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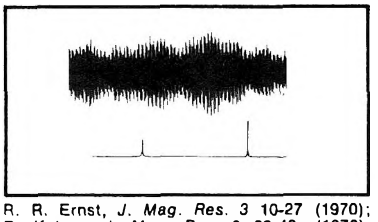

R. R. Ernst, *J. Mag. Res.* 3 10-27 (1970); R. Kaiser, *J. Mag. Res.* 3 28-40, (1970); J. Cooper and R. Addleman, 13th Experimental Nmr Conference (1972); E. Lippmaa, private communication.

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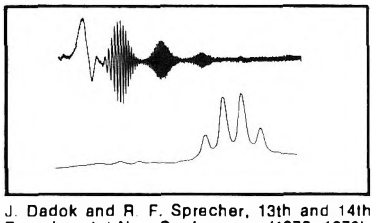

J. Dadok and R. F. Sprecher, 13th and 14th Experimental Nmr Conferences (1972, 1973); E. Becker, paper in press.

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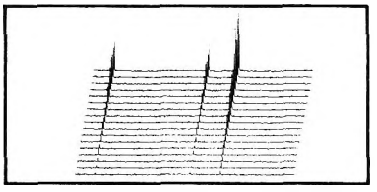

J. L. Markley, W. J. Horsley and M. P. Klein *J. Phys. Chem. 55* 3604 (1971); R. Freeman and H. D. W. Hill, *Ibid. 54* April (1971); G. G. McDonald and J. S. Leigh, Jr., *J. Mag. Res. 9* 358 (1973).

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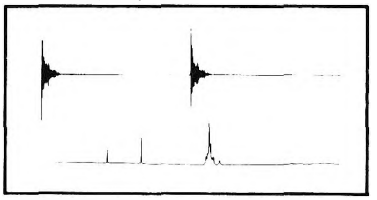

J. Schaeffer and E. O. Stejskal, 15th Experimental Nmr Conference (1974), and *J. Mag. Res.* March (1974) (In press). J. D. Ellett, et al. *Adv. Mag. Res.* 5 117 (1971)

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# THE JOURNAL OF Organic Chemistry





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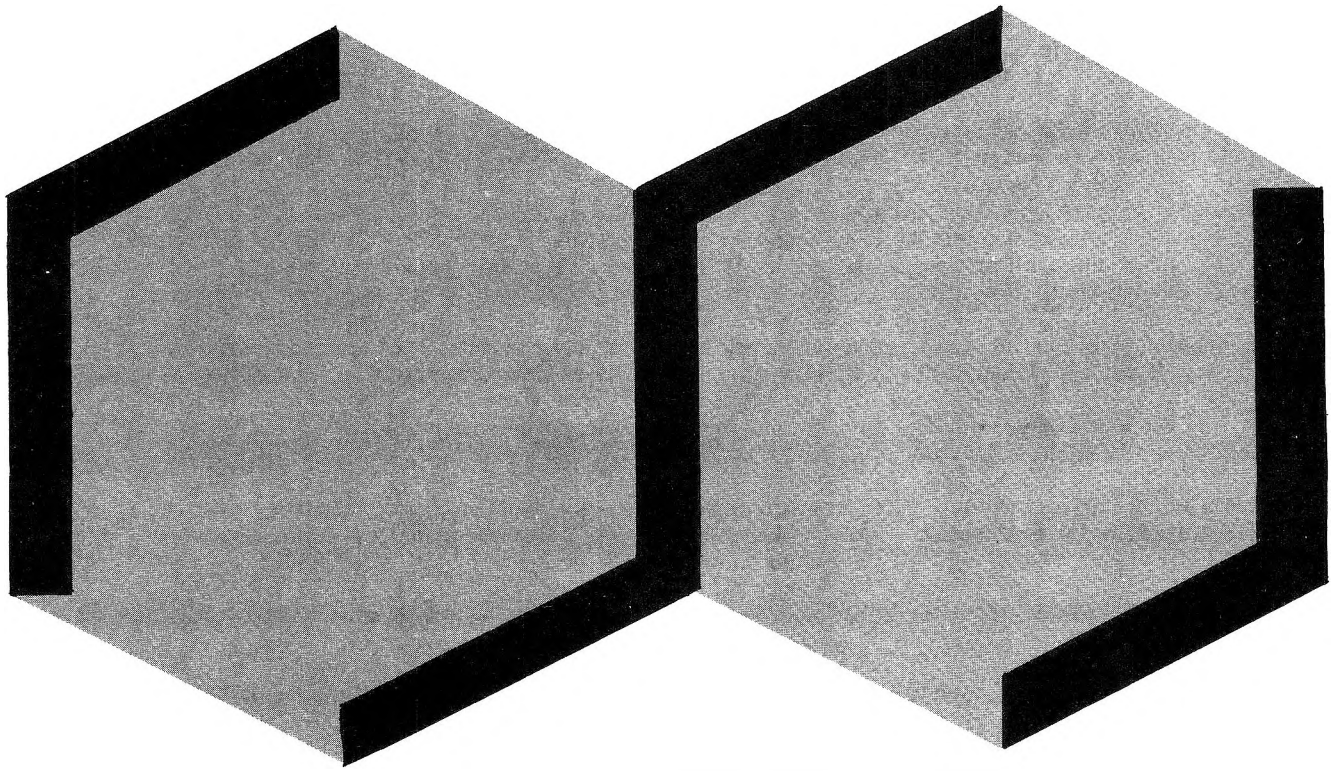

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THE JOURNAL OF Organic Chemistry®

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# Oxidation of Nucleic Acid Bases by Potassium Peroxodisulfate in Alkaline Aqueous Solution[1]

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*Received November 6, 1973*

The kinetics and products of peroxodisulfate oxidation of the common nucleic acid bases have been investigated in alkaline aqueous solution. The oxidations are first order in peroxodisulfate and first order in nucleic acid base. Relative rates in 1 *N* KOH at 40° follow: adenine, 1; thymine, 5.5; uracil, 5.2; cytosine, 8.6; guanine, 338. Values for the apparent second-order rate constants decrease with decreasing hydroxide ion concentration at constant ionic strength, suggesting involvement of the ionized base as the kinetically significant reactant. No significant reaction between peroxodisulfate and any nucleic acid base is observed under neutral or acidic conditions at 40°. Radical traps have no effect on either the rate or extent of peroxodisulfate disappearance or on the rate or extent of product formation. Uracil and cytosine were oxidized to uracil 5-sulfate and cytosine 5-sulfate, respectively. Urea was the only identified product of adenine and thymine oxidation. Oxidation of guanine produced ammonia, carbon dioxide, urea, guanidine, and 2,4-diamino-*s*-triazine-6-carboxylic acid. Triazinecarboxylic acid formation was also observed in 8-hydroxyguanine oxidation.

Chemical oxidation of the nucleic acid bases guanine, cytosine, adenine, uracil, and thymine has received considerable attention.[2] A partial list of the reagents employed to oxidize these materials includes potassium permanganate,[3-11] osmium tetroxide,[12-16] hydrogen peroxide,[17-19] and various organic peracids.[20-23] Potassium peroxodisulfate (persulfate, peroxydisulfate), a potent oxidant whose reactivity and utility are quite varied,[24-26] has received only limited use as an oxidant of purines or pyrimidines of biological origin. Biltz and Schauder[27,28] document its use as an oxidant of uric acid in acetic acid solution and more recently Hull[29] studied its reactions with substituted pyrimidines under alkaline conditions.

Work in our laboratory has recently been concerned with the investigation of reactions between nucleic acid components and a number of reagents[16,19,21,30] with the intention of devising or elaborating particular reactions which show promise as selective modifiers of nucleic acids. We therefore undertook a survey of the reactivity of the nucleic acid bases with peroxodisulfate. We report here the results of our observations on the kinetics and products of these reactions.

## Results

**Kinetics.** Under pseudo-first-order conditions with all bases except thymine, semilog plots for the disappearance of peroxodisulfate with time showed good linearity for at least 2 half-times. Initial concentrations were varied by at least a factor of 4 (Table I). Neither EDTA nor acrylamide, a sulfate radical ion trap,[19,31,32] had any significant effect on the rate of peroxodisulfate disappearance.

Semilog plots of peroxodisulfate disappearance in reaction with thymine in 1.0 *N* KOH at 40° showed satisfactory linearity for only approximately 10% of the reaction. Values for the apparent second-order rate constant for thymine oxidation were evaluated from these linear regions. Following this "induction" period, semilog plots of peroxodisulfate disappearance became concave downward. EDTA ($1 \times 10^{-4}$ *M*) and acrylamide ($5 \times 10^{-4}$ *M*) had no effect on the rate or extent of peroxodisulfate disappearance under these reaction conditions.

The kinetics of peroxodisulfate disappearance in reaction with thymine in 0.1 *N* KOH were also measured at 60°. Semilog plots of peroxodisulfate concentration *vs.* time were again concave downward, the induction periods varied depending on the reagents employed, and satisfactory linearity in the initial slopes of peroxodisulfate *vs.* time plots was generally not observed.

Oxygen exerted a significant retarding effect on the rate of peroxodisulfate disappearance in the presence of thymine in 0.1 *N* KOH at 60°. Both a lengthening of the observed induction period and a decrease in the maximum slope of semilog plots of peroxodisulfate concentration *vs.* time were observed. In contrast to the lack of linearity observed in its absence, thymine oxidations carried out in the presence of EDTA showed reasonable first-order dependence on peroxodisulfate for at least 1 half-time. These results suggest that metal ion catalyzed decomposition of peroxodisulfate is significant at this temperature in the absence of a sequestering agent such as EDTA.

While no definitive conclusion can be drawn as to the mechanism of thymine oxidation at 60° in 0.1 *N* KOH, the effects of EDTA and oxygen imply significant involvement by free radicals and metal ions in peroxodisulfate disappearance and present evidence that the mechanism of thymine oxidation at 40° is different from that at 60°.

The curvature observed in plots of peroxodisulfate disappearance *vs.* time for the oxidation of thymine at 40° in 1 *N* KOH is attributed to further oxidation of an initially formed product and not to free-radical decomposition. There are precedents in the literature for kinetics of this

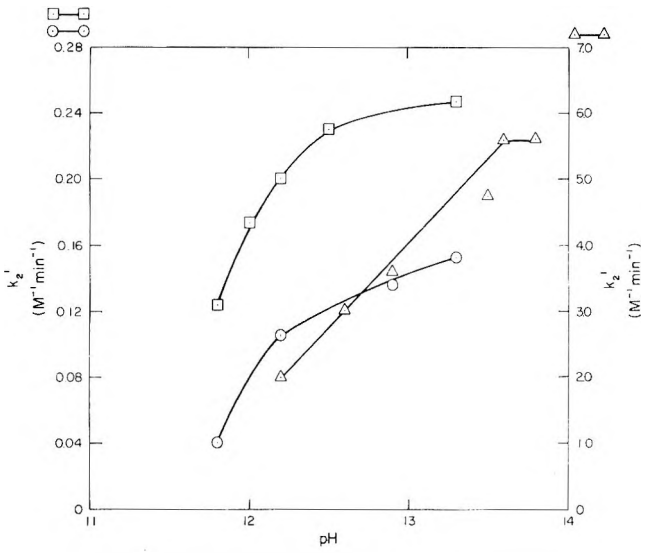



**Figure 1.** Apparent second-order rate constants as a function of pH: ⊙—⊙, uracil, 40°; ⊡—⊡, cytosine, 40°; △—△, guanine, 25°.

type.[26] This conclusion is consistent with the lack of effect EDTA and acrylamide on the rate of peroxodisulfate disappearance and with the observed stoichiometry of thymine oxidation, which will be presented in an accompanying section.

**Substrate Dependence.** Linearity in semilog plots of the concentration of peroxodisulfate *vs.* time suggests that peroxodisulfate disappearance may be described by the relationship $-d[S_2O_8^{2-}]/dt = k\psi[S_2O_8^{2-}]$, where $k\psi$ is the pseudo-first-order rate constant. The data of Table I suggest that $k\psi$ is a linear function of substrate concentration. The rate law for the disappearance of peroxodisulfate which satisfies these results is given by $-d[S_2O_8^{2-}]/dt = k_2'[\text{substrate}]_{\text{total}}[S_2O_8^{2-}]$, where $k_2' = k\psi/[\text{substrate}]_{\text{total}}$. For all cases considered, the disappearance of peroxodisulfate was first order in peroxodisulfate and first order in substrate. The rate law held for a minimum of 2 half-lives for each substrate. Guanine is the most reactive substrate with peroxodisulfate under these reaction conditions. The nucleic acid pyrimidines are oxidized at similar rates. Adenine is the least reactive substrate.

**pH Dependence.** Figure 1 shows the variation in the apparent second-order rate constant as a function of pH for the oxidation of uracil and cytosine at 40° and guanine at 25°. The data for cytosine and guanine show a plateau in the pH range 12.5–13 and 13.5–13.8, respectively. Half-maximal rates are observed near pH 11.8 for cytosine and 12.6 for guanine. A p$K_a$ of 11.7 for proton loss from cytosine was calculated for 40° using the heat of ionization for cytosine presented by Izatt and Christensen.[33] Izatt, Christensen, and Rytting[34] include a p$K_a$ of 12.62 for the second proton loss from guanine at 20°.

Uracil shows no well-defined plateau over the pH range investigated. The p$K_a$ for the second proton loss from uracil is greater than 13[34] at 25° and Shapiro and Kang[35] conclude it is probably nearer 14. These data, together with our observed two-fold rate increase for uracil oxidation over the pH range 12.2–13.3, suggest that the uracil dianion is more reactive toward peroxodisulfate than the singly ionized form. Similarly, only the cytosine anion is significantly reactive. These conclusions are supported by our observations[36] that the nucleosides of these bases do not react with peroxodisulfate at a significant rate in 1 *M* $Na_2CO_3$ solution.

Figure 1 shows that the guanine dianion is more reactive than the singly ionized form, although our findings[36] for guanosine (the nucleoside) suggest that the singly ionized form is appreciably reactive.

More limited data for thymine and adenine also suggest that it is the di- and monoanion, respectively, which are the reactive species. None of the substrates showed any detectable reaction with peroxodisulfate under neutral or acidic conditions at 40°.

**Table I**
**Kinetics of the Peroxodisulfate Oxidation of Nucleic Acid Bases[a]**

| Substrate | Concn range, *M* | $k_2'$, $M^{-1}$ min$^{-1}$ | Relative rate |
|---|---|---|---|
| Adenine | 0.025–0.100 | 0.029 ± 0.005 | 1 |
| Thymine | 0.0099–0.100 | 0.16 ± 0.03[b] | 5.5 |
| Uracil | 0.025–0.114 | 0.15 ± 0.006 | 5.2 |
| Cytosine | 0.0107–0.100 | 0.25 ± 0.02 | 8.6 |
| Guanine | 0.03 | 9.8 ± 0.3 | 338 |
| | 0.005–0.0200 | 5.16 ± 0.4[c] | |

[a] General conditions: [substrate]/[$K_2S_2O_8$] = 10, $T$ = 40°, 1.0 *N* KOH. [b] Evaluated from linear region of semilog plots of [$K_2S_2O_8$] *vs.* time. [c] 25°.

**Table II**
**Peroxodisulfate Oxidation of the Nucleic Acid Bases. Temperature Dependence[a]**

| Substrate | Temp, °C | $k_2'$, $M^{-1}$ min$^{-1}$ | $E_a$, kcal mol$^{-1}$ | $\Delta S^*$, cal mol$^{-1}$ deg$^{-1}$ |
|---|---|---|---|---|
| Guanine | 40 | 9.8 | 9.3 ± 0.3 | −34 ± 1 |
| | 25 | 5.2 | | |
| Cytosine | 50 | 0.49 | 13.5 ± 1.4 | −28 ± 5 |
| | 40 | 0.25 | | |
| Uracil | 50 | 0.30 | 13.9 ± 1.1 | −28 ± 4 |
| | 40 | 0.15 | | |
| Thymine | 40 | 0.16[b] | 11 ± 1.5 | −28 ± 5 |
| | 30 | 0.09[b] | | |
| Adenine | 50 | 0.058 | 13.9 ± 1.4 | −31 ± 4 |
| | 40 | 0.029 | | |

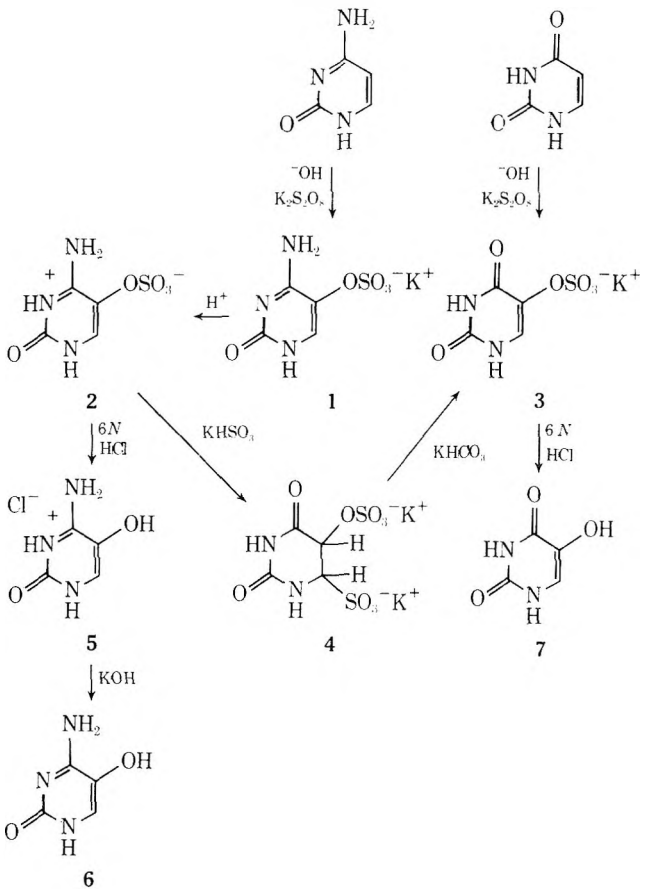
[a] General conditions: [substrate]/[$K_2S_2O_8$] = 10, 1 *N* KOH. Values are averages of two runs. [b] Evaluated from initial slopes of semilog plots of peroxodisulfate concentration *vs.* time.

**Ionic Strength Dependence.** The rates of oxidation of all of the bases increase with increasing ionic strength as expected for reaction between ions of like charge. Plots of the logarithm of the rate constants *vs.* the square root of ionic strength are linear in spite of the fact that the ionic strengths involved are far in excess of those for which the Debye–Hückel limiting law was derived.[37] The magnitude of the ionic strength effect is illustrated by the following data: guanine, 1.0 *M* KOH, $k_2' = 5.5\ M^{-1}$ min$^{-1}$, $\mu = 1$; same conditions but $\mu$ increased to 2.3 by the addition of KCl, $k_2' = 10.6\ M^{-1}$ min$^{-1}$.

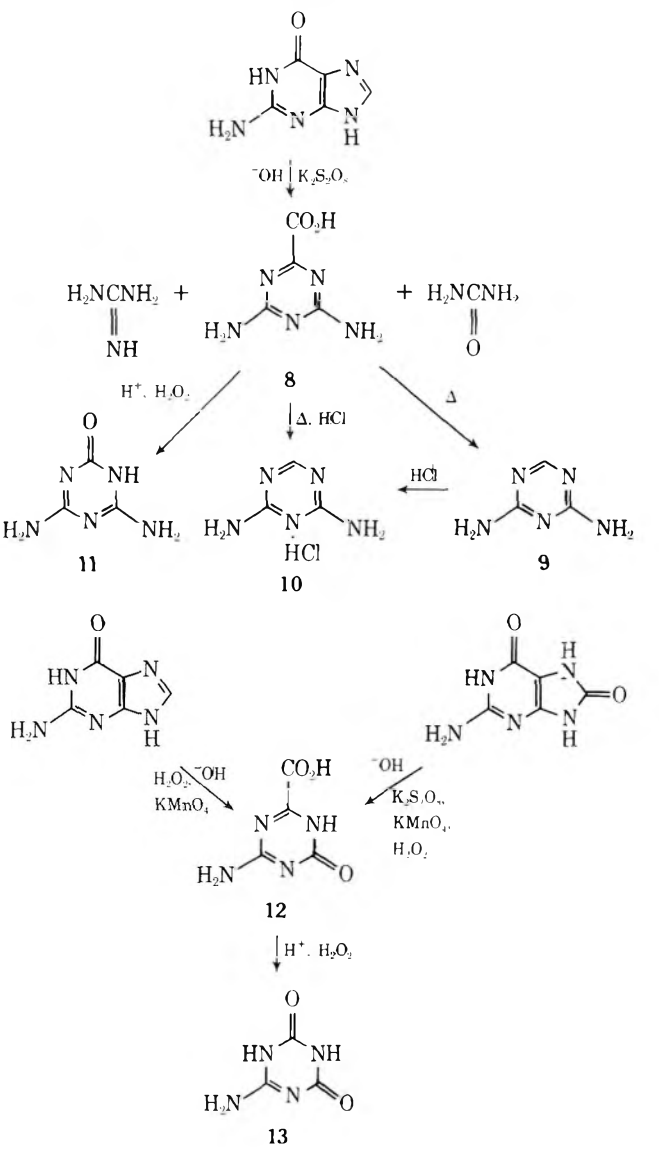
**Temperature Dependence.** The variation of the apparent second-order rate constants with temperature for adenine, thymine, uracil, cytosine, and guanine is presented in Table II along with the derived activation parameters.

**Products. Cytosine and Uracil.** Cytosine and uracil react with peroxodisulfate in 1 *N* KOH to yield the potassium salts of cytosine 5-sulfate (1) and uracil 5-sulfate (3), respectively (Scheme I). Paper chromatography of the reaction mixtures in solvent I showed starting material and the corresponding 5-sulfate to be the only ultraviolet-absorbing materials present in both reactions. No other products were detected when chromatograms were sprayed with either Ehrlich's reagent or the nitroprusside–ferricyanide–hydroxide spray. The 5-sulfates are the expected products based on the work of Hull.[29] At a substrate/peroxodisulfate ratio of 10 (the kinetic conditions), the yields of the 5-sulfates were 87 (cytosine) and 72%

**Scheme I**



**Scheme II**



(uracil). The yields dropped to 62 (cytosine) and 41% (uracil) at a substrate/peroxodisulfate ratio of 1. Cytosine 5-sulfate was isolated both as the free acid (2) and as the corresponding potassium salt (1). Uracil 5-sulfate was isolated as the potassium salt (3). The structures were assigned on the basis of ir spectra, nmr spectra in DMSO-$d_6$ and $D_2O$, elemental analyses, and hydrolysis of each material in 6 *N* HCl to known compounds, namely, 5-hydroxycytosine (6)[38] and 5-hydroxyuracil (isobarbituric acid, 7).[39,40] Further proof of the structures of these sulfates was obtained by the conversion of cytosine 5-sulfate to uracil 5-sulfate through the intermediacy of the bisulfite adduct, dipotassium 5-sulfo-6-sulfono-5,6-dihydrouracil (4). This material was prepared by incubating cytosine 5-sulfate (2) in 1 *M* $KHSO_3$ solution at 40° for 15 hr. The solid collected at the end of this incubation showed only end absorption in the ultraviolet. Its nmr spectrum in $D_2O$ showed the absence of the characteristic H-6 resonance typical of 5-substituted pyrimidines. The spectrum showed instead a pair of doublets centered at 4.80 and 5.55 ppm, $J$ = 6 Hz, resulting from coupling of two adjacent carbon-bound protons at positions 5 and 6 of a saturated pyrimidine ring. On addition of NaOD the doublets disappeared and a single H-6 resonance appeared. The elemental analysis for the product was correct for $C_4H_4N_2O_9S_2K_2$. On heating this material in 1 *M* $KHCO_3$ solution, a solid precipitated on cooling whose ir, uv, and nmr spectra and whose chromatographic behavior in solvent I were indistinguishable from those of the potassium salt of uracil 5-sulfate. These transformations are consistent with the known chemistry of bisulfite addition to pyrimidine rings.[41]

**Thymine.** Thymine reacts with peroxodisulfate in 1 *N* KOH to give ring-cleavage products. Paper chromatography of oxidation solutions showed the presence of three products. Two of the products were detected by Ehrlich's reagent. One of the Ehrlich-positive spots was identified as urea by its chromatographic mobility ($R_f$ in solvent I, 0.58), by its color development with Ehrlich's reagent, and by its destruction by the enzyme urease. The second Ehrlich-positive material ($R_f$ in solvent I, 0.18) became pink shortly after spraying with Ehrlich's reagent and became blue on standing in air for 3–4 hr. While this material was not identified, it should be pointed out that a compound with identical chromatographic mobility and color development properties can be prepared by incubation of *cis*-thymine glycol in 1 *N* KOH for 1 hr, conditions sufficient for complete degradation of thymine glycol.[9] The third component detected chromatographically appeared as a dark spot when viewed with an ultraviolet light source ($R_f$ in solvent I, 0.05). This material was not identified. Ultraviolet maxima at pH 1, 7, and 14 were obtained following elution of this material from paper chromatograms: $\lambda_{max}$ (pH 1) 273, $\lambda_{max}$ (pH 7) 270, $\lambda_{max}$ (pH 14) 291 nm.

Although hydroxyacetone and pyruvic acid have been observed as products of thymine oxidation in other systems,[3,19] we failed to detect either material. Control experiments showed that neither pyruvic acid nor hydroxyacetone survives incubation in 1 *N* KOH at 40° in the presence or absence of peroxodisulfate.

**Adenine.** The reaction of adenine with peroxodisulfate in 1 *N* KOH is complex and has not been elucidated here.

The reaction solutions are deep red in color and were shown chromatographically to be mixtures of a number of colored materials. Unchanged adenine was detected in reaction mixtures after 24-hr incubation in the presence of 2 equiv of peroxodisulfate in 1 *N* KOH at 40°. The red color of the alkaline reaction mixtures is immediately discharged by the addition of sodium dithionite or by acidification of the alkaline solutions but no readily recognizable materials were identified. Only urea was identified unambiguously.

**Guanine.** Products characterized in the alkaline peroxodisulfate oxidation of guanine were guanidine, urea, ammonia, carbon dioxide, and a material which is proposed to be 2,4-diamino-*s*-triazine-6-carboxylic acid. Guanidine was identified by its chromatographic mobility ($R_f$ in solvent I, 0.52), by its color development with the nitroprusside–ferricyanide–hydroxide spray, and by isolation as its crystalline picrate.[5] Ammonia was detected by its odor. Carbon dioxide was characterized by its liberation from acidified reaction solutions and by isolation as barium carbonate in a barium hydroxide trap.

A precipitate having properties consistent with the structure 2,4-diamino-*s*-triazine-6-carboxylic acid (8) (Scheme II) is obtained on acidification of guanine–peroxodisulfate oxidation mixtures. While neither this material nor those resulting from its various chemical transformations were isolated in adequate purity to provide acceptable elemental analyses, the infrared and mass spectra of the materials produced showed excellent agreement with known compounds.

The impure solid (8) which precipitates on acidification of guanine–peroxodisulfate product mixtures is sparingly soluble in acidic or neutral aqueous solution at room temperature but freely soluble in neutral buffered aqueous solution at pH greater than 6. It does not melt and shows no signs of decomposition at temperatures below 310°. At temperatures above 310° it decomposes with the liberation of dense white vapor. This vapor can be condensed on a cold-finger. The white sublimate shows a parent peak in its mass spectrum at *m/e* 111 and an ir spectrum identical with that of formoguanamine (guanamine, 2,4-diamino-*s*-triazine, **9**).

The impure, acid-precipitable solid (8) dissolves in hot 1 *N* HCl with the liberation of 50% of the theoretical amount of carbon dioxide. The ir spectrum of solid recovered following decarboxylation is virtually identical with that of authentic formoguanamine hydrochloride (**10**).

Oxidative decarboxylation of the guanine–peroxodisulfate precipitate (8) in $HCl$–$H_2O_2$ solution produces a material whose mass and ir spectra[42] are virtually identical with those of ammeline (2,4-diamino-6-hydroxy-*s*-triazine, **11**).

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Experimental Section

Chemicals.---Adenine (6-aminopurine), uracil (2,4-dioxypyrimidine), thymine (2,4-dioxy-5-methylpyrimidine), cytosine (2-oxy-4-aminopyrimidine), and guanine (2-amino-6-oxypurine) were purchased from the Sigma Chemical Company, St. Louis, Missouri. P and L Biochemicals Inc., Milwaukee, Wisconsin, Calbiochem, La Jolla, California, and Schwarz/Mann, Orangeburg, New York in pure form as determined by their ultraviolet spectra[58]. Guanidine hydrochloride was obtained from Heico, Inc., Delaware Water Gap, Pennsylvania. Dimethylsulfoxide, tetramethylsilane, 8-hydroxyguanine (2-amino-6,8-dioxypurine) and 2,4-diamino-6-chloro-*s*-triazine were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin. Dimethylsulfoxide was rendered anhydrous by storing over type 4-A molecular sieves obtained from Fisher Chemical, Fair Lawn, New Jersey. Deuterated dimethylsulfoxide (99.5% D) was purchased from Diaprep, Inc., Atlanta, Georgia, Prochem Ltd., Lincoln Park, New Jersey, and Norell Chemical Company, Inc., Landing, New Jersey. Deuterium oxide (99.8% D) was obtained from Norell Chemical Company, Landing, New Jersey. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate was obtained from Merck, Sharp and Dohme of Canada, Ltd., Montreal, Canada. Sodium deuteroxide (99% D) was purchased from E. Merck, Darmstadt, Germany. Potassium bromide (Optronic Grade) and phosphonium iodide were products of Alpha Inorganics-Ventron, Beverly, Massachusetts. Potassium peroxodisulfate was a Baker Analyzed Reagent, Phillipsburg, New Jersey and was recrystallized from water for use in kinetic experiments. All other inorganic chemicals were Baker Analyzed Reagents and were used without further purification.

Ammeline[59] (2,4-diamino-6-hydroxy-*s*-triazine) was prepared from 2,4-diamino-6-chloro-*s*-triazine by alkaline hydrolysis. Formoguanamine[59] (guanamine) (2,4-diamino-*s*-triazine) was prepared by reduction of 2,4-diamino-6-chloro-*s*-triazine using the hydriodic acid–

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phosphonium iodide method of Diels[60]

Instrumentation.---Ultraviolet absorption spectra were measured using a Perkin-Elmer Model 202 Spectrophotometer. Colorimetric measurements were carried out on a Klett-Summerson Colorimeter. Infrared spectra were recorded on a Perkin-Elmer Model 237-B Grating Infrared Spectrophotometer using potassium bromide discs as sample supports. Mass spectra were obtained on a Finnegan Model 1015SL Quadrupole Mass Spectrometer at 75 eV. Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 Spectrometer (60 MHz) at 35°. Tetramethylsilane was used as an internal standard in deuterated dimethylsulfoxide and sodium 2,2-dimethyl-2-silapentane-5-sulfonate in deuterium oxide.

Methods.---Kinetic runs were carried out in a water bath held to within 0.1° of the indicated temperature. Reactions were followed by measuring the disappearance of peroxodisulfate with time using a modification of the iodometric method of Kolthoff and Carr[51,61]. Blank corrections were in the range of 0.20 to 1.20 ml of 0.001 N thiosulfate. Kinetics were run under pseudo-first-order conditions by maintaining a substrate to peroxodisulfate ratio greater than or equal to 10. Values for the pseudo-first-order rate constants ($k\psi$) were obtained from the slopes of semi-log plots of the concentration of peroxodisulfate *vs.* time. Apparent-second-order rate constants ($k_2$) (no correction for per cent ionized) were obtained by division of the appropriate $k\psi$ values by total substrate concentration.

The variation in the determination of rate constants for reactions involving peroxodisulfate at concentrations of $10^{-3}$ M were generally of the order of ± 8%.

Urea was determined by the colorimetric method of Coulombe and Favreau[62]. Guanidine was determined by the colorimetric method of Marston[63] as presented by Snell and Snell[64]. In both cases, batchwise

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pretreatment of neutralized reaction aliquots with excess anion exchange resin (Bio-Rad AG 1-X8, 200-400 mesh, chloride form) to remove unreacted peroxodisulfate was required since peroxodisulfate interfered with both determinations.

The yields of cytosine-5-sulfate and uracil-5-sulfate were determined by reaction with the Folin phenol reagent[51] following hydrolysis in 3N HCl to the corresponding 5-hydroxy compounds. Uracil and cytosine do not interfere.

Paper chromatography (ascending) was performed on Whatman 3 MM paper in the machine-cut direction at 25° using isopropanol/ammonium hydroxide (58%)/water 7:1:2 v/v as solvent I. Dried chromatograms were sprayed with Ehrlich's reagent[65] for the visualization of urea and urea derivatives and the nitroprusside-ferricyanide-hydroxide spray[66] for the visualization of guanidine.

Elementary analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tennessee and Heterocyclic Chemical Company, Harrisonville, Missouri.

Hydrogen cytosine-5-sulfate monohydrate (2).---To a solution of 2.0 g cytosine (0.018 moles) in 100 ml 1.0 N KOH was added 7.3 g $K_2S_2O_8$ (0.027 moles) as a solid. The solution was stirred at room temperature for 18 hours. The pale yellow solution was brought to approximately pH 2 by the addition of 9 ml concentrated hydrochloric acid. When the solution was cooled a pale yellow precipitate formed. The solid was filtered, washed with cold water, acetone, and ether to afford 3.3 g (89%) of crude hydrogen cytosine-5-sulfate (2). One crystallization from 45 ml water afforded 2.6 g (70%) of pure product. Rf in Solvent I, 0.23; cytosine, 0.40. uv $\lambda_{max}^{pH\,1}$ 288 nm (ε 8950), $\lambda_{max}^{pH\,6.8}$ 277 nm (ε 5400), $\lambda_{max}^{pH\,14}$ 290 nm (ε 7700); ir (KBr) 3625, 3400, 3200, 3100, 1710, 1670, 1600, 1265, 1200, 1050, 850, 712 $cm^{-1}$; nmr (DMSO-$d_6$) δ 7.3 (broad, 4) 7.4 (s, 1, 6-H).

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Anal. Calcd for $C_4H_4N_3O_5S \cdot H_2O$: C, 21.33; H, 3.14; N, 18.66; S, 14.24. Found: C, 21.09; H, 2.30; N, 18.40; S, 14.23.

Potassium cytosine-5-sulfate monohydrate (1).---To a rapidly stirred suspension of 2 g hydrogen cytosine-5-sulfate (2) (0.01 mole) in 40 ml $H_2O$ was added 4 N KOH dropwise until the pH of the solution remained constant at pH 7. The solution was warmed to insure complete dissolution of all suspended solid and the pH readjusted to pH 7 by the additon of 4 N KOH. The resulting warm solution was diluted with 100 ml boiling ethyl alcohol and allowed to cool slowly to room temperature. The white solid which precipitated was filtered, washed with ethanol and ether and dried under vacuum over $P_2O_5$ for 15 hours to yield 2 g (85%) of potassium cytosine-5-sulfate monohydrate (1). ir (KBr) 3575, 3450, 3150, 1675, 1660, 1270, 1245, 1220, 1050, 840, 725 $cm^{-1}$; nmr (DMSO-$d_6$) δ 7.2 (s, 1, 6-H), 7.5 (broad, 3).

Anal. Calcd for $C_4H_4N_3O_5SK \cdot H_2O$: C, 18.25; H, 2.30; N, 15.96, S, 12.18. Found: C, 18.54; H, 2.10; N, 16.14; S, 12.58.

Dipotassium-5-sulfo-6-sulfono-5,6-dihydrouracil (4).---Hydrogen cytosine-5-sulfate (2), 0.5 g (0.0024 moles), was heated in 50 ml 1 M $KHSO_3$ solution until it dissolved completely. The solution was stored at 40°. Any solid which settled out of solution during the first 4 hours of incubation was redissolved by heating. Incubation at 40° was continued for a total of 15 hours. A white solid which was present at the end of this time was collected, washed with 10 ml water and acetone and dried under vacuum over $P_2O_5$ for 4 hours. The weight of dry solid was 0.35 g (40%). An analytical sample of dipotassium-5-sulfo-6-sulfono-5, 6-dihydrouracil (4) was prepared by one crystallization from water. ir (KBr) 3275, 3175, 3100, 1725, 1250, 1230, 1200, 1145, 1115, 1080, 1050, 1035, 865, 755, 700 $cm^{-1}$; nmr ($D_2O$) δ 4.80 (d, 1, J = 6 Hz, 5-H), 5.55 (d, 1, J = 6 Hz, 6-H); nmr ($D_2O$-NaOD) δ 7.6 (s, 1, 6-H).

Anal. Calcd for $C_4H_4N_2O_8S_2K_2$: C, 13.11; H, 1.10; N, 7.65; S, 17.50. Found: C, 13.12; H, 1.10; N 7.58; S, 17.67.

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Potassium uracil-5-sulfate (3).---To a solution of 2 g uracil (0.018 moles) in 100 ml 1 N KOH was added 9.6 g $K_2S_2O_8$ (0.036 moles) as a solid and the solution was stirred at 40° for 24 hours. The resulting colorless solution was neutralized with concentrated sulfuric acid and diluted to 200 ml by the addition of 100 ml methyl alcohol. The precipitated $K_2SO_4$ was removed by suction filtration and the methanol removed by evaporation under reduced pressure at 40°. The volume of the aqueous condensate was restored to 100 ml with water and a solution of 0.7 g $BaCl_2 \cdot 2H_2O$ in 20 ml of water was added with constant stirring. The precipitate was removed by gravity filtration and the filtrate condensed to dryness under reduced pressure at 40°. The solid residue was dissolved in 20 ml hot distilled water and was diluted to 100 ml with boiling acetone with rapid stirring. A semi-solid separated at once, and the hot supernatant suspension was decanted immediately and allowed to cool slowly to room temperature. The amorphous white solid which separated was redissolved in 20 ml hot water and reprecipitated by the addition of 80 ml boiling acetone. The isolated yield of crude potassium uracil-5-sulfate (3) was 0.7 g (14%). An analytical sample was prepared by recrystallization from water. Rf Solvent I, 0.125; uracil 0.43; uv $\lambda_{max}^{pH\,1}$ 268 nm (ε 7650), $\lambda_{max}^{pH\,6.8}$ 268 nm (ε 7650), $\lambda_{max}^{pH\,14}$ 283 nm (ε 7250); ir (KBr) 3180, 3090, 1730, 1710, 1315, 1290, 1270, 1245, 1230, 1065, 875, 730, 665 $cm^{-1}$; nmr (DMSO-$d_6$) δ 7.4 (s, 1, 6-H), 10.9 (broad, 2, 1 and 3 NH); nmr ($D_2O$-NaOD) 7.4 (s, 1, 6-H),

Anal. ---Calcd for $C_4H_3N_2O_5SK$: C, 19.51; H, 1.23; N, 11.38; S, 13.02. Found: C, 19.52; H, 1.25; N, 11.35; S, 13.22.

Potassium uracil-5-sulfate (3) from dipotassium-5-sulfo-6-sulfono-5, 6-dihydrouracil (4).---A solution prepared by heating 0.2 g dipotassium-5-sulfo-6-sulfono-5, 6-dihydrouracil (4) (0.0006 moles) in 2 ml 1 M $KHCO_3$ was kept warm in a boiling water bath with continuous stirring for approximately 5 minutes until all effervescence ceased. One drop of glacial acetic acid was added and the solution was allowed to cool

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slowly to room temperature and then chilled on ice until no further settling of white solid was evident. The solid was filtered, washed with 2 ml of distilled water, acetone, ether, and air dried to afford 0.08 g (57%) of potassium uracil-5-sulfate (3).

5-hydroxyuracil (isobarbituric acid) (7).---To a hot solution containing 1.2 g (0.005 moles) of crude potassium uracil-5-sulfate (3) in 7 ml water was added an equal volume of concentrated hydrochloric acid. A solid separated immediately from the hot solution and heating was continued for an additional 5 minutes. The solid was collected by filtration, washed with water until the odor of HCl was no longer detectable and dried over $P_2O_5$-KOH for 15 hours to yield 0.40 g (64%) of 5-hydroxyuracil (7). uv $\lambda_{max}^{pH\,1}$ 278 nm (ε 6550), $\lambda_{max}^{pH\,6.8}$ 278 nm (ε6300), $\lambda_{max}^{pH\,14}$ 305 nm (ε4750); ir (KBr) 3460, 3100, 3000, 2900, 2810, 1690, 1670, 1280, 1240, 1155, 830 $cm^{-1}$; nmr (DMSO-$d_6$) δ 6.8 (d, 1, 6-H), 7.2 (broad, 1, 5-OH), 10.1 (broad, 1, 1-NH), 11.1 (broad, 1, 3-NH).

Anal. Calcd for $C_4H_4N_2O_3$: C, 37.50; H, 3.15; N, 21.87. Found: C, 37.32; H, 2.98; N, 21.76.

5-hydroxycytosine (6).---A solution of 3 g hydrogen cytosine-5-sulfate (2) (0.014 moles) in 7 ml 6 N HCl was heated in a boiling water bath for 15 minutes. The resulting solution was chilled on ice to afford 2 g (85%) of water soluble 5-hydroxycytosine hydrochloride (5). This solid was dissolved in 30 ml warm distilled water and the pH of the stirred solution adjusted to pH 7 by the dropwise addition of 4 N KOH. The free base precipitated, was washed with water, acetone, and ether and dried under vacuum over $P_2O_5$ for 15 hours to afford 1.2 g (77%) of 5-hydroxycytosine (6). uv $\lambda_{max}^{pH\,1}$ 300 nm (ε8000), $\lambda_{max}^{pH\,6.8}$ 288 nm (ε5000), $\lambda_{max}^{pH\,14}$ 322 nm (ε5950); ir (KBr) 3175, 2850, 1725, 1600, 1475, 1445, 1200, 812 $cm^{-1}$.

Anal. Calcd for $C_4H_5N_3O_2$: C, 37.79; H, 3.97; N, 33.06. Found: C, 37.51; H, 3.74; N, 32.91.

These data and the analogies between the chemical transformations observed for the guanine-oxidation product and for the triazinecarboxylic acid isolated in the alkaline oxidation of uric acid[43-48] provide compelling evidence that 2,4-diamino-*s*-triazine-6-carboxylic acid is a product of guanine oxidation under the conditions employed here.

Peroxodisulfate consumption is virtually complete in the reaction with guanine over a period of 7 hr at 40° in 1.0 *N* KOH with 0.05 *M* peroxodisulfate and 0.01 *M* guanine. One mole of guanine consumes 2.4 mol of peroxodisulfate. This figure is unchanged if the reaction is carried out in 1 *M* sodium carbonate.

The molar ratios of product formed per mole of guanine oxidized follow: urea, 0.25; guanidine, 0.55; and 2,4-diamino-*s*-triazine-6-carboxylic acid, 0.13. Neither urea nor guanidine is oxidized by peroxodisulfate under the reaction conditions. If we assume that these three products are formed by independent routes, then they account for 93% of the guanine oxidized.

Among the bases, the largest overall consumption of $K_2S_2O_8$ is observed in the reaction with thymine in 1 *N* KOH. The ratio of peroxodisulfate consumed per mole of substrate approaches 4 over a 24-hr period. In the presence of a five-fold molar excess of peroxodisulfate, adenine consumes 2 equiv of peroxodisulfate over the same time period. Under these conditions, 0.37 mol of urea is formed per mole of thymine while 0.25 mol of urea is formed per mole of adenine.

Acrylamide had no significant effect on the rate or extent of product formation in these reactions though the overall consumption of peroxodisulfate was greater in the presence of acrylamide than in its absence. Control experiments showed that peroxodisulfate is consumed in the presence of acrylamide alone in 1 *N* KOH at 40° over a 24-hr period. No significant loss of peroxodisulfate in 1 *N* KOH at 40° was observed over the same time period in the absence of acrylamide.

**Oxidations with Some Related Oxidants and Substrates.** The permanganate oxidation of guanine in 1 *N* KOH at 40° produces guanidine, urea, and 2-amino-4-hydroxy-*s*-triazine-6-carboxylic acid (**12**). The amount of urea and guanidine produced was not measured. The yield of triazinecarboxylic acid as determined by the weight of acid-precipitable solid following guanine oxidation is approximately 20%. Oxidation of guanine by hydrogen peroxide in 1 *N* KOH at 40° affords 2-amino-4-hydroxy-*s*-triazine-6-carboxylic acid (**12**) and urea as identified products. The yield of triazinecarboxylic acid with this latter oxidant is approximately 11%. Unreacted guanine (70%) is

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2,4-diamino-s-triazine-6-carboxylic acid (8) (Method I).--- To a solution of 1 g guanine (0.0066 moles) in 100 ml of 1 N KOH was added 5.3 g $K_2S_2O_8$ (0.02 moles) as a solid and the mixture was stirred at room temperature until all the $K_2S_2O_8$ dissolved. The homogeneous solution was then stored at 40° for 18 to 24 hours. At the end of this time the resulting pale yellow solution was acidified to pH 2 by the addition of concentrated hydrochloric acid. Acidification was accompanied by the evolution of $CO_2$ and the precipitation of a pale yellow amorphous solid. This solid was collected by suction filtration, washed with water, acetone, and ether and dried under vacuum over $P_2O_5$ for 4 hours to afford 0.27 g of dry solid. uv: 12.8 mg of solid was dissolved in 100 ml hot water. After cooling, aliquots of solution were diluted 1/10 with either 0.1 N HCl, pH 6.8 buffer or 1 N KOH; $\lambda_{max}^{pH\ 1}$ 210 nm (broad end absorption), $\lambda_{max}^{pH\ 6.8}$ 256 nm; $\lambda_{max}^{pH\ 14}$ 254 nm.

Anal. Calcd for $C_4H_5N_5O_2$: C, 30.97; H, 3.23; N, 45.16. Found: C, 26.12; H, 4.61; N, 41.84.

2,4-diamino-s-triazine (formoguanamine) (9).---Dry, finely powdered pH 2 precipitate (8) was heated with a burner flame in a sublimation apparatus below a cold finger cooled by running water. The flame was removed at the first appearance of white vapor. When vaporization ceased, heat was again applied until the formation of additional vapor began. This process was cautiously repeated until no additional white vapor appeared after brief heating. A dark brown non-volatile residue (16 mg)(20%) remained. A white sublimate (8 mg) (9) was recovered. Mass spectrum:m/e 111; ir (KBr) 3440, 3370, 3120, 1670, 1590, 1550, 1475, 1370, 1325, 1270, 1160, 1060, 1000, 815, 720 $cm^{-1}$.

Decarboxylation of 2,4-diamino-s-triazine-6-carboxylic acid (8). ---To 6 ml of 1 N HCl in a 12 ml test tube was added 0.060 g of the pH 2 precipitate (8) The stoppered tube was connected by tubing to two 12 ml test tubes in series each containing 10 ml 6% $Ba(OH)_2 \cdot 8H_2O$ solution.

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The entire system was purged with nitrogen prior to and during the decarboxylations. The tube containing the suspended solid sample was supported in a boiling water bath and the evolved $CO_2$ collected until all of the solid sample had dissolved in the acid solution (45 minutes). No additional $CO_2$ could be collected if heating was continued after all solid had dissolved. By this method, 0.036 and 0.039 g $BaCO_3$ were obtained from two 0.060 g portions of sample The average weight of $BaCO_3$ collected corresponded to 50% of theoretical if all the solid sample were pure 2,4-diamino-s-triazine-6-carboxylic acid. Therefore, assuming that the quantitation of evolved $CO_2$ provided an accurate measure of the triazine carboxylic acid present, then approximately 50% (0.13 g) of the total dry weight of the pH 2 precipitate was 2,4-diamino-s-triazine-6-carboxylic acid. This weight corresponds to an overall yield of 13% based on the amount of guanine oxidized.

2,4-diamino-s-triazine-6-carboxylic acid (8) (Method II) ---To a solution of 4 g guanine (0.027 moles) in 400 ml 1 N KOH was added 21.2 g $K_2S_2O_8$ (0.079 moles) as a solid and the resulting mixture stirred at room temperature until all $K_2S_2O_8$ had dissolved. The solution was stored at 40° for 24 hours. At the end of this incubation, the alkaline reaction solution was mixed with 9 g Norit-A (acid washed) charcoal and the mixture stirred for 10 minutes. The charcoal was filtered by suction filtration. The collected charcoal was slowly eluted on the same filter with 150 ml hot distilled water. The eluent was filtered through celite to remove any suspended charcoal and the pH of the resulting filtrate adjusted to pH 2 by the addition of concentrated HCl. A white precipitate formed and the solution was chilled on ice until no further settling of solid was detected. The precipitate was collected by filtration, washed with water, acetone, and ether and air dried to afford 0.30g of white powder. Mass spectrum:m/e 44 ($CO_2$) and m/e 111 (P-44); ir (KBr) 3700-2500 (broad), 1650, 1575, 1480, 1380, 1350, 1330,

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1075, 990, 940, 780 $cm^{-1}$.[67] Decarboxylation of 0.0398 g of this material produced 0.0391 g of $BaCO_3$ or 77% of theoretical.

Anal. Calcd for $C_4H_5N_5O_2$: C, 30.97; H, 3.23; N, 45.16. Found: C, 29.95; H, 3.41; N, 41.15.

2,4-diamino-s-triazine hydrochloride (formoguanamine hydrochloride) (10).---To 5 ml of 1 N HCl in a 12 ml test tube was added 0.08 g of crude charcoal-eluted pH 2 precipitate. The suspension was heated in a boiling water bath for 45 minutes, withdrawn, and cooled to room temperature. A solid (0.008 g) precipitated, was filtered and discarded. The filtrate was evaporated twice to dryness with water and the white residue was dried for 12 hours under vacuum over $P_2O_5$-KOH to afford 0.05 g of solid whose ir spectrum was essentially identical to the spectrum of 2,4-diamino-s-triazine hydrochloride (10). ir (KBr) 3250, 3120, 2750, 1675, 1630, 1600, 1550, 1500, 1440, 1370, 1220, 1160, 1040, 1000, 960, 840, 790, 675 $cm^{-1}$.

2,4-Diamino-6-hydroxy-s-triazine (Ammeline) (11) by Oxidative Decarboxylation of (8).---To 3 ml 1 N HCl in a 12 ml test tube was added 0.03 g of charcoal-eluted pH 2 precipitate (8) (Method II) and 0.5 ml 30% $H_2O_2$. The mixture was heated on a boiling water bath for 30 minutes. The pH of the resulting homogeneous colorless solution was adjusted to pH 4 by neutralization with 0.3 ml 10 N KOH and 1 drop of glacial acetic acid. A white precipitate formed immediately and was filtered, washed with water, acetone, ether and air dried to yield 0.018 g of white powder. The powder was dissolved in 2 ml hot 0.5 M $Na_2CO_3$ solution and allowed to cool slowly to room temperature. The solid which separated on cooling was filtered, washed with water, acetone, and ether and air dried to afford 0.008 g of white powder. Mass spectrum: m/e 111, 127. The mass spectrum of authentic ammeline showed the same prominent peaks. The ir spectrum was in agreement with that presented by Padgett and Hamner[42].

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2,4-Diamino-6-hydroxy-s-triazine (Ammeline) (11) by Alkaline Hydrolysis of 2,4-Diamino-6-chloro-s-triazine. ---To a solution of 100 ml 1.0 N KOH was added 1 g (0.007 moles) of 2,4-diamino-6-chloro-s-triazine. The solution was boiled with vigorous stirring until all the solid had dissolved and allowed to cool slowly to room temperature. When cool, the pH of the resulting solution was adjusted to pH 6 by the addition of concentrated hydrochloric acid. The white solid which precipitated was collected by filtration and washed with water, acetone, and ether to afford 0.78 g(89%) of ammeline. The infrared spectrum of this material was in good agreement with the spectrum presented by Padgett and Hamner[42] although the spectrum of ammeline prepared by the above method showed greater resolution.

2-Amino-4-hydroxy-s-triazine-6-carboxylic acid hemihydrate (12) by Hydrogen Peroxide Oxidation of Guanine. ---To a solution of 100 ml 1 N KOH was added 2 g guanine (0.013 moles) and 9 ml 30% hydrogen peroxide (0.08 moles). The homogeneous solution was kept at 40° for 24 hours. At the end of the incubation the excess hydrogen peroxide was destroyed with $MnO_2$ and the alkaline solution filtered. The pH of the resulting filtrate was adjusted to pH 6 by the addition of concentrated HCl. Unreacted guanine precipitated and was filtered. The pH of the resulting filtrate was adjusted to pH 2 by the addition of concentrated HCl. The white solid which precipitated was collected by filtration, washed with water, acetone, and ether and air dried to afford 0.23 g (11%) of solid. ir (KBr) 3600-2000 (broad) 3150, 1750, 1675, 1600, 1525, 1455, 1375, 1350, 1220, 1120, 1055, 1010, 925, 830, 780, 770 $cm^{-1}$.

Anal. Calcd for $C_4H_4N_4O_3 \cdot 1/2\ H_2O$: C, 29.09; H, 3.03; N, 33.94. Found: C, 29.39; H, 3.12; N, 34.50.

2-Amino-4,6-dihydroxy-s-triazine (Ammelide) (13) by Oxidative Decarboxylation of (12). ---To a solution of 3 ml 1 N KOH in a 12 ml test tube was added 0.08 g (12) and 0.5 ml 30% hydrogen peroxide. The

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mixture was heated on a boiling water bath until all material dissolved (15 minutes), removed, and allowed to cool slowly to room temperature. The pH of the colorless solution was adjusted to pH 4 by neutralization with 0.3 ml 10 N KOH and 1 drop of glacial acetic acid. A solid separated immediately, and the solution was allowed to stand at room temperature until no further settling of solid was apparent. The precipitate was collected by filtration, washed with water, acetone, and ether and air dried to afford 0.043 g (61%) of white powder whose ir spectrum was in excellent agreement with the spectrum for ammelide (13) (2-amino-4,6-dihydroxy-s-triazine) presented by Padgett and Hamner[42].

Anal. Calcd for $C_3H_4N_4O_2$: C, 28.12; H, 3.12; N, 43.75. Found: C, 27.92; H, 3.10; N, 43.83.

2-Amino-4-hydroxy-s-triazine-6-carboxylic acid (12) by Permanganate Oxidation of Guanine ---Oxidation of 2 g (0.013 moles) guanine in 100 ml 1.0 N KOH by 2 equivalents of potassium permanganate for 24 hours at 40° produced 0.4 g (20%) of (12).

2-Amino-4-hydroxy-s-triazine-6-carboxylic acid (12) by Oxidation of 8-hydroxyguanine with Potassium Peroxodisulfate, Potassium Permanganate, and Hydrogen Peroxide. ---To 100 ml of 1 N KOH was added 2 g of 8-hydroxyguanine (0.012 moles) and 6.5 g $K_2S_2O_8$ (0.024 moles). The solution was stirred at room temperature until all the $K_2S_2O_8$ had dissolved. The homogeneous solution was stored at 40° for 24 hours. Following the incubation, the pH of the pale-green solution was adjusted to pH 6 with concentrated HCl. Any precipitated solid was filtered and the pH of the filtrate adjusted to pH 2 by the addition of concentrated HCl. A white solid precipitated immediately and the solution was allowed to stand at room temperature until settling of solid was complete. The white solid was collected by filtration, washed with water, acetone, and ether and air dried to afford 0.33 g (17%) of (12) as confirmed by its ir spectrum.

Oxidation of 2 g (0.012 moles) 8-hydroxyguanine in 100 ml 1.0 N KOH by 2 equivalents of potassium permanganate for 24 hours at 40°

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produced 0.7 g (37%) of 2-amino-4-hydroxy-s-triazine-6-carboxylic acid.

Oxidation of 2 g 8-hydroxyguanine by 4 equivalents of hydrogen peroxide under identical reaction conditions produced 0.6 g (32%) of the same triazine carboxylic acid.

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67. This ir spectrum is identical to the ir spectrum of authentic material prepared according to Brüning's method[57b] by $KMnO_4$ oxidation of acetoguanamine (2,4-diamino-6-methyl-s-triazine).

We thank the American Cyanamid Co. for a generous supply of acetoguanamine.

recovered after 24 hr of hydrogen peroxide oxidation even in the presence of a fourfold molar excess of peroxide.

Urea and 2-amino-4-hydroxy-*s*-triazine-6-carboxylic acid are products of 8-hydroxyguanine oxidation in 1 *N* KOH at 40° when either potassium peroxodisulfate, potassium permanganate, or hydrogen peroxide is used as oxidant. Unreacted 8-hydroxyguanine is recovered when hydrogen peroxide is used as an oxidant. A schematic summary of these transformations is included in Scheme II. Oxidative decarboxylation of 2-amino-4-hydroxy-*s*-triazine-6-carboxylic acid produced a material whose ir spectrum is in excellent agreement with that presented for ammelide[42] (2-amino-4,6-dihydroxy-*s*-triazine, **13**). The elemental analysis is also correct for ammelide.

## Discussion

A reasonable mechanism for the formation of uracil 5-sulfate and cytosine 5-sulfate from the reactions of uracil and cytosine with peroxodisulfate in 1 *N* KOH involves bimolecular nucleophilic displacement by the cytosine anion or the uracil dianion on the peroxide oxygen of peroxodisulfate. A similar mechanism has been invoked in the peroxodisulfate oxidation of phenols[49,50] and aromatic amines[51] in alkaline solution. Nucleophilic displacements on peroxide oxygen are well known and have been reviewed by Edwards,[52] Curci and Edwards,[53] and Behrman and Edwards.[54]

Neither cytosine 5-sulfate or uracil 5-sulfate has been previously described. The hydrolysis of cytosine 5-sulfate in 6 N HCl provides a convenient method for the synthesis of 5-hydroxycytosine, a material available previously in low yield through a multistep procedure.[38] Cier, *et al.*,[55] report this material as a product formed from the reaction of the Fenton reagent on cytosine. Ekert and Monier[56] suggest that it is one of the products formed from cytosine in aerated aqueous solution under the influence of X-rays, although no evidence was given.

We suggest that the peroxodisulfate oxidations of guanine, thymine (at 40°), and adenine also proceed *via* initial bimolecular nucleophilic displacement on the peroxide oxygen of peroxodisulfate. The site of attack by peroxodisulfate cannot be described with certainty for any of these substrates. Neither the rate of peroxodisulfate consumption nor the rate or extent of ring-cleavage product formation is affected by the presence of acrylamide, a known free-radical trap. This suggests that for at least the major part of these reactions a free-radical mechanism is not involved. If any of the product-forming steps in these reactions involved a significant free-radical contribution, then the introduction of a radical trap known to react with sulfate radical ions ($SO_4\cdot^-$) or hydroxyl radicals ($HO\cdot$) would result in a decrease in both the yield and rate of formation of the ring-cleavage products in these reactions. The increases observed in the overall consumption of peroxodisulfate in the presence of acrylamide and nucleic acid bases in 1 *N* KOH indicates that peroxodisulfate reacts with acrylamide under these reaction conditions but the reaction between peroxodisulfate and nucleic acid base is not significantly altered.

The observed activation energies for the oxidation of all the nucleic acid bases are in the range of 9–14 kcal $mol^{-1}$. The entropies of activation are in the range −28 to −34 cal $mol^{-1}$ $deg^{-1}$. These values are consistent with a large number of activation energies and entropies of activation for reactions involving nucleophilic displacement on peroxide oxygen[52-54] and are very similar to the values obtained for the peroxodisulfate oxidation of phenols[49,50] and aromatic amines[51] in alkaline solution. Activation energies for reactions involving formation of sulfate-anion radicals ($SO_4\cdot^-$) by homolysis of peroxodisulfate in the rate-limiting step are commonly of the order of 25 kcal $mol^{-1}$.[26]

Guanine reacts more rapidly with peroxodisulfate than any of the other nucleic acid bases under the conditions employed in this investigation. The identified products are urea, guanidine, and 2,4-diamino-*s*-triazine-6-carboxylic acid.

2-Amino-4-hydroxy-*s*-triazine-6-carboxylic acid has evidently not been previously described. 2,4-Diamino-*s*-triazine-6-carboxylic acid has been reported in the patent literature.[57] The structural assignment for 2,4-diamino-*s*-triazine-6-carboxylic acid is based on evidence that it decarboxylates in hot acidic solution to formoguanamine (2,4-diamino-*s*-triazine). It is oxidatively decarboxylated under the same conditions in the presence of hydrogen peroxide to ammeline (2,4-diamino-6-hydroxy-*s*-triazine). These transformations are analagous to those reported for oxonic acid (2,4-dihydroxy-*s*-triazine-6-carboxylic acid).[43-48] Oxonic acid decarboxylates in acid solution to allantoxaidin (2,4-dihydroxy-*s*-triazine). Oxidative decarboxylation in the presence of hydrogen peroxide affords cyanuric acid (2,4,6-trihydroxy-*s*-triazine). Thus, the oxidation of uric acid,[43-48] guanine, and 8-hydroxyguanine in alkaline solution afford triazinecarboxylic acids as oxidation products.

The formation of 2,4-diamino-*s*-triazine-6-carboxylic acid by peroxodisulfate oxidation of guanine in alkaline solution is particularly interesting since the permanganate and hydrogen peroxide oxidation of guanine produce 2-amino-4-hydroxy-*s*-triazine-6-carboxylic acid under the same reaction conditions. We failed to detect any deamination of 2,4-diamino-*s*-triazine-6-carboxylic acid to the 2-amino-4-hydroxy compound after 24-hr incubation in 1 *N* KOH at 40° and conclude that the formation of the former triazinecarboxylic acid by peroxodisulfate oxidation of guanine must proceed by a pathway which differs from the pathway of hydrogen peroxide and permanganate oxidation.

There is little justification for presentation of a mechanism for the peroxodisulfate oxidation of guanine analagous to Brandenberger's proposed mechanism for the alkaline oxidation of uric acid.[47] We can, however, rely on the previous investigations of Brandenberger[44-46] and Cannelakis and Cohen[43] to lend support to our contention that the mechanisms for the oxidation of either purine are probably similar.

Brandenberger and Cannelakis and Cohen demonstrated that carbons 2, 4, and 8 of uric acid were incorporated in the triazine ring of the oxonic acid formed as a result of the alkaline oxidation of uric acid using either hydrogen peroxide or potassium permanganate as an oxidant. It seems reasonable that the same carbons of guanine are incorporated in the triazine ring of 2,4-diamino-*s*-triazine-6-carboxylic acid as a result of the alkaline oxidation of guanine by potassium peroxodisulfate.

This conclusion is based on the following evidence. Both urea and guanidine are liberated in the peroxodisulfate oxidation of guanine, although the molar ratio of urea or guanidine produced per mole of guanine oxidized is less than 1. Control experiments indicate that neither urea nor guanidine is attacked by peroxodisulfate in 1 *N* KOH or in 1 *M* $Na_2CO_3$ solution. Guanidine, however, is degraded by prolonged incubation in 1 *N* KOH in the absence of peroxodisulfate. Paper chromatograms of 1% guanidine hydrochloride solutions incubated at 40° for 24–48 hr in 1 *N* KOH reveal the presence of guanidine and at least two materials which are detected by Ehrlich's reagent. Although one of the Ehrlich-positive spots is urea, we point out that the production of urea from guanidine degrada-

tion is not significant over the time period used to measure the complete oxidation of guanine in 1 *M* $Na_2CO_3$ solution and since the same stoichiometries are observed for the degradation of guanine in both 1 *N* KOH and 1 *M* $Na_2CO_3$, we conclude that the urea liberated in both cases is not exclusively due to the alkaline degradation of guanidine. Hence, guanidine liberation represents destruction of the pyrimidine portion of the guanine molecule while urea production must represent oxidative degradation of the imidazole ring.

The molar ratio of urea and guanidine liberated per mole of guanine oxidized is 0.25 and 0.55, respectively. Under the assumption that the urea liberated contains carbon 8 of the guanine molecule and that the guanidine liberated contains carbon 2, then no more than a 20% yield of 2,4-diamino-*s*-triazine-6-carboxylic acid could be produced if carbons 2 and 8 of the guanine skeleton were incorporated into the triazine ring of 2,4-diamino-*s*-triazine-6-carboxylic acid. The measured yield of this material by determination of the amount of carbon dioxide liberated from weighed samples of acid-precipitable guanine oxidation product is about 13%.

While the measured amounts of guanidine and urea are identical for the peroxodisulfate oxidation of guanine in either 1 *N* KOH or 1 *M* $Na_2CO_3$ solution, no solid can be collected on acidification of reactions following oxidation in 1 *M* $Na_2CO_3$ solution. We conclude that the formation of triazinecarboxylic acid by guanine oxidation under these conditions must either not take place or takes place to a lesser extent than in the case of guanine oxidation in 1 *N* KOH. Similarly, no 2-amino-4-hydroxy-*s*-triazine-6-carboxylic acid can be isolated from acidic solution when 8-hydroxyguanine is oxidized by potassium peroxodisulfate in 1 *M* $Na_2CO_3$ solution. It is reasonable to conclude that solutions of higher alkalinity are required for the formation of triazinecarboxylic acid by oxidation of either purine.

Urea production in the case of thymine oxidation by potassium peroxodisulfate in 1 *N* KOH at 40° indicates destruction of the pyrimidine ring but again the molar ratio of urea produced per mole of substrate oxidized is less than 1. Urea production in the alkaline oxidation of adenine represents degradation of the original molecule, but the structure of the intact adenine ring system presents at least two possible sites for oxidative release of urea under alkaline conditions.

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**Registry No.**—**1**, 51392-10-0; **2**, 51392-11-1; **3**, 51392-12-2; **4**, 51392-13-3; **5**, 51392-14-4; **6**, 13484-95-2; **7**, 20636-41-3; **8**, 13055-81-7; **9**, 504-08-5; **10**, 51392-15-5; **11**, 645-92-1; **12**, 42240-01-7; **13**, 645-93-2; adenine, 73-24-5; thymine, 65-71-4; uracil, 66-22-8; cytosine, 14987-28-1; guanine, 73-40-5; potassium peroxodisulfate, 7727-21-1.

**Miniprint Material Available.** Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1983.

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# *trans*-Di-*tert*-butylcyclopropanone. Preparation, Properties, Resolution, and Reaction with Nucleophiles[1]

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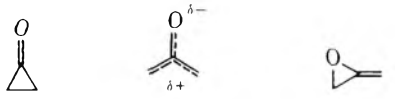
*trans*-Di-*tert*-butylcyclopropanone (1) has been prepared by reaction of potassium *tert*-butoxide with α-bromodineopentyl ketone. Partial resolution has been effected by reaction with *d*-amphetamine and with diisopinylcampheylborane. Reaction of 1 with water affords the hydrate (rates and equilibrium constants are reported in Table I). Reaction of 1 with alcohols affords the hemiketals, isolable for primary alcohols (relative rates of formation of hemiketals in alcohol solution at 25° follow: methanol, 90; ethanol, 20; isopropyl alcohol, 1; *tert*-butyl alcohol, 0). The rate of reversion of the methanol hemiketal to 1 in methanol has been determined by use of deuterium-labeled hemiketal. Under basic conditions the hemiketals are converted to the ring-opened Favorskii ester 2, under acidic conditions to α-alkoxy ketone 3. Reaction of 1 with potassium *tert*-butoxide in *tert*-butyl alcohol-*O*-*d* affords ester 3 of deuterium content $d_0$ 3%, $d_1$ 50%, $d_2$ 31%, $d_3$ 16%, pointing to some attack at α hydrogen. The cyclopropanone is stable to oxygen; the hydrate and hemiketals are not.

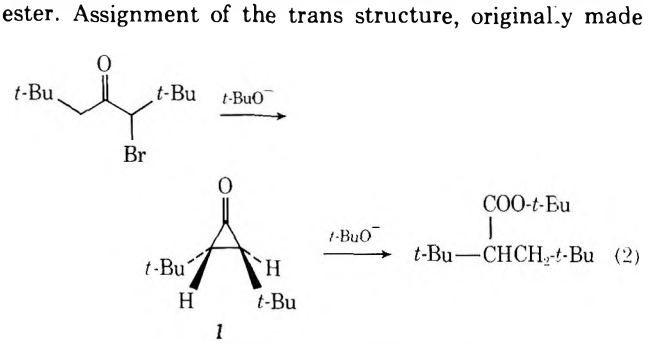
The cyclopropanone functionality has been an elusive one. Considerable interest attaches to this class, however, because of the possible breadth of reactions associated with the carbonyl group in a three-membered ring and the synthetic relevance to the Favorskii reaction. Cyclopropanones might be expected to possess three points of reactivity: (1) the carbonyl group, (2) the hydrogens α to the carbonyl group, and (3) the C-2–C-3 bond. The possibility of reactivity of C-2–C-3 is associated with the question of small-ring valence isomerization of the type shown in eq 1.



(1)

Various aspects of cyclopropanone reactions have been examined and reviewed[2] over the past few years, primarily with cyclopropanones containing small substituents. The high reactivity of these cyclopropanones has precluded isolation and has often involved special methods of preparation.[2a,3] In 1967 we reported the preparation of *trans*-di-*tert*-butylcyclopropanone,[4a] an isolable cyclopropanone of moderate stability. In this and following papers[5] we describe the preparation, properties, and a number of reactions of this cyclopropanone.

**Preparation and Properties.** *trans*-Di-*tert*-butylcyclopropanone may be prepared by the action of potassium *tert*-butoxide on α-bromodineopentyl ketone. The reaction may be carried out heterogeneously in ether or homogeneously in *tert*-butyl alcohol (eq 2). The latter case corresponds to conditions of the Favorskii reaction.[6] Use of 1 equiv of base affords the cyclopropanone; use of even a small excess of base results in complete conversion to the ester. Assignment of the trans structure, originally made



(2)

on nmr evidence of the hemiketal from benzyl alcohol,[4] is confirmed by the partial resolution of the cyclopropanone (see below).

**Chart I**

**Physical Data for *trans*-Di-*tert*-butylcyclopropanone (1)**

mp 24–26°, bp 75–77° (20 mm)
*d* 0.8380 (26°)
$^1$H nmr ($CCl_4$) 0.96 (s, 18 H), 1.55 (s, 2 H)
$^{13}$C nmr ($CS_2$, downfield from TMS) 28.4 ($CH_3$), 30.1 [$C(CH_3)_3$], 30.8 ($C_2$ and $C_3$), 215.2 ppm ($C_1$)
ir ($CCl_4$) 1822 cm$^{-1}$
uv (isooctane) $\lambda_{max}$ 354 nm (ε 33)
RD and CD (0.053 *M* in isooctane at 25°; values are for a sample of ~9% optical purity)
RD $[\Phi]_{450}$ +96°, $[\Phi]_{400}$ +221°, $[\Phi]_{373}$ +530°, $[\Phi]_{328}$ −483°, $[\Phi]_{285}$ −267°
CD $[\theta]_{396}$ 0°, $[\theta]_{354}$ +870°, $[\theta]_{285}$ 0°; bandwidth at half-maximum 41 nm
Major species in mass spectrum at 70 eV: *m/e* (rel intensity) 168 (1.7, molecular ion), 125 (75), 83 (100), 70 (90), 69 (91), 57 (90), 55 (90), 41 (90)

The n → π* maximum at 354 nm is at considerably longer wavelength than that for other ketones (cyclobutanone, 290 nm;[7a] cyclohexanone, 285 nm;[7b] tetrapropylcyclohexanone, 310 nm),[7b] and indeed somewhat longer than other cyclopropanones (cyclopropanone, 310 nm; tetramethylcyclopropanone, 340 nm).[2a] The $^{13}$C nmr shows the carbonyl carbon at 215.2 ppm (downfield from TMS)[7c] *vs.* cyclopropenone C-1 155.1, C-2 158.3,[8] cyclobutanone 208.2,[9] cyclopentanone 213.9 ppm.[9]

The cyclopropanone 1 has been partially resolved by asymmetric destruction with *d*-amphetamine.[4b] The RD and CD values are summarized in Chart I. The degree of optical purity was determined by reduction to the corresponding cyclopropanol and determination of enantiomeric composition by the methods of Dale, Dull, and Mosher[10] (conversion to the diastereomeric esters with optically pure 2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride and nmr analysis) and of Whitesides and Lewis[11] (nmr analysis with optically active lanthanide shift reagent). Both methods indicate an optical purity of 9 ± 1%. (+)-Cyclopropanone of 90–100% optical purity was obtained by partial reduction with (+)-diisopinocampheylborane,[12] but the product from this route was much harder to purify.

The RD and CD values given in Chart I are for cyclopropanone 1 of 9% optical purity, indicating values for optically pure 1 of $[\Phi]_{373}$ +5890°, $[\theta]_{354}$ +9660°; differential dichroic absorption, $\Delta\epsilon$ 2.92; optic anisotropy, $\Delta\epsilon/\epsilon$ 0.089; molecular amplitude, $a_{obsd}$ +112°, *a* (calculated from $a = 0.0122[\theta]$) +117°.[13] The absolute configuration of the cyclopropanone is not known. The configuration of (+)-1 as *R,R* (shown in eq 2) is that suggested by the octant rule.

**Table I**
**Hydration of *trans*-Di-*tert*-butylcyclopropanone (1) in Aqueous Dioxane**

A. Rates

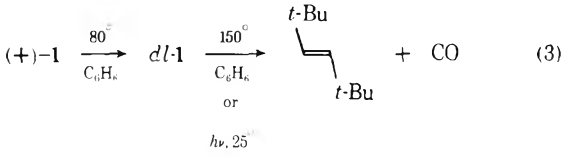
| [$H_2O$], $M$ | [1], $M^a$ | $k \times 10^5$, sec$^{-1}$ 46° | 80° |
|---|---|---|---|
| 1.46 | 0.0367 | 2.3 | 4.4 |
| 2.33 | 0.0381 | 6.4 | 13.6 |
| 2.76 | 0.0501 | 8.7 | 17.8 |

B. Equilibria[b]

| [$H_2O$], $M$ | [1], $M^a$ | $K^b$, $M^{-1}$ 27° | 46° | 80° |
|---|---|---|---|---|
| 1.46 | 0.0367 | 8.6 | 5.3 | 2.3 |
| 2.33 | 0.0435 | 7.8 | 5.0 | 2.1 |
| 2.76 | 0.0501 | 7.4 | 5.3 | 2.1 |
| 6.73 | 0.3035 | 4.7 | | |
| 10.51 | 0.282 | 2.3 | 2.0 | |
| 13.42 | 0.262 | 2.1 | 1.9 | |

[a] Initial concentration, moles/liter. [b] 1 + $H_2O$ ⇌ hydrate.

(+)-Cyclopropanone 1 racemizes at 80°.[4b,c] A detailed study is reported in a forthcoming paper.[5] At higher temperatures the cyclopropanone decomposes cleanly to *trans*-di-*tert*-butylethylene and carbon monoxide ($t_{1/2}$ 9.5 hr in benzene at 150°), eq 3. Irradiation at 25° also effects clean decarbonylation.



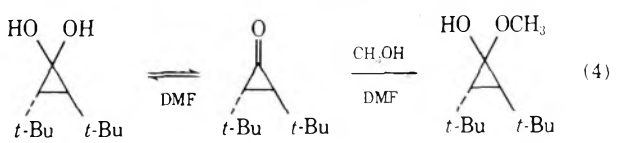
(3)

**Reaction with Nucleophiles. General Considerations.** Cyclopropanone 1 has two features of consequence in reactions with nucleophiles. The contraction of the C–C–C angle of the ketone from the preferred 120° to 60° provides strong driving force for nucleophilic addition to the carbonyl group. The trans-oriented *tert*-butyl groups, however, shield the carbonyl from attack. The net effect is a carbonyl group that might be expected to be inert toward large nucleophiles but reactive toward small ones.

A variety of results are obtained upon addition to the carbonyl group. The adduct may be stable, or may undergo ring opening at $C_{1-2}$, ring expansion, fragmentation, or dehydration. Reaction with water and alcohols are considered in this paper. In a following paper we describe examples in which addition is followed by some of the other possibilities.

**Reaction with Water.** The cyclopropanone hydrates readily. The hydrate, a solid of mp 105–107°, decomposes in air (see below). It is also sensitive to acids and bases. In a vessel of carefully cleaned surface a solution of the hydrate in dioxane or DMF was unchanged after 3 days at 80°. Heating an aqueous dioxane solution of the hydrate containing acid results in clean conversion to a α-hydroxydineopentyl ketone.

Reversibility of hydrate formation is seen in the conversion (slow) of the hydrate to the hemiketal upon addition of methanol to a solution in DMF (eq 4).



(4)

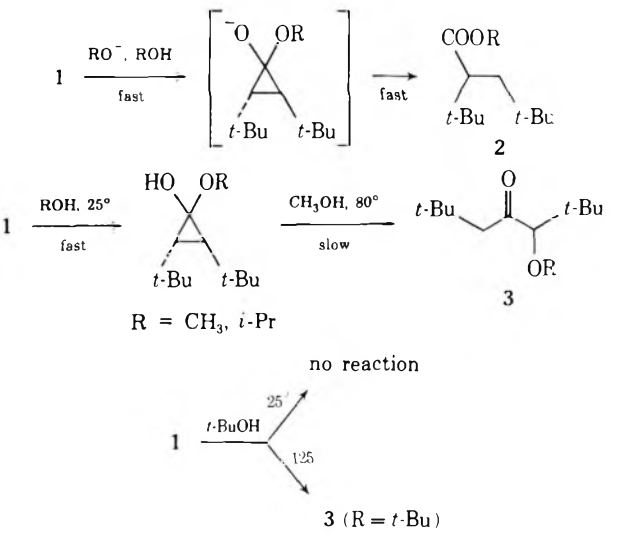
A brief study has been made of the hydration of the cyclopropanone in degassed aqueous dioxane. Rate and equilibria data are summarized in Table I. The data were obtained by determination of cyclopropanone concentration by ultraviolet analysis at 354 nm.

The principal conclusions are that hydration does not go to completion in aqueous dioxane at low water concentration; *e.g.*, at 2.33 $M$ water in dioxane, $t_{1/2}$ for hydration is 3 hr at 46°, and at equilibrium approximately 8% of the initial cyclopropanone remains as free cyclopropanone. Increase in temperature shifts the equilibrium toward free cyclopropanone. The concentration equilibrium "constant" is shifted to lower values by increasing water content, a not unexpected type of change in view of the substantial medium changes involved.[14]

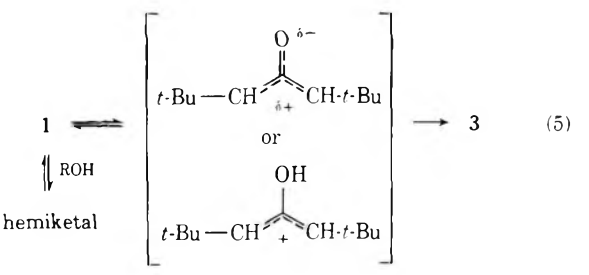
**Reaction with Alcohols.** The cyclopropanone reacts rapidly with primary alcohols, more slowly with secondary alcohols, and is unreactive with *tert*-butyl alcohol at 25°. The hemiketals from the primary alcohols may be isolated. The hemiketals and the hydrate are unstable in the presence of oxygen.

Under neutral conditions in a degassed solution containing an excess of the alcohol, no further change in the hemiketals is observed at 25°. Upon heating, the hemiketal is converted to the α-alkoxy ketone and/or the Favorskii ester. Under basic conditions the hemiketal undergoes rapid ring opening to the Favorskii ester. Under acid conditions α-alkoxy ketone is formed. Both hemiketal formation and conversion to alkoxy ketone are accelerated by acid.

**Chart II**




The results are summarized in Chart II. Conversion of hemiketal under basic conditions (*i.e.*, *via* the alkoxide species) to ester is rapid, and is easily understood.[15,16] Conversion of hemiketal to alkoxy ketone is slow, and the mechanism is less apparent. It probably involves reversion to the cyclopropanone, ring opening to oxyallyl species or the corresponding protonated form, and capture by solvent (eq 5).[17,18]



(5)

The rates of addition of methanol to cyclopropanone 1

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## EXPERIMENTAL SECTION

Dineopentyl Ketone. -- The iron carboxylate pyrolysis procedure was used.[23] 3,3-Dimethylbutric acid (58.1 g, 0.5 mol), iron powder (15.4 g, 0.27+ mol, Fisher electrolytically reduced) and boric acid (approx 15 mg) were heated at reflux under $N_2$ for 4 hr. The pot temp was raised to 360° and the volatile components were collected by distillation. Pyrolysis began at 275°. The distillate was added to pentane, filtered, washed with 1N NaOH, dried ($MgSO_4$), concentrated and distilled: Fraction 1, bp 65-75°C/95 mm, 1 g, identified by ir and nmr as methyl neopentyl ketone; Fraction 2, bp 105-115°C/95 mm, 14 g (30% yield), dineopentyl ketone (lit.[25] 75-79 at 20 mm); Fraction 3, bp 115-120°C/95 mm, 3 g, identified as 2-tert-butyl-5-neopentylfuran: ir ($CCl_4$) 3100 (w), 2960 (s), 1550 (s), 1475 (s), 1460 (s), 1390 (m), 1360 (s), 1275 (s), 1225 (s), 1200 (s), 1140 (s), 1025 (s), 1010 (s), 965 (s) $cm^{-1}$; nmr ($CCl_4$) δ 5.7 (2H, s), 2.4 (2H, s), 1.25 (9H, s), 0.90 (9H, s); mass spectrum, m/e (rel intensity) 194(18), 179(23), 138(17), 137(100), 123(32), 122(10), 95(10), 57(13), 43(34), 41(13); uv (isooctane) $\lambda_{max}$ 224 nm (log ε = 4).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41
Found: C, 80.28; H, 11.58.

Fraction 4, bp 120-125°C/95 mm, 4 g, was identified by ir and nmr as tert-butylacetic anhydride.

Dineopentyl ketone was also prepared by the slow addition of ethereal neopentylmagnesium chloride solution to 3,3-dimethylbutyryl chloride.[25]

α-Bromodineopentyl Ketone. -- To a 12.61 g (0.074 mol) sample of dineopentyl ketone in 50 ml of $CCl_4$ was added a solution of bromine (11.85 g, 0.072 mol) in 60 ml $CCl_4$ over a period of 30 min while flushing with nitrogen to help eliminate the hydrogen bromide. After addition was completed, more nitrogen was flushed for 48 hr. The $CCl_4$ was evaporated and the product distilled, affording 14.0 g (0.056 mol) of α-bromodineopentyl ketone in 78% yield; bp 48-47° (0.11 mm); ir ($CCl_4$), 1722, 1710 $cm^{-1}$; nmr ($CCl_4$), 1.05 (s, 9H), 1.18 (s, 9H), 2.5 (s, 2H), 4.1 (s, 1H).

Anal. Calcd for $C_{11}H_{21}BrO$: C, 53.02; H, 8.50; Br, 32.07
Found: C, 53.19; H, 8.48; Br, 32.34.

The residue was found to be mostly one component. Crystallization from pentane afforded a white solid α,α'-dibromodineopentyl ketone, mp 70-71° (lit.[25] 70-71°).

trans-2,3-Di-tert-butylcyclopropanone (1). -- To α-bromodineopentyl ketone (33.6 g, 0.135 mol) in a flame-dried flask ($N_2$) equipped with magnetic stirrer

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over an ice-water bath was slowly added (30 min) 128 ml of a solution of 1.0 M potassium tert-butyl alcohol (prepared by the addition of potassium metal to freshly distilled, sodium dried tert-butyl alcohol and standardized by back titration of an aliquot acidified with an aliquot of 0.1 N HCl). When the mixture solidified, the ice-bath had to be removed. The mixture was concentrated (ca 60°C, 25 mm) and trap-to-trap distilled (0.1 mm, 25-100°C). Recrystallization of the distillate from pentane (-78°C) yielded 16.8 g (75% yield) of cyclopropanone 1. The yield is variable (30-75%). It is imperative not to exceed 0.95 equivalents of base and to add the base slowly. Physical data on the cyclopropanone are summarized in Chart I.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98
Found: C, 78.70; H, 12.08.

Partial Resolution of trans-2,3-Di-tert-butylcyclopropanone by d-Amphetamine. -- d-Amphetamine (1.10 ml, 1.03 g, 7.6 mmol) was added to trans-2,3-di-tert-butylcyclopropanone (3.9 g, 23 mmol) ($N_2$). After completion of reaction the mixture was trap-to-trap distilled at 50°C and 0.1 mm yielding the cyclopropanone, and approximately 200 mg of a second phase (water). The organic fraction was separated and found to be greater than 98% cyclopropanone, $[\alpha]^{25}_{436}$ +76° (c 0.5, $CCl_4$). From another run, $[\alpha]^{25}_{436}$ +68° (c, 0.44 in isooctane), $[\alpha]^{25}_{373}$ +344 (c, 0.28 in isooctane). Additional RD and CD data are summarized in Chart I.

The residue from the trap-to-trap distillation was added to 2 ml of pentane and cooled to -78°C. The resulting precipitate was recrystallized from pentane (-78°C) to yield 900 mg of waxy solid, mp 37.5-46°C, trans-2,3-di-tert-butyl-N-(1-methyl-2-phenylethyl) cyclopropanimine. A second recrystallization (pentane, -20°C) raised the melting point to 39-40°C. Sublimation (40°C) yielded material of mp 44-46.5°: ir ($CCl_4$) 3030 (w), 2970 (s), 1775 (m) $cm^{-1}$; nmr ($CCl_4$) δ 7.07 (5H, s), 3.40 (1H, m), 2.75 (2H, d, see below), 1.34 (3H, d, J = 6Hz), 0.90 (9H, s), 0.70 (9H, s).

Anal. Calcd for $C_{20}H_{31}N$: C, 84.14; H, 10.95; N, 4.91
Found: C, 83.95; H, 11.19; N, 5.06.

Nmr analysis ($C_6F_6$, Varian HA-100) indicated that the downfield part of the "doublet" at δ 2.75 was actually two lines. When the multiplet at δ 3.50 was irradiated, the pattern at δ 2.75 merged to two lines of approximately equal intensity, separated by 2 Hz. This observation suggests that the imine sample is a mixture of low diastereomeric purity; attempted fractional crystallization of the diastereomers was unsuccessful.

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Partial resolution of the cyclopropanone was also effected by use of l-α-phenylethyl amine and by d-α-(1-naphthyl) ethylamine.

trans-2,3-Di-tert-butylcyclopropanol was prepared by reduction of the cyclopropanone with $LiAlH_4$, mp 49-51°, nmr ($CCl_4$) 3.28 (1H, doublet of doublets), 1.0 and 0.87 (two sharp peaks of equal area; integrated area from 0.7 to 1.1 is 20 H, 9 for each of two different tert-butyl groups and 2 for the cyclopropyl hydrogens.

Anal. Calcd for $C_{11}H_{22}O$: C, 77.57; H, 13.02
Found: C, 77.17; H, 13.19.

Determination of Optical Purity. NMR Method of Whitesides and Lewis.[11] To a solution of trans-2,3-di-tert-butylcyclopropanol in $CCl_4$ [obtained by $LiAlH_4$ reduction of cyclopropanone of $[\alpha]^{25}_{373}$ +344° (C, 0.28 in isooctane)] was added tris-[3-(tert-butylhydroxymethylene)-d-camphorato] europium (III). In the presence of approximately 0.2M europium compound, the signal for the tert-butyl group trans to the hydroxyl (originally at δ 0.82) appears as a broad singlet at δ 1.15, and the tert-butyl group cis to the hydroxyl (originally at δ 1.00) appears as an enantiomeric pair of signals at 1.98 and 2.10. Integration of the signals at a sweep width of 100 Hz using a planimeter indicated a ratio of 54.7/45.3 or a percent optical purity of 9.3±1. Analysis of the same solution at 100 MHz gave a separation of 12 Hz and an optical purity of 9.6%.

Nmr Method of Dale, Dull, and Mosher.[10] trans-2,3-Di-tert-butylcyclopropyl α-methoxy-α-trifluoromethylphenylacetate. -- To trans-2,3-di-tert-butylcyclopropanol (85 mg, 0.5 mmol) was added a mixture of the acid chloride of (±)-MTPA (235.6 mg, 0.9 mmol) and pyridine (0.5 ml, freshly distilled from $CaH_2$). After 1 hr, water (1 ml) was added and the mixture extracted with ether (20 ml). The ether extracts were washed with dil aq HCl, sat'd aq $Na_2CO_3$ solu, and water, dried ($MgSO_4$), and concentrated. The mixture of diastereomeric esters was purified by preparative gc, mp 72-78°C: ir ($CCl_4$) 3060 (w), 3030 (w), 2950 (s), 2905 (m), 2865 (m), 1750 (s), 1440 (m,b), 1388(w), 1360 (m), 1250 (s,b), 1185 (s), 1165 (s), 1115 (m), 1100 (m), 1075 (w), 1050 (w), 1015 (m), 960 (w), 910 (w), 890 (w); nmr (proton, $CCl_4$) δ 7.37 (5H, s, broad), 4.13 (1H, m), 3.57 (3H, s, broad), 0.87 and 0.80 (two sharp signals of equal area; integrated area from 0.6 to 1.0 is 20H, 9 for each of two different tert-butyl groups and 2 for the cyclopropyl hydrogens); fluorine, 56.45 MHz, $CCl_4/C_6F_6$) two diastereomeric $CF_3$ singlets 91 ppm downfield from $C_6F_6$ and separated by 0.25 ppm (14.1 Hz).

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Anal. (Mixture of Diastereomers): Calcd for $C_{21}H_{29}O_3F_3$: C, 65.26; H, 7.56 Found: C, 65.07; H, 7.57.

When the diastereomeric esters were prepared starting from (+)-trans-2,3-di-tert-butylcyclopropanone, $[\alpha]^{25}_{373}$ +344° (C, 0.28 isooctane), resolved by partial asymmetric destruction with 0.33 equivalents of d-amphetamine and (-)-α-methoxy-α-trifluoromethylphenylacetyl chloride,[10] measurement of the relative intensities of the diastereomeric $CF_3$ signals gave an optical purity of 9.2±1% (planimeter) or 9.4±1% (peak height) for the cyclopropanone. (The peak farthest downfield from $C_6F_6$ was the more intense).

Asymmetric Reduction of trans-2,3-Di-tert-butylcyclopropanone with Diisopinocampheylborane. -- To a solution of (-)-2-pinene (2.46 g, 18.1 mmol, 10% excess) in 5 ml of THF (freshly distilled from $LiAlH_4$) was added 3.82 ml of 1.08M diborane in THF (8.25 mmol of $BH_3$) at 0°C. After 4 hr at 0°C the mixture was cooled to -78°C and trans-2,3-di-tert butylcyclopropanone (2.78 g, 16.5 mmol) was added. When the mixture was warmed to 0° the precipitated organoborane quickly dissolved. The solution was maintained at 0° for 2 hr and at room temperature for an additional 2 hr, concentrated, and trap-to-trap distilled. The distillate (analyzed by glc, uv, and ir) contained approx equal amounts of the cyclopropanone and 2-pinene (total, 1.8 g). Attempted fractional crystallization at -78°C was not successful. The cyclopropanone could be purified by gc without racemization under the following conditions: 2' x 1/4" column of 20% SE 30 on 60/80 mesh Chromosorb W, 50°C, 150 cc He/min, injector at 70°C, detector at 65°C, retention time = 3 min. Cyclopropanone which was collected neat decomposed rapidly (as did samples of racemic material) so that it was necessary to collect it directly into isooctane solution $[\alpha]^{25}_{373}$ +3,950° (c 0.28, isooctane). For cyclopropanone of 9.1% optical purity, $[\alpha]^{25}_{373}$ +344° (c 0.28, isooctane) so that the optical purity of the recovered cyclopropanone is approximately 100% (±11%).

Decomposition of trans-di-tert-butylcyclopropanone, Thermal. -- A solution of 0.1470 g (0.88 mmol) of the cyclopropanone and 0.1409 g n-nonane in 5.0 ml benzene (freshly distilled from sodium) in Pyrex tubes was degassed and sealed (-78°, 0.05 mm), and heated at 150±4°. Analysis (glc, SE 30 on Chromosorb W, 70°) showed the disappearance of the cyclopropanone ($t_{1/2}$, 9.5 hr) and the appearance of trans-1,2-di-tert-butylethylene (95% after 45.5 hr at 150°), identified as the trans isomer by comparison of ir and nmr spectra with those of authentic samples. No other products were observed.

Photochemical. -- A solution of 0.0155 g (0.092 mmol) of the cyclopropanone and 0.0145 g n-decane was degassed and sealed in Pyrex tubes and irradiated

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at ambient temperature with a 275 watt General Electric sunlamp. Analysis (glc) after 6 hr showed only the cyclopropanone (52%; retention time, 7 min) and trans-1,2-di-tert-butylethylene (48%; retention time, 2 min). In a parallel experiment a solution of 1 in $CCl_4$ was degassed, sealed and irradiated under the above conditions. Analysis (nmr) after 6 hr showed the cyclopropanone and trans-1,2-di-tert-butylethylene only.

Stability of Cyclopropanone 1 in Dioxane at 100°. -- A 0.0374 M solution of cyclopropanone 1 in dioxane (distilled from sodium and benzophenone) was degassed and sealed in a Pyrex uv cell, $\lambda_{max}$ = 350 nm (ε = 41.0). Only 20% of the cyclopropanone was destroyed in 30 days at 100°. Analysis by glc indicated the only product was trans-di-tert-butylethylene.

In Triethylamine. -- A sealed tube containing the cyclopropanone and triethylamine was heated to 100° for 2 hr. Infrared analysis indicated no reaction had occurred.

Di-t-butylcyclopropanone Hydrate. -- All glassware employed in this experiment was soaked for two days in distilled water which had been distilled from $KMnO_4$ and stored in a drying oven prior to use. A mixture of 0.168 g (1.0 mmole) of cyclopropanone 1, 0.40 g (22 mmole) of distilled water and 3.0 ml of dioxane in a 25 ml flask was allowed to stand at room temperature under a positive nitrogen pressure for 48 hr. The addition of 10 ml of water afforded a white fluffy precipitate, isolated by filtration under a nitrogen atmosphere and dried under a stream of rapidly flowing nitrogen. The solid, 0.162 g (0.87 mmole), 87% yield, mp 105-107 (sealed tube) shows ir bands in $CCl_4$ at 3750 $cm^{-1}$ and 3360 $cm^{-1}$. Exposure of a 25-mg sample of the hydrate to the air for 30 min resulted in complete destruction. The infrared spectrum of the residue shows two strong carbonyl peaks at 1790 $cm^{-1}$ and 1700 $cm^{-1}$.

Formation of α-Hydroxydineopentyl Ketone from trans-Di-tert-butylcyclopropanone. -- A solution of cyclopropanone 1 (152 mg, 0.90 mmol) in 3 ml of 90% aqueous dioxane containing 5 mg of toluenesulfonic acid monohydrate (0.026 mmol) was degassed, sealed in a Pyrex tube, and heated at 80° for 60 hr. The organic material was extracted with ether, washed once with water and dried with $K_2CO_3$. Evaporation of the solvents yielded an oil which gave a single peak on glc. Sublimation yielded α-hydroxydineopentyl ketone: mp 40-42°; ir ($CCl_4$) 3480 m broad, 2950 s, 1705 s, 1480 s, 1390 m, 1365 s, 1060 s, 1020 $cm^{-1}$; nmr ($CCl_4$) 0.90 (9H, s), 1.00 (9H, s), 2.33 (2H, ABqΔν = 10 Hz, J = 16 Hz), ~3 [concentration-dependent (1H, broad)], 3.90 (1H, broad) ppm identical with an authentic sample prepared by hydrolysis of α-acetoxydineopentyl ketone.

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Methanol Hemiketal of trans-di-tert-butylcyclopropanone. -- A solution of 0.168 g (1.0 mmole) of cyclopropanone (99% pure by vpc) and 0.32 g (10 mmole of methyl alcohol distilled from sodium was allowed to react at room temperature under a positive nitrogen pressure for two hr. The excess methenol was removed under reduced pressure, affording 0.195 g (97%) of a white crystalline solid, mp 94-96° (sealed tube); ir ($CCl_4$) 3570 (s), 3360 (br), and 1125 (s) $cm^{-1}$; nmr ($CDCl_3$), 0.95 and 1.00 (doublet, 20 H), 2.87 (s, 1H), 3.40 (s, 3H).

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07
Found: C, 72.08; H, 12.08.

The material decomposed when exposed to the atmosphere for several hours. A degassed solution of the hemiketal in deuterochloroform was unchanged after heating for three days at 80°.

Benzyl Alcohol Hemiketal of trans-2,3-Di-t-butylcyclopropanone. -- The cyclopropanone (0.1572 g, 0.935 mmol) and benzyl alcohol (0.101 g, 0.935 mmol) were mixed neat. After 2 hr the reaction mixture was filtered, affording 0.1665 g (65% yield) of crude product, mp 93-98°. Recrystallization gave pure trans-2,3-di-t-butylcyclopropanone benzyl alcohol hemiketal, mp 102-103°, ir ($CCl_4$) 3550 (no carbonyl absorption); nmr ($CCl_4$), 0.97 and 1.02 (two sharp peaks of equal area; integrated area from 0.8 to 1.6 is 20 H, 9 for each of two different t-butyl groups and 2 for the cyclopropyl hydrogens) 2.8 (s, 1H), 4.6 (quartet, 2H), 7.1 (s, 5H).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; mol. wt., 276
Found: C, 78.04; H, 10.35; mol. wt. 279.

The hemiketal was found to be unstable in solution; ir and nmr spectra had to be measured immediately after the solid had been dissolved.

Reaction of trans-di-tert-butylcyclopropanone with potassium tert-butoxide. -- Addition of the cyclopropanone to tert-BuOH-tert-BuOK results in rapid conversion to the ester, tert-butyl 2-tert-butyl-4,4-dimethylpentanoate: ir ($CCl_4$) 1725 (s); nmr ($CCl_4$) 0.88 (s, 9H), 0.92 (s, 9H), 1.43 (s, 9H), 1.0-2.1 (mult, 3H).

Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.33; H, 12.48
Found: C, 74.42; H, 12.30.

With tert-butyl alcohol. -- A sample of the cyclopropanone in t-BuOH was degassed, sealed, and heated at 100° for 6 days. Evaporation of the solvent and analysis (glc) indicated a single product, identified as α-tert-butoxydineopentyl ketone: ir ($CCl_4$) 2960 (s), 1710 (s), 1475 (m), 1365 (s), 1190 (s), 1080 (s), 1020 $cm^{-1}$; nmr ($CCl_4$) 0.90 (9H, s), 1.00 (9H, s), 1.13 (9H, s), 2.43 (2H, ABqΔν = 19 Hz, J = 19 Hz), 3.27 (1H, s) ppm; uv (tert-butanol) $\lambda_{max}$ ~ 309 (ε ~ 92.0).

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Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.33; H, 12.47
Found: C, 74.28; H, 12.42.

With Ethanol. -- Cyclopropanone 1 in EtOH, degassed and sealed, heated at 80° for 60 hr, afforded a single product, α-ethoxy dineopentyl ketone: ir ($CCl_4$) 2960 (s), 1710 (s), 1480 (s), 1360 (s), 1215 (s), 1120 (m), 1095 (s) $cm^{-1}$; nmr ($CCl_4$) 0.90 (9H, s), 1.00 (9H, s), 1.16 (3H, t), 2.32 (2H, s), 3.03 (1H, s), 3.36 (2H, m) ppm.

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.83; H, 12.25
Found: C, 72.78; H, 12.45.

With Isopropyl alcohol, acidic conditions. -- Cyclopropanone 1 in 1 ml of a $1.7 \times 10^{-2}$ M solution of toluenesulfonic acid monohydrate in 2-propanol degassed and sealed, heated at 80° for 2.5 hr, afforded a single product α-isopropoxydineopentyl ketone: ir ($CCl_4$) 2960 (s), 1710 (s), 1470 (m), 1360 (s), 1180 (s) $cm^{-1}$; nmr ($CCl_4$) 0.90 (9H, s), 1.00 (9H, s), 1.11 (6H, dd), 2.35 (2H, partially resolved ABq), 3.10 (1H, s), 3.40 (1H, septet) ppm.

With Isopropyl alcohol, basic conditions. -- Reaction of the cyclopropanone with i-PrOH, i-PrONa rapidly afforded isopropyl tert-butyl-neopentylacetate: ir ($CCl_4$) 2960 (s), 1720 (s), 1480 (m), 1370 (s), 1180 (m), 1150 (s), 1105 (m) $cm^{-1}$; nmr ($CCl_4$) 0.83 (9H, s), 0.92 (9H, s), 1.20 (6H, d), 1.3-2.2 (3H, m), 4.95 (1H, septet) ppm.

Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.67; H, 12.36
Found: C, 73.51; H, 12.66.

With Isopropyl alcohol, neutral conditions. -- Cyclopropanone 1 in isopropyl alcohol, degassed and sealed, heated at 80° for 5 days afforded α-isopropoxydineopentyl ketone (30%), isopropyl tert-butylneopentyl acetate (30%) and 8 minor products.

With Methanol. -- Cyclopropanone 1 in $CH_3OH$, degassed, sealed, heated at 80° for 60 hr afforded a single product α-methoxydineopentyl ketone: ir ($CCl_4$) 2960 (s), 1715 (s), 1490 (s), 1370 (s), 1105 (s) $cm^{-1}$; nmr ($CCl_4$) 0.90 (9H, s), 1.01 (9H,s), 2.40 (2H, ABqΔν = 10 Hz, J = 15 Hz), 2.99 (1H, s), 3.33 (3H, s) ppm; uv (dioxane) $\lambda_{max}$ = 316 nm (ε = 44.0).

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07
Found: C, 71.91; H, 12.14.

When the methanol hemiketal of cyclopropanone was pre-formed in flame-dried glassware, washed with pentane, dissolved in neutral methanol and heated at 80°, less than 2% formation of the methoxy ketone was observed by uv after 10 days. This observation implies a maximum rate of methoxy ketone formation of $2 \times 10^{-8}$ $sec^{-1}$, i.e., the preparation of the methoxy ketone described above is catalyzed by

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some extraneous acid. The preparation was repeated several times with the same results.

Methanolysis of α-Bromodineopentyl Ketone. -- α-Bromodineopentyl ketone (0.55 g, 2.2 mmol) and 0.75 g of $AgNO_3$ (4.4 mmol) in 5 ml of methanol was degassed and sealed in a Pyrex tube and heated at 100° for 48 hr. The methanol was evaporated and the organic products were obtained by trituration with pentane. Analysis (glc) showed bromo ketone (70%) and three products in the ratio of 23:33:44. Samples of each of these peaks were collected for spectral analysis. The first peak was assigned as 2,3,6,6-tetramethyl-2-hepten-4-one on the basis of its spectral properties: ir ($CCl_4$) 2960 (s), 1710 (s), 1640 (m), 1480 (m), 1366 (m), 900 (s) $cm^{-1}$; nmr ($CCl_4$) 0.90 (9H, s), 1.15 (3H, s), 1.60 (3H, s), 2.10 (2H, s), 2.20 (3H, s) ppm.

The second peak was found to be identical to α-methoxydineopentyl ketone by ir and nmr. The third peak was identified as 2,3,6,6-tetramethyl-2-methoxy-4-heptanone: ir ($CCl_4$) 2960 (s), 1715 (s), 1460 (m), 1360 (s), 1190 (s), 1070 $cm^{-1}$; nmr ($CCl_4$) 0.95 (9H, s), 1.05 (3H, d, J = 7 Hz), 1.10 (6H, s), 2.33 (2H, s), 2.66 (1H, q, J = 7 Hz), 3.05 (3H, s) ppm.

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.07
Found: C, 71.73; H, 12.26.

Nmr Study of the Formation of α-Methoxydineopentyl Ketone. -- Cyclopropanone 1 (60 mg, 0.36 mmol) and toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) were dissolved in 1 ml of methanol in an nmr tube. The formation of α-methoxydineopentyl ketone was followed at room temperature by nmr ($t_{1/2}$ was about 96 hr). After mixing, only the methanol hemiketal (singlets at 0.95 and 1.00 ppm) was visible in the nmr spectrum; no cyclopropanone remained. As the reaction proceeded the spectrum of the methoxy ketone appeared (singlets at 0.90 and 1.01 ppm). At no time were any peaks other than those of the solvent, the hemiketal, and the methoxy ketone observed in the nmr spectrum.

Kinetics of Hemiketal Formation at 25° from Cyclopropanone 1. -- trans-2,3-Di-tert-butylcyclopropanone (approximately 50 mg) was placed in a dry uv cell. Approximately 3 ml of the anhydrous alcohol was added at 25° and the disappearance of the cyclopropanone was followed by uv at 350 nm. The solutions were not degassed and were sealed only with rubber serum caps. The results are summarized in Table III.

Exchange of Deuterated Methanol Hemiketal of Cyclopropanone 1. -- Cyclopropanone 1 (108 mg, 0.64 mmol) was allowed to react with 1 g of methanol-$d_4$ for 1 hr

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at 25° in a flame-dried flask. The excess alcohol was evaporated and 1 ml of pentane was added. The white solid hemiketal was allowed to stand under the pentane at 0° for 16 hr. The pentane was drawn off with a canula and the resulting solid dissolved in 5 ml of unlabeled methanol. This solution was degassed and sealed in five tubes and placed in a 25° oil bath. The tubes were removed from the bath at various times and the methanol evaporated. The hemiketal thus obtained was dissolved in $CCl_4$ and examined by nmr: time in hrs, fraction of label present, k x $10^7$ $sec^{-1}$ (0, 1.0; 73, 0.88, 4.86; 167, 0.74, 5.00; 359, 0.537, 4.81; 573, 0.314, 5.61) $k_{av} = 5.1 \times 10^{-7}$ $sec^{-1}$. A similar experiment at 80° had a $k_{av}$ = $9.8 \times 10^{-5}$ $sec^{-1}$.

Kinetics of Hydration of Cyclopropanone 1 in Dioxane at 80°. -- Stock solutions of cyclopropanone 1 in dioxane and $H_2O$ in dioxane were made up by weight in flame-dried flasks stoppered with serum caps. In calculating the molarity the volumes are assumed to be additive. Equal aliquots (1.5 ml) of each solution were transferred by syringe to oven-dried Pyrex uv cells, degassed, and sealed. The solutions were allowed to warm to room temperature and the initial absorbance was read. The cells were heated in an oil bath at 79.6° for predetermined time intervals (60 seconds allowed for warm-up time) and then quenched by cooling in an ice bath. The absorbance was read quickly and the cell returned to the oil bath. Absorbance values at infinite time were taken after at least 10 half lives. The results are summarized in Table I.

The equilibrium constants for the hydration reaction were calculated by the following formula: $K' = \frac{A_i - A_f}{A_f - A_c}$; $K = K'/[H_2O]$. Where $A_i$ is the initial absorbance, $A_f$ is the absorbance after 10 half-lives and $A_c$ is the absorbance of the cell filled with pure dioxane. This procedure avoids the need to determine the extinction coefficient for the cyclopropanone in each aqueous dioxane mixture used.

Kinetics of Methanol Hemiketal Formation from Cyclopropanone 1 in Dioxane at 80°. -- The procedure given above for the hydration was used here with freshly distilled methanol (from magnesium methoxide) replacing the distilled water. In this case equilibrium constants could not be obtained directly since the cyclopropanone concentration at equilibrium was too small.

Deuterium Exchange of trans-Di-tert-butylcyclopropanone with Potassium tert-Butoxide in tert-Butanol-O-d. -- A solution of potassium tert-butoxide (0.07 N by titration) was prepared by reaction of 13 mg of potassium metal with 6 ml of tert-butanol-O-d, 98% deuterated by nmr. Cyclopropanone 1 (43.8 mg, 0.26 mmol) was added to 2 ml of this solution and allowed to react for 20 min at room temperature. The alcohol was then evaporated and the residue triturated with pentane. The tert-butyl

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tert-butyl-neopentylacetate was collected from gc and analyzed for deuterium content by mass spectroscopy. Since the ester had no molecular ion in the mass spectrum, fragment ions had to be used to determine deuterium content. Ions at 171 and 130 m/e in the undeuterated compound were used since these are rather intense peaks formed by fragmentations involving only the tert-butyl groups which show relatively small M + 1 peaks (less than 15%): 3% $d_0$, 51% $d_1$, 30% $d_2$, and 16% $d_3$ at the 130 fragment, and 5% $d_0$, 48% $d_1$, 31% $d_2$, and 16% $d_3$ at the (less reliable, large M-2) 171 fragment. A sample of the ester prepared from undeuterated reactants showed no deuterium incorporation when subjected to this same procedure.

Oxidation of Di-tert-butylcyclopropanone in Hexane in the Presence of Water. -- A solution of 0.760 g (4.5 mmole) of di-t-butylcyclopropanone in 4.00 ml of freshly distilled hexane in a 10.0 ml flask was attached to a manometer for measuring uptake of oxygen. The system was flushed with oxygen and equilibrated followed by the addition of 40 µl (2.2 mmol) of water: time in minutes, volume of $O_2$ absorbed in ml (0,0; 10,0; 25, 9.8; 35, 14.8; 45, 21.4; 56, 26.0; 72, 29.0;

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130, 34.0; 186, 36.5; 216, 39.5; 1000, 39.5 ml (1.61 mmol)]. [A solution containing 0.830 g (4.93 mmole) of cyclopropanone to which no water had been added absorbed only a trace of oxygen in 6 hr.] During the oxidation a white crystalline solid precipitated, tentatively assigned the structure 2-tert-butyl-3-hydroxy-4,4-dimethylpentanoic acid, 0.030 g, mp 222-223.5°, ir bands at 1675 $cm^{-1}$ and a broad band between 2500 and 3200 $cm^{-1}$.

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.30; H, 10.96. Found: C, 64.98; H, 10.98.

Analysis of the hexane solution (glc, SE 30 on Chromosorb W, 120°, 65 cc/min) showed five components with retention times 1.60 (pivaldehyde), 2.25 (unknown), 4.40 (di-tert-butylacetaldehyde), 5.0 (tert-butyl neopentyl ketone), 24.2 min (tert-butyl-neopenylacetic acid), identified by comparison of retention times and infrared spectra with authentic samples. A second solution of 0.175 g (1.045 mmole) of the cyclopropanone, 0.10 g (5.6 mmole) of water, 0.0225 g decane (internal standard) in 4.0 ml of pentane was exposed to $O_2$ atmosphere for 24 hr: analysis (glc)

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showed pivaldehyde (0.192 mmole), di-tert-butylacetaldehyde (0.038 mmol), tert-butyl neopentyl ketone (0.030 mmol), tert-butylneopentylacetic acid (0.485 mmol).

tert-Butyl Neopentyl Ketone was prepared in 57% yield by the reaction of tert-butyllithium with tert-butylacetyl chloride: ir ($CCl_4$) 1708, 1475, 1462, 1387, 1362, 1358 $cm^{-1}$; nmr ($CCl_4$) 1.01 (s, 9H), 1.10 (s, 9H), 2.37 (s, 2H).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90 Found: C, 76.86; H, 12.90

tert-Butylneopentylacetic Acid was prepared by hydrolysis of 3 g of the corresponding tert-butyl ester in 25 ml of conc. $H_2SO_4$ at 25° for 1 hr. Addition to 200 ml of ice-water, collection of the precipitate, washing and recrystallization from methanol-water afforded the acid in 45% yield, mp 62-64°, further purified by sublimation, mp 66.6-67°: ir 1700 (s); nmr ($CDCl_3$) 0.89 (s, 9H), 0.97 (s, 9H), 1.1-2.3 (mult, 3H), 11.6 (s, 1H).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.91; H, 11.91 Found: C, 71.16; H, 11.91.

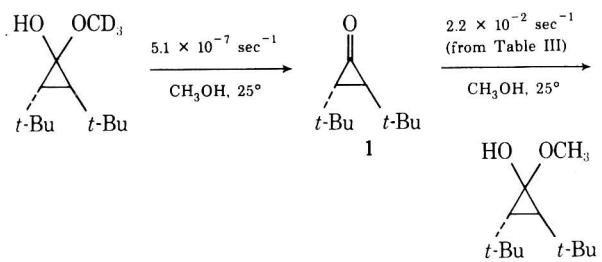
**Table II**
**Formation of Methanol Hemiketal from Cyclopropanone 1 in Dioxane at 80°**

| $[CH_3OH]$, $M$ | $k \times 10^5$, $sec^{-1}$ |
|---|---|
| 1.08 | 7.06 |
| 1.60 | 21.3 |
| 1.89 | 36.2 |

in dioxane at low methanol concentration to give the hemiketal are reported in Table II. The rate constants for both methanol addition (Table II) and water addition (Table I) are markedly dependent on the concentration of the nucleophile; rough interpolation indicates a severalfold faster rate of addition for the methanol. The amount of free cyclopropanone at equilibrium is too low for direct measurement in the methanol–dioxane studies.

Rates of addition of a few simple alcohols to the cyclopropanone in alcohol solution are summarized in Table III. In order to obtain an indication of the relative importance of changes in medium *vs.* changes in steric effects, the cyclopropanone was subjected to methanol–isopropyl alcohol mixtures (last two entries, Table III), following both the rate of disappearance of the cyclopropanone and analyzing for the relative amounts of the two hemiketals. The resulting rate constant for the methanol addition in isopropyl alcohol, $\sim 4 \times 10^{-4}$ $M^{-1}$ $sec^{-1}$, is within a factor of 2 of the corresponding rate constant in pure methanol, suggesting that much of the observed change in rate constants (relative $k_{ROH}$ in methanol, 90; ethanol, 20; isopropyl alcohol, 1; *tert*-butyl alcohol, 0) is associated with steric factors.

The equilibrium constant for cyclopropanone 1 $\rightleftharpoons$ methanol hemiketal could not be measured directly but was obtained by exchange experiments with deuterium-labeled methanol hemiketal (eq 6), following the rate of




(6)

appearance of the undeuterated methoxyl group by nmr analysis of the hemiketal isolated at various times. The equilibrium constant for methanol hemiketal formation from the cyclopropanone 1 in methanol solution at 25° is thus $4.3 \times 10^4$ (or $1.7 \times 10^3$ $M^{-1}$ if methanol concentration is included in the expression).

**Attempted Removal of $\alpha$ Hydrogen of Cyclopropanone 1.** Exchangeability of the $\alpha$ hydrogens was of interest both with regard to the acidity of these hydrogens and to the possible use of the enolate anion in subsequent synthetic reactions. In general, attack at $\alpha$ hydrogen and attack at a carbonyl carbon are competitive reactions, markedly dependent on the nature of the attacking base.

**Table III**
**Hemiketal Formation from Cyclopropanone 1 in Neat Alcohols at 25°**

| ROH | $k_{obsd} \times 10^4$, $sec^{-1}$ | [ROH], $M$ | $k_{obsd} \times 10^4/ROH$, $M^{-1}$ $sec^{-1}$ |
|---|---|---|---|
| $CH_3OH$ | 219 | 25.4 | 8.62[d] |
| $C_2H_5OH$ | 35.3 | 17.1 | 2.06 |
| *i*-PrOH | $1.24 \times 10^{-4}$ | 13.1 | 0.095 |
| *t*-BuOH | 0.[a] | 10.6 | |
| $CH_3OH$, *i*-PrOH | 7.33 | 1.41[b] | 4.37[e] |
| $CH_3OH$, *i*-PrOH | 3.58 | 0.60[c] | 3.95[f] |

[a] No observable reaction at 25° or at 80°. [b] 1.41 $M$ $CH_3OH$, 12.3 $M$ *i*-PrOH. [c] 0.60 $M$ $CH_3OH$, 12.8 $M$ *i*-PrOH. [d] $k'_{CH_3OH}$ (calculated from $k_{obsd} = k'_{CH_3OH}[CH_3OH] + k_{i\text{-}PrOH}[i\text{-}PrOH]$ and assuming that $k_{i\text{-}PrOH}$ is the same as the value in pure *i*-PrOH. [e] (methyl hemiketal/isopropyl hemiketal) observed by nmr = 5:1; calculated on assumption in footnote *d*, 5.3:1. [f] (methyl hemiketal/isopropyl hemiketal) observed = 2:1; calculated on assumption in footnote *d*, 1.95:1.

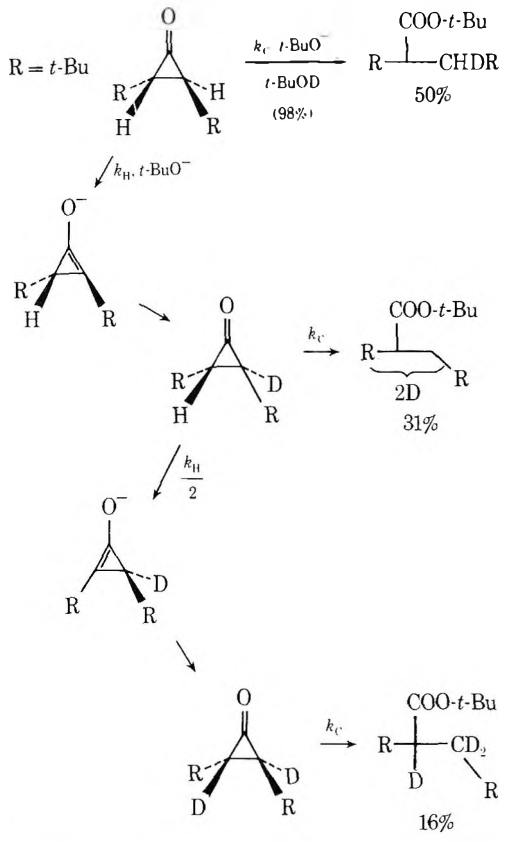
An immediate difficulty in the study of these reactions with a cyclopropanone is the irreversible conversion to ring-opened products—Favorskii ester or $\alpha$-alkoxy ketone —under basic or acidic conditions. We have nevertheless attempted the removal of the $\alpha$ hydrogens under a variety of conditions. No exchange was observed upon exposure of the cyclopropanone to triethylamine (which does not add to the cyclopropanone) and deuterium oxide, to deuterium oxide in DMF, or to *tert*-butyl alcohol-*O*-*d*. Triphenylmethyllithium in dimethoxyethane rapidly destroyed the cyclopropanone but no volatile products were obtained on quenching with acetic anhydride. Lithium diisopropylamide in dimethoxyethane effected the reduction of the cyclopropanone to the cyclopropanol rather than $\alpha$-hydrogen exchange.

**Evidence for Exchange of $\alpha$ Hydrogens of Cyclopropanone 1 by *tert*-Butoxide in *tert*-Butyl Alcohol.** In view of the difficulties described above, we examined the question of exchangeability of the $\alpha$ hydrogens in the overall process of conversion of 1 to the Favorskii ester. The extent of attack on $\alpha$ hydrogen should be reflected in the extent of deuteration of the ester. Subjection of the cyclopropanone to *tert*-butoxide in *tert*-butyl alcohol-*O*-*d* afforded ester with the deuterium content $d_0$ 3%, $d_1$ 50%, $d_2$ 31%, $d_3$ 16%. Samples of undeuterated ester subjected to the reaction conditions for a time period severalfold longer than the reaction were shown not to undergo exchange. Thus the di- and trideuterated ester *must have come from cyclopropanone molecules which had undergone exchange.*

It is of interest to see what the results imply about the relative rates of attack at carbonyl carbon with ring opening and attack at $\alpha$ hydrogen. The finding that the ester product contains approximately equal amounts of monodeuterated material (the result of attack at carbonyl carbon followed by ring opening, $k_C$) and of higher deuterated material (the result of initial attack at $\alpha$ hydrogen, $k_H$) indicates that $k_C$ and $k_H$ are approximately equal. The observed values of dideuterated ester (31%) and trideuter-

ated ester (16%) are also consistent with a value of $k_C \cong k_H$. The results and interpretation are summarized in Chart III.[19] Chart III and the brief derivations assume either noninvolvement of *cis*-di-*tert*-butylcyclopropanone[19] or $(k'_C/k'_H)_{cis\text{-cyclopropanone}} \cong (k_C/k_H)_{trans\text{-cyclopropanone}}$.

**Chart III**




$$\%d_1 = \frac{k_C}{k_C + k_H} \times 100 \cong 50 \quad \therefore \quad \frac{k_C}{k_H} = 1$$

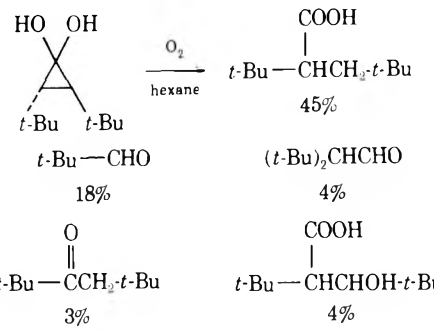
$$\%d_2 = \left(\frac{k_H}{k_C + k_H}\right)\left(\frac{k_C}{k_C + k_{H/2}}\right) \times 100$$

$$\%d_3 = \left(\frac{k_H}{k_C + k_H}\right)\left(\frac{k_{H/2}}{k_C + k_{H/2}}\right) \times 100$$

| | Obsd | Calcd for $k_C/k_H = 1$ |
|---|---|---|
| $\%d_2$ | 31 | 33 |
| $\%d_3$ | 16 | 17 |

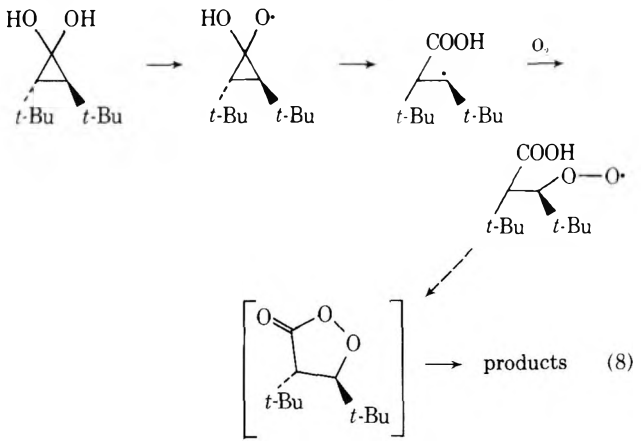
In a study of the stereochemistry of ring opening of cyclopropanols and hemiketals,[16] the cyclopropanone 1 was subjected to sodium methoxide in methanol-*O*-*d* and to sodium ethylene glycolate in ethylene glycol-$O$-$d_2$. Only monodeuterated esters were observed in contrast to the di- and trideuterated esters in the present study. Apparently the ratio of $k_C/k_H$ increases with decreasing size of R in the attacking $RO^-$, ROH.

**Reaction of the Cyclopropanone Hydrate with Oxygen.** Because of the instability of the cyclopropanone 1 in air, the effect of oxygen was briefly examined in the presence and absence of water. Under anhydrous conditions the cyclopropanone is stable to oxygen.[20] Shaking of a hexane solution of the cyclopropanone with water in the presence of oxygen resulted in the absorption of ~0.3 mol of oxygen per mole of 1 in 3.5 hr. Subjection of the reaction solution to glc analysis afforded a complex mixture (eq 7). The major product was the ring-opened isomer of the hydrate, 2-*tert*-butyl-4,4-dimethylpentanoic acid.




(7)

The products of oxidation are derivable by hydrogen atom abstraction from hydrate with ring opening and reaction of the carbon radical with oxygen, followed by various routes, possibly including a peroxylactone (eq 8).




(8)

The presence of such a species was suggested by ir absorption at 1790 $cm^{-1}$ in the crude reaction mixture. Good analogy for the products *tert*-butyl neopentyl ketone and di-*tert*-butylacetaldehyde is found in studies of decomposition of peroxy lactones.[21] Reaction of the methanol hemiketal of tetramethylcyclopropanone with oxygen has been reported to yield the ring-opened $\beta$-hydroperoxy ester, which was cyclized to a peroxy lactone in a subsequent step.[22] Lability of cyclopropanone hemiketals to oxygen also has been reported by de Boer.[2d] The major product from oxygen and 2,2-dimethylcyclopropanone methylhemiketal is the hydroperoxy ester, methyl 3-hydroperoxy-3-methylbutyrate. Under radical initiation but insufficient oxygen, the major products are the ring-opened esters, methyl 3-methylbutyrate and methyl pivaloate, isomers of the starting hemiketal.[2d]

**Registry No.**—1, 14743-58-9; 3,3-dimethylbutyric acid, 1070-83-3; methyl neopentyl ketone, 590-50-1; dineopentyl ketone, 4436-99-1; 2-*tert*-butyl-5-neopentylfuran, 51392-18-8; $\alpha$-bromodineopentyl ketone, 33712-48-0; *trans*-2,3-di-*tert*-butyl-*N*-(1-methyl-2-phenylethyl)cyclopropanimine, 51392-19-9; *trans*-2,3-di-*tert*-butylcyclopropanol, 51392-20-2; *trans*-2,3-di-*tert*-butylcyclopropyl $\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetate, 51392-21-3 (*R* isomer), 51547-28-5 (*S* isomer); diisopinocampheylborane, 1091-56-1; $\alpha$-hydroxydineopentyl ketone, 51392-23-5; *trans*-di-*tert*-butylcyclopropanone methanol hemiketal, 51392-24-6; *trans*-2,3-di-*tert*-butylcyclopropanone benzyl alcohol hemiketal, 51392-25-7; potassium *tert*-butoxide, 865-47-4; *tert*-butyl 2-*tert*-butyl-4,4-dimethylpentanoate, 51392-26-8; *tert*-butyl alcohol, 75-65-0; $\alpha$-*tert*-butoxydineopentyl ketone, 51392-27-9; ethanol, 64-17-5; $\alpha$-ethoxydineopentyl ketone, 51392-28-0; isopropyl alcohol, 67-63-0; $\alpha$-isopropoxydineopentyl ketone, 51392-29-1; isopropyl *tert*-butylneopentyl acetate, 51392-30-4; methanol, 67-56-1; $\alpha$-methoxydineopentyl ketone, 51392-31-5; 2,3,6,6-tetramethyl-2-hepten-4-one, 51392-32-6;

2,3,6,6-tetramethyl-2-methoxy-4-heptanone, 51392-33-7; *tert*-butyl neopentyl ketone, 868-91-7; *tert*-butyllithium, 594-19-4; *tert*-butylacetyl chloride, 7065-46-5; *tert*-butylneopentylacetic acid, 51392-34-8.

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(15) For example, see C. Rappe, L. Knutsson, N. J. Turro, and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2032 (1970).
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(18) The question of ring opening to oxyallyl is taken up in detail in a forthcoming publication (ref 5).
(19) It is not possible from these results to determine whether reprotonation of the enolate anion affords *cis*- or *trans*-cyclopropanone. Generation of the *cis*-cyclopropanone might be expected to lead to rapid attack at the greatly deshielded carbonyl, but by the same token the hydrogens are also more exposed. In a somewhat related case, reprotonation of the enolate from *trans*-di-*tert*-butylcyclobutanedione (ref 5) affords only the trans compound. On this basis, one might expect the di-*tert*-butylcyclopropanone enolate to be reprotonated with regeneration of the *trans*-cyclopropanone.
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# Reactions of 2,3-Dibromoindole Derivatives with Bromine and Other Oxidizing Agents. 2,3-Dibromoindole → 3,3-Dibromooxindole Transformation


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When an excess of bromine was allowed to react with 2,3-dibrominated polybromoindoles in acetic acid, the corresponding 3,3-dibrominated oxindoles were isolated. Only in one case, both oxidation and substitution took place. 2,3-Dibrominated polybromoindoles were the main reaction products when the bromination was carried out in anhydrous carbon tetrachloride. Present results confirm a previously proposed pathway according to which a 3,3-dibrominated indolenine (6) is the possible intermediate in the formation of 3,3-dibrominated oxindoles by reaction of some indoles with excess bromine. When 2,3-dibrominated polybromoindoles were treated with chromic anhydride or with peracetic acid the corresponding 3,3-dibrominated oxindoles were isolated in fairly good yields. This method could be used as a diagnostic tool in the structure determination of 2,3-dibromoindoles.


Halogenation of the indole nucleus has been extensively studied. Several halogenating agents, in aqueous and nonaqueous media, have been employed, and beside substitution products oxindole derivatives were almost always found.[1,2] It is known that an aqueous medium favors oxidation and an anhydrous one bromination, and that the two reactions are always competitive, neither one being completely excluded. However, more than one pathway has been proposed to explain the formation of 3-halooxindoles from indoles.[1b,2a,b,d] We have now investigated the behavior of some 2,3-dibrominated polybromoindoles with bromine in aqueous (acetic acid) and in nonaqueous media (carbon tetrachloride).

When excess bromine was added to an acetic acid suspension of 2,3,5,6-tetrabromoindole (**1a**),[1a] 3,3,5,6-tetrabromooxindole (**2a**, 67% yield) was formed. Compound **2a** was hydrolyzed with alkali to 5,6-dibromoisatin (**3a**)[1a] and led, with phenylhydrazine, to a β-phenylhydrazone identical with an authentic sample prepared from **3a**; these facts indicate that two bromine atoms in compound **2a** are in the 3 position.[1b] The infrared spectrum of **2a** shows strong N–H and C=O peaks at 3200 and 1730 cm$^{-1}$, respectively, in good agreement with those found for other 3,3-dibrominated oxindoles.[1b,3]

The main product of the reaction of **1a**[1a] with excess bromine in anhydrous $CCl_4$ was a nonoxindolic material

JOC-22-1

## Experimental Section[1,2]

([1,2]) Melting points are uncorrected. Ir spectra were obtained on a Perkin-Elmer Infracord 137, in Nujol mulls. Comparison between compounds were made on the basis of their infrared spectra. $MgSO_4$ was used as drying agent, unless stated otherwise.

Isatin-β-phenylhydrazones.—All β-phenylhydrazones were obtained according to the general procedure described by Da Settimo and Nannipieri for the preparation of 5,6-dibromo-1-methylisatin-β-phenylhydrazone.[1b]

Reactions with Bromine in Acetic Acid.—These reactions were all carried out in an open erlenmeyer flask at room temperature, unless stated otherwise. Commercial acetic acid (ca. 98%) was not previously dried.

Reactions with Bromine in Carbon Tetrachloride.—These reactions were all performed in anhydrous conditions. Carbon tetrachloride was previously dried with $CaCl_2$.

1,3,5,6-Tetrabromooxindole (2a). A. By Treatment of 2,3,5,6-Tetrabromoindole (1a) with Bromine in Acetic Acid.— To a well-stirred suspension of 0.1 g (0.23 mmol) of 1a[1a] in 2 ml of acetic acid 0.62 g (3.90 mmol) of bromine was added. The resulting solution was stored at room temperature for 15 hr; a precipitate formed which was collected by filtration, washed with acetic acid and water, and dried to yield 0.07 g (67.5%) of practically pure 2a. An analytical sample, pale yellow prisms darkening above 210° without melting, was crystallized from acetic acid. The ir spectrum showed bands at ca. 3200 (N-H) and 1730 $cm^{-1}$ (C=O).

Anal. Calcd for $C_8H_3Br_4NO$: C, 21.40; H, 0.67; Br, 71.22. Found: C, 21.67; H, 0.75; Br, 71.31.

The hydrolysis of 2a, carried out according to Stollé,[9a] with a mixture of ethanol and 2N aqueous sodium hydroxide, gave 5,6-dibromoisatin (3a)(85% yield), mp 288–290° (lit.[1a] mp 288–290°).

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The β-phenylhydrazone obtained from 2a was identical with that obtained from 1a; an analytical sample, orange needles, mp 266–268°, was obtained after crystallization from ethanol.

Anal. Calcd for $C_{14}H_9Br_4N_3O$: C, 42.53; H, 2.28; Br, 40.55. Found: C, 42.69; H, 2.30; Br, 40.61.

B. By Oxidation of 1a with Chromic Anhydride.—A suspension of 0.2 g of 1a in a mixture of 3 ml of acetic acid and 1 ml of water was treated, with stirring, with small portions (0.4 g total) of chromic anhydride. The suspension was heated slightly, stored at room temperature for 24 hr, and then poured into water. A precipitate formed which was collected by filtration, washed with water, and dried to give 0.15 g (72%) of practically pure 2a.

C. By Oxidation of 1a with Peracetic Acid.—To a suspension of 0.2 g of 1a in 6 ml of acetic acid, 1 ml of 36% hydrogen peroxide was added. After storage at room temperature for 5 days, the resulting solution was concentrated under reduced pressure; a precipitate formed which was collected by filtration, washed with acetic acid and water, and dried to yield 0.075 g (36%) of practically pure 2a. The acetic mother liquor was evaporated in vacuo to give an additional 0.05 g (60% total yield) of crude 2a.

Bromination of 1a in Carbon Tetrachloride. 2,3,5,6,7-Pentabromoindole (1b) and 1,3,5,6-Tetrabromooxindole (2a).—A suspension of 1.0 g (2.30 mmol) of 1a[1a] in 30 ml of anhydrous $CCl_4$ was treated with 2.5 g (15.6 mmol) of bromine. After 72 hr at room temperature with occasional stirring 0.115 g (11%) of 2a was collected by filtration. The filtrate was concentrated on a steam-bath to about 5 ml to give 0.5 g of practically pure 1b. The mother liquor was evaporated and the residue was dissolved in benzene and passed through a column of neutral

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alumina (grade I); elution with benzene gave additional 0.06 g (47% total yield) of pure 1b. An analytical sample, white crystals, mp 206–207.5°, was crystallized from benzene; the ir spectrum showed a band at ca. 3600 $cm^{-1}$ (N-H).

Anal. Calcd for $C_8H_2Br_5N$: C, 18.75; H, 0.39; Br, 78.2. Found: C, 19.00; H, 0.32; Br, 77.8.

1,3,5,6,7-Pentabromooxindole (2b). A. By Treatment of 2,3,5,6,7-Pentabromoindole (1b) with Bromine in Acetic Acid.—To a suspension of 0.1 g (0.195 mmol) of 1b in 2.5 ml of acetic acid 0.39 g (2.44 mmol) of bromine was added with stirring. Stirring was continued at room temperature for 24 hr. The mixture was then poured into 40 ml of water to give a precipitate which was collected by filtration, washed, and suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.08 g (78%) of practically pure 2b. A sample crystallized from acetic acid gave yellow needles darkening above 220° with decomposition without melting. The ir spectrum showed bands at ca. 3100 (N-H) and 1745 $cm^{-1}$ (C=O).

Anal. Calcd for $C_8H_2Br_5NO$: C, 18.20; H, 0.38; Br, 75.80. Found: C, 18.45; H, 0.45; Br, 76.01.

The β-phenylhydrazone obtained from 2b was crystallized from dimethylformamide to give orange needles melting at 312–314° with decomposition.

Anal. Calcd for $C_{14}H_8Br_5N_3O$: C, 35.42; H, 1.69; Br, 50.60. Found: C, 35.60; H, 1.71; Br, 50.89.

B. By Treatment of 7-Bromoindole (4) with Bromine in Acetic Acid.—To an ice-cold solution of 4.65 g (29.0 mmol) of bromine in 6 ml of acetic acid, 3 ml of acetic acid containing 0.3 g (1.53 mmol) of 4[9] was added dropwise with stirring. The mixture was allowed to warm to 25° and stand for 3 hr, while being stirred. It was then poured into water; a precipitate formed which was collected by filtration, and

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suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.47 g (58%) of 2b.

Several attempts to brominate 4 by adding bromine to a solution of the compound in acetic acid gave only brown amorphous products.

C. By Oxidation of 1b with Chromic Anhydride.—When 0.2 g of 1b was treated exactly as described for the chromic oxidation of 1a, 0.145 g (71%) of 2b was obtained.

D. By Oxidation of 1b with Peracetic Acid.—Compound 2b was obtained in 68% yield from 0.1 g of 1b as described for the oxidation of 1a with peracetic acid, except that the mixture was left at room temperature for 30 days.

2,3,5,6,7-Pentabromo-1-methylindole (1c).—To a suspension of 0.4 g of 1b in 4 ml of 2N sodium hydroxide, 0.4 ml of dimethyl sulfate was added with stirring. Stirring was continued for 12 hr while small amounts of 2N sodium hydroxide and of dimethyl sulfate were again added at intervals. After storage at room temperature overnight, the precipitate was collected by filtration, washed with water and dried to yield 0.35 g (86%) of 1c. A sample crystallized from benzene, and then from hexane, gave white needles, mp 160°.

Anal. Calcd for $C_9H_3Br_5N$: C, 20.60; H, 0.76; Br, 76.00. Found: C, 20.80; H, 0.95; Br, 76.19.

1,3,5,6,7-Pentabromo-1-methyloxindole (2c). A. By Treatment of 2,3,5,6,7-Pentabromo-1-methylindole (1c) with Bromine in Acetic Acid.—To a suspension of 0.05 g (0.095 mmol) of 1c in 4 ml of acetic acid 0.30 g (1.88 mmol) of bromine was added with stirring. Stirring was continued for 24 hr at room temperature. The mixture was then poured into water and a precipitate formed which was collected by filtration, and suspended in a 3% solution of sodium thiosulfate; the resulting

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compound was again collected, washed with water, and dried to give 0.035 g (67.5%) of practically pure 2c. It was crystallized twice from acetic acid to give colourless needles darkening above 210° without melting. The ir spectrum showed a band at ca. 1740 $cm^{-1}$ (C=O).

Anal. Calcd for $C_9H_4Br_5NO$: C, 20.00; H, 0.74; Br, 74.00. Found: C, 20.16; H, 0.70; Br, 74.01.

The β-phenylhydrazone obtained from 2c was crystallized twice from acetic acid to give orange crystals, mp 192–193°.

Anal. Calcd for $C_{15}H_{10}Br_5N_3O$: C, 36.90; H, 2.04; Br, 49.10. Found: C, 36.79; H, 1.98; Br, 49.40.

B. By Oxidation of 1c with Chromic Anhydride.—A suspension of 0.15 g of 1c in a mixture of 4 ml of acetic acid and 1 ml of water was treated with 0.3 g of chromic anhydride. The mixture was stored at room temperature for 48 hr, and then poured into water. A precipitate formed which was collected by filtration, washed with water, and dried to yield 0.140 g (92%) of practically pure 2c.

C. By Oxidation of 1c with Peracetic Acid.—To a suspension of 0.1 g of 1c in 1.5 ml of acetic acid, 0.5 ml of 36% hydrogen peroxide was added. After storage at room temperature for 30 days, a precipitate was collected by filtration, washed with water, and dried to give 0.08 g (77.5%) of 2c.

Reaction of 2,3,5,6-Tetrabromo-1-methylindole (1e) with Bromine. A. In Acetic Acid. Constant-melting Mixture of 1,3,5,6-Tetrabromo-1-methyloxindole (2e) and 3,3,4,5,6-Pentabromo-1-methyloxindole (2d).—To a suspension of 0.5 g (1.12 mmol) of 1e[1b] in 15 ml of acetic acid 0.5 g (3.12 mmol) of bromine was added. After 48 hr at room temperature with occasional stirring, a precipitate was collected by filtration, washed with acetic acid and water, and dried to yield 0.390 g of a mixture of 2e[1b] and 2d. The acetic mother liquor was concentrated under reduced pressure to give an additional 0.05 g of

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the same mixture. All attempts to separate the components of such mixture both by column chromatography and by fractional crystallization were unsuccessful. When the mixture was crystallized twice from acetic acid, crystals were obtained softening at 210–215° with darkening (the melting range remained unchanged through several crystallizations); the ir spectrum showed band at ca. 1735 $cm^{-1}$ (C=O). Both the melting range and the ir spectrum of the mixture were identical with those of an artificial mixture containing 2e and 2d in 7:3 ratio. Compounds 2e and 2d were obtained in 54 and 19.5% yield respectively [yields were based on 7:3 ratio (w/w) of 2e to 2d].

B. In Carbon Tetrachloride. 2,3,4,5,6-Pentabromo-1-methylindole (1d) and Constant-melting Mixture of 2e and 2d.—To a well-stirred suspension of 2.0 g (4.47 mmol) of 1e[1b] in 50 ml of anhydrous $CCl_4$ 3.12 g (19.5 mmol) of bromine was added. Stirring was continued for 48 hr at room temperature. A precipitate was collected by filtration and suspended in a 3% solution of sodium thiosulfate; the resulting compound was again collected, washed with water, and dried to give 0.8 g of practically pure 1d. The mother liquor was concentrated under reduced pressure to about 25 ml, and treated with additional 1.87 g (11.7 mmol) of bromine. After 48 hr at room temperature a precipitate was collected by filtration, and worked up as described above to yield an additional 1.0 g (76% total yield) of practically pure 1d. It was crystallized twice from benzene to give white needles, mp 214–216°.

Anal. Calcd for $C_9H_4Br_5N$: C, 20.60; H, 0.76; Br, 76.00. Found: C, 20.78; H, 1.02; Br, 76.02.

The mother liquor (from which compound 1d was collected) was allowed to evaporate slowly at room temperature; the residue consisted of 0.4 g of the constant-melting mixture of 2e and 2d described in A.

1,3,4,5,6-Pentabromo-1-methyloxindole (2d). A. By Treatment of 2,3,4,5,6-Pentabromo-1-methylindole (1d) with Bromine in Acetic Acid.—

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To a well-stirred suspension of 0.8 g (1.52 mmol) of 1d in 16 ml of acetic acid 0.64 g (4 mmol) of bromine was added. After 72 hr at room temperature with stirring a precipitate was collected by filtration, and worked-up as described for the treatment of 1b with bromine in acetic acid to yield 0.65 g (79%) of practically pure 2d. An analytical sample, yellow crystals darkening above 220° with decomposition and without melting, was crystallized from acetic acid; the ir spectrum showed a band at ca. 1745 $cm^{-1}$ (C=O).

Anal. Calcd for $C_8H_4Br_5NO$: C, 20.00; H, 0.74; Br, 74.00. Found: C, 19.92; H, 0.80; Br, 73.65.

The β-phenylhydrazone obtained from 2d was crystallized from acetic acid to give orange needles, mp 215–217°.

Anal. Calcd for $C_{14}H_9Br_5N_3O$: C, 36.90; H, 2.04; Br, 49.10. Found: C, 37.01; H, 1.98; Br, 48.95.

B. By Oxidation of 1d with Chromic Anhydride.—A suspension of 0.5 g od 1d in 13 ml of acetic acid was treated, with stirring, with small portions (0.6 g total) of chromic anhydride. The suspension was heated slightly for 1 hr and then poured into 100 ml of water. After storage at room temperature overnight, a precipitate was collected by filtration, washed with water, and dried to give 0.253 g (49%) of practically pure 2d.

C. By Oxidation of 1d with Peracetic Acid.—A suspension of 0.2 g of 1d in 3 ml of acetic acid was treated with 2 ml of 36% hydrogen peroxide. After storage at room temperature for 7 days, a precipitate was collected by filtration, washed with acetic acid and water, and dried to yield 0.2 g (97%) of practically pure 2d.

1,3,4,5,6-Pentabromooxindole (2f).—To an ice-cold solution of 9.4 g (58.8 mmol) of bromine in 10 ml of acetic acid, 10 ml of acetic acid containing 1.22 g (6.21 mmol) of 4-bromoindole (5)[7] was added dropwise with stirring. The mixture was allowed to warm to 25°

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and stored for 40 hr, while being stirred. It was then poured into water; a precipitate formed which was collected by filtration, suspended in a 3% solution of sodium thiosulfate, again collected, washed with water, dried, dissolved in benzene and passed through a column of silica gel (1.6 x 40 cm); elution with benzene gave 1.04 g (31.5%) of practically pure 2f. A sample crystallized from acetic acid gave yellow brown crystals darkening above 230° without melting; the ir spectrum showed bands at ca. 3200 (N-H) and 1730 $cm^{-1}$ (C=O).

Anal. Calcd for $C_8H_2Br_5NO$: C, 18.20; H, 0.38; Br, 75.80. Found: C, 18.36; H, 0.55; Br, 75.43.

Several attempts to brominate 5 by adding bromine to a solution of the compound in acetic acid gave only brown amorphous products.

The β-phenylhydrazone obtained from 2f was crystallized twice from dimethylformamide to give orange crystals, mp 293–295°.

Anal. Calcd for $C_{14}H_8Br_5N_3O$: C, 35.42; H, 1.69; Br, 50.60. Found: C, 35.64; H, 1.74; Br, 50.91.

4,5,6-Tribromo-1-methylisatin (3b). A. From 1,3,4,5,6-Pentabromo-1-methyloxindole (2d).—The hydrolysis of 2d was carried out according to Stollé,[9a] with a mixture of ethanol and 2N sodium hydroxide. The pure isatin 3b, obtained in 27% yield as red needles after sublimation at 220°/3 mm and crystallization from benzene, melted at 253–255°. The ir spectrum showed band at ca. 1750 $cm^{-1}$ (C=O).

Anal. Calcd for $C_9H_4Br_3NO_2$: C, 27.16; H, 1.01; Br, 60.26. Found: C, 27.41; H, 1.10; Br, 60.44.

The β-phenylhydrazone obtained from 3b was identical with a sample prepared from 2d.

B. From 1,3,4,5,6-Pentabromooxindole (2f).—When 0.5 g of 2f was treated as described for the methylation of 2,3,5,6,7-pentabromoindole (1b), except that the mixture was stirred for 24 hr, a solution formed which was diluted with water, and acidified with sulfuric acid;

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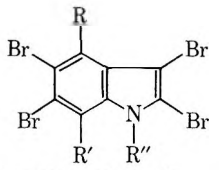
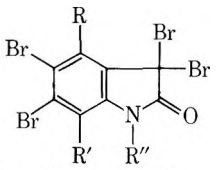
a red precipitate formed which after sublimation at 240°/3 mm and crystallization from benzene gave 0.03 g (8%) of pure 3b.

Oxidation of 2,3,5,6-Tetrabromo-1-methylindole (1e). A. With Chromic Anhydride.—A suspension of 0.5 g of 1e[1b] in a mixture of 15 ml of acetic acid and 2 ml of water was treated with 0.5 g of chromic anhydride. The mixture was heated slightly in order to dissolve the solid, then allowed to cool to 25°, and poured in 100 ml of water. After storage at room temperature overnight a precipitate was collected by filtration, washed with water, and dried to yield 0.28 g of a mixture of 5,6-dibromo-1-methylisatin (3c) and 3,3,5,6-tetrabromo-1-methyloxindole (2e). Fractional crystallization of the mixture from methanol yielded first 0.15 g (29%) of compound 2e, darkening above 220° with slow decomposition (lit.[1b] darkening above 220° with slow decomposition), and then 0.12 g (33.5%) of compound 3c, mp 255–256° (lit.[1b] 255–256°).

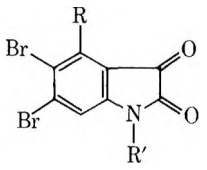
B. With Peracetic Acid.—Compound 2e was obtained in 63% yield from 0.3 g of 1e as described for the oxidation of 1a with peracetic acid, except that the mixture was stirred at room temperature for 3 days.



**1a**, R = R′ = R″ = H
**b**, R = R″ = H; R′ = Br
**c**, R = H; R′ = Br; R″ = $CH_3$
**d**, R = Br; R′ = H; R″ = $CH_3$
**e**, R = R′ = H; R″ = $CH_3$



**2a**, R = R′ = R″ = H
**b**, R = R″ = H; R′ = Br
**c**, R = H; R′ = Br; R″ = $CH_3$
**d**, R = Br; R′ = H; R″ = $CH_3$
**e**, R = R′ = H; R″ = $CH_3$
**f**, R = Br; R′ = R″ = H



**3a**, R = R′ = H
**b**, R = Br; R′ = $CH_3$
**c**, R = H; R′ = $CH_3$

(47% yield) (no C=O peak, N-H stretching at 3600 $cm^{-1}$) to which structure **1b** was assigned. Although the reaction was carried out under dry conditions, a small amount (11% yield) of the oxindole **2a** was isolated.[4] Structure **1b** was assigned to the nonoxindolic material, because it gave, with excess bromine in acetic acid suspension, the pentabromooxindole **2b**, which was also obtained by adding 7-bromoindole (**4**)[5] to an excess of bromine in acetic acid solution. Compound **2b** gave with phenylhydrazine 5,6,7-tribromoisatin β-phenylhydrazone.

When an acetic acid suspension of 2,3,5,6,7-pentabromo-1-methylindole (**1c**), obtained by methylation of **1b**, was treated with an excess of bromine, 3,3,5,6,7-pentabromo-1-methyloxindole (**2c**) (C=O peak at 1740 $cm^{-1}$, 67% yield) was isolated. Two bromine atoms are in the 3 position because compound **2c** gave, with phenylhydrazine, 5,6,7-tribromo-1-methylisatin β-phenylhydrazone.

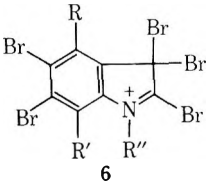
The reaction of 2,3,5,6-tetrabromo-1-methylindole (**1e**)[1b] with excess bromine was also solvent dependent. When the reaction was carried out in acetic acid, an oxindolic material (C=O band at 1735 $cm^{-1}$), whose melting range remained unchanged through several crystallizations, was isolated. This material was identified as a mixture of 3,3,5,6-tetrabromo-1-methyloxindole (**2e**)[1b] and 3,3,4,5,6-pentabromo-1-methyloxindole (**2d**). Its infrared spectrum and melting range were identical with those of an artificial mixture containing **2e** and **2d** in 7:3 ratio (w/w). Similar constant-melting mixtures of isomeric and nonisomeric bromoindoles have been already described.[1,5]

Structure **2d**[6] (C=O peak at 1745 $cm^{-1}$) was assigned to the minor product of the reaction of **1e** with bromine on the basis of its elemental composition and of the fact that it was different from **2c**; **2d** was hydrolyzed with alkali to isatin **3b**, which gave the same β-phenylhydrazone as **2d**. Structure **3b** was proved as follows: 4-bromoindole (**5**)[7] was added to an excess of bromine in acetic acid solution to yield 3,3,4,5,6-pentabromooxindole (**2f**) (N-H band at 3200 $cm^{-1}$, C=O band at 1730 $cm^{-1}$); compounds **2f** and **2b** are isomers; compound **2f** gave a β-phenylhydrazone with phenylhydrazine, and isatin **3b** by methylation with dimethyl sulfate in alkaline medium (hydrolysis of **2d** to **3b** accompanies the methylation).

When the reaction of **1e** with excess bromine was carried out in anhydrous $CCl_4$, 2,3,4,5,6-pentabromo-1-methylindole (**1d**, 76% yield) and the same mixture (from the mother liquor) of **2e**[1b] (13.5% yield) and **2d** (5% yield) were formed. Structure **1d** was assigned, because **1d** and **1c** are isomers, and **1d** led, with excess bromine in acetic acid, to the oxindole **2d** (79% yield).

When the results of the reactions of 2,3,5,6-tetrabromo-1-methylindole (**1e**) with bromine and of the unmethylated analog **1a** are compared, it can be seen that the bromination of the aromatic ring occurs at the 7 position in the nonmethylated and at the 4 position in the N-methylated compound. These results can be explained with the assumption that there is a preference for electrophilic attack on position 7 but that the *N*-methyl group exerts a sufficiently strong steric hindrance to prevent substitution at the 7 position, making attack at carbon 4 competitive.

In a previous paper we found that, when 1-methylindole was treated with excess bromine, 3,3,5,6-tetrabromo-1-methyloxindole (**2e**) was obtained; in one case also 2,3,5,6-tetrabromo-1-methylindole (**1e**) was isolated from the reaction mixture.[1b] The mode of conversion of 1-methylindole to the oxindole **2e** is an interesting problem. Using a 5:1 molar ratio of reagent to substrate, bromination of the benzene ring took place;[1b] when bromine atoms substitute on the benzene ring they have a very marked stabilizing effect, so that hydrolysis of 2,3-dibrominated polybromoindoles requires very drastic conditions.[1b] Therefore it was excluded that oxindole **2e** was formed by bromination of the 3 position of 3,5,6-tribromo-1-methyloxindole; in fact, the latter compound should be formed by hydrolysis of 2,3,5,6-tetrabromo-1-methylindole (**1e**); it was excluded also that oxindole 2e was formed by bromination of a simple intermediate nonbrominated oxindole,[8] because, when simple oxindoles are brominated, bromine attacks only positions 3, 5, and 7.[1b,9] The formation of oxindole **2e** was believed to involve electrophilic attack on position 3 of indole **1e** to give an intermediate 3,3-dibrominated indolenine **6** (R = R′ = H; R″ = $CH_3$), followed by rapid attack of a nucleophile ($H_2O$ or $BrO^-$). The same hypothetical intermediate **6** satisfactorily ra-



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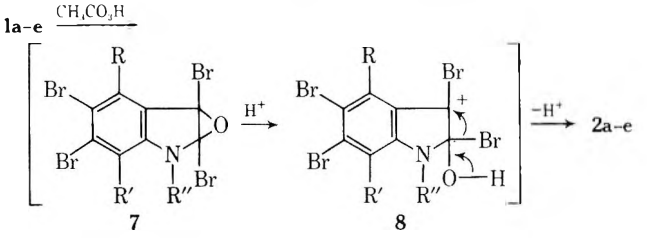
tionalizes the formation of oxindoles **2a–e** from the corresponding indoles **1a–e**. Then the present results seem to confirm the previously proposed pathway, whereas the mechanisms proposed by other authors[8] appear to be not effective in this case.

A matter of particular interest is the action of two oxidizing agents, chromic anhydride and peracetic acid, on 2,3-dibrominated indoles **1a–e**. Although in these compounds bromine atoms (electron-attracting substituents) substitute on the benzene ring, position 2 is substituted, and compounds **1c–e** are N-substituted also (such factors promote generally oxidation of some indole derivatives to o-acylamino ketones or to anthranilic acids);[1a,2a,10] nevertheless the reaction of **1a–e** with chromic anhydride and with peracetic acid did not yield usual products of oxidation.

When products **1a–d** were treated with chromic anhydride or with peracetic acid the corresponding 3,3-dibromooxindoles **2a–d** were isolated in yields ranging from 49 to 90%. Compound **1e** gave 3,3,5,6-tetrabromo-1-methyloxindole (**2e**, 83% yield) when the reaction was carried out with peracetic acid, whereas compound **2e** (29% yield) and 5,6-dibromo-1-methylisatin (**3c**, 33% yield) were isolated by reaction with chromic anhydride.

Since all 2,3-dibromoindoles were converted to 3,3-dibromooxindoles, this method could be used as a diagnostic tool in the structure determination of 2,3-dibromoindoles.

One possible explanation of the unusual oxidative reaction could involve the formation of an epoxide intermediate 7, followed by opening of the epoxide ring to give a carbonium ion 8, a 1,2 shift, and expulsion of the proton

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to yield the observed 3,3-dibromooxindole. Similar molecular rearrangements have been already observed in the peracid epoxidation of several haloalkenes.[11]

**Acknowledgment.** This work was supported by a grant from the Consiglio Nazionale delle Ricerche.

**Registry No.**—**1a**, 17826-06-1; **1b**, 51417-37-9; **1c**, 51417-38-0; **1d**, 51417-39-1; **1e**, 25055-55-4; **2a**, 51417-40-4; **2a** β-phenylhydrazone, 51417-41-5; **2b**, 51417-42-6; **2b** β-phenylhydrazone, 51417-43-7; **2c**, 51417-44-8; **2c** β-phenylhydrazone, 51417-45-9; **2d**, 51417-46-0; **2d** β-phenylhydrazone, 51417-47-1; **2e**, 25055-56-5; **2f**, 51417-48-2; **2f** β-phenylhydrazone, 51417-49-3; **3b**, 51417-50-6; **4**, 51417-51-7.

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# Stereochemistry and Mechanism of the Thermal [1,3] Alkyl Shift of Stable 1,4-Dialkyl-1,4-dihydropyrazines[1a,b]

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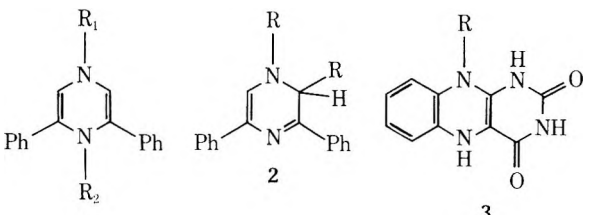
Stable 8-π-electron 1,4-dialkyl-1,4-dihydropyrazines are readily prepared by reaction of *N*-benzyldiphenacylamine hydrobromide with primary aliphatic amines provided care is taken to avoid the subsequent rearrangement. The previously postulated intermediacy of 1,4-dibenzyl-1,4-dihydro-2,6-diphenylpyrazine (**1a**) in the rearrangement to 1,2-dihydropyrazine **2a** is demonstrated and the reaction proceeds in 95 ± 2% yield with first-order kinetics. Crossover recombination experiments show 12 ± 6% intermolecular contribution from a radical dissociation–recombination process which is prevented with butanethiol scavenger. Chiral **24** rearranges in the presence of the scavenger with ≥95% stereospecificity and with inversion of the migrating group indicating an 88 ± 6% component of a concerted [1,3] sigmatropic shift with suprafacial allylic utilization.

We wish to report the general synthesis and chemistry of novel 1,4-dialkyl-2,6-diphenyl-1,4-dihydropyrazines[1] **1** and a study of the stereochemistry and mechanism of their thermally induced rearrangement to the isomeric 1,2-dialkyl-3,5-diphenyl-1,2-dihydropyrazines **2**. Compounds of structure **1** are of interest in possessing an 8π available electron system which is potentially antiaromatic[2] or homoaromatic.[3] In addition, the structural similarity between the 1,4-dihydro-1,4-dialkylpyrazines and the reactive ring of the isoalloxazine portion of the reduced flavin coenzymes 3[4] and the marked propensity of both to undergo redox reactions (which see) renders **1** of interest as model compounds for the latter. The structurally related 5,10-dihydrophenazines **4** have been employed as analogs of riboflavin.[4,5] The recent discovery of the importance of the 1,4-dihydropyrazine moiety in the biolumi-

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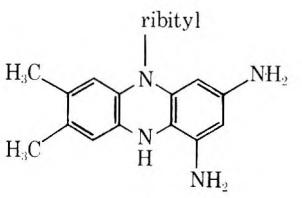


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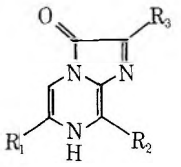
**Table I**
**1-Benzyl-4-alkyl-2,6-diphenyl-1,4-dihydropyrazines[c] (1, $R_1$ = $CH_2Ph$)**

| Compd | $R_2$ | Mp, °C | Yield, % | $\lambda_{max}$,[a] nm | Log ε | δ |
|---|---|---|---|---|---|---|
| **1a** | $CH_2Ph$ | 107–108.5 | 73 | 442<br>338 | 3.22<br>3.48 | ($C_6D_6$) 3.20 (s, 2 H, $-CH_2Ph$), 3.76 (s, 2 H, $-CH_2Ph$), 5.57 (s, 2 H, vinylic, $C_3$ and $C_5$ H), and 7.17–7.57 (m, 20 H, aromatic |
| **1b** | $(CH_2)_2Ph$ | 135–137 | 90 | 427<br>339<br>237 | 3.49<br>3.41<br>4.17 | ($C_5D_5N$) 3.25 [br s, 4 H, $-(CH_2)_2Ph$], 4.26 (s, 2 H, $-CH_2Ph$), 6.57 (br s, 2 H, vinylic H, $C_3$ and $C_5$ H), and 6.96–7.85 (m, 20 H, aromatic |
| **1c** | $(CH_2)_2CH_3$ | 103–105 | 64.4 | 428<br>338<br>238 | 3.41<br>3.29<br>4.22 | *b* |
| **1d** | $(CH_2)_3CH_3$ | 115–117 | 78.1 | 428<br>338<br>237 | 3.53<br>3.38<br>4.27 | *b* |
| **1e** | $CH_2CH(CH_3)_2$ | 106–107.5 | 79.4 | 429<br>337<br>239 | 3.21<br>3.51<br>4.21 | *b* |
| **1f** | $(CH_2)_2CH(CH_3)_2$ | 126–128 | 68.7 | 429<br>341<br>237 | 3.21<br>3.47<br>4.17 | *b*<br>*b* |
| **1g** | $CH_3$ | 133–135 | 22.3 | 428<br>340<br>237 | 3.41<br>3.51<br>4.15 | *b* |
| **1h** | c-$C_3H_5$ | 111–112.5 | 77.2 | 428<br>340<br>238 | 3.42<br>3.48<br>4.17 | *b* |
| **1i** | c-$C_5H_9$ | 107–108.5 | 30.4 | 409<br>329<br>245 | 3.64<br>3.47<br>4.09 | ($C_6D_6$) 0.92–2.02 (m, 8 H, cyclopentyl), 3.20–3.60 (br, 1 H, methine), 3.80 (s, 2 H, $CH_2Ph$), 6.35 (s, 2 H, vinylic H, $C_3$ and $C_5$ H), and 6.96–7.79 (m, 15 H, aromatic) |
| **1j** | c-$C_6H_{11}$ | 138–139.5 | 36.5 | 410<br>328<br>245 | 3.61<br>3.48<br>4.11 | ($C_6D_6$) 0.77–2.21 (m, 10 H, cyclohexyl), 2.64–3.30 (br, 1 H, methine), 3.76 (s, 2 H, $CH_2Ph$), 6.30 (2, 2 H, vinylic H, $C_3$ and $C_5$ H), and 6.95–7.91 (m, 15 H, aromatic) |
| **1k** | c-$C_7H_{13}$ | 120–121.5 | 31.4 | 409<br>329<br>243 | 3.61<br>3.45<br>4.08 | *b* |
| **1l** | c-$C_8H_{15}$ | 96–97.5 | 15.2 | 425<br>327<br>244 | 3.58<br>3.44<br>4.12 | *b* |

[a] Measured in $CH_3CN$. [b] The nmr signals were not visible owing to paramagnetic broadening by the odd-electron species present. [c] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table: Ed.



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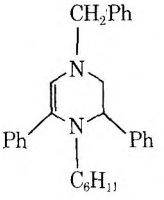
nescence of certain luciferins, *e.g.*, **5**, increases the general interest of the present study.[6] The logical approach to the synthesis of a representative of **1**, *e.g.*, the condensation of benzylamine with *N*-benzyldiphenacylamine hydrobromide, originally considered to afford 1,4-dihydro-1,4-dibenzylpyrazine,[7] has been shown to give the 1,2-dibenzyl-3,5-diphenyl-1,2-dihydropyrazine[8,9] (**4**, R = $PhCH_2$) and a 1,3-alkyl migration from the initially formed but unisolated 1,4-dibenzyl-1,4-dihydropyrazine isomer was postulated.[8]

We found that, in a general reaction with *N*-benzyldiphenacylamine, primary aliphatic amines, containing groups which are less prone to migrate, react to give the series of 1,4-dialkyl-1,4-dihydropyrazines indicated in Table I, often in excellent yield.[1] The simplicity of the nmr spectra is consistent with the $C_{2v}$ symmetry of structures of type **1**. Catalytic hydrogenation of **1j** at atmospheric pressure over Pd/C afforded the 1,2,3,4-tetrahydropyrazine **6** as an oil in 84% yield. The addition of only 1 equiv of hydrogen under these conditions is held to be characteristic of a 1,4-dihydropyrazine.[9] The new 1,4-dialkyl-1,4-dihydropyrazines described in Table I are stable as orange-red solids in the crystalline state but are sensitive to light and atmospheric oxygen and are reactive in solution, especially with halogen-containing solvents. The solutions are readily oxidized in air to stable paramagnetic species which give persistent epr signals. The sensitivity to oxygen of compounds **1a–f** results in considerable paramagnetic nmr line broadening in many cases even though they analyze correctly. Structure proof was, however, obtained with two additional representative examples, **1d** and **1h**, by catalytic hydrogenation to the 1,2,3,4-tetrahydro compounds, the nmr spectra of which were normal.[10] The epr spectra of the paramagnetic species formed by oxidation of **1j** (Table II) gave *g* values of 2.0025, close to the free-electron value of *g* = 2.00232,[11] indicative of an organic free radical, and the spectrum width for **1h**, 51 G, closely corresponds to those values previously reported for the reduction in concentrated sulfuric acid solutions of substituted pyrazines.[12] These analogies, together with



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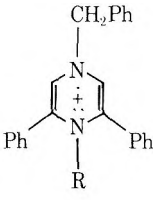

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**Table II**
**Esr Data on Paramagnetic Species Formed from the Oxidation of 1,4-Dialkyl-2,6-diphenyl-1,4-dihydropyrazines 1 in Benzene**

| Substrate | Spectrum width, G | Appearance |
|---|---|---|
| **a** | 62.5 | Multiplet |
| **b** | 110.0 | Multiplet |
| **c** | 167.0 | Multiplet |
| **d** | 68.0 | Multiplet |
| **e** | 58.0 | Multiplet |
| **f** | 87.0 | Multiplet |
| **g** | 64.5 | Multiplet |
| **h** | 51.0 | 8 lines, hfs 7.5 G |
| **i** | 48.0 | 7 lines, hfs 7.5 G |
| **j**[a] | 50.0 | Multiplet |
| **m**[b] | 72.0 | 9 lines, hfs 8.6 G |

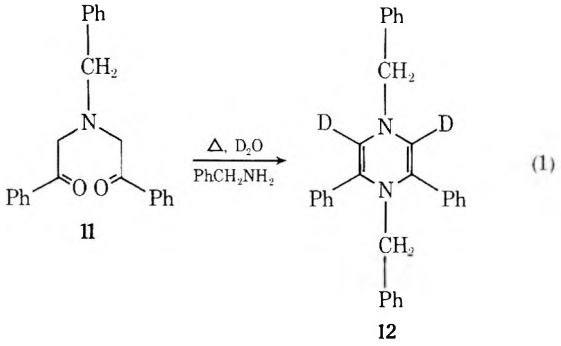
[a] $g$ value = 2.0025. [b] 1,4-Dimethyl-2,6-dipheny-1,4-dihydropyrazine.

the recent announcement that stable pyrazine radical cations may be generated under mild conditions by the action of daylight,[13] point to the 7-$\pi$-electron radical cation structure (**7**) for these species.

It was possible by employing lower reaction temperatures to isolate the very reactive 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine (**1a**) as an orange, crystalline solid. This permits confirmation of the previously postulated mechanism[8,9] and an examination of this unusually facile [1,3] alkyl shift.

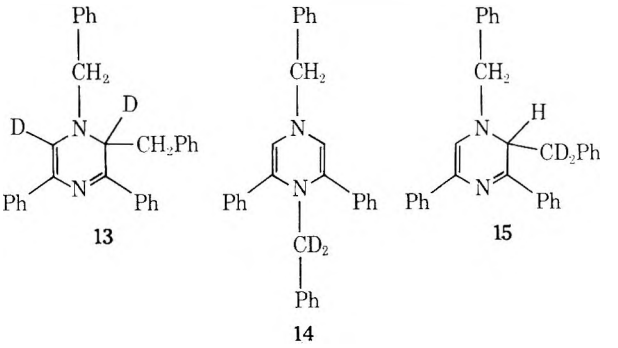
Examples of thermally induced [1,3] shifts involving heteroatoms at the migration origin or terminus have been reported in several cases.[14,15] However, in very few of these cases has it yet been established whether the rearrangements are concerted or proceed *via* a radical mechanism.[16] Thus we hoped to contribute to the general problem of [1,3] shifts. The 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine rearranges smoothly in benzene in the temperature range of 40–80° to **2** (R = $PhCH_2$) in a yield of ≥95 ± 2% as determined spectroscopically. Because of the photosensitivity and propensity of 1,4-dialkyl-1,4-dihydropyrazines to air oxidize to stable odd-electron species[1,13] it was necessary to degas carefully and protect the solution from the light.

To establish whether the reaction is intramolecular or intermolecular we performed a crossover recombination experiment with differentially deuterium-labeled 1,4-dialkyl-1,4-dihydropyrazines. The ring-labeled compound **12** was formed readily by deuterium exchange (eq 1) with



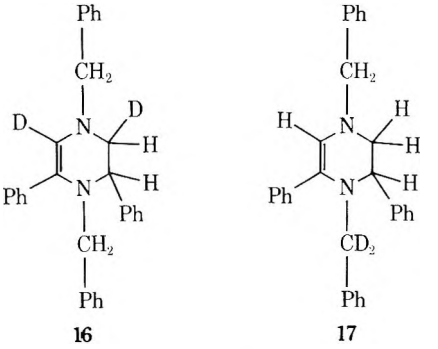

(1)

≥80% incorporation as shown by nmr, which showed the diminution of the 2 H singlet at $\delta$ 6.25. Rearrangement of **12** in benzene gave a quantitative yield of the 2,6-dideuterio-1,2-dihydropyrazine **13**, which allowed assignment of the methine and vinyl nmr absorptions in **2a** as $\delta$ 4.76 and 6.55, respectively. The isotopic labeling isomer of **12**, compound **14**, was prepared by treating **11** with $PhCD_2NH_2$ and contained 100 ± 2% deuterium incorporation at the 1-benzyl methylene positions. Thermal rearrangement of **14** to **15** proceeded smoothly and permitted assignment of




the methylene group nmr signals at the 1 and 2 positions of **2a** as $\delta$ 3.96 ($J$ = 15.5 Hz) and 2.70 ($J$ = 14.0 Hz), respectively.

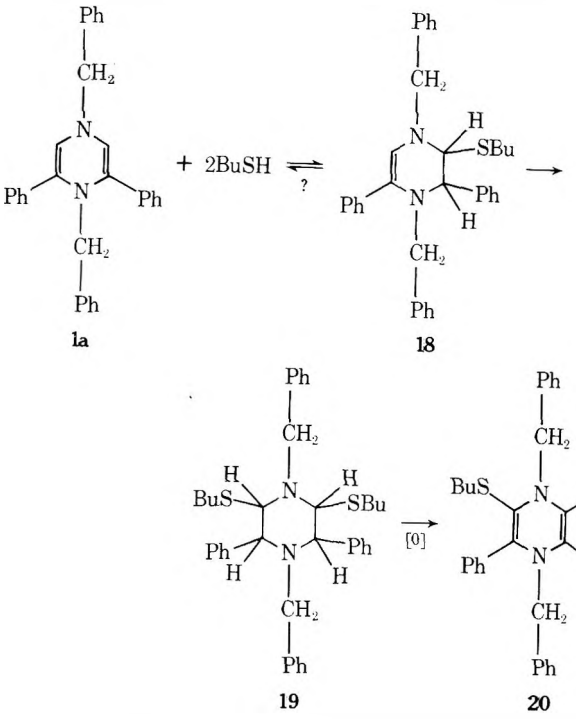
Additional assignments of the vicinal coupling constants were readily accessible by rapid catalytic hydrogenation of compounds **12** and **14**. Under these conditions 1,4-dihydropyrazines add only 1 equiv of hydrogen[9] and no deuterium scrambling was observed, giving compounds **16** and **17** from **12** and **14** respectively. An intimate mixture




**of 12** and **14** in a ratio of 5:4 was heated in benzene at 55° until the rearrangement was completed and the product mixture was examined by mass spectrometry. The isotopic content was consistent only with 12% being formed by crossover recombination.[17]

The results therefore indicate a largely intramolecular reaction with a small intermolecular component. Since free radicals are implicated in the extra cage reaction by scavenging experiments (which see), the crossover recombination evaluates the extent to which the initially formed radicals in the intermediate are independent (*i.e.*, escape the solvent cage). Similar crossover experiments in hexane (14%) and tetrahydrofuran (12% crossover) indicate that the somewhat higher figure for the former solvent may reflect its lower viscosity.[18] Combination of pyrazinyl radicals to form a dimer was not detected. The 10% or so of free pyrazinyl radicals formed may tend to scavenge benzyl radicals rather than permit the formation of detectable quantities of bibenzyl. The measured M + 4 peak, after correction for the $^{13}C$ isotope peak,[19] represents ¼ of the rearrangement product formed outside the solvent cage. In agreement with this interpretation it was found that, when the rearrangement of the mixture of **12** and **14** was performed in the presence of the radical scavenger butanethiol, crossover recombination, represented by the M + 4 peak, was prevented completely, and with the formation of butane disulfide. Since the yield of **2a** in the presence of the scavenger was 75 ± 3%, corresponding fairly well to a 95 ± 2% yield diminished by the extra-cage yield, this would tend to rule out a free-radical chain mechanism. A competing slow addition of the butanethiol

to the 1,4-dihydropyrazine is evident when a large excess of the thiol (20 equiv) is used, resulting in the formation of 1,4-dibenzyl-2,6-diphenyl-3,5-di(butylthiol)-1,4-dihydropyrazine (**20**) in 36% yield.[20] The loss of hydrogen from




**18** or **19** to form **20** may be due to disproportionation or air oxidation. This ready reversion of adducts of **1** to the 1,4-dihydrostructure, particularly when they bear five or more ring substituents, is surprising but common and attests to the unexpected stability of this new heterocyclic system.

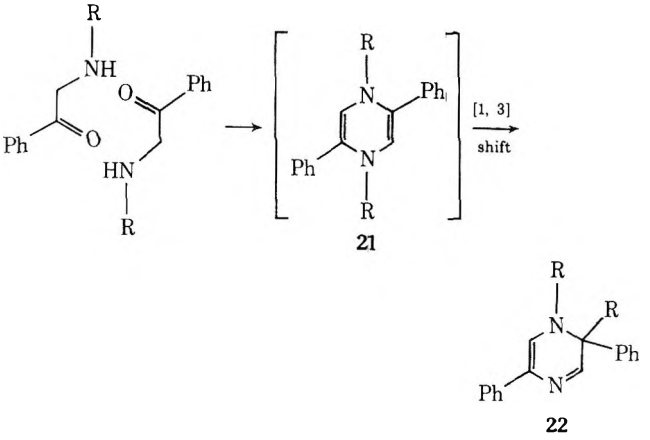
With firm evidence for the intervention of free radicals in the rearrangement an estimate of their lifetime was sought using CIDNP. The experimental conditions were established first by a control with picoline *N*-oxide–acetic anhydride system.[21] Rearrangement of the latter in benzene at 83° gave a strong CIDNP emission signal. However, in the present system no sign of a CIDNP effect was detected under a variety of conditions. In view of recent caveats concerning the conclusions to be drawn from such experiments[22] this negative result does not rule out the possibility of a rapid intramolecular rearrangement involving a tight radical pair. Closs[23] recently estimated the limiting lifetime of a free radical detectable by CIDNP at $10^{-10}$ sec. Owing to the tendency of benzyl groups to cleave as benzyl radicals, additional migrating alkyl groups were examined, namely cyclohexyl and cyclopentyl. The corresponding 1,4-dihydropyrazines rearranged smoothly to the 1,2-dihydropyrazines, both in good yield.

The kinetic order of the rearrangements was established conveniently by measuring the rate of disappearance of **1** by absorption spectrophotometry at 500 nm at which wavelength there was no overlap with the product. Compounds **1a**, **1i**, and **1j** obeyed Beer's law. The rearrangement of **1a** to **2a** strictly obeyed first-order kinetics over 80% of the reaction and at 55.4° gave $k = 6.44 \times 10^{-4}$ $sec^{-1}$. Measurement of the reaction rate in the temperature range 40.4–75.3° allowed the evaluation of Arrhenius parameters of $\Delta E^* = 15.6$ kcal $mol^{-1}$ and $\Delta S^* = -16.3$ eu.[24] The cyclopentyl and cyclohexyl analogs **1i** and **1j** similarly rearrange at somewhat higher temperatures but again strictly according to first-order kinetics.

These examples indicate that relief of steric compression of the groups at the 1, 2 and 6 positions may contribute to the driving force of the migration, since the direction of migration is such as to favor formation of less stable migrating radical and migration terminus. By comparison the analogous rearrangement of the symmetrical 2,5-diphenyl substituted 1,4-dihydropyrazines **21** is regiospecific, giving exclusively migration to the substituted carbon in **22**. In view of the proposed intermediacy of ion

**Table III**

| Rates (55.4°) | Solvent | Dielectric constant |
|---|---|---|
| $6.44 \times 10^{-4}$ | $C_6H_6$ | 2.28 |
| $7.95 \times 10^{-4}$ | Tetrahydrofuran | 7.95 |
| $11.80 \times 10^{-4}$ | $o$-$Cl_2C_6H_4$ | 9.93 |




pairs in certain rearrangements of analogous 1,2-dihydropyridines[25] and of ostensibly antiaromatic 2-azirines,[26] the effects of changes in solvent dielectric constant on the rate of rearrangement of **1a** to **2a** at 55.4° was examined (Table III). A slight trend toward higher rate at higher dielectric constant was observed but was clearly insufficient to warrant consideration of the intervention of charged species. The rate of a concerted [1,3] sigmatropic shift or of a stepwise reaction involving radical intermediates where no significant charge build-up develops should be relatively independent of solvent polarity.[27] As remarked upon above, unless care is exercised to exclude air from solutions of 1,4-dialkyl-1,4-dihydropyrazines, strong and persistant epr signals are detected.[1] Thus the possibility of a molecule-induced homolysis mechanism must be considered.[28] However, the rate of rearrangement of **1** in the presence of 2.5 equiv of the scavenger butanethiol (measured by the rate of disappearance of the dihydropyrazine) at the midrange temperature was comparable with that observed in the absence of the scavenger. The small rate difference is probably not due to a solvent effect, since a slight rate enhancement should have been anticipated on the basis of the study of solvent dielectric constant on rate. We rather attribute the rate reduction to the slow competing reversible addition of the scavenger to **1** discussed in the preparative experiment.

The above data point to an unusually facile unimolecular rearrangement which proceeds to the extent of ≥88% in an intracage process with a 12% contribution from intermolecular extracage free-radical pathway. Orbital symmetry theory recognizes two thermally allowed pathways for a [1,3] sigmatropic shift in an allylic moiety,[29] inversion at the migrating center with suprafacial allylic utilization and retention at the migrating carbon with antarafacial allylic participation. The latter alternative is excluded by geometrical constraints. Recently interest has

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## EXPERIMENTAL SECTION

### General

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer, and only the principal sharply defined peaks are reported. Nuclear magnetic resonance spectra were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on approximately 10–15% (w/v) solutions in $CDCl_3$ with tetramethylsilane as a standard. Line positions are reported in parts per million from the reference. Absorption spectra were recorded in "Spectro" grade solvents on a Beckman DB recording spectrophotometer. Mass spectra were determined on an Associated Electrical Industries MS-12 double-focusing high resolution mass spectrometer. The ionization energy, in general, was 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. Eastman Kodak precoated sheets were used for thin layer chromatography. Microanalyses were carried out by Mrs. D. Mahlow of this department.

### N,N-Diphenacylbenzylamine

To a suspension of 8.5 g (20 mmole) of diphenylacylbenzylamine hydrobromide in cold water was added dropwise a 10% sodium bicarbonate solution (50 ml). The free base was extracted with ether and dried ($MgSO_4$). Removal of the solvent in vacuo gave a yellow oil 6.2 g (91%) of N,N-diphenylacylbenzylamine; which turns dark on standing at room temperature; nmr $\delta_{TMS}$ ($CDCl_3$): 4.01 (s, 2H, $-N-CH_2Ph$), 4.25 (S, 4H, $-CH_2-COPh$), and 7.25 – 8.05 (m, 15H, aromatics); ir($CHCl_3$) 1670 $cm^{-1}$ (C=O).

Anal. Calcd. for $C_{23}H_{21}NO_2$ (mol. wt: 343.1756). Found (343.1751, mass spectrum).

### 1,4-Dialkyl-1,4-dihydropyrazines

A representative preparation of one of the more stable examples is given, thereafter the physical data on other compounds similarly prepared are summarized in Table I.

### 4-Benzyl-1-phenethyl-2,6-diphenyl-1,4-dihydropyrazine

To a solution of 4.25 g (10 mmole) of diphenacylbenzylamine hydrobromide in 5 ml of toluene was added 2.45 g (20 mmole) of phenethylamine. The reaction mixture was heated under nitrogen in an oil bath at 100 ± 1° for 4 h. The thick oil was treated with benzene and washed twice with cold water. The dark red solution was dried ($Na_2SO_4$). Removal of the solvent in vacuo gave an oil

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which on trituration with 95% ethanol deposited the dihydropyrazine 1b as a dark red solid 3.89 g (90%) m.p. 135–7°. Mass spectrum (70 eV) 428.2245 (calcd. for $C_{31}H_{28}N_2$, 428.2253).

Anal. Calcd. for $C_{31}H_{28}N_2$: C, 86.88; H, 6.58; N, 6.54. Found: C, 86.74, H, 6.70; N, 6.21.

### 1,4-Dibenzyl-1,4-dihydro-2,6-diphenylpyrazine

To a suspension of 4.25 g (10 mmole) of diphenacylbenzylamine hydrobromide in 5 ml of benzene [44] was added 2.15 g (20 mmole) of benzylamine. The mixture, in a pressure bottle was kept in an oil bath maintained at 40 ± 1° for 18 h. The reaction mixture was cooled to room temperature, diluted with 200 ml of ether and the precipitated benzylamine hydrobromide removed by filtration. The filtrate was washed with 50 ml of cold water and dried ($Na_2SO_4$). Removal of the solvent in vacuo at ambient temperature yielded a red semi-solid which was purified by chromatography on 100 g of B.D.H. alumina using benzene:hexane (1:9) as eluant. The initial colorless eluant was discarded then further elution gave a red solution. Removal of the solvent from the first 100 ml of the colored solution in vacuo at 35 ± 1° gave 1a as a red solid, 2.45 g (59%) m.p. 109–110.5° (95% ethanol) [45]; nmr $\delta_{TMS}$ (pyridine-$d_5$): 3.85 (s, 2H, 4-benzyl $CH_2$); 3.96 (s, 2, 1-benzyl $CH_2$), 6.23 (s, 2,3 and 5 protons); 7.16 – 7.9 (m, 20, aromatic protons); $\lambda_{max}$ ($C_6H_6$) 442 (log ε 3.53) and 338 (log ε 3.84); mass spectrum (70 eV) 414.2106 (calcd for $C_{30}H_{26}N_2$, 414.2096).

Anal. Calcd. for $C_{30}H_{26}N_2$: C, 86.92; H, 6.32; N, 6.76; Found: C, 87.07; H, 6.20; N, 6.96.

Continued elution and following the procedure described above gave a mixture of 1a and the rearranged product 2a, 0.900 g (80:20) as estimated by nmr. The pure 1,4-dihydropyrazine 1a was stable indefinitely at 0° and in the dark, otherwise it became gummy and discolored either by oxidation or due to a photochemical process.

### Thermal Rearrangement of 1,4-Dibenzyl-1,4-dihydro-2,6-diphenylpyrazine

A solution of 0.725 g (1.75 mmol) of 1a in 50 ml of benzene was heated under reflux for 4 h. Removal of the solvent in vacuo gave a red oil, trituration of which with 95% ethanol gave 1,2-dibenzyl-1,2-dihydro-3,5-diphenylpyrazine 4 as an orange solid 0.643 g (89%) m.p. 105-106.5° [lit. m.p. 94–98° [6,7]. The nmr spectrum of 2a was identical with that reported by Chen and Fowler.[8] Absorption spectrum $\lambda_{max}$ ($C_6H_6$): λ 422 nm (log ε = 3.785), and 327 (log ε 4.08).

In a separate control experiment the yield of 2a as determined spectroscopically was 92 ± 3%.

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### Thermal Rearrangement of 1,4-Dibenzyl-1,4-dihydro-2,6-diphenylpyrazine in the Presence of Butanethiol

A solution of 0.731 g (1.75 mmol) of 1a and 0.183 g (2 mmol) of butanethiol in 50 ml of benzene was heated under reflux for 4 h. Removal of the solvent in vacuo afforded a red oil. The yield of 2a determined spectroscopically was found to be 75 ± 3%. Chromatography of the red oil on 50 g of B.D.H. alumina and elution with benzene:hexane (1:5) gave first a colorless fraction which provided butane disulfide 0.055 g, m/e = 178 (mass spectrum). Further elution with benzene:hexane (1:5) gave pure 2a as an orange oil 0.496 g (67%) which solidified on standing to give an orange solid m.p. 108–109.5°.

### 1,4-Dibenzyl-3,5-dideuterio-1,4-dihydro-2,6-diphenylpyrazine

To a suspension of 6.3 g (15 mmol) of diphenacylbenzylamine hydrobromide in 15 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added 3.8 g (35 mmol) of benzylamine in 25 ml of deuterium oxide (99.7%, Merck, Sharp and Dohme of Canada). The mixture was stirred at room temperature for 7 days. The usual work-up procedure and chromatography on B.D.H. alumina gave the labelled 1,4-dihydropyrazine 1z as a dark red solid, 3.26 g (54%) m.p. 107.5–109°. nmr $\delta_{TMS}$ (pyridine-$d_5$): 3.86 (s, 2,4-benzyl $CH_2$); 3.97 (s, 2,1-benzyl $CH_2$), 6.25 (s, 0.4, 3 and 5 protons, 80% ring deuterium incorporation); 7.17–7.94 (m, 20, aromatic protons). Mass spectrum (70 eV) 416.2219, (calcd. for $C_{30}H_{24}D_2N_2$, 416.2221).

### 1,2-Dibenzyl-2,6-dideuterio-1,2-dihydro-3,5-diphenylpyrazine

To a solution of 6.6 g (20 mmol) of di(phenacyl-1-$d_2$)-benzylamine (80% deuterium incorporation, prepared by treating diphenacylbenzylamine with deuterium oxide in dry tetrahydrofuran solution with a trace of sodium hydroxide as catalyst), in 50 ml of tetrahydrofuran was added 4.5 g (45 mmol) of benzylamine in 40 ml of deuterium oxide. The reaction mixture was heated under reflux for 24 h. The usual workup procedure gave compound 13 5.75 (70%) m.p. 105-106.5°, nmr $\delta_{TMS}$ ($CDCl_3$): 2.69 (ABq, $J_{AB}$ = 14.0 Hz, 2;2-benzyl methylenes); 3.95 (ABq, $J_{AB}$ = 15.0 Hz, 2:1-benzyl methylenes), 6.85–8.01 (m, 20, aromatic protons). Mass spectrum (70 eV) 416.2218 (calcd. for $C_{30}H_{24}D_2N_2$, 416.2221).

### 1-(Benzyl-α,α-$d_2$)-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine

To a solution of 3.3 (10 mmol) of diphenacylbenzylamine in 5 ml of benzene was added 1.1 g (10 mmol) of α,α-$d_2$-benzylamine prepared by a literature procedure.[46] The solution was set aside at 40 ± 1° for 18 h. The usual workup procedure gave the benzyl labelled 1,4-dihydropyrazine 1q 2.63 g (60% yield) m.p.

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108-109.5°, nmr $\delta_{TMS}$ (pyridine-$d_5$): δ 3.87 (s, 2;4-benzyl methylenes), 6.22 (s, 2; 3 and 5 proton); 7.18-7.92 (m, 20, aromatic protons). The disappearance of the 3.96 absorption represents 100% incorporation of deuterium. Mass spectrum (70 eV) 416.2217 (calcd. for $C_{30}H_{24}D_2N_2$, 416.2221).

### 1-Benzyl-2-(benzyl-α,α-$d_2$)-1,2-dihydro-3,5-diphenylpyrazine

The thermal rearrangement of compound 14 carried out in the usual manner gave compound 15 in 80% yield, m.p. 105-106.5, nmr $\delta_{TMS}$ ($CDCl_3$): 3.96 (ABq, $J_{AB}$ = 15.0 Hz, 2;1-benzyl methylenes); 4.78 (s, 1;2 methine), 6.61 (d, $J_{2,6}$ = 1.5 Hz, 6-proton) and 6.87-7.97 (m, 20 aromatic protons).

### Catalytic Hydrogenation of 1,4-Dibenzyl-2,6-diphenyl-3,5-dideuterio-1,4-dihydropyrazine 12 and 14

(i) A solution of 0.60 g (1.41 mmole) of 12 in 80 ml of ethyl acetate was hydrogenated over 100 mg of 10% palladium on charcoal at atmospheric pressure for 48 h. The residual oil, obtained by filtration through Celite and removal of the solvent in vacuo, was chromatographed on 40 g of B.D.H. alumina. Elution with benzene:hexane gave 1,2,3,4-tetrahydro-3,5-dideuterio-1,4-dibenzyl-2,6-diphenylpyrazine 16 as an oil 0.302 g (50%); nmr $\delta_{TMS}$ ($CDCl_3$): 3.05 (d, 1H, $J_{2,3}$ = 2.0 Hz, $C_2H$), 3.55 and 4.33 (two doublets, 2H, J = 13.5 Hz, $N-CH_2Ph$), 3.85 (ABq, 2H, J = 12.5 Hz, $-NH-CH_2Ph$), 4.10 (d, 1H, J = 2.0 Hz, $C_2H$) and 6.94 - 7.78 (m, 20H, aromatics).

Anal. Calcd. for $C_{30}H_{26}D_2N_2$ (mol. wt. 420.2504). Found: (420.2509, mass spectrum).

(ii) A similar catalytic hydrogenation of 1-(α,α-dideuteriobenzyl)-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine 14 gave 1,2,3,4-tetrahydro-1-(α,α-dideuteriobenzyl)-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine 17 as an oil in 52% yield; nmr $\delta_{TMS}$ ($CDCl_3$) 2.85–3.25 (m, 2H, $C_3H$), 3.87 (center of ABq, 2H, J = 12.5 Hz), $-NHCH_2Ph$), 4.11 (t, 1H, J = 2.0 Hz, $C_2H$), 6.07 (s, 1H, $C_5H$) and 6.94–7.81 (m, 20H, aromatics).

Anal. Calcd. for $C_{30}H_{26}D_2N_2$ (mol. wt. 420.2504). Found: (420.2511, mass spectrum).

### Cross-over Recombination Experiments with Deuterium Labelled 1,4-Dibenzyl-1,4-dihydropyrazines.

A solution of 0.104 g (0.25 mmol) of 12 (99% deuterium incorporation) and 0.131 g (0.316 mmol) of 14 (80% deuterium incorporation) in 25 ml of the solvent (benzene, hexane, or tetrahydrofuran) was heated under reflux for 6 h. Removal

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of the solvent in vacuo and trituration of the residual oil with 95% ethanol resulted in the crystallization of the rearranged labelled products m.p. 105-106.5° The product was examined by high resolution mass spectrometry as summarized in Table III.

### Reaction of 1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine with Butanethiol

A solution of 0.83 g (1 mmole) of 1a and 1.38 g (15 mmole) of butanethiol in 5 ml of benzene was set aside at room temperature for 4 days. Removal of the solvent in vacuo gave a red oil which was subjected to chromatography on 60 g of B.D.H. alumina. Elution with hexane:benzene (2:1) gave a light yellow oil, 0.501 g (42%) (of 1,4-dibenzyl-2,6-diphenyl-3,5-dibutylthio-1,4-dihydropyrazine 20); nmr $\delta_{TMS}$ ($CDCl_3$) 0.91 (t, 6H, $CH_3$), 1.12-1.85 (m, 8H, $-(CH_2)_2-$), 1.85 (t, 4H, $-CH_2-S-$), 4.24 (bs, 2H, $-CH_2Ph$), 4.64 (bs, 2H, $-CH_2Ph$) and 6.96-7.98 (m, 20H, aromatics).

Anal. Calcd. for $C_{39}H_{42}N_2S_2$ [32] (mol. wt. 590.2790). Found: (590.2815, mass spectrum).

### Chemically Induced Dynamic Nuclear Polarization (CIDNP) Experiments

#### (i) Control Experiment with γ-Picoline-N-oxide

A degassed solution of 100 mg of γ-picoline-N-oxide [47] m.p. 180–182° in 250 µl of acetic anhydride and 100 µl of benzene-$d_6$ was sealed in an nmr tube. In 35 sec after the sample tube had been placed in the heated (83°) cavity of the Varian 100 MHz nmr spectrometer, there appeared emission signals at δ 4.97 and 2.58 which reached a maximum in 120 sec and gradually disappeared.[21]

#### (ii) 1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine

Similarly a degassed solution of 125 mg of 1a in 0.7 ml of benzene-$d_6$ was sealed in an nmr tube and placed in the nmr cavity at 83°. The spectral data were stored in a computer at 5 sec intervals for a period of 10 min. The reproduction of these data did not show any emission and enhancement signals. However, at the end of the 10 min period approximately 85% of 1a had been converted into 2a.

### Thermal Rearrangement of 4-Benzyl-1-cyclohexyl-2,6-diphenyl-1,4-dihydropyrazine 11

A solution of 1.05 g (1 mmole) of 11 in 30 ml of o-xylene was heated under reflux in an atomosphere of nitrogen for 10 h. Removal of the solvent in vacuo gave an orange oil which was subjected to chromatography on 50 g of BDH alumina.

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Elution with benzene:hexane (1:2) gave a light yellow oil 0.468 g (46.5%) which on trituration with ethanol and on cooling deposited yellow crystals of 1-benzyl-2-cyclohexyl-3,5-diphenyl-1,2-dihydropyrazine 23, m.p. 127–8.5°, nmr $\delta_{TMS}$ ($CDCl_3$): 0.81-2.01 (m, 11H, $C_6H_{11}$), 4.32 (dd, 1H, J = 8.5, $J_{2,6}$ = 1.5 Hz, $C_2H$), 4.52 (q, 2H, $J_{AB}$ = 12.5 Hz, $-CH_2Ph$), 6.53 (d, 1H, $J_{2,6}$ = 1.5 Hz, $C_6H$), and 6.98-7.81 (m, 15H, aromatics).

Anal. Calcd. for $C_{29}H_{30}N_2$ (mol. wt. 406.2409) C, 85.66; H, 7.42; N, 6.92. Found: (406.2413, mass spectrum): C, 84.91; H, 7.33; N, 7.17.

### Kinetic Studies

$(1.0 - 5.0) \times 10^{-2}$ Molar solutions of the 1,4-dihydropyrazines were prepared in benzene or the other appropriate solvents at room temperature and transferred in 5 ml aliquots to reaction tubes which were sealed and protected from the light with aluminum foil. The reaction tubes were placed in a Colora constant temperature bath, and after thermal equilibrium was attained, one tube was withdrawn, quenched in a methanol-ice bath and the initial absorbance recorded. Seven or eight reaction tubes were withdrawn at convenient intervals and the concentration of the 1,4-dihydropyrazine established by absorption spectrophotometry using balanced 1 cm cells. The analysis was performed at 500 nm region where the rearranged 1,2-dihydropyrazine isomer had a negligible extinction coefficient. It was established that the three 1,4-dihydropyrazines studied obeyed Beer's Law in the optical density range of 0.04–1.2. The reactions followed good first order kinetics for the disappearance of the 1,4-dihydropyrazine and showed a linear relationship for log $(E_t/E_0)$ versus time, where $E_0$ = the initial optical density and $E_t$ = the optical density at time t. A representative run is shown in full in Table IV, and subsequent kinetic data are summarized in Table V.

### Stereochemistry Experiments

#### 1-[(+)α-d-Benzyl]-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine

To a solution of 3.3 g (10 mmol) of diphenacylbenzylamine in 5 ml of benzene was added 1.1 g (10 mmol) of (S)(+)α-d-benzylamine $[\alpha]_D^{20}$ = +0.738 (neat) prepared by the prescribed procedure.[32] The mixture was set aside for 18 h at 40 ± 1°. The workup procedure described previously afforded the chiral 1,4-dihydropyrazine (S)-24 2.51 g (60%) m.p. 108.5–110°; nmr $\delta_{TMS}$ (pyridine-$d_5$) 3.86 (s, 2;4-benzylmethylene), 3.97 (s, 1.2H, 1-benzyl methine, 80% deuterium label), 6.24 (s, 2;3 and 5 protons); 7.19-7 92 (m, 20, aromatic protons). Mass spectrum (70 eV) 415.2153 (calcd. for $C_{30}H_{25}DN_2$, 415.2159).

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### Rearrangement of (S)1-(α-d-Benzyl)-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine in the Presence of Butanethiol.

A solution of 0.415 g (1 mmole) of the dihydropyrazine (S) 24 and 0.092 g (1 mmole) of butanethiol in benzene was heated under reflux in a nitrogen atmosphere for 8 h. Removal of the solvent in vacuo gave a red oil which was subjected to chromatography on 40 g of B.D.H. alumina. Elution with benzene:hexane (1:2) gave a light yellow oil 0.279 g (67%) of the 1-benzyl-2-(α-d-benzyl)-3,5-diphenyl-1,2-dihydropyrazine (-)(R) 25 which on trituration with ethanol gave yellow crystals m.p. 108-109.5° $[\alpha]_D^{25}$ -0.76 (c, 5.75, $C_6H_6$).

### (-)-(R)-3-Phenyl-3-deuteriopropiophenone

The title compound was prepared by the following sequence of reactions.

(a) (+)-(S)-α-d-Benzylamine 23 (80%d) = $[\alpha]_D^{25}$ + 0.73 (£1, neat); $[\alpha]_D^{25}$ + 0.71 (£1, 4.01, $C_6H_6$) was prepared by the prescribed procedure.[32]

(b) (-)-(S)-N,N-Dimethyl-α-d-benzylamine 26 (80%d), b.p. 71-73°/17mm, (85% yield), $[\alpha]_D^{25}$ - 1.94 (£1, 7.0, $C_6H_6$) was prepared by the methylation of (+)-(S)-α-d-benzylamine by treatment with formic acid and formaldehyde [48], nmr $\delta_{TMS}$ ($CDCl_3$): 2.68 (s, 6H, $N(CH_3)_2$), 3.37 (t, 1.20H, $J_{HD}$ = 1.7 Hz-CHD), and 7.25 (s, 5H, aromatic).

(c) (+)-(S)-N,N-Dimethyl-N-phenacyl-α-d-benzylammonium bromide 27. This compound was prepared from the (+)-(S)-N,N-dimethyl-α-d-benzylamine by reaction of phenacylbromide in benzene, as a white granular solid m.p. 160–2° [49] (89%) $[\alpha]_D^{25}$ + 0.50 (£1, 7.62 $CH_3OH$).

(d) (+)-(S)-α-Dimethylamino-β-deutero-β-phenylpropiophenone 28. This compound was obtained by heating the quaternary salt with 10% excess of 1N sodium hydroxide. The propiophenone was crystallized from hot methanol as needles m.p. 67-68° (80%). $[\alpha]_D^{25}$ -3.34 (£1, 10.1, $C_6H_6$), nmr $\delta_{TMS}$ ($CDCl_3$) = 2.40 [s, 6H, $-N(CH_3)_2$], 2.80-3.20 (b, 1.2H, -CHD), 4.21-4.51, (b, 1H, -CH-), and 7.17-7.97 (m, 10H, aromatics).

Anal. Calc. for $C_{17}H_{18}DNO$: C, 80.63; H, 7.50; N, 5.53. Found: C, 80.56; H, 7.79; N, 5.65.

(e) (-)-(R)-β-Deutero-β-phenylpropiophenone 29. A magnetically stirred solution of 0.509 g (2 mmole) of the aminoketone in 25 ml of glacial acetic acid was heated under reflux with 0.49 g (6.1 mmole) of zinc dust for 45 min. The hot solution was filtered from the inorganic precipitate and excess zinc. The filtrate was diluted with an ice-water mixture (125 ml) to yield a yellow semi-solid which was taken up in ether dried ($MgSO_4$) and the solvent removed to give

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29 0.315 g (75%). Repeated recrystallization from ether-petroleum ether gave a pure sample as white needles, m.p. 67-68.5° (lit. m.p. 69-71°). $[\alpha]_D^{25}$ -1.387 (£1, c, 5.3 $C_6H_6$).

### Attempted Acid Catalyzed Hydrolysis of 1,2-Dibenzyl-3,5-diphenyl-1,2-dihydropyrazine.

A solution of 0.63 g (1.52 mmole) of the 1,2-dihydropyrazine 2a in 50 ml of tetrahydrofuran and 20 ml of concentrated hydrochloric acid was heated under reflux for 18 h. The red solution was diluted with water and extracted with ether. The organic layer was washed twice with 5% sodium hydrogen carbonate solution, dried ($MgSO_4$), concentrated in vacuo to give a light yellow oil, 0.35 g which solidified on standing. Trituration with methanol-petroleum ether gave a light colored solid m.p. 145-146.5°, $\delta_{TMS}$ ($CDCl_3$): 4.23 (s, 4H, $CH_2Ph$), 7.13 (s, 10H, aromatic) and 7.26 - 7.55 (m, 10H, aromatic).

Anal. Calcd. for $C_{30}H_{24}N_2$: C, 87.35; H, 5.82; N, 6.79. Found: C, 87.41; H, 5.73; N, 6.51.

Possible structures for this product are 2,6-dibenzyl-3,5-diphenylpyrazine m.p. 146-7° or 3,6-dibenzyl-2,5-diphenyl pyrazine m.p. 145-147°.[8]

### Ozonolysis of 1,2-Dibenzyl-3,5-diphenyl-1,2-dihydropyrazine at -50 + 2°

A slow stream of ozone was passed into a solution of 1.0 g (2.36 mmole) of the dihydropyrazine 2a in 40 ml of ethyl acetate placed in a dry ice-acetone bath until moistened potassium iodide-starch paper gave a positive iodine test (approximately 9-10 min). The reaction mixture was then poured into 150 ml of water containing 2 g of zinc dust. The mixture was stirred at room temperature for 24 h. The filtered solution was extracted with ether to give an oil, which was purified by chromatography on BDH alumina. Elution with benzene:hexane (7:3) gave 0.483 g of an oil 31a nmr $\delta_{TMS}$ ($CDCl_3$) 2.67-3.57 (m, 2H, $-CH_2Ph$), 4.41 (ABq, J = 14.5 Hz, $N-CH_2Ph$), 4.72-5.45 (m, 0.5H), 5.33 (t, 0.5H, J = 8.0 Hz), 7.09-8.09 (m, 15H, aromatics) 8.23 (s, 0.6H, -CHO) and 8.40 (s, 0.4H, CHO).

Anal. Calc. for $C_{23}H_{21}NO_2$ (mol. wt. 343.1862. Found: (343.1871, mass spectrum).

Compound 31 was taken up in dry tetrahydrofuran and treated with potassium carbonate and deuterium oxide and the mixture heated under reflux for 10 h allowed to cool and extracted with ether. The extract was dried ($MgSO_4$) and the solvent removed to give an oil 31c nmr $\delta_{TMS}$ ($CDCl_3$) 2.67-3.58 (m, 2H, $-CH_2Ph$), 4.41 (ABq, J = 14.5 Hz, $-NCH_2Ph$), 7.05-8.09 (m, 15H, aromatics), 8.23 (s, 0.6H) and 8.40 (s, 0.4H) (-CHO).

Similarly, the ozonolysis of 1,2-dibenzyl-3,5-diphenyl-2,6-dideuterio-1,2-

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dihydropyrazine under the conditions given above gave 31b nmr $\delta_{TMS}$ ($CDCl_3$): 2.67-3.58 (m, 2H, $-CH_2Ph$), 4.41 (ABq, J = 14.5 Hz, $NCH_2Ph$), 4.72-5.45 (m, 0.5H), 5.33 (t, 0.5H, J = 8.0 Hz), and 7.05-8.09 (m, 15H, aromatics).

### Ozonolysis of 1,2-Dibenzyl-3,5-diphenyl-1,2-dihydropyrazine at Ambient Temperatures.

A slow stream of ozone was passed into a solution of 1.0 g (2.36 mmole) of 2a in 40 ml of ethyl acetate until moistened potassium iodide-starch paper gave a positive test. The reaction mixture was then poured into a flask containing 2 g of zinc dust and 50 ml of glacial acetic acid. The mixture was stirred at room temperature for 24 h, filtered and the filtrate diluted with 250 ml of water. The solution was extracted with ether and the extract washed with 5% aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent removed. Chromatography of the residual oil on BDH alumina and elution with benzene gave an oil, which on trituration with methanol deposited 32 0.280 g as a white solid m.p. 102-103.5°, nmr $\delta_{TMS}$ ($CDCl_3$): 3.56 (ABq, 2H, J = 14.0 Hz), 4.58 (ABq, 2H, J = 14.0 Hz) and 7.15-8.01 (m, 15H, aromatics), ir ($CHCl_3$) 1667 $cm^{-1}$ (C=O).

Anal. Calcd. for $C_{22}H_{19}NO$ (mol. wt. 313.1555). Found: (313.1551), mass spectrum).

Evaporation of the filtrate afforded 31a as an oil identified by its spectral characteristics.

Further elution of the column with benzene:ethanol (9:1) gave benzoic acid m.p. 119–120°, mmp with an authentic sample undepressed.

### Reduction Cleavage of 1-Benzyl-2(α-d-benzyl)-3,5-diphenyl-1,2-dihydropyrazine with Zinc and Acetic Acid.

A magnetically stirred solution of 0.830 g (2 mmole) of the dihydropyrazine 25 in 40 ml of glacial acetic acid was heated under reflux with 1.31 g (20 mmole) of zinc dust for 2 h, during which time the solution became colorless. The hot solution was filtered and the filtrate diluted with ice-water. The solution upon standing overnight deposited a yellow semi-solid which was taken up in ether. The extract was washed twice with 5% aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent removed to give a light yellow oil, which was subjected to chromatography on 60 g of BDH alumina. Elution with hexane:benzene (3:1) gave an oil which solidified on standing (+)-(S)-α-phenyl-α-deuteriopropiophenone 33. Repeated recrystallization from ether-petroleum ether afforded the pure ketone as white crystals m.p. 67-68.5°, $[\alpha]_D^{25}$ + 1.387 (£1, 1.86, $C_6H_6$).

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Further elution with benzene:hexane (1:1) gave a yellow oil which on trituration with ethanol and cooling gave yellow crystals of 1,2-dibenzyl-2,5-diphenyl-1,2-dihydropyrazine, m.p. 99-102°, mmp with an authentic sample[15] was undepressed.

TABLE III

(M+4) Peak [% of Base Peak M]

| Compound | Isotope Peak Calcd | | Observed | Average | Increase |
|---|---|---|---|---|---|
| 13 | 5.6 | (i) | 5.9 | 5.9 | - |
| | | (ii) | 5.8 | | |
| | | (iii) | 6.0 | | |
| 15 | 5.6 | (i) | 3.9 | 6.0 | - |
| | | (ii) | 6.0 | | |
| | | (iii) | 6.1 | | |
| Cross-over | | | | | |
| 12 + 14 (Benzene) | 5.6 | (i) | 9.6 | 9.63 | 3.63 |
| | | (ii) | 9.7 | | |
| | | (iii) | 9.6 | | |
| 12 + 14 (THF) | 5.6 | (i) | 9.7 | 9.70 | 3.70 |
| | | (ii) | 9.6 | | |
| | | (iii) | 9.8 | | |
| 12 + 14 (Hexane) | 5.6 | (i) | 10.2 | 10.1 | 4.1 |
| | | (ii) | 9.9 | | |
| | | (iii) | 10.0 | | |
| | | (iv) | 10.2 | | |
| 12 + 14 (Benzene with Butanethiol Scavenger) | 5.6 | (i) | 5.9 | 6.06 | ~0 |
| | | (ii) | 6.1 | | |
| | | (iii) | 6.2 | | |

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TABLE IV

Kinetics of Rearrangement of 1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine[a] 1a in Benzene at 55.3 ± 0.1°

| Time (min) | Optical Density (500 nm) | k x $10^4$ $sec^{-1}$ |
|---|---|---|
| 0 | 0.83 | - |
| 10 | 0.54 | 7.16 |
| 20 | 0.40 | 6.08 |
| 30 | 0.27 | 6.23 |
| 40 | 0.20 | 6.15 |
| 50 | 0.13 | 6.17 |
| 65 | 0.065 | 6.51 |
| 80 | 0.04 | 6.32 |

a Initial concentration = 1.0 x $10^{-2}$ M.

REFERENCES TO EXPERIMENTAL


(44) Use of larger volumes of benzene results in the formation of substantial quantities of the rearranged product 2a.

(45) The 1,4-dibenzyl-1,4-dihydro-2,6-diphenylpyrazine should not be left in contact with ethanol for prolonged periods, since it undergoes a slow reversible addition.

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TABLE V

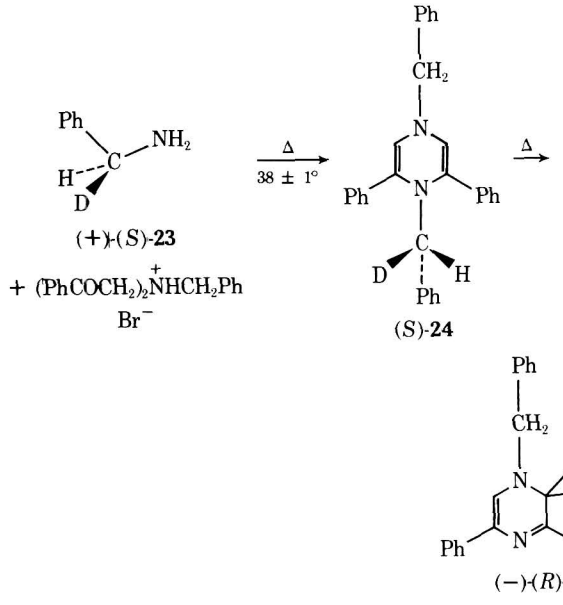
Summary of the Rate Constants

| Reactant and Initial Concentration | T°C | Rate constant (k x $10^4$ $sec^{-1}$) |
|---|---|---|
| 1a (1.0-1.15) x $10^{-2}$ M | 40.4 ± 0.1 | 1.96 |
| | 50.4 ± 0.1 | 4.62 |
| | 55.3 ± 0.1[a] | 6.37 |
| | 60.1 ± 0.1 | 8.02 |
| | 70.2 ± 0.1 | 14.58 |
| | 85.3 ± 0.1 | 36.71 |
| 11 (4.5-5.0) x $10^{-2}$ M | 99.8 ± 0.1 | 1.12 |
| | 110.1 ± 0.1 | 1.78 |
| | 120.2 ± 0.1 | 2.84 |
| | 129.8 ± 0.2 | 2.99 |
| | 140.2 ± 0.2 | 4.88 |
| | 150.1 ± 0.2 | 7.05 |
| 11 (4.5-5.0) x $10^{-2}$ M | 100.1 ± 0.1 | 2.96 |
| | 110.2 ± 0.1 | 4.51 |
| | 120.3 ± 0.1[b] | 5.52 |
| | 130.4 ± 0.2 | 6.54 |
| | 140.3 ± 0.2 | 7.85 |
| | 150.3 ± 0.2 | 10.87 |

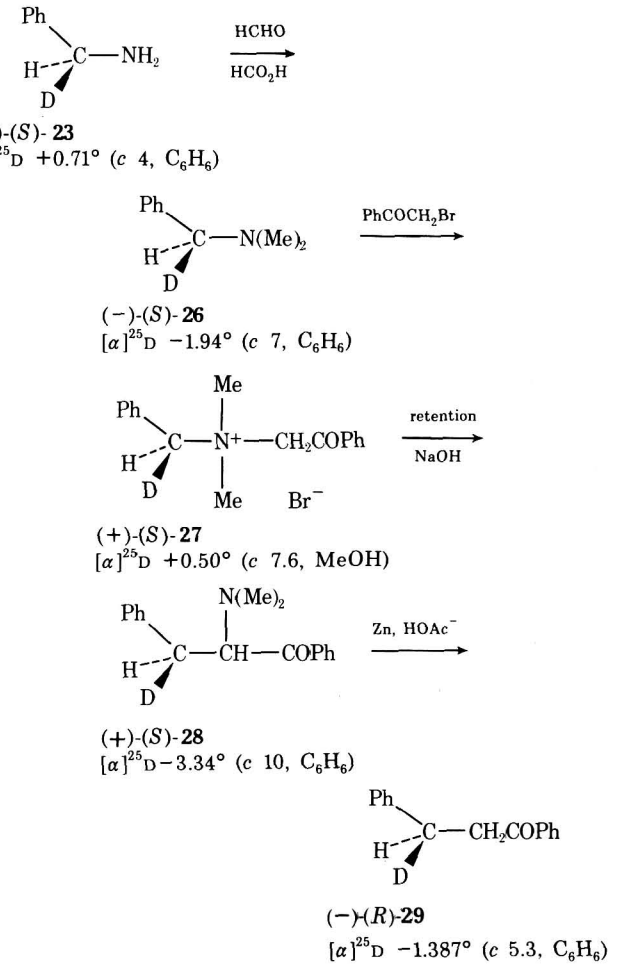
a) In the presence of BuSH (3 mole) the rate of constant was 4.72 x $10^{-4}$ $sec^{-1}$.

b) In the presence of BuSH (3 mole) the rate of disappearance of this 1,4-dihydropyrazine was 3.14 x $10^{-4}$ $sec^{-1}$.

been shown in the stereochemical consequences of intracage radical processes.[30] A stepwise reaction involving cleavage of the C–N bond to give a pair of radicals should lead to loss of optical acitivity only if the radical pair has a sufficiently long lifetime to permit reorientation of the planar radicals to occur.[30] A completely free radical necessarily results in racemization.[31] Thus the stereochemistry of the rearrangement permits a sensitive test of mechanism. An optically active product showing partial or total retention signifies a radical intracage mechanism where the radical lifetime is short compared with the rate of rotation, whereas overall inversion would only signify participation of the sigmatropic pathway inside the cage. The chiral 1,4-dibenzyl-1,4-dihydropyrazine **24** was prepared from chiral benzylamine-$\alpha$-*d*-(+)-(*S*)-benzylamine-$\alpha$-*d* **23** which has been prepared in 65% optical purity by Streitwieser and Wolfe.[32] and the absolute configuration established by Gerlach.[33] Upon heating compound **24** the labeled rearrangement product **25** was obtained quantitatively and proved to be optically active, $[\alpha]^{25}D$ −0.68 ± 0.01° (*c* 5.7, $C_6H_6$). To assess the degree of stereochemical integrity maintained inside the solvent cage, the rearrangement of **24** was examined in the presence of the butanethiol scavenger. From the crossover recombination experiments this must remove that portion of the rearranged product which is necessarily racemized by the extracage reaction. The rearranged product **25** under these conditions showed an increased specific rotation, $[\alpha]^{25}D$ −0.76 ± 0.02° (*c* 5.7, $C_6H_6$), in accord with this view. The configuration of the $\alpha$-*d*-benzyl group in **25** prepared in the presence of butanethiol was related to that in chiral 3-phenylpropiophenone-*3*-*d* by a Stevens rearrangement (Scheme I).



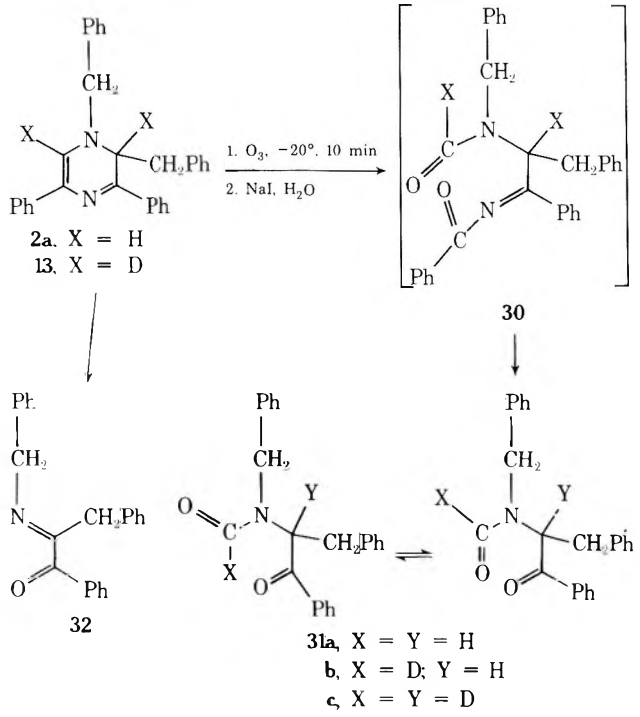

**Scheme I**



The scheme is based on a procedure developed by Brewster and Kline.[34] N-Methylation of the chiral benzylamine **23** afforded **26** in 85% yield, which was then quaternized with phenacyl bromide to give (−)-(*R*)-**27** quantitatively and converted into (−)-(*R*)-**29** as shown.[35]

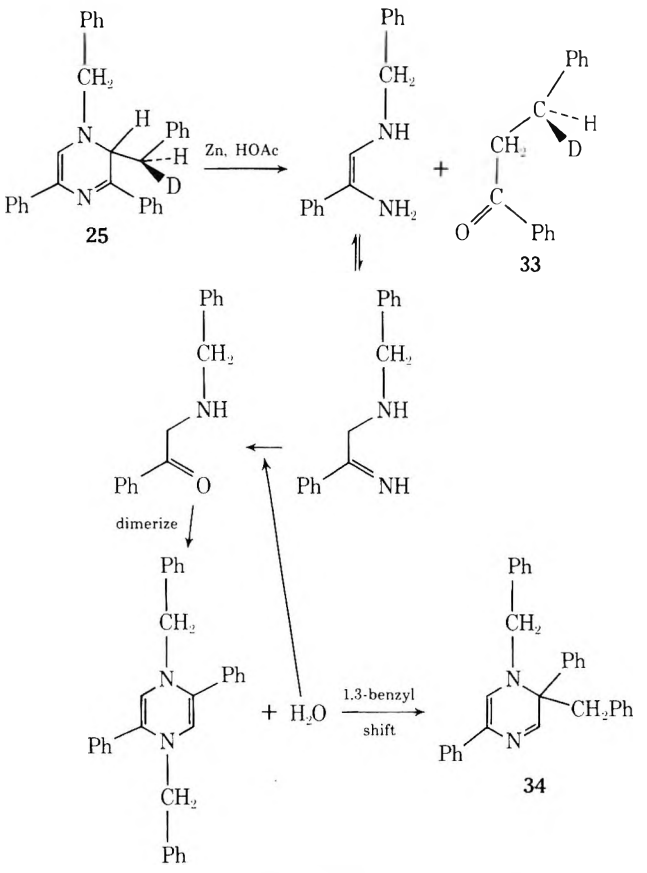
Attempts were made to relate the configurations of **25** and **29** directly by degradation of the former. Acid-catalyzed hydrolysis of **25** was found to be unsatisfactory, leading only to a dibenzyldiphenylpyrazine. Ozonolysis of **2a** in ethyl acetate solution at −20° resulted in the desired selective cleavage of the 5-6 bond and mild reductive work-up with sodium iodide and water (which was accompanied by hydrolysis of the intermediate **30**) afforded compound **31a** in about 65% yield. The nmr spectrum revealed a concentration-dependent equilibrium between the two possible geometrical isomers of **31a**, showing typically two formyl signals at δ 8.23 and 8.40 in a ratio of 60:40.

The ozonolysis must be carefully controlled, since at ambient temperatures and with longer exposure to ozone, further oxidative action affords **32**. Structure proof of **31a**



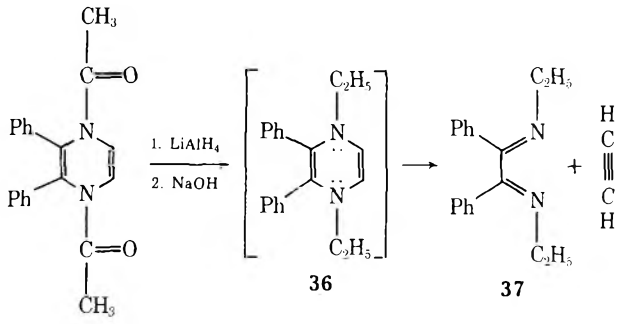

was provided by a parallel low-temperature ozonolysis of **13**, which gave **31b**. Inspection of the nmr spectrum showed that the formyl proton was completely exchanged with deuterium whereas the methine position α to the nitrogen was completely exchanged for protium. That this was due to base-catalyzed enolization of **31c** during work-up was confirmed by reverse exchange with potassium carbonate and deuterium oxide when Y was exchanged for deuterium. The formyl group in **31a** proved resistant to all attempts to convert it into the *N*-methyl compound, a prerequisite to the projected zinc and acetic acid reductive cleavage. Instead carefully controlled zinc and acetic acid cleavage of **25** afforded a mixture of the desired chiral ketone **26** and the known isomeric 1,2-dihydropyrazine[15] **34**. Compound **34** plausibly arises as shown in Scheme II. Chromatographic separation of **33** and **34** on alumina gave (+)-(*S*)-3-phenylpropiophenone-*3-d* (**33**), $[\alpha]^{25}D$ 1.37 ± 0.02° (*c* 1.86, $C_6H_6$). Assuming 96% retention in the Stevens rearrangement, then the specific rotation of (*R*)-**29** with 42% enantiomeric excess would be −1.45 ± 0.02°. Therefore that part of the rearrangement of **1** to **2** that proceeds intramolecularly proceeds with ≥95% stereospecificity and with inversion of configuration which demands a [1,3] sigmatropic shift with suprafacial allylic utilization.[29]

**Scheme II**



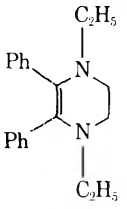

As far as we are aware this represents the first clear-cut example of a [1,3] sigmatropic shift with inversion involving nitrogen at the migrating center. The rearrangement therefore proceeds by a combination of sigmatropic and dissociative mechanisms and the contribution of the latter would be expected to be a function of the nature of the migrating group and reaction temperature. Baldwin and coworkers have encountered several examples of dual competing mechanisms in the rearrangement of ylides.[36]

**Nature of the 1,4-Dihydropyrazine System.** Theoretical considerations suggest that 4n-π cyclic systems in general are antiaromatic,[2,37] *i.e.*, destabilized by increased electron delocalization. Molecular orbital calculations by Streitwieser on the 1,4-dihydropyrazine structure predicts thermodynamic destabilization in that the last two electrons must be placed in an antibonding orbital.[38] However, this presupposes that the geometry of the 1,4-dialkyl-1,4-dihydropyrazine allows the nitrogen lone pairs to interact conjugatively with the π electrons of the ring. Some pieces of evidence suggest this may be so in certain structures. In contrast to the relative stability of the 1,4-dialkyl-1,4-dihydropyrazines described here, marked thermodynamic instability is inferred for the 1,4-diethyl-2,3-diphenyl-1,4-dihydropyrazine (**36**) postulated as a product of reduction of lithium aluminum hydride of the corresponding 1,4-diacetyl compound **35**.[9] While the electron-withdrawing 1,4 groups in **35** appear to stabilize the 1,4-dihydropyrazine system, compound **36** apparently undergoes a spontaneous retro Diels–Alder reaction and the diimine **37** was isolated. This implies destabilizing conjugative interaction of the nitrogen lone pairs of the π electrons of the ring. This instability of **36** may also be con-




35 36 37

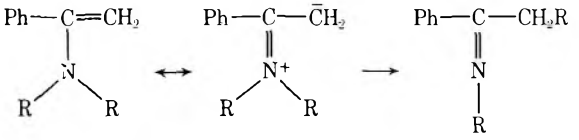
trasted with complete stability of **38**.[9] Evidently compounds **1** owe their relative stability and insolability to



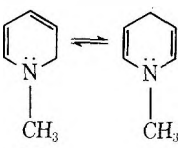
**38**

their substitution pattern, which imposes restrictions on full $\pi$ conjugation possibly owing to steric hindrance interactions at the 1, 2 and 6 positions. Further indications of this phenomenon follow from the regioselectivity of the [1,3] sigmatropic alkyl shift from **1** to **2**, implying relief of steric compression. The further contrast between the marked stability of **1** with the lability of the isomeric 1,4-dialkyl-2,5-diphenyl-1,4-dihydropyrazines[39] serves to emphasise this point. It is also tempting to suggest that destabilization inherent in **1** is relieved by the rapid oxidation to the 7-$\pi$ radical cation structures **7** described above.

An assessment of the role of the enamine to imine change of **1** to **4** must be made, however, Enamines are destabilized relative to the isomeric imine and Wittig has established a [1,3] shift in an acyclic example.[40] It must be

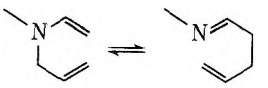


considered, therefore, that the unusual ease with which the groups migrate in **1a** could be due to the instability of the enamine moiety in **1a** compared to the imine in **2a**. Fowler points out that since **2a** is also an enamine containing and *N*-benzyl substituent its nonrearrangement under the reaction conditions indicates that there may be additional instability associated with enamine **1**.[8,9] However, the enediamine moiety of **1** may be different in character from a normal enamine. 1,4-Dihydropyridines show no tendency to rearrange to the 1,2 isomer. In equilibration, the *N*-methyl-1,4-dihydropyridine **40** is 2.29 ± 0.01 kcal mol$^{-1}$ more stable than the 1,2 isomer **39** at 91.6°.[41]



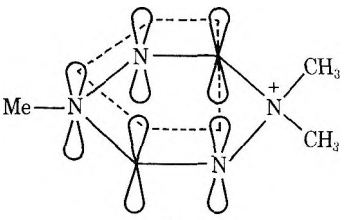
**39** **40**

Compounds of structure similar to **40** show unexpected stability which may be due to homoaromaticity or hyperconjugation.[41] The fact that the enamine to imine changes is not sufficient to account for the ease of rearrangement of **1** to **2** is also indicated by a comparison of the amino-Claisen rearrangement with the Claisen rearrangement. The former has an activation energy about 6 kcal mol$^{-1}$ higher than the latter and therefore is not so generally observed.[42] In conclusion, the evidence on the

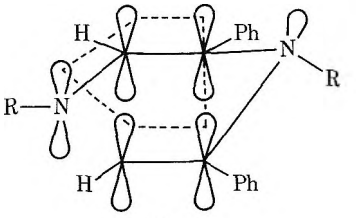


nature of the 1,4-dihydropyrazine system suggests a sensitive dependence of stability (determined by the extent of conjugative interaction of the nitrogen lone pairs) on the geometry of the heterocycle, which in turn is governed by the positioning of the substituents on the ring. For example, with two phenyl groups, 2,6 substitution confers stability[1] whereas 2,5[39] and2,3[8,9] substitution confers instability.

In a recent paper Kohn and Olofson[43] considered the geometry of the related 1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazine (**41**). Among other evidence, preferential N-alkylation at the substituted nitrogen may indicate a nonplanar homoaromatic structure for **41**. A similar nonplanar structure **42** would appear to be plausible for the 1,4-dihydropyrazine structure at this time.



**41**



**42**

**Registry No.**—**1a**, 49570-21-0; **1b**, 38283-66-8; **1c**, 38283-67-9; **1d**, 38283-68-0; **1e**, 38283-69-1; **1f**, 38283-70-4; **1g**, 51381-06-7; **1h**, 38283-71-5; **1i**, 40312-97-8; **1j**, 38350-61-7; **1k**, 51381-07-8; **1l**, 51381-08-9; **1m**, 40312-93-4; **2a**, 25827-91-2; **2j**, 51381-09-0; **11**, 19264-38-1; **11** hydrobromide, 51381-10-3; **12**, 51381-11-4; **13**, 51381-12-5; **14**, 51381-13-6; **15**, 51381-14-7; **16**, 51381-15-8; **17**, 51381-16-9; **20**, 51464-56-3; (+)-(*S*)-**23**, 3481-14-9; (*S*)-**24**, 51381-17-0; **25**, 49570-23-2; (−)-(*S*)-**26**, 49570-26-5; (+)-(*S*)-**27**, 49570-27-6; (+)-(*S*)-**28**, 51424-69-2; (−)-(*R*)-**29**, 49570-24-3; **31a**, 51381-18-1; **31b**, 51381-19-2; **31c**, 51381-20-5; **32**, 51381-21-6; **33**, 51424-70-5; benzylamine, 100-46-9; phenethylamine, 64-04-0; propylamine, 107-10-8; butylamine, 109-73-9; isobutylamine, 78-81-9; isopentylamine, 107-85-7; methylamine, 74-89-5; cyclopropylamine, 765-30-0; cyclopentylamine, 1003-03-8; cyclohexylamine, 108-91-8; cycloheptylamine, 5452-35-7; cyclooctylamine, 5452-37-9; di(phenacyl-*1*-$d_2$)benzylamine, 51381-22-7; benzylamine-$\alpha,\alpha$-$d_2$, 15185-02-1; butanethiol, 109-79-5; 2,6- (or 3,6-) dibenzyl-3,5- (or 2,5-) diphenylpyrazine, 51380-76-8.

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# Synthetic and Mechanistic Aspects of the Sodium Hydride Promoted Acylation of Methylated Heteroaromatics[1]

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A series of representative $\alpha$- and $\gamma$-methylated heteroaromatic azines and diazines were acylated with benzoate, trifluoroacetate, nicotinate, oxalate, and phthalate esters using sodium hydride as the condensing agent to afford heteroarylmethyl ketones, ethyl heteroarylpyruvates, and 2-heteroaryl-1,3-indandiones, respectively. Rates of acylation of quinaldine, as determined by hydrogen-evolution measurements, were shown to be independent of alkoxide concentration, but dependent upon both the concentration and polarity of the carbonyl group of the acylating ester. These results are attributed to accelerated ionization of a lateral proton from a complex involving ester and heterocycle.

Acylations of methylated heteroaromatics to afford ketones can be accomplished by initial lateral metalation of the heterocycle with a strong base, followed by treatment of the resulting carbanionic intermediate with an ester.[2] Essentials of the generally accepted mechanism for such reactions are illustrated in Scheme I by the acylation of quinaldine (**1**) with methyl benzoate.[3] On the basis of extensive studies by Levine and coworkers, alkali amides or alkali salts of certain dialkylamines currently appear to be the most satisfactory reagents for effecting these condensations.[4] Organolithium reagents have found some utility with heterocycles that are not susceptible to nucleophilic addition,[5] while alkoxides have been used in several instances where the acidity of side-chain protons is en-

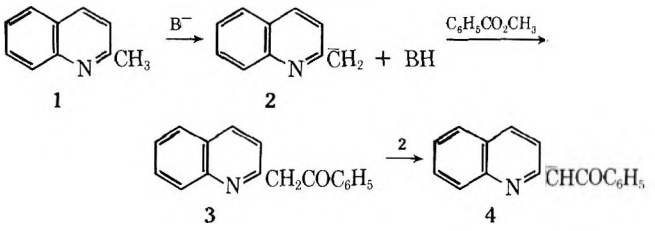
**Table I**
**Acylation of Methylated Heteroaromatics to Form Ketones and α-Keto Esters 6[a]**

| No. | Product— Het | R | Mp or bp, °C (mm) | Yield, % | Rxn time, hr | Recrystn solvent |
|---|---|---|---|---|---|---|
| **6a** | 2-Quinolyl | $C_6H_5$ | 119–120[b] | 93 | 18 | 70% EtOH |
| **6b** | 2-Quinolyl | $p$-$ClC_6H_4$ | 163–164[c] | 72 | 8 | EtOH |
| **6c** | 4-Quinolyl | $C_6H_5$ | 116–117[d] | 98 | 48 | $i$-PrOH |
| **6d** | 2-Pyridyl | $C_6H_5$ | 190–192[e] (7) | 92 | 48 | |
| **6e** | 4-Pyridyl | $C_6H_5$ | 115–116[f] | 92 | 48 | Benzene |
| **6f** | 2-Pyrazyl | $C_6H_5$ | 80–82[g] | 80 | 8 | DMF |
| **6g** | 2-Quinoxalyl | $C_6H_5$ | 152–153[h] | 82 | 2 | EtOH |
| **6h** | 3-Methyl-2-quinoxalyl | $C_6H_5$ | 125–126[i,j] | 52 | 7 | Hexane |
| **6i** | 2-Benzoxazolyl | 3-Pyridyl | 133–135[k] | 78 | 4 | $i$-PrOH |
| **6j** | 2-Quinoxalyl | $CF_3$ | 150–152[l] | 79 | 1 | 95% EtOH |
| **6k** | 2-Quinoxalyl | $CO_2Et$ | 164–165[m] | 72 | 4 | Heptane |
| **6l** | 3-Methyl-2-quinoxalyl | $CO_2Et$ | 126–128[n] | 88 | 4 | 50% EtOH |

[a] Acylating esters were methyl benzoate, methyl $p$-chlorobenzoate, ethyl nicotinate, ethyl trifluoroacetate, and diethyl oxalate. [b] Lit.[2b] mp 114–116°. [c] *Anal.* Calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.26; N, 4.97. Found: C, 72.52; H, 4.20; N, 4.78. [d] Lit.[2b] mp 115°. [e] Lit.[2b] bp 150–160° (3–4 mm). [f] Lit.[5d] mp 112–113°. [g] Lit.[5c] mp 82–83°. [h] *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.42; H, 4.84; N, 11.29. Found: C, 77.59; H, 4.97; N, 11.19. [i] Lit.[2a] mp 125.6–126.5°. [j] Diphenacyl derivative **7a** (32%) was isolated from this reaction, mp 205–207° (lit.[2a] mp 204.5–205.2°). [k] *Anal.* Calcd for $C_{14}H_{10}N_2O_2$: C, 70.59; H, 4.20; N, 11.76. Found: C, 70.84; H, 4.17; N, 12.04. [l] *Anal.* Calcd for $C_{11}H_7F_3N_2O$: C, 55.0; H, 2.94; N, 11.67. Found: C, 55.21; H, 2.69; N, 11.80. [m] Lit. mp 162°: N. J. Leonard and J. H. Boyer, *J. Amer. Chem. Soc.*, **77**, 2980 (1950). [n] Lit. mp 129°: G. M. Bennet and G. H. Willis, *J. Chem. Soc.*, 1928 (1960).

hanced by *N*-oxide,[6] nitro,[7] and carboalkoxy[8] functions or a second heteroatom.[9]

**Scheme I**




However, even with amide bases, these acylations suffer from an inherent disadvantage in that carbanions such as **2** usually abstract a methylene proton from intermediates of type **3**, to form weakly basic carbanions **4**, more rapidly than they react with ester. Thus, when a 1:1:1 molar ratio of heterocycle to base to ester is employed, only one-half of the heteroaromatic and ester are consumed. Attempts to circumvent this problem by using an extra equivalent of base have met with limited success owing to the tendency of many commonly employed bases to react with the acylating agent.[10] Consequently, these condensations are routinely carried out with a 2:2:1 molar ratio of heterocycle to base to ester. Although such procedures increase the efficiency of ester consumption, a molecular equivalent of starting heterocycle remains unchanged, and must be removed from the desired product. Moreover, if the heterocyclic reactant is precious, the disadvantage of such a sequence is obvious.

It seemed to us that the key to overcoming the unfavorable stoichiometry of these acylations, especially those utilizing esters having no α hydrogens, might be found in the use of sodium hydride as the condensing agent. This was based on the fact that sodium hydride is a strong base, but weakly nucleophilic,[11] and might therefore be used in excess without attacking either the ester carbonyl or the nucleus of the heterocyclic substrate. In spite of such potentially favorable properties, sodium hydride has been rarely employed in the acylation of alkylated heteroaromatics,[12] perhaps because of reports that weakly acidic heterocycles such as α- and γ-picoline and quinaldine (**1**) give little or no evidence of salt formation with sodium hydride in DMF,[13] THF,[14] or HMPA.[15]

We now wish to report that sodium hydride is a very effective base for acylations of a variety of methylated heteroaromatics, and that the mechanism of one such reaction is more complex than the series of steps shown in Scheme I.

## Results and Discussion

**Synthetic Applications.** In accord with results of other investigators,[13-15] we observed that less than 0.5 molar equiv of hydrogen was generated upon treatment of quinaldine (**1**) with excess sodium hydride in refluxing 1,2-dimethoxyethane (DME) for 18 hr. However, addition of a mixture of **1** and methyl benzoate (1:1.2 molar ratio) to excess sodium hydride in refluxing DME resulted in evolution of 2 molar equiv of hydrogen in 18 hr, and 2-phenacylquinoline (**6a**) was produced in 93% yield based on **1**. The generality of this procedure was demonstrated by acylations of a representative series of methylated heteroaromatics (**5**) with benzoate, picolinate, trifluoroacetate, and oxalate esters to afford ketones **6a–j** and α-keto esters **6k,l**. Results of these experiments are summarized in

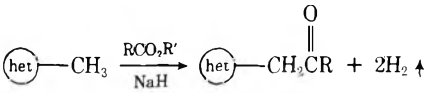



Table I, where it may be seen that yields of acylated products were quite satisfactory. Reaction times necessary for complete hydrogen evolution varied with acidity of the heterocyclic substrate and nature of the acylating ester. For example, reaction of methyl benzoate with 2-methylquinoxaline to give **6g** was essentially complete after 2 hr, while acylation of α-picoline with the same ester to give **6d** required 48 hr for complete hydrogen evolution. Reaction of **1** with methyl $p$-chlorobenzoate to afford **6b** proceeded significantly faster than the analogous acylation of **1** with methyl benzoate.

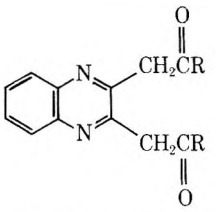
Twofold acylations of 2,3-dimethylquinoxaline with excess methyl benzoate and diethyl oxalate gave **7a** and **7b**, respectively. However, 2,6-lutidine underwent mainly monobenzoylation to afford **8** (39%) accompanied by only

**Table II**
**Acylation of Methylated Heteroaromatics with Diethyl Phthalate**

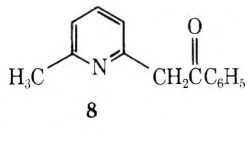
| Product No. | Het | Mp, °C | Yield, % | Rxn time, hr | Recrystn solvent |
|---|---|---|---|---|---|
| **10a** | 2-Pyridyl | 295–296[a] | 44 | 60 | 95% EtOH |
| **10b** | 4-Pyridyl | 323–324[b] | 72 | 80 | 95% EtOH |
| **10c** | 2-Quinolyl | 242–243[c] | 78 | 18 | Benzene |
| **10d** | 4-Quinolyl | 318–319[d] | 82 | 24 | 95% EtOH |
| **10e** | 2-Pyrazyl | 313–314[e] | 93 | 15 | MeOH |
| **10f** | 2-Quinoxalyl | 309–310[f] | 65 | 7 | HOAc |
| **10g** | 3-Methyl-2-quinoxalyl | 224–225[g] | 64 | 7 | EtOH |
| **10h** | 2-Benzothiazolyl | 363–364[h] | 78 | 2 | DMF |

[a] Lit.[16b] mp 292°. [b] Lit.[16b] mp 325°. [c] Lit.[18] mp 238–239°. [d] *Anal.* Calcd for $C_{18}H_{11}NO_2$: C, 79.12; H, 4.03; N, 5.13. Found: C, 79.40; H, 4.03; N, 5.11. [e] Lit.[17] mp 309–310°. [f] *Anal.* Calcd for $C_{17}H_{10}N_2O_2$: C, 74.45; H, 3.65; N, 10.22. Found: C, 74.62; H, 3.72; N, 10.35. [g] *Anal.* Calcd for $C_{18}H_{12}N_2O_2$: C, 75.0; H, 4.17; N, 9.72. Found: C, 74.76; H, 4.05; N, 9.90. [h] Lit. mp >320°: P. Jacobson, *Ber.*, **21**, 2630 (1888).

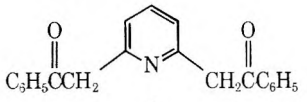
6% of diphenacyl derivative **9** upon prolonged treatment with excess methyl benzoate.



**7a**, R = $C_6H_5$
**b**, R = $CO_2Et$

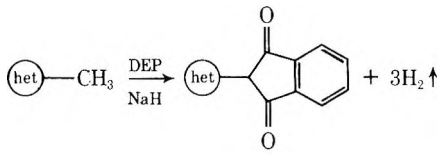


**8**



**9**

Reaction of diethyl phthalate (DEP) with a series of methylated heteroaromatics afforded 2-hetercaryl-1,3-indandiones **10** in good yields (Table II). Previous synthetic methods leading to compounds **10** have involved condensations of heteroaryl aldehydes with phthalides,[16] reaction of heteroarylacetic acids with phthalic anhydride,[17] and treatment of 1,3-indandiones with azine *N*-oxides in the presence of acetic anhydride.[18] In instances where comparisons can be made, the present yields are comparable to or better than those obtained in such syntheses. The sodium hydride method is also attractive because of the ready availability of starting materials.



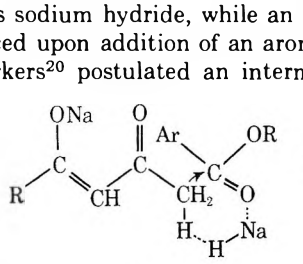
**10**

Several limitations discovered in the present synthetic endeavors are worthy of note. For example, β-picoline failed to undergo appreciable acylation with either methyl benzoate or DEP. Thus, it would appear that methyl groups β to an azomethine function will be acylated with difficulty by this method, whereas reactions at α- and γ-methyl groups occur readily (Tables I and II). Attempted reaction of α-picoline with *n*-propyl nitrate failed to yield any of the expected oxime.[12b] 2-Methylbenzimidazole was recovered unchanged following treatment with methyl benzoate and excess sodium hydride. In this case, initial ionization of the nuclear NH proton apparently reduces the acidity of the methyl protons to the point where sodium hydride cannot effect their removal.

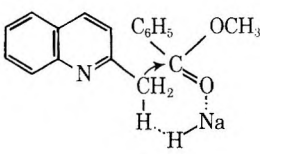
**Mechanistic Studies.** As pointed out in the previous section, the rate of hydrogen evolution observed upon treatment of **1** with sodium hydride in DME increased rapidly when methyl benzoate was present in the reaction mixture. Of ocurse, this would be expected to some degree since reaction of carbanion **2** with ester should form ketone **3**, which would then lose a methylene proton to generate carbanion **4** and release an equivalent amount of hydrogen. If formation of **2** were the rate-determining step, as it appeared to be on the basis of results with sodium hydride alone, then the rate of hydrogen evolution in the presence of ester should never be greater than twice that observed in its absence. This twofold maximum should likewise not be exceeded in the presence of excess ester. Comparisons of the rates of hydrogen release obtained by treating **1** with sodium hydride alone, with sodium hydride and 1.2 equiv of methyl benzoate, and with sodium hydride and 2.4 equiv of methyl benzoate clearly demonstrated that the rates of hydrogen production in the presence of ester exceeded the expected twofold increase. Moreover, the rate of hydrogen evolution was obviously related to ester concentration (Figure 1).

It has been shown that certain Claisen-type condensations employing sodium hydride proceed best in the presence of a catalytic amount of alcohol. In these instances alkoxide is probably the ionizing base, and sodium hydride serves mainly to force the reaction to completion.[19] It seemed possible that methoxide ion, which could be generated either by reaction of methyl benzoate with carbanion **2** or reaction of sodium hydride with traces of methanol present in the ester, might be responsible for the increased rate of hydrogen evolution observed with **1** and methyl benzoate. Comparison of the rates of hydrogen evolution obtained upon treatment of **1** with sodium hydride alone, and with sodium hydride in the presence of either 10 or 100 mol % of sodium methoxide, revealed that methoxide *did not* increase the rate of hydrogen production. Therefore, the rapid hydrogen release in the presence of methyl benzoate cannot be caused by alkoxide.

In an attempt to explain why only 1 equiv of hydrogen was evolved when certain diketones were treated with excess sodium hydride, while an additional 2 equiv was produced upon addition of an aromatic ester. Hauser and coworkers[20] postulated an intermediate such as **11**. It was



**11**



**12**

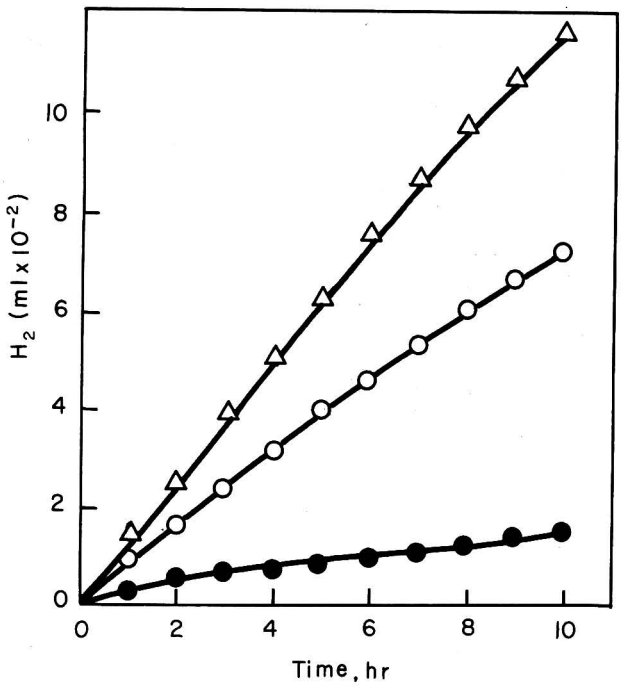



**Figure 1.** Effect of methyl benzoate concentration on the rate of hydrogen evolution from **1** (0.025 mol) in the presence of excess sodium hydride: ●, without methyl benzoate; ○, with 0.03 mol of methyl benzoate; △, with 0.06 mol of methyl benzoate.

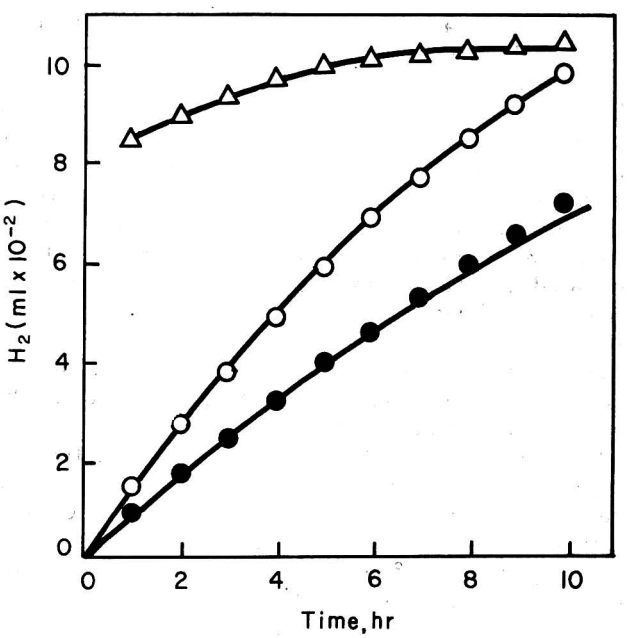
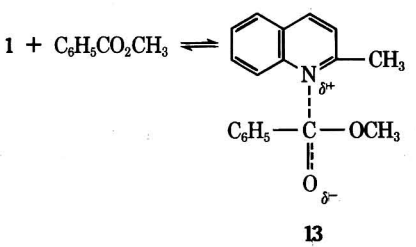



**Figure 2.** Effect of acylating ester on the rate of hydrogen evolution from **1** (0.025 mol) in the presence of excess sodium hydride: ●, of methyl benzoate (0.03 mol); ○, methyl *p*-chlorobenzoate (0.03 mol); △, ethyl trifluoroacetate (0.03 mol).

proposed that coordination of sodium with ester carbonyl might increase the basicity of hydride ion, thereby facilitating abstraction of a methyl proton to form a terminal carbanion in close proximity to the electrophilic site of the ester. A similar species, **12**, could be imagined for **1**, sodium hydride, and methyl benzoate. If such complexation were important it appeared that the role of metal as a mechanistic component might be probed by using lithium hydride. Although lithium hydride is a weaker base than sodium hydride, the greater tendency for coordination expected of lithium might compensate for differences in basicity.[21] Comparable reaction rates for these two bases would then provide strong evidence for the existance of such a coordinative mechanism. However, acylation of **1** with methyl benzoate and lithium hydride proceeded so much slower than the sodium hydride reaction that only 24% of the theoretical amount of hydrogen was evolved after 50 hr.

Although the results with lithium hydride do not definitely rule out a mechanism involving metal complex **12**, we feel that a more attractive explanation of the role of ester might involve interaction between ester and heterocycle in a preionization event. It is suggested then that a complex such as **13** is formed prior to ionization and that




**13**

the resulting electron deficiency at ring nitrogen facilitates ionization of a methyl hydrogen in a manner similar to that observed upon quaternization of **1**.[22] Complexes related to **13** have been proposed to account for changes in

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EXPERIMENTAL SECTION

General. -- Melting points were taken with a Mel-Temp apparatus and are corrected; boiling points are uncorrected. Infrared spectra were taken on Beckman IR-5A and IR-20A-X spectrophotometers. Pmr spectra were obtained on a Varian Associates A-60 spectrometer with tetramethylsilane as internal standard. Microanalyses were performed in this laboratory by Miss Q. H. Tan employing a Perkin Elmer 240 Elemental Analyzer. All reagents were commercial reagent grade. In studies of hydrogen evolution rates, reagents were purified immediately prior to use. 1,2-Dimethoxyethane (DME) was distilled from sodium ribbon and then from sodium hydride. Sodium hydride, as a 50% dispersion in mineral oil, was obtained from Ventron Corporation, Beverly, Mass.

General Procedure for Sodium Hydride Promoted Acylations. -- In a 500 ml three-necked flask equipped with a magnetic stirrer, a pressure-equilizing addition funnel, heating mantle and a reflux condenser, connected at its upper end through a cold trap (Dry Ice-acetone) to a Precision Scientific wet-test meter filled with water, were placed 200 ml of freshly distilled DME and 0.25 mol of sodium hydride (prepared by washing 12 g of the commercial dispersion free of mineral oil with petroleum ether). A solution of the appropriate methylated heterocycle (0.05 mol) and ester (0.07 mol) in 100 ml of DME was placed in the addition funnel. The system was flushed with dry nitrogen, then closed to the atmosphere. The solvent in the reaction flask was heated to reflux, and when thermal equilibrium had been established the gas meter was set to zero. The solution of heterocycle and ester was then added over a period of 20 min and the resulting suspension was refluxed until hydrogen evolution ceased. The reaction flask was then cooled in an ice-water bath and 100 ml of ether was added. Next 7.5 g of acetic acid was added dropwise (Caution!), followed by 75 ml of cold water. Finally, an additional 7.5 g of acetic acid and 75 ml of water were added. The resulting two-phase mixture was stirred well and solid products which separated between the layers were collected by suction filtration. The two layers of the filtrate were separated and the aqueous layer extracted with two 150 ml portions of ether. The ethereal extracts and the original organic layer were combined, dried ($Na_2SO_4$) and concentrated. The last traces of ester and acetic acid were removed at 50-75° (1 mm). The crude product resulting from this operation was added to that which separated between the layers, and the combined material was recrystallized from the appropriate solvent or distilled (Tables I and II).

Twofold acylation of 2,3-dimethylquinoxaline with methyl benzoate was carried out using 7.90 g (0.05 mol) of heterocycle, 21.76 g (0.16 mol) of ester and 12 g of sodium hydride dispersion in 300 ml of DME. The reaction period was 8 hr. Recrystallization of the crude product from absolute ethanol gave 11.45 g (62%) of (7a): mp 206-207.5° (lit.[28] mp 204.5-205.2°); pmr ($CDCl_3$) δ 8.15-7.05 (m, 14H, aromatic) and 6.45 ppm (s, 2H, vinyl H of

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enol); ir ($CHCl_3$) 6.25 and 6.48 μ (enol).

Similar twofold acylation of 2,3-dimethylquinoxaline with diethyl oxalate was carried out with 0.05 mol of heterocycle, 20.44 g (0.14 mol) of ester, and 12 g of sodium hydride dispersion. After 3 hr the reaction was processed in the usual manner to afford 4.50 g (21%) of 7b as blue-black crystals from absolute ethanol: mp 167-168°; pmr ($CDCl_3$) δ 12.60 (s, 2H, NH or OH), 8.35-7.30 (m, 4H, aromatic), 6.95° (s, 2H, vinyl H of enol), 4.55-3.85 (m, 4H, $OCH_2CH_3$) and 1.60-0.80 ppm (m, 6H, $-OCH_2CH_3$); ir 5.78 μ (ester C=O) and 6.25 - 6.40 μ (enol).

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 60.34; H, 5.03; N, 7.82. Found: C, 60.60; H, 4.78; N, 7.65.

Attempted dibenzoylation of 2,6-lutidine was conducted using 26.75 g (0.25 mol) of heterocycle, 81.60 g (0.60 mol) of methyl benzoate and 60 g of sodium hydride dispersion in 1000 ml of DME for 120 hr. After the usual work-up the resulting oily, crude product was vacuum distilled. The distillate collected at 194-294° (7mm) solidified on standing and was then recrystallized from hexane to give 20.45 g (39%) of 8: mp 73-76° (lit.[26] mp 77-78°); pmr ($Cl_2CCOCCl_2$) δ 8.05-6.68 (m), 6.26 (s), 5.92 (s) (total 10H) and 2.50 ppm (s, 3H, $CH_3$); ir ($CHCl_3$) 5.80 (C=O) and 6.00 μ (enol). To the distillation residue was added 100 ml of 95% ethanol and crystals soon formed. They were collected and recrystallized from absolute ethanol to give 4.41 g of diphenacyl derivative 9: mp 83-84° (lit.[27] mp 87°); pmr ($Cl_2CCOCCl_2$) δ 8.05-6.68 (m, 6.26 (s), 5.92 (s) (total 15H), and 4.36 ppm (s, 2H, $CH_2$; ir ($CHCl_3$) 5.94 (C=O) and 6.12 μ weak (enol).

In addition to the correct analytical data (Tables I and II), new compounds 6b, 6g, 6i, 6j, 10d, 10f and 10g had spectral characteristics consistent with the assigned structures. Ketones of type 6 had a weak ir band at 5.8-5.9 μ accompanied by several strong enol bands at 6.10-6.40 μ. Indandiones 10 exhibited similar absorption at 6.10-6.40 μ but had a much stronger carbonyl band at 5.85-5.95 μ. The pmr ($CDCl_3$) spectra of ketones 6 were characterized by fractional methylene proton resonances at 4.96-4.25 and vinyl proton absorptions at 6.56-5.94 ppm.

Hydrogen Evolution Studies. -- The apparatus described in the previous section was charged with 250 ml of freshly distilled DME and 0.125 mol of washed sodium hydride, and the resulting slurry was brought to reflux. Following attainment of thermal equilibrium, a solution of 1 (0.025 mol) alone or in combination with 0.030 mol of the appropriate ester in 100 ml of DME was added from the addition funnel over a period of 20 min. The cummulative volume of hydrogen evolved was recorded at hourly intervals along with the temperature of the meter and the atmospheric pressure. When hydrogen release stopped, the final meter readings were corrected to standard temperature and pressure and for the vapor pressure of water. In the series of experiments represented in Figure 1, the temperature of the gas

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meter varied from 21.8 to 22.8° and the atmospheric pressure varied from 709.6 to 711.5 mm. Under these conditions the theoretical volume of 2 equiv of hydrogen is between 1328 and 1339 ml, while that for 1 equiv of hydrogen is between 664 and 669 ml. In the experiments for which data is given in Figure 2, the temperature varied from 23.3 to 27.8° and the pressure varied over the range of 707.7 to 712 mm. The theoretical volume for 2 equiv of hydrogen under these conditions is between 1333 and 1371 ml. Reactions were processed in the usual fashion and products or starting materials were isolated. Acylation of 1 with ethyl trifluoroacetate gave 6 (R=$CF_3$): mp 129-130°; pmr ($CDCl_3$) δ 8.07-6.9 (m, 6H) and 5.86 ppm (s, 1H, enol CH).

Anal. Calcd. for $C_{12}H_6NOF_3$: C, 60.25; H, 3.38; N, 5.86. Found: C, 60.40; H, 3.29; N, 6.12.

Hydrogen evolution experiments involving the possible effects of methoxide on the sodium hydride promoted ionization of 1 were conducted on the same scale as described above. The appropriate molar quantities of methoxide were prepared in situ by adding methanol to the sodium hydride-DME slurry prior to attainment of thermal equilibrium and addition of 1.

Attempted benzoylation of 1 using lithium hydride was conducted with molar quantities of reactants identical to those given above.

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(27) G. S. Scheuing and L. Winterhalter, Ger. Patent 594849 (1934); Chem. Abstr. 28, 4542 (1934).

the pmr spectra of amides upon addition of pyridine,[23] shifts in the electronic spectrum of pyridazine in the presence of benzophenone,[24] and the rapid rate of which β-keto alcohols effect displacement of halide from 2-halopyridines.[25] As a test of this mechanism we examined the rates of hydrogen evolution accompanying acylations of **1** with methyl *p*-chlorobenzoate and ethyl trifluoroacetate, anticipating that the more positive carbonyl groups of these two esters would favor complex formation. If this occurred, the rates of hydrogen release should exceed the rate observed with methyl benzoate. The indeed proved to be the case, as shown in Figure 2, where it may be seen that the reaction with trifluoroacetate was greater than 60% complete after only 1 hr. It should also be noted that excess methyl benzoate should favor formation of complex **13**, thereby increasing the rate of hydrogen evolution as is observed. Thus, the course of the sodium hydride promoted benzoylation of **1** *via* complex **13** appears to be consistent with our experimental findings. It is also possible that acylations of β-diketone monoenolates in the presence of excess sodium hydride might also involve similar complex formation prior to removal of a terminal methyl proton, since the rates of such reactions are dependent on ester concentration.[20]

**Registry No.**—**1**, 91-63-4; **6a**, 1531-38-0; **6b**, 51425-11-7; **6c**, 7543-20-6; **6d**, 1620-53-7; **6e**, 1620-55-9; **6f**, 40061-45-8; **6g**, 16310-38-6; **6h**, 51425-12-8; **6i**, 51425-13-9; **6j**, 51425-14-0; **6k**, 7248-83-1; **6l**, 13119-79-4; **7a**, 51425-15-1; **7b**, 51425-16-2; **8**, 1083-25-6; **9**, 51425-17-3; **10d**, 51425-18-4; **10f**, 51425-19-5; **10g**, 51425-20-8; 4-methylquinoline, 491-35-0; 2-methylpyridine, 109-06-8; 4-methylpyridine, 108-89-4; 2-methylpyrazine, 109-08-0; 2-methylquinoxaline, 7251-61-8; 2,3-dimethylquinoxaline, 2379-55-7; methyl benzoate, 93-58-3; methyl *p*-chlorobenzoate, 1126-46-1; ethyl nicotinate, 614-18-6; ethyl trifluoroacetate, 383-63-1; diethyl oxalate, 95-92-1; diethyl phthalate, 84-66-2; 2,6-lutidine, 108-48-5; 2-methylbenzoxazole, 95-21-6.

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## References and Notes


(1) (a) Taken in part from the Ph.D. dissertation of D. E. P., Virginia Polytechnic Institute and State University, 1972. (b) Supported by Public Health Service Research Grants GM 14340 and NS-10197.
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# Chemistry of 2-Tetrahydropyranthiol


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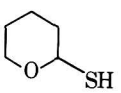
Hydrogen sulfide reacts with 2,3-dihydropyran to form 2-tetrahydropyranthiol (1). 1 has been shown to be a useful reagent for direct introduction of a protected mercaptan into a variety of organic compounds. Addition reactions under ionic and free-radical conditions and displacement reactions have been studied. Subsequent facile cleavage utilizing neutral aqueous silver nitrate followed by treatment of the mercaptide with hydrogen chloride gave the desired mercaptans.


2,3-Dihydropyran reacts with aliphatic and aromatic hydroxyl or sulfhydryl groups under acidic conditions to form alkyl or aryl tetrahydropyranyl ethers[2] or sulfides,[3] respectively. These cyclic acetals and monothioacetals are readily hydrolyzed, in most instances, under mild acid conditions to yield the free alcohol or mercaptan.

It seemed possible that the same protected thiol function might be prepared directly by addition of 2-tetrahydropyranthiol (1) to multiple bonds or by appropriate displacement reactions. Of perhaps greatest interest was the possibility of preparing derivatives of otherwise unstable tautomers such as enethiols or thioimidates. Although our

original efforts[4] in the latter direction were inconclusive, there were, nevertheless, indications of potential utility.

2-Tetrahydropyranthiol (1) can be prepared in 40–60% yield by treating a four- to fivefold excess of hydrogen sulfide with dihydropyran in the presence of an acid catalyst. A mixture of *p*-toluenesulfonic acid and trifluoroacetic acid gave the best results. The other product in significant quantities appears to be the bis(2-tetrahydropyranyl) sulfide (2). 1 is relatively stable but undergoes gradual dis-



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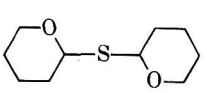

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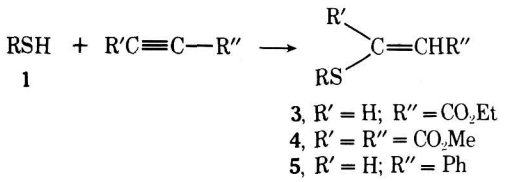
proportionation to 2 and decomposition to polymeric material. The thiol 1 is stable when stored under nitrogen in the cold for several weeks.

With the potential reagent in hand a study of its addition reactions under ionic and free-radical conditions was undertaken. The addition products of 1 and acetylenes are the corresponding substituted vinyl 2-tetrahydropyranyl sulfides (3, 4, and 5). All base-catalyzed additions of 1 to the acetylenes gave predominantly the product from trans

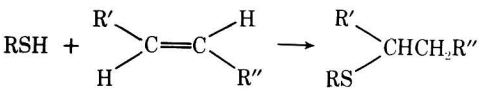


1

3, R′ = H; R″ = $CO_2Et$
4, R′ = R″ = $CO_2Me$
5, R′ = H; R″ = Ph

addition, as anticipated from the work of Truce[5] on similar reactions with simpler thiols. The cis/trans ratios were determined for both ionic and free-radical additions by analysis of the nmr spectra which was in some cases confirmed by glc analysis.

Addition reactions of the thiol 1 were also studied with diethyl maleate and styrene as representative olefins. The expected tetrahydropyranyl derivatives of diethyl 2-mercaptosuccinate (6) and β-phenylethanethiol (7) were obtained in good yield.



1

6, R′ = R″ = $CO_2Et$
7, R′ = H; R″ = Ph

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## EXPERIMENTAL[10]

2-Tetrahydropyranthiol (1). Hydrogen sulfide (90 g) was liquefied in a 200 ml stainless steel cylinder placed in an acetone-dry ice bath. 2,3-Dihydropyran (30 g) was added dropwise to the cylinder over a period of 10 min. Five to ten drops of trifluoroacetic acid and 50 mg of *p*-toluenesulfonic acid were added, the cylinder valve was closed and the reaction mixture was allowed to attain and remain at ambient temperature for 12 hr. The unreacted $H_2S$ was released slowly and the resulting liquid distilled at reduced pressure to yield 25 g (51%) of the desired product, bp 58° (15 mm) $n_D^{25}$ 1.4973; nmr δ 5.02 (m, 1, CH), 3.78 (m, 2, $CH_2O$), 2.17 (d, 1, SH), 1.66 (br, 6 $(CH_2)_3$); ir 2545 $cm^{-1}$ (SH).

Anal. Calcd for $C_5H_{10}OS$: C, 50.80; H, 8.53; S, 27.13
Found: C, 50.82; H, 8.58; S, 27.28.

A second fraction, presumed to be bis-2-tetrahydropyranyl sulfide (2) was obtained, bp 105° (1.5 mm), $n_D^{25}$ 1.5107; nmr δ 5.05 (q, 1, CH), 3.72 (m, 2, $CH_2O$), 1.6 (m, 6, $(CH_2)_3$).

Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.36; H, 8.97; S, 15.85
Found: C, 58.79; H, 8.82; S, 14.14.

Ethyl cis and trans-3-(2′-Tetrahydropyranylthio)propenoate (3). A. Base Catalyzed Addition. A mixture of 5.8 g (50 mmol) of ethyl propiolate, 5 g anhydrous $K_2CO_3$, and 300 ml THF distilled from $LiAlH_4$ was placed in a 3-neck 500 ml round bottom flask equipped with a magnetic stirrer, a nitrogen inlet tube, and a pressure equalizing dropping funnel. To this reaction mixture was added 5.9 g (50 mmol) of 1 dissolved in 50 ml of THF over a period of 1 hr. The mixture was stirred for 6 hr at ambient temperature, washed with 3 volumes of saturated NaCl solution, and dried with $MgSO_4$. The THF was evaporated and the remaining yellow oil was chromatographed on silica gel using $CHCl_3$ as solvent to afford 10.9 g (100%) of a cis:trans (70%:30% calculated from pmr and glc data) mixture of the addition products. Separation of the isomers was accomplished by preparative glc using a column temp of 175°, a detector and injector temp of 225°, and a collector temp of 230°. Bp trans 98-100° (5 μ) and cis 134-138° (25 μ); nmr δ trans 7.97 and 6.15 (2d, 2, olefinic, J = 16 Hz), 5.45 (m, 1, CH-O), 4.32 and 1.33 (q and t, 2 and 3, $C_2H_5$), 4.03 (m, 2, $CH_2O$), 1.80 (m, 6 $(CH_2)_3$); cis 7.51 and 6.09 (2d, 2, olefinic, J = 10 Hz), 5.23 (m, 1, CH-O), 4.33 and 1.33 (q and t, 2 and 3, $C_2H_5$), 4.04 (m, 2, $CH_2$-O), 1.80 (m, 6, $(CH_2)_3$). The elemental analysis was obtained on the cis/trans mixture.

Anal. Calcd for $C_{10}H_{16}O_3S$: C, 55.55; H, 7.46; S, 14.80
Found: C, 55.47; H, 7.21; S, 14.74.

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B. Radical Initiated Addition. A mixture of 5.8 g (50 mmol) of ethyl propiolate, 5.9 g (50 mmol) of 1, 0.136 g (1 mmol) azobisisobutyronitrile, and 10 ml of THF distilled from $LiAlH_4$ was sealed in a 20 ml ampoule which had been flushed with nitrogen. The ampoule was placed in an oil bath at 50°. At the end of 1 hr the ampoule was opened, the THF evaporated, and the contents distilled at reduced pressure to afford 6 g (55%) of a 20%/80% cis/trans mixture (calculated from the pmr spectrum).

cis- and trans-Dimethyl (2-Tetrahydropyranylthio)butendioate (4). A. Base Catalyzed Addition. A mixture of 7.1 g (50 mmol) of freshly distilled dimethyl acetylenedicarboxylate, 1 g of anhydrous $K_2CO_3$, and 300 ml of THF distilled from $LiAlH_4$ was placed in a 3-necked 500 ml round bottom flask equipped with nitrogen inlet tube, a magnetic stirrer, and a pressure equalizing dropping funnel. To this mixture was added dropwise 5.9 g (50 mmol) of 1 in 50 ml of THF at -10 to -15° over a period of 30 min. The mixture was stirred for 8 hr, washed with saturated NaCl solution, dried ($Na_2SO_4$), and chromatographed on a silica gel column using 50-50 ether-petroleum ether (30-70°) for elution. The column afforded 8.5 g (64%) of a 35%/65% cis/trans mixture.

Anal. Calcd for $C_{11}H_{16}O_5S$: C, 50.77; H, 6.20; S, 12.29
Found: C, 50.86; H, 6.07; S, 12.28.

Separation was accomplished on a silica gel (60-200 mesh) column using $CHCl_3$ as a solvent. The cis isomer gave nmr δ 6.08 (s, 1, CH), 5.45 (m, 1, CH-O), 3.68 (s, 3, $CH_3$), 3.02 (s, 3, $CH_3$), 3.85 (m, 2, $OCH_2$), 1.77 (m, 6, $(CH_2)_3$); ir 1451, 795 $cm^{-1}$. The trans isomer gave nmr δ 6.34 (s, 1, CH), 5.50 (m, 1, CH-O), 3.75 (s, 3, $CH_3$), 3.80 (s, 3, $CH_3$), 3.78 (m, 2, $CH_2$-O), 1.73 (m, 6, $(CH_2)_3$); ir 1356, 1005 $cm^{-1}$.

B. Radical Initiated Addition. A mixture of 5.9 g (50 mmol) of 1, 1.42 g (10 mmol) dimethyl acetylenedicarboxylate, and 0.13 g (1 mmol) of azobisisobutyronitrile was placed in a 20 ml ampoule, flushed with nitrogen, and sealed. The ampoule was placed in an oil bath at 60° and heated for 10 min. The yellow material was then chromatographed on a silica gel column using 50-50 ether-petroleum ether (30-70°) for elution. The column afforded 3.6 g (84%) of a 50%/50% cis/trans mixture.

2-Phenylvinyl 2-Tetrahydropyranyl Sulfide (5). A. Base Catalyzed Addition. Freshly distilled phenylacetylene (5.1 g, 50 mmol), 1 (5.9 g, 50 mmol) and $K_2CO_3$ (1.36 g, 10 mmol) were stirred in 250 ml THF for 5 hr. After washing (saturated NaCl), drying ($Na_2SO_4$), concentration, and distillation (250 μ, 128-130°) there

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was obtained 6.1 g (55%) of an 80/20 cis/trans mixture. Attempts to separate the isomers were not successful. Nmr δ cis 6.57, 6.44 (2d, 2, vinylic H, J = 10.5 Hz), 4.98 (t, 1, CH-O); trans 6.97, 6.71 (2d, 2, vinylic H, J = 15.7 Hz), 5.12 (t, 1, CH-O).

Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.52
Found: C, 70.97; H, 7.28; S, 14.49.

B. Photolytic Addition. Phenylacetylene (5.1 g, 50 mmol) and 1 (5.9 g, 50 mmol) sealed in a nitrogen flushed ampoule at 0° was allowed to remain at 25° for 3 days. Volatile materials were removed under vacuum (20°) and the residue was taken up in $CHCl_3$ and washed with 5% NaOH, 5% HCl and saturated NaCl. After drying and evaporation there was obtained 4 g (40%) of a 80/20 cis/trans mixture. Variations in reactant ratios has very little effect on the yield.

cis- and trans-Ethyl 3-Mercaptopropenoate. To 4.32 g (20 mmol) cis-trans 3 in 20 ml $CH_3OH$ was added 3.4 g (20 mmol) $AgNO_3$ in 40 ml of water. The precipitate was removed by filtration, suspended in 10 ml $CHCl_3$, and cooled to 0°. Excess HCl was bubbled into the suspension. This mixture was filtered through filter aid and the $CHCl_3$ filtrate was washed with saturated $KHCO_3$ and concentrated to give 2.6 g (99%) of an oil which could not be distilled or chromatographed on silica gel without decomposition. Ir data: 2562, 2517 (SH); 1751, 1712 (C=O); 966 (CH-trans) and 762 $cm^{-1}$ (CH-cis); nmr δ 7.08 (m, 1, SH, exchanged with $D_2O$), 5.88 (m, 2, olefinic), 4.28 and 4.27 (2q, 4, $CH_2$), 1.30 and 1.28 (2t, 6, $CH_3$).

Anal. Calcd for $C_5H_8O_2S$: C, 45.46; H, 6.10; S, 24.22
Found: C, 45.69; H, 5.96; S, 24.04.

Dimethyl Mercaptofumarate. To 5.2 g (20 mmol) of a mixture of 35% cis/65% trans 4 in 25 ml MeOH was added 3.4 g (20 mmol) of $AgNO_3$ in 50 ml of water. The precipitate was collected and suspended in 100 ml $CHCl_3$ at 0°. Excess HCl was bubbled through the suspension and the precipitate (AgCl) was removed by filtration. The $CHCl_3$ was washed with water until the washings became neutral, dried ($Na_2SO_4$) and evaporated. The resulting liquid sublimed to form a colorless solid upon distillation at reduced pressure thus affording 1.5 g (43%) of the desired product. Subsequent attempts to resublime the product provided an oil, bp 80-82° (15 mm); nmr δ 6.82 (s, 1, CH), 6.32 (s, 1, SH, exchanged with $D_2O$), 3.90 (s, 3, $CH_3$), 3.80 (s, 3, $CH_3$); ir 2488, 1733, 1594 $cm^{-1}$.

Anal. Calcd for $C_6H_8O_4S$: C, 40.90; H, 4.58; S, 18.16
Found: C, 41.18; H, 4.50; S, 18.08.

2-Phenylethenethiol. Cleavage of 5 with $AgNO_3$ as described for 4 afforded 59% of a cis-trans mixutre, $n_D^{24}$ = 1.6357, bp 57-60° (0.3 mm), nmr δ 7.25 (m, 5, $C_6H_5$), 6.32 (m, 2, vinyl), 2.99 (m, 1, SH, exchanged with $D_2O$); ir 2555 $cm^{-1}$ (SH). There was no evidence for a thiocarbonyl group.

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Anal. Calcd for $C_8H_8S$: C, 70.58; H, 5.92; S, 23.50
Found: C, 70.48; H, 6.03; S, 23.32.

Diethyl 2-(2′-Tetrahydropyranylthio)succinate (6). To 8.6 g (50 mmol) of freshly distilled diethyl maleate, 5 g anhydrous $K_2CO_3$, and 200 ml of THF distilled from $LiAlH_4$ in a 500 ml three-necked round bottom flask equipped with a nitrogen inlet tube, pressure equalizing dropping funnel, and magnetic stirrer was added 5.9 g (50 mmol) of 1 in 50 ml of THF dropwise into the reaction mixture over a period of 15 min. This mixture was stirred for 8 hr at ambient temperature. It was then extracted with 3 volumes of saturated NaCl solution and the THF dried with anhydrous $Na_2SO_4$. The THF was evaporated and the resulting liquid distilled at reduced pressure to afford 10.3 g (72%) of a colorless liquid, bp 128-130° (100 μ); $n_D^{23}$ 1.4086; nmr δ 5.16 (m, 1, CH-O), 4.16 (2q, 4, $OCH_2$), 3.83 (m, 2, $CH_2O$), 3.92 (m, 1, CH), 2.90 (m, 2, $CH_2$), 1.67 (m, 6, $(CH_2)_3$), 1.23 (2t, 6, $CH_3$).

Anal. Calcd for $C_{13}H_{22}O_5S$: C, 53.77; H, 7.64; S, 11.04.
Found: C, 53.55; H, 7.68; S, 10.91.

2-Phenylethyl 2-Tetrahydropyranyl Sulfide (7). Styrene (5.2 g, 50 mmol), 1 (5.9 g, 50 mmol), benzene (250 ml), and azobisisobutyronitrile (0.25 g, 1 mmol) in a 500 ml flask was flushed with nitrogen and heated in an oil bath for 5 min at 50°. The reaction mixture was allowed to stand at 25° for 4 days and then distilled to give 10 g (90%) of the addition product, bp 124-125° (250 μ), nmr δ 7.18 (m, 5, Ph), 4.92 (m, 1, CH-O), 3.75 (m, 2, $CH_2$-O), 2.82 (m, 4, $(CH_2)_2$), 1.68 (m, 6, $(CH_2)_3$).

Anal. Calcd for $C_{13}H_{18}OS$: C, 70.24; H, 8.16; S, 14.39
Found: C, 69.99; H, 8.09; S, 14.58.

Diethyl Mercaptosuccinate. To 5.8 g (20 mmol) of 6 in 20 ml $CH_3OH$ was added 3.4 g (20 mmol) $AgNO_3$ dissolved in water. The silver mercaptide was collected, suspended in 100 ml $CHCl_3$, and cooled to 0°. Excess HCl was bubbled into the suspension and the solid (AgCl) was removed by filtration. The $CHCl_3$ was dried ($Na_2SO_4$), evaporated, and the resulting liquid was distilled at reduced pressure to afford 3.6 g (85%) of the desired product, bp 62-64° (50 μ), $n_D^{25}$ 1.4581 (lit.[11] $b_{2\mu}$ 130°-135°), nmr δ 4.16 (2q, 4, $CH_2$), 3.72 (t, 1, CH), 2.86 (m, 2, $CH_2$), 2.72 (d, 1, SH, exchanges with $D_2O$), 1.27 (2t, 6, $CH_3$); ir 2562 $cm^{-1}$ (SH).

2-Phenylethanthiol. Cleavage of 7 with $AgNO_3$ gave 90% of the desired product, bp 41° (125 μ) (lit.[12] 95-98° at 12 mm), nmr δ 7.15 (m, 5, $C_6H_5$), 2.75 (m, 4, $(CH_2)_2$), 1.17 (m, 1, SH, exchanged with $D_2O$); ir 2551 $cm^{-1}$.

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Ethyl 2-(2′-Tetrahydropyranylthio)propionate (8). A mixture of 5.9 g (50 mmol) of 1, 9.05 g (50 mmol) of ethyl 2-bromopropionate, 3.5 g (25 mmol) $K_2CO_3$, and 100 ml acetone were placed in a 200 ml round bottom flask equipped with a magnetic stirrer and a condenser. This mixture was refluxed for 12 hr. The KBr which formed was removed by filtration, the acetone evaporated, and the resulting liquid distilled at reduced pressure to afford 7 g (64%) of the desired product, bp 78-80° (100 μ), nmr δ 5.09 (m, 1, CH-O), 4.11 (q, 2, $CH_2$), 3.73 (m, 2, $CH_2$-O), 3.43 (q, 1, CH-S), 1.68 (m, 6, $(CH_2)_3$), 1.32 (m, 6, $CH_3$).

Anal. Calcd for $C_{10}H_{18}O_3S$: C, 55.03; H, 8.31; S, 14.46
Found: C, 54.82; H, 8.11; S, 14.52.

n-Butyl 2-Tetrahydropyranyl Sulfide (9). To a solution of 2.7 g (50 mmol) of $CH_3ONa$ and 5.9 g (50 mmol) of 1 in 100 ml $CH_3OH$ was added, with stirring, 6.85 g (50 mmol) of 1-bromobutane in 50 ml $CH_3OH$. After heating under reflux for 6 hr the mixture was diluted with 200 ml of saturated NaCl and extracted with ether-benzene (3:1). The extract was dried ($MgSO_4$) and evaporated and the residue distilled to give 5.5 g (63%), bp 48° (250 μ), nmr δ 4.98 (1), 3.92 (2), 2.72 (2), 1.67 (10), 0.96 (3).

Anal. Calcd for $C_9H_{18}OS$: C, 62.04; H, 10.41; S, 18.37
Found: C, 61.97; H, 10.37; S, 18.41.

Benzyl 2-Tetrahydropyranyl Sulfide (10). α-Chlorotoluene (3.1 g, 24 mmol), 1 (2.8 g, 24 mmol), and $K_2CO_3$ (1.65 g, 12 mmol) in 50 ml acetone was stirred under reflux for 14 hr. Removal of KCl and acetone followed by distillation gave 2.3 g (47%) of the substitution product, bp 109-111° (250 μ), nmr δ 7.44 (5), 4.8 (1), 3.92 (2), 3.87 and 3.84 (2), 1.68 (6).

Anal. Calcd for $C_{12}H_{16}OS$: C, 69.21; H, 7.74; S, 15.37
Found: C, 69.16; H, 7.61; S, 15.42.

Ethyl 2-Mercaptopropionate. To 4.4 g (20 mmol) of 8 dissolved in 20 ml of $CH_3OH$ was added 3.4 g (20 mmol) of $AgNO_3$ dissolved in 50 ml of water. The precipitate was collected, suspended in 100 ml $CHCl_3$, and cooled to 0°. Excess HCl was bubbled through the suspension and the precipitate (AgCl) was removed by filtration. The $CHCl_3$ layer was washed with water until the washings became neutral, dried ($Na_2SO_4$) and evaporated. The resulting liquid distilled at reduced pressure to afford 2.5 g (92%) of the desired product, bp 90° (60 mm), lit.[13] 54° (6 mm), identical in all respects to an authentic sample.

1-Butanethiol. Cleavage of 9 with $AgNO_3$ gave 84% of the butanethiol identical in all respects to an authentic sample.

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α-Toluenethiol. Cleavage of 10 with $AgNO_3$ gave 89% of α-toluenethiol, bp 60-61° (2mm) identical in all respects to an authentic sample.

Bis-2-Tetrahydropyranyl Dithiooxaldiimidate (11). Into 3.0 g (26 mmol) of freshly distilled 1 and two drops of butylamine in 250 ml of heptane at -80° was passed 1.44 g (30 mmol) of cyanogen gas. Vigorous stirring was maintained throughout the addition, which required about 30 min and for two additional hrs at -80°. After settling, the solvent was decanted, leaving a white solid in the reaction flask to be used immediately in the next reaction.

In a previous experiment an effort was made to isolate the diimidate. After standing three hrs at -80° the reaction mixture was permitted to warm to room temperature. A portion of the solid material was collected on a filter and washed with heptane, which caused the material to liquify. A portion of the oil was crystallized using a mixture of heptane and benzene, to give colorless needles, mp 100-104°. Further attempts to recrystallize the product gave only dithiooxamide.

5-Benzylideneamino-2-phenyl-4(2-tetrahydropyranylmercapto)oxazole (12). 11 prepared from 3.0 g (26 mmol) of 1 was refluxed for 3 hr with 7 g (66 mmol) of benzaldehyde in 50 ml of dry benzene in a flask equipped with a Dean-Stark trap. A dark brown oil collected in the trap and on the base of the reflux condenser. The benzene was evaporated from the reaction mixture leaving a dark brown, viscous oil. The oil was crystallized from ethanol to give yellow rosettes, mp 152-155°. Additional material was obtained from the mother liquor. Four recrystallizations, two from ethanol followed by two from acetone, gave yellow needles, mp 157-158°. The yield was 2.75 g (59% based on 1). Nmr δ 8.57 (s, 1, N=CH), 7.94 and 7.40 (m, 10, Ph), 5.91 (t, 1, CH), 3.4 and 3.6 (m, 2, $CH_2O$), 1.8 (m, 6, $(CH_2)_3$).

Anal. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.20; H, 5.53; N, 7.69; S, 8.80
Found: C, 69.13; H, 5.53; N, 7.69; S, 8.13.

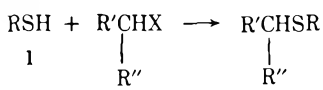
10. Elemental analyses were performed at the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. All nmr spectra for analysis of cis/trans ratios were obtained on a Varian model A-60A spectrometer using $CDCl_3$ with TMS as internal standard except for the analysis of cis and trans 4 (5) which was carried out on a Jeolco Model JNM 4H-100 MHz spectrometer. Glc analysis of cis and trans 3 was accomplished using a 10′ X 1/4″ aluminum column packed with 10% polyethylene glycol succinate on Chromsorb W 40/60 mesh.

11. A. Emr and F. Roubinek, Chem. Listy, 50, 664 (1956).

12. M. Kulka, Can.J.Chem., 34, 1093 (1956).

13. M. M. Kreevoy, B. E. Eichinger, F. E. Story, E. A. Katz, and J. H. Elstedt, J.Org.Chem., 29, 1641 (1964).

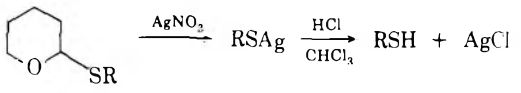
Substitution reactions using **1** with ethyl 2-bromopropionate, *n*-butyl bromide, and benzyl chloride provided the expected products **8**, **9**, and **10**, respectively.



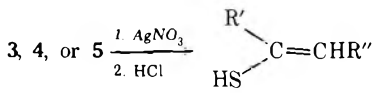
**8**, R′ = $CH_3$; R″ = $CO_2Et$; X = Br
**9**, R′ = *n*-$C_3H_7$; R″ = H; X = Br
**10**, R′ = Ph; R″ = H; X = Cl

Having established that the thiol reacts in the expected ways to provide a series of thio ethers, it was then necessary to demonstrate that cleavage to the free mercaptan could be accomplished in satisfactory yield. In contrast to the facile cleavage of acetals by hydrochloric acid, mercaptals and monothioacetals are generally more resistant to this acid.[6,7] The use of silver nitrate to form the mercaptide of a monothioacetal has been reported.[8]

During our preliminary attempts to cleave the 2-tetrahydropyranyl sulfides, including the heterocyclic system discussed below, this resistance to mild acid treatment was borne out. Most systems were resistant to aqueous, ethanolic or gaseous hydrogen chloride and aqueous or ethanolic *p*-toluenesulfonic acid. However, the silver salts of the mercaptans are easily obtained by addition of an equivalent amount of aqueous silver nitrate to a methanolic solution of the sulfide. The precipitated mercaptide is then suspended in chloroform through which excess gaseous hydrogen chloride is passed. After filtration of silver chloride the mercaptan is recovered from the chloroform.

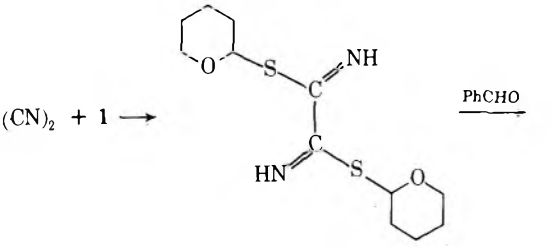


In the case of enethiols derived from cleavage of the addition of **1** and acetylenic compounds there was no evidence

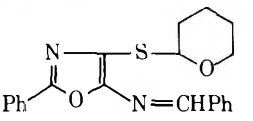


for the formation of tautomeric thioketones or thio aldehydes. With these substances, all of which contain substituents expected to stabilize the enethiol tautomer, this is not surprising. Since preparation of protected enethiols appears to be one of the more useful applications of **1** we plan to conduct a more complete study of such substances and their cleavage products.

The potential use of the reagent is further illustrated by preparation of the protected mercapto oxazole **12**. Previous reactions with dialkyl and diaryl dithiooxaldiimidates[9] provided alkyl- or arylmercaptooxazoles which could not possibly provide the free thiol. Reaction of **1** with cyanogen provided the expected thioimidate **11**, which was too unstable to be characterized completely. However, it reacted with benzaldehyde in the usual way to give the fully characterized heterocyclic product **12**. This and other uses of the reagent are the subject of continuing studies.



**11**



**12**

**Acknowledgment.** The authors wish to acknowledge the technical assistance of Steve Foreland and L. E. Harris.

**Registry No.**—**1**, 40446-64-8; **2**, 51380-90-6; *cis*-**3**, 51380-91-7; *trans*-**3**, 51380-92-8; *cis*-**4**, 51380-93-9; *trans*-**4**, 51380-94-0; *cis*-**5**, 51380-95-1; *trans*-**5**, 51380-96-2; **6**, 51380-97-3; **7**, 51380-98-4; **8**, 51380-99-5; **9**, 16315-52-9; **10**, 1927-50-0; **11**, 51464-54-1; **12**, 51381-00-1; hydrogen sulfide, 7783-06-4; 2,3-dihydropyran, 110-87-2; ethyl propiolate, 623-47-2; dimethyl acetylenedicarboxylate, 762-42-5; phenylacetylene, 536-74-3; dimethyl mercaptofumarate, 51381-01-2; *cis*-ethyl 3-mercaptopropenoate, 51381-02-3; *trans*-ethyl 3-mercaptopropenoate, 51381-03-4; *cis*-2-phenylethenethiol, 51381-05-6; *trans*-2-phenylethenethiol, 51381-04-5; styrene, 100-42-5; diethyl mercaptosuccinate, 23060-14-2; 2-phenylethanethiol, 4410-99-5; ethyl 2-bromopropionate, 535-11-5; 1-bromobutane, 109-65-9; α-chlorotoluene, 100-44-7.

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# Antileukemic Pseudoguaianolides from *Hymenoxys grandiflora* (T. & G.) Parker. Application of Lanthanide-Induced Shifts to Structure Determination[1,2]

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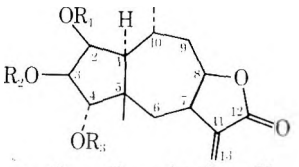
*Received January 21, 1974*

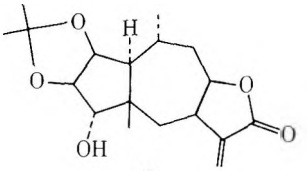
*Hymenoxys grandiflora* (T. & G.) Parker yielded three new pseudoguaianolides, hymenograndin, florigrandin, and hymenoflorin, and the previously known pseudoguaianolide glucoside paucin. Structures and stereochemistry of the new compounds were established by a combination of chemical transformations and physical methods. In particular, the stereochemistry of hymenograndin at C-4 was deduced by interpreting lanthanide-induced shifts using the modified McConnell equation. Structure determination of hymenoflorin and florigrandin which were correlated required nmr spectrometry at 270 MHz. Hymenoflorin exhibited significant *in vivo* activity against L-1210 lymphocytic leukemia, paucin against P-388 leukemia.

The genus *Hymenoxys* is rich in sesquiterpene lactones of the pseudoguaianolide and modified pseudoguaianolide type.[3-5] In the present communication we report the isolation and structure determination of three new pseudoguaianolides, **1a**, **5a**, and **6a**, which we have named hymenograndin, florigrandin, and hymenoflorin, from *Hymenoxys grandiflora* (T. & G.) Parker (old-man-of-the-mountain). This is a previously uninvestigated species which enjoys a brief flowering period in the alpine tundra of the Rocky Mountains during July and early August. The known[3,4,6] pseudoguaianolide glucoside paucin (**11**) was also found.[7]

Hymenograndin, $C_{19}H_{26}O_7$, mp 153–154°, $[\alpha]D$ +80.7°, the least polar constituent, had a tendency to form solvates, which complicated determination of the empirical formula and initially interfered with interpretation of the nmr spectrum. It was a diacetate (high-resolution mass spectrum, two three-proton resonances at 2.08 and 2.03 ppm) and had a free hydroxyl group (ir spectrum, conversion to a triacetate **1b**). The nmr spectrum also exhibited the typical doublets of an exocyclic methylene group conjugated with a lactone function (H-13a and H-13b of formula **1**), a multiplet near 4.8 ppm, presumably the signal of hydrogen under the lactone ether oxygen which remained stationary during acetylation while a doublet originally at 3.62 ppm (hydrogen under a secondary hydroxyl group) moved downfield into a two-proton cluster in the range 4.8–5.1 ppm (hydrogens under the acetates, assignment confirmed by hydrolysis to **1c** which resulted in the expected upfield shift). Since the two esterified secondary hydroxyl groups, one free secondary hydroxyl group, and the lactone function accounted for all the oxygen atoms of the empirical formula, the absence of additional double bonds and the presence, in the nmr spectrum, of a methyl singlet at 0.97 ppm and a methyl doublet at 1.08 ppm indicated that hymenograndin was an eudesmanolide or a pseudoguaianolide.



**1a**, $R_1 = R_2 = Ac$; $R_3 = H$
**b**, $R_1 = R_2 = R_3 = Ac$
**c**, $R_1 = R_2 = R_3 = H$



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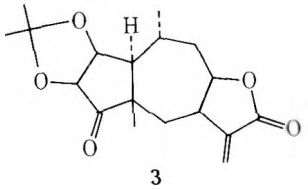

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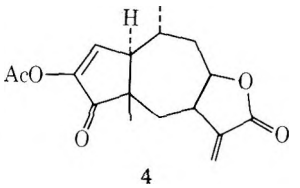

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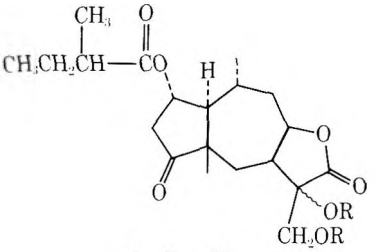
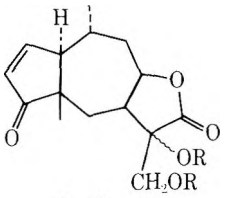
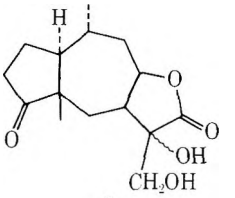


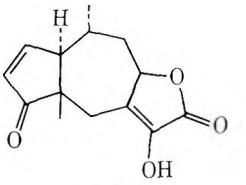
**5a**, R = H
**b**, R = Ac



**6a**, R = H
**b**, R = Ac
**c**, R = $B_2$



**8**



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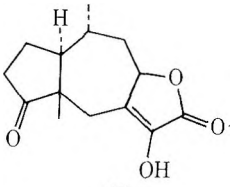

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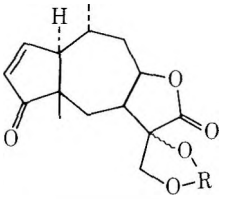
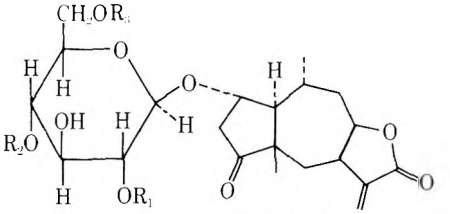


**7a**, R = >CHCH$_3$
**b**, R = O=S



**11**. $R_1 = R_2 = H$; $R_3 = Ac$
or $R_1 = R_3 = H$; $R_2 = Ac$
or $R_2 = R_3 = H$; $R_1 = Ac$

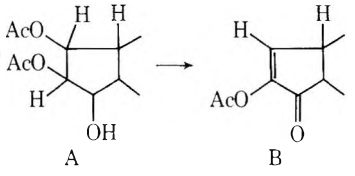
Acid hydrolysis of hymenograndin in aqueous acetone or treatment of **1c** with acetone–toluenesulfonic acid afforded an acetonide **2** whose nmr spectrum (see Experimental Section) indicated that only the newly freed hydroxyl groups but not the hydroxyl group originally present in

**Table I**
**Nmr Spectrum of 2[a]**

| | | |
|---|---|---|
| H-1 | 6.79 | $J_{1,10} = 11.5$ |
| H-2 | 9.93 | $J_{1,2} = 6.6$ |
| H-3 | 15.93 | $J_{2,3} = 8.0$ |
| H-4 | 14.68 | $J_{3,4} = 4.9$ |
| H-6$\alpha$ | 6.79 | $J_{6\alpha,6\beta} = 14 \pm 0.5$, $J_{6\alpha,7} = 4 \pm 0.5$ |
| H-6$\beta$ | 4.26 | $J_{6\beta,7} = 15.5 \pm 0.5$ |
| H-7 | 5.17 | $J_{7,13a} = 2.4$, $J_{7,13b} = 2.2$ |
| H-8 | 6.67 | $J_{7,8} = 8 \pm 0.5$ |
| H-9$\alpha$ | 4.18 | $J_{8,9\alpha} = 4 \pm 0.5$, $J_{9\alpha,9\beta} = 13.4 \pm 0.5$ |
| H9$\beta$ | *b* | $J_{8,9\beta} = 11 \pm 0.5$ |
| H-10 | 4.82 | $J_{9\beta,10} \leq 0.7$, $J_{9\beta,10} \leq 6$ |
| H-13a | 4.06 | $J_{10,14} = 6.6$ |
| H-13b | 6.42 | $J_{13a,13b} \leq 0.2$ |
| H-14[c] | 3.43 | |
| H-15[c] | 5.40 | |
| Acetonide methyls[c] | 5.91, 7.31 | |
| OH | 23.7 | |

[a] Run at 90 MHz in $CDCl_3$ with TMS as internal standard at $Eu(DPM)_3$ concentrations of 0, 0.16, 0.36, 0.41, 0.80, and 0.95 mol/mol of **2**. Chemical shifts are those observed in the 0.95 *M* solution; coupling constants (hertz) were determined by direct observation or double irradiation in whatever solution gave the best separation of the signals being observed. [b] Not determined. [c] Three protons.

hymenograndin had participated in acetal formation. Oxidation of **2** resulted in genesis of a cyclopentanone **3** (lactone and ketone bonds superimposed at 1760 $cm^{-1}$); the accompanying downfield shifts of the ether signals and their appearance (AB system in which B but not A was coupled to a third proton C) suggested that formation of the acetonide involved oxygens $\alpha$ and $\beta$ to the new carbonyl function, *i.e.*, that hymenograndin possessed partial structure A where the acetate functions must be cis. Confirmation for this inference was provided by the transformation of **1a** with chromic acid to an $\alpha$-acetoxy-$\alpha,\beta$-unsaturated cyclopentenone of type B ($\lambda_{max}$ 240 nm, new infrared frequencies at 1720 and 1610 $cm^{-1}$, replacement of the two-proton cluster of A near 5 ppm by a one-proton doublet at 7.00 ppm) as the result of $\beta$-elimination of acetic acid.



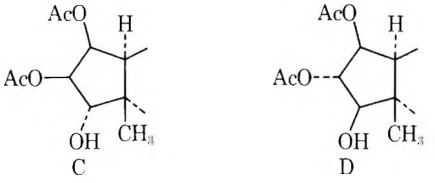

The complete structural formula of hymenograndin was deduced by extensive spin-decoupling studies on the acetonide **2** at various concentrations of the lanthanide shift reagent $Eu(DPM)_3$.[8] The results, presented in Table I, were obtained in the usual way; *i.e.*, irradiation at the frequencies of H-13a and H-13b permitted identification of H-7 and irradiation at the frequency of H-7 established the presence of an adjoining methylene group, neither one of whose protonic components (rendered visible at higher concentrations of shift reagent) was coupled to other protons, and established the remaining vicinal proton as the proton under the lactone ether oxygen (H-8). Irradiation at the frequency of the latter not only collapsed the H-7 signal, but established the presence of neighboring H-9$\alpha$ and H-9$\beta$. The chemical shift of H-10, close to that of H-9$\alpha$ and H-9$\beta$ at low concentrations of shift reagent, was established by irradiation at the frequency of the methyl doublet; observation of H-10 and one of the H-9 protons (H-9$\alpha$) at high concentrations of shift reagent permitted determination, by irradiation at the frequency of H-8, of the values of $J_{8,9\alpha}$, $J_{9\alpha,10}$, $J_{9\alpha,9\beta}$, and $J_{9\beta,10}$.

Samek's rule[9] that $J_{7,13}$ trans $\geq 3$ Hz $\geq J_{7,13}$ cis indicated that the lactone ring of hymenograndin was cis fused; if H-7 is $\alpha$ as in all pseudoguaianolides of authenticated stereochemistry, this is in agreement with the observation of a negative Cotton effect at 255 nm associated with the $n,\pi^*$ transition of a cis-fused, $\alpha,\beta$-unsaturated lactone closed to C-8.[11] Construction of Dreiding models and comparison of the observed coupling constants with those predicted from the dihedral angles of the models led to the conclusion that the observed coupling constants are best satisfied if the seven-membered ring assumes a boat conformation in which the cis-lactone ring is somewhat flexible and if H-1 and C-10 methyl are $\alpha$, as in all other pseudoguaianolides from *Helenium* and related species.

The remaining problem was the stereochemistry at C-2, C-3, and C-4, which, because only the C-2 and C-3 hydroxyl groups formed an acetonide, had to be either that shown in C or in D. Knowledge of the coupling constants involving H-1, H-2, H-3, and H-4 was not sufficient to decide between these alternatives. However, development of a method based on the quantitative prediction of lanthanide shifts[13] using the modified McConnell equation[14]

$$\left(\frac{\Delta H}{H}\right)_i = \frac{K(3\cos^2\chi_i - 1)}{r_i^3} \qquad (1)$$

so as to determine the configuration of a hymenograndin derivative capable of coordinating with the ion appeared to have promise.[15,16] The best for this purpose of the available derivatives of hymenograndin appeared to be **2** because of the expectation that it would form a single coordination complex involving only the alcohol oxygen atom.[17]




To provide a basis for using the method of lanthanide-induced shifts to the determination of the configuration of hymenograndin, we decided to determine initially how well eq 1 correlated with the lanthanide-induced shifts of 26 protons, not subject to contact shift, in four model compounds studied by Demarco and coworkers[18] (their compounds 1-4). These data were also useful for evaluating the model necessary for the computations.

The assumption was made that the complex formed between $Eu(DPM)_3$ and **2** would be similar in geometry and interaction kinetics to the complexes formed between $Eu(DPM)_3$ and the four compounds studied by Demarco, *et al.* It was also assumed that there would be either free rotation about the O–C* bond of the complex or that complexes would be formed between $Eu(DPM)_3$ and all rotational isomers of the alcohol. Since in all instances reported so far chemical exchange has been faster than nmr time, the mathematical treatment of both possibilities would be the same. To allow for easier computation, the rotational capability was treated in terms of two static models, one corresponding to closest approach of the europium atom and the proton in question, the other to the greatest distance between the europium, while still coordinated, and the same proton.

The computer program was written[19] such that the spatial parameters needed were the C*-O-$H_i$ angle, the O-$H_i$ bond distance, and an initial estimate of both the C*-O-Eu angle and the Eu-O distance. Conversion of input data to the two europium positions is accomplished within the program by trigonometric manipulation. Use was made of Dreiding models and other published data[20] to obtain initial estimates of the C*-O-Eu angle (125°) and the Eu-O distance (2.50 Å) in the complexes. These estimates were substituted in eq 1 to calculate individual values of $K$ for the 26 protons, not subject to contact shift, listed by Demarco, *et al.*[18] The standard deviation of an individual result for $K$ was calculated from the set of $K$'s generated using the initial estimates of europium angle and distance. A small increment (0.035 radian and 0.1 Å, respectively) was then added to angle and distance and a new set of $K$'s was calculated. The process was continued on an iterative basis until a minimum standard derivation for $K$ had been reached; further refinement was performed using incremental values of 0.0035 radian and 0.01 Å. This process yielded 1530 as a value for $K$ with a standard deviation of 11% and values of 139° for the angle and 4.19 Å for the distance.

Spectra of **2** were measured at 90 MHz using $CDCl_3$–TMS solutions containing 0, 0.16, 0.36, and 0.41 mol of $Eu(DPM)_3$ per mole of **2**. Since exchange was more rapid than nmr time, the spectra contained only a single time-averaged set of resonances for **2** and its complexed form. Only a limited number of signals could be followed over the range of shift concentrations. These are listed in Table II; assignments were confirmed by double irradiation as discussed earlier.

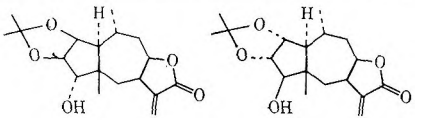
The magnitude of induced shift was measured at each $Eu(DPM)_3$ concentration and a linear least-squares fit for the data was obtained. Following convention, the induced shift was extrapolated to a 1:1 mole ratio of shift reagent compared with shifts calculated by using the values of $K$, Eu-O distance, and Eu-O-C* angle obtained from the four model compounds and by using C(4)-O-$H_i$ angles and O-$H_i$'s measured from models of **2** (based on C, column 3) and **2′** (based on D, column 5).

While the agreement between calculated and observed shifts for H-3 and H-4 is somewhat less than was hoped for and the differences between the two sets of calculated values are, on the whole, not great, one significant datum emerges immediately on inspection of Table II. The observed shift of the C-5 methyl group, in close proximity to the hydroxyl group on C-4, is reasonably close to that predicted for formula **2**, while vastly different from the value predicted for formula **2′**. Consequently, we feel that there is little doubt that the C-4 hydroxyl group of **2** is $\alpha$ and that hymenograndin is correctly represented by formula **1a**.

Contrary to our previous experience with lanthanide-induced shifts of $\alpha,\beta$-unsaturated lactones, the observed shifts of the exo-methylene protons H-13a and H-13b of **2** were upfield, as were the values calculated for these protons. Although the numerical agreement was not particularly good for H-13a, the circumstance that the upfield shifts predicted by the method were in fact observed experimentally lends credibility to the chosen model and to the assumptions that were employed.

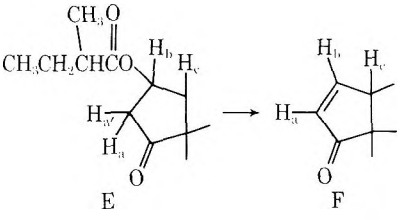
Florigrandin, $C_{20}H_{30}O_7$, mp 173–175°, and hymenoflorin, $C_{15}H_{20}O_5$, mp 197–199°, are conveniently discussed together since treatment of the former with acetone-HCl (or preparative tlc of florigrandin) resulted in conversion to the latter by $\beta$-elimination of a saturated five-carbon ester side chain. While florigrandin was a saturated ketone ($\lambda_{max}$ 282 nm, $\epsilon$ 120), hymenoflorin was clearly an $\alpha,\beta$-unsaturated cyclopentenone of type F because of its ir bands at 1700 and 1574 $cm^{-1}$, the uv spectrum ($\lambda_{max}$ 217.5 nm), and the typical nmr doublets of doublets at 7.76 ($\beta$ proton) and 6.06 ppm ($\alpha$ proton) which disappeared on catalytic hydrogenation to dihydrohymenoflorin (**8**). In the nmr spectrum of florigrandin these signals were replaced by a multiplet at 5.11 ppm which represented the proton at the point of attachment of the ester side chain, undoubtedly at the $\beta$ position of the cyclopentanone ring as in E (for confirmation, *vide infra*).

**Table II**
**Lanthanide-Induced Shifts of 2**

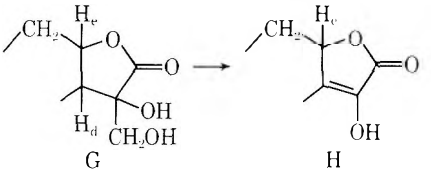


2 2′

| Proton | $\Delta_{obsd}$ | $\Delta\delta_{calcd}$ | Difference | $\Delta\delta_{calcd}$ | Difference |
|---|---|---|---|---|---|
| H-2 | 6.4 | 6.8 | 0.4 | 6.8 | 0.4 |
| H-3 | 12.8 | 16.2 | 3.4 | 15.6 | 2.8 |
| H-4 | 11.7 | 15.1 | 3.4 | 15.7 | 3.0 |
| C-5 Me | 6.4 | 7.1 | 0.7 | 17.0 | 10.6 |
| C-10 Me | 2.7 | 3.1 | 0.4 | 3.4 | 0.7 |
| H-13a | −1.6 | −4.0 | 2.4 | | |
| H-13b | −0.1 | −0.7 | 0.8 | | |
| Acetonide | 5.1 | 3.4 | −1.7 | 3.3 | −1.8 |
| Me | 5.2 | 3.5 | −1.7 | 4.3 | −0.9 |



E F



G H

The nature of the five carbon ester side chain was not immediately evident from the nmr spectrum of florigrandin, as its signals, regardless of solvent, were superimposed on those of a methyl singlet and a methyl doublet also displayed in the nmr spectra of hymenoflorin and its derivatives. However, use of chemical shift reagents demonstrated that the side chain gave rise to a methyl doublet and a methyl triplet, thus identifying florigrandin as a 2-methylbutanoyl ester of type E.

Florigrandin and hymenoflorin were diols (ir spectra, conversion to diacetates). The nmr spectra revealed an AB quartet near 3.6 ppm which was shifted downfield on transformation to the diacetates **5b** and **6b**. Hence the grouping $R_3C\text{-}CH_2OH$, where $R \neq H$, was present. The absence of other paramagnetic shifts as the result of acetylation indicated that the second hydroxyl group was tertiary and, because of the facility with which it underwent acetylation, $\alpha$[21] to the $\gamma$-lactone group (ir band near 1770 $cm^{-1}$). Hence a plausible partial structure was G.

Confirmation for the presence of the $\alpha$-glycol function G was provided by the formation, from hymenoflorin, of an ethylidene derivative **7a** and a thiocarbonate **7b** in whose nmr spectra all signals except those of the $-CH_2OH$ group were essentially unchanged. Moreover, periodate oxida-

tion of hymenoflorin and dihydrohymenoflorin resulted in transformation to norenol lactones of type H. This was accompanied by a paramagnetic shift and simplification of a complex signal, previously found near 4.78 ppm, to a triplet at 5.25 ppm. Hence the lactone ring of florigrandin and hymenoflorin must be closed to C-8 if these substances are pseudoguaianolides like hymenograndin and they can be formulated as **5a** and **6a**, respectively, exclusive of stereochemistry.

This conclusion was confirmed by extensive spin decoupling experiments on **6b** at 90 and 270 MHz which provided the data[22] reproduced in Table III and permitted independent deduction of the carbon skeleton of hymenoflorin and thereby that of florigrandin.

With respect to the stereochemistry, the CD curve of hymenoflorin exhibited the strong negative Cotton effect near 325 nm characteristic of the trans-fused cyclopentenone system and absolute stereochemistry (H-1$\alpha$, C-5 methyl $\alpha$) depicted in the formula, an inference supported by the inversion of the Cotton effect which accompanied

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## EXPERIMENTAL[25]

Extraction of Hymenoxys grandiflora. -- A) Dried and ground Hymenoxys grandiflora (T. & G.) Parker, wt. 1.1 kg, collected by Dr. B. H. Braun on August 2, 1962 on the tundra off Trail Ridge Drive, Rocky Mountain National Park, with permission of the National Park Service, was extracted with chloroform and worked up in the usual way.[26] The crude gum, wt. 47 g, was chromatographed over 500 g of silicic acid (Mallinckrodt 100 mesh), 300 ml fractions being collected. *Elution with benzene to benzene-$CHCl_3$ (1:3; fractions 1-7) gave 2.8 g of gummy* mixture. Elution with benzene-$CHCl_3$ (1:3) to $CHCl_3$ (fractions 8-23) gave 10.5 g of crude hymenograndin (1a) which was recrystallized from acetone-ether, mp 149-150°, $[\alpha]_D$ +80.7° (C 1.48). Hymenograndin formed solvates with ethyl acetate and acetone which initially complicated interpretation of the nmr spectrum. However, repeated recrystallization from methanol-water eliminated the problem and furnished crystals which melted at 153-154°, uv $\lambda_{max}$ 213 nm (ε 14000), ir bands at 3490 *(hydroxyl)*, 1750 *(γ-lactone)*, 1734, 1712 *(ester)* and 1650 $cm^{-1}$ *(double* bond), nmr signals (90 MHz, $CDCl_3$) at 4.83-5.08 ppm (2 overlapping protons, H-2 and H-3), 3.62d (5.0, H-4), 3.19m (H-7), 4.77m (H-8), 5.62d (2.0) and 6.27d (2.5, H-13), 1.08d (6.5, H-14), 0.97 (H-15), 2.08 and 2.03 (acetates), CD curve (0.7 mg/ml), $[\theta]_{300}$ 0; $[\theta]_{275}$ -1550; $[\theta]_{265}$ -2790; $[\theta]_{255}$ -3450 (min); $[\theta]_{240}$ -1730; $[\theta]_{236}$ 0; $[\theta]_{230}$ +920 (last reading).

Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.68; H, 7.15; O, 30.57; MW 366. Found: C, 62.88; H, 7.14; O, 30.71; MW *(chemical ionization)*, 366.

*The high resolution* mass spectrum of hymenograndin lacked a peak corresponding to the molecular ion, but exhibited significant peaks at 324.1587 (2.5%, M-$C_2H_2O$), 306.1436 (base peak, M-$C_2H_4O_2$), 264.1354 (75%, M-$C_2H_2O$-$C_2H_2O$) and 246.1248 (65.2%, M-2$C_2H_4O_2$).

Elution with $CHCl_3$-MeOH (99:1, fractions 24-27) gave a gummy mixture. Elution with $CHCl_3$-MeOH (97:3, fractions 28-29) gave 1.67 g of crude florigrandin which after recrystallization from acetone-ether had mp 173-175°, $[\alpha]_D$ 187° (C 1.44), ir bands at 3380, 3295 (hydroxyls), 1768 (γ-lactone) and 1734 $cm^{-1}$ (double intensity, ester and cyclopentanone, uv $\lambda_{max}$ 282 nm (120), nmr signals (90 MHz, $CDCl_3$) at 5.11td ($\delta^{27}$,$\delta^{27}$,$J^{27}$, H-2), 3.23dd ($J^{27}$,$\delta^{27}$,H-3a), 2.01dd ($J^{27}$,$J^{27}$,H-3b), 4.74m (H-8), 3.75br (2p, H-13, *split into AB quartet centered at 4.26 ppm in pyridine-$d_5$*), 1.16d (7, H-14), 1.06 (H-15), 1.19d (7) and 0.91t (7 methyls of ester side chain).

Anal. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91; O, 29.28; MW, 382. Found: C, 63.64; H, 7.67; O, 29.09; MW (mass spectrometry), 382.

Other significant peaks in the mass spectrum of florigrandin were 364 (M-$H_2O$), 352 (M-$CH_2O$), 325 (M-$C_4H_9$), 280 (M-$C_5H_{10}O_2$), 265 (M-$C_5H_{10}O_2$-$CH_3$), 262 (M-$H_2O$-$C_5H_{10}O_2$).

Fraction 30 ($CHCl_3$-MeOH, 97:3) gave a gummy mixture. Further elution with the same solvent (fractions 31 and 32) gave 8.2 g of crude hymenoflorin which was recrystallized from acetone and then had mp 197-199°, $[\alpha]_D$ -54.3° (C 0.92), ir bands at 3540-3700 (broad hydroxyl), 1772 (γ-lactone), 1700 and 1574 $cm^{-1}$ (cyclopentenone), uv $\lambda_{max}$ 217.5 nm (ε 9050), CD curve (0.49 mg/ml), $[\theta]_{380}$ 0; $[\theta]_{350}$ -2850; $[\theta]_{325}$ -5420 (min); $[\theta]_{300}$ -2660; $[\theta]_{275}$ -570 (max); $[\theta]_{250}$ -2090 (last reading), nmr signals (90 MHz, DMSO-$d_6$) at 7.76dd (6.0, 1.5, H-2), 6.06dd (6.0, 2.8, H-3), 4.78m (H-8), 3.5br (2p, H-13), 1.23d (6.5, H-14), 1.08 (H-15), 5.15t (6.0, -$CH_2OH$, disappears on $D_2O$ exchange), 5.07 (3° OH, disappears on $D_2O$ exchange).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; O, 28.54; MW, 280 Found: C, 65.22; H, 6.90; O, 28.29; MW, 280.

Other significant peaks in the mass spectrum were 265 (M-$CH_3$), 250 (M-$CH_2O$), 249 (M-$CH_2OH$), 235 (M-$CH_3$-$CH_2O$) and 232 (M-$CH_2O$-$H_2O$).

Further elution with $CHCl_3$-MeOH (93:7 and 19:1, fractions 33-36) gave a gummy mixture. MeOH-$CHCl_3$ (19:1, fractions 37-40) gave 2.5 g of crude paucin mp 144-146°, $[\alpha]_D$ +19.2° (C 0.625), ir 1760 and 1655 (unsaturated lactone), 1730 (acetate), 1720 and 1610 $cm^{-1}$ (cyclopentenone), uv $\lambda_{max}$ 214 and 240 nm (ε 11000 and 5400), nmr signals (60 MHz) at 7.00d (1.5, H-2) 3.32m (H-7), 4.70 m (H-8), 5.55d (2.0) and 6.16d (2.5, H-13), 1.23d (6.0, H-14), 1.23 (H-15), 2.21 ppm (acetate).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; O, 26.28; MW, 304.1310 Found: C, 67.12; H, 6.64; O, 26.26; MW, 304.1332.

Other significant peaks in the mass spectrum were at 262.1210 (base peak, M-$C_2H_2O$), 244.1091 (11.5%, M-$C_2H_4O_2$) and 234.1245 (24.5%, M-$C_2H_2O$-CO).

Diacetylflorigrandin (5b). -- Acetylation of 0.1 g of 5a in 1 ml of pyridine with 0.6 ml of acetic anhydride at room temperature overnight and work-up in the usual way afforded 0.12 g of crude 5b which was recrystallized from ethyl acetate, mp 161°, $[\alpha]_D$ +75° (C 1.00), nmr signal (90 MHz, $CDCl_3$), at 5.12td (8, 8, 7, H-2), 3.25dd (19.5, 8, H-3a), and 2.08m (H-3b), 2.6m (H-7), 4.74m (H-8), 4.34 (center of AB quartet, $J$ = 11, H-13), 1.17d (6.5, H-14), 1.01 (H-15), 1.20d and 0.92t (methyls of side chain).

Anal. Calcd for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35; O, 30.86; MW, 466 Found: C, 61.02; H, 7.44; O, 30.95; MW, 466.

Other significant peaks in the mass spectrum were 451 (M-$CH_3$), 437 (M-$C_2H_5$), 424 (M-$C_2H_2O$), 409 (M-$C_4H_9$), 406 (M-$C_2H_4O_2$), 394 (M-$C_2H_2O$-$CH_2O$), 382 (M-2$C_2H_2O$), 364 (M-$C_5H_{10}O_2$), 346 (M-2$C_2H_4O_2$), 322 (M-$C_5H_{10}O_2$-$C_2H_2O$), 304 (M-$C_5H_{10}O_2$-$C_2H_4O_2$), 280 (M-$C_5H_{10}O_2$-2$C_2H_2O$), 262 (M-$C_5H_{10}O_2$-$C_2H_2O$-$C_2H_4O_2$), 244 (M-$C_5H_{10}O_2$-2$C_2H_4O_2$).

Conversion of Florigrandin to Diacetylhymenoflorin. -- A solution of 0.045 g of 5a in 2 ml of MeOH and 0.6 ml of conc HCl was stirred at room temperature overnight, *diluted with water and extracted with ethyl acetate. The washed* and dried extract was *evaporated in vacuo and the residue was acetylated with* acetic anhydride-pyridine in the usual manner. Purification by preparative tlc yielded a gummy product which was identical in every respect with authentic 6b.

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which was recrystallized from acetone, mp 177-179°, identical in all respects with material previously isolated from Hymenoxys odorata DC.[3]

B) Repetition of the extraction with 9 kg of H. grandiflora collected by Professor F. R. Stermitz on July 6, 1972 in Rocky Mountain National Park 1/2 mile off Trail Ridge Road at an altitude of 11000 ft with permission of the National Park Service (FRS-42 on deposit in herbaria of Colorado State University and Florida State University) gave 200 g of crude gum which partially crystallized on standing. Chromatography over 3.4 kg of silicic acid gave 80 g of hymenograndin, 3.2 g of florigrandin, 6.2 g of hymenoflorin and 3.2 g of paucin.

Hydrolysis of Hymenograndin. -- A solution of 0.2 g of 1a in 1.5 ml of methanol and 5 ml of water containing 0.385 g of $Na_2CO_3$ was allowed to stand at room temperature for 20 min, diluted with water, acidified with dil. HCl and extracted with ethyl acetate. The washed and dried extract was concentrated and the residue was chromatographed over silica gel. Elution with $CHCl_3$-MeOH (9:1) gave 1c as a colorless gum which could not be crystallized, mol. wt. (mass spectrum) 282, calcd for $C_{15}H_{22}O_5$, 282; nmr peaks (60 MHz, acetone-$d_6$), complex system of 3 protons in range 4.35-3.40 ppm (H-2, H-3 and H-4), 3.07m (H-7), 4.72m (H-8), 5.52d (2) and 5.97 (2.5, H-13), 1.18d (6.0, H-14), 0.83 (H-15).

Acetylation of 0.21 g of 1c with pyridine-acetic anhydride at room temperature and work-up in the usual way gave a gum which was chromatographed over 5 g of silica gel. Elution with benzene-chloroform (1:1) gave a triacetate 1b, wt. 0.185 g, which could not be induced to crystallize and was identical with material prepared by *direct acetylation of* 1a, $[\alpha]_D$ +76.9 (C 1.30), *ir bands* ($CHCl_3$) at 1768, 1750 (very strong) and 1668 $cm^{-1}$ (double bond), nmr signals (60 MHz, $CDCl_3$) complex system of 3 protons in range 4.90-5.30 ppm (H-2, H-3 and H-4), 3.17m (H-7), 4.73m (H-8), 5.50d (2.0) and 6.17d (2.5, H-13), 1.07d (6.5, H-14), 1.00 (H-15), 1.97, 2.03, 2.08 (acetates).

Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91; O, 31.34. Found: C, 61.62; H, 6.98; O, 31.50.

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Treatment of 1c with acetone-toluenesulfonic acid gave a quantitative yield of the acetonide 2 (vide infra).

Preparation of 2. -- A solution of 0.315 g of 1a in 4 ml of acetone-water (1:1) and 10 ml of conc. HCl was allowed to stand at room temperature overnight, diluted with water and extracted with ethyl acetate. The washed and dried solvent was evaporated; the residue (2) was recrystallized from ethyl acetate, mp 168.5-170°, $[\alpha]$ +80.9° (C 1.05), ir bands ($CHCl_3$) at 3640, 3585 (OH), 1754 and 1658 $cm^{-1}$ (conjugated γ-lactone), nmr signals (90 MHz, $CDCl_3$) 4.26dd (6.5, 8, H-2), 4.41dd (8, 5, H-3), 3.76d (5, H-4), 3.21m (H-7), 4.77m (H-8), 6.26d (2.4, H-13a), 5.59d (2.2, H-13b), 1.13d (6.5, H-14), 0.92 (H-15), 1.49 and 1.29 (acetonide methyls).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13; O, 24.81. Found: C, 66.78; H, 8.25; O, 25.18.

Oxidation of 0.096 g of 2 in 1 ml of pyridine by treatment with 0.086 g of $CrO_3$ in 1 ml of pyridine overnight followed by dilution with water, extraction with *ethyl acetate and concentration of the washed and dried extract in vacuo* gave 0.087 g of 3 which was recrystallized from ethyl acetate, mp 178.5-180°, $[\alpha]_D$ +58.3° (C 1.235), ir bands ($CHCl_3$) at 1760 (strong, lactone and cyclopentanone) and 1661 $cm^{-1}$, nmr signals (90 MHz, $CDCl_3$) at 4.58t (8.0, H-2), 4.89d (8.0, H-3), 3.10m (H-7), 4.80m (H-8), 5.71d (2.0) and 6.27d (2.5, H-13), 1.25d (6.5, H-14), 1.09 (H-15), 1.36 and 1.48 (methyls of acetonide).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; O, 24.97. Found: C, 66.90, H, 7.27; O, 24.81.

Oxidation of Hymenograndin. -- A solution of 0.25 g of 1a in 2 ml of pyridine was allowed to stand at room temperature with 0.23 g of $CrO_3$ in 1.5 ml of pyridine for 2 days. The work-up described in the previous paragraph gave a gum which was chromatographed over 5 g of silica gel. Elution with benzene-chloroform (4:1) gave crystalline 4 which was recrystallized from ethyl acetate, was hydrogenated in the presence of 0.12 g of 10% Pd-C at room temperature and atmospheric pressure until hydrogen uptake ceased. Filtration followed by evaporation at reduced pressure gave solid, 8, wt. 0.215 g, which was recrystallized from acetone, mp 192-193°, $[\alpha]_D$ +72° (C 1.36), ir bands at 3450, 3365 (hydroxyls), 1770 (γ-lactone) and 1735 $cm^{-1}$ (cyclopentanone), nmr signals (60 MHz in DMSO-$d_6$) at 4.75m (H-8), 3.50 (2p, AB quartet of H-13 after addition of $D_2O$), 1.05d (5.0, H-14), 0.88 (H-15), 5.33t (6.0, *primary -OH*), 5.73 (*tertiary OH*), CD curve (0.3 mg/ml), $[\theta]_{350}$ 0; $[\theta]_{320}$ +56; $[\theta]_{295}$ +586 (max); $[\theta]_{275}$ +237, $[\theta]_{250}$ +13 (min); $[\theta]_{227}$ 42 (max), $[\theta]_{215}$ 0 (last reading).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85; O, 28.33; MW, 282. Found: C, 64.06; H, 7.51; O, 28.30; MW, 282.

Other significant peaks in the mass spectrum were at 252 (base peak, M-$CH_2O$) and 233 (M-$CH_3$-$CH_2O$).

*The gummy acetonide could not be induced to crystallize.*

Periodate Oxidations. -- A) A solution of 0.12 g of 6a in 2 ml of MeOH and 0.1 g of sodium metaperiodate in 1 ml of methanol and 0.3 ml of water was allowed to stand overnight, diluted with water and extracted with ethyl acetate. The washed and dried extract was evaporated and the solid residue (9) was recrystallized from acetone, yield 0.105 g, mp 247-249°, $[\alpha]_D$ -110° (C 1.22), *ir bands at* 3230 (hydroxyl), 1760 (α,β-unsaturated lactone, 1686 and 1575 $cm^{-1}$ (α,β-unsaturated cyclopentenone), uv $\lambda_{max}$ 231 nm (ε 21300), nmr signals (60 MHz, DMSO-$d_6$) at 8.00dd (6.0, 2.0, H-2), 6.32dd (6.0, 2.5, H-3), 5.25t (7.5, 6.0, H-8), 1.32d (6.0, H-14), 1.00 (H-15), 9.88br (enolic-OH).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50; O, 25.78 Found: C, 68.26; H, 6.29; O, 25.29.

B) Oxidation of 0.11 g of 8 with *sodium metaperiodate in the same manner* and recrystallization from acetone afforded the enol lactone 10, mp 217-219°, $[\alpha]_D$ +51° (C 1.09), ir bands at 3450, 3370 (hydroxyl), 1760 (unsaturated lactone) and 1734 $cm^{-1}$ (cyclopentanone), uv $\lambda_{max}$ 237 nm (ε 22400), nmr signals (90 MHz, DMSO-$d_6$) at 3.24d (15.2, H-6a), 4.94t (7, H-8) 1.20d (6.0, H-14), 0.98 (H-15).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25; O, 25.57 Found: C, 67.54; H, 7.27; O, 24.96.

Diacetylhymenoflorin (6b). -- Acetylation of 0.1 g of 6a with 0.4 ml of acetic anhydride and 1.5 ml of pyridine in the usual way followed by preparative tlc of the crude product gave a gum which could not be induced to crystallize, nmr signals (270 MHz) in Table III, ir bands at 1760 (γ-lactone), 1735 (ester), 1680 and 1575 $cm^{-1}$ (cyclopentenone).

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64; O, 30.73 Found: C, 62.08; H, 6.68; O, 30.73.

Dibenzoylhymenoflorin (6c). -- Benzoylation of 0.1 g of 6a with 0.18 g of benzoyl chloride in 2 ml of pyridine at 0° overnight followed by the usual work-up gave a gum which was purified by preparative tlc and had nmr signals (90 MHz, $CDCl_3$) at 7.5m (H-2, partially superimposed on 10 aromatic protons), 6.03dd (6.0, 2.5, H-3), 2.52dd (15, 4.5, H-6), 1.58t (15, 13.5, H-6), 3.06m (H-7), 4.88m (H-8 partially superimposed on H-13), 4.69 (center of AB quartet, $J$ = 11, H-13), 1.17d (H-14), 1.04 ppm (H-15), CD curve (0.28 mg/ml, MeOH), $[\theta]_{375}$ 0; $[\theta]_{350}$ -2190; $[\theta]_{325}$ -4720 (min); $[\theta]_{300}$ -2190; $[\theta]_{280}$ 0; $[\theta]_{250}$ -1950 (last reading).

Anal. Calcd for $C_{29}H_{28}O_7$ : C, 71.30; H, 5.78; O, 22.92; MW, 488.1 Found: C, 72.06; H, 5.45; O, 22.71; MW, 488.1835.

Other significant peaks in the mass spectrum were at 366.1031 (M-$C_7H_6O_2$) and 244.1046 (M-2$C_7H_6O_2$).

Preparation of 7a. -- A mixture of 0.075 g of 6a and 0.15 g of anhydrous zinc chloride in 4 ml of acetaldehyde was left overnight at room temperature, concentrated in vacuo and extracted with ethyl acetate. The washed and dried extracts were evaporated and the solid residue of 7a, wt. 0.07 g, was recrystallized *from ethyl acetate, mp 190-193°, $[\alpha]_D$ -57.8° (C 0.64), ir bands at 1783* (γ-lactone), 1706 and 1584 $cm^{-1}$ (cyclopentenone), nmr signals (60 MHz) at 7.55dd (6.0, 1.5, H-2), 6.18dd (6.0, 2.0, H-3), 4.81m (H-8), 4.08 (2p, center of AB quartet, H-13), 1.27d (6.0, H-14), 1.27 (H-15), 5.20q (5.0, methinyl of ethylidene), 1.49d (5.0, methyl of ethylidene).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11 Found: C, 66.25; H, 7.27; O, 26.30.

Preparation of 7b. -- Thionyl chloride (0.5 ml) was added dropwise with stirring to a solution of 0.11 g of 6a in 1.5 ml of pyridine at 0°. After an additional ten minutes, the mixture was poured into ice water and extracted with ethyl acetate. The washed and dried extracts were evaporated; the residual gum was *chromatographed over 5 g of silica gel.* Benzene-$CHCl_3$ (1:1) eluted solid 7b which was recrystallized from ether-ethyl acetate, mp 146-148°, $[\alpha]_D$ -55.6° (C 0.90), ir bands at 1790, 1710 and 1584 $cm^{-1}$, nmr signals (60 MHz, $CDCl_3$) at 7.40dd (6.0, 2.0, H-2), 6.02dd (6.0, 2.5, H-3), 4.77m (H-8), 4.70 (2p, center of AB quartet of H-13), 1.27d (5.0, H-14), 1.22 (H-15).

Anal. Calcd for $C_{15}H_{18}O_6S_2$: C, 55.20; H, 5.56; O, 29.41 Found: C, 54.80; H, 5.60; O, 29.47.

Dihydrohymenoflorin (8). -- A solution of 0.32 g of 6a in 20 ml of EtOAc

**Table III**
**Nmr Spectrum of 6b[a]**

| | | |
|---|---|---|
| H-1 | 2.22 m | $J_{1,10} \cong 10$[b] |
| H-2 | 7.51 dd | $J_{1,2} = 1.5$, $J_{2,3} = 6$ |
| H-3 | 6.08 dd | $J_{1,3} = 2.5$ |
| H-6$\alpha$ | 2.39 dd | $J_{6\alpha,6\beta} = 15$, $J_{6\alpha,7} = 4.5$ |
| H-6$\beta$ | 1.48 t | $J_{6\beta,7} = 13.5$ |
| H-7 | 2.74 m | $J_{7,8} = 7$ |
| H-8 | 4.77 septet | $J_{8,9\alpha} = 3.5$, $J_{8,9\beta} = 11$ |
| H-9$\alpha$ | 2.45 m | $J_{9\alpha,10} = 0.8$ |
| H-9$\beta$ | 2.66 m[c] | |
| H-10 | 2.05 m | $J_{10,14} = 6.5$ |
| H-13[d] | 4.31 br[e] | |
| H-14[f] | 1.26 d | |
| H-15[f] | 1.14 | |
| Acetates | 2.19, 2.09 | |

[a] Run at 270 MHz in $CDCl_3$ with TMS as internal standard. Signals are given in parts per million, coupling constants in hertz. Multiplicities are indicated by the usual symbols. [b] Estimate from line width of H-1 when H-2 and H-3 were decoupled. [c] $J_{9\beta,10}$ and $J_{9\alpha,9\beta}$ could not be determined satisfactorily. [d] Two protons. [e] Center of AB quartet. [f] Three protons.

reduction to dihydrohymenoflorin. Because of the large value of $J_{1,10}$, the C-10 methyl group must be $\alpha$ as is the case in all other pseudoguaianolides from *Hymenoxys* and related species. Hence the supposition that the C-7 side chain is $\beta$ oriented as in other substances of this type is logical.

Cis fusion of the lactone ring in hymenoflorin and florigrandin was deduced as follows. First, the observed coupling constants for the seven-membered rings of **2** and **6b** were astonishingly similar (see Tables I and III). Secondly, construction of Dreiding models of **6b** with cis- and trans-fused lactone rings revealed that the observed coupling constants are satisfied if ring B of **6b** is in the boat form of a cis-fused lactone, while several observed coupling constants are at variance with coupling constants predicted from the measured dihedral angles in the two chair forms of the cis-fused lactone and the somewhat flexible chair form and the boat form of a trans-fused lactone.

Double-resonance experiments on florigrandin established $J_{1,2}$, $J_{2,3a}$, and $J_{2,3b}$ as 8, 8, and 7 Hz, respectively, but the orientation of the C-2 ester side chain could not be deduced with certainty from this information. Conclusive evidence for the existence of a cis relationship between H-2 and the C-5 methyl group, *i.e.*, for the $\beta$ orientation of H-2, was provided by the demonstration of a relatively strong NOE arising from the spatial proximity of these two groups. Irradiation at the frequency of the C-5 methyl group produced, for **5b**, a 19.6% enhancement in the integrated intensity of H-2, but no enhancement in the intensity of the H-8 signal. The absence of an NOE between H-8 and the C-5 methyl group can be taken as additional evidence for a cis-lactone ring fusion.

The remaining problem, that of determining the stereochemistry at C-11, could not be solved satisfactorily. An attempt to use the method of Nakanishi and coworkers[23] for determining the configuration of acyclic diols failed when it was found that the CD curve of **6a** after addition of $Pr(dpm)_3$ did not exhibit new maxima of opposite sign and equal magnitude near 310 and 280 nm. In an attempt to apply the dibenzoate chirality rule,[24] which depends on the signs of two Cotton effects near 225 nm produced by two interacting benzoate chromophores, the dibenzoate **6c** was prepared and exhibited the expected physical properties. However, the CD curve could not be measured satisfactorily below 250 nm, although the usual minimum near 325 nm was seen due to the n, $\pi^*$ transition of the cyclopentenone chromophore.

**Acknowledgment.** We wish to thank Professor F. R. Stermitz (Colorado State University) for carrying out a large-scale collection of *Hymenoxys grandiflora*.

**Registry No.**—**1a**, 51292-55-8; **1b**, 51292-56-9; **1c**, 51292-57-0; **2**, 51292-58-1; **3**, 51292-59-2; **4**, 51292-60-5; **5a**, 51292-61-6; **5b**, 51292-62-7; **6a**, 51292-63-8; **6b**, 51364-37-5; **7a**, 51292-64-9; **7b**, 51292-65-0; **8**, 51292-66-1; **9**, 51292-67-2; **10**, 51292-68-3.

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(27) By spin decoupling.

# Synthesis of 5α-Cholesta-7,24-dien-3β-ol and Cholesta-5,7,24-trien-3β-ol[1]

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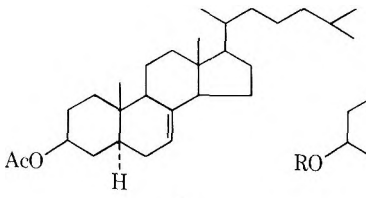
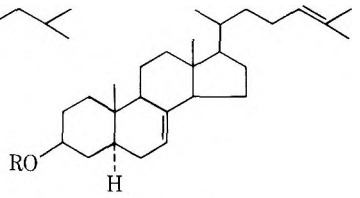
*Received January 17, 1974*

The title compounds were synthesized and were utilized for the identification of products of the *in vitro* incubation of mevalonic acid with yeast homogenates.

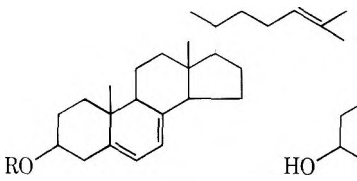
In the course of studies of the biosynthesis of sterols from (3*RS*,2*R*)-[2-$^{14}$C,2-$^{3}$H]mevalonic acid (MVA) and (3*RS*,2*S*)-[2-$^{14}$C,2-$^{3}$H]MVA in yeast homogenates, an unknown metabolite was obtained in a significant radioactive yield.[3] Frequently the metabolite contained *ca.* 20% of the total $^{14}$C radioactivity of the nonsaponifiable residue. The acetate of the unknown on hydrogenation over nickel sponge in ethyl acetate[4] gave 5α-cholest-7-en-3β-ol acetate (**1**), thus revealing a $C_{27}$ structure.[3] Analysis of the tritium content of the 7-en-3β-ols (**1**) derived from the *R* and the *S* metabolites indicated the incorporation in each case of four isotopic hydrogens. On theoretical grounds the presence of a tritium atom at C-26 of the metabolite and in **1** was assumed *a priori*. We have determined[3] the distribution of the isotopic hydrogens at C-1 and C-7 of **1** and have also deduced the distribution of $^{3}$H at C-15. Based on our data it became clear that the metabolite retained both the 2-pro *R* and 2-pro *S* hydrogens of MVA at C-22. This establishes that the unknown does not have a C-22 double bond.[5] In view of the fact that the biosynthetic product had a $C_{27}$ and *not* a $C_{28}$ framework, it seemed reasonable to assume that it still retained the C-24 unsaturation required for the introduction of the 24-alkyl moiety.[6] The body of the available evidence suggested therefore either 5α-cholesta-7,24-dien-3β-ol (**2a**) and/or cholesta-5,7,24-trien-3β-ol (**3a**) as the likely structure for the metabolite.




**1**




**2a**, R = H
**b**, R = $CH_3CO$




**3a**, R = H
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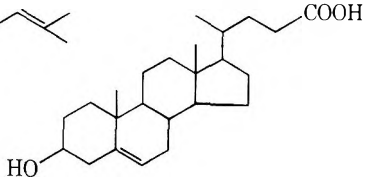
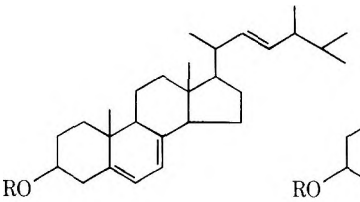


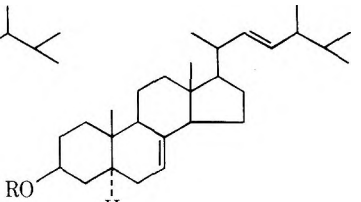

**4**

Cholesta-5,7,24-trien-3β-ol (**3a**) was previously prepared by Scallen.[7] Selective hydrogenation of the 5(6) double bond of **3a** afforded[8] 5α-cholesta-7,24-dien-3β-ol (**2a**). Since we required somewhat larger amounts of the diene **2a** and the triene **3a**, we undertook the preparation of these compounds and concentrated first on the synthesis of 5α-cholesta-7,24-dien-3β-ol (**2a**). We projected several approaches (*e.g.*, using 4 as starting material); however, the availability of ergosterol (**5a**) influenced our decision on a route *via* **7a** which we planned to couple with $(CH_3)_2C{=}CHCH_2X$.

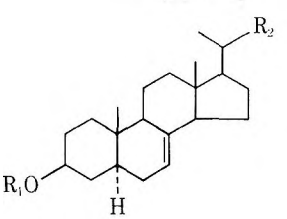
With this in mind, a benzene solution of ergosteryl benzoate (**5b**) was hydrogenated in the presence of tris(triphenylphosphine)rhodium chloride catalyst[9] to give 5α-ergosta-7,22-dien-3β-ol benzoate (**6**) in nearly quantitative yield. The diene **6** was dissolved in methylene chloride–pyridine[10] and ozonized at −78°. Following a reductive work-up, the aldehyde **7a** was isolated and subsequently reduced with sodium borohydride to the alcohol **7b**. The alcohol **7b** was converted to the bromide **7c** by two methods. The less convenient, two-step procedure involved the preparation first of the 22-tosyl ester 3β-benzoate **7d**. Displacement of the tosyl moiety was then carried out by warming a mixture of **7d**, lithium bromide, and dimethyl sulfoxide[11] to yield **7c** in *ca.* 70–75% yield. The preferred procedure consisted of treating the 22-hydroxy-3β-benzoate **7b** with carbon tetrabromide and triphenylphosphine.[12]



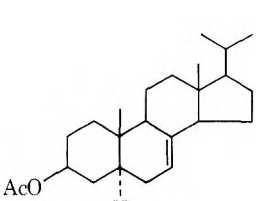

**5a**, R = H
**b**, R = $C_6H_5CO$
**c**, R = $CH_3CO$
**d**, R = $p$-$CH_3C_6H_4SO_2$




**6**, R = $C_6H_5CO$




**7a**, $R_1$ = $C_6H_5CO$; $R_2$ = CHO
**b**, $R_1$ = $C_6H_5CO$; $R_2$ = $CH_2OH$
**c**, $R_1$ = $C_6H_5CO$; $R_2$ = $CH_2Br$
**d**, $R_1$ = $C_6H_5CO$; $R_2$ = $CH_2C_6H_4SO_2$




**8**

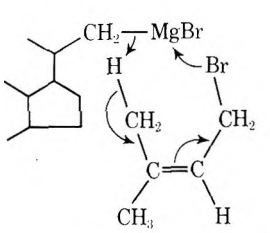
The coupling of the bromide **7c** with γ,γ-dimethylallyl bromide [$(CH_3)_2C{=}CHCH_2Br$] was carried out in the presence of magnesium.[13] In general the reaction posed some problems mainly due to self-condensation of dimethylallyl bromide. Also, under certain conditions, the C-3 benzoate moiety seemed to react preferentially with dimethylallylmagnesium bromide. When the reaction was carried out as described in the Experimental Section, two major steroidal products were formed, and these were resolved by argentation layer chromatography of their acetates.

The more polar product was **2b,** which after saponification gave the required **2a,** mp 96–98° (reported[8] mp 99–102°). The product **2a** gave a single peak on glc. Its mass spectrum had a peak for the molecular ion (*m/e* 384, $M^+$) and the fragmentation pattern was consistent with the assigned structure.[14] More important, however, was the nmr spectrum, which showed a multiplet at 5.25 ppm corresponding to the two vinylic hydrogens at C-7 and C-24. The crucially important signals for the vinylic 26- and 27-methyls were located at 1.60 (3 H) and 1.68 (3 H) ppm. Finally the chemical shifts of 0.54 ppm of the 18-methyl and 0.8 ppm of the 19-methyl are in good agreement with the calculated[15] and reported[26] values of 0.55 and 0.80 ppm, respectively. The presented evidence fully supports structure **2a.**

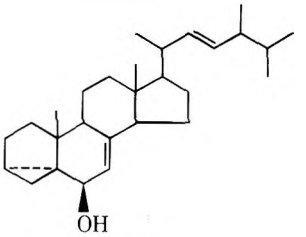
The less polar major product of the coupling reaction was identified as 20-methyl-5α-pregn-7-en-3β-ol acetate (**8**), mp 122–123°. The mass spectrum of **8** had a peak at *m/e* 358 for the molecular ion which corresponds to $C_{24}H_{38}O_2$. The nmr spectrum in $CDCl_3$ had a signal at 5.15 ppm for the C-7 vinylic proton and a pair of doublets at 0.86 ($J$ = 6 Hz, 3 H) and 0.95 ppm ($J$ = 6 Hz, 3 H) for the 21 and 22 secondary methyls. Finally, the chemical shifts of the 18- and 19-methyls are also in agreement with the proposed structure.[15]

The formation of the 20-methylpregnene is mechanistically interesting, since it seems to involve the reductive elimination of the 22-bromide from **7c.** A possible rationalization of the results is presented in **9.**

For the synthesis of cholesta-5,7,24-trien-3β-ol (**3a**) initially we again considered ergosterol as the starting material. We planned to protect the sensitive 5,7-diene moiety by converting ergosterol (**5a**) to isoergosterol[16] (**10**). However, ozonization[10] of **10** and work-up of the ozonide with zinc and acetic acid gave mainly the dehydrated cyclodiene **11.** In view of this difficulty and the anticipated difficulties of coupling the steroidal $C_{22}$ bromide with dimethylallyl bromide, we abandoned this approach.




**9**

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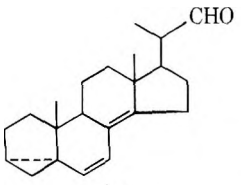
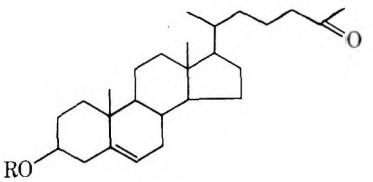



**11**

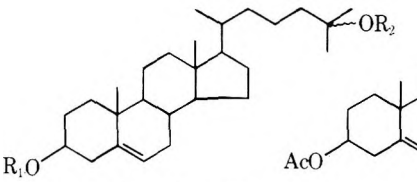



**12a,** R = H
**b,** R = $CH_3CO$
**c,** R = tetrahydropyranyl

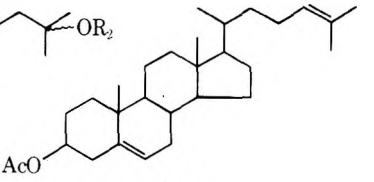
An alternative route from 26-norcholest-5-en-25-on-3β-ol (**12a**) was considered and explored. We planned to introduce the C-7 double bond first, then carry out a Grignard reaction[17] with $CH_3MgI$ on the 25-ketone and finally dehydrate the C-25 hydroxyl.

Prior to embarking on this route it was necessary to devise a procedure for the selective dehydration of the 25-hydroxyl without disturbing the homoannular diene system of ring B. From the outset we omitted mineral acids from our considerations, since these are known to cause isomerization of 5,7-dienes.[18] The dehydration procedures with acetic anhydride–acetic acid[19] or with methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt[20,21] (**20**) seemed more promising. Therefore the stability of cholesta-5,7-dien-3β-ol acetate (**21**) toward these reagents was tested, and the reaction was followed by uv and argentation tlc. In the course of the prolonged boiling with acetic anhydride–acetic acid[19] required for the removal of a 25-hydroxyl, the 5,7-diene **21** rearranged, as evidenced by the disappearance of the characteristic uv absorption. In contrast, treatment of **21** with reagent **20** did not cause rearrangement and the starting material was recovered in good yield.

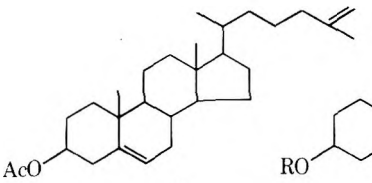
However, the question of the relative yields of $\Delta^{24}$ and $\Delta^{25}$ isomers still remained. For this purpose the 3β-acetoxy 25-ketone **12a** was treated with methylmagnesium iodide[17] and the resulting 3β,25-diol **13a** was acetylated with pyridine and acetic anhydride. In addition to the expected 3β-monoacetate **13b,** about 10% of the 3β,25-diacetate **13c** was also formed. The monoacetate **13b** was then dehydrated by the method of Burgess, *et al.*,[20] to yield a mixture of olefinic products. The mixture was resolved by argentation layer chromatography and two diene acetates were isolated. The more mobile diene (43%) proved to be desmosterol acetate (**14**), mp 96–98°, *m/e* 366 ($M^+$ − acetate). The less mobile product (46%) was the 5,25-diene acetate **15,** mp 108–109°, *m/e* 366 ($M^+$ − acetate). The nmr spectrum of **15** had a signal for the 26-methylene hydrogens at 4.75 ppm (2 H) and a singlet for a single vinylic methyl at 1.73 ppm (3 H).



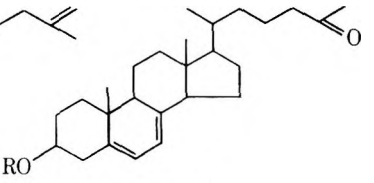

**13a,** $R_1 = R_2$ = H
**b,** $R_1$ = $CH_3CO$; $R_2$ = H
**c,** $R_1 = R_2$ = $CH_3CO$




**14**




**15**



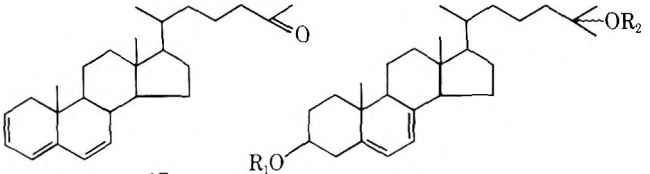

**16a,** R = H
**b,** R = $CH_3CO$

With this information at hand we proceeded with the synthesis of the 5,7,24-triene **3b** using the 3β-tetrahydropyranyl ether **12c** as a protective group for the 3-hydroxyl. Hence the ether **12c** was treated with *N*-bromosuccinimide in the presence of pyridine. The recovered mixture of bromides was dehydrobrominated with collidine in boiling xylene.[22] The uv spectrum of the crude dehydrohalogenation residue showed absorption maxima at 250, 272, and 283 nm. The absorption at 272 and 283 nm was interpreted as indicative of the presence of the required 5,7-diene

group. Fractionation of the crude residue by argentation layer chromatography showed a single product, which was recovered and identified as the triene **17**. The triene **17**, mp 97–98°, had uv absorption maxima at 294, 307, and 320 nm. The mass spectrum had a peak at *m/e* 366 for the molecular ion, revealing the elimination of the tetrahydropyranoxy moiety. The absence of this moiety was confirmed by the nmr spectrum, which showed the presence of five vinylic protons as expected for **17**. A similar, but minor reaction was observed in the course of *N*-bromosuccinimide bromination and dehydrobromination of cholesteryl acetate.[23] Apparently, in the present case, exposure of the product to argentation tlc ($AgNO_3$–$SiO_2$) promoted the elimination and resulted in the formation of the triene as the main product.

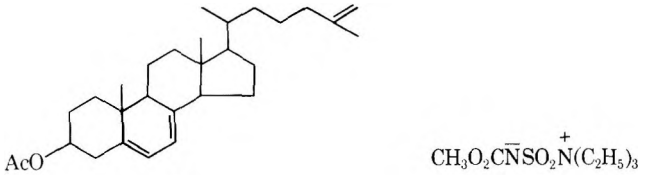
Under the circumstances we abandoned the use of the tetrahydropyranyl moiety as a protective group and prepared 26-norcholesta-5,7-dien-25-on-3β-ol acetate (**16b**) from acetate **12b** by *N*-bromosuccinimide bromination followed by dehydrobromination. The obtained 25-keto-5,7-diene **16b** was treated in the dark under nitrogen with methylmagnesium iodide.[17] The resulting diol **18a** was immediately reacetylated with pyridine and acetic anhydride to yield the 3-monoacetate **18b** as well as about 10% of the diacetate **18c**.

The 3-monoacetate-25-ol **18b** was treated with methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt (**20**) and again the dehydration proceeded toward C-24 and C-25. The two trienes (**3b** and **19**) were resolved by argentation layer chromatography. The less polar fraction (35%) was the required cholesta-5,7,24-trien-3β-ol acetate (**3b**), mp 78–81°. The product showed ultraviolet absorption maxima at 265, 272, and 283 nm as expected for the 5,7-diene. The nmr spectrum of **3b** had signals for the three vinylic hydrogens at C-6, C-7, and C-24, and for the 26 and 27 vinylic methyls.[26] Saponification of 3b provided[7] **3a**. The more polar compound was cholesta-5,7,25-trien-3β-ol acetate (**19**, 31%), mp 91–96°. The ir, nmr, and mass spectra fully support structure **19**.

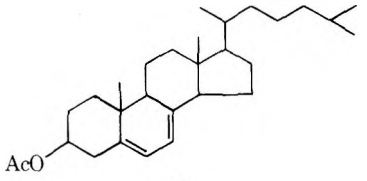



**17**

**18a**, $R_1 = R_2 = H$
**b**, $R_1 = CH_3CO$; $R_2 = H$
**c**, $R_1 = R_2 = CH_3CO$




**19** **20**




**21**

It is worthy of note that **18b** can be conveniently used in the synthesis of vitamin D metabolites and its analogs.

Finally we wish to report that the major unknown yeast metabolite was identified as the triene **3a**. In addition a small amount of the metabolite diene **2a** was also isolated. The results of the biosynthetic studies will be reported elsewhere.

## Experimental Section

**Physical Measurements.** Melting points were taken on a hot-stage apparatus and are corrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer as KBr wafers.[24] Absorption frequencies are quoted in reciprocal centimeters. Ultraviolet (uv) spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer in methanol solutions. Nuclear magnetic resonance (nmr) spectra were recorded in $CDCl_3$ on a Varian DA-60 or an EM 360 spectrometer at 60 MHz. Chemical shifts are quoted in parts per million downfield from tetramethylsilane as internal standard (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet).

Mass spectra were recorded on a Du Pont 21-491 or a Varian M-66 instrument using the direct probe insertion system with a temperature of source of 210° and an ionization voltage of 70 eV. The masses of eliminated fragments are given in brackets after the molecular ion.

**Chromatography.** Analytical thin layer chromatography (tlc) was carried out on precoated silica I B-F Baker Flex plates in the indicated solvent systems. The products were detected under ultraviolet light and by spraying with an ethanolic solution of phosphomolybdic acid or aqueous sulfuric acid. Preparative layer chromatography was carried out on plates coated with silica gel (Merck $HF_{254+336}$).

The purity of steroidal samples was tested by gas–liquid chromatography (glc) on a Hewlett-Packard 7620A instrument using a 6-ft glass column (o.d. 6 mm, i.d. 2 mm) packed with 3% OV-101 on Gas Chrom Q (80–100 mesh) support or 1% SE-30 on Gas Chrom Q (80–100 mesh) support. The temperature was set isothermally at 230° and the helium flow was 30 ml/min.

**5α,6-Dihydroergosteryl Benzoate (6).** Ergosteryl benzoate (**5b**, 25 g) in benzene (750 ml) was hydrogenated in the presence of tris(triphenylphosphine)rhodium chloride (3.0 g) at room temperature and atmospheric pressure. One equivalent of hydrogen was absorbed in 16 hr. The solution was then evaporated to dryness, and the residue was slurried with ether. The resultant suspension was filtered through a column of 1 kg of alumina. The product was eluted with ether (10 l.). Removal of the solvent gave a nearly quantitative yield of 5α,6-dihydroergosteryl benzoate (**6**). The uv spectrum of the product indicated the absence of absorption at 272 and 284 nm.

**23,24-Dinor-5α-chol-7-en-22-al-3β-ol Benzoate (7a).** 5α,6-Dihydroergosteryl benzoate (**6**, 31.27 g) in dichloromethane (10 l.) containing pyridine (5.9 ml) was cooled to −78°. Ozone (1.5 equiv) was passed through the solution at a rate of 42 mg/min (determined by iodometry) for 110 min. The excess of ozone was removed by bubbling nitrogen for 10 min and then the solution was treated for 3 hr with dimethyl sulfide (20 ml) and methanol (20 ml). During this period the temperature was progressively increased to 22°. The solution was evaporated to dryness, and the resulting residue was dissolved in chloroform (600 ml)–methanol (300 ml) and shaken with saturated sodium bisulfate (400 ml) for 10 min. The viscous mixture was extracted with ether (4 × 1000 ml) and each time centrifuged for 5 min at 500 rpm to break the resultant emulsion. The ether extract was dried and evaporated, giving unreacted 5α,6-dihydroergosteryl benzoate (**6**, 10 g). The aqueous phase was neutralized with sodium hydroxide and brought to pH 8 with saturated sodium bicarbonate. The solution was then extracted with 3 × 1000 ml of chloroform and again centrifuged. The organic extract was washed once with water, dried over sodium sulfate, and evaporated to leave a crude material which after preparative tlc (hexane–ethyl acetate, 9:1) yielded 8.5 g of purified aldehyde **7a**. Finally crystallization from chloroform–methanol gave a homogeneous product: mp 200–202°; ir 2700, 1730, 1720 $cm^{-1}$; nmr δ 0.6 (s, 3 H, 18-$CH_3$), 0.88 (s, 3 H, 17-$CH_3$), 1.15 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 4.86 (m, 1 H, 3α-H), 5.15 (m, 1 H, 7-H vinylic), 9.65 (m, $J$ = 3 Hz, 1 H, 22-CHO); mass spectrum *m/e* 434 ($M^+$) (−15, −28, −58, −122).

**23,24-Dinor-5α-chol-7-ene-3β,22-diol 3-Benzoate (7b).** To a solution of the 22-aldehyde **7a** (8.4 g) in chloroform (200 ml) and methanol (150 ml) at room temperature, was added sodium borohydride (750 mg). After 30 min a second portion of sodium borohydride (750 mg) was added. The reaction was terminated (after a total of 60 min) with a solution of ammonium chloride (5 g) in water (200 ml). Chloroform (200 ml) was added and the organic phase was washed with water, dried over sodium sulfate, and evaporated, giving the crude alcohol **7b** (7.5 g). This material was

further purified by preparative tlc (hexane–ethyl acetate, 4:1) and crystallized from a methanol–chloroform mixture (needles): mp 207–209°; ir 3640, 3480, 1715 $cm^{-1}$; nmr δ 0.575 (s, 3 H, 18-$CH_3$), 0.86 (s, 3 H, 19-$CH_3$), 1.06 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.6 (s, 1 H, 22-OH, $D_2O$ exchangeable), 3.58 (m, 2 H, 22-$CH_2$), 4.9 (m, 1 H, 3α-H), 5.2 (m, 1 H, 7-H vinylic); mass spectrum $m/e$ 436 ($M^+$) (−15, −59, −122, −137, −181).

**23,24-Dinor-5α-chol-7-ene-22-bromide-3β-ol Benzoate (7c).** A. A mixture of the 22-alcohol **7b** (7.3 g), carbon tetrabromide (17.8 g), and triphenylphosphine (13.2 g) in ether (5 l.) was stirred at room temperature for 1 hr, and then the solution was evaporated. The product was first filtered through a column of silica gel (800 g) from which it was eluted with chloroform, and was then purified by preparative tlc (hexane–ethyl acetate, 25:1). The obtained 22-bromide **7c** (3.0 g) was crystallized twice from a methanol–chloroform mixture to yield 2.7 g (white needles): mp 199–201°; ir 1715, 765 $cm^{-1}$; nmr δ 0.58 (s, 3 H, 18-$CH_3$), 0.86 (s, 3 H, 19-$CH_3$), 1.12 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 3.6 (m, 2 H, 22-$CH_2$), 4.96 (m, 1 H, 3α-H), 5.2 (m, 1 H, 7-H vinylic); mass spectrum $m/e$ 500 ($M^+$), 498 (−123, −122, −137, −245, −287, −395).

B. The 22-alcohol **7b** (180 mg) and *p*-toluenesulfonyl chloride (500 mg) in 10 ml of dry pyridine were kept at 4° for 12 hr. After the usual work-up the tosylate **7d** (200 mg) was crystallized from methanol–chloroform (needles): mp 148–150°; ir 1715, 960 $cm^{-1}$.

The tosylate **7d** (200 mg) in dry dimethyl sulfoxide (10 ml) was treated with lithium bromide (39 mg) at 70° for 6 hr. The mixture was poured into water and extracted with ether, and the extract was washed with water (4 × 20 ml), then dried and evaporated. The product was separated by preparative tlc (hexane–ethyl acetate, 9:1), giving the bromide **7c** (160 mg) and recovered tosylate **7d** (88.6 mg). Bromide **7c** was crystallized from methanol–chloroform and its physical constants were as above.

**20-Methyl-5α-pregn-7-en-3β-ol Acetate (8).** To magnesium turnings (10 g) in dry ether (20 ml) and dry tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added γ,γ-dimethylallyl bromide (2 ml). The reaction started immediately and the temperature was lowered to 4° by immersion in an ice–water bath. After 15 min, 22-bromide **7c** (561 mg) in ether (25 ml) and tetrahydrofuran (25 ml) were added all at once, along with γ,γ-dimethylallyl bromide (4 ml). The reaction mixture was stirred at room temperature and additional γ,γ-dimethylallyl bromide (6 ml) in ether (25 ml) was added dropwise during 8 hr. Stirring was continued for 12 hr, and the reaction was stopped by addition of aqueous ammonium chloride. The product was extracted with chloroform, and the extract was washed with water (3 × 70 ml), dried (sodium sulfate), and evaporated. A sterol fraction (261 mg) slightly less mobile than cholesterol was isolated by preparative tlc (hexane–ethyl acetate, 5:1).

This fraction was treated with acetic anhydride (7 ml) and pyridine (3.5 ml) at 50° for 1 hr. The volatile components were removed under reduced pressure, and the residue was fractionated by argentation tlc (silica gel–20% silver nitrate; chloroform–petroleum ether (bp 60–90°)–acetic acid, 25:75:0.5; developed three times). The mixture was resolved into the less polar **8** and the more polar **2b**.

The less polar 20-methyl-5α-pregn-7-en-3β-ol acetate (**8**, 172 mg) was crystallized from methanol–chloroform (white plates): mp 122–123°; ir 1733 $cm^{-1}$; nmr δ 0.53 (s, 3 H, 19-$CH_3$), 0.80 (s, 3 H, 18-$CH_3$), 0.86 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 0.95 (d, $J$ = 6 Hz, 22-$CH_3$), 2.01 (s, 3 H, 3β-acetoxy), 4.66 (m, 1 H, 3α-H), 5.15 (m, 1 H, 7-H vinylic) [in benzene solution peaks appeared at 0.55 (s, 3 H, 18-$CH_3$), 0.72 (s, 3 H, 19-$CH_3$), 0.88 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 0.975 (d, $J$ = 6 Hz, 3 H, 22-$CH_3$), 1.75 (s, 3 H, 3β-acetoxy), 4.83 (m, 1 H, 3α-H), 5.18 (m, 1 H, 7-H vinylic)]; mass spectrum $m/e$ 358 ($M^+$) (−15, −33, −60, −103).

**5α-Cholesta-7,24-dien-3β-ol (2a).** The more polar **2b** (93.4 mg), recovered from the above coupling experiment, was dissolved in tetrahydrofuran (10 ml) and treated with potassium hydroxide in methanol (5%, 10 ml). The mixture was stirred overnight, then acidified and diluted with water. The product was extracted with chloroform (100 ml) and after the usual work-up **2a** was obtained. Crystallization from methanol provided 5α-cholesta-7,24-dien-3β-ol (**2a**, 55 mg) (needles); mp 96–98° (lit.[8] mp 99–102°); ir 3350 $cm^{-1}$; nmr δ 0.54 (s, 3 H, 18-$CH_3$), 0.8 (s, 3 H, 19-$CH_3$), 0.95 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.60 and 1.68 (s, 6 H, 26-$CH_3$ and 27-$CH_3$), 1.68 (s, 1 H, 3β-OH, $D_2O$ exchangeable), 3.56 (m, 1 H, 3α-H), 5.25 (m, 2 H, 7, 24-H vinylics) [reported[26] δ 0.554 (s, 3 H, 18-$CH_3$), 0.813 (s, 3 H, 19-$CH_3$)]; mass spectrum $m/e$ 384 ($M^+$) (−18, −68, −113, −129).

**Ergosteryl Tosylate (5d).** Ergosterol (**5a**, 5 g) and *p*-toluenesulfonyl chloride (8.1 g, freshly crystallized from hexane) in pyridine (80 ml, distilled over sodium hydroxide) were stirred for 12 hr at 4° in the dark. The mixture was then poured into a cold solution (400 ml) of sodium bicarbonate (4%). After 15 min the precipitate was quickly filtered, washed with cold water, and dried in a stream of air for a short time. The product was dissolved in chloroform (200 ml) and filtered through a mixture of sodium sulfate–magnesium sulfate, and removal of the solvent gave impure ergosteryl tosylate (**5d**).

The tosylate is unstable and decomposes during tlc. Repetitive crystallizations from acetone yielded 1.25 g of ergosteryl tosylate (**5d**), mp 90–100°.

**3,5α-Cycloergosta-7,22-dien-6β-ol (Isoergosterol, 10).** To a refluxing mixture of sodium bicarbonate (400 mg), water (50 ml), and acetone (200 ml), ergosteryl tosylate (**5d**, 800 mg) was added in one portion. The boiling was continued for 5 min; then the condenser was removed and 100 ml of acetone was distilled under reduced pressure.

After cooling, water (100 ml) was added and the product was collected by filtration. The solid was washed with water (2 × 50 ml) and dried for 3 hr at 80°. Crystallization from hexane gave isoergosterol (**10**, 600 mg): mp 129–130° (lit.[16] mp 129–130°); ir 3480 $cm^{-1}$; nmr δ 0.65 (s, 3 H, 18-$CH_3$), 0.83 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.08 (s, 3 H, 19-$CH_3$), 151 (s, 1 H, 6β-OH, $D_2O$ exchangeable), 3.4 (m, 1 H, 6α-H), 5.2 (m, 2 H, 22-, 23-H vinylics), 5.45 (m, 1 H, 7-H vinylic); mass spectrum $m/e$ 396 ($M^+$) (−18, −33, −59, −143, −197).

**23,24-Dinor-3,5α-cyclocholesta-6,8(14)-dien-22-al (11).** Ozone was admitted for 100 sec to a solution of isoergosterol (**10**, 213.3 mg) in dichloromethane (100 ml) cooled to −78° at a rate of 19.4 mg/min (determined by iodometry) (1.25 equiv). The excess of ozone was removed by bubbling nitrogen; then zinc (500 mg) and acetic acid (1.5 ml) were added. The mixture was stirred under nitrogen for 10 min at −78°, then for 1 hr at 0°. The zinc was filtered and the filtrate was washed with saturated sodium bicarbonate and water and dried (sodium sulfate). Removal of the solvent gave a residue which was purified by preparative tlc (hexane–ethyl acetate, 3:4).

From the more mobile zone ($R_f$ 0.61) **11** was isolated. Crystallization from methanol yielded 23,24-dinor-3,5α-cyclocholesta-6,8(14)-dien-22-al (**11**, 65 mg): mp 105°; uv $\lambda_{max}$ 260 nm (ε 21,200); ir 2680, 1730 $cm^{-1}$; nmr δ 0.78 (s, 3 H, 18-$CH_3$), 1.11 (s, 3 H, 19-$CH_3$), 1.15 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 5.23 and 6.15 (d, $J$ = 10 Hz, 2 H, 6-, 7-H vinylics), 9.53 (d, $J$ = 4 Hz, 1 H, 22-H aldehyde); mass spectrum $m/e$ 310 ($M^+$) (−15, −57, −67).

**26-Norcholest-5-en-25-on-3β-ol Tetrahydropyranyl Ether (12c).** 26-Norcholest-5-en-25-on-3β-ol (**12a**, 12.0 g) was added to a benzene solution (250 ml) containing dihydropyran (15 g, distilled over sodium hydroxide) and *p*-toluenesulfonic acid monohydrate (200 mg). After 6 hr the resultant solution was poured into ice-cold aqueous sodium bicarbonate and the product was extracted with ether (500 ml). After the usual work-up, crystallization from ethanol–ether yielded 9.22 g of **12c**: mp 108–109°; ir 2910, 1705 $cm^{-1}$; nmr δ 0.66 (s, 3 H, 18-$CH_3$), 1.0 (s, 3 H, 19-$CH_3$), 3.53 (m, 1 H, 3α-H), 4.66 (m, 1 H, pyran CH—O), 5.31 (m, 1 H, 6-H vinylic).

**26-Norcholesta-2,4,6-trien-25-one (17).** A mixture of 26-norcholest-5-en-25-on-3β-ol tetrahydropyranyl ether (**12c**, 206 mg), petroleum ether (10 ml, bp 64–67°, distilled over sulfuric acid),[22] pyridine (0.67 ml), *N*-bromosuccinimide (300 mg, freshly crystallized from water), and bromine (1 drop) was refluxed under nitrogen. The mixture was irradiated with a sunlamp (250 W) for 20 min and then cooled (10°) and diluted with petroleum ether (30 ml). The solution was washed with water (3 × 25 ml) and dried over sodium sulfate. The solvent was distilled (below 10°) under reduced pressure.

The resulting oily residue was rapidly added to a boiling mixture of xylene (10 ml) and collidine (0.4 ml) and refluxing was continued for 30 min under nitrogen. After cooling, ether (100 ml) was added and the organic extract was washed with dilute hydrochloric acid (50 ml, 0.01 *N*), then with water (3 × 50 ml), and dried. Removal of the solvent gave an oil which showed maximal uv absorption at 250, 272, and 283 nm.

This oil was fractionated by tlc (silica gel–15% silver nitrate, hexane–ethyl acetate, 10:3; developed twice). The plates indicated a single product, which was eluted and crystallized from MeOH to yield 26-norcholesta-2,4,6-trien-25-one (**17**, 122 mg): mp 97–98°; uv $\lambda_{max}$ 294 nm, 307 (ε 15,300), 320; nmr δ 0.71 (s, 3 H, 18-$CH_3$), 0.95 (s, 3 H, 19-$CH_3$), 0.95 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 2.15 (s, 3 H, 27-$CH_3$), 5.5–6.13 (m, large, 5 H, 2-, 3-, 4-, 6-, 7-H vinylic); mass spectrum $m/e$ 366 ($M^+$) (−15, −113, −128).

**26-Norcholesta-5,7-dien-25-on-3β-ol Acetate (16b).** A mixture

of 26-norcholesta-5-en-25-on-3β-ol acetate (**12b**, 1 g), petroleum ether (100 ml), and pyridine (1.5 ml) was treated with *N*-bromosuccinimide (1.5 g) as described for **17**. The obtained brominated product was dissolved in xylene (50 ml) containing collidine (2 ml) and refluxed for 30 min under nitrogen in the dark. The dehydrobrominated product was purified by argentation tlc (silica gel–15% silver nitrate, hexane–ethyl acetate, 4:1; developed three times). Two bands with $R_f$ 0.62 and 0.52, respectively, were detected.

Elution of the band with $R_f$ 0.62 gave an oily residue (132 mg). The nmr spectrum indicated that the product still contained some impurity. However, judging from the nmr (chemical shifts of 18- and 19-methyls, the number of vinylic protons), the uv, and the mass spectra, the major component (*ca.* 70–80%) of the mixture was tentatively identified as 26-norcholesta-4,6-dien-25-on-3β-ol acetate.

The product from the slower band was crystallized from methanol to yield **16b** (238 mg): mp 135–136°; uv $\lambda_{max}$ 263 nm (ε 7590), 272 (11,200), 283 (11,620), 294 (6810); ir 1730, 1710 $cm^{-1}$; nmr δ 0.63 (s, 3 H, 18-$CH_3$), 0.96 (s, 3 H, 19-$CH_3$), 2.05 (s, 3 H, 3β-acetate), 2.15 (s, 3 H, 27-$CH_3$), 4.66 (m, 1 H, 3α-H), 5.35 and 5.55 (d, $J$ = 6 Hz, 2 H, 6-, 7-H vinylic); mass spectrum $m/e$ 426 ($M^+$) (−60, −75, −173).

**Cholesta-5,7-diene-3β,25-diol (18a).** A solution of methyl iodide (3 g, 21.2 mmol) in dry ether (50 ml) was slowly added to a stirred suspension of magnesium turnings (520 mg, 21.2 mmol) in dry ether (50 ml) under nitrogen. Addition of a crystal of iodine initiated a vigorous reaction. The solution was maintained at reflux until the magnesium was consumed (30 min). Then 26-norcholesta-5,7-dien-25-on-3β-ol acetate (**16b**, 750 mg, 1.77 mmol) in dry ether (75 ml) was added dropwise and the reaction mixture was refluxed for 3 hr in the dark under nitrogen. The stirring was continued for 7 hr at room temperature and the reaction was terminated with a saturated solution of ammonium chloride (200 ml). The product was extracted with ether to yield, after work-up, a crude residue (524 mg) which was stored at −10° under vacuum in the dark.

A portion of this material (24 mg) was resolved by tlc (hexane–ethyl acetate, 3:2) into two bands. The minor zone ($R_f$ 0.66) contained the saponified starting material (**16a**).

The second zone ($R_f$ 0.38) was identified as cholesta-5,7-diene-3β,25-diol (**18a**): mp 165–166°; uv $\lambda_{max}$ 263 nm (ε 7590), 273 (11,310), 283 (11,820), 295 (6905); ir 3350 $cm^{-1}$; nmr δ 0.68 (s, 3 H, 18-$CH_3$), 0.99 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.01 (s, 3 H, 21-$CH_3$), 1.23 (s, 6 H, 26-, 27-$CH_3$), 3.53 (m, 1 H, 3α-H), 5.36 and 5.6 (d, $J$ = 6 Hz, 2 H, 6-, 7-H vinylic); mass spectrum $m/e$ 400 ($M^+$) (−18, −33, −36, −51, −147).

**Cholesta-5,7-diene-3β,25-diol 3-Acetate (18b).** A mixture of the crude **18a** (500 mg), acetic anhydride (12 ml), and pyridine (6 ml) was stored in the dark under nitrogen for 16 hr. The reagents were distilled *in vacuo* and the residue was then purified by preparative tlc (hexane–ethyl acetate, 4:1, developed twice). Two fractions (with $R_f$ 0.73 and 0.44) were isolated.

The residue of the less polar zone ($R_f$ 0.73) was crystallized from methanol to yield cholesta-5,7-diene-3β,25-diol diacetate (**18c**, 50 mg): uv $\lambda_{max}$ 263, 274, 283, and 295 nm; ir 1730 $cm^{-1}$; nmr δ 0.61 (s, 3 H, 18-$CH_3$), 0.96 (s, 3 H, 19-$CH_3$), 1.43 (s, 6 H, 26-, 27-$CH_3$), 1.96 (s, 3 H, 25-acetate), 2.05 (s, 3 H, 3β-acetate), 4.66 (m, 1 H, 3α-H), 5.36 and 5.6 (d, $J$ = 6 Hz, 2 H, 6-, 7-H vinylic); mass spectrum $m/e$ 424 ($M^+$ − acetate) (−60, −75, −171).

The residue of the second zone ($R_f$ 0.44) was crystallized from methanol–chloroform to yield cholesta-5,7-dien-3β,25-diol 3-acetate (**18b**, 401 mg): mp 108–110°; uv $\lambda_{max}$ 265 nm (ε 7700), 273 (11,370), 283 (11,510), 295 (6810); ir 3440, 1730 $cm^{-1}$; nmr δ 0.68 (s, 3 H, 18-$CH_3$), 0.95 (s, 3 H, 19-$CH_3$), 1.21 (s, 6 H, 26-, 27-$CH_3$), 2.03 (s, 3 H, 3β-acetate), 4.66 (m, 1 H, 3α-H), 5.35 and 5.6 (d, $J$ = 6 Hz, 2 H, 6-, 7-H vinylic); mass spectrum $m/e$ 424 ($M^+$ − water) (−60, −78, −93, −171).

**Cholest-5-ene-3β,25-diol 3β-Acetate (13b).** Treatment of cholest-5-en-25-on-3β-ol acetate (**12b**) with methylmagnesium iodide as described above gave the diol **13a**, mp 172–174° (lit.[17] mp 172–174°). The diol **13a** was then acetylated to yield as the main product **13b**: mp 134–136° (lit.[17] mp 138–140°); ir 3440, 1730 $cm^{-1}$; nmr δ 0.66 (s, 3 H, 18-$CH_3$), 1.01 (s, 3 H, 19-$CH_3$), 1.20 (s, 6 H, 26- and 27-$CH_3$), 1.8 (s, 3 H, 3β-acetate), 4.56 (m, 1 H, 3α-H), 5.36 (m, 1 H, 6-H vinylic); mass spectrum $m/e$ 384 ($M^+$ − acetate) (−15, −18, −33, −129, −131, −139, −171).

**Cholesta-5,24-dien-3β-ol Acetate (14).** A mixture of cholest-5-en-3β,25-diol 3β-acetate (**13b**, 150 mg) and methyl(carboxysulfamoyl)trimethylammonium hydroxide inner salt[20] (**20**, 500 mg) in benzene (40 ml) was refluxed under dry nitrogen. After 10 min the starting material was consumed as evidenced by tlc (hexane–ethyl acetate, 4:1). The reaction was stopped by addition of water (10 ml). The organic phase was washed with saturated sodium chloride (2 × 20 ml) and water (2 × 20 ml), dried, and concentrated. The residue was fractionated by tlc (silica gel–18% silver nitrate, hexane–ethyl acetate, 4:1, developed twice). Two major bands with $R_f$ 0.62 and 0.50 were observed.

The product from the $R_f$ 0.62 zone was crystallized from methanol–chloroform to yield cholesta-5,24-dien-3β-ol acetate (**14**, 65 mg): mp 96–98° (lit.[25] mp 99–100°); ir 1730 $cm^{-1}$; nmr δ 0.7 (s, 3 H, 18-$CH_3$), 0.96 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.03 (s, 3 H, 19-$CH_3$), 1.63 and 1.7 (s, 6 H, 26- and 27-$CH_3$). 2.03 (s, 3 H, 3β-acetate), 4.62 (m, 1 H, 3α-H), 4.75 (t, $J$ = 6 Hz, 1 H, 24-H vinylic), 5.36 (m, 1 H, 6-H vinylic); mass spectrum $m/e$ 366 ($M^+$ − acetate) (−15, −68, −85, −113, −121, −138, −153).

The product from the second zone ($R_f$ 0.50) was crystallized from methanol to yield cholesta-5,25-dien-3β-ol acetate (**15**, 70 mg): mp 108° (lit.[25] mp 112°); ir 1730 $cm^{-1}$; nmr δ 0.7 (s, 3 H, 18-$CH_3$), 0.95 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.03 (s, 3 H, 19-$CH_3$), 1.73 (s, 3 H, 27-$CH_3$) 2.03 (s, 3 H, 3β-acetate), 4.62 (m, 1 H, 3α-H), 4.65 (s, 2 H, 25-$CH_2$), 5.36 (m, 1 H, 6-H vinylic); mass spectrum $m/e$ 366 ($M^+$ − acetate) (−15, −42, −71, −85, −111, −113, −121, −138, −153).

**Treatment of Cholesta-5,7-dien-3β-ol Acetate (21) with Methyl(carboxysulfamoyl)triethylammonium Hydroxide Inner Salt (20).** A mixture of cholesta-5,7-dien-3β-ol acetate (10 mg) and **20** (100 mg) in benzene (2 ml) was refluxed under nitrogen for 40 min. Aliquots were removed at 5-min intervals and tested by tlc (hexane–ethyl acetate, 5:1); only the starting material was detected. After the termination of the reaction the starting material was recovered.

**Cholesta-5,7,24-trien-3β-ol Acetate (3b).** A mixture of cholesta-5,7-diene-3β,25-diol 3-acetate (**18b**, 250 mg) and **20** (250 mg) in dry benzene (20 ml) was refluxed under nitrogen. After 15 min a sample of the reaction mixture was removed and tlc (hexane–ethyl acetate, 4:1) revealed the absence of starting material. The reaction was stopped and the mixture was worked up as described above. The crude product was purified by tlc (silica gel–18% silver nitrate, hexane–ethyl acetate, 4:1, developed twice). Two major bands were observed and eluted.

The residue of the less polar zone was crystallized from methanol to give cholesta-5,7,24-trien-3β-ol acetate (**3b**, 85 mg): mp 78–81°; uv $\lambda_{max}$ 265 nm, 272 (ε 10,980), 283 (11,400), 294 (6650); ir 1730 $cm^{-1}$; nmr δ 0.63 (s, 3 H, 18-$CH_3$), 0.95 (s, 3 H, 19-$CH_3$), 0.95 (d, $J$ = 6 Hz, 21-$CH_3$), 1.61 (s, 3 H, 26-$CH_3$), 1.68 (s, 3 H, 27-$CH_3$), 2.03 (s, 3 H, 3β-acetate), 4.66 (m, 1 H, 3α-H), 5.1 (t, $J$ = 6 Hz, 1 H, 24-H vinylic), 5.36 and 5.57 (d, $J$ = 6 Hz, 2 H, 6-, 7-H vinylic); mass spectrum $m/e$ 424 ($M^+$) (−60, −75, −101, −145, −171).

The residue of the more polar fraction was crystallized from methanol and yielded cholesta-5,7,25-trien-3β-ol acetate (**19**, 78 mg): mp 91–96°; ir 1730 $cm^{-1}$; nmr δ 0.63 (s, 3 H, 18-$CH_3$), 0.95 (s, 3 H, 19-$CH_3$), 0.95 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.7 (s, 3 H, 27-$CH_3$), 2.03 (s, 3 H, 3β-acetate), 4.66 (m, 1 H, 3α-H), 4.66 (s, 2 H, 26-$CH_2$), 5.36 and 5.56 (d, $J$ = 6 Hz, 2 H, 6-, 7-H vinylic); mass spectrum $m/e$ 424 ($M^+$) (−60, −75, −101, −145, −171).

**Cholesta-5,7,24-trien-3β-ol (3a).** A mixture of cholesta-5,7,24-trien-3β-ol acetate (**3b**, 20 mg), tetrahydrofuran (5 ml), and lithium aluminum hydride (100 mg) was refluxed in an atmosphere of nitrogen in the dark for 2 hr. To the cold reaction mixture was added saturated sodium sulfate (25 ml) and the obtained residue was removed by filtration. The filtrate was washed with water (2 × 25 ml) and dried and the solvent was removed to yield a powder (15.2 mg). The residue was crystallized from methanol to yield **3a** (needles): mp 98–99° (lit.[7] mp 102–102.5°); ir 3400 $cm^{-1}$; nmr δ 0.62 (s, 3 H, 18-$CH_3$), 0.96 (s, 3 H, 19-$CH_3$), 1.01 (d, $J$ = 6 Hz, 3 H, 21-$CH_3$), 1.62 (s, 3 H, 26-$CH_3$), 1.7 (s, 3 H, 27-$CH_3$), 3.66 (m, 1 H, 3α-H), 5.1 (t, $J$ = 6 Hz, 1 H, 24-H vinylic), 5.36 and 5.46 (d, $J$ = 6 Hz, 2 H, 6-, 7-H vinylic) [reported[7,26] δ 0.62 (s, 3 H, 18-$CH_3$), 0.955 (s, 3 H, 19-$CH_3$), 1.63 (s, 3 H, 26-$CH_3$), 1.69 (s, 3 H, 27-$CH_3$)]; mass spectrum $m/e$ 382 ($M^+$) (−15, −18, −33, −59, −129, −131, −171).

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**Registry No.**—**2a**, 651-54-7; **2b**, 51373-26-3; **3a**, 1715-86-2; **3b**, 17137-77-8; **5a**, 57-87-4; **5b**, 5035-30-3; **5d**, 51373-27-4; **6**, 4356-17-6; **7a**, 51373-28-5; **7b**, 32308-36-4; **7c**, 51373-29-6; **7d**, 51373-30-9; **8**, 51373-31-0; **10**, 2774-59-6; **11**, 32308-45-5; **12a**, 7494-34-0; **12b**,

7548-94-9; **12c**, 51464-63-2; **13a**, 2140-46-7; **13b**, 10525-22-1; **14**, 2665-04-5; **15**, 10525-24-3; **16b**, 24281-79-6; **17**, 51373-32-1; **18a**, 22145-68-2; **18b**, 24281-78-5; **18c**, 34679-19-1; **19**, 51373-33-2.

### References and Notes


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# Pyrazolopyrimidine Nucleosides. V. Methylation of the C-Nucleoside Antibiotic Formycin and Structural Elucidation of Products by Magnetic Circular Dichroism Spectroscopy[1]


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The direct methylation of formycin (**9**) has furnished the two monomethyl derivatives, 7-amino-1-methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (**10**) and 7-amino-2-methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (**12**). An unequivocal assignment of the above structures was made by a comparison of the magnetic circular dichroism (MCD) curves obtained for the model compounds 7-amino-2,3-dimethylpyrazolo[4,3-*d*]pyrimidine (**6**) and 7-amino-1,3-dimethylpyrazolo[4,3-*d*]pyrimidine (**7**) with the MCD spectra of **10** and **12**. The unequivocal synthesis of **6** and **7** was accomplished by ring annulation of the appropriately substituted pyrazole precursors. The synthesis of 1,3-dimethylpyrazolo[4,3-*d*]pyrimidin-7-one (**8**) and 2-methyl-3-(β-D-ribofuranosyl)-pyrazolo[4,3-*d*]pyrimidin-7-one (**11**) was accomplished by an unusual displacement of the exocyclic amino group in 1 *N* sodium hydroxide.


The antibiotics formycin and formycin B were isolated[3] from *Norcardia interforma* and found[4-6] to be C-nucleosides which were isomeric with the naturally occurring nucleosides adenosine and inosine, respectively. These antibiotics are of considerable interest since they are C-nucleosides and belong to the same class of compounds as showdomycin,[7] pseudouridine,[8] and pyrazomycin.[9] Formycin has demonstrated inhibition of Ehrlich carcinoma, mouse leukemia L-1210, Yoshida rat sarcoma, HeLa cells, and *Xanthomonas oryzae* as well as some antiviral activity.[3,12] Formycin 5′-triphosphate acts as a source of biological energy[13] and ribopolynucleotides with formycin replacing adenosine, at the binding site of t-RNA to ribosomes, have shown[14] no mistranslation of the messenger. In fact, formycin has shown the ability to act as a substrate for a number of enzymes specific for adenosine, including adenosine kinase[11] and, unfortunately, adenosine deaminase.[10] The resemblance of formycin to adenosine is thus apparent in many biological systems. Since formycin is such an excellent substrate for adenosine deaminase, this would suggest that although formycin hydrobromide has been found to exist in the syn conformation, there must be a population of formycin in the anti conformation in solution and *in vivo*. In fact, a recent X-ray study[15] has revealed that formycin, *per se*, exists on the average somewhere between the classical syn and anti forms (amphi form[16]) in the solid state. A recent study has established that adenosine derivatives in the syn conformation are not substrates for adenosine deaminase and this prompted us to initiate a study[17] designed to restrict rotation around the glycosyl (carbon–carbon) bond of formycin and increase the per cent of nucleoside in the syn conformation.

The isomeric purine nucleosides, when alkylated on an imidazole nitrogen, form salts with a positively charged heterocyclic ring[18] which can then undergo a facile ring opening.[19] However, formycin presents a unique opportunity to alkylate a ring nitrogen of a bicyclic nucleoside without the usual quaternization. These alkylated derivatives of formycin should be chemically very similar to formycin and yet the 2-alkyl derivative should exhibit

**Table I**
**Ultraviolet Absorption Spectral Data for Some Substituted Pyrazolo[4,3-*d*]pyrimidines**

| Compd | pH 1 $\lambda_{max}$, nm | $\epsilon \times 10^{-3}$ | pH 11 $\lambda_{max}$, nm | $\epsilon \times 10^{-3}$ | MeOH $\lambda_{max}$, nm | $\epsilon \times 10^{-3}$ |
|---|---|---|---|---|---|---|
| **9** | 295 | 10.15 | 302 | 7.90 | 304 | 7.20 |
| | 232.5 | 8.28 | 234 | 17.90 | 293.5 | 10.55 |
| | | | | | 286[a] | 9.88 |
| | | | | | 230 | 5.87 |
| **3** | 282 | 7.80 | 282 | 8.47 | 278 | 8.96 |
| **5** | | | 282.5 | 7.66 | 290 | 6.00 |
| | | | 230 | 13.70 | 230 | 6.88 |
| **7** | 305 | 9.45 | 315[a] | 6.04 | 315[a] | 6.04 |
| | 241.5 | 12.55 | 303 | 9.30 | 303 | 9.48 |
| | | | 295[a] | 8.80 | 297[a] | 9.08 |
| | | | | | 233 | 9.62 |
| **2** | 278 | 6.96 | 278 | 7.89 | 272 | 6.48 |
| **4** | | | 278 | 4.49 | 276 | 4.49 |
| | | | 255[a] | 2.72 | 255[a] | 3.00 |
| **6** | 305 | 9.80 | 316[a] | 6.20 | 316[a] | 6.54 |
| | 270[a] | 4.90 | 304 | 10.10 | 304 | 10.10 |
| | 258 | 6.54 | 294 | 8.65 | 294[a] | 8.65 |
| | 234 | 15.10 | 232 | 8.50 | 232 | 7.84 |
| **12** | 305 | 11.24 | 317[a] | 8.45 | 317[a] | 8.85 |
| | 270 | 5.90 | 305 | 12.90 | 305 | 13.80 |
| | 260 | 6.05 | 295[a] | 11.24 | 295[a] | 11.80 |
| | 231 | 10.95 | 237 | 5.61 | 237 | 6.05 |
| **10** | 302 | 6.32 | 314[a] | 3.93 | 314[a] | 3.65 |
| | 236 | 7.03 | 301 | 6.46 | 301 | 6.18 |
| | | | 293[a] | 6.19 | 293[a] | 5.75 |
| | | | 232 | 6.51 | 231 | 5.20 |
| **11** | 284.5 | 9.30 | 310[a] | 8.60 | 283 | 10.15 |
| | | | 299 | 13.80 | | |
| | | | 291[a] | 12.70 | | |
| | | | 228.5 | 7.05 | | |

[a] Shoulder.

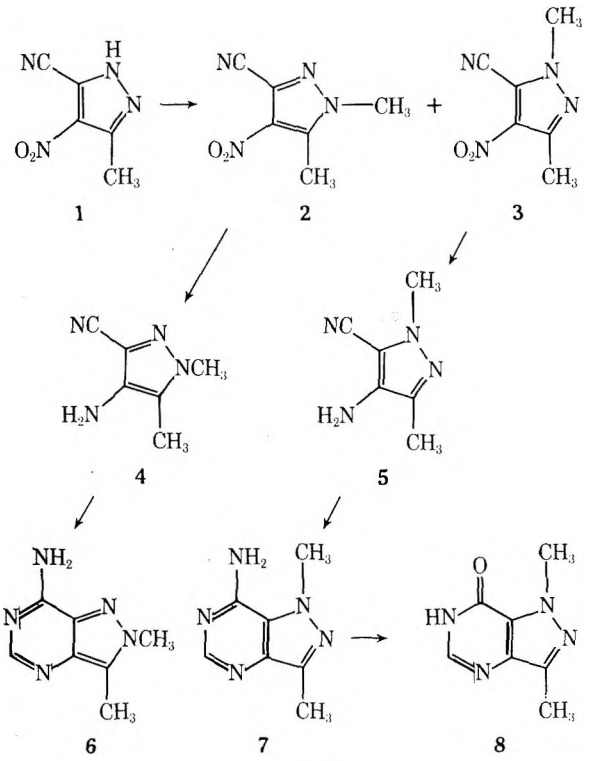
some steric restriction toward rotation around the glycosyl bond and decrease the population of nucleoside in the anti conformation.

## Results and Discussion

Since alkylation of formycin could lead to a number of products, depending on the pH of the solution and the alkylating agent used, we selected conditions designed to facilitate preferential alkylation of the pyrazole moiety. The monosodium salt of formycin was prepared and then alkylated by the addition of excess methyl iodide. Chromatography (tlc) of the reaction mixture revealed the presence of three products. The two major components were isolated and purified by dry column chromatography while the third product was not isolated, since it was estimated to be present in only a very small quantity. Therefore, with the isolation of two products, we were required to establish the actual site of methylation for each product.

The initial structural elucidation studies[5] of formycin and formycin B confirmed the similarity of their ultraviolet spectra with the ultraviolet spectra of the corresponding 7-substituted 3-methylpyrazolo[4,3-*d*]pyrimidines.[20] This prompted us to synthesize the appropriate 3-methylpyrazolo[4,3-*d*]pyrimidines [7-amino-1,3-dimethylpyrazolo[4,3-*d*]pyrimidine (7) and 7-amino-2,3-dimethylpyrazolo[4,3-*d*]pyrimidine (6)] in order to establish the actual site of methylation of formycin (*vide supra*). It has been established that the most facile synthesis of the pyrazolo[4,3-*d*]pyrimidine moiety can be accomplished by ring annulation of the appropriately substituted pyrazole precursor.[20,21] Therefore, we selected 5-cyano-1,3-dimethyl-4-nitropyrazole[22] (3), which had been prepared by the nucleophilic displacement of a chloro group by cyanide, as our starting material for the synthesis of the model compound 7. The nitro group was reduced with sodium hydrosulfite to furnish 4-amino-5-cyano-1,3-dimethylpyrazole (5) and treatment of 5 with formamidine acetate afforded a good yield of 7(Scheme I).

Scheme I




The synthesis of 3-cyano-1,5-dimethyl-4-nitropyrazole (2) by a similar route was then initiated. The synthesis of 3-chloro-1,5-dimethyl-4-nitropyrazole was accomplished, but repeated attempts to displace the chloro atom with cyanide in dimethylformamide under the same and even more forceful conditions as those that yielded 3 were not successful. The synthesis of this compound (2) was finally accomplished by methylation of 5-cyano-3-methyl-4-nitropyrazole[21] (1). The isomeric 5-cyano-1,3-dimethyl-4-nitropyrazole (3) was also formed but only in a very low yield. The nitro group of 2 was reduced with sodium hydrosulfite and ring closure with formamidine acetate yielded 6.

As stated above, when this investigation was initiated, we had expected to ascertain the actual site of methylation of formycin by a comparison of the ultraviolet spectra of the formycin derivatives with the ultraviolet spectra of the model compounds 6 and 7. However, unlike the closely related pyrazolo[3,4-*d*]pyrimidine ring system, the ultraviolet spectra of the model compounds 6 and 7 were found to be very similar (Table I). Therefore, a comparison of the ultraviolet and pmr spectra of the monomethyl derivatives of formycin (*vide supra*) and the model compounds 6 and 7 allowed us to make only a very tentative assignment of structure for the specific methylformycins.

Formycin has been reported[13] to be fluorescent; therefore, owing to the difference in their structures, we expected the methylformycins to produce dissimilar fluorescent spectra. However, fluorescent spectra of the methylformycins and the model compounds 6 and 7 were obtained and no definitive conclusions could be drawn as to their unequivocal structural assignment.

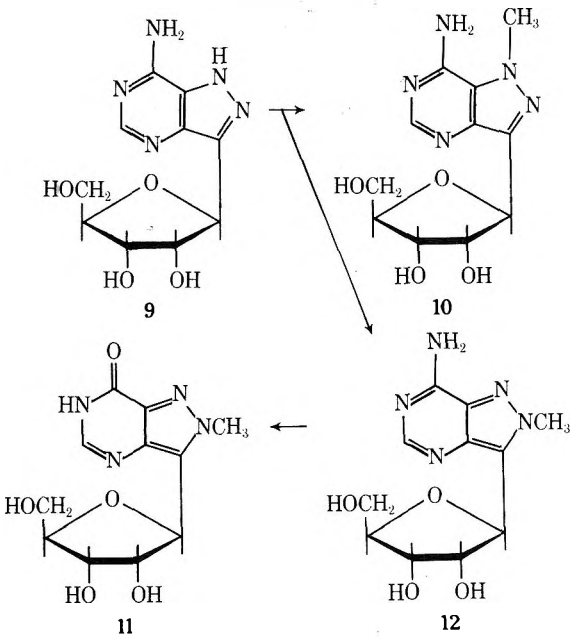
We have recently observed a very close similarity between the magnetic circular dichroism (MCD) spectra of 7-methylpurine[23] and 7-(β-D-ribofuranosyl)purine[24] in our laboratory. MCD should theoretically provide more information than that obtained by the usual spectrophotomet-

ric techniques owing to negative bonds and the increased sensitivity to changes in electronic structure. This sensitivity of MCD spectra to the precise chromophoric structure has been shown to provide definitive spectra for isomeric compounds, *e.g.*, the *N*-methyl (1, 3, 7, and 9) derivatives of purine. Therefore, although the MCD spectra of 7-methylpurine and 7-(β-D-ribofuranosyl)purine are very similar, there was observed a significant difference between 7-methylpurine and the isomeric 1-, 3-, and 9-methylpurines. This prompted us to obtain the MCD spectra of **6**, **7**, and the methylated formycins. The MCD spectra (Figure 1) have provided a very clear distinction between the two methylated derivatives of formycin and allowed us to make definite structural assignments.[25]

Of particular interest is the fact that the spectra observed for 7 and 1-methylformycin are very similar to the spectrum observed for formycin, *per se*. Since the spectra for **6** and 2-methylformycin are so dissimilar to those of formycin and 1-methylformycin, this would suggest that formycin in solution under the present conditions probably exists predominantly with the proton residing on the N-1 nitrogen of the pyrazole moiety. It is of interest that studies[26,27] on the tautomerism of formycin, *per se*, by $^{13}C$ nuclear magnetic resonance has revealed that prototropic tautomerism can be a function of temperature and solvent. Therefore, although MCD spectroscopy may be very useful in the elucidation of tautomeric structures, considerable effort must be expended in this area before any of these preliminary observations can be corroborated and firmly established.

On treatment of **6**, **7**, **10**, and **12** individually with 1 *N* sodium hydroxide at reflux temperature, the position of the ultraviolet maxima was found to shift to lower wavelengths in each case. In view of the structures assigned these compounds (Scheme II), a Dimroth rearrangement

**Scheme II**[a]




[a] All nucleosides have been drawn in the syn conformation, although **9** and **10** probably exist predominantly in either the anti or amphi conformations as per the Discussion Section.

was not deemed possible. This prompted us to conduct the reaction on a larger scale with **7** and **12** and the isolated products were identified as 1,3-dimethylpyrazolo[4,3-*d*]pyrimidin-7-one (**8**) and 2-methyl-3-(β-D-ribofuranosyl)-

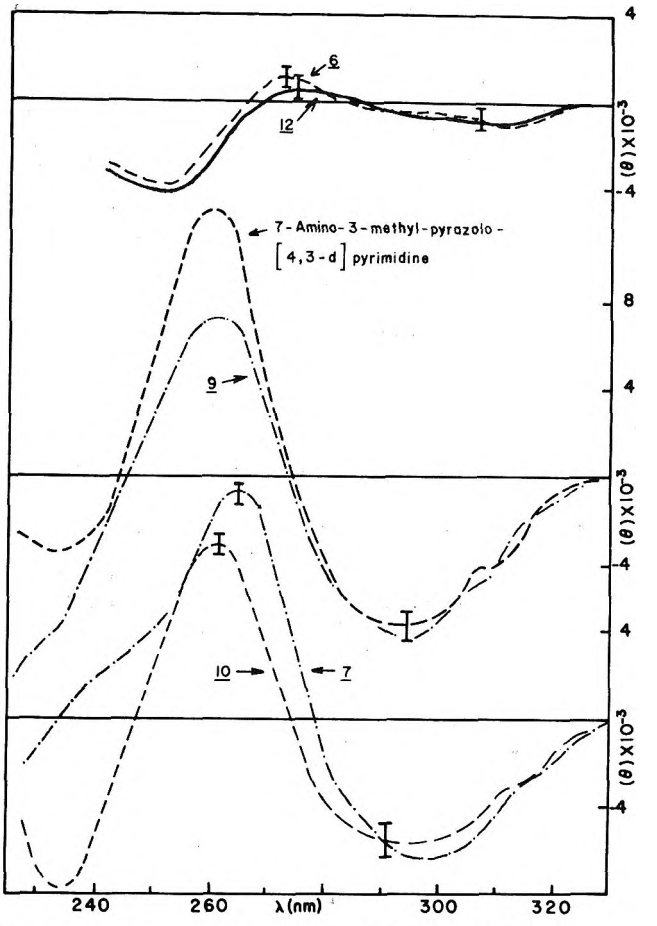



**Figure 1.** MCD spectra of some pyrazolo[4,3-*d*]pyrimidines.

pyrazolo[4,3-*d*]pyrimidin-7-one (**11**). The conversion of an amino group into a hydroxyl function under basic conditions is not normally observed in heterocyclic chemistry, although this conversion has been reported[28] to occur for 3-methylguanine *via* an apparent nucleophilic displacement. The possibility of a ring opening followed by ring closure could not be demonstrated, since chromatography (tlc) of the reaction solutions of **7** and **12** revealed only starting material and product. Apparently, in this case, a nucleophilic displacement of the amino group by base does occur.

It has been observed that **12** exhibited a higher T/C against leukemia L-1210 than **10**, although whether this difference is due to a difference in conformation (syn or anti) or their ability to act as substrates for specific catabolic and anabolic enzymes, etc., will be determined by additional studies.

## Experimental Section[29]

**3-Cyano-1,5-dimethyl-4-nitropyrazole (2).** 5-Cyano-3-methyl-4-nitropyrazole (**1**, 5.0 g) was dissolved in water (100 ml) containing sodium hydroxide (1.4 g) and to this solution was added 3.76 ml of dimethyl sulfate. The solution was stirred for 45 min and then extracted with $CHCl_3$ (2 × 200 ml). The combined $CHCl_3$ extracts were washed with $H_2O$ (100 ml), dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The white solid was dissolved in a minimum amount of boiling MeOH and allowed to stand at 0° for 16 hr. The solid which had separated was removed by filtration. The filtrate was evaporated to *ca.* half volume and the solid was again collected by filtration. The presence of a very small amount of **2** and **3** was detected in the filtrate by tlc. The combined solid was dried at room temperature in a vacuum desiccator over phosphorus pentoxide to yield 3.78 g (69.2%) of **2**. An analytical sample was prepared by three recrystallizations from EtOH–$H_2O$, mp 113–114°.

*Anal.* Calcd for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.39; H, 3.98; N, 33.61.

**4-Amino-3-cyano-1,5-dimethylpyrazole (4).** 3-Cyano-1,5-dimethyl-4-nitropyrazole (**2**, 1.0 g) was treated by the same procedure (A) which yielded **5**. The product was recrystallized from $H_2O$ for analysis to yield 0.23 g (28.8%) of **4**, mp 144–145°.

*Anal.* Calcd for $C_6H_8N_4$: C, 52.94; H, 5.93; N, 41.15. Found: C, 52.68; H, 6.13; N, 41.20.

**4-Amino-5-cyano-1,3-dimethylpyrazole (5). Method A.** 5-Cyano-1,3-dimethyl-4-nitropyrazole[30] (**3**, 2.5 g) was slurried in boiling $H_2O$ (25 ml) and then stirred rapidly during the gradual addition of sodium hydrosulfite (8.7 g). The temperature of the reaction mixture was maintained between 75 and 80° by the rate of addition. After the final addition of sodium hydrosulfite, the solution was filtered immediately and then allowed to stand at 0° for 16 hr. The solid was collected by filtration and recrystallized from $H_2O$ to yield 0.58 g (28.2%) of **5**. Recrystallization from $H_2O$ produced an analytical sample which was dried *in vacuo* at 100°, mp 116–117°.

*Anal.* Calcd for $C_6H_8N_4$: C, 52.94; H, 5.93; N, 41.15. Found: C, 52.70; H, 5.91; N, 41.28.

**Method B.** A solution of **3** (1.66 g) in 100 ml of MeOH was hydrogenated at 1 atm over 5% Pd/C (0.8 g). After the calculated amount of hydrogen had been absorbed, the mixture was filtered through a Celite pad and the pad was washed with warm MeOH (2 × 50 ml). The filtrate and washings were combined and evaporated to dryness. The crude product (mp 115–118°) was recrystallized from $H_2O$ to provide **5** (0.95 g, 69.8%), mp 117–119°, identical in all respects with the sample obtained from method A.

**7-Amino-2,3-dimethylpyrazolo[4,3-*d*]pyrimidine (6).** 4-Amino-3-cyano-1,5-dimethylpyrazole (**4**, 0.18 g) and formamidine acetate (0.2 g) were heated in EtOH (20 ml) at reflux temperature for 2 hr. The EtOH was removed *in vacuo* and the resulting solid was recrystallized from $H_2O$ to yield 0.14 g (65.1%) of **6**. An analytical sample was prepared by two recrystallizations from $H_2O$, mp 289–290° dec.

*Anal.* Calcd for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.75; H, 5.49; N, 43.20.

**7-Amino-1,3-dimethylpyrazolo[4,3-*d*]pyrimidine (7). Method A.** 4-Amino-5-cyano-1,3-dimethylpyrazole (**5**, 1.06 g) and formamidine acetate (1.15 g) were heated in EtOH (50 ml) at reflux temperature for 1 hr. The EtOH was removed *in vacuo*. EtOH (50 ml) was added, and again evaporated to dryness with this procedure being repeated three times. The residue was added to EtOAc (200 ml) at reflux temperature and the small amount of insoluble material was removed by filtration. The filtrate was reduced in volume to *ca.* 100 ml and allowed to stand at 5° for 16 hr. The yellow solid was collected by filtration and recrystallized from EtOAc to yield 0.6 g of **7**, mp 242–244°.

*Anal.* Calcd for $C_7H_9N_5$: C, 51.52; H, 5.56; N, 42.92. Found: C, 51.49; H, 5.50; N, 43.20.

**Method B.** 4-Amino-5-cyano-1,3-dimethylpyrazole (**5**, 0.5 g) and formamidine acetate (0.58 g) were dissolved in absolute EtOH (50 ml) and the solution was heated at reflux temperature. The reaction was monitored by tlc; after 3 hr an additional portion of formamidine acetate (104 mg) was added. The reaction mixture was heated at reflux temperature for an additional 1 hr (total 4 hr). The reaction mixture was evaporated to dryness and the residue was then dissolved in hot EtOAc (*ca.* 100 ml), filtered, and let stand at room temperature for 18 hr. The crystalline material was collected by filtration and air dried to yield **7** (0.53 g, 88.5%), mp 242–244°. This compound was identical in all respects with the sample obtained by method A.

**1-3-Dimethylpyrazolo[4,3-*d*]pyrimidin-7-one (8).** 7-Amino-1,3-dimethylpyrazolo[4,3-*d*]pyrimidine (**7**, 1.1 g) was added to 10 ml of 1 *N* sodium hydroxide and the solution was then heated at reflux temperature for 3 hr. The solution was allowed to cool at room temperature, and Dowex 50W-X4 was added (*ca.* 10 ml of washed resin) with stirring until the pH of the solution was *ca.* 7. The resin was removed by filtration and washed with 40 ml of hot $H_2O$. The filtrate and washings were combined and evaporated to dryness. EtOH (50 ml) was added, and again evaporated to dryness. The resulting solid was dissolved in hot $H_2O$ (30 ml) all insoluble material was removed by filtration, and the solution was allowed to stand at 5° for 18 hr. The solid was collected by filtration and dried at 110° *in vacuo* to yield 0.38 g of **8**, mp 303–304°.

*Anal.* Calcd for $C_7H_8N_4O$: C, 51.22; H, 4.88; N, 34.15. Found: C, 51.19; H, 4.89; N, 33.99.

**2-Methylformycin (12) and 1-Methylformycin (10).** Formycin (**9**, 4.0 g) and sodium (0.44 g) were added to EtOH (100 ml) and the mixture was stirred to effect a clear solution. Methyl iodide (1 ml) was then added and the solution was stirred at room temperature. An additional quantity of methyl iodide (1 ml) was added at the end of the first and the second hour and the solution was then stirred for an additional 16 hr. The solid was removed by filtration, recrystallized from isopropyl alcohol, and dried to yield 1.13 g (24.4%) of 2-methylformycin (**12**). An analytical sample was prepared by two additional recrystallizations from isopropyl alcohol and dried *in vacuo* at 110°, mp 205–206°.

*Anal.* Calcd for $C_{11}H_{15}N_5O_4$: C, 46.98; H, 5.37; N, 24.91. Found: C, 47.01; H, 5.51; N, 25.16.

The filtrate, after removal of the 2-methylformycin (**12**), was evaporated to dryness following the addition of silica gel[31] (3 g). The residue was applied to the top of a dry column (silica gel, 1.5 × 24 in.) and eluted with the upper phase of an ethyl acetate–1-propanol–water (4:1:3) mixture. The fractions were monitored with tlc on SilicAR 7GF in the same solvent system, fractions containing only the compound of $R_f$ 0.48 were collected and combined, and the solvent was removed *in vacuo*. The solid was recrystallized twice from EtOAc–MeOH and dried *in vacuo* at 110° to yield 0.16 g (3.8%) of 1-methylformycin[32] (**10**), mp foams 170–173°, dec >200°.

*Anal.* Calcd for $C_{11}H_{15}N_5O_4$: C, 46.98; H, 5.37; N, 24.91. Found: C, 46.79; H, 5.69; N, 25.03.

**2-Methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidin-7-one (11) (2-Methylformycin B).** 2-Methylformycin (**12**, 0.4 g) was added to aqueous 1 *N* sodium hydroxide (10 ml) and the solution was heated at reflux temperature for 3 hr. The solution was cooled to room temperature, Dowex 50W-X2 ($H^+$, 10 ml, previously washed with 100 ml of $H_2O$) was added, and the mixture was stirred until the pH was adjusted to *ca.* 4. The resin was removed by filtration and washed with boiling $H_2O$ (50 ml). The combined filtrate and washing was evaporated to dryness, and EtOH (50 ml) was added and removed *in vacuo*. This process was repeated again and the resulting solid was recrystallized twice from a mixture of MeOH–EtOAc to yield 0.064 g (16%) of **11**, mp 213–215°.

*Anal.* Calcd for $C_{11}H_{14}N_4O_5$: C, 46.85; H, 5.00; N, 19.87. Found: C, 46.82; H, 5.04; N, 20.18.

**Acknowledgment.** The authors wish to thank Dr. R. P. Panzica for several helpful suggestions.

**Registry No.**—**1**, 28668-15-7; **2**, 51222-23-2; **3**, 32183-13-4; **4**, 51222-24-3; **5**, 32183-14-5; **6**, 51222-25-4; **7**, 51222-26-5; **8**, 51222-27-6; **9**, 6742-12-7; **10**, 51222-28-7; **11**, 51481-59-5; **12**, 42204-46-6.

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(1) This research was supported by Research Contract No. PH-43-65-1041, No. C-72-3710 with the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Public Health Services, and Research Grant No. GM-12862-08, National Institutes of Health.
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# Cyano Adducts of 1-Substituted Pyridinium Salts[1a]

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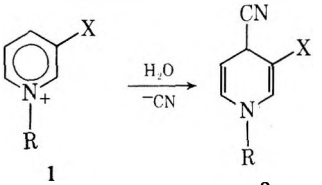
The isolation and characterization of several cyano adducts **11a–e** of 1-substituted pyridinium salts **10** is described. These represent the first examples of this type of compound. In addition, the first Reissert-like compound (**12a**) from pyridine is reported. Contrary to earlier suggestions, the title compounds are relatively stable. An explanation of the stability on the basis of interaction of the N substituent with the reactive dihydropyridine ring is presented.

The synthesis of stable, simple dihydropyridines has received increased attention recently.[2] Such compounds are of interest theoretically[2,3] and as precursors in synthetic applications.[2,4]

It has been shown that cyanide reacts with 1,3-disubstituted pyridinium salts **1** to afford the corresponding 4-cyano adducts **2**.[2] Only salts related to **1** yield isolable



**1** **2**

R = alkyl
X = $CONH_2$, $CO_2Me$, CN, COMe, COPh

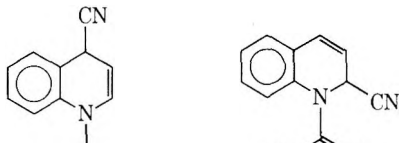
products.[2] That adducts of other salts were not observed was assumed to be due both to the low electrophilicity of the salt and the lack of resonance stabilization of the corresponding cyano adduct which is only possible in species such as **2**.[5]

While 3-unsubstituted pyridinium salts **3** had been found to be unreactive with cyanide,[5] related reactions are

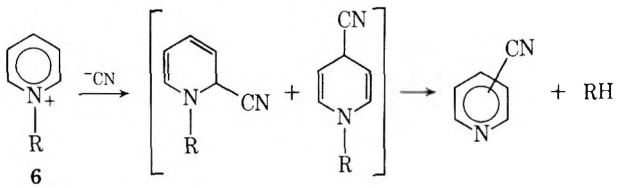
**3**

R = alkyl, aryl, acyl

known. Thus, the corresponding quinolinium adducts (**4**, **5**) have been known for many years,[6,7] while 1-alkoxy- and 1-amidopyridinium salts **6** yield transient cyano adducts which decompose with loss of an alcohol or amide to



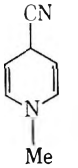
**4** **5**



**6**

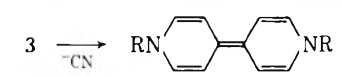
R = OR, RNCOR′

produce cyanopyridines.[8] In contrast to Gauthier's results, cyano adduct **7** was found to be stable in DMSO.[9]



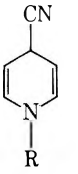
**7**

Within the last several years it has been reported that **3** (R = alkyl or aryl) reacts with cyanide to afford dihydrobipyridine **8** or its oxidized derivatives.[10,11] Although



**8**

there are several possible mechanisms,[10,11b] the initial reaction in each is the formation of a 4-cyano adduct **9**. We now wish to report several examples of **9** which are



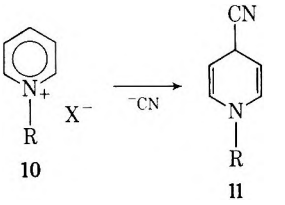
**9**

R = alkyl, aryl

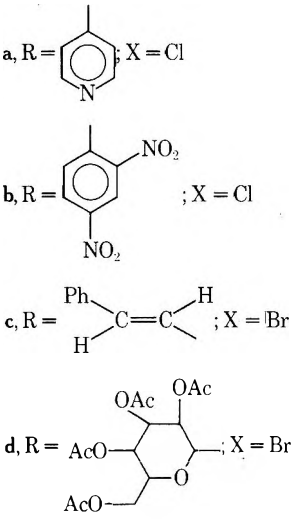
relatively stable and can be readily isolated. These adducts represent a new class of simple dihydropyridines.

## Results

When aqueous solutions of pyridinium salts **10a–e** were treated with sodium cyanide, the corresponding 4-cyano adducts **11** were obtained. The yields ranged from 24% for **11e** to 92% for **11b** as shown in Table I. Since reaction



**10** **11**



times of greater than 2 hr afforded impure **11e** and pyridinium salts dimerize in the presence of cyanide, presumably *via* a cyano adduct as described above, further efforts to obtain a higher yield of **11e** were not made.

The structures of the products were established on the basis of spectroscopic information. An infrared band was noted at 1680–1690 $cm^{-1}$ which has been found to be diagnostic for simple 1,4-dihydropyridines.[1a,12] A $M^+$ peak was observed for each adduct except **11b**, indicating that the compounds were indeed covalent and not ionic. The nmr spectra (Table I) are consistent with the assigned structures and related 1,4-dihydropyridines.[1a,2,4a,12] The observed ultraviolet spectra (Table I) likewise give good agreement with previously published results.[2,4a,12]

The reactions of **10f–i** with cyanide were only partially successful. Reaction of **10f** with cyanide furnished **11f**, which was free from dihydrobipyridine 8 (R = Ph) by infrared and mass spectroscopy.[13] However, as soon as the solid was dissolved, an intense green solution of phenylviologen cation radical was formed. It is known that cyanide induces the dimerization of **10f** to 8 (R = Ph) which

**Table I**
**Properties of 4-Cyano-1,4-dihydropyridines (11)**[a]

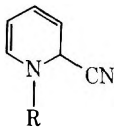
| Compd | R | Yield, % | Solvent | Nmr spectra, chemical shift, τ | | | | Ir max (KBr), $cm^{-1}$ | Uv max ($CHCl_3$), nm (ε) | Decomposition point, °C |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | $H_2$ | $H_3$ | $H_4$ | R | | | |
| **11a** | 4-Pyridyl | 79 | $(CD_3)_2CO$ | 3.0 (d, $J$ = 9.0 Hz) | 5.0 (m) | 5.5 (m) | 2.85 (d, 2, $J$ = 5.0 Hz), 1.50 (d, 2, $J$ = 5.0 Hz) | 2230, 1690 | 289 (8000), 345 (300) | 75–80 |
| **11b** | DNP[b] | 92 | $(CD_3)_2SO$ | 2.2 (m) | 2.7 (m) | 3.5 (m) | 1.4 (m, 1), 1.0 (m, 1), 0.5 (m, 1) | 2220, 1670 | 240 (sh, 18,000),[e] 290 (sh, 10,000),[e] 375 (10,300)[e] | 100 |
| **11c** |  | 50 | $CDCl_3$ | 3.5 (d, $J$ = 7.0 Hz) | 5.2 (m) | 5.6 (m) | 4.0 (d, 1, $J$ = 14.5 Hz), 3.40 (d, 1, $J$ = 14.5 Hz), 2.6 (s, 5) | 2240, 1685 | 315 (23,000) | 75 |
| **11d** | TAG[c] | 63 | $CDCl_3$ | 3.7 (d, $J$ = 7.5 Hz) | 5.3 (m) | 5.5 (m) | 7.9 (q, 12), 6.2 (m, 1), 5.7 (m, 3), 4.7 (m, 3) | 2235, 1760, 1690 | 280 (2400) | 140 |
| **11e** | $CH_2OMe$ | 24 | $CDCl_3$ | 3.8 (d, $J$ = 7.5 Hz) | 5.5 (m) | 5.5 (m) | 6.7 (s, 3), 5.6 (s, 2) | 2250,[d] 1685[d] | 243 (2600), 286 (2000) | |
| **11g** | $CH_2OAc$ | Trace | $CDCl_3$ | 3.8 (d, $J$ = 7.5 Hz) | 5.4 (m) | 5.6 (m) | 7.8 (s, 3), 5.25 (s, 2) | | | |
| **11h** | $CH_2CN$ | Trace | $CDCl_3$ | 3.9 (d, $J$ = 7.0 Hz) | 5.3 (m) | 5.7 (m) | 5.9 (s, 2) | | | |
| **11i** | $CH_2CO_2Et$ | Trace | $CDCl_3$ | 4.0 (d, $J$ = 7.5 Hz) | 5.6 (m) | 5.6 (m) | 8.7 (t, 3, $J$ = 7), 6.2 (s, 2), 5.7 (q, 2, $J$ = 7 Hz) | | | |

[a] Acceptable elemental analyses were obtained for **11a–e**. [b] DNP = 2,4-dinitrophenyl. [c] TAG = tetracetylglucosido. [d] Neat. [e] $CH_3CN$.

is oxidized to the cation radical in solution.[11a] Even with short reaction times, **11f** could not be obtained pure.

Salts **10g–i** yielded less than 5% of the corresponding adducts **11** on exposure to cyanide. The structures were assigned by nmr (Table I) and mass spectroscopy. A small amount of uncharacterized polymeric material was obtained from **10j** and cyanide.

The successful preparation of the above cyano adducts encouraged us to attempt the synthesis of the pyridine analogs of Reissert compounds **5.** Popp[14] has prepared a large number of such compounds by mixing the appropriate acid chloride and quinoline in methylene chloride with aqueous sodium cyanide and stirring the resulting mixture for several hours. This technique was utilized in the attempted synthesis of **12.** Thus, when pyridine, ethyl chloroformate, and cyanide were combined as above, 1-carbethoxy-2-cyano-1,2-dihydropyridine (**12a**) was obtained in 25% yield. The elemental analysis and spectral data are consistent with the assigned structure. An infrared absorption at 1650 $cm^{-1}$, which has been found to be characteristic of 1,2-dihydropyridines,[1a,12] was noted. A $M^+$ peak at $m/e$ 178 was observed. The observed $\lambda_{max}$ at 302 nm is consistent with that of similar 1-acyl-1,2-dihydropyridines,[4a,15] as is the nmr spectrum.[4a,15,16]



12

a, R = $CO_2Et$
b, R = $CONMe_2$
c, R = PhCO
d, R = $PhSO_2$
e, R = $NO_2PhCO$
f, R = o-$NO_2PhSO_2$
g, R = MeCO
h, R = $Me_3Si$
i, R = NO
j, R = CN

The attempted syntheses of **12b–j** were unsuccessful. The reactions led to uncharacterized mixtures of starting material, hydrolysis products of the acid chloride, or polymeric materials. The nmr spectra of the crude mixture from the attempted synthesis of **12i** and **12j** suggested the presence of a small amount of 2-cyanopyridine. While mass spectral data indicated that the desired **12d, 12f, 12i,** and **12j** were not obtained, a peak was observed at $m/e$ 104 as expected for cyanopyridine. These data suggest that in these cases some of the desired product was formed but decomposed with loss of RH (R = $PhSO_2$, o-$NO_2PhSO_2$, NO, CN) in a manner analogous to the 1-alkoxy- and 1-amidopyridinium salts described above. No evidence for either cyano adducts or cyanopyridine was observed in the other reactions.

It is known that benzoyl chlorides react with cyanide in the presence of pyridine to afford a complex mixture of products which does not contain pyridine.[17] Such a mixture was obtained from benzoyl chloride, *p*-nitrobenzoyl chloride, and probably dimethylcarbamoyl chloride.

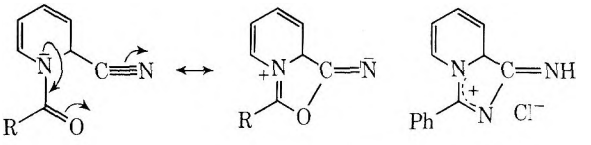
The reaction of ethyl chloroformate and dimethylcarbamoyl chloride, which is known to form a stable salt with pyridine,[18] with cyanide and pyridine was investigated in other systems in an effort to achieve the desired result. Thus, the reagents were combined in methanol, tetrahydrofuran, dichloromethane, and dichloromethane and 1 equiv of $SbCl_5$. However, **12b** was not obtained nor was their any evidence for cyanopyridine observed. While **12a** was obtained in all cases except in the presence of $SbCl_5$, the yield was no better. In addition, Popp's method with reaction times up to 16 hr still gave the same yield of **12a** and afforded none of the desired **12b.**

## Discussion

**Position of Attack.** It is unclear why 1-alkyl- and 1-arylpyridinium salts (**10**) afforded 4-cyano adducts (**11**) while 1-carboethoxypyridinium chloride furnished a 2-cyano adduct (**12a**). Identical behavior is observed in the quinolinium system (**4, 5**). However, again there is no explanation for this dichotomy, although it has been suggested that the carbonyl function guides the cyanide to the 2 position.[7]

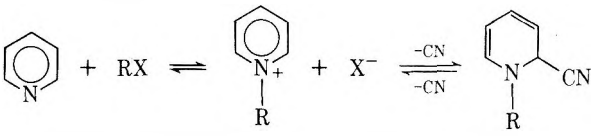
It has been established that 2-cyano adducts (kinetic product) rearrange to the more stable (thermodynamic product) 4-cyano adducts, at least for compounds similar to **2.**[2] Since it has been shown that the 1,4-dihydropyridine structure is about 2 kcal/mol more stable than the 1,2-dihydropyridine structure,[3] it is reasonable that the 4-cyano adducts (**11**) should represent the products from thermodynamic control.

A wide variety of enolate anions and related species have been observed to attack the 4 position of 1-acylpyridinium salts.[19a] However, evidence of initial attack at the 2 position in some cases has been reported.[19b] The stability of 2-cyano adducts[7] as opposed to 4-cyano adducts may be due to a favorable interaction between the carbonyl and cyano groups as shown. This interaction has been suggested to account for the stability of **13.**[19c]



13

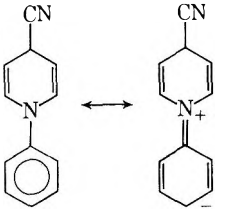
**Unreactive Pyridinium Salts.** The lack of reactivity of 1-acylpyridinium salts might be due to two factors. First, formation of the salt is an equilibrium reaction[20] which could be coupled to an equilibrium between salt and adduct[2] as shown. Unfavorable equilibria for either reaction



would make it difficult to obtain the desired cyano adducts **12.** A second difficulty encountered is attack of cyanide or other nucleophiles ($H_2O$), not on the ring, but at R to give acyl cyanides and related compounds.[17,21] However, 1-acylpyridinium salts have been found to react with several different nucleophilic species to furnish dihydropyridines,[19a] which implies that conditions might be found which would allow the isolation of the corresponding cyano adducts.

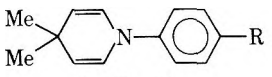
The apparent lack of reactivity of **10g–j** is presumably due to relatively low electrophilicity of the salt. Other workers have noted this behavior.[5,9]

**Stability of the Adducts.** Since simple dihydropyridines are generally unstable[2] and cyanide was predicted to be unreactive toward simple salts like **10,**[5] yet the adducts **11a–e** and **12a** are readily obtained, there are obviously some stabilizing factors in these compounds. Resonance stabilization as shown below is obviously one factor.



Such resonance interaction would decrease the electron density of the reactive dihydropyridine, thus minimizing the importance of decomposition reactions usually observed with simply dihydropyridines.

This explanation is completely analogous to the stabilizing effect of substituents at the 3 and 5 positions which are capable of electron withdrawal by resonance interaction (*i.e.*, **2**).[2,5] Kosower[12c] has interpreted the uv spectra of 1-aryl-1,4-dihydropyridines **14** in terms of resonance interaction between the substituents and the electron pair on nitrogen. The resistance of 1-phenyl-1,4- and 1,2-dihydropyridines (**15a** and **15b**) to reduction by sodium bor-



**14a**, R = H
b, R = $NO_2$
c, R = CN

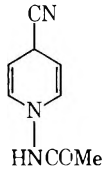
**15a**

**15b**

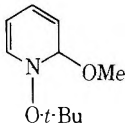
ohydride has been attributed to conjugation of the phenyl and dihydropyridine rings.[23]

The stability of **11d** and **11e** is unique. Since no resonance interactions are possible, perhaps inductive electron withdrawal is responsible for stabilizing the adducts. However, this does not explain why **11g-i** are not equally as stable. Tetracetylglucosido (TAG) is particularly effective in stabilizing the dihydropyridine ring.[24] As judged from its decomposition point and inertness upon recrystallization, **11d** appears to be the most stable adduct isolated. Wallenfels[25] has reported that TAG's stabilizing effect is due to inductive electron withdrawal which makes the pyridinium salt highly electrophilic and, therefore, highly reactive with nucleophiles.[25] In the corresponding dihydropyridine, the electron-withdrawing effect by TAG reduces the electron density of the ring, thus making oxidation (and presumably dimerization, etc.) more difficult relative to other 1-alkyl (or related) dihydropyridines.[25b]

Compounds **16** and **17** have been isolated, although they readily decompose to the corresponding pyridines.[26,27]



**16**



**17**

The limited stability of these compounds is also presumably due to inductive electron withdrawal.

While one can envision some stabilization due to inductive effects, it is not easy to understand why they are apparently so important in compounds with ether substituents (**11d, 11e**). The possible biological implications of the tremendous stabilizing ability of TAG are obvious.

## Experimental Section[28]

**1-(4-Pyridyl)-4-cyano-1,4-dihydropyridine (11a).** A solution of 3.0 g (15.6 mmol) of **10a** (Aldrich) in 35 ml of water was outgassed for 10 min with nitrogen. The addition of potassium cyanide (2.0 g, 30.0 mmol) caused a red solid to precipitate. The flask was stoppered and left in the dark overnight at room temperature. The solid was collected and dried under vacuum to afford 2.25 g (79%) of red **11a**: mass spectrum (70 eV) *m/e* (rel intensity) 183 ($M^+$, 15), 182 (21), 157 (30), 79 (15), 78 (19), 27 (100), 26 (17).

A solution of 1.15 g (5 mmol) of **10a** hydrochloride (Aldrich) and 0.42 g (5 mmol) of sodium bicarbonate in 20 ml of water was filtered[29] and purged with nitrogen for 30 min. To this solution was added 0.49 g (10 mmol) of sodium cyanide. The solution was stirred for 15 min while being flushed with nitrogen. The resulting red solid was collected, washed well with water, and dried under vacuum to afford 0.49 g (53%) of **11a**.[30]

**1 - (2,4 - Dinitrophenyl) - 4 - cyano - 1,4 - dihydropyridine (11b).**[31] After a solution of **10b** (1.40 g, 5 mmol) in 20 ml of water was purged with nitrogen for 30 min, sodium cyanide (0.49 g, 5 mmol) was added. The solution was stirred under nitrogen for 5 min to afford a brown solid, which was collected and dried under vacuum to yield 1.25 g (92%) of **11b**: mass spectrum (70 eV) *m/e* (rel intensity) 184 (70), 79 (82), 78 (100), 27 (40).

**1-(*trans*-2-Styryl)-4-cyano-1,4-dihydropyridine (11e).** After a solution of 0.54 g (1.93 mmol) of **10c** hydrate[32] in 10 ml of water was purged with nitrogen for 5 min, sodium cyanide (0.15 g, 3.06 mmol) was added. The solution was shaken for 1 min, then kept under nitrogen for 5 min, and finally extracted with chloroform (2 × 15 ml). The extracts were dried ($MgSO_4$) and concentrated to afford 0.20 g (50%) of **11c**: mass spectrum (70 eV) *m/e* (rel intensity) 208 ($M^+$, 2), 182 (25), 103 (13), 79 (13) 77 (12), 28 (100), 27 (41).

**1-Tetracetylglucosido-4-cyano-1,4-dihydropyridine (11d).** A solution of 2.71 g (5.53 mmol) of **10d**[33] in 10 ml of water was layered with 20 ml of methylene chloride. To the stirred mixture was added dropwise over 20 min 10 ml of water containing 0.50 g (10.2 mmol) of sodium cyanide. After the resulting mixture was stirred for 10 min, the layers were separated and the water layer was extracted with 20 ml of methylene chloride. The extracts were combined, dried (sodium carbonate), and concentrated under vacuum to yield 1.51 g (63%) of brown, crystalline solid. Recrystallization of 0.50 g from acetone-water afforded 0.25 g of tan plates of **11d**: mass spectrum (70 eV) *m/e* (rel intensity) 436 ($M^+$, 1) 79 (44), 43 (100), 27 (56).

**1-Methoxymethyl-4-cyano-1,4-dihydropyridine (11e).** Pyridine and chloromethyl methyl ether were combined to afford 1-methoxymethylpyridinium chloride (**10e**). A solution of **10e** (3.6 g, 22.5 mmol) in 20 ml of water was layered with 70 ml of methylene chloride and outgassed with nitrogen for 5 min. To the stirred mixture was added under nitrogen 10 ml of water containing 1.1 g (22.5 mmol) of sodium cyanide. After stirring for 2 hr under nitrogen, the mixture was poured into ether and the solution was washed with water. The ether was dried ($MgSO_4$) and concentrated to afford 0.8 g (24%) of green oil **11e**: mass spectrum (70 eV) *m/e* (rel intensity) 150 ($M^+$, 50), 124 (25), 119 (100), 45 (90). The oil darkened on standing.

**Attempted Synthesis of 1-Phenyl-4-cyano-1,4-dihydropyridine (11f).** A solution of 0.96 g (5.0 mmol) of **10f**[34] in 20 ml of water was purged with nitrogen for 15 min. Sodium cyanide (0.49 g, 10.0 mmol) was added and the flask was stoppered. After standing at room temperature in the dark overnight, impure **11f** as a waxy, brown solid (0.13 g) was obtained. Solutions of this material exhibited the characteristic uv spectrum of phenylviologen cation radical:[11c] ir (neat) 2230 (CN), 2120, 1680 $cm^{-1}$ (1,4-dihydropyridines); mass spectrum (70 eV) *m/e* (rel intensity) 182 ($M^+$, 74), 181 (86), 156 (100), 77 (47), 27 (76).

*Anal.* Calcd for $C_{12}H_{10}N_2$: C, 79.12; H, 5.49; N, 15.38. Found: C, 78.68; H, 5.26; N, 11.55.

A solution of 0.85 g (4.50 mmol) of **10f** in 5 ml of water was layered with 20 ml of methylene chloride and purged with nitrogen for 10 min. To the stirred mixture under nitrogen was added dropwise over 10 min 5 ml of water containing 0.32 g (6.50 mmol) of sodium cyanide. After 10 min the layers were separated and the aqueous layer was extracted with 20 ml of methylene chloride. The extracts were dried ($K_2CO_3$) and concentrated to afford 0.3 g of brown solid. The infrared and mass spectra were identical with those above. Solutions of the solid again exhibited the spectrum of phenylviologen cation radical.

**1-Acetoxymethyl-4-cyano-1,4-dihydropyridine (11g).** Pyridine and bromomethyl acetate were mixed in ether to afford **10g**. A solution of **10g** (2.3 g, 10 mmol) in 10 ml of water was layered with 35 ml of methylene chloride and outgassed with nitrogen for 5 min. Sodium cyanide (0.5 g, 10 mmol) in 10 ml of water was added and the reaction was carried out as in the synthesis of **11e** above to yield a small amount of green oil **11g** which darkened on standing; mass spectrum (70 eV) *m/e* 119, 104, 93, 79, 78, 57, 26; ir ($CHCl_3$) 2270 (CN), 1705 $cm^{-1}$; uv max ($CHCl_3$) 240, 290 nm (sh).

**1-Cyanomethyl-4-cyano-1,4-dihydropyridine (11h).** Chloroacetonitrile and pyridine were added to THF to afford 1-cyanomethylpyridinium chloride (**10h**). Sodium cyanide (0.2 g, 4 mmol) and 0.6 g (4 mmol) of **10h** were allowed to react as above

to afford a small yield of green oil **11h** which darkened on standing: mass spectrum (70 eV) *m/e* 119, 79, 57, 49, 47, 44, 26; ir ($CHCl_3$) 2285 (CN), 2205 (CN), 1685 $cm^{-1}$ (1,4-dihydropyridines); uv max ($CHCl_3$) 243, 290 nm (sh).

**1-Carboethoxymethyl-4-cyano-1,4-dihydropyridine (11i).** Ethyl chloroacetate and pyridine were combined in THF to yield **10i.** Sodium cyanide (0.7 g, 14 mmol) and 2.8 g (14 mmol) of **10i** were allowed to react as above to furnish a small amount of green oil **11i** which darkened on standing: mass spectrum (70 eV) *m/e* 192 ($M^+$), 191, 166, 163, 138, 119, 105, 93, 29, 26; ir ($CHCl_3$) 2270 (CN), 1740 (C=O), 1685 $cm^{-1}$ (1,4-dihydropyridine); uv max ($CHCl_3$) 243, 290 nm (sh).

**1-Carboethoxy-2-cyano-1,2-dihydropyridine (12a).** A solution of 6.3 g (80 mmol) of pyridine and 12.0 g (245 mmol) of sodium cyanide in 40 ml of water was layered with 60 ml of methylene chloride. After the mixture was purged with nitrogen for 5 min, 17.5 g (163 mmol) of ethyl chloroformate was added dropwise (*ca.* 20 min) under nitrogen with stirring. The resulting mixture was stirred for an additional 1 hr, poured into 200 ml of water, and extracted with 200 ml of ether. The extract was concentrated under vacuum, poured into dilute hydrochloric acid (*ca.* $10^{-3}$ *M*), and extracted with ether. The ether solution was washed with saturated sodium bicarbonate and water, dried, and concentrated under vacuum to afford 3.5 g (25%) of **12a** as a red liquid: ir ($CHCl_3$) 1720 (C=O), 1650 $cm^{-1}$ (1,2-dihydropyridine); uv max ($CHCl_3$) 304 nm; nmr ($CDCl_3$) $\tau$ 8.70 (t, 3, $J$ = 7.0 Hz), 5.65 (q, 2, $J$ = 7.0 Hz), 4.35 (m, 3), 3.75 (m, 1) 3.00 (d, 1, $J$ = 7.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 178 ($M^+$, 6), 105 (32), 79 (100), 78 (61).

*Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.62. Found: C, 60.17; H, 5.74.

**Registry No.**—**10a,** 22752-98-3; **10b,** 4185-69-7; **10c,** 26154-94-9; **10d,** 51364-78-4; **10e,** 51364-79-5; **10f,** 13958-90-2; **10g,** 51364-80-8; **10h,** 17281-59-3; **10i,** 27032-03-7; **11a,** 51364-81-9; **11b,** 51364-82-0; **11c,** 51364-83-1; **11d,** 51381-70-5; **11e,** 51364-84-2; **11f,** 51364-85-3; **11g,** 51364-86-4; **11h,** 51364-87-5; **11i,** 51364-88-6; **12a,** 51364-89-7.

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(1) (a) Taken in part from the Ph.D. Thesis of R. H. R., Drexel University, 1972. (b) NSF Predoctoral Fellow, 1968–1971. (c) Address all correspondence to this author at Department of Chemistry, Virginia Commonwealth University, Academic Center, Richmond, Va. 23220.
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(28) All melting points were determined using a Buchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Ultraviolet spectra were determined on a Perkin-Elmer 402 spectrometer. Nuclear magnetic resonance spectra were recorded using a Varian A-60A spectrometer. The chemical shifts are relative to TMS as internal standard. The mass spectra were obtained with a RMU-6 mass spectrometer. Elemental microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.
(29) Solutions of **10a** hydrochloride and sodium bicarbonate precipitated an amorphous brown sludge.
(30) When using **10a** hydrochloride, it was necessary to isolate the product within 1 hr or **11a** was obtained impure.
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# Cycloaddition of 1-Azirines to 1,3-Diphenylisobenzofuran and Rearrangement of the Adducts[1]


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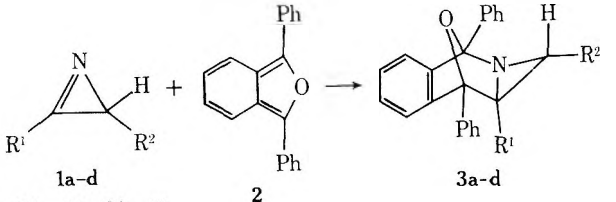
1-Azirines **1** and 1,3-diphenylisobenzofuran (**2**) react smoothly and efficiently in refluxing toluene to afford the simple 1:1 adducts **3,** possessing the exo configuration. Two of the adducts, **3a** and **3b,** were found to rearrange in the presence of neutral alumina, to give the epoxybenzo-2*H*-azepines **20a** and **20b.** Chemical reactions (water, alcohol, $LiAlH_4$) of the adducts **3** generally involved initial opening of the oxido bridge in a regiospecific manner. When more vigorous conditions were used, rupture of the aziridine ring usually followed.


The role of 1-azirines **1** as dienophilic components in Diels–Alder reactions with cyclopentadienones has recently been demonstrated and developed by us[2-5] and others.[6] The products were 3*H*- or 2*H*-azepines but only indirect evidence for the intermediacy of Diels–Alder adducts (7-norbornanones) was obtained. In an effort to isolate related Diels–Alder adducts, we examined, concurrently with our investigations of the cyclopentadienone system, 1,3-diphenylisobenzofuran (**2**) as the diene component. In the meantime a note has appeared[7] on this very same reac-

tion. We describe here our detailed results on the reaction of **1a-d** with **2**, and a novel rearrangement of some of the initial adducts **3**, catalyzed by neutral alumina.

## Results and Discussion

**A. Structures.** When azirines **1a-d** and isobenzofuran **2** were allowed to react in refluxing toluene for 2–24 hr, the 1:1 adducts **3a-d** were obtained in 80–90% yield. The



**1a-d** **2** **3a-d**

a, $R^1$ = Ph; $R^2$ = H
b, $R^1$ = Ph; $R^2$ = Me
c, $R^1$ = H; $R^2$ = Ph
d. $R^1$ = H; $R^2$ = *t*-Bu

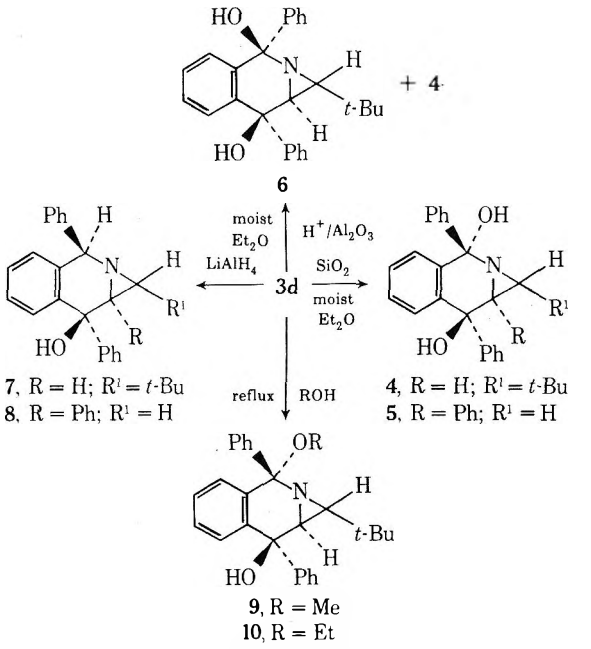
products were thermally stable in refluxing toluene (for 15 days) and though unstable to neutral alumina (see below), they could be purified by passage through a column of Merck acid-washed alumina. The structures of **3** were assigned in analogy with **3b**[7] and on the basis of spectra and chemical reactions.[8] For instance, the low-field position ($\tau$ 6.48) of the quartet in **3b** indicated considerable deshielding of this portion by the oxido bridge,[9] demonstrating the exo relationship. Similar deshielding effects have been observed[10-14] in cyclopropene adducts of **2**. The nmr analyses of the other adducts, **3a**, **3c**, and **3d**, contributed additional structure proof for the exo configuration. For example, the singlets at $\tau$ 7.70 and 6.66 in **3a**, although unresolved even at 100 MHz, were coupled ($J_{gem}$ < 0.2 Hz) as indicated by the fact that irradiation of either peak did cause an increase in the amplitude of the other. It is well known[15,16] that geminal coupling in aziridines is low (0–2 Hz). The adducts **3c** and **3d** (formed by the *in situ* generation of the azirines **1c** and **1d** from the terminal vinyl azides[4]) possessed small vicinal coupling constants of 2.4 and 2.7 Hz, respectively, thus proving the trans arrangement of the aziridine ring protons.

3,3-Dimethyl-2-phenylazirine failed to react with **2** in refluxing toluene. A similar inertness to reaction of this azirine with cyclopentadienones was also observed[2] and explanations were offered[5] to account for this.

In order to have a diagnostic probe for the nmr, most of the subsequent chemical reactions were conducted with the *tert*-butyl adduct **3d**.

**B. Oxido Bridge Opening.** When the crude reaction mixture containing **3d** was chromatographed over silica gel, a small amount of diol **4** (in addition to pure **3d**) was isolated. This reaction was carried out more efficiently by stirring the adduct **3d** with silica gel in USP-grade ether. An analogous product **5** was also noted from the reaction of **3a** on silica gel. The trans-diol structure assignment is based on the assumption that the more stable trans diol will be formed preferentially and in analogy with hydride opening of the oxido bridge, which is expected to proceed in a trans manner. When crude **3d** was chromatographed on Merck acid-washed alumina, and solvent mixtures containing undistilled ether were used as eluents, two isomers indicating the incorporation of one molecule of water were separated. The minor one, mp 171°, corresponded to **4** while the major component (mp 130°) had similar ir and nmr properties, and has tentatively been assigned the isomeric cis-diol structure **6**.[17]

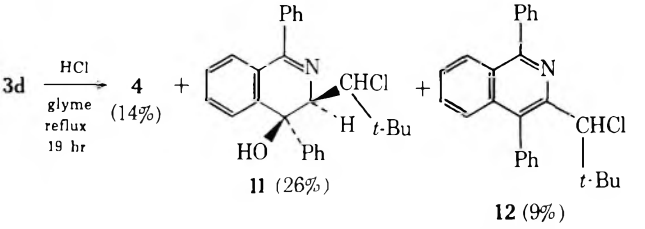
The utility of this reaction was examined with other nucleophiles such as alkoxide and hydride. By refluxing **3d** in an appropriate alcohol, opening of the oxido bridge oc-



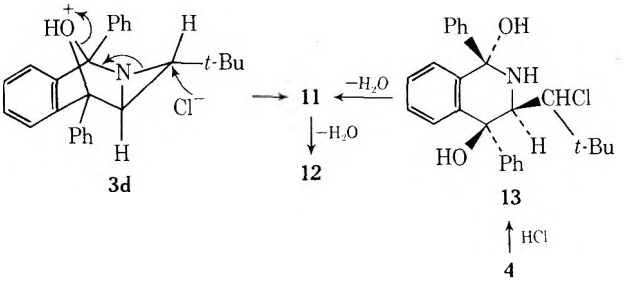

curred regiospecifically with the incorporation of a molecule of solvent to give the adducts **9** and **10**.

To prove the regiochemistry of opening we selected hydride as the nucleophile. Opening of **3b** by $LiAlH_4$ was postulated[7] to proceed to **8** on the basis of the chemical shift of the benzylic hydrogen. We were able to verify this assignment by the isolation of **7**, from the reduction of **3d**. The singlet ($\tau$ 5.63) for the benzylic hydrogen clearly indicated that hydride had entered at the carbon atom of the oxido bridge next to the aziridine ring nitrogen. The regioselective opening of the oxido bridge by $H_2O$, alkoxide, or hydride vicinally to the aziridine N suggests that the latter is capable of stabilizing adjacent incipient positive charges without undergoing ring opening. Backside trans opening of the oxido bridge is assumed.

Treatment of **3d** with concentrated HCl in refluxing glyme for 19 hr produced three products, **4**, **11**, and **12**, separated by ptlc. The first product **4** corresponded to that isolated from the hydration of **3d** on silica gel. The second product **11**, to which the dihydroisoquinoline structure has been assigned, may have been formed directly from **3d** as outlined, or indirectly from **4** *via* **13**.



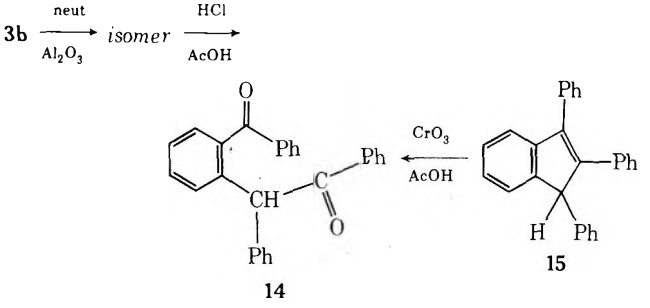

Opening to a seven-membered ring was ruled out by the nmr spectra. When **4** was treated under the reaction conditions it was smoothly converted to **12**, presumably via **11** which on dehydration yielded **12**. Similarly **11** was converted to **12**.



**C. Isomerization of Adducts.** As mentioned earlier, the adducts **3a-d** were purified by chromatography over Merck acid-washed alumina. We have found that this technique conveniently removes excess azirine from the product and that the azirines are not eluted from the column even when methanol is used as eluent (considerable amount of azirine still contaminated **3a** and **3b** after chromatography on silica gel). However, when the crude reaction mixture containing **3b** was chromatographed over Woelm neutral alumina (activity I) (or the pure adduct **3b** was merely stirred in solution with the chromatographic support) a colorless, crystalline isomer, mp 158°, was obtained very quickly (<1 hr) and in good yield (50-60%). Spectra comparison, chemical conversions, and synthetic schemes discussed below led to the elucidation of its structure as **20b.**

The ir spectrum indicated the absence of the OH, NH, and C=O moieties, while the nmr spectrum clearly indicated the intactness of the -CHMe- unit (three-proton doublet, $J$ = 6.5 Hz) at $\tau$ 8.68 and one-proton quartet at $\tau$ 6.35. The aromatic region displayed a 17 H multiplet at $\tau$ 3.10-2.30 and a low-field 2 H multiplet at $\tau$ 2.25-2.00, characteristic of the ortho protons of a benzene ring attached to a C=N, as observed in 3*H*- and 2*H*-azepines.[5]

Furthermore, the isomer failed to react with $LiAlH_4$, dilute HCl-methanol reflux, or refluxing KOH-MeOH, and it was unchanged by thermolysis in refluxing xylene. However upon treatment with refluxing glacial acetic acid containing a few drops of concentrated HCl it was converted to the diketone **14** [$\nu_{max}$ (KBr) 1672 and 1650 $cm^{-1}$]. The latter was independently synthesized by the chromic acid oxidation of 1,2,3-triphenylindene (**15**). This degradation gave a clue as to the structure of one side of the molecule, but since the other part (containing the methyl group) had been lost it was necessary to examine whether the same isomerization process can be observed with the other adducts **3.**

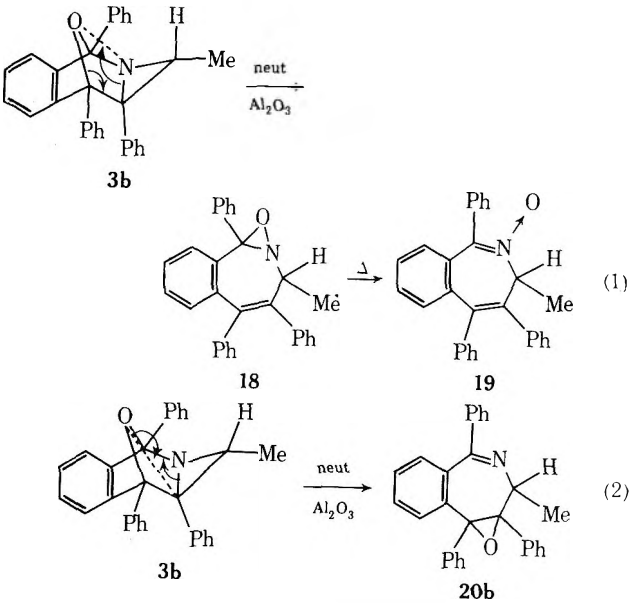


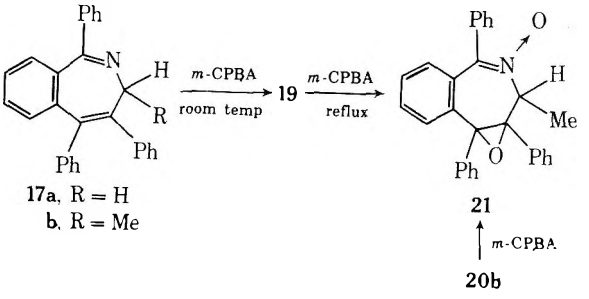

**14** **15**

Unfortunately, the isomerizations of **3a, 3c,** and **3d** were neither as clean nor as rapid as with **3b.** However, in analogy with **3b,** they all gave colorless solutions in chloroform or ether which rendered a blue-green fluorescence on treatment with neutral alumina. The *tert*-butyl adduct **3d** showed no rearrangement (by nmr or tlc) after 5 days. However, on exposure of **3a** to neutral alumina, a crystalline isomer (**20a**) was isolated in low yield. Whereas the nmr spectrum of **3a** had shown two singlets at $\tau$ ($CDCl_3$) 7.70 and 6.66 for the aziridine ring protons, the isomer displayed two doublets ($J$ = 10.5 Hz, each 1 H) at $\tau$ ($CDCl_3$) 6.42 and 5.22. It proved fortunate that this work was conducted concurrent with our study on cyclopentadienones,[2] since it was soon recognized that the nmr spectra of the isomers of **3a** and **3b** were very similar to those of the 2*H*-azepine adducts **17a** and **17b** derived from 1,3-diphenylinden-2-one (**16**) and the azirines **1a** and **1b.**[3,5] For example, **17a** showed two doublets ($J$ = 10 Hz, each 1 H) at $\tau$ 6.40 and 5.06; **17b** had a doublet ($J$ = 6.5 Hz, 3 H) at $\tau$ 8.55 and a quartet (1 H) at $\tau$ 6.40.

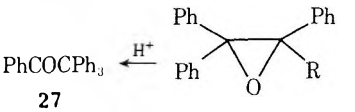
Two structures, the *N*-oxide **19** arising *via* **18** or the epoxide **20** formed by direct rearrangement of **3** (see Scheme I), would fit all the data described. In fact **19,** conveniently prepared as colorless crystals, mp 218°, from the 2*H*-azepine **17b,** possessed different physical and chemical properties than those of the isomer of **3b.** This excluded path 1. A direct synthesis of **20b** (path 2) from **17b** was not possible; however, when the 2*H*-azepine **17b** was heated in $CHCl_3$ with excess *m*-chloroperbenzoic acid (*m*-CPBA) it was slowly converted to the epoxide **21** (*via* **19**).

**Scheme I**



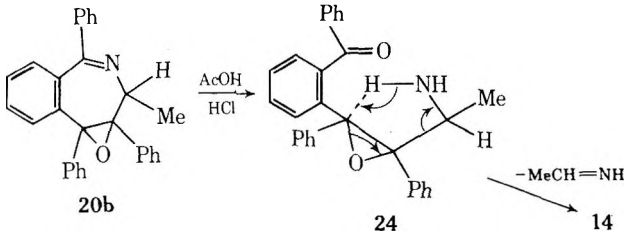

When the isomer of **3b** was treated with *m*-CPBA in chloroform at 25° it was converted to the same *N*-oxide **21.** It was therefore concluded that the isomerization of the adducts **3a** and **3b** on neutral alumina affords the epoxy-2*H*-azepines **20a** and **20b.** Scheme I (path 2) points out again the ability of the aziridine N to participate in the opening of the oxido bridge. The inertness of **20b** to acid, base, and $LiAlH_4$ may be compared to the resistance of tetraphenylethylene oxide (**22**) to these three reagents.[8] Similarly, 1-methyl-1,2,2-triphenylethylene oxide (**23**) was reported[19] to be "relatively stable" to aqueous $H_2SO_4$.




**27**

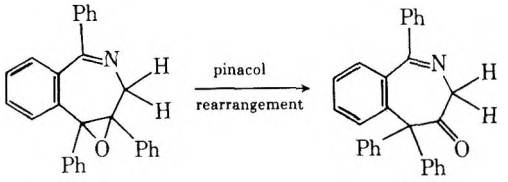
**22**, R = Ph
**23**, R = Me

Several processes may be postulated to account for the production of the diketone **14** on AcOH-HCl hydrolysis of **20b,** one of which is shown. It involves initial hydrolysis of the C=N bond to afford **24,** which then undergoes a hydrogen transfer with elimination of acetaldehyde imine to give **14.**

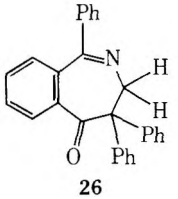



20b 24 14

When the crude adduct **3a** was adsorbed in a column of neutral alumina and allowed to stand overnight, elution the following day produced a small amount of the epoxide **20a.** However, the major product isolated turned out to be yet another isomer of **3a.** This material was obtained as colorless crystals, mp 176°, $\tau$ ($CDCl_3$) 5.23 (s, 2 H), 3.20–2.40 (m, 19 H). This isomer has been assigned the cyclic ketone structure **25,** rather than the regioisomer **26,** on the




20a 25




26

basis of its ir adsorption (1710 $cm^{-1}$). Both may be interpreted as being formed *via* a pinacol-type rearrangement of **3a.**[20] Similar rearrangements have been observed in other epoxides,[18a] for example **22** → **27,** and in adducts of 1,3-diphenylisobenzofuran (**2**) with cyclopropenes,[11] although in this latter case the opposite regioisomer was formed. The appearance of the methylene ring protons of **25** as a singlet in the nmr spectrum showed that ring inversion was fairly rapid on the nmr time scale when compared to the epoxy compound **20a** and the 2*H*-azepine **17a.**

## Experimental Section[21]

**Reaction of 2-Phenyl-1-azirine (1a) with 1,3-Diphenylisobenzofuran (2). Adduct 3a.** $\alpha$-Azidostyrene (2.0 g, 13.8 mmol) was converted to **1a** by heating[22] under reflux in toluene (25 ml) for 2 hr, at which time gas evolution had ceased, and the furan (2.70 g, 10 mmol) was added. The mixture was refluxed for an additional 17 hr until the blue-green fluorescence due to **2** disappeared. The solvent was removed to yield an orange oil, which was chromatographed over Merck acid-washed alumina. Ether–hexane (1:2) eluted a colorless foam (3.60 g, 93%). Trituration in hexane with cooling gave a white solid. Recrystallization from hexane gave the exo adduct **3a** (3.25 g, 84%) as colorless crystals: mp 94°; nmr ($CDCl_3$) $\tau$ 7.70 (s, 1 H), 6.66 (s, 1 H), 3.40–3.10 (m, 2 H), 3.00–1.90 (m, 17 H); $\nu_{max}$ (KBr) 1451, 1311, 1020, 1007, 995, 769 (s), and 710 $cm^{-1}$ (s); mass spectrum *m/e* (rel intensity) 387 (17), 386 (13), 359 (17), 285 (13), 284 (54), 282 (20), 271 (77), 270 (100), 252 (10), 241 (39), 239 (17), 206 (14), 173 (16), 165 (21), 117 (20), 105 (18), 103 (11), 77 (22).

*Anal.* Calcd for $C_{28}H_{21}NO$: C, 86.8; H, 5.5. Found: C, 86.6; H, 5.4.

**Reaction of 3-Methyl-2-phenyl-1-azirine (1b) with 2. Adduct 3b.** The furan and the azirine[22] were refluxed in toluene for 24 hr as for **3a.** Chromatography and elution with hexane–ether (3:1) gave a colorless foam (3.70 g, 92%), which on cooling and trituration with hexane gave large, colorless crystals (3.60 g, 90%). Recrystallization from hexane produced the pure exo adduct **3b** as colorless crystals: mp 110° (lit.[7] mp 192–194°);[8] nmr ($CDCl_3$) $\tau$ 8.95 (d, $J$ = 6.0 Hz, 3 H), 6.48 (q, $J$ = 6.0 Hz, 1 H), 3.55–3.20 (m, 2 H), 3.10–1.90 (m, 17 H); $\nu_{max}$ (KBr) 1450, 1312, 1021, 760 (s), and 710 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 401 (14), 359 (8), 296 (12), 283 (9), 271 (23), 270 (100), 241 (12), 239 (7), 165 (8), 131 (36), 130 (10), 115 (5), 105 (6), 104 (6), 103 (9), 77 (11).

*Anal.* Calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.8. Found: C, 86.9; H, 5.9.

**Reaction of 3-Phenyl-1-azirine (1c) with 2. Adduct 3c.** The furan (1.0 g, 3.72 mmol) and *trans*-$\beta$-azidostyrene[23] (0.90 g, 6.19 mmol) were heated in toluene (15 ml) for 1.5 hr. Work-up as described for **3a** gave 1.2 g of **3c,** and after recrystallization 0.94 g (65%) as colorless granules: mp 145°; nmr ($CDCl_3$) $\tau$ 7.16 (d, $J$ = 2.4 Hz, 1 H), 6.07 (d, $J$ = 2.4 Hz, 1 H), 2.95–2.00 (m, 19 H); $\nu_{max}$ (KBr) 1454, 1316, 990, 756, and 707 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 387 (21), 384 (24), 283 (100), 282 (33), 271 (14), 270 (51), 241 (13), 178 (10), 165 (14), 105 (26), 77 (27).

*Anal.* Calcd for $C_{28}H_{21}NO$: C, 86.8; H, 5.5. Found: C, 86.8; H, 5.5.

**Reaction of 3-*tert*-Butyl-1-azirine (1d) with 2. Adduct 3d.** *trans*-1-Azido-3,3-dimethylbut-1-ene[22] (2.1 g, 16.8 mmol) and the furan (2.7 g, 10 mmol) heated in toluene (15 ml) for 16 hr and worked up as above produced **3d** as a white solid (3.01 g, 82%), recrystallized from hexane: colorless needles, mp 104°; nmr ($CDCl_3$) $\tau$ 9.04 (s, 9 H), 7.40 (d, $J$ = 2.7 Hz, 1 H), 7.25 (d, $J$ = 2.7 Hz, 1 H), 3.00–2.70 (m, 4 H), 2.60–1.90 (m, 10 H); $\nu_{max}$ (KBr) 1450, 1313, 987, 763, 751, and 707 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 367 (7), 284 (24), 283 (100), 282 (5), 271 (8), 270 (28), 241 (7), 239 (5), 165 (7), 105 (8), 77 (5); m* 218.5 is 367 → 283.

*Anal.* Calcd for $C_{26}H_{25}NO$: C, 85.0; H, 6.9. Found: C, 85.0; H, 6.95.

**Hydration of the *tert*-Butyl Adduct 3d on Silica Gel.** The adduct **3d** (510 mg) was stirred in USP-grade ether (40 ml) in the presence of Fisher silica gel (10 g, 28–200 mesh) for 21 hr, after which time the silica was filtered and washed with anhydrous ether (50 ml). Removal of the solvent gave a foam (510 mg, 95%) which rapidly solidified on trituration with hexane. Recrystallization from hexane gave the pure trans diol **4** (373 mg, 70%) as colorless crystals: mp 171°; nmr ($CDCl_3$) $\tau$ 9.04 (s, 9 H), 7.55–7.25 (br, 2 H), 2.85–2.10 (m, 14 H); addition of $D_2O$ resolved the broad adsorption at $\tau$ 7.55–7.25 into two sharp doublets ($J$ = 3.8 Hz, each 1 H) at $\tau$ 7.46 and 7.36; $\nu_{max}$ (KBr) 3400–2700 (br d), 1460, 1450 (sh), 1210, 1065, 1058, 973, 948, 922, 767, and 710 $cm^{-1}$; mass spectrum *m/e* 385, 367, 328, 287, 283 (100), 270, 235, 209, 105; m* 252 is 328 → 287, m* 218.5 is 367 → 283.

*Anal.* Calcd for $C_{26}H_{27}NO_2$: C, 81.0; H, 7.1. Found: C, 80.8; H, 7.1.

**Hydration of the *tert*-Butyl Adduct 3d on Acid-Washed Alumina.** The crude reaction mixture containing **3d** [formed from the furan **2** (1.0 g, 3.7 mmol) and the vinyl azide (2.0 g, 16 mmol) in refluxing toluene (15 ml) for 5 hr] was chromatographed over Merck acid-washed alumina. Ether–hexane (1:4) eluted the exo adduct **3d** (700 mg, 51%). Increasing amounts of ether (up to 100%) eluted an oil (712 mg) from which the trans diol **4** separated (47 mg, 3%). The residual oil was subjected to ptlc and the fastest running component was removed, giving a colorless solid (222 mg, 16%). Recrystallization from hexane yielded colorless crystals of the cis diol **6:** mp 130°; nmr ($CDCl_3$) $\tau$ 9.00 (s, 9 H), 7.95 (br d, 1 H), 7.32 (br d, 1 H), 2.85–2.05 (m, 14 H); addition of $D_2O$ resolved the two broad doublets ($J$ = 3.4 Hz); $\nu_{max}$ (KBr) 3500–3000 (br), 1462, 1210, 1202, 1049, 910, 775, 761, and 707 $cm^{-1}$; mass spectrum *m/e* 385, 367, 328, 310, 300, 287, 283 (100%), 270, 241, 235, 209, 195, 178, 165, 152, 105, 99; m* 350 is 385 → 367, m* 218.5 is 367 → 283.

*Anal.* Calcd for $C_{26}H_{27}NO_2$: C, 81.0; H, 7.1; N, 3.6. Found: C, 81.2; H, 7.2; N, 3.7.

**Reaction of the *tert*-Butyl Adduct 3d with Methanol.** The adduct **3d** (200 mg) was heated under reflux in absolute methanol (15 ml) for 24 hr. Removal of the solvent and crystallization of the residue from hexane yielded the trans methoxy alcohol **9** (84 mg, 39%) as colorless crystals: mp 118°; nmr ($CDCl_3$) $\tau$ 9.01 (s, 9 H), 7.68 (br d, $J$ = 3.0 Hz, 1 H), 7.48 (br d, $J$ = 3.0 Hz, 1 H), 6.66 (s, 3 H), 2.80–2.20 (m, 14 H); addition of $D_2O$ resolved the two broad doublets; $\nu_{max}$ (KBr) 3285, 1450, 1076, 990 (s), 763, and 709 $cm^{-1}$; mass spectrum *m/e* 399, 367, 310, 300, 283 (100%), 270, 241, 193, 178, 165, 105, 77; m* 218.5 is 367 → 283.

*Anal.* Calcd for $C_{27}H_{29}NO_2$: C, 81.2; H, 7.3. Found: C, 81.2; H, 7.4.

**Reaction of the *tert*-Butyl Adduct 3d with Ethanol.** The adduct **3d** (700 mg) heated in ethanol (25 ml) for 2 hr afforded 573 mg (72%) of the trans ethoxy alcohol **10:** mp 145°; nmr ($CDCl_3$) $\tau$ 9.00 (s, 9 H), 8.85 (t, $J$ = 7 Hz, 3 H), 9.20–8.50 (v br, 1 H), 7.80–7.40 (v br, 2 H), 6.70–6.15 (2 q, AB, $J$ = 7.0 and 2.5 Hz, 2 H),

2.85–2.20 (m, 14 H); upon addition of $D_2O$ the broad signal at $\tau$ 9.20–8.50 disappears and the broad signal at $\tau$ 7.80–7.40 is resolved into two doublets ($J$ = 3.0 Hz, each 1 H) at $\tau$ 7.66 and 7.51; $\nu_{max}$ (KBr) 3275, 1076, 994, 882, 768, and 711 $cm^{-1}$; mass spectrum $m/e$ 413, 384, 367, 315, 287, 283 (100%), 270, 241, 209, 193, 178, 165, 105; m* 269.5 is 367 → 315, m* 261.5 is 315 → 287, m* 252 is 287 → 270, m* 218.5 is 367 → 283.

*Anal.* Calcd for $C_{28}H_{31}NO_2$: C, 81.3; H, 7.6; N, 3.4. Found C, 81.5; H, 7.7; N, 3.5.

**Reduction of the *tert*-Butyl Adduct 3d with $LiAlH_4$.** The adduct **3d** (256 mg, 0.7 mmol) was heated under reflux for 24 hr in tetrahydrofuran (15 ml) containing $LiAlH_4$ (40 mg, 1.05 mmol). An aqueous work-up provided a colorless foam (200 mg, 78%) which on extended trituration and cooling to −78° produced crystals. Recrystallization from hexane yielded the pure aziridino alcohol **7** as colorless crystals: mp 66°; nmr ($CDCl_3$) $\tau$ 9.00 (s, 9 H), 8.39 (d, $J$ = 3.0 Hz, 1 H), 7.90 (s, 1 H, OH), 7.14 (d, $J$ = 3.0 Hz, 1 H), 5.63 (s, 1 H), 3.00–2.45 (m, 13 H), 2.20–1.95 (m, 1 H); $\nu_{max}$ (KBr) 3450 (br), 1491, 1450, 1011, 768, 740, and 707 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 369 (48), 352 (13), 326 (25), 312 (10), 285 (24), 284 (100), 283 (13), 271 (11), 201 (24), 206 (36), 193 (16), 179 (16), 178 (16), 165 (11), 105 (13), 86 (61), 71 (29).

*Anal.* Calcd for $C_{26}H_{27}NO$: C, 84.5; H, 7.4. Found: C, 84.5; H, 7.5.

**Treatment of the *tert*-Butyl Adduct 3d with HCl. A.** The aziridine **3d** (200 mg, 0.545 mmol) was heated under reflux for 19 hr in glyme (5 ml) containing 3 drops of concentrated HCl. The solvent was removed and the yellow-green foam was extracted with chloroform–water. The organic layer was washed with dilute $Na_2CO_3$ solution and dried over $MgSO_4$ to give a yellow foam (159 mg). The foam was applied to a silica gel preparative plate (20 × 20 × 0.2 cm) and eluted with ether–hexane (1:1). Three bands were extracted with ether; the slowest (30 mg, 14%) was shown to be the trans diol **4**, mp 171°. The center band provided colorless crystals (59 mg, 26%) from hexane of **3-chloroneopentyl-4-hydroxy-1,4-diphenylisoquinoline (11):** mp 163°; nmr ($CDCl_3$) $\tau$ 8.80 (s, 9 H), 6.30 (v br, -OH), 5.95 (d, $J$ = 5.3 Hz, 1 H), 5.07 (d, $J$ = 5.3 Hz, 1 H), 2.80–2.20 (m, 14 H); $\nu_{max}$ (KBr) 3580 (w), 1606, 1446, 1327, 1320, 1164, 963, 797, 777, 764, and 710 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 403 (1), 388 (2), 369 (14), 368 (48), 352 (2), 346 (3), 310 (5), 271 (23), 270 (100), 241 (9), 193 (5), 165 (7), 105 (8); characteristic $^{35}Cl$ and $^{37}Cl$ pattern for $m/e$ 403, 388, 346, and 310 peaks.

*Anal.* Calcd for $C_{26}H_{26}NOCl$: C, 77.2; H, 6.5. Found: C, 77.3; H, 6.5.

The fastest component (21 mg, 9%) afforded colorless crystals from hexane of **3-chloroneopentyl-1,4-diphenylisoquinoline (12):** mp 182°; nmr ($CDCl_3$) $\tau$ 8.87 (s, 9 H), 5.10 (s, 1 H), 2.75–1.60 (m, 14 H); $\nu_{max}$ (KBr) 1385, 777, 756, and 710 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 385 (6), 350 (7), 335 (5), 334 (10), 332 (7), 331 (26), 330 (23), 329 (100), 328 (22), 296 (14), 295 (57), 294 (47), 293 (45), 292 (45), 291 (22), 290 (10), 258 (6), 71 (10); m* 261 is 329 → 293; $^{35}Cl$ and $^{37}Cl$ patterns for $m/e$ 385, 370, and 329 peaks.

*Anal.* Calcd for $C_{26}H_{24}NCl$: C, 81.0; H, 6.3. Found: C, 81.1; H, 6.4.

**B.** When the reaction was allowed to proceed for 68 hr before work-up, the isoquinoline **12** was isolated (85%) directly. Neither the trans diol **4** nor the dihydroisoquinoline **11** was detected by tlc or nmr after 68 hr at reflux.

**Reaction of the Trans-Diol 4 with HCl.** The diol **4** (205 mg, 0.53 mmol) was heated under reflux in glyme (5 ml) containing 6 drops of concentrated HCl for 22 hr. Removal of the solvent gave a yellow solid, which was dissolved in chloroform and washed with dilute $Na_2CO_3$ solution. The organic layer was dried with $MgSO_4$ and the solvent was removed to afford a yellow oil (200 mg) which rapidly solidified. (Nmr analysis of this solid showed it to be at least 90% pure isoquinoline **12.**) Recrystallization from hexane gave the pure isoquinoline **12,** mp 182°.

**Hydration of 3a on Silica Gel.** $\alpha$-Azidostyrene (1.5 g, 10.3 mmol) was heated under reflux for 2 hr in toluene. The furan (2.0 g, 7.4 mmol) was added and the mixture was refluxed for an additional 23 hr. The solvent was removed and the oil was chromatographed on silica gel. Ether–hexane (1:4) eluted the adduct **3a** (900 mg) contaminated with a small amount of azirine **1a.** Increasing amounts of ether (USP grade) eluted a foam (1.9 g) which was mainly **3a.** However, the later fractions crystallized on trituration with hexane. In this manner there was obtained a sand-like material (400 mg). Recrystallization (with charcoal) from chloroform–hexane gave colorless needles (286 mg, 10%) of the trans diol **5:** mp 186°; nmr ($CDCl_3$) $\tau$ 9.30–8.55 (v br, 1 H), 7.85 (br s, 1 H), 6.93 (br s, 1 H), 3.30–2.92 (m, 3 H), 2.92–2.16 (m, 16 H); the high-field signal $\tau$ 9.30–8.55 disappears with $D_2O$ and the two broad singlets become sharp; $\nu_{max}$ (KBr) 3320, 1450, 1211, 1061, 993, 969, 946, 791, 779, 766, 710, and 625 $cm^{-1}$; mass spectrum $m/e$ 405, 387, 386, 359, 284, 282, 271, 270, 252, 241, 239, 209, 206, 193, 178, 165, 152, 135, 119, 117, 105, 91, 77.

*Anal.* Calcd for $C_{28}H_{23}NO_2$: C, 82.9; H, 5.7; N, 3.5. Found: C, 82.8; H, 5.8; N, 3.5.

**Isomerization of the Adduct 3b to 20b with Neutral Alumina. A.** The reaction mixture containing crude **3b** [formed from the azirine **1b** (500 mg, 3.8 mmol) and the furan **2** (950 mg, 3.5 mmol) in refluxing toluene (15 ml) for 24 hr] was chromatographed over Woelm neutral alumina (activity I). Upon absorption, the chromatographic support acquired a brilliant green-blue fluorescence. Elution with benzene caused the fluorescent material to move down the column. There was obtained a blue-green fluorescent oil which rapidly solidified (600 mg, 81%). Recrystallization from hexane gave colorless crystals of **3,4-epoxy-2-methyl-3,4,7-triphenylbenz[*e*]-2*H*-azepine (20b):** mp 158°; nmr ($CDCl_3$) $\tau$ 8.68 (d, $J$ = 6.5 Hz, 3 H), 6.35 (q, $J$ = 6.5 Hz, 1 H), 3.10–2.30 (m, 17 H), 2.25–2.00 (m, 2 H); $\nu_{max}$ (KBr) 1594, 1567, 1448, 1295, 960, 767, and 700 $cm^{-1}$; mass spectrum $m/e$ 401, 359, 296, 286, 283, 275, 252, 209, 165, 152, 131, 105, 77.

*Anal.* Calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.8; N, 3.5. Found: C, 86.8; H, 5.8; N, 3.4.

**B.** The pure aziridine **3b** (211 mg) was stirred at 25° in benzene (20 ml) containing Woelm neutral alumina (10 g, activity I). The mixture rapidly acquired a blue-green fluorescence. After 2 hr the color had faded. The mixture was filtered to yield (after recrystallization from hexane) the epoxy-2*H*-azepine **20b** (115 mg, 55%). The time required for completion of this isomerization was variable (1–50 hr) depending upon the alumina and the solvent.

**Reaction of the Epoxy-2*H*-azepine 20b with Concentrated HCl–Acetic Acid.** The epoxide **20b** (126 mg, 0.315 mmol) was heated under reflux for 4 hr in glacial acetic acid (2.5 ml) containing 2 drops of concentrated HCl. The solvent was removed to give an orange oil, which was taken up in chloroform, washed with dilute $Na_2CO_3$ solution, and dried over $MgSO_4$. There was obtained a fluorescent yellow-green gum (95 mg) which slowly solidified. Recrystallization from hexane yielded **1-(*o*-benzoylphenyl)-1-phenylacetophenone (14)** as colorless crystals: mp 91°; nmr ($CDCl_3$) $\tau$ 3.33 (s, 1 H), 2.80–1.85 (m, 19 H); $\nu_{max}$ (KBr) 1672, 165 1274, 1223, 937, and 707 $cm^{-1}$; mass spectrum $m/e$ 376, 271, 255, 254, 241, 194, 165, 105, 93, 86, 77.

*Anal.* Calcd for $C_{27}H_{20}O_2$: C, 86.1; H, 5.4. Found: C, 85.9; H, 5.4.

**Oxidation of 1,2,3-Triphenylindene (15).**[24] The indene (500 mg, 1.45 mmol) and chromium trioxide (450 mg, 4.5 mmol) were stirred in glacial acetic acid (15 ml) at 50–70° for 15 min, at which time the hot mixture was poured into ice water (50 ml). Extraction with ether, followed by washing with water and dilute NaOH solution, gave a brown oil (450 mg). This was applied to a preparative tlc plate (silica, 20 × 20 × 0.2 cm) and eluted with ether–hexane (3:7). The faster band afforded the diketone **14** (100 mg, 18%), mp 91°. The slower band yielded 1,2-dibenzoylbenzene (133 mg, 22%).

**Isomerization of 3a to 20a on Neutral Alumina.** The furan **2** (1.0 g, 3.7 mmol) and the azirine **1a** (0.7 g, 6.0 mmol) were heated under reflux in toluene (12 ml) for 24 hr. The solvent was removed and the crude adduct **3a** was dissolved in chlorform. The solution was added to a dry column of Woelm neutral alumina (activity I) and the column was allowed to stand for 20 hr before eluting. The adsorbed material turned orange. Elution with ether afforded the furan **2** (100 mg, 10%) closely followed by a colorless oil (200 mg, 14%) which soon solidified. Recrystallization gave pure **3,4-epoxy-3,4,7-triphenylbenz[*e*]-2*H*-azepine (20a)** as colorless prisms from hexane: mp 152°; nmr ($CDCl_3$) $\tau$ 6.42 (d, $J$ = 10.5 Hz, 1 H), 5.22 (d, $J$ = 10.5 Hz, 1 H), 3.00–1.90 (m, 19 H); $\nu_{max}$ (KBr) 1600, 1447, 1309, 946, 770, and 705 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 387 (17), 285 (22), 284 (100), 282 (21), 270 (29), 252 (12), 207 (38), 206 (57), 193 (22), 178 (14), 105 (14).

*Anal.* Calcd for $C_{28}H_{21}NO$: C, 86.8; H, 5.5. Found: C, 87.0; H, 5.6.

Methanol eluted an amorphous orange solid (900 mg). Attempted purification by recrystallization (with charcoal) from methanol gave orange, leafy needles (36 mg), mp 165°. An analytical sample was prepared by ptlc and provided **4,4,7-triphenylbenz[*e*]-2*H*-azepin-3-one (25)** as cream needles: mp 176°; nmr ($CDCl_3$) $\tau$ 5.23 (s, 2 H), 3.20–2.40 (m, 19 H); $\nu_{max}$ (KBr) 1710, 770, and 704 $cm^{-1}$; mass spectrum $m/e$ (rel intensity) 388 (10), 387 (33), 360 (12), 359 (56), 358 (100), 282 (7), 281 (13), 280 (6), 268 (8), 253 (6), 252 (9), 118 (5), 75 (8).

*Anal.* Calcd for $C_{28}H_{21}NO$: C, 86.8; H, 5.5. Found: C, 86.5; H, 5.5.

**Oxidation of the 2*H*-Azepine 17b with *m*-CPBA. A.** The azepine **17b**[3,5] (129 mg, 0.335 mmol) was dissolved in chloroform (5 ml) at 25° and *m*-chloroperbenzoic acid (100 mg, 0.66 mmol) was added to the stirred solution. After 1.5 hr the solution was washed with dilute $Na_2CO_3$ solution and dried over $MgSO_4$. Removal of the solvent gave an oil (135 mg) which rapidly solidified. Recrystallization from chloroform–hexane gave pale yellow-green crystals (79 mg, 59%) of **2-methyl-3,4,7-triphenylbenz[*e*]-2*H*-azepine *N*-oxide (19):** mp 219°; nmr ($CDCl_3$) $\tau$ 8.50 (d, $J$ = 7.0 Hz, 3 H), 5.52 (q, $J$ = 7.0 Hz, 1 H), 3.10–2.00 (m, 19 H); $\nu_{max}$ (KBr) 1490, 1480, 1445, 1226 (N → O), 780, 757, and 704 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 401 (100), 385 (32), 384 (79), 369 (10), 359 (14), 357 (19), 356 (20), 343 (11), 324 (25), 285 (37), 284 (41), 283 (13), 280 (19), 278 (12), 270 (11), 269 (17), 268 (59), 267 (13), 265 (15), 252 (17), 290 (12), 165 (14), 117 (10), 115 (18), 105 (40), 91 (19), 83 (11), 77 (34).

*Anal.* Calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.8. Found: C, 86.6; H, 5.9.

**B.** Oxidation of 243 mg (0.635 mmol) of **17b** with 2.62 mmol of the peracid led to quantitative conversion to the *N*-oxide **19** (by tlc). Refluxing of the reaction mixture for 6 hr produced 253 mg of a foam, which on trituration with ether–hexane and recrystallization from chloroform–hexane provided greenish crystals (144 mg, 55%) of **3,4-epoxy-2-methyl-3,4,7-triphenylbenz[*e*]-2*H*-azepine *N*-oxide (21):** mp 231°; nmr ($CDCl_3$) $\tau$ 8.62 (d, $J$ = 6.7 Hz, 3 H), 5.45 (q, $J$ = 6.7 Hz, 1 H), 3.05–2.20 (m, 17 H), 2.05–1.80 (m, 2 H); $\nu_{max}$ (KBr) 1493, 1446, 1276, 1255, 1236, 770, 760, and 709 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 417 (11), 359 (11), 270 (13) 268 (15), 165(10), 117 (22), 115 (25), 105 (100), 91 (23) 77 (54).

*Anal.* Calcd for $C_{29}H_{23}NO_2$: C, 83.4; H, 5.55. Found: C, 83.2; H, 5.65.

**Oxidation of the Epoxy-2*H*-azepine 20b with *m*-CPBA.** Reaction of the epoxide **20b** (300 mg, 0.75 mmol) with the peracid (1.52 mmol) in chloroform (15 ml) for 5 hr afforded a foam (284 mg, 91%) which on trituration with hexane and recrystallization gave the epoxy-2*H*-azepine *N*-oxide **21** (198 mg, 63%), mp 231°, identical in all spectral properties with that obtained in the previous experiment, **17b → 19 → 21.**

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**Registry No.**—**1a,** 7654-06-0; **1b,** 16205-14-4; **1c,** 18886-64-1; **1d,** 50805-53-3; **2,** 5471-63-6; **3a,** 50805-46-4; **3b,** 34806-16-1; **3c,** 50805-47-5; **3d,** 50805-48-6; **4,** 50805-49-7; **5,** 50805-50-0; **6,** 51018-04-3; **7,** 50805-51-1; **9,** 50883-39-1; **10,** 50805-52-2; **11,** 50805-38-4; **12,** 50805-39-5; **14,** 50805-40-8; **15,** 38274-35-0; **17b,** 39934-15-1; **19,** 50805-41-9; **20a,** 50805-42-0; **20b,** 50805-43-1; **21,** 50805-44-2; **25,** 50805-45-3.

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(8) Our product **3b** melted at 110° and we were unable to obtain the melting point (192–194°) for this adduct as reported,[7] in spite of the fact that satisfactory spectral and elemental analyses were obtained by us. However, the nmr spectral data were in agreement. Similar dimorphism has been observed with the adduct **28** obtained from cyclopropene and 1,3-diphenylisobenzofuran. See ref 14.
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# Stevens Rearrangement of Carbamoylaminimides

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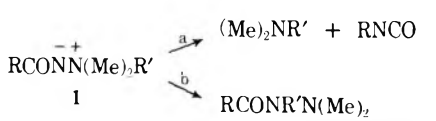
Carbamoylaminimides (**7**) with 1-allyl and 1-benzyl substituents undergo thermal Stevens rearrangements to give semicarbazides (**8**). Thermolysis of 1-(3-methyl-2-butenyl)- and 1-(2-butenyl)aminimides (**9** and **11**) give products resulting from allyl retention, thus ruling out a concerted mechanism for the $N_1 \rightarrow N_2$ allyl rearrangement.

Thermolysis of aminimides derived from carboxylic acids (**1**) has been extensively studied.[1] Isocyanates (or isocyanurates) are obtained from thermolysis of 1,1,1-trimethylamine acylimides[2] and 1-aryl-1,1-dimethylamine acylimides[3] *via* a Curtius-type rearrangement initiated by loss of a tertiary amine (path a). Thermolysis of acylaminimides with 1-allyl[4] and 1-benzyl[5] substituents results in Stevens rearrangement products (path b). Thermolysis of certain 1-benzyl-substituted acylaminimides gives both




Stevens and Curtius products.[6] Products which cannot be rationalized by a Curtius-type mechanism are obtained from thermolysis of 1,1,1-trimethylamine-2-arylcarbamoylimides (**2**). We have found that the major products from the thermolysis of 1,1,1-trimethylamine-2-phenylcar-

bamoylimide (**2a**) are trimethylamine, nitrogen, carbon monoxide, and 1,3-diphenylurea.[7] A thorough study of the latter has been recently reported by Wawzonek, Plaisance, and Boaz,[8] who identified several minor products from the thermolysis of **2a** and observed analogous results for the 1-naphthyl analog (**2b**). The latter workers also reported that thermolysis of the N,N-disubstituted compounds (**3**) affords indazoles (**5**) which result from cyclization of amino isocyanates (**4**).

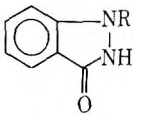
$$\text{RNHCONN}^{-+}(\text{Me})_3 \longrightarrow (\text{Me})_3\text{N} + \text{CO} + \text{N}_2 + \text{PhNHCONHPh}$$

**2a**, R = Ph
**b**, R = 1-naphthyl

$$\text{PhRNCONN}^{-+}(\text{Me})_3 \xrightarrow[-(\text{Me})_3\text{N}]{} [\text{PhRNNCO}] \longrightarrow$$

**3a**, R = Ph
**b**, R = Me

**4**



**5**

This paper reports the results of our study of the thermal Stevens rearrangement of carbamoylaminimides.

The carbamoylaminimides (**7**) were prepared by neutralization of the appropriate 1,1,1-substituted semicarbazonium salts (**6**). The series included carbamoylaminimides with phenylcarbamoyl, *N,N*-dimethylcarbamoyl and *N,N*-diphenylcarbamoyl substituents.

All of the 1-allyl- and 1-benzyl-substituted aminimides underwent thermal Stevens rearrangements to give semicarbazides (**8**). Thermolysis of the propargyl compound (**7f**) gave unidentified tars. No other products could be isolated from these reactions, thus indicating that the thermolysis pathway for these compounds is apparently not dependent on the carbamoyl substituents as was observed for **2** and **3**. The properties of the semicarbazides (**8**) obtained from the thermal rearrangements are given in Table III. In most instances these compounds were also prepared by carbamoylation of the appropriate trisubstituted hydrazine.

$$\text{R}_1\text{R}_2\text{NCONHN}^{+}(\text{Me})_2\text{R}_3\text{X}^- \xrightarrow{\text{OH}^-} \text{R}_1\text{R}_2\text{NCONN}^{-+}(\text{Me})_2\text{R}_3 \xrightarrow[\Delta]{\text{(except 6f)}} \text{R}_1\text{R}_2\text{NCONR}_3\text{N(Me)}_2$$

**6** **7** **8**

a. $R_1 = R_2 = Me$; $R_3 = CH_2CH{=}CH_2$
b. $R_1 = R_2 = Me$; $R_3 = CH_2Ph$
c. $R_1 = R_2 = Ph$; $R_3 = CH_2CH{=}CH_2$
d. $R_1 = Ph$; $R = H$; $R_3 = CH_2CH{=}CH_2$
e. $R_1 = Ph$; $R = H$; $R_3 = CH_2Ph$
f. $R_1 = Ph$; $R = H$; $R_3 = CH_2C{\equiv}CH$

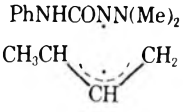
The Stevens rearrangement of allyl-substituted aminimides may proceed by either an allowed concerted [2,3] suprafacial rearrangement or by a nonconcerted radical dissociation-recombination pathway. Baldwin, Brown, and Cordell[9] have reported convincing evidence for a radical mechanism in the Stevens rearrangement of 1-allylic-substituted acylaminimides. Radical trapping[10] and CIDNP[11] have also been employed to support a radical process in the rearrangement of 1-benzyl-substituted acylaminimides.

We have conducted experiments that rule out a simple concerted process for the Stevens rearrangement of 1-allyl-substituted carbamoylaminimides. The 1-(3-methyl-2-butenyl) compound (**9**) was found to thermally rearrange with complete allyl retention to give **10**. Thermolysis of the 1-(2-butenyl) compound (**11**) afforded a mixture that contained 1,1-dimethyl-2-(2-butenyl)-4-phenylsemicarbazide (**12**) and 1,1-dimethyl-2-(1-methyl-2-propenyl)-4-phenylsemicarbazide (**13**) in a ratio of 1:3. Both **12** and **13** were synthesized by the reaction of phenyl isocyanate with the appropriate trisubstituted hydrazine and were found to be stable at 145° (thermolysis temperature) and 185°. Although our results do not lend themselves to detailed mechanistic interpretation (except to exclude a concerted process) the radical dissociation-recombination pathway proposed by Baldwin, Brown, and Cordell[9] could satisfactorily account for the results. The formation of both **12** and **13** in the thermolysis of **11** could be accounted for by assuming competitive concerted and radical processes[12] or by recombination of the radical pair **14** at both

$\text{PhNHCONN}^{-+}\text{R(Me)}_2$ **9**, R = $CH_2CH{=}C(Me)_2$; **11**, R = $CH_2CH{=}CHMe$

$\text{PhNHCONRN(Me)}_2$ **10**, R = $CH_2CH{=}C(Me)_2$; **12**, R = $CH_2CH{=}CHMe$; **13**, R = $CHMeCH{=}CH_2$

$$\mathbf{11} \longrightarrow \text{PhNHCONN(Me)}_2 \longrightarrow \mathbf{12} + \mathbf{13}$$



**14**

the 1 and 3 positions of the crotyl radical. The exclusive formation of **10** from the thermolysis of **9** could be accounted for by selective recombination of the radical pair to give the more stable allylic isomer.[13]

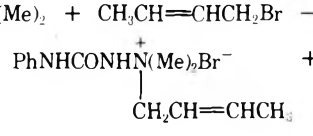
The formation of products resulting from both allylic inversion and retention has also been reported for 1-(2-butenyl)-1,1-dimethylamine-2-acetimide[14] and 1-(3-phenyl-2-propenyl)-1,1-dimethylamine-2-acetimide.[15]

Further evidence to support a radical process for these allylic rearrangements was not obtained from CIDNP experiments on **7a**. Compound **7a** failed to give evidence of CIDNP at 104° ($t_{1/2}$ *ca.* 9 min) or 127° ($t_{1/2}$ 1–2 min). Failure to observe CIDNP with this compound does not preclude a radical process for its rearrangement to **8a**.[16]

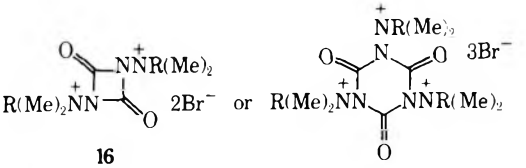
Compound **7a** was recovered unchanged after irradiation[17] in benzene.

Reaction of crotyl bromide with 1,1-dimethyl-4-phenylsemicarbazide repeatedly gave low yields of an insoluble salt whose analytical and spectral[18] properties seem to be best accommodated by either a symmetrically substituted dimer[19] (**16**) or trimer (**17**) of the quaternary isocyanate (**18**). Compound **18** could form by elimination of aniline from **15**. Infrared evidence (carbonyl bands at 1690 and 1740 $cm^{-1}$) excludes **18** from consideration. Analogous behavior in the reaction of other semicarbazides with allylic halides was sought but not found.

$$\text{PhNHCONHN(Me)}_2 + \text{CH}_3\text{CH}{=}\text{CHCH}_2\text{Br} \longrightarrow$$



**15**



**16** **17**

$$\mathbf{15} \xrightarrow[-\text{PhNH}_2]{?} [(\text{Me})_2\text{RNNCO Br}^-] \longrightarrow \mathbf{16} \text{ or } \mathbf{17}$$

**18**

R = $CH_2CH{=}CHMe$

**Table I**
**Semicarbazonium Salts (6)[a]**

$R_1R_2NCONHN^+(Me)_2R_3X^-$

| Structure | Mp, °C | Recrystn solvent | Yield, % | Formula | Nmr, δ |
|---|---|---|---|---|---|
| **6a** $Br^-$ | 105-106 | Acetone | 94 | $C_8H_{18}BrN_3O$ | 2.94 (s, 6), 3.79 (s, 6), 4.86 (d, 2), 5.5-5.9 (m, 3), 9.6 (s, 1) ($CDCl_3$) |
| **6b** $Br^-$ | 155–156 | Acetone | 82 | $C_{12}H_{20}BrN_3O$ | 3.71 (s, 6), 2.98 (s, 6), 5.40 (s, 2), 9.9 (broad, 1), 7.20–7.60 (m, 5) ($CDCl_3$) |
| **6d** $Br^-$ | 76–78 | EtOH–ether | 94 | $C_{12}H_{18}BrN_3O$ | 3.56 (s, 6), 4.60 (d, 2), 5.69 (m, 3), 7.33 (m, 5), 9.47 (s, 1), 10.0 (broad, 1) (DMSO-$d_6$) |
| **6e** $Cl^-$ | 133–135 | Acetone | 51 | $C_{16}H_{20}ClN_3O$ | 3.58 (s, 6), 5.18 (s, 2), 6.7-7.5 (m, 10), 9.8 (s, 1), 10.74 (broad, 1) (DMSO-$d_6$) |
| **6f** $Br^-$ | 151-153 | EtOH | 68 | $C_{12}H_{16}BrN_3O$ | 3.68 (s, 6), 4.08 (t, 1), 5.08 (d, 2), 6.9–7.4 (m, 5), 9.53 (s, 1), 10.2 (s, 1) (DMSO-$d_6$) |
| **9** HCl[b] | 50–58 (hygroscopic) | | 70 | $C_{14}H_{22}ClN_3O$ | 1.68 (s, 3), 1.73 (s, 3), 3.51 (s, 6), 4.5 (d, 2), 5.35 (m, 1), 6.8–7.4 (m, 5), 9.84 (s, 1), 10.66 (s, 1) (DMSO-$d_6$) |
| **15** | Hygroscopic oil | | 90 | $C_{13}H_{20}BrN_3O$ | 1.7 (d, 3) 3.5 (s, 6), 5.3–6.3 (m, 2), 4.45 (d, 2), 7.1–7.4 (m, 5), 9.33 (s, 1, NH), 9.7 (s, 1 NH) (DMSO-$d_6$) |

[c] Compounds **15** and 9 HCl did not give satisfactory analyses. Other compounds analyzed satisfactorily (±0.3%) for C, H, and N. [b] Tabulated as aminimide salt.

**Table II**
**Aminimides (7)[a]**

$R_1R_2NCONN^+(Me)_2R_3^-$

| Structure | Yield, % | Mp, °C | Formula | Nmr, δ |
|---|---|---|---|---|
| **7a** | 100 | Hygroscopic solid | $C_8H_{17}N_3O$ | 2.62 (s, 6), 3.19 (s, 6), 4.2 (d, 2), 5.10–5.95 (m, 3) ($CDCl_3$) |
| **7b** | 52 | 128–129 | $C_{12}H_{17}N_3O$ | 2.72 (s, 6), 3.11 (s, 6), 4.69 (s, 2), 7.26 (s, 5) ($CDCl_3$) |
| **7c** | 91 | 93–94 | $C_{18}H_{21}N_3O$ | 3.05 (s, 6), 3.95 (d, 2), 5.0–5.8 (m, 3), 6.7–7.4 (m, 10) ($CDCl_3$) |
| **7d** | 100 | 128–130 | $C_{12}H_{17}N_3O$ | 3.15 (s, 6), 4.15 (d, 2), 5.1–6.3 (m, 3), 6.5–7.4 (m, 6) ($CDCl_3$) |
| **7e** | 83 | 145–148 | $C_{16}H_{19}N_3O$ | 3.45 (s, 6), 5.03 (s, 2), 6.8–7.4 (m, 10), 9.64 (broad, 1) (DMSO-$d_6$) |
| **7f** | 95 | 117–118 | $C_{12}H_{15}N_3O$ | 3.21 (s, 6), 3.58 (t, 1), 4.60 (d, 2), 6.3–7.5 (m, 6) ($CDCl_3$) |
| **9** | 72 | 155–156 | $C_{14}H_{21}N_3O$ | 1.68 (s, 3), 1.72 (s, 3), 3.11 (s, 6), 4.20 (d, 2), 5.3 (m, 1), 6.18 (s, 1), 6.8–7.4 (m, 5) ($CDCl_3$) |
| **11** | 40 | 128-130 | $C_{13}H_{19}N_3O$ | 1.65 (d, 3), 3.11 (s, 6), 4.05 (d, 2), 5.6 (m, 2), 6.20 (s, 1), 6.6–7.3 (m, 5) ($CDCl_3$) |

[a] With the exception of **7a**, all compounds gave satisfactory (±0.3%) analyses for C and H.

## Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. Nmr spectra were determined with a Perkin-Elmer R-20 spectrometer utilizing hexamethyldisiloxane as the internal standard.

**1,1,4,4-Tetramethylsemicarbazide.** *N,N*-Dimethylcarbamoyl chloride (107.5 g) was slowly added to a stirred, ice-cooled solution containing 60.1 g of 1,1-dimethylhydrazine and 101.2 g of triethylamine in 400 ml of dry benzene. After the addition was complete, stirring was continued for 1 hr at room temperature. The triethylamine hydrochloride was filtered off and washed with dry benzene. Evaporation of the filtrate and combined washings gave 139.5 g of product that crystallized on standing: bp 131-133° (26 mm); mp 68-70°; nmr ($CDCl_3$) δ 2.51 (s, 6), 2.81 (s, 6), 6.4 (broad, 1).

*Anal.* Calcd. for $C_5H_{13}N_3O$: C, 45.8; H, 10.0; N, 32.0. Found: C, 45.5; H, 9.6; N, 32.0.

**Synthesis of Semicarbazonium Salts (6).** Equimolar mixtures of either 1,1,4,4-tetramethylsemicarbazide, 1,1-dimethyl-4,4-diphenylsemicarbazide,[8] or 1,1-dimethyl-4-phenylsemicarbazide[8] and the appropriate halide were heated on the steam bath under reflux for 1-2 hr. The cooled reaction mixtures were treated with dry ether and scratched to induce crystallization. The properties of the salts are given in Table I. The reaction of 1,1-dimethyl-4,4-diphenylsemicarbazide with allyl bromide gave a gum that was not characterized but converted directly to **7c**. Treatment of 1-(2-butenyl)-1,1-dimethyl-4-phenylsemicarbazonium bromide

**Table III**
**Semicarbazides (8)[a]**

$R_1R_2NCONR_3N(Me)_2$

| Structure | Thermolysis conditions | Mp (recrystn solvent) or bp, °C (mm) | Yield,[b] % | Formula | Nmr, δ |
|---|---|---|---|---|---|
| **8a** | 130° (2.5 hr) | 110–120 (20) | 41 (T)[c] 22 (S) | $C_8H_{17}N_3O$ | 2.36 (s, 6), 2.78 (s, 6), 3.67 (d, 2), 4.7–6.1 (m, 3) (neat) |
| **8b** | 165° (3.5 hr) | 98–99 (ligroin) | 63 (T) 39 (S) | $C_{12}H_{19}N_3O$ | 2.41 (s, 6), 2.79 (s, 6), 4.13 (s, 2), 7.17 (s, 5) ($CDCl_3$) |
| **8c** | 135° (1 hr) | 133–134[d] (EtOH) | 69 (T) 47 (S) | $C_{24}H_{24}N_6O_8$[d] | 2.28 (s, 6), 3.80 (d, 2) 4.8–5.3 (m, 3), 6.5–7.4 (m, 10), 7.70 (s, 1, NH), 8.5 (s, 2) (DMSO-$d_6$) |
| **8d** | 150° (3 hr) | 190–194 (22) | 40 (T) 100 (S)[e] | $C_{12}H_{17}N_3O$ | 2.42 (s, 6), 3.86 (d, 2), 4.8–6.4 (m, 3), 6.7–7.7 (m, 5), 8.90 (s, 1) (DMSO-$d_6$) |
| **8e** | 175° (1 hr) | 76–77 (EtOH) | 62 (T) 73 (S) | $C_{16}H_{19}N_3O$ | 3.6 (s, 6), 5.38 (s, 2), 6.9–7.7 (m, 10), 9.18 (s, 1) ($CDCl_3$) |
| **10** | 160° (1.5 hr) | 45–47 (ligroin) | 50 (T) | $C_{14}H_{21}N_3O$ | 1.58 (s, 6), 2.41 (s, 6), 2.87 (d, 2), 5.20 (m, 1), 6.6–7.5 (m, 5), 8.48 (s, 1) ($CDCl_3$) |
| **12** | | 83–84 (ligroin) | 53 (S) | $C_{13}H_{19}N_3O$ | 2.60 (m, 3), 2.40 (s, 6), 3.85 (m, 2), 5.5 (m, 2), 6.7–7.5 (m, 5), 8.48 (s, broad, 1) ($CDCl_3$) |
| **13** | | 142–145 (0.05) | 53 (S) | $C_{13}H_{19}N_3O$ | 1.36 (d, 3), 2.37 (s, 6), 3.9 (m, 1), 5.0 (m, 2), 6.20 (m, 1), 6.8–7.6 (m, 5), 8.71 (s, 1) (DMSO-$d_6$) |

[a] All compounds gave satisfactory (±0.4%) analyses for C and H. [b] Yields of recrystallized or distilled products. [c] T = thermolysis product; S = synthetic product. [d] Picrate. [e] Undistilled product (identical with thermolysis product).

and 1-(3-methyl-2-butenyl)-1,1-dimethyl-4-phenylsemicarbazonium bromide (both hygroscopic) with ethanolic picric acid resulted in precipitation of **1,1-dimethyl-4-phenylsemicarbazide picrate.** Recrystallization from *N,N*-dimethylformamide–water gave yellow crystals, mp 197–198°.

*Anal.* Calcd for $C_{15}H_{16}N_6O_8$: C, 44.2; H, 4.0. Found: C, 44.2; H, 4.3.

**Reaction of 1,1-Dimethyl-4-phenylsemicarbazide with Crotyl Bromide.** The reaction was conducted as described in the previous section. Treatment of the crude dark reaction mixture with dry acetone (10 ml/g of semicarbazide) gave white crystals (1.6 g from 10 g of semicarbazide), mp 231–234°. The oily, hygroscopic semicarbazonium salt was obtained by evaporation of the acetone and could not be induced to crystallize. The acetone-insoluble material (**16** or **17**) was recrystallized from acetone–pentane: mp 235–236°; nmr (DMSO-$d_6$) δ 1.75 (m, 3), 3.45 (s, 6), 4.90 (m, 2), 6.50 (m, 2); ir (KBr) 1690 and 1740 $cm^{-1}$ (s, C=O); *m/e* (20 eV, 200°) highest mass 140 ($C_7H_{13}N_2O^+ - 1$).

*Anal.* Calcd for $(C_7H_{13}BrN_2O)_n$: C, 38.0; H, 5.9; Br, 36.1; N, 12.7. Found: C, 37.8; H, 5.8; Br 35.9; N, 12.7.

**Preparation of Aminimides.** The semicarbazonium salts were treated with excess 6 *N* NaOH (2 ml/g of salt) and the aminimides were extracted with chloroform. The combined extracts were dried ($MgSO_4$). Evaporation of the solutions at reduced pressure gave the aminimides (Table II). Compound **7a** was obtained as an extremely hygroscopic solid that did not give satisfactory analytical data.

**Thermolysis of the Aminimides.** Thermolyses of neat samples of the aminimides were conducted under the conditions given in Table III. The composition of the mixture obtained from the thermolysis of the 1-(2-butenyl) compound (**11**) was determined by comparison of the integrated intensity ratios of the -CH=CH- and $=CH_2$ signals of the nmr spectra of **12** and **13**, respectively. The nmr spectrum of the mixture was found to be identical with the additive spectrum of authentic samples of **12** and **13**.

**1,1-Dimethyl-2-(2-butenyl)hydrazine.** A solution containing 15.0 g of crotonaldehyde *N,N*-dimethylhydrazone[20] in 100 ml of dry ether was added over 1.5 hr to a stirred suspension of 13 g of lithium aluminum hydride in 150 ml of dry ether. The reaction mixture was heated under reflux for 5 hr and then stirred at room temperature for 12 hr. Shorter reaction times and lower concentrations of hydride gave a product that was contaminated (by glc) with starting material. The reaction mixture was cooled in ice, stirred vigorously, and cautiously treated successively with 6 ml of water, 6 ml of 6 *N* NaOH, and 18 ml of water. The inorganic material was filtered off and washed with ether. The filtrate and combined washings were dried ($MgSO_4$) and the ether was removed by distillation at atmospheric pressure. The product was distilled through a 24-in. Vigreux column, giving 10.0 g of product as a colorless liquid: bp 131–133°; nmr ($CDCl_3$) δ 3.05 (m, 3), 2.10 (broad, exchangeable, 1), 3.31 (s, 6), 3.22 (m, 2), 5.45 (m, 2), minor impurities at 2.7 (m), 2.60 (s), and 2.78 (s). The compound rapidly darkened and did not give a satisfactory analysis.

The hydrazine was converted to **1,1,1-trimethyl-2-(2-butenyl)hydrazinium iodide** by reaction with methyl iodide. The salt was obtained as air-sensitive white crystals which were recrystallized from ethanol: mp 188–189°; nmr ($CDCl_3$) δ 1.63 (broad d, 3), 3.58 [s $(Me)_3N^+$ superimposed on the $-CH_2N<$ multiplet, 11], 5.5 (m, 2), 6.41 (m, 1, NH).

*Anal.* Calcd for $C_7H_{17}N_2I$: C, 32.8; H, 6.7; N, 10.9. Found: C, 33.0; H, 6.5; N, 11.0.

**1,1-Dimethyl-2-(1-methyl-2-propenyl)hydrazine.** We were unable to prepare the hydrazine by rearrangement of 1,1-dimethyl-1-(2-butenyl)hydrazinium bromide in aqueous sodium hydroxide.[21] Cordell[22] has reported the preparation of an impure product by rearrangement of the hydrazinium salt in ethanolic potassium *tert*-butoxide. The following procedure also afforded a crude product that when treated with phenyl isocyanate gave **13** in 53% yield.

A suspension of 11.4 g of crude 1,1-dimethyl-1-(2-butenyl)hydrazinium bromide[23] in 140 ml of dry ether was vigorously stirred under nitrogen and treated with 47 ml of a 1.7 *M* *n*-butyllithium–hexane solution by dropwise addition conducted over 2 hr. Stirring was continued overnight and the reaction mixture was cautiously treated with 20 ml of water. The layers were separated, the aqueous layer was extracted with ether, and the combined ether solution was dried ($MgSO_4$). The solvents were removed by distillation through a Vigreux column. Distillation of the residue gave a wide-boiling, colorless fraction, bp 80–110°. A sample with bp 109° gave the following nmr data (neat): δ 0.98 (d, $J$ = 7 Hz, 3), 2.28 [s (superimposed on a broad NH), 7], 3.30 (m, 1), 4.9 (m, 2), 5.6 (m, 1); impurities in low concentration; 1.82 (s), 2.70 (s), and 0.5–1.8 (m).

**Synthesis of Semicarbazides (Table III).** 1,1,-Dimethyl-2-

benzylhydrazine and 1,1-dimethyl-2-(2-propenyl)hydrazine were prepared by the published procedure.[24]

The preparation of compounds **8d**, **8e**, **12**, and **13** was accomplished by treating phenyl isocyanate with an equimolar quantity of the appropriate hydrazine.

Compounds **8a**, **8b**, and 8c were prepared by heating a mixture of either dimethylcarbamoyl chloride or diphenylcarbamoyl chloride with 2 equiv of the appropriate hydrazine at 100° for 1-2 hr. The products were isolated by extracting the crude reaction mixture with boiling petroleum ether.

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**Registry No.**—**6a**, 51433-78-4; **6b**, 51433-77-3; **6c**, 51433-50-2; **6d**, 51433-51-3; **6e**, 51433-52-4; **6f**, 51433-53-5; **7a**, 51433-54-6; **7b**, 51433-55-7; **7c**, 51433-56-8; **7d**, 51433-57-9; **7e**, 51433-58-0; **7f**, 51433-59-1; **8a**, 51433-60-4; **8b**, 51433-61-5; **8c**, 51433-63-7; **8d**, 51433-64-8; **8e**, 51433-65-9; **9**, 51433-66-0; 9 hydrochloride, 51472-52-7; **10**, 51433-67-1; **11**, 51433-68-2; **12**, 51433-69-3; **13**, 51433-70-6; **15**, 51433-71-7; **18**, 51433-76-2; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; benzyl chloride, 100-44-7; 3-propynyl bromide, 106-96-7; 1,1,4,4-tetramethylsemicarbazide, 27827-93-6; *N,N*-dimethylcarbamoyl chloride, 79-44-7; 1,1-dimethylhydrazine, 57-14-7; 1,1-dimethyl-4,4-diphenylsemicarbazide, 37934-75-1; 1,1-dimethyl-4-phenylsemicarbazide, 6297-20-7; 1-(2-butenyl)-1,1-dimethyl-4-phenylsemicarbazonium bromide, 51433-71-7; 1-(3-methyl-2-butenyl)-1,1-dimethyl-4-phenylsemicarbazonium bromide, 51472-53-8; 1,1dimethyl-4-phenylsemicarbazide picrate, 51433-72-8; crotyl bromide, 4787-77-4; 1,1-dimethyl-2-(2-butenyl)hydrazine, 51433-73-9; crotonaldehyde *N,N*-dimethylhydrazone, 74422-95-9; 1,1,1-trimethyl-2-(2-butenyl)hydrazinium iodide, 51433-74-0; 1,1-dimethyl-2-(1-methyl-2-propenyl)hydrazine, 15848-66-5; phenyl isocyanate, 103-71-9; 1,1-dimethyl-1-(2-butenyl)hydrazinium bromide, 27828-89-3; *N,N*-diphenylcarbamoyl chloride, 83-01-2; 1,1-dimethyl-2-(2-propenyl)hydrazine, 2736-72-3; 1,1-dimethyl-2-benzylhydrazine, 28082-45-3.

## References and Notes

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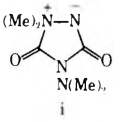
(14) Z. H. Gegelyan, K. P. Kizamidzhyan, M. G. Indhikyan, and A. Babayan, *Arm. Khim. Zh.*, **23**, 1010 (1970); *Chem. Abstr.*, **75**, 5176 (1971). It has been suggested (ref 1, p 270) that this result can be explained by invoking competitive concerted and radical processes.
(15) J. E. Brown, Ph.D. Thesis, The Pennsylvania State University, 1971, p 86.
(16) For a recent review of CIDNP and its interpretation when applied to rearrangements of aminimides, see A. R. Lepley in "Chemically Induced Dynamic Nuclear Polarization," A. R. Lepley and G. L. Closs, Ed., Wiley, New York, N. Y., 1973, p 356.
(17) A 450-W Hanovia medium-pressure mercury arc lamp (Pyrex filter) was employed.
(18) The mass spectrum of the salt did not display high mass ion radicals corresponding to cations **16** or **17**. The highest mass peak observed was *m/e* 140, which corresponds to the monomeric cation (**18**) − 1. Depolymerization of **16** or **17** on electron impact apparently occurs. We have found that the mass spectrum of triphenyl isocyanaurate displays $C_6H_5NCO\cdot^+$ as the parent peak together with a $(C_6H_5NCO)_3\cdot^+$ peak which is 50% less intense.
(19) Dimethylamino isocyanate does not form a diazetidinedione dimer. W. S. Wadsworth and W. D. Emmons [*J. Org. Chem.*, **32**, 1279 (1967)] have established the ylide structure (i) shown below for the



i

dimethylamino isocyanate dimer. The nmr spectrum of the salt obtained by us displays equivalent methyl and crotyl groups; hence a dialkylated derivative of i can be excluded.
(20) Prepared in 80% yield by the procedure described by R. F. Smith and L. E. Walker, *J. Org. Chem.*, **27**, 4372 (1962). The compound had bp 66–67° (27 mm). B. J. Ioffe and K. N. Zelenin, *Dokl. Akad. Nauk SSSR*, **141** 1369 (1961), give bp 70–71° (29 mm).
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(23) Obtained as an oil from the reaction of crotyl bromide and 1,1-dimethylhydrazine in refluxing acetonitrile (ref 22, p 69).
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# 1-Oxadecalins and 1-Oxa-4-decalones. Syntheses and Conformational Analyses

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A general synthetic route to 6- and 7-carbomethoxy-*trans*-1-oxadecalins (**9** and **12**) is presented. Base-catalyzed equilibrations and pmr data are used to evaluate conformational equilibria and relative configurations in several *cis*- and *trans*-1-oxadecalins and 1-oxa-4-decalones. The trans-fused ring system is thermodynamically favored in all instances.

The *trans*-decalin ring system has often been used as a conformationally fixed system for the study of the relative reactivities of equatorial and axial substituents[1] and the relative energies of substituents in a pair of equatorial and axial orientations at a given carbon atom.[2] Similarly, analogs of *trans*-decalin containing an atom other than carbon at a known position in the ring not containing the attached substituents provide the opportunity to evaluate the influences of the heteroatoms on the relative reactivities and relative energies of the substituents. These effects

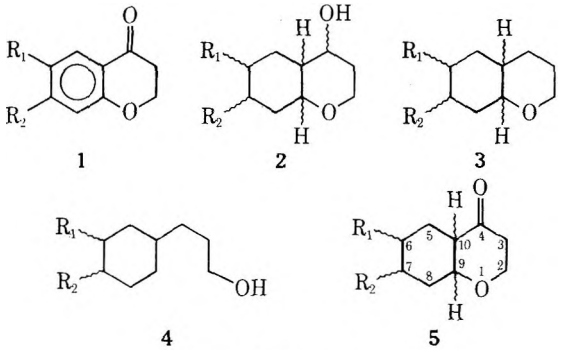
**Table I**
**Representative 4-Chromanone Hydrogenations**

| Compd | Yield, % 2 | 3 | 4 |
|---|---|---|---|
| **1a** | 95 | Not observed | 5 |
| **1b** | 60 | 25[a] | 15 |
| **1c** | 45 | 35[b] | 20 |

[a] Composed of a single cis-fused compound by glpc. [b] Composed of two cis-fused compounds in a 4:1 ratio by glpc.

would result from changes in ring structure and from polar effects, the latter of which probably can be accounted for using a field model[3] and the Kirkwood-Westheimer formalism.[3]

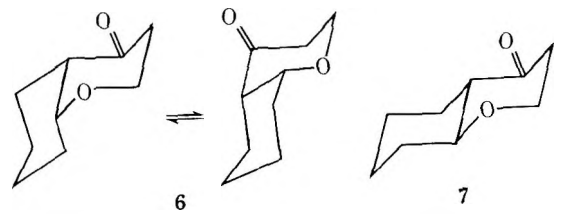
As the first phase of such a study of *trans*-heteradecalins, the syntheses and conformational analyses of representative 1-oxadecalins have been explored. Several 4-chromanones (**1a–c**) have been prepared and subjected to catalytic hydrogenation over ruthenium.[4] The major product in each instance (45–95% of isolated product) was a mixture of 4-hydroxy-1-oxadecalins (**2**), while significant amounts (5–35%) of 1-oxadecalins (**3**) and saturated monocyclic alcohols (**4**) were also isolated (Table I). In each series, the 4-hydroxy-1-oxadecalins were complex mixtures containing primarily cis ring fusions. Jones oxidation[5] of each alcohol mixture reduced the number of epimers[6] and somewhat simplified stereochemical assignments.



**1** **2** **3** **4** **5**

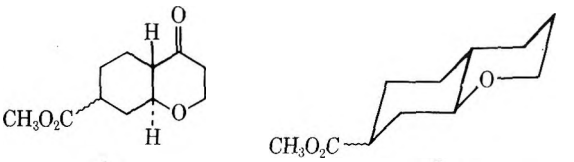
a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CO_2CH_3$
c, $R_1 = CO_2CH_3$; $R_2 = H$

Ketone **5a** appeared to be primarily[8] the cis isomer[9] **6**, since H-9 appeared as an obscured narrow multiplet at $\delta$ 3.80 in the pmr spectrum. Treatment of ketone **5a** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), a strong nonnucleophilic base,[10] in refluxing benzene resulted in a 90% recovery of trans-fused[8] **7**, which exhibited H-9 as the X portion of an ABMX pattern ($J$ = 4, 10, and 10 Hz) at $\delta$ 3.23 in the pmr spectrum.[11] A mixture of ketones **5a** and **7** was similarly treated with DBN to establish that equilibration was occurring. The greater stability of the *trans*-1-oxa-4-decalone (**7**) under equilibration conditions qualitatively parallels that of the 1-decalone system[12] and appears to be quantitatively[8] greater than in this hydrocarbon analog.



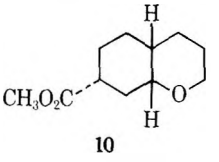
**6** **7**

In the 7-carbomethoxy series, ketone **5b** was chromatographically homogeneous, cis fused, and a mixture of the carbomethoxy epimers (see below). Equilibration of **5b** with DBN in benzene gave a mixture of ketones which was chromatographically homogeneous and almost exclusively trans fused. Pure trans-fused material (**8**) was obtained by one recrystallization, and exhibited H-9 as a multiplet in the pmr spectrum at $\delta$ 3.29 ($J$ = 4, 10, 10 Hz). Again the trans-fused ketone was more stable than the cis-fused.



**8** **9**

Deoxygenation of **8** without bridgehead epimerization was required to obtain the desired *trans*-1-oxadecalin structure. A recently reported procedure[13] involving sodium cyanoborohydride reduction of the tosylhydrazone was investigated for stereospecificity.[14] Application of this procedure to **8** resulted in 76% conversion to a single pure 7-carbomethoxy-*trans*-1-oxadecalin (**9**). In order to check the stereospecificity, the mother liquors from which **8** had been obtained were deoxygenated. The product consisted of two epimers in addition to the major product **9**. One of these, a *cis*-1-oxadecalin, was identical with the oxadecalin **3** obtained directly from the hydrogenation of **1b**, and is assigned structure **10** based on the pmr spectrum and the known[15] preference for cis hydrogenation over ruthenium. The other isomer was not identified. The small amounts of these isomers formed from the mother liquors and the absence of these isomers in the deoxygenation of pure **8** indicate negligible, if any, epimerization at C-10 under these deoxygenation conditions.



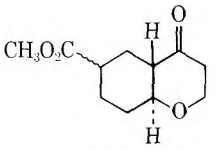
**10**

Several attempts were made to investigate the equatorial or axial nature of the carbomethoxy substituent in **9**. Ester **9** was treated with DBN in order to see whether the ester had been equilibrated simultaneously with the ring fusion (**5b** ⇄ **8**). No change was observed, compound **9** being recovered quantitatively. Treatment of **9** with sodium methoxide in methanol, the conditions used by Sicher[2] to equilibrate the *trans*-decalyl esters, resulted in the appearance of a new compound comprising approximately 20% of the mixture (by glpc). Mass spectral evidence supports assignment of the epimeric trans-fused structure to this compound. Unfortunately, equilibrium was probably not achieved because of decomposition of one of the esters under the reaction conditions. Nevertheless, these results support lack of ester epimerization with DBN. The pmr spectrum of ester **9** provides suggestive evidence that the ester functionality is equatorial. The C-7 methine hydrogen appears as a multiplet centered at $\delta$ 2.45 with coupling constants consistent only with an axial location ($J$ = 3.5, 3.5, 12, 12 Hz).

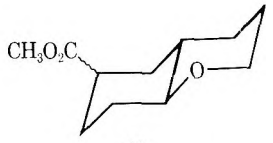
In the 6-carbomethoxy series, ketone **5c** obtained on Jones oxidation[5] of alcohol **2c** was a mixture of three compounds in a 3:6:1 ratio. Epimerization with DBN changed this ratio to 6:3:1. The major isomer was obtained in 90% purity by several recrystallizations and identified as a trans-fused compound (**11**) by the H-9 multiplet at $\delta$ 3.24[11] ($J$ = 4.5, 10, 10 Hz) in the pmr.

Deoxygenation[13] of a mixture of 6-carbomethoxy-1-oxa-

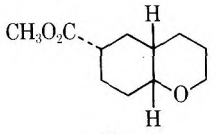
4-decalones containing 80% of trans-fused **11** produced two products in a ratio of 85:15, while deoxygenation of a 1:1 mixture of the trans and cis ketones resulted in a 1:1 mixture of deoxygenated products. Preparative glpc permitted identification of the major component in the trans-enriched reaction as a 6-carbomethoxy-*trans*-1-oxadecalin (**12**). The minor component was found to be identical with the major component in the 1-oxadecalin mixture (**3**) obtained directly on hydrogenation of ketone **1c** (Table I). Based on the well-known preference for cis hydrogenation,[15] this compound may be assigned structure **13** and the minor component from the direct hydrogenation would be **14**.



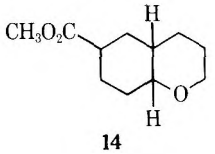
**11**



**12**



**13**



**14**

The ester functionality in 6-carbomethoxy-*trans*-1-oxadecalin (**12**) is tentatively assigned an axial orientation based on pmr spectral comparisons. The C-6 methine hydrogen is not discernible. However, the carbomethoxy methyl appears as a clean singlet at $\delta$ 3.72 in **12** and at $\delta$ 3.70 in precursor trans ketone **11**. By contrast, the methyl signal occurs at $\delta$ 3.67–3.68 in the 7-carbomethoxy analogs **8** and **9** in which the ester group is believed to be equatorial (see above). In addition, cis-fused systems **5b**, **10**, **5c**, and **13** all exhibited methyl singlets at $\delta$ 3.67 or 3.68. Using the reasonable assumption that conformational equilibria in cis systems (as shown for **6**) will result in a preponderance of that conformer in which any single attached substituent would be equatorial, the data from these cis systems reinforces the axial assignment to the ester group in **12**.

The result that the carbomethoxy group is equatorial in the 7 series (**9**) and axial in the 6 series (**12**) is consistent with another line of reasoning. If all-cis hydrogenation is assumed to predominate,[15] those isomers of **5b** and **5c** would be formed which would lead on DBN equilibration to the trans-fused ketonic precursors of **9** and **12** without any change in the ester stereochemistry. A perfect 1:1 correlation exists through both reaction sequences between ester stereochemistry in the major (all-cis) isomer of **5** and the final 1-oxadecalins **9** and **12**, thereby providing further substantiation of the proposed C-6 and C-7 stereochemistry and of all the assumptions made concerning reaction stereochemistry.

## Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using solutions in deuteriochloroform. Chemical shifts are assigned in Table II and coupling constants are shown in Table III except where either is included with the compound or mixture. Infrared spectra were determined with a Beckman IR-10 spectrophotometer, with only major absorptions being cited. Mass spectral analyses were obtained at 70 eV. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. The glpc column used was a 6 ft × 0.25 in. 10% NPGS w/w on Chromosorb W (60/80 mesh) column.

**Previously Unreported Glpc Retention Times for 1-Oxadecalins (3) Isolated from the Hydrogenation of 4-Chromanones (1b and 1c).** 7-Carbomethoxy-*cis*-1-oxadecalin (**10**) (175°), 8.3 min; mixture of epimers of 6-carbomethoxy-*cis*-1-oxadecalin (**3c**) (175°), 6.7 and 8.9 min (1:4).

**Table II**
**Nmr Chemical Shifts of 1-Oxadecalins[a]**

| Compd | H-2e[b] | H-2a | H-3e | H-7 | H-9 | H-10 | $CO_2CH_3$ |
|---|---|---|---|---|---|---|---|
| **5a** | 4.29 | 3.73 | 2.19 | | 3.80 | 2.77 | |
| **5b** | | | | | | | 3.68 |
| **5c** | | | | | | | 3.67 |
| **7** | 4.29 | 3.73 | 2.28 | | 3.23 | 2.82 | |
| **8** | 4.35 | 3.75 | 2.33 | | 3.29 | 2.73 | 3.68 |
| **9** | 4.00 | 3.40 | | 2.45 | 2.93 | | 3.67 |
| **10** | 3.65 | | | | | | 3.67 |
| **11** | 4.34 | 3.75 | | | 3.24 | | 3.70 |
| **12** | 4.00 | 3.41 | | | 2.93 | | 3.72 |
| **13** | 4.05 | 3.55 | | | | | 3.68 |

[a] In parts per million. [b] e and a have been used to designate equatorial and axial protons.

**Hydrogenation of 1a.** The general procedure of Hirsch and Schwartzkopf[4] was used for the hydrogenation of 2.0 g (14 mmol) of **1a**. Chromatography on silica gel (Woelm) of 1.9 g of crude product gave 50 mg (3%) of crude 3-cyclohexyl-1-propanol (**4a**) in the 10% ethyl acetate–methylene chloride fractions as an oil: ir (neat) 3400 (O–H) and 1070 $cm^{-1}$ (C–O); nmr $\delta$ 3.69 (t, $J$ = 6 Hz, $CH_2CH_2OH$), 3.31 (s, OH).

The 20–100% ethyl acetate–methylene chloride fractions contained 1.42 g (67%) of 4-hydroxy-1-oxadecalin isomers (**2a**) as an oil, ir (neat) 3400 $cm^{-1}$ (O–H).

*Anal.* Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.33. Found: C, 69.07; H, 10.41.

**6-Carbomethoxy-1-oxa-4-decalone (5c).** A stirred solution of 1.57 g (7.33 mmol) of the isomer mixture **2c** in 20 ml of acetone was treated with 3,4 ml (9.5 mmol) of Jones reagent[5] (2.8 *M*) over a few minutes at 0–10°. The ice bath was removed and stirring was continued for 1 hr. The mixture was treated with 20 drops of isopropyl alcohol and diluted with ether. The ethereal extract was washed with saturated sodium bicarbonate and dried ($MgSO_4$). Concentration of the ethereal extract gave 1.06 g of crude product. Chromatography on silica gel (Woelm) using 10% ethyl acetate–methylene chloride gave 940 mg (60%) of a mixture of three isomers of **5c** as an oil: ir (neat) 1730 $cm^{-1}$ (C=O); glpc retention times (225°) 8.4, 10.2, and 11.1 min (3:6:1).

*Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.04; H, 7.48.

**7-Carbomethoxy-*cis*-1-oxa-4-decalone (5b).** This epimer mixture was prepared from isomer mixture **2b** in 67% yield by the method used for **5c**. A pure product was obtained without chromatography: ir (neat) 1730 $cm^{-1}$ (C=O); nmr $\delta$ 3.87–4.33 (m, 2, H-2), 3.68 (s, 3, $OCH_3$), 2.71 (m, H-9a), 2.45 (t, $J$ = 6 Hz, H-3); glpc retention time (225°) 9.4 min (only one peak observed).

*Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.14; H, 7.60.

***cis*-1-Oxa-4-decalone (5a).** This compound was prepared from the isomer mixture **2a** by the method used for **5c**. Chromatography on silica gel (Woelm) of the 1.61 g of crude product obtained gave 670 mg (45%) of **5a** in the 2% ethyl acetate–methylene chloride fractions as an oil: ir (neat) 1730 $cm^{-1}$ (C=O); glpc retention time (180°) 3.9 min.

*Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.01; H, 9.15.

**Equilibration of 6-Carbomethoxy-1-oxa-4-decalone (5c).** A solution of 640 mg (3.02 mmol) of isomer mixture **5c** and 0.6 ml of 1,5-diazabicyclo[4.3.0]non-5-ene in 35 ml of dry benzene was refluxed for 18.5 hr. The cooled solution was extracted with 3 *N* HCl and the aqueous phase was washed with benzene. The combined benzene extracts were washed with saturated sodium bicarbonate and dried ($MgSO_4$). The benzene extract was concentrated, giving 560 mg (88%) of an equilibrated mixture of the three isomers: glpc retention times (225°) 8.4, 10.2, and 11.1 min (6:3:1).

*Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.09; H, 7.52.

The mixture was recrystallized from carbon tetrachloride–petroleum ether, then twice more from hexane, giving 40 mg (7% recovery) of primarily **11**: mp 73–76°; ir (Nujol) 1715 $cm^{-1}$ (C=O); glpc retention times (225°) 8.4, 10.2, and 11.1 min (9:1:trace).

**Table III**
**Coupling Constants of 1-Oxadecalins[a]**

| Compd | $J_{2a,2e}$[b] | $J_{2a,3a}$ | $J_{2a,3e}$ | $J_{2e,3a}$ | $J_{2e,3e}$ | $J_{3a,3e}$ | $J_{5a,10}$ | $J_{5e,10}$ | $J_{9,10}$ | $J_{8a,9}$ | $J_{8e,9}$ | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | 11 | 11 | 3.5 | 7 | 2.5 | 15 | 8 | 3 | 7.5 | H-9 | $W_{1/2} < 13$ | |
| **7** | 11.5 | 11.5 | 3.5 | 7 | 1.5 | 14 | 13 | 4.5 | 10 | 10 | 4 | |
| **8** | 11 | 11 | 3.5 | 7 | 2 | 14.5 | 12 | 4.5 | 10 | 10 | 4 | |
| **9** | 10 | | | | | | | | | H-9 | $W_{1/2} = 18$ | $J_{6a,7a} = J_{7a,8a} = 12$<br>$J_{6e,7a} = J_{7a,8e} = 3.5$ |
| **11** | 11 | 11 | 3.5 | 7 | 2 | | | | 10 | 10 | 4.5 | |
| **12** | 10 | | | | | | | | | H-9 | $W_{1/2} = 18$ | |
| **13** | 10 | | | | | | | | | | | |

[a] In hertz. [b] e and a have been used to designate equatorial and axial protons.

*Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.41; H, 7.52.

**Equilibration of 7-Carbomethoxy-*cis*-1-oxa-4-decalone (5b).** Equilibration was carried out as with **5c**, giving, after one recrystallization from hexane, a 36% yield of **8**: mp 104–106°; ir (Nujol) 1735 $cm^{-1}$ (C=O); glpc retention time (225°) 9.4 min (only one peak observed).

*Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.41; H, 7.62.

**Equilibration of cis-1-Oxa-4-decalone (5a).** Equilibration was carried out as with **5c**, giving a 90% yield of *trans*-1-oxa-4-decalone (**7**) as an *oil*. The analytical sample was chromatographed on silica gel (Woelm) using 2% ethyl acetate–methylene chloride: glpc retention time (180°) 3.9 min.

*Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.20; H, 9.13.

**6-Carbomethoxy-*trans*-1-oxadecalin (12).** A mixture of 60 mg (0.3 mmol) of **5c** (*ca.* 80% trans isomer), 60 mg (0.3 mmol) of *p*-toluenesulfonylhydrazide, 10 mg of *p*-toluenesulfonic acid hydrate, 0.7 ml of sulfolane, and 0.7 ml of dry dimethylformamide was stirred at room temperature for 1 hr. The mixture was then treated with 70 mg (1.1 mmol) of sodium cyanoborohydride and was stirred in a 100–105° bath for 2 hr more. The cooled solution was diluted with water and extracted with cyclohexane. The cyclohexane extracts were washed three times with water and dried ($MgSO_4$). Concentration gave 40 mg (70%) of primarily **12** as an oil: ir (neat) 1748 $cm^{-1}$ (C=O); glpc retention times (175°) 7.5 and 8.9 min (85:15).

Application of this procedure to 350 mg (1.6 mmol) of **5c** (*ca.* 50% trans isomer) gave 230 mg (72%) of a mixture of **12** and **13** (1:1). The isomers were partially separated by preparative glpc. The trans isomer (**12**) was obtained in 80% purity: glpc retention times (175°) 7.5 and 8.9 min (4:1).

*Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.15. Found: C, 66.78; H, 9.27.

The cis isomer (**13**) was also obtained in 80% purity: glpc retention times (175°) 7.5 and 8.9 min (1:4).

*Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.15. Found: C, 66.83; H, 9.25.

**7-Carbomethoxy-*trans*-1-oxadecalin (9).** This compound was prepared from **8** in 76% yield by the method used for **12**. Material of greater than 99% purity was obtained as a low-melting solid (melts near room temperature) by chromatography on silica gel (Woelm) using 2% ethyl acetate–methylene chloride: ir (neat) 1725 $cm^{-1}$ (C=O); glpc retention time (175°) 9.4 min (only one peak observed).

*Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.15. Found: C, 66.74; H, 9.21.

Application of this procedure to 340 mg (1.6 mmol) of the mother liquors from the recrystallization of **8** gave 150 mg (47%) of an isomer mixture: nmr $\delta$ 3.67 (s, $OCH_3$); glpc retention times (175°) 7.0, 8.3, and 9.4 min (16:28:56).

**Base-Catalyzed Equilibrations of 9.** A solution of 18 mg of **9** [glpc (175°) indicated 98% of the isomer with retention time of 9.4 min] in 2 ml of 2.5 *N* $NaOCH_3$–$CH_3OH$ was refluxed under $N_2$ for 7 days. The cooled solution was treated with 3 ml of 0.3 *N* HCl and 2 ml of brine and extracted with cyclohexane. The cyclohexane extracts were dried ($MgSO_4$) and concentrated to give only 0.7 mg of material which was not further investigated.

When the equilibration was repeated as above, with a reflux period of 1 hr, a 76% recovery was realized. The recovered material contained 13% of a new glpc peak at 7.0 min (175°) in addition to 87% of the starting isomer peak. Gas chromatography–mass spectra showed that this new peak was an isomer of **9**: new peak mass spectrum *m/e* (rel intensity) 198 (30), 167 (15), 139 (23), 111 (100), 97 (59), 84 (7); starting isomer peak mass spectrum *m/e* (rel intensity) 198 (12), 167 (14), 139 (32), 111 (55), 97 (100), 84 (12). On extending the reflux time to 4 hr only a 14% recovery of material which contained 21% of the new peak was possible.

Application of the equilibration technique used for ketones **5** led to recovered starting isomer with none of this new peak present.

**Acknowledgments.** One of us (G. S.) wishes to express appreciation to Merck and Co. for financial assistance. We are grateful to Merck and Co. for permitting use of their gas chromatography–mass spectra facilities and to Mr. Jack L. Smith for running these spectra.

**Registry No.**—**1a**, 491-37-2; **2a**, 51599-61-2; **2b**, 41118-34-7; **2c**, 41118-27-8; **3c** cis epimer 1, 51600-14-7; **3c** cis epimer 2, 51600-15-8; **4a**, 1124-63-6; **5a**, 51600-16-9; **5b** cis epimer 1, 51600-17-0; **5b** cis epimer 2, 51600-18-1; **5c**, 51599-62-3; **7**, 51600-19-2; **8**, 51599-63-4; **9**, 51600-20-5; **10**, 51600-21-6; **11**, 51600-22-7; **12**, 51600-23-8; **13**, 51600-15-8.

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(7) A. van der Gen, K. Wiedhaup, J. J. Swoboda, H. C. Dunathan, and W. S. Johnson, *J. Amer. Chem. Soc.*, **95**, 2656 (1973).
(8) Under optimum conditions, the presence of both ketones **6** and **7** could be shown by glpc in a synthetic mixture. However, the peaks were not well separated enough for quantification. Only one isomer was evident in the pmr spectrum of **6** or **7**.
(9) The stereochemical designations at the bridgeheads and all other positions are not meant to imply absolute configurations.
(10) J. A. Hirsch and L. Y. Lin, *J. Chem. Soc., Perkin Trans. 1*, 1366 (1973).
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(14) Following completion of this work, a similar analysis of deoxygenation stereospecificity using a related procedure on 1-octalones was reported.[7]
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# Syntheses of 6- and 7-Carbomethoxy-1-azadecalins and 6- and 7-Carbomethoxy-1-aza-4-decalones

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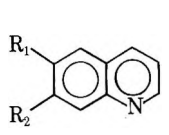
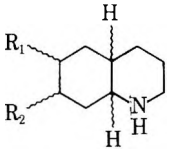
Synthetic routes to the title compounds have been investigated and all gross structures have been obtained. Problems of stereochemical assignments and epimer separations have been encountered, resulting in an inability to isolate definitive trans-fused isomers in pure form.

As part of a study of substituted *trans*-1-heteradecalins,[1] we have explored several synthetic routes to 6- and 7-carbomethoxy-1-azadecalins. Several examples of this ring system are known, with the critical reactions in their method of preparation being ring closure of nonaromatic monocyclic material,[2] Michael addition,[3] and ring closure of aromatic monocyclic material.[4] Because of our success in the 1-oxadecalin series[1] with procedures based on hydrogenation[5] of systems produced by ring closure of aromatic monocyclic material, we have pursued similar routes with the nitrogen analogs.

Initial efforts centered on hydrogenation of 6-carbomethoxyquinoline (**1a**) and 7-carbomethoxyquinoline (**1b**) in the hope that small amounts of *trans*-decahydroquinolines could be separated from the product mixture or that known reactions could be applied to the cis products to convert them into trans isomers. Quinoline-6-carboxylic acid was obtained by a modified Skraup reaction[6] on *p*-aminobenzoic acid, while quinoline-7-carboxylic acid was prepared by oxidation[7] of commercially available 7-methylquinoline. Both acids were esterified and the esters were subjected to hydrogenation at room temperature and low pressure in glacial acetic acid containing some concentrated sulfuric acid over an equal weight of Adams catalyst.[8] Good yields of mixtures of decahydroquinolines (**2a** and **2b**, respectively) were obtained.[9] In each case, glpc indicated the presence of 20% of a single isomer with a retention time shorter than that of two overlapping peaks which constituted 80% of the product mixture. Based on the behavior of the unsubstituted decahydroquinolines,[10] the earlier peak was believed to be the desired trans-fused structure.



**1**



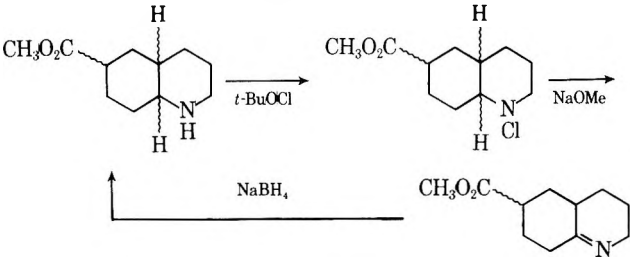
**2**

**a**, $R_1 = CO_2CH_3$; $R_2 = H$
**b**, $R_1 = H$; $R_2 = CO_2CH_3$

When the mixture of 6-carbomethoxy-1-azadecalins (**2a**) was treated in a manner expected to increase the amount of trans material (Scheme I), the material with the shorter glpc retention time was enhanced to 40% of the mixture. Nevertheless, a method of separating the isomers was still required. Column chromatography on deactivated aluminas[11] permitted separation of the two pure cis isomers, but the supposed trans isomer could not be obtained in better than 50% purity. Preparative glpc was equally unrewarding since rechromatography of collected "trans material" indicated the presence of two new peaks.

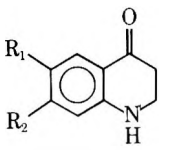
Chromatography of the mixture of 7-carbomethoxy-1-azadecalins (**2b**) on deactivated aluminas[11] resulted in pure cis isomers and a mixture containing 60% of the trans material.

**Scheme I**

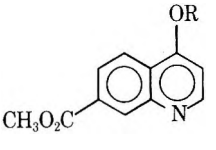



In both isomeric series (**2a** and **2b**), spectral data did not assist stereochemical assignment. The nmr (including with shift reagent), ir, and mass (including glpc–mass) spectra were all remarkably similar.

Since the above hydrogenation approach appeared unpromising, hydrogenation of 2,3-dihydro-4-quinolones along lines similar to the 4-chromanones[1,5] was investigated. Carboxylic acid **3b** was synthesized from nitroterephthalic acid with reasonable dispatch by modification of a literature method.[4] However, the decarboxylative cyclization constituting the last step in this sequence was found to be unreliable with more than 10 g of material.



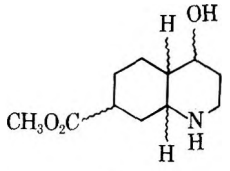
**3a**, $R_1 = CO_2H$; $R_2 = H$
**b**, $R_1 = H$; $R_2 = CO_2H$
**c**, $R_1 = CO_2CH_3$; $R_2 = H$
**d**, $R_1 = H$; $R_2 = CO_2CH_3$



**4a**, R = H
**b**, R = $CH_3$

Conversion of acid **3b** to methyl ester **3d** using concentrated sulfuric acid as the catalyst (as reported[4] for formation of the ethyl ester) was inefficient. Attempts to increase the conversion were successful, but resulted in product of lower purity since significant amounts of quinoline **4a** were formed. Use of boron trifluoride–methanol complex[12] at reflux as the esterification reagent led to quinoline **4b** as the isolated product. Dimethylformamide dimethyl acetal[13] provided pure product **3d**, but again in low conversion. The method finally chosen involved use of a polysulfonic acid resin (Bio-Rad AGMP-50) with methanol and a Soxhlet extractor.

Hydrogenation of ester **3d** over ruthenium[5] (1.7 g catalyst/g ester) led cleanly to a decahydroquinolinol mixture (**5**) containing no aromatic material and less than 4% of benzylically hydrogenolyzed ester **2b**. Oxidation of unblocked[14] crude 7-carbomethoxy-1-aza-4-decalol (**5**) with Jones reagent[15] resulted in a low yield of a mixture con-



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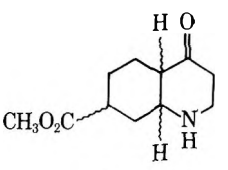

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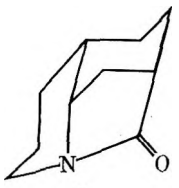

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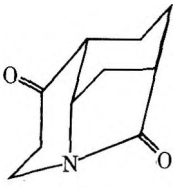
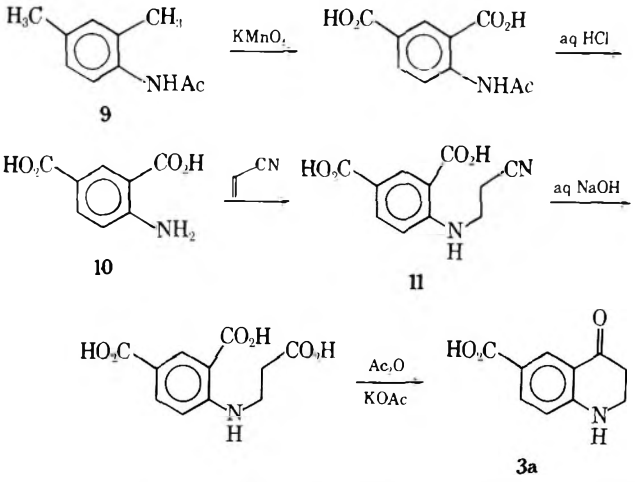


8

taining four isomeric ketones (6) and two lactams (7 and 8), lactam 7 evidently resulting from ring closure of hydrogenolyzed material[16] **2b** and lactam 8 from ring closure of one isomer of ketone **6**. Glpc–mass spectroscopy confirmed the structures of all of these products, but no information was obtained pertinent to stereochemical assignments in the ketone isomers, none of which were obtained in pure form.

Carboxylic acid **3a**, an unknown compound, was prepared in three ways. Application of a decarboxylative cyclization procedure[4] (Scheme II) analogous to that used

**Scheme II**

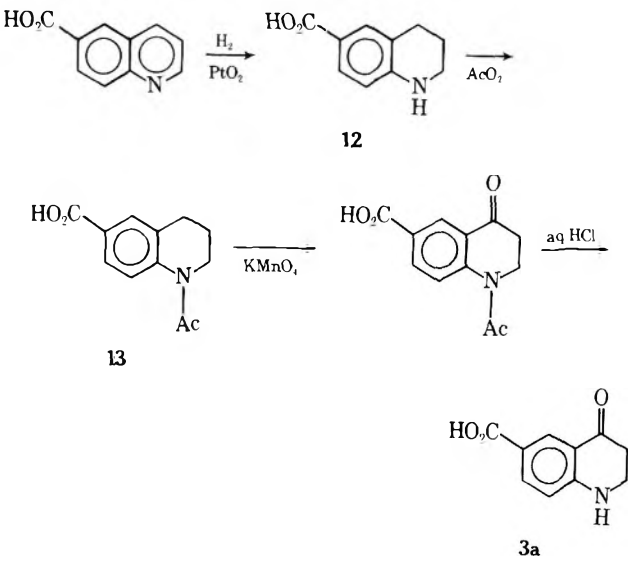


for **3b** produced the desired product in 29% yield from blocked xylidine **9**. The Michael addition (**10** → **11**) provided some difficulty, as a maximum 50% conversion could be obtained. However, repetitive additions of base and acrylonitrile to the reaction mixture produced repetitive 50% conversions so that good yields could be achieved. Use of $\beta$-propiolactone[17] instead of acrylonitrile was unsuccessful.

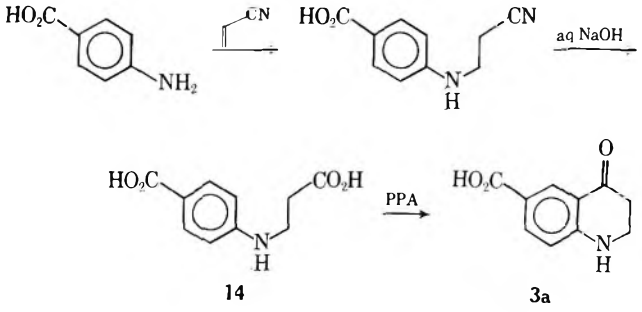
A second route (Scheme III) to acid **3a** utilized tetrahydroquinoline **12**, which could be obtained[9] from quinoline-6-carboxylic acid. Buffered permanganate oxidation[16] of blocked tetrahydroquinoline **13** proceeded satisfactorily at the benzylic position to provide acid **3a** in 37% yield from quinoline-6-carboxylic acid.

A third route, the ultimate method of choice because of its simplicity, involved intramolecular cyclization of a $\beta$-anilinopropionic acid (**14**) (Scheme IV) in a manner analogous to that used in the oxygen series.[1,5] Michael addition of *p*-aminobenzoic acid to acrylonitrile followed by hydrolysis produced acid **14**. After unsuccessful cyclization of **14** with hot sulfuric acid and of acetylated **14** with polyphosphoric acid, a technique[18] using hot polyphosphoric acid on **14** was found to give usable yields of **3a**, the overall yield for this synthetic route being 37%.

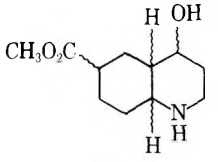
**Scheme III**



**Scheme IV**



Conversion of acid **3a** to methyl ester **3c** was achieved using the dimethylformamide dimethyl acetal method.[13,19] Hydrogenation of ester **3c** over ruthenium produced a decahydroquinolinol mixture (**15**) containing no more than 6% of hydrogenolyzed ester **2a**. Jones oxidation[15] gave a low yield of ketone mixture **16**. Column chromatography permitted separation of two fractions each containing better than 90% of the same two ketone isomers, but in different proportions (4:1 and 1:4). Equilibration[1] of these two mixtures with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) produced no change in either the pmr spectra or the thin layer chromatograms, suggesting that these isomers were trans fused[20] (**17** and **18**) and that equilibration had occurred earlier in the sequence,[21] presumably during the Jones oxidation. Unfortunately, the spectral data provided no stereochemical information.



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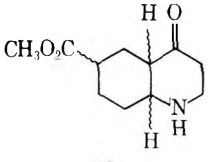

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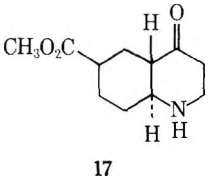

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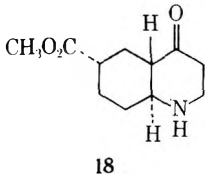

18

## Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using solutions in deuteriochloroform unless otherwise stated. Hexadeuterated dimethyl sulfoxide was

used where DMSO is specified. Infrared spectra were determined with a Beckman IR-10 spectrophotometer, with only major absorptions being cited. Mass spectral analyses were obtained at 70 eV. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. The glpc column used was a 6 ft × 0.25 in. 10% *m*-polyphenyl ether (five rings) w/w on an Anakrom ABS (60/70 mesh) column.

**6-Carbomethoxyquinoline (1a).** Quinoline-6-carboxylic acid was prepared from *p*-aminobenzoic acid in 83% yield by the method of Cohn[6] and was obtained from methanol as a buff solid, mp 291–295° (lit.[22] mp 290–291°). Conversion to the methyl ester, a white solid, was effected in 61% yield by the method of Haug and Fürst,[23] mp 86–88° (lit.[24] mp 86–87°).

**7-Carbomethoxyquinoline (1b).** Quinoline-7-carboxylic acid was prepared from 7-methylquinoline in 37% yield by the method of Siebert and coworkers,[7] mp 250–255° (lit.[7] mp 252–254°). Conversion to the methyl ester was effected in 57% yield by the method of Haug and Fürst,[23] giving a white solid, mp 73–76° (lit.[24] mp 73.5–74.5°).

**6-Carbomethoxy-1-azadecalin (2a).** A solution of 1.00 g (5.34 mmol) of **1a** in 10 ml of glacial acetic acid containing 5 drops of concentrated $H_2SO_4$ was hydrogenated for 1–2 hr at 10–50 psig at room temperature over 1.00 g of $PtO_2$. Hydrogen uptake was *ca.* 6 equiv (the catalyst was not prereduced). The mixture was diluted with $CH_2Cl_2$ and the catalyst was removed by filtration. The filtrate was treated with 10 ml of 19 *N* NaOH in the cold and extracted with $CH_2Cl_2$. The extracts were concentrated, giving 1.06 g (100%) of the epimers of **2a**, glpc retention times (175°) 13.6, 17.4, and 18.3 min (1:2:2).

*Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.82; H, 9.53; N, 7.10.

Chromatography on neutral alumina (Woelm, activity grade III) of 500 mg of this epimer mixture gave 160 mg (32%) of a single cis isomer as an oil in the 50% ethyl acetate–methylene chloride fractions: ir (neat) 1745 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (13), 166 (11), 138 (7), 110 (3), 96 (100), 83 (33); glpc retention time (175°) 18.3 min.

The 5–10% methanol–ethyl acetate fractions contained 240 mg (48%) of a mixture of the other cis isomer and a trans isomer of **2a**. Chromatography on neutral alumina (Woelm, activity grade V) of this new mixture gave 30 mg (6%) of the cis isomer in the 60% benzene–heptane fractions as a white solid: ir (Nujol) 1745 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (8), 166 (7), 138 (2), 110 (2), 96 (100), 83 (17); glpc retention time (175°) 17.4 min.

The 80–90% benzene–heptane fractions contained 30 mg (6%) of a mixture of this cis isomer and the trans isomer, glpc retention times (175°) 13.6 and 17.4 min (1:1).

**7-Carbomethoxy-1-azadecalin (2b).** This compound was prepared from **1b** in 99% yield by the method used for **2a**, glpc retention times (169°) 13.0, 15.4, and 16.9 min (1:4; the latter two peaks were not well defined and were combined for this ratio).

Chromatography on neutral alumina (Woelm, activity grade IV) of 500 mg of this isomer mixture gave 200 mg (40%) of a mixture of one of the cis isomers and a trans isomer as an oil in the 0–50% methylene chloride–benzene fractions, glpc retention times (169°) 13.0 and 16.9 min.

One 50% ethyl acetate–methylene chloride fraction contained 50 mg (10%) of the other cis isomer as an oil: ir (neat) 3440 (N–H) and 1750 $cm^{-1}$ (C=O); nmr $\delta$ 3.67 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (10), 166 (4), 138 (7), 110 (3), 96 (100), 83 (8); glpc retention time (169°) 15.4 min.

*Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.97; H, 9.70; N, 7.04.

Chromatography on neutral alumina (Woelm, activity grade III) of the previously mentioned 200 mg of isomer mixture gave 40 mg (8%) of a pure cis epimer in the $CH_2Cl_2$ fractions as an oil: ir (neat) 1750 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (13), 166 (7), 138 (5), 110 (6), 96 (100), 83 (10); glpc retention time (169°) 16.9 min.

The 10% methanol–ethyl acetate fractions contained 20 mg of a mixture of the latter cis isomer and the trans isomer, glpc retention times (169°) 13.0 and 16.9 min (3:2). The mass spectrum of the pure trans isomer of **2b** was recorded using gas chromatography–mass spectra: *m/e* (rel intensity) 197 (10), 110 (10), 96 (100).

**Partial Isomerization of 6-Carbomethoxy-1-azadecalin (2a).** A stirred solution of 207 mg (1.05 mmol) of isomer mixture **2a** in 2 ml of dry ether was treated dropwise with a solution of 120 mg (1.1 mmol) of *tert*-butyl hypochlorite in 2 ml of dry ether over 5 min in an ice bath. Stirring was continued in the cold for 30 min, and the resulting solution of 6-carbomethoxy-1-aza-1-chlorodecalin was then treated dropwise with a solution of 62 mg (1.1 mmol) of $NaOCH_3$ in 4 ml of dry methanol over a few minutes. Most of the ether was removed, and the solution was then refluxed for 30 min. The resulting solution was cooled and treated with 200 mg (5.3 mmol) of $NaBH_4$ and 1 drop of water. The mixture was stirred for a few minutes at room temperature, then kept at 5° for 22 hr. The mixture was treated with 1 ml of glacial acetic acid and concentrated. The residue was treated with ice and 2.5 *N* NaOH, then extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($NaSO_4$) and the solvent was evaporated, giving 130 mg (63%) of a crude mixture, glpc retention times (175°) 13.6, 17.4, and 18.3 min (4:3:3).

**7-Carbomethoxy-2,3-dihydro-4(1*H*)-quinolone (3d).** A stirred mixture of 3.56 g (18.7 mmol) of **3b**[4] and 11.4 g (56 mmol) of Bio-Rad AGMP-50 (50–100 mesh granular, $H^+$ form, 52–56% moisture content) in 400 ml of methanol was refluxed through a Soxhlet extractor containing 3A molecular sieves for 49 hr. The cooled mixture was filtered and the resin was washed with methanol. The filtrate and extracts were concentrated and the residue was dissolved in $CH_2Cl_2$. The solution was washed with 5% aqueous $NaHCO_3$ and brine, and then dried ($NaSO_4$). Concentration gave 2.02 g (53%) of crude **3d**, which was purified by a single recrystallization from methanol: mp 142–143°; ir (Nujol) 3380 (N–H), 1730, and 1660 $cm^{-1}$ (C=O); nmr $\delta$ 7.89 (d, 1, $J$ = 8 Hz, H-5), 7.40 (m, 1, H-8), 7.35 (m, 1, H-6), 4.91 (broad s, 1, NH), 3.90 (s, 3, $OCH_3$), 3.62 (t, 2, $J$ = 7 Hz, $NHCH_2CH_2$), 2.72 (t, 2, $J$ = 7 Hz, $CH_2CH_2C$=O).

*Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.26; H, 5.45; N, 7.00.

**Hydrogenation of 3d.** The standard procedure[5] was used for the hydrogenation of 410 mg (2.0 mmol) of **3d** over 700 mg of 5% Ru/C. Since the product had considerable water solubility, the aqueous methanol concentration residue was treated with a small amount of brine and extracted several times with $CH_2Cl_2$. The extracts were dried ($NaSO_4$) and evaporated, giving 190 mg (45%) of a mixture of isomers of **5** as an oil (additional **5** could be obtained by ethyl acetate extraction of the brine solution): ir ($CHCl_3$) 3390 [O(N)–H] and 1743 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$), 3.66 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 213 (10), 197 (5), 195 (14), 182 (12), 154 (13), 126 (10), 112 (100), 98 (24), 96 (71).

*Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 8.98; N, 6.56. Found: C, 62.03; H, 9.00; N, 6.71.

Alternatively the aqueous methanol filtrate from the hydrogenation was simply concentrated under vacuum until most of the water had been removed. This procedure gave 72% of a solid that appeared to be an hygroscopic hydrate of **5**, but which had a comparable pmr.

**7-Carbomethoxy-1-aza-4-decalone (6). Method A.** A stirred solution of 180 mg (0.84 mmol) of epimer mixture **5** in 4 ml of acetone was treated sequentially with 0.35 ml of $H_2O$, 0.07 ml (1.3 mmol) of $H_2SO_4$, and 0.39 ml (1.1 mmol) of Jones reagent[15] (2.8 *M*) in an ice bath. After being stirred in an ice bath for 5 hr, the mixture was treated with isopropyl alcohol, and then with excess $K_2CO_3$ and brine. The mixture was extracted with $CH_2Cl_2$ several times and the organic extracts were dried ($Na_2SO_4$). Concentration of the extracts gave 130 mg of a crude oil. Chromatography on activity grade III alumina (Woelm) using $CH_2Cl_2$ gave 40 mg (*ca.* 20%) of a mixture of isomers **6** and lactam **7**. This mixture was resolved by gas chromatography–mass spectra: mass spectrum *m/e* (rel intensity) first isomer of **6** 211 (8), 180 (3), 152 (3), 124 (3), 110 (100), 97 (11); second isomer of **6** 211 (8), 180 (3), 152 (3), 124 (3), 110 (100), 97 (8); third isomer of **6** 211 (24), 180 (24), 152 (24), 124 (100), 110 (50), 97 (10); fourth isomer of **6** 211 (13), 180 (11), 152 (16), 124 (100), 110 (67), 97 (10); lactam **7** 165 (100), 137 (24), 94 (72), 80 (51), 67 (45).

**Method B.** A stirred mixture of 830 mg (3.9 mmol) of **5** hydrate and 20 ml of acetone was treated sequentially with 1.1 ml of $H_2O$, 0.22 ml (3.9 mmol) of concentrated $H_2SO_4$, and 2.8 ml (7.8 mmol) of Jones reagent[15] (2.8 *M*) in an ice bath. The ice bath was removed and stirring was continued for 2 hr. The mixture was treated with isopropyl alcohol followed by excess $NaHCO_3$. This mixture was concentrated at room temperature and the solid residue was extracted with $CH_2Cl_2$. The remaining solid was slurried with aqueous $K_2CO_3$ and further extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried ($Na_2SO_4$) and evaporated, giving 860 mg of a crude oil. Chromatography on neutral alumina (Woelm, activity grade III) gave substantial amounts of an unidentified, volatile oil in the benzene fractions. The early $CH_2Cl_2$ fractions contained 60 mg of a mixture of **7**, **8**, and one isomer of **6**. The mixture was resolved by gas chromatography–mass spec-

tra. Lactam 7 exhibited the previously described mass spectrum (method A). Keto lactam 8 had mass spectrum *m/e* (rel intensity) 179 (100), 151 (20), 115 (25), 101 (65), 99 (54). The **6** present was either the first or the second isomer by mass spectrum (see method A).

The later $CH_2Cl_2$ fractions contained 50 mg (6%) of a mixture of two isomers of **6** (the third and fourth isomers): ir (neat) 1730 and 1710 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 3.68 (s, $OCH_3$).

**4-Aminoisophthalic Acid (10).** A stirred mixture of 30 g (0.18 mol) and 2′,4′-acetoxylidide[25] (**9**) and 1.5 l. of water was treated portionwise with 175 g (1.10 mol) of $KMnO_4$ over 7 hr at 80–85°. After the $KMnO_4$ had been consumed, the mixture was filtered hot. The cooled filtrate was made strongly acidic with concentrated HCl and the precipitated 4-acetylaminoisophthalic acid was washed with water. The crude moist solid was treated with 300 ml of concentrated HCl and 200 ml of ethanol and heated on a steam bath for 3.5 hr. The solution was filtered hot and the filtrate was treated with saturated sodium acetate solution to pH 3–4. The precipitated solid was aged and washed with water, giving 23.6 g (72% from **9**) of a solid: ir (Nujol) 3520, 3480, 3400, 3360 (N–H), 1690, and 1635 $cm^{-1}$ (C=O); nmr (DMSO-$CDCl_3$) $\delta$ 8.85 [broad s, O(N)H], 8.54 (d, $J$ = 2 Hz, H-2), 7.84 (dd, $J$ = 2, 9 Hz, H-6), 6.84 (d, $J$ = 9 Hz, H-5).

**4-[(2-Cyanoethyl)amino]isophthalic Acid (11).** A hot, stirred suspension of 13.1 g (72.4 mmol) of **10** and 2.95 g (73.6 mmol) of NaOH in 145 ml of water was treated with 9.6 ml (140 mmol) of acrylonitrile and refluxed on a steam bath for 18 hr. This mixture was further treated with 1.43 g (35.5 mmol) of NaOH and 4.8 ml (72 mmol) of acrylonitrile and heated for an additional 24 hr. This solution was stirred in an ice bath and acidified to pH *ca.* 4 with glacial acetic acid. The precipitated solid was washed with water and dried. Recrystallization from methanol gave 10.2 g (60%) of white crystals: mp 254° dec; ir (Nujol) 3360 (N–H), 2280 (C≡N), and 1680 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 9.36 [broad s, O(N)H], 8.51 (d, $J$ = 2 Hz, H-2), 7.93 (dd, $J$ = 2, 9 Hz, H-6), 6.94 (d, $J$ = 9 Hz, H-5), 3.67 (m, $NHCH_2CH_2$), 2.86 (t, $J$ = 6 Hz, $CH_2CH_2CN$).

*Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.26; H, 4.49; N, 11.90.

**4-[(2-Carboxyethyl)amino]isophthalic Acid.** A solution of 10 g (42 mmol) of **11** in 200 ml of 2.5 *N* NaOH was refluxed for 4 hr. The cooled solution was filtered and the filtrate was acidified to pH *ca.* 3 with concentrated HCl. The precipitated solid was washed with water, giving 11.1 g (100%) of a white solid: ir (Nujol) 1690 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 10.3 [broad s, O(N)H], 8.58 (d, $J$ = 2 Hz, H-2), 8.00 (dd, 1, $J$ = 2, 9 Hz, H-6), 6.89 (d, 1, $J$ = 9 Hz, H-5), 3.58 (m, 2, $NHCH_2CH_2$), 2.66 (t, $J$ = 6 Hz, $CH_2CH_2CO_2H$).

**1-Acetyl-6-carboxy-1,2,3,4-tetrahydroquinoline (13).** A mixture of 7.00 g (40.5 mmol) of quinoline-6-carboxylic acid (see **1a**) and 45 ml of glacial acetic acid was hydrogenated for 55 min at 5–48 psig at room temperature using 560 mg of $PtO_2$. The catalyst was removed by filtration and the filtrate was concentrated, giving crude tetrahydro compound **12**. A solution of crude **12** in 45 ml of acetic anhydride was heated on a steam bath for 1 hr. The cooled solution was treated with water and aged. The aqueous phase was decanted and the residual oil and solid were dissolved in $CH_2Cl_2$. The $CH_2Cl_2$ extract was washed with water, dried ($MgSO_4$), and concentrated, giving 5.6 g of a crude solid. The solid was washed with ether, giving 4.95 g (56% from quinoline-6-carboxylic acid) of a solid: mp 176–179° (lit.[26] mp 187°); ir (Nujol) 2640 (O–H), 1715, and 1640 $cm^{-1}$ (C=O); nmr (DMSO-$CDCl_3$) $\delta$ 7.71 (m, 2, H-5 and H-7), 7.54 (d, 1, $J$ = 9 Hz, H-8), 3.73 (t, 2, $J$ = 6.5 Hz, H-2), 2.76 (t, 2, $J$ = 6.5 Hz, H-4), 2.22 (s, 3, $COCH_3$), 2.08 (quintet, 2, $J$ = 6.5 Hz, H-3).

**1-Acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone.** A stirred solution of 2.19 g (10.0 mmol) of **13**, 450 mg (11 mmol) of NaOH, and 7.20 g (60.0 mmol) of anhydrous $MgSO_4$ in 90 ml of water was treated with a solution of 3.16 g (20.0 mmol) of $KMnO_4$ in 180 ml of water at *ca.* 10°. After 5 min the ice bath was removed and stirring was continued for 20 hr. The solution was further treated with 1.0 g (6.4 mmol) of solid $KMnO_4$ portionwise over 2.5 hr and stirred for another 12 hr. The mixture was filtered and the filtrate was acidified to *ca.* pH 2 with concentrated HCl. The resulting turbid solution was saturated with NaCl and extracted with ethyl acetate. The ethyl acetate extracts were dried ($MgSO_4$) and concentrated, giving 1.85 g (79%) of crude 1-acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone: nmr (DMSO) $\delta$ 8.45 (d, $J$ = 2 Hz, H-5), 8.13 (dd, $J$ = 2, 8.5 Hz, H-7), 7.90 (d, $J$ = 8.5 Hz, H-8), 4.21 (t, $J$ = 6 Hz, H-2), 2.86 (t, $J$ = 6 Hz, H-3), 2.38 (s, $COCH_3$).

**4-[(2-Carboxyethyl)amino]benzoic Acid (14).** A hot solution of 15 g (0.11 mol) of *p*-aminobenzoic acid and 4.2 g (0.10 mol) of NaOH in 150 ml of water was treated with 7.8 ml (0.18 mol) of acrylonitrile and refluxed on a steam bath for 20 hr. This solution was stirred in an ice bath and acidified to pH *ca.* 4 with glacial acetic acid. The precipitated solid was washed with water. A solution of this moist nitrile and 30 g of NaOH in 300 ml of water was refluxed for 4 hr. The solution was filtered, cooled, and acidified to pH *ca.* 3 with concentrated HCl. The precipitated solid was washed with water and recrystallized from aqueous methanol, giving 15.4 g (67%) of white crystals: mp 206° dec (lit.[27] mp 206–207° dec); ir (Nujol) 1685 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 7.68 (d, $J$ = 9 Hz, H-2 and H-6), 6.58 (d, $J$ = 9 Hz, H-3 and H-5), 6.33 [broad s, O(N)H], 3.32 (t, $J$ = 7 Hz, $NHCH_2CH_2$), 2.50 (t, $J$ = 7 Hz, $CH_2CH_2CO_2H$).

**6-Carboxy-2,3-dihydro-4(1*H*)-quinolone (3a). From 1-Acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone.** A mixture of 1.85 g (7.94 mmol) of 1-acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone in 18 ml of 6 *N* HCl was heated on a steam bath for 1 hr. This suspension was cooled in an ice bath and neutralized to *ca.* pH 3 with 19 *N* NaOH. The precipitated solid was washed with water, giving 1.27 g (84%) of a solid: ir (Nujol) 3380 (N–H) and 1675 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 8.26 (d, $J$ = 2 Hz, H-5), 7.83 (dd, $J$ = 2, 8.5 Hz, H-7), 7.51 (broad s, NH), 6.85 (d, $J$ = 8.5 Hz, H-8), 3.56 (t, $J$ = 7 Hz, H-2), 2.62 (t, $J$ = 7 Hz, H-3).

**From 4-[(2-Carboxyethyl)amino]isophthalic Acid.** The desired compound was prepared from 4-[(2-carboxyethyl)amino]isophthalic acid in 65% yield by the method used for **3b**.[4] The nmr spectrum was as previously described.

**From 14.** A mixture of 1.00 g (4.79 mmol) of **14** and 10.8 g of polyphosphoric acid was heated on a steam bath for 20 hr. The cooled solution was treated with ice, and the solid which gradually separated was washed with water, giving 510 mg (56%) of **3a**; ir spectrum was as previously described.

**6-Carbomethoxy-2,3-dihydro-4(1*H*)-quinolone** (3c). A mixture of 5.04 g (37.9 mmol) of **3a**, 9.0 ml (*ca.* 2 equiv) of dimethylformamide dimethyl acetal,[13] and 25 ml of DMF was stirred at room temperature for 20 hr. This solution was diluted with 5% aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was pumped at 70–80° under vacuum to remove DMF. The remaining residue was recrystallized from methanol, giving 1.13 g (20%) of yellow-brown crystals: mp 157–158°; ir (Nujol) 3395 (N–H), 1725, and 1665 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 8.21 (d, 1, $J$ = 2 Hz, H-5), 7.79 (dd, 1, $J$ = 2 and 9 Hz, H-7), 7.55 (broad s, 1, NH), 6.83 (d, 1, $J$ = 9 Hz, H-8), 3.80 (s, $OCH_3$), 3.56 (dt, $J$ = 2 and 7 Hz, $NHCH_2CH_2$), 2.60 (t, $J$ = 7 Hz, $CH_2CH_2C$=O).

*Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.25; H, 5.40; N, 7.00.

**Hydrogenation of 3c.** The standard procedure[5] was used for the hydrogenation of 1.10 g (5.36 mmol) of **3c** over 1.9 g of 5% Ru/C. Since the product had no great water solubility, the aqueous methanol concentration residue was simply extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried ($Na_2SO_4$) and evaporated, giving 530 mg (46%) of a mixture of isomers **15** as an oil: ir (neat) 3330 [O(N)–H] and 1740 $cm^{-1}$ (C=O); nmr $\delta$ 3.67 (s, $OCH_3$).

*Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 8.98; N, 6.56. Found: C, 62.19; H, 9.01; N, 6.46.

**6-Carbomethoxy-1-aza-4-decalone (16).** This isomer mixture was prepared from isomer mixture **15** by method A used for **6**. Chromatography of the 590 mg of crude **16** obtained on neutral alumina (Woelm, activity grade III) gave an unidentified volatile oil in the benzene fractions. The 90% $CH_2Cl_2$–benzene fractions contained 50 mg (10%) of a mixture of **17** and **18** as an oil: nmr $\delta$ 3.68 (s, $OCH_3$); tlc (silica gel, 8:2:1 heptane–EtOAc–diethylamine) $R_f$ minor 0.14, major 0.20, unknown 0.29.

The $CH_2Cl_2$ fractions contained 70 mg (14%) of a mixture of **17** and **18** as a low-melting solid: ir (Nujol) 3400 (N–H) and 1730 $cm^{-1}$ (C=O); nmr $\delta$ 3.67 (s, $OCH_3$); tlc (silica gel as above) $R_f$ major 0.14, minor 0.20; gas chromatography–mass spectra *m/e* (rel intensity) major 211 (12), 180 (17), 152 (17), 124 (65), 110 (100), 97 (35); minor 211 (23), 180 (4), 152 (22), 124 (26), 110 (100), 97 (34).

**Attempted Equilibration of Mixtures of 17 and 18.** Equilibrations were carried out as before.[1] The DBN was removed by chromatography on neutral alumina (Woelm, activity grade III) using $CH_2Cl_2$.

Application of this technique to the 50-mg sample of **17** + **18** resulted in the recovery of 40 mg (80%) of material that showed

no change in nmr or tlc from that of the starting mixture. Gas chromatography–mass spectra of the recovered material: *m/e* (rel intensity) major identical with that of the minor component of the 70-mg sample; minor 211 (15), 180 (15), 152 (9), 124 (26), 110 (100), 97 (31).[28]

Application of this technique to the 70-mg sample of **17** + **18** likewise resulted in no change in tlc.

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**Registry No.**—**1a**, 38896-30-9; **1b**, 51552-68-2; **2a** cis epimer 1, 51552-69-3; **2a** cis epimer 2, 51552-70-6; **2a** trans epimer, 51552-71-7; **2b** cis epimer 1, 51552-72-8; **2b** cis epimer 2, 51552-73-9; **2b** trans epimer, 51552-74-0; **3a**, 51552-75-1; **3b**, 19384-65-7; **3c**, 51552-76-2; **3d**, 39011-44-4; **5**, 51552-77-3; **6** isomer 1, 51552-78-4; **6** isomer 2, 51552-79-5; **6** isomer 3, 51552-80-8; **6** isomer 4, 51552-81-9; **7**, 51552-82-0; **8**, 51552-83-1; **9**, 2050-43-3; **10**, 33890-03-8; **11**, 51552-84-2; **13**, 51552-85-3; **14**, 51552-86-4; **15**, 51552-87-5; **17**, 51552-88-6; **18**, 51552-89-7; 4-[(2-carboxyethyl)amino]isophthalic acid, 51552-90-0; quinoline-6-carboxylic acid, 10349-57-2; 1-acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone, 51552-91-1.

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(28) This spectrum should be identical with that of the major component of the 70-mg sample of **17** + **18**. The differences that are observed are presumably because of the presence of the $R_f$ 0.29 unknown reported in the experimental data for **16**.

# An Improved Synthesis of Indenes. II. Alkyl-Substituted Indenes[1]

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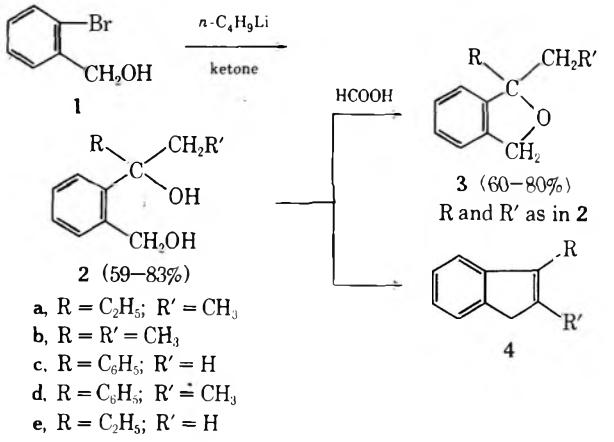
Dialkylphthalans **3**, unlike their spiro analogs, are stable to both hot formic acid and boron trifluoride etherate. Dialkyl indenes **4** (R and R′ alkyl) can, however, be prepared from diols **2** by a new procedure which involves heating the derived monoacetate **6** with hot acetic anhydride–formic acid. While this procedure is not efficient for the preparation of 3-arylindenes, the latter can be prepared in good yield from the corresponding diol **2** or phthalan **3** by use of either sulfuric acid–carbon tetrachloride (0°) or polyphosphoric acid (60°).

While fused indenes can be easily prepared[2] from spirophthalans analogous to **3**, or from the corresponding diols analogous to **2**, our initial attempts to extend this synthesis to simple acyclic indenes **4** were unsuccessful; results consistent with earlier reports.[3] We have now studied a series of acyclic diols **2** and phthalans **3** (Scheme I) and have defined useful conditions for their conversion to indenes **4**.

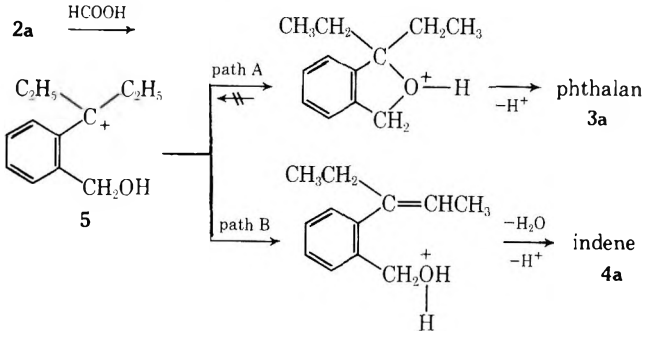
Phthalans **3a** and **3b** (where R = alkyl), in sharp contrast[2] to their cyclic analogs, are quite stable to hot formic acid and to hot boron trifluoride etherate in hot benzene; no evidence of decomposition or indene formation was noted. With stronger acids (PPA, $H_2SO_4$) these phthalans gave small amounts of indenes; however, higher condensation products predominate and the procedure is of no synthetic value.

It was observed that reaction of diol **2a** with hot formic acid gave **3a** and, significantly, some indene **4a** (8%). Since **3a** does not give **4a** under these conditions, it was concluded that diols **2** could be converted to indenes **4** by a process not involving phthalans **3**, and that successful conversion of **3a** to indene depended upon inhibiting path A relative to path B in Scheme II. Replacement of the primary hydroxyl group in **2** by acetoxy, as in **6** (Scheme III), was investigated since $CH_3C{=}O^+$ would be a poorer leaving group than $H^+$ which, consequently, should inhibit path A relative to path B (Scheme II). Satisfactory yields of indenes **4a** (60%) and **4b** (59%) were formed to-

**Scheme I**

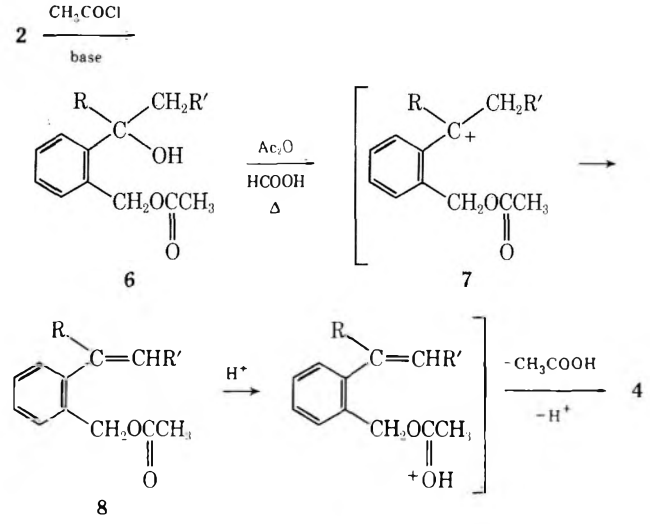


**Scheme II**



gether with some corresponding phthalan by the procedure outlined in Scheme III; 2,3-dimethylidene (**4b**) formed to the exclusion of 3-ethylidene (**4e**).

**Scheme III**



The acetate procedure, summarized in Scheme III, was not satisfactory for preparation of the 3-arylindenes. Reaction of the corresponding monoacetate **6c** (R = $C_6H_5$; R′ = H) and the eneacetate **8c** (R = $C_6H_5$; R′ = H) with hot acetic anhydride and formic acid gave principally phthalan **3c** with only low conversion to indene. Presumably, the greater stability of 7 where R = aryl, relative to 7 where R = alkyl, is sufficient to permit reaction of the type shown in path A (Scheme II) to dominate in these cases.

3-Arylindenes of type **4c** and **4d** can be prepared from diols of type 2 or the corresponding phthalans 3 by use of stronger acids. Both Pittman and Miller[4] and Bertoli and Plesch[5] have studied spectral behavior of 3-arylindenes in acid media at low temperature. The result of these studies indicate that 3-arylindenes are stable over long periods of time at low temperature (−50 to 0°) in strong acid. Reaction of diol **2c** and phthalan **3c** in a two-phase system in carbon tetrachloride and sulfuric acid[6] at 0° gave 57 and 59%, respectively, of **4c**; the dialkyl phthalans **3a** and **3b** gave complex mixtures under these conditions.

In certain cases polyphosphoric acid can be employed to give 3-arylindenes. Reaction of phthalan **3c** with PPA at 30° resulted in no reaction; reaction at 60° gave a complex mixture. By contrast, reaction of 3-phenyl-3-ethylphthalan (**3d**) with PPA at 60° gave an 82% yield of 2-methyl-3-phenylindene (**4d**). Polyphosphoric acid at 30° is not effective for conversion of either **3c** or **3d** to indenes; its use at higher temperature is limited to the preparation of indenes which are stable to higher reaction temperatures in such strong acid medium.

## Experimental Section

Diols 2 were prepared essentially as previously described[2] for related compounds.

**1-(2-Hydroxymethylphenyl)-1-phenylethanol (2c):** 59% yield; mp 109–110° (lit.[7] mp 109–110°) from petroleum ether[8]–acetone; pmr δ 7.9–7.0 (m, aromatic H, 8.9), 5.20 (broad s, OH, 0.97), 4.03 (broad s, $C_6H_5CH_2$ and OH, 3.0), 1.83 (s, $CH_3$, 3.0).

*Anal.* Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.90; H, 6.99.

**1-(2-Hydroxymethylphenyl)-1-phenylpropanol (2d):** 76% yield; mp 89–90.5° from petroleum ether[8]–acetone; pmr δ 7.8–7.1 (m, aromatic H, 8.9), 4.13 (s, $C_6H_5CH_2$, 1.9), 3.90 (broad s, OH, wt 1.9), 2.26 (q, $CH_2CH_3$, wt 2.1), 0.83 (t, $CH_2CH_3$, wt 2.9).

*Anal.* Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.56; H, 7.48.

**2-(2-Hydroxymethylphenyl)butan-2-ol (2b):** 80% yield; bp 100–103° (0.07 mm); pmr δ 7.13 (m, aromatic H, 3.9), 4.70 (q, $C_6H_5CH_2$, 1.9), 4.06 (broad s, OH, 1.9), 1.90 (q, $CH_2CH_3$, 2.1), 1.55 (s, $CH_3$, 3.1), 0.78 (t, $CH_2CH_3$, 3.1).

*Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.48; H, 9.06.

**3-(2-Hydroxymethylphenyl)pentan-3-ol (2a):** 84% yield; mp 78–79° (lit.[9] mp 81–82°) from petroleum ether;[8] pmr δ 7.20 (m, aromatic H, 4.0), 4.77 (s, $C_6H_5CH_2$, 1.9), 3.97 (broad s, OH, 1.93), 1.92 (q, $CH_2CH_3$, 4.0), 0.78 (t, $CH_2CH_3$, 6.1).

*Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.14.

**Phthalans 3** were prepared from 2 (0.28 mol) in boiling formic acid[2] (90%, 100 ml) for 2.5 hr; **3b** was prepared by reaction of **2b** (0.05 mol) with boron trifluoride etherate (0.05 mol) in benzene (150 ml) for 20 hr at room temperature.

**1-Methyl-1-phenylphthalan (3c):** 88% yield; bp 93–95° (0.2 mm) [lit.[7] bp 122–123° (2 mm)]; analytical sample purified by gc[10] (150°); pmr δ 7.83–7.00 (m, aromatic H, 9), 5.13 (s, $C_6H_5CH_2O$, 2.0), 1.83 (s, $CH_3$, 2.9).

*Anal.* Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.91; H, 6.57.

**1-Ethyl-1-phenylphthalan (3d):** 66% yield, bp 90–92° (0.12 mm); analytical sample purified by gc[10] (160°); pmr δ 7.83–7.00 (m, aromatic H, 9), 5.13 (s, $C_6H_5CH_2O$, 2.0), 1.83 (s, $CH_3$, 2.9).

*Anal.* Calcd for $C_{16}H_{16}O$: C, 85.68; H, 6.71. Found: C, 85.91; H, 6.57.

There was also obtained a higher boiling fraction [bp 103–115° (0.12 mm), ~⅓ weight of **3d**] that appeared to be (pmr) a mixture of **3d** and 1-(2-formyloxymethylphenyl)-1-phenylprop-1-ene; however, this product was not examined further.

**1-Ethyl-1-methylphthalan (3b):** 73% yield; bp 49–50° (1.4 mm); analytical sample purified by gc[10] (120°); pmr δ 7.31–6.93 (m, aromatic H, 3.9), 5.04 (s, $C_6H_5CH_2O$, 1.9), 1.78 (q, $CH_2CH_3$, 2.0), 1.44 (s, $CH_3$, 3), 0.78 (t, $CH_2CH_3$, 3).

*Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.24; H, 8.49.

**1,1-Diethylphthalan (3a):** 60% yield; bp 60–63° (1.4 mm); analytical sample prepared by gc[10] (135°); pmr δ 7.50–6.83 (m, aromatic H, 4), 5.08 (s, $C_6H_5CH_2O$, 1.9), 1.80 (q, $CH_2CH_3$, 4), 0.73 (t, $CH_2CH_3$, 5.9).

*Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.93; H, 8.97.

Distillation of the pot residue gave (1) a mixture (pmr) of **3a** and indene **4a** [~1/10 weight of **6a**, bp 63–70° (1.4 mm)] and (2)

3-ethyl-2-methylindene [**4a**, 8.4% yield, bp 70–73° (1.4 mm)].

**Monoacetates 6a and 6b** were prepared from the corresponding diols **2** in ether by using acetyl chloride (2 equiv) and *N,N*-dimethylaniline to trap hydrogen chloride.[11]

**2-(2-Acetoxymethylphenyl)butan-2-ol (6b):** 88% yield; bp 90–93° (0.11 mm); analytical sample purified by liquid chromatography;[12] pmr $\delta$ 7.5–7.1 (m, aromatic H, 4.0), 5.54 (s, $C_6H_5CH_2O$, 2.0), 2.46 (broad s, OH, 1.0), 2.09 (s, $O_2CCH_3$, 2.9), 1.92 (q, $CH_2CH_3$), 1.62 (s, $CH_3$, total weight at 1.92 and 1.62 = 5), and 0.83 (t, $CH_2CH_3$, 3.0); ir $\nu_{OH}$ 3500, $\nu_{C=O}$ 1745 $cm^{-1}$.

*Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.23; H, 7.96.

**3-(2-Acetoxymethylphenyl)pentan-3-ol (6a):** 90% yield; bp 97–100° (0.07 mm); analytical sample prepared by liquid chromatography;[12] pmr $\delta$ 7.6–7.2 (m, aromatic H, 3.8), 5.50 (s, $C_6H_5CH_2O$, 2.0), 2.52 (broad s, OH, 1.0), 2.08 (s, $O_2CCH_3$) and 1.92 (q, $CH_2CH_3$, combined weight = 7), and 0.79 (t, $CH_2CH_3$, 5.9); ir $\nu_{OH}$ 3500, $\nu_{C=O}$ 1740 $cm^{-1}$.

*Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.33; H, 8.43.

**1-(2-Acetoxymethylphenyl)-1-phenylethanol (6c):** 92% yield; mp 86–87° from petroleum ether;[13] pmr $\delta$ 7.9–7.0 (aromatic H, 9), 4.85 (AB quartet, $C_6H_5CH_2O$, 1.8), 3.35 (s, OH, 1.2), and 1.90 (s, $CH_3$ and $-O_2CCH_3$, 6.3); ir $\nu_{OH}$ 3500, $\nu_{C=O}$ 1740 $cm^{-1}$.

*Anal.* Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.38; H, 6.59.

**$\alpha$-(2-Acetoxymethylphenyl)styrene (8c)** was prepared from **2c** with acetyl chloride (solvent) as described for **6c**. Excess acetyl chloride was removed by distillation prior to extraction and removal of salt and excess *N,N*-dimethylaniline. The crude product was distilled to give essentially pure **8c**: 91% yield; bp 113–118° (0.08 mm); analytical sample prepared by gc[10] (160°); pmr $\delta$ 7.3–7.05 (aromatic H, 9), 5.85 (d, =CH–, 1), 5.27 (d, =CH–, 1) 4.98 (s, $C_6H_5CH_2O$, 1.9), and 1.88 (s, $O_2CCH_3$, 3.0); ir $\nu_{=CH_2}$ 915, $\nu_{C=O}$ 1740 $cm^{-1}$.

*Anal.* Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.67; H, 6.24.

**2,3-Dimethylindene (4b).** A solution of monoacetate **6b** (1.00 g, 4.49 mmol) in acetic anhydride was stirred at 120° for 4 hr. Formic acid (10 ml, 90%) was added cautiously and the resulting mixture was heated at the reflux temperature for an additional 4 hr. The cooled mixture was added to water (70 ml) and the resulting mixture was stirred for 1.5 hr. The mixture was extracted with petroleum ether[12] (4 × 25 ml) and the combined extracts were washed with saturated aqueous sodium bicarbonate (25 ml) and then dried ($MgSO_4$) and concentrated to give 0.75 g of crude indene (the nmr spectrum showed **4b**, a small amount of phthalan **3b**, and no **4e**). Indene **4b** was purified by column chromatography (Alcoa F-20, 60 g, eluted with petroleum ether);[13] concentration of the initial fractions gave pure (by nmr) indene **4b** (0.38 g, 59% yield). The analytical sample of **4b** was obtained by preparative gas chromatography[10] (130°); pmr $\delta$ 7.57–6.96 (m, aromatic H, 4.1), 3.15 (s, $C_6H_5CH_2$, 2.0), and 2.01 (s, $CH_3$, 5.9).

*Anal.* Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.58; H, 8.37.

**3-Ethyl-2-methylindene (4a)** was prepared from **6a** as described above for **4b**: 60% yield; pmr $\delta$ 7.77–6.88 (m, aromatic H, 4.2), 3.12 (s, $C_6H_5CH_2$, 2.0), 2.46 (q, $CH_2CH_3$, 2), 1.96 (s, $CH_3$, 2.9), and 1.11 (t, $CH_2CH_3$, 2.9).

*Anal.* Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.14; H, 9.07.

**3-Phenylindene (4c).** A solution of 1-methyl-1-phenylphthalan (**3c**, 1.00 g, 4.7 mmol) in carbon tetrachloride (15 ml) was added slowly to a cold (0°), stirred mixture of concentrated sulfuric acid (3.68 g) in carbon tetrachloride (10 ml) and the resulting mixture was stirred at 0° for 45 min. A solution of sodium hydroxide (2.95 g) in water (10 ml) was added to neutralize the acid and after 30 min of stirring the organic layer was separated and washed with saturated aqueous ammonium chloride. The crude product (0.95 g) obtained from the dried ($Na_2SO_4$) carbon tetrachloride was 3-phenylindene contaminated with a small amount of unchanged **3c**. The indene was purified by column chromatography (Alcoa F-20, 50 g, petroleum ether[12] as eluent). Concentration of early fractions gave pure 3-phenylindene (**4c**) 0.52 g, 57% yield): pmr $\delta$ 7.6–7.0 (m, aromatic H, 9), 6.48 (t, =$CHCH_2$, 1), and 3.12 (d, $C_6H_5CH_2$, 2).

*Anal.* Calcd for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found: C, 93.59; H, 6.45.

When diol **2c** was used instead of phthalan **3c**, the yield of **4c** was 59%.

**2-Methyl-3-phenylindene (4d).** A mixture of 1-ethyl-1-phenylphthalan (**3d**, 3.50 g, 0.156 mmol) and polyphosphoric acid (5.3 g) was stirred at room temperature for 10 min and was then maintained at 60° for 45 min. The cooled mixture was stirred with water (150 ml) and extracted with chloroform (4 × 35 ml). The combined extract was washed with saturated aqueous sodium bicarbonate (50 ml), dried ($Na_2SO_4$), and concentrated to give 3.55 g of a yellow oil. Distillation of the oil gave **4d** (2.65 g, 82% yield); bp 101–103° (0.12 mm); mp 56–56.5° from acetone (lit.[14] mp 57.5°); pmr $\delta$ 7.63–7.05 (m, aromatic H, 9.2), 3.35 (s, $C_6H_5CH_2$, 1.8), and 2.05 (s, $CH_3$, 2.9).

*Anal.* Calcd for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.04; H, 7.00.

**Registry No.**—**2a**, 51293-49-3; **2b**, 51293-50-6; **2c**, 25770-18-7; **2d**, 51293-51-7; **3a**, 51293-52-8; **3b**, 42502-57-8; **3c**, 51293-53-9; **3d**, 51293-54-0; **4a**, 51293-55-1; **4b**, 4773-82-4; **4c**, 1961-97-3; **4d**, 35099-60-6; **6a**, 51364-44-4; **6b**, 51293-56-2; **6c**, 51293-57-3; **8c**, 51293-58-4.

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(12) An 8 ft × 0.25 in. Porasil A, 1:1 chloroform–petroleum ether (bp 30–60°), 1.5 ml/min.
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# Synthesis of Benzoylbenzoic Acids

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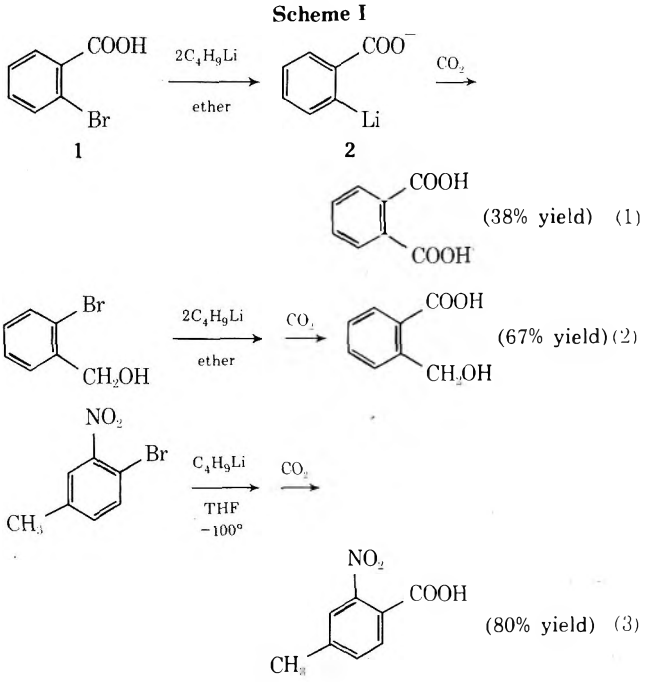
Bromine–lithium exchange in the isomeric bromobenzoic acids with *n*-butyllithium in tetrahydrofuran occurs selectively at −100°. The fate of these ions as a function of temperature has been examined. The dianions are stable at −75° but self-condense readily at −20° to give directly, and in good yield, *o*-, *m*-, and *p*-benzoylbenzoic acid, respectively. Anthraquinone is formed directly from o-bromobenzoic acid at higher temperature (0 to −20°).

In his pioneering work in organometallic chemistry, Gilman[1] and his coworkers established that halogen–metal interchange could be achieved with substituted halobenzene derivatives, and that the derived anions could be used as intermediates in synthesis as shown in Scheme I. A variety of halobenzene derivatives were employed in this work containing OH, CN, $NH_2$, $SO_2NH_2$, and $SO_2N(C_2H_5)_2$ functional groups; diethyl ether was used as solvent and temperatures of metalation varied from room temperature to −78°. While syntheses from organometallic intermediates of type 1 are potentially quite valuable, the procedure utilizing functionalized aryl halides has largely been overlooked, probably owing to the highly variable yields of benzoic acid derivatives (14–78%) obtained upon carbonation. In 1970, Kobrich and Buck[2] showed that *o*-nitrobromobenzene derivatives could be metalated in high yield (tetrahydrofuran at −100°) (eq 3, Scheme I) while *m*- or *p*-nitrobromobenzene derivatives undergo a redox reaction under these conditions.

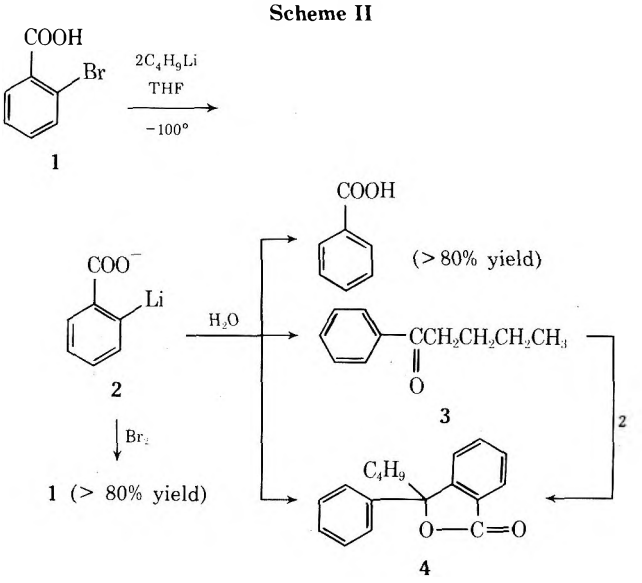
We conclude that bromine–lithium exchange should be highly selective for many substituted halobenzenes at very low temperature (−100°, liquid $N_2$), and that the variable yields of products previously reported were a consequence of side reactions of derived anions of type 2 with themselves or with solvent. We have, accordingly, reexamined halogen–metal interchange of the isomeric bromobenzoic acids and evaluated the product distribution as a function of temperature.

Reaction of *o*-bromobenzoic acid was studied in detail. When metalation of 1 was conducted at −100° in tetrahydrofuran and the reaction mixture maintained at −75°,

**Scheme I**




**Scheme II**




metalation was complete. The product distribution obtained subsequent to quenching the mixture with water is shown in Scheme II.

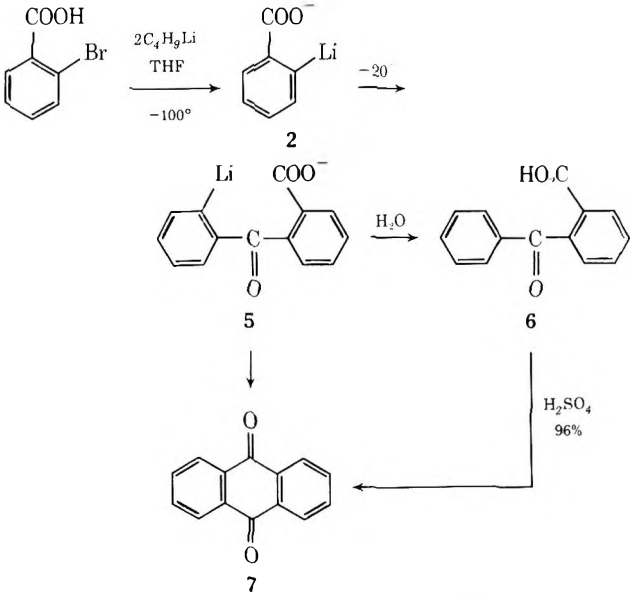
When the anion 2 was added to bromine in carbon tetrachloride, o-bromobenzoic acid was formed and isolated in >80% yield. Two minor side products, valerophenone (3, 6%) and lactone 4 (4.5%), were detected in the neutral fraction of the product obtained by addition of 2 to water. Valerophenone was undoubtedly formed by the slow addition of excess butyllithium to the anion 2, and the lactone 4 by addition of 2 to valerophenone. Evidence supporting the latter assumption was obtained by the independent synthesis of 4 (67% yield) by addition of 2 to valerophenone.

The fate of the anion 2 was found to be quite sensitive to temperature (Scheme III). Thus, while the anion 2 is quite stable at −75°, it condenses with itself[3] as the temperature is raised to −20°. Quenching the mixture obtained at −20° with water gave benzoic acid (8.4%), formed from unreacted 2, *o*-benzoylbenzoic acid (6, 63% yield, pure), anthraquinone (7, 2.3% yield) formed by self-condensation of 5, valerophenone (4%), and lactone 4 (7%).

When the temperature of the above reaction mixture was brought to 0°, none of the anion 2 survived nor was there any loss of anion 2 by abstraction of hydrogen from solvent, since no benzoic acid was obtained after addition of water; the yield of anthraquinone rose only slightly to 5.6%, and the yield of o-benzoylbenzoic acid was not changed appreciably (64% pure 6).

Attempts to effect a more efficient direct conversion of 5 to 7 were only partly successful, and this is attributed to interaction of 5 with solvent at higher temperature (−20°) to give the salt of 6. Addition of bromine to the solution of

**Scheme III**



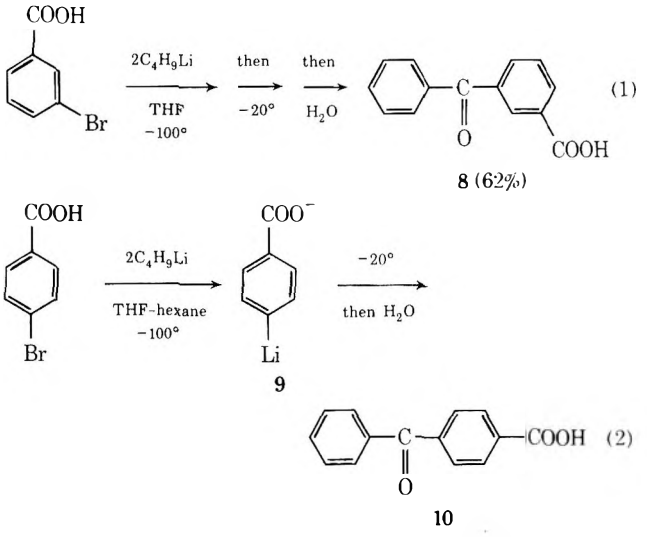

2 prepared at −100° but then warmed up to −20° gave 6 but no detectable amount of bromo acid derived from 5. Studies with *p*-bromobenzoic acid, discussed subsequently, substantiate loss of anion by reaction with solvent. When the solution of 2, prepared at −100°, was heated at the reflux temperature (24 hr) prior to addition of water, the yield of anthraquinone was raised to only 15%; the yield of o-bromobenzoic acid was reduced to 58%. The stability of anion 2 does appear to be a function of tetrahydrofuran concentration, since the yield of anthraquinone was increased to 44% (26% yield of 6) when metalation was effected at −100° in a mixture of tetrahydrofuran-hexane (40:60), and the mixture subsequently brought to reflux. Direct formation of anthraquinone (7) is of little synthetic consequence, since 7 can be formed[4] essentially quantitatively by reaction of 6 with concentrated sulfuric acid; however, utilization of the derived anion 5 directly for further synthetic transformations does not appear to be feasible.

This efficient one-step synthesis of o-benzoylbenzoic acid is of considerable synthetic consequence, since, in view of Gilman's[1] earlier work, it is anticipated that a number of substituted *o*-bromobenzoic acids can be employed which will provide direct access to substituted *o*-benzoylbenzoic acids and, subsequently, to substituted anthraquinones. This is important since the only practical direct synthesis of anthraquinones is the phthalic anhydride synthesis,[5] which is limited by the usual orientation problems and inhibiting action of negatively substitututed benzenes associated with Friedel-Crafts acylation reactions.

The direct formation of benzoylbenzoic acids is by no means limited to *o*-benzoylbenzoic acids. Thus, we have observed (Scheme IV) that *m*-benzoylbenzoic acid (8, 62% yield) and *p*-benzoylbenzoic acid (10, 55–60% yield) can be obtained directly by obvious modification of the procedure.

The anion 9 was found to be more reactive with solvent tetrahydrofuran than the corresponding anion derived from *o*- and *m*-bromobenzoic acids. Thus, when anion 9, formed at −100° in tetrahydrofuran at the same concentration used for the preparation of 3 and 8, was warmed to −20° prior to addition of water the yield of 10 was only 40%; benzoic acid was isolated in 30% yield. When the amount of solvent was increased twofold, only benzoic acid was obtained. Optimum conversion of *p*-bromobenzoic acid to 10 (55–60%) was realized by using a mixture

**Scheme IV**




of tetrahydrofuran-hexane (60:40); in this case a small amount (5%) of high-melting acid was formed.

Benzoylbenzoic acids of such orientation are not readily prepared by other methods, and it is anticipated that a variety of substituted aroylbenzoic acids can now be conveniently prepared.

## Experimental Section

**Reaction of *o*-Bromobenzoic Acid with *n*-Butyllithium. A.** *n*-Butyllithium (12.5 ml of ~2 *M* solution in hexane, ~0.025 mol) was slowly added (~1 hr) to a solution of 1 (2.5 g, 0.0125 mol) in tetrahydrofuran (50 ml, distilled from $LiAlH_4$). The mixture was maintained under nitrogen and the temperature was controlled by a liquid nitrogen–diethyl ether bath and was not allowed to rise above −95°. The mixture was then allowed to warm to −75° for 2 hr and was then poured into 5% aqueous hydrochloric acid (50 ml). The resulting mixture was extracted with chloroform (100 ml) and the chloroform extracts were washed with water (50 ml). The chloroform solution was extracted with cold 10% aqueous sodium hydroxide (25 ml) to remove acid products, and then washed with water and dried. Acidification of the alkaline extract gave essentially pure benzoic acid (1.25 g, mp 119–120°, 83% yield; 1.21 g after recrystallization from water, 79% yield, mp and mmp 120–122°).

The oil obtained from the chloroform extract was chromatographed on silica gel [preparative tlc, petroleum ether[6]–diethyl ether (80:20) as eluent] to give valerophenone (122 mg, 6%), identified by nmr and infrared, and lactone 4 as an oil; nmr showed butyl group and nine aromatic hydrogens; ir showed five-membered lactone at $\lambda_{C=O}$ 1770 $cm^{-1}$.

*Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.97; H, 6.66.

**B.** When the above reaction mixture was allowed to warm to −20 to −30° and maintained at this temperature for 5 hr prior to quenching, there was obtained (1) benzoic acid (8.4%), (2) o-benzoylbenzoic acid [6, 68% yield, mp 124–129° by chromatography, silica gel, petroleum ether[6]–ether (80:20) as eluent; 63% from benzene–petroleum ether[6], mp and mmp 128–129° (lit.[7] mp 127°)], along with the ketone 3 (4.2%), the lactone (7%), and anthraquinone (2.3%), mp and mmp 282–285°.

**C.** When the above mixture was maintained at room temperature for 6 hr prior to addition of water, there was obtained o-benzoylbenzoic acid (6, 64%), ketone 3 (4%), lactone 4 (8%), and anthraquinone (8.8%).

**D.** When the above mixture was heated at reflux (24 hr) prior to quenching, the yield of 6 was 55% and the yield of anthraquinone was 15%.

**E.** The optimum direct conversion of 1 to anthraquinone (44%) was obtained in experiments similar to D but by using tetrahydrofuran–hexane (40:60) as solvent; the yield of 6 was reduced to 26%.

**Preparation of Lactone 4.** Valerophenone (0.81 g, 0.005 mol) was added at −75° to a solution of 2 (~0.005 mol) as prepared in A above. The mixture was allowed to warm to room temperature. The lactone 4 was converted to the salt in warm aqueous base which was reconverted to lactone on acidification, yield of 4 67%.

**Conversion of 2 to *o*-Bromobenzoic Acid.** A solution of 2 was prepared as described in A and prior to quenching was added to bromine (excess in carbon tetrachloride). The acid 1 was isolated by conventional means and obtained in nearly quantitative yield.

***m*-Benzoylbenzoic acid** was prepared from *m*-bromobenzoic acid (0.0125 mol) by a procedure essentially identical with that described in B; the mixture was maintained at −20 to −10° (5 hr) prior to quenching with water. There was obtained (1) benzoic acid (mp 118–120°, 9.2%), (2) *m*-benzoylbenzoic acid [8, 69%, mp 155–158°; 63% from chloroform–petroleum ether,[6] mp and mmp 161–162° (lit.[8] mp 161–162°)]. The neutral fraction contained only trace quantities of products other than valerophenone (9%).

***p*-Benzoylbenzoic acid** was prepared from *p*-bromobenzoic acid as described for 8. The acid fraction on chromatography [silica gel, petroleum ether[6]–diethyl ether (70:30) as eluent] gave *p*-benzoylbenzoic acid [40%, mp 199–201° (lit.[9] mp 197–200°)] and benzoic acid (30%).

When the amount of tetrahydrofuran was increased twofold, only benzoic acid was obtained.

When the procedure was carried out as described for 8 but with a mixture of tetrahydrofuran–hexane (60:40) the yield of *p*-benzoylbenzoic acid was 55–60% (multiple runs).

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**Registry No.**—**1**, 88-65-3; **2**, 51310-60-2; **4**, 51310-61-3; **6**, 85-52-9; **8**, 579-18-0; **10**, 611-95-0; *n*-butyllithium, 109-72-8; benzoic acid, 65-85-0; *m*-bromobenzoic acid, 585-76-2; *p*-bromobenzoic acid, 586-76-5.

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# Synthesis of Isomeric Methyl Benzoylbenzoates and Substituted *o*-, *m*-, and *p*-Benzoylbenzoic Acids

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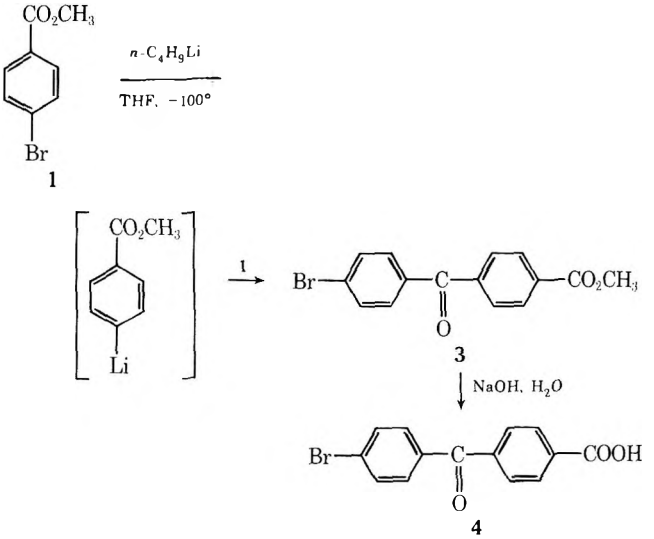
*n*-Butyllithium reacts selectively at −100° with isomeric methyl bromobenzoates by halogen–metal exchange. The corresponding anions derived from the meta and para isomers react readily with methyl ester functions at −100°; however, the anion derived from the ortho isomer reacts only slowly at this temperature, which permits complete metal–halogen interchange. The self-condensation of isomeric methyl bromobenzoates, and the reactions of dianions derived from the isomeric bromobenzoic acids with substituted methyl benzoates, provide ready access to a wide variety of *o*-, *m*-, and *p*-benzoylbenzoic acids.

In a previous communication[1] we reported a convenient procedure for a one-step conversion of bromobenzoic acids to *o*-, *m*-, and *p*-benzoylbenzoic acids. While it is apparent that this concept can be extended to a variety of substituted halobenzene derivatives, we were particularly interested in examining comparable reactions of the isomeric methyl bromobenzoates with *n*-butyllithium; it was anticipated that an understanding of competitive halogen–metal exchange *vs.* carbonyl addition reactions in such systems would permit a more versatile procedure for the preparation of a variety of isomeric aroylbenzoic acids.

**A. Self-Condensation of Methyl Bromobenzoates.** Methyl esters are considerably more reactive to anion addition reactions than carboxylate ions previously studied;[1] nevertheless, reaction of methyl *p*-bromobenzoate with *n*-butyllithium in tetrahydrofuran at −100° is selective in that the primary reaction involves halogen–metal interchange rather than addition of alkyllithium to the carbonyl ester function. The derived anion **2** did, however, react as formed at the ester function of unreacted **1**, as shown in Scheme I.

**Scheme I**




The principal product, methyl 4-(*p*-bromobenzoyl)benzoate (3), obtained pure in 63% yield when 0.75 molar equiv of *n*-butyllithium was employed, was unknown, and was further characterized by hydrolysis (~100% yield) to the corresponding acid **4**. The yield of **3** was optimum with approximately 0.75 molar equiv of *n*-butyllithium. The yield of **3** dropped to 49% when 0.6 molar equiv of *n*-butyllithium was employed, and in this case 9% of **1** was recovered unchanged; when 1 molar equiv of *n*-butyllithium was employed the yield of **3** was 57%.

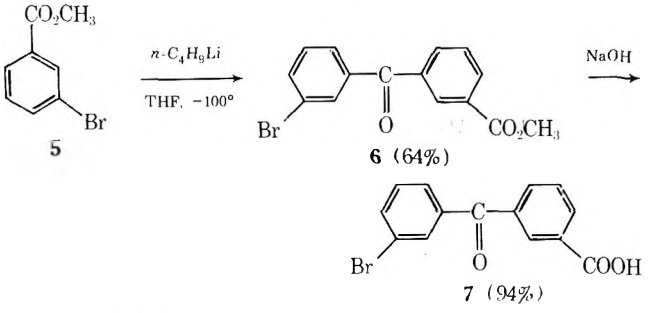
The temperature of the above reaction was found to be critical if high yields of bromo ester **3** are to be obtained.

When 1 was treated with *n*-butyllithium at −75° the yield of 3 was only 10–15%. The principal product in this case was a neutral oil which contained OH, $n$-$C_4H_9$, and $CO_2CH_3$ functions (by ir and nmr), establishing competitive reactions of *n*-butyllithium with ester or carbonyl functions; however, this material gave an oily acid on hydrolysis and was not examined further.

The above sequence provides a remarkably easy route to methyl 4-(*p*-bromobenzoyl)benzoate (3) and it is assumed that the method can be extended to related compounds containing substituents less reactive to anion addition than the ester function.

The sequence is by no means limited to the synthesis of benzoic acids substituted in the para position. Thus, when methyl *m*-bromobenzoate was treated similarly with 0.75 molar equiv of *n*-butyllithium at −100°, no unchanged bromo ester 5 was detected and methyl 3-(*m*-bromobenzoyl)benzoate (6) (Scheme II) was obtained directly in 64% yield (pure). The ester 6 was unknown and was further characterized by conversion to the new acid 7.

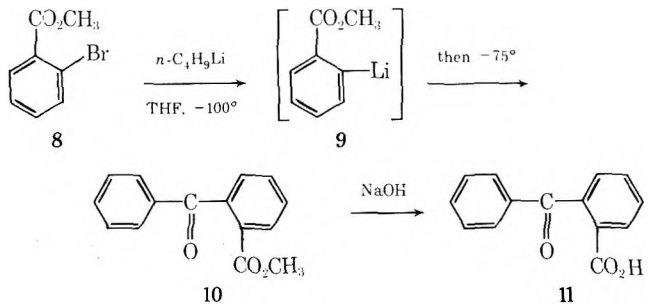
**Scheme II**




5 6 (64%) 7 (94%)

The reaction of methyl *o*-bromobenzoate (8) with *n*-butyllithium followed a different course than that observed for the meta and para isomer, although as for reactions of 1 and 5, metal–halogen interchange occurred rather than direct addition of alkyllithium to the ester function (Scheme III). Reaction of the intermediate anion 9 with unchanged bromo ester 8 was slow at −100°, as anticipated from steric considerations, which permitted complete metalation of 8 to 9. When the mixture was warmed to −75° the anion 9 self condensed and, subsequent to addition of water, there was obtained an 88% yield of methyl o-benzoylbenzoate (10). Although we could not induce this low-melting ester to crystallize, it was pure by nmr, and was hydrolyzed in essentially quantitative yield to *o*-benzoylbenzoic acid (11).

**Scheme III**

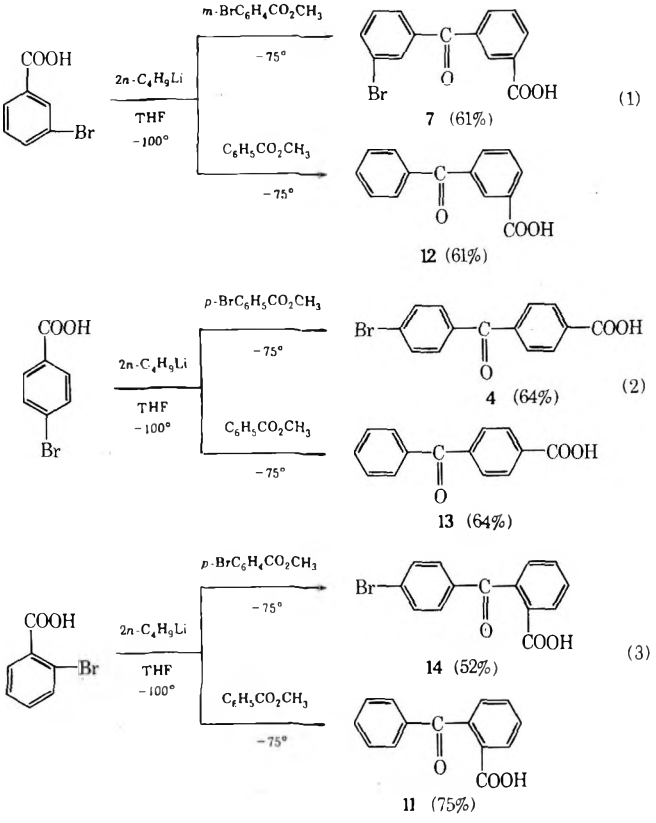



8 9 10 11

In the above experiment it was found expedient to use 1 molar equiv of *n*-butyllithium; use of 0.75 molar equiv of *n*-butyllithium gave 10 in 49% yield and appreciable starting ester 8 (31%).

**B. Crossover Experiments.** In view of the stability of the dianions prepared from the isomeric bromobenzoic acids[1] at −100° and the reactivity of the methyl ester group toward aryl anions observed at −100 to −75°, it became apparent that a seemingly broad spectrum of substituted benzoic acids could be prepared by crossover experiments. While we have not yet defined the scope of this method, we have demonstrated its utility by the examples outlined in Scheme IV.

**Scheme IV**

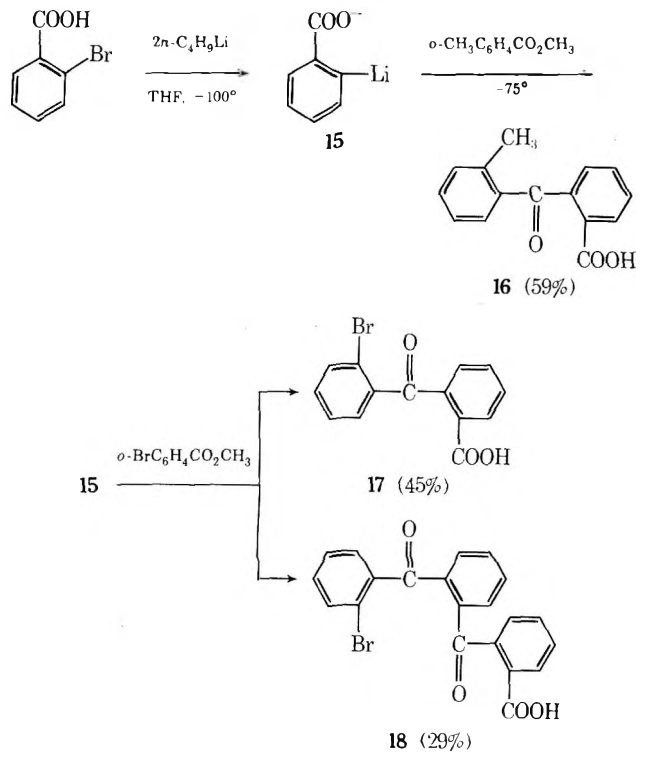



Since the only obvious limitation to this synthesis of isomeric aroylbenzoic acids is that the ester moiety contain functional groups less reactive toward nucleophilic addition than the ester function itself, it is apparent that this scheme constitutes a useful method, based on Gilman's pioneering work, for the synthesis of aromatic compounds. In view of the limited scope of the only other practical synthesis of anthraquinones (from *o*-benzoylbenzoic acids prepared by the Friedel–Crafts phthalic anhydride synthesis[2]) this procedure should prove of value for the preparation of precursors to anthraquinones and polynuclear aromatic systems not easily available by other routes.

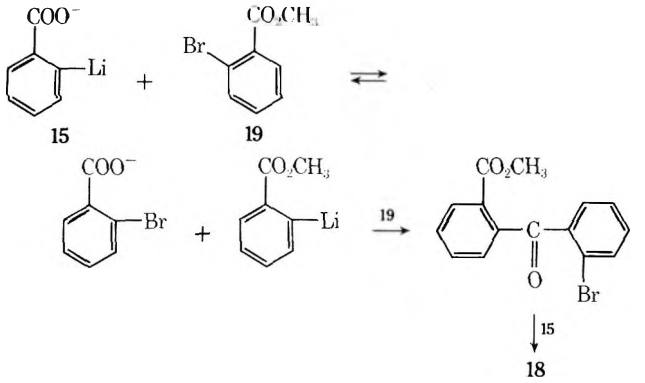
The procedure is also applicable for the preparation of the more hindered ortho,ortho-substituted cases summarized in Scheme V. Thus, reaction of 15 with methyl *o*-toluate gave 16 (59%, pure). Reaction of 15 with methyl *o*-bromobenzoate was of interest since in addition to the expected acid 17 (45%), there was also obtained an appreciable quantity (29%) of trimer acid 18. While 18 could theoretically form by addition of 15 to the salt of 17, this seems unlikely, since in no other case have we observed such addition to carboxylate functions at −75°. It seems more likely that 18 is formed by competitive lithium exchange reactions as, for example, shown in Scheme VI; however, this possibility has not been examined.

It would appear that the condensation of dianions of type 15 with acid halides is not as efficient for the preparation of *o*-benzoylbenzoic acids as is condensation with the corresponding ester. Formation of considerable amounts of 23 (19%) along with 16 (41%) by addition of 20

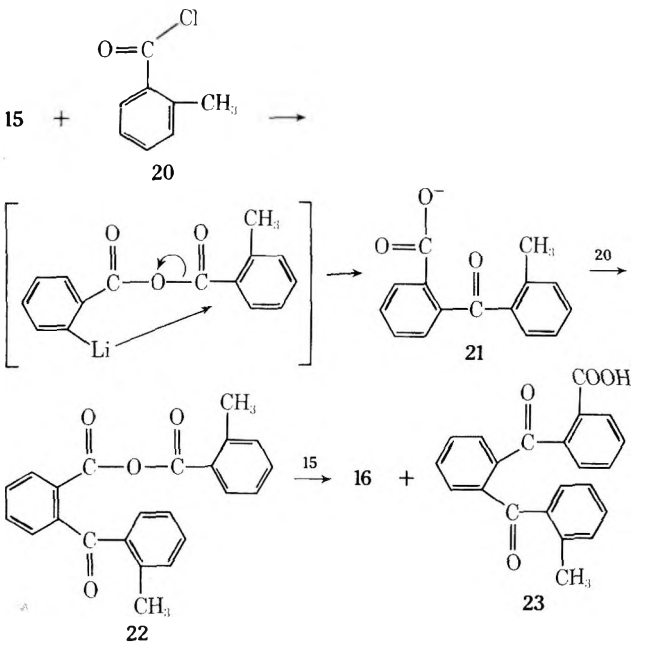
**Scheme V**



**Scheme VI**



**Scheme VII**



to **15** at −75° is consistent with the conclusion that anhydride formation is faster (or competitive) with carbanion addition as summarized in Scheme VII. Similarily, addition of *o*-bromobenzoyl chloride to **15** at −75° gave a mixture of **17** (31%) and **18** (29%).

## Experimental Section

**Self-Condensation of Methyl Bromobenzoates. Reaction of Methyl *p*-Bromobenzoate (1) with *n*-Butyllithium.** *n*-Butyllithium (9.4 ml of ~2 *M* solution in hexane, ~0.0185 mol) was slowly added (1 hr) to a solution of **1** (5.4 g, 0.025 mol, predried) in tetrahydrofuran (50 ml, distilled from $LiAlH_4$). The mixture was under nitrogen and the temperature was not allowed to rise above −95° (liquid $N_2$, diethyl ether). The mixture was allowed to warm to −75° and after 3 hr was poured into 5% aqueous hydrochloric acid (50 ml). The resulting mixture was extracted with ether and the extracts were dried ($MgSO_4$). The white solid (5.2 g, mp 110–130°) obtained by removal of ether was recrystallized from chloroform–methanol to give 2.5 g of methyl 4-(*p*-bromobenzoyl)benzoate (**3**, 63% yield, mp 177–178°).

*Anal.* Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.66; H, 3.63; Br, 24.95.

When 0.6 molar equiv of *n*-butyllithium was used, the yield of **3** was 49%; 9% of **1** was recovered; with 1 molar equiv of *n*-butyllithium the yield of **3** was 57%.

**4-(*p*-Bromobenzoyl)benzoic acid** (**4**, 96% yield, mp 274° from chloroform–methanol) was obtained from **3** by alkaline hydrolysis.

*Anal.* Calcd for $C_{14}H_9BrO_3$: C, 55.10; H, 2.97; Br, 26.19. Found: C, 54.77; H, 3.28; Br, 26.29.

**Methyl 3-(*m*-bromobenzoyl)benzoate** (**6**, 64% yield, mp 98–99° from methanol) was obtained from methyl *m*-bromobenzoate (**5**) as described above for **3**.

*Anal.* Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.22; H, 3.67; Br, 25.21.

**3-(*m*-Bromobenzoyl)benzoic acid** (**7**, 94% yield, mp 231–232° from chloroform–methanol) was obtained from **6** by alkaline hydrolysis.

*Anal.* Calcd for $C_{14}H_{19}BrO_3$: C, 55.10; H, 2.97; Br, 26.19. Found: C, 54.93; H, 3.07; Br, 26.34.

**Methyl *o*-Benzoylbenzoate (10).** Reaction of methyl o-bromobenzoate with *n*-butyllithium (0.75–1.0 molar equiv) was carried out as described above for **3** to give a yellow oil which showed one major and two minor components by tlc [silica gel, petroleum ether[3]–diethyl ether (80:20)]. The product was chromatographed on silica gel to give 0.264 g (88% yield) of **10** as a light yellow oil (lit.[4] mp 52°) which showed no impurities by nmr. Hydrolysis of the ester with aqueous sodium hydroxide gave quantitative conversion to o-benzoylbenzoic acid (mp and mmp[5] 128–129°).

**Crossover Experiments. 3-(*m*-Bromobenzoyl)benzoic Acid** (**7**). In a typical experiment *m*-bromobenzoic acid (2.5 g, 0.0125 mol) was converted to the corresponding dianion with *n*-butyllithium (0.25 mol) as previously described.[1] The temperature was allowed to warm to −75° for 2 hr and a solution of methyl *m*-bromobenzoate (2.7 g, 0.0125 mol) in dry tetrahydrofuran (10 ml) was added sufficiently slowly to maintain the mixture at −75 to −70°. The resulting mixture was stirred for 2 hr at −75° then allowed to warm to −20° and poured into 5% aqueous hydrochloric acid (100 ml); the resulting mixture was extracted with ether (400 ml total) which was in turn washed with water (50 ml). Acidic products were removed from the ether extract by extraction with 10% aqueous sodium hydroxide (50 ml) and the acids were regenerated (dilute hydrochloric acid) and collected by filtration. The crude acids (3.5 g, mp 205–220°) was recrystallized from chloroform–methanol to give 3-(*m*-bromobenzoyl)benzoic acid (61% yield, mp and mmp 232°).

***m*-Benzoylbenzoic acid** [**12**, 61% pure, mp and mmp 161–162° by chromatography (preparative tlc, silica gel using petroleum ether[3] as eluent, lit.[6] mp 161–162°)] was obtained from *m*-bromobenzoic acid and methyl benzoate.

**4-(*p*-Bromobenzoyl)benzoic acid** (**4**, 64% yield, mp and mmp of product obtained from methyl *p*-bromobenzoate was 274°) was obtained from *p*-bromobenzoic acid and methyl *p*-bromobenzoate.

***p*-Benzoylbenzoic acid** [**13**, 64% yield, mp 198–201°, by chromatography on silica gel, petroleum ether[3]–diethyl ether (80:20) as eluent, lit.[7] mp 197–200°] was prepared from *p*-bromobenzoic acid and methyl benzoate.

**2-(*p*-Bromobenzoyl)benzoic acid** (**14**, 52% yield, mp 170–172° from chloroform–petroleum ether,[3] lit.[8] mp 172–173°) was prepared from *o*-bromobenzoic acid and methyl *p*-bromobenzoate.

*o*-**Benzoylbenzoic acid** (75% yield, mp 127–129° from benzene–petroleum ether,[3] lit.[5] mp 128–129°) was prepared from *o*-bromobenzoic acid and methyl benzoate.

**2-(*o*-Methylbenzoyl)benzoic Acid (16) and the Acid 23. A.** The acidic product obtained as described for **7** by reaction of methyl *o*-toluate with the dianion prepared from *o*-bromobenzoic acid was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (70:30) as eluent] to give 2-(*o*-methylbenzoyl)benzoic acid (**16**), 59% yield, mp 107–109°[9] from benzene–petroleum ether.[3] No appreciable amount of **23** was isolated.

*Anal.* Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; neut equiv, 240.02. Found: C, 75.03; H, 5.25; neut equiv, 238.

**B.** When *o*-toluoyl chloride was used instead of methyl *o*-toluate and the acidic product was chromatographed as in A the yield of **16** was 41% and the acid **23** was obtained in 19% yield, mp 240–242° from ethanol–water.

*Anal.* Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; neut equiv, 344.3. Found: C, 76.58; H, 4.89; neut equiv, 345.

**2-(*o*-Bromobenzoyl)benzoic Acid (17) and the Acid 18. A.** The acidic product obtained as described for **7** by reaction of methyl o-bromobenzoate (2.77 g, 0.125 mol) with the dianion prepared from o-bromobenzoic acid was recrystallized from methanol–chloroform to give **18** as a white solid, 29% yield, mp 284–286°[c].

*Anal.* Calcd for $C_{21}H_{13}BrO_4$: C, 61.63; H, 13.20; Br, 19.45; neut equiv, 409.2. Found: C, 61.43; H, 3.67; Br, 19.16; neut equiv 408.

The mother liquor obtained above was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (60:40) as eluent] to give 2-(*o*-bromobenzoyl)benzoic acid (**17**), 45%, mp 134° from chloroform–petroleum ether.[3]

*Anal.* Calcd for $C_{14}H_9BrO_3$: C, 55.10; H, 2.97; Br, 26.19; neut equiv, 305.1. Found C, 54.89; H, 2.91; Br, 26.00; neut equiv, 304.

**B.** When o-bromobenzoyl chloride was used instead of methyl *o*-bromobenzoate, the yield of **18** was 27–30% and the yield of **17** was 40–44% (multiple runs including addition of the dianion at −75° to the acid chloride solution in hexane at room temperature, *i.e.*, reversed addition).

**Acknowledgment.** The authors would like to express their appreciation to the U. S. Army Research Office through Grant DAHCO4 74 GD128 for partial support of this work.

**Registry No.**—**1**, 619-42-1; **3**, 51310-29-3; **4**, 51310-30-6; **5**, 618-89-3; **6**, 51310-31-7; **7**, 51310-32-8; **10**, 606-28-0; **16**, 5469-51-2; **17**, 51310-33-9; **18**, 5130-34-0; **23**, 51310-35-1; *n*-butyllithium, 109-72-8; methyl *o*-bromobenzoate, 610-94-6; *m*-bromobenzoic acid, 585-76-2; methyl benzoate, 93-58-3; *p*-bromobenzoic acid, 586-76-5; *o*-bromobenzoic acid, 88-65-3; methyl o-toluate, 118-90-1; *o*-toluoyl chloride, 933-88-0; *o*-bromobenzoyl chloride, 7154-66-7.

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(2) *Cf.* E. Barnett, "Anthracene and Anthraquinones," Baillierè, Tindall and Cox, London, 1921.
(3) Boiling point 30–60°.
(4) I. M. Heilbron, "Dictionary of Organic Compounds," Vol. 1, 4th ed, Oxford University Press, London, 1953, p 357.
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(8) C. F. H. Allen and J. W. Gates, Jr., *J. Amer. Chem. Soc.*, **65**, 422 (1943).
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# Stereochemistry of Amino Carbonyl Compounds. IX.[1] Lithium Aluminum Hydride and Lithium Trialkoxyaluminum Hydride Reduction of α-Asymmetric β-Aminopropiophenones

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The stereochemical course of the reduction by lithium aluminum hydride ($LiAlH_4$), lithium trimethoxyaluminum hydride (TMH), and lithium tri-*tert*-butoxyaluminum hydride (TBH) of some α-asymmetric β-amino ketones has been investigated by varying hydride concentration, solvent, and reaction temperature. The stereoselectivity was found to be strongly dependent on the nature of the substrate and, to a lesser extent, on the other factors. Some considerations concerning the transition states are given.

Several papers concerning asymmetric induction of the reaction between acyclic asymmetric ketones bearing a heteroatom in the β position and nucleophilic reagents (organometallics and hydrides) have been published.[2] The discussion of the mechanism of such reactions is complicated, with respect to the corresponding substrates not containing heteroatoms, by the possibility of additional complexing and solvating effects which may affect the nature of the species involved.[3] In particular, an important question which arises whenever a rationalization of the stereochemical course of the reaction is attempted is concerned with the situation of the reducing species in the transition state.

In this connection we have investigated the role played by such factors as nature of the hydride, concentration of the reducing agent, solvent, and reaction temperature.

## Results and Discussion

The reduction of the amino ketones **1–3** (Scheme I) was performed with hydride concentrations of about 0.01, 0.1, and 0.5 *M*, at 0° and at reflux in THF, and at 0° in $Et_2O$. The results are collected in Table I and graphically depicted in Figure 1.

The relative amounts of the obtained diastereomeric 1-phenyl-3-dialkylaminopropan-1-ols **4–6** were determined on the crude reaction mixture[4] by integration of the nmr signal due to the proton bonded to C-1, as described in a previous paper.[2h]

Most of the reaction yields were quantitative (nmr) in amino alcohols, except when the reduction was carried out with the alkoxy hydrides, particularly at low concentrations and at 0° (Table I). In such cases longer reaction times as well as higher temperatures (room temperature) were required in order to obtain appreciable amounts of product. The diastereomeric ratios, however, were not affected by the reaction time, thus confirming that no equilibration occurred under the adopted conditions.

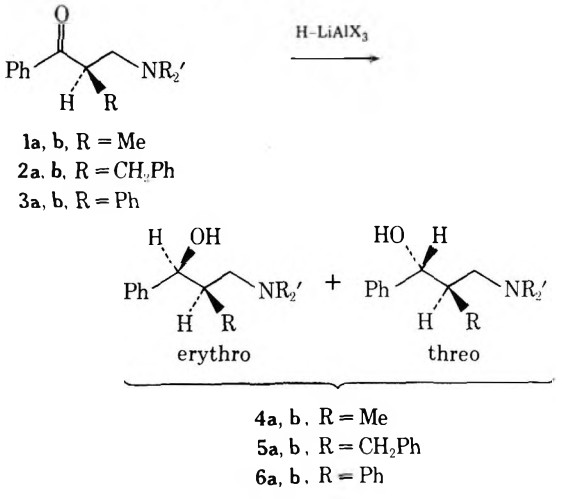
The experimental results show a general predominance of the erythro amino alcohols **4–6** and, in addition, allow the following observations to be made.

**Table I**
**Per Cent of Erythro Amino Alcohols 4–6 by Reduction of the Amino Ketones 1–3[a]**

| Amino ketone | Reaction temp, °C | —LiAlH$_4$ (Et$_2$O)[h]— 0.01 | 0.10 | 0.45 | —LiAlH$_4$ (THF)[h]— 0.01 | 0.09 | 0.44 | —TMH (THF)[h]— 0.01 | 0.10 | 0.45 | —TBH (THF)[h]— 0.01 | 0.10 | 0.45 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | 0 | 58 | 59 | 60 | 62 | 63 | 60 | 49 | 52 | 54 | 52[b] (70) | 52[c] | 53[d] |
| | Reflux | | | | 58 | 59[e] | 54[e] | 63 | 60 | 57 | 55[d] (36) | 55 | 55 |
| **1b** | 0 | 57 | 55 | 55 | 53 | 52 | 55 | 51 | 50 | 48 | 45[b] (52) | 45[c] (95) | 46[d] |
| | Reflux | | | | 53 | 50[e] | 53[e] | 53 | 49 | 50 | 46[f] (55) | 47 | 48 |
| **2a** | 0 | 67 | 71 | 69 | 67 | 67 | 64 | 82 | 78 | 79 | 79[b] (28) | 79 (17)<br>81[c] (78) | 85[d] (80) |
| | Reflux | | | | 61 | 61 | 61[e] | 86 | 80 | 77 | 73 (42) | 72 | 72 |
| **2b** | 0 | 60 | 57 | 57 | 46 | 49 | 46 | *g* | 62 | 61 | 63[b] (39) | 66 (12)<br>66[c] (78) | 68[d] (57) |
| | Reflux | | | | 48 | 49 | 51[e] | 60 | 59 | 56 | 55[f] (28) | 57 | 58 |
| **3a** | 0 | 87 | 89 | 89 | 97 | 94 | 94 | 99 | 98 | 98 | *b, g* | 92[d] (67)<br>92[f] (75) | 95[e] |
| | Reflux | | | | 92 | 91 | 90<br>87[e] | 97 | 95 | 95 | 85 (38) | 91 | 90 |
| **3b** | 0 | 87 | 87 | 84 | 95 | 93 | 94 | *g* | 94 | 95 | *b, g* | 92[e] (47) | 91[e] (93) |
| | Reflux | | | | 89 | 93 | 88[e] | 95 (55) | 97 | 93 | 85[f] (43) | 88 | 90 |

[a] Limit error ±3%. When not quantitative, the reaction yields are reported in parentheses. Reaction time 1 hr, except when otherwise indicated. [b] 24 hr at room temperature. [c] Reaction time 8 hr. [d] Reaction time 3 hr. [e] Inverted addition of reactants (see Experimental Section). [f] Reaction time 5 hr. [g] No reaction. [h] Hydride (solvent) at various molar concentrations.

**Scheme I[a]**




a, $NR_2' = NMe_2$; b, $NR_2' = N(CH_2)_5$

X = H, lithium aluminum hydride ($LiAlH_4$)
X = OMe, lithium trimethoxyaluminum hydride (TMH)
X = $OCMe_3$, lithium tri-*tert*-butoxyaluminum hydride (TBH)

[a] Only one enantiomer of the racemic pair is here represented.

(1) The stereoselectivity is always higher with the dimethylamino derivatives than with the corresponding piperidino derivatives and increases, with only one exception, passing from R = Me to $CH_2Ph$ to Ph.

(2) The alkoxy hydrides behave similarly, whereas $LiAlH_4$ in THF exhibits a different trend. In the $LiAlH_4$ reductions the change of solvent from THF to $Et_2O$ causes in some cases relevant variations of stereoselectivity.

(3) The dependence of stereoselectivity on the hydride concentration is very small, usually within the error of determination.

(4) The general decrease of the predominant diastereomer which is observed when the reaction temperature is raised from 0° to the boiling point of the solution does not substantially affect the trend of Figure 1 (I and III *vs.* II and IV, respectively). This indicates that the diastereomeric transition states are not considerably altered.

For similar α- or β-asymmetric ketones bearing NH, OH, or OR in the β position, the stereochemical results deriving from the reactions with hydrides or organometals have been interpreted on the basis of various cyclic transition states in which the metal hydride is bonded to the β heteroatom,[2c] or links both carbonyl oxygen and β heteroatom.[2a,b,f,i] Further, a competition has been proposed between cyclic and open-chain models.[2b]

Our results enable us to discuss the behavior of the reactants involved, so as to throw some light on the diastereomeric transition states.

The variation of stereoselectivity, sometimes very pronounced, which is observed (Figure 1) passing from the dimethylamino to the piperidino derivatives is indicative of the presence in the transition state of coordinated nitrogen. The effective difference of steric requirements between $CH_2N(CH_3)_2$ and $CH_2N(CH_2)_5$ seems to us less important than the different availability for the coordination of the nitrogen lone pair. The 1–3 diaxial interactions between the piperidine ring and the coordinated group, which are absent in the dimethylamino derivatives, could in fact induce conformational changes of the ring, thus leading to other forms of transition state. In this respect it is noteworthy that the $LiAlH_4$ reduction of a series of asymmetric α-dialkylamino ketones affords large changes of stereoselectivity depending on the structure of the dialkylamino moiety.[5] Further evidence of the presence of N-coordinated transition states is given in the hydride reduction of some aziridinyl ketones[6] and 2-dialkylaminocyclohexanones.[7]

The influence of the R substituent on stereoselectivity can be related with the increasing steric requirements passing from R = Me to $CH_2Ph$ to Ph, although such a trend is affected by the nature of the reducing agent. In the reactions with $LiAlH_4$ a deviation from the "regular" sequence observed with the alkoxy hydrides is afforded for the benzyl derivatives 2 and particularly when the piperidino group is also present in the substrate (**2b**).

The similar diastereomeric ratios afforded by TMH and TBH suggest that the alkoxy hydrides have comparable effective bulk, different from the one exhibited by $LiAlH_4$. Analogous behavior was observed in the reduction of some cycloalkanones with $LiAlH_4$ and with a large number of trialkoxy hydrides.[8] In particular, we have found that the alkoxy hydrides appear to be more selective ("larger") than $LiAlH_4$ when R = $CH_2Ph$, whereas generally smaller selectivities are observed when R = Me. This can be interpreted assuming that the alkoxy hydrides have a "long-range" larger hindrance and a "short range" similar or

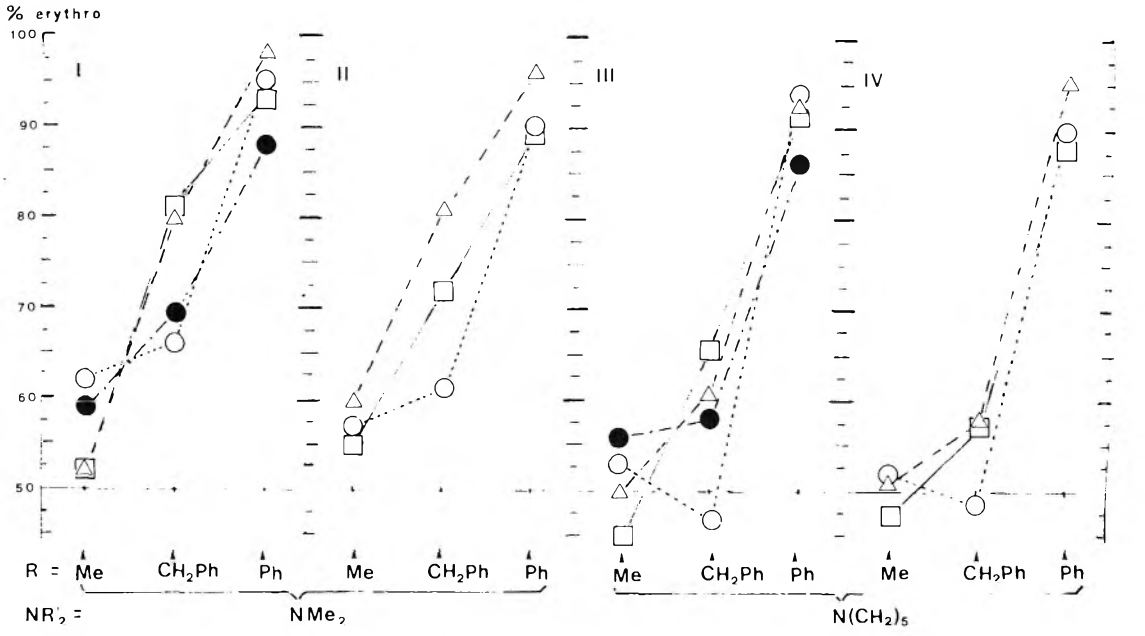



**Figure 1.** Dependence of stereoselectivity on the R substituent and $NR_2'$ group in the hydride reductions of the amino ketones 1–3 (mean values from Table I) (I and III at 0°; II and IV at reflux): ●-·-·-·, $LiAlH_4$ in $Et_2O$; ○·····, $LiAlH_4$ in THF; □———, TBH in THF; △------, TMH in THF.

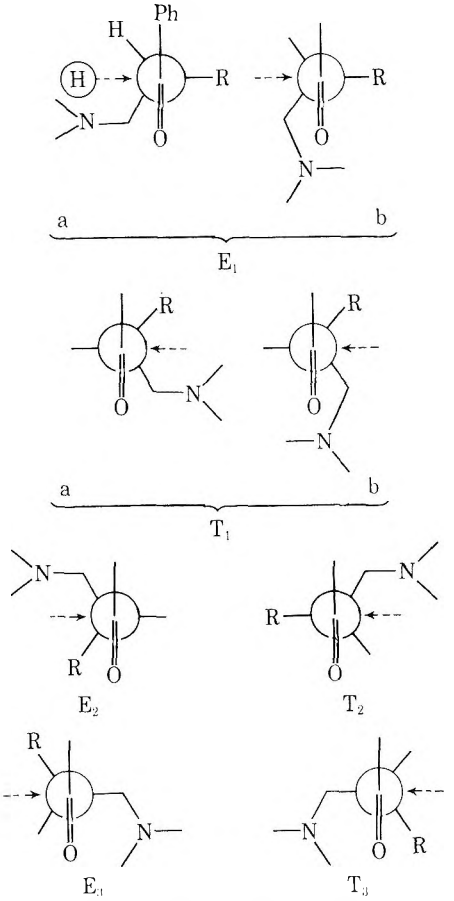
smaller hindrance with respect to $LiAlH_4$. Thus, when R = $CH_2Ph$ (a large group at "long range") the alkoxy hydrides exhibit higher selectivity than $LiAlH_4$. When, on the contrary, R = Me (a smaller substituent) the alkoxy hydrides exhibit analogous or lower selectivity than $LiAlH_4$. The phenyl derivatives **3a,b** afford in all the cases high diastereomeric ratios owing to the large steric requirement of the phenyl group, which levels any difference among the reducing species.

Carbonyl systems containing heteroatoms are expected[3] to afford strong variations of stereoselectivity associated with changes of solvent. Such variations are observed in our $LiAlH_4$ reductions which resulted in effects largely dependent on the substituents. This is again particularly evident for the benzyl piperidino derivative **2b.**

We have also investigated how the stereoselectivity is affected by changes of the hydride concentration. It is known[9] that TBH in THF is monomeric over the entire range of concentrations investigated and that both $LiAlH_4$ and TMH display an increasing degree of association as the concentration increases. Our results (Table I) show very small selectivity variations with the dilution (usually within the limit error), thus demonstrating, reputing as unlikely an equal steric requirement by both monomeric and polymeric species, that the reactant in THF is always monomeric in the transition state. $LiAlH_4$ in $Et_2O$ has been reported[10] as dimeric in the range 0.1–0.4 *M*. In this case we can only say that the reducing agent is always in the same state of aggregation, but it cannot be ascertained whether it is in the monomeric form or dimeric form.

A discussion on the diastereomeric transition states of the reduction should take in account the considerations above made, such as, mainly, (a) the participation, in some way, of coordinated nitrogen, (b) the monomeric state (at least in THF) of the reducing agents, and (c) the remarkable effects of the solvent. Such discussion would, however, require, to be well defined, the knowledge of several data which at the moment are unavailable. A first problem is, for example, whether the same molecule of reagent coordinates simultaneously both amino and carbonyl group and, in this case, whether one of both of the metal atoms are engaged. This would lead to stabilization of those conformations in which the nitrogen atom is close or far away, respectively, with respect to the carbonyl oxygen. Another problem is whether the hydride enters through an inter- or intramolecular mechanism.

If we assume that the torsional strain in the transition state tends to a minimum,[11] the following conformers of the substrate can be depicted.




(E and T forms afford erythro and threo diastereomers, respectively, according to the depicted direction of attack.)

Such forms allow either the coordination between nitrogen and carbonyl oxygen (in forms $E_2$ and $T_2$ the simultaneous participation of both Li and Al would be requested) or the anchimeric assistance by the coordinated nitrogen toward the entering species ($E_{1a}$, $T_{1a}$, $E_2$, $T_2$).

Although it is difficult to determine what forms are important in affecting the diastereomeric ratios, $E_{1a}$ appears, however, to show the minimum of interactions both in the substrate and between the reacting species. It could be therefore responsible for the generally observed predominance of the erthro amino alcohols, but does not explain how the substituent R affects the stereoselectivity of the reaction. For this reason, it is necessary to envisage the participation to the transition state of other forms which allow for the possibility of interaction between R and entering species (*e.g.*, $T_1$, $E_2$, etc.).

Another important interaction can occur in some forms (*e.g.*, $E_{1b}$, $T_{1a}$, etc.) between R and the *N*-alkyl groups, particularly when in the molecule are present substituents as $CH_2Ph$ and piperidino. Such groups could in fact strongly interact at long distance from the reaction center in rigid and "curled" conformations of the transition state. This could explain the deviations from the "regular" sequence observed in the $LiAlH_4$ reductions, especially when in the substrate are simultaneously present both benzyl and piperidino group. The above forms are therefore to be considered more important when R and/or the dialkylamino group have smaller steric requirements (*e.g.*, R = Me, amino group = $NMe_2$).

In conclusion it appears that the stereochemical course of the reaction cannot be interpreted on the basis of only one transition state. A number of different conformations could in fact be stabilized or destabilized by the concomitant intervention of steric and polar interactions and therefore participate with different weights in the overall diastereomeric balance.

## Experimental Section[12]

**Materials.** The amino ketones 1–3 and the amino alcohols 4–6 were previously described and characterized.[2h]

Solvents diethyl ether and tetrahydrofuran (THF) were purified by refluxing over sodium wire, followed by distillation from lithium aluminum hydride under a nitrogen atmosphere.

The lithium aluminum hydride (Fluka A.G.) and lithium tri-*tert*-butoxyaluminum hydride (Fluka A.G.) solutions were prepared by stirring slurries for 1 day, followed by removal of solids by filtration. Lithium trimethoxyaluminum hydride in THF was prepared by slow addition of the calculated amount of absolute MeOH[13] to $LiAlH_4$ solutions of the required concentration in THF.[14]

The hydride solutions were then stored under a nitrogen atmosphere in the apparatus devised by Dillard,[15] from which the required aliquots may be exactly withdrawn, and titrated by the iodometric method described by Felkin.[16]

**Reduction Procedure.** A 0.2 *M* solution of the amino ketone was added by a dropping funnel, under a nitrogen flow, to the hydride solution (ratio hydride ion/amino ketone = 4:1, *i.e.*, molar ratio $LiAlH_4$/amino ketone = 1:1 or alkoxy hydride/amino ketone = 4:1). An inverted order of addition was found to be convenient when the required volume of hydride solution was so small as to prevent a regular reflux of the solvent.

The mixture was kept at the desired temperature (by ice cooling or refluxing the solvent) for 1 hr (for the exceptions see Table I) and then cautiously hydrolyzed with $H_2O$ under cooling. After filtration of the inorganic material, the THF solutions were diluted with aqueous HCl and the organic solvent was evaporated under reduced pressure. The residual solution was then made alkaline with 10% aqueous NaOH and ether extracted. The ethereal solution was finally dried ($Na_2SO_4$) and evaporated to give the crude reaction mixture, which was submitted to nmr analysis.

Every reaction was repeated at least twice in order to check the reproducibility of the diastereomeric ratios.

**Nmr Determinations.** Nmr spectra were performed on a Jeol C60-HL spectrometer, using $CCl_4$ as solvent ($CDCl_3$ for the compounds **5a**) with TMS as internal standard.

The relative amounts of diastereomeric amino alcohols were directly determined by integration of the H-C(1) signals.[2h]

The amount of unreacted amino ketone was analogously dosed, when present, by integration of the signals due to the aromatic protons ortho to the carbonyl group, which appear at lower field with respect to all the remaining aromatic protons of the mixture. For the α-phenyl derivatives a complication arose, owing to superimposition between the resonance of the proton α to the carbonyl group of the unreacted amino ketone (**3a,b**) and the resonance due to the H-C(1) protons of the amino alcohols (**6a,b**). The determination was then made possible by repeated treatments, at room temperature for several hours, of the reaction mixture in THF with $NaOD$-$D_2O$, until complete deuteration of the α proton of the amino ketone was obtained.

**Acknowledgment.** We thank C. N. R. (Rome) for financial support.

**Registry No.**—**1a,** 51371-02-9; **1b,** 51371-03-0; **2a,** 51293-59-5; **2b,** 51293-60-8; **3a,** 51293-61-9; **3b,** 51293-62-0; $LiAlH_4$, 16853-85-3; TMH, 12076-93-6; TBH, 17476-04-9.

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# Synthesis and Stereochemistry of Tricyclo[3.2.2.0$^{2,4}$]nonane Derivatives[1]

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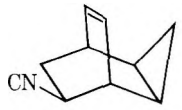
The four isomeric tricyclo[3.2.2.0$^{2,4}$]nonan-6-ols have been prepared along with two related tricyclo[3.2.2.0$^{2,4}$]-non-8-en-6-ols. The compounds with an exo cyclopropyl ring were prepared *via* the ketone, *exo*-tricyclo[3.2.2.0$^{2,4}$]-non-8-en-6-one, by $LiAlH_4$ reduction and hydrogenation. The endo cyclopropyl compounds were derived from *endo*-tricyclo[3.2.2.0$^{2,4}$]non-6-ene *via* standard methods. The stereochemistry of these alcohols has been elucidated with the aid of the nmr spectra of the $Eu(fod)_3$ complexes.

The chemistry of bridged polycyclic compounds containing a cyclopropane ring has provided considerable insight into the nature of the ability of this three-membered carbocycle to stabilize cationic species.[2] As an outgrowth of our previous work on the tricyclo[3.2.1.0$^{2,4}$]octyl system, synthetic work toward the closely related tricyclo-[3.2.2.0$^{2,4}$]nonyl skeleton was undertaken.

Two major problems exist: (1) the construction of the tricyclo[3.2.2.0$^{2,4}$] carbon skeleton, and (2) the elucidation of the stereochemistry of the four isomeric tricyclo-[3.2.2.0$^{2,4}$]nonan-6-ols.

**Synthesis.** The most common routes into this type of tricyclic system involve either cyclopropanation of bicyclic olefins or Diels–Alder and [2 + 2 + 2] cycloadditions. Our experience with the cyclopropanation of bicycloheptadiene[2a] led us to prefer the second general pathway. The scheme leading to the successful synthesis is given in Scheme I.

The tricyclic unsaturated ketone **2** was chosen as the point of entry into the compounds which we term the exo cyclopropyl series. This ketone was prepared from the acrylonitrile adduct of cycloheptatriene.[3] This [2 + 2 + 2] cycloaddition reaction reaction produces three major products in a 3:3:1 ratio. It was clear that the two most prevalent materials were the exo and endo isomers of 8-cyanotricyclo[3.2.2.0$^{2,4}$]non-6-ene (**13** and **14**). Recently,

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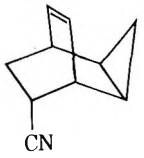
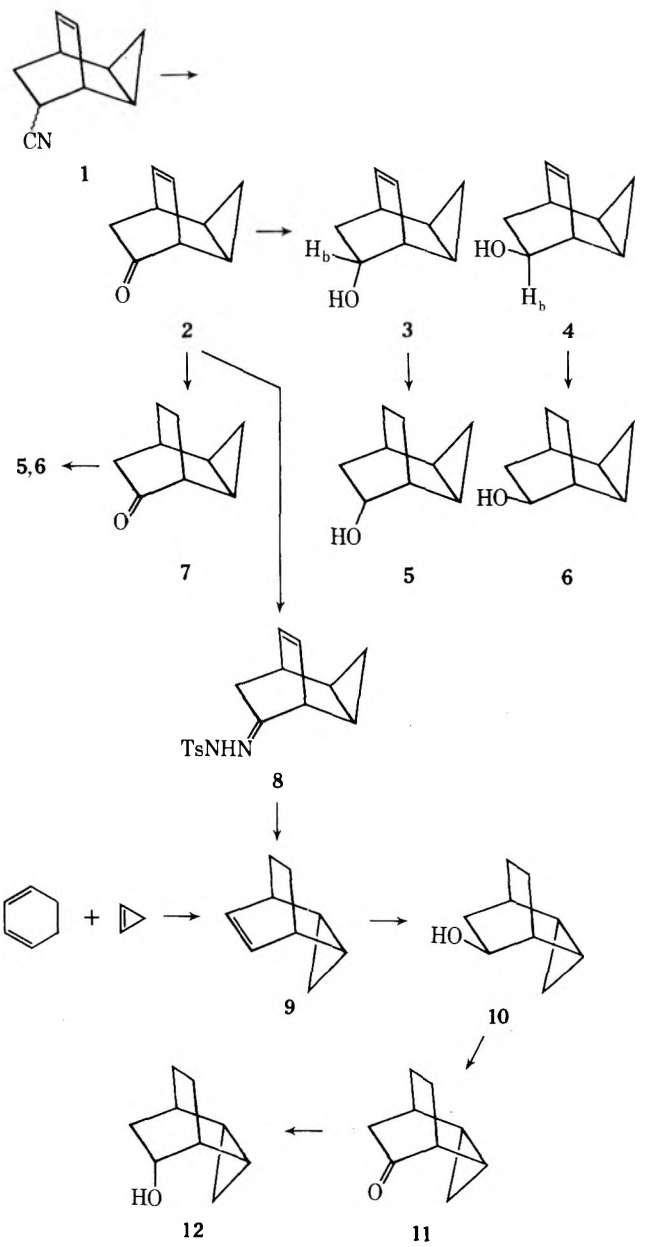


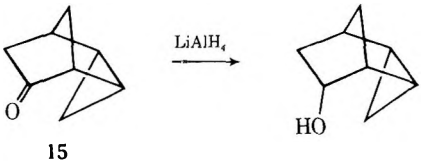

**14**

during the course of our work, Bellus, Helferich, and Weiss published a detailed study of this reaction bearing out our results as well as indicating the correct structure for the third product as 7-*endo*-cyanobicyclo[4.2.1]nona-2,4-diene.[4] This study also gave support for the exo or syn geometry for the cyclopropane ring in **2**. Their assignments based on nmr shifts agree well with our observations of the nmr spectra of related compounds. Furthermore, this stereochemistry is expected to predominate in this [2 + 2 + 2] cycloaddition, as is borne out by a number of examples.[3,4,5] Any doubt about this assignment being correct has been removed by consideration of the behavior of **2** and **7** upon reduction with $LiAlH_4$.

$LiAlH_4$ reduction of **7** is quite nonselective and yields a ~1:1 mixture of alcohols, *exo,endo*-tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (**5**) and *exo,exo*-tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (**6**).[6] This is consistent with the exo configuration for the cyclopropane ring, since models indicate that both faces of the carbonyl groups in **7** are quite similar; thus little reductive selectivity would be expected. From previous work[2a] on the reduction of ketone **15** we knew that an endo orientation of the cyclopropane ring, as in **11**, would lead to a large predominance of a single alcohol upon $LiAlH_4$ reduction. Whereas the nonselectivity in reduction of **7** served the purpose of indicating the exo orientation of the

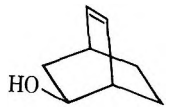
**Scheme I**




**15**

cyclopropane ring in 7 (and hence 2), it was not very useful for synthetic purposes. However, the $LiAlH_4$ reduction of 2 would be expected to be somewhat more selective based on the known reduction of bicyclo[2.2.2]oct-7-en-5-one, which produced a 3:1 mixture of exo and endo alcohols (16, 17).[7] It was quite gratifying to find that $LiAlH_4$

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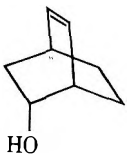



17

reduction of 2 at −65° produced a 5:1 mixture of 4 and 3. The orientation of the alcohol groups follows from their modes of production and is borne out by the observation that the $\tau$ value for hydrogen $H_b$ is slightly higher in 3 than in 4.[4] Furthermore, the vinyl hydrogens of 4 show a greater degree of nonequivalence in the nmr spectra than in 3 as expected if 4 contains an exo hydroxyl. Although these differences are convincing, the use of lanthanide shift reagents proved useful and decisively indicated that the initial assignment of geometry was correct (see the section on shift reagents). Hydrogenation of samples of 3 and 4 led to the desired exo series alcohols, 5 and 6.

The synthesis of the two endo cyclopropyl alcohols, 10 and 12, was quite direct. The Diels–Alder reaction between cyclopropene and cyclohexadiene[8] proceeded to yield the endo olefin 9 in approximately 10% yield. The structure of 9 is borne out by the 60-Hz nmr, which exhibited the following bands: 4.1 (2), 7.1 (2), 8.45 (4), 9.0 (2), 9.8 ppm (2). The endo configuration was expected on the basis of the analogous reaction of cyclopropene with cyclopentadiene[2a] and the previous synthesis by Rhodes.[8a] Convincing proof that this was indeed the correct stereochemistry for 9 came from direct conversion of 2 to 9 *via* the tosylhydrazone 8. Clearly, if 2 is as depicted above, then 9 must have the cyclopropane ring endo. Although this sequence served to correlate 2 and 9, in our hands it proved inadequate for the production of quantities of 9, for the yield was low and the product was difficult to purify. The endo orientation of the cyclopropane ring was further indicated in a striking fashion by the use of shift reagents on the alcohols 10 and 12. These could be prepared easily by hydroboration–oxidation of the tricyclic olefin 9 with diborane to yield >90% of a single alcohol (10). Further Sarett oxidation of 10 produced the endo ketone 11, which upon $LiAlH_4$ reduction produced 12 stereoselectively. The production of 12 upon $LiAlH_4$ reduction of 11 to the virtual exclusion of 10 again supports the endo configuration for the cyclopropane ring in 12.

**Nmr Shift Reagents[9] and Stereochemistry.** In order to supply additional evidence regarding the relative[9] stereochemistry of these compounds, alcohols 3, 4, 10, and 12 were studied using the lanthanide shift reagent $Eu(fod)_3$.[10] Alcohols 3 and 4 were chosen as representatives of the exo cyclopropyl series mainly because their nmr spectra were somewhat easier to interpret than those of 5 and 6 owing to the absence of the methylene groups which absorb in the $\tau$ 8–9 region.

Since initially only small quantities of the exo cyclopropyl series alcohols 3 and 4 were available, we chose to purify these compounds just prior to use by passing them through a glpc column and directly into carbon tetrachloride. This procedure was necessary owing to the tendency of 3 and 4 to form aerosols unless collected in a solvent. Secondly, this procedure excluded water, which has an adverse affect on the use of shift reagents.[11] For this reason the absolute concentration of the alcohols was known only within about ±10%. In all cases the concentration of the alcohol was similar but was not known absolutely. Observation with alcohols of the tricyclo[3.2.1.0$^{2,4}$]octyl skeleton of *known stereochemistry* indicated that this procedure using similar concentrations was adequate for gross stereochemical assignments so long as the lanthanide shifts to be compared were large as they are for the critical protons in 3, 4, 10, and 12. Since we worked in the region of low L/S ratios (L = lanthanide shift reagent, S = substrate) the shifts observed were essentially linear with L/S ratios.[9,12,13] This many times allows the estimation of an optimum L/S ratio for clear band separation without recourse to high L/S ratios where maximum shifts are observed. As is common in this type of work it is assumed that the stoichiometry of the LS complex[14] is the same for all alcohols. This would appear a safe assumption owing to the near equality of the two bridges in these molecules. The possible exception would be with compound 12, where it might be less probable to have $LS_2$ complexes owing to interference of the cyclopropyl methylene hydrogens with the $Eu(fod)_3$. If it were true that 12 formed $LS_1$ or predominantly $LS_1$ complexes rather than $LS_2$, then we should have observed smaller shifts for 12 at comparable L/S ratios for hydrogens b, c, and c′.[15] This was not observed. Furthermore, at low L/S ratios $LS_2$ complexes would be expected to predominate.[14]

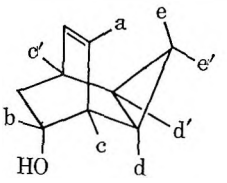
With the assumptions above, the shift data can be analyzed qualitatively. (For quantitative evaluation see ref 16)

Since all L/S ratios were probably within 10–15% of one another as shown by the relative constancy of the shifts for b, c, and c′ protons,[17] the observed shift of proton b will be used as essentially an internal standard. The shifts in hertz are taken as the shift in the center of gravity of a peak in the presence of $Eu(fod)_3$.

It is quite evident that the alcohol assigned the endo hydroxyl (3) exhibits an extraordinarily large shift for the d and d′ cyclopropyl hydrogens (118 Hz), whereas the exo alcohol 4 shows a much smaller shift (26 Hz). Furthermore, the signals for these hydrogens clearly separate from one another in the endo alcohol 3 but remain together in 4. It must be emphasized that since the concentrations of the alcohol relative to the europium compound are not exactly the same, the absolute values of the shifts are not extremely meaningful. The relative values are important, particularly when compared to the shift of $H_b$ in the two alcohols, 135 Hz for 4 *vs.* 181 Hz for 3. Since at equal L/S ratios these values would have been nearly equal,[18] it is apparent that the shifts expected for d and d′ in compound 3 would still be large, around 90 and 44 Hz, respectively, at concentrations equal to 4. These large shifts are accompanied by less spectacular shifts for other groups of protons, as seen in Table I. Note that the olefin hydrogens, a, of 4 are shifted by a larger amount than those for 3. It is also of interest to note that the olefin pattern of 4 becomes much more similar to that for 3 after addition of europium reagent. The exact origin of this effect is not clear; however, the greater shift for the a proton in 4 relative to 3 support the assigned structures. Note also that the e and e′ hydrogens are shifted by a small amount in both 3 and 4. This is to be contrasted sharply with the data for 10 and 12 presented in Table II.

Owing to greater overlapping of bands with these two alcohols (10, 12) it is more difficult to assign the bands when using $Eu(fod)_3$. However, it is quite clear that $H_e$ and $H_{e'}$, which overlap in both the endo,exo (10) and the endo,endo compound (12), behave in a strikingly different manner in the two compounds in the presence of the europium reagent. For the alcohol 10 these bands remain together and shift about 26 Hz, whereas for the alcohol 12

**Table I**
**Eu(fod)$_3$ Shift Study for Alcohols 3 and 4**



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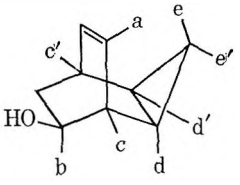
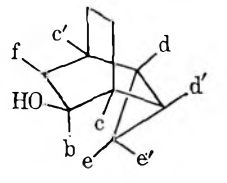


4

| H | ΔHz | H | ΔHz |
|---|---|---|---|
| $H_b$ | −181 | $H_b$ | −135 |
| $H_a$ | −31 | $H_a$ | −50 |
| $H_c$ | −101 | $H_c$ | −92 |
| $H_{c'}$ | −34 | $H_{c'}$ | −30 |
| $H_d$ | −118 | $H_d$ | −26 unresolved |
| $H_{d'}$ | −55 | $H_{d'}$ | −26 unresolved |
| $H_{e,e'}$ | (−34) unresolved | $H_{e,e'}$ | (−18) unresolved |

**Table II**
**Eu(fod)$_3$ Shift Study for Alcohols 10 and 11**[a]



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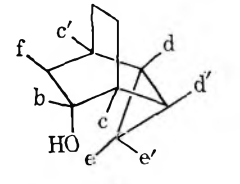

12

| H | ΔHz | H | ΔHz |
|---|---|---|---|
| $H_b$ | −177 | $H_b$ | −176 |
| $H_c$ | −124 | $H_c$ | −129 |
| $H_{c'}$ | −30 | $H_{c'}$ | −48 |
| $H_{d,d'}$ | −32 | $H_{d,d'}$ | −53 |
| $H_e$ | −29 | $H_e$ | −181 (133)[b] |
| $H_{e'}$ | −29 | $H_{e'}$ | −56 |
| $H_f$ | −161 | $H_f$ | −67 |

[a] The relative concentration of alcohol to Eu(fod)$_3$ would appear to be quite similar for these two alcohols, as can be seen from the similar values for the shift for both $H_b$ and $H_c$. This does assume a similar position for the Eu atom relative to protons $H_b$ and $H_c$, which is certainly very reasonable for $H_b$ (see ref 14 for similar case) and not surprising for $H_c$. [b] Since there is some overlap of bands, it is difficult to be totally certain of the assignment of this band. The 181 value appears more consistent with the values of $H_c$ and $H_{c'}$ considering reasonable positions for the Eu atom and estimated distances from models.

(endo OH) they clearly separate. In fact it appears that $H_e$ in **12** exhibits the greatest shift (181 Hz) of any hydrogen in these molecules. Even if the value of 133 Hz is used rather than 181 Hz, assuming an alternate assignment, it is obvious that $H_e$ in **12** must be quite proximate to the europium atom, as could only be possible for the endo,endo alcohol. Furthermore, the considerably smaller spread in shifts for $H_d$ and $H_{d'}$ in these two compounds relative to **3** and **4** again clearly indicates that the geometries of **10** and **12** are as depicted. Thus even in the absence of accurate knowledge of relative concentrations of reagents it appears that Eu(fod)$_3$ is quite useful not only in resolving overlapping bands but also in supplying confirmation of the assumed gross geometry of rigid systems of this type.

The synthesis and stereochemistry of these compounds complete the first phase of this work. Data regarding solvolysis behavior will be presented elsewhere.

## Experimental Section

All melting points are uncorrected. Nmr spectra were recorded on a Varian A-60A spectrometer with internal standard TMS in $CCl_4$. Chemical shifts are reported in $\tau$ values with the number of protons in parentheses. The europium shift reagent [Eu(fod)$_3$] was supplied by Norell. Infrared spectra were obtained on a Perkin-Elmer Model 137 grating spectrophotometer. Microanalysis were by Galbraith Laboratories, Knoxville, Tenn. The following glpc columns were employed: FFAP (15%) 10 ft × 0.375 in. (A); FFAP (10%) 30 ft × 0.375 in. (B); XF-1150 (20%) 5 ft × 0.25 in. (C); Carbowax 20 M (15%) 10 ft × 0.375 in. (G); Dow 710 5 ft × 0.25 in. (F).

**Tricyclo[3.2.2.0$^{2,4}$]non-8-en-6-one (2).** The procedure of Freeman[3] was followed and the purity was ascertained by glpc on columns B, C, and G. Nmr data agrees with those reported in ref 3.

***exo*-Tricyclo[3.2.2.0$^{2,4}$]nonan-6-one (7).** To a prehydrogenated suspension of 0.1 g of 5% palladium on carbon was added a solution of 2.42 g of **2** in 35 ml of dry ether. Hydrogenation was allowed to proceed until no further hydrogen was absorbed. Filtration and ether washing of the catalyst led upon evaporation of the ether to the product which was distilled at 80° (1 Torr) to yield 1.87 g (76%) of pure **7**: mp 113–114°; glpc (B) indicated one compound; nmr $\tau$ 7.59–7.95 (4) m, 8.5 (4) m, 8.7–9.6 (4) broad m; ir 3010, 2950, 1730, 1745 cm$^{-1}$.

*Anal.* Calcd for $C_9H_{12}O$: C, 79.41; H, 8.82. Found: C, 79.52; H, 8.89.

***exo,exo*-Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol and *exo,endo*-Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol. A. Reduction of 7 with LiAlH$_4$.** A mixture of 1.9 g of $LiAlH_4$ in 250 ml of anhydrous ether was added, dropwise, to a solution of 6.7 g of **7** in 35 ml of diethyl ether. The resulting suspension was stirred for 27 hr at room temperature and then treated with excess saturated sodium sulfate solution. Filtration followed by the removal of the solvent gave a soft solid, which was subjected to glpc on column B. Two products were present in a 1:1 mixture. These could be separated with difficulty by glpc; hence these two alcohols are better prepared by method B.

**B. Reduction of 2 with LiAlH$_4$.** ***exo*- and *endo,exo*-Tricyclo[3.2.2.0$^{2,4}$]non-8-en-6-ol.** To a solution of $LiAlH_4$ in ether at −65° was added dropwise a solution of 1.9 g of **2** in 35 ml of ether. After stirring for 24 hr at −65° the solution was allowed to warm and was worked up as in A to yield a quantitative yield of crude product. Preparative glpc separation (B) lead to **4** and **3** in the ratio of 5:1 with melting points of 87–90 and 104–107°, respectively: nmr (**4**) $\tau$ 4.25 (2) m, 6.15 (1) 2 t, 7.17 (3) m, 8.0 (1) m, 8.79 (1) t, 9.22 (2) m, 9.85 (2) m; nmr (**3**) $\tau$ 4.2 (2) t, 6.18 (1) 5, 7.2 (2) m, 8.21 (1) m, 8.7 (1) m, 8.85 (2) m, 9.9 (2) m.

*Anal.* Calcd for $C_9H_{12}O$ (**4**): C, 79.41; H, 8.82. Found: C, 79.25; H, 8.70.

*Anal.* Calcd for $C_9H_{12}O$ (**3**): C, 79.41; H, 8.82. Found: C, 79.54; H, 8.58.

**Hydrogenation of 3 and 4.** Hydrogenation of ethanol solutions of pure **3** and **4** over 5% Pd/C was carried out at atmospheric pressure until the uptake of 1 mol of hydrogen was complete. Filtration and removal of the solvent led to quantitative yields of **5** and **6**. Glpc (B) data indicated a single compound in each instance. The melting points of glpc (pure) samples follow: **6**, 155–185.5° (softens at 150°); **5**, 144–147° (softens at 130°).

*Anal.* Calcd for $C_9H_{14}O$ (**5**): C, 78.26; H, 10.14. Found: C, 78.65; H, 9.99.

*Anal.* Calcd for $C_9H_{14}O$ (**6**): C, 78.26; H, 10.14. Found: C, 78.23; H, 10.19.

***endo*-Tricyclo[3.2.2.0$^{2,4}$]non-6-ene (9). A. Diels–Alder Reaction.** A slow stream of cyclopropene in nitrogen, generated from 23 g of allyl chloride and 12 g of $NaNH_2$ at 85–105° according to the procedure of Closs,[19] was passed into a stirred solution of 11.0 g (0.136 mol) of 1,3-cyclohexadiene in 150 ml of dry methylene chloride at room temperature. After the production of cyclopropene was complete (5 hr) the system was flushed with $N_2$ for another 2 hr. The methylene chloride solution was then washed successively with cold 10% hydrochloric acid, 10% sodium carbonate, and water and then dried over magnesium sulfate. Removal of the solvent at atmospheric pressure followed by distillation up to 79° led to recovered diene. Distillation at 20 Torr at 120–130° led to 3.1 g (11% based on allyl chloride) of **9**, which crystallized and exhibited a melting point of 54°. Glpc (A) indicated a single compound, nmr $\tau$ 3.05 (2) t, 7.1 (2) m, 8.4 (4) m, 9.0 (2) m, 9.85 (2) t.

**B. Reduction of Tosylhydrazone 8.** To a stirred solution of 2.7 g (0.01 mol) of tosylhydrazone **8** in 75 ml of tetrahydrofuran was added 5.0 g (0.13 mol) of $LiAlH_4$. This mixture was refluxed for 40 hr followed by cooling and work-up with saturated sodium sulfate solution. The organic layer was washed with dilute acid and 10% $Na_2CO_3$ solution followed by water and then dried with magnesium sulfate. Removal of the solvent led to recovery of unreacted **8**, which was separated by filtration. The residual oil was shown by glpc (A and F) to consist of two products in the ratio of 4:1. The major component, present in 57% overall yield, was **9** as

shown by nmr and ir spectra. Purification of this product other than by glpc proved difficult.

*endo,exo*-**Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (10).** A solution of 7.2 g of olefin **9** in 100 ml of tetrahydrofuran at 0° was treated with a stream of diborane generated from a solution of 4.75 g of $NaBH_4$ in diglyme and 25 ml of $BF_3$·$Et_2O$ in 30 ml of diglyme according to the procedure previously used.[2a] This led to 7.31 g (87%) of a solid which upon crystallization from pentane had mp 165–168°. Glpc (B) of the original mixture indicated greater than 90% of a single alcohol, **10**, nmr $\tau$ 6.4 (1) m, 6.95 (1) 5, 8.15 (3) m, 8.5 (3) m, 8.88 (1) m, 8.18 (2) m, 9.8 (2) m.

*Anal.* Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 77.98; H, 10.05.

*endo*-**Tricyclo[3.2.2.0$^{2,4}$]nonan-6-one (11).** To a stirred suspension of 25 g of chromic acid in 250 ml of pyridine at 0° was slowly added a solution of 7.3 g of alcohol **10** in 80 ml of pyridine. The mixture was stirred for 39 hr at room temperature followed by addition of 100 ml of water and extration ten times with 150-ml portions of pentane. The pentane extracts were washed with cold 10% hydrochloric acid, 10% sodium carbonate, and water. After drying and removal of the solvent through a Vigreux column, 5.86 g of crude ketone **11** was obtained. Glpc (B) indicated only 65% purity. Distillation at 100° (0.5 Torr) yielded the pure ketone: $n^{24}D$ 1.5094; nmr $\tau$ 7.55 (2) m, 8.15 (2) d, 8.31 (4) m, 8.91 (2) m, 9.72 (2) m.

*Anal.* Calcd for $C_9H_{12}O$: C, 79.41; H, 8.82. Found: C, 79.52; H, 8.99.

*endo,endo*-**Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (12).** To a solution of lithium aluminum tri-*tert*-butoxyhydride at −65°, prepared according to the procedure of Brown,[20] was added 0.9 g (0.007 mol) of ketone **11** in 15 ml of tetrahydrofuran. After 24 hr at this temperature the reaction mixture was warmed to room temperature and worked up as in the other reductions. Glpc analysis indicated 79% of a single alcohol, mp 136–140°, nmr $\tau$ 6.3 (1) m, 7.08 (1) s, 8.0 (2) m, 8.5 (5) m, 8.9 (1) t, 9.2 (2) m, 9.7 (2) m.

*Anal.* Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 78.42; H, 10.31.

**Europium Shift Reagent Studies.** The $Eu(fod)_3$ used was taken directly from a fresh bottle supplied by Norell. The alcohols were subjected to glpc purification directly before use and then dissolved in $CCl_4$ for analysis. The shift reagent was weighed out and added in increments of about 10 mg, after which the nmr was observed and recorded. Since in many instances the peaks were broad, the centers of gravity of the peaks were used and shift values were deduced from these.

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**Registry No.**—**2**, 50744-35-9; **3**, 50744-41-7; **4**, 50898-31-2; **5**, 51260-36-7; **6**, 51260-35-6; **7**, 51260-37-8; **8**, 50744-36-0; **9**, 27019-95-0; **10**, 51260-33-4; **11**, 51260-38-9; **12**, 51260-34-5; cyclopropene, 2781-85-3; 1,3-cyclohexadiene, 592-57-4.

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(17) This also probably indicates a similar position for the Eu atom (relative to $H_c$, $H_{c'}$, $H_b$) in all cases. This is certainly reasonable for **3**, **4**, and **10**.
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# Synthesis and Relative Stereochemical Assignment of the Four Isomeric Cyclopropane-Bridged Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ols[1,2d]

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The four isomeric tricyclo[3.2.2.0$^{2,4}$]nonan-6-ols, containing a cyclopropane ring fused in a homocyclopropylcarbinyl relationship to the alcohol functionality, have been synthesized from the corresponding alkenes. Stereochemical assignments are accomplished by chemical means and with the aid of nmr shift reagents.

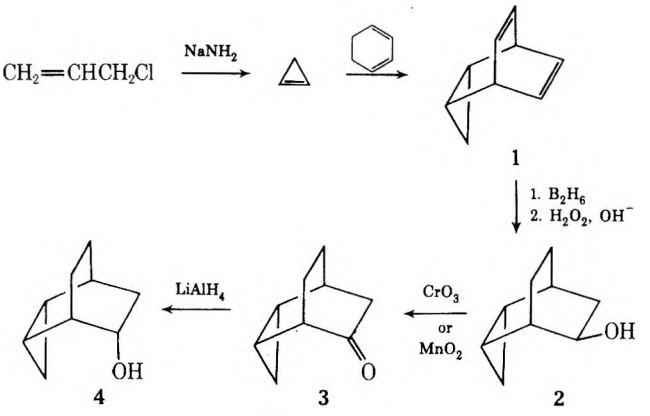
Reactivity studies[3] of various policyclic compounds containing bridged or fused cyclopropane rings have revealed the great diversity of reactivity of 2-cyclopropylethyl derivatives from the highly activated and reactive[3a,b,e-h] to the highly deactivated and unreactive[3c,d] systems. Despite the inherent problems of dissecting strain effects from electronic interaction effects and neighboring group effects, we have extended our earlier work[4] with conformationally unrestrained 2-cyclopropylethyl systems to studies using compounds with structural frameworks that have geometries and relative orientations of reactive groups that are well defined, namely, the four isomeric tricyclo[3.2.2.0$^{2,4}$]nonan-6-ols (*endo,endo-*, *endo,exo-*, *exo,endo-*, and *exo,exo-*)[5] in which there are four correspondingly different homocyclopropylcarbinyl geometrical orientations. Solvolyses of the parent 2-bicyclo[2.2.2]octyl system are not strongly assisted by neighboring carbon participation and thus any resultant cyclopropane participation should appear in rate and product studies of the solvolyses and should not be swamped[6a] by the dominant

reactivity patterns or by the structural symmetry of the corresponding hydrocarbon system, as is the case for the 2-norbornyl systems,[6b] to which the present study is homologous.

In this paper the synthesis of the four isomeric tricyclo[3.2.2.0$^{2,4}$]nonan-6-ols (**2**, **4**, **8**, and **9**) from the requisite olefins,[7] characterization, and relative stereochemical assignment are reported. The acetolyses of the corresponding brosylate esters will be reported separately.

**Synthesis of the Cyclopropyl Endo Epimers.** The epimeric cyclopropyl endo alcohols, *endo,exo-* (**2**) and *endo,endo*-tricyclo[3.2.2.0$^{2,4}$])nonan-6-ol (**4**), were synthesized by a route similar to that employed by Wiberg and Wenzinger[6b] in the synthesis of the corresponding tricyclo[3.2.1.0$^{2,4}$]octan-6-ols. This route is shown in Scheme I. Cyclopropene, generated by the procedure of Closs,[8a] was added to 1,3-cyclohexadiene to form *endo*-tricyclo[3.2.2.0$^{2,4}$]non-6-ene (**1**). The overall yield of this reaction, which was quite low (1–5%, based on sodium amide[8b]), was sensitive to a number of variables, notably the manufacturer, individual lot, and shelf age of the commercial sodium amide used.[8c] In this case, despite the low overall yield, sufficient quantities of **1** were obtained, since the reaction proved amenable to large-scale operation. The 220-MHz nmr spectrum of **1**[7] confirms the expected endo configuration of the cyclopropane ring.

**Scheme I**



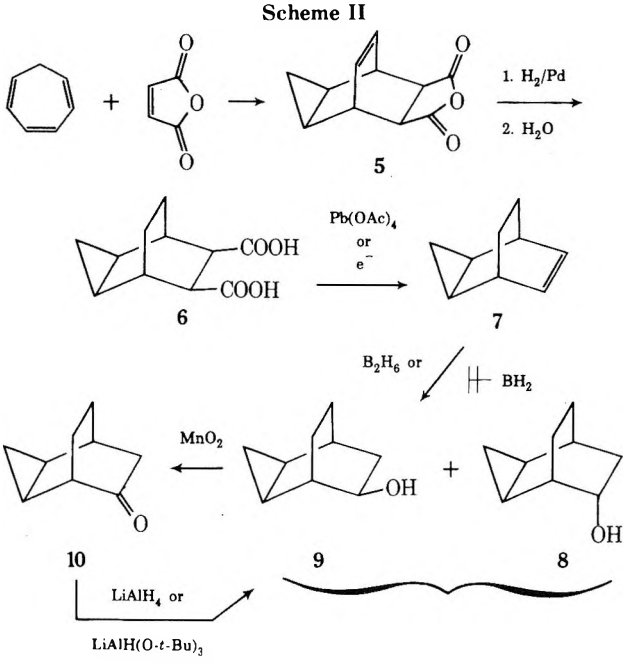

Hydroboration-oxidation[9] yielded the endo,exo alcohol **2** as the only product. The stereospecificity of this reaction is a consequence of the endo cyclopropane ring, which shields the endo side of the double bond from attack by diborane. The exo orientation of the hydroxyl group, while not required by the spectrometric evidence, is established through the proof of orientation for the endo,endo epimer (**4**), described below.

*endo*-Tricyclo[3.2.2.0$^{2,4}$]nonan-6-one (**3**) was synthesized by the oxidation of **2**, either by chromium trioxide in pyridine[10] or activated manganese dioxide in pentane,[11] in 75–80% yield. Although the yields for both procedures were comparable, the manganese dioxide method is much the simpler and cleaner one. The physical and spectrometric properties of **3** are in excellent agreement with those reported independently.[8c,12]

Reduction of **3** with lithium aluminum hydride in ether yielded only the endo,endo alcohol (**4**). The nmr spectrum of this alcohol enables the assignment of the relative orientation of the cyclopropane ring and the hydroxyl group to be made unambiguously: the endo or interior secondary cyclopropyl proton of **4** is deshielded by 0.84 ppm (relative to the corresponding proton in the endo,exo epimer **2**). This shift, indicative of the close proximity[13] of the oxygen atom and the interior cyclopropyl methylene proton to each other in **4**, confirms the endo,endo configuration of this compound.

**Synthesis of the Cyclopropane Exo Epimers.** The cyclopropane exo epimers, *exo,endo-* (**8**) and *exo,exo*-tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (**9**), were not isolated separately, but rather were obtained as mixtures of the two alcohols (which resisted all attempts at preparative separation), as was anticipated from inspection of molecular models. It is apparent from models that there may be only a slight steric advantage toward the endo side of **7**. The identification and composition of these mixtures was determined through the use of an nmr shift reagent, Eu(fod)$_3$, described in detail below. Mixtures of **8** and **9** were synthesized according to procedures outlined in Scheme II.

**Scheme II**



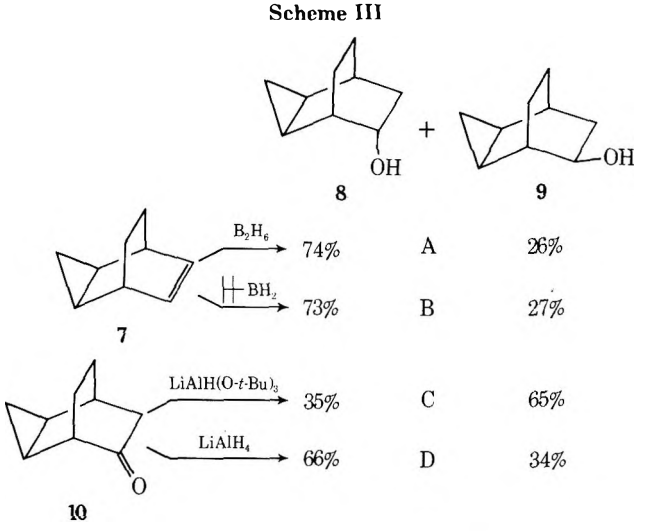

*exo*-Tricyclo[3.2.2.0$^{2,4}$]non-6-ene (**7**)[7] was prepared *via* the decarboxylation of the diacid **6**[14] by two methods: anodic oxidation[15] and lead tetraacetate decarboxylation.[16] Although the yields for the two routes are comparable (30–40%) on a small scale, the lead tetraacetate procedure was found to be more convenient for larger scale preparations, owing to difficulties encountered in large-scale electrolyses. The anticipated exo configuration of the cyclopropane ring is confirmed by the 220-MHz nmr spectrum, the details of which have been reported.[7]

Hydroboration-oxidation[9] of **7** yielded a product (in better than 80% yield) whose physical and spectrometric properties were consistent with a mixture of *exo,endo-* (**8**) and *exo,exo*-tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol; this result is not surprising, since **7** lacks the obvious steric bias between exo and endo attack present in endo olefin **1** or in norbornene. This epimeric mixture (mixture A) was shown *via* nmr shift reagent analysis to consist of 74% **8** and 26% **9** (see below). In order to maximize the effect of any steric bias inherent in **7**, the hydroboration was performed with the bulky 2,3-dimethyl-2-butylborane[17] (thexyl borane), followed by oxidation. The product (mixture B) appeared to be identical with mixture A, described above; shift reagent analysis showed it to consist of 73% **8** and 27% **9**. The apparent lack of effect of the bulkier thexyl borane on the composition of the mixture may indicate that the preference of endo attack by boron on **7** is electronic in origin, perhaps involving interaction with the cyclopropane ring, or that the stereochemistry of the reactions is determined by product control and is insensitive to the steric bulk of the reagents.

The mixture of exo,endo and exo,exo alcohol from conventional hydroboration-oxidation (mixture A) was clean-

ly oxidized by $MnO_2$ in pentane to a single ketone, *exo*-tricyclo[3.2.2.0$^{2,4}$]nonan-6-one (**10**), whose spectrometric properties were consistent with this structure.[18] This ketone was reduced with lithium aluminum tri-*tert*-butoxyhydride in ether, again in an effort to take advantage of any steric bias present in **10**. The product (mixture C), which in other respects appeared to be identical with mixture A, was shown by shift reagent analysis to have the composition 35% **8** and 65% **9**. This result, which indicates a preference for endo attack of hydride on the carbonyl group of **10**, may be anticipated from inspection of models of **10**: the tertiary cyclopropyl protons are held somewhat further away and at a wider angle from the reactive site than are the protons of the saturated C-8–C-9 bridge. The stereoselectivities of these reactions are summarized in Scheme III. Thus it may be seen that the stereochemistry of reactions A, B, and D are determined by product development control, while in reaction C, showing the result of a steric bias, the stereochemical preference is determined by steric approach control. Similar hydride reduction selectivities are noted in the accompanying paper by Wenzinger and Ors.[1]

**Scheme III**




**Identification and Composition of Mixture of Cyclopropane Exo Epimers.** The mixtures described above were characterized through analysis of their nmr spectra taken in the presence of a paramagnetic rare-earth chelate complex: tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-5-octa-4,6-dionato)europium(III), or Eu(fod)$_3$. A similar europium chelate [with 2,2,6-6-tetramethyl-3,5-heptanedione, Eu(thd)$_3$], first described by Eisentraut and Sievers,[20] produces downfield shifts in proton nmr spectra. The use of this and other europium chelates produces little line broadening [owing to the short relaxation time of Eu(III)] and little effect on coupling constants. Hinckley[21] observed large shifts for compounds with heteroatoms bearing unshared electrons (especially alcohols and amines, with smaller shifts for carbonyls and ethers). A postulated mechanism[21] involves reversible incorporation of the heteroatom in the europium coordination sphere. Shift magnitudes correlate linearly with the relative concentration of substrate to chelate. The magnitude of the shifts for individual protons correlates with the estimated distance of the proton from the metal atom.

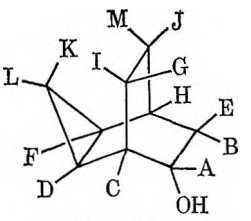
DeMarco and coworkers[22] have shown that the Eu(thd)$_3$-induced shifts ($\Delta\delta_{Eu}$, in parts per million, for equimolar solutions of alcohol and chelate) of the protons of a series of rigid secondary alcohols can be correlated with the distance $R$, in Å) of each proton from the oxygen atom in each alcohol. For rigid, monofunctional alcohols in deuteriochloroform, they observed a linear correlation between log $\Delta\delta_{Eu}$ and log $R$, over a wide range of shifts (0.7–20 ppm) and distances (2–10 Å). The hydroxyl and carbinol methine (OHOH) protons deviated significantly from the linear plot and are more strongly shifted than anticipated. Deviations probably result from failure to include an angle function (3 cos$^2$ − 1) and from measurement of distances to the alcohol oxygen instead of to the europium atom. Rondeau and Sievers[23] have discovered that Eu(fod)$_3$ gives larger shifts with weak donors; this chelate is a stronger Lewis acid, owing to the electron-withdrawing fluorine substituents. It is also appreciably more soluble in carbon tetrachloride than Eu(thd)$_3$. The use of these reagents and common assumptions and limitations on their use have been reviewed recently.[23b]

The nmr spectra of mixture A and mixture C in the presence of approximately 0.25 equiv of Eu(fod)$_3$ are described in detail in the Experimental Section. For simplicity we will assume that which is subsequently proven: that the major isomer in mixture A is **8**, and the major isomer in mixture C is **9**. Mixture A is thus 74% **8** and 26% **9**, while mixture C is 35% **8** and 65% **9**. These are the ratios of the areas of the peaks at 12.1 and 10.1 ppm in each spectrum, corresponding to the CHOH proton in **8** and **9**, respectively.[24] By a careful analysis of the multiplicity and relative areas of peaks and through decoupling of the shifted spectra it is possible to make structural assignments of the remaining regions in each spectrum of the different mixtures (A and C) and determine the number of protons from either **8** or **9** absorbing in each region. Through double-irradiation experiments, it was possible to determine a number of the coupling constants accurately. For compound **8** the following coupling constants may be assigned: $J_{AE}$ = 9.1, $J_{BE}$ = 13.5, and $J_{AB}$ = 2.3 Hz. For compound **9** the corresponding coupling constants are $J_{A'E'}$ = 10.0, $J_{B'E'}$ = 13.0, and $J_{A'B'}$ = 2.3 Hz. Coupling constants for geminal protons in medium-size rings are typically 11–14 Hz; vicinal coupling constants in such systems vary with dihedral angle. Typical values are 8–10 Hz for $\phi$ = 0°, 2–3 Hz for $\phi$ = 60°, 120°, and near zero for $\phi$ = 90°. These partial coupling patterns for both **8** and **9** are consistent with the structures shown.

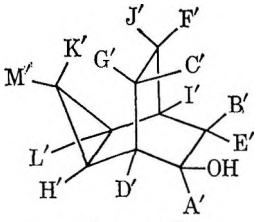
The results of additional double-irradiation experiments provide more information about the relationships between the protons of **8** and **9**. Irradiation at 6.0 ppm in the spectrum of mixture C ($H_{B'}$ and $H_{C'}$), in addition to decoupling $H_{A'}$ and $H_{E'}$ (from $H_{B'}$; see Table I), results in the collapse of a doublet ($J$ = 10 Hz) at 4.1 ppm ($H_{F'}$) and the collapse of a doublet ($J$ = 12–13 Hz) at 3.1 ppm ($H_{G'}$). Thus $H_{G'}$ is geminal to $H_{C'}$, and $H_{F'}$ is vicinal to $H_{C'}$, at a dihedral angle of about 0°. The isolated position in the shifted spectrum and coupling pattern (triplet, $J$ = 7–8 Hz) of $H_{M'}$ suggest that it is the exterior secondary cyclopropyl proton of **9**. Irradiation in the 5.8–6.4-ppm region of mixture A ($H_D$) resulted in changes in the splitting pattern in the 1.7–2.2-ppm region ($H_K$, $H_L$, $H_M$; see Table I). However, it was not possible to obtain any coupling constants or definite assignments owing to the complexity of this region.

Thus far the shift reagent has been used solely as a tool to modify spectral appearance to simplify analyses and the corresponding assignments. In addition, if these chelate complexes are similar to those studied by DeMarco,[22] there should be correlation of the distance of the proton from the chelate. It is inherent in these assumptions that there is only one (or one predominant) chelate complex formed for each alcohol and that the conformations involved are similar. (In the accompanying paper by Wenzinger and Ors[1] magnitudes of shifts were shown to be linear with concentration of shift reagent for similar compounds.) Utilizing the data and postulates summarized

**Table I**




(exo, endo)




(exo, exo)

| Δδ, ppm | Proton[a] | Region, ppm rel to Eu(fod)$_3$ | Proton[a] | Δδ, ppm |
|---|---|---|---|---|
| 8.2 | $H_A$ | 11.8–12.4 | | |
| | | 9.9–10.3 | $H_{A'}$ | 6.1 |
| 5.6 | $H_B$ | 7.6–7.9 | | |
| 4.8 | $H_C$ | 6.7–6.9 | | |
| 4.7–5.0 | $H_D$ | 5.8–6.4 | $H_{B'}$, $H_{C'}$ | 4.0 |
| | | 5.5–5.7 | $H_{D'}$ | 3.7 |
| 4.0 | $H_E$ | 4.9–5.4 | | |
| | | 4.3–4.8 | $H_{E'}$ | 3.1 |
| 2.8–2.9 | $H_F$, $H_G$ | 3.7–4.1 | $H_{F'}$ | 2.3 |
| 1.2–1.6 | $H_H$, $H_I$, $H_J$ | 2.4–3.6 | $H_{G'}$, $H_{H'}$, $H_{I'}$ | 1.9, 1.5–1.6 |
| 0.5–1.5 | $H_K$, $H_L$, $H_M$ | 1.7–2.2 | $H_{J'}$, $H_{K'}$, $H_{L'}$ | 1.0–1.4 |
| | | 1.0–1.4 | $H_{M'}$ | 0.5 |

[a] Letter assignments are used for protons to indicate magnitudes of observed shifts; A protons are shifted the most in the spectra.

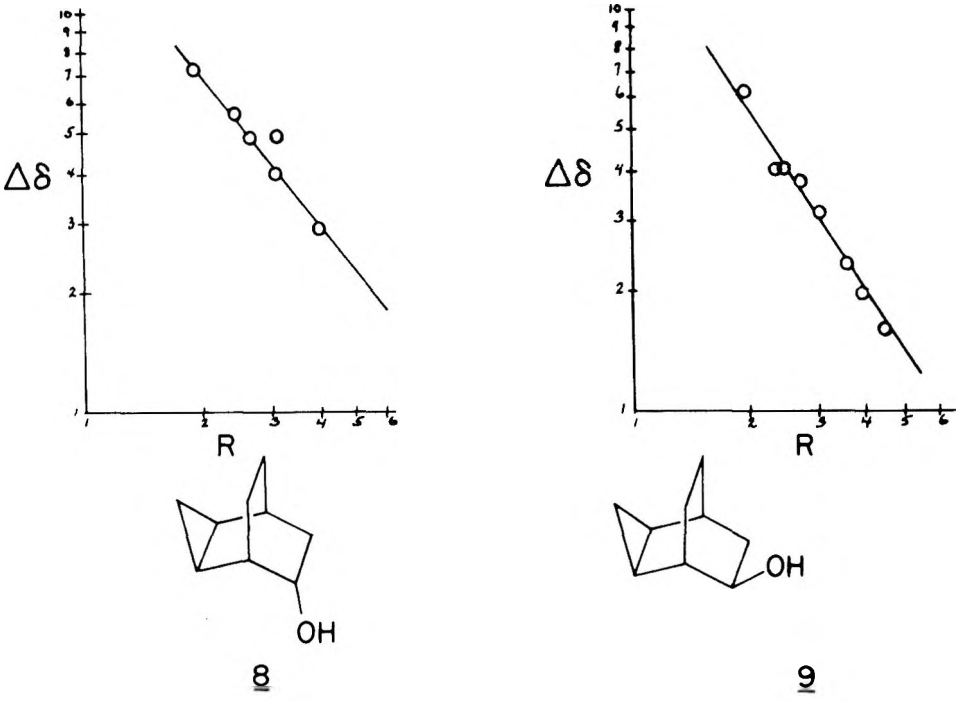



Figure 1.

above,[23b] the proton assignments listed in Table I, and the estimated chemical shift differences due to the paramagnetic reagent (Δδ) in Table I, may be correlated with the distances of each proton from the oxygen atom (estimated from models). Shift differences were evaluated as the chemical shift in the presence of chelate (relative to the chelate proton resonance) minus the chemical shift in the absence of chelate (relative to TMS) for each proton. The use of the chelate resonance as a reference position leads to some difficulties. The position of the chelate protons is 0.5 ppm upfield from TMS (in the absence of alcohol). DeMarco[22] has demonstrated that the chelate position does vary with the relative concentrations of chelate and alcohol, but the variation is not large. Thus, although precise quantitative results (Δδ per mole) are not obtainable from the obtained data, the qualitative correlations observed should be relatively insensitive to this choice of reference.

Using the values in Table I, plots of log Δδ *vs.* log *R* (Figure 1) show good linearity, as observed by DeMarco and coworkers,[22] especially for the exo,exo alcohol **9**, for which the greater number of firm chemical shift assignments (eight) may be made. Measured Δδ values were used directly, rather than extrapolated to unit concentration of chelate, since extrapolation based on only one concentration of chelate is not justified (however, see ref 1). Although distances should obviously be measured from the protons to the europium atom, this is not possible with these systems, as spacial orientation and distances are not known for these complexes. The slopes of the plots are about −2, which is typical.[23b]

The assignments for both isomers, based on analyses of

peak multiplicities, chemical shifts, and peak areas for both mixtures A and C, are in good agreement with correlation of induced shifts *vs.* distance from the oxygen atoms for both alcohols 8 and **9**, with the exception of $H_D$ in 8, the nearer tertiary cyclopropyl proton, which is shifted downfield about 1 ppm more than anticipated. This suggests greater proximity of this cyclopropyl proton and the europium atom, further supporting the stereochemical assignments of 8 and **9**. These stereochemical assignments are further supported by the products of solvolyses of the corresponding brosylates (to be reported later), providing also a mechanistic consistency for the assignments of these structures.

The fact that the CHOH proton in one isomer (8) is shifted about 2 ppm further downfield than the corresponding proton in the other isomer (**9**) cannot be a consequence of a difference in their respective distances from the oxygen. A plausible explanation for this difference is that the europium chelate complexes preferentially with isomer 8, *i.e.*, the equilibrium constant for incorporation of 8 into the coordination sphere of the europium is larger than the equilibrium constant for incorporation of **9**, resulting in greater shifts for alcohol 8. This may be readily accounted for in terms of a steric effect. The oxygen of 8 is in a sterically less crowded environment, as may be seen from models. This is also consistent with the observed steric effects in the hydride reductions.

## Experimental Section

Nmr spectra were recorded on a Varian Associates A-60 spectrometer or a Hitachi Perkin-Elmer R-20B spectrometer. All decoupling experiments were performed on the latter instrument. Chemical shifts are reported in units of $\delta$ (parts per million) downfield from TMS. Spectral data are presented as follows: chemical shift, splitting pattern (number of protons or relative area, coupling constant $J$ in hertz, assignment where known). Infrared spectra were recorded on a Perkin-Elmer 337 grating infracord spectrophotometer or a Beckman IR-5 spectrophotometer. Mass spectra were recorded on a Varian Associates Model M-66 spectrometer and are reported as follows: peak, $m/e$ (per cent of base peak). Melting points are uncorrected.

*endo*-**Tricyclo[3.2.2.0$^{2,4}$]non-6-ene (1).** Cyclopropene was generated by a modification of the method used by Closs and Krantz[8a] as adapted by DiFate.[8c] Sodium amide (400 g, 10 mol) was suspended in light paraffin oil in a flask fitted with dropping funnel, dry nitrogen source, mechanical stirrer, and Dry Ice–carbon tetrachloride condenser. 3-Chloropropene (800 g, 10.4 mol) was added dropwise over 12–15 hr to the stirred suspension, which was maintained at 90–100°. The resultant gas was passed through the Dry Ice condenser and through 2 l. of 25% sulfuric acid. The gas was then passed into 1,3-cyclohexadiene (125 g, 1.56 mol) and stirred at 0° in an ice–water bath with a magnetic stirrer. After generation was complete the mixture was dried with anhydrous potassium carbonate, kept at 0–5° for 12 hr, and filtered. Atmospheric distillation through a 6-in. Vigreux column gave 1,3-cyclohexadiene at 60–80° (80–100 g) and *endo*-tricyclo[3.2.2.0$^{2,4}$]non-6-ene at 160–170° as a waxy solid (collected with an air condenser heated intermittently with a hot-air pistol to prevent plugging), average yield of 17 g. The yield of product varied from 5 to 40 g depending chiefly on the commercial sodium amide used.[8c] The average yield of 17 g (0.14 mol) represents a 1.4% yield based on sodium amide, or 14% based on Closs' estimate of 10% yield of cyclopropene generated. Spectral details are identical with those reported.[7,8c]

*endo,exo*-**Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (2).** Diborane, generated by the addition of sodium borohydride (2.5 g, 0.066 mol) dissolved in 50 ml of dry diglyme to boron trifluoride–ethyl ether (20 g, 0.141 mol) in 50 ml of dry diglyme, was passed into a solution of *endo*-tricyclo[3.2.2.0$^{2,4}$]non-6-ene (15.0 g, 0.125 mol) in 300 ml of dry tetrahydrofuran, stirred at 0°. (Excess diborane was passed into running water.) After generation was complete (about 1 hr), the tetrahydrofuran solution was stirred under a dry nitrogen atmosphere at room temperature for an additional 2 hr. The solution was cooled to 0°, and 15 ml of 10% aqueous sodium hydroxide was carefully added dropwise, followed by the careful dropwise addition of 15 ml of 30% aqueous hydrogen peroxide. This mixture was then stirred at 0° for 3 hr and at room temperature for 1 hr. The mixture was then diluted with 1 l. of water and extracted with five 200-ml portions of ether. The combined ether extracts were washed with five 500-ml portions of water and once with 500 ml of saturated sodium chloride solution. The ether layer was dried over anhydrous potassium carbonate and the solvent was removed *in vacuo*. The residue (10 g, 59%) was crystallized from purified pentane, mp 155–160° (sealed tube).

*Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.44; H, 10.57.

Nmr 0.33, m (2 H, secondary cyclopropyl protons), 0.95, m (2 H, tertiary cyclopropyl protons), 1.20–2.20, broad m (8 H, methylene and bridgehead protons), 3.00, sharp s (1 H, hydroxyl proton), 3.75 ppm, m (1 H, CHOH proton).

Ir spectrum 3610, 3070, 3010, 2940, 2865, 1460, 1405, 1345, 1100, 1020, 1000 cm$^{-1}$.

*endo*-**Tricyclo[3.2.2.0$^{2,4}$]nonan-6-one (3). A.** To a stirred suspension of chromic anhydride–pyridine complex,[10] prepared by the careful addition of chromic anhydride (11.0 g, 0.11 mol) to 60 ml of dry pyridine, was added **2** (3.0 g, 0.022 mol) in 15 ml of dry pyridine. The mixture was stirred at room temperature under nitrogen for 24 hr. Water (100 ml) was added and the aqueous solution was extracted with ten 50-ml portions of purified pentane. The pentane extracts were washed with 200-ml portions of 10% HCl solution, water, and saturated sodium bicarbonate. The pentane solution was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The product was crystallized from pentane and purified by sublimation at atmospheric pressure, yield (white solid) 2.3 g (75%), mp 122–124° (sealed tube).

*Anal.* Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.49, 78.28; H, 9.26, 9.56.

The nmr, ir, and mass spectra are identical with those reported.[8,12]

**B.** **2** (5.0 g, 0.0362 mol) was dissolved in 300 ml of purified pentane. Activated manganese dioxide[11,25] (50 g) was added, and the mixture was stirred at room temperature for 100 hr. The reaction mixture was filtered and solvent was removed *in vacuo*. The infrared spectrum of the crude product showed the presence of unreacted alcohol (*ca.* 10%). The residue was dissolved in 50 ml of pentane and stirred with 2 g of activated alumina for 10 min, then filtered. The alumina was washed with a few milliliters of pentane, the pentane layers were combined, and solvent was removed *in vacuo*. The product showed no OH stretching bands in the infrared, yield 4.0 g (81%). The product was identical in all respects with the ketone prepared by the preceding method.

*endo,endo*-**Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (4).** A solution of **3** (2.0 g, 0.015 mol) in 30 ml of dry ether was added dropwise at room temperature to a stirred suspension of lithium aluminum hydride (0.30 g, 0.008 mol) in 30 ml of dry ether. After the addition was complete (about 15 min) the mixture was stirred for an additional 15 min, then cooled to 0° with an ice–water bath. Water and wet sodium sulfate (to a total of about 50 ml) were added carefully. The ether layer was separated, washed with 50-ml portions of water and saturated sodium chloride solution, and dried over anhydrous potassium carbonate. The ether was removed *in vacuo*, and the residue was crystallized from pentane, yield 1.5 g (75%), mp 173–175° (sealed tube).

*Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.26; H, 10.40.

Nmr 0.30, complex m (1 H, exterior cyclopropyl proton), 0.83, m (2 H, tertiary cyclopropyl protons), 1.17, m (1 H, interior cyclopropyl proton), 1.3–1.8, m (6 H, methylene protons), 2.05, broad s (2 H, bridgehead protons), 2.67, sharp s (1 H, hydroxyl proton), 3.71 ppm, m (1 H, CHOH proton):

Ir spectrum 3620, 3360, 2015, 2925, 2880, 1464, 1440, 1120, 1080, 1037, 1009 cm$^{-1}$.

*exo*-**Tricyclo[3.2.2.0$^{2,4}$]non-8-ene-*exo*-6,*exo*-7-dicarboxylic Anhydride[14] (5).** Maleic anhydride (255 g, 2.6 mol) and cycloheptatriene[26] (270 g, 2.9 mol) were dissolved in 1000 ml of xylene. The mixture was heated at reflux for 90 hr. The solution was cooled to 5° and the crystals were isolated by vacuum filtration, yield 300 g (62%), mp 101–103° (lit. mp 101°).[14]

*exo*-**Tricyclo[3.2.2.0$^{2,4}$]nonane-*exo*-6,*exo*-7-dicarboxylic Anhydride.[14] 5** (10.0 g, 0.526 mol), dissolved in 75 ml of acetone, and palladium (10% on activated charcoal, 0.6 g, prereduced) in 100 ml of acetone were mixed and stirred under hydrogen at atmospheric pressure. Hydrogen was absorbed over a period of 3 hr (1.20 l., 0.053 mol, 101%). The mixture was filtered and the acetone was removed *in vacuo*, yield (white solid) 10.0 g (99%). A small sample was recrystallized from 50% ether–pentane to give long, flat needles, mp 137–139° (lit. mp 140).[14]

Nmr ($CDCl_3$) 0.67–1.05, complex m (2 H, secondary cyclopropyl protons), 1.1–1.5, m (2 H, tertiary cyclopropyl protons), 1.47, broad s (4 H, methylene protons), 2.72, broad s (2 H, bridgehead protons), 3.43 ppm, broad s (2 H, anyhydride methine protons).

***exo*-Tricyclo[3.2.2.0$^{2,4}$]nonane-*exo*-6,*exo*-7-dicarboxylic Acid (6).** *exo*-Tricyclo[3.2.2.0$^{2,4}$]nonane-*exo*-6,*exo*-7-dicarboxylic anhydride (20 g, 0.104 mol) was added to 500 ml of distilled water containing sodium hydroxide (12 g, 0.30 mol). The mixture was heated to 75–85° and stirred until solution was complete. The hot solution was filtered and acidified to pH 1 (hydrion A paper) with 37% HCl (approximately 40 ml). The diacid immediately appeared as a fine white precipitate. After cooling to 5°, the product was isolated by vacuum filtration, washed thoroughly with distilled water, and dried to constant weight in a vacuum desiccator,[27] yield (white solid) 20.0 g (95%). A small portion was recrystallized from distilled water, mp 173° dec (lit. mp 173–174°).[14]

***exo*-Tricyclo[3.2.2.0$^{2,4}$]non-6-ene (7). A.** A modification of the procedure of Grob[16] was used. To a cooled suspension (ice-water bath) of 6 (21 g, 0.10 mol) in 500 ml of dry benzene containing dry pyridine (40 g, 0.51 mol) was added lead tetraacetate (containing acetic acid, 10% by weight, 75 g, 0.17 mol). The stirred mixture was slowly heated. Between 40 and 50° the mixture turned to a clear yellow-orange solution. Between 65 and 70° the reaction became exothermic, and gas was rapidly evolved. The mixture thickened, and a voluminous tan precipitate appeared. The mixture was stirred at 75–80° for 2 hr, cooled to room temperature, and filtered by suction. The solid was washed with 100 ml of benzene. The combined benzene solutions were washed with 500-ml portions of water, 5% NaOH (twice), water, 10% HCl (twice), water, saturated sodium bicarbonate, and saturated sodium chloride solution. The benzene layer was dried over anhydrous potassium carbonate and distilled at atmospheric pressure. The product, a waxy solid, was distilled using an air condenser heated with a hot air pistol, yield 4.3 g (36%), bp 162–168°.

Nmr spectrum 0.53 ppm, complex m (1 H, exterior secondary cyclopropyl proton), 0.82 ppm, m (1 H, interior secondary cyclopropyl proton), 0.95–1.55, m (6 H, tertiary cyclopropyl and methylene protons), 2.60, broad s (2 H, bridgehead protons), 6.32 ppm, AB d (2 H, vinyl protons).

Ir spectrum 3050, 3010, 2940, 2865, 1640, 1550, 1460, 1435, 1368, 1318, 1250, 1160, 1088, 1040, 1000, 953, 860 $cm^{-1}$.

Mass spectrum *m/e* (rel intensity) 120 (56), 105 (78), 93 (10), 92 (58), 91 (66), 80 (12), 79 (100), 78 (38), 77 (36), 66 (22), 65 (14), 51 (14), 41 (8), 39 (20).

**B.** 6 (3.0 g, 0.015 mol) was dissolved in 150 ml of 90% aqueous pyridine containing 2 ml of triethylamine. The solution was electrolyzed,[15] with a platinum mesh anode and a platinum wire cathode, at initial values of 70 V DC and 1.8 A. After 4.5 hr, the values were 100 V and 0.25 A. The solution was diluted with 500 ml of cold water and extracted with two 250-ml portions of pentane. The combined pentane layers were washed with 250-ml portions of water, 10% HCl (twice), water, and saturated sodium bicarbonate solutions. The pentane layer was dried over anhydrous $K_2CO_3$, and solvent was removed *in vacuo*. The residual yellow oil was distilled at atmospheric pressure through an air condenser to give the product (0.64 g, 37%), which was identical in all respects with that obtained above.

***exo,endo*- and *exo,exo*-Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (8, 9). A.** *Via* **Diborane, Mixture A.** Diborane, generated by the addition of sodium borohydride (5.0 g, 0.13 mol) in 175 ml of dry diglyme to boron trifluoride–ethyl ether (30.0 g, 0.21 mol) in 50 ml of dry diglyme, was passed into a solution of 7 (28.0 g, 0.233 mol) in 250 ml of dry tetrahydrofuran. The solution was stirred at room temperature under nitrogen for 2 hr after addition was complete, then cooled in an ice–water bath. Aqueous sodium hydroxide (10%, 40 ml) was added dropwise, followed by 40 ml of 30% hydrogen peroxide. The mixture was stirred at 0° for 2 hr. The mixture was added to 1 l. of water and extracted with five 200-ml portions of ether. The combined ether extracts were washed with five 1-l. portions of water and one portion of saturated sodium chloride solution. The ether layer was dried over anhydrous potassium carbonate, and the solvent was removed *in vacuo*, yield (crude) 28.6 g (89%). The product was recrystallized from pentane (60–70% yield), mp 159–164°.

*Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.83; H, 10.10.

Nmr 0.1–0.7, complex m (2 H, secondary cyclopropyl protons), 0.7–2.5 (major peaks at 1.25 and 1.97), m (10 H, tertiary cyclopropyl, methylene, and bridgehead protons), 2.55, s (1 H, hydroxyl proton), 3.90 ppm, m (1 H, CHOH proton).

Ir spectrum 3620, 3360, 3080, 3010, 2940, 2880, 1478, 1452, 1350, 1235, 1110, 1040, 1030, 975 $cm^{-1}$.

Mass spectrum *m/e* (rel intensity) 138 (29), 120 (29), 105 (26), 95 (23), 94 (68), 93 (28), 92 (47), 91 (45), 83 (13), 81 (15), 80 (21), 79 (100), 78 (32), 77 (29), 70 (13), 67 (19), 66 (29), 55 (13), 53 (13), 41 (19), 39 (17).

A solution of the above alcohol mixture (0.13 g, 0.000943 mol) and $Eu(fod)_3$ (0.21 g, 0.000201 mol, molar ratio of shift reagent to alcohol 0.215) in spectrophotometric grade carbon tetrachloride was prepared. The nmr spectrum of the mixture is reported below, with relative peak areas given. (Note: the chemical shifts are given relative to an external standard, TMS in $CCl_4$).

Nmr −1.3 [$Eu(fod)_3$ protons], −0.15, m (0.7 H), 0.6–1.1 (peaks at 0.75 and 0.95), m (3.8 H), 1.47, m (3.8 H), 1.6–2.4, m (2.0 H), 2.79, *m* (2.6 H), 4.02, *AB d* (1.3 H, $J$ = 9, 13.5 Hz), 4.60 *m* (0.4 H), 4.8–5.3, m (1.6 H), 5.96, broad s (1.0 H), 6.75, d (1.0 H, $J$ = 13.5 Hz), 9.25 ppm, m (0.3 H), 11.20, m (1.0 H, $J$ = 9 Hz).

**B.** *Via* **Thexyl Borane,[17] Mixture B.** Diborane, generated by the addition of sodium borohydride (1.50 g, 0.0395 mol) dissolved in 50 ml of dry diglyme to boron trifluoride–ethyl ether (5.69 g, 0.040 mol) in 50 ml of dry diglyme, was passed into a solution of 2,3-dimethyl-2-butene (3.68 g, 0.0438 mol) in 100 ml of dry tetrahydrofuran, with a stream of dry nitrogen. After the addition was complete, the solution was stirred at room temperature under nitrogen for 2.5 hr. 7 (2.51 g, 0.021 mol) dissolved in 15 ml of dry tetrahydrofuran was then added in one portion to the above solution. The mixture was stirred at room temperature for 20 hr. The mixture was then cooled to 0° (ice–water bath), and 10 ml of a 10% NaOH solution was added dropwise, followed by 10 ml of 30% hydrogen peroxide. The mixture was stirred for 3 hr at 0° and 1 hr at room temperature. It was then diluted with 300 ml of water and extracted with five 50-ml portions of purified pentane. The combined pentane layers were washed with five 200-ml portions of water and with saturated sodium chloride solution. The pentane extract was dried over anhydrous potassium carbonate and filtered, and the solvent was removed *in vacuo* (*tert*-hexyl alcohol was also removed in this process). The product, a pasty solid, was dissolved in $CCl_4$ along with approximately 0.2 equiv of $Eu(fod)_3$. The nmr spectrum of this mixture was very similar to that of the alcohol mixture produced by conventional hydroboration (see above), yielding a ratio of exo,endo to exo,exo alcohol of 2.7:1.0. It was not purified further, yield 1.7 g (59%).

***exo*-Tricyclo[3.2.2.0$^{2,4}$]nonan-6-one (10).** A mixture of *exo,endo*- and *exo,exo*-tricyclo[3.2.2.0$^{2,4}$]nonan-6-ols (mixture A, 5.00 g, 0.0366 mol) was dissolved in 300 ml of pentane. Activated manganese dioxide (50 g) was added and the mixture was stirred at room temperature for 120 hr. The mixture was then filtered and the residue was washed with an additional 100 ml of pentane. Activated alumina (1 g) was added and the solution was swirled for 2 min to remove any unreacted alcohol. The mixture was filtered and the solvent was removed *in vacuo*, yield 4.18 g (84%). The product was further purified by sublimation at atmospheric pressure, mp 119–121°.

*Anal.* Calcd for $C_9H_{12}O$: C, 79.37, H, 8.88. Found: C, 78.23, 78.05; H, 9.01, 8.82.

Nmr 0.38–0.96, m (6 H, tertiary cyclopropyl, C-8 and C-9 methylene), 2.15, m (2 H, C-7 methylene protons, adjacent to carbonyl), 2.15, m (2 H, C-7 methylene protons, adjacent to carbonyl), 2.30 ppm, broad s (2 H, bridgehead protons).

Ir spectrum 3065, 3015, 2938, 2865, 1730, 1463, 1410, 1285, 1114, 860 $cm^{-1}$.

Mass spectrum *m/e* (rel intensity) 136 (92), 108 (40), 94 (55), 93 (54), 92 (23), 91 (20), 80 (24), 79 (63), 77 (20), 67 (22), 66 (25), 54 (22), 53 (12), 41 (18), 39 (21), 32 (28), 28 (100).

***exo,endo*- and *exo,exo*-Tricyclo[3.2.2.0$^{2,4}$]nonan-6-ol (9, 8). A.** *Via* **Lithium Aluminum Tri-*tert*-Butoxyhydride, Mixture C.** 10 (2.86 g, 0.00212 mol) was dissolved in 60 ml of dry ether. Lithium aluminum tri-*tert*-butoxyhydride (6.00 g, 0.00236 mol) was added and the mixture was stirred at room temperature for 67 hr. A saturated aqueous solution of ammonium sulfate was added dropwise (to a total of 60 ml) and the layers were separated. The aqueous layer was washed with two 25-ml portions of ether. The combined ether layers were washed with water and saturated sodium chloride solution and dried over anhydrous potassium carbonate, and the solvent was removed *in vacuo*. The product was recrystallized from pentane, yield 2.18 g (75%), mp 159–164°.

Nmr 0.2–0.7 complex m (1.5 H, secondary cyclopropyl protons), 0.8–2.3 (peaks at 0.88, 1.29, 2.00), m (10.5 H, tertiary cyclopropyl, methylene, and bridgehead protons), 3.95, sharp s (1 H, hydroxyl proton), 3.8–4.3 m (1 H, CHOH proton).

A solution of this alcohol mixture (0.141 g, 0.00102 mol) and

$Eu(fod)_3$ (0.248 g, 0.00024 mol, molar ratio of shift reagent to alcohol 0.235) was prepared. The description of the nmr spectrum of that solution follows.

Nmr −2.70 [$Eu(fod)_3$ protons], −1.47, m (1.7 H), −0.74, m (5.1 H), 0.0–1.4, m (8.9 H, 1.88, AB d (1.3 H), 2.47, AB d (0.6 H), 2.8–3.7, m (4.0 H), 4.27, broad s (0.5 H), 5.00, d (0.5 H, $J$ = 13–14 Hz), 7.40, m (1.0 H), 9.20 ppm, m (0.5 H). Irradiation at 9.20 ppm yields a doublet at 2.47 ppm ($J$ = 13.5 Hz). Irradiation at 1.88 ppm yields a broad singlet at 7.40 ppm, and the coalescence of two peaks ($J$ = 13 Hz) in the 2.8–3.7-ppm multiplet to a singlet. Irradiation at 3.30 ppm yields a broad singlet at 1.15 ppm (collapse of doublet, $J$ = 12 Hz), and the collapse of a doublet ($J$ = 12 Hz) at 0.40 ppm.

**B.** *Via* **Lithium Aluminum Hydride, Mixture D. 10** (1.05 g, 0.00772 mol) in 10 ml of dry ether was added dropwise to a stirred suspension of lithium aluminum hydride (0.15 g, 0.00395 mol) in 10 ml of dry ether. After addition was complete, the mixture was stirred for an additional 15 min, then cooled in an ice–water bath. Water and wet sodium sulfate were added, and the layers were separated. The water layer was washed with an additional 20 ml of ether, and the combined ether layers were washed with water and saturated sodium chloride solution. The ether layer was dried over anhydrous potassium carbonate and solvent was removed *in vacuo*. The product was recrystallized from pentane, yield 0.80 g (75%), mp 158–163°. The nmr spectrum of this mixture in the presence of $Eu(fod)_3$ (0.35 equiv) was similar to that of the mixture produced *via* hydroboration–oxidation (see mixture A); the ratio of exo,endo to exo,exo alcohol was 2.0:1.

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**Registry No.**—**1**, 7092-05-9; **2**, 51260-33-4; **3**, 51260-38-9; **4**, 51260-34-5; **5**, 944-41-2; **6**, 51175-60-1; **7**, 27019-94-9; **8**, 51260-36-7; **9**, 51260-35-6; **10**, 51260-37-8; 3-chloropropene, 107-05-1; 1,3-cyclohexadiene, 592-57-4; maleic anhydride, 108-31-6; cycloheptatriene, 544-25-2; *exo*-tricyclo[3.2.2.$0^{2,4}$]nonane-*exo*-6,*exo*-7-dicarboxylic anhydride, 944-40-1.

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(25) Obtained from Winthrop Laboratories, Inc.
(26) We gratefully acknowledge the generous gift of cycloheptatriene from the Shell Chemical Corp., Calif.
(27) Caution: desiccation under high vacuum for extended periods leads to substantial dehydration to the anhydride. Observation of R. Leight in this laboratory.

# Conformational Analysis of Some Bicyclo[4.2.0]octanes by Hydrogen-1 Nuclear Magnetic Resonance

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7,7-Diphenyl-2,5-dioxabicyclo[4.2.0]octane (**1**), 7,7-diphenyl-2,5,8-trioxabicyclo[4.2.0]octane (**2**), and 7,7-dimethyl-2,5,8-trioxabicyclo[4.2.0]octane (**3**) were shown to exist as cis-fused chairs. The conformational analyses were accomplished by a combination of $Eu(fod)_3$ shift ratios and the Buys $R$ method. The $Eu(fod)_3$ was shown to have no effect on the conformation. The bicyclooctanes were synthesized through the photocycloaddition of acetone, benzophenone, and 1,1-diphenylethylene to 1,4-dioxene.

Buys[2] and Lambert[3] have developed methods for determining the conformation of rigid six-membered ring systems, containing heteroatoms in the 1 and 4 positions, by nmr. These methods relate the ratio of the average trans and cis vicinal coupling constants to the conformation.

Slessor and Tracy[4] have written a computer program,

Dihedral Angle Estimation by the Ratio Method (DAERM), for the conformational analysis of a $CHR_2CH_2R$ system. This method is based on the assumption that the ratio of Karplus constants for the cis and trans dihedral angles is a constant (0.9). Conformational analysis of some four-membered-ring compounds gave results consistent with those obtained by X-ray and dipole moment studies.[5]

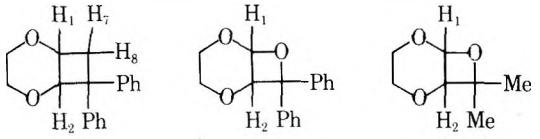
Simplification of complex spectra through the application of the shift reagent, $Eu(fod)_3$, is an established technique.[6] Compounds with two binding sites have been dealt with by Williams, *et al.*[7] They have shown that competition between sites can be detected by a plot of shift *vs.* the molar ratio of shift reagent to substrate.

These systems present the possibility of competition between various sites, some of which may be favored on steric considerations, others on electronic.

The conformations of the dioxane portion of compounds 1–3 were determined by Buys and Lambert's methods and *the conformation of the cyclobutane portion of* 1 by DAERM. The coupling constants were obtained from the $Eu(fod)_3$ shifted spectra and refined through the program NMRIT.[8]

## Results and Discussion

The 60-MHz nmr spectra of compounds 1–3 are shown in Figure 1. The partial spectra for the oxetanes 2 and 3




1 2 3

consist of two doublets, for the bridgehead protons, and a complex four-spin pattern (ABCD) for the methylene protons. The spectrum of the cyclobutane 1 is composed of two independent four-spin sets, an ABCD pattern for the dioxane methylene portion and a first-order pattern for the cyclobutane protons. The protons at 4.95 ppm in the spectra of 1 and 2 are assigned to H-2. The protons at 5.53 and 5.63 ppm are assigned to H-1 of compound 2 and 3, respectively; the remaining protons, compound 1, 4.2 ppm, H-1, and compound 3, 4.22 ppm, H-2.

The chemical shift difference between the A proton and the BCD envelop of the oxetanes 2 and 3 is attributed to the anisotropy of the oxetane ring. This difference is 25 Hz for compound 2 in deuteriochloroform, increasing to 45 Hz in hexadeuteriobenzene. These differences become 92 and 165 Hz ($\Delta\nu/J$, 8.4 and 15), respectively, at 220 MHz; however, this system is too strongly coupled for the A proton to become first order. The spectra of compounds 2 and 3 were simplified through the addition of the $Eu(fod)_3$ shift reagent.

The shifts of the bridgehead and methylene protons for compounds 1–3 were plotted against the molar ratio of $Eu(fod)_3$ to substrate. These plots gave straight lines, indicating that only one binding site was involved over the concentration range studied. Comparison of the slopes for *H-1* and *H-2* reveals that oxygen-5 does not complex the $Eu(fod)_3$, as expected in view of the steric hindrance of the R groups. Caple,[9] in a study of rigid bicyclic ethers, developed a model for the europium–ether complex in which europium lies in the C–O–C plane 3.0 Å from the oxygen and equidistant from the carbons. The slopes of H-1 and H-4 for the cyclobutane 1 are consistent with this model (refer to A (1 and 2) and B for proton numbering system). However, for the oxetanes 2 and 3, the slopes for H-1 are greater than those for either H-3 or H-4. The binding site for oxetanes 2 and 3 apparently consists of

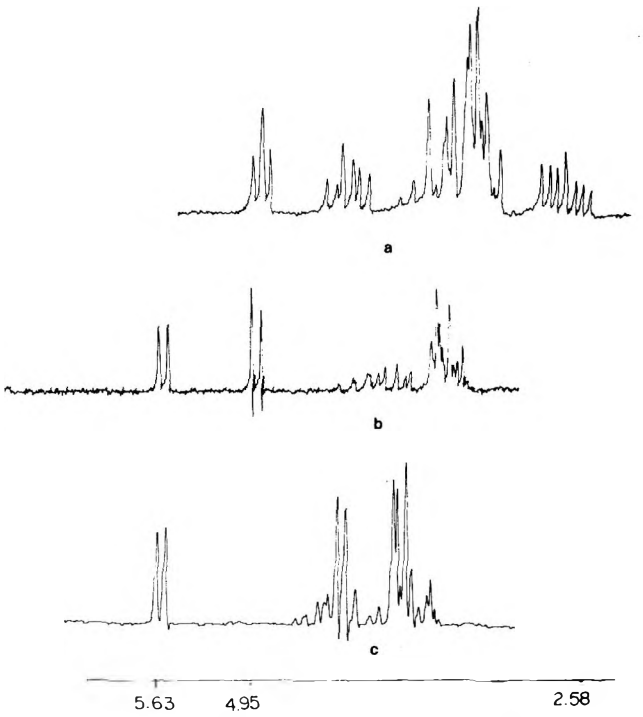
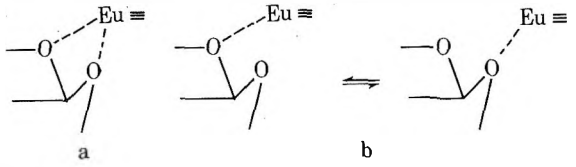



**Figure 1.** Partial 60-MHz nmr spectra: (a) 7,7-diphenyl-2,5-dioxabicyclo[4.2.0]octane (1); (b) 7,7-diphenyl-2,5,8-trioxabicyclo[4.2.0]octane (2); (c) 7,7-dimethyl-2,5,8-trioxabicyclo[4.2.0]octane (3).

oxygen-2 and oxygen-8. While it is impossible from our data to differentiate between a bidentate complex, a, and the time average of two 1:1 complexes, b, a model in which




a b

the europium lies equidistant (3.0 Å) from both oxygens and close to the intersection of the C–O–C planes of the oxetane and dioxane rings is consistent with the data.

As a result of the synthetic method, the ring juncture in the bicyclo[4.2.0]octane systems may be either cis or trans (*vide infra*). A trans ring juncture would lock the six-membered ring into the twist-boat or chair conformers while either boat or chair conformers are possible with a cis juncture.

Examination of Dreiding models of the complexes (*vide supra*) for the various conformations of the bicyclooctanes revealed that a trans ring juncture would require H-2 to have a greater shift than either H-3 or H-4. Since this was not observed in these systems, the trans ring juncture can be excluded. The band widths in the europium simplified, first-order spectra (25 and 16 Hz) demonstrate that the dioxane rings exist in the chair conformation.

In the 60-MHz spectra the BCD envelopes for compounds 1–3 are approximately 25 Hz wide; therefore, the chemical shift differences for these protons are less than 25 Hz. After the addition of $Eu(fod)_3$, these protons are separated by at least 25 Hz in the first-order spectra; therefore, the relative shift orders can be obtained directly. The decreasing proton shift orders follow: cyclobutane 1 (4, 3, 5, 6); diphenyloxetane 2 (3, 4, 5, 6); and dimethyl-*oxetane 3 (5, 3, 4, 6).*

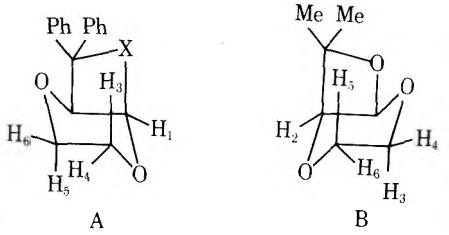
Correlation of these empirical shift orders and the slopes from a least-squares treatment of the chemical shift *vs.* the molar ratio of europium reagent to substrate demonstrates that the cyclobutane 1 and the diphenyloxetane

**Table I**
**NMRIT Refined Coupling Constants for Compounds 1–3**

| Compd | Coupling constants, Hz | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1,2 | 1,7 | 1,8 | 2,7 | 2,8 | 3,4 | 3,5 | 3,6 | 4,5 | 4,6 | 5,6 |
| **1** | 3.66[a] | 7.7[a] | 6.74[a] | 0.0[a] | −3.78[a] | −12.36 | 9.68 | 2.15 | 2.11 | 1.34 | −12.15 |
| **2** | | | | | | −12.39 | 10.85 | 2.36 | 2.41 | 2.34 | −12.08 |
| **2**[b] | 4.0 | | | | | −11.61 | 11.0 | 1.73 | 2.45 | 2.11 | −12.14 |
| **3** | 4.0 | | | | | −11.43 | 11.53 | 2.22 | 2.27 | 0.95 | −12.20 |

[a] Confirmed by spin decoupling, $J_{7,8} = -10.96$ Hz. [b] Calculated for uncomplexed diphenyloxetane **2**.

**2** exist as the frozen chair conformer A and the dimethyloxetane **3** exists as the alternate conformer B.




A B

1, X = $CH_2$
2, X = O

The assumption that Eu(fod)$_3$ will not affect the coupling constants is an accepted practice.[6] However, it was desired to demonstrate this by calculating the spectrum of the diphenyloxetane **2** in the absence of europium reagent. The (NMRIT[8]) refined values of the coupling constants from the europium-shifted spectra of **2** were used as input and the chemical shifts were adjusted by trial and error. The calculation was performed for the 220-MHz spectrum of **2** obtained in deuteriochloroform (Figure 2). The iterated solution approximates the experimental spectrum. The refined and calculated coupling constants are given in Table I.

A difference in the coupling constants obtained for the diphenyloxetane **2** from the europium-shifted spectrum and by calculation is evident in Table I. This deviation between solutions is believed to be a reflection of the precision of the method owing to inaccuracy in determining line positions in the experimental spectra. The main sources of the error are broadening by europium and hidden lines in the 220-MHz spectrum.

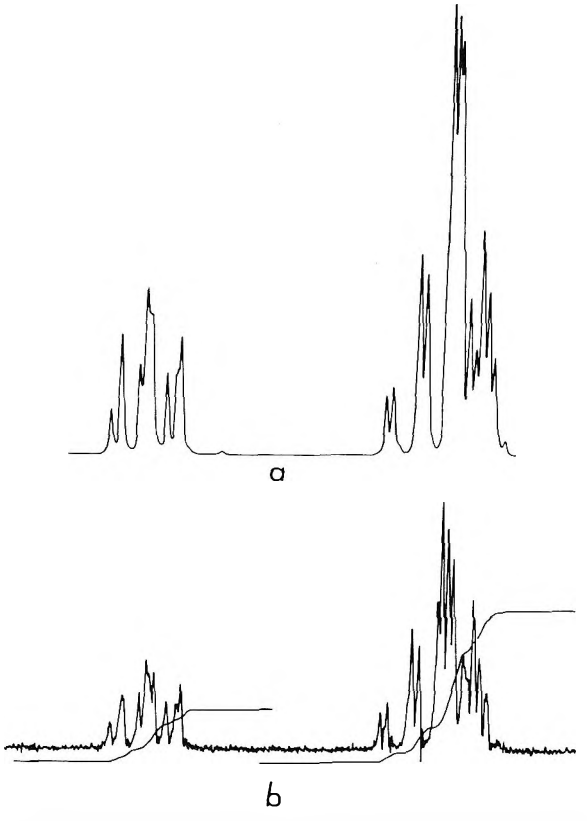



**Figure 2.** Partial 220-MHz nmr of 7,7-diphenyl-2,5,8-trioxabicyclo[4.2.0]octane (**2**): (a) calculated; (b) experimental in $CDCl_3$.

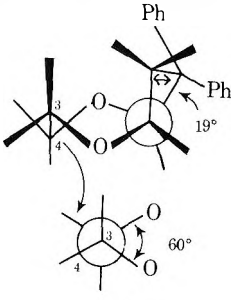
**Table II**
**Calculated Ring Dihedral Angles (O-$CH_2$-$CH_2$-O) for Compounds 1–3 by Buys' *R* Method**

| Compd | *R* | Dihedral angle, deg |
|---|---|---|
| **1**[a] | 2.59 | 60 |
| **2** | 2.79 | 61 |
| **2**[b] | 2.82 | 62 |
| **3** | 2.78 | 61 |

[a] A cyclobutane dihedral angle of 19° was calculated by the Slessor and Tracy method: $\omega = 127.6°$, $K/K' = 0.9$. [b] 220-MHz spectrum of diphenyloxetane **2**.

While the coupling constants calculated for the uncomplexed 220-MHz spectrum and the europium-shifted spectrum of the diphenyloxetane **2** differ by as much as 0.6 Hz for the axial-equatorial coupling constant, the dihedral angles obtained from the Buys *R* method (Table II) differ only by the nominal value of one degree. Therefore, conformational insensitivity to the europium reagent has been confirmed for this system.

The conformation of the cyclobutane **1** is shown by **1a**.




**1a**

The Karplus constant calculated by DAERM for the ring juncture in the cyclobutane is 4.41 Hz. Solution of the Karplus equation using this value gives a dihedral angle of 9.9° for the oxetanes. However, the variation of the Karplus constant with electronegativity and orientation of substituents has been established.[10] This variation is demonstrated in the cyclobutane by a Karplus constant of 4.41 Hz for the $H_1$-C-C-$H_2$ dihedral angle and 8.97 Hz for the $H_1$-C-C-$H_7$ dihedral angle. Since it is impossible to estimate the effect of the oxetane oxygen on the Karplus constant for the $H_1$-C-C-$H_2$ dihedral angle, the value of 9.9°, calculated with a Karplus constant of 4.41 from the cyclobutane, is a qualitative estimate at best. It has been shown that oxetanes have a greater tendency for planarity than cyclobutanes;[11] therefore, the cyclobutane dihedral angle of 19° is probably a reasonable upper limit for the dihedral angle in the oxetanes.

**Stereospecificity.** The photocycloadditions of benzophenone, 1,1-diphenylethylene, and acetone to olefins have been examined.[12-14]

The intermediacy of the triplet state of benzophenone

in the Paterno–Buchii reaction has been established.[12] In addition Servé has shown by quenching experiments that the triplet state of 1,1-diphenylethylene is involved in the formation of 7,7-diphenyl-2-oxabicyclo[4.2.0]octane.[13] However, the expected mixture of cycloadducts with cis and trans ring junctures was not obtained in the present cases.

Turro, *et al.*,[14] have shown that singlet as well as triplet mechanisms may operate in oxetane formation from acetone and enol ethers. Thus, the cis-fused 7,7-dimethyl-2,5,8-trioxabicyclo[4.2.0]octane (3) could be explained by a singlet mechanism. However, the factors which resulted in the isolation of only cis-fused 6:4 ring systems, by an apparent triplet mechanism, are not clear. Examination of the crude reaction mixtures did not reveal the presence of additional isomers.

**Summary.** The bicyclooctanes 1–3 have been shown to be amenable to europium shift reagent simplification and the coupling constants have been calculated by the programs NMRIT and NMREN1.[8] The presence of the phenyl substituent in the 7 positions of 1 provides sufficient steric hindrance to cause preferential complexation with the oxygen in the 2 position.

The anticipated distortion[15a] of the six-membered ring in a cis-fused 6:4 system is demonstrated by an $R$ value range of 2.6–2.8, whereas a trans-fused ring would be expected to have $R$ values less than 2.20.[15b]

Lambert's and Buys' methods have been applied to fused 6:4 ring systems[16] and in conjunction with $Eu(fod)_3$ shift data demonstrate the absolute conformation of these bicyclooctanes.

## Experimental Section

**General.** Photolyses were conducted in an immersion well reactor with a 450-W Hanovia medium-pressure mercury lamp fitted with a Pyrex filter sleeve and in a Srinivasan-Griffin reactor. The reactions were run with a nitrogen sweep. The nitrogen was bubbled through a vanadyl sulfate solution to remove oxygen.[17]

The nmr spectra were determined on Varian Associates A-60, HA-100, and HR-220 MHz spectrometers. The spectra were determined in deuteriochloroform or hexadeuteriobenzene with tetramethylsilane as an internal standard. Infrared spectra were determined with a Perkin-Elmer 337 grating infrared spectrometer on chloroform solutions or KBr disks. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Micro-Analysis, Inc., Wilmington, Del. All melting points are uncorrected. $Eu(fod)_3$ was purified by sublimation and transfers were made in a nitrogen atmosphere. The theoretical calculations were performed on IBM 370-165 and IBM 360-70 computers.

**Synthesis of 7,7-Diphenyl-2,5-dioxabicyclo[4.2.0]octane (1).** Dioxene (1.025 g, 0.012 mol) and 1,1-diphenylethylene (2.115 g, 0.012 mol) were dissolved in 50 ml of thiophene-free benzene and irradiated at 3000 Å in a Srinivasan-Griffin reactor for 69.5 hr. The solvent was removed under vacuum on a rotary evaporator and the residue was chromatographed on a 20 × 3 cm column containing 20 g of silica gel. The column was eluted with 50 ml of low-boiling petroleum ether–benzene (3:1), 50 ml of benzene, and 50 ml of benzene–chloroform (3:1) to yield a tacky white solid which sublimed at 80° (0.1 mm), giving 0.3 g (10% yield) of 1: mp 83.5–84.5°; ir (KBr) 3048, 3030, 2985, 2959, 2907, 2849, 1594, 1490, 1447, 1389, 1370, 1284, 1250, 1235, 1163, 1149, 1136, 1093, 1070, 1001, 943, 893, 774, 876, 844, 704, 650, and 617 $cm^{-1}$.

*Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77; mol wt, 254. Found: C, 81.29; H, 6.93; mol wt, 256 (benzene).

**Synthesis of 7,7-Diphenyl-2,5,8-trioxabicyclo[4.2.0]octane (2).** Dioxene (3.174 g, 0.037 mol) and benzophenone (6.67 g, 0.037 mol) were dissolved in 600 ml of thiophene-free benzene. The solution was irradiated in a Hanovia immersion well photoreactor fitted with condenser and nitrogen sweep for 34 hr (92% consumption of dioxene by glc). The solvent was removed under vacuum on a rotary evaporator, yielding 7.443 g (82%) of 2 as white crystals. The solid was recrystallized from chloroform and then from ethyl acetate: mp 145–146°; ir (KBr) 3049, 3030, 2985, 1594, 1488, 1447, 1399, 1379, 1294, 1269, 1235, 1160, 1087, 1044, 1001, 928, 870, 793, 769, 749, 723, 707, 694, 658, and 641 $cm^{-1}$.

*Anal.* Calcd for $C_{17}H_{16}O_3$: C, 76.12; H, 6.01. Found: 76.05; H, 6.12.

**Synthesis of 7,7-Dimethyl-2,5,8-trioxabicyclo[4.2.0]octane (3).** A solution of dioxene (2.12 g, 0.25 mol) in 600 ml of reagent-grade acetone was placed in the immersion well photoreactor fitted with a condenser and nitrogen sweep. The mixture was irradiated for 5 days. The acetone was removed under vacuum on a rotary evaporator and the product was distilled to give a clear, colorless liquid which solidified in the receiver: bp 44° (1.0 mm); yield 2.36 g (66%); ir ($CHCl_3$) 2985, 2963, 2933, 2874, 1455, 1404, 1381, 1368, 1297, 1282, 1259, 1223, 1170, 1146, 1108, 1042, 995, 976, 946, 926, 909, 879, and 844 $cm^{-1}$.

*Anal.* Calcd for $C_7H_{12}O_3$: C, 58.33; H, 8.33; O, 33.33. Found: C, 57.96; H, 8.27; O, 33.31.

**Acknowledgment.** We wish to thank Dr. Kermit C. Ramey of the Atlantic Richfield Co. for his helpful discussions and the 100-MHz work. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

**Registry No.**—1, 51175-63-4; 2, 51175-64-5; 3, 51175-65-6; dioxene, 543-75-9; 1,1-diphenylethylene, 530-40-3; benzophenone, 119-61-9; acetone, 67-64-1.

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# Chiroptical Properties of Cyclic Esters and Ketals Derived from (*S*)-1,2-Propylene Glycol and (*S,S*)- and (*R,R*)-2,3-Butylene Glycol

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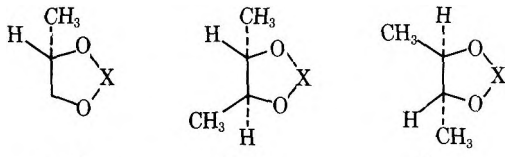
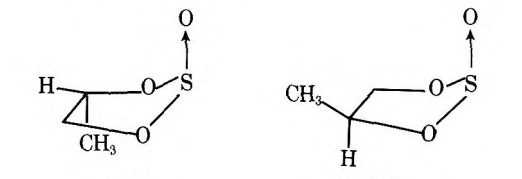
The optically pure five-membered ring thionocarbonates (**1a–3a**), carbonates (**1b–3b**), sulfites (*cis*- and *trans*-**1c, 2c, 3c**), phosphite (**2d**), and 2-bromo- and 2-chloromethyl-1,3-dioxolanes (*cis*- and *trans*-**1e, 2e, 2f**) were prepared from the three title diols by standard methods and their uv and CD spectra were measured in various solvents over the range 185–400 mμ at room temperature. The CD spectra of **1a–3a** display two well-defined Cotton effects of opposite signs and of diverse intensities centered at 222–235 and 325 mμ, related to the uv $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively. The sign of the long-wavelength Cotton effect is associated with the chirality of the heterocycle ring. A positive ellipticity for the $n \rightarrow \pi^*$ transition is assigned to thionocarbonates of *R* configuration, and vice versa, a negative one for the *S* series. Cyclic carbonates do not show CD maxima above 185 mμ; the curves of dichroic absorption for the *R* and *S* forms are antipodal and their signs correlate with those of the long-wavelength Cotton effect of the corresponding thionocarbonates. The condensation of (*S*)-1,2-propylene glycol with thionyl chloride gave rise to the expected isomers of opposite rotations, assigned the *cis*- and *trans*-**1c** structures, exhibiting similar dichroic bands centered at 212–225 and 195–200 mμ. The complex chiroptical properties of **1c–3c** and **2d** are discussed in terms of ring conformation and asymmetric solvation of the chromophore. The condensation of (*S*)-1,2-propylene glycol with bromoacetaldehyde again led to the expected cis and trans isomers. The dichroic curves of the geometric isomers and of **2e** do not correspond to those of the uv spectra. A CD study of the title glycols is herein included.

There is considerable interest in the application of chiroptical methods of configurational assignments in chiral alcohols and polyols.[1] The uv absorption of an oxy chromophore at a saturated carbon occurs below 200 mμ, and thus it is not expected to observe maxima in their CD spectra in this region. This was borne out in the cases of optically active acetals, ethers, and alcohols.[1a,2] However, recently[1b] it has been demonstrated that some secondary and tertiary alcohols show well-defined Cotton effects in the region of 185–192 mμ. It is worthy of note that the production of CD and ORD data of saturated oxy compounds is more readily obtained *via* derivatization of these compounds to form new chromophores such as carboxyl,[3] thionocarbonate,[4,5] and mono- and dioxycarbonylbenzenes,[6] and also by complex formation.[7]

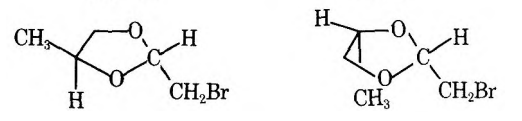
Following our concern in structural effects on reactivity in organic carbonates[8] and sulfites,[9,10] we became interested in exploring the possibility of deduction of stereochemistry in optically active diols by chiroptical methods. We thought that this goal could successfully be obtained if the oxy chromophore is part of a cyclic ester, such as thionocarbonate, carbonate, sulfite, and phosphite, or of a dioxolane system. For this purpose we converted the optically pure forms of the three known compounds (*S*)-(+)-1,2-propylene glycol (**1**), (*S,S*)-(−)-2,3-butylene glycol (**2**), and (*R,R*)-(+)-2,3-butylene glycol (**3**) into their corresponding optically pure five-membered ring thionocarbonates (**1a–3a**), carbonates (**1b–3b**), sulfites (*cis*- and *trans*-**1c, 2c,** and **3c**), phosphite (**2d**), 2-bromomethyl-1,3-dioxolanes (*cis*- and *trans*-**1e, 2e**), and a 2-chloromethyl-1,3-dioxolane (**2f**), and measured their circular dichroism spectra in various solvents.



**1a, 1b** **2a–f** **3a–c**

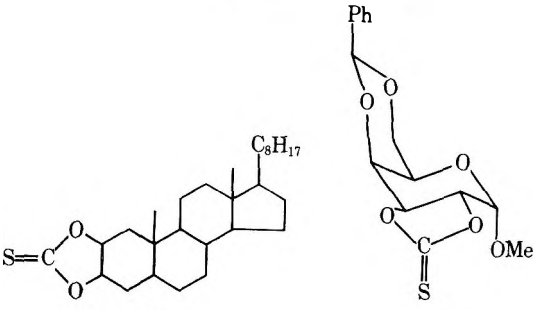


*trans*-**1c** *cis*-**1c**



*trans*-**1e** *cis*-**1e**

**a**, X = CS; **b**, X = CO; **c**, X = SO; **d**; X = $POCH_3$; **e**, X = $CHCH_2Br$; **f**, X = $CHCH_2Cl$



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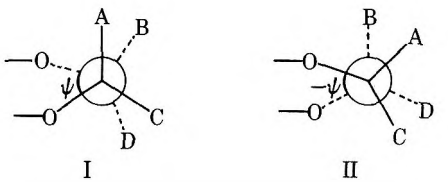


I II

## Results and Discussion

**Cyclic Thionocarbonates and Carbonates.** Chiral cyclic thionocarbonates[4,5] have been reported to exhibit one $n \rightarrow \pi^*$ and one $\pi \rightarrow \pi^*$ dichroic band. The signs of the Cotton effects associated with these bands were related to the chirality of the ring. For the $n \rightarrow \pi^*$ transition it was shown, using rigid systems, that conformation I causes a positive Cotton effect, while conformation II exhibits a negative one.

In flexible systems, where conformational equilibrium between two limiting conformations resembling the above given I and II exists, a decrease in the absolute value of

**Table I**
**Spectral Properties of Cyclic Thionocarbonates**

| Compd | Solvent | n → π* λmax, mμ | n → π* Δε | n → π* $10^{40}R^a$ | π → π* λmax, mμ | π → π* Δε | π → π* $10^{40}R^a$ |
|---|---|---|---|---|---|---|---|
| **1a** | Hexane | 325 | −0.047 | −0.12 | 222 | +0.83 | +2.56 |
| **2a** | Hexane | 325 | −0.73 | −2.75 | 235 | +3.13 | +10.06 |
| | Dioxane[b] | 315 | −1.21 | | 240 | +3.33 | |
| | Methanol | 307 | −0.55 | | | | |
| **3a** | Hexane | 324 | +0.75 | +2.46 | 235 | −3.33 | −8.86 |
| **4**[c] | Dioxane | 315 | +2.3 | +6.1 | 238 | −14.12 | |
| **5**[c] | Dioxane | 323 | +2.8 | +7.6 | | | |

[a] $R$ in cgs units. [b] In ref 5; $\lambda_{max}$ = 313 mμ; Δε = −0.8. [c] Reference 4.

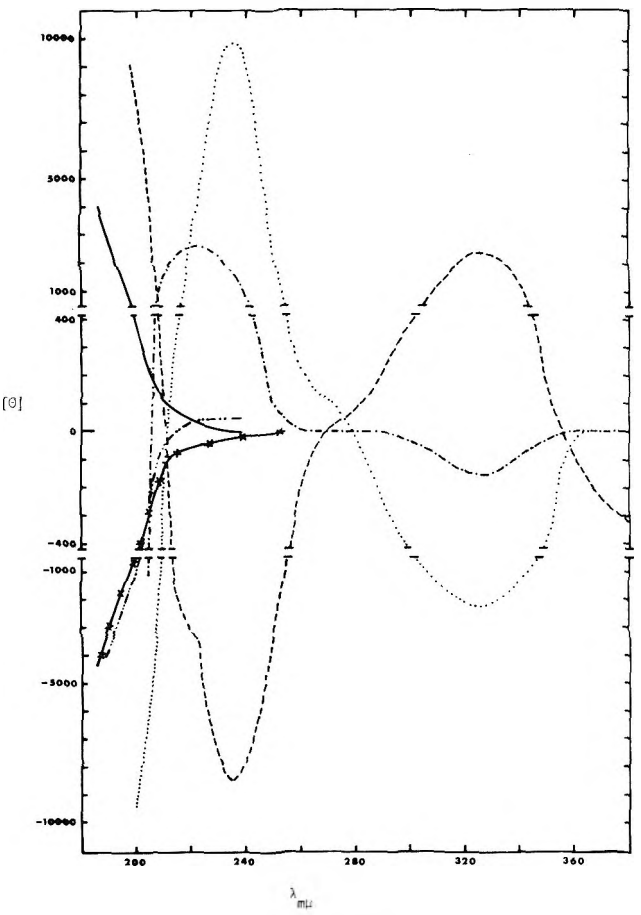



**Figure 1.** CD curves of (a) (*S*)-methylethylene thionocarbonate (**1a**) (-·-·-); (b) (*S,S*)-1,2-dimethylethylene thionocarbonate (**2a**) (····); (c) (*R,R*)-1,2-dimethylethylene thionocarbonate (**3a**) (----); (d) (*S*)-methylethylene carbonate (**1b**) (-·····); (e) (*S,S*)-1,2-dimethylethylene carbonate (**2b**) (x-x-x); (f) (*R,R*)-1,2-dimethylethylene carbonate (**3b**) (——) in hexane.

the rotational strength $R$ and in Δε would be expected compared to rigid systems. Thus, the pseudorotation of the five-membered ring thionocarbonates should decrease the chiroptical properties of both the n → π* and the π → π transitions. The low rotational strength observed in compounds **2a** and **3a** (see Figure 1 and Table I) is in accordance with this assumption when compared to the $R$ and Δε values reported by Haines and Jenkins[4] for the two puckered five-membered ring thionocarbonates 5α-cholestane-2β,3β-diol thionocarbonate (**4**) and 4,6-*O*-benzylidene-α-D-galactopyranoside 2,3-thionocarbonate (**5**).

In spite of pseudorotation, substitution on the ring carbons undoubtedly causes the cyclic thionocarbonates to attain a preferred conformation. For both **2a** and **3a** the anti form seems more stable than the gauche one; *i.e.*, conformation II (B = C = Me; A = D = H) should be more populated in the case of **2a** and I (A = D = Me; B = C = H) in the case of **3a**. This implies a negative Cotton effect in **2a**, and a positive one in **3a**.

**Table II**
**Coupling Constants and Calculated Dihedral Angles of Cyclic Carbonates**

| Cyclic carbonate | $J_{H-H}$ (cis) | $J_{H-H}$ (trans) | ψ, deg |
|---|---|---|---|
| Ethylene[a] | 8.9 | 7.4 | 18.5 |
| 1-Methylethylene[b] | 7.6 | 7.1 | 28.8 |
| 1-Phenylethylene[c] | 8.07 | 7.78 | 25.4 |
| *trans*-2,3-Dimethylethylene[d] | | 7.2 | 31.5 |
| *cis*-2,3-Dimethylethylene[d] | 7.35 | | 30.5 |

[a] Reference 14. [b] Reference 8. [c] Reference 15. [d] Reference 16; the methyls were assumed to be in an axial conformation and therefore the constant for $J_{H-H}$ (cis) was used in the calculation.

Compound **1a** shows an even greater decrease in the $R$ and Δε values than that shown by **2a** and **3a**. However, unlike the latter, in **1a** the chiroptical properties of the n → π* transition and those of the π → π* transition are unevenly affected. This will be explained later in the discussion.

Because of the flexibility of five-membered rings, conformational assignments based on nmr analysis in such systems should be taken with care. However, valuable information concerning conformational preference or time-averaged conformation of five-membered ring cyclic phosphites, dioxolanes, and dithiolanes has been obtained by nmr measurements.[11-13] It seems that even if absolute values of the dihedral angle, ψ, of five-membered ring carbonates cannot be calculated from the Karplus equation, using Haake's parameters[12] and nmr coupling constants, the influence of substituents on ψ could nevertheless be estimated by this method. The results obtained for some carbonates are presented in Table II. Calculation of the dihedral angles of the same cyclic carbonates by another method based on the $R$ values[17] shows a degree of skewness higher by at least 10°, but the influence of the substituents on ψ is similar to that observed in Table II. X-Ray analysis of ethylene carbonate in the solid state[18] gave a value of 26.2° for the dihedral angle ψ, which is also higher than the value appearing in Table II. The results represented in Table II indicate only a small change in the puckering of 1-methylethylene carbonate compared to that of *trans*-2,3-dimethylethylene carbonate. The torsional angles of the analogous thionocarbonates **1a** and **2a** are similarly assumed to differ from each other to a small extent only, *i.e.*, by ~3°. This shows that the difference in the chiroptical properties between the monosubstituted thionocarbonate **1a** and the disubstituted thionocarbonates **2a** and **3a** could not originate from differences in their conformation alone. It seems that the low intensity of the dichroic band of **1a** results also from the low chirality of the chromophore in this molecule which contains only one asymmetric carbon. While differences in the degree of puckering should affect the intensity of the CD n → π* and π → π* transitions to the same extent, the number of asymmetric centers should influence each transition in a different manner.

**Table III**
**Spectral Properties of Five-Membered Ring Sulfites**

| Compd | Solvent | $\lambda_{max}$, mμ | ε | $\lambda_{max}$, mμ | $10^2\ \Delta\epsilon$ | $\lambda_{max}$, mμ | $10^2\ \Delta\epsilon$ |
|---|---|---|---|---|---|---|---|
| *cis*-**1c** | Hexane | 215 | 300 | 217.5 | +6.1 | 197.5 | −130.3 |
| | Isooctane | 216 | 296 | 217.5 | +5.5 | 197.5 | −130.3 |
| | | 217[a] | 122[a] | | | | |
| | Acetonitrile | 217 | 182 | 212 | +12.1 | 192 | −125.0 |
| | Ethanol | 217 | 77 | 212 | +9.1 | | |
| *trans*-**1c** | Hexane | 218 | 114 | 226 | +1.5 | | |
| | Isooctane | 218 | 112 | 225 | +1.4 | 197 | −121.2 |
| | | 216[a] | 49[a] | | | | |
| | Acetonitrile | 216 | 83 | 222 | +1.3 | 195 | −112.4 |
| | Ethanol | 218 | 61 | 222 | +1.2 | | |
| **2c** | Hexane | 214 | 240 | 225 | −2.4 | 198 | +266.6 |
| | | | | 220[a] | −3.2[a] | 195[a] | +236.3[a] |
| | Isooctane | 214 | 238 | 223 | −2.6 | 198 | +263.6 |
| | | 214[a] | 58[a] | 221[a] | −3.8[a] | 193[a] | +245.4[a] |
| | Acetonitrile | 213 | 177 | 217 | −2.6 | 197 | +242.4 |
| | | 214[a] | 124[a] | 220[a] | −2.6[a] | 195[a] | +236.3[a] |
| | Ethanol | 213 | 137 | 222 | −2.6 | | |
| | | 215[a] | 67[a] | | | | |
| **3c** | Hexane | 214 | 240 | 225 | +2.5 | 197.5 | −303.7 |

[a] Data obtained for samples containing 3 μl of TFA.

Addition of 5 μl of TFA to **3a** in 3 ml of hexane causes a decrease of the $\Delta\epsilon$ values of both transitions by a factor of 1.8. This could suggest that the main effect of TFA is not a consequence of its asymmetrical solvation of the chromophore, but probably results from its influence on the equilibrium of the conformers in solution.

The cyclic five-membered ring carbonates **1b** and **2b** show uv absorption in hexane at 215 mμ with molar extinction coefficients of 5 and 8, respectively. A shift in $\lambda_{max}$ to 207 mμ is observed in ethanol. This is in accord with the calculation of Pople[19] for the n → π* transition of carbonic acid.

The CD curves of **1b**, **2b**, and **3b** (Figure 1) show no maxima at 215 mμ. However, an absorption is observed up to 185 mμ for the three compounds which could be attributed to an n → σ* transition. An n → π* dichroic band is perhaps submerged in this absorption. Thionocarbonates show in addition to the two CD absorptions mentioned earlier another absorption below 200 mμ (see Figure 1) which presumably corresponds to an n → σ* transition. The sign of the Cotton effect in this region is identical with that of the n → π* transition of the same molecule. As the short-wavelength CD absorption of the thionocarbonates and that of carbonates have the same sign for a given chirality, it seems that the same effects influence the chiroptical properties of the electronic transitions in both cyclic thionocarbonates and cyclic carbonates.

**Cyclic Sulfites.** We deemed it of interest to compare the uv spectra of the sulfites **1c**, **2c**, and **3c** with those of saturated dialkyl sulfoxides and sulfinates. Unlike the sulfoxides, which exhibit two absorption bands, a shoulder at 210–220 mμ and a maximum below 210 mμ (ethanol),[20,21] the cyclic sulfites show only one maximum at 213–218 mμ (see Table III). The short-wavelength absorption band in sulfoxides, attributed to an n → π* transition, exhibits a blue shift with increasing polarity of the solvent,[20] and the molar extinction coefficients (ε) are much larger than those in cyclic sulfites. It seems that the electronic transition of the cyclic sulfites resembles more the long-wavelength absorption band of dialkyl sulfoxides, which is characterized by a low ε and is less sensitive to solvent effects. Dialkyl sulfinates, like cyclic sulfites, show only one maximum (at 215 mμ, in ethanol), but in contrast to cyclic sulfites this transition is sensitive to a solvent effect.[20]

In dissymmetric dialkyl sulfoxides only the Cotton effect at long wavelength was assumed to be associated with the dissymmetric alkyl group, while the short-wavelength band is attributed to the chirality of the sulfur atom.[22] In contrast, in cyclic sulfites both transitions seem to be associated with the asymmetric perturbation of the chromophores caused by the chiral alkyl moiety of the ring. This is indicated by the CD curves of **2c** and **3c** (Figure 2). When S→O becomes a chiral center, as in *cis*- and *trans*-**1c**, an essential change in the CD spectra is observed. The two **1c** isomers, although identical with **2c** in the alkyl moiety configuration, differ from **2c** in their chiroptical

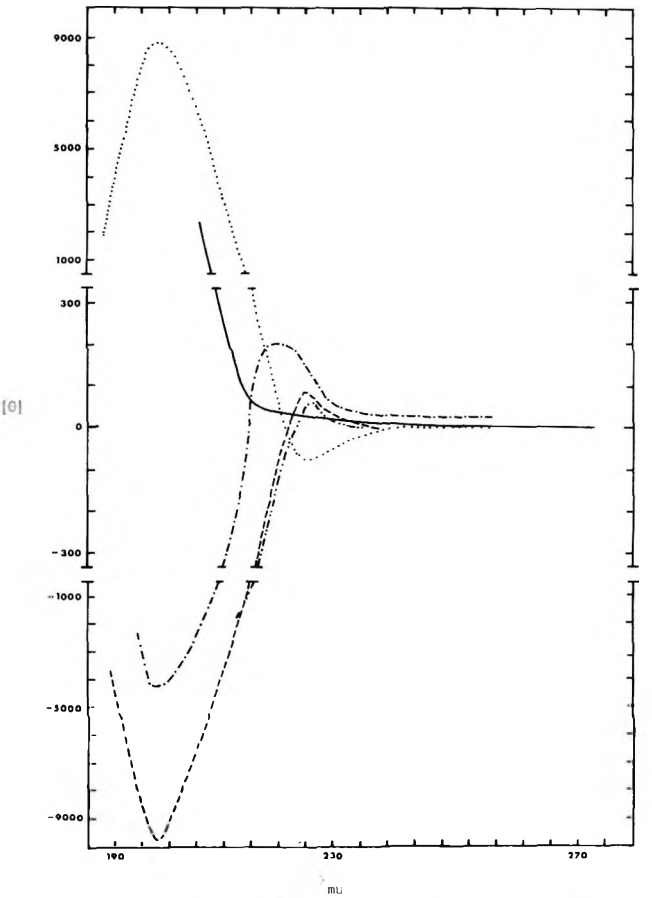



**Figure 2.** CD curves of (a) *cis*-(*S*)-methylethylene sulfite (*cis*-**1c**) (- · - · -); (b) *trans*-(*S*)-methylethylene sulfite (*trans*-**1c**) (- · · - · · -); (c) (*S,S*)-1,2-dimethylethylene sulfite (**2c**) (·····); (d) (*R,R*)-1,2-dimethylethylene sulfite (**3c**) (----); (e) (*S,S*)-1,2-dimethylethylene methyl phosphite (**2d**) (——) in benzene.

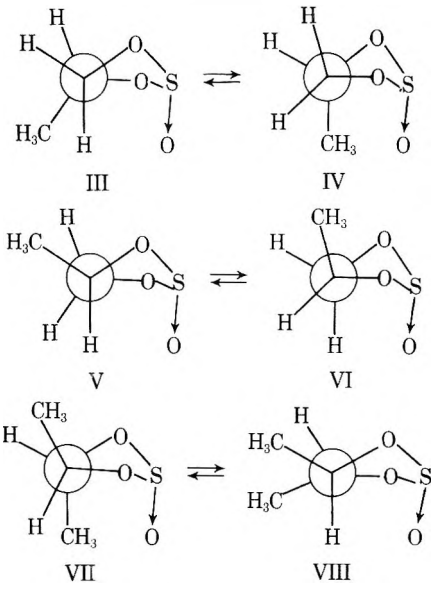
properties. Also, in contrast to **2c** and **3c**, *trans*-**1c** and *cis*-**1c** do not exhibit an antipodal relationship. This is not surprising, as the two are in fact diastereoisomers: they possess the same dissymmetric alkyl moiety but differ from each other by the S→O configuration, which is *S* in *trans*-**1c** and *R* in *cis*-**1c**. Even so, none of the CD bands of one compound is antipodal to the respective band in the spectrum of the other compound. Comparison of the two spectra shows that the effect of the asymmetric center at the sulfur atom is reflected mainly in the long-wavelength band of the CD spectra. In this region the spectra of the two diastereoisomers differ from each other in $\lambda_{max}$ as well as intensity, the cis isomer showing the dichroic band of shorter wavelength and higher intensity, yet the sign of the Cotton effect is positive in both. As in other ring systems[5,23-25] the chirality of the ring may be the factor determining the sign of the Cotton effect in cyclic sulfites. In the **1c** isomers the change in the configuration at the sulfur atom may bring about conformational changes in the molecules, from which a correlation between the conformation of the cyclic sulfites and the signs of Cotton effects displayed by them could result. This would be in analogy to cyclic and open-chain sulfoxides,[22,26] where restriction in rotation around the C–S bond and spatial interaction of the chromophore with the surrounding alkyl groups influence the Cotton effect.

Nmr analysis of ethylene sulfite[12] and sultones[27] has shown that these rings are not planar. Recently it was suggested by Green and Hellier, on the basis of nmr and ir analysis, that in ethylene sulfite as well as in other five-membered ring sulfites the S→O bond is axially orientated to the ring.[28] This is in analogy to six-membered ring sulfites, such as trimethylene[29] and 4-methyltrimethylene sulfite,[9] where the preference of rigid chair conformation with axial S→O orientation is clearly demonstrated. Average cis and trans vicinal coupling constants obtained for the five-membered ring sulfites[28] could indicate that the substituents on the two ring carbons are not eclipsed. On this basis and in analogy to five-membered ring phosphites, which are believed to exist in a twist-envelope conformation,[11,12] it can be assumed that the preferred conformation for **1c**, **2c**, and **3c** is the twist-envelope with S→O axial.

Since in the synthesis of **1c** the cis and trans isomers are obtained in a 1:2 mixture, it is clear that the two differ greatly in the steric interaction between the methyl and S→O groups. Therefore, it is expected that each of the isomers will attain different twist-envelope forms. In the case of *cis*-**1c** it seems that as a result of strain due to $CH_3 \cdots S \rightarrow O$ interaction, conformation IV is of higher energy than conformation III (Scheme I). If the chirality of the five-membered ring is defined as positive in conformation III and negative in IV, then *cis*-**1c** should exhibit a positive Cotton effect. In *trans*-**1c** similar steric interactions should considerably be diminished and therefore almost equal population of conformers of structures V and VI is to be expected. The observed small positive Cotton effect in this case suggests a slight preference of conformation V over VI. Looking at models reveals that the nonbonded interaction between the sulfur atom and the methyl group is greater in VI than in V.[30]

Compound **2c** can be described by the two limiting twist-envelope conformations VII and VIII. In the latter there is an increase in energy due to the gauche form, while in VII there exists nonbonded interaction between methyl and S→O groups. However, since nonbonded interaction is strongly dependent on the distance between the interacting groups, the energy would be lowered if the molecule attained a less puckered form with the S→O group farther removed from the methyl group. Thus conformation VII seems to be the more populated form of **2c**. Since the sign of the dihedral angle of VII is opposite to that of the dihedral angle of III and V, the CD absorption bands of **2c** are expected to be of opposite signs to those of the **1c** isomers, as found experimentally.

Scheme I




On the basis of conformational equilibrium it seems reasonable that increasing solvent polarity should lead to an increase in the intensity of the long-wavelength dichroic band in *cis*-**1c**, since owing to solvation of the chromophore there is a stronger nonbonded interaction between the S→O and the methyl group, and the dihedral angle is increased. This is indeed observed. In *trans*-**1c** no solvent effect is observed, since steric hindrance even in the solvated molecule is very small.

The effect of solvent in **2c** is not clear. No effect is observed on increasing solvent polarity, while addition of TFA causes an increase in the negative absorbance of the long-wavelength band and a small decrease in the dichroic band at short wavelength. A very small decrease in the absorbance at short wavelength is observed also in *cis*- and *trans*-**1c** on increasing the solvent polarity. It seems that the solvent effect in cyclic sulfites can be attributed not only to conformational changes but also to an asymmetric solvation of the chromophore which affects the two dichroic bands differently.

It is important to note that cyclic sulfites are highly associated in solution.[31] However, neither in a concentration range of $3.5\text{–}35 \times 10^{-3}$ *M* (*n*-hexane), used for measuring the long-wavelength band, nor in a concentration range of $6\text{–}17 \times 10^{-4}$ *M*, used for the short-wavelength band, could any significant changes in the CD spectra be observed on changing the sulfite concentration.

The phosphite **2d** exhibits a Cotton effect in the short-wavelength range of the same sign as that of the respective cyclic sulfite, **2c**. No absorption was found in the long-wavelength region.

**Diols and Dioxolanes.** Kirk, Mose, and Scopes have lately demonstrated the existence of well-defined Cotton effects in a long series of secondary and tertiary steroidal and terpene alcohols in the region 185–203 mμ.[1b] The ellipticity values ($\Delta\epsilon$) of these alcohols vary remarkably, from 0.12 in 3α-hydroxy-5α-cholestane up to 4.19 in the case of 5α,17β*H*-pregnan-20β-ol. The situation differs, however, when the oxy chromophore is attached to the side chain carbon 20, in which case the epimeric diols

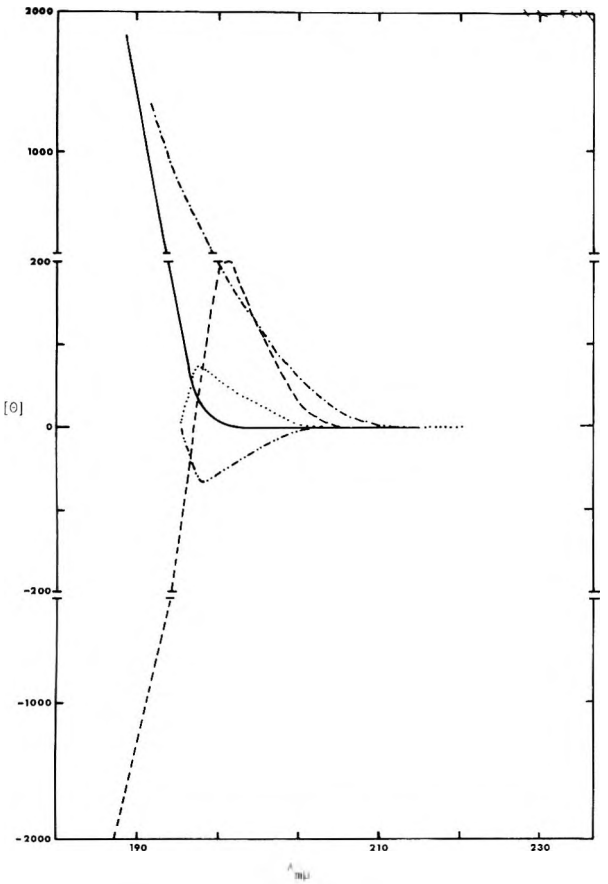



**Figure 3.** CD curves of (a) (−)-(*S,S*)-2,3-butylene glycol (**2**) (····); (b) (+)-(*R,R*)-2,3-butylene glycol (**3**) (-·-·-·); (c) *trans*-(−)-(*S*)-2-bromomethyl-4-methyl-1,3-dioxolane (*trans*-**1e**) (————); (d) *cis*-(−)-(*S*)-2-bromomethyl-4-methyl-1,3-dioxolane (*cis*-**1e**) (-·-·-); (e) (−)-(*S,S*)-2-bromomethyl-4,5-dimethyl-1,3-dioxolane (**2e**) (-----) in hexane.

(20*R*)- and (20*S*),24-dihydroxycholane display at 190–200 mμ only "end absorptions" of negative and positive signs, respectively.[32] By variance, the corresponding cyclic ethers, (20*R*)- and (20*S*),24-oxidocholane, exhibit well-defined Cotton effects of opposite signs in the 195–200-mμ region. The Δε values of these ethers vary significantly from −0.085 in the 20*R* case to +0.291 in the case of (20*S*),24-oxidocholanes.[33]

In the saturated diols **1–3** we observed Cotton effects in the region of 198 mμ only in the cases of **2** and **3** and none in the case of **1**. Moreover, in contrast to the steroidal monofunctional alcohols the Δε values found for **2** and **3** were notably low (0.022).

On the basis of prevailing views, the above variances could be explained in terms of conformational effects. Thus, the preferred conformation for both **2** and **3** is most likely with the methyls anti, the dihedral angle between the two oxy groups in **2** would assume an opposite sign to that of **3**, and they should obviously give rise to antipodal CD curves, as is the case. In analogy to (*R*)-phenylethylene glycol,[34] the lack of Cotton effect in **1** could reasonably be attributed to a near to zero value of the dihedral angle between the oxygen atoms owing to hydrogen bonding. In diols **2** and **3**, by contrast, a small but significant dihedral angle does exist owing to torsional effects stemming from Me···Me interactions.

The uv curves of the bromodioxolanes *cis*-**1e**, *trans*-**1e**, and **2e** in hexane show maxima at 220–235 mμ with normal absorption coefficients of 47–105. The appearance of the uv maximum in the chlorodioxolane **2f** at 212.5 mμ (ε 38) is in line with maxima shown by halogenoalkanes in which the n → σ* transition of the chlorine chromophore occurs at a lower wavelength than that of bromine.[35] The bathochromic shift in the uv absorption of the dioxolanes compared to that of alkyl halides[35] can be explained in terms of electronic or dipole–dipole interactions between the halogen and the ring oxygen atoms.

The dichroic curves of *cis*-**1e**, *trans*-**1e**, and **2e** (Figure 3) do not correspond to those of the uv spectra. Thus, **2e** exhibits a positive Cotton effect at 203 mμ (Δε 0.06) and an absorption of opposite sign at lower wavelength. Significantly, both *cis*- and *trans*-**1e** display only such an absorption, of positive sign. The cis isomer, however, shows the beginning of a positive Cotton effect below 220 mμ, while in *trans*-**1e** there is no absorption above 200 mμ. The absorption in *cis*-**1e** could be related to two positive superimposed Cotton effects. This then implies that (a) the long-wavelength absorption is not due to an additional asymmetric center in the dioxolane ring (at position 2 in the monomethyl dioxolanes); and (b) the dichroic band at longer wavelength originates from an n → σ* transition of the halogen.

The differences in the CD spectra of *cis*-**1e**, *trans*-**1e**, and **2e** could also be explained by different preferred conformations of these compounds *per se*, or by a different net overlap of the nonbonding 2p orbitals of oxygen resulting from conformational changes.[36] The nmr chemical shift data of these compounds are, however, very similar and do not allow any conclusion concerning differences in conformation.

The chiral five-membered ring sulfites and dioxolane systems included in this study display significant variations in their dichroic properties when an asymmetric center other than those of the diol residue is introduced into the molecule. In sulfites these differences are pronounced both in the shorter and in the longer wavelengths, whereas in the case of the dioxolanes they are noticed in the short wavelengths only.

## Experimental Section

The optically active 1,2-glycols used were (+)-(*S*)-1,2-propylene glycol (Aldrich), (−)-(*S,S*)-2,3-butylene glycol (Burdick and Jackson), and (+)-(*R,R*)-2,3-butylene glycol prepared from dibutyl L-tartrate according to literature procedures, by way of 2,3-*O*-isopropylidene-L-threitol 1,4-bis(methanesulfonate)[37] and subsequent reduction and hydrolysis.[38]

Ir spectra were recorded on a Perkin-Elmer Model 237 spectrometer, uv spectra on a Unicam Model Sp 800 A spectrometer, nmr spectra on a JEOL C-60-H spectrometer, and mass spectra on a Varian MAT CH-5 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter and CD spectra with a Cary 60 recording spectropolarimeter.

**Thionocarbonates.** The thionocarbonates were prepared according to the method of Staab and Walther.[39] To a solution of *N,N*-thiocarbonyldiimidazole (10–13 mmol) in toluene (10 ml) an equimolar amount of the glycol was added, and the reaction mixture was refluxed under nitrogen for 2 hr. The solvent was partially evaporated and the product was separated from the reaction mixture and purified by preparative vpc (2 ft × 0.25 in. 10% SE-30 column).

**(*S*)-Methylethylene thionocarbonate (1a)** was a colorless liquid: retention time 4.5 min on the above-mentioned column at 110° (gas flow rate 40 ml/min); $n^{22}$D 1.520; $\nu_{max}$ 1250 (C=S) and 1400 cm$^{-1}$; $\lambda_{max}$ (hexane) 235 mμ (ε 6150) and 315 (54); nmr ($CCl_4$) δ 1.5 (3 H, d, $J$ = 6 Hz, $CH_3$), 4.18 and 4.66 (2 H, dd, dd, $CH_2$), 5.0 ppm (1 H, m, CH); mass spectrum M$^+$ 118.

*Anal.* Calcd for $C_4H_6O_2S$: C, 40.68; H, 5.085; S, 27.12. Found: C, 40.50; H, 5.06; S, 27.20.

**(*S,S*)-1,2-Dimethylethylene thionocarbonate (2a)**[5] was a colorless liquid: retention time 5 min on the above-mentioned column at 120° (gas flow rate 45 ml/min); $n^{22}$D 1.512; $\nu_{max}$ 1250 and 1400 cm$^{-1}$; $\lambda_{max}$ (hexane) 230 mμ (ε 6000) and 325 (20); nmr ($CCl_4$) δ 1.5 (6 H, d, $J$ = 6 Hz, $CH_3$), 4.50 ppm (2 H, m, CH); mass spectrum M$^+$ 132.

**(*R,R*)-1,2-Dimethylethylene thionocarbonate (3a)** had vpc, ir, nmr, and mass spectral data identical with those of **2a**.

*Anal.* Calcd for $C_5H_8O_2S$: C, 45.45; H, 6.06; S, 24.24. Found: C, 45.37; H, 6.08; S, 24.30.

**Carbonates.** The carbonates were prepared by a transesterification reaction of the diol with diethyl carbonate.[40] A mixture of glycol (13 mmol) and diethyl carbonate (1.7 g, 14 mmol) was kept at 100° overnight, while ethanol was slowly distilled. The reaction mixture was then fractionally distilled under low pressure.

**(−)-(*S*)-Methylethylene carbonate (1b)** was obtained in a yield of 87%: bp 100–105° (25 mm); $\nu_{max}$ 1800 (C=O), 1100 cm$^{-1}$ (CO); $\lambda_{max}$ (dioxane) 215 mμ (ε 5); nmr ($CCl_4$) δ 1.49 (3 H, d, $J$ = 6 Hz, $CH_3$), 4.04 and 4.57 (2 H, dd, dd, $CH_2$), 4.87 ppm (1 H, m, CH); mass spectrum M$^+$ 102; $[\alpha]^{25}D$ −1.7° (*c* 0.92, EtOH).

*Anal.* Calcd for $C_4H_6O_3$: C, 47.06; H, 5.88. Found: C, 47.20; H, 5.94.

**(+)-(*S,S*)-1,2-Dimethylethylene carbonate (2b)** was obtained in a yield of 70%: bp 68° (0.5 mm); retention time 12 min on a column of 100% Carbowax 1500 M on Chromosorb P 60–80 (6 ft × 0.25 in.) at 150° (gas flow rate 60 ml/min); $n^{19}D$ 1.4185; $\nu_{max}$ 1800 (C=O), 1050 cm$^{-1}$ (CO); $\lambda_{max}$ (dioxane) 215 mμ (ε 8); nmr ($CCl_4$) δ 1.41 (6 H, d, $J$ = 6 Hz, $CH_3$), 4.36 ppm (2 H, m, CH); mass spectrum M$^+$ 116; $[\alpha]^{25}D$ +35° (*c* 1.09, EtOH). For data of the racemic compound see ref 21.

*Anal.* Calcd for $C_5H_8O_3$: C, 51.72; H, 6.90. Found: C, 51.82; H, 6.92.

**(−)-(*R,R*)-1,2-Dimethylethylene carbonate (3b)** had boiling point, vpc, ir, nmr, and mass spectral data identical with those of 2b, and $[\alpha]^{25}D$ −36.2° (*c* 1.0, EtOH).

*Anal.* Calcd for $C_5H_8O_3$: C, 51.72; H, 6.90. Found: C, 51.80; H, 6.95.

**Sulfites.** The sulfites were obtained by the reaction of thionyl chloride and the appropriate diol without solvent.[41] To the glycol (13 mmol) freshly distilled thionyl chloride (2.2 g, 18 mmol) was slowly added dropwise at room temperature. The reaction mixture was kept at 60° for 30 min and then fractionally distilled under low pressure.

**(*S*)-1-Methylethylene Sulfites (1c).** A 0.73-g (45%) yield of a 1:2 mixture of the cis and trans sulfite isomers was obtained, bp 68° (25 mm).[42] The isomers were separated by vpc (20 ft × 0.25 in. 10% Carbowax 1500 M at 120°, gas flow rate 50 ml/min). *cis*-(+)-(*S*)-Methylethylene sulfite (*cis*-**1c**) had retention time 83 min; $n^{19}D$ 1.4380; $\nu_{max}$ 1200 cm$^{-1}$ (S=O); $\lambda_{max}$ (EtOH) 215 mμ (ε 55); nmr ($CCl_4$) δ 1.59 (3 H, d, $J$ = 6 Hz, $CH_3$), 4.2–4.7 ppm (3 H, m, $CH_2$ and CH); mass spectrum M$^+$ 122; $[\alpha]^{25}D$ +3.0° (*c* 0.275, hexane). *trans*-(−)-Methylethylene sulfite (*trans*-**1c**) had retention time 91.7 min; $n^{19}D$ 1.4383; $\nu_{max}$ 1200 cm$^{-1}$ (S=O); $\lambda_{max}$ (EtOH) 215 mμ (ε 61); nmr ($CCl_4$) δ 1.41 (3 H, d, $J$ = 6 Hz, $CH_3$), 3.8 (1 H, q, one of the $CH_2$ protons), 4.63 (1 H, four lines, one of the $CH_2$ protons), 5.07 ppm (1 H, sextet, CH); mass spectrum M$^+$ 122; $[\alpha]^{25}D$ −3.5° (c 0.73, hexane).

*Anal.* Calcd for $C_3H_6O_3S$: C, 29.51; H, 4.92; S, 26.23. Found (for isomeric mixture): C, 29.38; H, 4.90; S, 26.40.

**(+)-(*S,S*)-1,2-Dimethylethylene sulfite (2c)** had bp 70° (25 mm); $n^{19}D$ 1.4332; $\nu_{max}$ 1200 cm$^{-1}$ (S=O); $\lambda_{max}$ (dioxane) 225 mμ (ε 17); nmr ($CCl_4$) δ 1.47 and 1.55 (6 H, two d, $J$ = 5 Hz, $CH_3$), 3.98 (1 H, m, CH), 4.60 ppm (1 H, m, CH); mass spectrum M$^+$ 136; $[\alpha]^{25}D$ +20.1° (c 0.54, hexane).

*Anal.* Calcd for $C_4H_8O_3S$: C, 35.29; H, 5.88; S, 23.53. Found: C, 35.13; H, 5.90; S, 23.62.

**(−)-(*R,R*)-1,2-Dimethylethylene sulfite (3c)** had boiling point, ir, uv, nmr, and mass spectral data identical with those of **2c** and $[\alpha]^{25}D$ −20.3° (*c* 0.55, hexane).

*Anal.* Calcd for $C_4H_8O_3S$: C, 35.29; H, 5.88; S, 23.53. Found: C, 35.40; H, 5.84; S, 23.60.

**(+)-(*S,S*)-1,2-Dimethylethylene methyl phosphite (2d)** was prepared by transesterification according to the following. A mixture of (−)-(*S,S*)-2,3-butylene glycol (2 g, 22 mmol) and trimethyl phosphite (3.2 g, 26 mmol) was kept at 100° overnight, while methanol was slowly distilled. The cyclic phosphite (1.8 g, 54% yield) was separated from the reaction mixture by fractional distillation, bp 55° (25 mm), and was further purified by vpc (10 ft × 0.25 in. 10% Carbowax 20 M at 110°, gas flow rate 40 ml/min): retention time 10 min; $n^{18}D$ 1.4375; $\nu_{max}$ 1200 ($POCH_3$), 1000 cm$^{-1}$ (O–P–O); $\lambda_{max}$ (hexane) 210 mμ (ε 41); nmr ($CCl_4$) δ 1.29 and 1.37 (6 H, two d, $J$ = 5 Hz, $CH_3$), 3.45 (3 H, d, $J$ = 11 Hz, $POCH_3$), 3.8 ppm (2 H, m, CH); $[\alpha]^{25}D$ +42° (*c* 0.97, dioxane), $[\alpha]^{25}D$ +65° (c 0.67, hexane).

*Anal.* Calcd for $C_5H_{11}O_3P$: C, 40.0; H, 7.33. Found: C, 39.8; H, 7.30.

**1,3-Dioxolanes** were prepared by the transacetalation method of Paquette and Houser.[43]

**2-Bromomethyl-1,3-dioxolanes.** A mixture of glycol (26 mmol), bromoacetaldehyde diethyl acetal (5.0 g, 26 mmol), and a few drops of concentrated sulfuric acid was kept at 120° for 4 hr, while ethanol was slowly distilled. The reaction mixture was cooled, diluted with ether, and washed twice with water and then with concentrated bicarbonate solution. After the ether solution was dried ($Na_2SO_4$) and evaporated the dioxolane was separated from the residue by fractional distillation at low pressure. Further purification of the dioxolane was carried out by preparative vpc (6 ft × 0.25 in. 10% Carbowax 20 M).

***trans*-(−)-(*S*)-2-Bromomethyl-4-methyl-1,3-dioxolane (*trans*-1e)** had retention time at 85° 25 min; $n^{25}D$ 1.4662; $\nu_{max}$ 1100 (O–C–O), 750 cm$^{-1}$ (CBr); $\lambda_{max}$ (hexane) 225 mμ (ε 47); nmr ($CCl_4$) δ 1.27 (3 H, d, $J$ = 5 Hz, $CH_3$), 3.23 (2 H, d, $J$ = 4.5 Hz, $CH_2Br$), 3.37 and 4.15 (3 H, two m, O–CH–$CH_2$–O), 5.15 ppm (1 H, t, $J$ = 6 Hz, O–CH–O); mass spectrum M$^+$ 181 and 183; $[\alpha]^{25}D$ −30.6° (*c* 0.78, hexane).

*Anal.* Calcd for $C_5H_9BrO_2$: C, 32.97; H, 4.95; Br, 44.51. Found: C, 33.20; H, 4.95; Br, 44.26.

***cis*-(−)-(*S*)-2-Bromomethyl-4-methyl-1,3-dioxolane (*cis*-1e)** had retention time at 85° 27 min; $n^{22}D$ 1.4658; ir and uv data identical with those of *trans*-**1e**; nmr ($CCl_4$) δ 1.3 (3 H, d, $J$ = 5 Hz, $CH_3$), 3.26 (2 H, d, $J$ = 4 Hz, $CH_2Br$), 3.2–4.4 (3 H, two m, O–CH–$CH_2$–O), 4.99 ppm (1 H, t, $J$ = 5 Hz, O–CH–O); mass spectrum M$^+$ 181 and 183; $[\alpha]^{25}D$ −24° (*c* 1.170, hexane).

*Anal.* Calcd for $C_5H_9BrO_2$: C, 32.97; H, 4.95; Br, 44.51. Found: C, 33.10; H, 4.93; Br, 44.30.

**(−)-(*S,S*)-2-Bromomethyl-4,5-dimethyl-1,3-dioxolane (2e)** had bp 80° (25 mm); $n^{25}D$ 1.4597; retention time 10 min at 120° (6 ft × 0.25 in. 10% Carbowax 20 M, flow rate 70 ml/min); $\nu_{max}$ 1100 (O–C–O) and 770 cm$^{-1}$ (CBr); $\lambda_{max}$ (hexane) 225 mμ (ε 85) and 275 (65); nmr ($CCl_4$) δ 1.20 and 1.25 (6 H, two d, $J$ = 6 Hz, $CH_3$), 3.21 (2 H, d, $J$ = 4 Hz, $CH_2Br$), 3.58 (2 H, m, O–CH–CH–O), 5.07 ppm (1 H, t, $J$ = 5 Hz, O–CH–O); mass spectrum M$^+$ 195 and 197; $[\alpha]^{25}D$ −10° (*c* 0.975, hexane).

*Anal.* Calcd for $C_6H_{11}BrO_2$: C, 36.73; H, 5.61; Br, 41.32. Found: C, 36.56; H, 5.62; Br, 41.02.

**(*S,S*)-2-Chloromethyl-4,5-dimethyl-1,3-dioxolane (2f)** was prepared from (*S,S*)-2,3-butylene glycol and chloroacetaldehyde diethyl acetal by a procedure identical with that given for the 2-bromomethyl-1,3-dioxolanes: retention time at 120° 12 min (6 ft × 0.25 in. 10% Carbowax 20 M, flow rate 70 ml/min); $\lambda_{max}$ (hexane) 213 mμ (ε 38); $\lambda_{max}$ (AcCN) 217 mμ (ε 119); nmr ($CCl_4$) δ 1.22 and 1.27 (6 H, two d, $J$ = 6 Hz, $CH_3$), 3.40 (2 H, d, $J$ = 4 Hz, $CH_2Cl$), 3.62 (m, 2 H, O–CH–CH–O), and 5.13 ppm (1 H, t, $J$ = 4.5 Hz, O–CH–O).

*Anal.* Calcd for $C_6H_{11}O_2Cl$: C, 47.84; H, 7.30; Cl, 23.58. Found: C, 47.62; H, 7.51; Cl, 23.34.

**Registry No.**—**1a,** 51175-86-1; **1b,** 51260-39-0; *cis*-**1c,** 51260-40-3; *trans*-**1c,** 51260-41-4; *cis*-**1e,** 51260-42-5; *trans*-**1e,** 51260-43-6; **2a,** 51175-87-2; **2b,** 51261-82-6; **2c,** 51260-44-7; **2d,** 51260-45-8; **2e,** 51260-46-9; **2f,** 51175-88-3; **3a,** 35677-60-2; **3b,** 51260-48-1; **3c,** 51260-47-0; **4,** 24410-91-1; **5,** 32588-95-7.

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# Synthesis of Macrocyclic Polythiaethers[1]

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Macrocyclic polythiaethers have been synthesized and some of their properties have been determined. The compounds reported comprise a homologous series containing two, four, or six sulfur atoms in the macrocyclic ring. One example of a five sulfur atom macrocyclic is included. The synthetic methods allow for symmetrical or unsymmetrical bridging of the ring sulfur atoms by ethylene, tri-, tetra-, penta-, and hexamethylene bridges. These methods are contrasted to previously reported methods for macrocyclic polyoxaether and mixed polyoxa–polythiaether synthesis.

The preparation and properties of numerous macrocyclic polyoxaethers have been previously reported.[2] In addition, a limited number of macrocyclic polythiaethers[3,4] and mixed azo–oxa–thia macrocyclic[2b,3a] and macrobicyclic[5] polyethers containing four or more sulfur atoms in the macrocyclic ring have been described.

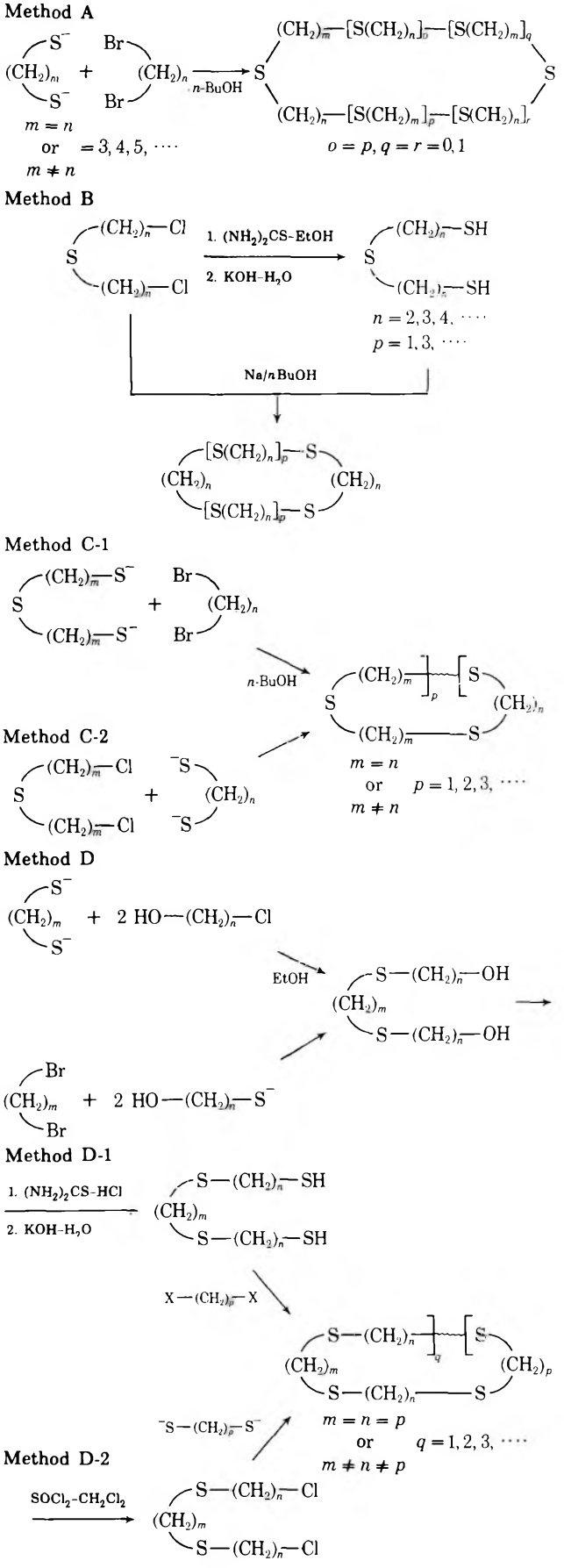
The macrocyclic polyoxaethers have generated particular interest through stable complex formation with cations of the alkali and alkaline earths, ammonium, and silver.[2,6] As model compounds, they have allowed extensive thermodynamic correlations to structurally related macrocyclics, both biological and synthetic in origin, which exhibit varying degrees of biological activity in the processes of active ion transport.[7] Relative to the oxaethers, the thia and mixed oxa–thia macrocyclics exhibit lower selectivity and coordinatability of active metal ions.[2c,6] To date, macrocyclic polythiaethers have not been given consideration as possible ion transport agents owing to their less discriminating coordination chemistry and lack of defined biologically related macrocyclics. However, in the absence of other ring heteroatoms, macrocyclic polythiaethers exhibit substantial coordinatability[3a,5] and selectivity[1,8] toward posttransitional element cations in agreement with hard and soft acids and bases theory.[9] On the basis of the established correlations between biological activity and macrocyclic structure,[7,10] more detailed selectivity and coordinatability studies and chemotherapeutic evaluations of macrocyclic polythiaethers, as related to purging of Hg(II) from test animals, are presently in progress in our laboratories. The scope and purpose of this paper is to report on the convenient preparation of a series of new and some previously reported macrocyclic polythiaethers containing no azo- or oxaether functionality which may be exploited for other than active metal coordination chemistry.

## Results and Discussion

A search of the literature has disclosed only several references to macrocyclic polythiaethers containing four or more sulfur atoms. With the exception of thioformaldehyde polymerization,[11] all other methods of thiaether ring closure were based on $\alpha$-mercaptide displacement of an $\omega$-halide function. The $\alpha$-mercapto-$\omega$-halopolythiamethylene intermediates are available only by *in situ* generation from condensation of $\alpha,\omega$-dihaloalkanes with active metal sulfide,[4a] $\alpha,\omega$-polymethylene dimercaptides,[4b] or precondensed $\alpha,\omega$-polythiapolymethylene dimercaptides.[3]

Unlike the strong template effect and corresponding high yields of macrocyclic polyoxaethers offered by oxygen coordination of alkali metal ion during cyclization of polyoxa units,[2,12] low sulfur-active metal ion coordination renders template effects of little consequence. Thus, the competition between cyclization and predominant linear polymerization is more statistically defined, entropy constraints of cyclization favoring linear polymerization whereas high dilution favors cyclization kinetically.[13] However, no prior study has elaborated the specific factors effecting relative distribution of cyclic products for the present reaction. By the methods outlined in Scheme

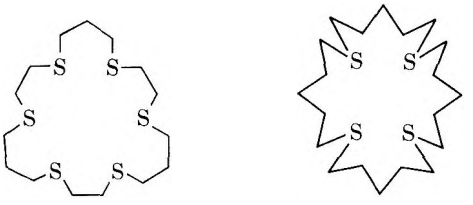
**Scheme I**




I, we have defined these factors and have refined practical synthetic routes to macrocyclic polythiaethers, particularly those of greater than trimethylene bridges.

Table I summarizes the macrocyclics isolated. Significantly, only two examples of macrocyclic hexathiaethers had been previously reported.[3a,4b] Since many of these polythiaethers have very cumbersome names, the proposed abbreviated nomenclature in Table I is designed to impart some of the salient structural formula features during repeated reference.[14] The terms of the trivial name in Chart I refer, in order, to (1) the number of sulfur atoms contained in the cyclic structure, (2) consecutive sequence of polymethylene bridging between sulfur atoms found as a repeated unit, and (3) total number of atoms comprising the polythiaether ring.

**Chart I**
**Relation of the Trivial Name to Structure**



7
$S_6$-Ethano-Propano-21

15
$S_4$-Pentano-24

In the absence of template effects, the entropy of cyclization may be considered to parallel the enthalpy of the end product and a relative assessment of these thermodynamic factors is provided by cyclic product distribution obtained by method A, Scheme I. Table II summarizes product ratios of two-sulfur codimerization to four- and six-sulfur copolymerization cyclic products at conditions experimentally optimized to favor cyclization kinetically.

Method A is most suitable for the preparation of tetra- and pentamethylene-bridged macrocyclic tetrathia- and hexathiaethers and may be disregarded as a method for the large ethylene- or trimethylene-bridged rings. The $S_4/S_2$ product ratios are in agreement with internal ring strain, which is at a minimum for 6, 14, and greater than 17 polymethylene rings.[15] With inclusion of two through four sulfur atoms, internal crowding would minimize ring strain in the 9- through 13-ring atom systems.[16] The entropy constraints of cyclization appear to converge with the kinetics of linear polymerization at macrocyclic polythiaethers of greater than approximately 24 ring atoms.

In order to avoid six- and seven-membered ring formation by method A in the ethylene- and trimethylene-bridged system, and to improve the overall kinetics of cyclization, methods B–E were investigated. Cyclization of the minimum number of precondensed polythia units would exclude two sulfur medium-ring products. Methods B and D should yield rings containing even numbers of sulfur atoms, whereas methods C and E could yield both odd and even sulfur atom numbers.

Method C-1 has been utilized previously for the synthesis of $S_6$-ethano-18 (3).[3a,4b] We have reinvestigated method C-1 and devised alternative method C-2 with results tabulated in Table III. Although identical products are isolated, total conversion to cyclic products and product distribution differs as a function of halide group leaving ability, bromide (28.9%) *vs.* chloride (15.2%). The unexpected and previously unreported formation of 1 and 2 can be rationalized in terms of cyclic sulfonium ion formation[17] (Scheme II) by means of chain-interior thia displacement of an ω-halo group from the linear intermediates.

Sulfonium ion formation should be more favored in polar media. Accordingly, 1 to 3 product ratios of 2:1 and 5:1 were found respectively in 1-butanol and ethanol media. Parallel leaving group and solvent effects were also

**Table I**
**Code Numbers and Systematic and Trivial Nomenclature of Cyclic Polythiaethers**

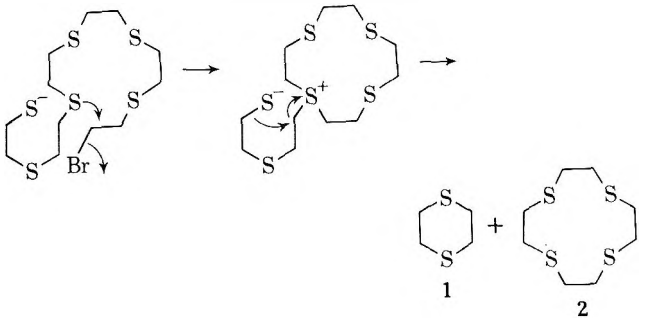
| Compd | Systematic name | Trivial name |
|---|---|---|
| **1** | *p*-Dithiane | $S_2$-Ethano-6 |
| **2** | 1,4,7,10-Tetrathiacyclododecane | $S_4$-Ethano-12 |
| **3** | 1,4,7,10,13,16-Hexathiacyclooctadecane | $S_6$-Ethano-18 |
| ***4*** | *1,4,7,10,13-Pentathiacyclopentadecane* | $S_5$-Ethano-15 |
| **5** | 1,4-Dithiepane | $S_2$-Ethano-Propano-7 |
| **6** | 1,4,8,11-Tetrathiacyclotetradecane | $S_4$-Ethano-Propano-14 |
| **7** | 1,4,8,11,15,18-Hexathiacycloheneicosane | $S_6$-Ethano-Propano-21 |
| **8** | 1,5-Dithiocane | $S_2$-Propano-8 |
| **9** | 1,5,9,13-Tetrathiacyclohexadecane | $S_4$-Propano-16 |
| **10** | 1,5,9,13,17,21-Hexathiacyclotetracosane | $S_6$-Propano-24 |
| **11** | 1,6-Dithiacyclodecane | $S_2$-Butano-10 |
| **12** | 1,6,11,16-Tetrathiacycloeicosane | $S_4$-Butano-20 |
| **13** | 1,6,11,16,21,26-Hexathiacyclotriacontane | $S_6$-Butano-30 |
| **14** | 1,7-Dithiacyclododecane | $S_2$-Pentano-12 |
| **15** | 1,7,13,19-Tetrathiacyclotetracosane | $S_4$-Pentano-24 |
| **16** | 1,7,13,19,25,31-Hexathiacyclohexatriacontane | $S_6$-Pentano-36 |
| **17** | 1,8-Dithiacyclotetradecane | $S_2$-Hexano-14 |
| **18** | 1,8,15,22-Tetrathiacyclooctacosane | $S_4$-Hexano-28 |
| ***19*** | *1,8,15,22,29,36-Hexathiacyclodotetracontane* | *$S_6$-Hexano-42* |

**Table II**
**Product Ratios of Four- and Six-Sulfur to Two-Sulfur Cyclothiaether Products by Method A**

| Bridge size | Ring size: Compd $S_2$ | Compd $S_4$ | Compd $S_6$ | Product ratios[a,b]: $S_6/S_2$ | $S_4/S_2$ |
|---|---|---|---|---|---|
| Ethylene | 6 | 12 | 18 | 0.065 | 0.0069 |
| Ethylene–Trimethylene[c] | 7 | 14 | 21 | 0.277 | 0.284 |
| Trimethylene | 8 | 16 | 24 | 0.850 | 1.19 |
| Tetramethylene | 10 | 20 | 30 | 1.05 | 2.02 |
| *Pentamethylene* | *12* | *24* | *36* | *1.21* | *7.00* |
| Hexamethylene | 14 | 28 | 42 | 1.16 | 0.867 |

[a] Based on quantitative separation and recovery, subpreparative scale, utilizing liquid–liquid chromatography. [b] $\alpha,\omega$-Dimercaptide, 0.2 *M* in 1-butanol at room temperature, $\alpha,\omega$-dibromide, 1 *M* in 1-butanol, 3 ml/min addition rate. [c] From ethanedithiol and 1,3-dibromopropane reactants.

**Scheme II**
**Intrachain Cyclization**




observed *via* method D for the mixed ethylene–trimethylene rings: **5** was isolated in 13.6% yield in addition to 12.6% of **6**. Consistent with lesser nucleophilic character of the oxa relative to the thia function, and further nucleophilic deactivation of the former by alkali metal ion coordination and resulting template effects, intrachain cyclization does not appear to intervene in macrocyclic polyoxaether synthesis.[2] Since the anticipated yield[3a] of **3** could not be attained even at extreme dilution by method C, method F, Scheme III, was devised.

Method F minimizes intrachain cyclization by appropriate choice of chloride leaving group and solvent polarity, thus yielding **3** as the smallest ring product from normal cyclization of reactants **21** and **23**. The method offers greatly simplified bulk isolation of **3** by liquid–liquid chromatography owing to virtual elimination of smaller ring products. However, the commercially unavailable intermediates, **21**, **22**, and **23**, are *potent vesicants* which require extreme care in handling.

**Table III**
**Product Distribution for Ethylene-Bridged Cyclopolythiaethers *via* C Methods[a]**

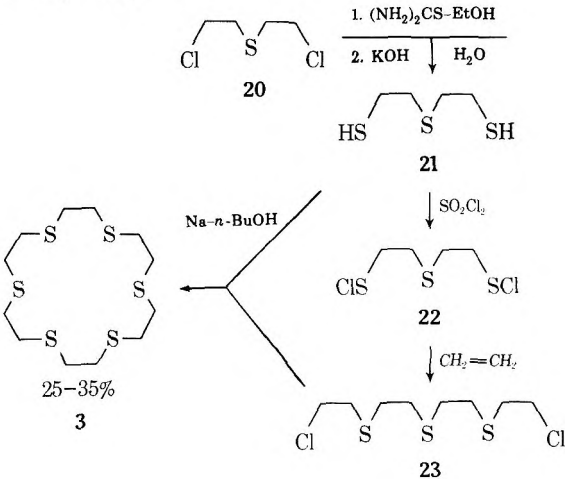
| Product[b] | Yield, %: Method C-1 | Method C-2 |
|---|---|---|
| **1** | 16.0 | 8.1 |
| **2** | 4.8 | 1.2 |
| **3** | 8.1[c,d] | 5.9 |
| Linear polymer and larger rings | 64.0 | 78.0 |

[a] Based on liquid–liquid chromatography isolation. [b] No 1,4,7-trithiacyclononane was observed by methods C-1 or C-2. [c] A 31% yield reported under identical conditions.[3a] [d] A 1.7% yield reported in ethanol media.[4b]

**Scheme III**

Method F

$SCl_2 + CH_2{=}CH_2 \longrightarrow$




Some optimized yields of macrocyclic polythiaethers synthesized by the methods outlined in Schemes I and II are summarized in Table IV. Only representative examples are cited. All methods of Scheme III are of general utility by adapting procedures outlined in the Experimental Section.

**Table IV**
**Macrocyclic Polythiaethers Isolated by Liquid–Liquid Chromatography**

| Compd[a] | Mp, °C[b] | Method | Elution solvent[c] | Yield, %[d] |
|---|---|---|---|---|
| **2** | 224–225 | B | Methylene chloride | 6.3[e] |
| **3** | 91–93 | A | 10:90 ethyl acetate–hexane | 0.8 |
| | | C-1 | | 8.1[f] |
| | | C-2 | | 21.7 |
| | | F | | 35.0 |
| **4** | 97.5–99 | E (B + D-2) | 20:80 ethyl acetate–hexane | 11.0 |
| **5** | 47–49 | A | 5:95 ethyl acetate–hexane | 16.2[g] |
| **6** | 121–122.5 | A | | 4.6 |
| | | D-2 | | 22.1[h] |
| **7** | 64–65 | A | 5:95 ethyl acetate–hexane | 0.5 |
| | | D (D-1 + D-2) | | 9.7 |
| **8** | bp 86–87 (1 Torr) | A | 5:95 ethyl acetate–hexane | 5.2[g] |
| **9** | 57.5–59 | A | 5:95 ethyl acetate–hexane | 6.2 |
| | | D-2 | | 19.5 |
| **10** | 29–30 | A | 5:95 ethyl acetate–hexane | 7.3 |
| | | C-2 | | 15.1 |
| **11** | 94–95.5 | A | 1:99 ethyl acetate–hexane | 1.9[g] |
| **12** | 31–32 | A | 1:99 ethyl acetate–hexane | 3.9[i] |
| **13** | 67–70 | A | Hexane | 1.7 |
| **14** | 81–82.5 | A | Pentane | 0.8 |
| **15** | 33–33.5 | A | 50:50 pentane–hexane | 5.3 |
| | | D-1 | | 3.6 |
| **16** | 36.5–38 | A | 50:50 pentane–hexane | 6.8 |
| **17** | 77–78 | A | Pentane | 1.4[g] |
| **18** | 30–32 | A | Pentane | 3.9 |
| **19** | 56–59.5 | A | Pentane | 3.2 |

[a] Proof of structure based on acceptable elemental analysis and molecular weight measurements in solution, and consistent nmr and infrared spectra. [b] Uncorrected Thomas-Hoover capillary melting point values. [c] Volume ratios. [d] Based on the polymerization process, representing in hand-multigram quantities of analytical grade material. [e] Reference 3c reported 4% yield. [f] Reference 3a reported 31% yield. [g] By-product of $S_4$ and $S_6$ macrocyclics *via* method A. [h] Reference 3d reported 7.5% yield. [i] A 19.7% yield was obtained on a small reaction scale by simultaneous addition of reactants to a bulk diluting solution; effective concentration of reactants below *ca.* $10^{-3}$ *M*.

## Conclusions

The use of chloro leaving groups and low solvent polarity favored larger rings within total cyclic product. However, cyclic to linear product conversion was more favorable with a bromo leaving group. Under the former conditions, a number of eight-sulfur macrocyclics were isolated by methods C and D, although no quantitative or optimization attempts were made to isolate rings of greater than six sulfurs. For ring systems containing larger than propane bridging, formation of two-sulfur cyclic products is less favored than larger cyclic products owing to ring constraints. Thus, methods of greater synthetic complexity than method A would not generally justify the slightly improved yields of cyclic product. However, method A gives rise to complications during attempted isolation of pure products owing to similarity in physical properties of mixture components. Moreover, odd sulfur atom numbered rings are available only by method E.

## Experimental Section

**General.** Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates T-60 spectrometer with tetramethylsilane as internal reference. Infrared (ir) spectra were recorded on either a Beckman IR-8 or a Perkin-Elmer 727. Molecular weights were determined with a Hitachi Perkin-Elmer 115 vapor pressure osmometer and compared to values obtained by manual cryoscopic determinations based on colligative freezing point depression of purified solvents. Optimum chromatographic solvents were established on microanalytical air-dried tlc plates prepared by immersion coating in a chloroform suspension of Merck silica gel H (neutral). Iodine vapor was used for spot development. Preparative column chromatography was carried out on Baker Analyzed silica gel (60–200 mesh). Crystallization and chromatographic elution solvent mixtures are volume ratios.

**Intermediate Reactants.** When not obtained from commercial sources, $\alpha,\omega$-dibromoalkanes were prepared from the corresponding $\alpha,\omega$-dihydroxyalkanes by reaction with 48% hydrobromic acid according to a modification of the procedure by Kamm and Marvel.[18]

Generation of $\alpha,\omega$-bisisothiuronium bromides from the corresponding $\alpha,\omega$-dibromoalkanes and subsequent hydrolysis by a modification of the procedure as described by Speziole[19] yielded simple $\alpha,\omega$-dimercaptoalkanes. Hydrolysis of $\alpha,\omega$-bisisothiuronium chlorides prepared in like fashion from $\alpha,\omega$-dichloroalkyl sulfides (20) yielded $\alpha,\omega$-dimercaptoalkyl sulfides (21). Alternatively, $\alpha,\omega$-dihydroxyalkyl sulfides (3,7-dithianonane-1,9-diol) were converted directly to the dithiols by *in situ* generation and hydrolysis of $\alpha,\omega$-bisisothiuronium chlorides according to the procedure described by Rosen and Busch.[3b] All three methods are of general utility, affording preparative yields of $\alpha,\omega$-dimercaptoalkanes in excess of 50%.

Simple $\alpha,\omega$-disulfenyl chlorides, as well as $\alpha,\omega$-dichlorosulfenylalkyl sulfides (22), were prepared from the corresponding dithiols by a modification of the procedure according to Mueller and Dines.[20]

$\alpha,\omega$-Dichloroalkyl sulfides were prepared by two general methods. $\beta$-Chloroethyl sulfides (23) were prepared by reaction of the $\alpha,\omega$-disulfenyl chlorides with ethylene by a modification of the procedure according to Brintzinger, *et al.*[21] The preparation of 1,5-dichloro-3-thiapentane (20) from ethylene and sulfur dichloride is an extension of this procedure.[22] The alternative method involves reaction of $\alpha,\omega$-dihydroxyalkyl sulfides with thionyl chloride by a modification of the procedure according to Bennett and Whincap.[23] Extreme vesicant properties were observed for all halo sulfides prepared.

**Preparation of 1,4,7,10-Tetrathiacyclododecane (2). Method B.** To a sodium butoxide solution, generated and maintained under a nitrogen atmosphere by dissolving sodium (2.2 mol) in 2 l. of 1-butanol, was added 154 g (1 mol) of 3-thiapentane-1,5-dithiol (21). The solution was equilibrated for 1 hr and cooled to 5° and 168 g (1 mol) of 1,5-dichloro-3-thiapentane was added all at once. The reaction was stirred below 10° for the first 2 hr, then at room temperature for an additional 16 hr. The solution was filtered, the filtrate was concentrated, and the oil residue was taken up in 1 l. of chloroform, washed with 0.5 l. of water, and dried with magnesium sulfate. The filter cake was vigorously stirred with 3 l. of water to dissolve salts. Insoluble solids were recovered by filtration, air dried, and combined with the chloroform solution of filtrate residue. The chloroform mixture was refluxed for 2 hr and filtered hot and insolubles were discarded. The solvent was vacuum evaporated and the residue was leached under reflux

with 5 × 100 ml of 5:95 ethyl acetate–hexane. The leachings contained traces of **1**, **4**, and higher polymers. The residue containing **2** was refluxed for 1 hr with 130 ml of methylene chloride. From the cooled methylene chloride filtrate was recovered 15.1 g (6.3%) of **2** ($S_4$-Ethano-12) as a fine, white, granular product.

**Preparation of 1,4,7,10,13,16-Hexathiacyclooctadecane (3). Method C-1.** Dimercaptide **21** (61.7 g, 0.40 mol) was converted to the disodium salt in the usual fashion in 0.5 l. of 1-butanol. This solution was added simultaneously over 2.5 hr, with the dropwise addition of ethylene bromide (75.2 g, 0.4 mol) in 0.5 l. of 1-butanol, to 2 l. of 1-butanol under nitrogen. The reaction was maintained below 10° for the first 10 hr, then stirred at room temperature for 36 hr. The solution was filtered and the filtrate was concentrated under vacuum while the filter cake was treated with 2 l. of water. The filtrate residue and air-dried, salt-free solids were extracted with 6 × 400 ml of refluxing pentane. The combined extracts were concentrated, and the residue was taken up in 0.5 l. of methylene chloride, washed with 300 ml of 5% potassium hydroxide, dried with magnesium sulfate, and reconcentrated to a thick, oily mass of 53.8 g. The mixture was eluted through a silica gel column with 30:70 ethyl acetate–hexane to remove immobile polymers and reconcentrated to 32.2 g of residue. The residue was rechromatographed on silica gel. Elution with 280 ml of pentane yielded 7.65 g (16%) of **1**, followed by elution of **3** with 600 ml of 10:90 ethyl acetate–hexane. Crude **3** was recrystallized from 5:95 ethyl acetate–hexane, yielding 5.78 g (8.1%) of **3** ($S_6$-Ethano-18) as a single crop of white crystals. From the pentane extraction residue was recovered 4.60 g (4.8%) of **2** according to the procedure for **2**, method B.

**Method C-2.** Solutions of **20** (58.9 g, 0.37 mol) dissolved in 0.5 l. of 1-butanol and the disodium salt of 1,2-ethanedithiol, 34.8 g (0.37 mol) of dimercaptan treated with butoxide in 0.5 l. of 1-butanol in the usual fashion, were simultaneously added dropwise to 2 l. of 1-butanol under nitrogen over 2.5 hr below 10°. After stirring at room temperature for an additional 36 hr, products were isolated in identical fashion with method C-1. The final chromatographic elution yielded 3.60 g (8.1%) of crude **1** and 14.43 g (21.7%) of **3** after recrystallization of the crude elution product, and 1.15 g (1.2%) of **2** was recovered from extraction residues.

**Method F.** Dimercaptan **21** (30.8 g, 0.2 mol) was converted to the disodium salt in 2 l. of 1-butanol in the usual fashion. To the solution was added all at once 45.8 g (0.2 mol) dichloride **23** and the reaction mixture was stirred below 25° for 48 hr. Products were separated according to the procedures in method C-1. Only 0.15 g (0.6%) of crude **1** was isolated, while recrystallization of the crude column concentrates of **3** yielded 11.7 g (32.8%) of analytical product.

**Preparation of 1,4,7,10,13-Pentathiacyclopentadecane (4). Method E (B + D-2).** 1,8-Dichloro-3,6-dithiaoctane (50.4 g, 0.23 mol), prepared in 83% yield from the reaction of ethylene with 1,2-ethanedisulfenyl chloride[21] or in 96% yield from 3,6-dithiaoctane-1,8-diol reaction with thionyl chloride,[23] was dissolved in 400 ml of 50:50 ether–1-butanol. Dimercaptan **21** (35.5 g, 0.23 ml) was converted to the disodium salt in 400 ml of 1-butanol in the usual fashion. The two solutions were simultaneously added dropwise over 2.5 hr to 2.2 l. of 1-butanol at 60° under nitrogen. The reaction mixture was stirred for an additional 15 hr at 60° and cooled and solids were separated by filtration. The filtrate was concentrated under vacuum, while the filter cake was treated with 2 l. of water to dissolve salts. The combined residues were extracted with 5 × 300 ml of refluxing hexane. The combined extracts were concentrated, taken up in 300 ml of methylene chloride, washed with 5% potassium hydroxide, dried with magnesium sulfate, and reconcentrated. The oily residue was eluted through a silica gel column to remove immobile polymers with 50:50 ethyl acetate–hexane, then rechromatographed with 20:80 ethyl acetate–hexane to yield traces of **1** and **2** and a concentrated band of **4**. The crude **4** ($S_5$-Ethano-15), recrystallized from 10:90 ethyl acetate–hexane, yielded 7.59 g (11%) of fine white crystals in a single analytical batch.

**Preparation of 1,4,8,11-Tetrathiacyclotetradecane (6). Method D-2.** 1,9-Dichloro-3,7-dithianonane was prepared from 3,7-dithianonane-1,9-diol[3b] by the general method previously described.[23] The dichloride (69.9 g, 0.3 mol) was dissolved in 400 ml of anhydrous ether and added simultaneously with a 400-ml 1-butanol solution of 1,3-propanediol disodium salt (0.3 mol) to 0.5 l. of 1-butanol under nitrogen over 6 hr at room temperature. After 12 hr, the reaction mixture was filtered, the filtrate was concentrated, and the filter cake was treated with water. The salt-free filter cake residues were extracted with 300 ml of cold ethylene chloride and the extracts were combined with the original filtrate residue. The solution was washed with two 200-ml portions of 5% sodium hydroxide, dried with anhydrous sodium sulfate, and reconcentrated to yield 34.1 g of paste residue. The residue was eluted with ethyl acetate through a silica gel column to remove immobile polymers, then rechromatographed with 5:95 ethyl acetate–hexane to yield a trace (0.08 g) of **5** as the first eluent. Recrystallization from 10:80 ether–hexane of subsequent crude column concentrates yielded 17.8 g (22.1%) of **6** ($S_4$-Ethano-Propano-14) as a single crop of white crystals.

**Preparation of 1,4,8,11,15,18-Hexathiacycloheneicosane (7). Method D (D-1 + D-2).** Condensation intermediates, 3,7-dithianonane-1,9-dithiol and 1,10-dichloro-4,7-dithiadecane, were prepared from the corresponding diols as previously illustrated. The $\alpha,\omega$-dichloro precursor was prepared from 1,2-ethanedithiol disodium salt and 3-chloropropanol (Aldrich). In identical fashion with the preparation of **6** (method D-2), 400-ml solutions of 68.4 g (0.3 mol) of dithiol disodium salt and 73.8 g (0.3 mol) of dichloride were simultaneously added to 0.5 l. of 1-butanol. Following 16 hr of reaction, crude product was concentrated according to the procedure for **6**. This residue (95.4 g) was eluted with 30:70 ethyl acetate–hexane through a silica gel column to remove immobile polymers, then rechromatographed with 5:95 ethyl acetate–hexane. In order were recovered a small amount (0.34 g) of **5**, a trace (0.02 g) of **6**, and 11.7 g (9.7%) of **7** ($S_6$-Ethano-Propano-21) as a single crop of white crystals, the latter by crystallization of elution concentrates from 5:95 ether–hexane.

**Preparation of 1,6,11,16-Tetrathiacycloeicosane (12) and Isolation of By-products 11 and 13. Method A.** In 3.5 l. of 50:50 ethanol–1-butanol, 161 g (1.32 mol) of 1,4-butanedithiol was converted to the disodium salt. To the cooled solution was added all at once 282 g (1.32 mol) of 1,4-dibromobutane under nitrogen. The reaction mixture was stirred for 3 hr below 15°, then for an additional 14 hr at 50°. Products of interest (**11**, **12**, and **13**) were concentrated by combining filtrate oil residue with four 500-ml ether extracts of the filter cake residue. This solution was washed with three 500-ml portions of 10% potassium hydroxide, dried with sodium sulfate, and reconcentrated to 42.6 g of paste. Higher polymers were removed by elution through a silica gel column with 10:90 ether–hexane. Complete separation of components in order of ring size, **11** first, was achieved by rechromatographing with 1:99 ethyl acetate–hexane. Recrystallization of aliquot concentrates yielded 4.50 g (1.9%) of **11** ($S_2$-Butano-10) and 6.00 g (1.7%) of **13** ($S_6$-Butano-30) from hexane, and 8.99 g (3.9%) of **12** ($S_4$-Butano-20) from pentane. Products **11** and **12** were isolated as fine white needles, and **13** as a white powder.

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**Registry No.**—**1**, 505-29-3; **2**, 25423-56-7; **3**, 296-41-3; **4**, 36338-04-2; **5**, 6008-55-5; **6**, 24194-61-4; **7**, 51540-11-5; **8**, 6572-95-8; **9**, 295-91-0; **10**, 51472-63-0; **11**, 51472-64-1; **12**, 51472-65-2; **13**, 51472-66-3; **14**, 51472-67-4; **15**, 51472-68-5; **16**, 51472-69-6; **17**, 295-32-9; **18**, 51472-70-9; **19**, 51472-71-0; **20**, 505-60-2; **21**, 3570-55-6; **22**, 51472-72-1; **23**, 51472-73-2.

**Supplementary Material Available.** Tables V and VI, listing literature references to physical constants, elemental analysis and molecular weight data, and more detailed experimental, chromatographic, intermediate, and duplicate synthesis examples, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2079.

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# Intramolecular Aromatic and Aliphatic Ullmann Reactions[1]

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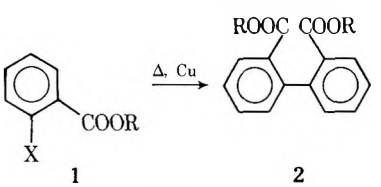
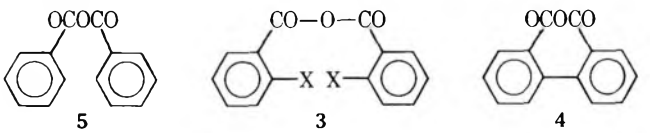
Intramolecular Ullmann cyclizations of several *o*-halobenzoic anhydrides have been shown to take place in high yields at temperatures near 60–70° in tetramethylethylenediamine (TMEDA), dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), hexamethylphosphoramide (HMPA), and pyridine. In all cases except that of pyridine, appreciable (10–30%) to large (50–82%) amounts of reduction products accompany the coupling product. The coupling of aliphatic $\alpha$-bromo-unsaturated anhydrides under comparable conditions has also been demonstrated.

The Ullmann coupling of 2-halo esters, **1**, to dialkyl diphenates, **2**, has often been effected.[3] In general the reaction has been carried out by long heating with copper at temperatures over 200°. We wished to find out if this type of reaction could be carried out under milder conditions than usual by changing the reaction from an intermolecular to an intramolecular type. In one case tried here earlier the synthesis of 6,6′-diethyldiphenic acid was markedly better when 3-ethyl-2-iodobenzoic anhydride was used instead of methyl 3-ethyl-2-iodobenzoate.[4] A few isolated cases in which intramolecular Ullmann reactions were tried are mentioned[3] but little study of this type of ring closure has been made. We had hoped that the synthesis of unsymmetrical diphenic acids might be improved by the use of unsymmetrical halo anhydrides, but this hope was not fully realized (see later, below).




1 2

We have found out that Ullmann reactions are carried out much more easily if anhydrides are used instead of halo esters. Two general types of reactions have been studied: method A, in which the 2-halobenzoic acid anhydrides, **3**, are cyclized to diphenic anhydrides, **4**, in a variety of nitrogenous solvents by heating with copper powder at 60–70°; and method B, in which the anhydrides, **3**, are heated with copper powder in benzene containing catalytic amounts of nitrogenous complexing agents. The complexing agents were chosen with the thought that they might complex with any hypothetical organocopper intermediate which might be involved in the reaction.[5-7] For analysis of the results of most experiments the reaction mixtures were treated with methanol and with diazomethane to convert anhydrides into the corresponding methyl esters.




5 3 4

The choice of solvent is important because the ratio of ring-closed product, a diphenic anhydride, **4**, to reduced product, a benzoic anhydride, **5**, is markedly solvent dependent.

The experiments (method A) which illustrate these points are listed in Table I. In our experience, the best solvent for this type of reaction is pyridine. In 1 hr at 60–70° not only is the starting anhydride almost completely reacted but the ratio of diphenic anhydride to benzoic anhydride formed is greatest (see expt 5, 11, and 17 in Table I). Surprisingly, appreciable to large amounts of reduction product were obtained in all of the other solvents studied.[8] That reduction occurs prior to, and not on, quenching of the reaction mixture with water was shown in the case of 2-bromobenzoic anhydride in tetramethylethylenediamine (TMEDA) by quenching with $D_2SO_4$ in $D_2O$.

**Table I**
**Effect of Solvent and Substrate in Ullmann Reactions of 2-Halobenzoic Anhydrides[a]**

| Expt | Substrate | Solvent | % reaction[b] | % coupling[c] | % reduction[d] |
|---|---|---|---|---|---|
| 1 | $(2\text{-}ClC_6H_4CO)_2O$[e] | Neat | 0 | 0 | 0 |
| 2 | $(2\text{-}ClC_6H_4CO)_2O$[e] | TMEDA | 43 | 83 | 17 |
| 3 | $(2\text{-}ClC_6H_4CO)_2O$[e] | DMF | 68 | 50 | 50 |
| 4 | $(2,4\text{-}Cl_2C_6H_3CO)_2O$ | DMF | 100 | 88 | 12 |
| 5 | $(2,4\text{-}Cl_2C_6H_3CO)_2O$ | Pyridine | 93 | 96 | 4 |
| 6 | $(2\text{-}BrC_6H_4CO)_2O$ | Neat | 0 | 0 | 0 |
| 7 | $(2\text{-}BrC_6H_4CO)_2O$ | TMED | 87 | 25 | 75 |
| 8 | $(2\text{-}BrC_6H_4CO)_2O$ | NMP[f] | 84 | 77 | 23 |
| 9 | $(2\text{-}BrC_6H_4CO)_2O$ | HMPA[g] | 79 | 77 | 23 |
| 10 | $(2\text{-}BrC_6H_4CO)_2O$ | DMF | 100 | 90 | 10 |
| 11 | $(2\text{-}BrC_6H_4CO)_2O$ | Pyridine | 100 | 98 | 2 |
| 12 | $(2\text{-}IC_6H_4CO)_2O$ | Neat | 0 | 0 | 0 |
| 13 | $(2\text{-}IC_6H_4CO)_2O$ | TMED | 100 | 18 | 82 |
| 14 | $(2\text{-}IC_6H_4CO)_2O$ | HMPA | 84 | 69 | 31 |
| 15 | $(2\text{-}IC_6H_4CO)_2O$ | DMF | 76 | 74 | 26 |
| 16 | $(2\text{-}IC_6H_4CO)_2O$ | NMP | 76 | 85 | 15 |
| 17 | $(2\text{-}IC_6H_4CO)_2O$ | Pyridine | 100 | 98 | 2 |

[a] The reaction conditions are those described in the Experimental Section under Ullmann Reactions. Method A. [b] Determined (glpc) by subtracting from 100 the per cent of recovered methyl halobenzoate corresponding to starting anhydride. [c] Determined (glpc) from the amount of dimethyl diphenate produced. [d] Determined (glpc) from the amount of methyl benzoate produced. [e] In reaction by method A, no reactions occurred in *N*-methylpyrrolidine (NMP) acid hexamethylphosphoric triamide (HMPA). [f] *N*-Methylpyrrolidone. [g] Hexamethylphosphoric triamide.

**Table II**
**Effect of Complexing Agent in Ullmann Reaction of 2-Bromobenzoic Anhydride[a,b]**

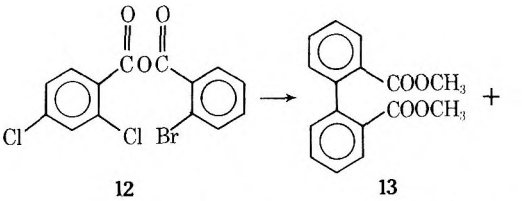
| Complexing agent | % reaction | % coupling | % reduction |
|---|---|---|---|
| DMF | 100 | 85 | 15 |
| HMPA | 100 | 87 | 13 |
| TMEDA | 86 | 32 | 68 |
| 4,5-Phenanthroline | 100 | 95 | 5 |
| 2,2′-Bipyridine | 100 | 98 | 2 |

[a] The per cent of reaction, coupling, and reduction were determined as described in Table I. [b] The reaction conditions are those described in the Experimental Section under Ullmann Reactions. Method B.

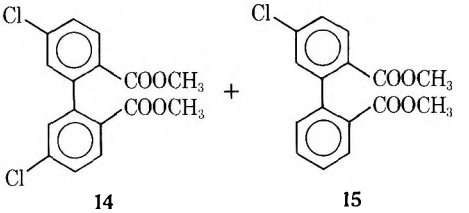
No deuterated methyl benzoate was detected. This experiment rules out the presence of an arylcopper species just prior to quenching. Any arylcopper compound formed under our reaction conditions (similar to expt 7, Table I) must have been reduced by the solvent prior to addition of $D_2SO_4$. This type of substitutive reduction in Ullmann-type reactions has been discussed.[6] Apparently $NCH_3$ groups in solvents readily engage in reductive processes.

As a standard experiment (method B) a solution of 2-bromobenzoic anhydride (**6**) in benzene containing less than 1 equiv of a complexing agent was held at reflux over copper powder for 24 hr. The results, summarized in Table II, indicate that the complexing agents of choice contain nitrogen-heterocyclic rings, *e.g.*, 4,5-phenanthroline and 2,2′-bipyridine. To show the generality of this type of reaction, 2,4-dichlorobenzoic anhydride (**7**) and 2-chloro-5-nitrobenzoic anhydride (**8**) in benzene containing 2,2′-bipyridine were converted into the corresponding 5,5′-dichlorodiphenic anhydride (**10**) and 4,4′-dinitrodiphenic anhydride (**11**) in excellent yields.

The results outlined above make it obvious that the Ullmann reaction to form diphenic acid derivatives is greatly facilitated by the use of anhydrides instead of esters. Accordingly, we next studied the use of unsymmetrical benzoic anhydrides[9] for obtaining unsymmetric diphenic anhydrides. Although the starting anhydrides used were undoubtedly mainly unsymmetric, on heating rapid disproportionation took place faster than coupling with the result that the two symmetric and the unsymmetric diphenic anhydrides were produced. For example, when the crude mixed anhydride, **12**, formed by treating 2,4-dichlorobenzoic acid in pyridine with 2-bromobenzoyl chloride[9] was heated under the conditions of method A or B a mixture of diphenic anhydrides was obtained. This mixture was hydrolyzed with alkali and the free acids obtained were esterified with diazomethane. Analysis of the esters showed that dimethyl diphenate (**13**), dimethyl 5,5′-dichlorodiphenate (**14**), and dimethyl 5-chlorodiphenate (**15**) were present in about the statistical ratio 1:1:2, respectively.



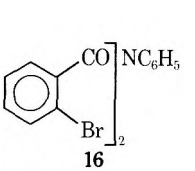

**12** **13**



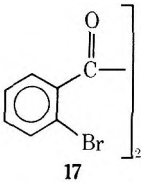

**14** **15**

The same mixture of **13**, **14**, and **15** was obtained when an equimolar mixture of **6** and **7** was used as starting material. This fact suggests that, for example, an excellent yield of **15** might be obtained if a mixture of **7** and an excess of **6**, or a mixture of **6** and an excess of **7**, were used. In a given case the choice as to which anhydride should be used in excess would depend on which anhydride was least valuable.

In an effort to use a derivative which might not disproportionate as readily as do anhydrides, we prepared *N*-phenyl-2-bromobenzimide (**16**). An attempt at cyclization (method B) yielded mainly recovered **16** and small



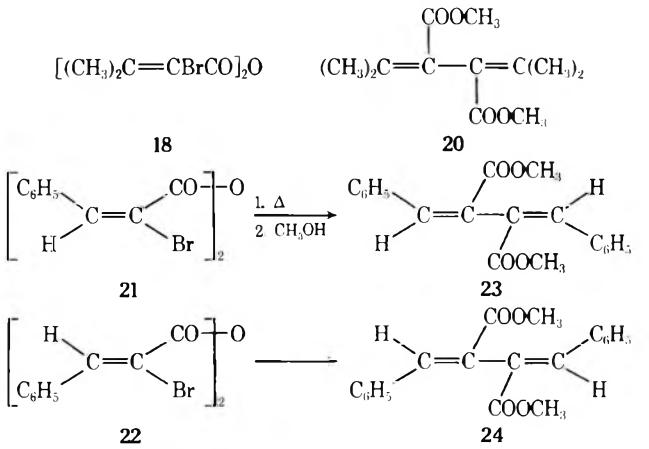

**16**




**17**

amounts of unidentified products, none of which corresponded to the desired *N*-phenyl diphenic imide. One attempt at cyclization of 2,2′-dibromobenzil (**17**) failed to produce any phenanthrenequinone.

Because of the success in the synthesis of diphenic anhydrides by intramolecular Ullmann reactions described above we carried out a few experiments in the aliphatic area. Intermolecular Ullmann reactions on substituted vinyl bromides and iodides have been carried out and the stereospecificity of the reactions determined and discussed.[5] We have found that 2-bromo-3-methylbutenoic anhydride (**18**) is readily coupled to 2,5-dimethylhexa-2,4-diene-3,4-dioic anhydride (**19**) as indicated by the isolation of dimethyl 2,5-dimethylhexa-2,4-diene-3,4-dioate (**20**) after treatment of the reaction product with methanol. The results of the attempted cyclizations of (*E,E*)-2-bromocinnamic anhydride (**21**) and the *Z,Z* isomer (**22**) were not very promising but are of some interest. The *E,E* anhydride, **21**, is not configurationally stable under the reaction conditions (method A). However, by chromatography of the methyl esters of the reaction product, a 22% yield of dimethyl (*Z,Z*)-1,4-diphenyl-1,3-butadiene-2,3-dioate (**23**) was isolated. The *Z,Z* anhydride, **22**, afforded 19% of dimethyl (*E,E*)-1,4-diphenyl-1,3-butadiene-2,3-oate (**24**).[10]




In each of the above coupling reactions some methyl cinnamate was produced. The proportion of this reduction product to coupled product was much larger in the case of the reaction involving **22**, undoubtedly because of greater hindrance to coupling because of the stereochemistry of the transition state which places the phenyl groups in opposition to each other.

The assignment of structures to **23** and **24** was made on the basis of uv and pmr spectra. The uv max for **23** (312 nm, log $\epsilon$ 3.5) lies at longer wavelength than that of **24** (278 nm, log $\epsilon$ 4.4), as does that of (*E,E*)-1,4-diphenyl-1,3-butadiene (328 nm) compared to (*Z,Z*)-1,4-diphenyl-1,3-butadiene (299 nm).[11] The *E,Z* form for either of the coupling products from **21** and **22** is ruled out because both **23** and **24** have singlets for the vinylic hydrogen at $\delta$ 6.92 and 7.92, respectively. If an *E,Z* compound were at hand there should be two singlets.

The fact that these reactions were effected in a short time (*ca.* 1.5 hr) at 80–90° as compared to the longer times at higher temperatures for intermolecular coupling[5] makes further study of intramolecular coupling of vinylic halides of interest.[12]

## Experimental Section[13]

**Preparation of Acid Chlorides.** In a typical experiment 38.5 g of 2-bromobenzoic acid was slowly added to a stirred slurry of 40 g of $PCl_5$ and 200 ml of dry $CH_2Cl_2$. When the mixture had become homogeneous (*ca.* 15 min after addition) the solvent and $POCl_3$ were removed under reduced pressure and the residue was distilled to yield 34.0 g (82%) of 2-bromobenzoyl chloride,[14] bp 130–133° (15 mm). In a similar way were prepared 2-chlorobenzoyl chloride,[15] bp 65° (0.05 mm), 2-iodobenzoyl chloride,[16] bp 145° (13 mm), 2,4-dichlorobenzoyl chloride,[17] bp 115–117° (13 mm), and 2-bromo-3-methyl-2-butenoyl chloride,[18] bp 78–80° (15 mm), ir (neat) 5.69 $\mu$ (1757 $cm^{-1}$).

**Preparation of Anhydrides.** The method[19] we used (method 1) to prepare some anhydrides is illustrated by the synthesis of 2-iodobenzoic anhydride.[20] To an ice-cold solution of 8.7 g of 2-iodobenzoic acid and 3 ml of pyridine in 20 ml of benzene was added a solution of 9.3 g of 2-iodobenzoyl chloride in 20 ml of benzene. After 10 min the mixture was filtered and the filtrate was worked up as usual to yield 14.9 g (88%) of 2-iodobenzoic anhydride, mp 71–75°. In a similar way 2-chlorobenzoic anhydride,[21] mp 78–79°, 2-bromobenzoic anhydride, mp 76.0–77.5°, and 2,4-dichlorobenzoic anhydride, mp 105.0–106.5°, were prepared.

*Anal.* Calcd for $C_{14}H_8Br_2O_3$: C, 43.7; H, 2.1; *m/e* 383. Found: C, 43.3; H, 1.8; *m/e* 383 (center of triplet). Calcd for $C_{14}H_6Cl_4O_3$: C, 46.2; H, 1.7; *m/e* 365. Found: C, 46.5; H, 1.6; *m/e* 365.

The mixed anhydrides, 2,4-dichloro-2′-bromobenzoic anhydride and 3-bromo-2-naphthoic-2′-bromobenzoic anhydride, were prepared by this method but were not analyzed or characterized because of rapid disproportionation on heating.

By treatment with ethoxyacetylene[22] (method 2), (*E*)-2-bromocinnamic acid was converted into (*E,E*)-2-bromocinnamic anhydride,[23] mp 71–73°, the *Z* isomer into (*Z,Z*)-2-bromocinnamic anhydride,[23] mp 101–102°, and 2-chloro-5-nitrobenzoic acid into 2-chloro-5-nitrobenzoic acid anhydride, mp 145–146°.

*Anal.* Calcd for $C_{14}H_6Cl_2N_2O_7$: Cl, 18.4; N, 7.3. Found: Cl, 18.3; N, 7.1.

**Ullmann Reactions. Method A (See Table I).** In a typical experiment (expt 10, Table I) a mixture of 1.0 g of copper powder[24] in 5 ml of pure DMF containing 1.4 g of 2-bromobenzoic anhydride (**6**) was stirred magnetically in a flask held in a bath at 60–70°. After 1.5 hr the cooled mixture was diluted with ether and filtered. The filtrate was washed with water and the water wash was reextracted with ether (repeated once). The combined ether layer was washed with saturated salt solution and filtered through anhydrous $MgSO_4$. After distillation of the ether, the residue was heated at reflux with aqueous methanolic KOH for 20 min. The acids, obtained by ether extraction of the acidified hydrolysis solution, were taken into ether. The dried ether solution was treated with a slight excess of diazomethane and the solvent was distilled. There remained 0.90 g (92%) of an oil which solidified on cooling. Analysis by glpc on a 30% SE-30 (a silicone oil) on Chrome-A support in a 8 ft × 0.25 in. column at 225° using helium revealed that approximately 10% of methyl benzoate was present along with 90% of dimethyl diphenate. No methyl 2-bromobenzoate was present. The identity of each fraction was determined by use of authentic samples. The experiment with **6** in which quenching with $D_2SO_4$ was used (see discussion) was of the method A type.

**Method B (See Table II).** In a typical experiment a solution of 1.0 g (2.6 mmol) of **6** and 0.2 g (1.0 mmol) of 2,2′-bipyridine in 75 ml of dry benzene was held at reflux over 0.7 g (10.4 mg-atoms) of copper for 24 hr. The reaction mixture was filtered. The filtrate was extracted with water and dilute HCl. After the benzene solution was filtered through $MgSO_4$, the reaction products were worked up as described for method A to yield approximately 98% of dimethyl diphenate and 2% of methyl benzoate (expt 5, Table II).

In a similar experiment except that the solvents were removed after the unused copper was removed by filtration, there was isolated by crystallization from benzene 0.5 g (86%) of diphenic anhydride,[25] mp 218–220°. Similarly, 2,4-dichlorobenzoic anhydride (**7**) yielded 5,5′-dichlorodiphenic anhydride,[26] mp 201–203°, and 2-chloro-5-nitrobenzoic anhydride (**8**) yielded 4,4′-dinitrodiphenic anhydride,[27] mp 234–236°, in 86 and 80% yields, respectively.

**Mixed Anhydride Experiments.** The experiments involving freshly prepared 2-bromo-2′,4′-dichlorobenzoic anhydride (**12**) were carried out in HMPA by methods A and B. The results were essentially the same in each case; about 10% of methyl benzoate and methyl 4-chlorobenzoate (reduction products) were formed in addition to dimethyl diphenate (**13**), dimethyl 5,5′-dichlorodiphenate, and dimethyl 5-chlorodiphenate (**15**), in the ratio of approximately 1:1:2. The structure of **15** was assumed from nmr ($CCl_4$), $\delta$ 7.9 and 7.3 (m, 7, ArH), 3.6 (s, 3, $OCH_3$), 3.52 (s, 3, $OCH_3$), and mass spectrum, *m/e* 304. When equimolar mixtures of **6** and **7** were treated as described for methods A and B, reac-

tion products closely analogous to those obtained with **12** were obtained.

*N*-**Phenyl-2-bromobenzimide (16).** To a slurry containing 0.2 g (5 mmol) of sodium hydride in 10 ml of DMF was added 1.3 g (4.9 mmol) of *N*-phenyl-2-bromobenzamide.[28] In a few minutes all of the hydrogen had been evolved and the mixture became homogeneous. To this was added 1.1 g (5 mmol) of 2-bromobenzoyl chloride. After standing overnight the mixture was heated to 65° for 30 min. After the usual work-up there was obtained about 2 g of an oil which was crystallized from benzene with little loss to yield **16,** mp 107–108°, which contained only ArH in the pmr, mass spectrum *m/e* 459, ir 5.92 $\mu$. This compound was recovered unchanged from experiments of type A and B above.

**2,2′-Dibromobenzil (17).** 2-Bromobenzaldehyde, bp 120–130°, was prepared in 48% yield (crude) by a slight modification (use of aqueous alcoholic potassium hydroxide) of the 2-nitropropane oxidation[29] of 2-bromobenzyl bromide. A mixture of 10.0 g of this aldehyde and 1.0 g of sodium cyanide in 50 ml of NMP was held at 90–100° for 9 hr. The mixture was diluted with an equal volume of water and the crude product, isolated as usual, was treated with saturated aqueous sodium bisulfite to remove unreacted aldehyde. The resulting crude benzoin was treated with 35 ml of concentrated $HNO_3$ for 1.5 hr at 90–100°. The product from this reaction, isolated as usual, was chromatographed over Florisil to yield 12% of pure **17,** mp 120–123°, *m/e* 368. No attempt at maximization of yield was made.

*Anal.* Calcd for $C_{14}H_8Br_2O_2$: C, 45.7; H, 2.2. Found: C, 45.5; H, 2.2.

**Dimethyl 2,5-Dimethylhexa-2,4-diene-3,4-dioate (20).** Pure 2-bromo-3-methyl-2-butenoic acid, mp 90–91°, prepared essentially as described,[30] was converted by method 2 (using ethoxyacetylene) into the anhydride **18,** 8.5 g of which was immediately added to 60 ml of DMF containing 6.4 g of copper. After 1.5 hr at 80°, 60 ml of methanol was added and the mixture was held at reflux for 30 min. After cooling and dilution with water the product was taken into ether. The ether extract was treated with diazomethane. After the usual work-up distillation afforded 2.9 g (50%) of pure **20,** mp 73–74°, ir (KBr) 5.83 $\mu$, nmr ($CCl_4$) $\delta$ 3.70 (s, 6, $OCH_3$), 2.15 (s, 6, $=CCH_3$), 1.68 (s, 6, $=CCH_3$), *m/e* 226, on crystallization from pentane.

*Anal.* Calcd for $C_{12}H_{18}O_4$: C, 63.6; H, 8.1. Found: C, 63.7; H, 8.0.

A small amount (*ca.* 10%) of reduction product, methyl 3-methyl-2-butenoate, was formed in the reaction as estimated by glpc (comparison of retention time with that of an authentic sample). When the reaction of **18** with copper was tried at reflux in benzene with 2,2′-bipyridine for 24 hr, no **20** was isolated, as tarry material was formed.

**Dimethyl (*Z*,*Z*)1,4-Diphenyl-1,3-butadiene-2,3-dioate (23).** (*E*)-2-Bromocinnamic acid, mp 115–116.5°, prepared essentially as described,[31] was converted into the anhydride with ethoxyacetylene (method 2 above). A mixture of 2.0 g of this and 1.6 g of copper in 10 ml of DMF was stirred at 85° for 1.5 hr. After the usual work-up and esterification to methyl esters, the product was chromatographed over silica gel. There could be isolated 0.4 g (22%) of **23,** mp 121–123°, uv max 318 nm (log $\epsilon$ 3.5), ir (KBr) 5.78 $\mu$, pmr $\delta$ 7.36 (s, 10, ArH), 6.92 (s, 2, =CH), 3.77 (s, 6, $OCH_3$), after recrystallization from ether–hexane. No attempt was made to maximize the yield of this reaction.

*Anal.* Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.7; H, 5.6.

**Dimethyl (*E*,*E*)-1,4-Diphenyl-1,3-butadiene-2,3-dioate (24).** On heating 8.0 g of (*E*)-2-bromocinnamic acid at 200° for 30 min, the product was crystallized from heptane to yield 5.5 g (69%) of (*Z*)-2-bromocinnamic acid,[31] mp 129–130°. After conversion to the anhydride with ethoxyacetylene (method 2 above), 5.0 g of the anhydride **22,** 4.0 g of copper, and 20 ml of DMF were held at 80–90° for 90 min. The mixture was diluted with methanol and refluxed for 1 hr. The resulting product was separated into neutral and acidic fractions by extraction with $K_2CO_3$ solution. The acid fraction was esterified with diazomethane and the esters were chromatographed on silica gel to yield 0.7 g (19%) of **24,**[32] mp 113–115°, uv max 278 nm (log $\epsilon$ 4.4), pmr $\delta$ 7.92 (s, 2, =CH), 7.33 (m, 10, ArH), 3.73 (s, 6, $OCH_3$).

**Registry No.**—$(2\text{-}ClC_6H_4CO)_2O$, 49619-43-4; $(2,4\text{-}Cl_2C_6H_3CO)_2O$, 51417-52-8; $(2\text{-}BrC_6H_4CO)_2O$, 49619-44-5; $(2\text{-}IC_6H_4CO)_2O$, 51417-53-9; **4,** 6050-13-1; **8,** 51417-54-0; **10,** 20872-20-2; **11,** 27007-55-2; **12,** 51417-55-1; **13,** 5807-64-7; **14,** 27007-54-1; **15,** 1035-83-2; **16,** 51417-56-2; **17,** 51417-57-3; **18,** 51417-58-4; **20,** 6117-26-6; **21,** 51417-59-5; **22,** 51417-60-8; **23,** 51417-61-9; **24,** 51417-62-0; Cu, 7440-50-8; 2-bromobenzoyl chloride, 7154-66-7; 2-chlorobenzoyl chloride, 609-65-4; 2-iodobenzoyl chloride, 609-67-6; (*E*)-2-bromocinnamic acid, 15894-30-1; (*Z*)-2-bromocinnamic acid, 15813-24-8; 2-chloro-5-nitrobenzoic acid, 2516-96-3; *N*-phenyl-2-bromobenzamide, 10282-57-2; 2-bromobenzaldehyde, 6630-33-7; 2-bromo-3-methyl-2-butenoic acid, 51263-40-2.

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# Aromatization of 4-Carboxybenzene Oxide

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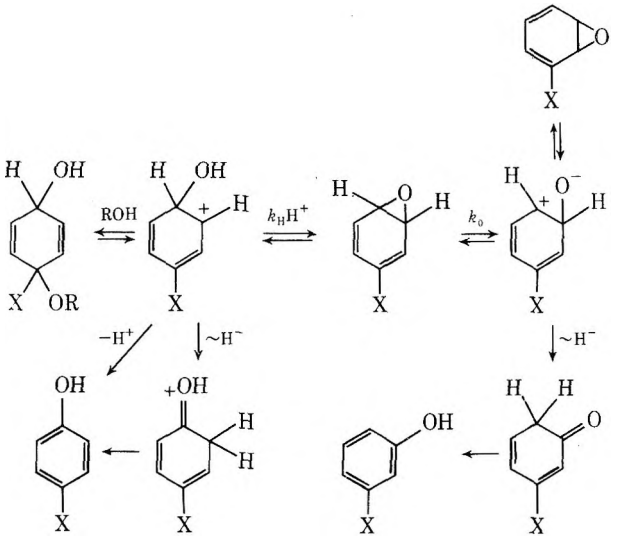
4-Carboxybenzene oxide (I) has been synthesized and the kinetics of its aromatization studied in the pH range of 0–10 ($H_2O$, 30°, $\mu$ = 0.2 KCl). General catalysis was found to be unimportant in both the acidic and basic regions of pH. The pH–log $k_{obsd}$ profile dictates three competitive pathways leading to phenols: specific acid-catalyzed aromatization of undissociated I (Ia) and its anion (Ib) as well as uncatalyzed aromatization of the anion. The lack of spontaneous aromatization of undissociated I is as predicted on the basis of a previous investigation of substituent effects upon the rate constants of both specific acid catalyzed and uncatalyzed aromatization of benzene oxides. The products of reaction were found to be *m*- and *p*-hydroxybenzoic acid (no ortho isomer). The ratio of meta:para isomers was found to be ~1:1 for both the acid-catalyzed and noncatalyzed reactions with Ib, while acid-catalyzed aromatization of Ia yields predominantly the meta isomer. The product analysis as well as the lack of importance of spontaneous aromatization of undissociated I is in accord with a previous suggestion of formation of resonance-stabilized carbonium ions as being rate determining in the aromatization of benzene oxides.

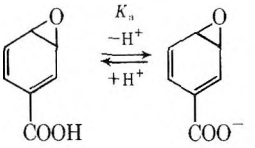
Arene oxides have been proposed as metabolic intermediates involved in necrosis,[1] mutagenesis,[2] and carcinogenesis.[3] Detailed studies of the kinetics for the aromatization of these intermediates indicate that the reaction proceeds *via* both specific acid catalyzed ($k_H$) and spontaneous ($k_o$) pathways.[4] Both pathways involve oxirane ring opening to form carbonium ions in the rate-determining step. In the spontaneous path, the carbonium ion may undergo intramolecular hydride transfer to give a ketone, which then enolizes to form the phenol (NIH shift). In competition with the NIH shift the carbonium ion may collapse to form isomeric arene oxides.[5] In the acid-catalyzed path, the intermediate carbonium ion may undergo intramolecular hydride transfer to give the protonated ketone, simply lose a proton to give the phenol directly, or reversibly trap solvent to give a diol.[6] The overall reaction is shown in Scheme I.

**Scheme I**




Support for the rate-determining formation of the carbonium ion lies in the observation of strong substituent effects ($\rho \simeq -7$) on the aromatization of several substituted benzene oxides.[7] The intermediacy of a ketone was proposed to account for the NIH shift[8] which has been observed to occur during the aromatization of these compounds. In certain instances the ketone may be observed.[9] For indan oxide the ketone has been established to reside along the reaction path.[5,10]

If the mechanism involving rate-determining carbonium ion formation through both spontaneous and acid catalysis is correct, then the presence of an ionizable substituent should result in two species, each of which may react by either of two different pathways. Herein is reported the dependence on pH of both reaction rate and product ratio in the aromatization of 4-carboxybenzene oxide (I).




Ia Ib

## Experimental Section

**Materials.** Reagent grade potassium chloride, ferric chloride, and potassium hydroxide were used without further purification. The *o*- and *p*-hydroxybenzoic acids were purchased from Eastman, the *m*-hydroxybenzoic acid from Aldrich, and the 2,4-dihydroxybenzoic acid from Matheson Coleman and Bell. These compounds were also used without further purification. The former acid buffer was prepared from formic acid (Matheson Coleman and Bell) and sodium formate (B and A grade, Specialty Chemicals Division, Allied Chemical Co.) while the acetic acid buffer was prepared from glacial acetic acid (B and A grade, General Chemical Division, Allied Chemical Co.) and sodium acetate trihydrate (Analytical Reagent, Mallinckrodt Chemical Works). Dioxane was refluxed over and distilled from sodium prior to use.

**3,4-Oxo-2,5-dihydrobenzoic Acid (2).** To a suspension of 84.2 g (0.68 mol) of 2,5-dihydrobenzoic acid[11] and 10 g of anhydrous NaOAc in 1250 ml of $CHCl_3$ was added dropwise 168 g (0.88 mol) of 40% peracetic acid. The mixture was stirred overnight at room temperature, extracted with two 300-ml portions of saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated to give off-white crystals that were recrystallized from $CHCl_3$ to give 65.5 g (69%) of **2**: mp 149–150°; ir ($CHCl_3$) 3600–2300 (broad), 1700, 1655, 1425, 1305, 1275, 950, 885 $cm^{-1}$; nmr ($CDCl_3$, DMSO-$d_6$) $\delta$ 9.16 (broad s, 1 H), 6.80 (m, 1 H), 3.30 (m, 2 H), and 2.70 ppm (m, 4, H).

*Anal.* Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.82; H, 5.55.

**Trimethylsilyl 3,4-Oxo-2,5-dihydrobenzoate (3).** A mixture of 59.0 g (0.42 mol) of **2** and 55.0 g (0.42 mol) of *N*-(trimethylsilyl)-acetamide in 450 ml of $CCl_4$ was heated under reflux for 1 hr. The mixture was cooled, the acetamide was filtered, the solvent was evaporated, and the residual oil was distilled to give 72.1 g (81%) of **3**: bp 77–82° (0.15 mm); ir ($CCl_4$) 2990, 2955, 2895, 2800, 1695, 1660, 1440, 1420, 1410, 1395, 1365, 1345, 1300, 1265, 1250, 1210, 1080, 1050, 1005, 950, 850 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 6.83 (m, 1 H), 3.38 (m, 2 H), 2.73 (m, 4 H), and 0.33 ppm (s, 9 H).

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**4-Carboxyoxepin-4-Carboxybenzene Oxide (1).** To a solution of 5.43 g (25.5 mmol) of 3 in 50 ml of $CCl_4$ was added 4.54 g (25.5 mmol) of *N*-bromosuccinimide and the mixture was heated under reflux and irradiated for 0.5 hr. The mixture was cooled, the succinimide was filtered, and the solvent was evaporated to give a bromide mixture which was used without further purification. The bromide mixture was dissolved in 50 ml of ether, 3.34 g (33 mmol) of triethylamine was added, and the mixture was stirred overnight at room temperature. The precipitated triethylamine hydrobromide was removed by filtration and the ether was evaporated to give a red-brown oil that was triturated with hexane. The hexane solution was decanted and evaporated under reduced pressure to give a red-orange oil that was distilled under reduced pressure to give 1.65 g (31%) of **4**: bp 85–90° (0.1 mm); ir ($CCl_4$) 3030, 2950, 2885, 1695, 1635, 1575, 1450, 1320, 1280, 1255, 1235, 1100, 1075, 990, 950, 850 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 7.07 (d, 1 H, $J$ = 6 Hz), 6.18 (d, 1 H, $J$ = 6 Hz), 5.63 (m, 3 H), and 0.33 ppm (s, 9 H).

To a solution of 0.4 g (2 mmol) of 4 in 1 ml of $CCl_4$ was added 40 $\mu$l of water and 60 $\mu$l of $CH_3OH$. The mixture was kept at room temperature for 45 min with occasional shaking and the solvents and trimethylsilyl alcohol were evaporated under vacuum to give 0.28 g (100%) of 1 that was recrystallized from hexane as light orange needles: mp 94–98°; uv max (hexane) 306 nm ($\epsilon$ 2010); ir ($CCl_4$) 3350–2400 (broad), 1695, 1640, 1610, 1580, 1430, 1400, 1280, 1240, 1105, 1080, 950 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 11.10 (broad s, 1 H), 7.05 (d, 1 H, $J$ = 6 Hz), 5.95 (d, 1 H, $J$ = 6 Hz) and 5.42 ppm (m, 3 H).

*Anal.* Calcd for $C_7H_6O_3$: C, 60.86; H, 4.38. Found: C, 61.06; H, 4.15.

**Kinetic Measurements.** The kinetic reactions were run in either deionized and glass-distilled water or in 50% aqueous dioxane. In both solvents the temperature was held at 30.0 ± 0.1° and the ionic strength was maintained at $\mu$ = 0.2 with potassium chloride. With the exception of the buffer dilutions, all reactions were carried out in a thermostated pH-stat cell designed for use in a Cary 15 spectrophotometer.[12]

The reactions run in water were followed by monitoring the appearance of products at 233 nm below pH 6, and at 235 nm at higher pH values. Those run in 50% aqueous dioxane were followed by monitoring both product formation at 260 nm and arene oxide disappearance at 330 nm. These wavelengths were chosen because they represent the wavelengths at which the maximum change in absorbance occurs. Each reaction was initiated by the addition of a small amount of solid 4-carboxybenzene oxide to give a concentration of $10^{-5}$–$10^{-6}$ $M$.

The reactions were clearly first order without the intervention of any detectable intermediates. When the reactions were followed by repetitive scanning, tight isosbestic points were established. In water, the isosbestic points appeared at 280 nm at pH 4.0 and at 299 nm at pH 8.6. In 50% aqueous dioxane they appeared at 307 nm at pH 2.9 and at 300 nm at pH 10.3. Pseudo-first order rate constants for all reactions were calculated by least-squares analysis of plots of ln $(A_\infty - A_0)/A_\infty - A_t)$ *vs.* time on a Hewlett-Packard 9820A calculator. The plots were all linear over at least 2 half-lives.

For the buffer dilutions the reactions were run in cuvettes. At each pH, the reaction was run at five different buffer concentrations. The reactions were carried out in a Cary 16 spectrophotometer so that all five reactions could be run simultaneously. As before, the reactions were followed by monitoring the change in absorbance at 233 nm. Pseudo-first order rate constants were calculated for each reaction as described above.

**Product Analysis.** Product analysis was carried out spectrophotometrically. At the end of each reaction the pH was adjusted to 7.0 and the spectrum was recorded. The following simultaneous equations were then solved for the concentrations of *p*-hydroxybenzoic ($C^p$) and *m*-hydroxybenzoic acid ($C^m$) in solution. In

$$A_{235} = a^p_{235}bC^p + a^m_{235}bC^m$$

$$A_{245} = a^p_{245}bC^p + a^m_{245}bC^m$$

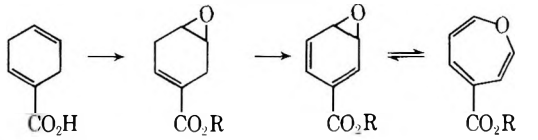
these equations, $A_{235}$ and $A_{245}$ are the absorbances at 235 and 245 nm, respectively, $b$ is the path length of the cell in centimeters, and $a^p$ and $a^m$ are the absorptivities of *p*- and *m*-hydroxybenzoic acids at the respective wavelengths. The products $a^p_{235}b$, $a^m_{235}b$, $a^p_{245}b$, and $a^m_{245}b$ were determined from the spectra of a set of standard solutions containing the same total concentration but different ratios of the isomeric *m*- and *p*-hydroxybenzoic acids. These particular wavelengths were chosen because calculations using the parameters determined at these wavelengths resulted in the best agreement when solutions of known concentrations were analyzed. The accuracy of this method is limited to ±5%.

The presence of o-hydroxybenzoic acid was analyzed for by mixing an aliquot of the reaction products with a 20% solution of ferric chloride in 0.1 *N* HCl.[13] Control runs using both salicylic acid and 2,4-dihydroxybenzoic acid resulted in the formation of a dark brown complex which absorbs strongly in the region 550–530 nm. When this test was applied to the products of the hydrolysis of 4-carboxybenzene oxide, no absorbance was detected in the specified region.

## Results

The synthesis of 1 was accomplished as indicated in Scheme II. Epoxidation of 2,5-dihydrobenzoic acid with peracetic acid afforded **2**, that was converted to **3** by reaction with *N*-trimethylsilyl acetamide. Allylic bromination of **3** with *N*-bromosuccinimide gave a mixture of monobromides which afforded **4** on treatment with triethylamine in ether. Ester **4** was hydrolyzed to the carboxylic acid **1** by treatment of a carbon tetrachloride solution with a small amount of aqueous methanol.

**Scheme II**




**2**, R = H
**3**, R = $Me_3Si$
**4**, R = $Me_3Si$
**1**, R = H

The rate of aromatization of 4-carboxybenzene oxide was measured over the pH range 0–10.5. The reactions were carried out in water at 30°, with $\mu$ = 0.2. The resulting log $k_{obsd}$ *vs.* pH profile is shown in Figure 1. The solid line which best fits the experimental data was generated by computer from eq 1, where $a_H$ = hydrogen ion activity

$$k_{obsd} = \frac{k_H a_H^2 + k'_H a_H K_a + k'_0 K_a}{K_a + a_H} \quad (1)$$

as determined with the glass electrode and $k_H$ = 8.50 × $10^{-2}$ $M^{-1}$ $sec^{-1}$, $k'_H$ = 4.25 $M^{-1}$ $sec^{-1}$, $k'_o$ = 3.50 × $10^{-4}$ $sec^{-1}$, and p$K_a$ = 3.70. The dotted line in Figure 1 was generated from eq 2 assuming $k_o$ = 3.50 × $10^{-4}$ $sec^{-1}$ and $k_H$ = 8.50 × $10^{-2}$ $M^{-1}$ $sec^{-1}$. The inability of eq 2 to fit the experimental data is evidence for observable, aromatization rates for both Ia and Ib.

$$k_{obsd} = k_0 + k_H a_H \quad (2)$$

The products of the aromatization of 4-carboxybenzene oxide are *m*- and *p*-hydroxybenzoic acid. The absence of o-hydroxybenzoic acid was shown by mixing aliquots of the reacton products with a 20% solution of ferric chloride in 0.1 *N* HCl. The lack of absorbance by the solutions in

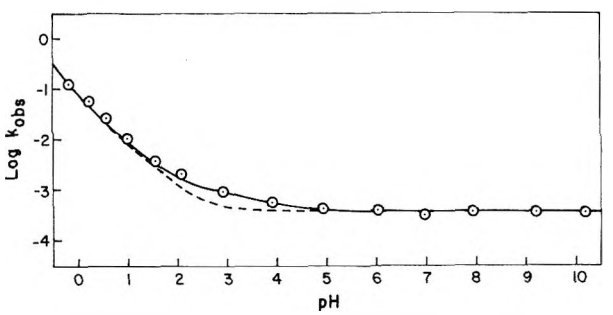



**Figure 1.** Plots of log $k_{obsd}$ *vs.* pH at 30°. The solid line was generated by computer from eq 1. The dashed line was generated by computer from eq 2.

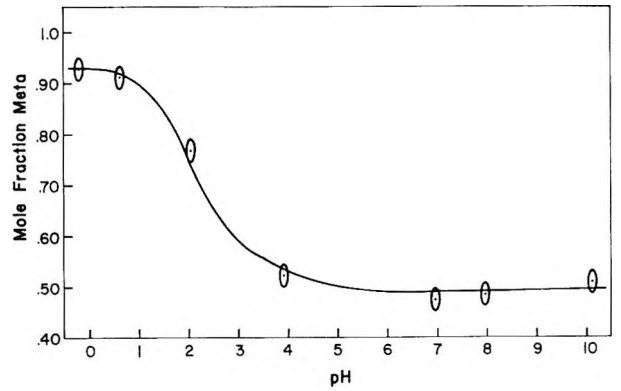



**Figure 2.** Plot of mole fraction meta *vs.* pH. The line was generated by computer from eq 3.

the region 530-550 nm is proof that o-hydroxybenzoic acid was not present in the products. The product ratio (*i.e.*, meta/para) was found to be pH dependent. A plot of mole fraction meta *vs.* pH is shown in Figure 2. The line which best fits the experimental data was generated from eq 3.

$$\text{Mole fraction meta} = \frac{Ak_H a_H^2 + Bk'_H a_H K_a + Ck'_0 K_a}{k_H a_H^2 + k'_H a_H K_a + k'_0 K_a} \quad (3)$$

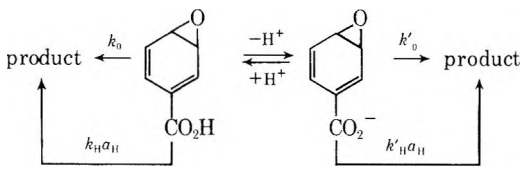
In this equation, $A$ is the mole fraction of meta isomer produced *via* $k_H$, $B$ is the mole fraction of meta produced *via* $k_H'$, and $C$ is the mole fraction of meta *via* $k'_0$. The values calculated for these constants are $A = 0.93$, $B = 0.56$, and $C = 0.49$.

The effect of total buffer concentration on the rate of aromatization is shown in Table I. The buffer at pH 4.41 was prepared from a mixture of acetic acid and sodium acetate, while the buffer at pH 3.42 consisted of formic acid and sodium formate. The lack of any significant concentration dependence is evidence that general acid catalysis is not operative with either acetic or formic acids.

## Discussion

The kinetics of the aromatization of 4-carboxybenzene oxide are essentially the same as those observed for the aromatization of benzene oxide. The only difference lies in the number of rate terms needed to describe the pH dependence of the reaction. Owing to the presence of an ionizable carboxyl group, 4-carboxybenzene oxide can exist in solution as either a neutral molecule (Ia) or as a negatively charged carboxylate anion (Ib). Since each of these species can react by both a spontaneous and an acid-catalyzed path, the overall reaction would be as shown in Scheme III. Thus, the rate expression used to describe

**Scheme III**




this reaction should incorporate all four rate constants, plus the equilibrium constant, $K_a$, for the acid dissociation. The equation derived for this reaction is eq 4. In this

$$k_{obsd} = \frac{k_H a_H^2 + k_0 a_H + k'_H a_H K_a + k'_0 K_a}{K_a + a_H} \quad (4)$$

equation $k_H$ and $k_0$ represent the acid-catalyzed and spontaneous aromatization of Ia, while $k'_H$ and $k'_0$ denote the corresponding rates for Ib.

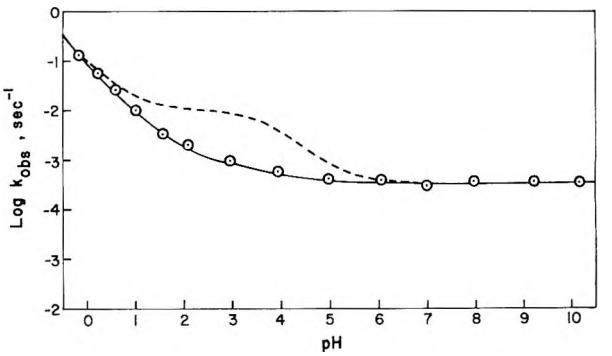



**Figure 3.** Plots of log $k_{obsd}$ *vs.* pH. The dashed line was generated from eq 4, where $k_H = 8.50 \times 10^{-2}\ M^{-1}\ sec^{-1}$, $k_0 = 9.00 \times 10^{-3}\ sec^{-1}$, $k'_H = 4.25\ M^{-1}\ sec^{-1}$, $k'_0 = 3.50 \times 10^{-4}\ sec^{-1}$, and $pK_a = 3.70$. The solid line is the same as that shown in Figure 1.

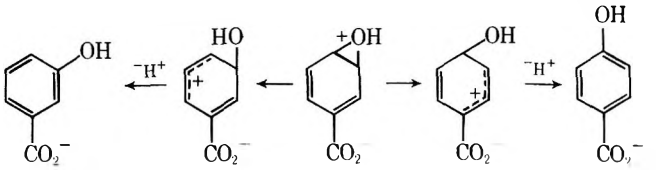
**Table I**
**Effect of Total Buffer Concentration on the Rate of Aromatization of 4-Carboxybenzene Oxide**

| Total buffer concn, $M$ | $k_{obsd} \times 10^4$, $sec^{-1}$ pH 3.42 | pH 4.41 |
|---|---|---|
| 0.01 | 5.84 | 4.01 |
| 0.0075 | 6.56 | 4.32 |
| 0.0050 | 6.37 | 4.30 |
| 0.0025 | 6.87 | 4.49 |
| 0.0010 | 6.67 | 4.58 |

If all four rate processes included in Scheme III (eq 4) are competitive with each other, then the log $k_{obsd}$ *vs.* pH profile predicted for I would be as shown in Figure 3, where $k_H = 8.50 \times 10^{-2}\ M^{-1}\ sec^{-1}$, $k_0 = 9.0 \times 10^{-3}\ sec^{-1}$, $k'_H = 4.25\ M^{-1}\ sec^{-1}$, and $k'_0 = 3.50 \times 10^{-4}\ sec^{-1}$. This profile contains plateau regions for both $k_0$ and $k'_0$, plus acid-catalyzed regions for $k_H$ and $k'_H$. The experimentally observed log $k_{obsd}$ *vs.* pH profile is shown in Figure 1. The only difference between the predicted and observed profiles occurs in the pH range 1.5-5.0. Although the observed profile does include an inflection in this region, a distinct plateau is not observed. The rate expression which best fits the experimental eq 1 differs from eq 4 in that the rate constant ($k_0$) for the spontaneous aromatization of Ia is absent. The omission of this rate constant may be justified if one considers the effect substituents have on the reaction rate. The $\rho$ for the aromatization of a series of substituted arene oxides has been determined to be $\sim -7.6$ in 50% dioxane-water. The value of $\sigma^+$ for the carboxyl group is +0.42, while the corresponding value for the carboxylate anion is −0.02. If $\rho = -7.6$, then $k'_0$ should be greater than $k_0$ by a factor of $\sim 1200$. Since $k'_0 = 3.50 \times 10^{-4}\ sec^{-1}$, the value for $k_0$ would be $\sim 4.2 \times 10^{-7}\ sec^{-1}$. A reaction associated with such a small rate constant would not be competitive with the other processes. Further justification for this treatment can be obtained by comparing the difference between $k_H$ and $k'_H$. Even if this 50-fold difference is all that applies to the spontaneous rates, that would still correspond to a $k_0$ of $\sim 7 \times 10^{-6}\ sec^{-1}$. It is unlikely that a reaction this slow would be observable under our conditions.

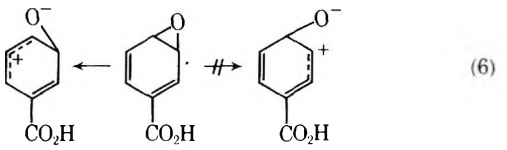
As shown in Figure 2, the product ratio is different for various reaction paths. While the ratio of *m*- to *p*-hydroxybenzoic acid is essentially 1:1 for both the acid-catalyzed and spontaneous aromatization of Ib, the meta isomer is the major product for the aromatization of Ia. Again, possible justification can be found in the electronic effects of the substituents. Since the carboxylate anion has a very small substituent constant ($\sigma^+ = -0.02$), its presence should have little influence on the $\pi$-electron system of the ring. Therefore, regardless of whether the oxirane ring

opens to form an incipient carbonium ion at the 1 or 2 position, both would be allylically stabilized by the adjacent double bond (eq 5). On the other hand, the protonated



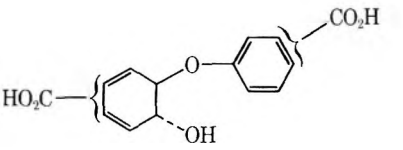
(5)

carboxyl is strongly electron withdrawing ($\sigma^+ = +0.42$). This effect should be particularly significant on the $\pi$ electrons of the double bond between carbons 3 and 4. As a result, these electrons would not be as available for stabilization of a positive charge as would the electrons in the $\pi$ bond between carbons 5 and 6. Consequently, the opening which leads to formation of the meta isomer would be of lower energy than the opening which leads to the *p*-hydroxybenzoic acid, as shown in eq 6.



(6)

In an effort to correlate the reaction of I with the reaction of previously studied arene oxides, the rate of aromatization of I was measured in 50% dioxane–water. At high pH the reaction was first order. Although the observed rate constant was smaller than that predicted from the $\sigma^+\rho$ plot, the agreement was not unreasonable. At pH 0.5, the reaction exhibited biphasic kinetics. This was possibly due to some type of nucleophilic participation by the dioxane oxygens. In conjunction with this, it was found that I also undergoes some sort of transformation on standing in THF. The reaction probably involves rearrangement of 1 to a mixture of *m*- and *p*-hydroxybenzoic acid that undergoes nucleophilic addition to 1 to afford a mixture of products (5). The transformation is analogous to the formation of *trans*-6-phenoxycyclohexa-2,4-dien-1-ol from oxepin–benzene oxide.[14]



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**Acknowledgment.** This work was supported by a National Institutes of Health grant to Thomas C. Bruice.

**Registry No.**—1, 51380-68-8; 2, 51380-69-9; 3, 51380-70-2; 4, 51380-71-3; 2,5-dihydroxybenzoic acid, 490-79-9.

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# Electron Spin Resonance Studies of Hydrogen Transfer to Alkoxy Radicals from the Hydroxyl Group of Alcohols

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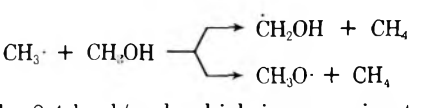
The esr spectra of *tert*-butyl radicals are observed during the reactions of various alkoxy radicals with tertiary alcohols containing one or more *tert*-butyl groups. The homolytic fragmentation of the alcohol is attributed to hydrogen transfer from the hydroxylic function to the alkoxy radical. Structural factors pertinent to the alcohol and alkoxy radical are explored in hydrogen transfer reactions of the hydroxyl group. Hydrogen bonding of alcohols to HF strongly inhibits the transfer of hydrogen from a hydroxylic function.

In solution, the majority of alcohols are preferentially attacked by free radicals at the $\alpha$-CH bond, with the exception of tertiary alcohols, of course. The resulting $\alpha$-hydroxyalkyl radicals have been trapped by olefins and their electron spin resonance spectra examined.[1-4]

Abstraction of the hydroxylic proton has been less commonly observed. For example, deuterium-labeling studies indicate that methanol reacts with methyl radicals in solution at the carbon–hydrogen bond 15 times faster than at the hydroxylic position at 30°.[5-7] The activation energy for hydrogen abstraction by methyl radical has been estimated to be 8.4 kcal/mol, which is approximately 3 kcal/mol higher than that of the corresponding reaction with methoxy radical.[8] Thermodynamic factors also favor abstraction from the $\alpha$-CH bond by 5–10 kcal/mol.[9,10]



(1)
(2)

In the gas phase, however, the relative rates of reactions 1 and 2 are reversed, and the O–H bond is preferentially broken. Solvent effects on the reactions of hydroxyl groups and free radicals could be partly accounted for by the dif-

**Table I**
**Reactions of Alkoxy Radicals with *tert*-Butylcarbinols**

| Alcohol $R^1R^2R^3COH$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | Registry no. | Alkoxy[a] radical | Registry no. | Radical observed | Registry no. | Hyperfine splitting,[b] G |
| $CH_3$ | $CH_3$ | $(CH_3)_3C$ | 594-83-2 | $Bu^tO\cdot$ | 3141-58-0 | $(CH_3)_3C\cdot$ | 1605-73-8 | $a_H$ = 22.73[c] |
| $CH_3$ | $CH_3$ | $(CH_3)_3C$ | | $PhC(CH_3)_2O\cdot$ | 16812-36-5 | $(CH_3)_3C\cdot$ | | |
| $CH_3$ | $CH_3$ | $(CH_3)_3C$ | | $CF_3O\cdot$ | 21811-29-0 | $\Delta\cdot$[d] | | $a_\alpha$ = 6.69, $a_\beta$ = 23.47 |
| | | | | | | $FCH_2CH_2CH_2\cdot$ | 38816-77-2 | $a_\alpha$ = 22.52, $a_\beta$ = 27.97 |
| $CH_3$ | $(CH_3)_2CH$ | $(CH_3)_3C$ | 29772-39-2 | $Bu^tO\cdot$ | | $(CH_3)_3C\cdot$ | | $a_H$ = 22.70 |
| $CH_3$ | $(CH_3)_2CH$ | $(CH_3)_3C$ | | $CF_3O\cdot$ | | $(CH_3)_2\dot{C}C(CH_3)(Bu^t)OH$ | 51392-63-3 | Not observed |
| $CH_3$ | $(CH_3)_3C$ | $(CH_3)_3C$ | 5857-69-2 | $Bu^tO\cdot$ | | $(CH_3)_3C\cdot$ | | $a_H$ = 22.76 |
| | | | | | | $\cdot CH_2C(Bu^t)_2OH$ | 51392-64-4 | Not observed |
| $CH_3CH_2$ | $(CH_3)_3C$ | $(CH_3)_3C$ | 32579-68-3 | $Bu^tO\cdot$ | | $(CH_3)_3C\cdot$, broad singlet[d] | | $a_H$ = 22.68 |
| $(CH_3)_2CH$ | $(CH_3)_3C$ | $(CH_3)_3C$ | 5457-42-1 | $Bu^tO\cdot$ | | $(CH_3)_3C\cdot$ | | $a_H$ = 22.74 |
| | | | | | | $(CH_3)_2\dot{C}C(Bu^t)_2OH$, broad singlet | 51392-65-5 | Not observed |
| | | | | | | $\Delta\cdot$, $FCH_2CH_2CH_2\cdot$ | | |
| $(CH_3)_2CH$ | $(CH_3)_3C$ | $(CH_3)_3C$ | | $CF_3O\cdot$ | | $(CH_3)_3C\cdot$ | | $a_H$ = 22.73 |
| $CH_3$ | $C_6H_5$ | $(CH_3)_3C$ | 21811-48-3 | $Bu^tO\cdot$ | | $(CH_3)_3C\cdot$ | | $a_H$ = 22.79 |
| $(CH_3)_3C$ | $(CH_3)_3C$ | $(CH_3)_3C$ | 41902-42-5 | $Bu^tO\cdot$ | | $(CH_3)_3C\cdot$ | | |
| | | | | | | $\Delta\cdot$, broad singlet | | |
| $(CH_3)_3C$ | $(CH_3)_3C$ | $(CH_3)_3C$ | | $CF_3O\cdot$ | | $\Delta\cdot$ | | |

[a] $Bu^tO\cdot$ from DTBP, $CF_3O\cdot$ from bis(trifluoromethyl) peroxide in cyclopropane solutions. [b] Measured at −80°, $g$ = 2.00276. [d] In addition to a 1:2:1 triplet with splitting of 21.95 G, $g$ = 2.00274. [e] Cyclopropyl radical.

ferences in hydrogen bonding in the initial and final states.[11,12] Methoxy radical has been established as the most abundant species produced in the γ-radiolysis of liquid methanol.[13,14]

$$CH_3OH \longrightarrow CH_3O\cdot + H\cdot$$

The competition between the removal of a hydrogen from an α carbon or oxygen is not readily ascertained. Thus, the esr spectra of alkoxy radicals, unlike those of alkyl radicals, are broadened beyond detection in solution, and this direct technique is not an adequate probe for detecting these oxygen-centered radicals in solution.[15] Chemical and spin traps have been used for alkoxy radicals derived from various alkyl peroxides and other precursors except alcohols.[16-18]

In the course of our investigations of oxygen-substituted alkyl radicals from tertiary alcohols,[19] we unexpectedly observed the esr spectra of alkyl radicals derived from the fragmentation of the alcohol, *e.g.*

$$(CH_3)_3CC(CH_3)_2OH + RO\cdot \rightsquigarrow (CH_3)_3C\cdot$$

The results are most readily accommodated by postulating the ready formation and subsequent β-scission of an alkoxy radical intermediate according to eq 3 and 4.

$$(CH_3)_3CC(CH_3)_2OH + RO\cdot \longrightarrow (CH_3)_3CC(CH_3)O\cdot + ROH \quad (3)$$

$$(CH_3)_3CC(CH_3)_2O\cdot \longrightarrow (CH_3)_3C\cdot + (CH_3)_2CO \quad (4)$$

In this paper we wish to present our study of the homolytic transfer of hydrogen from alcohols. After this work was largely completed, Griller and Ingold reported similar results.[20]

## Results and Discussion

The photolysis of di-*tert*-butyl peroxide (DTBP) with ultraviolet radiation constitutes a useful technique for the generation of *tert*-butoxy radicals in solution for a variety of esr studies.[21]

$$Bu^tOOBu^t \xrightarrow{h\nu} 2Bu^tO\cdot \quad (5)$$

$$Bu^tO\cdot + RH \longrightarrow Bu^tOH + R\cdot \quad (6)$$

**Hydrogen Transfer from tert-Butylcarbinols.** The intense esr spectrum of the *tert*-butyl radical shown in Figure 1 with resolved second-order splittings was obtained when a cyclopropane solution of DTBP and *tert*-butyldimethylcarbinol (triptyl alcohol) was irradiated in the cavity of the esr spectrometer. The spectrum appeared immediately upon irradiation of the solution and was essentially unchanged between −140 and −30°. The same spectrum was also observed when *tert*-butyldimethylcarbinol was treated with dicumyl peroxide, which shows unequivocally that the *tert*-butyl radical was derived from the carbinol. Furthermore, the esr spectrum of the *tert*-butyl radical was derived from a variety of tertiary carbinols containing one or more α-*tert*-butyl substituents as listed in Table I, including tri-*tert*-butylcarbinol, which has no β hydrogen. The latter precludes the possibility of the cleavage proceeding *via* a carbon-centered species such as that in eq 7. Furthermore, we did not observe the esr

$$(CH_3)_3C\overset{\cdot CH_2}{\overset{|}{C}}(CH_3)OH \longrightarrow (CH_3)_3C\cdot + CH_2{=}C(OH)CH_3 \quad (7)$$

spectrum of this parent species,[22] which is in accord with previous studies indicating that abstraction of methyl protons by *tert*-butoxy radicals to be a relatively slow and unimportant process.[21] The spectrum in Figure 1, how-

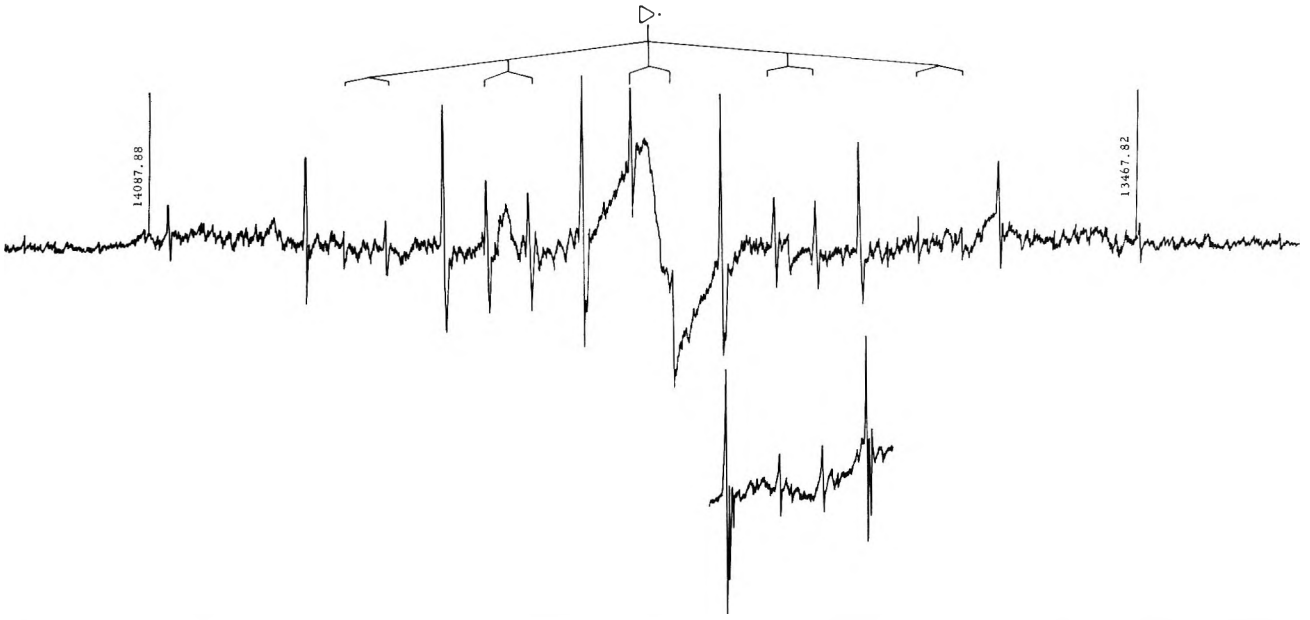
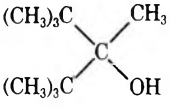



**Figure 1.** Esr spectrum of the *tert*-butyl radical and the cyclopropyl radical from the reaction of *tert*-butyldimethylcarbinol with *tert*-butoxy radical in cyclopropane solution. Inset below shows resolved second-order splittings for part of the spectrum of *tert*-butyl radical. Proton nmr field markers are in kilohertz.

ever, does show the presence of cyclopropyl radicals derived from the solvent, in addition to an unidentified broad absorption centered at $\langle g \rangle = 2.0028$, which we have been unable to resolve further. The products of the photolysis under these conditions were not examined quantitatively. However, qualitative analysis indicated that significant amounts of pinacolone and *tert*-butyl alcohol are derived from di-*tert*-butylmethylcarbinol, which is consistent with the process described in reaction 8.



$$+ \text{Bu}'\text{O}\cdot \longrightarrow \text{Bu}'\text{OH} + (\text{CH}_3)_3\text{C}\cdot + (\text{CH}_3)_3\text{CC}(=\text{O})\text{CH}_3 \quad (8)$$

Abstraction of hydrogen from alcohols was also examined with other oxygen-centered radicals. With *tert*-amyloxy radicals derived from di-*tert*-amyl peroxide, the rate of $\beta$-scission was apparently too fast to compete with hydrogen abstraction, and only the esr spectrum of the ethyl radical was observed in the presence of triptyl alcohol. Independent studies have shown that reaction 9 is roughly

$$\text{CH}_3\text{CH}_2\text{C}(\text{CH}_3)_2\text{O}\cdot \longrightarrow \text{CH}_3\text{CH}_2\cdot + (\text{CH}_3)_2\text{CO} \quad (9)$$

300 times faster than the cleavage of *tert*-butoxy radical and has an activation energy that is smaller by at least 10 kcal/mol.[23] Diisopropyl peroxide under the same conditions afforded only the spectrum of $\alpha$-hydroxyisopropyl radical, which is derived from isopropyl alcohol produced during the rapid induced decomposition of the peroxide,[24] *e.g.*

$$(\text{CH}_3)_2\text{CHO}\cdot + (\text{CH}_3)_2\text{CHOOCH}(\text{CH}_3)_2 \longrightarrow (\text{CH}_3)_2\text{CHOH} + (\text{CH}_3)_2\text{CHOO}\dot{\text{C}}(\text{CH}_3)_2 \quad (10)$$

$$(\text{CH}_3)_2\text{CHOO}\dot{\text{C}}(\text{CH}_3)_2 \longrightarrow (\text{CH}_3)_2\text{CO} + (\text{CH}_3)_2\text{CHO}\cdot$$

$$(\text{CH}_3)_2\text{CHO}\cdot + (\text{CH}_3)_2\text{CHOH} \longrightarrow (\text{CH}_3)_2\text{CHOH} + (\text{CH}_3)_2\dot{\text{C}}\text{OH}$$

Hydrogen peroxide (90%) was too insoluble in the hydrocarbon medium to be useful.

If polar effects in the transition state for hydrogen abstraction are considered, the rate should be enhanced by electronegative species such as trifluoromethoxy radicals owing to the participation of structures such as Ib. Considering this possibility, we were disappointed to find that photolysis of solutions of bis(trifluoromethyl) peroxide and *tert*-butylcarbinols afforded only the esr spectrum of the solvent-derived radicals, *i.e.*, cyclopropyl and $\gamma$-fluoropropyl. The latter is presumably derived from fluorine atom *via* fragmentation of the intermediate trifluoromethoxy radical followed by ring opening of cyclopropane. We interpret the lack of attack on alcohol under these conditions to the strong hydrogen-bonding properties of hydrogen fluoride liberated during the spontaneous decomposition of trifluoromethanol. Deactivation of the alcohol can be shown independently by the deliberate addition of anhydrous hydrogen fluoride to a pentane solution of triptyl alcohol and DTBP. Subsequent photolysis of the mixture afforded only the esr spectrum of the solvent-derived radical.

$$\text{RO}\cdot + \text{R}'\text{OH} \longrightarrow [\text{RO}\cdot\text{H}-\text{OR}' \longleftrightarrow \text{RO}^-\text{H}^+\text{OR}']^* \longrightarrow \text{products} \quad (11)$$

Ia Ib

$$\text{CF}_3\text{O}\cdot + \text{ROH} \longrightarrow \text{CF}_3\text{OH} + \text{R}\cdot \quad (12)$$

$$\text{CF}_3\text{OH} \xrightarrow{\text{fast}} \text{F}_2\text{CO} + \text{HF}$$

$$\text{ROH} + \text{HF} \longrightarrow \text{ROH}\cdots\text{F}\cdots\text{H}$$

**Structural Effects of the Alcohol in Hydrogen Transfer.** A variety of other alcohols listed in Table II were also examined in the presence of DTBP under similar conditions. In accord with previous studies, methyl alcohol afforded the esr spectrum of the hydroxymethyl radical and the spectrum of $\alpha$-hydroxyisopropyl radical was observed with isopropyl alcohol. No resolvable spectrum was obtained from *tert*-butyl alcohol with the use of either *tert*-butoxy or trifluoromethoxy radical as the abstracting agent. The absence of the spectrum of $\beta,\beta$-dimethyl-$\beta$-hydroxyethyl radical is in accord with the general inertness of methyl protons under these conditions (*vide supra*).

A number of simultaneous processes can be observed with isopropyldimethylcarbinol. Thus, this alcohol in the presence of *tert*-butoxy radical affords the spectrum of isopropyl radical in addition to that of the alcohol-derived radical II in eq 13. In the latter regard it is interesting to

**Table II**
**Reactions of Alcohols with Alkoxy Radicals**

| Alcohol $R^1R^2R^3COH$ | | | | Alkoxy | | | | |
|---|---|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | Registry no. | radical[a] | Radical observed | Registry no. | Hyperfine splitting, G | $\langle g \rangle$ |
| H | H | H | 67-56-1 | $Bu^tO\cdot$ | $HOCH_2\cdot$ | 2597-43-5 | $a_{CH_2} = 17.95$, $a_{OH} = 1.63$ | 2.00327 |
| H | H | H | | $CF_3O\cdot$ | $HOCH_2\cdot$ | | | |
| H | $CH_3$ | $CH_3$ | 67-63-0 | $Bu^tO\cdot$ | $HO\dot{C}(CH_3)_2$ | 5131-95-3 | $a_{CH_3} = 19.35$, $a_{OH} = 0.93$ | 2.00316 |
| H | $CH_3$ | $CH_3$ | | $CF_3O\cdot$ | $HO\dot{C}(CH_3)_2$ | | | |
| $CH_3$ | $CH_3$ | $CH_3$ | 75-65-0 | $Bu^tO\cdot$ | $CH_3\cdot$ | 2229-07-4 | Not observed | |
| $CH_3$ | $CH_3$ | $CH_3$ | | $CF_3O\cdot$ | $HO(CH_3)_2\dot{C}CH_2\cdot$ | 5723-74-0 | Not observed | |
| $CH_3$ | $CH_3$ | $(CH_3)_2CH$ | 594-60-5 | $Bu^tO\cdot$ | $(CH_3)_2\dot{C}H\cdot$ | 2025-55-0 | $a_\alpha = 21.87$, $a_\beta = 24.60$ | 2.00268 |
| $CH_3$ | $CH_3$ | $(CH_3)_2CH$ | | $CF_3O\cdot$ | $HO(CH_3)_2C\dot{C}(CH_3)_2$ Δ·, $FCH_2CH_2\dot{C}H_2\cdot$ | 51392-66-6 | $a_{CH_2} = 22.63$ | 2.00268 |

[a] $Bu^tO$ from DTBP, $CF_3O\cdot$ from bis(trifluoromethyl) peroxide in cyclopropane solutions. [b] Measured at −80°.

$$(CH_3)_2\dot{C}C(CH_3)_2OH + Bu^tOH \quad (13)$$

$$(CH_3)_2CHC(CH_3)_2OH + Bu^tO\cdot \quad II$$

$$(CH_3)_2CHC(CH_3)_2O\cdot + Bu^tOH \quad (14a)$$

$$(CH_3)_2CH\cdot + (CH_3)_2CO \quad (14b)$$

note that the *tert*-butylcarbinols in Table I containing more highly congested isopropyl groups did not afford esr spectra of analogous species. Variation of the temperature between −140 and −40° during photolysis did not appreciably alter the intensity of the esr spectrum of isopropyl radical relative to that of II.

Abstraction of hydrogen from the side chain appears to be a dominant process with other tertiary alkyldimethylcarbinols we examined. Thus, the benzyl-, alkyl-, and cyclopropyldimethylcarbinols on similar treatment afforded no spectrum of the alkyl radical resulting from fragmentation of the alcohol. Instead, only the spectra of the radicals derived by reactions at the alkyl groups were present, but their structures were not examined further.

**Rates and Intermediates in Hydrogen Transfer from Alcohols.** The simultaneous observation of the esr spectra of cyclopropyl and *tert*-butyl radicals during the photolysis of a cyclopropane solution of tri-*tert*-butylcarbinol and DTBP suggests that the rate of hydrogen transfer from the alcohol may be based on the following competitive scheme

$$Bu^tO\cdot + ROH \xrightarrow{k_1} RO\cdot + Bu^tOH \quad (15)$$

$$Bu^tO\cdot + SH \xrightarrow{k_2} S\cdot + Bu^tOH \quad (16)$$

$$RO\cdot + SH \xrightarrow{k_3} S\cdot + ROH \quad (17)$$

$$RO\cdot \xrightarrow{k_4} B\cdot + (CH_3)_2CO \quad (18)$$

$$S\cdot, B\cdot + \Sigma\chi_i \xrightarrow{k_5} \text{nonradical products} \quad (19)$$

where S· and B· represent cyclopropyl and *tert*-butyl radicals, respectively. The bimolecular rate constants $k_5$ are assumed to be the same for S· and B· and to include only interactions with other radical species $\Sigma\chi_i$ extant in solution. Under these simplifying conditions the steady-state concentrations of S· and B· are given by eq 20, if $k_2 \approx k_3$.

$$\frac{[S\cdot]}{[B\cdot]} = \frac{k_2[SH]}{k_4}\left(1 + \frac{k_3[SH] + k_4}{k_1}\frac{1}{[ROH]}\right) \quad (20)$$

Indeed, the relative concentration [S·]/[B·] at −80° is shown to be a linear function of 1/[ROH] in Figure 2. The slope of 0.07 is approximately equal to $k_2(SH)/k_1$, since $k_3/k_4$ is less than 1/300 according to the studies by Walling and Padwa.[25] Thus, we conclude that the rate of hydrogen transfer from tri-*tert*-butylcarbinol is about a factor of $10^2$ faster than transfer from cyclopropane.[26]

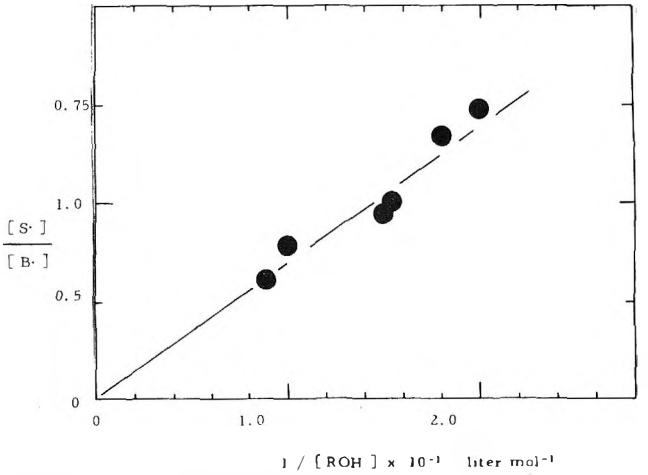



**Figure 2.** Relative concentrations of cyclopropyl and *tert*-butyl radicals from the reaction of tri-*tert*-butylcarbinol and *tert*-butoxy radical in cyclopropane solution at −80°. The linear plot was constrained to pass close to the origin, since $k_2[SH]/k_4$ in eq 20 is small.

Although the foregoing conclusion is based on the competitive kinetic scheme presented in eq 15–19, it is not necessary that the hydrogen transfer from the alcohol lead *directly* to an alkoxy radical as given in eq 15. Thus, an equivalent kinetic result is obtained if hydrogen transfer is accompanied by the simultaneous scission of the *tert*-butyl–$C_\alpha$ bond according to eq 21. Equation 21 is equivalent to the separate processes represented in eq 15 and 18.

$$[(CH_3)_3C]_3COH + Bu^tO\cdot \longrightarrow (CH_3)_3C\cdot + [(CH_3)_3C]_2CO + Bu^tOH \quad (21)$$

A necessary and sufficient condition for distinguishing between these two mechanisms is to show that an alkoxy radical is a discrete intermediate. The latter must be carried out by indirect experiments, since alkoxy radicals generally cannot be observed by esr studies in solution. Previous studies showed that trialkyl phosphites are efficient traps for alkoxy radicals and lead to phosphoranyl adducts III with large phosphorus splittings.[27] Griller and Ingold recently showed that the phosphorus splitting of $a_P$ = 890.3 G for the *tert*-butoxy adduct can be resolved from that of the triptyloxy adduct produced simultaneously during the photolysis of triptyl-*tert*-butyl peroxide in the presence of triethyl phosphite.[20,28]

$$RO\cdot + P(OR')_3 \longrightarrow \underset{III}{ROP(OR')_3} \quad (22)$$

**Table III**
**Esr Parameters of Alkoxy Adducts to Triethyl Phosphite**

| ROOR′ source | | | | Phosphoranyl adduct | | Hyperfine splitting | |
|---|---|---|---|---|---|---|---|
| R | R′ | Registry no. | Solvent[a] | ROP(OEt)$_3$ | Registry no. | $a_P$, G[b] | $\langle g \rangle$[c] |
| $(CH_3)_3C$ | $(CH_3)_3C$ | 110-05-4 | C–ROH | $(CH_3)_3C$ | 36761-40-7 | 884.6 | 2.003 |
| $(CH_3)_3C$ | $(CH_3)_3C$ | | C–MeOH | $(CH_3)_3C$ | | 886.0 | |
| $(CH_3)_3C$ | $(CH_3)_3CC(CH_3)_2$ | 6766-51-4 | C | $(CH_3)_3C$ | | 882.7 | |
| $(CH_3)_3C$ | $(CH_3)_3CC(CH_3)_2$ | | | $(CH_3)_3CC(CH_3)_2$ | 51392-68-8 | 897.0 | 2.003 |
| $CH_3$ | $(CH_3)_3C$ | 51392-67-7 | C | $(CH_3)_3C$[d] | | 884.6 | |
| $CH_3CH_2C(CH_3)_2$ | $CH_3CH_2C(CH_3)_2$ | 20639-96-7 | C | $CH_3CH_2C(CH_3)_2$ | 51392-69-9 | 887.4 | 2.003 |

[a] C = cyclopropane, ROH = triptyl alcohol. [b] Corrected to second order. [c] Corrected to second order using the Breit–Rabi equation: P. W. Atkins and M. C. R. Symons, "The Structure of Inorganic Radicals," Elsevier, Amsterdam, 1967. [d] Methoxy adduct may be unresolved.

We have been unable to trap triptyloxy radical as a phosphite adduct during photolysis of various mixtures of triptyl alcohol, DTBP, and triethyl phosphite at different temperatures. The esr spectrum consisted of the superposition of the spectrum of the *tert*-butoxy adduct III in Table III and that of the tert-butyl radical. The origin of the latter is ambiguous since it is known that the *tert*-butoxy adduct III (R = *tert*-butyl; R′ = ethyl) affords *tert*-butyl radicals by a competitive $\beta$-scission.[27] In order

$$(CH_3)_3COP(OEt)_3 \longrightarrow (CH_3)_3C\cdot + OP(OEt)_3 \qquad (23)$$

to obviate this difficulty, we employed di-*tert*-amyl, dicumyl, and bis(trifluoromethyl) peroxides in place of DTBP, but we were unable to observe the spectrum of either the triptyloxy adduct III or *tert*-butyl radical. We have also been unable to observe the spectrum of $\alpha,\alpha,\beta,\beta$-tetramethylpropyl radical possibly derived from the scission of the triptyloxy adduct III.[29]

The results up to this point unfortunately leave open the question of whether hydrogen transfer from alcohols is synchronous with the cleavage of an alkyl group.[30] Other competing reactions notwithstanding, the absence of alkyl cleavages in benzyl- and alkyldimethylcarbinols suggests that the driving force from such a contribution is probably not large.

## Summary and Conclusions

A variety of tertiary alcohols, especially those with one or more *tert*-butyl groups, are shown to be readily cleaved by photochemically generated *tert*-butoxy radicals. The reaction proceeds by hydrogen transfer from the hydroxylic function of the alcohol to *tert*-butoxy radicals. However, probing experiments have not yet proved whether hydrogen transfer and cleavage are synchronous processes. Examination of various alkoxy radicals from peroxidic precursors indicates that *tert*-butoxy is more effective than cumyloxy, *tert*-amyloxy, and trifluoromethoxy radicals. The ineffectiveness of *tert*-amyloxy radical is due to a competing $\beta$-scission. Hydrogen fluoride which is spontaneously formed from trifluoromethanol is strongly hydrogen bonded to alcohols and inhibits hydrogen transfer to trifluoromethoxy radical. Hydrogen bonding varies in alcohols owing to steric effects[32] and it may generally play a role in determining which alcohols are particularly susceptible to hydrogen transfer.[33] Quantitative knowledge of the steric crowding about the hydroxylic function and the nature of the hydrogen bonding in alcohols would help in establishing this relationship. This system merits further study to establish these points.

## Experimental Section

**Materials.** Di-*tert*-butyl peroxide was obtained from Shell Chemical Co., repeatedly washed with water, dried over calcium chloride, passed through an activated alumina column, and redistilled at reduced pressure prior to use. Bis(trifluoromethyl) peroxide was obtained from PCR, Inc. and used as such. Di-*tert*-amyl peroxide was prepared by the procedure of Raley, Rust, and Vaughan,[34] and was redistilled *in vacuo* and finally purified by elution of a pentane solution from an activated alumina column. Diisopropyl peroxide was prepared by the method of Pryor, *et al.*[24] Dicumyl peroxide was obtained from Hercules Chemical Co. and purified by alumina chromatography followed by recrystallization from pentane. Triethyl phosphite from Victor Chemical Co. was distilled once at atmospheric pressure under nitrogen and then redistilled from sodium metal at reduced pressure. Triptyl-*tert*-butyl peroxide was prepared by the method of Milas and Perry[35] and purified by redistillation at reduced pressure.

Triptyl alcohol was prepared from pinacolone and methylmagnesium bromide[36] and a pure sample was separated by preparative gas chromatography on a 5 ft 15% Carbowax 20M column on 30/60 mesh Chromosorb P (AW) at 150°. Triptyl alcohol, like others in the series, is extremely hygroscopic. Methyldi-*tert*-butylcarbinol, ethyldi-*tert*-butylcarbinol, methylisopropyl-*tert*-butylcarbinol, methyl-*tert*-butylphenylcarbinol, and dimethylisopropylcarbinol were prepared, characterized, and generously donated by Dr. G. F. Meier.[37] Tri-*tert*-butylcarbinol[38] and isopropyldi-*tert*-butylcarbinol were obtained as gifts from Professor V. J. Shiner, Jr., and purified by vacuum sublimation.

**Sample Preparation.** Samples were prepared on a vacuum line and thoroughly degassed using freeze–pump–thaw cycles. The sample composition, which consisted usually of 50–100 mg of alcohol: 0.2 ml of peroxide:1.5 ml of cyclopropane, was varied when necessary to optimize the signal-to-noise ratio. For trapping experiments the amount of triethyl phosphite added was varied from 0.05 to 0.2 ml for the above sample composition. For kinetic measurements, milligram quantities of tri-*tert*-butylcarbinol were transferred to the sample tubes by addition of a known volume of a standard solution of the alcohol in a volatile solvent (usually acetone) and removing it in vacuo. Di-*tert*-butyl peroxide (0.1 ml) was then added and after degassing cyclopropane was condensed into the tube to make the volume up to 1 ml at −78°.

**Esr Measurements.** The modified Varian X-band spectrometer, microwave frequency measurements, light source, and sample tubes were as described previously.[39] Perylene cation radical ($g$ = 2.00258)[40] was used as a standard for the $g$-value measurements in the configuration employed. The temperature measurements in the esr tube were calibrated with a thermocouple and are accurate to 5°. The ratios of [S·]/[B·] for the kinetic experiments were determined by averaging ten consecutive measurements of the relative intensities of selected esr lines for the different radicals, and correcting for their different degeneracies. The absence of line broadening by saturation or overmodulation was clear from the well-resolved second-order splittings in the concentration range studied. Since prolonged photolysis is expected to deplete the concentration of the alcohol, an experiment was conducted to follow the change of [S·]/[B·] with time of photolysis. The change after ten consecutive scans was found to be insignificant, compared to other experimental scatter and variations. An average for these ten values was employed rather than a value extrapolated to zero time.

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(29) It would be desirable to pursue this point with the use of isotopically (deuterium) labeled DTBP, since structural modifications of the peroxide apparently cause other complications described above.
(30) The trapping of triptyloxy by phosphite during photolysis of triptyl-*tert*-butyl peroxide[20] is not necessarily related to the production of free triptyloxy radicals, since the reaction may proceed *via* a peroxide–phosphite exciplex, reminiscent of the transition state in the well-known thermal reaction between phosphites and peroxides.[31] Trapping of triptyloxy derived from triptyl alcohol as a free alkoxy radical is less ambiguous.
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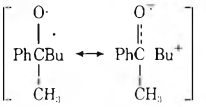

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# Organic Peroxides. X. Kinetics of Decomposition of Some Acyl-*p*-nitrobenzoyl Peroxides Containing Neophyl Groups


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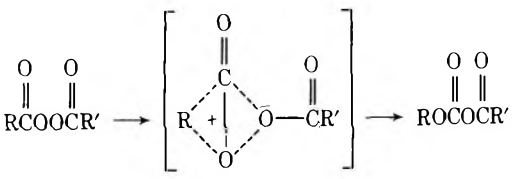
The kinetics of the thermal decompositions of a series of mixed β-(S-phenyl)isovaleryl *p*-nitrobenzoyl peroxides (S = *p*-$NO_2$, *m*-Br, *p*-Cl, H, *p*-$CH_3$, and *p*-$OCH_3$) in cyclohexane and in ethylbenzene were determined iodometrically in the temperature range 60–85° and at concentrations in the 0.002–0.02 *M* range. (Evidence is presented which shows that these peroxides initially form the carboxy-inversion compounds in good yield.) At these low concentrations, the kinetics (in both solvents) were found to be accurately first order, except in decompositions of the peroxide for which S = *p*-$NO_2$, in which case the first-order plots were curved so as to suggest a first plus higher order induced decomposition. The mathematical method used to correct for induced decomposition is presented. For the data obtained on the decompositions of five compounds at 75° in cyclohexane, an excellent correlation is obtained between log $k_d$ and Hammett σ's, when the corrected value of $k_d$ for the peroxide for which S = *p*-$NO_2$ is used, giving $\rho = -0.76 \pm 0.02$ ($r = 0.999$). However, for the data obtained at five temperatures in ethylbenzene, log $k_d$ correlates better with $\sigma^+$ ($r > 0.992$) than with σ ($r$ values near 0.97 at all five temperatures). The ρ values for the $\sigma^+$ correlations are −0.89, −0.85, −0.81, −0.77, and −0.74, respectively, at 60, 65, 70, 75, and 80°. The activation parameters obtained for the decompositions of these peroxides show good isokinetic behavior, with $\beta = 214°$. The rate constants obtained in ethylbenzene were extrapolated to 120° for comparison with rate constants obtained at that temperature on the decompositions of the corresponding *tert*-butyl peroxy esters by Rüchardt and Hecht. Although a log–log plot of the (extrapolated) peroxide and perester rate constants is not linear, a good correlation is obtained when log [$k_{peroxide}/k_{perester}$] is plotted against σ. The value of ($\rho_{peroxide} - \rho_{perester}$) obtained from this correlation (−0.61) indicates more sensitivity to substituents in the peroxide than in the perester series. Although this shows that the peroxide decompositions have more polar character than the decompositions of the peresters, the kinetics data presented here do not clearly delineate between identical and different transition states for the homolytic and carboxy-inversion product forming reactions of the β-phenylisovaleryl *p*-nitrobenzoyl peroxides.

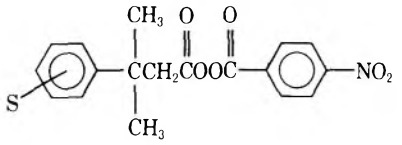

The formation of carboxy-inversion compounds in decompositions of diacyl peroxides has been the subject of a number of investigations during the past two decades.[3] Although some of the details involved in the mechanism

are still under discussion,[3o-s] it is generally recognized that the peroxide proceeds to a polar transition state which proceeds to give inversion compound.



In a recent paper from this laboratory which dealt with a series of isobutyrylaroyl peroxides,[3o] in which the aroate groups become anionoid in the polar intermediate, the rate constants obtained (determined spectrophotometrically by the excess stable radical method) were found to give excellent Hammett plots with $\rho$ values of +0.94 (±0.04), +0.89 (±0.01), 0.90 (±0.01), and +0.87 (±0.14), respectively, at 50, 55, 60, and 65°.

In this paper, we present the results of a rather extensive study of the kinetics of decomposition of peroxides of type 1.



Type 1 peroxides

| | S |
|---|---|
| **1a** | *p*-$OCH_3$ |
| **1b** | *p*-$CH_3$ |
| **1c** | H |
| **1d** | *p*-Cl |
| **1e** | *m*-Br |
| **1f** | *p*-$NO_2$ |

Since it was known that electron-withdrawing groups in the anionoid portion encourage inversion compound formation, it was decided to use *p*-nitrobenzoyl as one of the peroxide substituents. The decision to use ring-substituted β-phenylisovaleryl groups as the cationoid groups was based on the different effects of ring substituents (in neophyl groups) upon the rates of certain reactions. Thus, electron-releasing groups retard the rates of rearrangement of neophyl free radicals,[2b] although they enhance (slightly) the rates of thermal decomposition of the peresters from which they were derived.[2a] At the same time, electron-releasing ring substituents greatly enhance the rates of solvolysis of neophyl brosylates in acetic acid.[4] It was therefore felt that the neophyl system would offer certain advantages in comparing the carboxy-inversion reaction to purely free radical and ionic processes.

## Results

First, it should be explained that, although a number of attempts were made initially to perform kinetics-efficiency experiments using excess BDPA,[3o] difficulty was encountered in obtaining reproducibility in experiments.[5] The results of two pairs of such experiments which did seem to behave properly are probably worth mentioning. Thus, for a pair of decompositions of **1c** (S = H) at 75° in benzene, monitored at 860 nm ($\epsilon$ 1289), the following data were obtained: $10^4$ $k_d$ ($sec^{-1}$) = 4.77 and 5.05; efficiencies, $f$ = 0.169 and 0.156. A similar pair of runs conducted with BDPA and **1c** (S = H) at 65°, monitored at 490 nm ($\epsilon$ 23,700), gave $10^4$ $k_d$ ($sec^{-1}$) = 1.48 and 1.46; $f$ = 0.056 and 0.062. While we cannot explain the large disparity in the efficiencies obtained at the two different temperatures (and at different wavelengths), the rates obtained are in fair agreement with those obtained iodometrically in cyclohexane and in ethylbenzene, when the differences in polarizabilities of the solvents are properly considered.[6] These experiments tend to help establish that type 1 peroxides are in fact initiators of low free radical efficiency, and that inversion-compound formation can be a major reaction pathway.

The difficulties encountered in spectrophotometric kinetics experiments using BDPA led to the adoption of iodometric titration as our kinetic method. In the absence of an inhibitor (such as BDPA), radical-induced decomposition of the peroxide becomes possible,[7] and low peroxide concentrations (0.001–0.02 *M*) were used to minimize this phenomenon as much as possible.

The initial iodometric kinetics experiments were performed using cyclohexane as solvent, in the hope that the rate constants obtained using a nonpolar solvent of low polarizability would be more sensitive to substituents than would these obtained in a polarizable solvent. Although this anticipation was not later realized, the cyclohexane experiments gave data that fit the first-order law with precision, except for the decomposition of **1f** (S = *p*-$NO_2$), for which the first-order plot exhibited a barely discernible rate diminution at long times. (The method of treating this rate behavior mathematically is discussed subsequently.) The rate constants obtained from decompositions in cyclohexane which fit the first-order law are presented in Table I. That for **1f** (S = *p*-$NO_2$), which was corrected by a method discussed subsequently, is presented in Table II.

Having performed a few experiments in cyclohexane, it began to appear that a similarity of behavior was emerging between the rate constants obtained for type 1 peroxides at 75°, and the rate constants which were obtained previously by Rüchardt and Hecht on the decompositions of the corresponding *tert*-butyl peroxy esters in ethylbenzene at 120°.[2a] However, because of the disparity in conditions under which the rates in these two series were obtained, the decision was made to perform experiments on type 1 peroxides in ethylbenzene. The data obtained for all kinetics runs performed for all type 1 peroxides except for **1f** (S = *p*-$NO_2$) were found to fit the first-order law with precision. The results obtained by adjustment to the first-order law for decompositions of **1a–e** (S = *p*-$OCH_3$, *p*-$CH_3$, H, *p*-Cl, *m*-Br) in ethylbenzene are presented in Table I, along with the activation parameters deduced therefrom. Also listed in Table I are some rate constants extrapolated to temperatures other than those at which they were experimentally determined which are utilized in the plots presented in the discussion.

The rate data obtained on the decompositions of **1f** (S = *p*-$NO_2$) in ethylbenzene deviated seriously from first-order behavior; *i.e.*, first-order plots show rate diminutions at long times. This suggests adherence to the rate expression eq 1,

$$-d(P)/dt = k_i(P) + k_i(P)^x \quad (1)$$

the integral of which is eq 2,

$$\ln [(P)^{1-x} + \alpha] = -(1 - x)k_d t + \ln [(P)_0{}^{1-x} + \alpha] \quad (2)$$

in which $\alpha = k_i/k_d$; and, since the "first-order" rate constant diminishes with time, $x > 1$.

In going from a first-order to a first plus higher order reaction, the number of disposable parameters increases from two to four. It does not appear possible to obtain explicit solutions to the four constants [$x$, $\alpha$, $k_d$, and $(P)_0$] in eq 2 by the least-squares method, and it is necessary to make estimates by computer. The computer search is made somewhat less laborious if eq 2 is expanded by one

**Table I**
**Iodometric Kinetics Experiments on Type 1 Peroxides[a,b]**

| Peroxide | $(P)_0$ | $10^5$ ($k_d \pm \sigma$), $sec^{-1}$ | Temp, °C $\Delta H^*$, kcal, and $\Delta S^*$, eu |
|---|---|---|---|
| | | Solvent: Cyclohexane | |
| **1a** (S = *p*-$OCH_3$) | 0.0022 | 19.90 ± 0.63 | 75 |
| **1c** (S = H) | 0.0138 | 21.80 ± 0.15 | 80 |
| **1c** | 0.0157 | 11.80 ± 0.08 | 75 $\Delta H^* = 30.05 \pm 0.04$ |
| **1c** | 0.0137 | 5.96 ± 0.03 | 70 $\Delta S^* = 9.5$ |
| **1c** | 0.0148 | 3.16 ± 0.03 | 65 |
| **1d** (S = *p*-Cl) | 0.0043 | 7.78 ± 0.06 | 75 |
| **1e** (*m*-Br) | 0.0176 | 6.34 ± 0.05 | 75 |
| | | Solvent: Ethylbenzene | |
| **1a** (S = *p*-$OCH_3$) | | (4783.)[a] | 120 |
| **1a** | | (145.24) | 80 |
| **1a** | 0.00663 | 88.33 ± 0.35 | 75 |
| **1a** | 0.0058 | 53.07 ± 0.16 | 70 $\Delta H^* = 23.37 \pm 0.08$ |
| **1a** | 0.0058 | 31.82 ± 0.03 | 65 $\Delta S^* = -5.67$ |
| **1a** | 0.0058 | 18.26 ± 0.21 | 60 |
| **1b** (S = *p*-$CH_3$) | | (3013.) | 120 |
| **1b** | | (65.89) | 80 |
| **1b** | 0.0219 | 38.11 ± 0.30 | 75 |
| **1b** | 0.0122 | 22.01 ± 0.24 | 70 $\Delta H^* = 25.63 \pm 0.11$ |
| **1b** | 0.0122 | 12.54 ± 0.11 | 65 $\Delta S^* = -0.83$ |
| **1b** | 0.0798 | 6.79 ± 0.06 | 60 |
| **1c** (S = H) | | (2659.) | 120 |
| **1c** | | (45.34) | 80 |
| **1c** | 0.0030 | 25.68 ± 0.13 | 75 |
| **1c** | 0.0028 | 13.93 ± 0.03 | 70 $\Delta H^* = 27.35 \pm 0.22$ |
| **1c** | 0.0025 | 7.59 ± 0.01 | 65 $\Delta S^* = 3.28$ |
| **1c** | 0.0020 | 4.10 ± 0.01 | 60 |
| **1d** (S = *p*-Cl) | | (1509.) | 120 |
| **1d** | 0.0192 | 26.79 ± 0.17 | 80 |
| **1d** | 0.0186 | 14.90 ± 0.10 | 75 $\Delta H^* = 27.10 \pm 0.04$ |
| **1d** | 0.0198 | 8.38 ± 0.04 | 70 $\Delta S^* = 1.54$ |
| **1d** | 0.0201 | 4.58 ± 0.06 | 65 |
| **1d** | | (2.44) | 60 |
| **1e** (S = *m*-Br) | | (1310.) | 120 |
| **1e** | 0.0093 | 21.21 ± 0.20 | 80 |
| **1e** | 0.0021 | 12.01 ± 0.06 | 75 $\Delta H^* = 27.64 \pm 0.28$ |
| **1e** | 0.0079 | 6.65 ± 0.09 | 70 $\Delta S^* = 2.63$ |
| **1e** | 0.0088 | 3.51 ± 0.05 | 65 |
| **1e** | | (1.87) | 60 |

[a] Rate constants reported in this table for which standard deviations ($\sigma$) are given were obtained by adjustment of rate data to the first-order law; parenthesized rate constants were obtained by extrapolation from other temperatures using activation parameters given. [b] $(P)_0$ = initial molar concentration of peroxide.

of the subsequently discussed methods. The expansion of eq 2 by MacLaurin's series leads to the expression of ln (P) as a power series in *t*, *i.e.*, to eq 3,

$$\ln (P) = \sum_{1}^{n} b_n t^{n-1} \qquad (3)$$

in which the $b_n$ values can be related back to the original disposable constants, $x$, $\alpha$, $k_d$, and $(P)_0$.

Although the $b_n$ values can be obtained by standard computer programs, and the extension of eq 3 through four terms suffices to give estimates of the original constants, it was found that eq 3 does not converge as rapidly as a function which is derived as follows. First, eq 2 is *rearranged to eq 4*,

$$(P) = [Ce^{-ak_d t} - \alpha]^{1/a} \qquad (4)$$

where $C = (P)_0{}^a + \alpha$ and $a = 1 - x$. Equation 4 is then expanded by the binomial theorem to give a relation of the form of eq 5

$$(P) = A_1 e^{B_1 t} + A_2 e^{B_2 t} + A_3 e^{B_3 t} + \ldots \qquad (5)$$

in which the following relations hold

$$A_1 = C^{1/a} \qquad B_2 = -(1 - a)k_d$$
$$B_1 = -k_d \qquad A_3 = (1 - a)\alpha^2[C^{(1/a)-2}]/2a^2$$
$$A_2 = -\alpha[C^{(1/a)-1}]/a \qquad B_3 = -(1 - 2a)k_d$$

from which one can calculate

$$\alpha = A_2[1 + (B_2/B_1)]/A^{B_2/B_1}$$
$$(P)_0 = [A^{1+(B_2/B_1)} - \alpha]^{B_1/(B_1+B_2)}$$

The coefficients ($A_n$ and $B_n$) were established by using a subroutine based on the Marguard algorithm for a least-squares fit of a nonlinear curve to bivariant data.[8] The subroutine was designed to sweep values of $a = 1 - x = 1 + (B_2/B_1)$ through the range $-0.3 > a > -1$.

Considering the small amount of induced decomposition involved in the decompositions of **1f** (S = *p*-$NO_2$), it is not surprising that a definite, constant value of $x$ (*i.e.*, $a$) was not obtained in the four different runs reported in Table II. The effect of this treatment was to lower the value of $k_d$ (from those obtained when the rate data were adjusted to the first-order law) by less than 20% in each case.

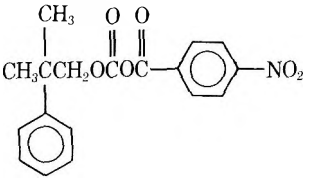
The evidence obtained through product studies to support the contention that type 1 peroxides form inversion

**Table II**
**Iodometric Kinetics Experiments on Peroxide 1f (S = *p*-$NO_2$)[a,b]**

| Peroxide | $(P)_0$ | $10^5 k_d$, $sec^{-1}$ | $a$ | $\alpha$ | Temp, °C | $\Delta H^*$, kcal, and $\Delta S^*$, eu |
|---|---|---|---|---|---|---|
| | | | Solvent: Cyclohexane | | | |
| **1f** (*p*-$NO_2$) | 0.0029 | 3.12 | −0.625 | 3.74 | 75 | |
| | | | Solvent: Ethylbenzene | | | |
| **1f** | | (854.9) | | | 120 | |
| **1f** | 0.0220 | 17.56 | −0.510 | 1.70 | 85 | $\Delta H^* = 30.22 \pm 0.37$ |
| **1f** | 0.0189 | 9.74 | −0.657 | 5.72 | 80 | $\Delta S^* = 8.32$ |
| **1f** | 0.0219 | 5.06 | −0.963 | 22.36 | 75 | |
| **1f** | | (2.64) | | | 70 | |
| **1f** | | (1.35) | | | 65 | |
| **1f** | | (0.67) | | | 60 | |

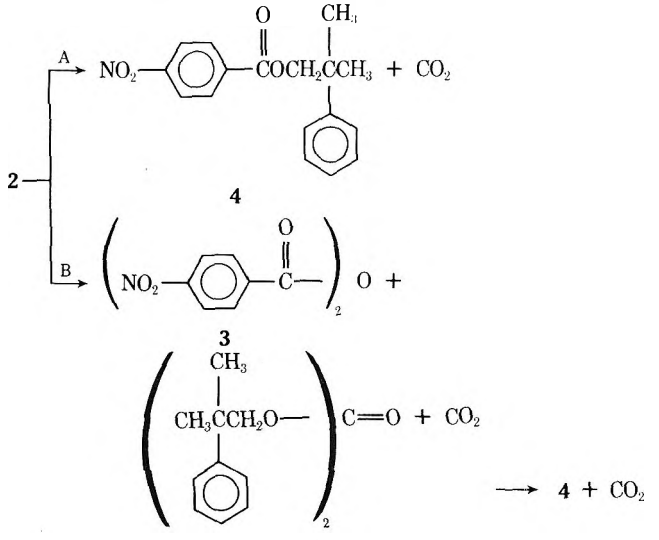
[a] The unparenthesized rate constants were obtained by adjustment of rate data to eq 5; the parenthesized rate constants were obtained by extrapolation of entries 3–5. [b] $(P)_0$ = initial molar concentration of peroxide; $a = 1 - x$; $\alpha = k_i/k_d$ (see eq 1–5).

compounds is rather indirect. Thus, the attempted synthesis of the inversion compound to be expected from **1c** (S = H), *i.e.*, *p*-nitrobenzoyl 2-methyl-2-phenyl-1-propyl carbonate (**2**), from neophyl chloroformate and *p*-nitro-



**2**

benzoic acid in the presence of triethylamine did not result in a pure compound. Rather, an oil was obtained from which there separated, upon sitting, white crystals which were identified as *p*-nitrobenzoic anhydride (**3**). When a sample of the oil was allowed to stand for 35 days, *p*-nitrobenzoic anhydride precipitated for the first 15 days, then began to redissolve. After 20 days or so, another compound began to precipitate which was later identified as neophyl *p*-nitrobenzoate (**4**). (The isolation of **4** is an indication that the neophyl group does not rearrange during the formation of the inversion product.) The de-



composition modes of **2** given above are precisely those which have been described by Tarbell and Longosz[9a,b] and by Windholtz[9c] for mixed carbonic carboxylic anhydrides.

Now when a 0.2 *M* solution of peroxide **1c** (S = H) in cyclohexane was decomposed completely (24 hr) at 75° in an evacuated tube, and the solvent and other volatile products were subsequently removed at the pump, there remained an oil whose infrared spectrum was almost identical with that of the oil obtained in the attempted synthesis of **2** described above. More particularly, there are at least 20 coincidental infrared bands in the two spectra, of which ten are the strongest bands in the spectra. Furthermore, solid samples of **1c** (S = H) were found to decompose slowly in the neat solid state to form a product which was found to be difficultly soluble in ether, and was likewise identified as *p*-nitrobenzoic anhydride (**3**).

## Discussion

The rates of decomposition of type 1 peroxides are consistently more rapid in the polarizable solvent, ethylbenzene, than in the solvent of low polarizability, cyclohexane, and as has been pointed out,[6] this is to be expected for peroxides which form the carboxy-inversion product. It is also not surprising that, for the decomposition of **1c** (S = H), the $\Delta H^*$ is lower and $\Delta S^*$ more negative in the solvent (ethylbenzene) in which the rates are faster (see Table I).

The activation parameters obtained for decompositions of type 1 peroxides in ethylbenzene show quite good isokinetic behavior (see Figure 1) except for the fact that the

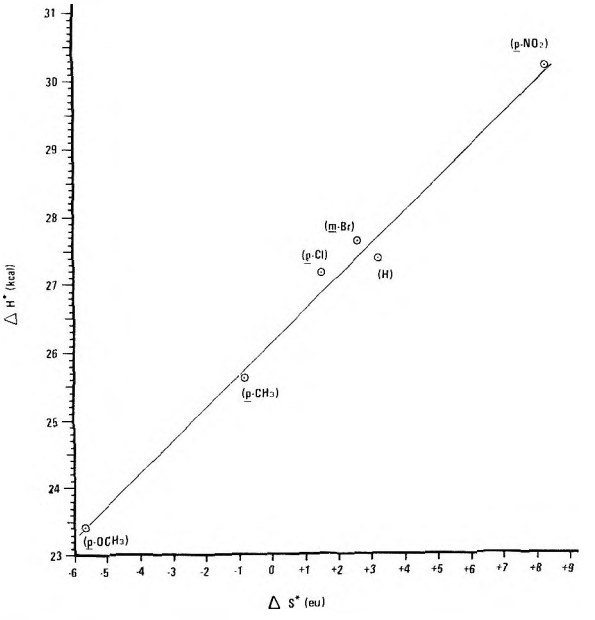



**Figure 1.** Isokinetic plot for decompositions of type 1 peroxides in ethylbenzene.

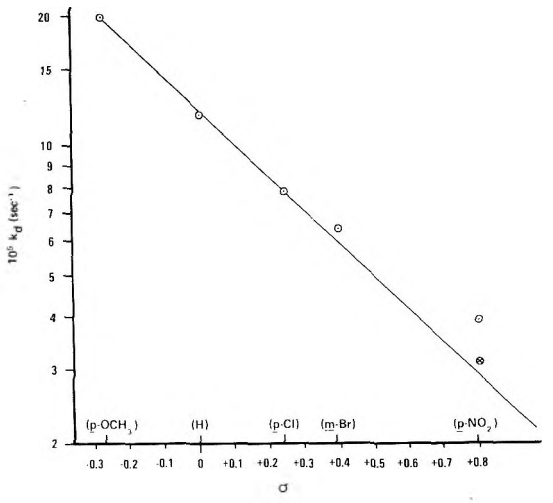



**Figure 2.** Semilog plot of $10^5$ $k_d$ *vs.* Hammett $\sigma$'s for decompositions of type 1 peroxides in cyclohexane at 75°: ⊙, $k_d$ obtained from correlation of rate data with first-order law; ⊗, $k_d$ obtained by adjustment of data to eq 5.

points for **1d** (S = *p*-Cl) and **1e** (S = *m*-Br) fall to the left of **1c** (S = H) on the plot, whereas they would be expected to fall to the right. Nevertheless, the correlation coefficient for the plot in Figure 1 is 0.995, and the slope defines the isokinetic temperature as 487 ± 25°K, or 214 ± 25°. Thus, the temperatures at which the kinetics experiments were performed on type 1 peroxides were more than 100° removed from the isokinetic temperature.[10]

The rate constants for the decompositions of **1a** and **1c-f** (S = *p*-$OCH_3$, H, *p*-Cl, *m*-Br, and *p*-$NO_2$) in cyclohexane at 75° give an excellent plot *vs.* Hammet $\sigma$'s if a correction is made for induced decomposition in the decomposition of **1f** (S = *p*-$NO_2$)[11] (see Figure 2). The $\rho$ value obtained for this correlation is −0.76 ± 0.02 ($r$ = 0.999). At the same time, the rate constants obtained for decompositions of type 1 peroxides in ethylbenzene (Figure 3) do not give good Hammett correlations, because the rate constants for **1a** (S = *p*-$OCH_3$) are too high. Actually, if the high $k_d$ values for **1a** (S = *p*-$OCH_3$) are ignored, better correlations are obtained with $\sigma$, but when all data are included, better correlations are obtained with $\sigma^+$.[12] The $\rho$ values and correlation coefficients for the $\sigma^+$ correlations at the five temperatures are as follows: $\rho$ = −0.89 ± 0.05 ($r$ = 0.994) at 60°; $\rho$ = −0.85 ± 0.04 ($r$ = 0.994) at 65°; $\rho$ = −0.81 ± 0.05 ($r$ = 0.994) at 70°; $\rho$ = −0.78 ± 0.05 ($r$ = 0.992) at 75°; and $\rho$ = −0.74 ± 0.04 ($r$ = 0.993) at 80°.

The behavior of the first-order rate constants for type 1 peroxide decompositions in ethylbenzene *vis-à-vis* $\sigma$ and $\sigma^+$ as described above can be more clearly illustrated in terms of the Yukawa-Tsuno equation,[13] *i.e.*, eq 6.

$$\log k = \log k_0 + \rho[\sigma + R(\sigma^+ - \sigma)] = \log k_0 + \rho(1 - R)\sigma + \rho R\sigma^+ \quad (6)$$

The rate constants in Tables I and II were used to calculate values of $\rho$ and $R$ from eq 6. In addition, activation parameters presented in the same tables were used to calculate (extrapolated) rate constants at 100 and 120°, and the latter, in turn, were used to calculate $\rho$ and $R$ values from eq 6 for those temperatures. The results of these calculations were presented in Table III, and plotted in Figure 4.

The Yukawa-Tsuno equation is designed such that $0 < R < 0.5$ indicates a better correlation with $\sigma$ than with $\sigma^+$, while $0.5 < R < 1$ indicates a better correlation with $\sigma^+$. Figure 4 indicates a fairly linear correlation of $R$ with temperature, which suggests that, although our rate data

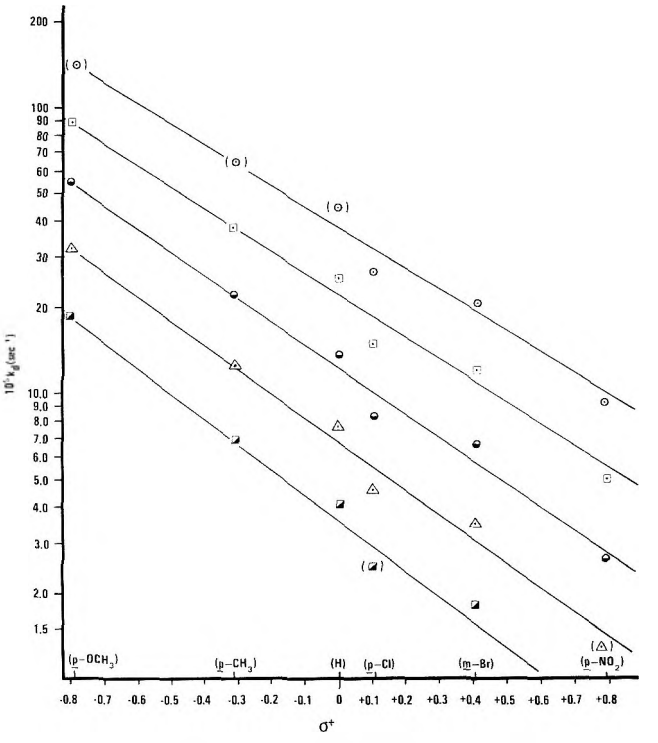



**Figure 3.** Semilog plot of $10^5$ $k_d$ for type 1 peroxides in ethylbenzene *vs.* $\sigma^+$ at five temperatures: ⊙, 80°; ⊡, 75°; ◒, 70°; ◭, 65°; ◪ 60°. The parenthesized points are extrapolated rate constants (see Tables I and II).

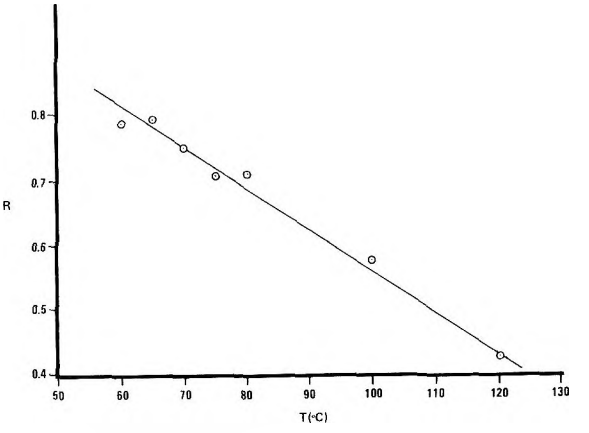



**Figure 4.** Plot of Yukawa-Tsuno $R$ *vs.* temperature.

on type 1 peroxides in ethylbenzene give a better correlation with $\sigma^+$ at the experimental temperatures (60-80°), at temperatures of 117° and above, better correlations would be obtained with $\sigma$.

It is instructive to compare the kinetic behavior of type 1 peroxides with that which has been described by Ru-

**Table III**[a]
**Adjustment of Rate Data for Type 1 Peroxides to the Yukawa-Tsuno Equation** $Y = a\sigma + b\sigma^+ + c$

| Temp, °C | $a$ | $b$ | $c$ | $R$ | $\rho$ |
|---|---|---|---|---|---|
| 60 | −0.206 | −0.755 | 0.592 | 0.786 | −0.961 |
| 65 | −0.195 | −0.727 | 0.861 | 0.788 | −0.922 |
| 70 | −0.218 | −0.667 | 1.122 | 0.753 | −0.885 |
| 75 | −0.250 | −0.609 | 1.377 | 0.709 | −0.859 |
| 80 | −0.237 | −0.580 | 1.622 | 0.710 | −0.817 |
| (100)[b] | −0.297 | −0.407 | 2.536 | 0.578 | −0.704 |
| (120)[b] | −0.340 | −0.255 | 3.365 | 0.428 | −0.595 |

[a] $Y = 5 + \log k$; $a = \rho(1 - R)$; $b = \rho R$; $c = 5 + \log k_0$. [b] Values of constants for 100 and 120° were obtained by adjustment of extrapolated rate constants to the equation.

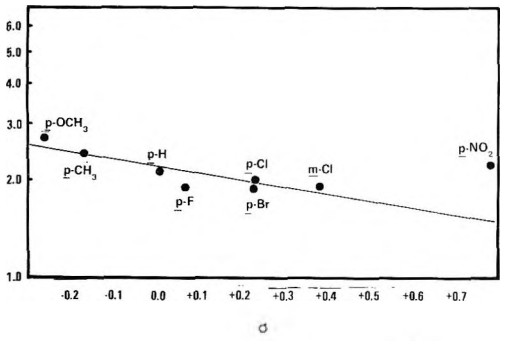



**Figure 5.** Semilog plot of $10^4$ $k_d$ *vs.* Hammett $\sigma$'s for decompositions of ring-substituted *tert*-butyl $\beta$-(S-phenyl)peroxyisovalerates in ethylbenzene at 120° (after Rüchardt and Hecht[2]).

chardt and Hecht[2] for the decompositions of the *tert*-butyl peresters of ring-substituted $\beta$-phenylisovaleric acids in ethylbenzene. First, it should be explained that the perester rate constants reported by Rüchardt and Hecht do not correlate well with either $\sigma$ or $\sigma^+$; the plot of log $k_d$ for the peresters *vs.* $\sigma$ is presented in Figure 5. In view of our experience with type 1 peroxides, however, it would seem reasonable to ascribe the high value of $k_d$ for the *p*-$NO_2$-substituted perester to induced decomposition. If the rate constant for the *p*-$NO_2$-substituted perester is ignored on this account, the following $\sigma$ correlation is obtained: $\rho = 0.21 \pm 0.05$ ($r = 0.871$).

Although the rate constants for both the peroxides and the peresters (at 120°) give somewhat better correlations with $\sigma$ than with $\sigma^+$, the log-log correlation between the 120° rate constants for the two series is very poor. However, there is a fairly good correlation between log [$k_{peroxide}/k_{perester}$] *vs.* $\sigma$, giving ($\rho_{peroxide} - \rho_{perester}$) = $-0.61 \pm 0.06$ ($r = 0.987$); the plot is presented in Figure 6.

It is necessary at this point to recall that Walling and coworkers[3p] have suggested that the formation of both radical and polar products (including the carboxy-inversion product) proceed from the same polar transition state and intermediate. The Walling mechanism was altered somewhat by Ward, Lawler, and Cooper,[3q] who failed to observe spin polarization in the inversion product formed in the decomposition of bis(isobutyryl) peroxide. Recently, Leffler and More[3r] expressed considerable doubt about the validity of the Walling mechanism, but, failing to discount a common transition state and intermediate (for homolysis and inversion product forming reactions) entirely, suggested somewhat different electronic structures for the intermediate.

Returning now to Figure 6, the difference in behavior of type 1 peroxides and the corresponding peresters as demonstrated in this plot can be interpreted in either of two ways. One of these is to suppose that a common intermediate mechanism holds for type 1 peroxide decompositions. If one adopts this view, then Figure 5 simply demonstrates that there is a significantly greater difference in polarities of the ground and transition states in the decompositions of type 1 peroxides than in decompositions of the corresponding perester.

This view is not without merit. One of the big differences between perester and diacyl peroxide decompositions is that an alkoxy group in perester is such a strongly basic "leaving" group that a transition state polarized in the direction R-$COO^+$ $^-$O-R simply cannot occur; and if it were possible, it is likely that dialkyl carbonates would be formed as rearrangement products. (The well-known Criegee rearrangement[14] requires polarization in the opposite direction, R-$COO^-$ $^+$O-R.) The "leaving" groups in the peroxide and perester series which are being compared in Figure 5 (*i.e.*, the *p*-nitrobenzoate and *tert*-butoxide anions) differ in basicity by several powers of ten. Thus, it is not unreasonable to assume that the transition state leading to radicals in the type 1 peroxide series is significantly more polar than the radical-producing transition state in the perester series, and it could conceivably lead to an intermediate which also produces inversion product. Along this line, curvature was not discernible in the ln ($k_d/T$) *vs.* $1/T$ plots over admittedly short (15°) temperature ranges, so that the $\Delta H^*$ values reported here for type 1 peroxides have a precision of ±1% or better.

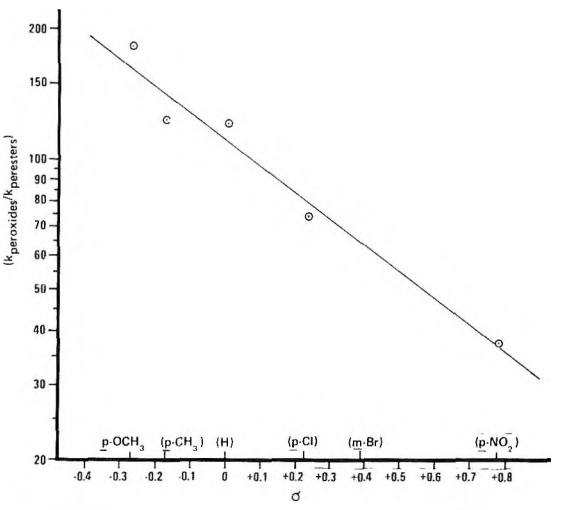



**Figure 6.** Plot of log [$k_{peroxides}/k_{peresters}$] *vs.* Hammett $\sigma$'s for type 1 peroxides and the corresponding *tert*-butyl peresters (after Rüchardt and Hecht[2]) in ethylbenzene at 120°.

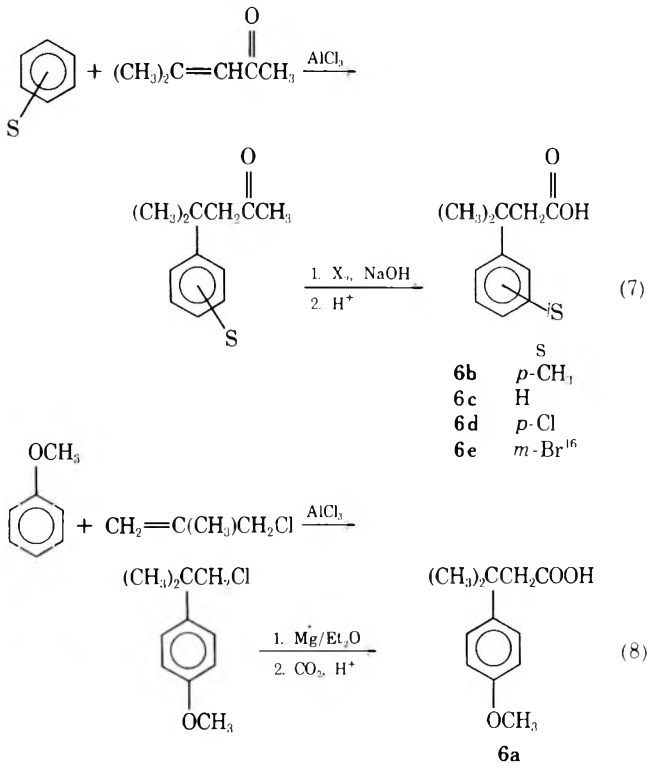
On the other hand, Rüchardt and Hecht showed that the peresters decompose exclusively by one-bond homolytic cleavage of the peroxide linkage, and one could reasonably argue that the plot in Figure 5 means that, when the substituent effect on the homolytic reaction is subtracted, the residual observed slope is to be ascribed to the carboxy-inversion reaction alone. The point is that the rate data presented here for type 1 peroxide decompositions do not clearly favor either the single or the double transition-state postulate, but if either is favored slightly, it is the former.

The substituent effects in type 1 peroxide decompositions, however, should be put in proper perspective. In the first place, the rate constant for the decomposition of **1c** (S = H) in cyclohexane is no more than a factor of three greater than that for bis(acetyl) peroxide.[7h] Secondly, the effect of ring substituents on type 1 peroxide decompositions, $\rho$ (*vs.* $\sigma^+$) = $-0.74$ to $-0.89$, more nearly approximates that of the corresponding perester decompositions, $\rho$ (*vs.* $\sigma$) = $-0.21$, than that of the solvolyses of the neophyl brosylates,[4] $\rho$ (*vs.* $\sigma^+$) = $-2.96$ (in acetic acid). The data do not suggest a high degree of bond breaking in the $-CH_2-C{=}O$ bond in the transition state for type 1 peroxide decompositions.

## Experimental Section[15]

**The ring-substituted $\beta$-phenylisovaleric acids** were synthesized by two different methods (eq 7[16] and 8).

In general, procedures were followed in the synthesis of the acids which were developed by Hoffman,[17] by Corse and Rohrmann,[18] and by Rüchardt and coworkers.[19] The $\beta$-(*p*-nitrophenyl)-isovaleric acid (**6f**, not shown) was obtained by nitration of the parent acid according to the Corse and Rohrmann procedure.[18] The methyl $\beta$-(S-phenyl)isobutyl ketones (eq 7) were transformed to the acid salts both by the sodium hypochlorite method of Newman and Holmes[20] and by the sodium hypobromite method described by Sandler and Karo.[21] The observed melting points of the acids were identical with or within 1° of those which have




been reported. The nmr spectra ($CCl_4$, S) exhibit 6 H singlet absorptions in the range of $\delta$ 1.40–1.48 for the *gem*-dimethyl groups and 2 H singlet absorptions in the $\delta$ 2.53–2.69 range for the methylene groups; **6a** (S = *p*-$OCH_3$) shows a 3 H singlet at $\delta$ 3.75 for the methoxyl group, and **6b** (S = *p*-$CH_3$) shows a singlet methyl absorption at $\delta$ 2.35. The aromatic protons exhibit a 4 H multiplet for **6a** (S = *p*-$OCH_3$) at $\delta$ 7.10, and **6b** at $\delta$ 7.20 (S = *p*-$CH_3$); a 5 H singlet at $\delta$ 7.21 for **6c** (S = H); a 4 H singlet at $\delta$ 7.22 for **6d** (S = *p*-Cl); a 4 H multiplet at $\delta$ 7.50 for **6e** (S = *m*-Br); and a 4 H multiplet for **6f** (S = *p*-$NO_2$) at $\delta$ 7.91. The ir spectra of the acids exhibit characteristic absorptions in agreement with assigned structures. The corresponding acid chlorides were prepared by treatment of the acids with excess thionyl chloride.[2a] The nmr spectra of the acid chlorides ($CCl_4$, S) show considerable similarity to those of the acids, except for the fact that the 2 H singlet absorptions for the methylene groups lie in the range $\delta$ 3.14–3.29. The mass spectra of four of the acid chlorides are described subsequently.

***p*-Nitroperoxybenzoic acid** was prepared from *p*-nitrobenzoic acid, hydrogen peroxide, and methanesulfonic acid by the method of Silbert, Siegel, and Swern,[22] except that double quantities of methanesulfonic acid were used, mp 138–139° (lit.[22] mp 138°).

**Type 1 peroxides** were synthesized by the treatment of *p*-nitroperoxybenzoic acid with the acid chlorides in the presence of pyridine. Thus, for the synthesis of **1c** (S = H), *p*-nitroperoxybenzoic acid (3.66 g, 0.02 mol) and $\beta$-phenylisovaleryl chloride (3.93 g, 0.02 mol) were dissolved in 100 ml of diethyl ether in a 300-ml three-necked flask equipped with stirrer, alcohol thermometer, and dropping funnel. The solution was cooled quickly to −20° in a Dry Ice–acetone bath, and pyridine (1.58 g, 0.02 mol), dissolved in 25 ml of diethyl ether, was added dropwise over a 15-min period. The mixture was allowed to stir for 5 hr while the flask was immersed in the Dry Ice–acetone bath (during which time the temperature was held below −30°), the bath was removed, and the solution was allowed to warm to 10°. The white precipitate was taken into solution by addition of more diethyl ether; the ether solution was transferred to a separatory funnel and washed respectively with 5% hydrochloric acid (3 × 50 ml), water (2 × 50 ml), 5% sodium bicarbonate (3 × 50 ml), and water (2 × 50 ml). The ether solution was dried over anhydrous sodium sulfate and filtered, and the ether was removed at the rotary evaporator. The pale yellow crystals thus obtained were recrystallized from an ether–pentane mixture, yield 4.4 g (65% of theory) of white crystals, mp 63–64°. Iodometric titration indicated a purity of 99.2%. The melting points of the peroxides are as follows: **1a** (S = *p*-$OCH_3$), 77–78°; **1b** (S = *p*-$CH_3$), 73–74°; **1c** (S = H), 63–64°; **1d** (S = *p*-Cl), 84–86°; **1e** (S = *m*-Br), 64–65°; **1f** (S = *p*-$NO_2$), 89–91°. The nmr spectra ($CCl_4$, TMS) exhibit 6 H singlet absorptions in the $\delta$ 1.53–1.61 region for the *gem*-dimethyl groups and 2 H singlet absorptions in the $\delta$ 2.79–2.92 region for the methylene groups; and all peroxides show a 4 H multiplet for *p*-nitrobenzoyl centered at $\delta$ 8.27. The $\beta$-(S-phenyl)isovaleryl groups show the following absorptions for aromatic hydrogens: **1a** (S = *p*-$OCH_3$), a 4 H multiplet at $\delta$ 7.14; **1b** (S = *p*-$CH_3$), a 4 H multiplet at $\delta$ 7.23; **1c** (S = H), a 5 H singlet at $\delta$ 7.39; **1c** (S = *p*-Cl), a 4 H singlet at $\delta$ 7.34; **1d** (S = *m*-Br), a 4 H multiplet at $\delta$ 7.37; **1f** (S = *p*-$NO_2$), a 4 H multiplet at $\delta$ 7.90.[23] There are additional 3 H singlet methyl absorptions for **1a** (S = *p*-$OCH_3$) and **1b** (S = *p*-$CH_3$) at $\delta$ 3.80 and 2.33, respectively, for the ring substituents. All of the ir spectra of the peroxides exhibit the following bands: a carbonyl-stretch doublet with one band in the 1795–1808 $cm^{-1}$ (m) region, and another in the 1767–1773 $cm^{-1}$ (s) region; an aryl-nitro band near 1530 $cm^{-1}$; a band in the 1460 $cm^{-1}$ (s) region due to $CH_3$– and $-CH_2-$; a $-CH_2C{=}O$ band near 1410 $cm^{-1}$ (w); a *gem*-dimethyl doublet in the 1390 (w) and 1370 $cm^{-1}$ (m) regions; and an aryl-nitro band near 1350 $cm^{-1}$ (w). Other ir bands also confirmed the assumed structures. Iodometric titration indicated purities above 98% for all the peroxides.

**Mass spectra** were obtained on the acid chlorides for which S = *p*-$OCH_3$, *p*-$CH_3$, *m*-Br, and *p*-$NO_2$, and on two type 1 peroxides, **1b** (S = *p*-$CH_3$) and **1e** (S = *m*-Br). The following ions (or their *m/e* equivalents) were obtained for all of these derivatives: $SC_6H_4C_4H_7^+$, $SC_6H_4C_3H_6^+$, $SC_6H_4CH_2^+$, $C_6H_5C_4H_6^+$, $C_6H_5C_3H_3^+$, $C_6H_5C_3H_2^+$, $C_6H_5CH_2^+$ (or tropylium$^+$), $C_6H_5^+$, and $CO^+$ (or $N_2^+$). The peroxide spectra also showed $CO_2^+$ and $NO_2C_6H_4COOH^+$. The 100% peak for all the acid chlorides corresponded to $SC_6H_4C_3H_6^+$; the 100% peak for the two peroxides, however, was a peak of *m/e* 131, corresponding to $C_6H_5C_4H_6^+$. The mass spectra of only two of these compounds showed small parent ions: the acid chlorides for which S = *p*-$NO_2$ and *p*-$OCH_3$.

**Neophyl alcohol (2-phenyl-2-methyl-1-propanol)** was prepared by oxygenation of neophylmagnesium chloride by the method of Cadogan and Foster,[24] mp of the *p*-nitrobenzoate 58–59.5°. The nmr spectra of the alcohol and the *p*-nitrobenzoate agree with the assigned structures.

**Neophyl chloroformate** was prepared by treating neophyl alcohol with phosgene in the presence of *N,N*-dimethylaniline, using a procedure similar to that described by Dodonov and Waters,[25] bp 82–85° (0.5 mm).

**Kinetics Runs.** Stock solutions of the peroxides were prepared at the concentrations indicated in Tables I and II, and 8-ml aliquots were injected into tared Pyrex vials, each of which had a previously constricted stem leading to a 10/30 ₸ joint. Each vial was weighed, attached to a vacuum manifold, immersed in liquid nitrogen, and carefully degassed. The stem was then sealed under vacuum.

For a given run, six to ten sealed vials were used. These were placed in a thermostated (±0.05°) bath at the same time, and removed at various times, quenched by immersing in a Dry Ice–acetone slurry, and subsequently titrated. For each titration, the contents of the tube were washed into an iodine flask with cold acetone saturated with carbon dioxide. A saturated solution of sodium iodide in acetone (5 ml), likewise kept cold and saturated with carbon dioxide using Dry Ice, was added. The iodine liberated was titrated with standard sodium thiosulfate solution.[26]

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**Registry No.**—**1a**, 51380-77-9; **1b**, 51380-78-0; **1c**, 51380-79-1; **1d**, 51380-80-4; **1e**, 51380-81-5; **1f**, 51380-82-6; **6a**, 1136-01-2; **6b**, 42288-08-4; **6c**, 1010-48-6; **6d**, 42288-16-4; **6e**, 42288-04-0; **6f**, 42288-06-2; $\beta$-(*p*-methoxyphenyl)isobutyl chloride, 51380-83-7; methyl $\beta$-(*p*-methylphenyl)isobutyl ketone, 10528-65-1; methyl $\beta$-phenylisobutyl ketone, 7403-42-1; methyl $\beta$-(*p*-chlorophenyl)isobutyl ketone, 6269-30-3; methyl $\beta$-(*m*-bromophenyl)isobutyl ketone, 51380-84-8; $\beta$-(*p*-methoxyphenyl)isovaleryl chloride, 4094-65-9; $\beta$-(*p*-methylphenyl)isovaleryl chloride, 51380-85-9; $\beta$-phenylisovaleryl chloride, 4094-64-8; $\beta$-(*p*-chlorophenyl)isovaleryl chloride, 4094-67-1; $\beta$-(*m*-bromophenyl)isovaleryl chloride, 51380-86-0; $\beta$-(*p*-nitrophenyl)isovaleryl chloride, 51380-87-1; *p*-nitroperoxybenzoic acid, 943-39-5; neophyl *p*-nitrobenzoate, 51380-88-2; neophyl chloroformate, 51380-89-3.

## References and Notes


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(6) It has been shown that, for decompositions of bis(isobutyryl) peroxide, a peroxide which forms the inversion compound in good yield, the rate constants obtained in a series of nonpolar solvents of different polarizabilities increase with increasing solvent polarizability, *i.e.*, benzene > toluene = *p*-xylene > carbon tetrachloride > cyclohexane. Therefore, for type 1 peroxides, the sequence benzene > ethylbenzene > cyclohexane is in complete agreement with the previously established series (*cf.* Figure 1 in ref 3n).

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(12) Thus, when all rate constants are included, the correlation coefficients for the correlations with $\sigma$ are near 0.97 at all five temperatures. However, if rate constants for **1a** (*p*-$OCH_3$) are ignored, the *r* values are near 0.997.

(13) *Cf.* J. Shorter, "Correlation Analysis in Organic Chemistry," Oxford University Press, London, 1973, pp 15–16. We have used capital *R* for the Yukawa–Tsuno constant to distinguish it from *r*, which is used in this paper to designate the correlation coefficient.

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(15) Infrared spectra were obtained using Perkin-Elmer Model 137 and Model 257 spectrophotometers; nmr spectra were obtained using Hitachi Perkin-Elmer Model R-20 and Varian Model A-60 spectrometers; Atlas Model CH-4 and CH-5 mass spectrometers were used to obtain mass spectra.

(16) Rüchardt and Trautwein showed that the acid obtained from bromobenzene by this procedure, mp 109–110°, is actually the meta isomer. The proof consisted of the oxidation of the decarbonylation products of the corresponding aldehyde to *m*-bromobenzoic acid, and by the independent synthesis of $\beta$-(*p*-bromophenyl)isovaleric acid, mp 68–69°, from $\beta$-(*p*-aminophenyl)isovaleric acid. *Cf.* C. Rüchardt and S. Eichler, *Chem. Ber.*, **95**, 1921 (1962).

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# Kinetics and Mechanisms of Reactions of 3-Buten-2-one and Related Compounds in Aqueous Perchloric Acid


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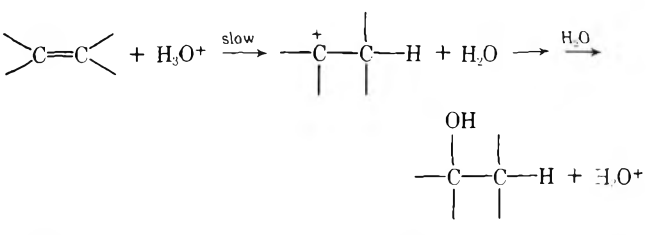
A detailed study of the hydration of homologs of 3-buten-2-one is reported. Rate constants for the hydration and dehydration reactions have been separated and activation parameters, precise solvent isotope effects, and acidity dependences have been measured over a wide range of acidity, 1–10 *M* perchloric acid. These mechanistic criteria are discussed in view of other olefin hydrations.


Hydration of olefins in aqueous acidic media has been studied extensively and the reaction mechanisms for several classes of olefins have been established.[1-5] For simple aliphatic olefins, dienes, and substituted styrenes, the mechanism of hydration has been shown to involve rate-determining proton transfer from hydronium ion to olefinic carbon, followed by addition of water to the carbonium ion thus formed[1-4] (Scheme I).

These reactions are characterized by solvent isotope effects, $k(H_2O)/k(D_2O)$, of 1.4–5 and entropies of activation of −5 to 0 eu. 3-Buten-2-one and its homologs are a special class of olefins having a carbonyl group conjugated with a double bond. Hydration of some $\alpha,\beta$-unsaturated ketones has been reported previously.[6-9] The compounds studied

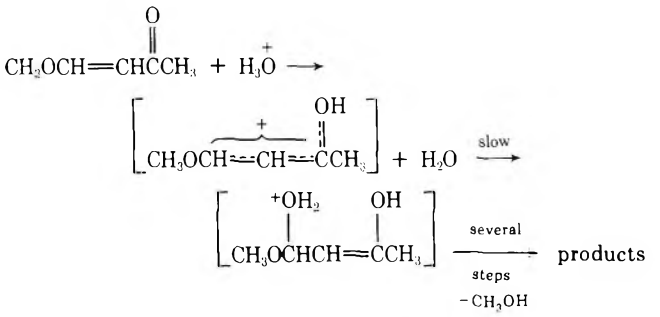
**Scheme I**



do not appear to hydrate by the type of mechanism accepted for hydration of aliphatic olefins, dienes, and styrenes.

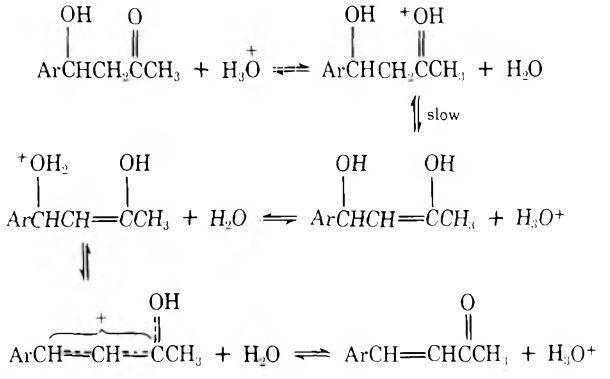
The alkoxy-substituted $\alpha,\beta$-unsaturated ketone 4-methoxy-3-buten-2-one undergoes a vinyl ether hydrolysis which proceeds *via* a 1,4 addition of water to the conjugated system followed by loss of methanol[6] (Scheme II). This reaction proceeds faster in deuterio solvent and exhibits an entropy of activation of −26 eu. It is significant that the rate-controlling step in this hydrolysis is attack by water on the conjugate acid of 4-methoxy-3-buten-2-one.

**Scheme II**



$\beta$-Aryl-$\beta$-hydroxy ketones are dehydrated reversibly by two mechanisms, the reverse of Scheme I and Scheme III.[7] Reactions occurring *via* Scheme III are characterized by entropies of activation of −20 eu and a nonlinear dependence of log $k$ on $-H_0$. Substitution of carbonium ion stabilizing groups on the carbon $\beta$ to the carbonyl favor reaction *via* Scheme I.

**Scheme III**



These facts, taken in conjunction with the considerable discussion surrounding the mechanism of hydration of simple aliphatic alkenes *vs.* substituted styrenes, demonstrate the importance of precisely elucidating the mechanism of hydration of simple aliphatic $\alpha,\beta$-unsaturated ketones *vs.* aryl-substituted $\alpha,\beta$-unsaturated ketones. In view of the conclusions regarding hydrolysis of 4-methoxy-3-buten-2-one, it is critical to establish not only whether a 1,2 or 1,4 addition of water occurs, but also whether attack by water or proton transfer from hydronium ion to carbon is rate controlling.

Hydration of 4-methyl-3-penten-2-one has been reported recently[8,9] but the results thus far are consistent with several interpretations.[9] Consequently, a complete detailed study of the hydration of homologs of 3-buten-2-one is now reported. Rate constants for the hydration and dehydration reactions have been separated and acidity dependences, activation parameters, and precise solvent isotope effects have been measured over a wide range of acidity, 1–10 $M$ perchloric acid. These mechanistic criteria are particularly useful when considered in light of results from other olefin hydrations.

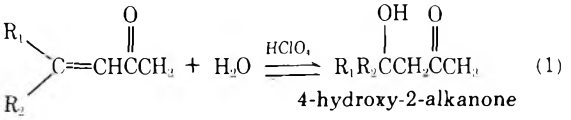
## Experimental Section

**Materials and Kinetic Method.** All substrates were obtained from Aldrich Chemical Co. and were molecularly distilled just prior to each kinetic run. The kinetic method employed was that described previously.[1] Deuterioperchloric acid solutions were made from deuterium oxide (99.8% $D_2O$, Stohler Isotope Chemicals) and concentrated deuterioperchloric acid, as described previously.[1]

**Product Analysis.** It was suspected that acetone was being formed from 4-methyl-3-penten-2-one in perchloric acid solutions greater than 8 $M$. Consequently, 1.0 g (0.01 mol) of 4-methyl-3-penten-2-one was dissolved in 5 ml of ethanol and this solution was added slowly to 1 l. of 10 $M$ perchloric acid accompanied by vigorous stirring. After about 10 half-lives of reaction time (100 hr at 25°), 300 mg (0.0015 mol) of 2,4-dinitrophenylhydrazine was added to a 100-ml aliquot of the 10 $M$ acid–ketone solution. Back-titration with 2 $N$ NaOH to about 80% neutralization yielded yellow-orange crystals which were recrystallized from ethanol–water and dried under vacuum. The yield of bright yellow dinitrophenylhydrazone was 195 mg (80%), mp 123–125° (lit.[10] mp 126°). Pmr spectra of this dinitrophenylhydrazone and authenic acetone dinitrophenylhydrazone were superimposable.

## Results

The reactions investigated are reversible and at equilibrium the product concentration is greater than the reactant concentration.



(1)

3-alken-2-one

4-hydroxy-2-alkanone

1. $R_1 = R_2 = H$
2. $R_1 = H$; $R_2 = CH_3$
3. $R_1 = R_2 = CH_3$

**Observed Rate Constants, $k_{obsd}$.** Pseudo-first-order rate constants were determined in the traditional way[1] and are tabulated in Table I. In order to measure the solvent isotope effect, $k_{obsd}$ was determined in $DClO_4$–$D_2O$ solutions. However, since the reaction is overall reversible, exchange of hydrogen for deuterium occurred on the substrate. To ensure that $k_{obsd}(D_2O)$ was measured prior to exchange becoming important, a computer program was developed[11] similar to the iterative type provided by Wiberg.[12] The pseudo-first-order rate constants in Table II are those calculated by computer and are true constants over at least 2 half-lives of reaction.

**Equilibrium Ratios, [4-Hydroxy-2-alkanone]/[3-Alken-2-one].** Since the reactant, 3-alken-2-one, is the only specie absorbing significantly at the wavelengths used, calculation of the equilibrium ratio (eq 2) is considerably simplified (data in Table III).

$$\frac{[\text{4-hydroxy-2-alkanone}]}{[\text{3-alken-2-one}]} = \frac{A_0 - A_e}{A_e} \qquad (2)$$

[4-hydroxy-2-alkanone] = molarity of the product at equilibrium

[3-alken-2-one] = molarity of the reactant at equilibrium

$A_0$ = absorbance at time zero (*i.e.*, upon mixing)

$A_e$ = absorbance at equilibrium (*i.e.*, at time "infinity")

The value of $A_e$ was not directly measurable in $DClO_4$–$D_2O$ solutions (owing to exchange of hydrogen for deuterium on the substrate); consequently, the value of $A_e$ calculated by the iterative computer program (see previous section) was used to calculate the equilibrium ratios in Table IV.

**Table I**
**Values of $k_{obsd}$ in Aqueous $HClO_4$[a]**

| $M_{HClO_4}$ | $-H_A$[b] | $10^4 k_{obsd}$ 3-Buten-2-one[c] | 3-Penten-2-one[d] | 4-Methyl-3-penten-2-one[e] |
|---|---|---|---|---|
| | | 15° | | |
| 4.03 | 1.64 | 5.87 | | |
| 6.28 | 2.42 | 15.4 | | |
| 8.26 | 3.24 | 32.3 | | |
| 9.30 | 3.59 | 42.9 | | |
| 9.96 | 3.83 | 46.9 | | |
| 11.10 | 4.20 | 36.1 | | |
| | | 20° | | |
| 2.57 | 1.09 | 4.91 | | |
| | | 25° | | |
| 9.30 | 3.59 | 97.6 | | |
| | | 30° | | |
| 2.57 | 1.09 | 12.5 | 2.89 | 4.54 |
| 6.28 | 2.42 | | | 14.0 |
| 8.26 | 3.24 | 114 | | |
| 9.30 | 3.59 | 147 | | |
| 9.96 | 3.83 | | | 0.187[f] |
| | | 40° | | |
| 1.05 | 0.31 | 9.72 | 2.85 | 3.90 |
| 2.57 | 1.09 | 27.8 | 6.95 | 10.3 |
| 4.03 | 1.64 | 55.0 | 12.5 | 19.1 |
| 6.28 | 2.42 | 144 | 21.7 | 31.8 |
| 7.48 | 2.92 | | 31.0 | 26.6[f] |
| 8.26 | 3.24 | 284 | 30.5 | 0.96[f] |
| 9.30 | 3.59 | | | 0.702[f] |
| 9.96 | 3.83 | | | 0.666[f] |
| | | 50° | | |
| 2.57 | 1.09 | | 15.5 | 22.2 |
| 6.28 | 2.42 | | | 61.1 |
| 9.96 | 3.83 | | | 1.54[f] |

[a] Means of replicate determinations; average deviations from mean values were $< \pm 2\%$. [b] Reference 14. [c] Followed at 210 nm. [d] Followed at 226 nm. [e] Followed at 243 nm. [f] Followed at 278 nm.

**Table II**
**Values of $k_{obsd}$ in $DClO_4$–$D_2O$ Solution at 40°[a]**

| $M_{DClO_4}$ | $10^4 k_{obsd}$ 3-Buten-2-one[b] | 3-Penten-2-one[c] | 4-Methyl-3-penten-2-one[d] |
|---|---|---|---|
| 1.05 | 4.71 | 0.979 | 1.33 |
| 4.70 | 28.9 | 6.88 | 8.51 |
| 9.39 | 63.8 | | 0.537 |

[a] Means of replicate determinations; average deviation from mean value were $< \pm 2\%$. [b] Followed at 210 nm. [c] Followed at 226 nm. [d] Followed at 243 nm. [e] Measured at 30° rather than 40°.

**Separation of $k_{hyd}$ and $k_{dehyd}$.** These rate constants were calculated from $k_{obsd}$ and the equilibrium ratios using the following relationships.[13]

$$k_{obsd} = k_{hyd} + k_{dehyd} \quad (3)$$

$$\frac{[\text{4-hydroxy-2-alkanone}]}{[\text{3-alken-2-one}]} = \frac{k_{hyd}}{k_{dehyd}} \quad (4)$$

$k_{hyd}$, the rate constant for the forward reaction in eq 1

$k_{dehyd}$, the rate constant for the reverse reaction in eq 1

Figure 1 shows the acidity dependence of $k_{hyd}$. $H_A$[14] is used as the measure of medium acidity, since it has been shown that $\alpha,\beta$-unsaturated ketones behave as Hammett bases when the extent of protonation is measured using $H_A$.[15,16]

**Table III**
**Equilibrium Measurements, [4-Hydroxy-2-alkanone]/[3-Alken-2-one[a]]**

| $M_{HClO_4}$ | [4-hydroxy-2-butanone]/[3-buten-2-one][b] | [4-hydroxy-2-pentanone]/[3-penten-2-one][c] | [4-hydroxy-4-methyl-2-pentanone]/[4-methyl-3-penten-2-one][d] |
|---|---|---|---|
| | 15° | | |
| 4.03 | 22.7 | | |
| 6.28 | 20.4 | | |
| | 20° | | |
| 2.57 | 22.2 | | |
| | 30° | | |
| 2.57 | 19.0 | 3.90 | 9.02 |
| 6.28 | | | 4.08 |
| | 40° | | |
| 1.05 | | 3.35 | 8.49 |
| 2.57 | 13.0 | 3.14 | 6.75 |
| 4.03 | | 2.46 | 5.21 |
| 6.28 | | 1.96 | 3.92 |
| 7.48 | | 1.06 | 1.36 |
| 8.26 | | 0.912 | |
| | 50° | | |
| 2.57 | | 2.67 | 5.15 |
| 6.28 | | | 2.52 |

[a] Means of replicate determinations; average deviations from mean values were $< \pm 2\%$. [b] Measured at 210 nm. [c] Measured at 226 nm. [d] Measured at 243 nm.

**Table IV**
**Equilibrium Measurements in $DClO_4$–$D_2O$ Solutions at 40°[a]**

| $M_{DClO_4}$ | [4-hydroxy-2-butanone]/[3-buten-2-one][b] | [4-hydroxy-2-pentanone]/[3-penten-2-one][c] | [4-hydroxy-4-methyl-2-pentanone]/[4-methyl-3-penten-2-one][d] |
|---|---|---|---|
| 1.05 | 6.55 | 1.67 | 2.92 |
| 4.70 | 3.91 | 0.96 | 2.07 |
| 9.39 | 3.25[e] | | |

[a] Means of replicate determinations; average deviations from mean values were $< \pm 5\%$. [b] Measured at 210 nm. [c] Measured at 226 nm. [d] Measured at 243 nm. [e] Measured at 30° rather than 40°.

At 15°, the equilibrium ratio for the hydration of 3-buten-2-one is sufficiently large (>20) so as to make calculation of $k_{hyd}$ from $k_{obsd}$ unnecessary (*i.e.*, $k_{obsd}$ essentially equals $k_{hyd}$); consequently the rate constants plotted for 3-buten-2-one are $k_{obsd}$. Two of these, at $H_A = -0.31$ and $-1.09$, are extrapolated from studies at higher temperatures (Table I).

Plots of log $k_{hyd}$ *vs.* $-H_A$ (Figure 1) for 3-buten-2-one, 3-penten-2-one, and 4-methyl-3-penten-2-one are linear through $H_A = -1.64$ (4.03 *M* $HClO_4$) with slopes of 0.58, 0.48, and 0.51, respectively. Though the significance of these slopes is discussed later, it is interesting to note that similar plots *vs.* $-H_0$ are nonlinear even in this moderate acid concentration range. The curvature in Figure 1 at greater acid concentrations is due to protonation of the substrate (discussion to follow and ref 16).

**Solvent Isotope Effects, $k_{hyd}(H_2O)/k_{hyd}(D_2O)$.** Calculation of solvent isotope effects given in Table V required interpolation of $k_{hyd}(H_2O)$ in 4.70 *M* $HClO_4$ at 40°[c] from

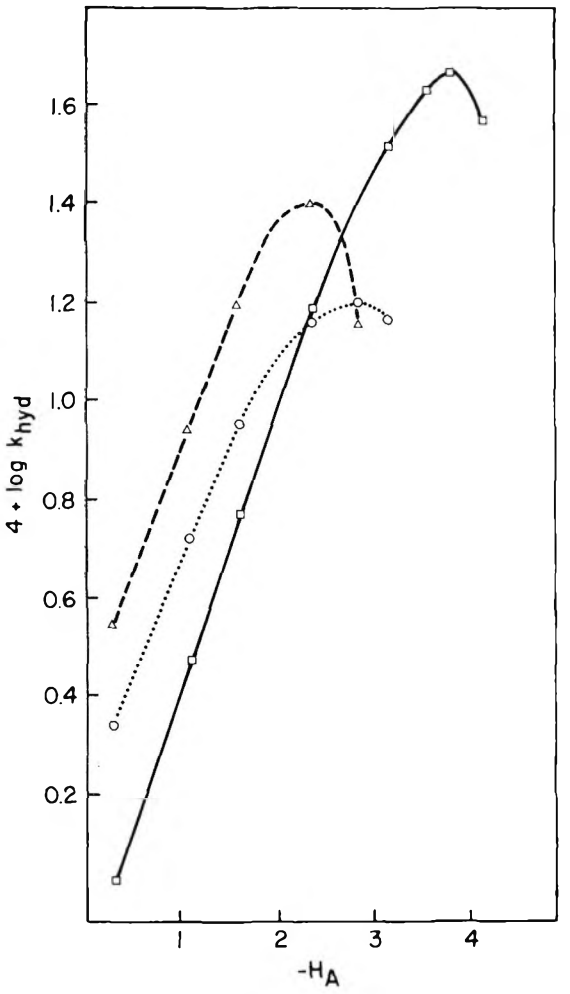



**Figure 1.** Acidity dependence of the hydration of 3-buten-2-one (□ ——, 0.58), 3-penten-2-one (○ · · · ·, 0.48), and 4-methyl-3-penten-2-one (△ - - - -, 0.51). The number in parentheses gives the slope of the straight line established by the first three points. Data for 3-buten-2-one are at 15°; other data are at 40°.

data reported in Tables I and III. The ratio $k_{hyd}(H_2O)/k_{hyd}(D_2O)$ thus represents the rate of hydration of a 3-alken-2-one in $HClO_4$–$H_2O$ solution divided by the rate of hydration of a 3-alken-2-one in a $DClO_4$–$D_2O$ solution of equal molarity.

**Activation Parameters.** Enthalpy and entropy of activation were calculated in the usual fashion[1] for the hydration of 3-alken-2-ones (*i.e.*, data in Table VI is based on $k_{hyd}$ values).

## Discussion

The mechanism by which hydration of simple aliphatic $\alpha,\beta$-unsaturated ketones proceeds is given in Scheme IV.

**Scheme IV**

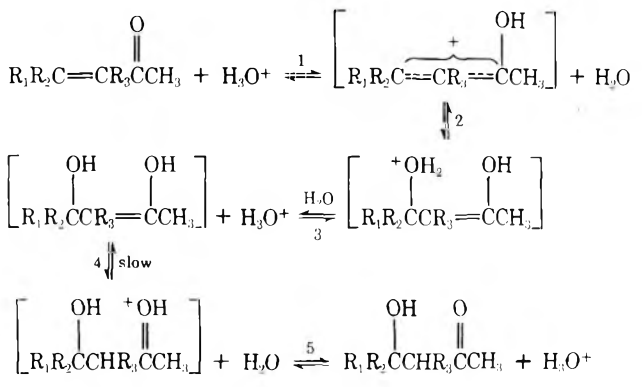



**Table V**
**Solvent Isotope Effects for the Hydration of 3-Alken-2-one at 40°**

| | $k_{hyd}(H_2O)/k_{hyd}(D_2O)$ | | |
|---|---|---|---|
| $M_{acid}$ | 3-Buten-2-one | 3-Penten-2-one | 4-Methyl-3-penten-2-one |
| 1.05 | 2.38 | 3.56 | 3.51 |
| 4.70 | 3.46 | 3.12 | 3.31 |
| 9.39 | 3.08[a] | | 1.28 |

[a] At 30°.

Below about 6 *M* perchloric acid, equilibrium 1 lies far to the left and step 4 is rate controlling, as shown by (a) the very large solvent isotope effect (Table V), (b) the very large negative entropy of activation (Table VI), and (c) the fact that 3-buten-2-one hydrates three times faster than 4-methyl-3-penten-2-one (Table I). The primary solvent isotope effect indicates that proton transfer to carbon is rate controlling. The large negative entropy is consistent with incorporation of a molecule of water into the transition state in addition to the hydronium ion. The somewhat greater reactivity of 3-buten-2-one over 4-methyl-3-penten-2-one demonstrates that reaction cannot occur *via* Scheme I (*e.g.*, isobutene hydrates $10^3$–$10^4$ times faster than propene).[17]

Above 6 *M* perchloric acid, some of the substrates are present increasingly as the conjugate acid (*i.e.*, equilibrium 1 lies to the right). The kinetic expression differs significantly from that of the reaction in dilute acid. Allowing S = substrate and $SH^+$ = protonated substrate

$$\text{when } [S] \gg [SH^+]\ v = \frac{k_1k_2k_3k_4}{k_{-1}k_{-2}k_{-3}}[S]A_{H_3O^+}A_{H_2O}\frac{f_s}{f_{tr^+}}$$

$$\text{when } [SH^+] \gg [S]\ v = \frac{k_2k_3k_4}{k_{-2}k_{-3}}[SH^+](A_{H_2O})^2\frac{f_{SH^+}}{f_{tr^+}}$$

Thus as long as the substrate is present as S (equilibrium 1 lies to the left), $k_{obsd}$ will increase with increasing acidity according to the term $A_{H_3O^+}A_{H_2O}$ ($f_s/f_{tr^+}$) above. However, when the substrate is present as $SH^+$ (equilibrium 1 lies to the right), $k_{obsd}$ will decrease with increasing acidity according to the term $(A_{H_2O})^2$ ($f_{SH^+}/f_{H_2O}$). This becomes of great significance when the kinetic expressions for dehydration are examined (*i.e.*, the reverse of Scheme IV). No matter whether the $\alpha,\beta$-unsaturated ketone is present as S or $SH^+$, $k_{obsd}$ for dehydration increases with increasing acidity according to the term $A_{H_3O^+}$ ($f_{ROH}/f_{tr^+}$), where ROH denotes the $\beta$-hydroxy ketone product of Scheme IV. Consequently as the acidity increases beyond 6 *M* $HClO_4$, a marked *decrease* in equilibrium constant (Table III) indicates that the substrate S is becoming increasingly $SH^+$ by equilibrium 1 shifting to the right. For 4-methyl-3-penten-2-one this occurs at about 6 *M* $HClO_4$; for 3-penten-2-one it occurs at *ca.* 7 *M* $HClO_4$. A forthcoming paper will discuss the basicities of these ketones in detail.[16] The only matter of consequence to Scheme IV is that as protonation of the $\alpha,\beta$-unsaturated ketone becomes significant, the rate of hydration will decrease with increasing acidity *and* the equilibrium constant will *decrease*, favoring the $\alpha,\beta$-unsaturated ketone over the $\beta$-hydroxy ketone. The curves in Figure 1 are in quantitative agreement with the reported $pK_b$ of $\alpha,\beta$-unsaturated ketones in aqueous perchloric acid; *i.e.*, the maxima in Figure 1 coincide with those expected based on $pK_b$ data[16] and the preceding discussion.

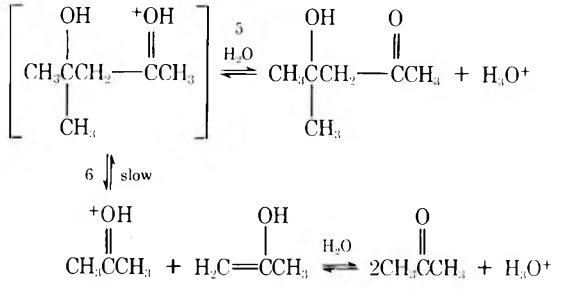
The reaction of 4-methyl-3-penten-2-one in acidities greater than 8 *M* $HClO_4$ is suprising. As previously discussed, the equilibrium constant is changing since $k_{dehyd}$ is becoming greater than $k_{hyd}$ and consequently in acidities much greater than 8 *M* there is no *apparent* hydration

**Table VI**
**Activation Parameters for the Hydration of 3-Alken-2-ones in Aqueous Perchloric Acid[a]**

| Compd | $M_{HClO_4}$ | $\Delta H^*$, kcal/mol[b] | $\Delta S^*$, eu[b] |
|---|---|---|---|
| 3-Buten-2-one | 2.57 | 15.2 ± 0.4 | −21.7 ± 1.4 |
| 3-Buten-2-one | 8.26 | 14.9 ± 0.7 | −18.2 ± 2.3 |
| 3-Buten-2-one | 9.30 | 13.6 ± 0.2 | −22.0 ± 0.6 |
| 3-Penten-2-one | 2.57 | 15.7 ± 0.4 | −22.8 ± 1.4 |
| 4-Methyl-3-penten-2-one | 2.57 | 14.8 ± 0.0 | −25.0 ± 0.1 |
| 4-Methyl-3-penten-2-one | 6.28 | 13.7 ± 0.7 | −26.3 ± 2.2 |
| 4-Methyl-3-penten-2-one | 9.96 | 20.1 ± 1.8 | −13.7 ± 5.9 |

[a] Calculated at 40°. [b] Enthalpy, entropy, and standard deviations were calculated using least-squares method, carried out on a CDC 3300 computer.

since the equilibrium constant strongly favors $\alpha,\beta$-unsaturated ketone. *However,* a slow reaction incurs at about this acidity which results in total destruction of $\alpha,\beta$-unsaturated ketone. This reaction is characterized by irreversibility (for practical purposes), small solvent isotope effect [$k$ ($H_2O$)/$k$($D_2O$) = 1.3], a very slight inverse acidity dependence [d(log $k$)/d(−HA) = −0.1], a negative entropy (−13 eu) significantly more positive than that for hydration (−25 eu), and acetone being the product (isolated as dinitrophenylhydrazone). These data all support the incursion of a retro aldol condensation as outlined below.



Recalling that at these acidities the reactant state is protonated $\alpha,\beta$-unsaturated ketone (>90% $SH^+$) and merging the above scheme with Scheme IV we have

$$v = \frac{k_2k_3k_4k_6}{k_{-2}k_{-3}k_{-4}} A_{H_2O}[SH^+] \frac{f_{SH^+}}{f_{tr^+}}$$

Tabulated values of $A_{H_2O}$ in $HClO_4$ solutions[18] give d(log $A_{H_2O}$)/d($-H_A$) = −1.0 in the region of acidity studied here. Consequently, for d(log $k$)/d($-H_A$) to equal −0.1 requires $f_{SH^+}/f_{tr^+}$ to increase significantly, compensating largely for the change in $A_{H_2O}$. This is very significant, since it demonstrates that in rather concentrated perchloric acid solution, activity coefficient *ratios* of similarly structured ions charge drastically with acid molarity (in this case, about as much as the activity of water changes). This is yet another example of the failure of the premise of the Zucker–Hammett hypothesis; previous reports have been in more dilute solutions.[19] It is also significant that this system is not a very sensitive one to changes in acidity. This is clear since protonation of $\alpha,\beta$-unsaturated ketones follows $H_A$, not $H_0$, and d($-H_A$)/d$M_{HClO}$ < d($-H_0$)/d$_{HClO}$ by about a factor of 3 in this region of acidity.[14,16]

Although not studied because of the slowness of reaction, 3-penten-2-one exhibits behavior similar to 4-methyl-3-penten-2-one in 10–11 $M$ $HClO_4$. That is, acid-catalyzed retro aldol condensation appears to be characteristic of $\alpha,\beta$-unsaturated ketones.

**Acknowledgments.** Financial support by the Long Beach Heart Association and California State University at Long Beach Foundation is gratefully acknowledged.

**Registry No.**—3-Buten-2-one, 78-94-4; 3-penten-2-one, 625-33-2; 4-methyl-3-penten-2-one, 141-79-7.

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## Effect of Added Dimethyl Sulfoxide on the Alkaline Hydrolysis of *p*-Nitroacetanilide

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The effect of added dimethyl sulfoxide on the alkaline hydrolysis of anilides has recently been examined by Gani and Viout.[1] They observed that at 1 *M* NaOH, addition of DMSO caused a rate increase for *N*-methyl-*p*-nitroacetanilide and a rate decrease for *N*-methyl-*p*-methoxyacetanilide and *N*-methylacetanilide. These effects were explained as indicating rate-determining addition of hydroxide ion for *N*-methyl-*p*-nitroacetanilide hydrolysis, but rate-determining breakdown of the intermediate for the anilides without electron-withdrawing substituents. This interpretation of the *p*-nitroanilide data has been challenged by Broxton and Deady[2] on the basis of effects of DMSO on the methanolysis of substituted 2,2,2-trifluoro-*N*-methylacetanilides. They argue that an increase in hydrolysis rate on addition of DMSO does not necessarily imply that the addition step is rate determining.

In order to resolve this controversy, we have determined the effect of added DMSO on the alkaline hydrolysis of *p*-nitroacetanilide under conditions where addition of hydroxide is known to be rate determining and under conditions where breakdown of the intermediate is known to be rate determining. Our data show that the effect of DMSO cannot be used as a probe for the rate-determining step in anilide hydrolysis. In addition, these results provide confirmatory evidence for different types of transition states in the breakdown of the tetrahedral intermediate in anilide hydrolysis depending on substituent.[3]

### Results

Pseudo-first-order rate constants were measured at 25.0 ± 0.2° in 50 vol % DMSO at an ionic strength 0.5 (NaCl) and hydroxide ion concentrations of 0.001–0.3 *M*. Reactions at higher hydroxide ion concentrations were followed to completion, but those at lower base concentrations were analyzed by measuring initial rates.

Although *p*-nitroacetanilide hydrolysis is complicated by ionization to give an unreactive anion (eq 1),[4] this side reaction can be easily corrected for. The equilibrium constant for eq 1 was measured and found to be 59 $M^{-1}$ in

$$CH_3\overset{\overset{O}{\|}}{C}NHAr + OH^- \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}\overset{-}{N}Ar \qquad (1)$$

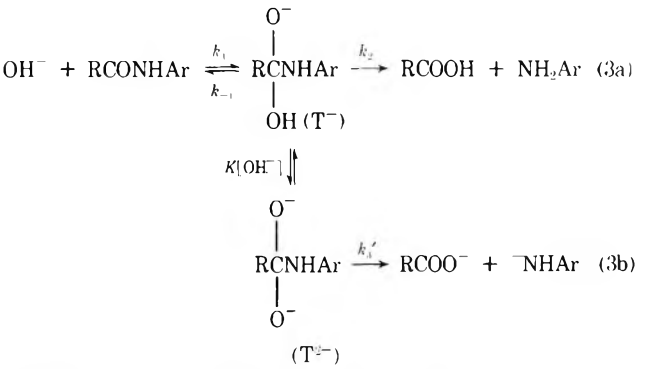
50% DMSO. The observed rate constants were then corrected for ionization of the anilide according to eq 2.

$$k^{corr} = k^{obsd}(1 + K_a[OH^-]) \qquad (2)$$

These rate constants are given in Table I and plotted in Figure 1, along with the rate constants for the entirely aqueous system.[4,5]

### Discussion

The alkaline hydrolysis of *p*-nitroanilides has been shown to proceed through two parallel paths:[4-7] (1) decomposition of the monoanion of the tetrahedral intermediate ($T^-$) with general acid catalysis to give the carboxylic acid and free amine (eq 3a); and (2) decomposition of the dianion ($T^{2-}$) without general catalysis to give carboxylate ion and anilide ion (eq 3b). This mechanism is




supported by the finding of buffer catalysis for path 3a with *p*-nitrotrifluoroacetanilide[6] and the much greater sensitivity of the dianion cleavage than of the monoanion cleavage to substituent effects in the ring.[4-7]

The present results may be accounted for by the mechanism of eq 3a and 3b. Application of the steady-state assumption gives eq 4, where $k_3 = k_3'K$. The calculated values of these parameters are given in Table II.

$$k^{corr} = \frac{k_1(k_2 + k_3[OH^-])[OH^-]}{k_{-1} + k_2 + k_3[OH^-]} \qquad (4)$$

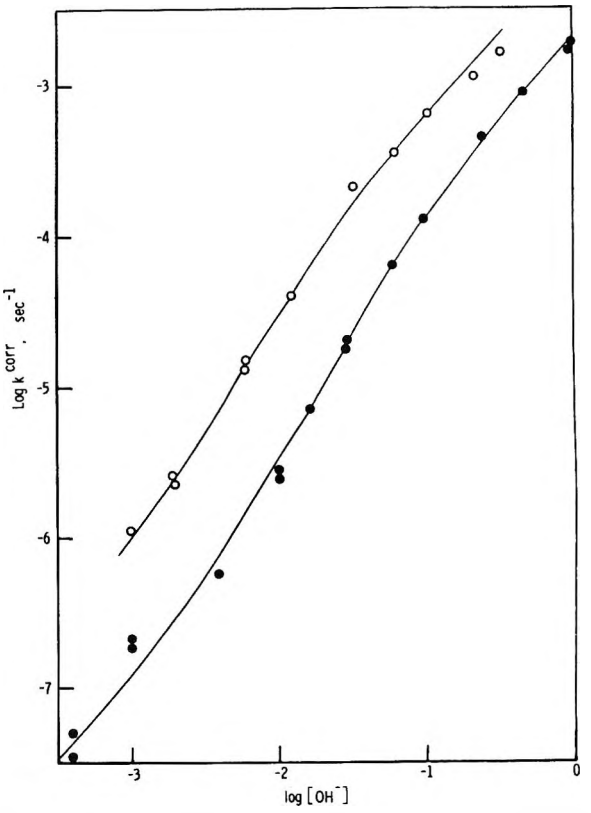



**Figure 1.** Plot of log $k^{corr}$ *vs.* log [$OH^-$] for the hydrolysis of *p*-nitroacetanilide in water (closed circles) and in 50% DMSO–water (open circles). Data for water is from ref 4 and 5. The lines are calculated from eq 4 using the parameters given in Table II.

**Table I**
**Rates of Alkaline Hydrolysis of *p*-Nitroacetanilide in 50% DMSO–Water at 25.0°**

| $[OH^-]$, $M$ | $k^{obsd}$, $sec^{-1}$ | $k^{corr}$, $sec^{-1}$ [a] | Method[b] |
|---|---|---|---|
| $3.00 \times 10^{-1}$ | $8.37 \times 10^{-5}$ | $1.58 \times 10^{-3}$ | C |
| $2.00 \times 10^{-1}$ | $8.75 \times 10^{-5}$ | $1.12 \times 10^{-3}$ | C |
| $1.00 \times 10^{-1}$ | $9.04 \times 10^{-5}$ | $6.28 \times 10^{-4}$ | C |
| $6.00 \times 10^{-2}$ | $7.59 \times 10^{-5}$ | $3.47 \times 10^{-4}$ | C |
| $3.00 \times 10^{-2}$ | $7.37 \times 10^{-5}$ | $2.05 \times 10^{-4}$ | C |
| $1.20 \times 10^{-2}$ | $2.37 \times 10^{-5}$ | $4.07 \times 10^{-5}$ | C |
| $6.00 \times 10^{-3}$ | $9.67 \times 10^{-6}$ | $1.31 \times 10^{-5}$ | I |
| $6.00 \times 10^{-3}$ | $1.06 \times 10^{-5}$ | $1.44 \times 10^{-5}$ | C |
| $2.00 \times 10^{-3}$ | $1.96 \times 10^{-6}$ | $2.19 \times 10^{-6}$ | I |
| $2.00 \times 10^{-3}$ | $2.45 \times 10^{-6}$ | $2.74 \times 10^{-6}$ | C |
| $1.00 \times 10^{-3}$ | $1.07 \times 10^{-6}$ | $1.13 \times 10^{-6}$ | I |

[a] Corrected by eq 2. [b] C = followed to completion; I = initial rate.

**Table II**
**Kinetic Parameters for the Alkaline Hydrolysis of *p*-Nitroacetanilide in Water and 50% DMSO–Water**

| | Water | 50% DMSO |
|---|---|---|
| $k_1$ | $2.2 \times 10^{-3}$ $M^{-1}$ $sec^{-1}$ | $7.6 \times 10^{-3}$ $M^{-1}$ $sec^{-1}$ |
| $k_2/k_{-1}$ | 0.045[a] | 0.09 |
| $k_3/k_{-1}$ | 14 $M^{-1}$ [b] | 53 $M^{-1}$ |

[a] Recalculated from ref 4 and 5. Value in ref 5 is 0.063. [b] Recalculated from ref 4 and 5. Value in ref 4 is 17 $M^{-1}$.

Evaluation of the kinetic parameters for water and 50% DMSO reveals that the rate constant for hydroxide addition ($k_1$) is increased by about 3.5-fold on changing the solvent from water to 50% DMSO. Under conditions where breakdown of the intermediate is rate determining ($k_3[OH^-] \ll k_{-1}$), the overall rate constant for reaction by pathway 3a $[k_1k_2/k_{-1} + k_2)]$ is increased sevenfold and by pathway 3b $[k_1k_3/(k_{-1} + k_2)]$ 12-fold.

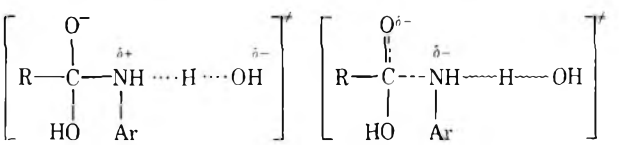
It is immediately obvious that addition of DMSO causes a rate enhancement for *p*-nitroacetanilide hydrolysis whether the rate-determining step is addition of hydroxide ion, breakdown of $T^-$, or breakdown of $T^{2-}$. These results support Deady's contention[2] that the effect of DMSO cannot be used to determine the identity of the rate-determining step in the alkaline hydrolysis of anilides.

It is of interest to analyze the effect of added DMSO on the different rate processes for this reaction. The addition of dipolar aprotic solvents such as DMSO to aqueous solutions of base is known to have a large effect on the basicity of the solution.[8] For example, the $H_-$ value of 0.011 $M$ tetramethylammonium hydroxide changes from 12 in water to 26 in 99.5 mol % DMSO.[9] This large increase in basicity has been attributed to the increased activity of hydroxide ion brought about by reduced solvation by DMSO.[9] Larger anions are less affected by a change in solvent since their solvation requirements are less than for hydroxide ion.

The rate variations observed in our work may be analyzed in the following way. An increase of the value for $k_1$ on going from water to DMSO is expected since the transition state is a larger anion than hydroxide ion, and large anions are destabilized less than small anions on transfer from water to water–DMSO solutions.[9] Consequently, solvation is less important in the transition state than the ground state and the reaction is accelerated by a less solvating medium.

For path 3b the rate enhancement due to added DMSO can be explained in an analogous manner. This process involves destruction of two hydroxide ions, with generation of water and a more diffuse anion in the transition state. Again, DMSO is expected to increase the rate due to lower solvation requirements of the transition state than the ground state.

The effect of DMSO on the first-order process for hydrolysis (eq 3a), however, cannot be explained so easily. In fact, a slight *decrease* in rate was found for the analogous process for *N*-methyl-*p*-methoxyacetanilide and *N*-methylacetanilide on going from water to 50% DMSO.[1] These results were explained by postulating a dual effect of DMSO. In addition to augmenting the activity of hydroxide ions, added DMSO decreases the activity of water. Since the rate-determining step for the hydrolysis of anilides with poor leaving groups involves slow proton transfer from water prior to C–N bond cleavage (I),[3] the diminished activity of water offsets the increased activity of hydroxide ions. Furthermore, a new hydroxide ion is being generated in the transition state and solvation of this incipient anion becomes important. The net result is a small effect on the overall reaction rate.



I II

In contrast to the results for *N*-methylacetanilide and *p*-methoxy-*N*-methylacetanilide, we find that DMSO increases the reactivity of *p*-nitroacetanilide by the process of eq 3a. The observed rate increase for *p*-nitroacetanilide hydrolysis may be explained in a manner similar to that used by Deady for the effect of DMSO on the methanolysis rates of *N*-methyl-*m*-nitro-2,2,2-trifluoroacetanilide.[2]

For good leaving groups (*p*-Cl, *m*-$NO_2$, etc.) the rate-determining step for breakdown of the intermediate is no longer proton transfer to the nitrogen as with poor leaving groups. Rather, it is C–N bond cleavage, with water acting simply to solvate the leaving group (II).[3] Here the transition state is a relatively large anion, with the negative charge spread out between the oxygen and the nitrogen. Although water is needed to solvate the nitrogen in II, it is clear that transition state II is a larger anion than hydroxide ion. Since the charge is more diffuse in II than in hydroxide ion, a rate increase on addition of DMSO for good leaving groups can be explained. For poor leaving groups (transition state I), on the other hand, charge localization is actually greater than for hydroxide ion and a rate decrease is expected. Consequently, the overall rate by the process of eq 3a is increased by addition of DMSO for good leaving groups and decreased for poor leaving groups.

## Experimental Section

*p*-Nitroacetanilide was synthesized by acylation of *p*-nitroaniline with acetic anhydride, mp 214° (lit.[4] mp 214–215°). Dimethyl sulfoxide was purified by distillation from calcium hydride at reduced pressure. Kinetic solutions were made up by pipetting 25 ml of a known concentration of aqueous sodium hydroxide into a 50-ml volumetric flask and diluting to the mark with DMSO.

The kinetics were followed spectrally at 390 nm and analyzed by a nonlinear least-squares regression program for those reactions followed to completion or by measuring initial rates (~2% reaction).[4] All reactions which were followed to completion gave stable infinity points and excellent first-order kinetics.

The equilibrium constant for the ionization of *p*-nitroacetanilide in 50% DMSO–water was determined spectrophotometrically at 390 nm by using hydroxide ion concentrations of 0.006–0.300 $M$ and a *p*-nitroacetanilide concentration of $3 \times 10^{-4}$ $M$. A plot of $1/A^{obsd}$ *vs.* $1/[OH^-]$ gave a slope of $1/(K)(A^-)$ where $A^{obsd}$ is the absorbance, $A^-$ is the absorbance of the anion, and $K$ is the equilibrium constant. A weighted least-squares analysis of this data gave $K = 59 \pm 6$ $M^{-1}$.

**Acknowledgment.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are also grateful to Dr. L. W. Deady for a preprint of ref 2 and Dr. H. B. Silber for helpful discussions.

**Registry No.**—*p*-Nitroacetanilide, 104-04-1.

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(1) V. Gani and P. Viout, *Tetrahedron Lett.*, 5241 (1972).
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(3) L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, **93**, 2014 (1971).
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## Organic Disulfides and Related Substances. 37. A Possible Counterpart of the Ene Reaction with Di-*n*-pentyl Disulfide and Maleic Anhydride[1]

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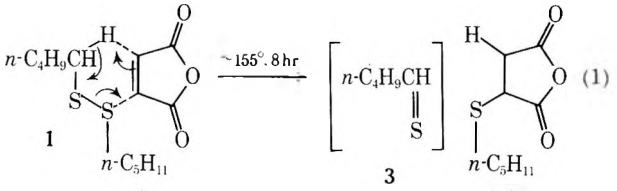
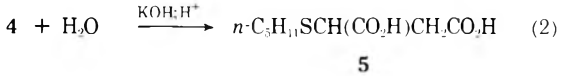
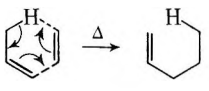
Interest in uncatalyzed reactions of disulfides with unsaturated systems prompted study of di-*n*-pentyl disulfide (1) with maleic anhydride (2) because the double-bond system of **2** seemed more likely than an isolated double bond to interact with unshared electrons of the sulfur atoms. The reaction that occurred is shown by eq 1 (with isolation of actual product, **5**, after hydrolysis by eq 2).




1 2 3 4 (1)



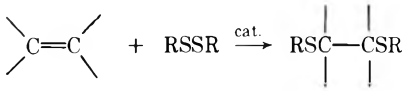

5 (2)




(3)

Although the reaction is neither particularly clean nor perhaps synthetically attractive in its present form, it is noteworthy in that the structural outcome suggests a relationship to the broadly important ene reaction (eq 3).[2] According to both eq 1 and 3, a hydrogen atom and the third atom from it add to the anhydride, a widely used enophile.[2] However, development of the new double bond requires cleavage of the S–S bond for **1** in contrast merely to the shift of bond for an alkene. So far as we know, a sulfur counterpart of the ene reaction has not been specifically recognized as such before, although a formulation resembling that of eq 1 was suggested for the reaction of di-*n*-butyl disulfide and acetylene,[3] which also is an enophile.[2] The arrows in eq 1 and 3 are intended merely to point up the similarity of the reactions, not to make a point about the direction of electron shift.

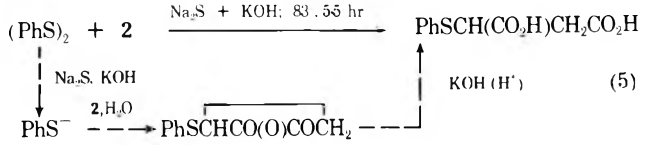
Disulfides have long been known to react with a double bond as shown by eq 4, with suitable catalysis (iodine,[4]




(4)

hydrogen fluoride,[5] cobalt sulfide,[6] or ethanesulfonic acid[7]). Free-radical addition also has been observed but leads only to poor yields of 1:1 adducts.[8]

The only reaction apparently reported for a disulfide with **2** is that of eq 5,[9] which also seems to be the only reaction where a disulfide has led to a mono- rather than a bisthio ether. The sequence probably is that of the dotted arrows (eq 5), involving merely reduction of the disulfide to the thiolate ion, which then adds conventionally to **2**.[10]




(5)

Table I, expt 1, shows conditions for the initial reaction when **1** was heated neat with **2** (eq 1). The fate of the presumed thio aldehyde **3** never became clear, not surprisingly, because **3** would be expected to be highly reactive. That the main product, after hydrolysis (eq 2), was 2-(*n*-pentylthio)succinic acid (**5**) was confirmed by independent synthesis.

Experiment 2 was done at lower temperature and with excess **1** (rather than the usual excess of **2**) to improve the conversion to **5**. The conversion was zero, but the result showed that the reactions of eq 1 and 5 must differ significantly (compare the conditions cited above the arrows). Indeed, when expt 1 was essentially repeated with diphenyl disulfide (15% excess) substituted for **1**, 99% of this disulfide was recovered; cleavage alone of this S–S bond thus did not suffice for a reaction like that of eq 1, so that the $\alpha$-$CH_2$ moiety of **1** clearly is essential. In expt 3, longer reaction at the lower temperature did lead to **5**, indeed with better results than in expt 1 (*cf.* Table I, footnote *h*).

There was a possibility that the hydrolysis and treatment with alkali used in isolating **5** (eq 2) actually might have led to conversion of **1**, only at this late point, to give *n*-pentanethiolate ion, which then could have added to **2** to produce **4**. Experiment 4 duplicated the isolation alone and, by giving no **5**, ruled out the possibility that **5** merely was an artifact of isolation. That **5** also did not originate during the reaction itself simply through thermally induced cleavage of **1** to 1-pentanethiol was shown by demonstrating high thermal stability of **1** at *ca.* 155° (*cf.* Experimental Section).

Experiments 5–7 were done to improve the conversion further. A plot of conversion against time for expt 1 and 4–7 indicated that the product **4** undergoes further reactions that destroy it when heating is prolonged and that the optimum time of reaction would be *ca.* 7 hr. Experiment 8, based on this inference, gave the best conversion encountered, 44%.

In expt 5, **1** and **2** were carefully purified to obviate possible misinterpretations. An effort then was made to isolate all products. No pure sulfur compound other than **5** could be isolated, despite reworking of mother liquors, capitalization upon differing solubilities, distillation, and chromatography. The material balance was 98%, but the

**Table I**
**Reaction of Di-*n*-pentyl Disulfide (1) with Maleic Anhydride (2)[a]**

| Expt | Molar proportions: Disulfide (1) | Molar proportions: Anhydride (2) | Reaction: Temp, °C[b] | Reaction: Time, hr | Product (5): Conversion, %[c] | Product (5): Approx yield, %[d] | Product (5): Mp, °C[e] |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 2 | 165[f] | 17 | 22 | | 100–103 |
| 2 | 3 | 1 | 115 | 23 | 0[g] | 0[g] | |
| 3[h] | 3 | 1 | 115 | 43 | 34 | | 103.5–107 |
| 4[i] | 1 | 2 | 25[i] | 0 | 0 | 0 | |
| 5 | 1 | 2 | 155 | 8.5 | 31 | ~79 | 106.5–107.5 |
| 6 | 1 | 2 | 155 | 6 | 31 | | 101–103.5 |
| 7 | 1 | 2 | 155 | 2.3 | 9 | | 103–105 |
| 8 | 1 | 8 | 155 | 7.6 | 44 | ~71 | 102.5–105 |
| 9 | 1 | 2 | To 190[j] | 17 | 2[k] | | 95–102.5 |
| 10[h,l] | 3 | 1 | 126 | 43 | 31 | ~81 | 103.5–105 |
| 11[m] | 1 | 2 | 155 | 6 | 32 | | 104.5–106 |
| 12[m] | 1 | 2 | 155 | 25 | 18 | | 95.5–100 |

[a] Heated neat unless otherwise stated. [b] Approximate average; usual range *ca.* ±5° unless otherwise stated. [c] On the assumption of **1** as the limiting reagent in eq 1, except for expt 2, 3, and 10, where **2** is assumed to be limiting. [d] On the assumption that *all* solvent-extractable neutral material is recovered **1** [ir showed that a little was unhydrolyzed anhydride(s)] and that **1** actually consumed is starting material less this neutral material. For example, in expt 5 neutral material extracted after hydrolysis amounted to *ca.* 61% of **1** used (yield of **5**, 79%); distillation reduced the 61% to 38% (yield of **5**, 50%). [e] Melting point of pure **5**, 108.5–109°. Identity of **5** checked by mixture melting point. [f] Range *ca.* ±15°. [g] Recovery of **1**, 88%. [h] A little sulfur was added in the hope of catalyzing eq 1 or of inhibiting polymerizations. However, it may have changed the mechanism of reaction. [i] Control experiment at 25° to assure that **5** was not an artifact of the usual procedure of isolation. [j] Range *ca.* 150–190°; for several hours the temperature was *ca.* 190°. [k] The pH of the aqueous solution after neutralization and extraction was *ca.* 10 (usually *ca.* 7), suggesting loss of part of the carboxyl function during reaction. The benzene-soluble material (13.9 g) atypically was mostly insoluble in $H_2O$, suggesting that the water-insoluble "black oil," which usually was a by-product, had become the major product. [l] In AcOH as solvent [m] In cumene as solvent.

crude hydrolysis product (eq 2) seemed to contain at least a dozen components. The usual black reaction product contrasts markedly with the negligible color **1** alone develops at *ca.* 155°. Early crops of **5** typically were contaminated by an intractable, water-insoluble "black oil" that could be removed reasonably well mechanically by washing and pressing and that seemed to contain at least four substances. Five recrystallizations were required to give the **5** reported in Table I.

Some other conclusions are possible. Experiment 9 (like expt 1 but at a temperature up to 25° higher) pointed to the bad effect on the conversion of too high a temperature; the amount of "black oil" was unusually large, confirming the probability that it arose from decomposition of **4**. Although 38–61% of **1** was recovered in expt 5 (*cf.* Table I, footnote *d*), use of the still larger excess of **2** in expt 8 did not influence the conversion or yield significantly, perhaps because the excess **2** was consumed in side reactions (comparison of expt 3 with expt 1 suggests that use of excess **1** also may have little effect). Experiment 10, with acetic acid as a solvent, gave much the same result as expt 3 done neat, showing that a proton source has little effect. Experiments 11 and 12 explored use of cumene as a solvent. The thought was that if eq 1 involved thiyl radicals in a homolytic process, abstraction of H· from cumene (instead of by destruction of other thiyl radicals to form **3**) could both improve the yield and indicate a homolytic nature for eq 1. "Cumene is normally particularly susceptible to side-chain hydrogen abstraction by free radicals . . . ."[12] However, the results of expt 11 were much like those of expt 6 done neat. It is worth adding that "the ene synthesis is little affected by solvent changes."[2] The implication from the negligible effect of cumene that homolysis may not play a major role in eq 1 was supported by the fact that no more than 2% of **5** could be isolated when **1** and **2** were strongly irradiated for 8 hr; in the perhaps analogous reaction mentioned of alkyl disulfides with acetylene, free-radical initiators had no effect.[3] Experiment 12 confirmed that too long a period of heating has the same bad effect as that mentioned of too high a temperature (*cf.* expt 11 and 12).

## Experimental Section[13]

**Reaction of Di-*n*-pentyl Disulfide (1) with Maleic Anhydride (2).[14] A. Typical Procedure with Excess 2 (Expt 8).** A clear solution in **1** (20.10 g, 97.4 mmol) of **2** (76.4 g, 780 mmol, 8 molar proportions) was heated (Glascol mantle) at 151–163° for 7.6 hr in a 500-ml flask protected from moisture ($CaCl_2$) and provided with a thermometer, stirrer, and air condenser. Cooling to *ca.* 25° then gave a mobile, dark liquid. Water (300 ml) was added, and the mixture was stirred vigorously for 1 hr. "Black oil" (**1**?), which separated in many experiments at this point, did not appear. An iced solution of KOH (88.5 g, 1580 mmol) and $H_2O$ (160 ml) then was added below 15° (to obviate attack on any **1** that remained). The mixture was stirred for 5 min (pH *ca.* 7) and extracted with $Et_2O$. The $Et_2O$ extract, washed with $H_2O$, dried, and evaporated, gave 7.6 g of dark liquid, which an ir spectrum showed to be largely **1** (38% recovery) containing some form of anhydride(s) (ir 1725, 1788 $cm^{-1}$). The combined aqueous layers were acidified with concentrated HCl (132 ml) and extracted with 100 ml of benzene, then thrice more with 50 ml.[17] The combined benzene extracts were washed twice with 10-ml portions of $H_2O$. Removal of the benzene (without drying, in expt 8, to obviate crystallization of the sparingly soluble **5**) left dark oil, which crystallized to a greasy solid (23.6 g). Three recrystallizations from $H_2O$ gave 9.42 g of 2-(*n*-pentylthio)succinic acid (**5**, 44% conversion, 71% yield assuming that the 7.6 g of liquid extracted was pure **1**),[18] mp 102.5–105°, undepressed by authentic **5**.

**B. Modifications.** In expt 3, a typical one with excess **1** (except that 0.5 g of sulfur also was used; *cf.* Table I, footnote *h*), **1** (27.62 g, 133.9 mmol) and **2** (4.37 g, 44.6 mmol) were heated at *ca.* 110–120° for 44 hr. **5** was isolated as in A, except that recrystallization of **5** was from $Cl(CH_2)_2Cl$ to the melting point in Table I, then from $H_2O$ and *n*-BuCl to a constant melting point (and mixture melting point) of 108–108.5°. *Anal.* Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.56; neut equiv, 110. Found: C, 48.92; H, 7.13; S, 14.64; neut equiv, 111.

Experiment 10 was essentially a repetition of expt 3 but with 25 ml of glacial AcOH as solvent. After the 43-hr reaction period (at the reflux temperature), AcOH was removed from the deep red solution, and isolation then was done as in A; $Et_2O$ extraction recovered 24.13 g of **1**. Experiment 11 was like expt 8 except for use of 19.00 g (194 mmol) of **2**, 100 ml of cumene as a solvent (at the reflux temperature), the different conditions noted in Table I, and longer periods of stirring with $H_2O$ (3 hr) and alkali (10 min) to achieve a neutral pH (~8) in the presence of the cumene; this cumene procedure seemed a clean one, promising for other studies. Experiment 12 was like expt 11 except for the longer reaction

period (Table I); the acidification led to *ca.* 35 g of a syrup that was insoluble in both $H_2O$ and benzene and presumably represented secondary reaction products.

**C. Effect of Light.** A mixture of **1** (8.33 g, 40.4 mmol) and **2** (1.98 g, 20.2 mmol) was irradiated with occasional swirling in a quartz flask at *ca.* 50–75° using a 6-in. distant 250-W Hg lamp [General Electric Co. UA-2 Uviarc; rated per cents of wattage (Å range) were 4.6 (<2800), 4.3 (2800–3200), and 3.4 (3200–3800)]. A brown oil began to separate after *ca.* 1 hr. Considerable carbonization seemed to occur. After 8 hr, a brown solid and pale yellow supernatant layer resulted. Addition of $H_2O$ (5 ml) and warming effected dissolution of the solid. An iced solution of KOH (2.29 g, 40.9 mmol) in $H_2O$ (25 ml) was added, and the mixture was extracted well with $Et_2O$. Acidification (pH 7) and benzene extraction gave 0.07 g of material, a *maximum* yield of only 2% of **5**.

**Authentic 2-(*n*-Pentylthio)succinic Acid (5).** Sodium hydroxide (5.3 g, 133 mmol) and purified *n*-pentyl iodide (27.8 g, 140 mmol) were added to a solution of mercaptosuccinic acid (19.4 g, 129 mmol)[19] and $Na_2CO_3$ (13.7 g, 129 mmol) in $H_2O$ (58 ml). The mixture was stirred at high speed under $N_2$ for 6 hr.[20] Heat was applied briefly at the outset to raise the temperature to 70°, after which the temperature remained at *ca.* 70–83°, mainly apparently because of the heat of stirring. The homogeneous mixture was washed with $Et_2O$, acidified, and extracted with benzene (300 ml) and $Et_2O$ (200 ml) in several portions (**5** is sparingly soluble). The combined extracts were washed ($H_2O$), dried ($MgSO_4$), and evaporated, yield, 20.0 g (70%), mp 105.5–107°. Recrystallization [$H_2O$, $Cl(CH_2)_2Cl$] gave **5** of constant mp 108.5–109°, undepressed by the analytically pure **5** described in B (lit. mp 99.5°,[11] 107°,[21] 107.7–108°[22]). *Anal.* Calcd for $C_9H_{16}O_4S$: C, 49.07; H, 7.32. Found: C, 49.26; H, 7.21.

When essentially the same mixture merely was shaken vigorously at ~25° for 28 hr, the yield of greasy **5** (mp 93–102°) was quite small.

**Thermal Stability of 1.** In a simulation of expt 1, **1** (7.45 g) was heated alone at 153–158° for 19 hr. In contrast to the dark color typically seen in less than 1 hr with **1** and **2** (*e.g.*, in expt 1 and 8), **1** became only very pale yellow; no odor of a thiol or of $H_2S$ was perceptible. Even the first fraction on distillation was pure **1** [0.46 g (6%), $n^{25}D$ 1.4872 (lit.[15] $n^{25}D$ 1.4868, 1.4875)], and remaining fractions were quite pure as well [6.42 g (86%), bp 140–145° (19 mm), $n^{25}D$ 1.4873, $n^{25}D$ for 1-pentanethiol, 1.4439[23]].

**Substitution of Diphenyl Disulfide for 1.** In a simulation of expt 1, recrystallized $(PhS)_2$ (7.68 g, 35.2 mmol) and **2** (3.00 g, 30.6 mmol) were heated at 160–170° for 23 hr. The $(PhS)_2$, isolated as in A, amounted to 7.62 g (99% recovery), mp and mmp 57–59°. Acidification of the aqueous layers and continuous $Et_2O$ extraction gave 2.92 g (82%) of maleic acid, mp and mmp 126.5–129°.

**Registry No.**—**1**, 112-51-6; **2**, 108-31-6; **5**, 5413-66-1; diphenyl disulfide, 882-33-7.

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(1) (a) Paper 36: P. K. Srivastava and L. Field, *J. Org. Chem.*, **37**, 4196 (1972). (b) This investigation was supported by the U. S. Army Research Office, Durham, N. C., and, in the last phases, by NIH Research Grant AM11685 from the National Institute of Arthritis, Metabolism, and Digestive Diseases.

(2) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

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(4) (a) B. Holmberg, *Ark. Kemi, Mineral. Geol.*, **12B**, No. 48 (1938); *Chem. Abstr.*, **32**, 4155 (1938); (b) *ibid.*, **13B**, No. 14 (1940); *Chem. Abstr.*, **34**, 2341 (1940).

(5) D. A. McCaulay and A. P. Lien, U. S. Patent 2,519,586 (1950); *Chem. Abstr.*, **44**, 10728 (1950).

(6) F. K. Signaigo, U. S. Patent 2,454,099 (1948); *Chem. Abstr.*, **43**, 1794 (1949).

(7) W. A. Proell, U. S. Patent 2,658,038 (1953); *Chem. Abstr.*, **48**, 3049 (1954).

(8) E. I. Heiba and R. M. Dessau, *J. Org. Chem.*, **32**, 3837 (1967).

(9) W. A. Proell and C. E. Adams, U. S. Patent 2,561,673 (1951); *Chem. Abstr.*, **46**, 3083 (1952).

(10) Chilcote has added thiols to **2** in the presence of enough aqueous KOH to engender thiolate ions (96°, 2 hr).[11]

(11) W. B. Chilcote, U. S. Patent 2,581,514 (1952); *Chem. Abstr.*, **47**, 4363 (1953).

(12) R. L. Dannley, J. E. Gagen, and O. J. Stewart, *J. Org. Chem.*, **35**, 3076 (1970).

(13) Melting points are corrected, and boiling points are uncorrected.

(14) Good commercial grades of **1** and **2** usually were used; as a check, however, for expt 5 the disulfide **1** was fractionally distilled (also used in expt 8), $n^{25}D$ 1.4869 (lit.[15] $n^{25}D$ 1.4868, 1.4875), and the anhydride **2** was recrystallized from $Cl(CH_2)_2Cl$, mp 52.5–54° (lit.[16] mp 52.8°).

(15) E. Miller, F. S. Crossley, and M. L. Moore, *J. Amer. Chem. Soc.*, **64**, 2322 (1942).

(16) "Handbook of Chemistry," 10th ed, N. A. Lange, Ed., McGraw-Hill, New York, N. Y., 1961, p 592.

(17) Benzene proved best for extracting crude **5**, while leaving maleic and fumaric acids mainly in the aqueous phase. However, it is a rather poor solvent and in some experiments (when the extract was dried) $Et_2O$ had to be added to preclude crystallization of 5.

(18) Typically, after the first recrystallization, products were washed with a little ice water and then pressed on a vacuum filter with a rubber dam. The water expressed carried more or less of the "black oil" that appeared in the filtrate in each such instance except in expt 11. Decolorizing carbon was used frequently in the recrystallizations.

(19) Kindly provided by Evans Chemetics, Inc., New York, N. Y.

(20) Apparatus of A. A. Morton, B. Darling, and J. Davidson, *Ind. Eng. Chem., Anal. Ed.*, **14**, 734 (1942).

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## Hydrolytic Reactions of Carbyl Sulfate


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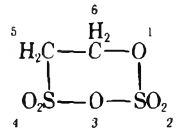
Carbyl sulfate (2,2,4,4-tetraoxo-1,3,2,4-dioxadithiane, **1**) is a colorless, crystalline solid, mp 107–108°, commonly prepared by the direct reaction of ethylene with $SO_3$.[1b,2] Crude "carbyl sulfate" of mp 80°[1b] has been shown to be complexed with excess $SO_3$.[2] The pure compound reacts vigorously with alcohols,[3] amines,[4] and other compounds possessing active hydrogens. The reaction of carbyl sulfate with water has been reported to produce ethionic acid ($HOSO_2OCH_2CH_2SO_3H$),[2,5] isethionic acid ($HOCH_2CH_2SO_3H$),[5,6] and/or vinylsulfonic acid or its sodium salt.[2,3,5-7] We have sought to elucidate the reactions of carbyl sulfate with water.



**1**

When 0.01 mol of purified carbyl sulfate is added to 200–400 ml of water at 0–80° a fast exothermic reaction goes to completion within seconds. Titration shows formation of 2 equiv of strong acid. Similar results are obtained when carbyl sulfate is predissolved in 1,2-dichloroethane or dioxane, and when water is replaced by dilute mineral acid. The reaction product is ethionic acid.

$$\overline{SO_2OCH_2CH_2SO_2O} + H_2O \longrightarrow HOSO_2OCH_2CH_2SO_3H \quad (1)$$

Dilute acidic aqueous solutions of ethionic acid are stable for days at room temperature. At about 60° and above, the ratio (equivalents of acid formed):(moles of carbyl sulfate reacted) slowly increases from 2.0 to 3.0, following pseudo-first-order kinetics. At 70° $k \cong 1 \times 10^{-6}$ $sec^{-1}$. The activation energy (70–90°) is approximately 33 kcal $mol^{-1}$. A solution of ethionic acid in water was held at 80° for 24 hr, then cooled and titrated with $BaCl_2$ to remove sulfate. The filtrate was neutralized with dilute NaOH and water was removed to yield sodium isethionate. The only reaction evident in hot acidic aqueous solutions is

simple ester hydrolysis. Under these conditions no vinylsulfonic acid is formed.

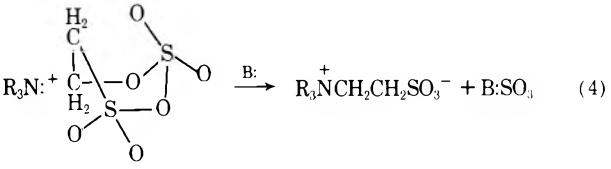
$$HOSO_2OCH_2CH_2SO_3H + H_2O \longrightarrow H_2SO_4 + HOCH_2CH_2SO_3H \quad (2)$$

Addition of carbyl sulfate to aqueous alkaline solutions at 25–90° (pH 12.0–13.3) resulted in rapid reactions yielding in all cases *mixtures* of ethionate and vinylsulfonate salts. No isethionate was detected and no secondary hydrolysis of ethionate was observed. The ratios (equivalents of acid formed):(moles of carbyl sulfate reacted) were in the range 2.5–2.8. These ratios were difficult to reproduce from one run to another, but ratios found in individual runs were reproducible and invariant with time. No systematic temperature dependency was evident. These observations are consistent with a competition between two fast irreversible processes, one forming ethionate and the other forming vinylsulfonate *directly from carbyl sulfate*.

$$\overbrace{SO_2OCH_2CH_2SO_2O} + OH^- \longrightarrow CH_2{=}CHSO_3^- + H_2SO_4 \quad (3)$$

In titrating alkaline ethionate solutions to neutrality it was observed that at about pH 9 and below additional acid was formed spontaneously. Similarly, titrations of acidic solutions of ethionic acid were characterized by fading end points. An acidic solution of ethionic acid was brought to pH 7.8–8.0 with a measured excess of $NaHCO_3$, allowed to stand for 15 min at 23°, then acidified and assayed for acid functions by a quick-titration method; the ratio (equivalents of acid formed):(moles of carbyl sulfate reacted) was found to have increased from 2.0 to 3.0. The organic product of this reaction is sodium vinylsulfonate. These observations indicate that ethionic acid in aqueous solutions is stable at pH's below about 5, and its anion is stable at pH's above about 10, but in the intermediate range (pH 6–9) a facile elimination occurs.

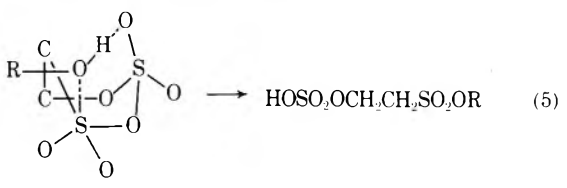
The foregoing, taken together with literature reports,[2-7] suggests that carbyl sulfate can undergo three distinct ring-opening attacks by Lewis bases. Soft bases which do not possess active hydrogens (for example, tertiary amines[4]) make a SN2 attack upon C-6 (eq 4), where B: is



(4)

excess amine or any other available base. In aqueous solutions this reaction is preempted by either or both of the following reactions.

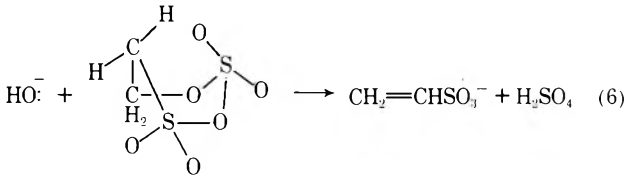
Soft bases possessing active hydrogens (alcohols, primary and secondary amines, water) have available to them another very facile ring-opening mechanism. We suggest that this may be an attack upon S-4 facilitated by interaction with the flagpole oxygen of S-2 (eq 5). With



(5)

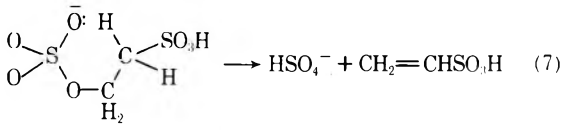
water (R = H) the product is ethionic acid, with alcohols the corresponding sulfonate esters.[3]

Hard bases such as hydroxide ion not only may attack sulfur to form ethionate ion, but also may attack the most acidic hydrogen at C-5, to produce vinylsulfonate (eq 6).



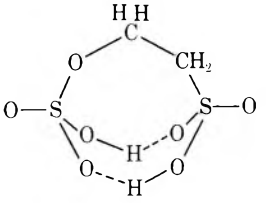
(6)

Another feature of the aqueous system is the fast elimination which ethionic acid undergoes in neutral solutions. The intramolecular elimination of the monoanion looks reasonable (eq 7). However, a rate optimum at pH 7–8 re-



(7)

quires that $K_1K_2 \cong 10^{-15}$, a smaller product than expected for a molecule containing a hydrogen sulfate and an alkylsulfonic acid function.[8] Furthermore, Geiger[9] has shown that the methyl half-ester of ethionic acid fails to undergo the corresponding elimination reaction under these conditions. A possible explanation lies in the conformations available to ethionic acid. This may assume a strainless conformation with two intramolecular hydrogen bonds (2). In conformation 2 one of the hydrogens adja-



2

cent to the sulfonic acid function is also anti to the sulfate function, that is, in favored position for elimination. Although the concentration of undissociated ethionic acid is very low in neutral solutions, the high susceptibility of 2 to E2 attack by $OH^-$ may compensate and thereby explain this fast elimination.

## Experimental Section

Commercial carbyl sulfate (brown crystals) was recrystallized three times from 1,2-dichloroethane under nitrogen, dried for 90 min under vacuum to remove all traces of solvent and occluded $SO_3$, then stored in sealed bottles at −20°. Carbyl sulfate purified in this manner is in the form of colorless crystals, mp 107–108°, nmr spectrum in dichloroethane consisting of two triplets (60 MHz), $\delta$ 2.48 and 5.09 ppm, and stable in dry storage for at least 1 year. With less rigorous purification or in the presence of moisture the compound deteriorates within a few weeks.

Ethionic acid, formed by the reaction of carbyl sulfate with water, decomposes upon isolation. Its aqueous solution was identified by its infrared spectrum (AgCl cell) with major $-SO_2-$ peaks at 1200, 1160, 1040, and 1020 $cm^{-1}$, its nmr spectrum, characterized by triplets at $\delta$ 3.35 and 4.42 ppm, the 2:1 stoichiometry of acid function per carbyl sulfate reacted, and its subsequent reactions noted below.

Isethionic acid was isolated from the reaction of 2.5 g of carbyl sulfate with 400 ml of 0.01 *M* sulfuric acid, after hydrolysis of the intermediate ethionic acid by refluxing for 12 hr and removal of sulfate by $BaCl_2$ precipitation. The aqueous filtrate was neutralized with NaOH. One portion was concentrated by evaporation at reduced pressure; its nmr spectrum showed two triplets at $\delta$ 3.29 and 4.09 ppm. A second portion was dried; the white, crystalline salt yielded (KBr pellet) infrared absorption peaks at 3300, 1180, 1040, and 740 $cm^{-1}$, in good agreement with published values.[10] Nmr and infrared spectra of a commercial sample of sodium isethionate were essentially identical with the above.

Vinylsulfonic acid was prepared and identified as follows. To 250 ml of 0.02 *M* sulfuric acid at 22° was added 0.020 mol of carbyl sulfate, to form ethionic acid. To this solution was added an

excess (0.080 mol) of $NaHCO_3$ and the buffered solution was stirred for 15 min. Analysis of an aliquot showed 3.0 equiv of acid per mole of carbyl sulfate. (This was confirmed with poor precision by a bisulfite additon assay.) The neutralized solution was dried at 50° and reduced pressure and the resulting salt mixture was subjected to a 12-hr Soxhlet extraction with methanol. The extract, containing the organic salt, was divided into aliquots. One portion, treated with *S*-benzylthiuronium chloride, formed the corresponding vinylsulfonate salt, mp 145–146° from ethanol, in good agreement with the reported value.[11] Another portion was dried; the white salt yielded (KBr pellet) major infrared maxima at 1190, 1045, 1620, and 755 $cm^{-1}$, in the expected regions for $-SO_2-$ asymmetric and symmetric stretch, vinyl, and S–O stretch, respectively. The remaining portion was examined in aqueous solution by nmr, yielding a seven-peak spectrum characteristic of vinyl splitting with $J_{gem} \cong 0$.[12] The three vinylic protons appeared at $\delta$ 6.00, 6.04, and 6.86 ppm, similar to those found for methyl vinyl sulfone (5.95, 6.13, and 6.70 ppm)[13] and reasonably close to the values predicted by the Pascual equation[14] for $CH_2{=}CH{-}SO_2-$ (6.23, 6.43, and 6.86 ppm).

Acid–base titrations were carried out using standard 0.10 *N* $Na_2CO_3$ or NaOH. Since ethionic acid undergoes an acid-generating elimination in near-neutral solutions, it was found useful to make one or two preliminary range-finding titrations, prior to carrying out rapid analytical titrations to first end points.

Reactions in dilute aqueous base were examined by addition of 2–3 mmol of pure carbyl sulfate to 100-ml portions of 0.10 *N* KOH, followed by titration with standard acid. At 25, 50, and 90° the average values of the ratio (equivalents of acid formed):(moles of carbyl sulfate reacted) were found to be 2.7, 2.6, and 2.7. (When carbyl sulfate is predissolved in 10 ml of dry dioxane and this solution is added to the aqueous base, this observed ratio falls to 2.0.) Identification of vinylsulfonate in the product mixture was made by infrared examination and by reaction with measured amounts of bisulfite ion to form potassium ethanedisulfonate.[15]

Quantitative information on the elimination of sulfate by ethionate in near-neutral solutions was sought by combining solutions of ethionic acid and phosphate buffers, then assaying these for vinylsulfonate by the semiquantitative bisulfite method.[15] Vinylsulfonate yields of 80–90% were obtained at pH 7.70, 70–78% at pH 7.01 and 8.90, 45–55% at pH 5.5 and 10.2, and 80–95% with authentic sodium vinylsulfonate. While these data suggest a maximum elimination in nearly neutral solutions, we were unable to obtain acceptably reproducible assays by this procedure.

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**Registry No.**—Carbyl sulfate, 503-41-3.

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## Ester Enolates. A New Preparation of Malonates, Phosphonoacetates, and α-Selenyl and Sulfinyl Esters

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The formation of α carbanions of carboxylic acids and esters by means of nonnucleophilic bases such as disubstituted lithium amides has recently been widely investigated owing to their great synthetic utility.

At the present time, the reactions of these anions with electrophilic substrates are restricted to alkyl halides,[1-6] halogens,[7] epoxides,[1] alkyl nitrates,[8] substituted ammonias,[9] alkyl silyl chlorides,[10] and carbonyl compounds such as $CO_2$,[11] esters,[8,12] acyl chlorides,[13] aldehydes,[14,15] and ketones.[15]

In this paper we wish to report the extension of this range of substrates to ethyl chloroformate, chlorophosphates, diphenyl disulfide, and benzeneselenenyl bromide. Also included are certain substrates that did not react satisfactorily. Esters of α-branched and straight-chain acids (isobutyric, hexanoic, and acetic acid) were employed to test the general applicability of the investigated reactions in relation with self-condensation reactions. The α anions were prepared with the readily available base lithium diisopropylamide (LDA) using published procedures.[5,6]

The reaction of ethyl chloroformate with these α anions was explored, leading to the expected substituted malonates in yields as high as 70% at −15° and 90% at −78°.

$$R_2CHCO_2R' \xrightarrow[2.\ ClCO_2Et]{1.\ LDA} R_2C(CO_2Et)CO_2R'$$

Of special interest is the facile preparation of ethyl *tert*-butyl malonate,[16] useful in β-keto ester synthesis.[17] This reagent can be obtained in a yield of 70–75%, whereas the normal three-step procedure[16] has an overall yield of 40–45%. This reaction can presumably be extended to the synthesis of other useful mixed malonates.

The synthetic utility of β-carboalkoxy phosphates (phosphonoacetates) and phosphinoxides as starting materials for olefination reactions suggested their preparation by treating the α anions with chlorophosphates and chlorophosphinoxides. Isobutyrates, on reaction with chlorophosphates, gave high yields of the expected products.

$$(CH_3)_2CHCO_2R \xrightarrow[2.\ (R'O)_2POCl]{1.\ LDA} (CH_3)_2C(CO_2R)P(O)(OR')_2$$

a. R = Et; R′ = Et, $CH_3$
b. R = $CH_3$; R′ = $CH_3$

The same reaction attempted with methyl hexanoate and ethyl acetate failed to give the expected products, thus detracting from synthetic use in olefination reactions. As self-condensation products were indicated by nmr spectra, we looked at the analogous *tert*-butyl esters, whose anions are known to be more stable.[5,6,18] The anion of *tert*-butyl acetate gave 65% of the desired reaction with $(EtO)_2P(O)Cl$, indicating the advantages of using hindered esters.

It was observed that $Ph_2P(O)Cl$ was unreactive with isobutyrate and acetate α anions, probably owing to steric crowding, $Ph_2P(O)OH$ being recovered after quenching of the reaction mixture with water. However, the obvious possibility of reaction on oxygen[19] by both sets of phosphorus chloride reagents must be considered, the intermediate phosphates being hydrolized during work-up. The relative success of esters sterically hindered on the α car-

**Table I**

| Ester | Electrophilic reagent | Product | (No.) | Yield, % |
|---|---|---|---|---|
| $(CH_3)_2CHCO_2Et$ | $ClCO_2Et$ | $(CH_3)_2C(CO_2Et)_2$ | (1) | 90 |
| $CH_3CO_2Et$ | $ClCO_2Et$ | $CH_2(CO_2Et)_2$ | (2) | 88 |
| $CH_3CO_2Bu$-$t$ | $ClCO_2Et$ | $CH_2(CO_2Et)CO_2Bu$-$t$ | (3) | 70–75 |
| $(CH_3)_2CHCO_2Et$ | $ClP(O)(OEt)_2$ | $(CH_3)_2C(CO_2Et)P(O)(OEt)_2$ | (4) | 80 |
| $(CH_3)_2CHCO_2Et$ | $ClP(O)(OCH_3)_2$ | $(CH_3)_2C(CO_2Et)P(O)(OCH_3)_2$ | (5) | 64 |
| $(CH_3)_2CHCO_2CH_3$ | $ClP(O)(OCH_3)_2$ | $(CH_3)_2C(CO_2CH_3)P(O)(OCH_3)_2$ | (6) | 62 |
| $CH_3CO_2Bu$-$t$ | $ClP(O)(OEt)_2$ | $CH_2(CO_2Bu$-$t)P(O)(OEt)_2$ | (7) | 65 |
| $(CH_3)_2CHCO_2Et$ | PhSeBr | $(CH_3)_2C(CO_2Et)SePh$ | (8) | 85 |
| $n$-$C_5H_{11}CO_2CH_3$ | PhSeBr | $n$-$C_4H_9CH(CO_2CH_3)SePh$ | (9) | 60 |
| $CH_3CO_2Et$ | PhSeBr | $CH_2(CO_2Et)SePh$ | (10) | 80 |
| $(CH_3)_2CHCO_2Et$ | PhSSPh | $(CH_3)_2C(CO_2Et)SPh$ | (11) | 80 |
| $CH_3CO_2Et$ | PhSSPh | $CH_2(CO_2Et)SPh$ | (12) | 70 |

bon (isobutyrates) or on alkyl oxygen (*tert*-butyl acetate) indicates steric impedance to Claisen condensation and/or oxygen alkylation as two important side-reactions.[5,6,10,18]

Our interest in organoselenium chemistry and the general synthetic utility of $\alpha$-thio and $\alpha$-seleno esters led us to investigate the reaction of ester enolates with diphenyl disulfide and phenyl selenenyl bromide. Recent publications[20-22] concerning similar reactions and the utility of the products in formation of $\alpha,\beta$-unsaturated ketones and esters prompt us to include our complementary results.

$$R_2CHCO_2Et \xrightarrow[2.\ PhSSPh]{1.\ LDA} R_2C(CO_2Et)SPh + PhS^- \xrightarrow{H_2O} PhSH$$

$R = CH_3$, H

$$RR'CHCO_2R'' \xrightarrow[2.\ PhSeBr]{1.\ LDA} RR'C(CO_2R'')SePh$$

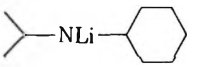
a, $R = R' = CH_3$; $R'' = Et$
b, $R = R' = H$; $R'' = Et$
c, $R = C_4H_9$; $R' = H$; $R'' = CH_3$

The two reactions gave the expected products in high yields. In the first case only half of the disulfide is converted, but the corresponding arylsulfenyl halides are more difficult to prepare.

Two attempted reactions to introduce a $\beta$-carbonyl and a $\gamma$-formyl functionality failed, giving only unidentified products.

$$R_2CHCO_2Et \xrightarrow[2.\ R'CN\ \ 3.\ H_2O/H^+]{1.\ base} R_2C(COR')CO_2Et$$

a, $R = CH_3$; $R' = CH_3$; base = LDA

b, $R = H$; $R' = Ph$; base = 

$$R_2CHCO_2Et \xrightarrow[2.\ XCH_2CH(OEt)_2\ \ 3.\ H_2O/H^+]{1.\ LDA} R_2C(CO_2Et)CH_2CHO$$

$R = CH_3$; X = Cl, Br

These results are in accord with the known lesser reactivities of nitriles and $\alpha$-haloacetals toward nucleophiles.

## Experimental Section

Infrared spectra were determined using a Perkin-Elmer Infracord or Perkin-Elmer Model 457-A spectrophotometer. Nmr spectra were obtained with a Varian T-60 or HA-100 spectrometer. Chemical shifts ($\delta$) are reported in parts per million downfield from tetramethylsilane (TMS) as internal standard, using conventional notation. Mass spectra were obtained on a Finnigan Model 1015 under the supervision of Dr. Herndon Williams, Universidade de Campinas, Campinas, Brasil. Microanalyses were performed in our department under the supervision of Dr. Riva Moscovici. Boiling points are quoted for the temperature of the oven during evaporative bulb-to-bulb (Kugelrohr) short-path distillation. The esters were prepared in the usual way, distilled, and stored over molecular sieves 4A. Dimethyl and diethyl chlorophosphate were prepared[23] from phosphorus oxychloride and methanol or ethanol, respectively, the products being stored over molecular sieves 4A. Benzeneselenenyl bromide was prepared[21] from diphenyl diselenide and bromine. Diphenyl disulfide was prepared from thiophenol and bromine ($CHCl_3$, 0°, 1 hr) in 75% yield, mp 58–59° (lit.[24] mp 60–61°).

The following general experimental procedure was employed for all the described reactions (see Table I).

To a 50-ml round-bottom flask equipped with septum inlet, magnetic stirring, dropping funnel, and $N_2$ inlet was added diisopropylamine (0.01 mol) in 10 ml of anhydrous THF and the solution was treated with the equivalent amount of $n$-butyllithium in hexane (0°, 15 min). The colorless solution was cooled with a Dry Ice–acetone bath and treated with the ester (0.01 mol) in 2 ml of THF and after 10 min with the electrophilic reagent (0.01 mol) in 2–5 ml of THF.

After 10–30 min of stirring at −78° the reaction solution was quenched with saturated $NH_4Cl$ solution, extracted with ether, dried with $MgSO_4$, filtered, and evaporated to give the crude product. Depending on purity, distillation or preparative thick plate chromatography and distillation were used to isolate the product in the specified yields.

Owing to water solubility problems the four carboalkoxy dialkylphosphonates were isolated with the minimum amount of water necessary to quench the reaction mixtures. Thiphenol, produced as a by-product in the formation of $\alpha$-thiophenyl esters, was extracted from the reaction mixture by washing with 10% $Na_2CO_3$.

Diethyl dimethylmalonate (1) from ethyl isobutyrate and ethyl chloroformate (90%): bp 90° (25 mm) [lit.[24] bp 97–98° (22 mm)]; nmr ($CCl_4$) $\delta$ 4.12 (q, 4, $J$ = 7 Hz), 1.35 (s, 6), 1.23 (t, 6, $J$ = 7 Hz).

Diethyl malonate (2) from ethyl acetate and ethyl chloroformate (88%): bp 80° (25 mm) (lit.[24] bp 199°); nmr identical with that of authentic sample.

Ethyl *tert*-butylmalonate (3) from *tert*-butyl acetate and ethyl chloroformate (70–75%): bp 105° (22 mm) [lit.[16] bp 98–100° (22 mm)]; nmr ($CCl_4$) $\delta$ 4.15 (q, 2, $J$ = 7 Hz), 3.13 (s, 2), 1.45 (s, 9), 1.28 (t, 3, $J$ = 7 Hz).

1-Carbethoxy-1-methylethyl diethyl phosphonate (4) from ethyl isobutyrate and diethyl chlorophosphate (80%): bp 55–57° (0.005 mm); nmr ($CDCl_3$) $\delta$ 4.22 (q, 2, $J$ = 7 Hz), 4.15 (q, 2, $J$ = 7 Hz), 3.92 (q, 2, $J$ = 7 Hz), 1.65 (s, 3), 1.62 (s, 3), 1.35 (t, 3, $J$ = 7 Hz), 1.33 (t, 3, $J$ = 7 Hz), 1.25 (t, 3, $J$ = 7 Hz); mass spectrum (20 eV) $m/e$ 252 (P).

*Anal.* Calcd for $C_{10}H_{21}O_5P$: C, 47.61; H, 8.41. Found: C, 46.23; H, 8.31. This compound, although chromatographically pure and spectroscopically consistent, gave inaccurate analyses.

1-Carbethoxy-1-methylethyl dimethyl phosphonate (5) from ethyl isobutyrate and dimethyl chlorophosphate (64%): bp 40–42° (0.005 mm); nmr ($CCl_4$) $\delta$ 3.90 (q, 2, $J$ = 7 Hz), 3.87 (s, 3), 3.70 (s, 3), 1.63 (s, 3), 1.58 (s, 3), 1.26 (q, 3, $J$ = 7 Hz); mass spectrum (20 eV) $m/e$ 224 (P).

*Anal.* Calcd for $C_8H_{17}O_5P$: C, 42.85; H, 7.60. Found: C, 42.73; H, 7.60.

1-Carbomethoxy-1-methylethyl dimethyl phosphonate (6) from methyl isobutyrate and dimethyl chlorophosphate (62%): bp 35–37° (0.005 mm); nmr ($CCl_4$) $\delta$ 3.86 (s, 3), 3.67 (s, 3), 3.60 (s, 3), 1.63 (s, 3), 1.58 (s, 3); mass spectrum (20 eV) $m/e$ 210 (P).

*Anal.* Calcd for $C_7H_{15}O_5P$: C, 40.00; H, 7.21. Found: C, 39.93; H, 7.25.

1-Carbo-*tert*-butoxymethyl diethyl phosphonate (7) from *tert*-butyl acetate and diethyl chlorophosphate (65%): bp 50–55° (0.05 mm) [lit.[25] bp 82–82.5° (0.05 mm)]; nmr ($CCl_4$) $\delta$ 4.20 (q, 2, $J$ = 7 Hz), 4.05 (q, 2, $J$ = 7 Hz), 2.73 (d, 2, $J$ = 22 Hz), 1.45 (s, 9), 1.34 (t, 3, $J$ = 7 Hz).

Ethyl α-selenophenylisobutyrate (8) from ethyl isobutyrate and benzeneselenenyl bromide (85%): bp 80–85° (0.025 mm); nmr ($CCl_4$) δ 7.1–7.6 (m, 5), 4.01 (q, 2, $J$ = 7 Hz), 1.52 (s, 6), 1.17 (t, 3, $J$ = 7 Hz).

*Anal.* Calcd for $C_{12}H_{16}O_2Se$: C, 53.13; H, 5.90. Found: C, 53.10; H, 5.99.

Methyl α-selenophenylhexanoate (9) from methyl hexanoate and benzeneselenenyl bromide (60%): bp 60–65° (0.05 mm); nmr ($CCl_4$) δ 7.1–7.7 (m, 5), 3.57 (s, 3), 1.0–2.0 (m, 7), 0.87 (t, 3, $J$ = 6 Hz).

*Anal.* Calcd for $C_{13}H_{18}O_2Se$: C, 54.74; H, 6.36. Found: C, 55.10; H, 6.41.

Ethyl α-selenophenylacetate (10) from ethyl acetate and benzeneselenenyl bromide (80%): bp 77–80° (0.025 mm); nmr ($CCl_4$) δ 7.3 (m, 5), 4.10 (q, 2, $J$ = 7 Hz), 3.50 (s, 2), 1.21 (t, 3, $J$ = 7 Hz).

*Anal.* Calcd for $C_{10}H_{12}O_2Se$: C, 49.43; H, 4.97. Found: C, 49.73; H, 5.05.

Ethyl α-thiophenylisobutyrate (11) from ethyl isobutyrate and diphenyl disulfide (80%): bp 80° (0.025 mm); nmr ($CCl_4$) δ 7.3 (m, 5), 4.06 (q, 2, $J$ = 7 Hz), 1.42 (s, 6), 1.20 (t, 3, $J$ = 7 Hz).

*Anal.* Calcd for $C_{12}H_{16}O_2S$: C, 64.28; H, 7.14. Found: C, 64.40; H, 7.21.

Ethyl α-thiophenylacetate (12) from ethyl acetate and diphenyl disulfide (70%): bp 80° (0.05 mm) [lit.[26] bp 118° (2.7 mm)]; nmr ($CCl_4$) δ 7.1–7.6 (m, 5), 4.07 (q, 2, $J$ = 7 Hz), 3.40 (s, 2), 1.18 (t, 3, $J$ = 7 Hz).

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**Registry No.**—**1**, 1619-62-1; **3**, 32864-38-3; **4**, 40226-07-1; **5**, 51364-90-0; **6**, 51364-91-1; **7**, 27784-76-5; **8**, 51364-92-2; **9**, 51364-93-3; **10**, 51364-94-4; **11**, 51364-95-5; **12**, 7605-25-6; ethyl isobutyrate, 97-62-1; ethyl chloroformate, 541-41-3; *tert*-butyl acetate, 540-88-5; diethyl chlorophosphate, 814-49-3; dimethyl chlorophosphate, 813-77-4; methyl isobutyrate, 547-63-7; benzeneselenenyl bromide, 34837-55-3; methyl hexanoate, 106-70-7; ethyl acetate, 141-78-6; diphenyl disulfide, 882-33-7.

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## Reaction of 1,3-Dimethyl-2-pyridone with *N*-Bromosuccinimide. A Reexamination

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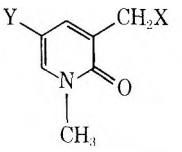
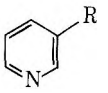
During our recent work on the total synthesis of camptothecin,[1] we had the opportunity to examine the reaction of 3-methyl-2-pyridone systems with *N*-bromosuccinimide (NBS). In a reported application of such a reaction,[2] 1,3-dimethyl-2-pyridone (**1**) was stated to react with NBS in the presence of dibenzoyl peroxide to yield 3-bromomethyl-1-methyl-2-pyridone (**2**). Since **1** had been chosen as a model compound, we sought to duplicate this experiment. On each of three attempts, following as closely as we could the experimental procedure described, the only product recovered was 5-bromo-1,3-dimethyl-2-pyridone (**3**). Comparison of this product with that previously reported proved difficult, since the characterization given[2] included only a melting point (98–99°) and an elemental analysis.





1, X = H; Y = H
2, X = Br; Y = H
3, X = H; Y = Br
4, X = OAc; Y = H
5, X = Cl; Y = H
6, X = OH; Y = H
7, X = OCH=CH$_2$; Y = H
10, X = $Ph_3P^+Br^-$; Y = H
11, X = OTs; Y = H
12, X = $Py^+Br^-$; Y = H
13, X = OMs; Y = H
8, R = CHO
9, R = $CH_2OH$

In characterizing the 5-bromo-1,3-dimethyl-2-pyridone (**3**) prepared in our study, the major additional datum was its nmr spectrum, which displayed singlets of three-proton intensity at δ 2.17 and 3.54 ppm. These correspond very closely with the methyl singlets at δ 2.14 and 3.52 in **1**. The position of the bromine atom in **3** is established by disappearance of a one-proton triplet at δ 6.06 when the spectrum is compared with that of **1**. The crude triplet at δ 7.2 corresponding to the remaining protons on the pyridone ring of **1** collapsed to a finely split doublet in the spectrum of **3**. To verify that our interpretation of the nmr spectrum of **3** was correct, a series of compounds was prepared, substituted on the 3-methyl group but not at the 5 position of the ring. These included 3-acetoxymethyl-, 3-chloromethyl-, 3-hydroxymethyl-, and 3-vinyloxymethyl-1-methyl-2-pyridone (**4**, **5**, **6**, and **7**, respectively). In each case, the corresponding nmr spectrum displayed a one-proton triplet near δ 6.0 for the proton on carbon 5 of the ring and a two-proton singlet in the δ 4.5–5.0 range for the methylene group bonded at carbon 3.

Finally, it was reported[2] that compound **2** gave a positive test with alcoholic silver nitrate. It is significant that our product also showed reactivity with alcoholic silver nitrate even after two recrystallizations from petroleum ether, the solvent reported as used for purifying **2**. However, an analytically pure sample of **3** prepared by recrystallization and sublimation followed by preparative gc failed to react with silver nitrate and had mp 106–107°

compared with 100–102° after purification by recrystallization and sublimation alone.

In an attempt to determine the actual melting point of 3-bromomethyl-1-methyl-2-pyridone (2), and thus establish whether or not it might have indeed been prepared as reported, considerable effort was expended toward its unambiguous synthesis. The starting material chosen for this study was 3-hydroxymethyl-1-methyl-2-pyridone (6), which is easily obtained from pyridine-3-carboxaldehyde (8) *via* a modification of the reported route.[3] Rather than using the reported reduction of ethyl nicotinate in preparing the intermediate 3-hydroxymethylpyridine (9), we found it advantageous to reduce 8 with sodium borohydride.[4] Conversion of 9 to 6 followed the previously reported steps.

A variety of methods for displacement of a primary hydroxyl group with bromine have been reported. The two methods initially examined were reaction of 6 with phosphorus tribromide in the presence of pyridine[5] and treatment of 6 with carbon tetrabromide and triphenylphosphine.[6] In the former case, a very low yield of a mixture of products was recovered. As 6 is known to have a distribution between water and organic solvents strongly favoring the aqueous phase, it seems probable that 2 either failed to form or was hydrolyzed back to 6 during the isolation. Reaction of 6 with carbon tetrabromide and triphenylphosphine in acetonitrile also gave a mixture of products which apparently included unreacted 6, a small amount of 2, and the phosphonium salt 10, from reaction of 2 with triphenylphosphine. Attempts to separate the desired product from the mixture resulted in the reconversion to 6.

As 3-chloromethyl-1-methyl-2-pyridone (5) was formed in the course of attempted mesylate preparation from 6 and methanesulfonyl chloride, synthesis of 2 by reaction of 6 with *p*-toluenesulfonyl bromide or methanesulfonyl bromide also seemed reasonable. *p*-Toluenesulfonyl bromide[7] reacted with 6 in the presence of pyridine,[8] but mild aqueous work-up again gave no product readily extractable into an organic solvent. If tosylate 11 or the bromide 2 were forming, it also rapidly converted into a water-soluble product such as 6 or 12 during the course of the reaction or subsequent isolation. Methanesulfonyl bromide was prepared from mesyl chloride,[9] and reaction with 6 in the presence of 1,8-(dimethylamino)naphthalene again failed to give any product which could be identified as 2 or as the mesylate 13.

While the results of these attempted syntheses have not provided the desired unambiguous source of 2, they do indicate that the bromine in 2 would be extremely labile and subject to displacement under very mild conditions. It is doubtful that this extraordinary reactivity would go unnoticed if pure 2 were prepared. Our own characterization of 3 verifies that carbon 5 is the active site of 1,3-dimethyl-2-pyridone (1) when it is treated with NBS in the presence of dibenzoyl peroxide. This observation is entirely consistent with reports that upon treatment of 2-pyridones[10] and 1-methyl-2-pyridones[2] with NBS both the 3 and 5 positions are substituted with bromine. Thus the reported formation of 5-bromomethyl-1-methyl-2-pyridone in the reaction of 1,5-dimethyl-2-pyridone with NBS in the presence of dibenzoyl peroxide[2] is in doubt.

## Experimental Section

Infrared absorption spectra were recorded on a Perkin-Elmer Infracord Model 137. The proton magnetic resonance spectra were recorded on a Varian T-60 nmr spectrometer, and chemical shifts are reported in $\delta$ units relative to internal tetramethylsilane. Mass spectra were obtained on a CEC-103 mass spectrometer. The glc analyses were performed on a Varian Aerograph gas–liquid chromatograph using helium as carrier gas. Elemental analyses were performed by the Analytical Laboratory, University of California, Berkeley, Calif.

**1,3-Dimethyl-2-pyridone (1).** This material was prepared from $\beta$-picoline:[11] gc on 5% QF-1 on Chromosorb W 80/100 AW-DMCS, 5 ft × 0.25 in., 123°, retention time 7.45 min; nmr ($CDCl_3$) $\delta$ 7.13 (d, $J$ = 6.5 Hz, 2 H), 6.06 (t, $J$ = 7 Hz, 1 H), 3.52 (s, 3 H), 2.14 (s, 3 H).

**5-Bromo-1,3-dimethyl-2-pyridone (3).** In a dry nitrogen filled flask was placed a solution of 0.83 g (6.7 mmol) of 1 in 12 ml of carbon tetrachloride which had been freshly distilled from $P_2O_5$. To the solution was added a mixture of 1.18 g (6.6 mmol) of NBS and 81 mg (0.34 mmol) of dibenzoyl peroxide. The mixture was then heated at 80° until reaction began, and the vigorous reaction was complete in about 5 min but reflux was continued for 0.5 hr. The hot mixture was filtered, the filtrate was evaporated, the residue was digested with petroleum ether–benzene and filtered hot, and the filtrate was evaporated. Recrystallization of the residue twice from petroleum ether (bp 40–60°) and sublimation gave material of mp 100–102°, raised to 106–107° after preparative gc: gc on 5% QF-1 on Chromosorb W 80/100, AW-DMCS 5 ft × 0.25 in., 175°, retention time 3.0 min; nmr ($CDCl_3$) $\delta$ 7.00–7.67 (m, 2 H), 3.54 (s, 3 H), 2.17 (s, 3 H); mass spectrum $m/e$ 203, 201 (P), 174, 172, 122, 94.

*Anal.* Calcd for $C_7H_8NOBr$: C, 41.6; H, 4.0; N, 6.9. Found: C, 41.7; H, 4.0; N, 6.9.

**3-Hydroxymethyl-1-methyl-2-pyridone (6).** This compound was prepared from 3-hydroxymethylpyridine.[3] Distillation of the crude product obtained by continuous extraction of the reaction mixture with methylene chloride provided a fraction boiling at 121–123° (0.2 Torr): mp 79–82° on recrystallization from benzene (lit.[3] mp 80°); gc on 5% QF-1 on Chromosorb W, AW-DMCS, 10 ft × 0.25 in., 184°, retention time 7 min. Gas chromatography of the distilled but not recrystallized product revealed the presence of a small impurity of the isomeric **5-hydroxy-methyl-1-methyl-2-pyridone:** retention time 11.5 min; nmr ($CDCl_3$) $\delta$ 7.13–7.24 (m, 2 H), 6.20 (t, $J$ = 6 Hz, 1 H), 4.06–4.76 (m, including s at 4.51, 3 H total), 3.54 (s, 3 H); nmr ($CDCl_3$–$D_2O$) $\delta$ 7.00–7.33 (m, 2 H), 6.06 (t, $J$ = 6 Hz, 1 H), 4.46 (s, 2 H), 3.50 (s, 3 H); ir ($CHCl_3$) 3435, 3001, 1645, 1579, 1399, 1181, 1101 $cm^{-1}$; uv (EtOH) 298, 230 nm; mass spectrum $m/e$ 139 ($M^+$).

**3-Hydroxymethylpyridine (9).** To a solution of 107 g (1.0 mol) of pyridine-3-carboxaldehyde (8) in 800 ml of absolute ethanol, cooled to 10° and flushed with nitrogen, was added 21 g (0.54 mol) of sodium borohydride at a rate to maintain the temperature below 25°. Most of the ethanol was evaporated at 40°, and the residue was poured into a solution of ice, salt, and ammonium chloride and stirred until hydrogen evolution ceased, 6 *N* HCl being added to maintain pH 5–6. The pH was adjusted to 7–8 with 4 *N* KOH and the 2 l. of aqueous solution was continuously extracted with methylene chloride for 24 hr. The dried extract was evaporated to give a quantitative yield of yellow oil pure by gc: bp 84–90° (0.1 Torr) [lit.[3] bp 110° (0.1 Torr)]; gc on 5% QF-1 on Chromosorb W, 10 ft × 0.25 in., 145°; nmr ($CCl_4$–$CDCl_3$) $\delta$ 8.33 and 8.22 (2 H), 7.62 (d, 1 H), 7.12 (d, 1 H), 6.06 (s, 1 H), 4.56 (s, 2 H).

**3-Acetoxymethyl-1-methyl-2-pyridone (4).** To a mixture of 2 ml of acetic anhydride and 4 ml of pyridine was added 140 mg (1.0 mmol) of 6, and the stoppered flask was allowed to stand for 24 hr. The excess reagents were removed *in vacuo*, leaving a solid residue which was sublimed to give 162 mg (92%) of 4: mp 79–82°; gc on 5% QF-1 on Chromosorb W, AW-DMCS, 10 ft × 0.25 in., 177°, retention time 9.5 min; nmr ($CDCl_3$) $\delta$ 7.42 (m, 2 H), 6.22 (t, $J$ = 7 Hz, 1 H), 5.05 (s, 2 H), 3.57 (s, 3 H), 2.12 (s, 3 H).

*Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.6; H, 6.1; N, 7.8.

**3-Chloromethyl-1-methyl-2-pyridone (5).** To a solution of 279 mg (2.0 mmol) of 6 in 10 ml of methylene chloride was added 304 mg (3.0 mmol) of triethylamine. To the cooled solution (0°) was added 300 mg (2.62 mmol) of mesyl chloride dissolved in 0.5 ml of methylene chloride, and after 10 min at 0°, the mixture was allowed to warm to room temperature. It was then again cooled and extracted successively with ice water, cold 2 *N* HCl, cold sodium bicarbonate solution, and saturated salt solution. The organic phase was dried over $MgSO_4$ and filtered and the solvent was removed to give 125 mg (40%) of 5: mp 79–80°; gc on 5% QF-1 on Chromosorb W 80/100, AW-DMCS, 5 ft × 0.25 in., 170°, retention time 3.6 min; nmr ($CDCl_3$) $\delta$ 7.45 (t, $J$ = 7 Hz, of d, $J$ = 2 Hz, 2 H), 6.18 (t, $J$ = 7 Hz, 1 H), 4.55 (s, 2 H), 3.57 (s, 3 H); mass spectrum $m/e$ 159, 157 (P), 122, 94, 93, 78, 67, 65, 51; high-resolution mass spectrum, $m/e$ 157.0292 (calcd for $C_7H_8ONCl$, 157.0294).

**3-Vinyloxymethyl-1-methyl-2-pyridone (7)** was prepared from 6 and ethyl vinyl ether using mercuric acetate as catalyst,[12] yield 34% as a yellow oil: gc on 5% QF-1 on Chromosorb W 80/100, 10 ft × 0.25 in., 168°, retention time 6.4 min; nmr ($CCl_4$) δ 7.00–7.43 (crude t, 2 H), 6.43 (d, $J_{cis}$ = 7 Hz, of d, $J_{trans}$ = 14 Hz, 1 H), 6.02 (t, $J$ = 7 Hz, 1 H), 4.59 (s, 2 H), 4.25 (d, $J_{gem}$ = 2 Hz, of d $J_{trans}$ = 14 Hz, 1 H), 4.00 (d, $J_{gem}$ = 2 Hz, of d, $J_{cis}$ = 7 Hz, 1 H), 3.47 (s, 3 H); ir (film) 1651, 1600, 1561, 1407, 1198, 766 $cm^{-1}$; mass spectrum $m/e$ 165 (P), 137, 122, 94.

*Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.1; H, 6.4; N, 8.4.

**Registry No.**—**1**, 6456-92-4; **3**, 51417-13-1; **4**, 51417-14-2; **5**, 51417-15-3; **6**, 36721-61-6; **7**, 51417-16-4; **8**, 500-22-1; **9**, 100-55-0; NBS, 128-08-5.

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## Steric and Electrostatic Interactions in Reactions of Carbohydrates. II.[1] Stereochemistry of Addition Reactions to the Carbonyl Group of Glycopyranosiduloses. Synthesis of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-β-D-mannopyranoside[2]


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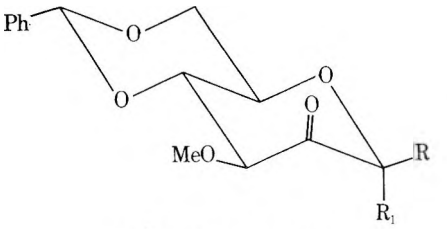
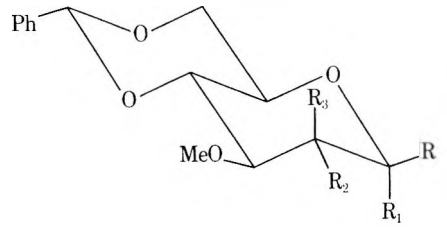
It has been reported that the reduction of benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-*lyxo*-hexopyranosid-2-ulose with lithium aluminum hydride gave benzyl 4,6-*O*-benzylidene-β-D-talopyranoside[3] (73%) whereas the reduction of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*arabino*-hexopyranosid-2-ulose with lithium aluminum hydride gave methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-glucopyranoside as the only product.[4] These observations, and our earlier observation on the dependence upon the anomeric configuration of the stereochemistry of the methyllithium and Grignard reagent additions to the C-4 carbonyl carbon atom of glycopyranosid-4-uloses,[1] prompted us to investigate the influence of the anomeric configuration on the stereochemical course of metal–hydride reduction of the C-2 carbonyl group of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α- and -β-*arabino*-hexopyranosid-2-ulose (**1** and **2**).[10] The following were the reasons for undertaking this investigation.

Presently, a view has been adopted that the transition-state geometry for reactions of metal hydrides (and organometalic reagents) with carbonyl groups resembles the geometry of the starting ketone, and that nonbonded steric interactions, torsional strain, and electrostatic interactions (dipole–dipole repulsions) are decisive factors in determining the direction from which a nucleophile will approach a carbonyl group.[5] In the case of D-glycopyranosid-2-uloses of the β series, *e.g.*, **2**, the axial approach of the metal hydride anion to the C-2 carbonyl carbon atom, resulting in the formation of the transition state **3**, requires that the negatively charged metal hydride ion approaches the C-2 carbonyl carbon atom from a direction bisecting the $C_1$–$O_1$ and $C_1$–$O_5$ torsional angle. Since the $C_1$–$O_1$ and $C_1$–$O_5$ bonds are polarized and act as two equally oriented dipoles, an approach which will apposition a negatively charged ion between them should be energetically unfavorable owing to electrostatic interactions. An "equatorial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of **2**, resulting in the formation of the transition state **4**, will be, however, not only free from the electrostatic interactions, but the torsional strain and nonbonding steric interactions will be at a minimum as well.

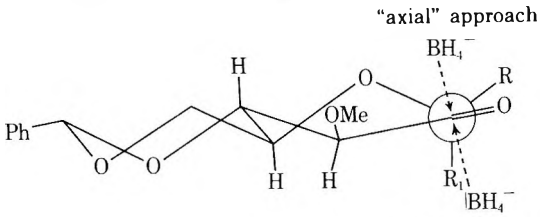



1, R = H; $R_1$ = $OCH_3$
2, R = $OCH_3$; $R_1$ = H




7, R = $R_3$ = H; $R_1$ = $OCH_3$; $R_2$ = OH
8, R = $OCH_3$; $R_1$ = $R_2$ = H; $R_3$ = OH
9, R = $OCH_3$; $R_1$ = $R_3$ = H; $R_2$ = OH

"axial" approach




"equatorial" approach

3, R = $OCH_3$; $R_1$ = H ("axial" approach)
4, R = $OCH_3$; $R_1$ = H ("equatorial" approach)
5, R = H; $R_1$ = $OCH_3$ ("axial" approach)
6, R = H; $R_1$ = $OCH_3$ ("equatorial" approach)

In the transition state **5**, which results from an "axial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of D-glycopyranosid-2-uloses of the α series, *e.g.*, **1**, the electrostatic interactions of the type described for the transition state **3** are not present. Furthermore, there will be no torsional strain. The only interaction present in **5** is one 1,3-nonbonding steric interaction between the axially oriented C-4 hydrogen atom and the incoming metal hydride anion. An "equatorial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of **1** resulting in the formation of the transition state **6** should give rise to generation of considerable torsional strain and dipolar interaction between the axially oriented C-1 methoxy group and the approaching metal hydride anion. Furthermore, in the transition state **6**, there will be two nonbonding steric interac-

tions between the approaching metal hydride anion and the axially oriented hydrogens at C-3 and C-5.

As a consequence, the metal hydride reduction of **1** should give methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**7**) as the preponderant, if not the only, product, whereas the metal hydride reduction of **2** should yield methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**8**) as the preponderant product.

The results of our studies are reported in this paper.

Methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranosid-2-ulose (**2**) was prepared by DMSO–$Ac_2O$ oxidation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**9**)[6] at room temperature. The reduction of **2** was effected with sodium borohydride in methanol. The reason for using sodium borohydride for reduction of **2** rather than lithium aluminum hydride was based on the observation that sodium borohydride produces more axial alcohol than lithium aluminum hydride in reductions of alicyclic ketones, indicating a greater effective size of the borohydride species.[7] The crude reduction product, as expected, consisted almost exclusively of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**8**) [the ratio of D-manno (**8**) to D-gluco derivative (**9**) was 19:1].

The sodium borohydride reduction of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**) in methanol, which was obtained by DMSO–$Ac_2O$ oxidation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**7**),[6] afforded the D-gluco derivative **7** as the only product.

It is interesting to note that Ekborg, *et al.*,[8] have recently reported the synthesis of methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside by catalytic hydrogenation of methyl 3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosid-2-ulose. The high stereoselectivity (D-manno to D-gluco ratio was 19:1) in catalytic hydrogenation of the C-2 carbonyl group of β-D-*arabino*-hexopyranosid-2-uloses observed first by Theander[9] and confirmed by Ekborg, *et al.*,[8] is probably due to steric interactions exclusively.

The observed high stereoselectivity in the sodium borohydride reduction of **2** not only provides a very convenient synthetic route for the preparation of a wide variety of alkyl and/or aryl β-D-mannopyranosides, but also makes the C-2 tritium- and deuterium-labeled β-D-mannopyranoside derivatives readily available.

## Experimental Section

**General.** The silica gel used for all column chromatography was E. Merck (Darmstadt, Germany) silica gel, grain size <0.08 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267; the nmr spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in parts per million.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranosid-2-ulose (2).** A solution of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**9**, 520 mg) in 2:1 methyl sulfoxide–acetic anhydride mixture (12 ml) was kept at room temperature for 17 hr. The solvents were removed *in vacuo* (bath temperature was 60°), and the crystalline residue was chromatographed on silica gel (50 g). Elution with 50:75:1 acetone–hexane–water afforded pure **2** (413 mg, 80%), which after recrystallization from acetone–isopropyl ether (needles) showed mp 167–169° dec; $[\alpha]^{27}D$ −73° (*c* 1.17, $CHCl_3$); ir ($CHCl_3$) 1753 $cm^{-1}$ (C=O stretch); nmr ($CDCl_3$) δ 7.7–7.2 (m, 5, phenyl), 5.58 (s, 1, methine H from benzylidene group), 4.82 (s, 1, H-1), 4.6–3.7 (m, 5, H-3, H-4, H-5, H-6, H-6′), 3.63 (s, 3, methyl from C-1 methoxy group), 3.60 (s, 3, methyl from C-3 methoxy group).

*Anal.* Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 60.94; H, 6.05.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-β-D-mannopyranoside (8).** To a solution of **2** (116 mg) in methanol (15 ml) a methanolic solution (10 ml) of sodium borohydride (50 mg) was added dropwise. After the reduction was finished (10 min; monitored by tlc using 95:5 benzene–2-propanol as eluent), the excess of sodium borohydride was destroyed with acetic acid, and the resulting solution was evaporated *in vacuo* to dryness. The solid residue was extracted with boiling ethyl acetate (3 × 30 ml) and combined extracts were evaporated *in vacuo*. The crude product (127 mg) was chromatographed on silica gel (20 g). Elution with 3:2 hexane–acetone gave three fractions. The first fraction (3.5 mg) was pure methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**9**) identical with an authentic sample (mixture melting point and ir spectra). The second fraction (18 mg) was a mixture of **8** and **9** (monitored by tlc using 95:5 benzene–2-propanol as eluent), whereas the third fraction (82 mg) was pure methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**8**). Rechromatography of the second fraction (18 mg) on silica gel (5 g) afforded 1.5 mg of **9** and 14.5 mg of **8**. Therefore, the total isolated amounts of **8** and **9** by sodium borohydride reduction of **2** were 96.5 mg of **8** (82%) and 5 mg of **9** (4%). The overall yield of reduction was 86%. Recrystallization of the methyl β-D-manno derivative **8** from acetone–isopropyl ether gave very fine needles: mp 187–188°; $[\alpha]^{27}D$ −70° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3575 $cm^{-1}$ (OH); nmr ($CDCl_3$) δ 7.9–7.2 (m, 5, phenyl), 5.58 (s, 1, methine H from benzylidene group), 4.45 (d, $J_{1,2} \leq 1$ Hz, 1, H-1), 3.53 (s, 6, C-1 and C-3 methoxy groups), 2.53 (broad s, 1, OH).

*Anal.* Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.59; H, 6.79.

**Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1).** Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**7**, 537 mg) was dissolved in 2:1 methyl sulfoxide–acetic anhydride mixture (12 ml) and the solution was kept at room temperature for 6 hr. The solvents were evaporated *in vacuo* (bath temperature was 60°) and the crystalline residue was chromatographed on silica gel (50 g). Elution with 120:80:1 hexane–acetone–water gave pure **1** (484 mg, 90%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether (needles): mp 133.5–134.5°; $[\alpha]^{27}D$ +42° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 1750 $cm^{-1}$ (C=O stretch); nmr ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 4.73 (s, 1, H-1), 4.5–3.7 (m, 5, H-3, H-4, H-5, H-6, H-6′), 3.59 (s, 3, methyl from C-3 methoxy group), 3.47 (s, 3, methyl from C-1 methoxy group).

*Anal.* Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.05; H, 6.14.

**Reduction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Sodium Borohydride in Methanol.** To a vigorously stirred methanolic solution (15 ml) of **1** (96 mg), a methanolic solution (8 ml) of sodium borjhydride (40 mg) was added drpwise. After the reaction was finished (5 min, monitored by tlc using 95:5 benzene–2-propanol as eluent), acetic acid was added to destroy the excess of sodium borohydride, and the resulting solution was evaporated *in vacuo* to dryness. The solid residue was extracted with three 30-ml portions of boiling ethyl acetate, and combined extracts were evaporated *in vacuo*. The crude reaction product (108 mg) was chromatographed twice on silica gel. Elution with 95:5 benzene–2-propanol gave pure **7** (80 mg, 82%), which after recrystallization from acetone–isopropyl ether (needles) showed mp 147–148° and was identical with an authentic sample[6] (mixture melting point and ir spectra). Even traces of methyl α-D-manno derivative were not present in the crude reaction mixture (examined by tlc using 95:5 benzene–2-propanol as eluent).

**Registry No.**—**1**, 29774-59-2; **2**, 29774-60-5; **7**, 20770-95-0; **8**, 51364-57-9; **9**, 35775-68-9.

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## Reactions of Naphthalene and Anthracene Derivatives with Trifluoromethyl Hypofluorite

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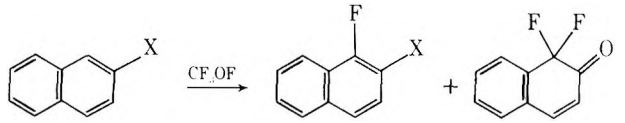
The recent discoveries that trifluoromethyl hypofluorite ($CF_3OF$) is useful in the fluorination of aromatic compounds[2,3] coupled with our interests in preparing fluoroaromatic compounds[4] led us to investigate the reaction of $CF_3OF$ with some naphthalene and anthracene derivatives. Barton and coworkers'[2] report on the preparation of 1-fluoro-2-acetylaminonaphthalene (**2a**) from reaction of $CF_3OF$ with 2-acetylaminonaphthalene (**1a**) led us to reinvestigate this reaction as a starting point for our own work.

Reaction of **1a** with $CF_3OF$ was carried out in chloroform solution at room temperature. The reaction was performed until all **1a** was consumed as discerned from glpc and tlc analyses of the reaction progress. When all **1a** had been consumed two major products were present, 1-fluoro-2-acetylaminonaphthalene (**2a**) and 1,1-difluoro-2-naphthone (**3**), in 25 and 43% yields, respectively. The structure of **2a** was confirmed by conversion to 1-fluoro-2-aminonaphthalene (**2b**). Compound **3** was identified by its spectral and elemental analyses and by spectral analysis of its hydrogenation product.




**1a**. X = $NHCOCH_3$
**b**. X = $NH_2$
**c**. X = OH

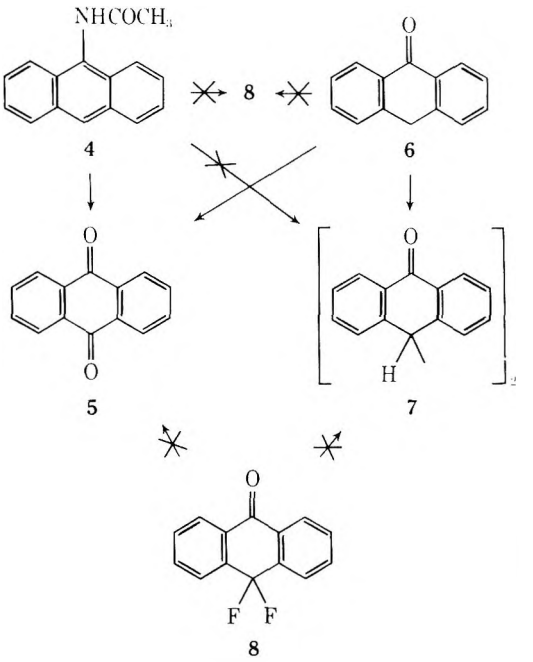
**2a-c** **3**

Reaction of 2-naphthylamine (**1b**) with $CF_3OF$ produced a mixture from which 1-fluoro-2-naphthylamine (**2b**) was obtained in 9% yield and **3** was obtained in 19% yield. Facile decomposition of **2b** on exposure to air may account partially for its low yield. 2-Naphthol (**1c**) reacted with $CF_3OF$ to yield 1-fluoro-2-naphthol (**2c**) in 14% yield and **3** in 20% yield. Analytical data established the composition of **2c**, but analogy with reaction products from **1a** and **1b** was used to determine the orientation of the fluorine atom. The hydroxyl proton showed long-range coupling to the fluorine atom, giving further evidence that the fluoro and hydroxyl groups are adjacent.[5] Attempts to prepare **2c** unambiguously from 1-amino-2-naphthol failed.

A gray solid (mp 295–298°) was formed in the reactions of **1a**, **1b**, and **1c** with $CF_3OF$. This material was insoluble in most organic solvents except dimethyl sulfoxide. The composition of the solid was not determined owing to slow continuous decomposition and our inability to obtain a pure sample. The infrared spectrum showed absorbances characteristic of an amine salt[6] at 2200 and 1800 $cm^{-1}$ if the spectrum was obtained on freshly prepared material. On standing, these absorbances disappeared.

Treatment of pure samples of **2a**, **2b**, **2c**, and **3** with $CF_3OF$ produced a complex mixture of at least seven components (tlc and glpc). We could therefore not show that **3** was formed by further fluorination of **2a**, **2b**, and **2c**. Yields of products are based on a parallel reaction scheme: **1** → **2**; **1** → **3**.

Reaction between 9-acetylaminoanthracene (**4**) and $CF_3OF$ yielded anthraquinone (**5**) in 95% yield. No other compound was detected by tlc or glpc. Attempts to determine a mechanism for this reaction were made by treating feasible intermediates with $CF_3OF$. Anthrone (**6**) produced both **5** (55%) and 10,10-bianthronyl (**7**, 30%) on reaction with $CF_3OF$. 10,10-Difluoroanthrone (**8**) and **7** are reported products from the reaction of **6** with sulfur tetrafluoride in the presence of radical scavengers.[7] We were unable to detect either **5** or **7** on reaction of **8** with $CF_3OF$. Our detection methods (tlc and glpc) could have detected at least 0.1% of the components as determined from standard solutions of **5** and **7**. Careful reexamination of the products from **4** failed to show any **7**. These results are presently taken as evidence against the intermediacy of either **6** or **8**. Investigations which should provide useful information regarding the mechanism and synthetic potential of these and similar reactions are in progress.




### Experimental Section

All temperature reading are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were determined on a Varian T-60 spectrometer using tetramethylsilane (δ 0.0) as an internal standard. Molecular weights were determined from mass spectra obtained on a Varian MAT-111 spectrometer. Infrared spectra were determined on a Perkin-Elmer Model 337 grating spectrophotometer using polystyrene for calibration. Trifluoromethyl hypofluorite was obtained from PCR, Inc., Gainesville, Fla. Aldrich spectroquality chloroform was used as the solvent in all reactions with $CF_3OF$. Glpc analyses were performed on a Varian 1440 flame ionization gas chromatograph using a 5 ft × 0.13 in. stainless steel column of 3% SE-30 on Chromosorb W and helium flow rate of 60 ml/min.

**Reactions with Trifluoromethyl Hypofluorite ($CF_3OF$). 2-Acetylaminonaphthalene (1a).** A solution of 1.5 g (7.2 mmol) of **1a** in 25–30 ml of chloroform was treated with $CF_3OF$ at room temperature. The reaction mixture became dark. The course of the reaction was followed by glpc and tlc (silica gel). Two major products were formed and all **1a** was consumed within 40–60min. Nitrogen was bubbled through the reaction mixture to assist in the removal of residual $CF_3OF$. The mixture was filtered to give 0.7 g of gray material, mp 295–298° dec. *Anal.* Found: C, 75.2; H, 4.7; N, 7.9; F, 3.6. This material was not identified because its properties (ir, nmr, melting point) continuously changed.

The filtrate was concentrated on a rotary evaporator, giving 1.8 g of brown oil. Trituration with petroleum ether (bp 40–60°) gave

a yellow solution and a dark residue. Recrystallization of the residue from benzene–cyclohexane furnished 0.4 g (25%) of 1-fluoro-2-acetylaminonaphthalene (**2a**), mp 117–120° (lit.[2] mp 120–121°). Hydrolysis of 0.25 g (1.1 mmol) of **2a** with 30 ml of 6 *N* hydrochloric acid followed by neutralization with sodium hydroxide solution furnished 0.17 g (96%) of 1-fluoro-2-naphthylamine (**2b**), mp 34–35°.[8] *Anal.* Calcd for $C_{10}H_8FN$: C, 74.5; H, 4.97; F, 11.8; N, 8.70; mol wt, 161. Found: C, 74.2; H, 5.04; F, 11.6; N, 8.66; mol wt, 161.

Reaction of **2b** (50 mg, 0.3 mmol) with isoamyl nitrite (0.5 mmol) in tetrahydrofuran[9] (1 ml) furnished 1-fluoronaphthalene (23%) which was identical with authentic material.

The cooled petroleum ether solution furnished 0.55 g (43%) of 1,1-difluoro-2-naphthone (**3**) as pale yellow needles, mp 49–50.5°. Sublimation at 40° (0.5 mm) furnished pure **3** with little loss of material: mp 50.5–52°; ir (melt between salt plates) 1700 $cm^{-1}$ (C=O); nmr ($CCl_4$) $\delta$ 6.12 (two sets of triplets, 1 H, C=CHC=O, $J_{H-H}$ = 10, $J_{H-F}$ = 2.8 Hz), 7.31–7.99 (m, 5 H, aromatic and CH=CC=O). Irradiation at $\delta$ 6.12 resulted in the collapse of a doublet centered at $\delta$ 7.36 among the aromatic protons. *Anal.* Calcd for $C_{10}H_6F_2O$: C, 66.7; H, 3.3; F, 21.1; N, 0.00; mol wt, 180. Found: C, 66.4; H, 3.4; F, 21.9; N, 0.05; mol wt, 180.

Reduction of 0.15 g of **3** in 30 ml of absolute alcohol using 0.1 g of 5% palladium on carbon at 15 psi for 2 hr furnished, after work-up, material which showed hydroxyl but no carbonyl absorption in its ir spectrum and no olefinic protons in its nmr spectrum. An analytically pure sample was not obtained.

**2-Naphthylamine (1b).** $CF_3OF$ was bubbled into a solution of 3.0 g (0.02 mol) of **1b** in 60 ml of chloroform. 2-Naphthylamine was consumed completely within 15–60 min. Glpc showed the presence of **3**, **2b**, and a third unidentified component in a 3:1:5 ratio, respectively. Filtration of the mixture furnished 1.2 g of gray residue. The filtrate was concentrated on a rotary evaporator at room temperature. The ir spectrum of the mixture showed strong absorptions at 2200 and 1800 $cm^{-1}$ characteristic of an amine salt.[6] Chromatography of the crude mixture on a 15 × 1 in. Florisil column (1:1 benzene–hexane) furnished 0.7 g (19%) of **3**. Benzene eluent furnished 1-fluoro-2-naphthylamine (**2b**, 9%). A pink solid (0.4 g) identical with the material filtered from the reaction mixture from **1a** was obtained on further elution with ether. The solid did not contain the 2200 and 1800 $cm^{-1}$ ir absorbances.

**2-Naphthol (1c).** $CF_3OF$ was slowly bubbled into a solution of 2.9 g (13.0 mmol) of **1c** in 30 ml of chloroform until glpc analysis no longer showed the presence of **1c**. Two major products were indicated by both glpc and tlc. Nitrogen was bubbled into the reaction mixture to facilitate the removal of residual $CF_3OF$. The reaction mixture was filtered (0.2 g residue) and concentrated on a rotary evaporator to give a dark, viscous oil. The crude material was chromatographed on a 8 × 0.5 in. column of neutral alumina [1:1 benzene–petroleum ether (60°)], furnishing 0.5 g (20%) of pure **3**. Chloroform–benzene (7:3) eluted 0.32 g of **2c**. Recrystallization from petroleum ether produced 0.3 g (14%) of **2c**: mp 74–75°; ir (KBr) 3250 $cm^{-1}$ (OH); nmr ($CDCl_3$) $\delta$ 5.2 (broad, 1 H, OH) and 7.1–8.2 (m, 6 H, aromatic). On careful drying, the $\delta$ 5.2 absorption appeared as a doublet, $J$ = 4 Hz. Since no change was observed in the aromatic portion of the spectrum, the coupling occurred between the hydroxyl proton and the fluorine atom. Intramolecular hydrogen bonding was negligable as deduced from the large hydroxyl proton chemical shift dependence on the concentration of the solution.

*Anal.* Calcd for $C_{10}H_7FO$: C, 74.1; H, 4.4; F, 11.7; mol wt, 162. Found: C, 74.3; H, 4.4; F, 12.0; mol wt, 162.

Attempted preparation of **2c** from 1-amino-2-naphthol hydrochloride by a Balz–Schiemann reaction failed in two attempts.

**9-Acetylaminoanthracene (4).** $CF_3OF$ was bubbled into a solution of 0.78 g (3.3 mmol) of **4** in 30 ml of chloroform. The reaction was monitored by tlc on silica gel (chloroform). Three products were detected but one major component accounted for more than 90% of the products. All **4** was consumed in 2 hr. Nitrogen was passed through the reaction mixture to remove residual $CF_3OF$. The solvent was removed on a rotary evaporator and the tan residue was chromatographed on a 10 × 0.5 in. column of alumina (benzene), furnishing a light yellow solid which after recrystallization from benzene yielded 0.65 g (95%) of **5**, mp 282–284°. The identity was proven by comparison with authentic anthraquinone.

**Anthrone (6).** A solution of 1.5 g (7.0 mmol) of **6** in 50 ml of chloroform was treated with $CF_3OF$ for 3 hr. Tlc on silica gel (chloroform) showed the presence of two components. Removal of the chloroform on a rotary evaporator gave 1.6 g of yellow solid. Chromatography on a 10 × 1 in. column of silica gel (benzene) furnished 0.9 g (55%) of yellow **6**. Benzene–chloroform (1:1) elution furnished an orange solid after removal of the solvents. Recrystallization from benzene–petroleum ether gave 0.55 g (35%) of 10,10-bianthronyl (**7**): mp 262–268° dec (lit.[10] mp *ca.* 270–275° dec); ir identical with a published spectrum; nmr ($CDCl_3$) $\delta$ 4.75 (s, 1 H, benzylic proton) and 6.7–8.0 (complex, 8 H, aromatic); mol wt, 386 (calcd mol wt, 386).

**Acknowledgment.** This research was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the office of Research and Projects, Southern Illinois University.

**Registry No.**—**1a**, 581-97-5; **1b**, 91-59-8; **1c**, 135-19-3; **2a**, 19580-15-5; **2b**, 14554-00-8; **2c**, 51417-63-1; **3**, 51417-64-2; **4**, 37170-96-0; **6**, 90-44-8; **7**, 4393-30-0; $CF_3OF$, 373-91-1.

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# Nitroxides. LVIII. Structure of Steroidal Spin Labels

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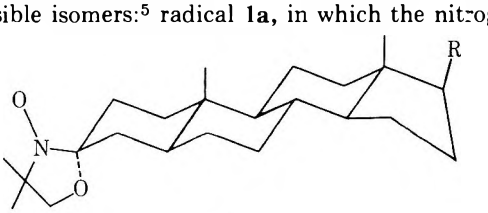
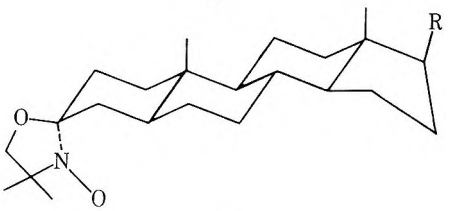
Spiro oxazolidine steroidal nitroxides[1] are widely used as spin labels in biological membranes.[2-4] In spite of its interest for orientation studies, the configuration of the spiro ring system has never been established. There are two possible isomers:[5] radical **1a**, in which the nitrogen is



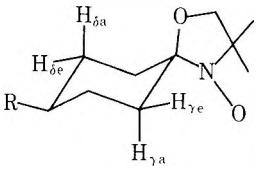

**1a**




**1b**

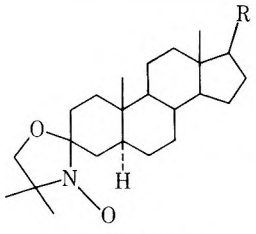
equatorial (e) relative to the steroid A ring, and radical **1b**, in which nitrogen is axial (a). Structure **1a** is generally postulated without experimental evidence.[6,7]

We have recently studied oxazolidinyloxy radicals prepared from substituted cyclohexanones.[8] We have shown by electron spin resonance (esr) and by nuclear magnetic resonance (nmr), through comparison with *tert*-butyl cyclohexyl nitroxide,[9] that only one isomer **2** is obtained, in which the cyclohexane is in the chair form, and nitrogen is equatorial. The following hyperfine coupling constants (hcc) have been measured: $a_{H\gamma a} = -0.7$ G; $a_{H\gamma e} = -0.65$ G; $a_{H\delta a} = +0.17$ G; $a_{H\delta e} = +1.06$ G.

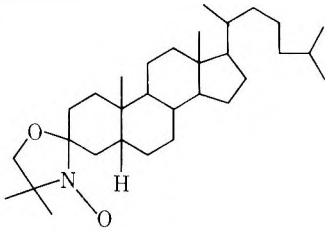


**2a**, R = H
**b**, R = *t*-Bu

We have studied radicals **3**[2] (mp 175°), **4**[1] (mp 176°), and **5** (mp 94–98°) prepared from 5$\alpha$-androstan-17$\beta$-ol-3-one, 5$\alpha$-cholestan-3-one, and 5$\beta$-coprostan-3-one. In each case, a single radical was obtained.



**3**, R = OH
**4**, R = $C_8H_{17}$

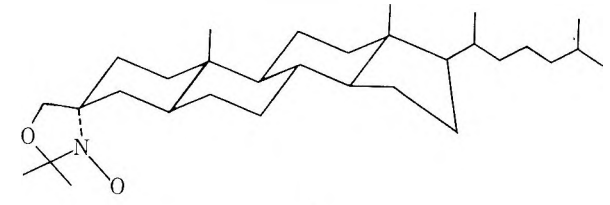


**5**

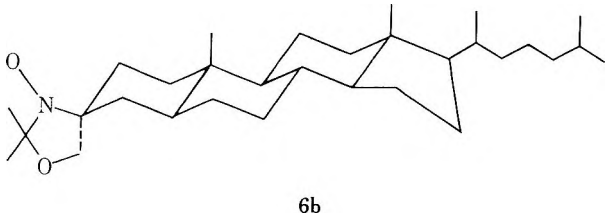
The esr spectrum of the three radicals is the normal nitroxide triplet, the hyperfine structure (Figure 1a) being identical for the three radicals. Although the 5$\alpha$ and 5$\beta$ isomers may look different, radicals **3**, **4**, and **5** have the same protons in the A ring (two axial $\gamma$, two equatorial $\gamma$, two axial $\delta$, and one equatorial $\delta$ proton). Since the electron-proton hcc are very stereospecific,[10,11] all three radicals probably have the same geometry.

If we assume the same configuration for radicals **3**, **4**, and **5**, and for radical **2b**, the esr spectrum of the former radicals should be reconstituted by using the $\gamma$ and $\delta$ hcc determined for radical **2b**: the computer-simulated spectrum (Figure 1d) is identical with the experimental spectrum.

This is the first evidence that the steroidal radicals studied have the same configuration as radical **2**, *i.e.*, configuration **1a** (equatorial nitrogen).



**6a**

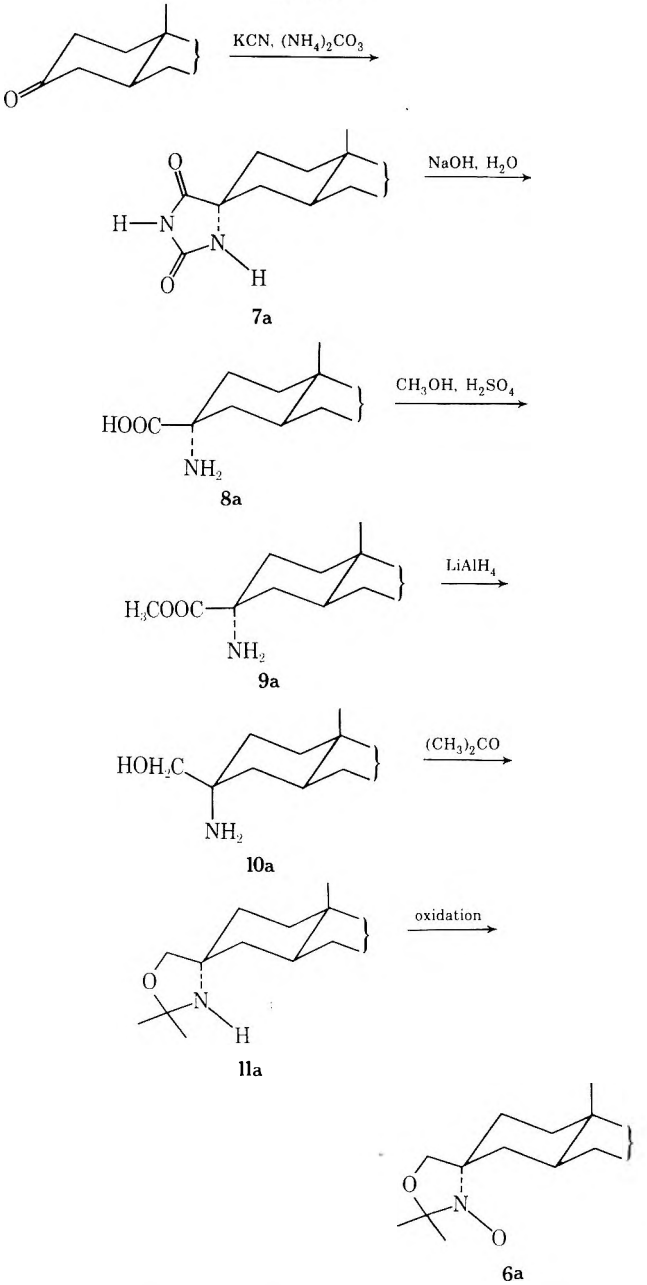


**6b**

In order to obtain some information on the other possible isomer, **1b** (axial nitrogen), we have prepared radicals **6a** and **6b** in which the only difference is a methylene-oxygen permutation, for which we expect a small influence on the proton hcc.

Chart I gives the different steps for the preparation of radical **6a**.

**Chart I**




It is known[12,13] that the hydantoin obtained from cholestanone is a mixture of isomers; the major product leads to the amino acid **8a** (mp 264°) in which the $NH_2$ group is axial (conclusion based on p$K$ values and hydrolysis rate constants for both epimeric amino acids[13]).

When the reaction sequence described in Chart I was carried out on the pure amino acid **8a** (mp 264°), radical **6a** (mp 188°) was obtained. Since this reaction sequence does not change the configuration at the steroid 3 position, this radical **6a** has an axial nitroxide group.

In order to obtain the other isomer, the same reaction sequence was carried out on the mixture of both epimeric hydantoins **7a** and **7b**. Two different radicals were obtained (in 86.5:13.5 ratio) and separated by thin layer chromatography. The first eluted radical was identical

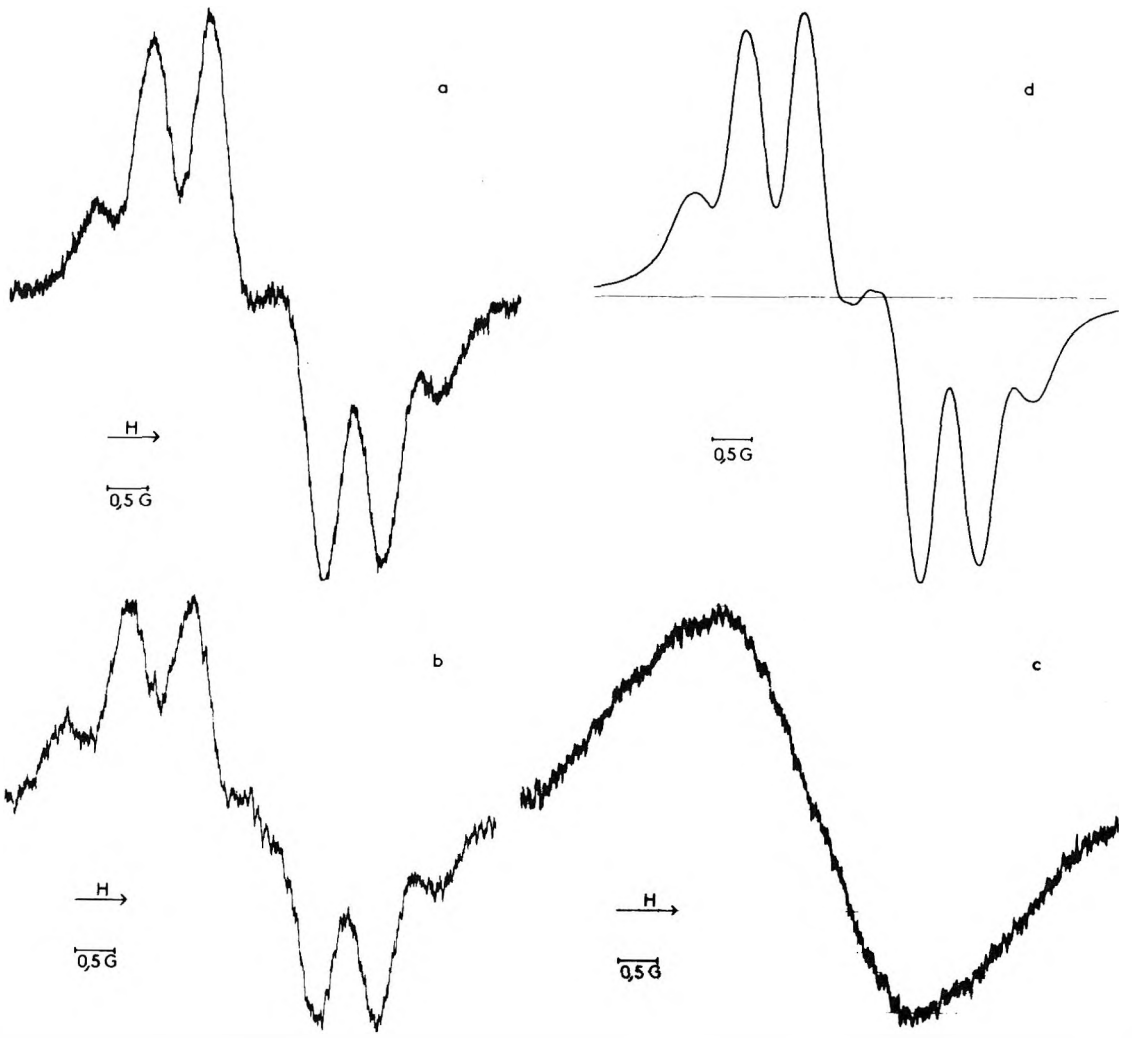



**Figure 1.** Low-field nitrogen line of the esr spectra, in degassed $CHCl_3$ at room temperature, of (a) radical **3**, (b) radical **6b**, (c) radical **6a**, (d) radical **3** (computer-simulated, $a_{H\gamma a} = a_{H\gamma e} = 0.7$ G; $a_{H\delta e} = 1.07$ G; $a_{H\delta e} = 0.2$ G; linewidth $\Delta H = 0.34$ G).

with **6a** (mp 188°) and the last eluted radical **6b** had mp 150–155°.

By comparing the yields of each step and the proportion of hydantoins **7a** and **7b**[13] and of radicals **6a** and **6b**, it can be safely concluded that the minor isomer comes from **7b**: the least abundant radical has an equatorial nitroxide group.

This minor isomer **6b** (mp 150–155°) displays a three-line esr spectrum, each line having a well-resolved hyperfine structure (Figure 1b) very similar to those of radicals **3**, **4**, and **5**. This confirms our hypothesis that methylene–oxygen permutation does not change hyperfine splittings. The major radical **6a** (mp 188°) displays the nitroxide three-line spectrum without resolution of the proton hyperfine structure (Figure 1c), the peak-to-peak linewidth being comparable to the one of radical **6b**. These results show that radical **1b**, if it exists, may have a three-line spectrum in which each line has no resolved proton hyperfine structure.

In conclusion, the synthesis of oxazolidine nitroxide from steroidal 3-ketones yields, in our hands, a single radical having an equatorial nitrogen relative to the steroid A ring.[14]

## Experimental Section

**4′,4′-Dimethylspiro(5α-cholestane-3,2′-oxazolidine).** According to Keana,[1] 5α-cholestan-3-one (0.5 g) and an excess of 2-amino-2-methylpropan-1-ol (1.1 g) in xylene solution (40 ml) with a trace of *p*-toluenesulfonic acid were boiled for 5 days. Water was removed by azeotropic distillation. After extraction, 0.58 g of crystals was obtained (crude yield 98%): mp 123–124° (lit.[1] mp 124–125°); ir (Nujol) $\nu_{NH}$ 3300 $cm^{-1}$; nmr ($CDCl_3$) $CH_3$(4′,4′) 1.22, $CH_2$(5′) 3.56 ppm; nmr ($C_6D_6$) $CH_3$(4′,4′) 1.08, $CH_2$(5′) 3.45 ppm. No trace of another isomer was detected by nmr.

Reflux, for 5 days, without azeotropic distillation, of the same products gave the same result.

**4′,4′-Dimethylspiro(5α-cholestane-3,2′-oxazolidine)-3′oxyl (4).** The crude amine (0.57 g) in ether solution was oxidized by *m*-chloroperbenzoic acid (0.32 g)[15] in ether solution. The radical concentration was followed by esr (oxidation time 6 hr). When the esr signal was maximum, the solution was washed with 5% sodium bicarbonate solution and dried over sodium sulfate. By thin layer chromatography (silica gel, 90% pentane–10% ether), 0.43 g of yellow crystals was obtained (yield 72%): mp 176° (methanol–ether) (lit.[1] mp 175–176°); uv (cyclohexane) λ 450 mμ (ε ~12); esr ($CHCl_3$, $M/1000)a_N = 14.9$ G.

Changes in oxidation time (0.25–48 hr) did not lead to detection of another radical by thin layer chromatography.

**4′,4′-Dimethylspiro(5β-cholestane-3,2′-oxazolidine)** was prepared in the same manner as the oxazolidine above. Azeotropic distillation with 0.28 g of ketone and 0.6 g of 2-amino-2-methylpropan-1-ol in xylene solution (40 ml), after 5 days, followed by extraction, gave 0.32 g of viscous product (crude yield 97%): ir (Nujol) $\nu_{NH}$ ~3200 $cm^{-1}$; nmr ($CDCl_3$) $CH_3$(4′,4′) 1.2, $CH_2$(5′) 3.5 ppm.

**4′,4′-Dimethylspiro(5β-cholestane-3,2-oxazolidine)-3′-oxyl (5)** was prepared in the same manner as the radical above (4) using 0.32 g of crude amine and 0.6 g of *m*-chloroperbenzoic acid. After 4 hr oxidation time and thin layer chromatography, 0.24 g of product was obtained (yield 72%): mp 94–98° (methanol–ether); uv (cyclohexane) λ 450 mμ (ε ~9); esr ($CHCl_3$, $M/1000$) $a_N = 14.9$ G.

*Anal.* Calcd for $C_{31}H_{54}NO_2$: C, 78.75; H, 11.51; O, 6.77; N, 2.96. Found: C, 78.76; H, 11.58; O, 6.52; N, 2.85.

**17β-Hydroxy-4′,4′-dimethylspiro(5α-androstane-3,2′-oxazolidine)** was prepared as described above using 0.6 g of ketone and

1.8 g of 2-amino-2-methylpropan-1-ol in xylene solution (50 ml). After 7 days, the mixture was extracted to give 0.73 g of product: mp 79°; ir (Nujol) $\nu_{OH}$ 3500, $\nu_{NH}$ 3200 $cm^{-1}$; nmr ($CDCl_3$) $CH_3(4',4')$ 1.23, $CH_2(5')$ 3.55 ppm.

**17β-Hydroxy-4',4'-dimethylspiro(5α-androstane-3,2'-oxazolidine)-3'-oxyl (3)** was prepared as described above, using 0.73 g of crude amine and 0.53 g of *m*-chloroperbenzoic acid (oxidation time 5 hr). Thin layer chromatography gave 0.48 g of yellow product (yield 63%): mp 175–176° (methanol–water) (lit.[2] mp 172–174°); uv (cyclohexane) λ 450 mμ (ε ~13); esr ($CHCl_3$, $M/1000$) $a_N$ = 14.9 G.

**Spiro(5α-cholestane-3,5'-hydantoin) (7a).** According to Maki,[13] a mixture of 5α-cholestan-3-one (3.86 g), ammonium carbonate (5.7 g), and potassium cyanide (2 g) in 80% ethanol (150 ml) was heated at 57–58° for 10 days. The precipitate was filtered, washed with water, and dried to give 4 g of white powder (yield 87%): mp 274°; ir (KBr) $\nu_{NH}$ 3200, $\nu_{CO}$ 1780 and 1730 $cm^{-1}$.

The crude product (0.200 g) was extracted repeatedly with ethyl acetate to give 0.125 g of white powder **7a**, mp 276° (lit.[13] mp 273–274°), ir (KBr) identical with that of crude product.

**3α-Amino-5α-cholestane-3β-carboxylic Acid (8a).** According to Maki,[13] **7a** (0.125 g, mp 276°), sodium hydroxyde (5 g), and water (5 ml) were heated for 1 hr with occasional addition of water. At the end of this time, a large amount of water was added and the mixture was filtered. The precipitate was dissolved by addition of 70% sulfuric acid. The sulfate obtained was treated with concentrated ammonia to give 0.100 g (yield 87%) of white product **8a**, mp 264° (lit.[13] mp 262–264°).

**Methyl 3α-Amino-5α-cholestane-3β-carboxylate (9a).** According to Maki,[13] a solution of **8a** sulfate in methanol (20 ml) and concentrated sulfuric acid (4 ml) was refluxed for 8 hr. The methanol was evaporated and the residue was extracted with ether after neutralization with sodium carbonate solution. A 0.100-g yield (95%) of white product **9a** was obtained: mp 141° (methanol) (lit.[13] mp 141–141.5°); ir (Nujol) $\nu_{NH_2}$ 3300, $\nu_{CO}$ 1725 $cm^{-1}$; nmr ($C_6D_6$) $CH_3$ carboxylate 3.44 ppm.

**3α-Amino-5α-cholestane-3β-hydroxymethyl (10a). 9a** (0.1 g, mp 141°) in ether solution was added to a suspension of lithium aluminum hydride (0.25 g) in ether solution (100 ml). The mixture was refluxed for 12 hr. The excess of hydride was decomposed,[16] the ether layer was filtered, and the solvent was removed. **10a** (0.084 g, yield 90%) was obtained: mp 155–158°; ir (Nujol) $\nu_{OH}$ ~3500 $cm^{-1}$; nmr ($C_6D_6$) $CH_2$ hydroxymethyl 3.12 ppm; nmr ($CDCl_3$) $CH_2$ 3.25 ppm.

**2',2'-Dimethylspiro(5α-cholestane-3,4'-oxazolidine) (11a).** Azeotropic distillation of **10a** (0.08 g) with an excess of acetone and a trace of *p*-toluenesulfonic acid gave 0.082 g (yield 95%) of viscous oil **11a**: ir (Nujol) $\nu_{NH}$ 3200 $cm^{-1}$; nmr ($C_6D_6$) $CH_3(2',2')$ 1.4, $CH_2(5')$ 3.53 ppm; nmr ($CDCl_3$) $CH_3(2',2')$ 1.45, $CH_2(5')$ 3.58 ppm.

**2',2'-Dimethylspiro(5α-cholestane-3,4'-oxazolidine)-3'-oxyl (6a).** **11a** (0.08 g) was oxidized using 0.045 g of *m*-chloroperbenzoic acid. Thin layer chromatography (silica gel, 90% pentane–10% ether) gave 0.040 g (yield 47%) of yellow crystals of **6a**: mp 188° (ethanol); uv (cyclohexane) λ 450 mμ (ε ~9.5); esr ($CHCl_3$, $M/1000$) $a_N$ = 15.2 G, no hyperfine structure (Figure 1c).

*Anal.* Calcd for $C_{31}H_{54}NO_2$: C, 78.75; H, 11.51; O, 6.77; N, 2.96. Found: C, 78.76; H, 11.56; O, 6.98; N, 2.85.

**2',2'-Dimethylspiro(5α-cholestane-3,4'-oxazolidine)-3'-oxyl (6a and 6b).** The same method as above was used on the crude hydantoin **7**, mp 274° (mixture of two epimeric hydantoins **7a** and **7b**), without purification of intermediate products. Hydrolysis of crude hydantoins (0.5 g, mp 274°) with sodium hydroxide gave 0.41 g of white product, mp 263° (mixture of two epimeric amino acids).

This crude mixture (0.41 g) in *ethanol* solution (100 ml) containing anhydrous hydrochloric acid was allowed to stand at room temperature overnight. The residue, obtained after evaporation of the ethanol, was extracted with ether to give 0.45 g of white product, mp 105° (mixture of epimeric amino esters): ir (KBr) $\nu_{CO}$ 1720 $cm^{-1}$; nmr ($CDCl_3$) $CH_3$ carboxylate 1.3 (triplet, $J$ = 6 Hz), $CH_2$ carboxylate 4.2 ppm (quadruplet, $J$ = 6 Hz).

This crude amino ester (0.12 g) was reduced with lithium aluminum hydride (0.25 g) to give 0.10 g of white solid, mp 155–157° (mixture of epimeric amino alcohols): ir (Nujol) $\nu_{OH}$ 3500 $cm^{-1}$; nmr ($CDCl_3$) $CH_2$ hydroxymethyl 3.25 ppm.

An azeotropic distillation of crude amino alcohols (0.1 g) with an excess of acetone gave 0.105 g of viscous product (mixture of two epimeric oxazolidines): ir (Nujol) $\nu_{NH}$ 3300 $cm^{-1}$; nmr ($CDCl_3$) $CH_3(2',2')$ 1.45, $CH_2(5')$ 3.57 ppm.

This mixture of oxazolidine (0.105 g) was oxidized with *m*-chloroperbenzoic acid (0.06 g). Thin layer chromatography (silica gel, 90% pentane–10% ether) gave two products in 86.5:13.5 ratio: 0.044 g of yellow crystals, mp 188° (ethanol), identical with **6a**, and 0.007 g of yellow crystals **6b**, mp 150–155°, esr ($CHCl_3$, $M/1000$) $a_N$ = 15.1 G, hyperfine structure (Figure 1b).

**Registry No.**—**3**, 39665-50-4; **4**, 51820-19-0; **5**, 51820-20-3; **6a**, 51231-13-1; **6b**, 51231-14-2; **7a**, 5119-47-1; **7b**, 5167-92-0; **8a**, 5071-18-1; **8b**, 5119-44-8; **9a**, 5071-19-2; **9b**, 5071-15-8; **10a**, 51231-15-3; **10b**, 51231-16-4; **11a**, 51231-17-5; **11b**, 51540-03-5; 4',4'-dimethylspiro(5α-cholestane-3,2'-oxazolidine), 51231-18-6; 5α-cholestan-3-one, 566-88-1; 2-amino-2-methylpropan-1-ol, 124-68-5; 4',4'-dimethylspiro-5β-chlolestane-3,2'-oxazolidine), 51231-19-7; 17β-hydroxy-4',4'-dimethylspiro(5α-androstane-3,2'-oxazolidine), 51231-20-0.

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## Trans Dehydration of Alcohols with Methyl(carboxysulfamoyl) Triethylammonium Hydroxide Inner Salt[1]


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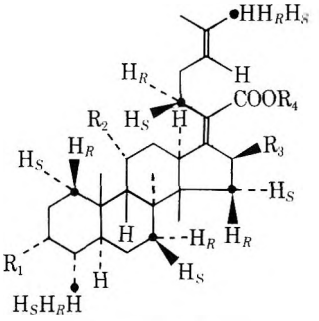
During the course of our investigations into the mode of incorporation of hydrogen atoms of biosynthetic precursors into polyprenoids, we required a procedure applicable to microscale operations allowing the introduction of a double bond *via* a cis elimination of an hydroxyl function. A novel and convenient procedure for the dehydration of secondary and tertiary alcohols utilizing methyl(carboxysulfamoyl) triethylammonium hydroxide inner salt (**6**) claimed to proceed *via* cis elimination has been reported by Burgess, *et al.*[3] Indeed, these authors have shown that the dehydration of *threo*- and *erythro*-2-deuterio-1,2-diphenylethanol is a cis-elimination process. Based on this observation, the generality of the cis elimination was suggested.[3,4]

Dehydration of steroidal alcohols with the reagent **6** has been accomplished without affecting other functional groups of the molecule, such as ketones, unsaturated ketones, acetylenes, and acetates.[4] Because of the potential utility of this reagent, we undertook an exploration of the stereochemistry of the process.

Treatment of 3α-acetoxymethyl fusidate (**1b**)[5,6] with the reagent **6** for 1.5 hr in refluxing benzene afforded the $\Delta^{9(11)}$ olefin (**2**)[5] in 90% yield. The crude reaction product was scrutinized for the $\Delta^{11}$ olefin but none could be isolated. In fusidic acid (**1a**) the 11α-hydroxyl and the

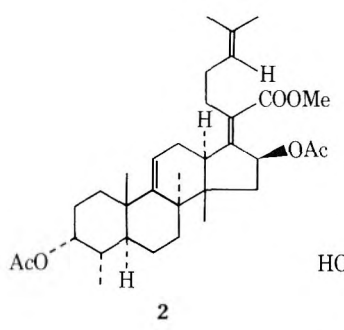


· carbon derived from C-2 of MVA

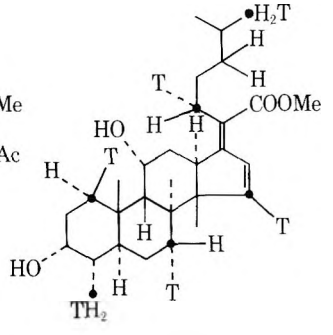
$H_R$ derived from 2-pro-*R* of MVA

$H_S$ derived from 2-pro-*S* of MVA

**1a**, $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = H$
**b**, $R_1 = OAc$; $R_2 = OH$; $R_3 = OAc$; $R_4 = CH_3$
**c**, no $\Delta^{24}$; $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = H$
**d**, no $\Delta^{24}$; $R_1 = R_2 = THPO$ (tetrahydropyranyloxy); $R_3 = OAc$; $R_4 = H$
**e**, $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = CH_3$
**f**, no $\Delta^{24}$; $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = CH_3$
**g**, no $\Delta^{24}$; $R_1 = R_2 = THPO$; $R_3 = OH$; $R_4 = CH_3O$
**h**, no $\Delta^{24}$; $R_1 = R_2 = THPO$; $R_3 = OAc$; $R_4 = CH_3O$



**2**



**3**

9β-hydrogen are trans diaxial,[5,6] and hence the isolated olefin is the product of a trans elimination.

Elimination of 11-hydroxyl functions in pregnane derivatives with the reagent **6** had been reported.[4] The 11β-hydroxyl derivative gave the $\Delta^{9(11)}$ olefin in 96% yield, while the 11α-hydroxyl derivative gave the $\Delta^{9(11)}$ olefin in only 9% yield. The results are contrary to those expected if one maintains the cis-elimination mechanism. The 11α-hydroxyl, being cis to the 9α-hydrogen, should be more readily eliminated than the 11β-hydroxyl. Crabbé, *et al.*,[4] could not satisfactorily explain the lack of reactivity of the 11α-hydroxyl; however the result with the 11β-hydroxyl was rationalized by assuming that a C-11 cation is formed first, and this is followed by an intramolecular hydrogen transfer from C-9 to C-11. Stabilization of the resulting C-9 cation was then postulated to occur *via* the loss of a C-11 hydrogen and $\Delta^{9(11)}$ bond formation. A more reasonable explanation consistent with our observations is that a trans elimination is operating in the case of the 11β-hydroxyl. This explanation is supported by the results obtained in the elimination of the 3α-hydroxyl of **4b** described below.

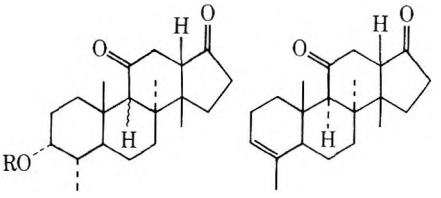
To evaluate the stereochemistry of the dehydration of the 3α-hydroxyl of **4b**, 3-acetoxymethyl fusidate (**1b**) was converted to **4a** as previously described.[7] The saponification of **4a** to **4b** was carried out under conditions which would ensure complete isomerization of the 9β-H to the more stable 9α-H.[8] Indeed, the physical properties (melting point, $[\alpha]_D$) of the product agreed with those reported[8] for **4b**. Exposure of **4b** to the reagent **6** for 1 hr in refluxing benzene yielded the $\Delta^3$ olefin **5**. In alcohol **4b**

**Table I**

| Compd | $^3H:^{14}C$ isotopic ratio[a] | $^3H:^{14}C$ atomic ratio |
|---|---|---|
| **1e** | 5.04 | 6.00:6 |
| **1f** | 5.03 | 6.00:6 |
| **1d** | 4.98 | 5.92:6 |
| **1h** | 4.96 | 5.90:6 |
| **3** | 4.96 | 5.90:6 |

[a] Isotopic ratios were determined on samples first purified by tlc and then repeatedly crystallized from a suitable solvent. Reported values are the average of three crystallizations.

the 3α-hydroxyl and the 4β-hydrogen are trans diaxial; hence the isolated product (**5**) is again the result of a trans elimination.



**4a**, R = Ac 9β
**b**, R = H 9α

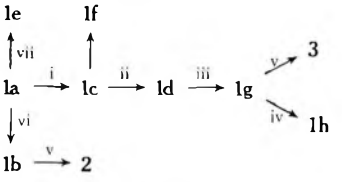
**5**

$MeO_2\bar{C}NSO_2\overset{+}{N}Et_3$
**6**

Considerations of the mode of formation of squalene and its oxidative cyclization to protosterols predict that the hydrogens derived from 2-pro-*R* and 2-pro-*S* protons of mevalonic acid (MVA) will be located in the derived fusidic acid[5,7] as shown in **1a**. Consequently, fusidic acid (**1a**) biosynthesized from (3*RS*,2*R*)[2-$^{14}$C,2-$^3$H]-MVA will have *inter alia* a $^3$H atom at the 15β position. In a previous study[9] we had indeed confirmed that [$^{14}C_6$,$^3H_6$]fusidic acid (**1a**) biosynthesized from (3*RS*,2*R*)[2-$^{14}$C,2-$^3$H]-MVA has a $^3$H atom at the 15β position. Proton magnetic resonance[10] and X-ray[11] studies of fusidane derivatives have indicated that the cis 16β-C–O and the 15β-C–H bonds have a rigid, nearly eclipsed orientation. It was felt that this stereochemistry should favor a cis elimination of the 16β-OH and 15β-$^3$H.

Consequently [$^{14}C_6$,$^3H_6$]fusidic acid[9] (**1a**; · $^{14}$C; $H_R$-$^3$H) biosynthesized from (3*RS*,2*R*)[2-$^{14}$C,2-$^3$H]mevalonic acid was converted to 16β-hydroxydihydrofusidate (**1g**) as outlined[8] in Scheme I. Treatment of the [$^{14}C_6$,$^3H_6$]-16β-ol

**Scheme I**



i, $H_2$/Pd on $BaCO_3$[6b]
ii, dihydropyran-*p*-toluenesulfonic acid
iii, $LiAlH_4$–tetrahydrofuran, $CH_2N_2$
iv, $Ac_2O$–pyridine (50°)
v, $MeO_2\bar{C}NSO_2\overset{+}{N}Et_3$–benzene[3]
vi, $Ac_2O$–pyridine[6b]
vii, ethereal $CH_2N_2$[6b]

**1g** (counted as **1h**) with reagent **6** for 2 hr in refluxing benzene yielded the [$^{14}C_6$,$^3H_6$] olefin **3**.[9] The $^3H:^{14}C$ ratios of the olefin **3** and the 16β-ol **1g** were identical (see Table I), indicating that $^3$H was not lost. It can be concluded that the $\Delta^{15}$ product isolated was obtained *via* loss of the 16β-OH and the gauche 15α-H and again the overall process is equivalent to a trans elimination.

Our results with **1g** do not preclude the possibility of the participation of an allylic cation in the $\Delta^{15}$ formation. However, the complete stereospecificity of the reaction which proceeded with retention of all of the $^3H$ would mitigate against this argument.

Thus in the three cases studied by us, products of an overall trans rather than the expected cis dehydration were isolated. The unlikely possibility that cis elimination occurs first and is followed by a subsequent isomerization is not ruled out by our results. However, it is apparent that based on the structures of the *isolated* end products, the generalization of the mechanism of the reaction as a cis-elimination process is not tenable.

## Experimental Section[12]

**Methyl 3-Acetoxy-$\Delta^{9(11)}$-fusidate (2).** To a stirred solution of methyl 3-acetoxyfusidate (**1b**,[5,6] 100 mg) in benzene (20 ml) under an atmosphere of $N_2$ was added dropwise a solution of methyl(carboxysulfamoyl) triethylammonium hydroxide inner salt (**6**, 50 mg) in benzene (20 ml). The solution was stirred at room temperature for 0.5 hr and refluxed for 0.5 hr. Additional reagent **6** (50 mg) was added and the reaction was refluxed for 1 hr and then terminated with water. The benzene layer was washed with $H_2O$ and dried over $Na_2SO_4$ and the solvent was removed. The olefin (90 mg) was purified by preparative tlc [silica gel, hexane–acetone (8:2)]. The olefinic zone was eluted with $CHCl_3$–EtOAc (4:1) and further fractionated by argentation tlc [silica gel–silver nitrate 15%; hexane–acetone (7:3)] to yield homogenous olefin **2**[5] (70 mg): ir 3020 $cm^{-1}$ (C=C); nmr 4.52 ppm (1 H, t, $J$ = 3 Hz, 11-H); $m/e$ 494 ($M^+$ − HOAc).

**3$\alpha$-Hydroxy-4$\alpha$,8,14-trimethyl-18-nor-5$\alpha$,8$\alpha$,14$\beta$-androstane-11,17-dione (4b).** To a stirred, under nitrogen, solution of 3$\alpha$-acetoxydione **4a**[7] (725 mg) in MeOH (160 ml) was added KOH (40 g) in $H_2O$ (40 ml). The stirring was continued overnight at room temperature under $N_2$ and then the mixture was refluxed for 1 hr. Water (200 ml) was added, and the mixture was neutralized and extracted with EtOAc. The combined extract was washed with $H_2O$ and dried ($Na_2SO_4$) and the solvents were removed. The resulting residue was fractionated on tlc [silica gel, hexane–acetone (7:3)]. The recovered 3$\alpha$-hydroxydione **4b**[8] (446 mg) was crystallized (MeOH): mp 230–232° (lit.[8] mp 237–239° uncorrected); $[\alpha]^{24}_{589}$ − 172° (0.1225 g/100 ml) (lit.[8] −176°); ir 3470 (OH), 1733 and 1685 $cm^{-1}$ (C=O); nmr 6.28 (1 H, broad s, 3$\beta$-H), 8.33, 8.80, 8.98, and 9.07 ppm (12 H, s, 4-, 8-, 14-, and 19-$CH_3$); $m/e$ 332 ($M^+$), 314 ($M^+$ − 18).

**4$\alpha$,8,14-Trimethyl-18-nor-5$\alpha$,8$\alpha$,14$\beta$-androst-3-ene-11,17-dione (5).** To a stirred solution of 3$\alpha$-hydroxydione **4b** (177 mg) in benzene (3 ml) the reagent **6** (200 mg) in benzene (10 ml) was added. The mixture was refluxed for 1 hr and processed as above. The recovered olefin (75 mg) was fractionated first by preparative tlc [silica gel, hexane–acetone (7:3)] and then by argentation preparative tlc (silica gel–silver nitrate 15%). The recovered $\Delta^3$ olefin **5** was crystallized (EtOAc–hexane): mp 145–149°; ir 1735 and 1693 $cm^{-1}$ (C=O); nmr 4.69 (1 H, broad s, 3-H), 8.14 (3 H, d, $J$ = 2 Hz, 4-$CH_3$), 8.80, 8.89, and 9.10 ppm (9 H, s, 8-, 14-, 19-$CH_3$); $m/e$ 314 ($M^+$), 299 ($M^+$ − 15).

**Methyl 24,25-Dihydro-3$\alpha$,11$\alpha$-dihydroxy[$^{14}C_6$,$^3H_4$]-16-deacetoxy-$\Delta^{15}$-fusidate (3).** A stirred solution of 16$\beta$-hydroxy dihydrofusidate **1g**[9] (93 mg) in benzene (10 ml) was treated with reagent **6** (50 mg) in benzene (10 ml). After stirring at room temperature for 0.5 hr, the mixture was refluxed for 2 hr and worked up as above. Preparative tlc [silica gel, hexane–acetone (4:1)] gave the $\Delta^{15}$ olefin **3**[9] (30 mg), which was crystallized (EtOAc): mp 160–161°; ir 1665 and 1610 (conjugated C=O), 980 $cm^{-1}$ (C=CH); nmr 3.62 (1 H, d, $J$ = 6 Hz, 16-H), 3.10 ppm (1 H, d, $J$ = 6 Hz, 15-H); uv (EtOH) 274 nm (ε 17,200); $m/e$ 472 ($M^+$).

**Registry No.** —**1b**, 51424-41-0; **1g**, 51373-34-3; **2**, 51373-35-4; **3**, 51373-36-5; **4a**, 13263-12-2; **4b**, 51424-42-1; **5**, 51381-68-1; **6**, 51373-37-6.

## References and Notes

(1) The very generous support of this work by the National Institutes of Health (Grants AM12156, CA13369, GM16928, and GM19882) and the National Science Foundation (Grants GB36201 and GB23801-A1) is gratefully acknowledged.

(2) (a) Postdoctoral Fellow, 1972–1974. (b) Postdoctoral Fellow, 1970–1973.

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(10) (a) The nmr spectra of fusidic acid derivates (see data below) reveals vicinal coupling between the 15$\alpha$ and 16$\alpha$ protons of 8 Hz

Chemical Shifts ($\tau$) and Coupling Constants ($J$) for the 16$\alpha$-H

| Compd | $\tau$ | $J$, Hz |
|---|---|---|
| **1a** | 4.14 (d) | 8 |
| **1b** | 4.08 (d) | 8 |
| **1d** | 4.22 (d) | 7 |
| **1h** | 4.21 (d) | 8 |
| **1e** | 4.18 (d) | 8 |

and *ca.* 1 Hz between the 15$\beta$ and 16$\alpha$ protons. Thus the dihedral angle between the 15$\alpha$ and 16$\alpha$ protons must approach zero. (b) W. von Daehne, H. Lorch, and W. O. Godtfredsen, *Tetrahedron Lett.*, 4843 (1968).

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(12) Melting points were taken on a hot stage and are corrected. Infrared spectra were recorded on KBr microdisks on a Perkin-Elmer Model 237 spectrometer. Mass spectra were obtained on a Du Pont 21-491 instrument. Nmr spectra were recorded on a Varian DA-60 spectrometer at 60 MHz with samples dissolved in $CDCl_3$. Glc analyses were performed on a Hewlett-Packard Model 7620A glc equipped with a flame ionization detector. A 6 ft silanized glass column of 1% SE-30 on Gas-Chrom Q was used for all analyses. Specific activities and $^3H$:$^{14}C$ ratios were determined on samples which were purified by tlc and crystallized to constant specific activity of $^{14}C$ and constant $^3H$:$^{14}C$ ratio.

# Aromatization of Cyclic Ketones. I. Alkylcyclohexanone

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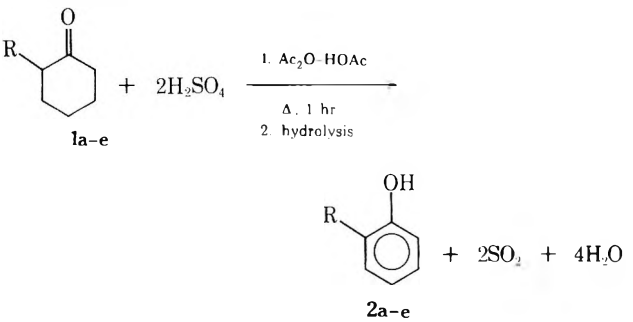
Several methods are reported in the literature for the aromatization of substituted cyclohexanones. In general, either high-temperature catalytic aromatizations[1] or a two-step process, halogenation-dehydrohalogenation,[2] were employed. Treatment of 3,3,5-trimethylcyclohexanone with 30% oleum for 7 days at room temperature followed by steam distillation gives about a 10% yield of trimethylphenol.[3]




a, R = $CH_3$
b, R = $C_2H_5$
c, R = $n$-$C_3H_7$
d, R = $n$-$C_4H_9$
e, R = 

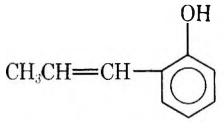
Several $\alpha$-alkylcyclohexanones **1** were subjected to the sulfuric acid–acetic anhydride aromatization procedure, whereby 2 mol of sulfuric acid and at least 2 mol of acetic

**Table I**
**Aromatization of α-Alkylcyclohexanones**

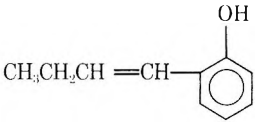
| Compd | Solvent | Moles of $H_2SO_4$ per mole of ketone | Yield, % | Product(s)[a] |
|---|---|---|---|---|
| **1a** | $Ac_2O$–HOAc | 2.0 | 90 | **2a** |
| **1a** | $Ac_2O$ | 2.0 | 80 | **2a** (64%), 3-methylcatechol (36%)[c] |
| **1b** | $Ac_2O$–HOAc | 2.0 | 50 | **2b** |
| **1c** | $Ac_2O$–HOAc | 2.0 | 60 | **2c** |
| **1c**[b] | $Ac_2O$–HOAc | 1.8 | 65 | **1c** (10%), **2c** (40%), **3** (22%) |
| **1d** | $Ac_2O$–HOAc | 2.0 | 65 | **2d** |
| **1d**[b] | $Ac_2O$–HOAc | 1.8 | 70 | **1d** (22%), **2d** (30%), **4** (20%) |
| **1e** | $Ac_2O$–HOAc | 2.0 | 90 | **2e** |

[a] Ratio of products based on glc analysis. [b] Several higher boiling materials detected by glc (28%) were not identified. [c] M. S. Kablaoui and H. Chafetz, unpublished results.

anhydride ($Ac_2O$) to 1 mol of ketone were employed. The major product isolated was the corresponding *o*-alkylphenyl acetate. Hydrolysis of the product yields the *o*-alkylphenols. Best yields were obtained when sulfuric acid was added, preferably at room temperature, to a solution of the ketone, $Ac_2O$, and acetic acid (HOAc)[4] in a dry nitrogen atmosphere. The use of 1.8 mol of $H_2SO_4$ for **1c** and **1d** gave appreciable amounts of the 2-(1-alkenyl)phenols (**3**, **4**)[5] as by-products. Results are shown in Table I.



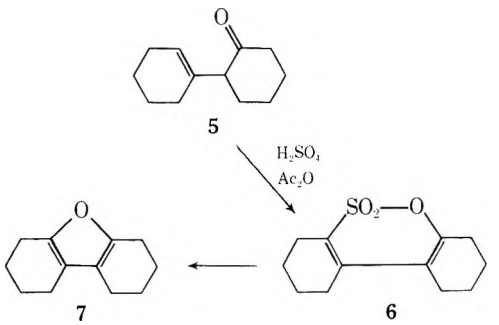

3




4

No aromatization occurred when sodium bisulfate, *p*-toluenesulfonic acid, or sulfoacetic acid was substituted for $H_2SO_4$, or when phthalic or succinic anhydride replaced $Ac_2O$.

Non-α-alkylated cyclohexanones exhibited different behavior. Thus cyclohexanone and 3-methyl- and 4-methylcyclohexanone as well as 2-(1-cyclohexenyl)cyclohexanone (**5**, aldol condensation product[6] of cyclohexanone), when subjected to the above aromatization procedure, gave high-boiling, nonphenolic materials. Such materials are believed[7] to be the sultone **6** and octahydrobenzofuran **7**. The literature[8] reported the formation of **6** by the reaction of **5** with cold concentrated $H_2SO_4$ and $Ac_2O$. Pyrolysis[8] of **6** gave **7**.




7 6

It seems that non-α-alkylated cyclohexanones give aldol condensation products when subjected to the above aromatization procedure. In the case of α-alkylated cyclohexanones, the corresponding o-alkylphenols are usually isolated. It is reasonable to assume that under the above conditions, non-α-alkylated cyclohexanones undergo aldol condensation faster than aromatization while α-alkylated cyclohexanones aromatize (or form the enol acetate) faster than forming aldol condensation products. The fact that non-α-alkylated cyclohexanones undergo aldol condensations faster than the α-alkylated is known in the literature.[9] To further verify this, cyclohexanone and 2-methyl- and 4-methylcyclohexanone were treated at room temperature with hydrogen chloride; cyclohexanone and 4-methylcyclohexanone formed the aldol dimer while 2-methylcyclohexanone was recovered unreacted.

Acetylation of the enol form of α-alkylcyclohexanone appears to be the first step of the aromatization. Thus, analysis of the products formed when refluxing began indicated the presence of only the enol acetate[10] (90%) and o-alkylphenyl acetate (10%). After 10 min of reflux, over 50% of the aromatized product was isolated. No enol acetate remained after 1 hr.

It is proposed that the aromatization of 2-alkylcyclohexanones involves O-acetylation of the enol form followed by two hydride abstractions giving first the diene followed by the product **2** and $SO_2$. Several mechanisms can be postulated for the hydride abstraction and formation of $SO_2$. One possibility could involve the sulfonation of the ketone or its enol acetate with concentrated $H_2SO_4$ or acetyl sulfate (the product of the reaction of $H_2SO_4$ with $Ac_2O$) followed by desulfonation[3,12] to give $SO_2$ and $H_2O$. Another alternative mechanism could involve hydride abstraction as in the formation of adamantanones from adamantane[13] or the action of *tert*-butyl chloride–aluminum bromide complex on isopentene.[14]

## Experimental Section

The ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer; the nmr spectra were obtained on a Varian Associates Model V-4311 spectrometer operating at 60 MHz. All glc analyses were run on a SE-30 column programmed from 100 to 250°.

**Aromatization of 2-Methylcyclohexanone.** Into a 300-ml, three-neck flask equipped with a magnetic stirrer, a gas sparger, a condenser, and a thermometer were charged 5.0 g (0.044 mol) of 2-methylcyclohexanone (2-MCH), 50 ml of acetic anhydride, and 50 ml of HOAc. Concentrated sulfuric acid (9.0 g, 0.09 mol) was slowly added at room temperature to the mixture. The reaction mixture was then heated to reflux for 1 hr while dry nitrogen was passed through at the rate of 140 ml/min. The work-up of the reaction mixture was done by quenching in 150 ml of ice–water and stirring for 30 min to decompose all the acetic anhydride followed by extraction with ether (4 × 50 ml). The combined ether extracts were washed once with 50 ml of saturated $NaHCO_3$ solution and once with saturated NaCl solution, dried, and stripped on a rotary evaporator to give a residue (6.5 g) whose glc analysis indicated the presence of one compound. Upon distillation of the residue, 6.0 g (90% yield) of *o*-cresyl acetate was isolated. The product was identified by comparison of its ir and nmr spectra with those of an authentic sample. When air was substituted for dry nitrogen in the above run, low yields (~50%) of o-cresyl acetate were isolated.

**Isolation of Intermediates in the Aromatization of 2-Methylcyclohexanone.** The aromatization of 2-MCH was repeated whereby samples were taken during the course of the aromatization. After work-up, the residue was analyzed. When the temperature of the reaction reached 50°, *o*-cresyl acetate (traces), the enol acetate of 2-MCH, and 2-MCH were isolated. At reflux, the enol acetate of 2-MCH (about 90%) and o-cresyl acetate (10%) were isolated. After 15 min of reflux, 58% of o-cresyl acetate was isolated.

**Aromatization of α-Substituted Cyclohexanones.** The aromatizations were carried out by the same procedure used for the aromatization of 2-MCH. Variations in solvent and amount of $H_2SO_4$ used are shown in Table I.

**Aromatization of 2-Propylcyclohexanone (1c).** The title compound (5.0 g, 0.35 mol), 6.6 g (0.066 mol) of $H_2SO_4$, 75 ml of $Ac_2O$, and 75 ml of HOAc were refluxed for 1 hr as in the case of 2-methylcyclohexanone. After work-up of the reaction mixture, a glc analysis indicated the presence of four compounds. The first (10%) and second (40%) were identified as the enol acetate of the

starting material and 2-propylphenyl acetate, respectively, by comparison of the ir and nmr spectra with those of authentic samples. The fourth compound (18%) was not identified. The third compound (22%) was identified as 2-(1-propenyl)phenyl acetate (3): ir (neat) 5.75 (-OAc), 6.1 μ (C=C); nmr ($CDCl_3$) δ 1.89 (d, 3 H, $CH_3C$=C-), 2.32 (s, 3 H, $CH_3COO$-), 6.3 (m, 2 H, -CH=CH-), and 7.25 (m, 4 H, aromatic).

When the above run was repeated using 7.7 g (0.077 mol) of concentrated $H_2SO_4$, only 2-propylphenyl acetate (70%) was isolated.

Aromatization of 2-butylcyclohexanone gave similar results (Table I).

**Reaction of Hydrogen Chloride with Methylcyclohexanones.** Into three separate test tubes were charged 5 ml each of cyclohexanone and 2-methyl- and 4-methylcyclohexanone. Hydrogen chloride was bubbled at room temperature into each of the test tubes for 15 min. Analysis of the products by ir and nmr indicated that cyclohexanone and 4-methylcyclohexanone gave different products than the starting material whereas 2-methylcyclohexanone was recovered unreacted.

**Registry No.**—**1a**, 583-60-8; **1b**, 4423-94-3; **1c**, 94-65-5; **1d**, 1126-18-7; **1e**, 90-42-6; **3** acetate, 35922-87-3; cyclohexanone, 108-94-1; 4-methylcyclohexanone, 589-92-4; hydrogen chloride, 7647-01-0.

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(4) The use of HOAc as solvent along with $Ac_2O$ (1:1 volume ratio) improves the yield of o-alkylphenol and minimizes the formation of alkylcatechols (Table I). This type of aromatization will be fully discussed in a separate paper.
(5) Identified by ir and nmr only.
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## Effect of Dichloromethane on the Reaction of Carbethoxynitrene with *trans*-1,2-Dimethylcyclohexane


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There is ample experimental evidence to support the statement that nitrenes, generated from a variety of precursors, can be made to cross from an initially formed singlet state to a lower energy triplet state by collisional deactivation with inert solvent molecules.[1-3] Collisional deactivation or destabilization of singlet states by inert solvents can mean the actual promotion of intersystem crossing by electronic interactions as with heavy-atom solvents or, as is more probably the case with dichloromethane, simply that the solvent by being inert allows intramolecular intersystem crossing to compete favorably with reactive collision, or both.

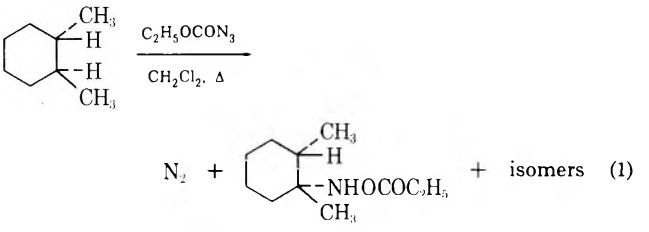
**Table I**
**Thermal Decomposition of Ethyl Azidoformate in Dichloromethane–*trans*-1,2-Dimethylcyclohexane (TDCH) Solutions[a]**

| Mol % TDCH | Stereospecificity (% trans insertion product) | Proportion of tertiary product[b] | Absolute yield %[c] |
|---|---|---|---|
| 100 | 96.5 | 38.7 | 26.2 |
| 89.9 | 98.5 | 39.6 | 37.3 |
| 79.9 | 97.8 | 35.6 | 34.4 |
| 66.7 | 96.2 | 38.1 | 30.0 |
| 51.0 | 94.5 | 35.4 | 38.0 |
| 39.5 | 95.6 | 33.7 | 37.5 |
| 19.2 | 96.4 | 28.2 | 35.2 |
| 8.1 | 92.0 | 22.6 | 37.7 |

[a] Reaction mixtures were carefully degassed and azide decomposition was carried out in evacuated, sealed tubes at 120° for 90 hr; analysis by vpc. [b] Proportion of tertiary C–H insertion product to other isomers; tertiary/(tertiary + secondary + primary). [c] Total absolute yield of all insertion products.

However, Breslow has recently reported that yields of insertion (singlet) products of carbalkoxynitrenes, ROCON, with cyclohexane are increased upon dilution with hexafluorobenzene.[4] Furthermore, in an accompanying communication, Lwowski demonstrates that dichloromethane acts to stabilize the singlet-state character of a number of alkanoylnitrenes, RCON, without removing their C–H insertion reactivity,[5] although it was noted that no such effect of dichloromethane on yields and product ratios had been observed from previous studies with carbethoxynitrene, ROCON, R = Et.[6]

As part of a long-range study of the factors which influence the singlet–triplet character of nitrenes, we now present evidence that dichloromethane has a noticeable effect on the reactions of a carbalkoxynitrene (ROCON) as well as alkanoylnitrenes (RCON). Table I summarizes results from a study of the reaction of thermally generated carbethoxynitrene with *trans*-1,2-dimethylcyclohexane (TDCH) at various dilutions with dichloromethane (eq 1).




The results given for each concentation of hydrocarbon are based on triplicate runs with an error of ±2% for the stereospecificity, ±2% for the proportion tertiary product, and ±5% for the absolute yields. From the data in Table I it is evident that changing the concentration of the hydrocarbon by dilution with dichloromethane does not affect the stereospecificity of the insertion; *i.e.*, little *cis*-1,2-dimethyl-1-cyclohexylurethane is formed from the trans hydrocarbon. This result supports the conclusion, based on a wealth of other experiments, that only singlet carbethoxynitrene inserts into unactivated C–H bonds.[7] Competition experiments established that the tertiary C–H bonds of *cis*-1,2-dimethylcyclohexane react 1.2 times faster than the corresponding bonds in the trans isomer; a factor of 1.7 was found for these hydrocarbons using cyanonitrene, NCN.[2] Otherwise, the cis and trans isomers gave similar product patterns on vpc analysis and the trans isomer was chosen for study. With pure (>99%)

trans hydrocarbon, the selectivity (corrected for numbers of hydrogens) for tertiary:secondary:primary C–H bonds was found to be 34:14:1, in good agreement with previous results.[8] However, Table I shows a steady decrease in the selectivity of the insertion, *i.e.*, the proportion of tertiary insertion product decreases with increasing dilution with dichloromethane. This contrasts with previous experiments in which no change in selectivity upon dilution with dichloromethane was observed for the thermal or photochemical decomposition of ethyl azidoformate in 3-methylhexane[9] nor for the reaction of 2-methylbutane with carbethoxynitrene generated by photolysis or $\alpha$-elimination.[10] The absolute yields in Table I show an initial increase followed by no evident increase or decrease down to a dilution of 8% hydrocarbon–92% dichloromethane. Breslow also observed an increase of insertion yield for the thermal decomposition of *n*-octadecyl azidoformate in cyclohexane upon dilution with hexafluorobenzene (at concentrations of 90, 75, and 50% hydrocarbon) and only when the concentration of hydrocarbon was reduced to 25% by dilution was the insertion yield lower than for 100% hydrocarbon.[4] An increase in insertion yield was also observed upon 50:50 dilution with hexafluorobenzene of a thermal decomposition reaction of ethyl azidoformate in cyclohexane.[4] However, yields of insertion products only decreased when dichloromethane was used to dilute reactions involving carbethoxynitrene generated from ethyl azidoformate with 3-methylhexane[9] and cyclohexene.[6]

## Discussion

Stabilization of nitrene singlet states by symmetrical interaction with two lone pairs has been proposed by Gleiter and Hoffmann[11] and such an effect has been invoked to explain the singlet stabilizing effect of hexafluorobenzene on carbethoxynitrenes[4] and of dichloromethane on alkanoylnitrenes.[5] A possible theoretical explanation of why dichloromethane seems to stabilize the singlet state of alkanoylnitrenes (RCON) but not (previous to our results) of carbalkoxynitrenes (ROCON) has been recently provided.[12] Based on LCAO–MO–SCF calculations, Alewood, *et al.*, concluded that singlet–triplet separations in carbalkoxynitrenes may be much smaller than for alkanoylnitrenes and that this may manifest itself in a reduced tendency of carbalkoxynitrenes to undergo intersystem crossing. Then, to explain the effect of hexafluorobenzene on carbalkoxynitrenes, these authors[12] point out that Breslow and Edwards[4] suggest the possibility that $C_6F_6$ might be acting as a radical (triplet) trap. Although Breslow and Edwards do discuss the radical-trap hypothesis, they finally concluded that the nitrene–halide complex hypothesis is the more likely one,[4] *i.e.*, $C_6F_6$ stabilizes singlet carbalkoxynitrenes by the same type of interaction[11] by which $CH_2Cl_2$ stabilizes singlet alkanoylnitrenes.

Based on the data in Table I, we conclude that dichloromethane has a singlet stabilizing effect on carbalkoxynitrenes as well as on alkanoylnitrenes. The singlet character of the insertion reaction of carbethoxynitrene, as determined by the stereospecificity, remains high throughout the range of dilution. The absolute yields also remain unchanged, after an initial increase similar to that observed in the hexafluorobenzene–carbethoxynitrene system. The lack of any trend of increasing or decreasing absolute yields with successive dilution is probably the result of a counterbalancing of the normally observed collisional deactivation (singlet destabilizing) effect of an inert solvent and the singlet stabilizing ability of this particular inert solvent, dichloromethane. That such an initial increase of insertion yield or the maintenance of high insertion yields upon dilution with dichloromethane of carbethoxynitrene–hydrocarbon reaction mixtures was not previously observed is probably due to the fact that there were no data presented in the region of 33–100 mol % hydrocarbon; *i.e.*, data are presented for 100 mol % hydrocarbon and then typically for dilutions of 33 or 25% hydrocarbon and less but none inbetween.[1,6,9,10,13] The effect of increased yield is observed at 50, 75, and 90% hydrocarbon with hexafluorobenzene[4] and at 90% and other concentrations in this work.

To support the statement that dichloromethane has no significant effect on insertion yields and stereospecificity,[5] reference is made to studies in which dichloromethane and neopentane are compared as "inert" diluents.[6,13] Yet in the one communication (ref 6) there are no common concentrations of dichloromethane and neopentane and the experiments which can be roughly compared are at concentrations of 10% hydrocarbon (cyclohexene) or less at which the collisional deactivation effect of dichloromethane probably predominates over any stabilizing effect and at which the C–H insertion yields with cyclohexene are difficult to compare because of the appreciable yields of neopentylurethan which form at these high dilutions. In an accompanying communication (ref 13) data is presented on the stereospecificity of the addition of carbethoxynitrene to *cis*- and *trans*-4-methyl-2-pentene which shows that at 1.5 mol % hydrocarbon and correcting for the neopentylurethan formed, the stereospecificity of the addition reaction is the same with dichloromethane and neopentane as diluents.[13] However, in a later paper, again reporting the results of reactions of carbethoxynitrene with the 4-methyl-2-pentenes and comparing neopentane and dichloromethane as diluents, Lwowski concluded that, if anything, dichloromethane seems to stabilize the singlet relative to neopentane.[1]

## Experimental Section

**Reagents.** Ethyl azidoformate, bp 40–41° (30 mm), was prepared from potassium azide and ethyl chloroformate.[14]

*trans*-1,2-Dimethylcyclohexane (Baker grade) was found to be >99% pure by vpc and was used without further purification.

Dichloromethane (Eastman reagent grade) was used without further purification.

**General Reaction Procedure.** Into a thick-wall tube was place approximately 2 g of *trans*-1,2-dimethylcyclohexane and approximately 0.2 g of ethyl azidoformate. The proper amount of dichloromethane was then added to give the desired mole fraction concentration of hydrocarbon. The tube was then degassed three times, sealed under vacuum, and heated for 90 hr at 120° in an oil bath. When the reaction was done at high dilution (50% hydrocarbon or less), the product mixture was concentrated by removing solvent to a volume of about 3 ml.

The products were analyzed by vpc (Aerograph A-700 gas chromatograph) with an XF-1150 column (8 ft × 0.25 in., 15% on 60/80 Chromosorb W, column temperature 155°, 60 ml/min He) and peak areas were determined by the "cut and weigh" technique. Nmr analysis of material collected from the gc was used to identify the C–H insertion products. For *trans*-1,2-dimethylcyclohexane, there is one product expected from insertion into the tertiary C–H bonds, four isomeric products from the secondary C–H bonds, and one from the primary. After the shorter retention time peaks due to solvent, unreacted hydrocarbon, and urethan are obtained, there is a large peak for the tertiary C–H insertion product (with good separation of *cis*- and *trans*-1,2-dimethylcyclohexyl-1-urethane on this column having been previously established) followed by a series of four smaller overlapping peaks (secondary insertion products) and one peak with the longest retention time (primary C–H insertion product). This order of elution (tertiary, secondary, primary) is the same as that observed by Lwowski for the isomeric 3-methylhexane urethanes.[9]

Chemical shifts, peak multiplicities, and integrated areas are consistent with the structures assigned to the insertion products collected from the gc: tertiary insertion product $\delta_{TMS}$ ($CCl_4$) 4.11

(q, $J$ = 7.5 Hz, 2, $CH_2$ of Et), 1.28 (t, $J$ = 7.5 Hz, 3, $CH_3$ of Et), 0.97 (d, $J$ = 7.0 Hz, 3, $CH_3$ on tertiary C with H), 1.23 (s, 3, $CH_3$ on tertiary C with $-NHCO_2Et$), 0.9–2.3 (m, 18, all H except NH, $CH_2$ of Et); secondary insertion product $\delta_{TMS}$ ($CCl_4$) 3.93 (q, $J$ = 7.5 Hz, 2, $CH_2$ of Et), 1.11 (t, $J$ = 7.5 Hz, $CH_3$ of Et), 0.87 (s, 6, $CH_3$'s on tertiary C's), 1.95 (s, 1, H on C with $-NHCO_2Et$). The two methyl groups on each of the four secondary insertion products should each appear as a doublet. The singlet listed at $\delta$ 0.87 is the envelope of these closely spaced, unresolved doublets. The primary insertion product was not present in sufficient quantity for analysis and assignment was based on retention time and selectivity data.

The stereospecificty and selectivity were then calculated from the peak areas in the usual manner. The absolute yield was determined by using acetophenone as an external standard. Total moles of insertion product was then calculated from the area/mol for acetophenone using the calibration factor of 0.78 for the products relative to acetophenone. It was assumed that all the insertion products have the same detector sensitivity.

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**Registry No.**—*trans*-1,2-Dimethylcyclohexane, 6876-23-9; ethyl azidoformate, 817-87-8; dichloromethane, 75-09-2.

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## Studies in Chemical Ionization Mass Spectrometry. Mechanisms in Ester Spectra

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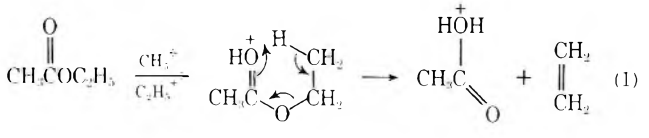
We wish to report deuterium labeling experiments on the methane chemical ionization (CI) mass spectrum of ethyl acetate which were designed to establish some of the mechanisms previously postulated to explain the observed products.[1] In the partial $CH_4$ CI mass spectrum of ethyl acetate (Table I) the major decomposition product is the protonated acid. It was suggested that this ion could be formed in the following manner.[2]



(1)

**Table I**
**$CH_4$CI Mass Spectra of Ethyl Acetates**

| | 100 $I_i/\Sigma_i$ | | |
|---|---|---|---|
| $m/e$ | $-CH_2CH_3$[a] | $-CD_2CH_3$[b] | $-CD_2CD_3$[c] |
| 61 | 44.8 | 45.0 | 2.3 |
| 62 | 1.1 | 4.6 | 30.4 |
| 63 | 0.7 | 1.0 | 1.2 |
| 87 | 0.4 | | |
| 88 | 0.6 | | |
| 89 | 44.8 | 3.3 | 0.3 |
| 90 | 2.3 | 1.0 | 2.4 |
| 91 | | 38.8 | 0.1 |
| 92 | | 1.8 | 0.4 |
| 93 | | | 2.6 |
| 94 | | | 49.4 |
| 95 | | | 3.2 |

[a] Registry no., 141-78-6. [b] Registry no., 51472-78-7. [c] Registry no., 51472-79-8.

An average $CH_4$ CI mass spectrum of $CH_3COOCD_2CH_3$ is also given in Table I. The major processes are the same for the deuterated and undeuterated species. It is apparent from Table I that reaction 1 is the dominant process, since very little deuterium is incorporated in the protonated acid ions.

From these and other data collected at different concentrations of ethyl acetate, repeller voltages of 0–2 V, source temperatures of 110–160°, and $CH_4$ pressures of 0.5–0.9 Torr, the average ratio of ionic abundances at $m/e$ 62 and 61 was 0.109 ± 0.006. With the appropriate correction of $^{13}C$, the ratio of abundances of species $(CH_3CO_2HD^+)/(CH_3CO_2H_2^+)$ is 0.086 ± 0.006. The specificity of the decomposition process is high, but not 100%: incorporation of the deuterium atom from the $\alpha$ carbon occurs about 8% of the time, and reaction 1 occurs about 92% of the time.

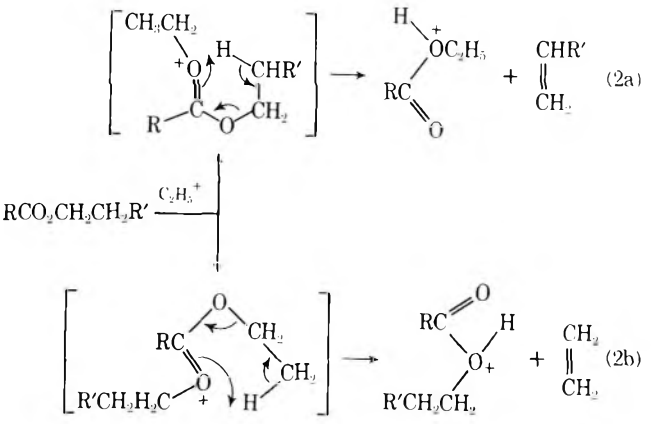
It is of interest to compare the rearrangement decomposition of protonated ethyl acetate in the $CH_4$ CI mass spectrum with the rearrangement decomposition of the moelcular ion of ethyl acetate in the electron ionization (EI) mass spectrum. The formation of $CH_3COOH^+$ from the molecular ion by the McLafferty rearrangement is the comparable process, involving the transfer of only one H (or D) atom. The observed ratio[3] for $(CH_3COOH^+)/(CH_3COOD^+)$ from the high-voltage EI spectrum of $CH_3COOCD_2CH_3$ was 0.7:0.3.

Appreciable scrambling occurs prior to decomposition of the radical molecular ions, $M\cdot^+$, produced by electron ionization. Little scrambling occurs prior to the decomposition of the even-electron $(M + H)^+$ ions produced in the methane CI spectra.

In the $CH_4$ CI spectra of alkyl esters, there were observed[1] ions of the type $RCOHOC_2H_5^+$. It was suggested that these "alkyl exchange" ions could be the result of the decomposition of an intermediate ethyl addition $(M + C_2H_5)^+$ ion (which is observed under some conditions in the $CH_4$ CI spectra of esters). This $(M + C_2H_5)^+$ ion can decompose in two ways (eq 2a and 2b).

Reactions 2a and 2b are, of course, indistinguishble for the unlabeled esters (R′ = H), but would give different products if the original alkyl group were propyl or higher (R′ = $CH_3$, ...). Differentiable products will be produced if the original alkyl group of the ester is labeled, $CH_3COOCD_2CH_3$ and $CH_3COOCD_2CD_3$.

If the proposed mechanism is correct, the displacement reaction (2a) should give $CH_3CO_2HC_2H_5^+$ ions at $m/e$ 89 in the spectrum of $CH_3CO_2CD_2CH_3$ and $CH_3CO_2DC_2H_5^+$ ions at $m/e$ 90 in the spectrum of $CH_3CO_2CD_2CD_3$. Reaction 2b will give $(M + H)^+$ ions at $m/e$ 91 and 94 for these two esters. Reaction 2b cannot be resolved from proton transfer from $CH_5^+$.



In the $CH_4$ CI spectrum of the $\alpha$-dideuterioethyl ester, the abundance of the ion at $m/e$ 89, although small, is significantly higher than the value for $(M - H)^+$ ions in the spectrum of the undeuterated ethyl acetate, $m/e$ 87. This increase in abundance at $m/e$ 89 in the spectrum of $CH_3CO_2CD_2CH_3$ is due to reaction 2a.

The ions expected from reaction 2a with $CH_3CO_2CD_2CD_3$ are observed at $m/e$ 90 and the relative abundance, 2.4% in Table I, is consistent with the amount of reaction 2a observed for $CH_3CO_2CD_2CH_3$, 2.9%.

The difference in relative abundances of $(M + H)^+$ and protonated acid ions between the $C_2D_5$ ester and the other two esters can be attributed to a lower inlet temperature. It was necessary to use lower temperatures for the $C_2D_5$ ester than for the others to reduce surface-catalyzed exchange reactions, which were demonstrated by significant abundances of ions at $m/e$ 89 and 61 from $CH_3COOC_2D_5$ and by the observation of changes in the abundances of these ions with temperature. A decrease in abundance of $(M + H)^+$ and an increase in abundance of $CH_3CO_2H_2^+$ with increasing temperature were observed previously[1] and were also noted in these studies.

In chemical ionization mass spectrometry, the reagent ions may also be labeled in order to study mechanisms. Such experiments have been reported with $CD_4$,[4] $ND_3$,[5] $D_2O$,[6] and $C_4D_{10}$.[7] We have obtained spectra with $CD_4$ of the three labeled ethyl acetates. These perdeuteriomethane spectra are not reported, however, because small amounts of partially deuterated methane and traces of water are present in the reagent and these impurities caused significant amounts of $(M + H)^+$ ions to be present in the spectra. In spite of this complication, several of the postulated[1] reactions can be confirmed.

In our $CD_4$ spectra, predominately $(M + D)^+$ ions are observed. This indicates that the protonated ethyl acetate obtains a hydrogen from the reactant ions. The observation of predominately $CH_3CO_2HD^+$ for $CH_3COOCH_2CH_3$ and $CH_3COOCD_2CH_3$ and of predominately $CH_3CO_2D_2^+$ for $CH_3COOCD_2CD_3$ indicates that one hydrogen of the protonated acid comes from the reactant ion and the other from the alkyl group as predicted by reaction 1. Small amounts of $CH_3CO^+$, $m/e$ 43, are observed (~5%) in the $CD_4$ spectra of the ethyl acetates. This confirms the observations of $CH_3CO^+$ made under high resolution in $CH_4$ CI spectra. Reaction 2a is indicated by the formation of small amounts of $CH_3COHOC_2D_5^+$ ions, $m/e$ 94, in the $CD_4$ spectra of $CH_3COOCH_2CH_3$ and $CH_3COOCD_2CH_3$.

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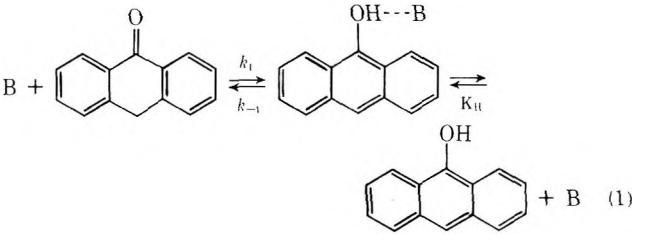
# Communications

## Proton Migration in an Aprotic Solvent Catalyzed by Very Weak Bases

*Summary:* Amides and other weak aqueous bases can in an aprotic solvent effectively catalyze an intramolecular migration of a proton from a carbon atom to a distant oxygen.

*Sir:* Association constants for complexation between *p*-fluorophenol and a wide variety of bases have provided a measure of base strength in $CCl_4$.[1] The logarithms of these constants ($pK_{HB}$'s) do not correlate with $pK_a$ values in water.[2] This has been attributed to a relatively small degree of proton transfer (<30%) within the hydrogen-bonded complexes.[1-3] An alternate explanation for the lack of correlation, namely hydration effects on aqueous basicity, has been rejected.[3,4] The strongest support for the "extent of transfer" hypothesis comes from the observation that upfield F nmr shifts of hydrogen-bonded ion pairs, formed between organic bases and *p*-fluorobenzenesulfonic acid in $CH_2Cl_2$, parallel $pK_a$ rather than $pK_{HB}$.[3]

We have found that extremely weak aqueous bases can assist proton removal from carbon acids in aprotic solvents. Thus, acetamide catalyzes the tautomerization of anthrone to anthranol in acetonitrile. The simplest mechanism for this reaction consistent with the kinetic data is given in eq 1.[5,6] Each of the following reaction variables was determined independently[7] for a variety of bases: $k_1$ (the rate of the base-catalyzed proton removal from the



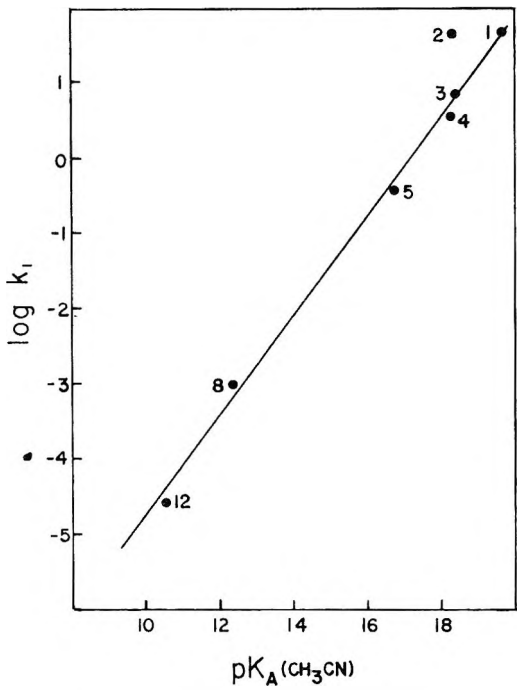



**Figure 1.** Plot of log $k_1$ ($M^{-1}$ sec$^{-1}$) for the base-catalyzed anthrone tautomerization in acetonitrile at 25.0° *vs.* $pK_a$ of the bases in acetonitrile. The numbers refer to the bases in Table I.

carbon acid); $K_1 = k_1/k_{-1}$ (the equilibrium constant relating anthrone with hydrogen-bonded anthranol); and $K_H$ (the association constant for hydrogen bonding between base and anthranol). Acetonitrile was selected as the solvent because this is the only aprotic medium in which $pK_a$ values for several nitrogen and oxygen bases are known.[8-10] Thus, we could compare the response of each of the reaction parameters to basicity as measured by the $pK_a$ in water, $pK_a$ in acetonitrile, and $pK_{HB}$ in carbon tetrachloride.[11] The data are presented in Table I, and the important relationships are summarized below.

1. A plot of log $k_1$ *vs.* $pK_a$ in $CH_3CN$ for *nitrogen* bases is linear with a slope $\beta$ equal to 0.67 (Figure 1).[12] This value of $\beta$ approximates (if the classical treatment is correct[13]) the extent to which the transition state resembles the ion-pair intermediate believed involved in the anthrone tautomerism.[6]

2. There is no correlation between log $k_1$ and $pK_{HB}$ even if one restricts the comparison to nitrogen bases. For example, *n*-butylamine and pyridine have rates differing by 3.56 log units, and yet their $pK_{HB}$ values are similar (2.11 and 1.88, respectively[1]). These results reflect more extensive proton transfer in the transition state of the $k_1$ step relative to that occurring during hydrogen bonding in $CCl_4$.[1-3]

3. Weak oxygen bases such as dimethyl sulfoxide ($pK_a$ = −2.6 in water[2]) and *N,N*-dimethylacetamide ($pK_a$ = −0.39 in water[14]) are surprisingly effective in removing the labile proton from the carbon acid.[15] For example, acetamide is a better catalyst than pyridine, although acetamide is a much weaker base than pyridine in both water and acetonitrile (Table I). A two-point Brønsted plot utilizing $k_1$ and $pK_a$ data in Table I for acetamide and benzamide (two bases of the same "family") shows that $\beta$ is near unity. This implies a large degree of proton transfer in the transition state for the amide-catalyzed proton migration in the aprotic solvent.

4. On the basis of rather limited data, it appears that log $k_1$ for weak bases is unrelated to ion-pair $\Delta$ values[3] (secured from F nmr shifts of *p*-fluorobenzenesulfonic acid ion paired with organic bases in $CH_2Cl_2$). Thus, although *N,N*-dimethylacetamide is a slightly better catalyst than pyridine, the pyridine ion pair displays a chemical shift 1.47 ppm larger than that of the amide.[3,16] The lack of a positive correlation is observed despite the fact that both $k_1$ and $\Delta$ describe ion-pair processes. Clearly, the relationship between basicity and catalytic activity in nonaqueous systems (where solvation does not exert a large leveling effect) can be extraordinarily complex.

**Table I**
**Dependence on Base of the Reaction Parameters for the Catalyzed Tautomerism of Anthrone in Acetonitrile at 25.0°**

| Base | $k_1$, $M^{-1}$ sec$^{-1}$ | $K_1$, $M^{-1}$ | $K_H$, $M^{-1}$ | $pK_A$ ($CH_3CN$) |
|---|---|---|---|---|
| Pyrrolidine | 49 | 36 | 1400 | 19.58[b] |
| Dabco[a] | 45 | 88 | 3500 | 18.29[b] |
| Triethylamine | 7.3 | 0.21 | 7.7 | 18.46[b] |
| *n*-Butylamine | 3.6 | 33 | 1000 | 18.26[b] |
| Benzylamine | $3.9 \times 10^{-1}$ | 8.1 | 340 | 16.76[b] |
| Acetamide | $2.2 \times 10^{-2}$ | 0.061 | 2.3 | 6.0[c] |
| *N,N*-Dimethylacetamide | $1.8 \times 10^{-3}$ | 0.036 | 2.1 | |
| Pyridine | $1.0 \times 10^{-3}$ | 0.13 | 4.7 | 12.33[b] |
| Dimethylsulfoxide | $5.5 \times 10^{-4}$ | 0.072 | 2.7 | 5.8[c] |
| *N,N*-Dimethylaniline | $1.3 \times 10^{-4}$ | 0.078 | 3.8 | |
| Benzamide | $1.2 \times 10^{-4}$ | 0.074 | 2.8 | 3.8[c] |
| Aniline | $2.7 \times 10^{-5}$ | 0.024 | 1.7 | 10.56[b] |

[a] Triethylenediamine. [b] Reference 8. [c] Reference 9.

5. Plots of log $K_1$ and log $K_H$ *vs.* $pK_a$ of nitrogen bases in $CH_3CN$ are linear and have slopes of 0.38 ± 0.05. These slopes, which indicate only moderate proton transfer from hydroxyl groups to amine, seem reasonable in light of previous work on acid-base behavior in acetonitrile.[17,18] Plots of log $K_1$ and log $K_H$ *vs.* $pK_a$ show large positive and negative deviations for Dabco and triethylamine, respectively. Undoubtedly, the peri hydrogens in proximity to the hydroxyl group of anthranol enhance the sensitivity of the hydrogen bonding to the steric properties of the bases.

In summary, we have found that weak aqueous bases in an aprotic solvent can effectively catalyze the migration of a proton from a carbon atom to a distant oxygen. The reaction occurs with considerable proton transfer to the bases. We presume that the bases associate with the labile proton as the proton migrates intramolecularly[6] along the anthrone orbitals from carbon to oxygen. The remarkable ability of extremely poor aqueous bases such as amides to promote the anthrone tautomerism supports the idea that weak bases might function catalytically at hydrophobic sites of enzymes.[11,19]

**Acknowledgment.** This work was supported in part by grants from the National Science Foundation and the National Institutes of Health.

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$$\frac{1}{(\epsilon_e - \epsilon_K)C_K d}\left(\frac{dA}{dt}\right)_{t=0} = k_1 B$$

(8) J. F. Coetzee and G. R. Padmanabhan, *J. Amer. Chem. Soc.*, **87**, 5005 (1965).
(9) I. M. Kolthoff and M. K. Chantooni, *J. Amer. Chem. Soc.*, **95**, 8539 (1973).
(10) On the other hand, acetonitrile has two (surmountable) disadvantages: anthrone tautomerizes spontaneously in this solvent and anthranol hydrogen bonds weakly to acetonitrile.
(11) See also P. W. Arana, C. W. Su, and J. W. Watson, *Chem. Commun.*, 363 (1970).
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(14) P. Haake, R. D. Cook, and G. H. Hurst, *J. Amer. Chem. Soc.*, **89**, 2650 (1967).
(15) A qualitative explanation for the reactivity of weak oxygen bases in terms of Linnett theory may be found in the Ph.D. thesis of R. F. Williams (see footnote 7).
(16) The magnitude of 1.47 ppm may be gauged from the 2.57-ppm shift of *sym*-tetramethylguanidine relative to that of *N,N*-dimethylacetamide (the strongest and weakest bases recorded in ref 3).
(17) Phenoxide is a stronger base than triethylamine in acetonitrile by more than 8 $pK_a$ units: J. F. Coetzee, *Progr. Phys. Org. Chem.*, **4**, 45 (1967).
(18) H. Baba, A. Matsuyama, and H. Kokubun, *Spectrochim. Acta*, **25A**, 1709 (1969), have found that *p*-nitrophenol and triethylamine form solvent-separated ion pairs in acetonitrile. However, anthranol (with a $pK_a$ in acetonitrile probably six units greater than that of *p*-nitrophenol)[17] would not be expected to form ion pairs.
(19) F. M. Menger and A. C. Vitale, *J. Amer. Chem. Soc.*, **95**, 4931 (1973).
(20) Recipient of a Camille and Henry Dreyfus Foundation Teacher-Scholar Grant and a National Institutes of Health Research Career Development Award.

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## Organoselenium Chemistry. Conversion of Cyclic Ketones and β-Dicarbonyl Compounds to Enones

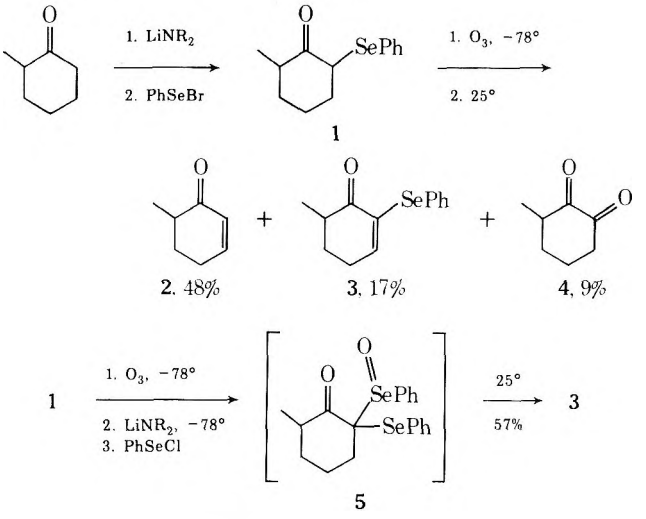
*Summary:* The selenoxide syn elimination method for the synthesis of enones has been extended to the preparation of β-dicarbonyl enones, cyclobutenones, and enone ketals; and an important limitation to the method has been found.

*Sir:* The syn elimination of selenoxides has been shown to be a convenient, mild, and high-yield method for the preparation of α,β-unsaturated carbonyl compounds.[1,2] The precursor α-phenylselenocarbonyl compounds can be prepared from ketones, aldehydes, and esters,[1,2] as well as from enol acetates[1b,2b] and acetylenes.[1b] We describe here some limitations of the method not heretofore recognized, as well as extensions to four-membered rings and β-dicarbonyl compounds.

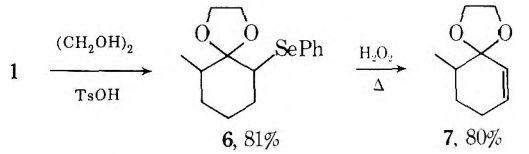
The necessity for achieving a cyclic transition state in the selenoxide elimination[3] may impose conflicting conformational demands on cyclic systems, and in fact only a limited range of cyclic enones (five- and six-membered rings) have been prepared. Our inability to achieve a high yield transformation of 2-methyl-6-phenylselenocylohexanone (**1**) to the enone (**2**)[1a] led us to examine this reaction in more detail (Scheme I). The formation of by-products **3** and **4** can be rationalized as resulting from a Pummerer-like reaction of the ketoselenoxide. 2-Phenyl-6-phenylselenocyclohexanone[6] also gives only a fair yield of enone, but the isomeric 2-phenylseleno compound, in which the phenyl substituent prevents the Pummerer reaction, gives enone in high yield (Table I). Scheme I also presents an alternate synthesis of the vinyl selenide **3** by selenenylation of the ketoselenoxide.

Both 2-phenylselenocycloheptanone and -cyclooctanone give only small amounts of enone (5–15%) under all conditions we have tried. If the oxidation is carried out using sodium metaperiodate buffered with sodium bicarbonate, 33 and 48%, respectively, of the vinyl selenides analogous to **3** are formed.

**Scheme I**




The occurrence of a facile Pummerer reaction depends on the acidifying effect of the carbonyl group on the α proton. Hence it is not surprising that the ketal **6** undergoes oxidation[8a] and elimination[8b] to enone ketal **7** in

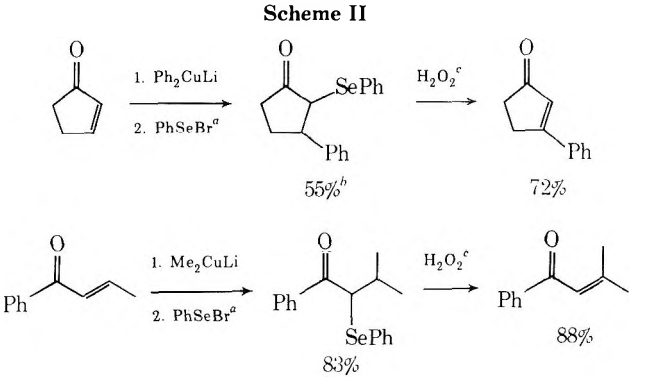



good yield. 2-Phenylselenocycloheptanone can similarly be converted to the ethylene ketal of cycloheptenone in 68% yield.

Table I shows several examples of the preparation of cyclopentenones[9a] and cyclobutenes. The great facility with which cyclobutanones undergo Baeyer–Villiger oxidation necessitates the use of ozone as oxidant[10] for the preparation of 3-phenyl-2-cyclobutenone.[11] Scheme II presents two examples which illustrate the ability to trap copper enolates with PhSeBr for the synthesis of β-substituted enones.

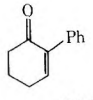
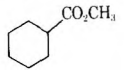
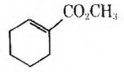
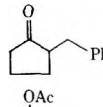
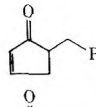
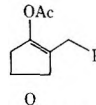
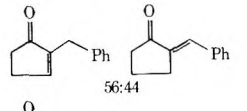
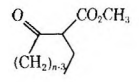
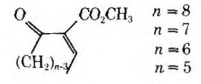
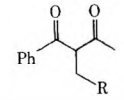
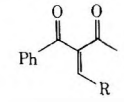
The extension of the selenoxide elimination to the synthesis of enediones from β-dicarbonyl compounds is an important one, since such transformations are difficult using classical methods.[12] The dehydrohalogenation in particular often fails because of instability of halodicar-

**Scheme II**




[a] Total quantity of PhSeBr used was 10% excess over RLi used in the preparation of the cuprate. A small amount of $Ph_2Se_2$ was added to suppress formation of α-halo ketones. [b] Both cis and trans isomers (1:4.5) appeared to give enone. [c] Reference 8a.

**Table I**
**Preparation of α,β-Unsaturated Carbonyl Compounds**

| Compd | Olefin | Yield,[a] % Selenide | Yield,[a] % Olefin |
|---|---|---|---|
|  |  | | 60[b-d] |
|  |  | 86[e] | 94[d] |
|  |  | | 96[b,e,f] |
|  |  | | 66[b-d] |
|  |  56:44 | 96[g] | 95[d] |
|  |  | 87[e] | 83[d] |
|  |  | 47[e] | 58[h] |
|  |  $n=8$ $n=7$ $n=6$ $n=5$ | 96[i] 90[i] | 93[d] 93[d] 81[b,f,g] 28[b,f,g] |
|  |  | 86[i] | 90[h] |
|  |  R = H R = *n*-Pr | 93[i] 96[i] | 80[d] 93[d,g] |

[a] All compounds were fully characterized by spectral methods. [b] Overall yield. [c] Selenide was prepared by the reaction of lithium enolate (LiN-*i*-Pr$_2$) with PhSeBr or PhSeCl at −78°. [d] Oxidation of selenide with $H_2O_2$ in $CH_2Cl_2$; see ref 8a. [e] Selenide was prepared by reaction of lithium enolate (from cleavage of enol acetate with MeLi) with PhSeBr at −78°. [f] One pot procedure described in ref 1a. [g] Selenide prepared by reaction of enol acetate with $PhSeO_2CCF_3$; see ref 1b. [h] Oxidation by ozonolysis in $CH_2Cl_2$ at −78°, followed by warming to 25°. [i] Selenide prepared by the reaction of sodium enolate (NaH) in THF with PhSeCl or PhSeBr. [j] A 95:5 mixture of geometric isomers is formed.

bonyl compounds or enones under the reaction conditions. We have found the method to work superbly for the eight, seven and six-membered 2-carboethoxycloalkenones, a result which underscores the conclusions reached above that reactions involving the acidic α hydrogen, were responsible for the failure to achieve high yield syntheses of cyloctenone or cycloheptenone itself. Hydrogen peroxide cannot to be used as oxidant for the five-[13] and six-membered cyclic ketones, since rapid epoxide formation and further degradation occurs. Here ozonolysis at −78° followed by warming is the best procedure[10] (elimination occurs at or below −10°).

An important consequence of the mild reaction conditions is that in all cases exclusively nonenolized β-dicarbonyl enones are formed, even though a number of these systems are known to be significantly or even predominantly enolic at equilibrium.[12] Other synthetic methods invariably give a mixture of keto and enol forms.

The preparation of α-phenylseleno-β-dicarbonyl compounds is conveniently carried out at room temperature by the addition of ketone to a suspension of NaH (excess) in THF. When hydrogen evolution is complete (<15 min) a solution of 1.05 equiv of PhSeCl (or PhSeBr) in THF is added dropwise, and the reaction is immediately poured into ether and saturated $NaHCO_3$ solution. Completion of the work-up gives the selenide in quantitative yield. Oxidation is then carried out either by the $H_2O_2$-$CH_2Cl_2$ method[8a] or by ozonolysis.

**Acknowledgment.** We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work, and the Du Pont Co. for a Du Pont Young Faculty Grant (to H. J. R.).

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(4) D. N. Jones, D. Mundy, and R. D. Whitehouse, *Chem. Commun.*, 86 (1970).
(5) K. B. Sharpless, M. W. Young, and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973).
(6) The deprotonation of 2-phenylcyclohexanone using LiN-*i*-Pr$_2$ in THF occurs 99:1 in favor of the secondary position (glc analysis of enol acetates). Acid-catalyzed ($HClO_4$) formation of enol acetates gives a 90:10 mixture, with phenyl-substituted olefin predominating. See B. Miller and H. S. Wong [*Tetrahedron*, **28**, 2369 (1972)] for a study of the bromination and dehydrobromination of 2-phenylcyclohexanone.

(7) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).
(8) (a) Oxidation was carried out by magnetically stirring a solution of the selenide in methylene chloride containing 2 equiv of pyridine with 5 to 10 equiv of 15% aqueous hydrogen peroxide for ~10 min, when oxidation is usually complete (in a few cases the thermal elimination requires somewhat longer reaction times). We have found these conditions for oxidation and elimination to be superior in convenience and purity and yield of products to other methods for any selenide where the olefin product is not attacked rapidly by hydrogen peroxide. (b) Oxidation at room temperature as above gave selenoxide; elimination was completed by refluxing for 5 min in $CCl_4$ containing 2 equiv of pyridine. This is the only selenoxide among those described here which does not eliminate readily at or below room temperature.
(9) (a) Positional control during synthesis of enones by dehydrobromination of α-halo ketones has been achieved using a similar technique.[9b] (b) P. L. Stotter and K. A. Hill, *J. Org. Chem.*, **38**, 2576 (1973).
(10) Under these conditions ⅔ of the selenium is recovered in the product as $Ph_2Se_2$; the remainder is removed as $PhSeO_2H$ in the workup.
(11) S. L. Manatt, M. Vogel, D. Knutson, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2645 (1964).
(12) (a) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957); (b) C. W. T. Hussey and A. R. Pinder, *ibid.*, 3525 (1961); (c) C. W. T. Hussey and A. R. Pinder, *ibid.*, 1517 (1962); (d) J. E. Brenner, *J. Org. Chem.*, **26**, 22 (1961); (e) D. Gorenstein and F. H. Westheimer, *J. Amer. Chem. Soc.*, **92**, 634 (1970).
(13) J. N. Marx, J. H. Cox, and L. R. Norman [*J. Org. Chem.*, **37**, 4489 (1972)] have dehydrogenated 2-carbomethoxycyclopentanone with $SeO_2$ in 48% yield. They also were unable to purify their reaction product.

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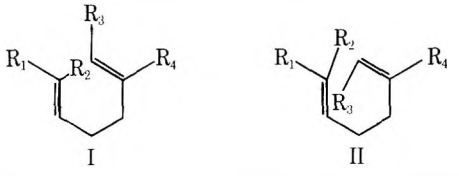
## A General 1,5-Diene Synthesis. Application to the Synthesis of Squalene

*Summary:* A new method for the preparation of geometrically pure 1,5-dienes *via* coupling of allylic sulfones with allylic halides followed by reductive cleavage of the allylated sulfones is described.

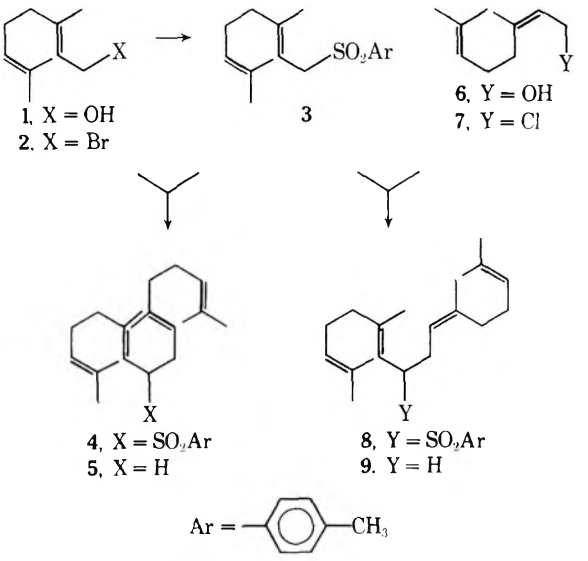
*Sir:* The construction of 1,5-dienes of types I and II involving over-all allyl alcohol coupling with geometrical and positional control has recently received attention as a result of the importance and general utility of such systems for the synthesis of juvenile hormones and cyclic terpenoid or steroidal precursors. In conjunction with another project we required a method for carbon–carbon bond formation with formation of a 1,5-diene unit.[1]




We wish to report a new method for the preparation of geometrically pure 1,5-dienes *via* coupling of allylic alcohol units which proceeds in good yields with essentially complete preservation of the geometry and position of the olefinic bonds.

The over-all synthetic sequence involves (1) conversion of the allylic alcohols to allylic bromides, (2) sulfone formation with one of the allylic bromides, (3) C-allylation of the desired stabilized allyl carbanion with another allylic bromide unit, and (4) reductive cleavage of the new sulfone. The complete process can be conveniently carried out in 60–70% yield with <1–2% isomerization, either positional or cis-trans.

Treatment of pure *trans*-geraniol (**1**) in anhydrous ether with $PBr_3$ at 0° afforded *trans*-geranyl bromide (**2**) in near-quantitative yield. Treatment of **2** with sodium *p*-toluenesulfinate in anhydrous DMF at ambient temperature for 18 hr gave *trans*-geranyl *p*-tolyl sulfone **3** in 98% yield. Metalation of sulfone **3** at −20° with *n*-butyllithium in tetrahydrofuran–hexamethylphosphoramide (4:1) followed by cooling to −78° and addition of *trans*-geranyl bromide resulted in formation of pure sulfone **4** (89%



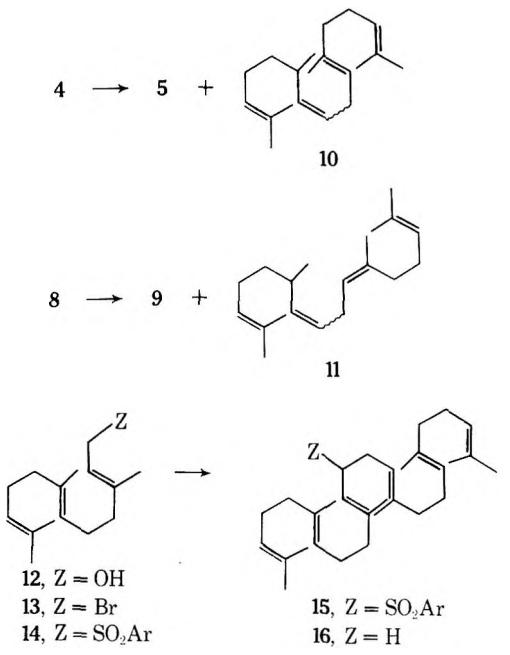

yield). Nmr analysis of the coupled sulfone revealed lack of aliphatic methyl resonance, a consequence of coupling at the γ position. In addition the nmr spectrum of **4** revealed no terminal vinyl resonance. Geometrical isomerization was rigorously ruled out by coupling of cis- and trans-allylic isomers and glpc comparison of the respective products derived from reduction cleavage of the sulfone moiety (*vide infra*).

The new sulfone **4** was purified and reduced at 0° with lithium in ethylamine under a nitrogen atmosphere. After stirring for 30 min the reaction mixture was worked up in the standard manner and the product chromatographed on silica gel to yield pure all-trans bisgeranyl **5**[2] (77%) [the ratio of cis:trans allylic methyl groups at δ 1.58 and 1.67 was 2.0:1.0 as anticipated for pure trans,trans compound].

Coupling of *trans*-geranyl sulfone **3** with neryl chloride[1d] **7** as described gave sulfone **8** (71%). Reductive cleavage of the sulfone provided an 82% yield of *cis,trans*-nerylgeranyl **9** [nmr ratio of cis:trans allylic methyl groups was 1.0:1.0 as expected for pure cis,trans compounds]. Bisgeranyl **5** and nerylgeranyl **9** are readily separable by glpc and the products of the above couplings indicated <1–2% contamination.

Although the cleavage of the carbon–sulfur bond with lithium in ethylamine proved to be satisfactory, we had initially hoped to be able to perform the required cleavage reaction under milder reaction conditions. Dabby and coworkers[3] have reported that the C–S bond of sulfones can be cleaved with sodium amalgam. To investigate this carbon–sulfur cleavage reaction sulfone **4** was treated with 3% sodium amalgam[4] in ethanol for 1.5 hr. In addition to the expected all-trans tetraene **5** there was obtained the rearranged tetraene **10** in a ratio of 9:4 (90%). making this procedure unattractive from a synthetic viewpoint. Use of hexamethylphosphoramide in ethanol (6:1) resulted in an 11:6 mixture of **5** and **10**, respectively. In the case of **8**, use of HMPA resulted in a 2:1 mixture of **9** and **11**.

In a similar fashion employing the procedures developed above, we have prepared *all-trans*-squalene **16** from pure *trans,trans*-farnesol **12**.[5]




Treatment of *trans,trans*-farnesol **12** in acetonitrile with carbon tetrabromide and triphenylphosphine[1f] afforded pure *trans,trans*-farnesyl bromide **13** in 90% yield. Reaction of the bromide with sodium *p*-toluenesulfinate in anhydrous dimethylformamide at ambient temperature overnight gave *trans,trans*-farnesyl *p*-tolyl sulfone **14** in 97% yield. Generation of the carbanion from **14** in tetrahydrofuran at −20° with *n*-butyllithium followed by cooling to −78° and addition of 1 equiv of *trans,trans*-farnesyl bromide **13** gave after gradual warming to 0° the pure coupled sulfone **15** in 86% yield after chromatography on silica gel. Nmr analysis of **15** revealed lack of aliphatic methyl resonance.

Cleavage of the carbon–sulfur bond of **15** was conveniently carried out at −78° with lithium in ethylamine. After stirring for 20 min, the reaction mixture was quenched with 1,3-butadiene and the crude product (96%) was chromatographed on silica gel to yield pure (homogeneous by glpc) *all-trans*-squalene **16** (80%), identical with an authentic sample by nmr (ratio of cis:trans allylic methyl groups 3.0:1.0).

**Acknowledgment.** We thank Eli Lilly and Co. for generous support of our research and Dr. Bernard J. Kane, Glidden-Durkee, Jacksonville, Fla., for generous gifts of pure geraniol and pure nerol.

## References and Notes

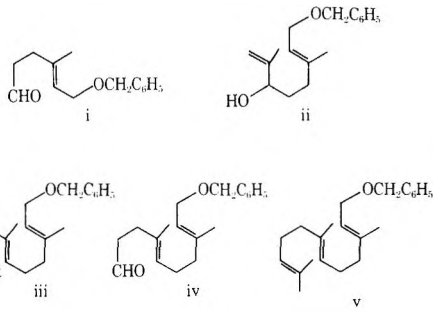
(1) For existing 1,5-diene syntheses see (a) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, **87**, 3277 (1965); (b) E. J. Corey and M. F. Semmelhack, *ibid.*, **89**, 2755 (1967); (c) K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, *ibid.*, **90**, 209 (1968); (d) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969); (e) J. F. Biellman and J. B. Ducep, *ibid.*, 3707 (1969); (f) E. H. Axelrod, G. M. Milne, and E. E. Tamelen, *J. Amer. Chem. Soc.*, **92**, 2139 (1970); (g) K. Hirai, H. Matsuda, and Y. Kishida, *Tetrahedron Lett.*, 4359 (1971); (h) J. A. Katzellenbogen and R. S. Lenox, *ibid.*, 1471 (1972).

(2) Satisfactory nmr, tlc, glpc, and analytical data were obtained for all compounds.

(3) R. E. Dabby, J. Kenyon, and R. F. Mason, *J. Chem. Soc.*, 4881 (1952); also see M. Julia and P. Ward, *Bull. Soc. Chim. Fr.*, 3065 (1973), and references cited therein.

(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1968, p 1030.

(5) Synthesis of *trans,trans*-farnesol: *trans*-geraniol was protected by O-benzylation[1c] (sodium hydride followed by benzyl bromide in glyme) followed by cleavage (ozone–methanol;[6] dimethyl sulfide[7]) of the isopropylidene terminus resulting in the formation of aldehyde *i*. The 6,7-trans-trisubstituted double bond was constructed by reaction with isopropenylmagnesium bromide affording allylic alcohol ii which upon Claisen rearrangement[8] with ethyl orthoacetate gave diene ester iii. Lithium aluminum hydride reduction followed by Collins oxidation[9] afforded the aldehyde iv. Reaction of iv with isopropyltriphenylphosphorane gave pure *all-trans*-farnesyl benzyl ether v, which was cleaved by treatment with lithium in ethylamine at −78°.




(6) G. Stork, M. Gregson, and P. A. Grieco, *Tetrahedron Lett.*, 1391 (1969).

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(8) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

(9) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

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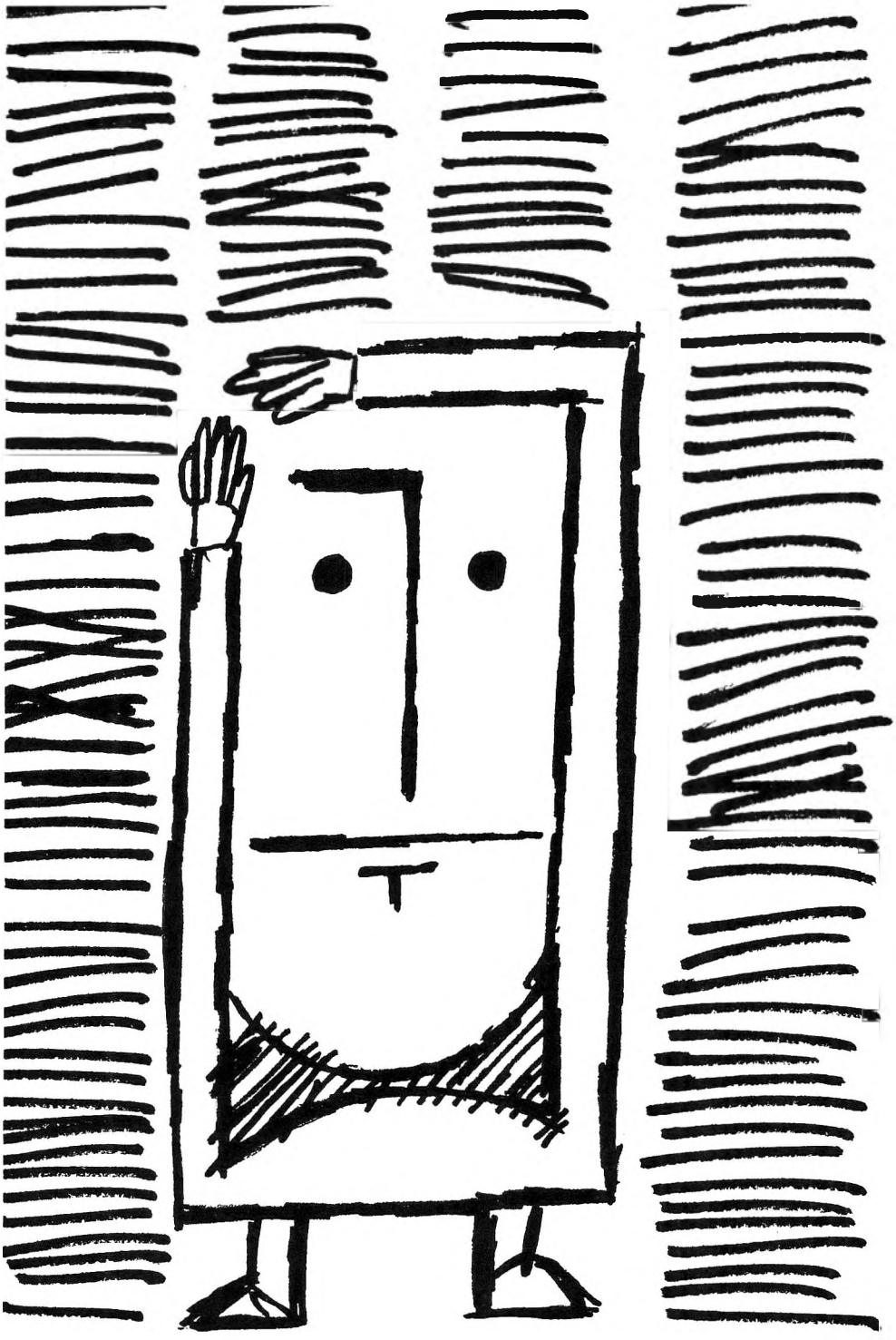

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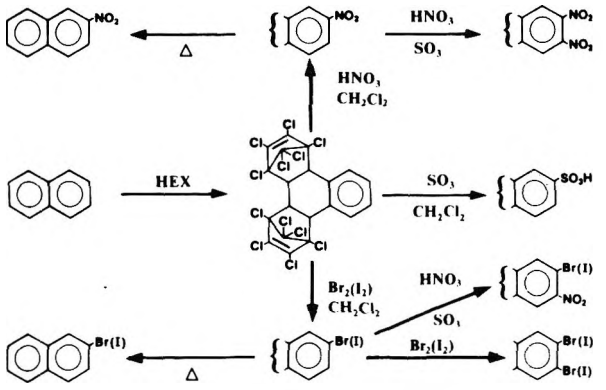
# The Great Aldrich Time Saver: DHA

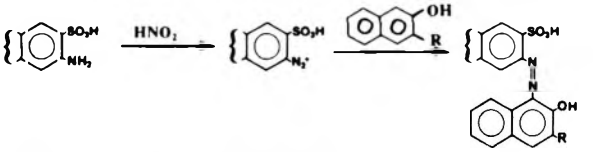
## β-Substituted Naphthalenes were once nearly unobtainable. But you'll find them listed in our book, ready for delivery.

No other bicyclic aromatic system has been studied as thoroughly as naphthalene; yet a number of simple derivatives such as 2-bromo- and 2-nitronaphthalene are exceedingly difficult to prepare and therefore have had limited use.[1] Hyman and co-workers[2] have shown that these compounds may be prepared *via* the Diels-Alder adduct of naphthalene and hexachlorocyclopentadiene (HEX). Naphthalene serves as a dienophile provided that the diene used is sufficiently stable to allow a high temperature reaction. Naphthalene reacts with HEX at high temperature to form a diadduct (DHA) which can then be nitrated and halogenated in the β-position of ring A.[1] Since the Diels-Alder reaction is reversible, pyrolysis of the 2-nitro- or 2-halogeno-DHA gives the otherwise difficult-to-synthesize 2-nitro- or 2-halogenonaphthalene.[1]

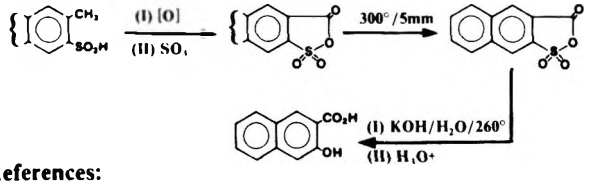



The DHA adducts may also be sulfonated or further halogenated or nitrated to give highly substituted DHA derivatives. Oxidation of the DHA adduct of 2-methylnaphthalene with concentrated nitric acid gives DHA-2-carboxylic acid which can be nitrated to give 3-nitro-DHA-2-carboxylic acid.[1] These DHA derivatives readily undergo reverse Diels-Alder reactions at 250 - 400° in a molecular still apparatus.[1]

DHA provides a means of avoiding the use of the carcinogenic β-naphthylamine in the preparation of dyestuffs. For example, 2-amino-DHA-3-sulfonic acid can be diazotized and coupled with phenols to give dyes with probable flame-retarding properties.[1]




In addition, sulfonated 2-methyl-DHA is the basis of a new process for synthesizing 3-hydroxy-2-naphthoic acid, an important dye intermediate.[1]

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1) M. Look, *Aldrichimica Acta*, 7, 22 (1974).
2) J. Hyman and A.A. Danish, U.S. Patent 2,658,927 (1953).


| | | |
|---|---|---|
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