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THE JOURNAL OF Organic Chemistry

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NOTES

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Thermal Decomposition of Tertiary Alkyl Peroxides. Substituent Effects in Peroxide Bond Homolysis and β Scission of Alkoxy Radicals

W. H. RICHARDSON,* M. B. YELVINGTON, A. H. ANDRIST,[1a] E. W. ERTLEY,[1b] R. S. SMITH, AND T. D. JOHNSON

Department of Chemistry, California State University, San Diego, San Diego, California 92115

Received May 11, 1973

Rate coefficients for the thermal decomposition of a series of substituted tertiary alkyl peroxides in chlorobenzene at 150° were obtained. The sum of the polar substituent constant ranged over approximately one unit for the peroxides to give $\log k + 4 = (-0.131 \pm 0.030)\Sigma\sigma^* + 0.578$. From this correlation, the reaction constants ρ_I and f were calculated to be −0.291 and −0.175, respectively. The corresponding reaction constants for meta-substituted benzoyl peroxides, obtained from a multiple-linear-regression analysis of published data in dioxane at 80°, are $\rho_I = -0.327$ and $f = -0.174$. For comparison to alkyl peroxides, the latter values were corrected to 150°, where $\rho_I = -0.273$ and $f = -0.145$. Considering the change in solvent and approximations in relating alkyl peroxide and benzoyl peroxide reaction constants, there appears to be little difference in substituent effects between these two types of peroxides. Alkyl peroxides of the type $(CH_3)_3COOC(CH_3)_2R$ with R = CH_2OH (**7**) or COOH (**8**) showed unusually fast rates of decomposition and enhanced yields of *tert*-butyl alcohol. The alcohol **7** also showed a small deuterium isotope effect ($k_H/k_D = 1.35$). Mechanistic schemes are considered to explain the kinetic data, as well as the products from **7** and **8**. Substituent effects in β scission of unsymmetrically substituted *tert*-alkoxy radicals, produced from alkyl peroxides, are reported. These data are considered in terms of a Polanyi relationship.

Certain peroxides undergo reaction by ionic pathways;[2] however, free-radical decomposition looms as an alternative process. In order to use kinetic data to distinguish between ionic and radical processes, it is sometimes necessary to estimate rates of radical decomposition of peroxides from substituent effect correlations. This situation arose in a study of the neighboring *tert*-butylperoxy group.[3] Although a substituent effect correlation is reported for the radical decomposition of benzoyl peroxides,[4,5] no such correlations are reported for alkyl peroxides. The reported kinetic data for alkyl peroxides are devoted to variations in alkyl and aryl alkyl hydrocarbon substituents, where there are small changes in the substituent constant.[5,6] Furthermore, primary and secondary alkyl peroxides are included in these data, which are subject to induced decomposition and can then lead to erroneous rate data.[5,6b] For these reasons, we have obtained kinetic data for the thermal decomposition of *tertiary* alkyl peroxides, where the sum of the polar substituent constant for the groups vary over approximately 1.0 σ^* unit.

In the course of this study, it was noted that peroxides of the type $(CH_3)_3COOC(CH_3)_2R$ with R = CH_2OH or COOH undergo unusually rapid decomposition and give enhanced yields of *tert*-butyl alcohol. Possible explanations for these observations are considered. In addition, product studies from the thermal decomposition of alkyl peroxides allowed us to calculate relative rates of β scission from unsymmetrically substituted *tert*-alkoxy radicals.

Results

Kinetic data were obtained by following the rate of disappearance of the peroxides by glc and the results are given in Table I. Tertiary alkyl peroxides are not highly susceptible to induced decomposition in most solvents,[5-7] but in order to suppress this potential reaction 2,6-di-*tert*-butyl-*p*-cresol or styrene were used as radical traps. The rate coefficient (4.6×10^{-4} sec^{-1}) for thermolysis of *tert*-butyl peroxide in benzene at 150°, calculated from reported activation param-

(1) National Science Foundation Undergraduate Research Participant: (a) summer 1965; (b) summer 1968.

(2) R. Curci and J. O. Edwards, "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, p 199.

(3) W. H. Richardson, M. B. Yelvington, J. J. Manness, and T. D. Johnson, unpublished data.

(4) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *J. Amer. Chem. Soc.*, **72**, 5426 (1950).

(5) For a review see W. H. Richardson and H. E. O'Neal, "Comprehensive Chemical Kinetics," Vol. 5, C. F. H. Tipper and C. H. Bamford, Ed., Elsevier, New York, N. Y., 1971, Chapter 4.

(6) For reviews see (a) P. Molyneux, *Tetrahedron*, **22**, 2929 (1966); (b) S. W. Benson and R. Shaw, "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, p 105.

(7) (a) S. H. Goh and S. H. Ong, *J. Chem. Soc. B*, 870 (1970); (b) S. H. Goh, *J. Org. Chem.*, **37**, 3098 (1972); (c) E. S. Huyser and C. J. Bredeweg, *J. Amer. Chem. Soc.*, **86**, 2401 (1964).

TABLE I

RATE COEFFICIENTS FOR THE THERMAL DECOMPOSITION OF TERTIARY ALKYL PEROXIDES IN CHLOROBENZENE AT 150°

Peroxide (P)[a]	$10^2[P]_0$, M	10^4k,[d] sec^{-1}	$\Sigma\sigma^*$
$(CH_3)_3COOC(CH_3)_3$ (1)[a]	7.93	4.45 ± 0.08	−0.600
$(CH_3)_3COOC(CH_3)_2CO_2$-CH_3 (2)[a]	6.24	4.68 ± 0.08	+0.234
$(CH_3)_3COOC(CH_3)_2CH_2Cl$ (3)[a]	4.99	4.15 ± 0.05	−0.115
$ClCH_2(CH_3)_2COOC$-$(CH_3)_2CH_2Cl$ (4)[a]	6.27	3.11 ± 0.08	+0.390
$(CH_3)_3COOC(CH_3)_2$-CH_2Br (5)[a]	4.98	3.63 ± 0.04	−0.133
$(CH_3)_3COOC(CH_3)_2$-CH_2OCOCH_3 (6)[a]	4.88	4.12 ± 0.08	−0.174
$(CH_3)_3COOC(CH_3)_2$-CH_2OH (7)[b]	7.62	16.1 ± 0.5	−0.296
$(CH_3)_3COOC(CH_3)_2$-CH_2OD (7D)[b]	5.11	12.3 ± 0.4[e]	−0.296
$(CH_3)_3COOC(CH_3)_2CO_2H$ (8)[c]	7.00	24.0	+0.550

[a] With 0.005 M 2,6-di-*tert*-butyl-*p*-cresol. [b] With 0.102 M styrene. [c] Without a radical trap and the rate coefficient is calculated from activation parameters: W. H. Richardson and R. S. Smith, *J. Amer. Chem. Soc.*, 91, 3610 (1969). [d] By least-squares fit with probable error. [e] 7D is 90% deuterated. No correction is made for partial deuteration; however the corrected value is $11.9 \pm 0.4 \times 10^{-4}$ sec^{-1}.

eters ($\Delta H^{\pm}$ = 35 kcal/mol and $\Delta S^{\pm}$ = 8 eu),[8] is in good agreement with our value (4.45×10^{-4} sec^{-1} at 150°) in chlorobenzene. These rate coefficients are greater than those calculated for *tert*-butyl peroxide at 150° in *tert*-butylbenzene (2.8×10^{-4} sec^{-1}, E_a = 38.0 kcal/mol, log A = 16.04)[9] and cumene (2.9×10^{-4} sec^{-1}, E_a = 37.5 kcal/mol, log A = 15.80).[9] The increased rate of decomposition of *tert*-butyl peroxide in chlorobenzene relative to *tert*-butylbenzene (1.4-fold at 110°) was noted previously.[7a] The origin of this increase in rate is uncertain in chlorobenzene and benzene, but induced decomposition was considered unlikely in the latter solvent.[7c]

Table I also includes the sum of the polar substituent constants for each peroxide. Where polar substituent constants are not reported[10] for R in ROOR, they are calculated.[11] With the omission of peroxides **7** and **8**, the data from Table I give $\rho^* = -0.131 \pm 0.030$ with probable error (eq 1). The mechanism of decomposition of the omitted peroxides **7** and **8** is considered later.

$$\log k + 4 = (-0.131 \pm 0.030)\Sigma\sigma^* + 0.578 \quad (1)$$

Yields of acetone and *tert*-butyl alcohol from thermolysis of the peroxides are given in Table II. Products from **3** were not determined, but yields of products can be reasonably estimated from the data for **1** and **4**. The latter two peroxides serve to predict acetone and *tert*-butyl alcohol yields from *tert*-butoxy and chloro-*tert*-butoxy radicals, respectively. Thus, the predicted yields of acetone and *tert*-butyl alcohol for **3** are 1.87 and 0.005 mmol/mmol **3**, respectively. We estimate the error in yields given in Table II to be approximately ±5%.

(8) E. S. Huyser, "Free-Radical Chain Reaction," Wiley-Interscience, New York, N. Y., 1970, p 272.

(9) J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, 70, 1336 (1948).

(10) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 222.

(11) Reference 10, p 224.

TABLE II

PRODUCT STUDIES FOR THE DECOMPOSITION OF ALKYL PEROXIDES AT 150° IN CHLOROBENZENE

Peroxide (P)	$10^2[P]_0$, M	Yield[a] CH_3COCH_3	Yield[a] t-C_4H_9OH
1	7.29	1.99	0.011
1[b]	6.44	1.86	0.23
2	6.24	1.91	0.055
4	6.27	0.87	
5	14.0	1.30	0.010
6	9.50	1.50	0.12
7	3.09	1.35	0.51
7[b]	7.62	1.74	0.39
8	7.00	1.30	0.73

[a] Millimoles of product/millimoles of peroxide. [b] With 0.102 M styrene.

Discussion

Substituent Effect Correlations.—Prior to this study, the effect of substituents on the rate of homolysis of the peroxide bond rested on the thermal decomposition of aroyl peroxides.[4] Although substituents have been varied in other peroxide decompositions, the kinetic data are unsuitable for LFE correlations with homolysis of the peroxide bond. In the alkyl peroxide series, changes in the substituents amounted to small changes in σ^*. Furthermore, the variations included primary and secondary groups, which are susceptible to induced decomposition.[5,6b] There are other instances where substituent effects were determined, but simple homolysis of the peroxide bond does not occur. For example, multibond homolysis occurs with certain substituted peresters, where both the peroxide bond and the alkyl carbon–acyl carbon bond are broken in the transition state.[5,12] Also, some acyl peroxides undergo an inversion mechanism in their decomposition, which is not simply related to O–O bond homolysis.[5,13]

Benzoyl peroxide decompositions were originally correlated by the Hammett equation to give $\rho = -0.38$ at 80° in dioxane with 0.2 M 3,4-dichlorostyrene.[4,14] Unfortunately, this ρ value cannot be directly compared to the ρ^* value obtained for alkyl peroxides. To relate substituent effects in benzoyl peroxides to those observed in alkyl peroxides, a common reaction constant must be employed first for both series. The ρ_I constant is appropriate for this purpose, where $\rho_I = \rho^*/0.45$.[16] Thus, from eq 1 the alkyl peroxides give $\rho_I = -0.291 \pm 0.067$ [= $(-0.131 \pm 0.030)/0.45$]. A multiple-linear-regression analysis of the rate coefficients for decomposition of meta-substituted benzoyl peroxides[4] with eq 2 gives $\rho_I = -0.317 \pm 0.056$ and $\rho_R = -0.361$

$$\log k/k_0 = \rho_I\sigma_I + \rho_R\sigma_R^0 \quad (2)$$

± 0.065 with a standard error in log k/k_0 of ±0.0520 and r (correlation coefficient) = 0.974. If the m,m'-

(12) *Cf.* (a) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, 80, 1398 (1958); (b) C. Rüchardt and H. Böck, *Chem. Ber.*, 104, 577 (1971); (c) A. I. Dalton and T. T. Tidwell, *J. Org. Chem.*, 37, 1504 (1972).

(13) (a) S. Oae, K. Fujimori, and S. Kozuka, *Tetrahedron*, 28, 5327 (1972); (b) S. Oae, K. Fujimori, and Y. Uchida, *ibid.*, 28, 532 (1972); (c) J. E. Leffler and A. A. More, More, *J. Amer. Chem. Soc.*, 94, 2483 (1972); (d) R. A. Cooper, R. G. Lawler, and H. R. Wards, *ibid.*, 94, 545 (1972); (e) C. Walling, H. P. Waits, J. Milovanovic, and C. G. Pappiaonnou, *ibid.*, 92, 4927 (1970).

(14) Thenoyl peroxides gave $\rho = -0.4$ by a Hammett correlation.[5,15]

(15) (a) R. D. Shuetz and D. M. Teller, *J. Org. Chem.*, 27, 410 (1962); (b) R. D. Shuetz, F. M. Gruen, D. R. Byrne, and R. L. Brennan, *J. Heterocycl. Chem.*, 3, 184 (1966).

(16) *Cf.* C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 338 (1964).

dimethoxybenzoyl peroxide is not included, one obtains $\rho_I = -0.327 + 0.046$, $\rho_R = -0.267 \pm 0.077$ with a standard error in log k/k_0 of ± 0.0428, and $r = 0.980$. Since reaction constants are expected to be proportional to $1/T$,[17a] the ρ_I values for benzoyl peroxides at 80° are corrected to 150° (the temperature employed for alkyl peroxide kinetics). This gives $\rho_I = -0.265 \pm 0.047$ and -0.273 ± 0.038 at 150° for the benzoyl peroxides with and without the *m,m'*-dimethoxy derivative, respectively. This places the ρ_I values derived from benzoyl peroxides and alkyl peroxides (-0.291 ± 0.067) within the error limits of each other.

Another means of relating substituent effects in these two series is through the field effect parameter f in the Swain–Lupton equation (eq 3).[18] A somewhat better

$$\log k/k_0 = f\mathcal{F} + r\mathcal{R} \quad (3)$$

correlation of the benzoyl peroxide meta-substituent effect data (excluding the *m,m'*-dimethoxy derivative) results with this equation, where $f = -0.174 \pm 0.027$, $r = -0.211 \pm 0.054$, r (correlation coefficient) = 0.985, and the standard error in log k/k_0 is ± 0.0377. A temperature correction from 80 to 150° gives $f = 0.145 \pm 0.022$ for the benzoyl peroxides. Swain and Lupton[18] find a good correlation between σ_I and $\mathcal{F}$, such that $\sigma_I = 0.60\mathcal{F}$. Since $\sigma_I = 0.45\sigma^*$,[16] it follows that $f = \rho^*(0.45/0.60)$ or $f = \rho^*/0.75$. From the ρ^* value given in eq 1, the alkyl peroxides give $f = -0.175 \pm 0.040$ [$= (-0.131 \pm 0.030)/0.75$] in chlorobenzene compared to $f = -0.145 \pm 0.022$ for benzoyl peroxides in dioxane at the same temperature (150°). Again the two values are within error limits of each other. Considering the change in solvent and the potential errors in relating the reaction constants, it appears that the field (or inductive) effect of the substituents does not change between alkyl and meta-substituted benzoyl peroxides.

The overall effect of substituents on alkyl peroxide decomposition is small compared with that observed for aroyl peroxides. This results from a large resonance contribution of the substituents in the aroyl peroxide series. The per cent resonance (%$\mathcal{R}$)[18] for meta-substituted benzoyl peroxides is 43%, which is significantly greater than obtained for ionization of meta-substituted benzoic acids (%$\mathcal{R}$ = 22%).[18] With para-substituted benzoyl peroxides,[4a] where through-resonance interactions are possible between the substituents and the carbonyl group, %$\mathcal{R}$ increases to 67% [$f = -0.145 \pm 0.044$, $r = -0.474 \pm 0.085$, r (correlation coefficient) = 0.967, standard error in log $k/k_0 = \pm 0.0798$]. This too is greater than for the ionization of para-substituted benzoic acids (%$\mathcal{R}$ = 53%).[18] Although electron release to the peroxide reaction site increases the rate and resonance contributions are significant for aroyl peroxides, it cannot be discerned whether this is due to an increase in the ground-state energy of the peroxides or a decrease in the transition-state energy. It is possible that electron release to the peroxide group increases the ground-state energy by increasing the electron repulsions between the peroxy oxygen atoms. Alternatively, the alkoxy or acyloxy radical, which is reflected in the transition state, is electron deficient and electron release may then stabilize the activated complex.

Decomposition of 7 and 8.—Both alcohol **7** and acid **8** decompose at rates faster than predicted from the Taft correlation (eq 1). The correlation predicts rate coefficients for **7** and **8** of $4.14 \pm 0.09 \times 10^{-4}$ and $3.21 \pm 0.13 \times 10^{-4}$ sec^{-1} compared to observed values of $16.1 \pm 0.5 \times 10^{-4}$ and 24.0×10^{-4} sec^{-1}, respectively. The alcohol **7** and the acid **8** then undergo decomposition by factors of 3.9 and 7.5 times faster, respectively, than predicted by eq 1. The significance of the carboxylic acid hydrogen atom in rate acceleration of **8** is seen by comparing **8** with its methyl ester **2**. The methyl ester is well correlated by eq 1, as opposed to the acid **8**. The involvement of the alcoholic hydrogen atom in rate acceleration of **7** is suggested by an isotope effect [$[k_H/k_D = 1.35$ (corrected)] when this atom is replaced by deuterium. The yield of *tert*-butyl alcohol is also significantly increased in the decomposition of **7** and **8** compared with *tert*-butyl peroxide. Production of only free *tert*-butoxy radicals from **7** and **8** cannot explain the unusually high *tert*-butyl alcohol yields.

As a starting point, two competing decomposition paths can be considered for **7** and **8**, namely, simple homolysis (eq 4 and 6) and cyclic decomposition (eq 5 and 7). Qualitatively, the latter paths (eq 5 and 7) will offer an explanation for enhanced yields of *tert*-butyl alcohol from **7** and **8** as well as the involvement of the OH hydrogen atom. Considering that **7** shows intramolecular hydrogen bonding between the hydroxyl and peroxide groups,[19] **7c** $^{\mp}$ and **8c** $^{\mp}$ appear reasonable.

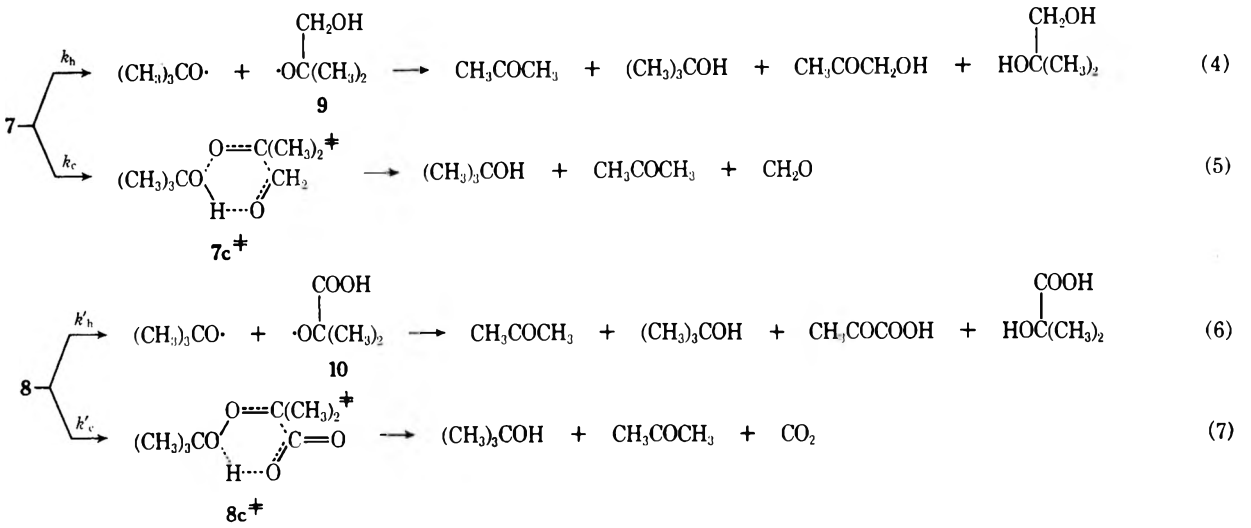
A further consideration of kinetic and product data indicates that these two modes of decomposition cannot wholly explain the results. For **8**, the per cent simple homolysis is given by $k'_h/k_{obsd} \times 10^2 = (3.21 \times 10^{-4})/(24.0 \times 10^{-4}) \times 10^2 = 13.4\%$, where k'_h is predicted from the LFER for homolysis and k_{obsd} is the observed rate coefficient. If **10** yields acetone exclusively,[20] then the simple homolysis of **8** will produce 0.27 mmol acetone/mmol **8** ($= 0.134 \times 1.99$) based on the acetone yield from *tert*-butyl peroxide. An insignificant amount of *tert*-butyl alcohol (0.0008 mmol $= 0.134 \times 0.006$) would be produced in eq 6, based on *tert*-butyl peroxide. In the cyclic decomposition (eq 7), equivalent yields of acetone and *tert*-butyl alcohol are predicted. Since 0.73 mmol of *tert*-butyl alcohol is produced per mmol of **8**, essentially this entire amount must arise from eq 7 and 0.73 mmol of acetone will be formed also in this step. The total yield of acetone from eq 6 and 7 is expected to be 1.00 mmol/mmol **8** ($= 0.27 + 0.73$), while 1.30 mmol of acetone/mmol **8** is observed. Thus, 0.30 mmol of acetone/mmol **8** is unaccounted for if only eq 6 and 7 are considered. Similarly, if it is assumed that **10** does not yield acetone, 0.44 mmol of acetone/mmol of **8** is unaccounted for by eq 6 and 7. By similar arguments it can be shown that 0.91–1.14 mmol of acetone/mmol **7** is unexplained by solely eq 4 and 5 with styrene present and 0.32–0.59 mmol of acetone/mmol **7**

(17) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968: (a) p 20; (b) p 3.

(18) C. G. Swain and E. C. Lupton, *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

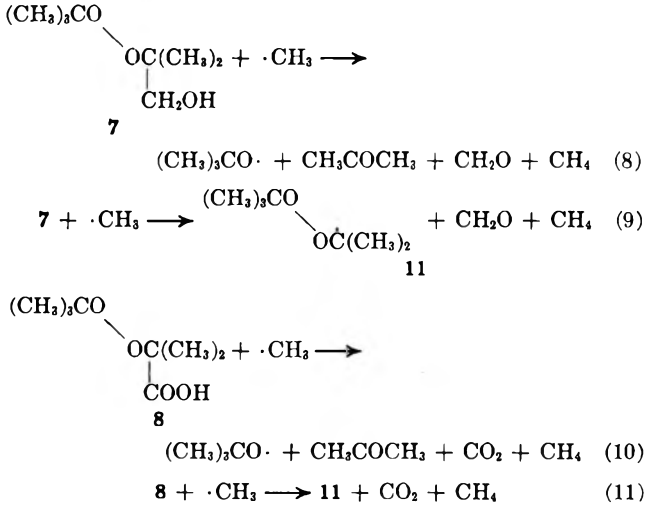
(19) W. H. Richardson and R. S. Smith, *J. Org. Chem.*, **33**, 3882 (1968).

(20) The difference in enthalpies of reaction ($\Delta\Delta H_r°$) for acetone formation less pyruvic acid production from **10** is the same (5.90 kcal/mol) as for the two similar processes from $(CH_3)_2(CO_2CH_3)CO\cdot$. The statistically corrected relative rates of acetone/methyl pyruvate formation from the latter radical is 23 (*cf.* β scission of alkoxy radicals). Thus, the relative amounts of these two products will be 11.5. Since $\Delta\Delta H_r°$ is the same for the two alkoxy radicals, the expected ratio of acetone/pyruvic acid from **10** is 11.5.



without styrene. The ranges in unaccounted acetone arise in each case by assuming that **9** gives exclusively or no acetone.[21]

A decomposition path for **7** and **8** must be considered, in addition to homolysis (eq 4 and 6) and cyclic decomposition (eq 5 and 7), to explain acetone formation without an appreciable amount of *tert*-butyl alcohol. The kinetics dictate that the rate of this reaction be faster than simple homolysis. Two possible reaction types for **7** and **8** that could accommodate these requirements are given below. The reactions are shown with methyl radicals, although radicals derived from scavengers could intervene. The *tert*-butoxy radical will yield almost exclusively acetone and methyl radical, according to the product study with *tert*-butyl peroxide. The radical **11** (eq 9 and 11) will yield acetone and a *tert*-butoxy radical, so that eq 8–11 will allow for the



formation of acetone with essentially no *tert*-butyl alcohol production. Normally hydrogen atom abstraction from carboxylic acid or alcoholic OH atoms is unfavorable.[22] However, π-carbonyl bond formation is expected to lower the activation energy of these reactions such that they may become favorable. Some insight into this proposal can be gained by calculating the enthalpies of reaction ($\Delta H_r°$) for eq 8–11 by group additivity methods.[23] For reactions 8 and 9 with peroxide **7**, the calculated $\Delta H_r°$ values are −33.9 and +25.1 kcal/mol, respectively. The calculated $\Delta H_r°$ values of reactions 10 and 11 for peroxide **8** are −55.2 and +3.8 kcal/mol, respectively. Although $\Delta H_r°$ cannot be simply related to E_a in these reactions, the large exothermicity of reactions 8 and 10 suggests a very low activation energy. For example, hydrogen atom abstraction from methane by fluorine atoms has an E_a value of 0.2 kcal/mol[24] with a $\Delta H_r°$ value of −31.8 kcal/mol.[25] Thus, reactions 8 and 10 would appear to be quite favorable in terms of activation energies. Although the heats of reactions for eq 9 and 11 (25.1 and 3.8 kcal/mol, respectively) set only the *minimum* activation energies, these reactions are likely to have activation energies less than that found in the simple homolysis of the peroxide bond.[5,6b] Thus, either two-bond (eq 9 and 11) or three-bond homolysis could contribute to accelerated rates of decomposition of **7** and **8**.

With a combination of simple homolysis (eq 4 and 6), cyclic decomposition (eq 5 and 7), and induced decomposition (eq 8–11), the product balance for **7** and **8** is good in the absence of styrene. As outlined above, 13.4% of **8** is decomposed by simple homolysis (eq 6) and 73% by cyclic decomposition (eq 7), so that 0.14 mmol of **8** [1.00 − (0.134 + 0.73)] is consumed by induced decomposition. Thus, 0.28 mmol of acetone (2 × 0.14) is expected from the latter process. By these three processes a total of 1.27 mmol of acetone/mmol **8** (0.26 + 0.73 + 0.28) is expected compared with the observed yield of 1.30 mmol. We have assumed that alkoxy radical **10** gives a 92% yield of acetone (11.5/11.5 + 1 × 10^2),[20] so that 0.26 mmol of acetone is produced by homolysis. For **7** without styrene, 25.5% of the peroxide decomposes by homolysis based on kinetic data (eq 4, k_h/k_{obsd} × 10^2) and 51% of the decomposition can be attributed to cyclic decomposition (eq 5) based on the *tert*-butyl alcohol yield. Thus, 0.235 mmol of **7** [1.00 − (0.255 + 0.51)] remains for induced decomposition, so that 0.470 mmol of acetone (2 × 0.235) is expected to be produced by this process. Assuming a 31% yield of acetone from **9**, 0.33 mmol of

(21) The $\Delta\Delta H_r°$ values **9** and $(CH_3)_2(CH_2Br)CO·$ are the same (1.3 kcal/mol) for acetone to hydroxy acetone or bromo acetone formation. By the same reasoning as given in ref 20, the relative yields of acetone/substituted acetone production (0.45) are expected to be equal.

(22) M. Simonyi and F. Tüdös, *Advan. Phys. Org. Chem.*, **9**, 127 (1971).

(23) S. W. Benson, "Thermochemical Kinetics," Wiley, New York, N. Y., 1968.

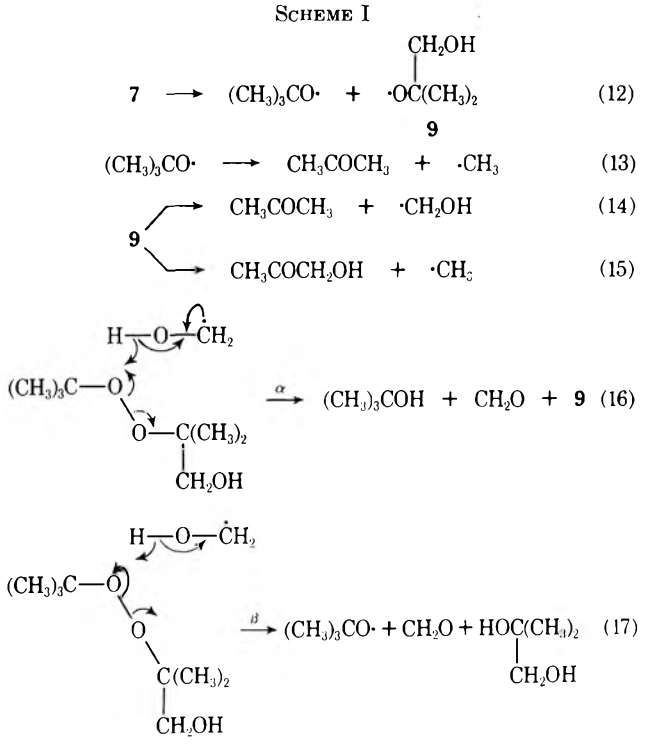
(24) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 155.

(25) Calculated by group additivities.[23]

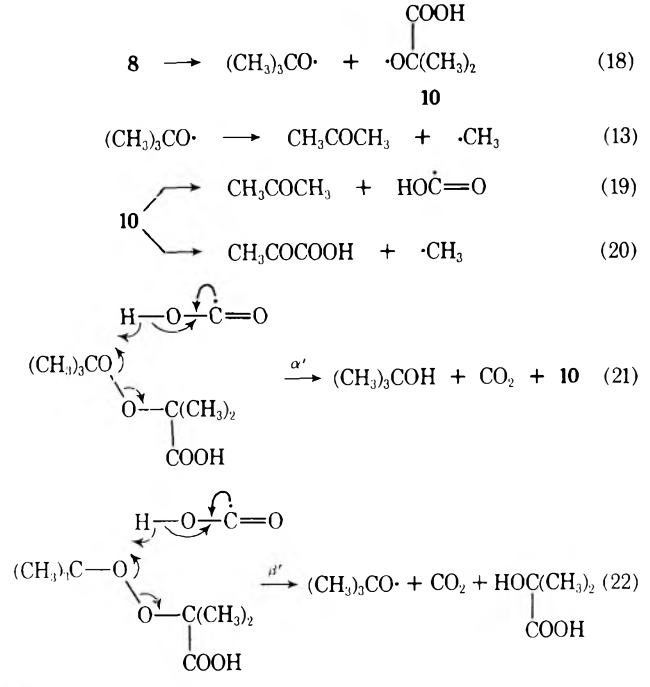
acetone/mmol **7** is expected from homolysis and the total acetone yield from the three processes is 1.31 mmol/mmol **7** (0.33 + 0.51 + 0.470) compared with the observed yield of 1.35 mmol. By similar reasoning, the product balance is poor with **7** in the presence of styrene. Here, the total expected acetone yield is 1.38 (0.31 + 0.36 + 0.710) compared with the observed yield of 1.74 mmol.

Although a combination of homolysis, cyclic decomposition, and induced decomposition can explain the data reasonably well for **7** and **8** (with the exception of **7** in the presence of styrene), alternative mechanisms (Schemes I and II) can be considered. Reactions 16 and 17 have been proposed to explain induced decomposition of *tert*-butyl peroxide in alcoholic solvents.[7e]

SCHEME I



SCHEME II



Reactions 21 and 22 are then analogous to these induced decompositions. In terms of calculated heats of reaction ($\Delta H_r°$), induced decompositions 16 and 17 for **7** are suggestive of processes with low activation energies (see Scheme I). The calculated $\Delta H_r°$ values for both reactions 16 and 17 are −34.5 kcal/mol. Similarly, low activation energies are expected for induced decompositions of **8** *via* eq 21 and 22, where the $\Delta H_r°$ values are −56.8 kcal/mol for both reactions.

The product balances for **7** and **8** based on Schemes I and II are less satisfactory than those based on eq 4–11. With the analysis presented above, the per cent **8** decomposed by (1) homolysis and (2) α'- and (3) β'-induced decomposition is 13.4% (from kinetic data), 73% (from *tert*-butyl alcohol yield), and 13.6% [1.00 − (0.134 + 0.73)], respectively. The millimoles of acetone/mmol **8** from (1) homolysis and (2) α'- and (3) β'-induced decomposition is then 0.26, 0.67 (0.92 × (0.73), and 0.136 mmol, respectively, for a total of 1.07 mmol, compared with 1.30 mmol of acetone observed. In the same manner for **7** without styrene, the per cent **7** decomposed along with (millimoles of acetone formed/mmol **7**) from (1) homolysis and (2) α- and (3) β-induced decomposition is calculated to be 25.5 (0.33), 51(0.16), and 23.5% (0.235), respectively, for a total of 0.73 mmol, compared with 1.35 mmol of acetone observed. With styrene, the per cent **7** decomposed along with (millimoles of acetone formed/mmol **7**) from (1) homolysis and (2) α- and (3) β-induced decomposition is calculated to be 25.5 (0.31), 36 (0.11), and 38.5% (0.385), respectively, for a total of 0.81 mmol relative to 1.74 mmol of acetone observed.

In summary, a combination of homolysis, cyclic decomposition, and induced decomposition (eq 4–11) best fits the existing data for **7** and **8**. It would be unwarranted to completely exclude the alternative Schemes I and II, based on product balances, since predicted total yields of acetone depend on knowing acetone yields from β scission of alkoxy radicals **9** and **10**. In our final analysis of the product balances for eq 4–11 and Schemes I and II, we have assumed a 31% yield of acetone from **9**[21] and a 92% yield from **10**.[20] This seems to be a reasonable estimate and the relationship between relative rates of β scission from unsymmetrical alkoxy radicals and calculated differences in enthalpies of reaction ($\Delta\Delta H_r°$) for these processes are discussed further in the next section. However, it should be noted that the product balances for Schemes I and II will be improved if it is assumed that alkoxy radicals **9** and **10** give exclusively acetone. For peroxide **8**, assuming only acetone production from **10**, Scheme II predicts a total of 1.14 mmol of acetone *vs.* 1.30 mmol observed. For **7**, assuming solely acetone formation from **9**, Scheme I predicts a total of 1.26 mmol of acetone without or with styrene compared with 1.35 and 1.74 mmol observed without and with styrene.

β Scission of Alkoxy Radicals.—Competitive β scission reactions (Scheme III) from a number of unsymmetrical *tert*-alkoxy radicals has been reported.[26] To our knowledge, previous studies include only alkyl

(26) (a) J. D. Bacha and J. K. Kochi, *J. Org. Chem.*, **30**, 3272 (1965); (b) J. K. Kochi, *J. Amer. Chem. Soc.*, **84**, 1193 (1962); (c) F. D. Greene, M. L. Savitz, H. H. Lau, F. D. Osterholtz, and W. N. Smith, *ibid.*, **83**, 2196 (1961); (d) C. Walling and A. Padwa, *ibid.*, 2207 (1961); (e) P. Gray and V. Williams, *Chem. Rev.*, **59**, 239 (1959).

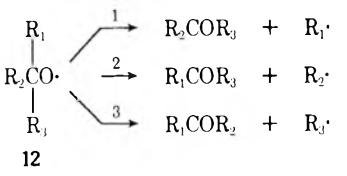
TABLE III

RELATIVE RATES OF β SCISSION OF 12 AND THERMOCHEMICAL PARAMETERS

	12					
Registry no.	R_1	R_2	R_3	k_1/k_2, 150°	$\Delta\Delta H_r°$[a,b]	ΔE_a[a,c]
42334-75-8	CO_2CH_3	CH_3	CH_3	23	5.9	3.4
42334-91-8	CH_2OCOCH_3	CH_3	CH_3	2.08	2.0	1.2
42334-92-9	CH_2Cl	CH_3	CH_3	1.54	2.3	1.3
42334-93-0	CH_2Br	CH_3	CH_3	0.90	1.3	0.75

[a] In kcal/mol. [b] $\Delta\Delta H_r° = \Delta H_{r_2}° - \Delta H_{r_1}°$. [c] $\Delta E_a = E_{a_2} - E_{a_1}$.

SCHEME III



12

hydrocarbon radicals (R_1, R_2, R_3). The yields of acetone from Table II now allow us to calculate rates of β scission, relative to $R_2 = CH_3$, for $R_1 = CO_2CH_3$, CH_2Cl, CH_2Br, and CH_2OCOCH_3. The statistically corrected rates (k_1/k_2) are given by $2(\text{acetone})_{12}/[1.00 - (\text{acetone})_{12}]$, where $(\text{acetone})_{12}$ is the millimoles of acetone/mmol 12. Where a *tert*-butoxy radical is produced from the peroxide, as well as 12, $(\text{acetone})_{12}$ is obtained by subtracting 1.99/2 (*cf. tert*-butyl peroxide) from the total acetone yield given in Table II.

Although Polanyi relationships[27] have met with varying success, they are potentially useful. Ideally one can calculate differences in enthalpies of reactions ($\Delta\Delta H_r°$)[23] and then determine differences in activation energies (ΔE_a) from eq 23, once sufficient data are

$$\Delta E_a = \alpha\Delta\Delta H_r° \quad (23)$$

available to empirically determine α. From the Arrhenius equation and eq 23, one can obtain eq 24.

$$2.303RT \log (k_1/k_2) = \alpha\Delta\Delta H_r° + 2.303RT \log (A_1/A_2) \quad (24)$$

Since our data were not determined as a function of temperature, the ratio of A factors is unknown. However, if the ratio A_1/A_2 is reasonably constant, eq 24 predicts a linear plot of $2.303RT \log (k_1/k_2)$ *vs.* $\Delta\Delta H_r°$. From such a plot from the data in Table III at 150°, $\alpha = 0.58 \pm 0.04$ and $A_1/A_2 = 0.40$ with r (correlation coefficient) = 0.989. The value of r indicates a satisfactory correlation.[17b] With this value of α and $\Delta\Delta H_r°$ quantities in Table III, ΔE_a for β scission can be calculated from eq 23 and recorded in Table III.

Experimental Section[28]

Materials.—Chlorobenzene (Matheson Coleman and Bell) was dried over Drierite. Styrene (Matheson Coleman and Bell) was distilled before use, bp 26° (5 mm) [lit.[29] bp 54° (30 mm)]. 2,6,Di-*tert*-butyl-*p*-cresol (Matheson Coleman and Bell) was sublimed at 70° (0.1 mm), mp 69.0–70.7° (lit.[30] mp 69.8–70.5°). *tert* Butyl peroxide (1) (Shell Chemical Co.) was purified by distillation, bp 52° (100 mm) [lit.[31] bp 109° (760 mm)]. Preparation of peroxides 2,[32a] 7,[19] and 8[32b] were previously reported from this laboratory.

Chloro-*tert*-butyl Peroxide (3).—This peroxide was isolated in 44% yield, based on consumed *tert*-butyl peroxide, from the photochlorination of the latter peroxide, bp 54–55° (20 mm) [lit.[33] bp 55° (20 mm)]. The purity was estimated to be 98–99% by glc after distillation through a 1 × 90 cm glass helice column (Todd Scientific Co.). Alternatively, 3 was prepared by slowly adding 18.8 g (0.151 mol) of chloro-*tert*-butyl hydroperoxide to 140 g of concentrated sulfuric acid and 53 g of water at 0° with stirring. Then 11.2 g (0.151 mol) of *tert*-butyl alcohol was added in 256 ml of chloroform. The reaction mixture was stirred for 48 hr at room temperature and the chloroform phase was separated. The aqueous phase was extracted with three 50-ml portions of chloroform and the combined chloroform phases were washed with three 50-ml portions of water and dried over magnesium sulfate. Rotoevaporation gave 20.7 g of crude product, which was chromatographed on 60 g of acid-washed Merck alumina by elution with *n*-hexane. The residue from the *n*-hexane fractions was distilled through a 1 × 90 cm glass helice column to give 9.48 g (35% yield) of 3, bp 54–55° (20 mm) [lit.[33] bp 55° (20 mm)]. The product was estimated to be 100% pure by glc: nmr δ 3.55 (s, 2.0, CH_2Cl), 1.28 [s, 6.0, $(CH_3)_2$], and 1.21 [s, 8.9, $(CH_3)_3$]. The ir (neat) of 3 showed the following significant absorptions: CH, 2975, 2935, 2870, 1470, 1360; CO, 1190, 1150; OO, 870; CCl, 730 cm^{-1}.

Anal. Calcd for $C_8H_{17}ClO_2$: C, 53.18; H, 9.48; Cl, 19.62. Found: C, 53.69; H, 9.76; Cl, 19.43.

Bis(chloro-*tert*-butyl) Peroxide (4).—The preparation and purification of 4 was the same as that given in the latter method for 3, except that 1-chloro-2-methyl-2-propanol[34,35] was used in place of *tert*-butyl alcohol. Peroxide 4 was obtained in 16% yield, with glc-estimated purities of 96–98%: bp 54–55° (2 mm);[36] nmr 3.57 (s, 4.0, CH_2Cl), 1.29 [s, 12.0, $(CH_3)_2$]; ir (neat) CH, 2980–2880, 1470, 1370; CO, 1140; OO, 870; CCl, 740 cm^{-1}; mass spectrum m/e (rel intensity) (the molecular ion is M) M + 4, 218 (0.55); M + 3, 217 (0.30); M + 2, 216 (3.2); M + 1, 215 (0.46); M, 214 (5.1); M − CH_3, 199 (0.40); M − CH_2Cl, 167 (11), 165 (62); M − $(CH_3)_2CCH_2Cl(O)$, 109 (17), 107 (56), 92 (100); M − $(CH_3)_2CCH_2Cl(OO)$, 93 (73), 91 (58), and 90 (67) where the absorptions of m/e 90–93 are complicated by ions with m/e ±1.

Anal. Calcd for $C_8H_{16}Cl_2O_2$: C, 44.67; H, 7.50. Found: C, 44.20; H, 7.21.

Analysis of the reaction mixture from the photochlorination of *tert*-butyl peroxide by glc (20% SE-30 on 60/80 mesh Chromosorb W, 5 ft × 0.25 in., column temperature 125°, helium flow 50 ml/min) indicated that 4 was obtained in 17% yield along with 3 in 50% yield, both based on consumed *tert*-butyl peroxide,

(27) (a) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **34**, 11 (1938); (b) H. E. O'Neal and S. W. Benson, "Free Radicals," Vol. II, J. K. Kochi, Ed., Wiley, New York, N. Y., 1973, Chapter 17.

(28) Melting points are corrected and boiling points are uncorrected Temperatures reported for kinetic measurements are corrected. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane as 0 ppm (δ scale). The nmr absorptions are given as parts per million, couplng, relative area. Infrared (ir) spectra were determined with a Perkin-Elmer 621 or 337 spectrometer and mass spectra were obtained with a Hitachi RMU-6E instrument (oven 25°, ionization voltage 70 eV). Nmr and ir spectra were obtained in carbon tetrachloride solvent (10% w/v), unless specified otherwise. Gas–liquid chromatography (glc) analyses were performed on a Varian Aerograph Hy-Fi III (FID) or an an A-90P (TC) instrument. Elemental analyses were obtained from C. F. Geiger, Ontario, Calif.

(29) H. B. Dykstra, *J. Amer. Chem. Soc.*, **56**, 1625 (1934).

(30) W. C. Sears and L. J. Kitchen, *J. Amer. Chem. Soc.*, **71**, 4110 (1949).

(31) N. A. Milas and D. M. Surgenor, *J. Amer. Chem. Soc.*, **68**, 205 (1946).

(32) (a) W. H. Richardson, R. S. Smith, G. Snyder, B. Anderson, and G. L. Kranz, *J. Org. Chem.*, **37**, 3915 (1972); (b) W. H. Richardson and R. S. Smith, *J. Amer. Chem. Soc.*, **91**, 3610 (1969).

(33) J. H. Raley, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **70**, 2767 (1948).

(34) W. H. Richardson and V. F. Hodge, *J. Amer. Chem. Soc.*, **93**, 3996 (1971).

(35) J. Burgin, G. Hearne, and F. Rust, *Ind. Eng. Chem.*, **33**, 385 (1941).

(36) A mixture of three isomeric dichloro-tert-butyl peroxides, obtained from photochlorination of *tert*-butyl peroxide, are reported to boil at 55–70° (4–5 mm).[33]

while 76% of the latter peroxide was consumed. Unfortunately, **4** could not be completely separated from the other isomeric dichloro-*tert*-butyl peroxides by the fractional distillation.

Bromo-*tert*-butyl Peroxide (5).[37]—A 500-ml three-necked flask was fitted with a thermometer, a fritted glass filter stick which was connected to a chlorine lecture bottle with Tygon tubing, a Y-addition tube which was fitted with a pressure-equilibrated addition funnel and a reflux condenser to which a nitrogen inlet was connected *via* a mercury valve. The flask was charged with 129 g (0.883 mol) of *tert*-butyl peroxide and a magnetic stirring bar, while the addition funnel was charged with 35.7 g (0.223 mol) of bromine. Chlorine was slowly bubbled through the *tert*-butyl peroxide and bromine was added in 1-ml portions with stirring, while the flask was irradiated with a 250-W sun lamp. After the bromine color was discharged, another 1-ml portion was added. Temperature of the reaction mixture was maintained at 40–44° by passing a stream of compressed air over the flask. After completion of the bromine addition, the reaction mixture was washed with two 20-ml portions of saturated sodium bicarbonate solution and then with three 10-ml portions of water. After drying over magnesium sulfate, the crude product was analyzed by glc (20% SE-30 on 60/80 mesh Chromosorb W, 5 ft × 0.25 in., column temperature 125°, helium flow 50 ml/min) using biphenyl as an internal standard. The analysis indicated 50% unreacted *tert*-butyl peroxide and the following yields are based on consumed *tert*-butyl peroxide: **5** (38%), **3** (31%), and **4** (2%). Distillation of the mixture through a 1 × 90 cm glass helice column gave 16.1 g (20% yield) of **3** in 95% purity and 43.5 g (44% yield) of **5** in purity ranging between 96.1 and 98.2%, bp 53–54° (10 mm). Yields are based on 50% consumed *tert*-butyl peroxide. The nmr and ir spectra of **5** showed the following absorptions: nmr δ 3.47 (s, 2.0, CH_2Br), 1.32 [s, 6.2 $(CH_3)_2$], 1.22 [s, 9.1, $(CH_3)_3$]; ir CH, 2980, 2935, 1465, 1360; CO, 1140; OO, 870; CBr, 670 cm^{-1}. A sample of **5** was purified for analysis by preparative glc (conditions as above, except column temperature 89°).

Anal. Calcd for $C_8H_{17}BrO_2$: C, 42.68; H, 7.61; Br, 35.49. Found: C, 42.42; H, 7.67; Br, 35.61.

2-Methyl-2-*tert*-butylperoxy Acetate (6).—Acetyl chloride (0.77 ml, 10.9 mmol) was added dropwise over 5 min to a stirred solution containing 1.76 g (10.9 mmol) of 2-*tert*-butylperoxy-2-methyl-1-propanol (**7**)[19] and 0.88 ml (10.9 mmol) of pyridine (distilled from barium oxide) in 3.0 ml of anhydrous ether. After the addition was completed, the mixture was heated under reflux for 2 hr and then the pyridine hydrochloride was filtered and washed with ether. The ethereal filtrate was washed with three 5-ml portions of water and dried over magnesium sulfate. Concentration of the ethereal solution with a rotoevaporator (bath 30°) gave 1.95 g of crude product, which was estimated to be 87% **6** (76% yield) by glc analysis (3% SE-30 on Chromosorb W, 5 ft × 0.125 in., column 50°, flow of nitrogen 28 ml/min). Distillation through a Holtzmann column gave 1.19 g of **6** (53% yield), bp 62.3° (3 mm), without an appreciable improvement in purity. By preparative glc (3% SE-30 on Chromosorb W, 5 ft × 0.25 in., column 70°, detector and injector 110°, helium flow 40 ml/min), **6** was obtained in 98.5–100% purity as estimated by glc: nmr 1.25 [s, 15.1, $(CH_3)_3$ and $(CH_3)_2$], 2.06 (s, 2.9, CH_3CO_2), 4.08 (s, 2.0, CH_2); mass spectrum molecular ion M, 204; (M − CH_2OCOCH_3) or [M − $(CH_3)_2$-CO], 131; [M − $(CH_3)_3COO$)], 115.

(37) The preparation of **5** is claimed in patents, but physical properties are not reported.[38]

(38) (a) F. F. Rust, W. E. Vaughan, and R. W. Wheatcroft, U. S. Patent 2,501,966 (1950); *Chem. Abstr.*, **44**, 5376*b* (1950). (b) W. E. Baughan and F. F. Rust, U. S. Patent 2,501,967; *Chem. Abstr.*, **44**, 5376*d* (1950).

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.93; H, 10.04.

2-*tert*-Butylperoxy-2-methyl-1-propanol-d_1 (7D).—Alcohol **7**[19] (150 mg, 0.773 mmol) in 1.0 ml of chlorobenzene was shaken three times with 0.1 ml (5.5 mmol) of deuterium oxide (99.5 mol %, Matheson Coleman and Bell) at room temperature for periods of 5, 5, and 60 min. The resulting sample was calculated to be 90% deuterated by using the ratio of absorbance of the free O–D stretching frequency in the ir to that of the sum of the O–D and O–H absorbances.

Product Studies.—Chlorobenzene solutions of the peroxides were prepared in 2-ml volumetric flasks and then sealed in melting point capillary tubes. The tubes were immersed in a thermostated Dow-550 silicone oil bath at 150° for 10–11 half-lives. Product analyses were performed by glc (FID) and yields were calculated relative to an authentic mixture of the products in chlorobenzene with the solvent as the internal standard. Areas were obtained from the chromatograms with a planimeter. The unreacted peroxide solutions were checked by glc for decomposition under the conditions of analysis. Only minor amounts of products were observed. The glc conditions for the decomposed peroxide solutions, along with product retention times (minutes), are as follows, where the flow rate of nitrogen is 28 ml/min: **1** [20% polypropylene glycol on Chromosorb W (PPG/CW), 5 ft × 0.125 in., column (C) 39°, injector (I), 100°], acetone (A) (3.5), *tert*-butyl alcohol (BA) (11), chlorobenzene (CB), (54), **1** (6.5); **2** (20% PPG/CW, 5 ft × 0.125 in., C 50°, I 100°), A (2.5), BA (4.4), CB (42); **4** and **7** (same conditions as **2**).

Kinetic Studies.—Chlorobenzene solutions of the peroxides, including radical traps, were sealed in capillary tubes and heated as described above. Tubes were removed from the bath (controlled to ±0.02°) at timed intervals and stored in a refrigerator, and analyses for the peroxides were performed by glc (FID). The peroxides were stable under the glc conditions as determined by checking the unreacted solutions. The glc conditions for analysis of the peroxides, including retention times (minutes) of the peroxide and the internal standard, are as follows, where the flow rate of nitrogen is 28 ml/min: **1** (20% PPG/CW, 5 ft × 0.125 in., C 50°, I 100°), **1** (5.8), CB (42); **2** (3% SE-30 on Varaport-30, 5 ft × 0.125 in., C 50°, I 100°), **2** (12), *p*-dichlorobenzene (DCB) (8.5); **3** and **6** (same conditions as **2**), **3** (7.6), **6** (19); **4** (3% SE-30 on Varaport-30, 5 ft × 0.125 in., C 65°, I 100°), **4** (21), DCB (6.6); **5** (same conditions as for **4**), **5** (11); **7** (10% SF-96 on Varaport-30, 5 ft × 0.125 in., C 80°, I 100°), **7** (10), DCB (15). The ratio of the areas of the peroxides to the internal standards from glc analyses and reaction times were processed by a first-order least-squares computer program. The rate coefficients were based on data collected over approximately 3 half-lives.

Acknowledgment.—We thank the U. S. Army Research Office (Durham) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank Professor H. Walba for valuable discussions and the use of his multiple linear regression analysis program. Pertinent comments by the referees are appreciated.

Registry No.—**1**, 110-05-4; **2**, 27492-18-8; **3**, 1068-41-3; **4**, 42334-69-0; **5**, 28531-45-5; **6**, 42334-71-4; **7**, 17393-39-4; **7D**, 42334-73-6; **8**, 16424-69-4.

Mobile Keto Allyl Systems. XIV.[1] The Kinetics and Mechanism of the Thermal Decomposition of *trans*-2-Benzal-3-cyclohexylamino-4,4-dimethyl-1-tetralone

GEORGE GLAROS

Department of Chemistry, Russell Sage College, Troy, New York 12180

NORMAN H. CROMWELL*

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

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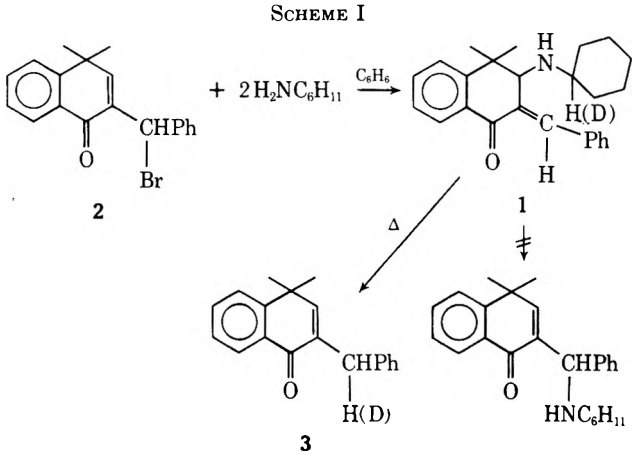
The thermal decomposition of the title compound was found to exhibit first-order kinetics: a large solvent effect, $k_{CHCl_3}/k_{isooctane} = 18$; as well as a primary isotope effect, $k_H/k_D = 2.2$. Possible mechanisms are discussed.

In an earlier paper in this series,[2] we described a thermal decomposition reaction of *trans*-2-*o*-methylbenzal-3-amino-4,4-dimethyl-1-tetralones as a retro-ene reaction involving the transfer of the hydrogen atom α to the nitrogen in the amino moiety to the benzylic position. It has also been shown[3] that this decomposition occurs in the corresponding unsubstituted benzal compounds. Four possible mechanisms were suggested[2] to account for the complete transfer of the α hydrogen, a proton transfer (path A), a hydride transfer (path B), a hydrogen atom transfer (path C), and a concerted cyclic transition state (path D). In this paper, we discuss the kinetics and mechanism of this thermal decomposition reaction.

Results and Discussion

The compound chosen for study was *trans*-2-benzal-3-cyclohexylamino-4,4-dimethyl-1-tetralone (**1**). Amino ketone **1** was prepared as previously described[3] from 2-(α-bromobenzyl)-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**2**) and 2 equiv of cyclohexylamine. Although reasonably stable to rearrangement and decomposition at room temperature,[3] amino ketone **1** decomposes in high yield to the known[4] 2-benzyl-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene (**3**), Scheme I.

SCHEME I



Compounds **1** and **3** have significantly different uv spectra (Figure 1), which allowed the rate of the reaction to be followed by observing the decrease in absorbance due to **1** with time. The reaction was shown to follow first-order kinetics for 2 to 3 half-lives.

In Table I are listed the results of the kinetics in isooctane and chloroform, as well as several control experiments. Neither the presence of glass wool, radical initiators, or radical traps appreciably alters the rate of the reaction. Thus, this reaction does not appear to be a surface-catalyzed or a radical chain reaction.

TABLE I

[E_a(isooctane) = 25.4 kcal/mol; $\Delta S^{\ddagger} = -17$ eu at 135°; $k_H/k_D = 2.2$[g]]

Solvent	ϵ_{20}[a]	Temp, °C	[1]	k, sec^{-1}	k, sec^{-1}
Isooctane	1.9	120	0.00446	2.4×10^{-5}	
		120	0.00092	2.5×10^{-5}	
		120	0.00230	2.4×10^{-5}	2.4×10^{-5}
		135	0.00203	1.4×10^{-4}	
		135	0.00403	1.6×10^{-4}	
		135	0.000755	1.6×10^{-4}	1.5×10^{-4}
		135[b]	0.00205	1.6×10^{-4}	
		135[c]	0.00221	8.5×10^{-5}	
		150	0.00264	2.1×10^{-4}	
		150	0.00138	1.5×10^{-4}	
		150	0.00332	2.2×10^{-4}	1.9×10^{-4}
Chloroform	4.8	120	0.000464	5.0×10^{-4}	
		120	0.00115	4.7×10^{-4}	
		120	0.00217	4.0×10^{-4}	4.5×10^{-4}
		120[d]	0.00110	2.1×10^{-4}	
		120[d]	0.000456	2.3×10^{-4}	2.2×10^{-4}
		120[e]	0.000346	2.9×10^{-4}	
		120[f]	0.00140	1.9×10^{-4}	

[a] Dielectric constants taken from A. A. Maeyott and E. R. Smith, "Table of Dielectric Constants of Pure Liquids," National Bureau of Standards Circular 514, Aug 10, 1951. [b] Sample tubes packed with glass wool. [c] Dibenzoyl peroxide added. [d] α-Deuterium compound. [e] Hydroquinone added. [f] Solution saturated with oxygen. [g] Corrected for isotopic purity, 98.3% atom/molecule as determined by mass spectral analysis.

The large solvent effect observed, $k_{CHCl_3}/k_{isooctane} = 18$, is indicative of a reaction in which charge is developed in the transition state.[5] Radical reactions are often characterized by their insensitivity to changes in solvent polarity.[6] Similarly, several examples[7] of a symmetry-allowed concerted 1,5-hydrogen shift[8] show little variation in rate with a large variation in solvent

(1) (a) For paper XIII in this series, see G. Glaros and N. H. Cromwell, *J. Org. Chem.*, **37**, 867 (1972). (b) Presented at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972.

(2) G. Glaros and N. H. Cromwell, *J. Org. Chem.*, **36**, 3033 (1971).

(3) G. Glaros and N. H. Cromwell, *J. Org. Chem.*, **37**, 862 (1972).

(4) A. Hassner and N. H. Cromwell, *J. Amer. Chem. Soc.*, **80**, 893 (1958).

(5) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 379.

(6) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 13.

(7) A. P. ter Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **82**, 741, 1189 (1963).

(8) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965).

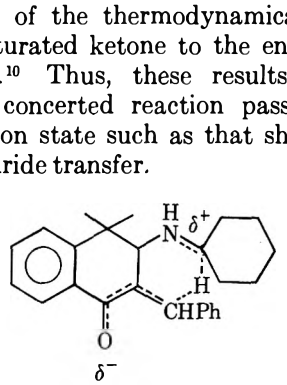
polarity. Thus, neither the hydrogen atom transfer (path C) nor the concerted 1,5-hydrogen shift (path D) seems to be involved in this reaction. The mechanisms which best explain the large solvent effect are the ionic pathways A and B.

When the reaction was carried out in ethanol, the decomposition was essentially complete in the 15 min usually allowed for temperature equilibration. Since the ethanol could act as a polar solvent or as an external source of hydrogen atoms or protons, the rate enhancement could be attributed to either property. When the decomposition was carried out in methanol-d_1, the product contained no deuterium. Thus, the rate enhancement is probably due to the increased polarity of the solvent. The primary isotope effect k_H/k_D = 2.2 is also considerably smaller than the maximum value of around 12 for highly concerted 1,5 shifts in which the hydrogen atom is equally bonded to both carbon atoms in the transition state.[9]

As a control experiment, the α-deuterio amino ketone **1** was decomposed with an equal molar amount of *trans*-2-*o*-methylbenzal-3-cyclohexylamino-4,4-dimethyl-1-tetralone.[2] The crude reaction mixture was analyzed by mass spectrometry and the 2-*o*-methylbenzyl-1,4-dihydro-4,4-dimethyl-1-ketonaphthalene obtained was shown to contain no deuterium.

Pathways C and D, which do not involve a large degree of charge separation, may be ruled out because of the large solvent effect. Path A, the proton transfer, may be ruled out, since the intermediate involves an unfavorable disposition of charges, and the most acidic hydrogen (the one on nitrogen or the methanol-d_1) is not transferred.[2] All the data are consistent with a hydride transfer to give a dipolar intermediate, which is resonance stabilized. Attempts to trap this intermediate with dimethyl acetylenedicarboxylate were unsuccessful. This may be due to the steric hindrance of the addition or the short life of the intermediate.

In this decomposition, the resonance effect in the ground state of the molecule makes the benzal position susceptible to nucleophilic attack by the hydride ion, and the main driving force of the reaction is probably the conversion of the thermodynamically less stable exocyclic unsaturated ketone to the endocyclic unsaturated ketone.[10] Thus, these results are best explained by a concerted reaction passing through a dipolar transition state such as that shown below, *via* path B, the hydride transfer.



Experimental Section[11]

Preparation of Materials.—Spectrograde isooctane was dried over sodium prior to use. Reagent grade chloroform was passed through a column of alumina (Woelm activity I) to remove water and ethanol and was used immediately after purification.

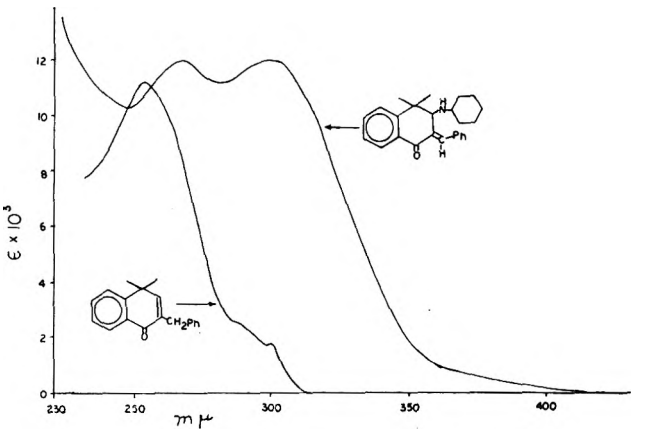


Figure 1.—Ultraviolet absorption spectra of amino ketone **1** and unsaturated ketone **3**, measured in isooctane.

Amino ketone **1** was prepared as previously described[3] and had mp 94–95° (lit.[3] mp 94–95°). The amino ketone was recrystallized from 95% ethanol, powdered, dried under vacuum, and stored in a desiccator. The deuterated amino ketone was prepared by the method previously described.[2]

Kinetic Method.—Aliquots of a stock solution of **1** were placed in test tubes; the tubes were sealed and placed in a constant-temperature bath. At appropriate intervals, tubes were removed from the bath and the reaction was quenched in Dry Ice–acetone. The tube was then opened and the contents were diluted to an appropriate volume. The concentration of **1** was determined spectrophotometrically at four wavelengths, λ 310, 312, 314, and 316 mμ.

The rate constants were obtained by plotting the log of the concentration of **1** *vs.* time. Activation parameters were calculated by standard methods[12] using the following expressions: $k_1 = A \exp(-E_a/RT)$, $E_a = \Delta H^{\ddagger} + RT$, $k_1 = kT/h \exp(-\Delta F^{\ddagger}/RT)$, and $\Delta F^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Reaction of 1 in Methanol-d_1.—A 0.238-g (0.66 mmol) sample of amino ketone **1** was dissolved in 1 ml of methanol-d_1 and heated at 135° for 45 min in a sealed tube. The tube was opened and the contents were passed through a column of Florisil. The resulting oil crystallized upon trituration and was recrystallized from 95% ethanol to yield 0.091 g (53%) of white crystals, mp 112–113° (lit.[4] mp 113–113.5°). The nmr spectrum follows: δ 1.4 (s, 6 H), 3.77 (d, 2 H, J = 0.6 Hz), 6.56 (t, 1 H, J = 0.6 Hz), 7.1–7.7 (m, 8 H), and 8.23 (1 H).

Reaction of 1 with Dimethyl Acetylenedicarboxylate.—A 0.359-g (1 mmol) sample of amino ketone **1**, 0.287 g (2 mmol) of dimethyl acetylenedicarboxylate, and 2 ml of isooctane were heated in a sealed tube at 135° for 4–5 hr. The tube was cooled and opened, and the contents were triturated with 95% ethanol to yield 0.102 g (39%) of a white solid, mp 109–110°. The nmr spectrum showed it to be **3**.

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Registry No.—**1**, 33240-02-7; **3**, 42262-37-3.

(9) (a) H. M. R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969); (b) W. R. Roth, *Chimia*, **20**, 229 (1966).

(10) N. H. Cromwell, R. P. Ayer, and P. W. Foster, *J. Amer. Chem. Soc.*, **82**, 130 (1960).

(11) Melting points were taken by the capillary method in a Mel-Temp melting point apparatus and are uncorrected. Ultraviolet spectra were taken on a Cary Model 14 recording spectrophotometer. For kinetics, a Beckman DB-G grating spectrophotometer was used. Proton magnetic resonance spectra were obtained on a Varian A-60D spectrometer employing $CDCl_3$ solutions and are reported in parts per million (δ) relative to internal TMS (0.0). Mass spectra were obtained with a Hitachi Model RMU-6D spectrometer. Rate constants were calculated by the least-squares method on an IBM-360 computer.

(12) W. J. Moore, "Physical Chemistry," 2nd ed, Prentice-Hall, Englewood Cliffs, N. J., 1955, pp 546 and 568.

The Electrophilic Addition of Bromine to Arylcyclopropanes. Kinetics and Mechanistic Implications

Robert T. LaLonde* and Anthony D. Debboli, Jr.

Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210

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The kinetics of the electrophilic addition of bromine to phenylcyclopropane in chlorinated solvents have been examined. The rate of bromination was observed to be first order in both bromine and phenylcyclopropane at 20° in chloroform ($k = 2.0 \times 10^{-3}$ l. M^{-1} sec^{-1}) and methylene chloride ($k = 7.3 \times 10^{-3}$ l. M^{-1} sec^{-1}). The resulting ring-opened products are 1,2,3-tribromo-1-phenylpropane and 1,3-dibromo-1-phenylpropane. Addition of bromine to *trans*-1,2-diphenylcyclopropane resulted in 1,3-dibromo-1,3-diphenylpropane with a *dl*/meso ratio of 1.0 as the major product. Bromine addition to *cis*-1,2-diphenylcyclopropane resulted in dibromide with a *dl*/meso ratio of 0.82. A mechanism is presented which involves electrophilic attack of bromine on the cyclopropane ring to give a free benzyl carbonium ion as the major intermediate.

Previously reported results[1] from this laboratory on the addition of bromine to phenylcyclopropane and 1,2-diphenylcyclopropane showed that changes in temperature, concentration, light, and solvent have drastic effects on the rate of reaction and on product distribution. These results were rationalized in terms of three major competing types of reactions. Type A was one which could be initiated either photolytically or thermally, results in addition of bromine to yield 1,3-dibromo-1-phenylpropane as the only product, and was favored in less polar solvents. This reaction type had some of the characteristics usually attributed to free-radical bromine addition. Reaction type B had characteristics of an electrophilic bromine addition which resulted in cyclopropane ring cleavage and was favored by more polar solvents. Reaction type C involved aromatic substitution resulting in the formation of *p*-bromoarylcyclopropane and was favored at low temperatures and in polar solvents.

Our recent efforts have been devoted to searching for conditions under which each of the three reaction types could be isolated and studied individually. This report presents results of our investigation of the reaction type B, the addition reaction having characteristics of an ionic process. An interpretation of the results in terms of a reaction mechanism is included.

Results

The conditions which were found favorable for isolating the ionic addition reaction were as follows: the use of chloroform and methylene chloride as solvents at concentrations between 0.1 and 0.5 M, temperatures between 5 and 30°, and the presence of isoamyl nitrite, a free-radical inhibitor.[2,3] Within the temperature and concentration range employed, aromatic substitution does not occur in carbon tetrachloride and occurs to only a minor extent in chloroform and methylene chloride. The results of our kinetic studies of the bromination of phenylcyclopropane under these conditions are presented in Table I.

Kinetics.—The two products resulting from the addition of bromine to phenylcyclopropane are 1,3-dibromo-1-phenylpropane and 1,2,3-tribromo-1-phenylpropane. One mole of bromine is required to convert 1 mol of phenylcyclopropane to dibromide and 2 mol are required in the conversion to tribromide and hydrogen bromide. The tribromide–dibromide ratio remains constant throughout the course of the reaction. The relation between the phenylcyclopropane concentration, P, and the bromine concentration, B, is given in eq 1. Symbols, ρ, P_0, and B_0 refer, respectively, to

$$P = P_0 - \frac{B_0 - B}{\rho + 1} \quad (1)$$

the ratio of tribromide to total bromides, initial phenylcyclopropane concentration, and initial bromine concentration. Equation 2 represents the second-order

$$\frac{dB}{dt} = kBP \quad (2)$$

rate expression for a reaction which is first order with respect to both P and B. Equation 3 is the integrated

$$kt = \frac{1}{P_0 - B_0/(1 + \rho)} \ln \frac{B_0}{P_0(1 + \rho)} + \left[\frac{P_0(1 + \rho) - (B_0 - B)}{B}\right] \quad (3)$$

form of eq 2 in which P was substituted by the quantity given in eq 1. Substituting P back into eq 3 yields the rate expression 4.

$$kt = \frac{1}{P_0 - B_0/(1 - \rho)} \ln (PB_0/BP_0) \quad (4)$$

Straight-line plots are obtained for more than 70% of the reaction in chloroform and methylene chloride when ln (PB_0/BP_0) is plotted against time. Derived second-order rate constants are given in Table I. Slight deviations from linearity appearing in some cases are attributed to competing aromatic substitution, which occurs to less than 10% when $B_0/P_0 \leq 1$. The extent of these deviations is represented by the coefficient of linear regression, R (Table I), determined for each kinetic run. Examination of the R values in Table I shows that the plots tend to deviate least from linearity for the smaller values of B_0/P_0. Coincidentally, the amount of competing aromatic substitution increases with increasing B_0/P_0.

The second-order rate constant for the bromination of phenylcyclopropane in ethanol-free chloroform is invariable for B_0/P_0 values of 0.25, 0.50, and 1.00 (runs 18–21, 31–34, and 28–30). Over 20% para substitution occurs in competition with ring opening when B_0/P_0 is 2.00 (runs 16–17). Consequently, the second-order rate constant was not determined. The presence

(1) R. T. LaLonde, P. Ferrara, and A. Debboli, Jr., *J. Org. Chem.*, **37**, 1094 (1972).
(2) M. S. Karasch, P. White, and F. Mayo, *J. Org. Chem.*, **3**, 33 (1938).
(3) D. Applequist and R. Searle, *J. Amer. Chem. Soc.*, **86**, 1389 (1964).

TABLE I[a]

KINETICS OF THE ADDITION OF BROMINE TO PHENYLCYCLOPROPANE

Solvent	Run no.	B_0[b]	P_0[b]	Temp, °C	k,[c] 10^3 l. M^{-1} sec^{-1}	R[d]	ρ[e]
$CHCl_2$	1–2	0.25	0.125	20.1			0.36 ± 0.02
	3–6	0.125	0.125	20.1	7.83 ± 0.25	0.995	0.36 ± 0.02
	7–8	0.125	0.250	20.1	7.82 ± 0.08	0.995	0.36 ± 0.02
	9–10	0.09	0.36	20.1	7.46 ± 0.05	0.998	0.36 ± 0.02
	11–13[f]	0.125	0.250	20.1	7.30 ± 0.30	0.997	0.38 ± 0.02
	14–15[f]	0.125	0.250	5.0	2.97 ± 0.03	0.989	0.38 ± 0.02
$CHCl_3$	16–17[f]	0.50	0.25	20.1			0.50 ± 0.02
	18–21[f]	0.10	0.40	20.1	1.87 ± 0.06	0.997	0.50 ± 0.02
	22–23	0.10	0.40	20.1	2.31 ± 0.01	0.997	0.38 ± 0.02
	24–25[f]	0.10	0.40	5.0	0.825 ± 0.015	0.998	0.50 ± 0.02
	26–27[f]	0.10	0.40	30.0	3.11 ± 0.17	0.997	0.50 ± 0.02
	28–30[f]	0.25	0.25	20.1	2.08 ± 0.06	0.993	0.50 ± 0.02
	31–34[f]	0.25	0.50	20.1	2.08 ± 0.06	0.995	0.50 ± 0.02
CCl_4	35–36	0.25	0.25	20.1	0.384 ± 0.013	0.999	0
	37–38[f]	0.25	0.25	20.1	0.0202 ± 0.0002	0.997	0.57 ± 0.02
	39[f,g]	0.25	0.25	20.1	0.0199	0.999	0.57 ± 0.02

[a] All experiments except run 39 were performed in the dark. [b] Initial concentration of bromine, B, and phenylcyclopropane, P, in moles per liter. [c] Rate constant reported with average deviation for multiple runs. [d] R = average coefficient of linear regression for multiple runs. [e] Mole ratio of tribromide product to total ring-opening products. [f] Contains 5 mol % isoamyl nitrite with respect to bromine. [g] In room light.

of isoamyl nitrite has the effect of decreasing k by 20% in chloroform (runs 18–21 and 22–23).

Likewise, the second-order rate constant remains invariable for the reactions carried out in methylene chloride solutions when B_0/P_0 is varied from 0.25 to 0.50 to 1.00 (runs 9–10, 7–8, and 3–6). However, when B_0/P_0 was 2.00, the second-order rate constant was not determined because of the nearly 30% para substitution occurring in competition with the addition reaction (runs 1–2). Added isoamyl nitrite in methylene chloride decreases the rate constant by approximately 7% (runs 11–13 and 7–8).

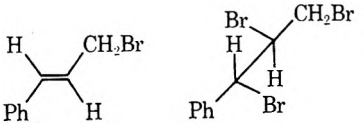
Using data from Table I the enthalpy of activation, $\Delta H^{\ddagger}$, and entropy of activation, $\Delta S^{\ddagger}$, were calculated according to the absolute rate equation.[4] The activation parameters for the reactions carried out in chloroform were $\Delta H^{\ddagger} = 8.3 \pm 0.8$ kcal mol^{-1} and $\Delta S_{293}{}^{\ddagger} = -43 \pm 3$ cal mol^{-1} °K^{-1} (runs 18–21, 24–27). The activation parameters for the reaction carried out in methylene chloride were $\Delta H^{\ddagger} = 9.3 \pm 0.8$ kcal mole^{-1} and $\Delta S_{293}{}^{\ddagger} = -36 \pm 3$ cal mol^{-1} °K^{-1} (runs 11–13, 14–15).

Straight-line plots are not observed when eq 4 is applied to the addition of bromine to phenylcyclopropane in carbon tetrachloride. However, plots of the reciprocal of the bromine concentration against time are linear. Rate constants in carbon tetrachloride were determined using the rate expression $kt = 1/B - 1/B_0$, which is derived from the rate equation $dB/dt = kB^2$. It is obvious that major kinetic differences exist between the bromine addition to phenylcyclopropane in carbon tetrachloride and in the other chlorinated solvents studied. We are not able at this time to rationalize this difference. Nevertheless, the rate constants for the carbon tetrachloride system are presented for comparative purposes.

The rate constant for the bromination of phenylcyclopropane in carbon tetrachloride in the dark is decreased by 95% when isoamyl nitrite is present (runs 35–38, Table I). Room light does not affect the rate when isoamyl nitrite is present (runs 37–39). However, without the added inhibitor room light has a drastic catalytic effect.[1]

Some interesting comparisons can be drawn from Table I concerning the effect of solvent on the rate of bromination. The second-order rate constants measured at 20° for the dark reaction increase with increasing solvent dielectric constants in the order $CCl_4 < CHCl_3 < CH_2Cl_2$ (runs 3–6, 22–23, and 35–36). Added isoamyl nitrite decreases the rate of bromination in each solvent without changing the overall order of the solvent effect (runs 37–38, 28–30, and 11–13). The ability of isoamyl nitrite to retard the rate of bromination is more pronounced in the solvents of lower dielectric constant. Added isoamyl nitrite decreases the rate constant by 95% in carbon tetrachloride, 20% in chloroform, and only 7% in methylene chloride.

Since cinnamyl bromide (1) appeared to be a probable precursor of the tribromide formed in the addition of bromine to phenylcyclopropane, the rate of bromine addition to 1 in chloroform at 22° in the dark was



1 2 3

measured. The addition is observed to follow the third-order kinetic expression $kt = 1/B^2 - 1/B_0{}^2$ when the initial concentration of 1 and bromine are equal. These results are consistent with reported third-order kinetics for the bromine addition to simple olefins in carbon tetrachloride.[5] A straight line is obtained when $1/B^2$ is plotted against time through 80% completion for runs where B_0 and the initial cinnamyl bromide concentration are 0.025 M. The rate constant is 8.25 l.$^2/M^2$ sec and the coefficient of linear regression, R, for the plot is 1.00.

cis- and *trans*-1,2-diphenylcyclopropane were brominated in the dark in chloroform at 20.1° with the initial bromine and hydrocarbon concentrations equal to 0.25 M. The time required for consumption of one

(4) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, pp 377–379.

(5) C. G. Gebelein and G. D. Frederick, *J. Org. Chem.*, **37**, 2211 (1972).

half of the bromine is 37 min for the trans and 12.5 min for the cis isomers. The bromine half-life for the addition to the trans and cis isomers is 25 and 16 min, respectively, when isoamyl nitrite was present.

Product Analysis.—The analysis and structure characterization of *dl*- and *meso*-1,2,3-tribromo-1,3-diphenylpropane, *p*-bromophenylcyclopropane, 1,3-dibromo-1-phenylpropane, and *dl*- and *meso*-1,3-dibromo-1,3-diphenylpropane have been presented in a previous paper.[1]

The erythro tribromide, **2**, isolated from the phenylcyclopropane bromination product, has identical physical and spectral properties with those of the erythro tribromide from the bromination of cinnamyl bromide, **1**. The dark addition of bromine to **1** in carbon tetrachloride gives a mixture of two tribromides, **2** and **3**. Since trans addition predominates under these conditions, the predominant diastereomer must be the erythro tribromide, **2**. Therefore the predominant downfield doublet (τ 4.69) in the nmr of the cinnamyl bromide product mixture is assigned to the erythro benzyl proton. Moreover, the doublet coupling constant for the erythro isomer is larger than the coupling constant for the threo isomer. This observation is consistent with the results from earlier nmr studies of erythro–threo dibromide pairs.[6]

The threo tribromide could not be separated from the phenylcyclopropane–bromine addition mixture. However, the spectral and chromatographic properties of the mixture are consistent with the presence of threo tribromide.

The tribromide–dibromide product ratio is affected by both solvent and the presence of isoamyl nitrite. Isoamyl nitrite increases the amount of tribromide in the product by 57% in carbon tetrachloride (runs 35–36 and 37–38), 12% in chloroform (runs 18–21 and 22–23), and 2% in methylene chloride (runs 11–13 and 7–8). The tribromide–dibromide ratio is the same for each of the three solvents at 50 and 100% completion and remains unchanged by temperature in the range 5–30° (runs 11–13, 14–15, 24–25, and 26–27).

Bromination of *trans*-1,2-diphenylcyclopropane in chloroform in the dark results in 100% conversion to 1,3-dibromo-1,3-diphenylpropane. The *dl*/meso ratio is 1.0. Under the same conditions with 5 mol % of isoamyl nitrite added the resulting product consists of 50% of 1,3-dibromo-1,3-diphenylpropane (*dl*/meso = 1.0), approximately 20% of 1,2,3-tribromo-1,3-diphenylpropane, and 30% of aromatic substitution products. Bromination of *cis*-1,2-diphenylcyclopropane in chloroform results in approximately 70% dibromide (*dl*/meso = 45/55) and 30% tribromide. Added isoamyl nitrite has no appreciable effect on the product composition.

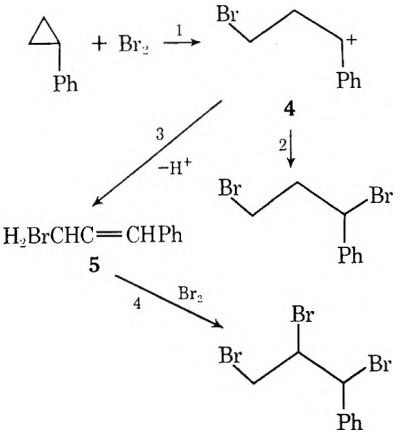
Pure 1,3-dibromo-1-phenylpropane and *erythro*-1,2,3-tribromo-1-phenylpropane were stable under the conditions employed for the addition of bromine. The stability of *dl*- and *meso*-1,3-dibromo-1,3-diphenylpropane under reaction conditions had been determined previously.[1]

Discussion

The results reported above for the dark bromination of arylcyclopropanes in chlorinated solvents in the presence of isoamyl nitrite show the following characteristics: (1) the formation of 1,3-dibromo-1-phenylpropane and 1,2,3-tribromo-1-phenylpropane as the main products from phenylcyclopropane; (2) the second-order kinetics, which are first order in both phenylcyclopropane and bromine concentration; (3) the increasing rate of bromine addition with increasing solvent dielectric constant, (4) the complete lack of stereospecificity in the addition to *trans*-1,2-diphenylcyclopropane and near lack of stereospecificity in the addition to the cis isomer.

These characteristics are consistent with addition occurring by electrophilic attack of bromine on arylcyclopropane and product formation involving intermediate ion **4**. The sequence of steps is summarized in Scheme I. The rate-determining step, step 1, is the

Scheme I



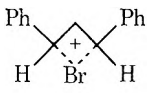
cleavage of the carbon–carbon single bond with accompanying carbonium ion formation.

Since bromine addition to cinnamyl bromide is fast relative to bromine addition to phenylcyclopropane, the ratio of tribromide to dibromide in the final product will depend on the relative rates of steps 2 and 3 and the extent to which the fast radical addition, reaction type A, competes with the much slower ionic reaction, reaction type B. Our earlier results coupled with those reported here demonstrate that reaction type A occurs photolytically or thermally and converts phenylcyclopropane completely to 1,3-dibromo-1-phenylpropane but is effectively retarded by isoamyl nitrite.

That the tribromide and dibromide products came from a common intermediate is consistent with the observations that the tribromide to dibromide ratio remains constant throughout the course of the reaction and is not effected by a change in the initial bromine–phenylcyclopropane ratio. Moreover, the dibromide was found to be stable to reaction conditions. Since the tribromide–dibromide product ratio is inversely related to the solvent dielectric constant, the amount of reaction proceeding by step 3 relative to step 2 decreases with increasing dielectric constant.

The complete lack of stereospecificity in the bromination of *trans*-1,2-diphenylcyclopropane would suggest that the carbonium ion intermediate, **4**, formed from phenylcyclopropane is symmetrical. Bromine atom participation such as in the bridged ring bromonium ion, **6**, would require a preference for trans stereo-

(6) R. C. Fahey and J. J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1968).



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specific addition and therefore can be eliminated as a plausible intermediate.

1,2-Dibromo-1-phenylpropane, an expected product of 1,2-cyclopropane addition, was undetected in product mixtures resulting from bromine addition to phenylcyclopropane. Yet as much as 2% of this dibromide could be detected by nmr in synthetic mixtures. 1,2-Cyclopropane addition is observed in additions to some alkylcyclopropanes.[7,8] The absence of such addition in the case of the arylcyclopropanes is undoubtedly the result of the increased stability of benzyl carbonium ions relative to the bridge ion species of the type offered as intermediates in 1,2 addition to alkylcyclopropanes.

Differences in product composition and the effects of light and isoamyl nitrite connected with the carbon tetrachloride reactions seem best explained as follows. The photochemically or thermally initiated reaction (type A) is the only effective one in carbon tetrachloride solution, the ionic reaction competing only very slowly. However, when isoamyl nitrite is added, reaction type A is strongly retarded and the decreased rate of bromine consumption and appearance of tribromide reflects the occurrence of the ionic pathway given in Scheme I. In contrast to the carbon tetrachloride reactions, type A reaction in chloroform and methylene chloride amounts to only 20 and 7%, respectively, since the reaction rates are decreased by 20 and 7% when isoamyl nitrite is present. The tribromide–dibromide product compositions of the chloroform reaction support this view. The observed tribromide–dibromide ratios in the absence of isoamyl nitrite is 0.61 ± 0.04. The expected ratio is 0.66 based on 20% reaction type A, which yields only dibromide, and 80% type B, which yields tribromide and dibromide in a 1:1 ratio when isoamyl nitrite is present.

Experimental Section

Spectra were obtained as follows: nmr in $CDCl_3$ solution (unless otherwise indicated), 1% TMS (τ 10.00), Varian A-60A, symbols s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; ir in CCl_4 solution (unless otherwise indicated) Perkin-Elmer 137, 0.05-mm sample and reference cells, symbols s, m, w, sh, and br refer to strong, medium, weak, sharp, and broad, respectively; mass spectrum at 70 eV and 160–165° with an all-glass heated inlet, Hitachi Perkin-Elmer RMU-6E.

Melting points were determined on a Köfler micro hot stage and are uncorrected. Vpc was performed on a Varian Aerograph Model 200 and high-speed liquid chromatography was performed on a Waters Associates ALC/GPC Model 502 using conditions as indicated. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Evaporation of solvent or concentration of solution was done at the flash evaporator at reduced pressures.

Materials.—All solvents were distilled over P_2O_5 through a 12-in. Vigreux column. Chloroform was washed successively with concentrated H_2SO_4, water, and 10% aqueous Na_2CO_3 followed by preliminary drying ($CaCl_2$) prior to distillation.

Bromine (reagent grade, Fisher) was used without further purification.

Phenylcyclopropane was purchased from Chemical Samples Co. and found to be at least 99% pure by vpc on both a Carbowax and a SE-30 column. 1,2-Diphenylcyclopropane was purchased from Chemical Samples Co. and separated on a spinning band column to obtain cis [bp 116° (0.2 mm)] and trans [bp 125° (0.2 mm)] isomers. The cis isomer was further purified by recrystallization from *n*-pentane. *cis*- and *trans*-1,2-Diphenylcyclopropane were found to be greater than 99% pure by vpc (0.25 in. × 8 ft, 5% SE-30 on Chromosorb W, 200°, flow rate of 1.4 ml/sec). Retention times of 5.2 min for the cis isomer and 6.4 min for the trans isomers were observed. Cinnamyl bromide was purchased from Aldrich Chemical Co. and distilled [bp 76° (0.3 mm)] immediately before its use.

Stock Solutions.—Stock solutions of approximately 0.5 *M* Br_2 in CCl_4, $CHCl_3$, and CH_2Cl_2 were prepared by pipeting 1.3 ml of Br_2 into 49 ml of the solvent in a ground glass stoppered volumetric flask. The concentration of the solution was determined by titration with 0.1 *N* $Na_2S_2O_3$ solution in the presence of excess KI.[9] These stock solutions were then diluted to the desired concentration.

Kinetic Procedure.—The reaction rates for the arylcyclopropane brominations were followed by determining the Br_2 concentration spectrophotometrically with a Cary 15 spectrophotometer. The absorbance of the reaction solution was determined in a 2-mm quartz cell with a 1.9-mm spacer in the solvent indicated at the following wavelengths: CCl_4, 415 nm; $CHCl_3$, 413 nm; CH_2Cl_2, 411 nm. The diluted Br_2 and arylcyclopropane solutions were allowed to equilibrate thermally in a thermostated water bath in a darkened room, and then mixed in a blackened glass stoppered reaction flask. Aliquots were removed periodically and the Br_2 absorbance was determined. The first reaction measurement was always made within 1 min of mixing. A fresh aliquot was removed for each measurement. The reaction product mixtures were isolated by flash evaporation of the solvent and excess bromine in the dark.

The rate constants for the $CHCl_3$ and CH_2Cl_2 systems were calculated using the expression $kt = 1/K \ln (B_0P/P_0B)$, where P and B are the arylcyclopropane and Br_2 concentrations, respectively, P_0 and B_0 refer to initial concentrations, t is the time, and $K = P_0 - B_0/(1 - \rho)$. The ratio of tribromide product to total ring opening products is ρ. The rate constants for the CCl_4 system were calculated using the expression $kt = 1/B + 1/B_0$. All reported rate constants are the average of multiple runs followed through at least 70% completion, and were determined using a least squares method.

Product Analysis.—The ratio of erythro and threo tribromides to dibromide was determined from the benzyl proton resonances in the nmr spectra of the crude product mixtures. The dibromide benzyl proton resonance appeared at τ 4.89 (d of d, J = 7.8 Hz). The benzyl proton of the erythro tribromide appeared at τ 4.69 (d, J = 9 Hz). The benzyl proton of the threo tribromide appeared at τ 4.47 (d, J = 4 Hz). Synthetic mixtures of tri- and dibromides of various ratios were prepared from the pure tri- and dibromides. The percentage compositions of these synthetic mixtures determined by nmr agreed within 3% with the compositions determined by weight.

erythro- (**2**) and *threo*-**1,2,3-Tribromo-1-phenylpropane** (**3**).—To 0.62 g of cinnamyl bromide in 6.6 ml of $CHCl_3$ was added 6.1 ml of a 0.52 *M* Br_2 in $CHCl_3$ solution. After decolorization (15 min) the solution was flash evaporated to yield 1.15 g (100% yield) of a white solid. Nmr analysis revealed the product to contain a 1:1 mixture of **2** and **3**. When the bromination was carried out in CCl_4, the resulting product contained 85% of **2** and 15% of **3**.

Recrystallization from pentane of the mixture containing 85% of **2** gave pure **2**: mp 123–124°;[10] white needles; nmr ($CDCl_3$) τ 2.65 (s, 5 H, ArH), 4.69 (d, 1 H, J = 9.0 Hz, ArCHBr), 5.28 (quintet, 1 H, J = 9.0, 4.5, and 4.5 Hz, C-2 H), 5.80 (q, 1 H, J = 11.5 and 4.5 Hz, C-3 H), 6.09 (q, 1 H, J = 11.5 and 4.5 Hz, C-3 H); ir (1% KBr pellet) 690 cm^{-1} (s, sh), 760 (m, sh), 825 (m, sh), 880 (m, sh), 1130 (m, sh), 1250 (m, sh), and 1410 (m, sh); mass spectrum m/e 354 (M^+), 356 ($M^+ + 2$), 358 ($M^+ + 4$), 350 ($M^+ + 6$), 375, 377, and 379 ($C_9H_8Br_2^+$), 169 and 171 ($C_6H_5CHBr^+$), 117 (base peak, $M^+ - Br_3$).

(7) R. T. LaLonde, *J. Amer. Chem. Soc.*, **87**, 4217 (1965).
(8) N. C. Deno and D. N. Lincoln, *J. Amer. Chem. Soc.*, **88**, 5357 (1966).
(9) H. H. Furan, "Scott's Standard Methods of Chemical Analysis," Vol. I, Van Nostrand, Princeton, N. J., 1959.
(10) T. Taguchi, M. Tomoeda, and I. Aratani, *J. Amer. Chem. Soc.*, **78**, 1468 (1956).

threo-1,2,3-Tribromo-1-phenylpropane (**3**) was purified by preparative liquid–solid chromatography employing a 0.0125 in. × 2 ft Corasil II column at a flow rate of 1.0 ml/min. The eluting solvent was *n*-hexane. The retention times for **2** and **3** were 2.6 and 2.1 min, respectively. In this manner pure **3** was obtained as a clear oil: nmr ($CDCl_3$) τ 2.68 (s, 5 H, ArH), 4.47 (d, 1 H, J = 4 Hz, ArCHBr), 5.65 (m, 1 H, C-2 H), 6.20 (m, 2 H, C-3 H); ir 695 (s, sh), 1220 (m, sh), 1435 (m, sh), 1450 (m, sh), 1495 cm^{-1} (m, sh); mass spectrum m/e 354 (M^+), 356 ($M^+ + 2$), 358 ($M^+ + 4$), 360 ($M^+ + 6$), 375, 377, and 379 ($C_9H_9Br_2^+$), 169 and 171 ($C_6H_5CHBr^+$), 117 (base peak, $M^+ - Br_3$). *Anal.* Calcd for $C_9H_9Br_3$: C, 30.28; H, 2.54; Br, 67.17. Found: C, 30.58; H, 2.57; Br, 67.06.

Stability of Ring-Opening Products to Reaction Conditions.—1,3-Dibromo-1-phenylpropane (200 mg) in 5 ml of a 0.25 *M* Br_2–$CHCl_3$ solution was allowed to stand at room temperature in the dark for 40 hr. Flash evaporation of the solvent and Br_2 yielded a clear oil which was determined to be the starting 1,3-dibromophenylpropane by comparative nmr and ir analysis.

2 (200 mg) in 5 ml of a 0.25 *M* Br_2–$CHCl_3$ solution was allowed to stand for 40 hr in the dark at room temperature. Flash evaporation of the solvent yielded a white, crystalline solid, mp 122–125°, which was determined to be the starting **2** by comparative nmr analysis.

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Registry No.—**1**, 4392-24-9; **2**, 42334-76-9; **3**, 42334-77-0; phenylcyclopropane, 873-49-4.

Stereochemistry of Reduction of Substituted Cyclohexanones with Triisobutylaluminum and Diisobutylaluminum Hydride

GEORGE E. HEINSOHN AND E. C. ASHBY*

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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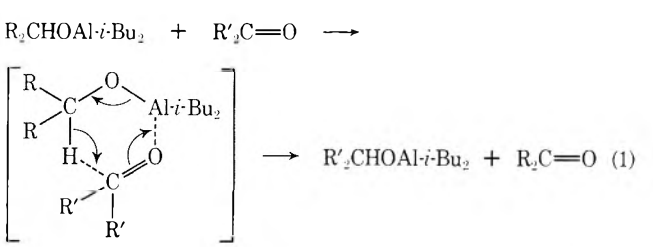
The reduction of 3,3,5-trimethylcyclohexanone and 4-*tert*-butylcyclohexanone with diisobutylaluminum hydride (DIBAH) and with triisobutylaluminum (TIBA) has been examined in ether and in benzene. Reduction of these ketones with DIBAH in 1:1 stoichiometry produces the epimeric alcohols in quantitative yield. The isomer ratio of the product mixture is essentially independent of solvent and reactant stoichiometry. On the other hand, reduction of these ketones with TIBA is more selective and is accompanied by some (~5%) formation of aluminum enolate. The isomer ratio of the product mixture is essentially independent of solvent, but dependent on the reactant stoichiometry and the initial concentration of TIBA. Evidence is presented which indicates that the epimeric ratio of alcohol products is influenced by the degree of association of TIBA, complex formation between TIBA and the aluminum alkoxide formed, and isomer equilibration by a Meerwein–Ponndorf–Verley pathway.

Since the reduction of chloral to 2,2,2-trichloroethanol by treatment with triethylaluminum etherate was first noted,[1] organoaluminum compounds have been investigated in considerable detail as reducing agents for a wide variety of organic functional groups. Although the reaction of organoaluminum reagents with carbonyl compounds can afford mixtures of alkylated and reduced products, the primary mode of reaction is that of reduction when the organometallic reagent has an available hydrogen at a branched β position,[2] or contains aluminum–hydrogen bonds.[3] Despite intensive investigation over a period of several decades, surprisingly little is presently known about the factors influencing the stereochemistry of reduction. The present study was undertaken with a twofold purpose in mind: (1) to systematically examine triisobutylaluminum (TIBA) and diisobutylaluminum hydride (DIBAH) as potential stereoselective reagents for the reduction of carbonyl compounds, and (2) to delineate the experimental parameters affecting the stereochemistry of reduction, particularly the effect of reactant stoichiometry on stereochemistry in hydrocarbon solvent.

Reduction of 2-methylcyclohexanone with DIBAH leads to predominant formation of *cis*-2-methylcyclohexanol, the least stable of the two expected alcohols.[4] However, because of the conformational mobility of 2-methylcyclohexanone, stereochemical interpretation of this result is at best uncertain. Furthermore, the isomer ratio of the product mixture was determined by measurement of density, a technique considerably less accurate than modern gas chromatographic methods. Haubenstock and Davidson[5] found that the composition of the product mixture obtained by reduction of 3,3,5-trimethylcyclohexanone with TIBA in benzene at 42° was dependent on the ratio of reactants. When TIBA was present in excess, the product mixture contained 96% of the least stable alcohol, *trans*-3,3,5-trimethylcyclohexanol. In the presence of excess ketone the isomeric ratio of the product mixture changed with time, approaching pure *cis*-3,3,5-trimethylcyclohexanol after 31 hr at 42°. This was attributed to thermodynamically controlled isomer equilibration *via* a Meerwein–Ponndorf–Verley type reduction involving



a six-center transition state. The authors concluded that hydride transfer in a kinetically controlled process occurs predominantly from the least hindered side of

(1) H. Meerwein, G. Hinz, H. Majert, and H. Sonke, *J. Prakt. Chem.*, **147**, 226 (1936).

(2) K. Zeigler in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, Chapter 5.

(3) W. L. Everson and E. M. Ramirez, *Anal. Chem.*, **37**, 806 (1965).

(4) L. I. Zakharkin and I. M. Khorlina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.*, 1144 (1961); *Chem. Abstr.*, **55**, 27135e (1961).

(5) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).

the ketone, affording *trans*-3,3,5-trimethylcyclohexanol as the major product.

Teisseire and coworkers[6] have reported the reduction of several terpenoid ketones with excess TIBA in hydrocarbon solvent. In agreement with the work of Haubenstock and Davidson,[5] hydride transfer was observed in all cases to occur predominantly from the least hindered side of the substrate, leading to the thermodynamically less stable alcohol. Since TIBA was employed in excess, equilibration of the product mixture was not observed. In those cases where comparative data were reported, reduction with TIBA was found to be more stereoselective than reduction with DIBAH, leading in the former case to a higher proportion of the less stable alcohol.

Recently we reported that a dramatic change in stereochemistry takes place when 4-*tert*-butylcyclohexanone is allowed to react with trimethylaluminum in benzene if the R_3Al:ketone ratio is changed from 1:1 to 2:1,[7] whereas no change in stereochemistry is involved in ether solvent under the same conditions. It was suggested that the reaction in 1:1 ratio proceeds *via* a four-center transition state whereas the reaction in 2:1 ratio proceeds *via* a six-center transition state. Since there is reason to believe that reaction of a ketone with diisobutylaluminum hydride proceeds *via* a four-center transition state and reaction with triisobutylaluminum proceeds *via* a six-center transition state,[8] it was considered particularly important to evaluate the stereochemistry of diisobutylaluminum hydride and triisobutylaluminum reduction of 4-*tert*-butylcyclohexanone in benzene solvent. Based on the stereochemical results observed in the reaction of 1 and 2 with $(CH_3)_3Al$ it was anticipated that diisobutylaluminum hydride would reduce 4-*tert*-butylcyclohexanone in benzene predominantly from the least hindered side of the molecule (equatorial attack to produce the axial alcohol) in 1:1 ratio with an increasing amount of axial attack as the R_2AlH:ketone ratio is changed to 2:1. It was further anticipated that the stereochemistry of triisobutylaluminum reduction in benzene would be independent of stoichiometry and that reduction with both reducing agents would be independent of stoichiometry in ether solvent.

Eliel and Senda[9] have suggested that, in the absence of other factors, attack on the carbonyl group in an asymmetric environment occurs predominantly from the sterically least hindered side. The importance of stereoselective attack of reducing agents on a carbonyl group from the least hindered side of the molecule is obvious. In this way the least stable alcohol is always formed which is the most difficult isomer to obtain. The most stable isomer, of course, can be easily obtained by equilibration of the epimeric alcohol mixture.

Results and Discussion

Table I summarizes the results obtained for reduction of 3,3,5-trimethylcyclohexanone (1) and 4-*tert*-butylcyclohexanone (2) with DIBAH. In each case, only the two expected reduction products were observed which together quantitatively account for the ketone consumed during reaction. It is evident from the data that reduction occurs in 1:1 stoichiometry. Failure to detect ketone after reaction with excess DIBAH indicates that formation of an aluminum enolate does not occur under these conditions, since quenching of the enolate would regenerate the ketone. As expected, a greater proportion of axial alcohol is obtained during reduction of 3,3,5-trimethylcyclohexanone than in the case of 4-*tert*-butylcyclohexanone, since axial attack is more hindered in the former case than in the latter.[10] Somewhat surprisingly, however, the stereochemistry of reduction is essentially independent of the nature of the solvent employed and not significantly influenced by reaction stoichiometry. Spectroscopic investigation[11] has shown that DIBAH exists as a cyclic hydrogen-bridged trimer (3) in the absence of donor solvents, but forms moderately stable 1:1 adducts (4) which exist in equilibrium with the associated species when aliphatic ethers are present. It is therefore likely that reduction in either solvent proceeds with prior formation of a complex analogous to the complex observed spectroscopically during reduction of benzophenone with TIBA.[8]

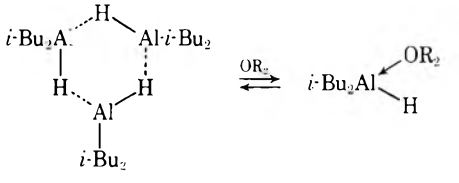
When 4-*tert*-butylcyclohexanone was allowed to react with trimethylaluminum in benzene solvent, dramatic changes occurred in the stereochemistry when

TABLE I[a]

REDUCTION OF 3,3,5-TRIMETHYLCYCLOHEXANONE (1) AND 4-*tert*-BUTYLCYCLOHEXANONE (2) WITH DIISOBUTYLALUMINUM HYDRIDE

Expt	Ketone	Solvent	DIBAH, mmol	Ketone recovered, %	Products, % Axial alcohol	Products, % Equatorial alcohol
1	1	Ether	0.5	56	70	30
2	1	Ether	1.0	17	69	31
3	1	Ether	2.0	0	74	26
4	1	Ether	5.0	0	75	26
5	1	Benzene	0.5	56	67	33
6	1	Benzene	1.0	7	68	32
7	1	Benzene	2.0	0	73	27
8	1	Benzene	5.0	0	77	23
9	2	Ether	0.5	51	25	75
10	2	Ether	1.0	0	28	72
11	2	Ether	2.0	0	29	71
12	2	Ether	5.0	0	26	74
13	2	Benzene	0.5	48	32	68
14	2	Benzene	1.0	5	30	70
15	2	Benzene	2.0	0	34	66
16	2	Benzene	5.0	0	31	69

[a] All runs employed 1.0 mmol of ketone and 10.0 ml of solvent; reaction time was 2 hr at 0° in ether and 2 hr at 22° in benzene; quenched with 5% HCl.



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(6) (a) P. Teisseire, A. Galfre, M. Plattier, and B. Corbier, *Recherches*, **15**, 52 (1966); P. Teisseire, A. Galfre, M. Plattier, and B. Corbier, *ibid.*, **16**, 59 (1967); (c) P. Teisseire, P. Roullier, and A. Galfre, *ibid.*, **16**, 68 (1967); (d) P. Teisseire, A. Galfre, M. Plattier, P. Roullier, and B. Corbier, *ibid.*, **16**, 119 (1967).

(7) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37**, 1918 (1972).

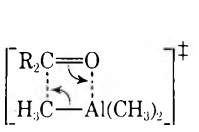
(8) E. C. Ashby and S. H. Yu, *J. Org. Chem.*, **35**, 1034 (1970).

(9) E. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).

(10) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Menlo Park, Calif., 1972, pp 54–68.

(11) E. G. Hoffman, *Z. Elektrochem.*, **61**, 1014 (1957).

the organoaluminum compound to ketone ratio was >1:1.[7] Under these circumstances a higher proportion of product resulted from transfer of a methyl group to the most hindered (axial) side of the substrate molecule. Kinetic evidence has been presented to support the idea that this is a result of a change in mechanism.[12] When excess trimethylaluminum is present, alkylation proceeds by a consecutive bimolecular reaction possibly *via* a six-center transition state (**6**) rather than the four-center transition state (**5**) postulated for the case



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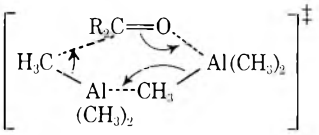

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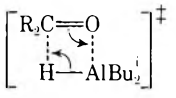
when equimolar quantities of reactants are employed. Although a similar change in mechanism is conceptually possible for ketone reduction with DIBAH (**7**, **8**), the



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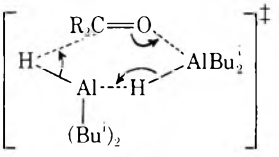

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data in Table I fail to supply evidence for its occurrence. The isomeric ratio of the product mixture is essentially independent of reactant ratio, and the small changes that are noted are in the direction opposite to that observed for alkylation with trimethylaluminum.

The results obtained in the reduction of **1** and **2** with TIBA (Table II) are qualitatively similar to the results

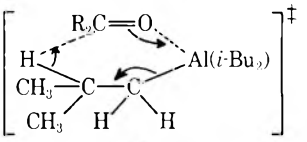
TABLE II[a]

REDUCTION OF 3,3,5-TRIMETHYLCYCLOHEXANONE (1) AND 4-*tert*-BUTYLCYCLOHEXANONE (2) WITH TRIISOBUTYLALUMINUM

					Products, %	
Expt	Ketone	Solvent	TIBA, mmol	Ketone recovered, %	Axial alcohol	Equatorial alcohol
17	1	Ether	0.5	40	63	37
18	1	Ether	1.0	5	67	33
19	1	Ether	2.0	5	86	14
20	1	Ether	5.0	2	90	10
21	1	Benzene	0.5	54	82	18
22	1	Benzene	1.0	8	90	10
23	1	Benzene	2.0	3	90	10
24	1	Benzene	5.0	2	93	7
25	2	Ether	0.5	52	14	86
26	2	Ether	1.0	11	35	65
27	2	Ether	2.0	12	36	64
28	2	Ether	5.0	10	44	56
29	2	Benzene	0.5	42	30	70
30	2	Benzene	1.0	11	39	61
31	2	Benzene	2.0	3	40	60
32	2	Benzene	5.0	3	41	59

[a] All runs employed 1.0 mmol of ketone and 10.0 ml of solvent; reaction time was 2 hr at 0° in ether and 2 hr at 22° in benzene; quenched with 5% HCl.

using DIBAH; *i.e.*, reduction of **1** involves predominant equatorial attack and reduction of **2** involves predominant axial attack with either TIBA or DIBAH. Since the reduction of ketones by TIBA is known to be first order in both ketone and TIBA and since the stereochemistry of reduction of **1** and **2** by DIBAH is not only similar to that observed for TIBA but also independent of stoichiometry, it is plausible that both reactions proceed *via* similar transition states, namely **8** and **9**. Although it was anticipated that the reaction



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of DIBAH with ketone would proceed *via* **7** at 1:1 stoichiometry and *via* **8** at 2:1 stoichiometry, it is not unreasonable to suggest that the reaction proceeds *via* **8** at all stoichiometries for two reasons: first, hydrogen is a much stronger bridging group than methyl (see **5** and **6**) and, secondly, if equilibrium 2 does not lie entirely to the right and pathway 4 is more rapid than pathway 3, then the reaction would be expected to proceed *via* pathway 4 involving transition state **8**.

$$R_2C{=}O + R'_2AlH \rightleftharpoons \underset{\text{(complex)}}{R_2C{=}O\cdots AlR_2H} \quad (2)$$

$$\text{complex} \longrightarrow [7]^{\ddagger} \longrightarrow \text{product} \quad (3)$$

$$\text{complex} + R_2AlH \longrightarrow [8]^{\ddagger} \longrightarrow \text{product} \quad (4)$$

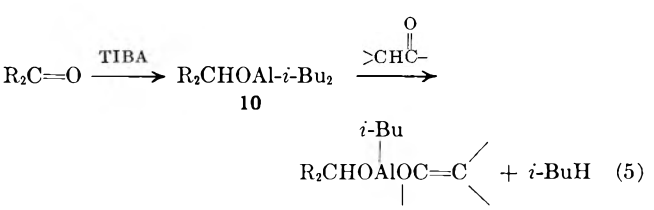
In agreement with previous reports, reduction with TIBA apparently proceeds in 1:1 stoichiometry. In all cases only the two expected reduction products were observed which together quantitatively account for the ketone consumed during reaction. Since the reduction reaction is rapid on the time scale of these experiments (Table III), recovery of ketone even when a fivefold

TABLE III

TIME DEPENDENCE OF PRODUCT ISOMER RATIO FOR REDUCTION OF 3,3,5-TRIMETHYLCYCLOHEXANONE WITH TRIISOBUTYLALUMINUM

Time, min	Axial alcohol, %	Equatorial alcohol, %	Unreacted ketone, mmol
3	72	28	0.26
10	68	32	0.25
20	67	33	0.26
120	66	34	0.19
240	66	34	0.23

excess of TIBA is employed provides compelling evidence for formation of an aluminum enolate. Ziegler, *et al.*,[13] have demonstrated that dialkylalkoxyaluminum compounds can abstract acidic protons from carbonyl-containing molecules, resulting in formation of an aluminum enolate. The enolization accompanying reduction with TIBA can then be explained as proton abstraction by the initially formed reduction product, diisobutylaluminum alkoxide.[8] Since DIBAH is far



(5)

(12) E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Amer. Chem. Soc.*, **90**, 5179 (1968).

(13) K. Zeigler, K. Schneider, and J. Schneider, *Justus Liebigs Ann. Chem.*, **623**, 9 (1959).

more reactive than TIBA toward ketones,[12] the aluminum alkoxide **10** is more able to compete with TIBA than with DIBAH for unreacted ketone. Consequently, enolization is observed during reduction with TIBA but not with DIBAH. In agreement with the results of previous workers,[5,6] comparison of Tables I and II demonstrates that the less reactive reducing agent, TIBA, is somewhat more selective than the more reactive one, DIBAH.

The most striking feature of Table II is that the stereochemistry of reduction with TIBA is apparently dependent on the ratio of reactants. In the presence of excess ketone, a higher proportion of the more stable equatorial alcohol is obtained. Several factors which might contribute toward this variation in stereochemistry were examined. The first of these is equilibration by a Meerwein–Ponndorf–Verley type reduction as previously observed over relatively long periods of time by Haubenstock and Davidson.[5] To determine whether equilibration of this type contributes significantly in determining the isomer ratios reported in Table II, 3,3,5-trimethylcyclohexanone (*ca.* 1.0 mmol) in ether was allowed to react with TIBA (*ca.* 0.75 mmol) and the stereochemical progress of the reaction was monitored by periodic withdrawal of samples. The results are summarized in Table III. Isomer equilibration does occur, and *cis*-3,3,5-trimethylcyclohexanol is continually produced at the expense of the trans isomer. However, even in the presence of 25 mol % of 3,3,5-trimethylcyclohexanone, equilibration is slow relative to the time scale of the reduction experiments (Table II). Consequently, other factors might be sought, operating in conjunction with isomer equilibration, to explain the variation of product composition with reactant ratio.

Since all the reduction experiments employed the same volume of solvent, the concentration of TIBA varied from 0.05 to 0.5 *M*. The change in stereochemistry might reflect differences in the state of association of the reducing agent. There is some disagreement in the literature concerning the degree of association of TIBA in benzene and in ether. Cryoscopic and other studies have indicated that TIBA is monomeric in both solvents over the concentration range of present interest.[14] However, more recent calorimetric studies have demonstrated considerable association of TIBA.[15] It might be expected that, because of increased steric requirement of an associated species, greater selectivity and hence a higher proportion of *trans*-3,3,5-trimethylcyclohexanol would result when the initial TIBA concentration is greater. Because of enhanced coordination ability of ether, it would be anticipated that such an effect might be more pronounced in benzene than in ether. Inspection of Tables I and II shows that a greater proportion of equatorial attack generally does occur when the solvent is benzene. To test the effect of association of the reducing agent on the stereochemistry of reduction, several experiments were conducted in which equimolar quantities of reactants were employed, but the amount of ether solvent and hence the degree of association of TIBA was varied. Table IV summarizes the results of these experiments.

TABLE IV[a]

EFFECT OF INITIAL TRIISOBUTYLALUMINUM CONCENTRATION ON REDUCTION OF 3,3,5-TRIMETHYLCYCLOHEXANONE

Expt	[TIBA]	Axial alcohol, %	Equatorial alcohol, %	Ether, ml
33[b]	1.0	65	35	1
34	0.2	68	32	5
35	0.1	67	33	10
36	0.05	62	38	20
37	0.025	58	42	40

[a] All runs employed 1.0 mmol of ketone and 1.0 mmol of TIBA. [b] Because of poor mixing and considerable heating, this result could not be consistently reproduced and should be taken *cum grano salis*.

Clearly, the stereochemistry of reduction of 3,3,5-trimethylcyclohexanone with TIBA does depend on the initial concentration of the reducing agent. At high concentration where considerable association of TIBA is expected, there is a greater preference for hydride transfer from the least hindered equatorial side of the substrate, leading to a higher proportion of *trans*-3,3,5-trimethylcyclohexanol. However, this effect is relatively minor over the range of initial TIBA concentration employed in the reduction experiments, and cannot be solely responsible for the stereochemical variation reported in Table II.

Another factor of potential stereochemical consequence is possible complex formation between the initially formed dialkylalkoxyaluminum and TIBA. In those cases where TIBA is not in excess, a complex such as **11** (joined *via* an alkoxy bridging group) might

$$R_2C{=}O \xrightarrow{\text{TIBA}} \underset{\mathbf{10}}{R_2CHOAl\text{-}i\text{-}Bu_2} \underset{\longleftarrow}{\overset{\text{TIBA}}{\rightleftharpoons}} \underset{\mathbf{11}}{R_2CHOAl\text{-}i\text{-}Bu_2\cdot i\text{-}Bu_3Al}$$

be the active reducing species leading to a different stereochemical result. *A priori*, formation of such a complex might seem unlikely, since, even in the presence of donor solvents, aluminum alkoxides such as **10** exhibit a very strong tendency to self-associate into unreactive dimers and/or trimers.[12] On the other hand, formation of stable mixed alkoxy–alkyl bridged systems of empirical formula $R_2AlOR\cdot AlR_3$ are known.[16] Therefore, one cannot discount the possibility of reduction by a small equilibrium concentration of a complex such as **11**. The extent of such reduction would depend on the ability of the complex to compete with TIBA for ketone, and hence on the ratio of TIBA to ketone. To test the significance of reduction by a complex such as **11**, 3,3,5-trimethylcyclohexanone was reduced in ether with a reagent formed by premixing 3,3,5-trimethylcyclohexanol (35% trans) with 2 equiv of TIBA. After correcting for the isomeric composition of the reagent, it was found that 60% hydride transfer to the ketone was from the equatorial side. In a parallel experiment, reduction with TIBA under identical conditions resulted in 66% hydride transfer from the equatorial side of the ketone. This result suggests that a definite but small fraction of the stereochemical variation in reduction of ketones with TIBA

(14) (a) E. G. Hoffmann, *Justus Liebigs Ann. Chem.*, **629**, 104 (1960); (b) R. Koster and P. Binger, *Advan. Inorg. Chem. Radiochem.*, **7**, 263, (1965).

(15) M. B. Smith, *J. Organometal. Chem.*, **22**, 273 (1970).

(16) E. C. Ashby, J. Laemmle, and G. Parris, *J. Organometal. Chem.*, **19**, 24 (1969).

may be attributed to intervention by a complex such as 11.

Thus it appears that the dependence of the isomeric composition of the product mixture obtained by reduction of 3,3,5-trimethylcyclohexanone or 4-*tert*-butylcyclohexanone with TIBA cannot be attributed to a single cause. At least three minor factors are operative: isomeric equilibration *via* a Meerwein–Ponndorf–Verley type reduction, association of the reducing agent, and complexation of TIBA by the initially formed aluminum alkoxide. Greatest selectivity is attained when TIBA is employed in excess and the reduction is performed in concentrated solution.

Experimental Section

Manipulations of air-sensitive compounds were performed either in a Kewaunee inert atmosphere box or by employing special bench-top techniques.[17] Reagents were transferred in flame-dried syringes which were cooled under nitrogen. Products were analyzed by glc utilizing a 20-ft column packed with 5% Carbowax 20M on Chromosorb G and a Hewlett-Packard Model 700 chromatograph. Ethyl benzoate was employed as internal standard in reduction of 3,3,5-trimethylcyclohexanone, and analyses were performed at 135°. Retention times for ketone, axial alcohol, and equatorial alcohol were 16.0, 25.2, and 31.1 min, respectively. For reduction of 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone was used as internal standard and analyses were performed at 150°. Retention times for ketone, axial alcohol, and equatorial alcohol were 22.6, 25.9, and 31.0 min, respectively.

Materials.—Reagent-grade ether and benzene were refluxed for 24 hr over $LiAlH_4$ and $NaAlH_4$, respectively, distilled through a 3-ft Vigreux column, and stored over sodium–lead alloy (J. T. Baker dri-Na) in a nitrogen atmosphere. Standard solutions of diisobutylaluminum hydride and triisobutylaluminum were prepared from the aluminum compounds as received (Ethyl Corp.). Aluminum analysis of the solutions by EDTA titration were in all cases satisfactory. Hydrolysis of an aliquot and analysis of the gases evolved indicated the presence of 2.7% active hydride in the triisobutylaluminum. 3,3,5-Trimethylcyclohexanone (Chemical Samples Co., 99%) was distilled through a 2-ft glass helices column and the middle fraction was used in this study. 4-*tert*-Butylcyclohexanone (Frinton Laboratories) was sublimed prior to use.

General Procedure for Reduction.—A 50-ml erlenmeyer flask containing a magnetic stirring bar was flame dried and allowed to cool under vacuum in the entry port of an inert atmosphere box. After transfer of the flask into the box, it was sealed with a rubber septum, removed from the box, and connected by means of a needle to a nitrogen-filled manifold equipped with an oil-filled bubbler. A solution of the appropriate ketone (1.00 mmol, *ca.* 1 ml of 1 *M* solution) was introduced into the reaction vessel followed by sufficient solvent to bring the final volume to 10.0 ml except in those cases where TIBA concentration was being studied. Stirring was initiated and the flask was immersed in a water bath at 0° for the reactions to be carried out in ether or at 22° for those to be carried out in benzene. After the flask had come to temperature equilibrium, a solution (*ca.* 1 *M*) of the appropriate organoaluminum reagent was introduced, allowed to react for 2.0 hr, and then quenched by addition of *ca.* 0.5 ml of 5% HCl. Internal standard was added and the product mixture was analyzed by glc.

Acknowledgments.—We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and to the Ethyl Corp. for generous samples of TIBA and DIBAH.

Registry No.—1, 873-94-9; 2, 98-53-3; diisobutylaluminum hydride, 1191-15-7; triisobutylaluminum, 100-99-2; axial 3,3,5-trimethylcyclohexanol, 767-54-4; equatorial 3,3,5-trimethylcyclohexanol, 933-48-2; axial 4-*tert*-butylcyclohexanol, 937-05-3; equatorial 4-*tert*-butylcyclohexanol, 937-06-4.

(17) D. F. Shriver, "The Manipulation of Air-Sensitive Compounds," McGraw-Hill, New York, N. Y. 1969.

The Stereochemistry of Electroreductions. IV. Carbon–Sulfur Single Bonds[1]

CHARLES M. FISCHER AND RONALD E. ERICKSON*

Department of Chemistry, University of Montana, Missoula, Montana 59801

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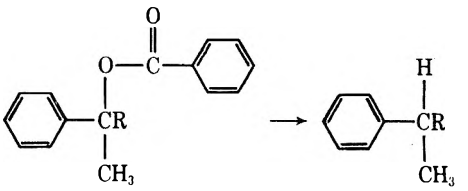
The stereochemistry of the electroreduction of optically active ethyl 2-phenylmercaptopropionate was investigated. Reaction proceeds with the formation of ethyl 2-phenylpropionate of low optical activity (2–4% stereospecificity–inversion of configuration being observed).

In an earlier paper,[1c] we reported the stereochemical features of the electroreduction of atrolactic acid derivatives. Controlled potential electrolysis of both *O*-benzoylatrolactic acid (I) and methyl *O*-benzoylatrolactate (II) resulted in cleavage of the carbon–oxygen bond and subsequent carbon–hydrogen bond formation (see Scheme I). The stereochemical results indicated that the reduction proceeded with almost complete loss of optical activity.

These results were in contrast to earlier reported reductions of cyclopropyl halides[1a,b] in which moderately high stereospecificities (56% inversion to 38% retention) were found. Also, Czochralska found that the electrochemical reduction of 2-chloro-2-phenylpropionic acid proceeded with a very high degree of

SCHEME I



I, R = COOH
II, R = $COOCH_3$

stereospecificity (77% to 92% inversion of configuration).[2]

The present paper reports the results obtained in a study of the stereochemistry of the electroreduction of carbon–sulfur single bond substrates. It was thought

(1) For earlier papers in this series see (a) R. Annino, R. E. Erickson, J. Michalovic, and B. McKay, *J. Amer. Chem. Soc.*, **88**, 4424 (1966); (b) R. E. Erickson, R. Annino, M. D. Scanlon, and G. Zon, *ibid.*, **91**, 1767 (1969); (c) R. E. Erickson and C. M. Fischer, *J. Org. Chem.*, **38**, 1604 (1970).

(2) B. Czochralska, *Chem. Phys. Lett.*, **1**, 239 (1967). We have attempted to repeat Czochralska's work but have been unsuccessful. Yields of the expected product were on the order of 50% and essentially no optical activity was found in the product mixture.

TABLE I

ELECTROCHEMICAL AND STEREOCHEMICAL DATA

Reactant	Reactant α_D (lit.)[a]	$e^{1}/_{2}$,[b] V	E_e,[c] V	e⁻/mol	Product (yield, %)	Product α_D (lit.)[d]
C_6H_5—C(SC$_6$H$_6$)(CH$_3$)—COOH		1.76	1.80–2.0	2.02	Starting material	
C_6H_5—C(SC$_6$H$_6$)(CH$_3$)—COOEt	56.2 ± 1.36° (89.8°)	1.92	1.9–2.0	1.96	C_6H_5—C(H)(CH$_3$)—COOH (90%); C_6H_5SH (90%)	+4.23 ± 1.84° (45.20)[d]
C_6H_5—C(SC$_6$H$_6$)(CH$_3$)—COOEt	56.2 ± 1.36° (89.8°)	1.92	2.0	2.00	C_6H_5—C(H)(CH$_3$)—COOH (90%); C_6H_5SH (90%)	+2.20 ± 0.68° (45.20)[d]

[a] Reference 4. [b] All polarograms obtained in 0.1 *M* TEAB in 95% ethanol. Measurements are in volts relative to a saturated ethanol calomel electrode. [c] Potentials are in volts relative to a commercial saturated calomel electrode. E_e symbolizes the value at which the voltage was controlled during electrolysis. [d] Literature[4] indicates an expected value of 72.2° (EtOH) if the ester were optically pure. The 45.2° (EtOH) value is what we would expect for a stereospecific reaction from 62% resolved starting material.

that this data would be valuable in terms of comparison with our earlier work. The compounds chosen for study were 2-phenyl-2-phenylmercaptopropionic acid and its ethyl ester. Studies correlating the configurations of these compounds with their expected reduction products, 2-phenylpropionic acid and its ethyl ester, were available in the literature.[3] Thus, the stereochemical features of the reduction of these substrates could be determined.

Experimental Section

Materials.—Eastman tetraethylammonium bromide (TEAB) was recrystallized several times from ethanol before use. Undenatured 95% ethanol was used without any further purification. Atrolactic acid was purchased from Pfaltz and Bauer and Aldrich Chemical Co.; *d*-(+)- and l-(−)-α-methylbenzylamine were purchased from Aldrich Chemical Co.

2-Phenyl-2-phenylmercaptopropionic Acid (III).—This acid was prepared according to the procedure of Bonner[4] in a yield of 72%, mp 100–103° (lit. mp 104.5–105°). The nmr spectrum of this compound in chloroform-*d* had the following signals: δ 1.83 (s), 7.39 (m), >8.00 (s).[5]

The acid was resolved using optically active α-methylbenzylamine according to the procedure of Bonner.[4] The resolved acid had $[\alpha]^{25}D$ +123.5 ± 2.8°, EtOH (lit. $[\alpha]^{25}D$ 165.5°, EtOH).

Ethyl 2-Phenyl-2-phenylmercaptopropionate (IV).—This ester was prepared according to the procedure of Bonner[4] in a yield of 92%. The nmr spectrum of this compound in chloroform-*d* had the following signals: δ 1.21 (t), 1.83 (s), 4.17 (q), 7.33 (m).

Optically active ethyl 2-phenyl-2-phenylmercaptopropionate was synthesized from optically active 2-phenyl-2-phenylmercaptopropionate acid according to the procedure of Bonner.[4] The acid, $[\alpha]^{25}D$ +123.5 ± 2.8° (EtOH), gave the ester having $[\alpha]^{25}D$ +56.2 ± 1.36° (Et_2O). The literature value for this ester is $[\alpha]^{25}D$ +89.8° (Et_2O).

2-Phenylpropionic Acid.—Ligroin (bp 35–55°) was added to 22.56 g of a sodium hydride–mineral oil (50:50) mixture. This was swirled by hand for approximately 15 min and the liquid was decanted, leaving 11.28 g of sodium hydride.

Benzyl cyanide (50 g, 0.427 mol) was dissolved in dimethylformamide. Sodium hydride (11.28 g, 0.47 mol) and 55.5 g (0.47 mol) of ethyl carbonate were added to this solution. The solution was kept cold until the evolution of hydrogen gas ceased. The solution was then stirred for an additional 1 hr at room temperature.

Methyl iodide (60.6 g, 0.427 mol) was added to the solution, and the reaction mixture was heated in a water bath for approximately 2.5 hr. The reaction mixture was then cooled and poured into water, and the product was extracted with benzene. The benzene extracts were dried with anhydrous magnesium sulfate and the dried extracts were evaporated *in vacuo*. The resulting residue was distilled *in vacuo* and 55.62 g (0.27 mol) of distillate was collected in the range of 109–118° (1–2 mm) [lit.[6] 139–152° (15 mm)]. The nmr data (chloroform-*d*) for 2-phenyl-2-cyanoethyl propionate was δ 1.24 (t), 1.96 (s), 4.23 (q), 7.45 (m).

2-Phenylethyl cyanide (21.1 g) was obtained by hydrolysis of 2-phenyl-2-cyanoethyl propionate according to the method of Delaby, *et al.*, bp 107–110° (12–16 mm) [lit. bp 109° (15 mm)].

2-Phenylethyl cyanide was hydrolyzed to 2-phenylpropionic acid by the method of Campbell and Kenyon,[7] and 15.1 g of the product (23.4% yield) was obtained, bp 153–155° (12–16 mm) [lit.[6] bp 145° (13 mm)]. The nmr data for this compound in chloroform-*d* were δ 1.49 (d), 3.70 (q), 7.23 (s), >8.00 (s).

2-Phenylpropionic acid was resolved using strychnine according to the method of Raper.[8] It has $[\alpha]^{25}D$ ±76.2° ($CHCl_3$). The acid was resolved giving $[\alpha]^{25}D$ +10.7° ($CHCl_3$, 14% resolved).

Ethyl 2-Phenylpropionate.—This ester was prepared from 2-phenylpropionic acid *via* Fisher esterification. 2-Phenylpropionic acid having $[\alpha]^{25}D$ +10.7 ± 1.4° (14% resolved) gave upon esterification the ester having $[\alpha]^{25}D$ +10.0 ± 0.7° (13.9% resolved).

Apparatus.—Polarographic analyses, controlled potential electrolyses, and cyclic voltammetry experiments were carried out as described in an earlier paper.[1c]

Optical rotations were measured on an O. C. Rudolph and Sons polarimeter, Model 80. Two cells were employed, one of 10 cm and the other 5 cm in length. Measurements were performed in the appropriate previously reported solvent.

Nuclear magnetic resonance spectra were recorded on a Varian HA-60 recording spectrometer as approximately 15% solutions in appropriate solvents.

Compounds III and IV were examined under the conditions of cyclic voltammetry.[1c] In both cases, scan reversal past the cathodic peak at speeds up to 5 V/sec resulted in no evidence of reoxidation.

Product Analysis.—In most instances, the electrolysis solution was analyzed immediately upon completion of the experiment. In those cases where this procedure was not followed, the solution was first neutralized with dilute sulfuric acid and was then placed in a refrigerator before analysis.

The procedure employed to isolate the product of reaction consisted of pouring the electrolysis solution into three times its volume of water followed by extraction with ether. When one of the acids was used as a starting material, the solution was made acidic with dilute sulfuric acid before extraction. The ether extracts were dried over anhydrous magnesium sulfate and evaporated under vacuum. Nmr spectra and optical rotation measurements, where appropriate, were obtained on this ether residue.

Results and Discussion

Table I summarizes the important electrochemical and stereochemical data obtained in this study.

(3) W. A. Bonner and R. A. Grimm, *J. Org. Chem.*, **32**, 3022 (1967).
(4) W. A. Bonner, *J. Amer. Chem. Soc.*, **74**, 1034 (1952).
(5) Splitting designations are s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.
(6) R. Delaby, P. Reynaud, and F. Lily, *Bull. Soc. Chim. Fr.*, 864 (1960).
(7) A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).
(8) J. Raper, *J. Chem. Soc.*, **123**, 2557 (1923).

Attempts to determine the electrolysis product of III were unsuccessful. Each time this compound was subjected to controlled-potential electrolysis (−1.76 V), the product isolated was the starting acid. This suggests that the polarographic wave for III at −1.76 V can be attributed to the reduction of the carboxylic acid proton to hydrogen. However, attempts to electrochemically reduce the anion of this acid also resulted in the isolation of starting acid.

The electrochemical reduction of ethyl 2-phenyl-2-phenylmercaptopropionate (IV) proceeded with rupture of the carbon–sulfur bond and subsequent carbon–hydrogen bond formation. The coulometric data in all cases was approximately 2 e/mol. Both of the reduction products, ethyl 2-phenylpropionate and thiophenol, were obtained in high yields and were identified by means of their nmr spectra.

Throughout this series of papers, the basis for investigating the mechanism of electroreductions has been the stereochemistry of the reaction. Bonner and coworkers[3,9] have established that (−)-atrolactic acid and (+)-2-phenylpropionic acid have the same configuration. They have also shown that (−)-2-phenyl-2-phenylmercaptopropanoic acid and (+)-2-phenylpropionic acid have identical configurations. Thus, by synthesizing the appropriate derivative (compound IV) from optically active starting materials *via* routes which do not disturb the configuration about the asymmetric carbon atom (see Experimental Section), the stereochemistry involved in the electroreduction of these substrates could be determined.

As can be noted in Table I, a small degree of inversion of configuration is found for carbon–sulfur single-bond reductions. Our results ranged from 9.35 ± 4.05% to 4.87 ± 1.33% inversion.

By subjecting the product of the reduction of the ester, *i.e.*, ethyl 2-phenylpropionate, to normal electrolysis conditions, it was found that this ester racemizes to some extent. The compound was found to undergo 50% racemization when subjected to conditions of pH 8–9 for 6 hr. However, it is still obvious that the electroreductions examined in this and previous[1c] work proceed with little or no stereospecificity. The value of 50% racemization does not explain the total lack of optical activity in the reduction products for atrolactic acid derivatives, and the percentage inversion for IV is low. Also, the duration of time required to perform the electrolyses of these compounds was usually less than 6 hr and those experiments where the pH was controlled at approximately 7 still resulted in the same relative lack of stereospecificity.

The stereochemical results for compound IV are in accord with the trends found earlier.[1a,b] We reported then a net inversion of configuration to occur in the electroreduction of methyl 1-bromo-2,2-diphenylcyclopropanecarboxylate. Those results were explained in terms of a mechanism involving an intermediate electrode complex with the same configuration as the reactant. The overall stereochemistry of the process was thought to be determined by a stereoselective reaction of a few electrode-shielded carbanions with solvent or proton. Other mechanisms have been suggested[10,11] and we had hoped that some light might be shed on the problem through the use of our substrates. Unfortunately, the picture is more clouded than ever. None of our systems show intermediates such as those found by Webb, Mann, and Walborsky[10] by cyclic voltammetry[12] and the one truly remarkable stereochemical result in the literature[2] could not be repeated.[2,13]

Acknowledgment.—The support of this work by the National Science Foundation is gratefully acknowledged.

Registry No.—(±)-III, 13479-08-8; (+)-III, 42253-92-9; (±)-IV, 42253-93-0; (+)-IV, 42253-94-1; benzyl cyanide, 140-29-4; ethyl carbonate, 105-58-8; methyl iodide, 74-88-4; 2-phenyl-2-cyanoethyl propionate, 15601-34-0; 2-phenyl ethylcyanide, 42253-96-3; (±)-2-phenylpropionic acid, 2328-24-7; (+)-2-phenylpropionic acid, 7782-24-3; ethyl 2-phenylpropionate, 42253-99-6.

(9) W. A. Bonner, J. A. Zdeiec, and G. A. Casaletto, *J. Amer. Chem. Soc.*, **74**, 5086 (1952).

(10) J. L. Webb, C. K. Mann, and H. M. Walborsky, *J. Amer. Chem. Soc.*, **92**, 2042 (1970).

(11) A. J. Fry and R. G. Reed, *J. Amer. Chem. Soc.*, **94**, 8475 (1972).

(12) Fry (ref 11) also found no evidence for organomercurials in the reduction of geminal dihalides.

(13) We are discontinuing work in this area. For those who wish to continue we suggest using substrates which are easily preparable in large quantities so that more time can be spent adjusting the electrochemical experimental parameters.

Study of the Alkaline Hydrolysis and Nuclear Magnetic Resonance Spectra of Some Thiol Esters[1]

JOHN P. IDOUX*

Department of Chemistry, Florida Technological University, Orlando, Florida 32816

PHILIP T. R. HWANG[2] AND C. KINNEY HANCOCK

Department of Chemistry, Texas A & M University, College Station, Texas 77843

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The alkaline hydrolysis rate constants at 35° in 40% aqueous *p*-dioxane and the nmr chemical shifts have been measured for nine thiolacetates, CH_3COSR', nine methyl thiol esters, $RCOSCH_3$, and seven disubstituted thiol esters, RCOSR'. Alkaline hydrolysis rate constants are controlled almost exclusively by steric effects of the R and R' groups. The nmr substituent chemical shifts (SCS) of thiol esters are controlled largely by steric and six-number effects of the R and R' groups. All of these correlations are discussed and compared with correlations previously reported for similar oxygen esters, RCOOR', on the basis of differences in various structural features of the two series. A contributing structure involving negative charge development at the sulfur atom is apparently not of importance for simple thiol esters.

In the alkaline hydrolysis of esters, RCOOR', the reaction site in the reactant state is trigonal and unsaturated while the reaction site in the intermediate is tetrahedral and saturated. Moreover, the rate-determining step in the mechanism[3] for the reaction is the coordination of the hydroxyl ion with the carbonyl carbon. Consequently, in the absence of α,β unsaturation in the R group, the alkaline hydrolysis rate constant for RCOOR' is affected by polar and steric effects of the R' group.

For example, eq 1 has been found[4] for the alkaline hydrolysis rate constants of nine methyl esters, $RCOOCH_3$, in 40% aqueous *p*-dioxane at 35°. In eq 1, k is the second-order rate constant, σ^* is Taft's polar substituent constant,[5a] E_s^c is Taft's steric substituent constant[5b] corrected[4] for hyperconjugative effects, n is the number of α hydrogens in the R group, R is the multiple correlation coefficient,[6a] and s is the standard deviation *from regression*.[6a] The numbers in parentheses below the three coefficients of eq 1 are the percentage confidence levels as determined by "Student's" t tests.[6b] It is apparent from eq 1 that log k is an almost exact function of σ^*, E_s^c, and $(n - 3)$, with each of these three independent variables being highly significant.

$$\log k = 1.25 + 1.75\sigma^* + 0.848\,E_s^c - 0.383\,(n - 3), \quad (1)$$
(100.0) (100.0) (100.0)
$$R = 0.998,\ s = 0.043$$

Further, Newman[7] has shown that, for the esterification of carboxylic acids and the hydrolysis of esters, the six number of a substituent (*i.e.*, the number of atoms in the six position from the carbonyl oxygen atom as atom one) makes a large contribution to the total steric effect of that substituent. For example, eq 2 has been found[8] for the alkaline hydrolysis rate constants of nine acetate esters, CH_3COOR', in 40% aqueous *p*-dioxane at 35°. In eq 2, $\Delta 6$ is the change in the six number, *i.e.*, the difference of the six number of a substituent in the R part of the ester minus the six number of the same substituent in the R' part of the ester. It is evident that eq 2 provides a quantitative relationship that is almost as exact as that of eq 1.

$$\log k = 1.35 + 0.688\sigma^* + 0.644\,E_s^c + 0.0477\,(\Delta 6), \quad (2)$$
(95.5) (100.0) (99.4)
$$R = 0.997,\ s = 0.070$$

For the nine acetate esters mentioned previously,[8] in addition to nine others, Rosado and his coworkers[9] have found eq 3 to apply to the measured substituent chemical shifts (SCS) of these acetates relative to methyl acetate. In eq 3, σ^* has the same meaning as before and C-6 no. is the number of carbon atoms in the six position.[7] Equation 3 indicates, as concluded by Kan,[10] that the SCS values of acetate esters are governed largely by polar and six number effects of the R' group. Rosado and his coworkers[9] have also measured the SCS of a series of methyl esters relative to methyl acetate and have found that eq 4 applies for this series.

$$\text{SCS (Hz)} = 0.953 + 20.4\sigma^* + 1.11\,(\text{C-6 no.}), \quad (3)$$
(100.0) (100.0)
$$R = 0.943,\ s = 0.659$$

$$\text{SCS (Hz)} = 0.446 + 18.4\sigma^* - 2.06\,(n - 3), \quad (4)$$
(100.0) (100.0)
$$R = 0.863,\ s = 0.415$$

In view of the differences and of the multitude of substituent effects exhibited by oxygen esters in alkaline hydrolysis and in substituent chemical shift correlations, we have made similar studies on the corresponding sulfur esters. The present paper is concerned with the results of these studies and with a

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(2) Abstracted in part from the Ph.D. Dissertation of P. T. R. H., Texas A & M University, Aug 1965.

(3) M. L. Bender, *J. Amer. Chem. Soc.*, **73**, 1626 (1951).

(4) C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Amer. Chem. Soc.*, **83**, 4211 (1961).

(5) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956: (a) p 619; (b) p 598.

(6) G. W. Snedecor, "Statistical Methods," 5th ed, The Iowa State College Press, Ames, Iowa, 1956: (a) Chapter 14; (b) pp 46, 418, and 441; (c) Chapter 6.

(7) M. S. Newman, *J. Amer. Chem. Soc.*, **72**, 4783 (1950).

(8) C. K. Hancock, B. J. Yager, C. P. Falls, and J. O. Schreck, *J. Amer. Chem. Soc.*, **85**, 1297 (1963).

(9) O. Rosado-Lojo, C. Kinney Hancock, and A. Danti, *J. Org. Chem.*, **31**, 1899 (1966).

(10) R. O. Kan, *J. Amer. Chem. Soc.*, **86**, 5180 (1964).

comparison of these results to those for the corresponding oxygen esters.

Results and Discussion

Alkaline Hydrolysis Rate Constants of Thiol Esters.—The alkaline hydrolysis rate constants at 35° in 40% aqueous *p*-dioxane for 24 thiol esters are shown in Table I and the various substituent parameters are shown in Table II.

TABLE I
ALKALINE HYDROLYSIS RATE CONSTANTS FOR 24 THIOL ESTERS IN 40% AQUEOUS *p*-DIOXANE AT 35°

	RCOSR′			k, l. mol^{-1} min^{-1},
Registry no.	No.	R	R′	av
625-60-5	1	CH_3	C_2H_5	9.58
2307-10-0	2	CH_3	n-C_3H_7	7.40
926-73-8	3	CH_3	i-C_3H_7	5.74
928-47-2	4	CH_3	n-C_4H_9	6.30
2432-37-3	5	CH_3	i-C_4H_9	6.23
2432-39-5	6	CH_3	s-C_4H_9	4.14
999-90-6	7	CH_3	t-C_4H_9	2.52
32362-99-5	8	CH_3	$C_6H_5CH_2$	12.59
1534-08-3	9	CH_3	CH_3	17.42
5925-75-7	10	C_2H_5	CH_3	11.49
2432-51-1	11	n-C_3H_7	CH_3	5.32
42075-42-3	12	i-C_3H_7	CH_3	3.46
42075-43-4	13	n-C_4H_9	CH_3	4.66
23747-45-7	14	i-C_4H_9	CH_3	1.32
42075-45-6	15	s-C_4H_9	CH_3	1.02
42075-46-7	16	t-C_4H_9	CH_3	0.45
5925-74-6	17	$C_6H_5CH_2$	CH_3	10.70
2432-42-0	18	C_2H_5	C_2H_5	5.93
2432-92-0	19	n-C_4H_9	C_2H_5	2.56
6330-43-4	20	n-C_3H_7	t-C_4H_9	0.506
2432-91-9	21	i-C_4H_9	s-C_4H_9	0.278
42075-51-4	22	s-C_4H_9	t-C_4H_9	0.0756
28058-96-0	23	t-C_4H_9	t-C_4H_9	0.0390
42075-53-6	24	n-C_4H_9	$C_6H_5CH_2$	4.86

TABLE II
SUBSTITUENT PARAMETERS

No.	Substituent	σ^{*a}	$E_s{}^b$	$E_s{}^{cc}$	$(n-3)^d$	$\Delta6^e$	$6\#^f$
1	C_2H_5	−0.100	−0.07	−0.38	−1	−3	0
2	n-C_3H_7	−0.115	−0.36	−0.67	−1	0	3
3	i-C_3H_7	−0.190	−0.47	−1.08	−2	−6	0
4	n-C_4H_9	−0.130	−0.39	−0.70	−1	0	3
5	i-C_4H_9	−0.125	−0.93	−1.24	−1	3	6
6	s-C_4H_9	−0.210	−1.13	−1.74	−2	−3	3
7	t-C_4H_9	−0.300	−1.54	−2.46	−3	−9	0
8	$C_6H_5CH_2$	0.215	−0.38	−0.69	−1	2	4
9	CH_3	0.000	0.00	0.00	0	0	0

[a] Reference 5a. [b] Reference 5b. [c] Reference 4. [d] n is the number of α hydrogens. [e] Reference 8. [f] Reference 7.

A. Thiolacetates, CH_3COSR'.—Since eq 2 provides a good correlation *via* the extended Taft equation for the alkaline hydrolysis of the oxygen esters, CH_3COOR', a similar correlation has been attempted for the corresponding thiolacetates (No. 1–9 of Table I) to give eq 5. Rejecting the least significant variable, Δ6, the

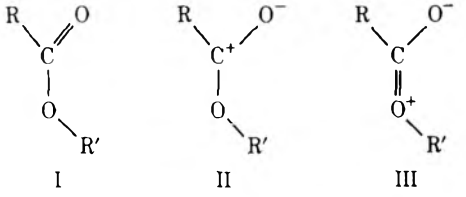
$$\log k = 1.14 + 0.675\sigma^* + 0.236\,E_s{}^c + 0.0032\,(\Delta6), \quad (95.9)\ (99.7)\ (26.6)$$
$$R = 0.977,\ s = 0.067 \quad (5)$$

correlation becomes eq 6. Rejecting the next least significant variable, σ^*, the correlation becomes eq 7. Statistical consideration of eq 5–7 indicates that Δ6

$$\log k = 1.15 + 0.314\,E_s{}^c,\ r = 0.936,\ s = 0.094 \quad (7)$$
$$(100.0)$$

is not significant, σ^* is significant, and $E_s{}^c$ is highly significant. Of the total variance of log k, 95.3% ($R^2 \times 100$) is accounted for by eq 6 and 87.6% is accounted for by eq 7. Thus, it appears that most of the variation in the log k's of the thiolacetates is due to steric effects. In contrast, for the corresponding acetates, CH_3COOR', log k is a good function of σ^*, $E_s{}^c$, and Δ6, as shown previously by eq 2.

The nine thiolacetates (with the exception of R′ = CH_3) used in the correlations to obtain eq 5–7 all undergo the alkaline hydrolysis reaction more rapidly than the corresponding acetates under the same experimental conditions. The greater reactivity of the thiolacetates is not due to mercaptide ion catalysis, since comparable rates were obtained between reactions run in the presence of initial concentrations of mercaptide ion of 0.006 M and reactions run in the absence of added mercaptide ion. These differences in reactivity as well as the predominant influence of steric effects over that of polar and six-number effects on the log k values of the thiolacetates compared to the importance of all three of these factors with regard to the acetates can be accounted for on the basis of differences in various structural features of the two series. That is, esters exist predominantly[11] in the cis conformation I and are resonance hybrids[12] with structures I, II, and III being the main contributors. While similar



I II III

contributors might be expected for thiol esters, a form such as III makes little contribution to the structure of a thiol ester relative to an oxygen ester, since the unshared electron pairs on the larger sulfur atom are not able to overlap as efficiently with the adjacent carbonyl group and form a double bond. At the same time, therefore, the relative importance of a form such as II should be more important for thiol esters than for the corresponding oxygen esters and should effectively render the carbonyl group of the thiol esters more polarizable. The observed greater reactivity of the thiolacetates toward alkaline hydrolysis relative to the acetates can be accounted for on this basis, since the rate-determining step in both reactions is coordination of the hydroxide ion with the carbonyl group. In addition to the relative importance of various contributing structures and on the basis of bond-angle data for sulfides and ethers[13,14] and bond-distance data for thiol acids and carboxylic acids,[15,16] one would

(11) J. M. O'Gorman, W. Shand, Jr., and V. Schomaker, *J. Amer. Chem. Soc.*, **72**, 4222 (1950).
(12) G. W. Wheland, "Resonance in Organic Chemistry," Wiley, New York, N. Y., 1955, p 236.
(13) L. O. Brockway and H. O. Jenkins, *J. Amer. Chem. Soc.*, **58**, 2036 (1936).
(14) L. Pauling and L. O. Brockway, *J. Amer. Chem. Soc.*, **58**, 2684 (1935).
(15) W. Gordy, *J. Chem. Phys.*, **14**, 560 (1946).
(16) I. L. Karle and J. Karle, *J. Chem. Phys.*, **22**, 43 (1954).

expect the C–S–C bond angle of a thiol ester to be smaller than the corresponding C–O–C bond angle in an oxygen ester and the carbonyl C–S bond in a thiol ester to be longer than the corresponding carbonyl C–O bond in the oxygen ester. Thus any polar effect from R′ will have to be transmitted over a longer distance in the case of thiol esters. This fact, along with the decreased importance of a contributing form such as III for thiol esters compared to oxygen esters, indicates that polar effects from R′ should be less important in thiol esters relative to oxygen esters. In essence, then, the sulfur atom in the thiol acetates appears to serve as an effective buffer of polar effects from R′.

The smaller C–S–C bond angle and the longer C–S bond in thiol esters relative to the corresponding C–O parameters in the oxygen esters have the effect of moving the R′ group of the thiol ester closer to the carbonyl oxygen and farther from the carbonyl carbon where the rate-determining coordination with the hydroxyl ion occurs. The result is that the relative importance of steric effects for the thiolacetates should be less than for the acetates. This is indeed reflected in the smaller δ^c values of eq 5–7 compared to that of 0.664 in eq 2. In addition, the bond-angle and bond-distance differences are probably responsible then for the insignificance of the effect of the changes in the six number, Δ6, in the case of the thiol esters since, as pointed out previously,[8] the six number of a particular group often changes when that group's position in the acyl portion of an ester is compared to its position in the alkyl portion.

B. Methyl Thiol Esters, $RCOSCH_3$.—Since eq 1 provides an excellent correlation for the methyl esters, $RCOOCH_3$, under the the same experimental conditions, a similar correlation for the corresponding methyl thiol esters (No. 9–17 of Table I) was carried out to give eq 8.

$$\log k = 1.14 + 0.947\sigma^* + 0.917\,E_s^c - 0.323\,(n-3), \quad R = 0.002,\ s = 0.083 \quad (8)$$
(98.2) (100.0) (98.4)

Rejecting $(n - 3)$ the correlation becomes eq 9.

$$\log k = 1.23 + 0.719\sigma^* + 0.599\,E_s^c, \quad R = 0.973,\ s = 0.143 \quad (9)$$
(83.3) (99.9)

Rejecting σ^*, the correlation becomes eq 10.

$$\log k = 1.25 + 0.691\,E_s^c,\ r = 0.961,\ s = 0.157 \quad (10)$$
(100.0)

Equation 8 accounts for 98.5% ($R^2 \times 100$) of the variance of log k and indicates that σ^* and $(n - 3)$ are significant while E_s^c is highly significant. Equation 10 accounts for 92.5% of the variance of log k and indicates that log k for the alkaline hydrolysis of $RCOSCH_3$, as in the case of the thiolacetates (CH_3COSR'), is controlled largely by steric effects of the substituent alkyl group. However, in contrast to the thiolacetates, the methyl thiol esters all undergo the alkaline hydrolysis reaction more slowly than the corresponding methyl acetates under the same experimental conditions. This is probably due in part to the slightly greater influence of steric effects in the acyl portion of a methyl thiolacetate relative to that in a methyl acetate (*i.e.* δ^c of eq 8 is 0.917 compared to 0.848 in eq 1.)

In general, steric effects are of preponderant influence in controlling the alkaline hydrolysis of any thiol ester (RCOSR′). This is confirmed by the correlation provided by eq 11, which is the multiple regression of log k for all the thiol esters of Table I on the appropriate steric substituent constants. Equation 11, with only two independent variables, accounts for

$$\log k = 1.24 + 0.704\,E_{s_R}^c + 0.410\,E_{s_{R'}}^c, \quad R = 0.980,\ s = 0.144 \quad (11)$$

96.1% ($R^2 \times 100$) of the variance of log k and is as significant as the multiple regression of log k on σ^*_R $(n - 3)_R$, $\sigma^*_{R'}$ $(\Delta 6)_{R'}$, $E_{s_R}^c$ and $E_{s_{R'}}^c$.

Nuclear Magnetic Resonance Spectra of Thiol Esters.—The substituent chemical shifts (SCS) of 17 thiol esters relative to methyl thiolacetate are given in Table III. Inspection of these data shows that the

TABLE III
SUBSTITUENT CHEMICAL SHIFTS (SCS) FOR 17 THIOL ESTERS

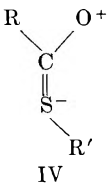
No.	Thiol ester RCOSR′ R	R′	Shift of RCOSR′ from CH_3COSCH_3, Hz, 37°, neat *vs.* TMS
1	CH_3	C_2H_5	1.7
2	CH_3	*n*-C_3H_7	1.4
3	CH_3	*i*-C_3H_7	−0.5
4	CH_3	*n*-C_4H_9	0.3
5	CH_3	*i*-C_4H_9	0.7
6	CH_3	*s*-C_4H_9	−0.4
7	CH_3	*t*-C_4H_9	−5.1
8	CH_3	$C_6H_5CH_2$	−10.7
9	CH_3	CH_3	0.0
10	C_2H_5	CH_3	−0.4
11	*n*-C_3H_7	CH_3	0.1
12	*i*-C_3H_7	CH_3	−1.0
13	*n*-C_4H_9	CH_3	−0.4
14	*i*-C_4H_9	CH_3	−0.2
15	*s*-C_4H_9	CH_3	−0.9
16	*t*-C_4H_9	CH_3	−3.3
17	$C_6H_5CH_2$	CH_3	−12.5

SCS for benzyl thiolacetate (no. 8) and methyl phenylthiolacetate (no. 17) are markedly different from those of the other 15 thiol esters. These large differences are due to the magnetic anisotropy[10] of the phenyl ring present in both of these thiol esters and absent in the other 15. Consequently, the data for these two thiol esters are omitted in all of the subsequent correlations involving the chemical shifts.

It is interesting to note that the acyl methyl hydrogens of the thiolacetates occur downfield relative to these hydrogens in the corresponding acetates. The greater importance of resonance forms such as II (positive charge development on the carbonyl carbon) and the decreased importance of forms such as III (multiple bond character of atoms between R and R′) for the thiolacetates relative to the acetates have the effect of causing less shielding of the acyl methyl hydrogens in the thiolacetates. As a result, these hydrogens experience a greater downfield shift relative to those in the acetates. On the other hand, the alkyl methyl hydrogens of the methyl esters occur downfield relative to these hydrogens in the methyl thiol esters. In this case, the greater importance of a resonance form (III) involving positive charge development on the alkyl oxygen of a methyl ester relative to such positive

charge development on the sulfur atom of a methyl thiol ester tends to decrease the shielding of the alkyl methyl hydrogens in a methyl ester and thus shifts them downfield.

We would like to point out that the contributing structure IV has been suggested[17] as being important



IV

for thiol esters relative to oxygen esters and has been considered when explaining differences between thiol esters and other acyl compounds.[18,19] Structure IV suggests negative charge development at the sulfur atom *via* electron donation from the carbonyl group into the sulfur 3d orbitals. The importance of such a structure could easily be invoked in explaining our reactivity and nmr data. However, we do not feel it necessary to do so but rather the fact that our data are explicable in terms of more conventional structures leads us to question the importance of IV as a significant factor in the ground-state stabilization of thiol esters. Wadsö[20] has reported heats of hydrolysis for thiol esters and oxygen esters which confirm this conclusion and more recently Collings[21] and his coworkers have questioned the importance of structure IV based on infrared studies on thiol esters and other acyl compounds.

A. Thiolacetates, CH_3COSR'.—In view of the fairly good correlation provided by eq 3 for the acetates, the correlation of the SCS of the acyl methyl protons of eight of the thiolacetates (benzyl thiolacetate omitted) was also attempted. σ^* and H-6 no., where H-6 no. (see Table IV) is the number of hydrogen atoms in the six position from the carbonyl oxygen atom as atom number one, were found to be insignificant variables.

TABLE IV

CARBON SIX NUMBERS AND HYDROGEN SIX NUMBERS FOR SUBSTITUENTS

	As R′ of CH_3COSR'		As R of $RCOSCH_3$	
Substituent	C-6 no.[a]	H-6 no.[b]	C-6 no.[a]	H-6 no.[b]
CH_3	0	0	0	0
C_2H_5	0	3	0	0
n-C_3H_7	1	2	0	3
i-C_3H_7	0	6	0	0
n-C_4H_9	1	2	1	2
i-C_4H_9	2	1	0	6
s-C_4H_9	1	5	0	3
t-C_4H_9	0	9	0	0

[a] Carbon six number, *i.e.*, the number of carbon atoms in the six position from the carbonyl oxygen atom as atom number one. [b] Hydrogen six number, *i.e.*, the number of hydrogen atoms in the six position from the carbonyl oxygen atom as atom number one.

The relationship which best fits the data is shown in eq 12. This equation accounts for 79% of the variance

$$\underset{(99.0)}{\text{SCS (Hz)} = 1.30 + 2.23\ E_s^c} + \underset{(90.5)}{1.21\ \text{(C-6 no.)}},$$
$$R = 0.889,\ s = 1.15 \quad (12)$$

in SCS and indicates that E_s^c is a significant variable while C-6 no. is almost significant. The significance of E_s^c for the chemical shifts of the thiolacetates is in agreement with its significance for the alkaline hydrolysis rate constants of the same compounds (see eq 7). The near significance of C-6 no. for the thiol esters is in agreement with its significance for the chemical shifts of the corresponding acetates (see eq 3). It is believed that C-6 no. would be a highly significant variable for a more extensive series of thiolacetates with a larger range of C-6 no. and SCS values. The data in the second column of Table IV show that there is very little variation of the C-6 no. values for the eight thiolacetates correlated by eq 12. Also, omitting the data for *tert*-butyl thiolacetate, the chemical shifts for the other seven thiolacetates given in the fourth column of Table III cover a range of only 2.3 Hz. The fact that σ^* is not a significant variable is expected and for the same reasons, as outlined previously, that it is not significant when considering the alkaline hydrolysis rate constants.

B. Methyl Thiol Esters, $RCOSCH_3$.—Correlation of the SCS of the alkyl methyl protons of eight methyl thiol esters relative to methyl thiolacetate (no. 9–16 of Table III) with σ^*, E_s^c, $(n - 3)$, and 6# gave an equation which showed that σ^* was the least significant variable (83% confidence level). Eliminating σ^* and repeating the correlation gave an equation with $(n - 3)$ as the next least significant variable (55% confidence level). Eliminating $(n - 3)$, the new correlation gives eq 13, which provides a fairly good fit for the data.

$$\underset{(99.9)}{\text{SCS (Hz)} = 0.097 + 1.25\ E_s^c} + \underset{(99.1)}{0.237\ \text{(C-6 no.)}},$$
$$R = 0.966,\ s = 0.336 \quad (13)$$

The standard deviation of 0.336 in eq 13 is only 10% of the range of 3.4 in hertz values involved. This range in hertz values is relatively small in comparison to the ranges in E_s^c and C-6 no. values. The reason for this is that the C-6 no. tends to become more positive as E_s^c becomes more negative, *i.e.*, the term 0.237 (C-6 no.) increases as the term 1.25 E_s^c decreases and these two effects tend to compensate for one another.

Thus, it appears that steric factors have the greatest influence on the chemical shifts of acyl or alkyl methyl hydrogens in thiol esters just as such factors are of most importance in controlling the alkaline hydrolysis of these compounds. These results are in marked contrast to similar studies on oxygen esters where polar effects were at least of equal importance.

Experimental Section

Materials.—Methyl and benzyl mercaptans (Distillation Products Industries) were purchased. The other seven mercaptans used in this study were donated by the Phillips Petroleum Co.

Methyl and ethyl thiolacetates (Wateree Chemical Co.) were purchased. The other 22 thiol esters were prepared by refluxing

(17) A. W. Baker and G. H. Harris, *J. Amer. Chem. Soc.*, **82**, 1923 (1960).
(18) I. Wallmark, M. H. Krackov, S. Chu, and H. G. Mautner, *J. Amer. Chem. Soc.*, **92**, 4447 (1970).
(19) W. P. Jencks, B. Schaffhausen, K. Tornheim, and H. White, *J. Amer. Chem. Soc.*, **93**, 3917 (1971).
(20) I. Wadsö, *Acta Chem. Scand.*, **16**, 487 (1962).
(21) A. J. Collings, P. F. Jackson, and K. J. Morgan, *J. Chem. Soc. B*, 581 (1970).

a mercaptan with an acyl chloride in pyridine solution.[22a] All of the thiol esters were purified as described previously.[4] The physical constants for nine of the esters agree with previously reported values and the constants for the other 13 previously unreported esters are given in Table V.

TABLE V
PHYSICAL CONSTANTS FOR 13 THIOL ESTERS, RCOSR'[a]

RCOSR'			
R	R'	$n^{25}D$	Bp °C (mm)
n-C_3H_7	CH_3	1.4595[b]	142–142.5 (757)
i-C_3H_7	CH_3	1.4559	132–132.1 (757)
n-C_4H_9	CH_3	1.4614[c]	165.2–165.4 (757)
i-C_4H_9	CH_3	1.4577	155.4–155.5 (756)
s-C_4H_9	CH_3	1.4585	153.8–154 (756)
t-C_4H_9	CH_3	1.4576	137–137.1 (756)
$C_6H_5CH_2$	CH_3	1.5592	112–112.2 (4)
n-C_4H_9	C_2H_5	1.4576	178–178.1 (757)
n-C_3H_7	t-C_4H_9	1.4505[d]	49.5–50 (4.5)
i-C_4H_9	s-C_4H_9	1.4556	77.1–77.2 (6.5)
s-C_4H_9	t-C_4H_9	1.4507	62.5–63.0 (6.0)
t-C_4H_9	t-C_4H_9	1.4695[e]	177.5–180 (757)
n-C_4H_9	$C_6H_5CH_2$	1.5347	159.1–159.5 (7.0)

[a] Satisfactory combustion analytical data for C, H, and S (±0.3%) were reported for all of the compounds in this table: Ed. [b] At 26°. [c] At 24°. [d] At 27°. [e] At 23°.

Standard sodium hydroxide solution and 40% aqueous p-dioxane were prepared as described previously.[4]

Determination of Alkaline Hydrolysis Rate Constants.—The apparatus and method of determination of the rate constants were the same as described previously,[4] except that (1) null points were obtained by a null indicator (Leeds and Northrup No. 8067), (2) the initial concentrations in the reaction mixture were 0.005 M thiol ester and 0.01 M sodium hydroxide.

(22) (a) P. N. Rylander and D. S. Tarbell, *J. Amer. Chem. Soc.*, **72**, 3021 (1950); (b) J. R. Schaefgen, *J. Amer. Chem. Soc.*, **70**, 1308 (1948).

It can be shown from previous studies[4,22b] that the integrated rate equation for this reaction is

$$(a/t)(1/R_0 - 1/R_t) = 2ak(1/R_t) - 2ak/R_\infty \qquad (14)$$

where R_0 and R_t are the resistance readings at time zero and at time t, a is the initial concentration of the thiol ester, k is the second-order rate constant, and R_∞ is the resistance reading after complete reaction (R_∞ is not required in this treatment). An approximate value of R_0 was obtained by measuring the resistance in the *same* conductivity cell of 0.01 M sodium hydroxide in 40% aqueous p-dioxane. Using this value of R_0, the *initial* plot of $(1/t)(1/R_0 - 1/R_t)$ *vs.* $1/R_t$ was always curved to some extent. If the curvature was concave upward, a slightly higher value of R_0 was then tried, and this procedure was repeated until linearity was obtained. If the initial plot was concave downward, slightly lower values of R_0 were tried until linearity resulted. The slope of the regression[6c] of $(1/t)(1/R_0 - 1/R_t)$ on $1/R_t$ was divided by 2a to obtain k.

Two or three rate-constant determinations were made on each thiol ester and the average k values are given in Table I. For the 24 thiol esters, the maximum deviation from the mean of replicate k values exceeded 2.0% only in the following four cases: $(CH_3)_2CHCOSCH_3$, 2.2%; $CH_3(CH_2)_3COSCH_3$, 2.9%; $(CH_3)_3CCOSCH_3$, 5.2%; and $CH_3(CH_2)_3COSCH_2CH_3$, 4.1%.

The following alkaline hydrolysis rate constants at 30° in 43 wt % aqueous acetone, determined by the titration method, have been reported previously: ethyl thiolacetate,[22b] 4.39; isopropyl thiolacetate,[22a] 2.42. Under the same conditions, except by the above-described conductivity method, k values of 4.49, 4.61, and 4.30 (av of 4.47) for ethyl thiolacetate and of 2.34 and 2.48 (av of 2.41) for isopropyl thiolacetate were found.

Nmr Spectral Measurements.—Using a Varian A-60 spectrometer, the chemical shifts of the thiol esters (neat), with respect to tetramethylsilane as internal standard, were measured at 37° at 250-Hz chart width and are accurate to about 0.2 Hz. The chemical shifts of methyl protons relative to those of methyl thiolacetate are shown in Table III.

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Aromatic Nitration with Nitric Acid and Trifluoromethanesulfonic Acid

CLIFFORD L. COON,* WILLIAM G. BLUCHER, AND MARION E. HILL

Chemistry Laboratory, Stanford Research Institute, Menlo Park, California 94025

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Nitration of aromatic compounds is accomplished by a nitrating reagent not previously reported. Two equivalents of trifluoromethanesulfonic acid (1) and one of HNO_3 combine to form a white, crystalline solid that has been identified as a mixture of nitronium trifluoromethanesulfonate (3) and the monohydrate of 1. 3 is an excellent nitrating reagent in inert organic solvents, H_2SO_4, or CF_3SO_3H, and has been used to nitrate toluene, benzene, nitrobenzene, chlorobenzene, m-xylene, and benzotrifluoride. Nitrations with 3 have been carried out over a temperature range of −110 to 30°, yields are consistently >98%, and exceptionally high positional selectivity has been demonstrated. For example, 3 reacts in 1 min with toluene in an inert organic solvent at −110, −90, or −60° to give quantitative yields of mononitrotoluene that contains only 0.23, 0.36, and 0.53% of the meta isomer, respectively. When the mononitration of toluene is carried out at −110, −90, −60, −30, and 0° followed by dinitration at 0°, the combined meta-isomer percentages are 0.33, 0.51, 0.75, 1.08, and 1.33, respectively.

In the course of work to find a method of reducing meta substitution in the mono- and dinitration of toluene, a study was made on the effect of various strong acids on isomer percentages. The recent availability of trifluoromethanesulfonic acid (1), prompted us to determine its effectiveness, relative to other acids, as a nitration solvent and catalyst. 1 is a strong monobasic acid and possesses an acid strength 427 times as great as that of nitric acid and 14 times as great as that of sulfuric acid.[1] This work resulted in the discovery of nitronium trifluoromethanesulfonate and its subsequent use as a reagent to effect aromatic nitration.

The use of nitronium salts for the nitration of aromatic compounds is well known and has recently been reviewed extensively in several articles concerned with the mechanism of aromatic nitration.[2–5] It has long

(1) T. Gramstad, *Tidsskr. Kjemi, Bergv. Met.*, **19**, 62 (1959); *Chem. Abstr.*, **54**, 12739 (1960).

(2) J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Scholfield, "Nitration Aromatic Reactivity," University Press, Cambridge, England, 1971.

(3) G. A. Olah and S. J. Kuhn in "Friedel–Crafts and Related Reactions," Vol. III, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, Chapter XLIII.

(4) G. A. Olah, *Accounts Chem. Res.*, **4**, 248 (1971).

(5) J. H. Ridd, *Accounts Chem. Res.*, **4**, 248 (1971).

TABLE I

MONONITRATION OF TOLUENE WITH 3 IN ORGANIC SOLVENTS[a]

Run	Mole ratio of 3 to toluene	Solvent	Time, min	Temp, °C	Yield, % MNT[b]	Isomer ratios, % o-MNT	p-MNT	m-MNT
1	4:1	$CFCl_3$	180	−110	>99	50.52	49.25	0.23
2	4:1	CH_2Cl_2	180	−90	>99	61.32	38.32	0.36
3	4:1	CH_2Cl_2	60	−60	>99	62.13	37.35	0.53
4	2.05:1	CH_2Cl_2	60	−60	>99	61.99	37.49	0.52
5	4:1	$CFCl_3$	1	−60	>99	61.88	37.61	0.51
6	4:1	$CFCl_3$	1	−110	>99	50.78	48.98	0.24

[a] A mixture of 3 and 4 was formed by adding 1 equiv of nitric acid to 2 equiv of 1 dissolved in an organic solvent. About 50 ml of solvent was used for each 10 g of 3 formed. [b] MNT = mononitrotoluene.

TABLE II

PREPARATION OF DINITROTOLUENE IN NITRATING MIXTURES CONTAINING CF_3SO_3H[a]

Run	Composition of nitrating mixture, wt % CF_3SO_3H	H_2SO_4	HNO_3	H_2O	Temp, °C	Yield, %	Isomer distribution 2,6	2,3–2,5	2,4	3,4	Total meta %
1	89.0	0	11.0	0	−5	>98	15.70	0.51	82.84	0.95	1.46
2	45.5	45.5	6.0	3.0	−20	>98	10.19	0.31	88.64	0.86	1.17
3	45.5	45.5	6.0	3.0	−20	99	14.85	0.64	83.42	1.10	1.74
4	22.7	68.3	6.0	3.0	−20	99.5	12.06	0.43	86.37	1.15	1.58
5[b]	0	90.6	6.3	3.1	−25	99	11.77	0.50	86.47	1.26	1.76
6	80	0	10	10	20	99.2	16.79	0.96	81.00	1.25	2.21
7	65	0	5	30	0	100	o-/m-/p-MNT = 58.86/1.96/39.18				
							o/p = 1.50				

[a] A 4:1 mole ratio of nitric acid to toluene was used, and reactions were run for 15 min. [b] Run for comparative purposes.

been realized that nitronium salts, such as NO_2HSO_4 and NO_2KSO_4, can be formed *in situ*, and that the attacking species in most nitrating systems is the nitronium ion. The use of stable nitronium salts for aromatic nitration was first mentioned by Goddard, Hughes, and Ingold[6] in 1950 and Olah, Kuhn, and Mlinko[7] in 1956. Subsequently, Olah and coworkers carried out extensive studies on nitration with nitronium salts, such as NO_2BF_4, NO_2PF_6, NO_2ClO_4, NO_2AsF_6, and $NO_2HS_2O_7$.[8-12]

In this paper we report the synthesis of nitronium trifluoromethanesulfonate and its general utility as a nitrating reagent for aromatic compounds, and we briefly examine the mechanism of nitration with this reagent.

Results

Two equivalents of trifluoromethanesulfonic acid (1) and one of anhydrous nitric acid combine to form a white, crystalline solid, 2. This reaction can be carried out between the neat reactants or in solvents such as CH_2Cl_2, CCl_4, H_2SO_4, and excess 1. 2 is very hygroscopic, melts at 60–65°, and partially sublimes at 60–70° (1–2 mm). 2 was shown to be a mixture of nitronium trifluoromethanesulfonate (3) and hydronium trifluoromethanesulfonate (4) by its elemental

$$\underset{1}{2CF_3SO_3H} + HNO_3 \longrightarrow \underset{3}{NO_2^+CF_3SO_3^-} + \underset{4}{H_3O^+CF_3SO_3^-} \quad (1)$$

analysis and Raman spectrum. Reaction 1 is similar to that described by Goddard, Hughes, and Ingold[1] in which nitric acid reacts with $HClO_4$ to give nitronium perchlorate (5) and the monohydrate of perchloric acid (6).

$$2HClO_4 + HNO_3 \longrightarrow \underset{5}{NO_2^+ClO_4^-} + \underset{6}{H_3O^+ClO_4^-} \quad (2)$$

For the purpose of clarity, 2 will refer to the mixture of nitronium trifluoromethanesulfonate and hydronium trifluoromethanesulfonate, and 3 will refer to nitronium trifluoromethanesulfonate.

The elemental analysis of 2 showed that it was composed of the elements of two molecules of 1 and one of nitric acid. The Raman spectrum gave a strong emission at 1409 cm^{-1}, which is characteristic of the symmetrical stretching vibration for the nitronium ion, and showed the presence of the CF_3- and $-SO_3$- group.

Although our initial work was concerned with the use of 1 as a catalyst and solvent for toluene nitration, the observance of 3 prompted us to investigate its effectiveness as a nitrating agent both in protonic acids and in organic solvents. 3 was found to effect aromatic nitration in a variety of solvents, including sulfuric acid, 1, aqueous 1, CH_2Cl_2, CCl_4, $CFCl_3$, CF_2Cl_2, and pentane, and over a temperature range of −110 to 30°. The

$$ArH + xNO_2CF_3SO_3 \longrightarrow Ar(NO_2)_x + xCF_3SO_3H \quad (3)$$

nitrating reagent was formed by adding 1 equiv of anhydrous HNO_3 to a solution of 2 equiv of 1 in a suitable solvent. This reaction could be carried out at ambient temperature, and no exotherm was observed. After an aromatic substrate was added and the mixture was stirred from 1 to 60 min, the reaction was quenched on ice and the products were isolated by extraction. Reaction yields were based on weights of isolated products, and isomer proportions were determined by gc. The reactions of 3 with a variety of aromatic compounds and over a wide range of reaction conditions are summarized in Tables I–V.

(6) D. R. Goddard, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2559 (1950).
(7) G. A. Olah, S. J. Kuhn, and A. Mlinko, *J. Chem. Soc.*, 4257 (1956).
(8) S. J. Kuhn and G. A. Olah, *J. Amer. Chem. Soc.*, **83**, 4564 (1961).
(9) G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Amer. Chem. Soc.*, **83**, 4571 (1961).
(10) G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Amer. Chem. Soc.*, **83**, 4581 (1961).
(11) G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **84**, 3684 (1962).
(12) G. A. Olah, S. J. Kuhn, S. H. Flood, and J. C. Evans, *J. Amer. Chem. Soc.*, **84**, 3687 (1962).

TABLE III

DINITRATION OF TOLUENE WITH 3 IN ORGANIC SOLVENTS

Run	Mole ratio of 3 to toluene[a]	Solvent	Time, min	Temp, °C	Yield, % DNT	Isomer content, % 2,6-DNT	2,4-DNT	Total meta isomers	2,4-/2,6-DNT ratio
1	4:1	CH_2Cl_2	60	25	>99	16.28	81.96	1.72	5.03
2	4:1	CH_2Cl_2	60	0	>99	16.51	82.16	1.33	4.98
3	4:1	CH_2Cl_2	60	−30	>99	15.75	83.17	1.08	5.28
			60	0					
4	4:1	CH_2Cl_2	60	−60		17.18	82.07	0.75	4.78
			60	0	100				
5	4:1	CH_2Cl_2	180	−90		17.67	81.82	0.51	4.63
			180	0					
6	4:1	$CFCl_3$	180	−110	>99	12.66	87.01	0.33	6.87
			60	0					
7	2.05:1	CH_2Cl_2	60	0	99	16.38	82.87	1.35	5.02
8	4:1	CCl_4	60	0	96[b]	15.98	82.82	1.20	5.52
9	4:1	$CFCl_3$	60	0	>99	16.47	82.36	1.17	5.00
10	4:1	CF_2Cl_2	60	−30[c]	c	*c*	*c*	c	
11	4:1	Pentane	60	0	*d*				
12	4:1	Pentane	60	25	98	16.72	81.54	1.74	4.88

[a] A mixture of 3 and 4 was formed by adding 1 equiv of nitric acid to 2 equiv of 1 dissolved in an organic solvent. About 50 ml of solvent was used for each 10 g of 3 formed. [b] Small amount of MNT present. [c] Reaction run at reflux temperature of CF_2Cl_2 (Freon 12). Product contained 80% MNT and 20% DNT. [d] Product contained 10% toluene, 69% MNT, and 21% DNT; isomer ratios not determined.

TABLE IV

NITRATION OF COMPOUNDS OTHER THAN TOLUENE WITH 3

Run	Compd, mmol	Registry no.	CF_3SO_3H, mmol	HNO_3, mmol	CH_2Cl_2, ml	Temp, °C	Time, hr	Products
1	PhH, 43	71-43-2	345	172	500	0	2	98% $PhNO_2$, 2% $C_6H_4(NO_2)_2$
2	$PhNO_2$, 8	98-95-3	40	20	60	25	5	84.8% $C_6H_4(NO_2)_2$ (*o*/*m*/*p* = 9.0/88.7/2.3), 15.2% $PhNO_2$
3	$PhNO_2$, 8		40	20	60	30	3	96.9% $C_6H_4(NO_2)_2$ (*o*/*m*/*p* = 10.0/87.4/2.5), 3.1% $PhNO_2$
4	PhCl, 8	108-90-7	40	20	60	25	2.5	56% $C_6H_4ClNO_2$, 44% $C_6H_3Cl(NO_2)_2$
5	PhCl, 20		42	21	63	25	2.5	97% $C_6H_4ClNO_2$ (*o*/*m*/*p* = 30.5/0.1/69.4%), 3% $C_6H_3Cl(NO_2)_2$
6	*m*-$C_6H_4(CH_3)_2$, 10	108-38-3	42	21	63	25	1	61.5% 4,6-dinitro-*m*-xylene, 37.4% 2,4-dinitro-*m*-xylene, <0.5% each of four other products
7	$PhCF_3$, 5	98-08-8	40	20	60	25	16	85.6% *m*-$C_6H_4CF_3NO_2$, 14.3% *o*-$C_6H_4CF_3NO_2$, 0.1% *p*-$C_6H_4CF_3NO_2$

TABLE V

EFFECT OF VARIOUS SULFONIC ACIDS ON THE NITRATION OF TOLUENE IN METHYLENE CHLORIDE[a]

Run	Nitrating mixture: Acid, mmol	Registry no.	HNO_3, mmol	Toluene, mmol	Time, min	Yield, MNT, %	Comments
1	CF_3SO_3H, 40	1493-13-6	20	5	60	100	*o*/*m*/*p* = 62.13/0.53/37.35
2	FSO_3H, 40	7789-21-1	20	5	120	89	*o*/*m*/*p* = 62.76/0.72/36.52
3	CH_3SO_3H, 104	75-75-2	52	13	150	20	Toluene recovered[b]
4	H_2SO_4, 40	7664-93-9	20	5	120	9	Toluene recovered[b]

[a] Reaction temperature −65 to −60°. [b] MNT isomer ratio not determined.

Discussion

Nitronium trifluoromethanesulfonate (3) proved to have excellent nitrating properties in each reaction medium investigated in this work. Product yields were nearly quantitative in a variety of solvent systems including sulfuric acid, 1, aqueous 1, methylene chloride, and $CFCl_3$, thus indicating the absence of side reactions. In sulfuric acid or mixtures of sulfuric acid and 1, dinitration of toluene occurred to give high yields of DNT. In aqueous 1, as in aqueous sulfuric acid, either mono- or dinitration could be made to occur depending on the concentration of the acid.

Although it is not surprising that 3 is an effective nitrating reagent in sulfuric acid, 1, or aqueous solutions of these acids, the use of 3 as a nitrating reagent in inert organic solvents has proven to be an exceptionally good nitrating system. In organic solvents, mono- or dinitration of toluene could be controlled by reaction temperature, as shown in Tables I and III. At −110 to −60° in methylene chloride, mononitration oc-

TABLE VI
NITRATION OF TOLUENE WITH NITRONIUM SALTS IN METHYLENE CHLORIDE

Run No.	Nitronium salt	Registry no.	Mmol	Toluene, mmol	Temp, °C	Time, min	Yield, %	MNT isomer ratio o-	m-	p-
1	NO_2BF_4	13826-86-3	14.85	3.47	−65	150	70.2	56.55	0.65	42.80
2	NO_2PF_6	19200-21-6	10.39	2.60	−65	150	88.5	46.44	0.81	52.75
3	$NO_2CF_3SO_3$	42262-35-1	19.99	4.99	−60	1	>99	62.18	0.54	37.28

curred accompanied by only a trace of DNT products; at 0° or higher, quantitative yields of DNT were obtained. At −30° mixtures of MNT and DNT were formed.

3 proved to be a slightly less effective nitrating agent in carbon tetrachloride at 0°. In pentane **3** reacted with toluene to give mixtures of MNT and DNT after 1 hr at 0°. At 25° the reaction of **3** with toluene in pentane gave a 98% yield of DNT (see runs 11–12, Table III).

The mononitration of toluene with **3** is very fast, as shown by the fact that in methylene chloride at temperatures from −110 to −60° mononitration of toluene is complete within 1 min. The dinitration step, that is, the nitration of nitrotoluenes, carried out at 0°, is somewhat slower; after 15 min it is 50% complete and requires about 30 min for completion. Although these results show that **3** is not as strong a nitrating agent as the H_2SO_4–HNO_3–0–5% H_2O, oleum–HNO_3, or oleum–metal nitrate systems in which the dinitration step is very fast, **3** in an inert solvent is a very strong nitrating system and one of the few that will convert toluene to DNT at 0°. Although oleum and sulfuric acid nitration systems are stronger than **3** in an organic solvent, these systems freeze and are impractical as nitration media much below −25°. The lowest temperature limit for the effective use of **3** as a nitrating agent is still under investigation.

Complete mono- or dinitration of toluene is possible without the use of excess nitrating reagent. For example, 2.05 equiv of **3** reacts with 1 equiv of toluene at 0° in CH_2Cl_2 to give a 99% yield of DNT after 1 hr (run 7, Table III). In addition, at −60° only a slight excess of **3** is needed for rapid mononitration of toluene.

3 shows a high degree of positional selectivity as a reagent for aromatic nitration. As with all other nitrating systems the amount of meta isomer produced in toluene nitration is directly dependent upon reaction temperature. At −60, −90, and −110° the reaction of **3** with toluene gives MNT that contains 0.53, 0.36, and 0.23% *m*-MNT, respectively (see Table I). The last value is the lowest that has been reliably recorded for a MNT synthesis. Since most meta substitution takes place in the mononitration stage, the final meta-isomer content in DNT can be greatly influenced by running the mononitration step at low temperatures followed by dinitration at 0–25°. Thus, when mononitration was carried out at −110, −90, −60, −30, 0, and 25° followed by dinitration at 0 or 25°, the resulting DNT products contained 0.33, 0.51, 0.75, 1.08, 1.33, and 1.72% meta isomers, respectively. The value 0.33% is the lowest that has been reliably recorded for meta isomers in a DNT synthesis. A similar relationship between reaction temperature and meta-isomer content was noted in nitrations carried out in a mixture of sulfuric acid and 1 shown in Table II.

The *o*-/*p*-MNT and 2,4-/2,6-DNT ratios of the reaction products from Tables I–III are of interest because they illustrate a trend that has not heretofore been noted. In the low-temperature nitration studies in Table I, we noted that at −110° the *o*-/*p*-MNT ratio was substantially different from those obtained at −90 and −60°. *E.g.*, the ortho/para ratios at −90 and −60° are 1.60 and 1.66, respectively, which are typical of *o*-/*p*-MNT ratios obtained from many other nitration systems. At −110° this ratio changes suddenly to 1.03, indicating that a greater selectivity for the para position occurs in the temperature range between −90 and −110°. In the series of reactions shown in Table III in which mononitration was carried out at low temperature followed by dinitration at a higher temperature, the 2,4-/2,6-DNT ratio varies only slightly between 4.63 and 5.28 except for the reaction in which mononitration is carried out at −110°. In this case the 2,4-/2,6 ratio is 6.87, indicating that the mononitration step gave an unusually low *o*-/*p*-MNT ratio. The significant point of these experiments is that in the temperature range from −90 to 25° the *o*-/*p*-MNT ratio appears to decrease slightly as the nitration temperature is lowered, but at −110° the *o*-/*p*-MNT ratio changes suddenly and para substitution predominates.

The positional selectivity of **3** in aromatic nitration (see Table IV) is slightly different from that of other nitrating systems. In general **3** tends to give less meta and more ortho substitution than other nitrating systems. For each aromatic substrate investigated, less meta substitution occurred than was obtained from other nitrating systems at comparable temperatures. In the case of toluene, in which mononitration with 1 equiv of **3** could not be carried out at 25° without formation of some DNT, a direct comparison could not be made. However, since meta isomers from DNT prepared at 25° total only 1.74%, the *m*-MNT percentage can be no larger than this. This decrease in meta substitution occurs for both ortho-, para- and meta-directing aromatic substrates and results in increased ortho, rather than para, substitution. This is especially true in the cases of nitrobenzene and benzotrifluoride, in which exceptionally high values for ortho substitution were recorded. The amounts of ortho substitution obtained for the nitration of toluene and chlorobenzene with **3** were comparatively high but typical of other nitrating reagents.

A short study was conducted to compare the effectiveness of **3** with NO_2BF_4 and NO_2PF_6 as nitrating agents for toluene in methylene chloride at −65° (see Table VI).

The results of this study show that **3** is a far more effective nitrating reagent in methylene chloride than either NO_2BF_4 or NO_2PF_6. Whereas **3** converts toluene to MNT in 1 min, nitrations with NO_2BF_4 and NO_2PF_6 give 70.2 and 85.5% yields, respectively, after 2.5 hr. In addition, **3** shows a higher positional selectivity than either NO_2BF_4 or NO_2PF_6, at least with regard to meta substitution. A meta-isomer per-

centage of 0.54 was formed with **3**, whereas NO_2BF_4 and NO_2PF_6 gave 0.65 and 0.81% *m*-MNT, respectively. At higher temperatures, **3** also appears to be more reactive than NO_2BF_4. Whereas Ciaccio and Marcus[13] have shown that excess NO_2BF_4 mononitrates nitrobenzene at 24° to give conversions of about 100, 75, and 50% after 30 min in sulfuric acid, methanesulfonic acid, and acetonitrile, respectively, a fourfold excess of $NO_2CF_3SO_3$ in CH_2Cl_2 gave a 100% conversion to DNT after 30 min.

The *o*-/*p*-MNT ratio obtained from the nitration of toluene with NO_2PF_6 (see Table V) was 0.88, one of the lowest values recorded. Others have reported the nitration of toluene with NO_2PF_6 in organic solvents, such as tetramethylene sulfone (TMS) at 25°, and found the ortho/para ratio to be 2.18.[10] It is not known if there is a gradual reduction in the ortho/para ratio in the mononitration of toluene with NO_2PF_6 as the temperature decreases and then a sudden change occurs to predominantly para substitution near −65°. This point will be the subject of additional research.

The reaction of **3** with an aromatic hydrocarbon is one of the few examples in which a reagent that is insoluble in the reaction medium is used to effect nitration. At most, only minute quantities of **3** are dissolved in methylene chloride. When **1** and nitric acid react in methylene chloride to form a mixture of **3** and **4**, the supernatant liquid, when separated by filtration, possesses no nitrating capabilities. If fresh methylene chloride is added to the mixture of **3** and **4**, the nitration of aromatic compounds proceeds in the expected manner. Olah, Kuhn, and Mlinko first reported heterogeneous nitrations involving a solid nitronium salt in ether.[7] Bachman and coworkers[14-16] also reported a heterogeneous nitration system in which the solid products from the reaction of BF_3 with N_2O_4 or N_2O_5 are used as nitrating agents in organic solvents such as $CHCl_3$, CCl_4, benzene, or nitromethane. Whereas in Bachman's work heating and long reaction times are necessary to obtain moderate yields, nitrations effected by **3** in inert solvents are very fast even at temperatures as low as −110°.

Since **3** proved to be an excellent nitrating reagent for toluene, several reactions were run to determine if less acidic sulfonic acids, such as fluorosulfonic acid (**7**), methanesulfonic acid (**8**), or sulfuric acid would react in the same manner. The conditions and results for these experiments are summarized in Table V. These systems were substantially different from those of HNO_3 and **1** in CH_2Cl_2 in that a solid, stable, nitronium salt did not form. The combination of HNO_3 and **7** in CH_2Cl_2, which formed a cloudy suspension, is an effective nitrating reagent giving an 89% yield of MNT after 1 hr at −60°. The combinations of HNO_3 and **8** or H_2SO_4 were somewhat less effective and formed only low yields of MNT. These low yields were probably due to poor mixing between a viscous second phase with the CH_2Cl_2 solution of toluene.

From the data presented in this paper it is difficult to determine the mechanism by which aromatic nitration with **3** in organic solvents occurs. The facts that **3** can be used as a suspended solid in organic solvents and that the nitrations are essentially between solid **3** and a dissolved aromatic compound set this reagent apart from other much-studied nitration systems. This heterogeneity makes comparisons of our observed data on relative reaction rates and isomer distributions with data from homogeneous systems difficult to interpret. In addition, the presence of **4** in the reaction mixture and the role it might take in the nitration processes are not known.

The major difference between aromatic nitration with **3** and other nitronium salts is reaction rate. The rate of nitration of toluene by **3** at −60 and −110° compared with that using NO_2BF_4 or NO_2PF_6 at −60° convincingly illustrates differences in the nitrating species involved. Because it must be assumed that the nitronium ion is present in the attacking species, the difference in reactivity must arise from the accompanying anion. Whether this difference can be attributed to solubility difference in the NO_2^+-containing species in CH_2Cl_2, the formation of a reactive complex between **3** and **4**, or the inherent reactivity of **3** will be a subject of future research.

Experimental Section

General.—Elemental analyses were determined by the Stanford University Microanalytical Laboratory. Infrared spectra were run on a Perkin-Elmer 237 spectrophotometer and Raman spectra on a Specs Ramalog 1401 Double Monochromator, Coherent Radiation Model 52, Mixed Gas Argon Krypton Laser. Vpc analyses were run on an Aerograph 1520 gas chromatograph equipped with a flame ionization detector. Mononitrotoluene, nitrochlorobenzene, dinitrobenzene, and nitrated xylene mixtures were analyzed on a 12 ft × 0.125 in., 4% QF-1 on 100/120 mesh Chromosorb G, acid-washed, DMCS-treated column. Dinitrotoluene and nitrobenzotrifluoride mixtures were analyzed on a 12 ft × 0.125 in. column packed with 4% poly-*m*-phenyl ether (six ring) on 80/100 mesh Chromosorb G, acid washed, DMCS treated. Base-line separation of all DNT isomers was obtained except for the 2,3 and 2,5 isomers, which had the same retention time. Each vpc analysis was compared with that of a standard that contained approximately the same isomer distribution.

Starting Materials.—Trifluoromethanesulfonic acid was obtained from the 3M Co. under the name of trimsylate acid (FC-24). It was analyzed as ~99% pure by preparation of its aniline salt and was used without further purification. Toluene was obtained from usual commercial sources and was distilled before use to obtain fractions that were pure by vpc analysis. Benzene (Matheson Coleman and Bell), nitrobenzene (Curtin Chemical Co.), chlorobenzene (Baker Chemical Co.), *m*-xylene (Matheson Coleman and Bell), and benzotrifluoride (Pierce Chemical Co.) were of sufficient purity for use as received.

Reaction of CF_3SO_3H with HNO_3. Method A.—Under an atmosphere of N_2, a 6.00-g sample (40 mmol) of trifluoromethanesulfonic acid was placed in a 50-ml flask equipped with a mechanical stirrer, N_2 inlet tube, and dropping funnel. To this stirred liquid was added dropwise 1.26 g (20 mmol) of anhydrous nitric acid. As the nitric acid was added a white, crystalline solid was continually formed. The resulting solid was allowed to stir for 1 hr to assure complete mixing and reaction. The product was shown to contain approximately the original weights of starting material by elemental analysis. It melted at 60–65° and sublimed at 60–70° (1–2 mm): ir (KCl pellet) 525 (m), 590 (m), 640 (s), 765 (m, very sharp), 830 (w), 850 (w), 880 (w), 1030 (w), 1150–1180 (vs), and 1230–1300 cm^- (s); Raman (crystalline) 321 (C–S), 351 (SO_3) 520 (CF_3), 580 (NO_2^+), 776 (CF_3), 1038 (SO_3), 1160, 1188 (SO_3), 1228 (CF_3), 1323, and 1409 cm^- (NO_2^+).

Anal. Calcd for $C_2H_3NO_9F_6S_2$: C, 6.61; H, 0.83; F, 31.39; N, 3.06; S, 17.66. Found: C, 6.59; H, 1.31; F, 34.9; N, 3.48; S, 16.44.

Method B.—Under an atmosphere of N_2, 6.00 g (40 mmol) of trifluoromethanesulfonic acid was dissolved in 100 ml of CH_2Cl_2 in a 200-ml flask equipped with a mechanical stirrer, N_2 inlet tube,

(13) L. L. Ciaccio and R. A. Marcus, *J. Amer. Chem. Soc.*, **84**, 1838 (1962).
(14) G. B. Bachman, H. Feuer, B. R. Bluestein, and C. M. Vogt, *J. Amer. Chem. Soc.*, **77**, 6188 (1955).
(15) G. B. Bachman and J. L. Dever, *J. Amer. Chem. Soc.*, **80**, 5871 (1958).
(16) G. B. Bachman and C. M. Vogt, *J. Amer. Chem. Soc.*, **80**, 2987 (1958).

thermometer, and addition funnel. To this solution was added dropwise at 25° 1.26 g (20 mmol) of anhydrous nitric acid; no exotherm was noted. The solution was stirred for 15 min and then filtered under N_2 to collect a white, crystalline solid. Not all of the solid was collected, since some adhered to the sides of the flask. The solid, 6.67 g, was dried under vacuum over P_2O_5 and NaOH, mp 60–64°. The ir spectrum of this product was identical with that obtained from the product from method A.

Anal. Calcd for $C_2H_3NO_9F_6S_2$: C, 6.61; H, 0.83; N, 3.06. Found: C, 6.58; H, 1.21; N, 3.29.

Preparation of Mononitrotoluene.—A solution containing 6.00 g (40 mmol) of trifluoromethanesulfonic acid dissolved in 100 ml of CH_2Cl_2 was placed in a 200-ml flask equipped with a mechanical stirrer, addition funnel, and thermometer. A 1.26-g sample (20 mmol) of anhydrous HNO_3 was added to this solution, causing a white, crystalline solid to separate from solution. The temperature of the mixture was lowered to −60° by means of a Dry Ice–acetone bath, and 0.46 g (5 mmol) of toluene was added in one portion. The mixture was stirred at −60° for 1 hr and then quickly poured onto 100 g of crushed ice. The resulting mixture was extracted with three 100-ml portions of CH_2Cl_2. These were combined and dried ($MgSO_4$), and the solvent was removed under vacuum, leaving 0.69 g (100%) of mononitrotoluenes. A gc analysis of this product showed that it contained 62.12% *o*-nitrotoluene, 0.53% *m*-nitrotoluene, and 37.35% *p*-nitrotoluene; a trace (<0.1%) of dinitrotoluene was present.

Preparation of Dinitrotoluene. Method A.—A nitrating mixture consisting of 42.63 g (284 mmol) of CF_3SO_3H, 42.75 g of 96% H_2SO_4, and 7.91 g (126 mmol) of anhydrous HNO_3 was prepared in a 100-ml flask equipped with a mechanical stirrer, addition funnel, and thermometer. The solution was cooled to −24° and 2.02 g (22 mmol) of toluene was added dropwise in 50 min. As the toluene was added, a solid product was formed and the nitrating mixture became partially frozen. Stirring was continued for 1 hr at −24 to −20° and the reaction mixture was poured onto 1200 g of crushed ice. The resulting mixture was extracted with three 250-ml portions of CH_2Cl_2; there were combined and dried ($MgSO_4$) and the solvent was evaporated, leaving 3.83 g (97%) of a light yellow solid that was identified as a mixture of dinitrotoluene isomers by its ir spectrum and elemental analysis. Gc analysis showed that this product contained 12.20% 2,6-DNT, 0.45% 2,3- and 2,5-DNT, 86.31% 2,4-DNT, and 1.04% 3,4-DNT. Total meta-isomer content was 1.49%.

Anal. Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.12; H, 3.33; N, 15.25.

Method B.—A nitrating mixture consisting of 50.0 g (333 mmol) of CF_3SO_3H and 6.30 g (100 mmol) of anhydrous HNO_3 was prepared in a 100-ml, three-necked flask equipped with a mechanical stirrer, addition funnel, and thermometer. The mixture consisted of an insoluble complex of $2CF_3SO_3H/HNO_3$ in CF_3SO_3H. The mixture was cooled to 0° and 4.00 g (43 mmol) of toluene was added over a 10-min period. The reaction mixture was stirred at 0° for 1 hr and quenched on 500 g of crushed ice. The resulting mixture was extracted with three 100-ml portions of CH_2Cl_2, which were combined and dried ($MgSO_4$). Removal of solvent left 7.75 g (98%) of a light yellow solid that was identified as a mixture of dinitrotoluene isomers by ir spectrum. A gc analysis of this product showed that it contained 15.70% 2,6-DNT, 0.51% 2,3- and 2,5-DNT, 82.84% 2,4-DNT and 0.95% 3,4-DNT.

Method C.—A mixture containing 6.00 g (40 mmol) of trifluoromethanesulfonic acid and 100 ml of $CFCl_3$ was prepared in a 200-ml flask equipped with a mechanical stirrer, addition funnel, and thermometer. A 1.26-g sample (20 mmol) of anhydrous HNO_3 was added at 25°, forming the $2CF_3SO_3H/HNO_3$ complex. The temperature of the reaction was lowered to 0° and 0.46 g (5.0 mmol) of toluene was added in one portion. The mixture was stirred for 1 hr at 0° and poured onto 100 g of crushed ice. Three 100-ml CH_2Cl_2 extractions were combined and dried over $MgSO_4$. The solvent was removed, leaving 0.90 g (99%) of a light yellow solid that was identified as a mixture of dinitrotoluene isomers by its ir spectrum. A gc analysis of this product showed that it contained 16.47% 2,6-DNT, 0.45% 2,3- and 2,5-DNT, 82.36% 2,4-DNT, and 0.72% 3,4-DNT. Total meta-isomer content was 1.17%.

Method D.—A solution containing 6.00 g (40 mmol) of trifluoromethanesulfonic acid in 100 ml of CH_2Cl_2 was prepared in a 200-ml, three-necked flask equipped with a mechanical stirrer, addition funnel, and thermometer. The addition of 1.26 g (20 mmol) of anhydrous HNO_3 caused the precipitation of the white, crystalline $2CF_3SO_3H/HNO_3$ complex. The temperature of the mixture was lowered to −60° by means of a Dry Ice–acetone bath and 0.46 g (5.0 mmol) of toluene was added in one portion. After the mixture was stirred at −60° for 1 hr, the reaction temperature was raised to 0° over a 10-min period and the mixture was stirred at 0° for 1 hr. The reaction mixture was poured onto 100 g of crushed ice, and the organic products were extracted into CH_2Cl_2 (3 × 100 ml). The CH_2Cl_2 extracts were combined and dried ($MgSO_4$), and the solvent was removed, leaving 0.91 g (100%) of a light yellow solid that was identified as a mixture of dinitrotoluenes by its ir spectrum. A gc analysis of this product showed that it contained 17.18% 2,6-DNT, 0.28% 2,3- and 2,5-DNT, 82.07% 2,4-DNT, and 0.47% 3,4-DNT. Total meta-isomer content was 0.75%.

Relative Reaction Rates of Toluene and Benzene toward 3.—A nitrating mixture was prepared from 4.80 g (32 mmol) of CF_3SO_3H and 1.01 g (16 mmol) of anhydrous HNO_3 in 40 ml of CH_2Cl_2. The resulting slurry was kept at −65° and added in portions over a 10-min period to a solution of 1.84 g (20.0 mmol) of toluene and 1.56 g (20.0 mmol) of benzene in 10 ml of CH_2Cl_2. During the mixing of the reactants and for an additional 1 hr, a stirring rate of ~2000 rpm was maintained. The reaction mixture was poured onto 200 g of ice water, and the organic products were extracted with three 50-ml portions of CH_2Cl_2. The extracts were combined and dried ($MgSO_4$) and the products were analyzed by gc without removing the solvent. Gc analysis showed a nitrotoluene to nitrobenzene ratio of 1.94; no dinitro products were present. Based on our work with toluene and benzene described above, we assumed that all of the nitric acid was consumed. Therefore, the amount of toluene and benzene remaining would be 9.5 and 14.5 mmol, respectively. A relative rate factor using the equation $k_t/k_b = (\log t - \log t_0)/(\log b - \log b_0)$ was found to be 2.3 (t, t_0, b, and b_0 equal final and initial concentrations of toluene and benzene).

Nitration of Chlorobenzene.—Chlorobenzene was nitrated according to method C. The reaction was run at 25° for 2.5 hr using 6.30 g (42 mmol) of CF_3SO_3H, 1.32 g (21 mmol) of anhydrous HNO_3, and 2.25 g (20 mmol) of chlorobenzene in 63 ml of CH_2Cl_2; product weight was 3.21 g (100% based on HNO_3). Gc analysis showed 3% dinitrochlorobenzene. The *o*-, *m*-, and *p*-nitrochlorobenzene percentages were 30.5, 0.1, and 69.4%, respectively.

Nitration of Nitrobenzene.—Nitrobenzene was nitrated according to method C. The reaction was run at 25° for 5 hr using 6.0 g (40 mmol) of CF_3SO_3H, 1.26 g (20 mmol) of anhydrous HNO_3, and 0.98 g (8.0 mmol) of nitrobenzene in 60 ml of CH_2Cl_2. Product weight was 1.25 g (84.8%). Gc analysis showed 8.96, 88.75, and 2.29% of *o*-, *m*-, and *p*-dinitrobenzene, respectively.

Nitration of Benzotrifluoride.—Benzotrifluoride was nitrated according to method C. The reaction was run at 25° for 16 hr; reaction times of 1–5 hr were not sufficient for complete nitration. The reaction was run using 6.00 g (40 mmol) of CF_3SO_3H, 1.26 g (20 mmol) of anhydrous HNO_3, and 0.73 g (5 mmol) of benzotrifluoride in 60 ml of CH_2Cl_2. Product weight was 0.98 g (theoretical weight of nitrobenzotrifluorides is 0.96 g). A gc analysis showed that the product contained 7.6, 92.3, and <0.1% of *o*-, *m*-, and *p*-nitrobenzotrifluoride, respectively.

Nitration of *m*-Xylene.—*m*-Xylene was nitrated according to method C. The reaction was run at 25° for 1 hr using 6.30 g (42 mmol) of CF_3SO_3H, 1.32 g (21 mmol) of anhydrous HNO_3, and 1.06 g (10 mmol) of *m*-xylene in 63 ml of CH_2Cl_2. The product weight was 1.98 g [the theoretical weight of dinitroxylene (DNX) is 1.96]. Gc analysis showed that the product contained 61.5% 2,6-DNX, 37.4% 2,4-DNX, and <0.5% each of 2,5- and 4,5-DNX and an unknown.

Registry No.—HNO_3, 7697-37-2; toluene, 108-88-3.

Effect of Polar Attraction on the Equilibria of Rigid Tetracyclic Hemiacetals

ANTHONY WINSTON,* WILLIAM D. RIGHTLER, FREDERICK G. BOLLINGER, AND RONALD F. BARGIBAND

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

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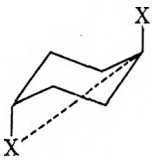
Tetracylic hemiacetals **14–24** were synthesized and their isomeric equilibria in DMSO-d_6 at 50° were studied by nmr techniques. Substitution of polar groups at the C_9-exo position caused the equilibrium to shift toward the lesser stable β isomer. This shift is interpreted on the basis of a stabilization of the β isomer through polar attraction between the electropositive carbon, C_9, and the electronegative oxygen of the nearby hydroxyl group. Halogen or mesyl substituents at C_9 cause a stabilization of 0.4–0.5 kcal/mol while hydroxyl imparts about 0.2-kcal/mol stabilization. These results are significant in understanding the forces responsible for hemiacetal and conformational equilibria.

Recent evidence has clearly shown that the position of conformational equilibria of pyranose derivatives and multisubstituted cyclohexanes cannot be predicted reliably on the basis of additive conformational free energies and anomeric effects. Pyranose derivatives substituted at C_1 with negative substituents, such as acetate, benzoate, and especially halogen, invariably prefer that conformation in which the C_1 substituent is axial, regardless of the fact that this often forces substituents at the other positions into axial conformations.[1-3] An extreme situation is encountered in the case of tri-*O*-acetyl- and tri-*O*-benzoyl-β-D-xylopyranosyl chloride, which at equilibrium contains 80 and 98%, respectively, of the *1C* conformer in which the three acetate (benzoate) groups, as well as the chlorine at C_1, are all axial.[3] According to Durette and Horton,[3] this would not have been predicted on the basis of conformational free energies[4,5] and the anomeric effect of the chloro group.[6]

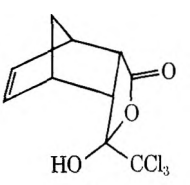
In the case of trifluoroacetoxycyclohexane the equilibrium is 80% in favor of the equatorial conformer, but, with two such substituents situated 1,4-trans, the equilibrium is only 55% in favor of the diequatorial conformer.[7] Stabilization of the diaxial conformer through polar attraction between an electropositive carbon and the electronegative substituent at the C_4 axial position as shown was suggested to account for this phenomenon.[7] The substantial stability of diaxial conformers of trans-1,2 and trans-1,4 disubstituted cyclohexanes is further confirmation of the complexity of the interactions involved.[8] Under circumstances where several interacting groups are present, predictions of the conformational preferences become hazardous.



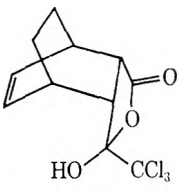
It is the purpose of this paper to present equilibria studies of hemiacetals of some rigid tetracyclic ring systems in which the stereochemistry and the polar interactions are strictly controlled. These results will then be interpreted to indicate the magnitude of the polar forces between a halogen substituted carbon and an electronegative hemiacetal hydroxyl group. With appropriate corrections for the distances involved in the interactions it is suggested that these results provide a further parameter for predicting, or justifying, the position of hemiacetal and conformational equilibria.

Results

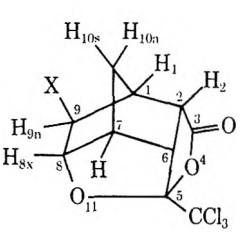
Synthesis and Characterization of Tetracyclic Lactones.—Trichloromethyl lactols **1** and **2** were starting materials for the preparation of lactones **3–13**. Lactols **1** and **2** were prepared through the reaction of sodium trichloroacetate with the Diels–Alder adducts of cyclopentadiene and 1,3-cyclohexadiene with maleic anhydride.[9,10]



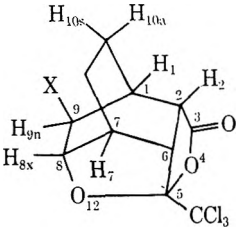
1



2



3, X = H
4, X = Cl
5, X = Br
6, X = I
7, X = OH
8, X = OMs



9, X = H
10, X = Cl
11, X = Br
12, X = I
13, X = OH

(1) C. V. Holland, D. Horton, and J. S. Jewell, *J. Org. Chem.*, **32**, 1818 (1967).
(2) P. L. Durette and D. Horton, *J. Org. Chem.*, **36**, 2658 (1971).
(3) P. L. Durette and D. Horton, *Carbohyd. Res.*, **18**, 57 (1971).
(4) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **91**, 344 (1969).
(5) E. L. Eliel, N. L. Allinger, S. F. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.
(6) C. B. Anderson and D. T. Sepp, *J. Org. Chem.*, **32**, 607 (1967).
(7) G. Wood, E. P. Woo, and M. H. Miskow, *Can. J. Chem.*, **47**, 426 (1969).
(8) H. J. Hageman and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **88**, 97 (1969); R. J. Abraham and T. M. Siverns, *J. Chem. Soc., Perkin Trans. 2*, 1587 (1972); M. J. T. Robinson, *Pure Appl. Chem.*, **25**, 635 (1971); L. J. Collins and D. N. Kirk, *Tetrahedron Lett.*, 1547 (1970); P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, *J. Chem. Soc., Perkin Trans. 2*, 58 (1972); P. L. Barili, G. Bellucci, G. Ingrosso, F. Mariono, and I. Morelli, *Tetrahedron*, **28**, 4583 (1972).
(9) A. Winston, J. P. M. Bederka, W. G. Isner, P. C. Juliano, and J. C. Sharp, *J. Org. Chem.*, **30**, 2784 (1965).
(10) A. Winston, J. C. Sharp, K. E. Atkins, and D. E. Battin, *J. Org. Chem.*, **32**, 2166 (1967).

Lactones **3** and **9** were prepared by a reaction of the lactols **1** and **2** with concentrated sulfuric acid as reported previously for the synthesis of lactone **3**.[11] The 9-halo lactones **4**–**6**, reported previously,[12] and **10**–**12** were prepared by the reactions of lactols **1** and **2** with the appropriate halogen in aqueous sodium carbonate in the presence of the corresponding potassium halide. The 9-hydroxy lactones **7**[12] and **13** were prepared by treatment of lactols **1** and **2** with peracetic acid. The mesyl lactone **8** was prepared from hydroxy lactone **7** by treatment with methanesulfonyl chloride in pyridine.

Significant nmr lines for lactones **3**–**13** are reported in Table I. Chemical shifts and coupling assignments

TABLE I

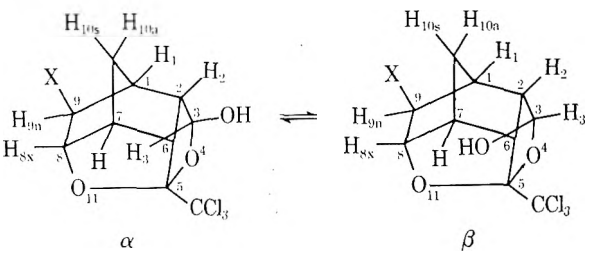
NMR DATA FOR TETRACYCLIC LACTONES

Compd	Solvent	Chemical shifts, τ: H_{8x} (multiplicities)	H_{9n}	Coupling constants, Hz: $J_{7,8x}$	$J_{9n,10}$	$J_{1,9n}$
3	DMSO-d_6	5.10 (m)	*a*			
4	DMSO-d_6	5.10 (d)	5.98 (d)	5.0	2.5	
5	DMSO-d_6	4.91 (d)	5.95 (d)	5.0	2.5	
6	DMSO-d_6	4.78 (d)	6.04 (d)	5.0	2.5	
7	DMSO-d_6	5.57 (d)		5.0		
8	DMSO-d_6	5.02 (d)	5.51 (s)	5.0		
9	$CDCl_3$	5.35 (t)	*a*	5.0		
10	$CDCl_3$	5.45 (d)	5.82 (d)	5.0		4.0
11	$CDCl_3$	5.22 (d)	5.73 (d)	5.0		4.0
12	$CDCl_3$	5.01 (d)	5.62 (d)	5.0		4.0
13	$CDCl_3$	5.70 (d)	5.94 (d)	5.0		4.0

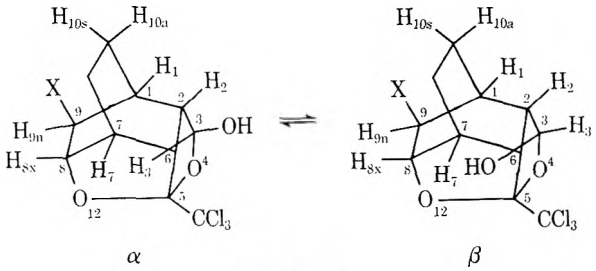
[a] Concealed in upfield multiplet.

of Table I are based in part upon a detailed nmr analysis of a structure closely analogous to the present series.[13] For lactones **4**–**8** and **10**–**13**, the H_{8x} protons are clearly evident as doublets (J = 5 Hz) coupled with the bridgehead protons H_7. The failure to observe coupling between H_{8x} and H_{9n} can reasonably be attributed to a dihedral angle close to 90°, caused by distortion of the bicyclic ring by the oxygen bridge. Similar lack of coupling of vicinal trans protons has been reported for other strained cyclic and bicyclic systems.[13,14] For lactones **4**, **5**, and **6**, H_{9n} appears as doublets (J = 2.5 Hz) through W coupling[15] with H_{10a}. For lactones **10**–**13** H_{9n} also appears as doublets of J = 4 Hz, which is a somewhat larger value than is ordinarily observed in W coupling. Examination of molecular models reveals that the dihedral angle between H_{9n} and H_1 changes from about 80° for the bicyclo[2.2.1]heptane series to about 50° for the bicyclo[2.2.2]octane series **9**–**13**. Hence, in the case of lactones **9**–**13**, it would seem more reasonable to assign the source of these doublets to coupling between the H_{9n} and H_1 rather than to W coupling with H_{10a}.

Synthesis, Characterization, and Equilibration of the Tetracyclo Hemiacetals.—The tetracyclic lactones were smoothly converted into the corresponding hemiacetals **14**–**24** by reduction with sodium borohydride. Even

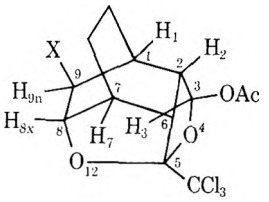


14, X = H
15, X = Cl
16, X = Br
17, X = I
18, X = OH
19, X = OMs



20, X = H
21, X = Cl
22, X = Br
23, X = I
24, X = OH

though excess sodium borohydride was often used, opening of the cyclic hemiacetal with further reduction of the aldehyde was never observed. The acetates **25** and **26** were prepared from hemiacetal **20** and **21** by treatment with acetic anhydride in pyridine.



25, X = H
26, X = Cl

The α–β equilibria of hemiacetals **14**–**24** are clearly revealed by their nmr spectra using DMSO-d_6 as solvent. Although the equilibria could also be detected using pyridine-d_5 and other solvents, DMSO-d_6 was the ideal choice, not only because of the good solubility of the compounds, but also because the C_3 hydroxyl protons appear far downfield and exhibit good splitting patterns.[16–18] The most significant feature is the doublet–triplet combination shown schematically in Figure 1 and listed in detail for each hemiacetal in Table II. Acetates **25** and **26**, which do not undergo equilibration, are also included in the table for comparison.

The origin of these lines and their assignments to particular protons of the two isomeric hemiacetals can

(11) A. Winston, J. C. Sharp, and R. F. Bargiband, *J. Org. Chem.*, **36**, 1714 (1971).
(12) R. F. Bargiband and A. Winston, *Tetrahedron*, **28**, 1427 (1972).
(13) K. C. Ramey, D. C. Lini, R. M. Moriarty, H. Gopal, and H. G. Welsh, *J. Amer. Chem. Soc.*, **89**, 2401 (1967).
(14) A. Winston and J. C. Sharp, *J. Amer. Chem. Soc.*, **88**, 4196 (1966).
(15) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 334.
(16) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).
(17) B. Casu and M. Reggiani, *Tetrahedron Lett.*, 2253 (1965).
(18) W. Mackie and A. S. Perlin, *Can. J. Chem.*, **44**, 2039 (1966).

TABLE II
NMR DATA FOR TETRACYCLIC HEMIACETALS AND DERIVATIVES IN DMSO-d_6

	Chemical shift, τ[a]			
Compd	OH-β (d)	OH-α (d)	H_3-β (t)	H_3-α (d)
14	2.90	3.34	4.33	4.58
15	2.48	3.12	4.30	4.37
16	2.49	3.11	4.33	4.38
17	2.51	3.14	4.35	4.38
18	2.76	3.27	4.37	4.52
19	2.47	3.07	4.31	4.32
20	3.00	3.45	4.38	4.70
21	2.47	3.13	4.32	4.46
22	2.51	3.19	4.31	4.46
23	2.51	3.18	4.31	4.52
24	2.86	3.41	4.42	4.65
25				3.86[b]
26				3.66[b]

[a] Coupling constants, $J(OH,H_3) = 5$ Hz; $J(H_3,H_2) = 5$ Hz. [b] Singlet.

be established by area ratios, spin decoupling, and splitting patterns. The two isomers have been arbitrarily designated α and β as shown in the structural drawings for compounds **14**–**26**. Referring to Figure 1, integration of the lines revealed that, in those cases in which the upfield triplet–doublet pair was sufficintly separated for measurement, the areas of A were always equivalent to the areas of C. Similarly, the areas B and D were always equivalent. In every case the total area of A and B was the same as the total area of C and D. These results indicate that lines A and C arise from one of the two isomers, while B and D are from the other. This idea was confirmed by spin decoupling. Irradiation of the doublet A caused triplet C to collapse to a doublet, while irradiation of triplet C caused doublet A to become a singlet. Similarly, irradiation of either of the doublets B or D caused the other to collapse to a singlet.

The lines can be assigned to a particular isomer, α or β, by analysis of the splitting pattern. The C_3-OH protons appear as doublets in both isomers as a result of coupling with H_3. Protons H_3 are correspondingly split by the OH protons. In the case of the β isomer, H_3 is again split by H_2, giving rise to the triplet C. For the α isomer, further splitting by H_2 is at a minimum due to a dihedral angle close to 90°. Hence, H_3 for the α isomer appears only as the doublet. Thus, doublet A and triplet C (Figure 1) arise respectively from the OH proton and H_3 of the β isomer, while doublets B and D are from the corresponding protons of the α isomer. For acetates **25** and **26**, which cannot undergo equilibration, only singlets were observed for H_3, characteristic of the α form. Only the α isomers of acetates **25** and **26** were ever isolated in the preparation. The β isomers, if they formed at all, were in low concentration and were not detected.

The presence of two isomeric hemiacetals in solution is undoubtedly a result of equilibration *after* formation of the hemiacetal by sodium borohydride reduction. Reduction by borohydride, being a kinetically controlled process, would be expected to occur by an approach of the reagent from the less hindered, convex, face of the tetracyclic lactone to form exclusively the β isomer as the kinetic product. Equilibration would normally be expected to occur during the isolation and purification procedures. If the conditions of the reduction and the isolation of the product are carefully controlled, a single isomer can be obtained. The pure β isomer of **19** was prepared by reduction of the lactone **8** in dioxane at 0°. Recrystallization from nonprotonic solvents at low temperatures produced a product, the nmr spectrum of which exhibited only the doublet–triplet combination of the β isomer. After 10 min at ambient temperatures (37°) in the nmr spectrometer the spectrum was still unchanged, indicating that under these conditions equilibration is reasonably slow. After heating the same sample for 10 min at 50° in the nmr tube the pair of doublets characteristic of the α isomer had appeared.

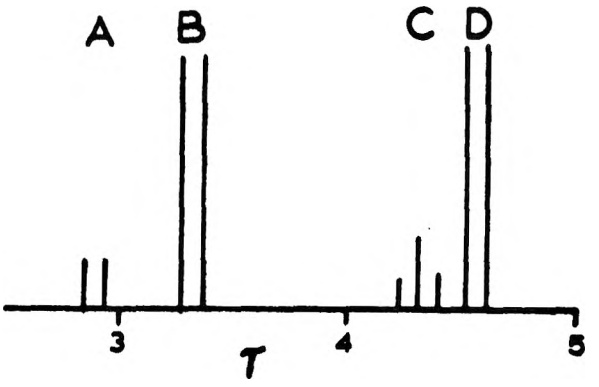


Figure 1.—General appearance of the downfield nmr lines of hemiacetals **14**–**24**.

A pure α isomer was also isolated by slow crystallization of hemiacetal **16** over a period of 2 months. The initial nmr spectrum of a sample of this material showed only the pair of doublets of the α isomer, but, after heating at 50°, lines for both isomers were then present.

The hemiacetals **14**–**24** were allowed to equilibrate in DMSO-d_6 at 50° and the nmr spectra were recorded periodically at ambient temperatures (37°) until no further changes in the line intensities could be noted (about 72 hr). The relative concentrations of the isomers were measured by integration of the sharp, well-resolved OH doublets (lines A and B in Figure 1). Each spectrum was integrated five times and the average values were taken. Deviations from the average were not greater than ±5%. The equilibrium constants and the $\Delta G°$ values at 50° are reported in Table III.

TABLE III
EQUILIBRIUM CONSTANTS AND FREE ENERGY VALUES FOR THE α–β EQUILIBRIA OF HEMIACETALS AT 50° IN DMSO-d_6

Compd	X	K_{eq}[a]	$\Delta G°$, kcal/mol
14	H	0.23	0.97
15	Cl	0.58	0.36
16	Br	0.67	0.25
17	I	0.61	0.34
18	OH	0.30	0.75
19	OMs	0.63	0.29
20	H	0.38	0.62
21	Cl	0.85	0.10
22	Br	0.88	0.08
23	I	0.84	0.11
24	OH	0.52	0.42

[a] $K_{eq} = [\beta]/[\alpha]$.

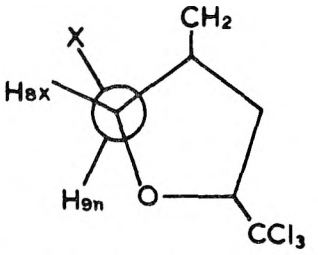


Figure 2.—Newman projection of the tetracyclic system showing the conformation about C_8 and C_9.

Discussion

Equilibria and thermodynamic data, Table III, clearly reveal that in every case the position of the α–β equilibrium is in favor of the α isomer. This is understandable since it is in this form that the C_3 hydroxyl group is directed away from the ring toward an area of relatively lower steric crowding. The position of the equilibrium, however, varies appreciably with the nature of the substituent at the C_9-exo site. Taking compounds **14** and **20** (X = H) as the standard, the β isomers show a marked increase in stability when X is changed to halogen or *O*-mesyl. A considerable, but somewhat lesser stability, is imparted to the β isomer by the hydroxyl group at C_9-exo. To arrive at a reasonable interpretation of these results requires a consideration of both steric and electronic factors.

The presence of bulky groups at the C_9-exo position should have little effect on the steric environment of the C_3 hydroxyl group of the β isomer. The lack of coupling between H_{8x} and H_{9n} indicates that the corresponding dihedral angle approaches 90°.[12-14] This would mean that the C_9-exo substituent is directed upward and situated in a slightly staggered conformation with respect to the H_{8x} substituents, Figure 2. Rotation about the C_8–C_9 bond in the other direction is not only sterically unfavorable due to the rigidity of the tetracyclic ring system, but is also contrary to the nmr results. If this were the case, the dihedral angle between H_{8x} and H_{9n} would have to approach 180°, and in such a situation coupling should have been observed. Also, since the steric requirements of the hydroxyl group and the *O*-mesyl group are about the same, the great difference in the equilibrium constants of hemiacetals **18** and **19** cannot be justified on steric grounds. It is thus clearly apparent that, in general, steric effects arising from C_9-exo substituents cannot be regarded as providing a significant contribution to stabilization of the β isomer.

On the other hand, consideration of polar effects provides a quite reasonable interpretation. The presence of an electronegative group at the C_9-exo position would induce a net positive charge on C_9. Attraction between positive C_9 and the nearby negative oxygen of the β isomer would provide a clear justification for the greater stability of the β isomer. Comparing **18** (X = OH) with **19** (X = OMs) the electronegativity of the oxygen at C_9-exo is increased substantially on converting the hydroxyl group to the *O*-mesyl group, thus increasing the induced positive charge at C_9 and resulting in a stronger attractive force between C_9 and the β-C_3 hydroxyl group.

The increased stabilization of the unfavorable β isomer through substitution at C_9 is of the order of

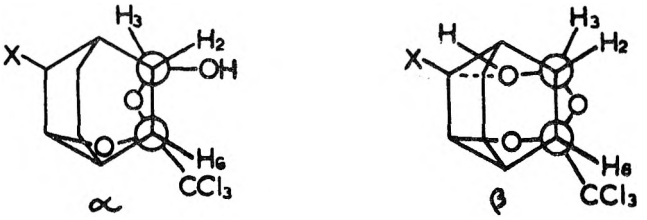


Figure 3.—Conformations of α and β isomers of tetracyclic hemiacetals.

0.4–0.5 kcal/mol for halogen and *O*-mesyl and 0.2 kcal/mol for hydroxyl. Although the equilibrium constants and $\Delta G°$ values may change somewhat for solvents other than DMSO, as it is well known that the nature of the solvent does influence hemiacetal equilibria;[18] nevertheless, the results clearly establish the existence of polar attractive forces. Appropriate application of these concepts to polysubstituted cyclohexanes, pyranoses, and other systems may well lead to a better understanding of the parameters involved in conformational preferences. For example, in the case of *trans*-1,4-bis(trifluoroacetoxy)cyclohexane, the conformational $\Delta G°$ value was found to be only 0.077 kcal/mol, whereas on the basis of additive conformational free energies it should have been 0.970 kcal/mol, based on 0.485 kcal/mol for each trifluoroacetoxy group.[7] The difference of 0.9 kcal can be accounted for on the basis of two polar attractive forces of 0.45 kcal each, clearly of the same magnitude as the energies found here for such attraction. Recently quantitative theoretical support for attractive nonbonded interactions has been provided[19] to account for various conformational populations, with particular reference to the "anomeric effect."[20] On this basis the involvement of longer range attractive forces in conformation and hemiacetal equilibria appears quite reasonable.

The nmr spectra also give information concerning the precise conformation of the hemiacetal ring system. In the α form the apparent lack of coupling between H_3 and H_2 would indicate that these protons lie at a dihedral angle close to 90°, and that the conformation approaches that of Figure 3, α. In the β form the 5-Hz coupling between H_3 and H_2 would indicate a dihedral angle of 20–30°. Since there is polar attraction between C_9 and the C_3–OH group, the most likely conformation would be represented as shown in Figure 3, β.

In comparing the two hemiacetal systems with each other we find that for series **14**–**19** the equilibrium constants indicate an energy consistently lower by about 0.2 kcal/mol than series **20**–**24**. This result can be accounted for by subtle steric differences in the positions of the protons H_{9n} in the two cases. Molecular models show that H_{9n} of **14**–**19**, derived from the bicyclo[2.2.1] system, is located somewhat further under the ring and closer to the C_3-β-hydroxyl group than H_{9n} of **20**–**24**, derived from the bicyclo[2.2.2] system. The C_3-β hydroxyl group of the bicyclo[2.2.1] series would appear to experience a greater

(19) S. Wolfe and A. Rauk, *J. Chem. Soc. B*, 136 (1971); S. Wolfe, *Accounts Chem. Res.*, **5**, 102 (1972).

(20) R. U. Lemieux and N. J. Chü, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, 31N; N. J. Chü, Ph.D. Thesis, Department of Chemistry, University of Ottawa, 1959.

steric crowding from H_{9n} than the corresponding hydroxyl group of the bicyclo[2.2.2] series and thus justify the generally lower stability of the β isomers of the [2.2.1] series.

Experimental Section

Melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were measured with the Beckman IR-8 spectrophotometer. Nmr spectra were recorded on the Varian T-60 and A-60 spectrometers, using TMS as internal standard. Yields, melting points, and ir carbonyl absorptions are given in Table IV.

TABLE IV
EXPERIMENTAL DATA FOR NEW COMPOUNDS[a]

Compd	Yield, %	Mp, °C	Ir, cm^{-1}, C=O (KBr)
2	25	175–176	1785[b]
8	98	140–141	1793
9	85	139–140	1794
10	94	134–135	1795
11	97	148–149	1790
12	97	197–198	1787
13	99	205–206	1787
14	72	185–186	
15	52	183–184	
16	61	192–193	
17	90	223–224	
18	73	216–217	
19	70	200–201	
20	45	152–153	
21	50	181–182	
22	46	184–185	
23	65	214–215	
24	63	229–230	
25	64	138–139	1744
26	42	151–152	1757

[a] Satisfactory analytical data were reported for all compounds listed: Ed. [b] $CHCl_3$.

endo-cis-Trichloroacetylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid lactol (1) was prepared from the reaction of sodium trichloroacetate with *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride in dimethoxyethane.[9] Lactone 3 was prepared by the action of concentrated sulfuric acid on lactol 1.[11] The *exo*-9-chloro, -bromo, and -iodo lactones 4, 5, and 6 were prepared by the action of the appropriate halogen on lactol 1 in the presence of the corresponding potassium halide in aqueous sodium carbonate.[12] The *exo*-9-hydroxy lactone 7 was prepared by the action of peracetic acid on lactol 1.[12]

5-Hydroxy-5-trichloromethyl-4-oxatricyclo[5.2.2.$0^{2,6}$]undec-8-en-3-one (2).—A solution of 17.8 g (0.1 mol) of *endo-cis*-bicyclo-[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride in 100 ml of anhydrous dimethoxyethane was stirred at 25° while 18.5 g (0.1 mol) of anhydrous sodium trichloroacetate was added in one portion. The resulting white slurry was stirred for 2 days at 25–30°. The solvent was removed *in vacuo* below 40°, and the solid product, 32.5 g, was pulverized and triturated with 400 ml of cold water for 0.5 hr. The insoluble solid was collected, washed with water, and dried to give 17.1 g crude product, mp 157–170°, 8.0 g after crystallizations from benzene–heptane.

***exo*-9-Mesyloxy-5-trichloromethyl-4,11-dioxatetracyclo[5.2.1.-$1^{5,8}$.$0^{2,6}$]undecan-3-one** (8).—A solution of 2.00 g (6.7 mmol) of hydroxy lactone 7 in 24 ml of dry pyridine was stirred at room temperature while 0.51 g (13.4 mmol) of mesyl chloride was slowly added. The mixture was warmed on the steam bath until dissolution was complete, and then the reaction mixture was allowed to stand at room temperature for 3 days. White crystals formed immediately upon the addition of 70 g of ice and water. The crystals were collected and the filtrate was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and then evaporated. The residue was combined with the collected crystals, and the entire product was treated with decolorizing carbon in ether. Recrystallization from ether–pentane afforded 2.48 g (6.55 mmol) of 9-*exo*-mesyl lactone 8.

5-Trichloromethyl-4,12-dioxatetracyclo[5.2.2.$1^{5,8}$.$0^{2,6}$]dodecan-3-one (9).—Concentrated sulfuric acid (30 ml) was added to 5.00 g (16.8 mmol) of lactol 2 over a period of 10 min with stirring. The lactol dissolved rapidly to give a straw-colored solution and the reaction was only slightly exothermic. The acid solution was chilled in an ice bath while 150 ml of cold water was added slowly, causing the precipitation of a white solid. After stirring 15 min the solid was collected, washed with water, and dried *in vacuo* at 60° for 3 hr to give 4.89 g of impure lactone 9. Crystallization from heptane–CCl_4 gave 4.24 g of pure lactone 9.

Preparation of *exo*-9-Chloro- (10), -9-Bromo- (11), -9-Iodo- (12), and -9-Hydroxy-5-trichloromethyl-4,12-dioxatetracyclo[5.2.2.-$1^{5,8}$.$0^{2,6}$]dodecan-3-one (13).—These compounds were prepared by treating the trichloromethyl lactol with chlorine, bromine, iodine, and peracetic acid, respectively, according to the methods presented in a previous publication.[12]

Preparation of Hemiacetals 14–24 through Sodium Borohydride Reduction of the Corresponding Lactones.—A solution of 6.00 mmol of lactone, dissolved in the minimum amount of 95% ethanol or anhydrous isopropyl alcohol (100–150 ml), was stirred at room temperature while 7.00 mmol of solid sodium borohydride was slowly added. Stirring was continued for 18–24 hr after which glacial acetic acid was added until effervescence ceased. After 15 min of additional stirring, 20 ml of water was added and the solution was evaporated to a small volume leaving a white crystalline solid suspended in acetic acid–water. The solid was collected, washed well with water, and dried *in vacuo* at 50°. The solid was then recrystallized from carbon tetrachloride, cyclohexane, or dimethoxyethane.

Preparation of Acetyl Derivatives 25 and 26 through Acetylation of Hemiacetals 20 and 21.—Acetic anhydride (1.2 ml) was added slowly with swirling to 1.14 mmol of hemiacetal 20 or 25 in 2 ml of pyridine with cooling. The flask was stoppered and allowed to stand in the ice bath for 8 hr. The cold solution was poured over 50 g of crushed ice, and the precipitated solid was stirred for 0.5 hr before filtering. The products were purified by crystallization from heptane.

Acknowledgment.—The authors gratefully acknowledge the contribution of the Monsanto Company for making available their laboratory facilities and otherwise contributing to the progress of F. G. Bollinger in his work toward the M.S. degree in chemistry, which he received in 1972.

Registry No.—1, 28795-87-1; 2, 42087-05-8; 3, 28795-88-2; 4, 36162-61-5; 5, 36162-62-6; 6, 36204-45-2; 7, 36162-63-7; 8, 42087-10-5; 9, 42117-35-1; 10, 42087-11-6; 11, 42087-12-7; 12, 42087-13-8; 13, 42087-14-9; α-14, 42087-15-0; β-14, 42087-16-1; α-15, 42087-17-2; β-15, 42087-18-3; α-16, 42087-19-4; β-16, 42087-20-7; α-17, 42087-21-8; β-17, 42087-22-9; α-18, 42087-23-0; β-18, 42087-24-1; α-19, 42087-25-2; β-19, 42087-26-3; α-20, 42183-74-4; β-20, 42087-27-4; α-21, 42087-28-5; β-21, 42087-29-6; α-22, 42087-30-9; β-22, 42183-75-5; α-23, 42087-31-0; β-23, 42087-32-1; α-24, 42087-33-2; β-24, 42087-34-3; 25, 42087-35-4; 26, 42087-36-5; *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, 129-64-6; *endo-cis*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride, 24327-08-0; sodium trichloroacetate, 650-51-1.

Enol Acetates, Enol Ethers, and Amines by Mercuration of Acetylenes

PAUL F. HUDRLIK* AND ANNE M. HUDRLIK

School of Chemistry, Rutgers University, New Brunswick, New Jersey 08903

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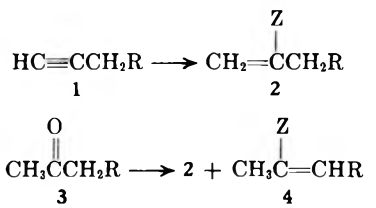
An improvement on the catalytic mercuration of terminal acetylenes to form enol acetates was developed, and solvomercuration–demercuration of terminal acetylenes was investigated and shown to be a useful method for the preparation of methyl enol ethers and, in lower yields, ethyl enol ethers and aziridine enamines. All enol derivatives prepared by these reactions were shown to be isomerically pure. 1-Octyne (**1a**) was converted into 2-acetoxy-1-octene (**2a**) by treatment with catalytic amounts of mercuric acetate and boron trifluoride etherate in acetic anhydride. Similarly, the tosylate (**1b**) of 3-butyn-1-ol was converted into enol acetate **2b**. The enol ethers **2c** and **2d** were prepared by treating 1-octyne with mercuric acetate in methanol and ethanol, respectively, followed by demercuration with alkaline sodium borohydride. Although the use of aziridine in a similar reaction gave the enamine **2e**, the use of pyrrolidine resulted in the formation of the saturated amine **8**.

In connection with another project, we needed synthetic methods for the preparation of enol acetates, enol ethers, and enamines having a terminal double bond (**2**). Enol derivatives are commonly prepared from the corresponding ketone (**3**).[1,2] However, as unsymmetrical ketones generally give a mixture of double bond isomers (**2** and **4**), we have investigated the solvomercuration reactions of terminal acetylenes as a route to these enol derivatives.

Although the preparation of vinyl derivatives from acetylene itself has been of some commercial importance,[3–5] the use of higher acetylenes is not common. Enol esters have been prepared on a laboratory scale from acetylenes and carboxylic acids in the presence of a catalytic amount of a mercury salt and a strong acid.[6–11,13] Although solvomercuration–demercuration and disputed.[3b,c,4j] Reactions of acetylenes with amines have yielded products for which enamines were postulated as intermediates.[3a,c,5,18] There is a recent report of the formation of a ketene acetal from ethoxyacetylene.[19] A few specialized examples are known of the formation of enol derivatives from certain acetylenes in the absence of mercury salt catalysis.[3–5,20,24–28]



a, R = C_5H_{11}; Z = OAc
b, R = CH_2OTs; Z = OAc
c, R = C_5H_{11}; Z = OMe
d, R = C_5H_{11}; Z = OEt
e, R = C_5H_{11}; Z = $N(CH_2)_2$

(1) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972.

(2) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(3) (a) J. A. Nieuwland and R. R. Vogt, "The Chemistry of Acetylene," Reinhold, New York, N. Y., 1945; (b) J. W. Reppe, "Acetylene Chemistry," Charles A. Meyer, New York, N. Y., 1949; (c) J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold, New York, N. Y., 1949; (d) S. A. Miller, "Acetylene Its Properties, Manufacture, and Uses," Vol. II, Academic Press, New York, N. Y., 1966; (e) T. F. Rutledge, "Acetylenes and Allenes," Reinhold, New York, N. Y., 1969.

(4) (a) W. Reppe, *Justus Liebigs Ann. Chem.*, **601**, 81 (1956); (b) C. W. Kruse and R. F. Kleinschmidt, *J. Amer. Chem. Soc.*, **83**, 213 (1961).

(5) I. A. Chekulaeva and L. V. Kondrat'eva, *Russ. Chem. Rev.*, **34**, 669 (1965).

(6) (a) G. F. Hennion and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **56**, 1802 (1934); (b) G. F. Hennion, D. B. Killian, T. H. Vaughn, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **56**, 1130 (1934); (c) G. F. Hennion, R. R. Vogt, and J. A. Nieuwland, *J. Org. Chem.*, **1**, 159 (1936); (d) E. A. Bried and G. F. Hennion, *J. Amer. Chem. Soc.*, **60**, 1717 (1938).

(7) H. Lemaire and H. J. Lucas, *J. Amer. Chem. Soc.*, **77**, 939 (1955).

(8) R. H. Wiley, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 853.

(9) (a) A. I. Bol'shukhin and V. L. Zhitorchuk, *Zh. Obshch. Khim.*, **25**, 1459 (1955); *Chem. Abstr.*, **50**, 4832 (1956); (b) A. I. Bol'shukhin and A. G. Egorov, *Zh. Obshch. Khim.*, **26**, 1121 (1956); *Chem. Abstr.*, **50**, 16665 (1956); (c) A. G. Egorov, *Uch. Zap., Leningrad. Gos. Pedagog. Inst. im. A. I. Gertsena*, **179**, 211 (1958); *Chem. Abstr.*, **55**, 3421 (1961).

(10) H. C. Haas, N. W. Schuler, and R. L. MacDonald, *J. Polym. Sci., Part A-1*, **7**, 3440 (1969).

(11) The intermediate organomercury compounds were isolated and characterized in some cases where the mercury salt was used in equivalent amounts and the strong acid was omitted.[12] The organomercury compounds resulting from the addition of hydrogen chloride to acetylene have also been characterized.[12,ab]

(12) (a) A. N. Nesmeyanov, "Selected Works in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1963; (b) A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **1**, 158 (1957); (c) G. Drefahl, G. Heublein, and A. Wintzer, *Angew. Chem.*, **70**, 166 (1958); see however G. Drefahl and S. Schaaf, *Chem. Ber.*, **90**, 148 (1957).

(13) Acetals and ketals have been prepared from acetylenes and alcohols by this method,[6b,c,14–16] and the synthesis of several enol ethers[3d,14i,17] and an enamine[18a] has been claimed. Several claims for the preparation of enol ethers in the early patent literature are questionable owing to the instability of enol ethers in strong acid. The yields were often poor and the products were accompanied by acetals;[3d] some of the reactions were later repeated

(14) (a) J. S. Reichert, J. H. Bailey, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **45**, 1552 (1923); (b) H. S. Hill and H. Hibbert, *ibid.*, **45**, 3108 (1923); (c) J. A. Nieuwland, R. R. Vogt, and W. L. Foohey, *ibid.*, **52**, 1018 (1930); (d) H. D. Hinton and J. A. Nieuwland, *ibid.*, **52**, 2892 (1930); (e) D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *ibid.*, **56**, 1384 (1934); (f) G. F. Hennion and J. A. Nieuwland, *ibid.*, **57**, 2006 (1935); (g) D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *ibid.*, **58**, 80 (1936); (h) *ibid.*, **58**, 1658 (1936); (i) G. F. Hennion and W. S. Murray, *ibid.*, **64**, 1220 (1942); (j) G. F. Hennion and F. P. Kupiecki, *J. Org. Chem.*, **18**, 1601 (1953).

(15) (a) S. Tamaru and Y. Tanaka, *J. Chem. Soc. Jap.*, **56**, 486 (1935); *Chem. Abstr.*, **29**, 4733 (1935); (b) A. Contardi and B. Ciocca, *Ric. Sci.*, (2) **7**, II, 610 (1936); *Chem. Abstr.*, **32**, 9039 (1938).

(16) D. D. Coffman, U. S. Patent 2,387,495 (1945); *Chem. Abstr.*, **40**, 1870 (1946); D. D. Coffman, G. H. Kalb, and A. B. Ness, *J. Org. Chem.*, **13**, 223 (1948).

(17) (a) Plausons Forschungsinstitut G. M. B. H., German Patent 338,281 (1923); *Chem. Abstr.*, **17**, 1804 (1923); (b) T. Henshall, British Patent 616, 853 (1949); *Chem. Abstr.*, **43**, 5414 (1949).

(18) (a) J. A. Loritsch and R. R. Vogt, *J. Amer. Chem. Soc.*, **61**, 1462 (1939); (b) H. B. Kagan, A. Marquet, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1079 (1960), and references cited therein.

(19) H. H. Wasserman, J. U. Piper, and E. V. Dehmlow, *J. Org. Chem.*, **38**, 1451 (1973).

(20) Some intramolecular reactions to give cyclic enol derivatives are known.[3c] Acetylenes conjugated with an activating group (such as trifluoromethyl or carbonyl) form addition products readily without metal catalysis. Examples are given in ref 3e, 5, and 21–23.

(21) A. L. Henne, J. V. Schmitz, and W. G. Finnegan, *J. Amer. Chem. Soc.*, **72**, 4195 (1950); A. L. Henne and M. Nager, *ibid.*, **74**, 650 (1952).

(22) A. G. Evans, E. D. Owen, and B. D. Phillips, *J. Chem. Soc.*, 5021 (1964).

(23) (a) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965); (b) R. Huisgen, B. Giese, and H. Huber, *Tetrahedron Lett.*, 1883 (1967); (c) B. Giese and R. Huisgen, *ibid.*, 1889 (1967).

(24) For an example of enol ester formation catalyzed by zinc salts, see E. S. Rothman, S. S. Hecht, P. E. Pfeffer, and L. S. Silbert, *J. Org. Chem.*, **37**, 3551 (1972).

(25) P. E. Peterson and J. E. Duddey, *J. Amer. Chem. Soc.*, **85**, 2865 (1963); P. E. Peterson and J. E. Duddey, *ibid.*, **88**, 4990 (1966).

(26) Moureu, *C. R. Acad. Sci.*, **138**, 288 (1904).

(27) M. D. Gauthier, *Ann. Chim. Phys.*, **16**, 289 (1909); *Chem. Abstr.*, **3**, 1873 (1909). See also ref 14j.

(28) (a) A. Favorsky, *J. Russ. Chem. Soc.*, 414 (1887); *J. Chem. Soc.*, **54**, 798 (1888); (b) A. Favorsky, *J. Prakt. Chem.*, (2) **37**, 382 (1888); (c) *ibid.*, (2) **37**, 531 (1888); (d) *ibid.*, (2) **44**, 208 (1891). See also D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **57**, 544 (1935).

reactions of olefins have been intensively studied in recent years,[1,29-35] the use of these reactions to prepare enol derivatives from acetylenes has not been been investigated.

For our purposes, we anticipated that the use of catalytic amounts of mercury salts in the presence of acid catalysts would be suitable for the preparation of enol acetates. For the preparation of the more acid-sensitive enol ethers and enamines, we decided to investigate the solvomercuration–demercuration of acetylenes.

Results

Enol Acetates.—The enol acetate of 3-hexanone has previously been prepared from 3-hexyne using mercuric acetate and boron trifluoride etherate in acetic acid.[7] When we applied this procedure to 1-octyne (**1a**), 2-octanone was the only product obtained. The same result was observed when acetic acid distilled from P_2O_5, or mixtures of acetic acid and acetic anhydride, were used as solvent. However, when acetic anhydride was used as the solvent, a good yield of the enol acetate **2a** was obtained, along with smaller amounts of 2-octanone (**3a**) and a product shown to be 3-decyn-2-one (**5a**)[36] by independent synthesis.

5a, R = C_5H_{11}
b, R = CH_2OTs

To check whether double bond isomers were formed, an authentic mixture of the isomeric enol acetates (**2a** and **4a**) of 2-octanone was prepared by quenching the potassium enolate in acetic anhydride. Comparison of the vpc and nmr spectra demonstrated that the acetoxymercuration product contained no detectable amount of the internal double bond isomers (**4a**).

Using the same mercuration procedure (with acetic anhydride), the tosylate (**1b**) of 3-butyn-1-ol was converted into the terminal enol acetate **2b**.

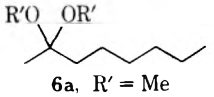
Alkoxymercuration–Demercuration.—We found that 1-octyne could be readily converted into the methyl enol ether **2c** by treatment with 1 equiv of mercuric acetate in methanol for 15 min, followed by reductive demercuration with sodium borohydride in aqueous sodium hydroxide. The product (formed in 65% yield) contained a small amount of the dimethyl ketal **6a** as the only impurity.

The use of other mercury salts was investigated in this reaction. Mercuric chloride gave a mixture of 2-octanol, 2-octanone, and the ketal **6a**. Mercuric nitrate and trifluoroacetate similarly gave little or no enol ether.

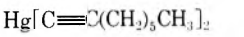
To determine the isomeric purity of the enol ether formed, a mixture of enol ethers (**2c** and **4c**) was prepared by cracking the dimethyl ketal **6a** of 2-octanone. No detectable amount of the internal double bond isomers was found in the methoxymercuration product.

The ethyl enol ether **2d** was prepared in an analogous manner from the reaction of ethanol with mercuric acetate and 1-octyne. The yield of enol ether (36%) was somewhat lower, and a considerable amount of white, crystalline material, which proved to be di-1-octynylmercury (**7**),[37] was also formed. The isomeric purity of the ethyl enol ether was established as before, by comparison with a mixture of enol ethers (**2d** and **4d**) prepared from the diethyl ketal **6b**.

Attempts to prepare a *tert*-butyl enol ether from 1-octyne and mercuric acetate in *tert*-butyl alcohol led to di-1-octynylmercury as the only characterized product.

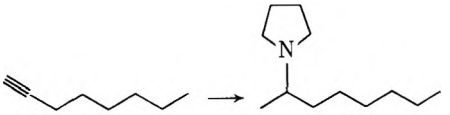


6a, R′ = Me
b, R′ = Et



7

Aminomercuration–Demercuration.—The reaction of 1-octyne with mercuric chloride in pyrrolidine, followed by alkaline sodium borohydride, produced a small amount of 2-octanol and a good yield of an acid-soluble product having ir and nmr spectra inconsistent with the desired enamine structure. The same compound was also obtained when mercuric acetate was used in place of mercuric chloride. The product was shown to be the saturated amine **8** by comparison with a sample prepared independently from pyrrolidine and 2-bromooctane.



1a **8**

Because of the possibility that the saturated amine was being produced by reduction of an intermediate iminium salt,[38] aminomercuration of 1-octyne with aziridine was attempted, since an iminium salt in this case would be much less favorable. Using mercuric acetate with short reaction times, the aziridine enamine **2e** was formed in 17.5% yield as the only volatile product. The structure of the enamine **2e** was established by its spectral and analytical data, and by hydrolysis to 2-octanone.

When the reaction of 1-octyne with mercuric acetate in aziridine was allowed to proceed for several hours, the yield of enamine dropped and a second volatile product was formed. Although never isolated pure, the ir and nmr spectra of the new compound, and its facile hydrolysis to 2-octanone, support the imine struc-

(29) Reviews: J. Chatt, *Chem. Rev.*, **48**, 7 (1951); N. S. Zerfirov, *Russ. Chem. Rev.*, **34**, 527 (1965); W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968).

(30) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **93**, 6902 (1971), and references cited therein.

(31) (a) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967); (b) H. C. Brown and M.-H. Rei, *ibid.*, **91**, 5646 (1969); (c) H. C. Brown and J. T. Kurek, *ibid.*, **91**, 5647 (1969); (d) H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).

(32) (a) F. G. Bordwell and M. L. Douglass, *J. Amer. Chem. Soc.*, **88**, 993 (1966); (b) G. M. Whitesides and J. San Filippo, Jr., *ibid.*, **92**, 6611 (1970).

(33) (a) J. J. Perie and A. Lattes, *Bull. Soc. Chim. Fr.*, 583 (1970), and references cited therein; (b) A. Dobrev, J. J. Perie, and A. Lattes, *Tetrahedron Lett.*, 4013 (1972), and references cited therein; (c) V. G. Aranda, J. B. Mur, G. Asensio, and M. Yus, *ibid.*, 3621 (1972), and references cited therein; (d) H. K. Hall, Jr., J. P. Schaefer, and R. J. Spanggord, *J. Org. Chem.*, **37**, 3069 (1972), and references cited therein.

(34) C. H. Heathcock, *Angew. Chem., Int. Ed. Engl.*, **8**, 134 (1969).

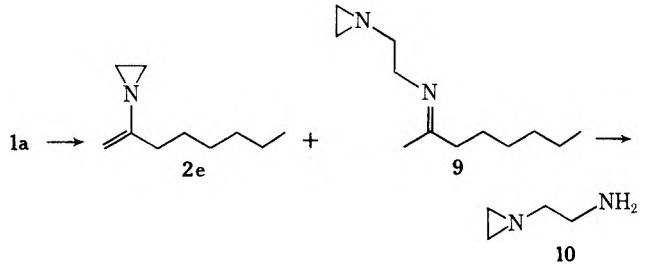
(35) D. H. Ballard and A. J. Bloodworth, *J. Chem. Soc. C*, 945 (1971).

(36) R. B. Davis and D. H. Scheiber, *J. Amer. Chem. Soc.*, **78**, 1675 (1956).

(37) (a) G. Eglinton and W. McCrae, *J. Chem. Soc.*, 2295 (1963); (b) T. H. Vaughn, *J. Amer. Chem. Soc.*, **55**, 3453 (1933).

(38) See, for example, R. D. Bach and D. K. Mitra, *Chem. Commun.*, 1433 (1971).

ture **9** for the product.[39] When a solution of **9** in carbon tetrachloride or benzene was stirred with deuterium oxide for 3 hr, the nmr spectrum of the organic layer showed mainly peaks corresponding to 2-octanone, while the nmr spectrum of the aqueous layer showed a symmetric pair of multiplets at δ 1.33 and 1.73 and a symmetric pair of multiplets at δ 2.32 and 2.78. The chemical shifts agree very well with those reported for 1-(2-aminoethyl)aziridine (**10**).[41]



Discussion

As discussed earlier, there are several reports of the synthesis of enol acetates from acetylenes and acetic acid in the presence of a mercuric salt and a strong acid. Most of these reports appeared before modern spectroscopic techniques, particularly nmr, became available, and the possibility of double bond isomerization could not be studied. In many of the reported procedures, a significant quantity of ketone was isolated along with the enol acetate.

The mercuric acetate–boron trifluoride etherate–acetic anhydride procedure appears to be a useful synthetic method for the preparation of terminal enol acetates. Double bond isomerization is not a problem, and in the acidic reaction conditions the mercury catalyst is continually regenerated, so that a full equivalent is not necessary.

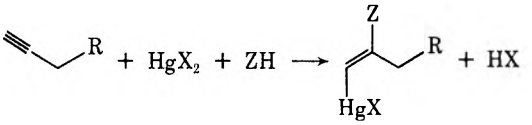
The mercury salt–strong acid catalyzed reactions would not be expected to be useful for the preparation of enol ethers and enamines from terminal acetylenes, since the double bonds would be more easily isomerized than those of enol acetates. We did not investigate this approach to enol ethers or enamines.[42]

The solvomercuration–demercuration approach promises to be a useful method for the preparation of methyl enol ethers from terminal acetylenes. With higher alcohols, the formation of the dialkynylmercury becomes a major competing reaction,[43] although a modest yield of the ethyl enol ether could be obtained.

We have so far been unsuccessful in preparing pyrrolidine enamines by this approach, presumably owing to the ease of formation of an iminium salt intermediate (for example, by addition of a proton or mercury ion to the initial aminomercuration adduct) which is easily reduced to a saturated amine. The use of aziridine rather than pyrrolidine effectively prevents the formation of an iminium salt because of the strain involved in generating an sp^2 center in a three-membered ring,[44] and the enamine can be isolated.

Aziridine enamines are relatively rare. The only previous examples of aziridine enamines of simple ketones are those of cycloheptanone and cyclooctanone.[40,45] The reluctance of the nitrogen atom in the three-membered ring to adopt the planar geometry necessary for maximum orbital overlap with the double bond manifests itself in the downfield chemical shift of the vinyl hydrogens[48] of the enamine **2e**.[49] The chemical shift of enamines has in turn been correlated with their reactivity toward electrophiles;[53] thus one would expect that the aziridine enamines would be comparatively unreactive (with respect to reactions at the carbon atom).

In the solvomercuration reactions, 1 equiv of acid is generated, as shown below. The initial adduct contains a double bond which could in principle undergo



protonation or further mercuration. In the alkoxymercuration reactions, this process, followed by reaction with alcohol, may be responsible for the formation of the small quantities of ketal **6** obtained after reduction. In the aminomercuration reactions with pyrrolidine, this process would lead to a relatively stable iminium salt[38] which is probably the precursor of the saturated amine **8**. It is conceivable that this process, followed by deprotonation, could lead to a product with an isomerized double bond (**4**); under our conditions, this does not appear to be a problem.

In conclusion, the mercuration of terminal acetylenes provides a useful synthetic method for isomerically pure enol acetates and methyl enol ethers with a terminal double bond and, in lower yields, ethyl enol ethers and aziridine enamines, all of which are difficult to prepare by other methods. The use of the solvomercuration–demercuration approach to the synthesis of other enol derivatives deserves more study.

(39) Imines of this type are known. See ref 40.

(40) S. C. Kuo and W. H. Daly, *J. Org. Chem.*, **35**, 1861 (1970).

(41) H. P. Fritz and G. Hierl, *Z. Naturforsch., B*, **26**, 476 (1971).

(42) The preparation of an enamine from the reaction of *N*-ethylaniline and 1-heptyne with mercuric oxide and boron trifluoride etherate has been reported;[18a] we were unable to repeat this with *N*-methylaniline and 1-octyne.

(43) This could be an intermediate in the methoxymercuration reaction.

(44) This property of aziridine derivatives has been used for a synthesis of aldehydes. See ref 1, p 81.

(45) Aziridine enamines which are vinylogous amides have been prepared by the uncatalyzed addition of aziridine to acetylenecarboxylic esters[23] and to β-chlorocyclohexenones,[46] and a ketene *N,O*-acetal, 1-aziridinyl-1-trimethylsiloxyethylene, is known.[47]

(46) (a) H. W. Whitlock, Jr., and G. L. Smith, *Tetrahedron Lett.*, 1389 (1965); (b) G. L. Smith and H. W. Whitlock, Jr., *ibid.*, 2711 (1966).

(47) P. F. Hudrlik and D. Peterson, unpublished results.

(48) For a correlation between the chemical shift of the vinyl hydrogens of enamines and the degree of overlap of the lone pair electrons on nitrogen, see W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967).

(49) The chemical shift of the vinyl hydrogens of **2e** is lower than those for the reported terminal enamines from other methyl alkyl ketones with morpholine and diethylamine.[50] The products resulting from the addition of various secondary amines to dimethyl acetylenedicarboxylate also showed the aziridine compounds to occur at low fields in the nmr,[23a,51] and the vinyl hydrogens of 1-aziridinyl-1-trimethylsiloxyethylene[47] occur downfield from those of the dialkylamino analogs.[52] Aziridine enamines of cycloheptanone and cyclooctanone also absorb at low fields.[40]

(50) (a) R. Jacquier, C. Petrus, and F. Petrus, *Bull. Soc. Chim. Fr.*, 2845 (1966); (b) H. Weingarten and W. A. White, *J. Org. Chem.*, **31**, 4041 (1966); W. A. White and H. Weingarten, *ibid.*, **32**, 213 (1967).

(51) (a) E. Winterfeldt and H. Preuss, *Angew. Chem., Int. Ed. Engl.*, **4**, 689 (1965); (b) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

(52) A. S. Kostyuk, Yu. I. Baukov, and I. F. Lutsenko, *J. Gen. Chem. USSR*, **40**, 598 (1970).

(53) M. E. Kuehne and T. Garbacik, *J. Org. Chem.*, **35**, 1555 (1970). See also A. I. Meyers and N. Nazarenko, *J. Amer. Chem. Soc.*, **94**, 3243 (1972).

Experimental Section[54]

Reagents.—Acetic anhydride was distilled (bp 139–140°) before use. Methanol and ethanol were distilled from their magnesium alkoxides. Pyrrolidine was distilled from barium oxide. Aziridine[55] was distilled from potassium hydroxide.

All mercuration reactions were run under a nitrogen atmosphere, and transfers of liquids and solutions were done with syringes which had been filled with nitrogen. Organic extracts were dried with sodium sulfate followed by magnesium sulfate unless otherwise indicated.

1-Octyne with Mercuric Acetate in Acetic Anhydride. 2-Acetoxy-1-octene (2a).—To a solution[56] of 17 mg (0.053 mol) of $Hg(OAc)_2$ in 10 ml of acetic anhydride was added 0.02 ml of $BF_3 \cdot Et_2O$, followed by 0.50 ml (0.37 g, 3.4 mmol) of 1-octyne (**1a**) added dropwise. The solution, which turned yellow, was stirred at room temperature for 3 hr,[57] diluted with 10 ml of ether, and injected into an an ice-cooled solution of 18 g of KOH in 200 ml of water overlaid with ether. The layers were separated, and the ether layer was washed with brine, dried, concentrated,[58] and evaporatively distilled (0.1 mm, 70°), yielding 0.51 g (89%) of colorless liquid having ir and nmr compatible with the enol acetate structure [with extra small peaks at 4.51 (**5a**) and 5.83 μ (**3a**) in the ir]. Vpc analysis (SE-30)[54a,b] showed three peaks having relative areas of 14:79:7. The 14% peak had the same retention time as 2-octanone (**3a**); the other two products were purified by vpc collection (SE-30).[54b]

The minor product had ir and nmr spectra and vpc retention time (SE-30)[54b] identical with those of 3-decyn-2-one (**5a**)[36] obtained from 1-octynyllithium plus CuI and acetyl chloride (room temperature, 22 hr, 64% yield).[59]

The major product was identified as 2-acetoxy-1-octene (**2a**):[9b,c] ir (CCl_4) 5.71, 6.02 μ; nmr (CCl_4) δ 4.65 (m, 2 H), 2.36–1.97 including singlet at 2.05 (5.3 H), 1.63–0.8 (11 H); mass spectrum m/e 170 (M^+, small), 128, 110, 71, 58, 43.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.24; H, 10.79.

An authentic mixture of the isomeric enol acetates of 2-octanone (**2a** and **4a**) was made by quenching the enolate (prepared by adding the ketone to a solution of triphenylmethylpotassium in dimethoxyethane) in acetic anhydride.[2] The enol acetates were separated from the triphenylmethane by evaporative distillation (0.1 mm, 60°). The distillate had ir (film) 5.7, 5.83 (small, **3a**), 6.0 μ; nmr (CCl_4) δ 4.90 (broad t, J = 7 Hz), 4.65 (m), 2.05 (s), 1.83 (broad s). Vpc analysis (SE-30)[54b] indicated a ketone–enol acetates peak area ratio of 20:80. The partially resolved mixture of three enol acetates[60] had an approximate peak area ratio (in order of increasing retention times) of 35:55:10. The major product from the acetoxymercuration was identical in retention time and on coinjection with the major enol acetate peak from the authentic mixture. No peaks due to the other enol acetate isomers could be detected in the vpc (or the nmr) of the acetoxymercuration product.

Tosylate of 3-Butyn-1-ol with Mercuric Acetate in Acetic Anhydride. 3-Acetoxy-3-buten-1-ol Tosylate (2b).—The tosylate (**1b**) of 3-butyn-1-ol[61] (0.19 g) was treated with 2.5 ml of a mercuric acetate solution [prepared by dissolving 17 mg of $Hg(OAc)_2$ in 10 ml of acetic anhydride and adding 0.02 ml of $BF_3 \cdot Et_2O$] for 3 hr. After work-up (as for **2a**), 0.21 g of a light yellow oil was obtained: ir (film) 4.51 (small, impurity of **5b?**), 5.71, 5.99 μ; nmr (CCl_4) δ 7.8–7.15 (4 H, aromatic), 4.77 (d, J = 2 Hz) and 4.70 (m) (1.3 H, vinyl H), 4.07 (t, 2.1 H, J = 6 Hz, CH_2O), 2.67–2.36 (m, $C{=}CCH_2$) and 2.42 (broad s, $ArCH_3$) (5.1 H total), 2.18 (small s, impurity of **5b?**), 2.0 (s, 2.9 H, CH_3CO).

A portion of the product was chromatographed on Florisil (benzene–methylene chloride), giving a colorless oil having the same ir and nmr spectra as before chromatography. The mass spectrum showed m/e 284 (M^+, very small), 242, 224 (small), 172, 155, 112, 91, 70, 43.

1-Octyne with Mercuric Acetate in Methanol. 2-Methoxy-1-octene (2c).—A mixture of 1.09 g (3.4 mmol) of $Hg(OAc)_2$ and 8 ml of methanol was stirred for 5 min, then cooled in ice, and 0.5 ml (0.37 g, 3.4 mmol) of 1-octyne was added dropwise. The ice bath was removed and the mixture was stirred for 15 min.[57] After cooling in ice again, 8 ml of pentane was added followed immediately by 140 mg of $NaBH_4$ in 3.4 ml of 3 M NaOH. Sodium chloride was added to saturate, the ice bath was removed, and the mixture was stirred for 15 min.[62] The pentane was separated and the remainder was extracted twice more with pentane. The combined pentane extracts were dried, concentrated,[58] and evaporatively distilled (0.1 mm, 70°) yielding 0.31 g (65%) of colorless liquid, ir (film) 6.05 μ. The nmr spectrum (CCl_4) indicated the product to be the terminal enol ether **2c** containing 9% of the dimethyl ketal **6a**. No other peaks were present; in particular, no peaks due to the double bond isomer(s) of the enol ether **4c** were detectable. Vpc (SE-30)[54a,b] showed two peaks assigned to the enol ether and ketal.[63]

The enol ether was purified by vpc collection (SE-30):[54b] ir (CCl_4) 6.05 μ; nmr (CCl_4) δ 3.76 (s, 2 H), 3.49 (s, 3 H), 2.25–0.7 (13.4 H); mass spectrum m/e 142 (M^+), 85, 72.

The analytical sample was prepared by vpc collection (Carbowax).[54c] *Anal.* Calcd for $C_9H_{18}O$: C, 75.99; H, 12.96. Found: C, 75.64; H, 13.16.

To prepare an authentic mixture of the isomeric methyl enol ethers of 2-octanone (**2c** and **4c**), the ketone was converted to the dimethyl ketal **6a** with trimethyl orthoformate.[64] A sample of the ketal free from ketone was obtained by percolation through Florisil in hexane: ir no carbonyl or hydroxyl; nmr (CCl_4) δ 3.08 (s, 6 H), 1.6–0.8 including s at 1.17 (16 H). This ketal was heated with a crystal of *p*-toluenesulfonic acid monohydrate in a distillation apparatus under nitrogen (175°, 30 min), and the residue was evaporatively distilled (0.1 mm, 40°), giving the mixture of enol ethers **2c** and **4c**: ir (film) 5.83 (small, **3a**), 6.01, 6.05 μ; nmr (CCl_4) δ 4.25 (broad t, J = 7 Hz, vinyl H of **4c**), 3.76 (s, vinyl H of **2c**), 3.49 (s, CH_3O of **2c**), 3.43 (s, CH_3O of **4c**), 3.08 (small s, CH_3O of **6a**), 2.25–0.7 including s at 1.70 (vinyl methyl of **4c**). The ratio of more substituted to less substituted double bond was approximately 1:1 and the percentage of ketal was less than 5% by the nmr integration.

1-Octyne with Mercuric Acetate in Ethanol. 2-Ethoxy-1-octene (2d).—1-Octyne (0.5 ml, 0.37 g, 3.4 mmol) was treated with 1.09 g (3.4 mmol) of $Hg(OAc)_2$ in 8 ml of ethanol for 15 min[57] according to the procedure used for the methyl enol ether **2c**. After work-up, when most of the pentane solvent was removed by distillation, white crystals precipitated and were filtered off and dried. The crystals (0.20 g) had spectra and melting point compatible with di-1-octynylmercury (**7**): ir (CCl_4) 4.64 μ; nmr (CCl_4) δ 2.5–2.1 (4 H), 1.8–0.7 (22 H); mp 81.5–82.5° (lit. mp 82–83°,[37a] 80.4–80.7°[37b]).

The mother liquor was concentrated and evaporatively distilled (0.1 mm, 60°) producing 0.19 g (36%) of colorless liquid and 0.16 g of crystalline pot residue. The distilled product had ir (film) 6.05 μ; nmr (CCl_4) δ 3.73 (s), 3.67 (q, J = 7 Hz), 3.39 (small q partially covered by previous q, J = 7 Hz, impurity of **6b**), 2.24–0.7. The integration indicated that about 6% of the diethyl ketal **6b** was present.[63] No peaks attributable to the double bond isomer(s) of the enol ether (**4d**) were detectable. The mass spectrum showed m/e 156 (M^+), 99, 71.

(54) Melting points were determined on a Fisher-Johns hot stage melting point apparatus. Infrared spectra were determined with a Perkin-Elmer Model 137 spectrometer. Nmr spectra were taken on a Varian T-60 spectrometer, using TMS as an internal standard, unless otherwise noted. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-7 instrument. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Vpc analyses were done on a Varian Aerograph Model 90-P3 gas chromatograph, using one of the following columns: (a) 10% SE-30 on Chromosorb W, 10 ft × 0.25 in.; (b) 5% SE-30 on Chromosorb W, 5 ft × 0.25 in.; (c) 20% Carbowax 20M on Chromosorb W, 10 ft × 0.25 in.

(55) The toxicity of aziridine is discussed in J. A. Riddick and W. B. Bunger, "Organic Solvents," 3rd ed, Wiley-Interscience, New York, N. Y., 1970.

(56) The components were stirred for 1 hr at room temperature (under nitrogen) to effect solution.

(57) A similar reaction with an internal standard present suggested that this was approximately the optimum time.

(58) Ir and nmr spectra were taken of the crude product before distillation to ascertain that the products were present in the reaction mixture and were not formed during distillation.

(59) J. F. Normant and M. Bourgain, *Tetrahedron Lett.*, 2659 (1970).

(60) H. Nakata and A. Tatematsu, *Org. Mass Spectrom.*, **4**, 211 (1970).

(61) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

(62) This *in situ* demercuration procedure is essentially that of Brown.[81]

(63) The vpc peak area ratios in duplicate runs were not always strictly reproducible, suggesting that the compounds were not completely stable to our vpc conditions; therefore vpc has not been used for quantitative determinations of product composition for this reaction.

(64) The procedure is analogous to that of House[2] for the preparation of diethyl ketals with triethyl orthoformate.

A sample was prepared for analysis by vpc collection (SE-30).[54b] *Anal.* Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.71; H, 13.18.

An authentic mixture of the ethyl enol ether isomers **2d** and **4d** of 2-octanone was prepared by the procedure[2] used for the methyl enol ethers **2c** and **4c**. The diethyl ketal **6b**[65] was made from triethyl orthoformate and 2-octanone and purified by percolation through Florisil: ir, no carbonyl or hydroxyl; nmr (CCl_4) δ 3.39 (q, J = 7 Hz, 3.3 H), 1.65–0.7 (22 H). The ketal was converted to the enol ethers by heating with *p*-toluenesulfonic acid as before, and the residue was evaporatively distilled (0.1 mm, 40°), giving the mixture of enol ethers **2d** and **4d**: ir (film) 5.83 (small, **3a**) 6.02, 6.05 μ; nmr (CCl_4) δ 4.25 (broad t, J = 7 Hz, vinyl H of **4d**), 3.73 (s, vinyl H of **2d**), 3.9–3.2 (appears to be three overlapping quartets, centered at 3.39, 3.62, and 3.68), 2.25–0.7 including broad s at 1.70 (vinyl methyl of **4d**).

1-Octyne with Mercuric Chloride in Pyrrolidine. *N*-2-Octylpyrrolidine (**8**).—To a solution of 1.84 g (6.8 mmol) of $HgCl_2$ in 16 ml of pyrrolidine was added 1.0 ml (0.74 g, 6.8 mmol) of 1-octyne dropwise. After stirring at room temperature for 3.5 hr, the reaction mixture was cooled in ice and 16 ml of pentane was added followed by a solution of 280 mg of $NaBH_4$ in 6.8 ml of 3 *M* NaOH. NaCl was added to saturate, the ice bath was removed, and the mixture was stirred for 15 min.[62] The pentane was separated and the remainder was extracted twice more with pentane. The combined pentane extracts were dried, concentrated,[58] and evaporatively distilled (0.1 mm, 70°) yielding 1.06 g (86%) of colorless liquid having ir and nmr spectra compatible with the saturated amine structure. Vpc analysis (SE-30 and Carbowax)[54a,c] showed two peaks, the smaller (10% of the peak area) having the same retention time as 2-octanol. The major product was purified by vpc collection (SE-30)[54a] and had ir, nmr, and vpc retention time identical with those obtained from the reaction product of 2-bromooctane and pyrrolidine (5.5 hr, 80–110°), nmr (benzene) δ 2.65–2.05 (5 H), 1.85–0.8 including doublet at 1.05 (J = 6 Hz) (20 H).

A sample was prepared for analysis by partitioning the aminomercuration product between ether and 1 *N* HCl. The aqueous layer was washed twice with ether and neutralized with NaOH. The neutralized solution was extracted with ether; the ether extract was dried, the solvent was removed, and the residue was evaporatively distilled (0.1 mm, 70°).

Anal. Calcd for $C_{12}H_{25}N$: C, 78.61; H, 13.75. Found: C, 78.82; H, 13.80.

1-Octyne with Mercuric Acetate in Aziridine. 2-Aziridinyl-1-octene (2e).—To an ice-cooled solution of 2.18 g (6.8 mmol) of $Hg(OAc)_2$ in 16 ml of aziridine was added 1.0 ml (0.74 g, 6.7 mmol) of 1-octyne dropwise. The ice bath was removed and the reaction solution was stirred for 20 min.[57] The solution was cooled in ice and 16 ml of pentane was added followed by a solution of 280 mg of $NaBH_4$ in 6.8 ml of 3 *M* NaOH. NaCl was added to saturate, the ice bath was removed, and the mixture was stirred at room temperature for 15 min.[62] The layers were separated and the aqueous layer was extracted twice with pentane. The combined pentane extracts were dried, concentrated,[58] and evaporatively distilled (0.1 mm, 80°), producing 0.18 g (17.5%) of a colorless distillate: ir (film) 5.83 (small, **3a**?), 6.15 μ; nmr (benzene) δ 4.28 (m, 1.5 H, vinyl H), 2.4–0.7 (17 H) including s at 1.52 (aziridine ring H) (in CCl_4 the vinyl protons occurred as a multiplet centered at δ 4.08); mass spectrum *m/e* 153 (M^+), 96, 55.

Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50. Found: C, 77.96; H, 12.76.

The nmr sample (CCl_4) of the enamine was stirred for 5 min with an equal volume of 6 *N* HCl. After neutralization with NaOH, the layers were separated. The organic layer was washed with 1 *N* HCl and dried (Na_2SO_4). The nmr was identical with that of 2-octanone and the vpc (SE-30)[54b] showed only a large peak at the same retention time as that of 2-octanone.

1-Octyne with Mercuric Acetate in Aziridine. Long Reaction Time.—To an ice-cooled solution of 0.82 g (2.6 mmol) of $Hg(OAc)_2$ in 6 ml of aziridine was added 0.38 ml (0.28 g, 2.5 mmol) of 1-octyne dropwise. The ice bath was removed and the reaction solution was stirred for 4.25 hr. After work-up as before (see **2e**),[58] the crude product was evaporatively distilled in two fractions: (1) 0.1 mm, 64–80°, 0.20 g; (2) 0.1 mm, 80°, 0.19 g. Vpc analysis[63] (SE-30)[54a,b] indicated the first fraction to contain a considerable amount of enamine and the second to contain mostly higher retention time substance. The spectra of the second fraction showed ir (film) 5.83 (small, **3a** impurity), 6.02 μ; nmr (CCl_4)[66] δ 3.37 (broad t, J = 7 Hz), 2.9–0.7 with broad s at 1.80.

The nmr sample of the second fraction was stirred with D_2O for 3 hr. The nmr[66] of the CCl_4 layer showed mainly peaks corresponding to 2-octanone while the spectrum[66] of the D_2O layer (relative to DSS) showed only two mirror-image multiplets centered at δ 1.33 and 1.73 (area ratio 1:1) and two mirror image multiplets centered at δ 2.32 and 2.78 (area ratio 1:1).

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Registry No.—**1a**, 629-05-0; **1b**, 23418-85-1; **2a**, 26735-84-2; **2b**, 42367-31-7; **2c**, 42401-58-1; **2d**, 42367-32-8; **2e**, 42434-73-1; **7**, 42367-33-9; **8**, 42367-34-0; mercuric acetate, 1600-27-7; mercuric chloride, 7487-94-7.

(65) H. E. Carswell and H. Adkins, *J. Amer. Chem. Soc.*, **50**, 235 (1928).

(66) Nmr spectra were taken on both JEOL MH-100 and Varian T-60 instruments.

Some Reactions of Organolithium Compounds with Nitrosamines[1a]

PETER R. FARINA[1b] AND HOWARD TIECKELMANN*

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

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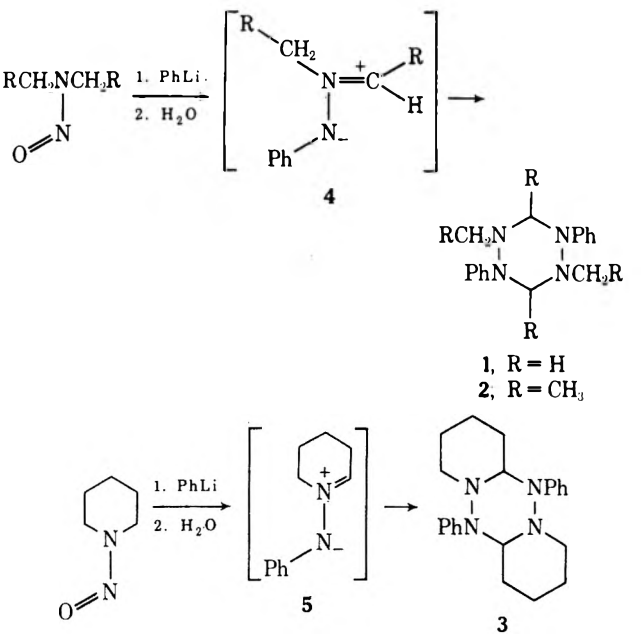
Secondary nitrosamines react with phenyllithium or *tert*-butyllithium to give N'-alkylated lithium salts which undergo elimination to form azomethine imines when treated with water or ethanol. When *N*-methyl-*N*-*tert*-butylnitroamines, *tert*-butyllithium, and ethanol are used, a stable compound, 1,2-di-*tert*-butyl-1-(ethoxymethyl)-hydrazine, can be isolated. The azomethine imines form *sym*-hexahydrotetrazines on standing or can be trapped with *N*-phenylmaleimide or dimethyl acetylenedicarboxylate.

The carcinogenic nature of certain nitrosamines has been well established.[2] These observations and the reported chemotherapeutic activity of other nitrosamines[3] stimulated our interest in the chemistry of these compounds.[4] Although spectroscopic studies are numerous, owing in part to the interest in restricted rotation around N–N bonds,[5] basic chemistry of this functional group remains largely unexplored. It has been, for example, only recently demonstrated that α protons of nitrosamines can undergo base-catalyzed H–D exchange, and α-C-alkylation with methyl iodide,[6] which has thus suggested the existence of an α-nitrosamino carbanion.[6,7] Seebach and Enders[8] have further substantiated this using dimethylnitrosamine (DMNA) and several electrophiles. However, they also observed that nucleophilic attack at the nitroso moiety of dimethylnitrosamine was competitive with metalation at the methyl group when organolithium reagents were employed. *N*-Butyraldehyde oxime was isolated as a by-product when *N*-butyllithium and benzophenone were added sequentially to DMNA in tetrahydrofuran at −80°. Such nucleophilic attack is not surprising, since in our previous communication[4] we reported that some simple alkylnitrosamines reacted with phenyllithium at the N=O moiety, in ether, at −65° to give symmetrical hexahydrotetrazines (**1**–**3**) in 30–40% yield.

Our results suggested[4] that intermediates such as **4** and **5** are formed and subsequently dimerize head to tail to form the *sym*-hexahydrotetrazines. The present investigation was undertaken to determine if the intermediate azomethine imines (**4**, **5**) might be detected or trapped.



Results

Assuming "normal" addition[9] of phenyllithium to the nitroso moiety, the azomethine imines may have been formed by an elimination reaction either before or after quenching with water. The former pathway was considered unlikely after consideration of the following data. When **4** was generated in the presence of excess phenyllithium (our reaction conditions), it was expected that the highly reactive dipolar species would be phenylated at the methyl group. The reaction of dimethylnitrosamine with phenyllithium did not yield 1-methyl-1-benzyl-2-phenylhydrazine.[10] The reaction of phenyllithium with several akyl nitrosamines gave transient colored species either prior to or after the addition of water.[11] Although the appearance of highly colored intermediates is reminiscent of colored aromatic azomethine imines,[12,13] no further characterization of these species was undertaken.

(1) (a) This investigation was supported in part by U. S. Public Health Service Grant No. CA-02857 and CA-10746 from the National Institutes of Health, National Cancer Institute. (b) Allied Chemical Corp. Fellow, 1970–1971.

(2) (a) P. N. Magee and J. M. Barnes, *Brit. J. Cancer*, **10**, 114 (1956); (b) H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schmahl, *Z. Krebsforsch.*, **69**, 103 (1967).

(3) (a) F. M. Schabel, T. P. Johnston, G. S. McCaleb, J. A. Montgomery, W. R. Laster, and H. E. Skipper, *Cancer Res.*, **23**, 725 (1963); (b) C. T. Bahner, D. Brotherton, and M. K. Brotherton, *J. Med. Chem.*, **11**, 401 (1968).

(4) For a preliminary report on this work see P. R. Farina, *Tetrahedron Lett.*, 4971 (1970).

(5) (a) C. E. Looney, W. D. Phillips, and E. L. Reilly, *J. Amer. Chem. Soc.*, **79**, 6136 (1957); (b) G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964); (c) H. W. Brown and D. P. Hollis, *J. Mol. Spectrosc.*, **13**, 305 (1964); (d) J. T. D'Agostino and H. H. Jaffe, *J. Amer. Chem. Soc.*, **92**, 5160 (1970).

(6) L. K. Keefer and C. H. Fodor, *J. Amer. Chem. Soc.*, **92**, 5747 (1970).

(7) R. R. Fraser and Y. Y. Wigfield, *Tetrahedron Lett.*, 2515 (1971).

(8) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **11**, 301 (1972).

(9) P. Buck and G. Köbrich, *Tetrahedron Lett.*, 1563 (1967), have suggested a reverse addition of phenyllithium to nitrosobenzene followed by the displacement of PhOLi with an additional 1 mol of PhLi to account for reaction products.

$$PhN{=}O \xrightarrow{PhLi} PhN(Li^+)OPh \xrightarrow{PhLi} Ph_2NLi + PhOLi$$

By analogy this would presumably give 1,1-dimethyl-2-phenylhydrazine from the reaction of DMNA with phenyllithium if a similar route were applicable and not the observed reaction product.

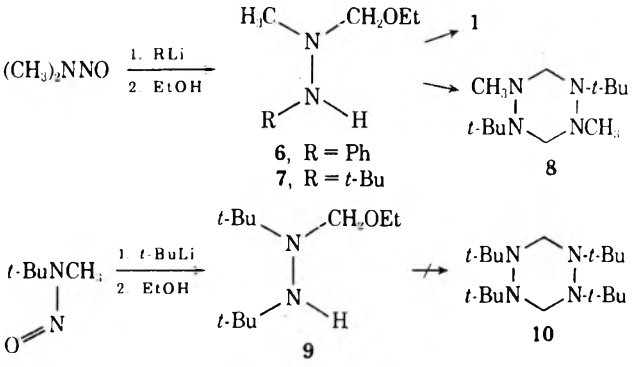
(10) This compound was the major product when PhMgBr was employed and is the subject for a future report.

(11) Orange, purple and blue-black for dimethylnitrosamine, diethylnitrosamine, and *N*-nitrosopiperidine, respectively.

(12) B. Singh, *J. Amer. Chem. Soc.*, **91**, 3670 (1969).

(13) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

Isolation of Ethoxymethylhydrazines.—A dipolar species generated during the water quench could be in equilibrium with its hydrated form.[14] Our attempts to detect such a species after reaction of dimethylnitrosamine with phenyllithium employing nmr spectroscopy were unsuccessful. Some azomethine imines, however, are known to form stable neutral adducts with alcohol.[13] The substitution of absolute ethanol for water in the quench of the reaction of DMNA with *tert*-butyllithium or phenyllithium resulted in the isolation of the corresponding unstable ethoxymethylhydrazines **6** and **7**, which were characterized by nmr.



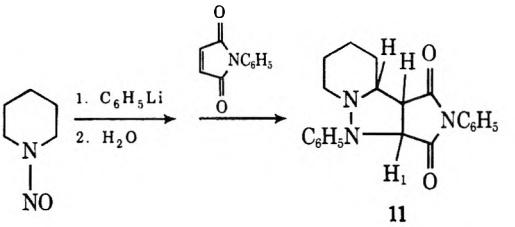
Compound **7** exhibited a singlet at δ 1.03 (9 H, *tert*-butyl) overlapping a triplet at δ 1.15 (3 H, J = 7.0 Hz, CCH_3), a singlet at δ 2.50 (3 H, NCH_3), a quartet at δ 3.52 (2 H, J = 7.0 Hz, OCH_2C), and a singlet at δ 4.02 (2 H, NCH_2O). After a short period of time the nmr spectrum began to change and was replaced in part by a new singlet at δ 2.84 and a peak at δ 3.9. Evaporation of the solvent gave **8**, hexahydro-1,4-dimethyl-2,5-di-*tert*-butyl-*s*-tetrazine, as a colorless liquid. Its nmr showed singlets at δ 1.01 (18 H, *tert*-butyl) and 2.84 (6 H, NCH_3), a mound at δ 3.85 (4 H, NCH_2N) which became a singlet on heating slightly above room temperature, and an AB quartet, J_{AB} = 11.5 Hz, on cooling. (See paragraph at end of paper regarding supplementary material.) Its infrared spectrum did not exhibit any NH absorption. This compound was clearly the product formed from **7** in solution or neat. However, if **7** was dissolved in methanol-d_4 its nmr spectrum remained unchanged even after several days in solution.

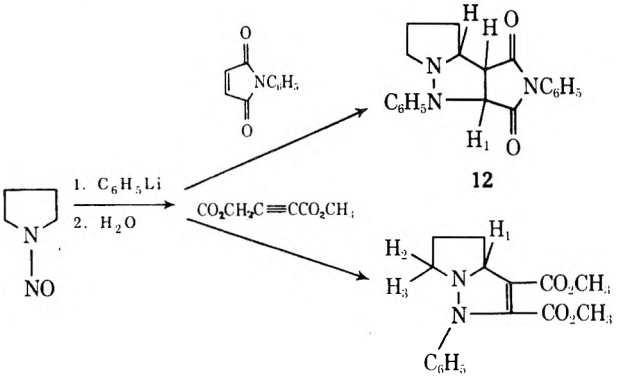
Similarly, **6** rapidly (half-life 1 hr, 30°, CCl_4) lost ethanol to form **1** which was independently synthesized from 1-methyl-2-phenylhydrazine and formaldehyde and therefore establishes structure **1** for a compound reported much earlier by Knorr and Weidel.[15]

When *N*-methyl-*tert*-butylnitrosamine was treated with *tert*-butyllithium and quenched with ethanol, 1,2-di-*tert*-butyl-1-(ethoxymethyl)hydrazine (**9**) was formed in almost quantitative yield. Surprisingly, this compound proved to be stable and was easily distilled at reduced pressure without decomposition. Its nmr spectrum (100 MHz) showed two singlets at δ 1.05 and 1.07 (18 H, *tert*-butyl) overlapping a triplet at δ 1.18 (3 H, J = 7.0 Hz, CH_3), a broad absorption at δ 3.10 (NH) which rapidly underwent exchange with D_2O, a quartet at δ 3.36 (2 H, J = 7.0 Hz, OCH_2C), and a singlet at δ 4.38 (2 H, NCH_2O). Its infrared spectrum showed a weak absorption at 3.05 μ attributed to NH. This compound did not eliminate ethanol to form **10** and was stable at room temperature.

Reactions with Dipolarophiles.—Certain *sym*-hexahydrotetrazines[12,13,16] are known to react with dipolarophiles presumably through dissociation to the 1,3-dipolar form to yield isolable adducts. Neither **1**, **2**, or **3** reacted with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide when refluxed in benzene solution. This was not unexpected, since dissociation is usually favored by appropriate, *i.e.*, aromatic, stabilization adjacent to both the dipolar centers.[12,13,16]

However, if the crude oils obtained from the reaction of phenyllithium with *N*-nitrosopiperidine or *N*-nitrosopyrrolidine followed by quenching with water were stirred with *N*-phenylmaleimide in ether, a white, crystalline solid began to precipitate after 10 min at





room temperature. These compounds were characterized as adducts **11** and **12** from the following data.

Adduct **11** was identified by its 100-MHz spectrum in trifluoroacetic acid which displayed a six-proton multiplet between δ 1.54 and 2.80, a three-proton multiplet between δ 2.88 and 4.12, a one-proton triplet at δ 4.36, a doublet at δ 5.26 (H_1, J = 8.2 Hz), and a ten-proton multiplet between δ 7.16 and 7.68.

The 100-MHz spectrum of adduct **12** in trifluoroacetic acid showed a four-proton multiplet between δ 2.16 and 2.88, a two-proton multiplet centered at δ 3.64, a one-proton doublet of doublets centered at δ 4.24 (J = 7.0 and 2.4 Hz), a one-proton multiplet at δ 5.20, and a doublet (H_1, J = 7.0 Hz) and a ten-proton multiplet between δ 7.12 and 7.60.

Dimethyl acetylenedicarboxylate was also an effective dipolarophile when refluxed in benzene with the oil obtained from the reaction of *N*-nitrosopyrrolidine and phenyllithium. The product, after purification by column chromatography, was characterized as dimethyl 3a,4,5,6-tetrahydro-1-phenyl-1*H*-pyrrolo[1,2-*b*]-pyrazole-2,3-dicarboxylate (**13**) from the following

(14) R. Grashey, R. Huisgen, K. K. Sun, and R. M. Moriarty, *J. Org. Chem.*, **30**, 74 (1965).

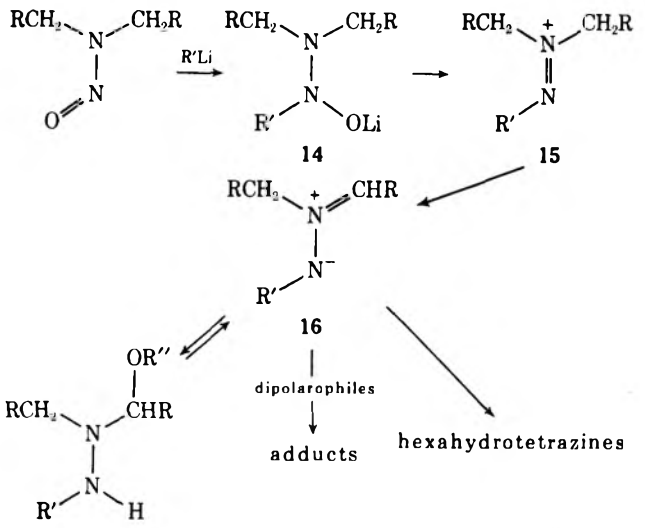
(15) L. Knorr and A. Weidel, *Chem. Ber.*, **42**, 3523 (1909).

(16) (a) R. Grashey, H. Leitermann, R. Schmidt, and K. Adelsberger, *Angew. Chem., Int. Ed. Engl.*, **1**, 406 (1962); (b) R. Grashey and K. Adelsberger, *ibid.*, **1**, 267 (1962).

spectral properties: ir (Nujol) 5.72 and 5.88 (ester C=O), 6.16 and 6.28 μ (unsaturation). The carbonyl values are in good agreement with those found by Singh[12] (5.72 and 5.91 μ) for a similar *N*-phenyl, α,β-unsaturated dimethyl dicarboxylate system. The nmr spectrum exhibited a four-proton multiplet between δ 1.5 and 2.3, a multiplet centered at δ 2.94 (H_2, H_3), two singlets at δ 3.58 and 3.67 (6 H, CH_3), a triplet at δ 4.75 (H_1), and a five-proton aromatic peak at δ 7.08.

Discussion

The reaction of simple alkyl nitrosoamines with phenyl- or *tert*-butyllithium to give *sym*-hexahydrotetrazines can be accommodated by the following scheme, outlined below. The first step involves attack by the organolithium reagent on the nitroso moiety to give **14**, which undergoes elimination to form the azomethine imine **16** (presumably through a diazenium salt **15**[17])



when quenched with a protic solvent such as water or ethanol. The 1,3-dipolar species which is generated is probably in equilibrium to some extent with its hydrate when water is employed. This is supported by the isolation of neutral ethoxymethylhydrazines when ethanol was substituted for water. Two of these hydrazines readily lose ethanol and dimerize to the same *sym*-hexahydrotetrazines which were obtained from the water quench of the reaction.

1,2-Di-*tert*-butyl-1-(ethoxymethyl)hydrazine is of particular interest, since it does not lose ethanol to form hexahydro-1,2,4,5-tetra-*tert*-butyl-*s*-tetrazine[18] on standing or when heated above room temperature. It is difficult to speculate at this time why **9** is so much more stable than **6** or **7**, although steric requirements of the two *tert*-butyl groups are most probably involved.

Cyclic aliphatic nitrosamines, such as *N*-nitrosopyrrolidine or piperidine, apparently form hydrates which are sufficiently long lived to permit reaction with dipolarophiles before dimerization to products. *N*-Nitrosopyrrolidine, however, does not yield an isolable hexahydrotetrazine.

It is noteworthy that nitrosamines can react with organometallics by two major routes: abstraction of an α proton to form an α-nitrosamino carbanion or nucleophilic attack on the NO moiety. The path is probably determined by the nucleophilicity of the reagent, polarity of the solvent, and the nature of the nitrosamine.

(17) G. Büttner and S. Hünig, *Chem. Ber.*, **104**, 1088 (1971).

(18) This product was also not observed when water was used as quenching agent.

Experimental Section

Infrared absorption spectra were determined using a Beckman IR-5A spectrophotometer and ultraviolet absorption spectra were determined using a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. A Varian A-60 or Jeolco 100 nuclear magnetic resonance spectrometer were used to record the nmr spectra. Mass spectra were obtained on a Hitachi Perkin-Elmer RMV. 6D mass spectrometer.

Melting points were determined on a Mel-Temp or Fisher-Johns melting apparatus and are uncorrected. Microanalyses were performed by Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn.

Dimethylnitrosamine, diethylnitrosamine, and *N*-nitrosopyrrolidine were purchased from Eastman Organics, Rochester, N. Y., and were used without further purification.[19a] *N*-Methyl-*tert*-butylnitrosamine was prepared according to a standard procedure.[19b] *tert*-Butyllithium (2 *M* in *n*-pentane) was purchased from Alfa Inorganics, Beverly, Mass.

Phenyllithium Reagent.—Phenyllithium was prepared according to a standard method[20] and titrated prior to use by the method of Gilman.[21] The following modifications were made: lithium wire was cut into pieces 0.5 cm long, argon was substituted for nitrogen, and the solution was allowed to settle overnight before it was siphoned into a container for storage.

***N*-Nitrosopyrrolidine.**—Pyrrolidine (44 g, 0.62 mol) was added slowly to a stirred solution of glacial acetic acid cooled by ice. The yellow solution was then heated to 90° and sodium nitrite (86 g, 1.2 mol) was added, maintaining the temperature between 90 and 95°. The solution was stirred until no more gas was evolved and then evaporated *in vacuo* at 60°. The residue was then extracted with ether. The extract was concentrated and anhydrous sodium carbonate was added to the stirred solution until carbon dioxide evolution was complete. The solution was then filtered and evaporated to a red-brown liquid.

The product was distilled, and the fraction boiling at 66–68° (2.0 mm) was collected, 62 g (80% yield), diluted with a small portion of ether, and stirred with anhydrous sodium carbonate overnight. Filtration and concentration as above, followed by distillation, gave the nitrosamine: bp 69–70° (1.0 mm); ir (film) 6.88 (m), 7.09 (s), 7.66 (s), 8.27, 10.30, 12.38, 13.94 μ; nmr (CCl_4) δ 1.7–2.2 (m, 4 H) and 3.1–3.5 (m, 4 H).

Hexahydro-1,4-dimethyl-2,5-diphenyl-*s*-tetrazine (1). A. From Dimethylnitrosamine.—A solution of dimethylnitrosamine (1.44 g, 19.5 mmol) in 100 ml of anhydrous ether was cooled to −45° with stirring under an argon atmosphere. Phenyllithium (40 ml, 0.96 mmol/ml) was added dropwise over a period of 25 min. After an additional 0.5 hr the solution was warmed to −10° and quenched with water. The ether layer was dried and evaporated *in vacuo*. The pale yellow oil crystallized immediately after trituration with methanol to give 1.0 g (40% yield) of **1**, mp 141–148°. Recrystallization from ligroin (bp 66–75°) gave the analytical sample: mp 151–151.5°; ir (Nujol) 6.24 (s), 8.79 (s), 12.75 (s), 13.41, and 14.51 μ (s); nmr (CCl_4) δ 2.55 (s, 6 H), 4.47 (s, 4 H), and 6.4–7.3 (m. 10); mass spectrum (70 eV) *m/e* (rel intensity) 268 (26), 135 (45), 134 (72), 120 (17), 105 (86), 91 (18), 77 (100). *Anal.* Calcd for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.53; H, 7.28; N, 20.69.

B. From 1-Methyl-2-phenylhydrazine and Formaldehyde.—The reaction conditions described by Knorr and Weidel[15] were employed using 1-methyl-2-phenylhydrazine[22] and aqueous formaldehyde. The product was recrystallized from hexane and was shown to be identical with **1** obtained from phenyllithium and dimethylnitrosamine.

Hexahydro-1,4-diethyl-3,6-dimethyl-2,5-diphenyl-*s*-tetrazine (2).—A solution of diethylnitrosamine (2.18 g, 21.4 mmol) in

(19) (a) Precautions in handling of nitrosamines should be undertaken owing to the carcinogenic properties of some of these compounds.[2] (b) D. F. Heath and A. R. Mattocks, *J. Chem. Soc.*, 4226 (1961).

(20) R. G. Jones and H. Gilman, *Org. React.*, **6**, 353 (1951).

(21) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Amer. Chem. Soc.*, **45**, 150 (1923).

(22) C. H. Schmidt, *Chem. Ber.*, **103**, 986 (1970).

100 ml of anhydrous ether was cooled to −50° with stirring under an argon atmosphere. Phenyllithium (50 ml, 0.85 mmol/ml) was added dropwise. After 1 hr the reaction mixture was quenched with water, producing an intense purple color which faded and changed to yellow as more water was added. The ether layer was dried and evaporated to a viscous oil. Trituration with methanol gave 2.87 g (30% yield) of the product (**2**), mp 168–171°. Recrystallization from hexane gave white cubic crystals: mp 184–185°; ir (Nujol) 6.28 (s) 7.31 (s), 8.84 (s), 13.50 (s), 14.58 μ (s); nmr (CCl_4) δ 1.04 (t, 6 H), 1.48 (d, 4 H), 2.89 (q, AB of q, 4 H) (J_{AB} = 12, J_{AX} = J_{BX} = 8 Hz), 4.70 (q, 2 H), 6.3–7.3 (m, 10 H); mass spectrum (70 eV) *m/e* (rel intensity) 324 (5), 190, (10), 163 (53), 162 (97), 161 (100), 147 (14), 133 (13), 118 (48), 117 (98), 77 (91). *Anal.* Calcd for $C_{20}H_{28}N_4$: C, 74.03; H 8.70; N, 17.27. Found: C, 74.01; H, 8.66; N, 17.44.

Reaction of *N*-Nitrosopyrrolidine with Phenyllithium.—A stirred solution of *N*-nitrosopyrrolidine (10.9 g, 109 mmol) in 300 ml of anhydrous ether was cooled to −65° under an argon atmosphere. Phenyllithium (218 mmol) in 230 ml of ether was added dropwise to this solution. After 2 hr the reaction was quenched with water and the ether layer was separated and dried. Evaporation of the ether *in vacuo* gave 10.1 g of crude oil. All attempts at purification to give a *sym*-hexahydrotetrazine were unsuccessful.

Dimethyl 3a,4,5,6-Tetrahydro-1-phenyl-1*H*-pyrrolo[1,2-*b*] pyrazole-2,3-dicarboxylate (13).—A solution of 80 ml of benzene containing 4.8 g of crude oil from the previous experiment and 4.3 g of dimethyl acetylenedicarboxylate was refluxed overnight. The brown residue was chromatographed on 450 g of deactivated neutral alumina[23] using carbon tetrachloride followed by 1:4 (volume) chloroform–carbon tetrachloride. The yellow band was collected to give 2.85 g of a pale yellow oil. Thin layer chromatography on silica gel (Eastman) with chloroform as eluent showed a spot having R_f 0.71 and two contaminants which were visualized using iodine. Further purification by thick layer on silica gel H gave the product as a single spot by tlc.

Trituration of the oil with several drops of hexane and cooling in the refrigerator for several days gave a low-melting solid, mp 54–55°. Recrystallization from 1:1 (volume) ethanol–water gave an analytical sample: mp 61–61.5°; ir (Nujol) 5.72 (s), 5.88 (s), 6.16 (s), 6.28 (s), 13.09 (s), 13.70 (m), 14.30 μ (s); uv (ethanol) λ_{max} 356 mμ (ε 13,600); nmr (CCl_4) spectral designations given in text; mass spectrum *m/e* (rel intensity) 312 (26, P), 273 (39), 243 (63), 229 (10), 215 (100), 211 (14), 198 (12), 144 (10), 77 (79), 72 (12). *Anal.* Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.76; H, 6.05; N, 9.14.

Hexahydro-*N*,1-diphenyl-1*H*-pyrrolo[1,2-*b*]pyrazole-2,3-dicarboximide (12).—*N*-Phenylmaleimide (1.2 g, 7.0 mmol) was added to a stirred solution of crude oil obtained from *N*-nitrosopyrrolidine (1.0 g, 0.6 mmol) and phenyllithium in 100 ml of ether. After 10 min of stirring at room temperature, a white, crystalline precipitate began to form. The reaction mixture was stirred overnight and then filtered to give 0.30 g of the adduct: mp 216–218° dec; ir (Nujol) 5.85 (s), 6.24 (m), 8.36 (s), 13.37 (s), 14.24 (w), 14.49 μ (m); nmr (CF_3COOH) spectral designations given in text; mass spectrum *m/e* (rel intensity) 333 (81, P), 172 (86), 158 (23), 157 (19), 129 (18), 117 (11), 93 (17), 91 (21), 81 (78), 78 (78), 77 (43), 69 (100). *Anal.* Calcd for $C_{20}H_{19}N_3O_2$: C, 72.10; H, 5.74; N, 12.60. Found: C, 72.29; H, 5.82; N, 12.55.

Dodecahydro-5,11-diphenyldipyrido[1,2-*b*:1′,2′-*e*]-*s*-tetrazine (3).—A solution of *N*-nitrosopiperidine (1.70 g, 15.0 mmol) in 150 ml of anhydrous ether was cooled to −65° with stirring under an argon atmosphere. To this solution was added 30 ml of phenyllithium (1.0 mmol/1 ml) over a 15-min period. The solution changed color from yellow to green to light blue to dark blue during the addition. After an additional 1 hr the solution was quenched with water which reversed the color changes. The ether layer was separated, dried, and evaporated to a viscous yellow oil. Trituration with hexane and cooling overnight gave 0.77 g (30%) of the hexahydrotetrazine **3** as white crystals, mp 135–140°. Recrystallization from hexane gave an analytical sample: mp 151–151.5°; ir (Nujol) 6.23 (s), 7.95 (m), 9.65 (m), 13.26 (s), 14.39 μ (s); nmr (CCl_4) δ 1.1–2.1 (m, 12 H), 2.83–3.21 (m, 4 H), 3.57 (d, 1 H), 4.03 (s, 1 H), 6.37–7.20 (m, 10 H); mass spectrum *m/e* (rel intensity) 348 (17, P), 173 (78, P/2), 174 (60), 172 (34), 135 (64), 130 (23), 122 (47), 117 (60), 105 (43), 93 (100), 77 (100), 66 (100). *Anal.* Calcd for $C_{22}H_{28}N_4$: C, 75.82; H, 8.10; N, 16.10. Found: C, 76.03; H, 8.06; N, 16.15.

Octahydro-*N*,1-diphenylpyrazolo[1,5-*a*]pyridine-2,3-dicarboximide (11).—*N*-Phenylmaleimide (1.7 g, 9.8 mmol) in 50 ml of ether was added to a stirred solution of crude oil from the above reaction (1.5 g, 7.9 mmol). After 45 min a white precipitate began to form. The reaction mixture was stirred overnight and then filtered, giving 0.7 g (25%) of the adduct, mp 225–227° dec. Recrystallization from acetonitrile gave an analytical sample: mp 228–229.5° dec; ir (Nujol) 5.84 (s), 6.25 (w), 7.23 (m), 8.38 (m), 13.71 (w), 14.47 μ (m); nmr (CF_3COOH) spectral designations given in text; mass spectrum *m/e* (rel intensity) 347 (78, P), 231 (13), 181 (55), 173 (39), 158 (11), 131 (78), 119 (14), 100 (21), 93 (16), 77 (24) 69 (100). *Anal.* Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.10; N, 12.10. Found: C, 72.74; H, 6.18; N, 12.18.

1-Methyl-1-ethoxymethyl-2-phenylhydrazine (6).—Dimethylnitrosamine (4.25 g, 0.575 mol) dissolved in 150 ml of anhydrous ether was cooled to −65° under an argon atmosphere. Over a period of 1 hr, 100 ml of 0.115 *M* phenyllithium was added to the well-stirred solution. After an additional 10 min, 25 ml of absolute ethanol (dried over 3A molecular sieves) was added to the white suspension. The solution color changed from orange to deep yellow to pale yellow during the addition of ethanol. When the addition was completed, water was added until the solution separated into two distinct layers. The ether layer was separated, dried over anhydrous potassium carbonate, and evaporated *in vacuo* at room temperature to a pale yellow oil: nmr (CCl_4) δ 1.13 (t, CCH_3), 2.57 (s, NCH_3), 3.40 (q, OCH_2C), 4.12 (s, NCH_2O), 5.1 (br s, NH). This compound rapidly loses ethanol on standing to form **1**.

1-Methyl-1-ethoxymethyl-2-*tert*-butylhydrazine (7).—Dimethylnitrosamine (7.4 g, 0.1 mol) was dissolved in 300 ml of anhydrous ether and cooled to −70° under an argon atmosphere. Over a period of 1 hr 47 ml of 2.34 *M tert*-butyllithium was added to the well-stirred solution. After an additional 1 hr the yellow solution was quenched with 25 ml of absolute ethanol and the temperature was brought to 0°. Water (50 ml) was then added to dissolve precipitated salts and the ether layer was separated and dried. The ether was evaporated *in vacuo* at room temperature to give the product (16 g, 84% yield): ir (film) 3.07 (w, NH), 7.25 (m) and 7.38 (s), 8.88 (m), 9.00 (m), 9.30 (s), 10.10 (m), 11.35 (s), 12.92 μ (w); nmr (CCl_4) spectral designations given in text.

Hexahydro-1,4-dimethyl-2,5-di-*tert*-butyl-*s*-tetrazine (8). A.—A solution of 2.50 g (0.0156 mol) of 1-methyl-1-ethoxymethyl-2-*tert*-butylhydrazine was stirred overnight in 25 ml of carbon tetrachloride. Evaporation of the solvent and distillation gave 1.24 g (71%) of **8** which was collected at 59° (0.05 mm).

B.—The same conditions employed for **7** were used, except that water was substituted for ethanol. This permitted the direct isolation of **8**: ir (film) 7.22 (m), 7.38 (s), 8.26 (s) 9.28 (s) 11.09 (m), and 13.80 μ (s); nmr (CCl_4) spectral designations appear in text; mass spectrum *m/e* (rel intensity) 228 (10, P), 171 (7), 115 (11), 114 (17), 99 (31), 71 (58), 70 (10), 58 (50), 57 (100), 41 (38), 39 (10). *Anal.* Calcd for $C_{12}H_{28}N_4$: C, 63.11; H, 12.36; N, 24.53. Found: C, 63.20; H, 12.53; H, 24.45.

1,2-Di-*tert*-butyl-1-(ethoxymethyl)hydrazine (9).—*N*-Methyl-*N*-*tert*-butylnitrosamine (4.64 g, 0.040 mol) was dissolved in 300 ml of anhydrous ether and cooled to −70° under an argon atmosphere. Over a period of 1 hr 19 ml of 2.34 *M tert*-butyllithium was added with stirring. After an additional 1 hr 10 ml of absolute ethanol was added and the temperature was brought to 0°. Water (50 ml) was added and the ether layer was separated, dried, and evaporated *in vacuo* to a pale yellow liquid, 6.2 g (77% yield). This material was distilled and the fraction boiling at 52–54° (2.0 mm) was collected: ir (film) 3.05 (w), 7.22 (m), 7.37 (s), 9.32 (s), 10.20 (m), 11.84 (m), 12.60 (m), and 13.80 μ (m); nmr (CCl_4) spectral designations appear in text; mass spectrum *m/e* (rel intensity) 176 (2), 129 (59), 85 (26), 73 (83), 71 (27), 57 (100), 46 (28), 45 (65), 41 (98), 39 (22), 31 (100). *Anal.* Calcd for $C_{11}H_{26}N_2O$: C, 65.30; H, 12.95; N, 13.84. Found: C, 65.08; H, 12.78; N, 13.61.

Hexahydro-1,4-dimethyl-2,5-diphenyl-*s*-tetrazine (1) from Halogen-Free Phenyllithium.—Dimethylnitrosamine was sim-

(23) Neutral alumina activity I (450 g) and 22.5 g of water were shaken until the powder appeared homogenous.

ilarly treated with phenyllithium which was halogen free.[24] The product isolated was identical with that obtained using phenyllithium prepared from bromobenzene and lithium metal.

Registry No.—1, 27377-48-6; 2, 30514-23-9; 3, 30514-22-8; 6, 42297-06-3; 7, 42297-07-4; 8, 42297-08-5; 9, 42297-09-6; 11, 42297-10-9; 12, 42297-11-0; 13, 42297-12-1; *N*-nitrosopyrrolidine, 930-55-2; pyrrolidine, 123-75-1; dimethylnitrosamine, 62-75-9; diethylnitrosamine, 55-18-5; dimethyl acetylenedicarboxylate, 762-42-5; *N*-phenylmaleimide, 941-69-5; *N*-nitrosopiperidine, 100-75-4; *N*-methyl-*N*-*tert*-butylnitrosamine, 7068-83-9.

(24) G. Wittig, F. J. Meyer, and G. Lange, *Justus Liebigs Ann. Chem.*, **571**, 167 (1951).

Supplementary Material Available.—Nmr data for compound 7 freshly dissolved in CCl_4 and after standing for 3 hr and 4 days and for compound 8 in CCl_4 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, 20× 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-73-4259.

Reactions of Lithium Diorganocuprates(I) with Oxiranes

CARL R. JOHNSON,* R. WILBUR HERR, AND DONALD M. WIELAND

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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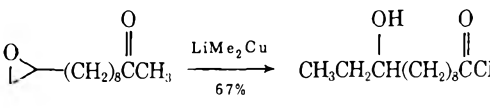
Lithium diorganocuprates have been shown to be highly effective reagents for the nucleophilic ring opening of oxiranes in the trans manner. These reactions occur more rapidly in diethyl ether than in tetrahydrofuran. Evidence and precedent for a mechanism involving the formation of a triorganocopper(III) intermediate is discussed. The selectivity of lithium diorganocuprates in reactions with substrates containing epoxide along with other electrophilic sites is discussed in terms of the hard and soft acid–base theory.

The nucleophilic ring opening of oxiranes by organometallic reagents is a frequently used method for the generation of new carbon–carbon σ bonds;[1] in many cases the utility of the reaction is curtailed owing to competing reactions arising from the Lewis acidity or the basicity of the organometallic reagent. We have observed that lithium diorganocuprates(I) are capable of ring opening of oxiranes under very mild conditions. In a series of preliminary communications,[2-4] we have demonstrated the ability of these reagents to circumvent many of the troublesome side reactions frequently encountered in the reactions of other organometallic reagents with oxiranes. In order to conserve journal space our published results will be summarized in a brief manner in the following paragraphs. The main body of this paper is largely concerned with extensions of our earlier results and mechanistic discussion. The Experimental Section of this paper includes details of certain key experiments described in the earlier communications.

In the introductory communication[2] the reactions of cyclohexene oxide with methyl- and phenyllithium were compared with the corresponding lithium diorganocuprates(I). The results indicated that the cuprates were more reactive toward oxiranes and were somewhat superior in terms of yields of trans nucleophilic addition products. Polymeric methylcopper and methylcopper complexes with trimethyl phosphite or tri-*n*-butylphosphine were unreactive toward cyclohexene oxide, whereas lithium methylcyanobis(triethyl phosphite)copper(I) reacted only slightly. In these ring-opening reactions of oxiranes the lithium ion is undoubtedly lending an electrophilic assist by coordination with the oxirane oxygen. In contrast to the coupling reactions of organocuprates and alkyl halides,[5] these oxirane reactions proceed more rapidly in diethyl ether than in THF. The latter solvates the lithium ion more effectively to the detriment of the lithium ion–oxirane complex. Perhaps the most significant observation was that lithium diorganocuprates could selectively ring open oxiranes in the presence of unprotected carbonyl functions (ester or ketone), *e.g.*, eq 1.



(1)

In the second communication[3] we compared the reactions of methylmagnesium, methyllithium, and methylcopper reagents with 1,2-epoxybutane and 1,2-epoxy-3-butene.[6] With the latter substrate methylmagnesium reagents gave 16–68% conjugate addition (mixture of *cis*- and *trans*-2-penten-1-ol), methyllithiums gave 20–55%, and lithium dimethylcopper gave 94%. The conjugate mode of addition of lithium dialkylcuprates to α,β-unsaturated carbonyl compounds,[7,8] allylic acetates,[9] and propargylic acetates[10] had already been documented. More recently we reported on the regio- and stereoselectivity of the reactions of methyl-

(1) (a) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part I, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, pp 386–417; (b) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 779 (1959); (c) N. G. Gaylord and E. I. Becker *ibid.*, **49**, 448 (1951).

(2) R. W. Herr, D. M. Wieland, and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 3813 (1970).

(3) R. W. Herr and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 4979 (1970).

(4) D. M. Wieland and C. R. Johnson, *J. Amer. Chem. Soc.*, **93**, 3047 (1971).

(5) (a) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); (b) *ibid.*, **90**, 5615 (1968); (c) G. M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Bashe, and H. O. House, *ibid.*, **91**, 4871 (1969).

(6) For a related study see R. J. Anderson, *J. Amer. Chem. Soc.*, **92**, 4978 (1970).

(7) (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (b) H. O. House and W. F. Fischer, Jr., *ibid.*, **33**, 949 (1968); (c) E. J. Corey and J. H. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969); (d) J. B. Siddall, M. Biskup, and J. H. Fried, *ibid.*, **91**, 1853 (1969).

(8) For a review see G. H. Posner, *Org. React.*, **19**, 1 (1972).

(9) P. Rona, L. Tokes, J. Tremble, and P. Crabbe, *Chem. Commun.*, 43 (1969); (b) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970).

(10) (a) P. Rona and P. Crabbe, *J. Amer. Chem. Soc.*, **90**, 4733 (1968); (b) *ibid.*, **91**, 3289 (1969).

and phenyllithium and lithium dimethyl-, diphenyl-, and di-*tert*-butylcuprates with 1,2-epoxy-3-cyclohexene.[4,11] The copper reagents were again found to react more rapidly and under milder conditions to give better yields of addition products than their organolithium counterparts. The methyl and phenyl reagents displayed high trans stereoselectivity in both the 1,2 and 1,4 additions. In regard to the 1,4 additions it should be noted that it has been generally accepted that the entering nucleophile bears a cis relationship to the leaving group in an SN2 reaction.[12,13]

Reactions of Cycloalkene Oxides.—Table I summarizes the nucelophilic ring opening reactions of fused

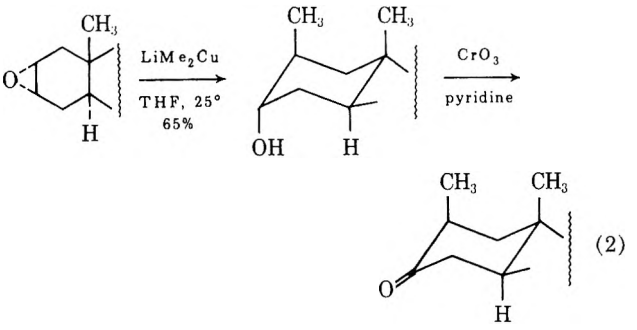
TABLE I
REACTIONS OF LITHIUM DIMETHYLCUPRATE WITH CYCLOALKENE OXIDES[a]

Oxirane	Time, hr	Oxirane recovered, %	Conversion, %	Product distribution Trans alcohol	Ketone
Cyclopentane oxide	6	0	85[b]	88	12
Cyclohexene oxide	14	0	82[b]	76	24
Cycloheptene oxide	48	11	81[c]	74	26
cis-Cyclooctene oxide	48	79	9[c]	60	40
cis-Cyclooctene oxide	30[d,e]	48	36[c]	60	40
exo-Norbornene oxide	24	100	0[c]		
exo-Norbornene oxide	5[d,f]	1	58[b]	100	
5α-Cholestane 2α,3α-oxide	24	0	86[b]	75[g]	25

[a] The reactions were 0.02 *M* in oxirane and 0.10 *M* in lithium dimethylcuprate (fivefold excess). The lithium dimethylcuprate solution was made at 0°, the oxirane was added dropwise, and then the reaction was allowed to warm to the desired temperature. All reactions were run under an argon or nitrogen atmosphere. The reactions were run in diethyl ether at 25° except where noted. [b] Isolated yield. [c] Vpc yield. [d] In dimethoxyethane. [e] At 70°. [f] At 55°. [g] See eq 2.

ring oxiranes with lithium dimethylcuprate(I). The only significant side reaction appears to be the formation of ketones by rearrangement of the epoxides. In each case the ring opening occurs cleanly in the trans manner. As would be typical of an SN2 process, these reactions were sluggish when back-side attack was sterically encumbered. In the case of *exo*-2,3-epoxynorcamphor and *cis*-cyclooctene oxide this sluggishness could be overcome to some extent by switching from diether ether to dimethoxyethane and increasing the reaction temperature.

The reaction of lithium dimethylcuprate with 5α-cholestane 2α,3α-oxide is of more than passing interest in steroid chemistry. The reaction results in the introduction of a methyl group in the 2 position of the steroid nucleus in the less stable axial orientation (eq 2). Reaction of the same epoxide with a Grignard reagent would most likely lead to ring contraction as the reaction pathway.[14] The same alcohol has recently been



synthesized from the epoxide in a two-step sequence—reaction with lithio-1,3-dithiane followed by Raney nickel desulfurization.[15] It should be pointed out that, while it is important that lithium dimethylcopper can open sterically hindered epoxides in steroids, the fact that ambient temperatures are required rules out the selective use of this reaction when other reactive function groups are present.

The emergence of a new factor—a competing reduction reaction— is noted in the reactions of lithium di-*n*-butylcuprate with epoxides (Table II). It has recently been shown that the tri-*n*-butylphosphine complex of *n*-butylcopper(I) undergoes thermal decomposition at 0° in ether *via* β elimination of copper(I) hydride.[16] The stability of *n*-butylcopper (the by-product of the reaction of the lithium di-*n*-butylcuprate with an epoxide) in ether solution is not known, but it is likely to be less stable than the complex. Copper hydride is an efficient reducing agent, and we suspect that its formation accounts for the cyclopentanol and cyclohexanol (Table II).[17]

As a possible method to prevent the formation of copper hydride under the reaction conditions it occurred to us to utilize an excess of the *n*-butyllithium, which would in effect "tie up" the *n*-butylcopper as it formed by converting it to the more stable lithium di-*n*-butylcuprate (Scheme I). The second and fourth entry in

SCHEME I

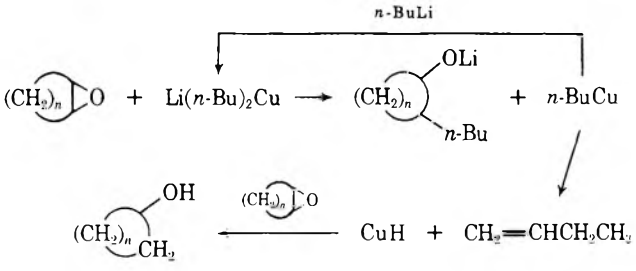


Table II indicate the excellent success of this approach—the reduction products were completely eliminated. The lithium di-*n*-butylcuprate is itself stable at −40° for an indefinite period. The lower temperatures utilized were not necessary to assure exclusion of reduction products, but were used to prevent rearrangement of the epoxide to ketone. These reactions show that small or even catalytic amounts of cuprous iodide and low temperatures may be used to effect the ring open-

(11) For a related study see J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).

(12) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).

(13) For a recent interesting commentary on SN2′ reactions see F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(14) For a related example see B. G. Christensen, R. G. Strachan, N. R. Trenner, B. H. Arison, R. Hirshmann, and J. M. Chemesda, *J. Amer. Chem. Soc.*, **82**, 3995 (1960).

(15) J. Jones and R. Grayshan, *Chem. Commun.*, 141 (1970).

(16) G. M. Whitesides, E. R. Stedronsky, C. P. Casey, and J. San Filippo, Jr., *J. Amer. Chem. Soc.*, **92**, 1426 (1970).

(17) The reduction of a ketone by lithium di-*n*-butylcuprate has been recently reported by L. T. Scott and W. D. Cotton, *Chem. Commun.*, 320 (1973).

TABLE II

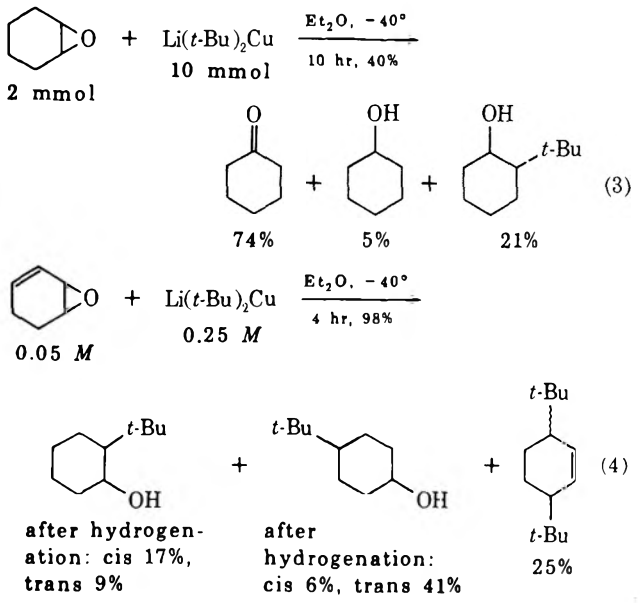
REACTION OF LITHIUM DI-*n*-BUTYLCUPRATE WITH CYCLOALKENE OXIDES[a]

Oxirane	Oxirane, mmol	CuI, mmol	*n*-BuLi, mmol	Time, hr	Temp, °C	Product distribution[b] *trans*-2-*n*-Butylcycloalkanol	Cycloalkanol	Cycloalkanone
Cyclopentene oxide	1.0	5.0	10.0	4	25	66	22	12
Cyclopentene oxide	1.0	0.5	10.0	4	−40	99	0	1
Cyclohexene oxide	1.0	5.0	10.0	4	25	73	19	8
Cyclohexene oxide	1.0	0.5	10.0	10	0	97	0	3
Cyclohexene oxide	1.0	0	5.0	14	25	13[c]		

[a] The solvent consisted of 43 mol of diethyl ether and 7 ml of hexane. The lithium *n*-butylcuprate was generated at −40°, the oxirane was added dropwise, and then the mixture was allowed to warm to the desired temperature. The reactions were run under an argon atmosphere. [b] Mesitylene was used as an internal standard. In all cases the conversions to the products shown were in the 80-90% range. [c] The major product was 2-cyclohexenol; for related results see R. L. Letsinger, J. G. Traynham, and E. Bobko, *J. Amer. Chem. Soc.*, **74**, 399 (1952).

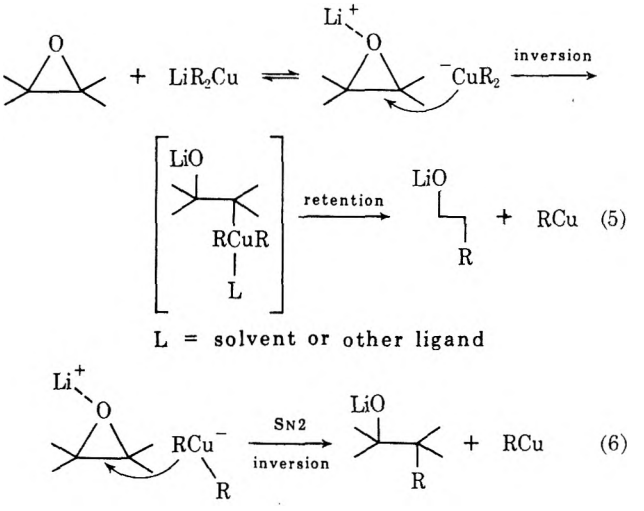
ing of epoxides with organolithium reagents. However, these conditions preclude the selective ring opening of epoxides in the presence of such functionalities as keto, ester, or nitrile.

The reactions of lithium di-*tert*-butylcuprate with cyclohexene oxide and 1,2-epoxy-3-cyclohexene are illustrated in eq 3 and 4. The production of 3,6-di-



tert-butylcyclohexene can be rationalized as involving a dianion[18] which collapses to a carbene or by displacement of LiO^-. The isolation of this product suggests[19] that the cis products formed in the reaction of lithium di-*tert*-butylcuprate with 1,2-epoxy-3-cyclohexene (eq 4) may arise by equilibration of the initially formed trans products *via* dianions. The vpc of the product mixtures exhibited the same number and relative areas of peaks before and after hydrogenation.

Discussion of General Mechanistic Aspects.—Although other mechanisms are certainly conceivable,[20] the reactions of lithium diorganocuprates(I) with oxiranes are most likely to proceed by one of the two possible mechanisms shown below (eq 5 and 6). Lithium



ion assistance in the ring opening is suggested by the facts that ether is a better solvent for these reactions than THF (the oxirane competes effectively with ethyl ether for the lithium ion) and sulfide or phosphine solubilized organocopper reagents are not effective in these reactions.

It is abundantly clear that organocopper reagents are different in their reactivity profile from the run-of-the-mill organometallics such as alkyllithiums and alkylmagnesium halides. The organocopper reagents are more effective at nucleophilic substitution at saturated carbon,[5,20] prefer to add in the conjugate manner to α,β-carbonyl compounds,[7,8] show greater preference for SN2′ reactions in vinyloxiranes[3,4,6,11] and allylic[9] and propargylic acetates,[10] and prefer reaction at the saturated carbon of an oxirane over addition to a carbonyl.[2] These rather dramatic differences in reactivity can be best explained by the assumption that with a typical organometallic, say an alkyllithium (R^-Li^+), it is the alkyl carbon that is acting as the nucleophile, whereas with a cuprate ($R_2Cu^-Li^+$) the copper atom is the nucleophilic site (eq 5). This latter idea has precedent. Pyridine[bis(dimethyl glyoximate)]cobalt(I) reacts with cyclohexene oxide to give the trans adduct (eq 7).[21a] There is also a good possibility that the so-called deconjugation reactions of substrates, such as isophorone by combinations of Grignard reagents and

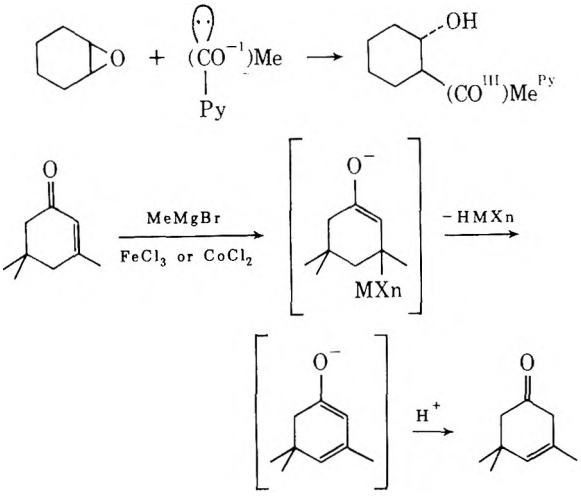
(18) The formation of dianions of allylic alcohols using *n*-butyllithium has been documented: D. R. Dimmel and S. B. Gharpure, *J. Amer. Chem. Soc.*, **93**, 3991 (1971); **94**, 5495 (1972).

(19) For an earlier suggestion see ref 4; H. O. House and M. J. Umen, *J. Amer. Chem. Soc.*, **94**, 5495 (1972), have recently provided new evidence favoring an electron transfer mechanism in the conjugate addition of cuprates to electrophilic olefins.

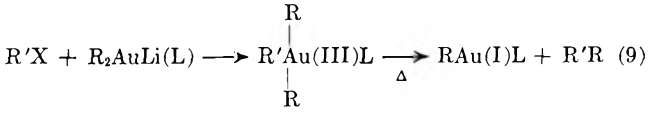
(20) For a related study on the reactions of lithium diorganocuprates and tosylates see C. R. Johnson and G. A. Dutra, *J. Amer. Chem. Soc.*, **95**, 7777, 7783 (1973).

(21) (a) F. R. Jensen, V. Maden, and D. H. Buchanan, *J. Amer. Chem. Soc.*, **92**, 1414 (1970); (b) M. S. Kharasch and P. O. Tawney, *ibid.*, **63**, 2308 (1941); (c) J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971).

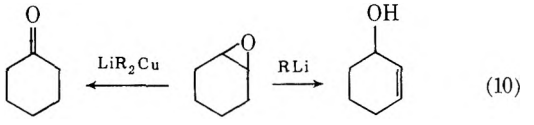
ferric or cobalt chloride, may occur *via* the formation of a metal–alkyl intermediate followed by elimination (eq 8).[21b,c]



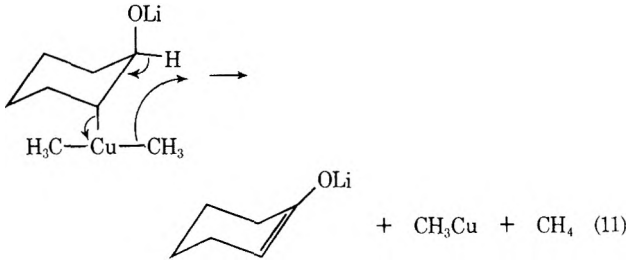
Clearly, the most pertinent examples of metal atom nucleophiles have been provided by the recent work of Tamaki and Kochi,[22] who found that lithium dialkylaurates(I) react with alkyl halides to provide a relatively stable gold(III) complex in which the original alkyl groups largely assume a trans orientation. The gold(III) complexes undergo thermally induced elimination to produce a new carbon–carbon bond (presumedly by coupling of two cis alkyl groups) (eq 9).



Major by-products from the reactions of lithium diorganocuprates with epoxides are ketones. For example, cyclohexanone is formed in the reaction of cyclohexene oxide with lithium dimethylcuprate. Note, however, that the typical product from the base-catalyzed rearrangement of cyclohexene oxide is cyclohexen-3-ol (eq 10).[3,23] If it is assumed that the



mechanism shown in eq 5 obtains, then enolate (and subsequently, ketone) formation can be nicely explained by a cyclic elimination mechanism from an organocopper(III) intermediate (eq 11). We have



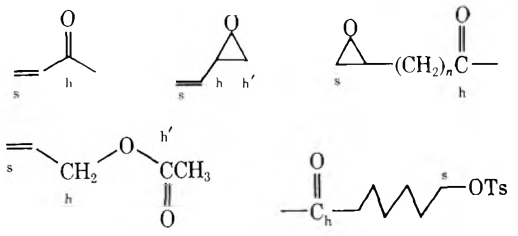
trapped the enolates in such reactions with acetic anhydride.

(22) A. Tamaki and J. K. Kochi, *J. Organometal. Chem.*, **51**, C39 (1973).

(23) R. P. Thummel and B. Rickborn, *J. Amer. Chem. Soc.*, **92**, 2064 (1970).

In a recent stereochemical, kinetic, and mechanistic study of the coupling reactions of lithium diorganocuprates and alkyl tosylates we concluded that these reactions also involve an initial SN2 reaction with the copper atom of the cuprate as the nucleophilic site.[20]

It appears to us that the hard and soft acid–base principle[24] may be useful to consider, at least from a predictive point of view, in comparing reactions of alkyllithiums and other organometallics with those of lithium organocuprates. If we consider that lithium dimethylcuprate is a softer base than methyllithium and hence prefers to react with the softer acid sites while methyllithium prefers to react at hard acid sites, then a good deal of the difference in their chemistry seems predictable. In the structures shown below we have added labels (s = soft, h = hard, h′ = harder) to indicate what we believe to be reasonable comparative designations of the hardness or softness of the acid sites.



Experimental Section

General.—Infrared spectra were obtained on a Perkin-Elmer 137 B spectrophotometer. The nmr spectra were obtained on a Varian T-60 spectrometer with TMS as the internal standard. The glc work was performed with a Hewlett-Packard Prepmaster, Jr., and a Perkin-Elmer F-11. All organometallic reactions were run under a dry nitrogen atmosphere. Solvents (ether and tetrahydrofuran) were dried by distillation from sodium dispersion. The melting points and boiling points are uncorrected. Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind. The 1,2-epoxy-3-butene was obtained from Aldrich Chemical Co. The cyclohexene oxide was obtained from Matheson Coleman and Bell. The methyl- and *n*-butyllithium reagents were obtained from Foote Mineral Co., the phenyllithium was from Alfa Inorganics, and *tert*-butyllithium was from Lithcoa. The methylmagnesium reagents were prepared from magnesium turnings (Fisher) and the methyl halides by the standard procedures. Lithium dimethylcuprate was prepared according to the procedure of House[7a] utilizing cuprous iodide purchases from Alfa Inorganics, Ventron, or Matheson and purified.[25] For details of methods used in the preparation of other cuprates see ref 20.

Reactions of Metallomethyl Reagents with 1,2-Epoxy-3-butene.—A solution of the organometallic reagent (excess) was added to a solution of the oxirane followed by refluxing the mixture in ether for 24 hr. Hydrolysis was effected with saturated ammonium chloride solution and the reaction was worked up in the usual manner.

The reaction of methylmagnesium iodide with 1,2-epoxy-3-butene is representative of the general procedure. To a magnetically stirred solution of 0.361 g (5 mmol) of 1,2-epoxy-3-butene in 10 ml of ether at room temperature, there was added, with a hypodermic syringe, 5 ml of ~3 *M* methylmagnesium iodide in ether (15 mmol). An exothermic reaction occurred upon addition of the Grignard reagent. The mixture was refluxed for 24 hr, cooled, and hydrolyzed with 5 ml of saturated ammonium chloride solution. Following extraction with ether and drying over anhydrous sodium sulfate, the ether was removed by distillation.

(24) (a) R. G. Pearson, *Science*, 151, 172 (1966); (b) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967); (c) B. Saville, *Angew. Chem., Int. Ed. Engl.*, **6**, 928 (1967); (d) R. G. Pearson, *Chem. Brit.*, **3**, 103 (1967).

(25) G. B. Rauffman and L. A. Teter, *Inorg. Syn.*, **7**, 10 (1963).

TABLE III

NMR DATA FOR THE PRODUCTS FROM THE REACTION OF 1,2-EPOXY-3-BUTENE WITH METALLOMETHYL REAGENTS[a]

Registry no.	Alcohol	Vinyl	CH_3	CH_2	CH	OH
616-25-1	A	5.5 (m, 3)	0.8 (t, 3)	1.4 (m, 2)	3.9 (q, 1)	3.2 (s, 1)
625-31-0	B	5.5 (m, 3)	1.1 (d, 3)	2.1 (t, 2)	3.7 (sex, 1)	3.0 (s, 1)
4516-90-9	C	5.5 (m, 3)	1.0 (d, 3)	3.3 (d, 2)	2.2 (m, 1)	4.0 (s, 1)
1576-96-1 (*E*)	D	5.5 (m, 2)	1.0 (t, 3)	2.0 (m, 2)		4.4 (s, 1)
1576-95-0 (*Z*)				4.0 (m, 2)		

[a] Chemical shift values are given in parts per million from TMS (δ).

The reaction of lithium dimethylcuprate with 1,2-epoxy-3-butene was varied slightly in that the reaction mixture was refluxed for only 30 min.

The reaction mixtures were separated into their components by preparative glc on a 6 ft × 0.75 in., 15% Carbowax 20M, on Chromosorb W, 45–60 mesh column. The column temperature was 85° with a nitrogen flow rate of 400 ml/min.

Product distribution was determined by glc analysis utilizing a 16 ft × 0.25 in., 20% diethylene glycol succinate on Chromosorb W, 60–80 mesh column. The column temperature was 100° with a helium flow rate of 60 ml/min.

Structure assignments of the products were made on the basis of the ir and nmr spectra (Table III). The stereochemical assignment of the cis–trans mixture of 2-penten-1-ol was based on the ir spectra. Two C=C bands were observed for the mixture from each reaction, with the stronger band at 1675 cm^{-1} and the weaker band at 1660 cm^{-1}. The trans/cis ratio was then determined by capillary glc using a 50 ft × 0.020 in. i.d. Perkin-Elmer support coated open tubular (SCOT) column (Carbowax 20M) with a column temperature of 80° and a nitrogen flow rate of ~1.5 cc/min. The product distribution data and reaction parameters are presented in Table II of ref 3.

Refractive indices for the four alcohols are as follows: 1-penten-3-ol (A), $n^{25}D$ 1.4234; 4-penten-2-ol (B), $n^{25}D$ 1.4230; 2-methyl-3-buten-1-ol (C), $n^{25}D$ 1.4257; 2-penten-1-ol (D), $n^{25}D$ 1.4347.

Reactions of Metallomethyl Reagents With 1,2-Epoxy-3-butene in Diethyl Ether.—The same general procedure was used as outlined for the reactions of 1,2-epoxy-3-butene. The product mixture was analyzed and separated by glc (16 ft × 0.25 in., 10% Carbowax 20M, on Chromosorb W, 60–80 mesh column; column temperature 90°, nitrogen flow rate 60 cc/min) and the products were identified by their infrared spectra and glc retention times. The reaction parameters and results are presented in Table I of ref 3.

Reactions of Organometallic Reagents with Cycloalkene Oxides.—The reactions were carried out by adding a solution of cycloalkene oxide to a solution of the organometallic reagent. Work-up and isolation were carried out in the usual manner. Products were usually separated by glc and identified by comparison of ir spectra with those of authentic samples of the compounds. The reaction parameters and results are presented in Table I of ref 2, Table I of ref 4, and Table I of this paper.

The following reaction of lithium dimethylcuprate with cyclohexene oxide illustrates the general procedure. To a solution of 5 mmol of lithium dimethylcuprate in 21 ml of ether, at 0°, there was added dropwise with stirring 0.263 g (2.5 mmol) of cyclohexene oxide in 20 ml of ether over a 10-min period. No reaction was immediately discernible, but after a few minutes a yellow solid began to precipitate from solution. The mixture was stirred for 5 hr at 0°, then hydrolyzed by addition of 20 ml of saturated ammonium chloride solution. This mixture was stirred for 2 hr at room temperature, then the aqueous layer was separated and extracted with two 10-ml portions of ether. The combined ether extracts were washed with 10 ml of saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the product mixture was analyzed by glc (8 ft × 0.25 in., 10% Carbowax 20M, on Chromosorb W, 60–80 mesh column, column temperature 125°, helium flow rate 60 ml/min). Three peaks were obtained with retention times of 4.3, 5.5, and 8.1 min. Material was collected from the glc and ir spectra obtained for the three compounds. Comparison with the ir spectra of authentic samples confirmed the following assignments: 4.3 min (8%), cyclohexene oxide; 5.5 min (22%), cyclohexanone. The remaining peak, 8.1 min (70%), was proven to be *trans*-2-methylcyclohexanol by comparison of its ir spectrum with Sadtler ir spectrum 13371. Analysis of the *trans*-2-methylcyclohexanol on a 50 ft × 0.020 in. i.d. Perkin-Elmer diethylene glycol succinate SCOT column (column temperature 85°, nitrogen flow rate ~1.5 ml/min) showed conclusively that no *cis*-2-methylcyclohexanol was present. With the conditions used, a mixture of *cis*- and *trans*-2-methylcyclohexanol was separated cleanly into its components.

By-product from the Reaction of Lithium Di-*tert*-butylcuprate with 1,2-Epoxy-3-cyclohexene.—A white solid (~25%) was observed to precipitate out of the ethereal solution of the crude reaction product. Ice cooling of this solution, filtration of the solid, and recrystallization from ether gave white crystals: mp 161–161.5°; nmr (CCl_4) δ 5.74 (m, 2), 1.70 (m, 6), 0.90 (s, 18); ir (KBr) 3020, 1390, 1360, 770, 685 cm^{-1}; mass spectrum (70 eV) *m/e* 194 (100%), 137, 80, 57. We suggest that this material is either *cis*- or *trans*-3,6-di-*tert*-butylcyclohexene.

Reaction of Methyl 10,11-Epoxyundecanoate with Lithium Dimethylcuprate.—To a solution of 20 mmol of lithium dimethylcuprate in 77 ml of ether there was added 2.161 g (10 mmol) of methyl 10,11-epoxyundecanoate (Aldrich) in 80 ml of ether at 0°. The mixture was stirred at 0° for 13.5 hr, then hydrolyzed and worked up as described for the reaction of cyclohexene oxide with lithium dimethylcuprate. Short-path distillation of the residue gave 0.843 g (37%) of methyl 10-hydroxydodecanoate, bp 114–116° (0.02 mm), white crystals with a broad melting range at about room temperature, ir (film) 3400 and 1725 cm^{-1}.

Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.77; H, 11.40. Found: C, 68.01; H, 11.23.

Reaction of Ethyl 2,3-Epoxybutyrate with Lithium Dimethylcuprate.—To a solution of 20 mmol of lithium dimethylcuprate in 84 ml of ether at 0° there was added over 30 min a solution of 1.309 g (10 mmol) of ethyl 2,3-epoxybutyrate (Aldrich) in 80 ml of ether over 30 min. The reaction was stirred for 3 hr at 0°, then hydrolyzed and worked up as described for the reaction of cyclohexene oxide with lithium dimethylcuprate. There was obtained 1.324 g of residue which analyzed as 74.6% ethyl 2-methyl-3-hydroxybutyrate by glc analysis (8 ft × 0.25 in., 10% Versamid 940 on Chromosorb W, 60–80 mesh column, column temperature 140°, helium flow rate 60 ml/min). The yield of ethyl 2-methyl-3-hydroxybutyrate based on the glc analysis was 67%. A sample of product was collected by preparative glc (6 ft × 0.75 in., Carbowax 20M on Chromosorb W, 45–60 mesh column, column temperature 110°, nitrogen flow rate 400 cc/min), ir (film) 3500 and 1730 cm^{-1}, $n^{25}D$ 1.4245.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.50; H, 9.67. Found: C, 57.51; H, 9.68.

Reaction of Ethyl 2,3-Epoxybutyrate with Methyllithium.—To a solution of 20 mmol of methyllithium (Foote, 1 equiv of LiBr) in 84 ml of ether at 0° there was added a solution of 1.312 g (10 mmol) of ethyl 2,3-epoxybutyrate in 80 ml of ether over 30 min. The reaction was stirred for 3 hr at 0°, then hydrolyzed and worked up. Glc analysis (8 ft × 0.25 in., 10% Versamid 940 on Chromosorb W, 60–80 mesh column, column temperature 125°, nitrogen flow rate 60 ml/min) revealed a mixture consisting of 45% ethyl 2,3-epoxybutyrate, 1% ethyl 2-methyl-3-hydroxybutyrate, and 54% of a complex mixture of unidentified products.

10,11-Epoxy-2-dodecanone.—To a solution of 0.12 mol (21.5 g) of dodecen-11-one[26] in 300 ml of methylene chloride in a 1-l., three-necked flask fitted with mechanical stirrer was added portionwise 0.18 mol (30.5 g) of *m*-chloroperbenzoic acid over a 30-min period while the reaction temperature was maintained at 5–10°. After addition of the acid, the temperature was raised to ambient and stirring was maintained for 19 hr. Excess *m*-chloroperbenzoic acid was reduced with 10% aqueous potassium bisulfite. The methylene chloride layer was separated and shaken with two 200-ml portions of brine solution and then dried over anhydrous magnesium sulfate. Removal of the solvent

(26) N. A. Sorensen and J. Mehlum, *Acta Chem. Scand.*, **2**, 140 (1948).

and distillation of the oily residue gave 17.5 g (75% yield) of clear, colorless oil: bp 119–123°; mp 27–28°; ir (film) 1720, 915, 835 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.69; H, 11.18. Found: C, 71.92; H, 11.13.

Reaction of Lithium Dimethylcuprate with 10,11-Epoxy-2-dodecanone.—To a solution of 5.34 mmol of lithium dimethylcuprate in 15 ml of absolute ether at −50° was added dropwise 2.67 mmol (506 mg) of 10,11-epoxy-2-dodecanone in 30 ml of ether. Following the 10-min addition, the reaction mixture was stirred for 30 min and then quenched with 40 ml of saturated ammonium chloride solution. The reaction mixture was warmed to ambient and stirred for 0.5 hr. The ether layer was decanted, shaken with 20 ml of water and 20 ml of brine solution, and then dried over sodium sulfate. Removal of the ether and column chromatography of the residue on silica gel G using 2% ether–98% methylene chloride as eluent gave 372 mg (68% yield) of 11-hydroxy-2-tridecanone: mp 44–45° (recrystallized from hexane); ir (CCl_4) 3500, 1720, 1355, 1160 cm^{-1}.

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 72.74; H, 12.20.

Reaction of Lithium Diphenylcuprate with 2,3-Epoxy-3-methylbutyronitrile.—To a solution of 10 mmol of lithium diphenylcuprate in 20 ml of ether and 10 ml of benzene at 0° was added 2,3-epoxy-3-methylbutyronitrile[27] (485 mg, 5 mmol) in 10 ml of ether over a 10-min period. After addition was complete the mixture was stirred for an additional 20 min. The usual work-up yielded a liquid residue which upon chromatography on a silica gel column, eluting with pentane–ether, yielded 3-hydroxy-3-methyl-2-phenylbutyronitrile (295 mg, 34%) [ir (film) 3400, 2225, 1150, 730, 690 cm^{-1}, nmr ($CDCl_3$) δ 7.37 (s, 5), 3.80 (s, 1), 2.56 (s, 1), 1.30 (s, 6)] and 2,2-dimethyl-3-benzoyloxirane (50 mg, 6%) [ir (neat) 1690, 1220, 680, 700 cm^{-1}, nmr ($CDCl_3$) δ 7.8 (m, 5), 4.15 (s, 1), 1.63 (s, 3), 1.28 (s, 3)].

Reaction of Lithium Dimethylcuprate with *exo*-Norbornene Oxide.—To a solution of 0.5 mmol (95 mg) of cuprous iodide and 20.0 mmol of methyllithium in 30 ml of anhydrous dimethoxyethane at 0° under nitrogen was added dropwise with stirring 9.0 mm (0.990 g) of *exo*-norbornene oxide. The reaction was warmed to 55° and maintained there for 5 hr. The reaction mixture was cooled to 0° and hydrolyzed with 10 ml of aqueous ammonium chloride. Fifty milliliters of ether and 30 ml of water were added to the mixture and shaken. The ether layer was collected and treated consecutively with 20 ml of water, 20 ml of saturated sodium chloride solution, and solid anhydrous Na_2CO_3. Solvent removal *in vacuo* gave a white solid which after sublimation (60°, 7 mm) gave 0.65 g (58%) of *endo*-3-methyl-*exo*-2-norbornanol: mp 96–100° (lit.[28] mp 95.5–97°); ir (CCl_4) 3300, 1070 cm^{-1}.

Reaction of *exo*-norbornene oxide (9 mmol) with methyllithium (20 mmol) in 30 ml of dimethoxyethane at 70° for 5 hr resulted in a recovery of 93% of starting material and 7% conversion to *endo*-3-methyl-*exo*-2-norbornanol and a trace of norcamphor.

Reaction of Lithium Dimethylcuprate with 5α-Cholestane 2α,3α-Oxide.—To a solution of lithium dimethylcuprate (5 mmol) in 20 ml of ether at 0° was added dropwise 387 mg (1.0 mmol) of 5α-cholestane 2α,3α-oxide[29] in 20 ml of ether. After addition was completed, the reaction mixture was warmed to room temperature and allowed to stir for 24 hr. Work-up gave 341 mg of a white solid which showed two major spots on tlc on silica gel. Column chromatography on silica gel using pentane–ether as eluent gave 5α-cholestan-2-one (82 mg, 22%), mp 128.5–129.5°, $[\alpha]^{25}D$ +50.6° (*c* 1.97, EtOH) (lit.[29] mp 130°, $[\alpha]D$ +50.7°), and 2β-methyl-5α-cholestan-3α-ol (260 mg, 65%), mp 117.5–118.0°, $[\alpha]^{25}D$ +42.9° (*c* 2.0, $CHCl_3$), ir (CCl_4) 3400 cm^{-1}. Oxidation of this alcohol with chromic anhydride–pyridine gave 2β-methyl-5α-cholestan-3-one,[30] mp 98.5–99° (lit.[15] mp 97.5–98.5°), ir (CS_2) 1715 cm^{-1}, $[\alpha]^{25}D$ +122° (*c* 1.51, $CHCl_3$).

Registry No.—Lithium dimethylcuprate, 15681-48-8; lithium di-*n*-butylcuprate 24406-16-4; 1,2-epoxy-3-butene, 930-22-3; lithium di-*tert*-butylcuprate 23402-75-7; 1,2-epoxy-3-cyclohexene, 6705-51-7; 3,6-di-*tert*-butylcyclohexene, 42334-56-5; methyl 10,11-epoxyundecanoate, 22663-09-8; methyl 10-hydroxydodecanoate, 27512-78-3; ethyl 2,3-epoxybutyrate, 19780-35-9; ethyl 2-methyl-3-hydroxybutyrate, 27372-03-8; 10,11-epoxy-2-dodecanone, 42334-61-2; dodecen-11-one, 5009-33-6; 11-hydroxy-2-tridecanone, 27372-05-0; lithium diphenylcuprate, 23402-69-9; 2,3-epoxy-3-methylbutyronitrile, 6509-07-5; 3-hydroxy-3-methyl-2-phenylbutyronitrile, 42334-65-6; 2,2-dimethyl-3-benzoyloxirane, 15120-98-6.

(27) V. F. Martynov and A. V. Shchelrunov, *Zh. Obshch. Khim.*, **27**, 1188 (1957).

(28) J. A. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *J. Amer. Chem. Soc.*, **89**, 2567 (1967).

(29) A. Furst and P. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(30) Y. Mayer and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 5220 (1958).

Preparation of Organocalcium Halides in Hydrocarbon Solvents

NARIYOSHI KAWABATA,* AKIRA MATSUMURA, AND SHINZO YAMASHITA

Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606, Japan

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Contrary to the description in the literature, the reaction of alkyl halides with calcium metal in hydrocarbon solvents was found to give the corresponding alkylcalcium halides in good yields. The reaction was not restricted to primary alkyl iodides. Bromides and chlorides also afforded alkylcalcium halides. Isopropyl halides were also converted into organocalcium halides. In the reaction with *tert*-butyl halides, however, the disproportionation to form the corresponding alkane and alkene far exceeded the formation of *tert*-butylcalcium halides. The reaction of calcium with aryl halides gave arylcalcium halides in poor yields.

In the preceding paper,[1] we demonstrated that the reaction of organic halides with calcium metal in tetrahydrofuran gave the corresponding organocalcium halides in much better yields than those available in the literature. The key ingredient appeared to be the

$$RX + Ca \longrightarrow RCaX \quad (1)$$

availability of higher purity calcium metal than was previously obtainable. The lower content of sodium in the calcium metal seemed to be an important factor in this improvement. Reaction 1 was shown to be not restricted to aryl and primary alkyl iodides contrary to the description in the literature. Bromides and chlorides also afforded organocalcium halides. In addition, isopropyl halides were first converted into organocalcium halides by the reaction.

Our experimental procedure showed several additional advantages. Previous authors described various approaches to the activation of calcium metal, *e.g.*, treatment with Grignard reagent,[2] amalgamation,[3–5] use of calcium–magnesium alloy,[3] and heating with

(1) N. Kawabata, A. Matsumura, and S. Yamashita, *Tetrahedron*, **29**, 1069 (1973).

(2) Z. C. Glacet, *Bull. Soc. Chim. Fr.*, **5**, 895 (1938).

(3) D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc.*, 577 (1963).

(4) R. Masthoff, H. Schüler, and G. Krieg, *J. Organometal. Chem.*, **13**, 37 (1968).

(5) M. Chastrette and R. Gauthier, *C. R. Acad. Sci., Ser. C*, **274**, 1101, 2013 (1972).

magnesium and mercury.[6-13] Therefore, there would be some organomercury or organomagnesium compounds mixed in with their organocalcium halides. On the other hand the amount of such extraneous organometallics would be minimized under our experimental conditions, because the activation of calcium metal was not necessary.[1] The yields of organocalcium iodides by previous workers were generally low especially in the aliphatic series, and a considerable amount of calcium iodide produced by the Wurtz-type coupling was present.[5,14] This too was avoided in our case due to the more reactive calcium metal. Thus, our experimental procedure would result in the formation of organocalcium halides in much purer state than was reported before by previous authors.

Nevertheless, a serious disadvantage of reaction 1 remained unsolved, which is the use of ethereal solvents as the reaction media. Although tetrahydrofuran and other ethereal solvents are convenient media for the preparation of organocalcium halides, they are readily cleaved by organocalcium reagents. Bryce-Smith and Skinner[3] reported the half-lives of phenyl- and methylcalcium iodide at 20° in tetrahydrofuran to be 13.5 and 13 days, respectively. According to our experiments,[15,16] about 77% of methylcalcium iodide was consumed by the reaction with tetrahydrofuran during a storage of 20 hr at 28° under a nitrogen atmosphere following the procedure described previously. This calcium compound was found to be somewhat more stable at lower temperature, about 25% being consumed by the reaction during a storage of 20 hr at −70°.[16] Therefore, it is necessary to use the organocalcium halides for further reactions immediately after the preparation in tetrahydrofuran. The present study was aimed at preparing organocalcium halides both in high yields and in a more stable state.

Results and Discussion

We first attempted to prepare methylcalcium iodide in diethyl ether using the calcium metal of higher purity, since diethyl ether appeared to be cleaved less readily than tetrahydrofuran by organocalcium halides. The preparation of organocalcium halides in the absence of ethereal solvents is quite desirable, but we felt at first that the preparation would be extremely difficult, because Bryce-Smith and Skinner[3] described that no reaction could be induced in the absence of ethereal media even between the activated calcium and various organic iodides.

These authors obtained methylcalcium iodide in 37% yield by the reaction of methyl iodide with their activated calcium in refluxing diethyl ether. The reaction of methyl iodide with the calcium metal of higher purity was very slow in diethyl ether at low temperature, while the reaction in tetrahydrofuran proceeded smoothly even at −70°.[1] The reaction in diethyl ether proceeded very slowly at low temperature even after the initiation by the addition of a small amount of the organic iodide at 35°. However, the reaction proceeded smoothly at 35° to give methylcalcium iodide in 61% yield over 3 hr. The activation of calcium metal was not necessary, but the yield was lower than that of the corresponding reaction in tetrahydrofuran at −70°. Since relatively higher temperature was necessary for the reaction in diethyl ether, the Wurtz-type coupling and the cleavage of ethereal bond were rather significant.

Contrary to our expectation, the stability of methylcalcium iodide in diethyl ether was still rather low. For example, about 40% of the calcium compound was consumed by the reaction with diethyl ether during a storage of 20 hr at 28° after the preparation.

It seemed, therefore, to be absolutely necessary to carry out reaction 1 in the absence of ethereal solvent in order to obtain organocalcium halides in a stable state. Kocheshkov and coworkers[17,18] prepared several organocalcium iodides by the treatment of calcium shavings with organic iodides in ethereal solvent. They isolated solvated organocalcium iodides and removed the ethereal solvent by heating under vacuum. Such a procedure would be, however, inconvenient for the practical use of organocalcium halides in organic syntheses.

Contrary to the description in the literature, we found that reaction 1 proceeded smoothly in toluene or benzene to give alkylcalcium halides in good yields when the higher purity calcium metal was used. The initiation of the reaction was not difficult, and the activation of calcium metal was not necessary even in toluene and benzene. Although a higher reaction temperature was necessary, the Wurtz-type coupling was not significant under our reaction conditions. Generally, a small amount of alkyl halide remained unchanged in the reaction mixture at the end of our preparation of alkylcalcium halide. Reaction 1 in the hydrocarbon solvents was found not to be restricted to primary alkyl iodides. Bromides and chlorides also afforded the corresponding organocalcium halides. Isopropyl halides were also converted into the corresponding organocalcium halides in good yields by the reaction in toluene. These alkylcalcium halides were found to be insoluble in hydrocarbon solvents.

It would be noteworthy that reaction 1 with isopropyl bromide in toluene proceeded smoothly without initiation by the addition of a small amount of the corresponding iodide. Isopropyl bromide appeared to be more reactive than *n*-propyl bromide in the reaction. Usually, organic bromides and chlorides are much less reactive than the corresponding iodides, and the initiation of reaction 1 by the addition of a small amount of the corresponding iodide is helpful. We adopted this

(6) L. N. Cherkasov, G. I. Pis'mennaya, Kh. V. Bal'yan, and A. A. Petrov, *Zh. Org. Khim.*, **6**, 1758 (1970).

(7) L. N. Cherkasov, G. I. Pis'mennaya, and Kh. V. Bal'yan, *Zh. Vses. Khim. Obshchest.*, **16**, 591 (1971); *Chem. Abstr.*, **75**, 151002b (1971).

(8) L. N. Cherkasov, *Zh. Org. Khim.*, **7**, 1319 (1971).

(9) L. N. Cherkasov, *Zh. Obshch. Khim.*, **41**, 1561 (1971).

(10) L. N. Cherkasov, S. I. Radchenko, G. I. Pis'mennaya, and Kh. V. Bal'yan, *Zh. Org. Khim.*, **7**, 1111 (1971).

(11) L. N. Cherkasov, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tecknol.*, **14**, 1117 (1971); *Chem. Abstr.*, **75**, 140173g (1971).

(12) L. N. Cherkasov, *Zh. Obshch. Khim.*, **42**, 1528 (1972).

(13) L. N. Cherkasov, *Zh. Vses. Khim. Obshchest.*, **17**, 111 (1972); *Chem. Abstr.*, **76**, 99010g (1972).

(14) R. Masthoff and Ch. Vieroth, *J. Prakt. Chem.*, **38**, 182 (1968).

(15) N. Kawabata, H. Nakamura, and S. Yamashita, *J. Org. Chem.*, **38**, 3403 (1973).

(16) N. Kawabata, A. Matsumura, and S. Yamashita, unpublished results.

(17) K. A. Kocheshkov, N. I. Sheverdina, and M. A. Zemlyanichenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2090 (1969).

(18) M. A. Zemlyanichenko, N. I. Sheverdina, I. M. Viktorova, V. A. Chernoplekova, N. P. Barminova, and K. A. Kocheshkov, *Dokl. Akad. Nauk SSSR*, **194**, 95 (1970).

technique throughout the preparation of organocalcium bromides and chlorides in tetrahydrofuran.[1]

On the other hand, the disproportionation to form the corresponding alkane and alkene was an important side reaction in reaction 1 with *tert*-butyl halides in toluene, and the yields of *tert*-butylcalcium halides were negligible as in the corresponding reaction in tetrahydrofuran.[1] Reaction 1 with benzyl halides in benzene gave the corresponding organocalcium halides in poor yields. Wurtz-type coupling was an important side reaction in this case.

The hydrocarbon solvents useful for reaction 1 are not restricted to aromatic compounds. We found that reaction 1 with several alkyl iodides proceeded smoothly in cyclohexane to give the corresponding alkylcalcium iodides in good yields. Initiation of the reaction was not difficult and the activation of calcium metal was again not necessary.

Unlike reaction 1 in hydrocarbon solvents with alkyl halides, that with aryl halides gave the corresponding organocalcium halides in poor yields. For example, the reaction of calcium with iodobenzene in toluene at 100° for 91 hr gave a trace of phenylcalcium iodide, and almost all of the iodobenzene remained unchanged in the reaction system. The reaction at 180° for 30 hr in tetralin gave phenylcalcium iodide but in only 15% yield. This is a disadvantage of reaction 1 in hydrocarbon solvents. Some of the main results are given in Table I.

TABLE I
PREPARATION OF ORGANOCALCIUM HALIDES BY REACTION 1 IN HYDROCARBON SOLVENTS[a]

Halide, RX	Registry no. (RX)	Solvent	Temp, °C	Time, hr	Yield, %[b]	Registry no. (RCaX)
CH_3I	74-88-4	Toluene	40	25.5	61–68[e]	20458-43-9
CH_3I		Toluene	40	43	77–84[e]	
CH_3I		Cyclohexane	40	43	71–76[f]	
C_2H_5I	75-03-6	Toluene	60	27	64	20458-44-0
C_2H_5I		Cyclohexane	60	45	70	
n-C_3H_7I	107-08-4	Toluene	95	41	88	20458-45-1
n-C_3H_7I		Cyclohexane	75	44	77	
n-C_3H_7Br[c]	106-94-5	Toluene	65	29	72	42282-72-4
n-C_3H_7Br[d]		Toluene	65	48	Trace	
n-C_3H_7Cl[c]	540-54-5	Toluene	45	46	50	42282-73-5
n-C_3H_7Cl[d]		Toluene	45	48	Trace	
i-C_3H_7I	75-30-9	Toluene	85	28	78	42177-27-5
i-C_3H_7Br[c]	75-26-3	Toluene	55	45	75	42398-30-1
i-C_3H_7Br[d]		Toluene	55	48	66	
i-C_3H_7Cl[c]	75-29-6	Toluene	33	47	75	42282-75-7
t-C_4H_9I		Toluene	95	17	0	
t-C_4H_9Cl[c]		Toluene	70	19	0	
$C_6H_5CH_2I$	620-05-3	Benzene	90	99	6	42282-76-8
$C_6H_5CH_2Br$[c]	100-39-0	Benzene	90	145	6	42282-77-9
$C_6H_5CH_2Cl$[c]	100-44-7	Benzene	90	94	2	42282-78-0
C_6H_5I	591-50-4	Toluene	120	96	3	24488-76-4
C_6H_5I		Toluene	160	46	3	
C_6H_5I		Tetralin	180	30	15	
C_6H_5Br[c]	108-86-1	Toluene	160	45	5	42282-79-1
C_6H_5Cl[c]	108-90-7	Toluene	130	43	3	42282-80-4

[a] Reaction conditions: organic halides, 5.0 mmol; calcium, 6.5 mmol; solvent, 10 ml. [b] Based on the organic halide. [c] In these cases, reaction 1 was initiated by the addition of 1 mol % of the corresponding iodides, respectively. [d] The initiation by the addition of the corresponding iodides was not adopted. [e] Three runs were carried out. [f] Two runs were carried out.

Experimental Section

Vapor phase chromatographic analyses were performed on a Shimadzu GC-4A gas chromatograph.

Materials.—Benzyl and *tert*-butyl iodides were prepared by a conventional procedure.[19] Commercial products of the other organic halides were purified by usual methods.[20] Calcium metal of higher purity was provided by Mitsuwa Chemicals, Ltd., Osaka. As was described in the preceding paper,[1] the calcium contained 0.493% magnesium and 0.0019% sodium. The calcium was rasped in dry liquid paraffin. Nitrogen was purified by passing through a tube containing copper turnings in a furnace at 170° followed by drying with phosphorus pentoxide. Tetrahydrofuran, diethyl ether, benzene, toluene, tetralin, and cyclohexane were purified by distillation in the presence of benzophenone sodium ketyl under a nitrogen atmosphere. Other chemicals were commercial products and were used without further purification.

Preparation of Organocalcium Halides by Reaction 1 in Hydrocarbon Solvents (General Procedure).—The reaction vessel was a two-necked flask equipped with two three-way cocks. Each three-way cock was connected with a nitrogen inlet and a rubber serum cap. The rasped calcium was placed in the flask. The reaction vessel was evacuated and filled with dry nitrogen, and the calcium was washed with the hydrocarbon used as the solvent for reaction 1 under a nitrogen atmosphere.

In the preparation of organocalcium iodides, about 1% of a solution of organic iodide (5.0 mmol) in the solvent (3.0 ml) was added *via* a hypodermic syringe at the prescribed temperature to this rasped calcium (0.26 g, 6.5 mmol) in the solvent (5.0 ml) without stirring. The mixture did not show the change in color noted in the preparation in tetrahydrofuran. After about 0.5 hr, 2.0 ml of the solvent was added. The rest of the organic iodide was then added *via* a hypodermic syringe over a period of 1 hr while stirring at the same temperature. Stirring was continued for several hours at this temperature. The reaction system afforded a fine black powder as the reaction proceeded. After the preparation, organocalcium iodide was decomposed by the addition of methanol, acetic acid, or a 2:1 mixture (volume ratio) of water and ethanol to the reaction mixture, and the products were analyzed. In the case of methyl, ethyl, and propyl derivatives, the total amount of the gas evolved after the decomposition was determined by a gas buret. The gas was analyzed by vapor phase chromatography. The gas usually contained a small amount (less than 1 mol %) of hydrogen. In other cases, the amount of hydrocarbon evolved after the decomposition was determined by vapor phase chromatography. Yield of organocalcium iodides was determined by the amount of hydrocarbon evolved after the decomposition.

Preparation of organocalcium bromides and chlorides was carried out in a similar manner. In some cases, however, the reaction was initiated by the addition of 1 mol % of the corresponding iodide. Such an initiation was very helpful in the preparation of *n*-propylcalcium bromide and chloride, but was not necessary in the preparation of isopropylcalcium bromide.

Preparation of Methylcalcium Iodide in Ether.—About 1% of a solution of methyl iodide (5.0 mmol) in diethyl ether (3.0 ml) was added at 35° without stirring. After the reaction started, 2.0 ml of the ether was added, and the remainder of methyl iodide was slowly added to the reaction system. Three runs of the preparation at 35° for 1.5 hr gave methylcalcium iodide in 54% yield in each case. The preparation at 35° for 3 hr gave the compound in 61% yield.

Registry No.—Calcium, 7440-70-2.

(19) H. Stone and H. Shechter, *Org. Syn.*, **31**, 31 (1951).

(20) J. A. Riddick and W. B. Bunger, "Organic Solvents," 3rd ed, Wiley-Interscience, New York, N. Y., 1970.

Organosilicon Compounds. XVIII. Silicon-Containing Dianhydrides

J. R. PRATT AND SHELBY F. THAMES*

University of Southern Mississippi, Polymer Science Department, Hattiesburg, Mississippi 39401

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Four new silicon-containing dianhydrides, bis(3,4-dicarboxyphenyl)dimethylsilane dianhydride (**4a**), bis(2,3-dicarboxyphenyl)dimethylsilane dianhydride (**6**), 1,4-bis(3,4-dicarboxyphenyldimethylsilyl)benzene dianhydride (**10**), and 1,3-bis(3,4-dicarboxyphenyl)-1,1,3,3-tetramethyldisiloxane dianhydride (**14**), were prepared by aqueous potassium permanganate–pyridine oxidations of corresponding tetramethyl intermediates to form tetracarboxylic acids, which were dehydrated to the dianhydrides.

The number of aromatic dianhydrides suitable for the synthesis of thermally stable polyimides is limited.[1] We have been interested in preparing new silicon-containing polyimide precursors, as methyl- and phenyl-substituted silanes have been reported to provide polymeric materials possessing good thermal and thermooxidative stabilities with good mechanical properties.[2,3] Furthermore, our experience has shown that the incorporation of silicon increases the solubility of polymers in organic solvents. Thus, this work represents an attempt to provide useful silicon-containing polyimide precursors. The synthesis of four new silicon-containing dianhydrides is reported herein.[4]

Results and Discussion

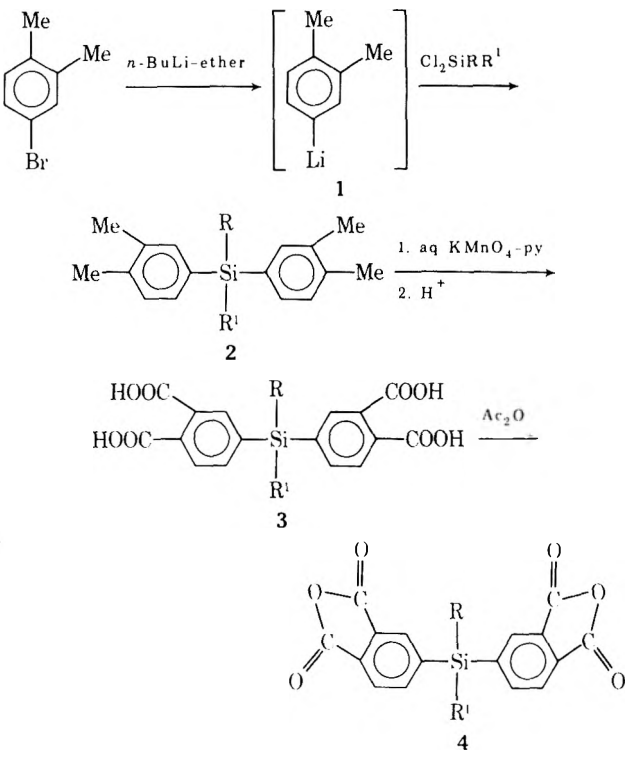
The preparation of **4** (Scheme I) was achieved by first treating *n*-butyllithium with 4-bromo-*o*-xylene *via* halogen–metal interchange to form 4-lithio-*o*-xylene (**1**). Treatment of 2 mol of **1** with 1 mol of the appropriate dichloro disubstituted silane produced the tetramethyl derivative (**2**). Aqueous potassium permanganate–pyridine oxidation of **2a** gave, after neutralization, the tetracarboxylic acid **3a**, which was then dehydrated in refluxing acetic anhydride to the dianhydride **4a**.

This oxidation is unusual in that it represents one of the few reported cases in which a tetramethyl aromatic compound has been completely oxidized to its tetracarboxylic acid with aqueous permanganate.

We were unable to prepare **3b** or **3c**. In each case a colorless, oily material or a low- and broad-melting solid which resisted purification was isolated. Likewise, we were unable to acquire pure dianhydride from the attempted cyclization of these two crude carboxylic acids. Our contention is that incomplete oxidation of aromatic methyl groups is affording a product mixture which has, to date, defied purification. This tenet was confirmed by the appearance of significant amounts of benzylic protons from unoxidized aromatic methyl groups in the nmr spectra of **3b** and **3c**.

Crude **3b** and **3c** both showed a strong ir siloxane stretch at 1060 and 1050 cm^{-1}, respectively. For this reason the possibility of nucleophilic attack on silicon–aromatic bonds of **3b** and **3c** (but not **3a**) by the OH^- produced during the $KMnO_4$ oxidation has not been ruled out. The mild electron withdrawal of the phenyl substituent would be expected to enhance nucleophilic attack on silicon by polarizing the silicon–phenyl bonds.

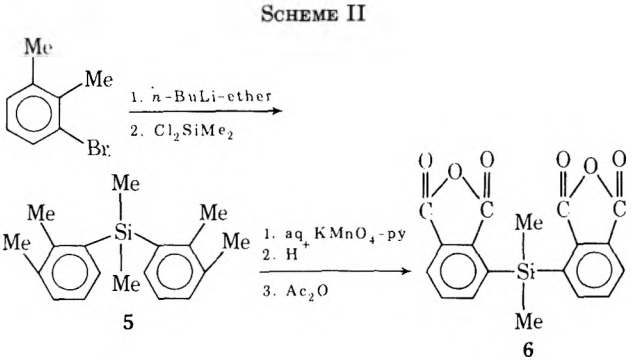
SCHEME I



a. R = R' = Me
b. R = Me; R' = Ph
c. R = R' = Ph

An isomer of **4a** (Scheme II) was produced in a similar fashion. The reaction of 3-bromo-*o*-xylene with *n*-butyllithium in ether, followed by dichlorodimethylsilane, formed bis(2,3-dimethylphenyl)dimethylsilane (**5**), which was oxidized to the tetracarboxylic acid as

SCHEME II



(1) C. E. Sroog, *J. Polym. Sci., Part C*, **16**, 1191 (1967).

(2) R. J. H. Voorhoeve, "Organohalosilanes, Precursors to Silicones," Elsevier, New York, N. Y., 1967, p 288.

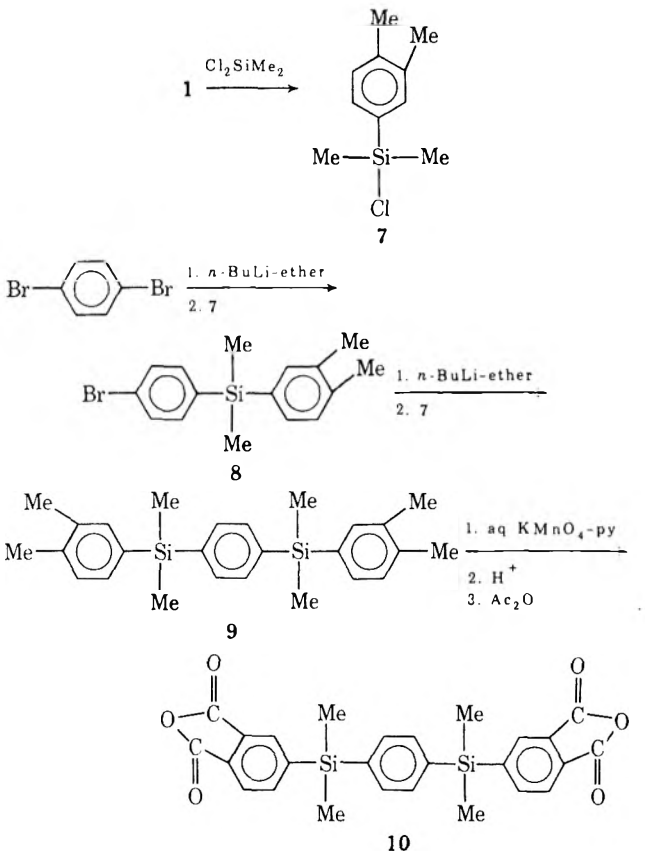
(3) H. N. Kovacs, A. D. Delman, and B. B. Simms, *J. Polym. Sci., Part A-1*, **6**, 2103 (1968).

(4) The polymerization of **4a**, **10**, and other silicon-containing precursors to polyimides was reported: N. J. Johnston and R. A. Jewel, Abstracts, 165th National Meeting of the American Chemical Society, Dallas, Tex., April 1973, ORPL-169.

before with permanganate and subsequently dehydrated to form the dianhydride **6**.

A dianhydride of higher silicon content was synthesized according to Scheme III. The starting material, chlorodimethyl(3,4-dimethylphenyl)silane (**7**), was prepared by the inverse addition (1:1) of 4-lithio-*o*-xylene to dichlorodimethylsilane at 0°. Although we were unable to purify **7** *via* vacuum distillation for a correct elemental analysis, it was of sufficient purity to be successfully employed in reactions with lithio species. Thus, by the stepwise formation of lithio species from *p*-dibromobenzene, followed by treatment with **7**, a third tetramethyl derivative (**9**) was prepared, which was then oxidized to the tetracarboxylic acid and dehydrated to the dianhydride **10**. The direct synthesis of **9** from *p*-dibromobenzene *via* the *p*-dilithio species led to a low yield (9%) of this material.

SCHEME III



The attempted synthesis of a thiophene-containing tetracarboxylic acid (**15**) *via* a similar aqueous permanganate–pyridine oxidation led to cleavage of the two silicon–thienyl bonds and isolation of the siloxane **13**, which was then dehydrated to the dianhydride **14** (Scheme IV). The cleavage of the silicon–thienyl bonds was not entirely unexpected, in view of the known instability of α-silyl heterocycles to potassium hydroxide solution in refluxing ethanol–dioxane–water.[5] The production of electron-withdrawing carboxylic acid salt groups as the oxidation progressed, no doubt, facilitated this cleavage reaction.[6]

We are continuing our efforts to synthesize silicon-containing dianhydrides, particularly the highly phenylated materials.

Experimental Section

General.—Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined on a Varian A-60D spectrometer using tetramethylsilane as the internal standard in CCl_4 unless otherwise specified at concentrations of approximately 30% by weight and are reported in parts per million. Microanalysis for silicon was performed by Galbraith Laboratories, Inc., Knoxville, Tenn.; all other analyses were performed by Chemalytics, Inc., Tempe, Ariz.

We have not reported analytical or spectral data on the tetracarboxylic acid, as we were unable in some cases to purify these materials. However, spectral data from the crude materials corresponded in all cases to those of the proposed structures.

Tables I and II contain experimental summaries of the tetramethylsilanes and the dianhydrides. In addition we have included a detailed procedure of typical syntheses.

Bis(3,4-dimethylphenyl)dimethylsilane (2a).—To a stirred solution of 4-bromo-*o*-xylene (185.1 g, 1 mol) in anhydrous ether (500 ml) was added *n*-butyllithium (424 ml, 1 mol) 2.36 *M* in hexane dropwise at 0° under nitrogen. After a 5-hr reaction period at ambient temperature, dichlorodimethylsilane (60.6 ml, 0.5 mol) was added dropwise. This solution was allowed to stir overnight before the LiCl was removed by filtration and the ether was removed *in vacuo*. Distillation afforded 90.4 g (68%) of **2a**, bp 120–124° (0.29 mm), which solidified on cooling, mp 51–54°. One recrystallization from ethyl acetate afforded pure **2a**, mp 54–56° (lit.[7] mp 54.5–55.5°).

Bis(3,4-dicarboxyphenyl)dimethylsilane Dianhydride (4a).—To a refluxing solution of **2a** (26.8 g, 0.1 mol) in pyridine (400 ml) and water (110 ml) was added $KMnO_4$ (190 g, 1.2 mol) portionwise to maintain a slow reflux. The solution was then refluxed for 1 hr before methanol (10 ml) was added to destroy any unreacted permanganate. After suction filtration of the MnO_2, followed by washing with boiling water, the pyridine was boiled off, adding water when necessary to prevent boiling to dryness. Acidification with 3 *N* HCl to pH 1 gave 30.2 g of crude tetracarboxylic acid **3a**, which was not recrystallized but cyclicized directly as follows.

Crude **3a** (18.2 g) was slowly refluxed for 1 hr with 60 ml of acetic anhydride, taking care to prevent discoloration caused by overheating. Following a vacuum distillation of the solvents, the product was recrystallized from benzene–hexane to afford 9.6 g (45%, based on **2a**) of **4a**, mp 180.5–181°.

Chlorodimethyl(3,4-dimethylphenyl)silane (7).—To a solution of 4-bromo-*o*-xylene (80.0 g, 0.43 mol) in anhydrous ether (180 ml) was added dropwise *n*-butyllithium (191 ml, 0.43 mol) 2.25 *M* in hexane at 0° under nitrogen. Following this 3-hr addition period the solution was allowed to warm to ambient temperature for an additional 3-hr period before it was inversely added dropwise to dichlorodimethylsilane (52.4 ml, 0.43 mol). After the usual work-up under anhydrous conditions, distillation afforded 47.6 g (56%) of crude **7**, bp 123–130° (31 mm), $n^{21}D$ 1.5157. Although this material could not be purified by fractional distillation for a correct elemental analysis, **7** was of sufficient purity to be utilized in the reaction with lithio species (see **8**, **9**, **11**, and **12**): nmr (CCl_4) δ 7.0–7.45 (3 H, m, aryl CH), 2.2 (6 H, s, aryl CH_3), 0.6 (6 H, s, silyl CH_3); ir (neat) 1248, 780 cm^{-1} (silyl CH_3).

Dimethyl(3,4-dimethylphenyl)(*p*-bromophenyl)silane (8).—To a solution of *p*-dibromobenzene (119 g, 0.5 mol) in anhydrous ether (450 ml) at −70° was added *n*-butyllithium (214 ml, 0.5 mol) 2.36 *M* in hexane dropwise. After the solution was stirred at −70° for an additional 6 hr, **7** (100 g, 0.5 mol) was added dropwise and the resultant solution was then allowed to stir overnight at ambient temperature. Following the usual work-up, fractionation afforded 128 g (80%) of **8**: bp 120–124° (0.03 mm);

(5) R. H. Meen and H. Gilman, *J. Org. Chem.*, **20**, 73 (1955).

(6) V. Bazant, V. Chvalovsky, and J. Rathousky, "Organosilicon Compounds," Vol. 1, Academic Press, New York, N. Y., 1965, p 233.

(7) A. V. Topchiev, N. S. Nametkin, C.-L. Gu, and N. A. Leonova, *Dokl. Akad. Nauk SSSR*, 118, 731 (1958); *Chem. Abstr.*, **52**, 11769i (1958).

SCHEME IV

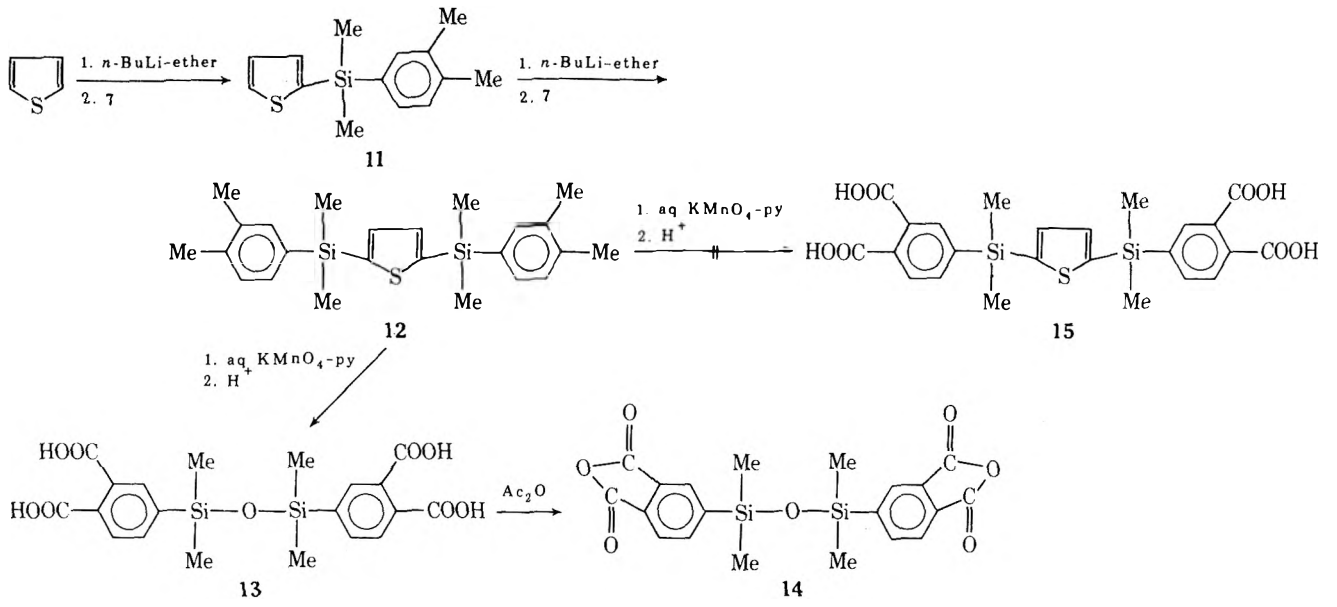


TABLE I[d]

EXPERIMENTAL SUMMARY OF ALKYL ARYL SILANES

Compd	Yield, %	Mp, °C	Bp, °C (mm)	$n^{27}D$	Nmr, δ (assignment)	Ir, cm^{-1} (assignment)
2a	68	54–56[e]			6.9–7.35 (6 H, m, aryl CH), 2.15 (12 H, s, aryl CH_3), 0.45 (6 H, s, silyl CH_3)	1260, 805 (silyl CH_3)[b]
2b	55	50.5–54.5			6.9–7.65 (11 H, m, aryl CH), 2.25 (12 H, s, aryl CH_3), 0.75 (3 H, s, silyl CH_3)	1420, 1088, 695 (silyl phenyl), 1240, 774 (silyl CH_3)[c]
2c	61	100–102			6.65–8.0 (16 H, m, aryl CH), 2.2 (12 H, s, aryl CH_3)	1422, 1098, 698, (silyl phenyl)[c]
5	29		106 (0.005)	1.5645	6.9–7.55 (6 H, m, aryl CH), 2.25 (12 H, s, aryl CH_3), 0.55 (6 H, s, silyl CH_3)	1249, 811 (center of multiplet, silyl CH_3)[b]
9	61	88–89			7.4 (4 H, s, aryl CH), 6.9–7.35 (6 H, m, aryl CH), 2.2 (12 H, s, aryl CH_3), 0.5 (12 H, s, silyl CH_3)	1240, 803 (silyl CH_3)[c]
11	36		107 (0.04)	1.5651	6.9–7.55 (6 H, m, aryl CH), 2.2 (6 H, s, aryl CH_3), 0.5 (6 H, s, silyl CH_3)	1254, 805 (silyl CH_3)[b]
12	77	57.5–58			6.95–7.4[a] (8 H, m, aryl CH), 2.25 (12 H, s, aryl CH_3) 0.55 (12 H, s, silyl CH_3)	1245, 796 (silyl CH_3)[c]

[a] DMSO-d_6. [b] Neat. [c] KBr. [d] Satisfactory analytical data for carbon and hydrogen were reported for all compounds listed in the table except **2a**, which is known. [e] Reference 7.

TABLE II[e]

EXPERIMENTAL SUMMARY OF SILICON-CONTAINING DIANHYDRIDES

Compd	Yield, %[a]	Mp, °C	Nmr, δ (assignment)	Ir,[d] cm^{-1} (assignment)
4a	45	180.5–181	8.05–8.15[b] (6 H, m, aryl CH), 0.8 (6 H, s, silyl CH_3)	1855 and 1765 (anhydride carbonyl), 1240 and 803 (silyl CH_3)
6	19	181.5–182	8.05–8.2[b] (6 H, m, aryl CH), 0.8 (6 H, s, silyl CH_3)	1855 and 1760 (anhydride carbonyl), 1240 and 810 (silyl CH_3)
10	35	199–200.5	7.95–8.35[c] (6 H, m, aryl CH), 7.7 (4 H, s, aryl CH), 0.7 (12 H, s, silyl CH_3)	1845 and 1770 (anhydride carbonyl), 1240 and 790 (silyl CH_3)
14	21	137–138	7.9–8.35[b] (6 H, m, aryl CH), 0.5 (12 H, s, silyl CH_3)	1850 and 1780 (anhydride carbonyl), 1250 and 795 (silyl CH_3), 1088 (siloxane)

[a] Based on the tetramethyl derivative. [b] $CDCl_3$–TMS. [c] Acetone-d_6–TMS. [d] KBr pellet. [e] Satisfactory analytical data for carbon and hydrogen were reported for all compounds listed in the table; in addition **4a** and **14** checked for silicon and **14** contained no sulfur.

$n^{26}D$ 1.5822; nmr (CCl_4) δ 7.35 (4 H, s, aryl CH), 7.05–7.3 (3 H, m, aryl CH), 2.2 (6 H, s, aryl CH_3), 0.5 (6 H, s, silyl CH_3); ir (neat) 1242, 795 cm^{-1} (silyl CH_3).

Acknowledgment.—We gratefully acknowledge the advice and encouragement of Drs. Norman Johnston and Vernon Bell of NASA, Langley Research Center, Hampton, Va. We are particularly grateful to NASA for making this investigation possible *via* NASA Grant 25-005-005-008. We also express appreciation to Dr. W. H. Daudt, Dow Corning Corp., for the organosilicon reagents.

Registry No.—2a, 18057-66-4; 2b, 42297-15-4; 2c, 42297-16-5; 3a, 42297-17-6; 4a, 42297-18-7; 5, 42297-19-8; 6, 42297-20-1; 7, 42297-21-2; 8, 42297-22-3; 9, 42297-23-4; 10, 42297-24-5; 11, 42297-25-6; 12, 42297-26-7; 13, 42297-27-8; 14, 42297-28-9; 4-bromo-*o*-xylene, 583-71-1; dichlorodimethylsilane, 75-78-5; dichloromethylphenylsilane, 149-74-6; dichlorodiphenylsilane, 80-10-4; 3-bromo-*o*-xylene, 576-23-8; *p*-dibromobenzene, 106-37-6; thiophene, 110-02-1.

Reactions of Alkyl Siliconium Ions under Chemical Ionization Conditions

T. J ODIORNE, D. J. HARVEY, AND PAUL VOUROS*

Institute for Lipid Research, Baylor College of Medicine, Houston, Texas 77025

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The chemical ionization mass spectra of the trimethylsilyl derivatives of various types of compounds have been determined in tetramethylsilane reagent gas. Data are presented showing the occurrence of intermolecular exchange reactions between sample trimethylsilyl groups and reagent gas ions, and involving part or all of the sample trimethylsilyl moiety. The extent of interaction between reagent siliconium ions and sample molecules is strongly influenced by steric effects.

In recent years there has been a growing interest in the chemistry of organosilicon compounds as applied to biochemistry and analytical organic chemistry. Most of this interest stems from the technique of trimethylsilylation, *i.e.*, replacement of labile hydrogens in organic compounds with trimethylsilyl groups for the purpose of application in gas chromatography–mass spectrometry.[1] The mass spectra of trimethylsilyl derivatives frequently exhibit rearrangements explainable by silyl cation attack on an electronegative center.[2] Indicative of the high reactivity of the siliconium center, these rearrangements have been shown to occur both intra- and intermolecularly.[3] We have taken advantage of the latter property by utilizing tetramethylsilane as a reagent gas in chemical ionization mass spectrometry.[4] Siliconium ions were produced at high pressures (0.1–0.5 Torr) from this gas and the resulting chemical ionization mass spectra were usually characterized by the predominance of the $[M + 73]^+$ adduct ions. This corresponds to the addition of a trimethylsiliconium ion $[(CH_3)_3Si]^+$. Other abundant adduct ions have also been observed at $[M + 131]^+$ and $[M + 145]^+$ corresponding to the addition of $(CH_3)_3Si{-}Si^+(CH_3)_2$ and $(CH_3)_3Si{-}Si^+(CH_3)_2(CH_2)$, respectively.

In our preliminary experiments we were able to obtain chemical ionization mass spectra in tetramethylsilane using microgram quantities of a variety of organic compounds, including steroids and prostaglandins.[4,5] Because of this demonstrated high reactivity of the siliconium ion there exists a good possibility for application to the analysis of biological compounds. In view of the fact that the vapor-phase analysis of many such compounds is conducted with their trimethylsilyl derivatives, it seemed logical to acquire some additional information about any interaction between sample trimethylsilyl groups and alkylsiliconium ions from the reagent, especially since considerable structural information is carried by ions containing the trimethylsilyl moiety.[6]

Results and Discussion

The extent of interaction between the reagent gas and sample is indicated not only by adduct ion formation, but also by the occurrence of silyl group exchange between the reagent gas and the trimethylsilyl group of the sample. Assessment of this interaction was made by using perdeuteriotrimethylsilyl derivatives of the sample.[7] The lability of the sample trimethylsilyl group possibly influences the amount and type of interaction, and as a consequence we investigated the reactions of two general types of trimethylsilyl groups, ethereal and the more labile acidic group. Compounds chosen from the first category included the perdeuteriotrimethylsilyl and/or trimethylsilyl derivatives of *n*-tetradecanol (**1**), *n*-hexadecanol (**2**), *n*-docosanol (**3**), 2-tetradecanol (**4**), 5-hexadecanol (**5**), and 5α-androstan-17β-ol (**6**). Compounds **1–3** contained a primary trimethylsilyloxy function whereas **4–6** had a secondary trimethylsilyloxy group. Compounds in the second category included the derivatives of *n*-tetradecanoic acid (**7**), L-α-glycerophosphate (**8**), phenylphosphonic acid (**9**), and benzylphosphonic acid (**10**).

Exchange Reactions.—Figure 1 shows the chemical ionization mass spectra of the trimethylsilyl derivative of *n*-tetradecanol (**1**, Figure 1a) and of its perdeuteriotrimethylsilyl analog (Figure 1b), obtained in tetramethylsilane reagent gas under similar conditions.

(1) A. E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Co., Rockford, Ill., 1968.

(2) See, for example, (a) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **34**, 3147 (1969); (b) W. P. Weber, R. A. Felix, and A. K. Willard, *J. Amer. Chem. Soc.*, **91**, 6544 (1969); (c) P. D. Woodgate, R. T. Gray, and C. Djerassi, *Org. Mass Spectrom.*, **4**, 257 (1970); (d) E. White, S. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **93**, 6340 (1971); (e) W. P. Weber, R. A. Felix, A. K. Willard, and H. G. Boettger, *J. Org. Chem.*, **36**, 4060 (1971), and references cited therein.

(3) (a) D. J. Harvey, M. G. Horning, and P. Vouros, *Chem. Commun.*, 898 (1970); (b) D. J. Harvey, M. G. Horning, and P. Vouros, *Anal. Lett.*, **3**, 489 (1970).

(4) T. J Odiorne, D. J. Harvey, and P. Vouros, *J. Phys. Chem.*, **76**, 3217 (1972).

(5) D. M. Desiderio, B. S. Middleditch, and P. Vouros, *Chim. Chron.*, in press.

(6) J. Diekman and C. Djerassi, *J. Org. Chem.*, **32**, 1005 (1967).

(7) J. A. McCloskey, R. N. Stillwell, and A. M. Lawson, *Anal. Chem.*, **40**, 233 (1968).

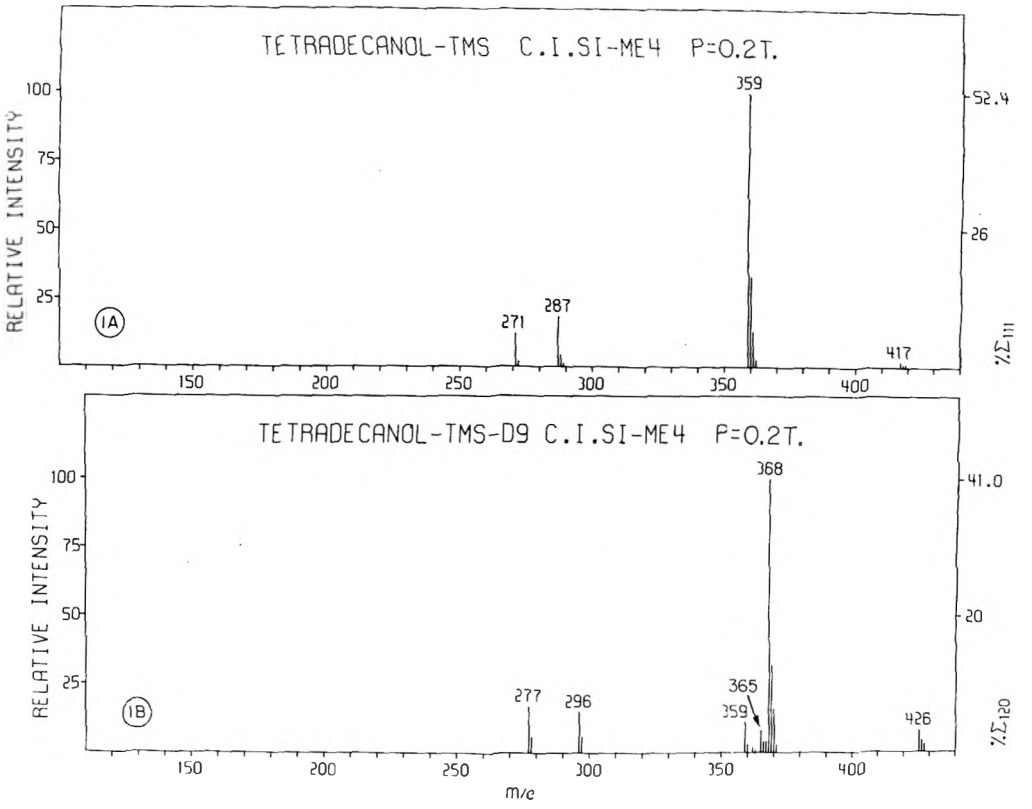
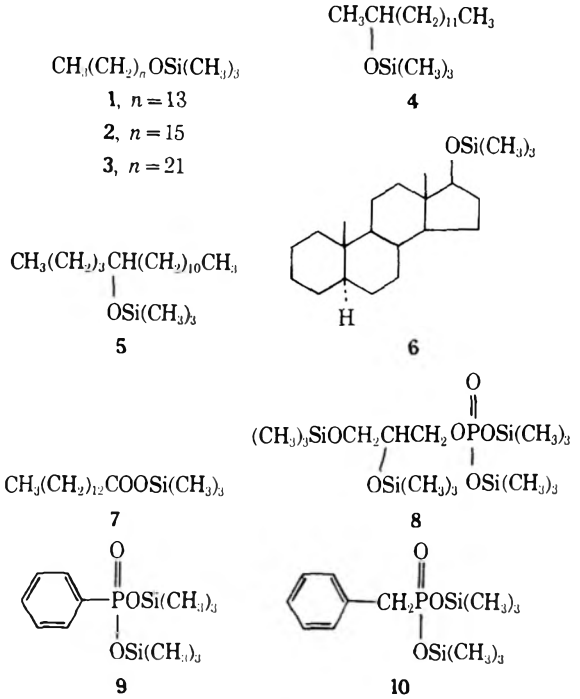


Figure 1.—The chemical ionization mass spectra with tetramethylsilane as the reagent gas of (a) the trimethylsilyl derivative of *n*-tetradecanol and (b) the perdeuteriotrimethylsilyl derivative of *n*-tetradecanol.



The $[M + 73]^+$ ion (*m/e* 359, Figure 1a) carries approximately 80% of the total ion current and a further 14% is carried by the $[M + 1]^+$ peak at *m/e* 287. Elimination of either CH_4 from $[M + 1]^+$ or $Si(CH_3)_4$ from $[M + 73]^+$ yields the peak at *m/e* 271 and both processes were indeed confirmed by metastable defocussing. Finally, the peak at *m/e* 417 corresponds to the $[M + 131]^+$ adduct ion. The spectrum (Figure 1b) of the perdeuteriotrimethylsilyl derivative showed the expected nine mass unit shift in the principal ions in agreement with sample analysis by electron impact mass spectrometry, which had indicated a perdeuteration greater than 99.9%. In addition, however, peaks were observed at *m/e* 359 and 365 corresponding to exchange of an entire trimethylsilyl group and of a methyl group, respectively. A much smaller peak at *m/e* 362 indicated exchange of two methyls of the silyl-d_9 function. Similar results were obtained with the other primary trimethylsilyl ethers **2** and **3**. This exchange was evident in mass spectra recorded at various ion source pressures ranging from 0.045 to 0.400 Torr.

Table I summarizes the types of exchange observed in the chemical ionization mass spectra of compounds **1–10**. The numbers in Table I should be taken as qualitative indicators, rather than precise measurements. In all cases where accurate intensity measurements could be made there was definite evidence for exchange of an entire silyl-d_9 function in the $[M + 1]^+$ and $[M + 73]^+$ adduct ions. It is of interest to note that in the spectra of the secondary trimethylsilyloxy derivatives (**4–6**) there was a marked decrease in the abundance of the $[M + 73]^+$ ions, coupled with a sharp increase in the relative intensity of $[M + 1]^+$. The latter ion in the spectra of **4–6** exhibited exchange of an intact silyl-d_9 function but no d_3-methyl exchange. In the spectra of compounds **7–10**, which contain more labile silyl functions, there was a measurable exchange of the entire silyl-d_9 groups but no detectable silyl methyl scramble with the reagent gas. Progressively decreasing in relative intensity, multiple silyl-d_9 exchanges were evident in compounds containing two or more trimethylsilyl groups (**8–10**).

The nonthermal nature of the observed group exchanges was confirmed by simulating the ion source conditions (less ionization) in an experiment which in-

TABLE I
TYPES OF EXCHANGE IN THE $[M + 1]^+$ AND $[M + 73]^+$ ADDUCT IONS OF THE PERDEUTERIOTRIMETHYLSILYL ANALOGS OF 1-10[a]

Compd	$[M + 73]$	$[M + 73 - 3]$[b]	$[M + 73 - 9]$[c]	$[M + 1]$	$[M + 1 - 9]$
1[d]	100	8	12	14	1
2[d]	100	9	7	*e*	*e*
3[d]	100	13	9	11	2
4	11		1	100	10
5[f]	*e*	*e*	*e*	74	3
6[f]	*e*	*e*	*e*	54	29
7	100		3	7	9
8[g]	100		24	25	8
9[g]	100		15	9	1
10[g]	100		8	6	0.5

[a] All peak intensities normalized to the base peak in the spectrum. The numbers should be treated qualitatively rather than quantitatively. [b] Indicates exchange of one silyl methyl from the perdeuteriotrimethylsilyl derivative. [c] Indicates exchange of the entire silyl-d_9 function from the perdeuteriotrimethylsilyl derivative. [d] Exchange of two methyl groups observed in minor amounts. [e] Peak intensities were too low to obtain accurate measurements. [f] Base peak corresponds to elimination of $(CH_3)_2SiOH$ from $[M + 1]^+$. [g] Exchange of two silyl-d_9 groups observed in the M + 73 adduct ions.

volved heating samples of the perdeuteriotrimethylsilyl derivatives in a closed container in the presence of tetramethylsilane and stainless steel at temperatures ranging from 100 to 120°. The samples were then analyzed by electron impact mass spectrometry, and even after 1 hr at this temperature less than 0.1% exchange of a trimethylsilyl function could be detected. As a comparison it may be noted here that this 1-hr period is obviously orders of magnitude longer than any possible residence time of sample molecules in the ion source. It is thus apparent that the group exchanges summarized in Table I are ionically induced.

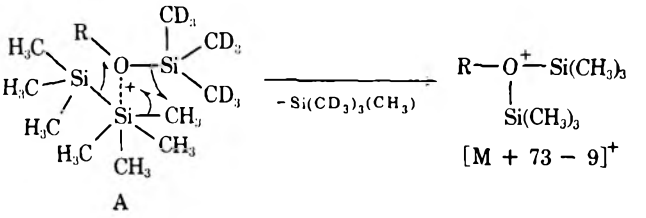
Probably the bulk of the $[M + 73]^+$ ions are formed by direct addition of the trimethylsiliconium ion to the sample molecules. The relatively high pressures used in chemical ionization provide collisional stabilization of the adduct ion. Furthermore, energy dissipation can be effected by equilibration throughout the vibrational modes of the polyatomic systems discussed here. The $[M + 73]^+$ ion, however, can also be formed by the unimolecular decomposition of activated complexes resulting from the reaction of secondary reagent gas ions with the sample. Metastable defocussing experiments were conducted and indeed confirmed the formation of $[M + 73]^+$ from adduct ions of the type $[M + 103]^+$, $[M + 131]^+$, $[M + 145]^+$, and $[M + 161]^+$. This is analogous with the findings of Bursey and coworkers,[8] who studied ion molecule reactions in butanedione utilizing ion cyclotron resonance spectrometry.

In line with this and based on a single collision argument and proper mass balance, a reasonable explanation for the observed exchange would involve participation of the most abundant secondary ion of *m/e* 161 $[(CH_3)_7Si_2]^+$ as shown in Scheme I. The proposed mechanism provides for elimination of tetramethylsilane, a process occurring readily under electron impact in systems possessing adjacent silyl groups as in the case of trimethylsilyl derivatives of phosphates.[9]

(8) M. M. Bursey, T. A. Elwood, M. K. Hoffman, T. A. Lehman, and J. M. Tesarek, *Anal. Chem.*, **42**, 1370 (1970).

(9) D. J. Harvey, M. G. Horning, and P. Vouros, *J. Chem. Soc., Perkin Trans. 1*, 1074 (1972).

SCHEME I



Bonding of the pentavalent silicon of the *m/e* 161 ion with the $ROSi(CD_3)_3$ oxygen can be justified by the ability of silicon to expand its valence shell and participate in bond formation with its 3d orbitals. In this case the silicon with the expanded valence shell in intermediate A (Scheme I) exists in an octahedral sp^3d^2 configuration and forms a bond with the oxygen.[10] The proximity of the various methyl groups in intermediate A can induce intramolecular methyl scramble and elimination of $Si(CH_3)_n(CD_3)_{4-n}$ (where $n = 1$–4) to give peaks at $[M + 73]^+$, $[M + 73 - 3]^+$, and $[M + 73 - 9]^+$ in compounds **1**–**3** (Table I). An analogous $[M + 161]^+$ intermediate can also be attained by considering a mechanism based on the direct reaction of the trimethylsiliconium ion with a sample molecule. The $[M + 73]^+$ adduct ion arising from the latter reaction can then collide with a neutral reagent gas molecule to form an $[M + 161]^+$-type ion analogous to A, which subsequently undergoes group exchange in the process of fragmenting to $[M + 73]^+$. It is not possible from the present data to distinguish between those two or other mechanisms without the employment of ion cyclotron resonance spectrometry, but the metastable defocussing experiments clearly show the participation of at least the $[M + 161]^+$ intermediate in the exchange process.

An interesting feature may be noted when examining the further loss of tetramethylsilane from the $[M + 73]^+$ ion to form the fragment ion of *m/e* 271 in the spectrum of the trimethylsilyl derivative of 1-tetradecanol (Figure 1a). The shift of *m/e* 271 to *m/e* 277 in the spectrum of the perdeuteriotrimethylsilyl derivative (Figure 1b) indicates the nonequivalence of the trimethylsilyl groups in the $[M + 73]^+$ system. Three possible fragmentation pathways are outlined in Scheme II. While the combined routes a and b seem attractive from Scheme I, the lack of any *m/e* 271 suggests the likelihood of route c. Thus it is apparent that other alternatives must be considered in addition to the normally conceptionalized silicon–oxygen bonding as in Scheme I.

Stereochemical Effects.—In most ionic organic reactions in solution steric factors have been shown to play a very significant role. Trimethylsilyl reactions in solution have also followed this pattern and thus it seemed reasonable to investigate steric parameters in gas-phase reactions as well. In compounds containing a secondary trimethylsilyloxy function (**4**–**6**) we observed virtually no formation of the $[M + 73]^+$ adduct ion but instead the spectrum was dominated by the $[M + 1]^+$ peak. This is exemplified by the spectra of the trimethylsilyl derivatives of 1-hexadecanol and 5-hexadecanol shown in Figure 2. The absence of the $[M + 73]^+$ ion can be rationalized by the increased

(10) J. F. Klebe, *Accounts Chem. Res.*, **3**, 299 (1970).

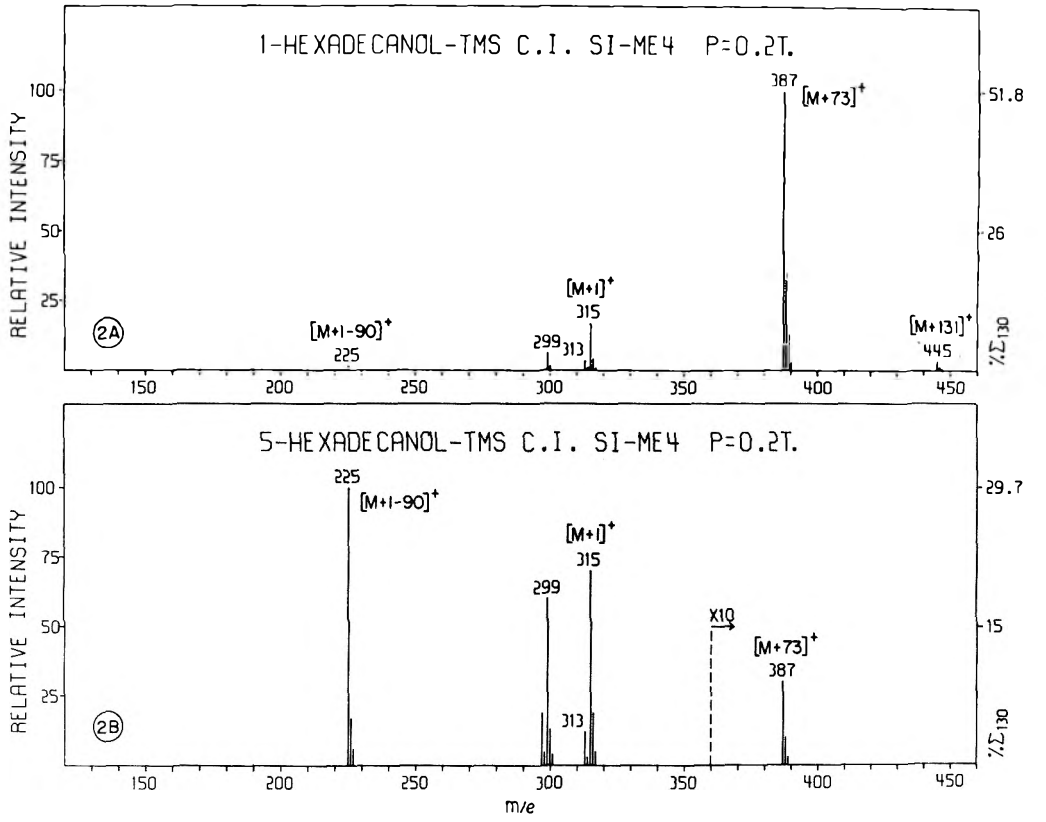
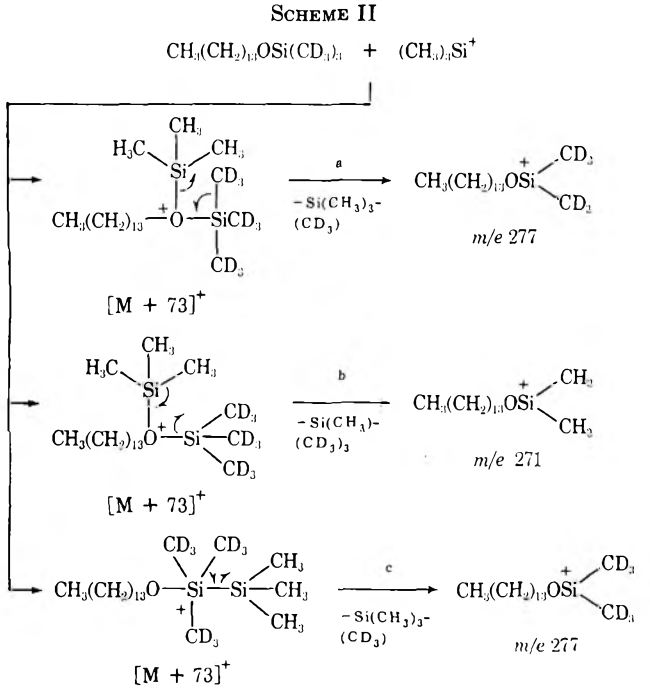


Figure 2.—The chemical ionization mass spectra with tetramethylsilane as the reagent gas of the trimethylsilyl derivative of (a) *n*-hexadecanol and (b) 5-hexacedanol.

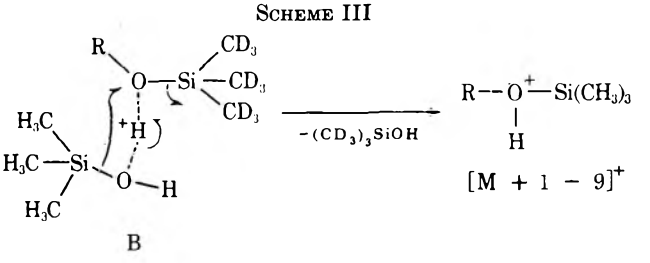
SCHEME II



steric hindrance, in view of the bulky groups involved in the adduct ion formation. The $[M + 1 - 90]^+$ peak in the spectrum of the trimethylsilyl derivative of 5-hexadecanol corresponds to elimination of trimethylsilanol from the protonated molecule.

The high relative abundance and, for that matter, even the presence of the intense $[M + 1]^+$ peak was somewhat puzzling, since sample protonation from the reagent gas ions would require transfer of a methyl hydrogen or possibly of a methylene hydrogen in the case of *m/e* 131. It is much more likely that the majority of the $[M + 1]^+$ ions are formed through participation of water impurities present in the system. Reaction of $(CH_3)_3Si^+$ with water yields protonated trimethylsilanol, $[(CH_3)_3SiOH_2]^+$, which reacts as a Brønsted acid with the sample to give $[M + 1]^+$. This hypothesis is supported by the presence of a strong peak at *m/e* 91 in the spectrum of the reagent gas. It was further confirmed by an experiment in which we introduced D_2O vapor into the system and correlated the ratio of $[M + H]^+$ and $[M + D]^+$ to that of $[(CH_3)_3SiOH_2]^+$ (*m/e* 91) and $[(CH_3)_3SiOD_2]^+$ (*m/e* 93). When the bulky alkyl siliconium ions are unable to react with sterically hindered heteroatoms, protonation from $[(CH_3)_3SiOH_2]^+$ becomes predominant (Scheme III). Intermediate B seems to be of sufficient lifetime

SCHEME III



to allow a trimethylsilyl scramble *via* elimination of the stable perdeuteriotrimethylsilanol as shown in Scheme III.

In spite of the low energy release upon protonation by $[(CH_3)_3SiOH_2]^+$ the difference in the steric environment between the primary and secondary trimethylsilyloxy isomers **2** and **4** is sufficient to produce significantly different amounts of fragmentation of the $[M +$

1]$^+$ ion. By contrast the methane chemical ionization mass spectra of both isomers are very similar, with the base peak occurring at [M + 1 − 90]$^+$. On the other hand the isobutane chemical ionization spectra of **2** and **4** were not informative because of the poor reactivity of the reagent.

Conclusions

The examples presented above provide new evidence about functional group interactions during ionic vapor-phase reactions of alkyl siliconium ions. The vapor-phase reaction of these ions with sample molecules containing a trimethylsilyl function results in exchange of methyl groups as well as the entire trimethylsilyl group. The extent of intermolecular exchange of either the methyl groups or the entire trimethylsilyl function is in part determined by the acidity of the trimethylsilyl derivative. This indicates that a finite lifetime is probably required for the postulated intermediates to effect methyl group scramble. Recognition of ionically induced trimethylsilyl group exchanges such as the ones reported here is important in analytical studies of trimethylsilyl derivatives, since in the spectra of the latter compounds much of the structural information is carried by ions containing the silyl function. The data presented also point out that stereochemical factors play a significant role in vapor-phase reactions. Unlike proton transfer reactions from NH_4^+ or CH_5^+, which are generally not sterically "sensitive", chemical ionization studies with alkyl siliconium ions may provide important information about stereochemical requirements in vapor-phase ionic reactions.

Experimental Section

Chemical ionization mass spectra were obtained with a modified CEC 21-110B mass spectrometer.[11] All spectra were recorded at ion source pressures of 0.2 Torr, temperatures of 100–135°, a repeller field of 10 V/cm, and ion-accelerating voltage of 8 kV. The total filament emission current was 100 μA and the electron energy was 400 V. The ion beam was focussed for maximum secondary ion intensity at *m/e* 161. The principal ions in the spectrum of tetramethylsilane at ion source pressure of 0.2 Torr and temperature of 125° occurred at *m/e* 73 (75% Σ_{40}), 131 (2.5% Σ_{40}), 145 (<1% Σ_{40}), and 161 (18% Σ_{40}). Trimethylsilyl derivatives of the compounds investigated were prepared according to established procedures.[12] The samples were introduced into the ion source *via* the standard solid probe inlet of the mass spectrometer.

Acknowledgment.—Financial support by the National Institutes of Health (GM-13901, GM-16216, and GM-02055) is gratefully acknowledged.

Registry No.—**1**, 6221-89-2; **2**, 6221-90-5; **3**, 42449-18-3; **4**, 42449-19-4; **5**, 42449-20-7; **6**, 7604-82-2; **7**, 18603-17-3; **8**, 29881-28-5; **9**, 42449-24-1; **10**, 18406-56-9.

(11) (a) J. H. Futrell and L. H. Wojcik, *Rev. Sci. Instrum.*, **42**, 244 (1971); (b) I. Dijidic, D. M. Desiderio, M. S. Wilson, P. F. Crain, and J. A. McCloskey, *Anal. Chem.*, **43**, 1877 (1971).

(12) E. M. Chambaz and E. C. Horning, *Anal. Biochem.*, **30**, 7 (1969).

Synthesis, Structure, and Conformation of 10,15-Dihydro-1,6,11-trihydroxy-2,7,12-trimethoxy-4,9,14-trimethyl-5*H*-tribenzo[*a*,*d*,*g*]cyclononene and Its Tripropyl Analog

J. F. MANVILLE* AND G. E. TROUGHTON

Department of the Environment, Canadian Forestry Service, Western Forest Products Laboratory, Vancouver, British Columbia

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Acid-catalyzed condensation of 6-hydroxymethyl-4-methylguaiacol produced a new cyclic trimer similar to cyclotriveratrylene (CTV). Its structure was determined by proton magnetic resonance spectroscopy and mass spectrometry to be 10,15-dihydro-1,6,11-trihydroxy-2,7,12-trimethoxy-4,9,14-trimethyl-5*H*-tribenzo[*a*,*d*,*g*]-cyclononene (**3**). In contrast to CTV, neither **3** nor its triacetate **3a** adopt rigid "crown" conformations normal for compounds of this type; nor do they form inclusion complexes. Similar properties were exhibited by the tripropyl analog, 10,15-dihydro-1,6,11-trihydroxy-2,7,12-trimethoxy-4,9,14-tripropyl-5*H*-tribenzo[*a*,*d*,*g*]cyclononene (**4**) and its triacetate **4a**.

Although originally described as a dimer[1] and subsequently as a hexamer,[2] the condensation product of veratrole with formaldehyde under acid conditions, with the general formula $(C_9H_{10}O_2)_n$, has been shown by Lindsey,[3] Erdtman, *et al.*,[4] and others[5–8] to be in fact a trimer (n = 3). The trivial name for this trimer, cyclotriveratrylene (CTV), was coined by Lindsey.[3]

The stereochemistry of this tribenzocyclononene system has been investigated by several groups.[3–8] On the basis of pmr spectra, CTV adopts a rigid "crown" conformation. This is also the most stable conformation for cyclononatriene,[9] although here interconversion between two equivalent "crown" conformations occurs at room temperature. However, unlike cyclononatriene, CTV does not show any tendency to invert its conformation, even at 200°.[5,6] CTV forms clathrate complexes with a large number of organic compounds[10] suggesting that this molecule must adopt a rigid nonplanar conformation.

An alternative conformation proposed in the literature is a flexible "saddle" form, which would be ex-

(1) G. M. Robinson, *J. Chem. Soc.*, **107**, 267 (1915).

(2) A. Oliverio and C. Casinovi, *Ann. Chim. (Rome)*, **42**, 168 (1952); **46**, 926 (1956).

(3) A. S. Lindsey, *J. Chem. Soc.*, 1685 (1965); *Chem. Ind. (London)*, 823 (1963).

(4) H. Erdtman, F. Haglid, and R. Ryhage, *Acta Chem. Scand.*, **18**, 1249 (1964).

(5) R. C. Cookson, B. Halton, and I. D. R. Stevens, *J. Chem. Soc. B*, 767 (1968); N. K. Anand, R. C. Cookson, B. Halton, and I. D. R. Stevens, *J. Amer. Chem. Soc.*, **88**, 370 (1966).

(6) B. Miller and B. D. Gesner, *Tetrahedron Lett.*, **No. 38**, 3351 (1965).

(7) T. Sato and K. Uno, *J. Chem. Soc., Chem. Commun.*, 579 (1972); *J. Chem. Soc., Perkin Trans. 1*, 895 (1973).

(8) A. Goldup, A. B. Morrison, and W. G. Smith, *J. Chem. Soc.*, 3864 (1965).

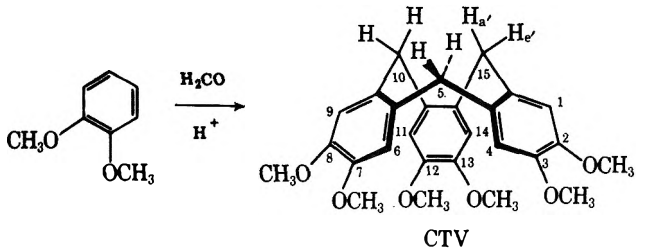
(9) P. Radlick and S. Winstein, *J. Amer. Chem. Soc.*, **85**, 344 (1963); K. G. Untch and R. J. Kurland, *ibid.*, **85**, 346 (1963).

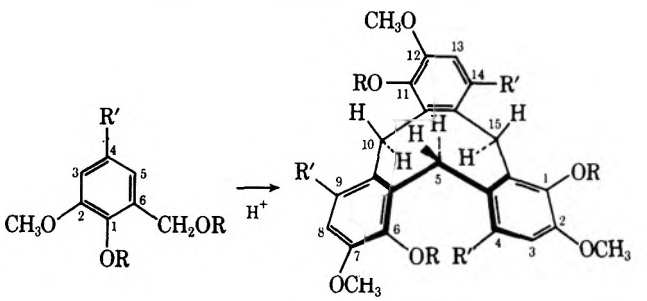
(10) V. Gaglioti, A. M. Liquori, N. Galo, E. Giglio, and M. Scrocco, *J. Inorg. Nucl. Chem.*, **8**, 572 (1958).

TABLE I

PMR SPECTRAL DATA. FIRST-ORDER CHEMICAL SHIFTS (δ VALUES, $CDCl_3$ SOLUTIONS)

	Aromatic(s)	Methylene	Methoxyl	Methyl	Propyl α	Propyl β	Propyl γ	OH(s)	Acetate(s)
1	6.55 (2)	4.58	3.70	2.20				6.05, 2.2	
1a	6.70 (2)	4.95	3.69	2.16					2.12, 1.98
2	6.56 (2)	4.64	3.78		2.46	1.58	0.82	6.25, 2.9	
2a	6.74, 6.69	4.96	3.72		2.48	1.58	0.92		2.23, 1.98
3	6.50	4.02	3.76	2.22				5.5	
3a	6.58	3.86	3.73	2.25					2.08
4	6.47	4.07	3.72		2.63	1.28	0.83	5.6	
4a	6.57	3.90	3.72		2.56	1.28	0.86		2.06





1,3, R = H, R′ = CH_3

1a,3a, R = $COCH_3$; R′ = CH_3

2,4, R = H; R′ = C_3H_7

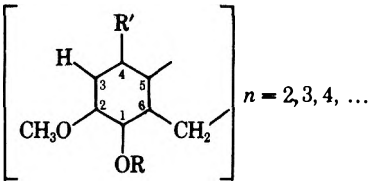
2a,4a, R = $COCH_3$; R′ = C_3H_7

pected to interconvert readily among three equivalent structures. Cookson, *et al.*,[5] found evidence for such a form for cyclotriveratrylen-5-one and the derived methylcarbinol; unlike the 5-methylene analog these showed no tendency to revert to "crown" conformations. They also observed that cyclotriveratrylen-5-ol preferentially adopts the rigid "crown" conformation (β alcohol). Although they were able, by carefully controlling the reaction conditions, to synthesize this secondary alcohol in the flexible "saddle" conformation (α alcohol), it readily and quantitatively converted into the rigid "crown" form. They did not observe any conversion of the β alcohol into the α alcohol.

During studies on resin formation from lignin hydrogenolysis products, the acid-catalyzed condensation of 6-hydroxymethyl-4-methylguaiacol (1) was examined. The resulting syrup was acetylated prior to gas–liquid chromatographic (glc) analysis. It was found to contain relatively low-molecular-weight products. This acetylated syrup, on standing in aqueous ethanol overnight, deposited crystals whose retention time of 51 min, although considerably longer than those of the acetylated dimeric products previously obtained[11] from 1 and alkali, was indicative of a relatively low degree of polymerization.

The structures of this crystalline product and of that produced from 6-hydroxymethyl-4-propylguaiacol (2) were established by pmr and mass spectrometry.

The pmr spectrum of **3a** (see Table I) is very simple: all five resonances are sharp singlets with an integrated ratio of 1:2:3:3:3. The signal at δ 6.58 corresponds to the aromatic protons while the signal for the methylene groups appears at δ 3.86. The remaining signals at δ 3.73, 2.25, and 2.08 are due to the methoxyl, methyl, and acetate groups, respectively. This is in full accordance with a flexible structure interconverting rapidly at room temperature with two other equivalent conformations (see above) making similar protons groupwise equivalent. Also, it indicates a 1,2,4-substitution pattern on each aromatic ring as in **3a**. However, these data do not specify the degree of polymerization, since any molecule in this series where $n = 2, 3, 4 \ldots$ undergoing rapid conformational inter-



conversions would exhibit these pmr parameters. However, the method of synthesis, similarities with CTV, and the retention time for **3a** (51 *vs.* 71 min for CTV) suggest that $n = 3$; this was confirmed by mass spectrometry.

CTV shows the two methylene protons as an AB quartet, with $J = 14$ Hz, at δ 4.70 and 3.45.[3-7] In **3**, **3a**, **4**, and **4a** the methylene protons are equivalent and appear close to the average of the shifts observed for CTV. Further, it has been shown[4-7] that CTV does not undergo conformational interconversions at temperatures up to 200°. CTV is locked in a "crown" conformation. In contrast, several conformations of compounds **3**, **3a**, **4**, and **4a** appear to be rapidly interconverting at room temperature, since all resonances [in $CDCl_3$, $(CD_3)_2CO$, C_6D_6, CS_2, and CD_2Cl_2] are groupwise equivalent.

Further evidence of this flexibility was obtained by observing the pmr spectra at low temperatures in CD_2Cl_2. The chemical shift(s) of the aromatic protons for **3a** and **4a** are temperature dependent and become separated into two discrete resonances. Table II lists these chemical shifts for **3a** and **4a** at the various temperatures studied. Compounds **3** and **4** were not at the slow exchange limit at −108.5°, broad singlets being observed at δ 6.50.

(11) G. E. Troughton and J. F. Manville, *Can. J. Forest Res.*, **2**, 271 (1972).

TABLE II

VARIABLE TEMPERATURE PMR DATA OF **3a** AND **4a**

Temp, °C	Aromatic proton chemical shifts(s)[a] 3a	4a
+35	6.63 (3)	6.60 (3)
−58.5	6.64 (3)	6.63 (3)
−68.5		6.64 (3)
−78.5	~6.67 (3)	~6.65 (3)
−88.5[b]	6.73 (1), 6.66 (2)	6.78 (1), 6.58 (2)
−98.5	6.75 (1), 6.66 (2)	6.80 (1), 6.58 (2)
−108.5[c]	6.87 (1), 6.66 (2)	6.82 (1), 6.58 (2)[d]

[a] Shifts in CD_2Cl_2–10% TMS. [b] At the slow exchange limit, two separate resonances for the aromatic protons might be expected. Examination of the Dreiding molecular models for these compounds shows that two of the aromatic rings are below the plane of the methylene groups, the third is above this plane. Thus it is reasonable to find two aromatic protons resonating together even though they are diastereotopic groups. [c] Compounds **3** and **4** were not at the slow exchange limit at this temperature and were observed as broad singlets at δ 6.50. [d] In CS_2 the chemical shifts (δ) are 6.62 (1) and 6.42 (2).

The cyclotribenzylene ring system can exist in five distinct conformational modes, two of which are rigid; the remaining three are conformationally mobile. These are given in Chart I together with the expected

CHART I

	No. of aromatic proton resonances: Fast	Slow
1. Rigid "saddle" (C_1 symmetry)	n.a.	2 (2:1) or 3 (1:1:1)
2. Rigid "crown" (C_3 symmetry)	n.a.	1
3. Interconverting "crown" ⇄ "crown"	1	No change
4. Interconverting "crown" ⇄ "saddle"	1	3; possibly 2 or 4
5. Interconverting "saddle" ⇄ "saddle"	1	2 (2:1) or 3 (1:1:1)

pmr observation for the aromatic proton resonance(s) at the exchange limits (intensity ratios in parentheses).

Scrutiny of Table II indicates that the first possibility is excluded by the room temperature pmr data. Conformations 2 and 3 are excluded by the two distinct resonances in a ratio of 2:1 obtained below −60°. Two possibilities remain, that of an interconverting "crown" ⇄ "saddle" conformational mode or a conformationally mobile "saddle" form.

Even though the pmr data do not exclude the interconverting "crown" ⇄ "saddle" conformation, literature data on this cyclotribenzylene ring system make this possibility unlikely. Thus, for molecules in this ring system to undergo "crown" ⇄ "saddle" conformational interconversions, a *necessary condition* is that at least one of the ring carbons C-5, C-10, or C-15 be an sp^2 carbon.[12] All other molecules studied, in this ring system, are either locked in the "crown" conformation[4-7] or exist solely in the flexible "saddle" conformation,[5-8] with no "crown" form observable. Examples are CTV and its methylcarbinol which are reported to be exclusively in the rigid "crown" and flexible "saddle" conformations, respecitvely.

Since compounds **3**, **3a**, **4**, and **4a** do not satisfy the necessary sp^2 condition for the interconverting "crown" ⇄ "saddle" conformational mode, and yet they are conformationally mobile, they must be interconverting between "saddle" conformations.

This result was not expected in view of the stability exhibited[4-7] by CTV in the "crown" conformation. Exclusive adoption of a flexible "saddle" conformation must reflect strong nonbonded interactions between the 4 and 6, 9 and 11, and 14 and 1 substituents on adjacent aromatic rings which would result if these molecules were to exist in the "crown" conformation. CPK Precision [Corey–Pauling atomic models with Kolton connectors (CPK)] and Dreiding molecular models of these compounds reveal that these nonbonded interactions are minimized in the "saddle" form.[13] Also it would be most difficult for these molecules to interconvert with the "crown" form due to the excessive bond/angle strain necessary to force these models to adopt this alternative conformation. In fact, it is not possible to construct a CPK molecular model of **3**, **3a**, **4**, and **4a** in the "crown" form due to the bulkiness of the substituents. Thus it is most likely that these molecules formed by acid-catalyzed ring closure of their respective benzyl alcohols exist exclusively in flexible "saddle" conformations.

Further evidence for the adoption of "saddle" conformations was obtained by attempts to determine clathrate formation for these compounds (**3a** and **4a**). Pmr spectroscopy was used to examine crystals obtained from several of the solvents listed by Gaglioti, *et al.*,[10] which are known to form inclusion complexes with CTV. Complete absence in the pmr spectra of signals due to the crystallizing solvent indicated that clathrate formation had not occurred for **3a** and **4a**. These results strongly suggest that their inability to form clathrate complexes is directly related to the fact that they do not adopt the "crown" conformation of CTV. Compounds **3** and **4** both exhibited pmr parameters consistent with a flexible conformation.

The mass spectrum of **3a** exhibited a molecular ion peak (M) at *m/e* 576, confirming that it is indeed a cyclic trimer. In contrast to the spectrum of CTV,[2] there is no M − 2 peak. The first major fragment occurs at *m/e* 534 which corresponcs to loss of ketene from one of the acetates. Peaks at *m/e* 193 and 383 (sum 576) arise from the fission of the molecule with formation of the ions $^1/_3$ M + 1 and $^2/_3$ M − 1, respectively. Similarly, for the decomposition of M − 42 ion, *m/e* 534, peaks arise at 151 and 383 or 193 and 341. The base peak at *m/e* 341 corresponds to $^2/_3$ M − 1 − ketene. The next abundant ion fragment *m/e* 299 (92%) corresponds to the further loss of ketene from the *m/e* 341 ion. A larger peak corresponding to loss of 32 mass units from the above (*m/e* 299) fragmention is observed at *m/e* 267. No metastable transitions were observed in the mass spectrum so that the origin of some peaks remains a matter of conjecture.

The mass spectrum obtained for **4a** exhibited major ion fragments analogous to those observed for **3a**, but at higher *m/e* values (multiples of 28 mass units) corresponding to the replacement of methyl with propyl groups.

We feel that the above data are consistent with the proposed structures and conformations for the crystal-

(12) Since the β alcohol does not convert into the "saddle" conformation,[5] cyclotriveratrylen-5-ol does not undergo "crown" ⇄ "saddle" conformational interconversions.

(13) A similar conclusion was formulated by Meth-Cohn[14] following recent studies on the cyclic trimer produced from 2,5-dimethylthiophene and formaldehyde.

(14) O. Meth-Cohn, *Tetrahedron Lett.*, **No. 2**, 91 (1973).

line products obtained from acid-catalyzed condensations of 4-alkyl-6-hydroxymethylguaiacols. This class of 1,2,4-trisubstituted cyclotribenzylenes appears to adopt only the flexible "saddle" conformation in contrast to CTV (2,3 disubstituted) which is locked in the "crown" conformation. This represents the first example of conformational control by aryl substitution pattern in the cyclotribenzylene system.

Experimental Section

The reaction mixtures were fully acetylated (pyridine–acetic anhydride 1:1 v/v) prior to pmr or glc analyses. Pmr spectra were normally recorded on a Varian HA-100 spectrometer using $CDCl_3$ as solvent and TMS as internal reference. The low-temperature experiments were recorded on a Varian XL-100 instrument in CD_2Cl_2 with 10% TMS. Glc analyses were obtained from a Varian Model 1520 gas chromatograph using a 6 ft × 1/8 in. stainless steel column packed with 5% SE-30 coated on Chromosorb W (60–80 mesh). The column was temperature programmed from 90 to 250° at 6°/min and then held isothermally. The nitrogen carrier-gas flow rate was 20 ml/min. The injector port was maintained at 230° and flame-ionization detection was used. Ir spectra (KBr pellet) were recorded on a Perkin-Elmer 521 spectrophotometer. Low-resolution mass spectra were run on a MS-12 spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

Cyclization.—6-Hydroxymethyl-4-methylguaiacol (1) and 6-hydroxymethyl-4-propylguaiacol (2) were prepared by the procedure of Marton, *et al.*,[15] and their purity checked by pmr spectroscopy. Cyclization was effected by heating 2 g of 1 or 2, 20 ml of water, and 7.5 ml of concentrated HCl under reflux for 2 hr. The reaction mixture was neutralized, extracted with ether, dried (Na_2SO_4), and evaporated (reduced pressure) to a syrup. After acetylation the reaction product was crystallized from ethanol. 10,15-Dihydro-1,6,11-triacetoxy-2,7,12-trimethoxy-4,9,14-trimethyl-5*H*-tribenzo[*a*,*d*,*g*]cyclononene (**3a**) (0.61 g, 27%) had mp 280–282°; ν_{max} 1745, 1585, 1445, 1352, 1300, 1120, 1090, 1000, 915, 870, and 820 cm^{-1}; M^+ 576; retention time 51 min.

10,15-Dihydro-1,6,11-triacetoxy-2,7,12-trimethoxy-4,9,14-tripropyl-5*H*-tribenzo[*a*,*d*,*g*]cyclononene (**4a**) (0.57 g, 25%) had mp 207–209°; ν_{max} 1745, 1585, 1440, 1352, 1295, 1165, 1090, 1010, 870, and 820 cm^{-1}; M^+ 660; retention time 91 min.

De-O-acetylation.—Compounds **3a** and **4a** were de-O-acetylated by treating them with excess $LiAlH_4$ in THF. After recrystallization from aqueous ethanol, **3** was obtained as white crystals, mp *ca.* 135° dec. Somewhat impure (rust color) **4** was obtained from **4a** and had a melting point range of >10° at *ca.* 190° dec. Pmr indicated only traces <5% of impurities.

10,15-Dihydro-1,6,11-trihydroxy-2,7,12-trimethoxy-4,9,14-trimethyl-5*H*-tribenzo[*a*,*d*,*g*]cyclononene (**3**) had ν_{max} 3430, 1585, 1440, 1280, 1230, 1200, 1175, 1090, 1025, 905, and 820 cm^{-1}; M^+ 450.

10,15-Dihydro-1,6,11-trihydroxy-2,7,12-trimethoxy-4,9,14-tripropyl-5*H*-tribenzo[*a*,*d*,*g*]cyclononene (**4**) had ν_{max} 3530, 3495, 1585, 1450, 1270, 1230, 1180, 1090, 1005, 900, and 820 cm^{-1}; M^+ 534.

Acknowledgments.—We thank L. Rozon and D. Watson for technical assistance in the preparation of these compounds, and Dr. Ian Armitage for helping to obtain the low-temperature pmr spectra at the University of British Columbia.

Registry No.—**1**, 7452-08-6; **1a**, 42214-44-8; **2**, 32359-71-0; **2a**, 42214-46-0; **3**, 42214-47-1; **3a**, 42214-48-2; **4**, 42214-49-3; **4a**, 42319-50-6.

(15) J. Marton, T. Marton, S. K. Falkenhag, and E. Adler, *Advan. Chem. Ser.*, **No. 59**, 125 (1966).

Photochemical and Acid-Catalyzed Rearrangements of Tricyclo[4.4.2.0]dodecanones[1,2]

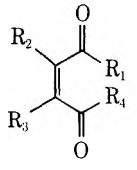
NORTON P. PEET AND ROBERT L. CARGILL*

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

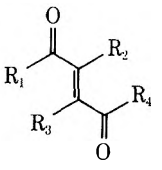
Received June 13, 1973

Photoannulations of transoid 2-ene-1,4-diones with ethylene and 2-butyne are described. An efficient synthesis of bicyclo[4.4.0]dec-1(6)-ene-2,7-dione (**7**) in two steps from 1,5-decalindiol has been accomplished. Acid-catalyzed and photochemical isomerizations of 11,12-dimethyltricyclo[4.4.2.0]dodec-11-ene-2,7-dione (**10**), the adduct of 7 and 2-butyne, are presented.

Although cycloaddition reactions of cisoid 2-ene-1,4-dione systems with acetylenes, olefins, and other enes are well documented,[3] the involvement of molecules containing transoid 2-ene-1,4-dione moieties in such reactions is not. In this paper we report that the latter enediones are effective partners in photocycloadditions with olefins and acetylenes.



cisoid 2-ene-1,4-dione



transoid 2-ene-1,4-dione

Irradiation of **1**[4] in hexane through uranium glass[5] at room temperature with 2-butyne very quickly and cleanly produced the β,γ-unsaturated dione **3**. Irradiation (Pyrex) of **1** at low temperature[6] in methylene chloride saturated with ethylene likewise gave a single adduct, **4** (Scheme I).

Since rearrangement studies with **3** and **4** would certainly be complicated by the presence of the angular methyl group, we required the parent enedione **7**. The electronic effect of the methyl group in methylfuran is apparently essential for conjugate addition to cyclohexenone to occur; thus furan could not be added to cyclohexenone under the same reaction conditions.

(1) Presented in part by N. P. Peet at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 30, 1972, Abstract ORGN 86.

(2) Grateful acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this research.

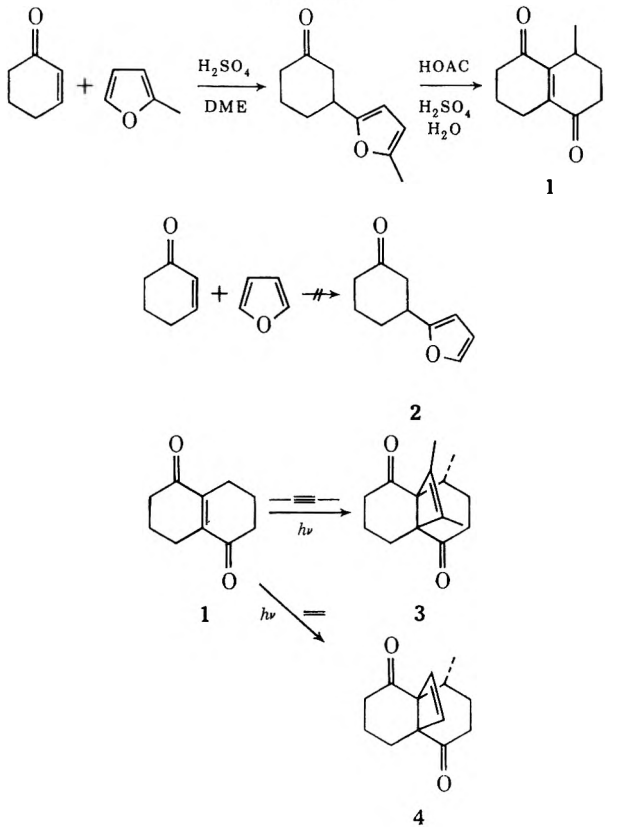
(3) Consider the number of examples in which quinones, benzoquinones, and maleic anhydrides have been used in photocycloaddition reactions: M. E. Kuehne and H. Linde, *J. Org. Chem.*, **37**, 4031 (1972); S. P. Pappas, B. C. Pappas, and N. A. Portnoy, *ibid.*, **34**, 520 (1969); I. W. J. Still, M. W. Kwan, and G. E. Palmer, *Can. J. Chem.*, **46**, 3731 (1968); W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966).

(4) M. A. Tobias, *J. Org. Chem.*, **35**, 267 (1970).

(5) When a Pyrex glass filter was employed in the preparation of **3**, two additional products were observed in the irradiation solution by glpc.

(6) The apparatus used for low-temperature irradiation was similar to that described by D. C. Owsley and J. J. Bloomfield, *J. Chem. Soc. C*, 3445 (1971).

SCHEME I

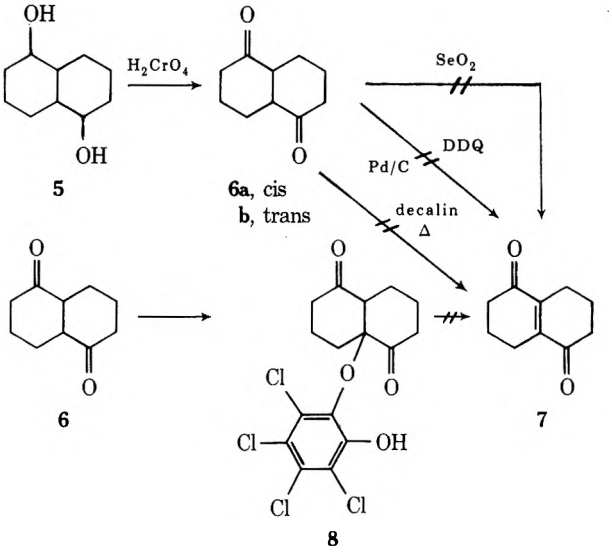


This negative result led us to explore alternate routes for the preparation of enedione **7**.

Enedione **7** is briefly mentioned only twice in the literature. Baumann and Prelog[7] reported its preparation in their laboratories by chloranil oxidation of 1,5-decalindione, but gave no experimental data. Campbell and Harris[8] report two oxidative processes for the production of **7** from $\Delta^{9,10}$-octalin, which gave overall yields of 3.5 and 0.5%.

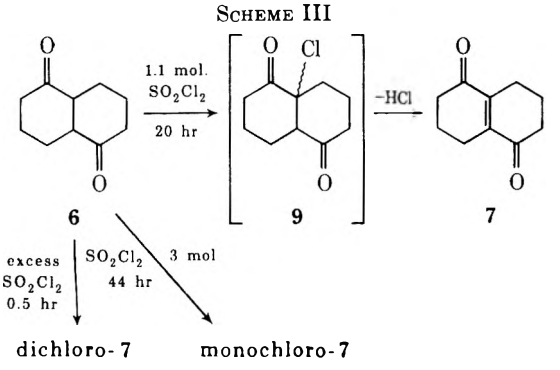
Commercially available 1,5-decalindiol (**5**) was converted into a mixture of *cis*- and *trans*-1,5-decalindiones (**6a** and **6b**, respectively) with Jones reagent.[9] Although selenium dioxide is reported to oxidize transoid 2-ane-1,4-diones to 2-ene-1,4-diones,[12] only trace amounts of **7** resulted from treatment of dione **6a** with selenium dioxide. Treatment of **6a** with 2,3-dichloro-5,6-dicyanoquinone (DDQ) yielded a small amount of **6b**, but no **7**. When **6a** was treated with 10% palladium on charcoal in decalin at reflux, dehydrogenation occurred but enedione **7** was not produced. Treatment of **6a** with *o*-chloranil in carbon tetrachloride gave a 52% yield of adduct **8**. Although treatment of **8** with base did yield a small amount of enedione **7** and provided supporting evidence for the structural assignment of adduct **8**, this did not constitute a practical synthesis of **7**. A probable side reaction of this base treatment is the abstraction of the phenolic proton followed by ether cleavage to regenerate *o*-chloranil and the enolate of **6**. Scheme II summarizes these unsuccessful routes to **7**.

SCHEME II



Treatment of **6** with sulfuryl chloride,[13] on the other hand, produced enedione **7** directly.[14] Treatment of **6** with excesses of sulfuryl chloride produced mono- and dichloro derivatives of **7** (Scheme III).

SCHEME III



Irradiation of enedione **7** with 2-butyne and ethylene (in the same manner as described for **1**) cleanly yielded the noval adducts **10** and **12**, respectively. Treatment of β,γ-unsaturated ketone **10** with *p*-toluenesulfonic acid (TsOH) in benzene at reflux rapidly produced the thermodynamically more stable enedione **11**, *via* a 1,2-vinyl shift followed by a Wagner–Meerwein shift.[15] Treatment of dione **12** with TsOH in the same manner resulted in two Wagner–Meerwein shifts[16] to produce dione **13** as the only product. Acid-catalyzed 1,3-acyl migration[15b,17] of **10** (*i.e.*, to product **14**) was

(7) P. Baumann and V. Prelog, *Helv. Chim. Acta*, **42**, 736 (1959).

(8) W. P. Campbell and G. C. Harris, *J. Amer. Chem. Soc.*, **63**, 2721 (1941).

(9) 1,5-Decalindiol (Aldrich) was treated with 8 *N* chromic acid[10] to give a mixture of 1,5-decalindiones (93% yield). Fractional crystallization separated pure *cis*- and *trans*-1,5-decalindiones in yields of 41 and 33%, respectively. This preparation of **6** represents an improvement over previously used procedures.[11]

(10) D. C. Kleinfelter and P. v. R. Schleyer, *Org. Syn.*, **42**, 79 (1962).

(11) W. S. Johnson, C. D. Gutsche, and D. K. Banarjee, *J. Amer. Chem. Soc.*, **73**, 5464 (1951).

(12) (a) C. S. Barnes and D. H. R. Barton, *J. Chem. Soc.*, 1419 (1953); (b) R. K. Hill, *J. Org. Chem.*, **26**, 4745 (1961).

(13) (a) A. J. Sisti and A. C. Vitale, *J. Org. Chem.*, **37**, 4090 (1972); (b) H. O. House and H. W. Thompson, *ibid.*, **26**, 3729 (1961).

(14) Chromatographic purification of **7** was necessary to free it of a minor impurity which could not be separated by recrystallization.

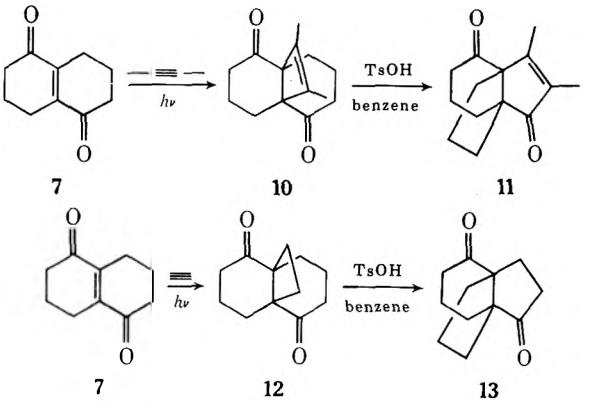
(15) (a) R. L. Cargill and J. W. Crawford, *J. Org. Chem.*, **35**, 356 (1970); (b) R. L. Cargill, D. M. Pond, and S. O. Legrand, *ibid.*, **35**, 359 (1970), and references cited therein.

(16) N. P. Peet, R. L. Cargill, and D. F. Bushey, *J. Org. Chem.*, **38**, 1218 (1973).

(17) (a) R. L. Cargill, M. E. Beckham, J. R. Damewood, D. M. Pond, W. A. Bundy, and J. Bordner, *J. Org. Chem.*, **37**, 78 (1972); (b) R. L. Cargill and A. B. Sears, *Tetrahedron Lett.*, 3555 (1972); (c) R. L. Cargill, M. E. Beckham, A. E. Siebert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965).

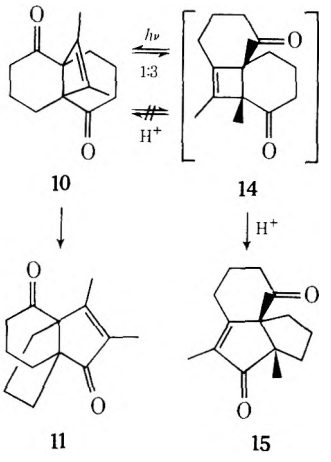
not observed (*vide infra*). The adducts of **7** and their rearrangements are summarized in Scheme IV.

SCHEME IV

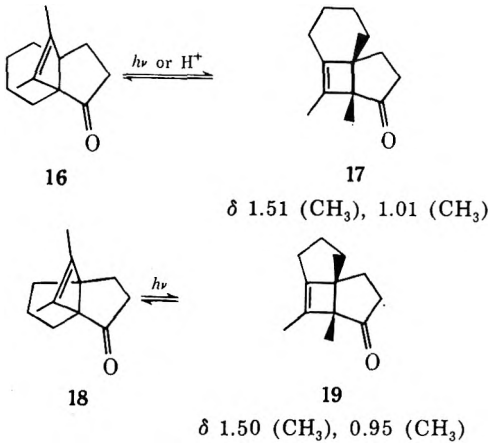


The ultraviolet spectrum of enedione **10** [299 nm (ε 472)] indicated efficient excited state mixing of olefinic and carbonyl orbitals (as was the case for enedione **3**) and we predicted that **10** would undergo a photochemical 1,3-acyl migration.[18-20] Irradiation (Pyrex) of **10** in hexane gave a mixture from which ketones **11** and **15** (Scheme V) were isolated by glpc in a

SCHEME V



1:3 ratio, respectively. Analysis of the reaction mixture on another column led to isolation of **10** and **15** in a 1:3 ratio. (The initial column was then shown to isomerize **10** to **11**.) Analysis of the methyl region of the nmr spectrum of the reaction mixture before glpc indicated the presence of **10**, the absence of **15**, and methyl singlets at δ 1.57 and 1.10. The nmr spectra of ketones **17**[17c] and **19**,[17b] which are photoisomers of **16** and **18**, respectively, show methyl singlets in similar regions. An infrared spectrum of the reaction mixture



indicated that the major component had a carbonyl stretching frequency of 1705 cm^{-1}. These data indicate the photochemical formation of **14**, and its subsequent isomerization to **15** during gas chromatography. Further analysis of the nmr spectrum of the photostationary mixture indicated the presence of **10** and **14** in a ratio of *ca.* 1:3.

The structures of **14** and **15** follow from the body of knowledge already obtained in these laboratories regarding photochemical and acid-catalyzed isomerizations of propellane systems such as the ones under discussion,[15-17] coupled with the spectroscopic data already described. Isolation of pure **14** was unsuccessfully attempted using a variety of glpc columns. Thick layer chromatography (silica gel) of the irradiation mixture also failed to separate **14**.

Since treatment of **11** with TsOH in benzene at reflux yielded no trace of **15**, and since **15** treated in the same manner yielded no trace of **11**, we conclude that the formation of **14** in the irradiation of **10** was not an acid-catalyzed isomerization. This result is interesting in view of the fact that similar compound sets, **16** ⇄ **17** and **18** ⇄ **19**, are equilibrated under acidic conditions. Furthermore, when a portion of the photostationary mixture was treated with TsOH in benzene at reflux, the resulting mixture contained **11** and **15** in a ratio of 1:3, respectively. This result again demonstrates that the acid-catalyzed interconversion of **10** and **14** has a barrier which is greater than those leading from **10** to **11** and from **14** to **15**.

Experimental Section[21]

5-Methylbicyclo[4.4.0]dec-1(6)-ene-2,7-dione (1).—Enedione **1**, mp 50–54° (lit.[4] mp 50–53.5°), was prepared in an overall yield of 13% from cyclohexenone.[4] Careful recrystallization of **1** (hexane) yielded a purer product, mp 58–60°, which was used in the subsequent reactions. Enedione **1** had mp 58–60°; ir (CCl_4) 1670 cm^{-1} (C=O); uv max (95% EtOH) 264 nm (ε 12,000); nmr ($CDCl_3$) δ 3.3–1.7 (m, 11, all protons except CH_3) and 1.17 (d, J = 7.2 Hz, 3, CH_3).

(18) For recent references to photoisomerizations of this type in rigid systems, see K. E. Hine and R. F. Childs, *Chem. Commun.*, 145 (1972); H. Hart and A. F. Naples, *J. Amer. Chem. Soc.*, **94**, 3256 (1972); and R. L. Cargill and T. Y. King, *Tetrahedron Lett.*, 409 (1970).

(19) For recent reports of 1,3-acyl photoisomerizations in nonrigid β,γ-unsaturated ketones, see J. R. Williams and G. M. Sarkisan, *J. Chem. Soc. D*, 1564 (1971); P. S. Engel and M. A. Schexnayder, *J. Amer. Chem. Soc.*, **94**, 4357 (1972); and P. S. Engel and M. A. Schexnayder, *ibid.*, **94**, 9252 (1972).

(20) (a) N. P. Peet, R. L. Cargill, and J. W. Crawford, *J. Org. Chem.*, **38**, 1222 (1973); (b) R. L. Cargill, T. Y. King, and A. B. Sears, *ibid.*, **36**, 1423 (1971); (c) N. A. LeBel, N. D. Ojha, J. R. Menke, and R. J. Newland, *ibid.*, **37**, 2896 (1972); (d) K. N. Houk, D. J. Northington, and R. E. Duke, *J. Amer. Chem. Soc.*, **94**, 6233 (1972).

(21) All boiling points and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. Infrared spectra were recorded using a Perkin-Elmer Model 257 grating spectrophotometer. All nmr spectra were determined using tetramethylsilane as an internal standard, with a Varian A-60 nmr spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 spectrophotometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 instrument. Analytical gas–liquid partition chromatograms were determined using a Varian Aerograph 1200 flame ionization chromatograph, and preparative glpc separations were conducted using a Varian Aerograph 90-P-3 chromatograph. Irradiations were carried out using a Hanovia high-pressure mercury arc (450 W), internal probe, type L, with the filter specified.

Attempted Preparation of 3-(2-Furyl)cyclohexanone (2).—A mixture of 113 g (1.18 mol) of cyclohexenone (Columbia Organic), 104 g (1.53 mol) of furan (MCB), 575 ml of dimethoxyethane, and 1 ml of concentrated H_2SO_4 was heated at reflux for 24 hr. The dark solution was cooled and stirred (30 min) with $NaHCO_3$ (10 g). The excess $NaHCO_3$ was removed by filtration, and the filtrate was fractionally distilled at reduced pressure. Distillates consisted largely of recovered starting materials, with only a small amount of material in the boiling point range expected for a 1:1 adduct of furan and cyclohexenone, which was not **2** (or **7**).

5,11,12-Trimethyltricyclo[4.4.2.0]dodec-11-ene-2,7-dione (3).—A solution of 0.912 g (5.12 mmol) of enedione **1** and 20 ml of 2-butyne (Columbia Organic) in 150 ml of hexane was irradiated (uranium glass filter) for 2.75 hr. The disappearance of **1** and the appearance of a single product was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 150°, 30 cc/min of He). Removal of the solvent left 1.14 g (96%) of **3** as an oily solid. Adduct **3** was purified by elution through a 2-g plug of alumina[22] with hexane, followed by low-temperature recrystallization[23] (hexane) and sublimation [75° (0.35 mm)]. Adduct **3** had mp 80.5–82°; uv max (95% EtOH) 235 nm (ε 3500) and 302 (500); nmr ($CDCl_3$) δ 2.8–1.3 (m, 19, all protons except angular CH_3, with CH_3 multiplets at 1.61 and 1.50) and 0.84 (d, J = 7.2 Hz, 3, angular CH_3); mass spectrum (70 eV) m/e 232 (molecular ion).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.72; H, 8.73.

5-Methyltricyclo[4.4.2.0]dodecane-2,7-dione (4).—A solution of 0.971 g (5.12 mmol) of enedione **1** in 150 ml of CH_2Cl_2 saturated with ethylene (Matheson) was irradiated (Pyrex filter) at low temperature for 2.25 hr. Progress of the addition was followed by glpc (3% DEGS, 8 ft × 0.125 in., 140°, 30 cc/min of He). The reaction solution was warmed to room temperature and dried ($MgSO_4$), and the solvent was removed to leave 1.13 g (99%) of **4** as a viscous oil, which solidified upon standing. Separation of **4** from minor impurities was accomplished by preparative glpc (20% SE-30, 5 ft × 0.25 in., 210°, 85 cc/min of He). Adduct **4** had mp 72–74°; uv max 296 nm (ε 55); ir (CCl_4) 1695 cm^{-1} (C=O); nmr (CCl_4) δ 2.6–1.3 (m, 17, all protons except CH_3) and 0.88 (d, J = 7.2 Hz, 3, CH_3); mass spectrum (70 eV) m/e 206 (molecular ion).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.73; H, 8.84.

Bicyclo[4.4.0]dec-1(6)-ene-2,7-dione (7).—A solution of 2.08 g (12.5 mmol) of *trans*-1,5-decalindione (**6**)[9] and 1.81 g (13.4 mmol) of sulfuryl chloride (MCB) in 50 ml of CH_2Cl_2 was stirred for 20 hr. Progress of the reaction was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 120°, 30 cc/min of He). The yellow reaction mixture was neutralized with saturated $NaHCO_3$, the layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated to leave 2.30 g of yellow solid. Recrystallization (hexane) yielded yellow material displaying a wide melting point range (85–100°) which was applied (CH_2Cl_2) to a 100-g column of alumina.[22] Elution with ether–hexane mixtures (1:9 to 1:1) afforded initial, intensely yellow fractions which were combined, concentrated, and recrystallized (hexane) in two crops to yield 0.738 g (36%) of **7** as yellow plates. Enedione **7** had mp 111–113° (lit. mp 110–111°[7] and 113–114°[8]); ir (CCl_4) 1680 cm^{-1} (C=O); uv max (95% EtOH) 265 nm (ε 12,000); nmr δ 2.7–2.3 (m, 8, CH_2 groups adjacent to C=O and C=C groups) and 2.3–1.7 (m, 4, remaining CH_2 groups); mass spectrum (70 eV) m/e 164 (molecular ion).

When a 1.04-g (6.25 mmol) quantity of **6b** was stirred with 2.81 g (20.8 mmol) of sulfuryl chloride in 50 ml of CH_2Cl_2 for 44 hr, the major product was monochloro-**7**. Progress of the reaction was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He). After 5 hr, the major product (95% by glpc) was **7**, and, after 44 hr, the major product (90% by glpc) was monochloro-**7**. Work-up of the reaction mixture as above yielded 1.37 g of oily, yellow solid which was recrystallized twice (ether–hexane and hexane) to yield 0.216 g of yellow prisms. Monochloro-**7** had mp 102–111°; ir (KBr) 1690 and 1675 (C=O), 1175, and 1155 cm^{-1}; mass spectrum (70 eV) m/e 198 (molecular ion).

When a 1.04-g (6.25 mmol) quantity of **6b** was stirred with 10 ml of sulfuryl chloride (neat) for 30 min, the major product (70% by glpc) was dichloro-**7**. (The remaining 30% was monochloro-**7**.) Work-up of the reaction mixture as above yielded 1.58 g of yellow solid which was recrystallized twice ($CHCl_3$–hexane and $CHCl_3$–ether) to yield 0.413 g of white solid which displayed a single peak on glpc (3% DEGS, 8 ft × 0.125 in., 150°, 30 cc/min of He). Dichloro-**7** had mp 153–156°; ir (KBr) 1690 (C=O) and 1155 cm^{-1}; mass spectrum (70 eV) m/e 232 (molecular ion).

Attempted Preparations of 7. Isolation of Adduct 8.—A 0.979-g (5.89 mmol) quantity of **6a** in 50 ml of absolute ethanol and 2.40 g (5.89 mmol) of selenium dioxide (MCB) were heated at reflux for 90 min. The reaction mixture was filtered, concentrated, and eluted through a plug of alumina[22] (ether). The eluent was concentrated and the residue was recrystallized (heptane) to yield 0.6 g of **6b**. An infrared spectrum of the concentrated mother liquor indicated the presence of a small amount of enedione **7**. The use of an acetic acid–hexane solvent system and excess selenium dioxide afforded no trace of **7**.

A 0.866-g (5.21 mmol) quantity of **6a**, 0.5 g of 10% palladium on carbon (Columbia Organic), and 25 ml of *cis*- and *trans*-decalin (MCB) were heated at reflux for 1.5 hr, during which time 150 ml of gas was evolved. (Theoretical gas evolution volume for conversion to enedione is *ca.* 115 ml.) The reaction mixture was cooled and filtered, and the concentrated filtrate was applied to a 25-g column of alumina.[22] Elution with ether and CH_2Cl_2 removed 0.712 g of white solid. Recrystallization (CH_2Cl_2–hexane) afforded 0.451 g of **6b**.

A 1.04-g (6.25 mmol) quantity of **6a** and a 1.52-g (6.69 mmol) quantity of 2,3-dichloro-5,6-dicyanoquinone[24] in 50 ml of benzene were heated at reflux for 1 hr. The red reaction solution was concentrated and applied to a 50-g column of alumina.[22] The column was eluted with ether to remove a small amount of **6b**.

A 0.954-g (5.74 mmol) quantity of **6a** and 1.46 g (5.95 mmol) of *o*-chloranil (Columbia Organic) in 50 ml of CCl_4 were stirred for 3 hr. The initially clear, red solution deposited a voluminous precipitate after 3 hr which was removed by filtration and washed with CCl_4 to yield 1.22 g (52%) of adduct **8**, which was recrystallized from ether: mp 240–242° dec; ir (KBr) 3650–3100 (OH), 1695 (C=O), 1590, and 1425 cm^{-1}. The material was not soluble in available nmr solvents. Adduct **8** exhibited a positive ferric chloride test.[25] When a small amount of **8** was slurried with ether and dilute KOH, the ether layer became yellow. Concentration of the ether phase gave a yellow solid whose infrared spectrum was identical with that of enedione **7**.

Anal. Calcd for $C_{16}H_{14}Cl_4O_4$: C, 46.63; H, 3.42; Cl, 34.41. Found: C, 46.76; H, 3.41; Cl, 34.41.

11,12-Dimethyltricyclo[4.4.2.0]dodec-11-ene-2,7-dione (10).—A solution of 1.01 g (6.16 mmol) of enedione **7** and 10 ml of 2-butyne in 150 ml of hexane was irradiated (uranium glass filter) for 1.3 hr. Progress of the addition was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He). Removal of the solvent left 1.38 g of clear oil which solidified on standing. The material was eluted through a 2-g plug of alumina[22] with ether–hexane and recrystallized (hexane) at low temperature[23] to yield 0.818 g (61%) of **10**. A sample was sublimed [70° (0.15 mm)] for elemental analysis. Adduct **10** had mp 71–75°; ir (CCl_4) 1690 cm^{-1} (C=O); uv max (95% EtOH) 230 nm (ε 3640) and 299 (472); nmr (CCl_4) δ 2.4–1.6 (m, 12, all protons except CH_3 groups) and 1.54 (s, 6, CH_3 groups); mass spectrum (70 eV) m/e 218 (molecular ion).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.88; H, 8.26.

8,9-Dimethyltricyclo[4.3.3.0]dodec-8-ene-2,7-dione (11).—A solution of 0.213 g (0.974 mmol) of **10** and 0.5 g of *p*-toluenesulfonic acid monohydrate (Baker, $TsOH \cdot H_2O$) in 45 ml of benzene was heated at reflux for 1.5 hr with azeotropic removal of water. Analysis of reaction solution aliquots by glpc (3% DEGS, 8 ft × 0.125 in., 130°, 30 cc/min of He) indicated that rearrangement was complete in less than 15 min. The cool reaction mixture was washed with saturated $NaHCO_3$ (30 ml) and water (30 ml), dried ($MgSO_4$), and concentrated to leave 0.167 g (79%) of **11**. To separate it from minor impurities originally present,[26] **11** was collected from glpc (20% SE-30, 5 ft × 0.25 in., 185°, 85 cc/min of He) as a clear oil. Enedione **11** had ir (CCl_4) 1700 (C=O groups) and 1645 cm^{-1} (C=C); uv max (95%

(22) Baker aluminum oxide (pH of 10% slurry at 25° 7.8) was used.

(23) Low-temperature recrystallization was accomplished by suspending the solution in a dewar flask containing Dry Ice and capped with a loose fitting plug.

(24) Prepared by J. L. Moore using the method of D. Walker and T. D. Waugh, *J. Org. Chem.*, **30**, 3240 (1965).

(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1956, p 127.

(26) Compound **10** partially deteriorated, upon standing for 3 weeks, to an oily solid.

EtOH) 247 nm (ε 10,300) and 296 (476); nmr (CCl_4) δ 2.4–1.0 (m, all protons, with CH_3 singlets at 1.90 and 1.72); mass spectrum (70 eV) *m/e* 218 (molecular ion).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.02; H, 8.22.

Tricyclo[4.4.2.0]dodecane-2,7-dione (12).—A solution of 0.886 g (5.39 mmol) of enedione **7** in 150 ml of CH_2Cl_2 saturated with ethylene was irradiated (Pyrex filter) at low temperature[27] for 1.5 hr. Progress of the addition was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He). The reaction solution was dried ($MgSO_4$) and the solvent was removed to leave 1.11 g of clear oil which solidified upon standing. The material was eluted through a 2-g plug of alumina[22] with ether–hexane and recrystallized (hexane) at low temperature[23] to yield 0.707 g (68%) of **12**. A portion of **12** was sublimed [60° (0.15 mm)] for elemental analysis. Adduct **12** had mp 45–48°; ir (CCl_4) 1705 cm^{-1} (C=O); uv max (95% EtOH) 296 nm (ε 59); nmr (CCl_4) δ 2.5–1.2 (m); mass spectrum (70 eV) *m/e* 192 (molecular ion).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.91; H, 8.22.

Tricyclo[4.3.3.0]dodecane-2,7-dione (13).—A solution of 0.076 g (0.395 mmol) of **12** and 0.5 g of $TsOH \cdot H_2O$ in 45 ml of benzene was heated at reflux for 1 hr with azeotropic removal of water. Progress of the rearrangement was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He). The cool reaction mixture was washed with saturated $NaHCO_3$ (30 ml) and water (10 ml), dried ($MgSO_4$), and concentrated to leave 0.070 g (92%) of **13**. Dione **13** was collected from preparative glpc (20% SE-30, 5 ft × 0.25 in., 170°, 85 cc/min of He) for characterization: mp 115–118°; ir (CCl_4) 1740 (cyclopentanone C=O) and 1705 cm^{-1} (cyclohexanone C=O); uv max (95% EtOH) 292 nm (ε 42); nmr (CCl_4) δ 2.5–1.2 (m); mass spectrum (70 eV) *m/e* 192 (molecular ion).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.27.

Preparation of Transient 2,3-Dimethyltricyclo[6.4.0.0^{3,8}]dodec-1-ene-4,9-dione (14) and Its Acid-Catalyzed Conversion to 1,3-Dimethyltricyclo[7.3.0.0^{4,9}]dodec-3-ene-2,8-dione (15).—A 0.814-g (4.96 mmol) quantity of enedione **7** was converted to adduct **10** as described, using a base-washed irradiation vessel. The uranium glass filter was removed and irradiation (Pyrex) was continued for 3.75 hr, until glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He) indicated a mixture of static integral intensity numbers. Collection of the smaller of the two major peaks (present in *ca.* a 1:3 ratio) from glpc (10% Apiezon M, 8 ft × 0.25 in., 220°, 85 cc/min of He) showed it to be enedione **11**, which had been formed from enedione **10** on the column. [This was proved by collection of **10** from another glpc system (20% SE-30, 5 ft × 0.25 in., 180°, 85 cc/min of He) which did not cause this conversion.] Collection of the larger peak yielded enedione **15**: bp 100° (0.2 mm); ir (CCl_4) 1705 (C=O) and 1650 cm^{-1} (C=C); uv max (95% EtOH) 251 nm (ε 7890), 221 (4470), and 315 (305); nmr (CCl_4) δ 3.0–1.0 (m, with CH_3 singlets at 1.71 and 1.07); mass spectrum (70 eV) *m/e* 218 (molecular ion).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.09; H, 7.90.

The finding that **14** was a labile precursor of **15** and the determination of the photostationary mixture of **10** and **14** (as 1:3, respectively) are presented in the discussion section.

Registry No.—**1**, 22242-82-6; **3**, 42249-31-0; **4**, 42245-83-0 **6a**, 42245-84-1; **6b**, 42245-85-2; **7**, 42245-86-3; monochloro-**7**, 42249-11-6; dichloro-**7**, 42249-12-7; **8**, 42245-87-4; **10**, 42245-88-5; **11**, 42245-89-6; **12**, 42245-90-9; **13**, 42245-91-0; **14**, 42245-92-1; **15**, 42245-93-2; cyclohexenone, 930-68-7; 2-butyne, 503-17-3; ethylene, 74-85-1.

(27) Low temperature was maintained by immersing the irradiation vessel in a Dry Ice–isopropyl alcohol bath, and circulating isopropyl alcohol, cooled indirectly with Dry Ice, through the probe.

Photochemical Addition of Dimethyl Maleate to 2,3-Dimethyl-2-butene. Use of a Chiral Shift Reagent

GERALD L. GOE[1]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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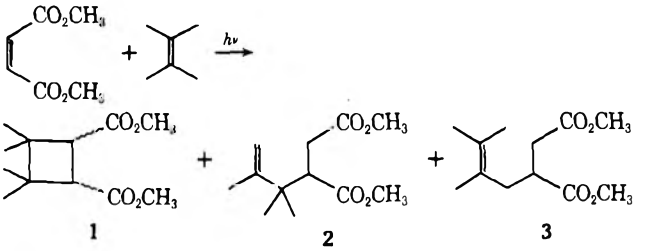
Irradiation (253.7 nm) of dimethyl maleate with excess 2,3-dimethyl-2-butene gave dimethyl (1,1,2-trimethylallyl)succinate (49% of product), dimethyl (2,3-dimethyl-2-butenyl)succinate (33%), and dimethyl 3,3,4,4-tetramethylcyclobutane-*trans*-1,2-dicarboxylate (18%) in 33% yield. The stereochemistry of the cyclic ester was proven by conversion to the corresponding cis ester by way of the cyclic anhydride. Proton nmr spectra of the trans ester with added tris(trifluoroacetylcamphorato)europium showed different shifts for the hydrogens of the enantiomers in the racemic modification of the compound; the corresponding cis (meso) ester, similarly treated, showed different shifts for the enantiotopic nuclei, the differential shifts being intramolecular as shown by coupling between the nonequivalent methine hydrogens in the shifted spectra.

In spite of the increasing number of ways in which instrumental methods can be applied to problems of structure elucidation, chemical degradations and even independent syntheses of degradation products are frequently necessary in difficult structure problems. In connection with another problem we recently required authentic samples of *cis*- and *trans*-3,3,4,4-tetramethylcyclobutane-1,2-dicarboxylic acid, and in the process of identifying these compounds practiced a recently proposed instrumental method that promises great savings in time and material as compared with traditional chemical methods.

The dimethyl ester (**1**) of one of the desired acids was produced, albeit as a minor product, by irradiation of a mixture of dimethyl maleate and 2,3-dimethyl-2-butene (tetramethylethylene, TME). The structures of the other products, **2** and **3**, were determined unambiguously by instrumental methods (see Experimental Section) and are consistent with the allylic abstraction–radical recombination mechanism proposed for the photoaddition of dimethyl maleate to cyclohexene[2] that was confirmed by labeling studies.[2d] Only a single isomer of **1** was produced in this reaction;



1 2 3

(1) Address correspondence to Reilly Tar and Chemical Corp., Indianapolis, Ind. 46204.

(2) (a) P. de Mayo, R. W. Yip, and S. T. Reid, *Proc. Chem. Soc., London*, 54 (1963); (b) J. A. Barltrop and R. Robson, *Tetrahedron Lett.*, 597 (1963); (c) P. de Mayo, *Pure Appl. Chem.*, **9**, 597 (1964); (d) G. Ahlgren and B. Åkermark, *Tetrahedron Lett.*, 1885 (1970).

since maleate and fumarate esters are rapidly interconverted under the reaction conditions and both are present in the reaction mixture, it made no difference whether maleate or fumarate esters were used as starting material.[3]

It remained to prove the stereochemistry of the isomer of **1** produced in the photochemical reaction and to prepare the other isomer, if possible. There are four classical methods for determining the stereochemistry of a vicinally disubstituted cyclic compound. The coupling constant in the proton nmr is frequently a useful guide to the stereochemistry of the substituents, and can sometimes be determined by examination of the ^{13}C satellite peaks in the case of identical disubstitution. Unfortunately, the cis and trans coupling constants in cyclobutanes are too similar to be used for this purpose.[4] A second method relies on conversion of the substituents to a cyclic functionality (*e.g.*, an ahydride) to demonstrate the spatial proximity of the original substituents. A third method depends on the symmetry properties of the substituted compound; in the absence of other unsuitable substituents, a cyclic compound with trans-like substituents possesses a twofold symmetry axis (before allowing for conformational effects) and no other symmetry element and therefore is not superposable with its mirror image and can support optical activity. Similarly, a suitable cis disubstituted compound will have a plane of symmetry and will be meso, incapable of supporting optical activity. Therefore, successful resolution of an unknown compound of suitable constitution to give observable optical activity can provide definitive proof of trans stereochemistry. The fourth method depends on conversion of the thermodynamically less stable isomer to the more stable, if the substituents are such that interconversion can take place and if the relative stabilities of the isomers are known. In the case of the cyclic vicinal dicarboalkoxy compounds, cis isomers are converted to trans isomers by alkoxide base.[5] Of these methods, all except the nmr method require considerable amounts of material and time, and, since a negative result is not always conclusive, the availability of both isomers is frequently a necessity.

The stereochemistry of **1** was proven to be trans by the reactions outlined in Scheme I. Treatment of the ester with sodium methoxide gave no detectable amount of another isomer, consistent with the trans stereochemistry. Since the equilibrium constant for the unsubstituted dimethyl cyclobutane-1,2-dicarboxylate is only 7.7–8.6 (temperature dependent),[5] the lack of detectable isomerization in the present case is consistent with much greater steric hindrance in *cis*-**1** than in the less substituted compound, because of the four methyl groups.

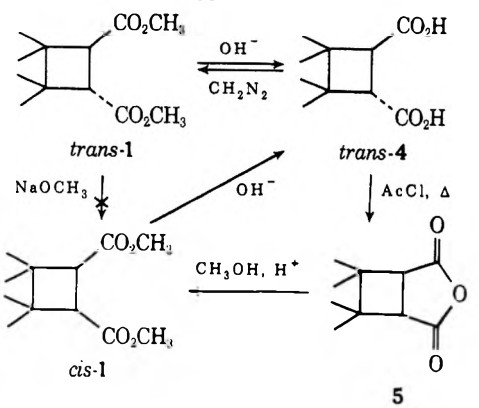
Saponification of the ester gave the diacid, *trans*-**4**, which could be transformed into the cis cyclic anhydride **5** by treatment with acetyl chloride under forcing conditions. Acid-catalyzed methanolysis of **5** gave the ester *cis*-**1**. Attempted saponification of *cis*-**1** gave concomitant isomerization, yielding *trans*-**4** exclusively;[6] this result was confirmed by esterification of the acid thus produced, to give back *trans*-**1**.

Recently, an instrumental substitute for optical resolution for proof of stereochemistry has been developed. Although a number of lanthanide compounds cause differential changes in the chemical shift of nonequivalent nuclei in the nmr spectra of compounds containing polar groups, if the ligands on the metal are chiral, then nuclei in enantiomeric molecules are shifted by different amounts.[7] Thus, as was first pointed out by Pirkle, *et al.*,[8] the racemic modification of a compound capable of supporting optical activity should demonstrate differential shifts for the two enantiomers when treated with a chiral shift reagent. A meso compound, under similar circumstances, might naively be expected to give no differential shifts. However, it must be noted that the symmetry plane common to meso stereoisomers causes symmetry-related groups to have an enantiotopic relationship to one another; although equivalent in achiral media, enantiotopic groups will reside in diastereomeric environments in a chiral medium and therefore will not be chemically equivalent; in principle, the enantiotopic nuclei will be anisochronous in the nmr.[9] Thus it should be expected that meso stereoisomers will also show differential shifts when treated with chiral shift reagents.

There is an important and observable difference between the ways in which *dl* and meso compounds are shifted, however, since the differential shifts in the *dl* compound are *inter*molecular—nuclei in the (+) and (−) molecules are shifted by different amounts—and the differential shifts in the meso compound are *intra*molecular—enantiotopic nuclei within the *same* molecule are shifted by different amounts. This difference allows a simple distinction between the two types of compounds, since nuclei in different molecules cannot couple with one another while nonequivalent nuclei within a single molecule can be coupled. If this coupling can be observed in shifted spectra, the stereochemistry of a meso compound can be confirmed.

This prediction and the stereochemistry elucidated by chemical means were confirmed by examining the

SCHEME I



(3) Attempted photochemical cycloaddition of TME to maleic anhydride was unsuccessful.

(4) H. Weitkamp and F. Korte, *Tetrahedron, Suppl.*, **No. 7**, 75 (1966).

(5) D. S. Seigler and J. J. Bloomfield, *J. Org. Chem.*, **38**, 1375 (1973), and references cited therein.

(6) Partial isomerization of cyclobutane-*cis*-1,2-dicarboxylic acid to the trans isomer under conditions of acid or heat has been observed: E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schlatter, *J. Amer. Chem. Soc.*, **64**, 2696 (1942).

(7) Review: R. von Ammon and R. D. Fischer, *Angew. Chem., Int. Ed. Engl.*, **11**, 675 (1972).

(8) M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Amer. Chem. Soc.*, **94**, 5924 (1972).

(9) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

nmr spectra of *cis*- and *trans*-**1** as influenced by the chiral shift reagent tris(trifluoroacetylcamphorato)-europium [Eu(tfac)$_3$]. Both isomers gave differentially shifted spectra for all the kinds of protons, but, while the methine hydrogens in *trans*-**1** gave differential shifts that were clearly intermolecular, the methine hydrogens of *cis*-**1** gave an obvious AB pattern [J_{AB} = 9.8 Hz, $\delta_A - \delta_B$ = 18.1 Hz at 100 MHz and 0.4 equiv of Eu(tfac)$_3$] in the shifted spectra (see Figure 1), confirming that the groups are enantiotopic by internal comparison, and therefore that the compound has a plane of symmetry and is meso and cis disubstituted. It is also worthy of note that the cis isomer is more shifted than the trans, as noted by Pirkle, *et al.*,[8] in a known system, probably because of greater ease of approach of the cis isomer to the metal.

Thus the use of chiral shift reagents to elucidate stereochemistry promises great savings in time and amounts of material needed, *if* the compounds of interest are such that additional coupling in the shifted spectra of the meso isomer can be observed. In contrast with other methods, assignment made by this method should always be reliable even if only one isomer is available, providing that the above conditions are met.

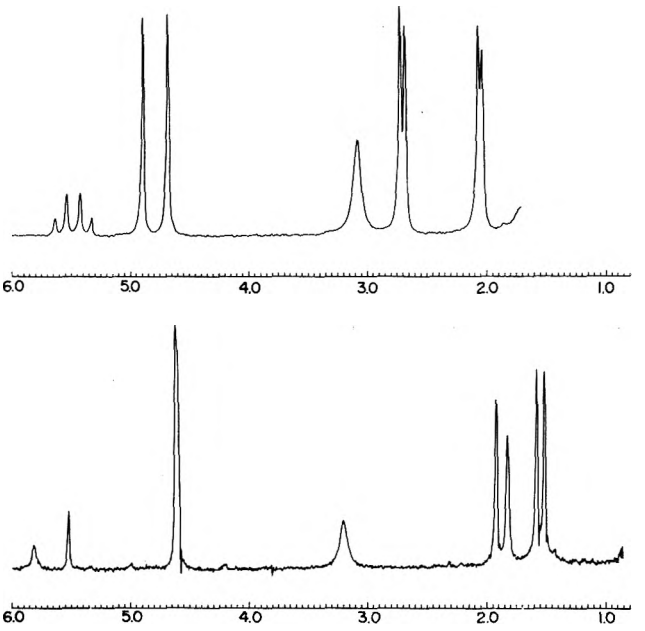


Figure 1.—Nmr spectra (100 MHz) of *cis*-**1** (top) and *trans*-**1** (bottom), each with 0.4 equiv of Eu(tfac)$_3$. Scale is in ppm downfield from TMS. Peak at 3.1–3.2 is due to shift reagent. The downfield peak for methine hydrogen in *trans*-**1** (δ 5.8 in the bottom spectum) is observably broader than other peaks at all shift reagent concentrations. Expansion of the peak at δ 4.6 in the spectrum of *trans*-**1** shows it to consist of two peaks separated by 0.6 Hz.

Experimental Section[10]

Irradiation of Dimethyl Maleate and 2,3-Dimethyl-2-butene.—A solution of 12.0 g (0.083 mol) of dimethyl maleate, 15.0 g (0.18 mol) of TME, and 2 ml of absolute EtOH (necessary for homogeneous solution) was sealed in a quartz tube with a serum cap and deaerated by nitrogen bubbling. The resulting solution was irradiated with a circular array of 16 G15T8 germicidal lamps for 14 days; aliquots were taken periodically for analysis by glpc [6 ft × 0.125 in. 5% diethylene glycol succinate (DEGS) on Chromosorb G, 140°]. Solvent and excess TME were removed under reduced pressure at room temperature, and the residue was distilled under reduced pressure. After a small forerun of maleate and fumarate esters a mixture of **1**, **2**, and **3** (6.2 g, 33%; glpc area ratio 18:49:33, using flame ionization detector) was distilled, bp 135–150° (18–20 mm). Pure samples of the products were obtained by preparative glpc (8 ft × 0.375 in. 10% DEGS on Chromosorb P, 150°); order of elution was **1**, **2**, and **3**. No *cis*-**1** could be detected in the mixture (limit of detection ~1%).

Dimethyl 3,3,4,4-Tetramethylcyclobutane-*trans*-1,2-dicarboxylate (*trans*-**1**).—The compound was further purified by recrystallization from MeOH–H$_2$O: mp 75.0–75.5°; ir 1735 cm^{-1}; nmr (60 MHz) δ 0.95 (s, 3), 1.05 (s, 3), 3.04 (s, 1), and 3.63 (s, 3); mass spectrum *m/e* (rel intensity) 228.136 (M$^+$, 9, calcd for $C_{12}H_{20}O_4$ 228.135), 115 (100), 114 (52), 84 (48), 83 (60).

Dimethyl (1,1,2-Trimethylallyl)succinate (**2**).—The liquid compound was further purified by preparative glpc (3 ft × 0.25 in. 10% silicone rubber SE-30 on Chromosorb P, 130°): ir (film) 3080, 1735, and 895 cm^{-1}; nmr (60 MHz) δ 1.05 and 1.08 (2s, 6), 1.77 (br s, 3), 2.03–3.05 (m, 3), 3.60 and 3.63 (2s, 6), and 4.76 (br s, 2); mass spectrum *m/e* (rel intensity) 228.139 (M$^+$, 3, calcd for $C_{12}H_{20}O_4$ 228.135), 83 (100).

Dimethyl (2,3-Dimethyl-2-butenyl)succinate (**3**).—The liquid compound was further purified by preparative glpc (conditions as for **2**, above): ir 1740 cm^{-1}; nmr (60 MHz) δ 1.63 (s, 9), 2.12–2.67 (m, 4), 2.72–3.17 (m, 1), and 3.62 (s, 6); mass spectrum *m/e* (rel intensity) 228.124 (M$^+$, 28, calcd for $C_{12}H_{20}O_4$ 228.135), 83 (100).

Attempted Isomerization of *trans*-1 with Sodium Methoxide.—A mixture of 5.6 mg (0.025 mmol) of *trans*-**1**, 5 ml of dry MeOH, and 0.1 ml (0.002 mmol of NaOMe) of a MeOH solution 0.02 *M* in NaOMe was heated under reflux in a nitrogen atmosphere. Aliquots (0.04 ml) were removed periodically and quenched with H$_2$O and CH_2Cl_2, the layers were separated, and the dried ($MgSO_4$) CH_2Cl_2 layers were analyzed by glpc. After 20 hr another 0.4 ml of NaOMe solution was added (total base 0.011 mmol) and heating was continued. After another 26 hr, the trans ester remained unchanged, and no *cis*-**1** could be detected by glpc.

3,3,4,4-Tetramethylcyclobutane-*trans*-1,2-dicarboxylic Acid (*trans*-**4**).—A mixture of 187 mg (0.82 mmol) of *trans*-**1**, 2 g of KOH, and 20 ml of 80% EtOH was heated under reflux for 4 hr. Most of the solvent was evaporated and the residue was diluted with H$_2$O. The resulting basic solution was extracted with CH_2Cl_2 and the organic layer discarded, acidified with concentrated HCl, and extracted continuously with CH_2Cl_2 for 48 hr. The extract was evaporated to yield 160 mg (98%) of crude *trans*-**4**, which was recrystallized from acetone–hexane, mp 212.5–213.5°.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found (Schwarzkopf Microanalytical Laboratory): C, 59.82; H, 8.05.

3,3,4,4-Tetramethylcyclobutane-*cis*-1,2-dicarboxylic Anhydride (**5**).—A mixture of *trans*-**4** (126 mg, 0.63 mmol) and 2.0 ml of acetyl chloride was heated under reflux with protection from atmospheric moisture for 4 hr. Excess acetyl chloride was removed by distillation and the residue was heated at 150° for 2 hr. This material was sublimed at 180–200° (0.1 mm) to yield 92 mg (~80%) of crude **5** (mp 124–130°) which appeared to contain some trans mixed anhydride (see below) but which was not further purified: ir 1857 and 1780 cm^{-1}; mass spectrum *m/e* (rel intensity) 182.094 (M$^+$, 0.1, calcd for $C_{10}H_{14}O_3$ 182.093), 154 (4), 110 (2), 83 (100).

Dimethyl 3,3,4,4-Tetramethylcyclobutane-cis-1,2-dicarboxylate (*cis*-**1**).—A mixture of 52 mg (0.29 mmol) of crude **5**, 5 ml of dry MeOH, and 0.05 ml of concentrated H_2SO_4 was heated under reflux with protection from moisture for 2 hr. The resulting solution was diluted with H$_2$O and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to yield 45 mg (69%) of *cis*-**1**, found to be contaminated with 27% (by nmr and glpc) of *trans*-**1**. Pure liquid *cis*-**1** was isolated by preparative glpc (9 ft × 0.25 in. 10% DEGS on Chromosorb P, 155°): ir 1740 cm^{-1}; nmr (60 MHz) δ 1.11 (br s, 6), 2.95 (s, 1), and 3.60 (s, 3); mass spectrum *m/e* (rel intensity) 228.138 (M$^+$, 1, calcd for $C_{12}H_{20}O_4$ 228.135), 115 (100), 114 (53), 84 (47), 83 (77).

(10) Melting points were taken on a Fisher-Johns apparatus that had been calibrated with known compounds. Nmr spectra were recorded using Varian A-60A (60 MHz) or XL-100 (100 MHz) spectrometers and CCl_4 solutions. Ir spectra were taken on CCl_4 solutions except as noted. Mass spectra were recorded on an AEI MS902 mass spectrometer at an ionizing voltage of 70 eV; the masses of molecular ions were measured by peak matching with the appropriate peak of tris(perfluorobutyl)amine reference.

Nmr Spectra of *cis*-1 and *trans*-1 with Eu(tfac)$_3$.—Solutions of *cis*-1 (18 mg) and *trans*-1 (26 mg), each in 0.35 ml of CCl_4 containing TMS, were prepared, and solutions of Eu(tfac)$_3$ (Willow Brook Laboratories) in CCl_4 were prepared such that 0.01 ml would contain 0.05 molar equiv of the shift reagent. Nmr spectra (100 MHz) of the esters were recorded after each addition of 0.01- or 0.02-ml aliquots of the shift reagent solution. The esters were recovered from the resulting solutions by column chromatography on silica gel, eluted with benzene. (The shift reagent could not be recovered by this procedure.)

3,3,4,4-Tetramethylcyclobutane-*trans*-1,2-dicarboxylic Acid (*trans*-4) from *cis*-1.—A mixture of *cis*-1 (16 mg, 0.07 mmol, recovered from the shifted nmr sample as described above) and 3 ml of a solution of 10% KOH in 80% EtOH was heated under reflux for 2 hr and diluted with H_2O. The basic solution was extracted with CH_2Cl_2 and the organic layer discarded, acidified with concentrated HCl, and extracted continuously with CH_2Cl_2 for 29 hr. The CH_2Cl_2 solution was evaporated to give 11 mg (79%) of crude *trans*-4, mp 210–211.5°, mmp with authentic *trans*-4 212–213°. A 2-mg sample of acid was esterified in MeOH solution with ethereal diazomethane to give only *trans*-1, identical with an authentic sample by glpc and ir.

Acknowledgment.—I wish to thank Mr. Don Schifferl for the mass spectra and for assistance with the 100-MHz nmr spectra.

Registry No.—*trans*-1, 42151-26-8; *cis*-1, 42151-27-9; 2, 42151-28-0; 3, 42151-29-1; *trans*-4, 42151-30-4; 5, 42151-31-5; dimethyl maleate, 624-48-6; 2,3-dimethyl-2-butene, 563-79-1; acetyl chloride, 75-36-5.

N-Acylation during the Addition of Carboxylic Acids to *N*-*tert*-Butylacylketenimines and the Use of the Reagent *N*-*tert*-Butyl-5-methylisoxazolium Perchlorate for Peptide Synthesis

DARRELL J. WOODMAN* AND A. I. DAVIDSON

Department of Chemistry, University of Washington, Seattle, Washington 98195

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Diacylamide precursors of amide impurities have been detected in spectral tests of the addition of carboxylic acids to *N*-*tert*-butylacylketenimines. Variations in the product distribution with an inefficient acylketenimine in media of differing acidity suggest that diacylamide formation involves a second intermediate adduct that does not convert rapidly to the desired enol ester. A high free acid concentration results in interception of the intermediate to give acid anhydrides. Partial deuterium incorporation at the vinylic position of the enol esters indicates that intramolecular *O,O*-acyl migration is relatively slow for the adducts of *N*-*tert*-butylacylketenimines, and possible substituent influences are discussed. The preparation of β-acyloxy-*N*-*tert*-butylcrotonamide enol ester acylating agents from *N*-*tert*-butyl-5-methylisoxazolium perchlorate succeeds with unprotected hydroxyl groups and the carboxamide function of glutamine. However, amide dehydration was observed in the case of asparagine and competing azlactone formation was detected with benzoylleucine. Crystalline esters were not obtained with Z-Ala-OH, Z-Tyr-OH, and Z-Met-OH. Test couplings have established compatibility of the enol esters with unprotected hydroxyl groups in the amine component but results are not markedly improved relative to *N*-ethyl-5-phenylisoxazolium 3′-sulfonate. A new side reaction, condensation of the amine component with the coupling by-product, is shown to be a likely source of impurities in the use of the esters of hindered carboxylic acids. The original zwitterionic isoxazolium salt reagent is much less susceptible to the side reaction.

Since the discovery of the facile conversion of carboxylic acids to enol ester acylating agents upon reaction with 3-unsubstituted isoxazolium salts,[1] there have been continuing attempts to obtain isoxazolium cations with superior properties for application as reagents in peptide synthesis. Following the development of the zwitterion *N*-ethyl-5-phenylisoxazolium 3′-sulfonate (NEPIS),[2] structural modifications have centered on the substituent on nitrogen,[3,4] benzisoxazolium cations,[5,6] and other ring-fused isoxazolium salts.[7] The issues of concern underlying these efforts have been the avoidance of rearrangement of the enol esters to diacylamides, the efficiency of enol ester formation, and the prevention of racemization *via* azlactones during the formation and reactions of enol esters of N-protected peptide acids. In contrast to the *N*-aryl heterocycles,[3] the *N*-*tert*-butyl compounds (**1**) were found to stabilize the enol esters relative to rearrangement.[4] However, examination of the reagent *N*-*tert*-butyl-5-methylisoxazolium (**1a**) perchlorate revealed *N*-*tert*-butylamides (**7**) as a side reaction product.[4] Our further examination of the *N*-*tert*-butyl system has led to the partial elucidation of the side reaction, the discovery of new complications in the reaction of the *N*-*tert*-butylacylketenimine intermediates (**2**) with carboxylic acids, and a definition of the limits of synthetic utility for **1a**.

A likely explanation of the side reaction observed in the *N*-*tert*-butyl series would involve *N*-*tert*-butyldiacylamides (**6**) as precursors of the amides **7**. Since the diacylamides were not themselves detected in the previous study, they would have to be relatively labile compounds. Consistent with this possibility, an attempt to force thermal rearrangement of the enol ester **4a** (R_3 = $ZNHCH_2$) of carbobenzoxyglycine to the corresponding diacylamide **6a** gave only the decomposition fragments amide **7** and *N*-*tert*-butylacetoacetamide (**5a**).[8] Spectral data in support of the proposed

(1) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron, Suppl.*, **7**, 415 (1966).

(2) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **No. 8**, 321 (1966).

(3) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

(4) D. J. Woodman and A. I. Davidson, *J. Org. Chem.*, **35**, 83 (1970).

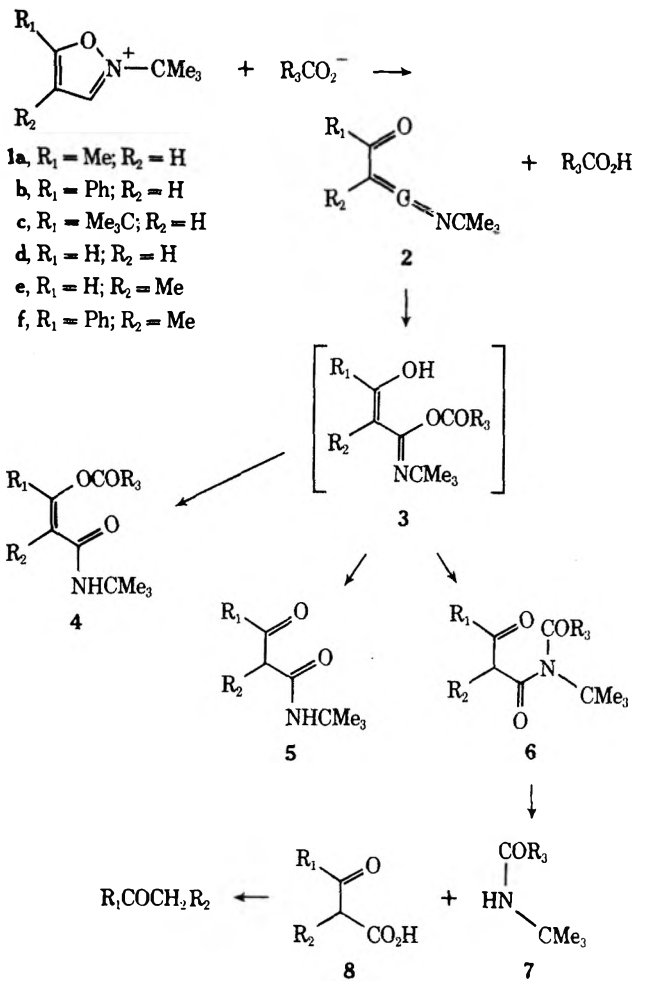
(5) D. S. Kemp, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1964.

(6) D. S. Kemp and S. W. Chien, *J. Amer. Chem. Soc.*, **89**, 2743 (1967).

(7) R. A. Olofson and Y. L. Marino, *Tetrahedron*, **26**, 1779 (1970).

(8) Other workers[9] have reported that the enol ester of 3,5-diamino-6-chloropyrazine-2-carboxylic acid similarly gives the *N*-*tert*-butylamide on treatment with triethylamine, but a compound assigned the diacylamide structure was obtained with methoxide in polar media. If the latter structure is correct, it remains unclear why fragmentation took place only in the former medium and what special factors account for imide stability in the latter experiment.

(9) K. L. Shepard, W. Halczenko, and A. J. Cragoe, Jr., *Tetrahedron Lett.*, 4757 (1969).



decomposition of the *N-tert*-butyldiacylamides was obtained from the addition of formic acid to the isolated intermediate acylketenimine **2a**. Combination of the reactants resulted in considerable effervescence, as in the dehydration of formic acid to carbon monoxide upon reaction with carbodiimides.[10] In addition to appreciable (52%) dehydration product **5a**, the nmr spectrum of the product mixture revealed signals for the formate enol ester **4a** (R_3 = H, 34%) and the HCO, Me_3C, and $COCH_2CO$ protons of the *N*-formyl diacylamide **6a** (12%). The formate ester **4a** proved unstable, decomposing completely within a few hours to give additional keto amide **5a** and diacylamide **6a** in roughly equal amounts. On longer standing, the peaks attributed to the diacylamide also disappeared, as corresponding amounts of acetone and the amide **7** were observed to form. On the basis of these spectral assignments, fragmentation to amide **7** appears the dominant mode of diacylamide decomposition, and the lifetime of diacylamide in this instance may reflect greater stability associated with the less crowded formyl derivatives.[11]

In contrast to the above reaction with formic acid, in the previous study it was found that enol esters of other acids did not rearrange to diacylamides or decompose to give the amide impurities under the reaction conditions.[4] In those cases, it would be necessary that the unstable diacylamides arise directly from the initial adduct **3**[12] *via* an iminoanhydride rearrangement[13] in competition with conversion to enol ester **4**. Proof of the formation of **6** by such a pathway was achieved using an acylketenimine (**2f**) that was found to give an adduct especially prone to side reactions.

A survey of the outcome of the addition of carbobenzoxyglycine to a variety of acylketenimines showed that small amounts of amide **7** (R_3 = $ZNHCH_2$) resulted with the *N-tert*-butylcumulenes **2a–c** from different 5-substituted isoxazolium salts **1a–c**. The quantities of amide from **2d** and **2e** were below the limits of nmr detection. While the lesser severity of the side reaction could be an indication that these latter formylketenimines might provide a more efficient route to enol esters, the formyl substituted structures would have little synthetic utility owing to the greater tendency of the coproducts **5d** and **5e** to condense with the amine components of coupling reactions (discussed below). Extension of the survey to the disubstituted ketenimine **2f** led to a surprising result, the formation of the anhydride of carbobenzoxyglycine. Up to now the detection of intramolecular side reactions has provided the only experimental support for the existence of the postulated high-energy intermediate **3** in the reaction leading to enol esters,[4,5,14] and the present finding of interception by unconsumed carboxylic acid constitutes the first case of intermolecular trapping of **3**. In addition, a large amount (32%) of amide **7** was produced when the acid was added slowly to **2f** to keep anhydride formation to a minimum.

Further examination of the ineffective ketenimine **2f** with formic acid again provided an observable diacylamide. When **2f** was added to excess formic acid, dehydration once more was encountered, leading exclusively to keto amide **5f**. With the reverse order of addition of formic acid to excess **2f**, the product mixture nmr spectrum was in accord with a 3:1 ratio of diacylamide **6f** (R_3 = H) and enol ester **4f**, along with some keto amide **5f**.[15] In this case, the diacylamide proved sufficiently stable for partial purification and confirmation of the nmr peak assignments. The infrared spectrum also revealed no NH or OH absorption, in accord with the diacylamide structure **6f**. Control experiments with mixtures of different proportions of diacylamide **6f** and ester **4f** in the presence of acid or base showed no rapid interconversion. Therefore, this diacylamide cannot have been formed by rearrangement of enol ester and must have arisen directly from an intermediate. The two detectable formyl imides **6a** and **6f** thus provide confirmation of the postulated origin and decomposition of *N-tert*-butyldiacylamides proposed as the source of amide impurities.

Additional evidence for diacylamide intervention in a more representative case was obtained from the study of the reaction of ketenimine **2f** with acetic acid. Addition of **2f** to excess acid again gave keto amide **5f** (about 50%) together with an equivalent amount of acetic anhydride. The nmr spectrum was consistent

(10) I. Muramatsu, M. Itoi, M. Tsuji, and A. Hagitani, *Bull. Chem. Soc. Jap.*, **37**, 756 (1964).

(11) In the series of salicylamide esters from the *N*-ethylbenzisoxazolium cation, the lesser steric requirements of the formyl group permits *O,N*-acyl migration.[5]

(12) The adduct is represented for simplicity as **3**, the form presumed[1] to be produced initially.

(13) D. Y. Curtin and L. L. Miller, *J. Amer. Chem. Soc.*, **89**, 637 (1967).

(14) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **34**, 2742 (1969).

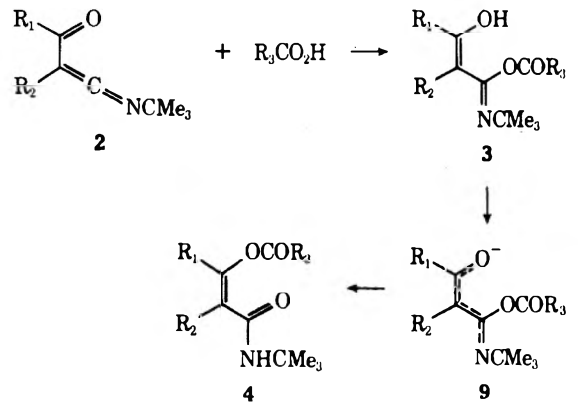
(15) The dependence of the outcome on the order of addition suggests that dehydration of formic acid involves the anhydride, following interception of the intermediate **3f** by formic acid.

with about a 2:1 ratio of the noninterception products, ester **4f** (R_3 = Me) and amide **7**, and the second diacylamide cleavage product **8f** was isolated from the reaction mixture.[16] Moreover, a transient *N-tert*-butyl peak was detected during nmr monitoring of the reaction. The complexity of the spectrum prevented a complete structural assignment on the basis of the nmr data, but the main change as the transient signal faded was the development of the amide *N-tert*-butyl peak, as would be expected for the diacylamide **6f**.

The occurrence of diacylamide formation with *N-tert*-butylacylketenimines presents the ironic result that the same structural factor which suffices to block *O,N*-acyl migration for most enol esters results in N-acylation as a side reaction of an earlier intermediate. Decomposition of an intermediate by N-acylation is only one example of the general situation that enol ester formation is less rapid relative to alternative reactions of the adducts from acylketenimines bearing the *N-tert*-butyl group. Previously it was found that azlactone formation was especially severe in the reaction of **2a** and hippuric acid.[14] The present results with formic acid and **2a** are consistent with a further new intermolecular reaction to give the acid anhydride. With the disubstituted ketenimine **2f**, both anhydride formation and increased N-acylation are clearly established.

The increased extent of side reactions in the *N-tert*-butyl series at least in part may be rationalized on the basis of the slow rate of the addition step and the accessibility of the transition state for rearrangement to enol esters. In the proposed[1] mechanism for the reaction of isoxazolium salts with carboxylate anions, it was argued that the most favorable direction of addition to the acylketenimines would give an adduct **3**[12] with the proper geometry for *O,O*-acyl migration. The simplest interpretation of a later finding,[5,14] that the intramolecular side reaction with peptide acids leading to azlactones was diminished by bases, would be favored conversion of the intermediate *via* its anion **9** to enol ester **4**. Accepting both these reasonable speculations, the most rapid pathway to enol ester, represented for the *N-tert*-butyl system, reduces to Scheme I. It has already been noted[14] that the

SCHEME I



relatively slow addition of carboxylic acids to the *N-tert*-butylcumulenes **2** gives rise to a medium effect. The intermediates from **2** undergo decomposition in the presence of a relatively high (drifting) concentration of unconsumed free acid, so that the environment may be less favorable for rearrangement to enol ester *via* the anion. In addition, the stability of the anion **9** relative to its conjugate acids would be reduced by the *N-tert*-butyl group. Both factors would tend to increase the importance of side reactions of **3** or its tautomers. These arguments could be extended to account for the still greater severity of side reactions with the disubstituted ketenimine **2f**, although an additional factor in that case might be the introduction of an unfavorable steric interaction in the anion **9**.

The simple picture of increased side reactions involving the conjugate acids of **9** is supported by partial isotope incorporation at the vinylic position of the enol ester **4a** (R_3 = $ZNHCH_2$) prepared in media containing exchangeable deuterium. In the original study of the reactions of isoxazolium salts,[1] the absence of such exchange established that the rearrangement was more rapid than equilibration with the CH tautomer of the initial adduct. The opposite result here shows that the *N-tert*-butyl substituent of **2a** does permit more favorable access to at least the CH tautomer prior to enol ester formation. The substituent influences cited above, then, probably are of general validity, but further scrutiny of the N-acylation side reaction has established that the foregoing analysis does not fully account for the behavior of the *N-tert*-butyl intermediates.

The extent of side reactions proceeding *via* the conjugate acids of **9**, according to Scheme I, should be subject to control by adjusting the acidity of the medium, as is dramatically true for azlactone formation.[14] However, testing this approach in the reaction of acetic acid with the ineffective ketenimine **2f** resulted in only a minor increase in the yield of enol ester when either excess ketenimine or even excess **2f** and **1** equiv of pyridine was employed.[17] At the same time the product distributions (Table I) for various conditions

TABLE I

Stoichiometry	Ester **4f**, %	Amide **7**, %	Keto amide **5f**, %
1.0 **2f** + 3.0 HOAc	35	9	56
1.0 **2f** + 2.0 HOAc	37	14	49
2.0 **2f** + 1.0 HOAc	46	40	14
2.0 **2f** + 1.0 HOAc + 1.0 pyridine	48	45	7

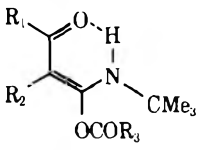
reveal a striking reversal of the proportions of amide **7** and keto amide **5f**. Although the magnitude of the side reactions is enhanced with the disubstituted ketenimine **2f**, the susceptibility of the N-acylation reaction to diversion to keto amide is not unique to this system. Previously a selective channeling of the less severe side reaction with cumulene **2f** was inferred from the increase of keto amide at the expense of amide as water was added to the reaction mixture.[4]

We consider the most likely explanation of these results to be that both by-products **3** and **7** are formed from a common intermediate that does not readily convert to enol ester **4**. The new results with **2f** make it unlikely that the intermediate in question is the

(16) While the involvement of adventitious moisture could lead to **8** directly, the spectral data show that the second fragment of diacylamide cleavage is the mixed anhydride of **8f** and acetic acid which undergoes hydrolysis during the work-up procedure.

(17) With **2a** and hippuric acid, the use of 1 equiv of pyridine results in a twofold decrease in the ratio of azlactone to enol ester.[14]

diacylamide **4** itself, since the observed transient species postulated to be diacylamide is not diverted to **5f** and anhydride in the presence of excess carboxylic acid. An attractive candidate instead would be an adduct **10** with the wrong geometry for *O,O*-acyl



10

migration. The results of Table I would reflect a competition for **10** between N-acylation to give diacylamide and interception to give anhydride that shows a dependence on free acid concentration similar to the situation in the addition of carboxylic acids to carbodiimides.[18] Possible routes to **10** would include isomerization of a common initial adduct (with the same acidity dependence as for rearrangement to enol ester) or direct formation by a different mode of addition to the acylketenimine. The latter possibility would permit an interpretation of the especially unfavorable outcome with the disubstituted cumulene **2f** in terms of the rotamer of the acylketenimine undergoing addition.[19] Still, a general explanation for the unfavorable influence of the *N-tert*-butyl group on N-acylation remains obscure. Moreover, whatever factors are actually responsible for the side reaction, they can be easily overridden, as shown by the clean formation of the enol ester **4f** (R_3 = Me_3C) from the disubstituted ketenimine **2f** and pivalic acid.

Regardless of the reasons for N-acylation in the *N-tert*-butyl series, the possibility of diverting the side reaction was utilized earlier to obtain improved yields in the formation of enol esters with the reagent *N-tert*-butyl-5-methylisoxazolium (**1a**) perchlorate. In our further study, we have examined the utility of **1a** in comparison with the original isoxazolium peptide reagent NEPIS.

For the preparation of enol esters (activation step), **1a** offers the special feature of an isolable intermediate acylketenimine (**2a**)[20] of potential value in cases where careful monitoring of the progress of addition to the cumulene or the avoidance of competitive ketenimine decomposition may be important. However, the previous studies have shown that utilization of the precursor isoxazolium salt itself for making enol esters does not detract from the results, in the general synthetic recipe developed to obtain maximum yields.[4] Tests with a variety of carboxylic acids and N-protected amino acids to date have shown that difficulty in product crystallization is sometimes a problem and, in three instances (Z-Ala-OH, Z-Tyr-OH, and Z-Met-OH), solid products have not been obtained. An additional practical concern was that the lower efficiency of enol ester formation with *N-tert*-butylcumulenes might result in side reactions with polyfunctional amino acids. Examination of this point has revealed that unprotected hydroxyl groups (Z-Tyr-OH and Z-Ser-OH) and the amide function of glutamine (Z-Gln-OH) do not lead to any complications. However, with the more sensitive acid asparagine (Z-Asn-OH), partial dehydration of the amide function was observed, in contrast to the successful use of this acid in couplings with NEPIS.[1] Similarly, it appears that application of **1a** to the preparation of esters of N-protected peptide acids is hazardous, despite the definition of special conditions (2-picoline solvent) that eliminated all traces of azlactone formation with hippuric acid.[14] Using the 2-picoline procedure with Young's test acid *N*-benzoylleucine as a representative sensitive case, short-wavelength azlactone absorption was detected in the infrared spectrum of the reaction mixture.

The general applicability of the β-acyloxy-*N-tert*-butylcrotonamide enol esters **4a** as acylating agents was shown previously by the quantitative conversion of the ester of Z-Gly-OH to the benzylamide.[5] The apparent second-order rate constant for the reaction with 1 equiv of benzylamine is approximately tenfold larger than that found[5] for the corresponding stable salicylamide ester from the *N*-ethylbenzisoxazolium cation under comparable conditions. Subsequent rate comparisons have shown the latter salicylamide esters to be on the order of 100-fold less reactive than the *p*-nitrophenyl esters.[6] The indirect rate comparison indicates that the enol esters **4a** themselves are relatively placid acylating agents. This modest level of reactivity may be useful where selectivity is desired, but could be an undesirable feature in couplings of hindered carboxyl components, where competing side reactions of the amine component could become important.

As a probe of the extent of amine component decomposition, the reaction of the unhindered ester of Z-Gly-OH with the dipeptide ester H-Gly_2-OEt, which is susceptible to diketopiperazine formation, was considered. Combination of equivalents of the reactants in MeCN (~0.2 *M* in each component), evaporation after 20 hr, and by-product **5a** removal by stirring with

water left 90% of Z-Gly_3-OEt of undepressed melting point—identical with the result for the same coupling mediated by NEPIS under similar conditions. Next, the compatibility of the esters with unprotected hydroxyl groups in the amine component was demonstrated by the similar (in EtOAc) preparation of pure Z-Gly-Ser-OMe in 80% yield. Finally, for comparison purposes, two couplings (to form Phth-Gly_2-OEt and Z-Gln-Tyr-OMe) were performed which had given relatively low yields (88 and 75%, respectively) with NEPIS.[1] The use of the purified esters **4a** did result in some yield improvement (92 and 82%, respectively) under comparable conditions, but with lower product purities as reflected in melting point depressions of 2–3°.

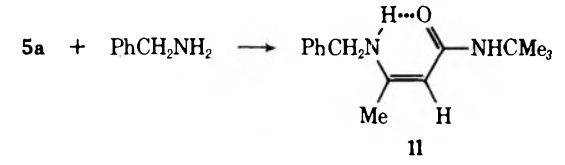
It is significant that couplings with the purified intermediate acylating agents do not provide marked improvement in contrast to the results for sequential activation and coupling with no intervening purification using NEPIS. The similarity of the outcome indicates that the extent of activation side reactions and enol ester decomposition are indeed small in the latter two-step procedure. The direct isolation of purer products with NEPIS follows from the efficiency of aqueous removal of by-products and side reaction products bearing the ionic sulfonate function. In con-

(18) D. F. Detar and R. Silverstein, *J. Amer. Chem. Soc.*, **88**, 1020 (1966).
(19) Olofson and Marino have presented arguments concerning the beneficial effects of the s-cis fused geometry on the outcome of the reaction.[7]
(20) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **88**, 3169 (1966).

trast, although the by-product **5a** is freely water soluble, traces of side reaction products in coupling with the esters **4a** may not be removed in the aqueous work-up.

Over-all, then, the main merit of the new reagent **1a** would be in cases where isolation of the intermediate enol esters is desirable for special reasons of convenience or for conducting couplings in solvents that do not readily bring NEPIS into solution. The isolable enol esters fail to provide significant improvement in the acylation of the amine component that would be desirable for stepwise peptide synthesis, and, given the lesser efficiency of enol ester formation with **1a**, overall yields for activation and coupling are lower than with NEPIS.

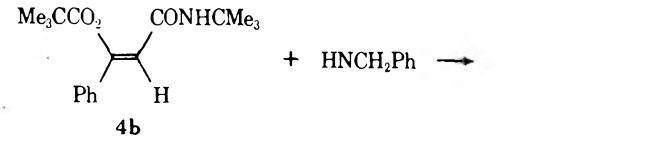
Scrutiny of possible side reactions in couplings with the enol esters also has brought to light a potential problem in applications to hindered acids. An obvious possibility would be condensation of amino acid esters with keto amide **5a**, as is well known for β-dicarbonyl compounds.[21,22] In the present case the enamine **11**



11

could be prepared in quantitative yield by evaporation of equivalents of **5a** and benzylamine in MeCN. As a measure of the severity of the side reaction, a bimolecular rate constant of approximately 5×10^{-3} l./mol min was estimated, which is roughly 3000 times smaller than for the rate of coupling with the enol ester of Z-Gly-OH. Even when coupling is 99% complete in this unhindered case, then, the desired reaction would be 30 times faster than the side reaction and only trace contamination results. At the opposite extreme, in the hindered case of pivalic acid, the reaction of the ester **4a** and benzylamine gave almost equimolar amounts of the amide and **11** after a 20-hr reaction time. On longer standing, drift toward the amide was observed as expected for the reversible condensation. Clearly, couplings with esters of hindered acids and nonselective, unhindered amine components should be avoided on account of the side reaction.

Finally, it should be stressed that the enamine side reaction is not a problem with the original isoxazolium salt reagent NEPIS. The ester **4b** (R_3 = Me_3C) was prepared as a stable model for hindered acylating agents from NEPIS. Only traces of the corresponding enamine could be detected in the coupling reaction with benzylamine. As a further test, under conditions where **5a** was 80% converted to **11**, the less reactive benzoylketo amide **5b** formed only **15%** of the condensation product in a much slower reaction. Thus, there is little likelihood that appreciable amounts of condensation product would result in the use of NEPIS and any traces of enamine would be effectively removed in the customary aqueous isolation.



4b **5b**

(21) E. Dane, F. Drees, P. Konad, and T. Dockner, *Angew. Chem., Int. Ed. Engl.*, **1**, 658 (1962).

(22) B. Halpern and L. B. Jones, *Nature (London)*, **202**, 592 (1964).

Experimental Section[23]

Thermal Decomposition of the Ester 4a of Carbobenzoxyglycine.—The ester[4] was heated in a vacuum (<0.1 mm) sublimation assembly having an ice water cold finger condenser. Above the melting point (89°) of the enol ester, condensate began to form, and heating was discontinued when bumping became severe (bath temperature 110°). The nmr spectrum of the condensate was consistent with a mixture of the known[4] compounds *N-tert*-butylacetoacetamide (**5a**) and carbobenzoxyglycine *N-tert*-butylamide (**7**, R_3 = $ZNHCH_2$).

Reaction of Acetyl-*N-tert*-butylketenimine (2a) and Formic Acid.—Formic acid (0.036 ml, 0.95 mmol) was added to **2a** (0.132 g, 0.95 mmol)[19] in 0.5 ml of $CDCl_3$ over a 6-min period. Considerable effervescence (presumably CO) was observed and the nmr spectrum of the solution revealed the characteristic signals of *N-tert*-butylacetoacetamide (**5a**) at δ 3.42 (s, CH_2), 2.22 (s, Me), and 1.32 (s, CMe_3), along with peaks expected for the enol ester **4a** (R_3 = H) at δ 8.15 (s, HCO, superimposed on signal for any remaining HCO_2H), 5.60 (br s, HC=C), 2.00 (m, MeC=C), and 1.32 (CMe_3, shown by integration to be superimposed on CMe_3 signal of **5a**). In addition there were peaks at δ 8.85 (s, HCO), 3.92 (s, CH_2), 2.22 (Me, shown by integration to be superimposed on Me signal of **5a**) and 1.57 (s, CMe_3), consistent with the diacylamide **6a** (R_3 = H). The integration was consistent with approximately 52 mol % **5a**, 34 mol % **4a**, and 12% **6a**. During a few hours, the peak attributed to **4a** disappeared while the ratio of **6a** (33%) to **5a** (65%) increased.

Attempts to separate **6a** from **5a** by trituration and/or distillation were unsuccessful.

Over a 10-day period, the nmr signals of the diacylamide **6a** disappeared completely as the spectrum showed a corresponding buildup of peaks for acetone and *N-tert*-butylformamide. The acetone was also identified by ir and isolation, after distillation from the reaction mixture, as the 2,4-DNP derivative.

Tests of Addition of Carbobenzoxyglycine to Acylketenimines 2a–e.—In all cases, 1 equiv of carbobenzoxyglycine was added at 0° to a stirred 2 *M* solution of the acylketenimine in $CDCl_3$. The reactions were monitored by nmr until **2** was consumed. The benzylic doublet, at slightly higher field (δ 3.68) than the corresponding signals for the enol esters **4** and carbobenzoxyglycine, was used to assay for **7** (R_3 = $ZNHCH_2$). Small signals amounting to a few per cent were detected along with the expected enol ester signals in the additions with *N-tert*-butylacetylketenimine (**2a**), *N-tert*-butylbenzoylketenimine (**2b**),[24] and *N-tert*-butylpivalylketenimine (**2c**),[24] but not with *N-tert*-butylformylketenimine (**2d**)[24] nor *N-tert*-butylformylmethylketenimine (**2e**).[24] Additional data are reported below for the new enol esters **4b** and **4e** which were isolated.

***N-tert*-Butyl-β-Carbobenzoxyglycyloxycinnamamide (4b, R_3 = $ZNHCH_2$).**—Evaporation of the reaction mixture above (from **2b**), dissolving the residue in CH_2Cl_2, and washing the solution with 5% $NaHCO_3$ then aqueous NaCl and drying (Na_2SO_4) left the crude ester. Recrystallization from benzene–petroleum ether (bp 30–60°) and then from EtOAc–heptane gave **4b** (R_3 = $ZNHCH_2$) as colorless needles: mp 139.5–140°; ir (CH_2Cl_2) 5.62 μ; nmr ($CDCl_3$) δ 7.28 (m, 10), 6.05 (s, 1), 5.83 (br, 2), 5.05 (s, 2), 4.23 (d, 2, J = 6 Hz), and 1.24 (s, 9).

Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.29; H, 6.40; N, 6.83. Found: C, 67.14; H, 6.38; N, 6.82.

***N-tert*-Butyl-β-Carbobenzoxyglycyloxymethacrylamide (4e, R_3 = $ZNHCH_2$).**—After the same work-up as above of the reaction mixture from **2e**, trituration of the residue with petroleum

(23) Melting points were determined with a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra were run on a Varian A-60 spectrometer, and chemical shifts are reported in τ values relative to tetramethylsilane as an internal standard. The ir spectra were recorded on a Perkin-Elmer 137 spectrophotometer and the rotations were measured with a thermostated Perkin-Elmer 141 automatic polarimeter. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

(24) D. J. Woodman and Z. L. Murphy, *J. Org. Chem.*, **34**, 3451 (1969).

ether left an 82% yield of 4e (R_3 = ZNHCH$_2$), mp 87.6–88°. Recrystallization from CCl_4–heptane gave material of mp 88.5–89°; ir (CH_2Cl_2) 5.62 μ; nmr ($CDCl_3$) δ 7.29 (m, 6), 6.28 (br, 1), 5.82 (br, 1), 5.10 (s, 2), 4.03 (d, 2, J = 6 Hz), 1.81 (d, 3, J = 1 Hz), 1.33 (s, 9).

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.04; H, 6.96; N, 8.04. Found: C, 62.24; H, 7.06; N, 8.20.

Reaction of Carbobenzoxyglycine with *N-tert*-Butylbenzoylmethylketenimine (2f).—Repetition of the nmr assay with **2f**[24] resulted in the formation of a precipitate, while the spectrum of the supernatant showed the presence of remaining **2f**. After evaporation of the $CDCl_3$, the ir spectrum of the residue contained shoulders at 5.47 and 5.68 μ for the anhydride of carbobenzoxyglycine. Approximately 13% of **7** (R_3 = ZNHCH$_2$) was also detectable by nmr. Evaporation of the solvent and addition of petroleum ether to an EtOAc solution of the residue resulted in the precipitation of close to 20% of the crude anhydride: mp 111–115° (mp 124–125° after two further recrystallizations) (lit mp 115–116°,[25] 118–119,[26] 120.5–124°[27]); ir (MeCN), 5.45 and 5.70 μ (lit.[21] 5.44 and 5.70 μ); nmr (MeCN) δ 7.33 (s, 5), 6.00 (br, 1), 5.00 (s, 2), and 4.00 (d, 2, J = 6 Hz). As reported by other workers, addition of Et_3N to an MeCN solution led to the disappearance[21] in the ir spectrum of the 5.47-μ peak and the development of new absorptions at 5.80, 5.88, 6.05, 6.25, and 8.35 μ.

When the experiment was repeated with slow addition (45 min) of the acid to **2f**, no precipitate was observed and a larger proportion (32%) of **7** was detected by nmr.

Reaction of Formic Acid and 2f.—The usual test reaction procedure with addition of **2f** over a 15-min period to excess formic acid resulted in considerable effervescence (presumably CO) and the product nmr spectrum contained only signals for keto amide. The nmr spectrum of the product mixture was consistent with unreacted **2f**, 38% of keto amide **5f** [δ 1.28 (CMe_3), 4.25 (q, CHMe, CH**Me** masked)], 15% of enol ester **4f** (R_3 = H) [δ 1.38 ($NCMe_3$), 1.98 (MeC=, HCO masked)], and 47% of diacylamide **6f** (R_3 = H) [δ 1.50 ($NCMe_3$), 1.40 (CH**Me**), 5.37 (C**H**Me), 8.8 (HCO)].

There was no change in composition of the above reaction mixture within 24 hr.

In a modified experiment, formic acid was added in portions to **2f** until the cumulene had all been consumed. Evaporation and repeated fractional crystallization of the residue from CCl_4–heptane provided crystalline **6f** (R_3 = H) (approximately 10 mol % impurity by nmr): mp 70.5–71°; ir (CCl_4) broad imide band centered at 5.92 μ; nmr ($CDCl_3$) δ 8.83 (s, 1, HCO), 8.20–7.43 (m, 5, ArH), 5.40 (q, 1, J = 7 Hz, CHMe), 1.57 (s, 9, CMe_3), and 1.44 (d, 3, J = 7 Hz, CH**Me**).

Diacylamide (**6f**) rich and 1:1 diacylamide–enol ester (**4f**) mixtures from the above fractional crystallization were each allowed to stand in $CDCl_3$ solution in the presence of added base (Et_3N) and acid (HCO_2H), but no changes in composition were observed by nmr within 24 hr.

2-Benzoyl-*N-tert*-butylpropionamide (5f).—An authentic sample of keto amide **5f** was prepared by ring opening 0.316 g (1.0 mmol) of *N-tert*-butyl-4-methyl-5-phenylisoxazolium (**2f**) perchlorate with 0.14 ml (1.0 mmol) of Et_3N in 10 ml of MeCN and adding excess water to the resulting solution. After 12 hr, the solvent was evaporated and the residue was stirred for 24 hr in 12 ml of water. Digestion of the precipitate on the steam bath and filtration gave 0.213 g (91%) of colorless crystals, mp 141.5–145° (some prior softening). Recrystallization from EtOH–water gave **5f**: mp 144–145.5°; nmr ($CDCl_3$) δ 8.23–7.30 (m, 5), 6.30 (br, 1), 4.28 (q, 1, J = 7 Hz), 1.52 (d, 3, J = 7 Hz), and 1.32 (s, 9).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.22; N, 6.00. Found: C, 71.96; H, 8.19; N, 5.98.

Reaction of Benzoyl-*N-tert*-butylmethylketenimine (2f) and Acetic Acid.—The usual test procedure with addition of **2f** over a 10-min period to 3 equiv of HOAc gave a solution that contained strong anhydride absorption at 5.45 μ in the ir spectrum. The nmr spectrum, in addition to the peak at δ 2.05 for excess HOAc, showed signals at δ 1.29 (s, CMe_3), 1.48 (d, J = 7 Hz, CH**Me**), and 4.30 (q, J = 7 Hz, CHMe) for the keto amide **5f** (56%) along with a corresponding strong peak at δ 2.18 for Ac_2O. Signals for the enol ester **4f** (R_3 = Me, 35%) were evident at δ 1.39 (s, CMe_3), 1.96 (s, MeC=C), and 2.14 (s, $MeCO_2C$). The amide **7** (R_3 = Me, 9%) was tentatively identified by its *tert*-butyl peak at δ 1.32 (s, CMe_3, **Me**CONH singlet at δ 1.87 apparent as a shoulder), and a low-field acetyl singlet at δ 2.38 was consistent with a corresponding amount of the mixed anhydride of **8f** and acetic acid. The assigned chemical shifts agreed with the nmr spectrum of an authentic solution of acetic anhydride, acetic acid, keto amide, and amide. As expected, reduced pressure evaporation of the reaction mixture removed the Ac_2O and HOAc. Further evaporation at 0.06 mm led to the partial removal of the peaks assigned to amide, and the nmr of the cold-trap condensate was the same as that of an authentic sample of amide.

Detection of an Intermediate in the Addition of Acetic Acid to 2f and Isolation of 2-Benzoylpropanoic Acid (8f).—Upon repetition of the above experiment with 2 equiv of HOAc, immediate nmr assay revealed a new *tert*-butyl peak at δ 1.15 and a methyl singlet at δ 1.88 consistent with the diacylamide **6f** (R_3 = Me) present in an amount between $^1/_3$ and $^1/_2$ that of the enol ester **4f** (R_3 = Me). At the outset, only a small *tert*-butyl signal for amide **7** (R_3 = Me) was evident, but within 30 min the signals attributed to **6f** disappeared as peaks for **7** increased in intensity relative to those for ester and keto amide.[28] In the same period, the acetyl methyl singlet assigned the mixed anhydride developed. Integration of the product spectrum indicated the pressure of 49% keto amide, 37% enol ester, and 14% amide.

A reaction mixture of the above stoichiometry was worked up by dilution with $CHCl_3$ and extraction with $NaHCO_3$. Acidification of the bicarbonate extract, back-extraction into $CHCl_3$, drying (Na_2SO_4) and evaporation of the organic phase, and recrystallization of the residue from benzene–petroleum ether gave 2-benzoylpropanoic acid (**8f**): mp 77–78.5° (lit.[29] mp 82–83°); nmr ($CDCl_3$) δ 8.80 (s, 1), 8.21–7.28 (m, 5), 4.43 (q, 2, J = 7 Hz), 1.49 (d, 3, J = 7 Hz). The acid was decarboxylated by heating on the steam bath for 20 min and passed through a short column of neutral alumina with ether. The residue upon evaporation of the solvent was identified as propiophenone by nmr and ir.

Addition of Acetic Acid to Excess 2f.—The usual test procedure with addition of HOAc over a 10-min period to 2 equiv of **2f** resulted in qualitatively the same outcome as above. A larger transient signal (roughly equivalent to the enol ester *tert*-butyl peak) was observed on rapid monitoring, and the proportion of keto amide and amide (and the corresponding coproducts) in the final product changed to 14 and 40%, respectively, together with 46% of enol ester.

Repetition of the experiment with an added 1 equiv of pyridine gave 7% keto amide, 45% amide, and 48% enol ester.

Formation of Enol Ester 4a (R_3 = ZNHCH$_2$) in the Presence of D_2O.—To a solution of 0.213 g (1.0 mmol) of carbobenzoxyglycine and 0.18 ml (1.3 mmol) of Et_3N in 10 ml of MeCN containing 1.8 ml (90 mmol) of D_2O was added 0.305 g (1.3 mmol) of the perchlorate salt of **1a**. After evaporation of the solvent, stirring the residue with water and recrystallization from benzene–petroleum ether, the nmr spectrum of the product **4a** (R_3 = ZNHCH$_2$) was in accord with only 0.3–0.4 vinyl hydrogens at δ 5.4, in comparison with the integration for the methylene signal at δ 4.08. In a control experiment, the enol ester was subjected to the work-up conditions, and no diminution of the δ 5.4 signal was observed.

***N-tert*-Butyl-β-trimethylacetoxy-α-methylcinnamamide (4f, R_3 = CMe_3).**—The usual test procedure adding pivalic acid to excess **2f** gave, after 3 hr, a product mixture that had nmr signals for unreacted **2f**, the expected product **4f** (R_3 = CMe_3), and no by-products. Precipitation with petroleum ether gave colorless needles, mp 102–105.3°. Recrystallization from heptane gave material of mp 104.5–106.5°: uv max (MeCN) 244 nm (ϵ 12,600); ir (CH_2Cl_2) 5.78 μ; nmr ($CDCl_3$) δ 1.22 (s, 9), 1.32 (s, 9), 1.87 (s, 3), 5.93 (br, 1), 7.23 (s, 5).

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.88; H, 8.59; N, 4.41. Found: C, 71.79; H, 8.39; 6, 4.51.

(25) D. F. DeTar, R. Silverstein, and J. Rodgers, Jr., *J. Amer. Chem Soc.*, **88**, 1024 (1966).

(26) M. Brenner, J. P. Zimmerman, J. Wehrmuller, P. Quitt, A. Hartmann W. Schneider, and J. Beglinger, *Helv. Chim. Acta*, **40**, 1497 (1957).

(27) J. Baddiley, J. G. Buchanan, R. Hodges, and J. F. Prescott, *J. Chem. Soc.*, 4769 (1957).

(28) A second, smaller signal at lower field was also observed to build in several cases where the disappearance of the transient was monitored, but the structure of the minor decomposition product has not been established.

(29) E. Hope and W. H. Perkin, Jr., *J. Chem. Soc.*, **95**, 2045 (1909).

Preparation of Enol Esters (4a).—The general procedure reported previously[4] was used for the acids below with the modifications noted.

tert-**Butyloxycarbonyl-L-leucine.**—The residue from the procedure with 2.07 g (8.0 mmol) of BOC-Leu-OH·H_2O (prepared according to the procedure of Schwyzer[30]), mp 78–82.5° (lit.[30] mp 78–81°), was taken up in 150 ml of EtOAc, and the solution was washed with aqueous NaCl and 5% aqueous $NaHCO_3$. After drying (Na_2SO_4), the solution was evaporated to a small volume and flooded with 80 ml of petroleum ether (bp 40–60°). Seeding, chilling overnight, filtration and drying gave 1.8 g (76%) of tan solid: mp 98–101° (mp 103–104° after recrystallization from CCl_4–heptane and EtOAc–petroleum ether); nmr ($CDCl_3$) δ 5.64 (br, 1), 5.42 (unresolved m, 1), 5.16 (unresolved m, 1), 4.41 (unresolved m, 1), 1.95 (unresolved m, 3), 1.70 (br, 3), 1.42 and 1.31 (both s, total 18), and 0.97 (d, 6).

Anal. Calcd for $C_{19}H_{34}N_2O_5$: C, 61.58; H, 9.27; N, 7.56. Found: C, 61.72; H, 9.21; N, 7.62.

Carbobenzoxy-L-serine.—The general procedure directly gave 87% of the ester: mp 77–81° (mp 81–83° after recrystallization from CCl_4 or C_6H_6 and petroleum ether); nmr ($CDCl_3$) δ 7.38 (s, 5), 5.86 (br, 2), 5.49 (unresolved m, 1), 5.18 (s, 2). 4.42 (br, 2), 3.89 (br, 1), 1.93 (s, 3), and 1.40 (s, 9); $[\alpha]^{19}D$ −92.3° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.29; H, 6 94; N, 7.40. Found: C, 60.16; H, 7.06; N, 7.28.

Carbobenzoxy-L-glutamine.—The general procedure (extraction work-up) followed by precipitation with $CHCl_3$–petroleum ether gave 73% of the ester: mp 96.5–98.5° after drying several days *in vacuo* (mp 103–105° after recrystallization from $CHCl_3$–petroleum ether); nmr (MeCN) δ 7.37 (s, 5), 5.53 (unresolved m, 1), 5.12 (s, 2), and 1.25 (s, 9); $[\alpha]^{24}D$ −42.2° (*c* 1, MeCN).

Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 59.97; H, 7.20; N, 9.99. Found: C, 59.81; H, 7.01; N, 9.87.

Carbobenzoxy-L-alanine, Carbobenzoxy-L-methionine, and Carbobenzoxy-L-tyrosine.—The general procedure gave oils showing the expected enol ester ir absorption near 5.65 μ but which resisted a variety of attempts at initiating crystallization.

Carbobenzoxy-L-asparagine.—To a solution of 0.266 g (1.0 mmol) of carbobenzoxy-L-asparagine and 0.14 ml (1.0 mmol) of Et_3N in 10 ml of MeCN was added 0.240 g (1.0 mmol) of *N-tert*-butylacetylketenimine After evaporation of the solvent, the residue was dissolved in EtOAc and washed with aqueous NaCl and 5% $NaHCO_3$. The nmr spectrum of the neutral residue showed keto amide to be a major constituent. Acidification of the $NaHCO_3$ phase, extraction with CH_2Cl_2, evaporation, and several recrystallizations of the residue gave 0.01 g of white powder, mp 125–126°, identical with authentic carbobenzoxy-β-cyanoalanine prepared by the method of Liberek.[31]

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.05; H, 4.88; N, 11.29. Found: C, 57.95; H, 4.78; N, 11.09.

Benzoyl-L-leucine.—To 0.169 g (1.21 mmol) of *N-tert*-butylacetylketenimine in 6 ml of 2-picoline was added with stirring 0.285 g (1.21 mmol) of benzoyl-L-leucine (prepared by the method of Williams and Young)[32] along with 6 ml more of solvent. After 20 hr, the solvent was evaporated. The ir spectrum (MeCN) of the residue contained weak azlactone absorption at 5.52 μ as well as a strong enol ester peak at 5.69 μ.

In a duplicate experiment, isolation of the enol ester possessing optical activity established, at least, that complete racemization *via* azlactone does not result under these conditions. Treatment of the reaction residue with petroleum ether gave 0.217 g (48%) of tan solid: mp 115–118.5° (needles of mp 118–119° after two recrystallizations from $CHCl_3$–heptane); nmr ($CDCl_3$) δ 8.30–7.17 (m, 6), 6.15 (s, 1), 5.49 (s, 1), 4 93 (unresolved m, 1), 1.88 (unresolved m, 6), 1.33 (s, 9), and 1.0 (m, 6); $[\alpha]^{23.1}D$ −84.5° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.34; H, 8.09; N, 7.48. Found: C, 67.16; H, 7.87; N, 7.46.

Coupling Tests.—As a general procedure for the preparation of the compounds below, exact equivalents each of the appropriate enol ester, the amino acid ester hydrochloride, and Et_3N were combined in MeCN (~0.2 *M* in each reactant). The solution was stirred overnight or for 24 hr and evaporated under reduced pressure. The product was isolated by thorough stirring with hot water, filtration, and drying over P_2O_5 *in vacuo*.

Carbobenzoxytriglycine Ethyl Ester.—The procedure gave 90% of the protected tripeptide, mp 168.5–169.5° with softening (mp 168–169° after recrystallization from EtOH).

Carbobenzoxyglycyl-L-serine Methyl Ester.—The residue from the general reaction procedure (EtOAc solvent) was partitioned between aqueous NaCl and EtOAc. The dried (Na_2SO_4) organic layer was evaporated and the residue was crystallized from CCl_4 at −20°. Recrystallization from benzene gave 80% of solid, mp 96–97°.

Phthaloyldiglycine Ethyl Ester.—The procedure gave 92% of white powder, mp 195–196.5° (fine needles, mp 197–199° after recrystallization from EtOH–H_2O).

Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.91; H, 4.87; N, 9.65. Found: C, 58.04; H, 4.84; N, 9.61.

Carbobenzoxy-L-glutaminyl-L-tyrosine Methyl Ester.—The procedure ($MeNO_2$ solvent) gave 82% of solid, mp 197–200° dec after recrystallization from DMF–H_2O.

Anal. Calcd for $C_{23}H_{27}N_3O_7$: C, 60.35; H, 5.96; N, 9.19. Found: C, 60.21; H, 5.87; N, 9.16.

β-Benzylamino-*N-tert*-butylcrotonamide (11).—A solution of 0.314 g (2.0 mmol) of *N-tert*-butylacetoacetamide (**5a**) and 0.22 ml (2.0 mmol) of $PhCH_2NH_2$ in 20 ml of MeCN showed carbonyl absorption for **5a** after standing overnight at room temperature. To force the reaction to completion, the solvent was evaporated under reduced pressure, leaving 0.49 g (100%) of white solid: mp 96–101° (mp 103–105° after recrystallization from CCl_4–petroleum ether); nmr ($CDCl_3$) τ 0.65 (br, 1), 2.72 (s, 5), 5.20 (br, 1), 5.65 (unresolved m, 3), 8.20 (s, 3), and 8.65 (s, 9).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.12; H, 9.01; N, 11.37. Found: C, 73.05; H, 8.75; N, 11.30.

Rate of Condensation of Benzylamine with *N-tert*-Butylacetoacetamide 5a.—A solution of 0.157 g (1.0 mmol) of **5a** and 0.107 g (1.0 mmol) of $PhCH_2NH_2$ in 10 ml of MeCN at ambient temperature (22°) was assayed by ir to estimate the concentration of **5a** from the corrected absorbance at 5.88 μ. A plot of 1/[**5a**] was linear over two half-lives, giving an apparent second-order rate constant of approximately 5×10^{-3} l./mol min.

Reaction of β-Pivaloxy-*N-tert*-butylcrotonamide[4] and Benzylamine.—A solution of 0.085 g (0.35 mmol) of the enol ester **4a** (R_3 = CMe_3) of pivalic acid[5] and 0.038 ml (0.35 mmol) of $PhCH_2NH_2$ in 0.5 ml of $CDCl_3$ was assayed by nmr. After 20 hr, the ratio of enamine **11** to desired amide was 3:4 with considerable unreacted enol ester remaining. On long standing, loss of **11** and enol ester accompanied by an increase in **5a** and amide (1:3 ratio after 3 weeks) was observed.

β-Pivaloxy-*N-tert*-butylcinnamamide (4b, R_3 = CMe_3).—To a solution of 0.21 ml (1.5 mmol) of Et_3N in 12 ml of MeCN was added 0.453 g (1.5 mmol) of *N-tert*-butyl-5-phenylisoxazolium perchlorate[33] with magnetic stirring. After addition of 1 equiv of pivalic acid, the solvent was immediately evaporated at room temperature, and the residual pale yellow oil was taken up in 30 ml of EtOAc and washed three times with 5 ml each of aqueous NaCl, 5% $NaHCO_3$, and aqueous NaCl. Evaporation of the dried (Na_2SO_4) organic solution and recrystallization of the residue from heptane gave 0.361 g (78%) of off-white crystals: mp 115–116.5° (colorless needles, mp 116–117° after recrystallization from CCl_4–heptane); nmr ($CDCl_3$) δ 7.47 (unresolved m, 5), 6.07 (s, 1), 5.88 (br, 1), and 1.42 (s, 18).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.88; H, 8.59; N, 4.41. Found: C, 71.79; H, 8.39; N, 4.51.

Spectral Tests of the Condensation Reaction with 5b.—After 48 hr, only trace peaks at δ 4.47 (s) and 4.18 (d, J = 6 Hz) assignable to the condensation product could be detected in the nmr spectrum of the product mixture from the reaction of 0.107 g (0.35 mmol) of **5b** (R_3 = CMe_3) and 0.038 ml (0.35 mmol) of $PhCH_2NH_2$ in 0.5 ml of $CDCl_3$.

After 15 hr, the nmr spectrum of a solution originally of 0.067 g (0.4 mmol) of **5b** and 0.044 ml (0.4 mmol) of $PhCH_2NH_2$ contained the above enamine signals corresponding to 15% conversion. In a comparison test with **5a** in place of **5b**, 80% transformation to **11** resulted in the same time.

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Registry No.—**1a** perchlorate, 10513-45-8; **1b**, 10514-54-2; **2a**, 10513-47-0; **2b**, 10513-46-9; **2e**, 42221-95-4; **2f**, 21555-07-7; **2f** perchlorate, 42221-97-6; **4a** (R_3 = H), 42221-98-7; **4a** (R_3 =

(30) R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959).

(31) B. Liberek, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **10**, 407 (1962).

(32) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).

(33) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966).

ZNHCH$_2$), 19625-78-6; **4a** (R$_3$ = CMe$_3$), 21995-77-7; **4a** (R$_3$ = *tert*-butyloxycarbonyl-L-leucyl), 42222-15-1; **4a** (R$_3$ = carbobenzoxy-L-seryl), 42222-16-2; **4a** (R$_3$ = carbobenzoxy-L-glutamyl), 42222-17-3; **4a** (R$_3$ = benzoyl-L-leucyl), 42222-19-5; **4a** (R$_3$ = carbobenzoxyglycylglycyl), 42222-24-2; **4a** (R$_3$ = phthaloylglycyl), 21995-78-8; **4a** (R$_3$ = carbobenzoxy-L-glutaminyl), 42222-17-3; **4b** (R$_3$ = ZNHCH$_2$), 42222-01-5; **4b** (R$_3$ = CMe$_3$), 42222-02-6; **4e** (R$_3$ = ZNHCH$_2$), 42222-03-7; **4f** (R$_3$ = H), 42222-04-8; **4f** (R$_3$ = CMe$_3$), 42222-05-9; **4f** (R$_3$ = Me), 42222-14-0; **5a**, 42222-06-0; **5b**, 42222-07-1; **5f**, 42222-08-2; **6a** (R$_3$ = H), 42222-09-3; **6f** (R$_3$ = H), 42222-10-6; **7** (R$_3$ = ZNHCH$_2$), 21995-76-6; **8f**, 4767-01-5; **11**, 42222-13-9; formic acid, 64-18-6; acetic acid, 64-19-7; carbobenzoxy-β-cyanoalanine, 3309-41-9; carbobenzoxytriglycine ethyl ester, 2503-35-7; carbobenzoxyglycyl-L-serine methyl ester, 10239-27-7; phthaloyldiglycine ethyl ester, 2641-02-3; carbobenzoxy-L-glutaminyl-L-tyrosine methyl ester, 42222-23-1; benzylamine, 100-46-9; pivalic acid, 75-98-9; carbobenzoxyglycine, 1138-80-3; carbobenzoxy-L-asparagine, 2304-96-3; benzoyl-L-leucine, 1466-83-7; glycine ethyl ester hydrochloride, 623-33-6; L-serine methyl ester hydrochloride, 5680-80-8; L-tyrosine methyl ester hydrochloride, 3417-91-2.

Synthesis of 2-Nor-2-formylpyridoxal 5'-Phosphate, a Bifunctional Reagent Specific for the Cofactor Site in Proteins

ANNA POCKER

Department of Biochemistry, University of Washington, Seattle, Washington 98195

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A facile and general procedure was developed for the preparation of vitamin B$_6$ amine oxides and their corresponding 2-carbinol rearrangement products. These compounds served as intermediates in the synthesis of the dicarboxaldehyde 2-nor-2-formylpyridoxal 5'-phosphate and of 2-nor-2-formyl-4-deoxypyridoxol 5'-phosphate, an isomer of pyridoxal 5'-phosphate. Both analogs were prepared for the purpose of exploring the spacial configuration of polypeptide chains at the pyridoxal 5'-phosphate site in glycogen phosphorylase (EC 2.4.1.1) and other enzymes.

The introduction of stable covalent bridges between amino acid residues has been recently utilized as a direct chemical tool to provide information about the spacial orientation of polypeptide chains in proteins.[1] It occurred to us that this approach, coupled with a systematic application of affinity labeling techniques, may reveal the architecture of important sites on enzymes and perhaps cont ribute to the elucidation of the catalytic mechanism. 2-Nor-2-formylpyridoxal 5'-phosphate (**9**) and 2-nor-2-formyl-4-deoxypyridoxol 5'-phosphate (**4**)[2] were synthesized as part of a project designed to probe the three-dimensional structure around the pyridoxal 5'-phosphate pocket in glycogen phosphorylase (EC 2.4.1.1)[3] and a number of other enzymes. Earlier investigations indicated that the absence of the 2-methyl group has little effect on the activity of the cofactor.[3,4] Consequently, an additional functionality was anchored at this position in the expectation that the enzyme will conserve a high degree of specificity for this analog and thus promote the formation of a bisazomethine cross-linkage at the PLP site.

The synthetic pathway, as depicted in Scheme I, is based on an improved two-step synthesis of 2-pyridine carbinol analogs serving as intermediates for the final products described herein. When *m*-chloroperbenzoic acid[5] is employed in either protic or aprotic solvents in the cold, a smooth N-oxidation of vitamin B$_6$ compounds proceeds. Although several syntheses of pyridoxol *N*-oxide had been published,[6,7] none would seem to equal the general applicability or good yields obtained with this reagent. Ethanol was frequently used as solvent from which the amine oxides crystallized out during the course of oxygenation. Protection of a formyl group was effected by hemiacetal formation; otherwise extensive oxidation to the corresponding carboxylic acid is the preferred pathway as noticed in the quantitative conversion of pyridoxal 5'-phosphate to 4-pyridoxic acid 5'-phosphate. On the other hand, carbinol groups are attacked only on a limited scale and the relatively small improvements in yield do not warrant the work involved in protection and deprotection. Thus several compounds in the vitamin B$_6$ group were readily converted to the amine oxides with the exception of the PLP diethyl acetal, which under a variety of conditions gave rise to low yields and a number of by-products. In a second step, an intramolecular rearrangement[8] of the amine oxides to the corresponding 2-pyridine carbinols was effected by trifluoroacetic anhydride [(TFA)$_2$O], a reagent which was not previously utilized for such conversions on a preparative scale.[9] We found this anhydride to be superior to acetic anhydride in that it required mild conditions for acylation and gave rise to fewer by-products.

With ω-hydroxypyridoxol readily available, attempts were made to oxidize **7c** to **8** by activated manganese dioxide. The complex mixture of products thus obtained was fractionated on an ion-exchange column and was found to include ω-hydroxypyridoxal (**7a**) and 2-nor-2-formylpyridoxol as well as other acidic components, but only small amounts of the desired dicarbox-

(1) F. Wold, *Methods Enzymol.*, **25B**, 623 (1972).

(2) Abbreviations used are as follows: ω-hydroxy indicates the introduction of a 2'-hydroxyl group and 2-nor-2-formyl, the replacement of a 2-methyl with a 2-formyl; PLP, pyridoxal 5'-phosphate; *m*-CPBA, *m*-chloroperbenzoic acid; PPA, polyphosphoric acid; THF, tetrahydrofuran; (TFA)$_2$O, trifluoroacetic anhydride.

(3) For previous work on this subject see A. Pocker and E. H. Fischer, *Biochemistry*, **8**, 5181 (1969); S. Shaltiel, J. L. Hedrick, A. Pocker, and E. H. Fischer, *ibid.*, **8**, 5189 (1969).

(4) E. E. Snell, *Vitam. Horm. (New York)*, **28**, 265 (1970); W. Dowhan, Jr., and E. E. Snell, *J. Biol. Chem.*, **245**, 4629 (1970).

(5) J. Cymerman Craig and K. K. Purushothaman, *J. Org. Chem.*, **35**, 1721 (1970).

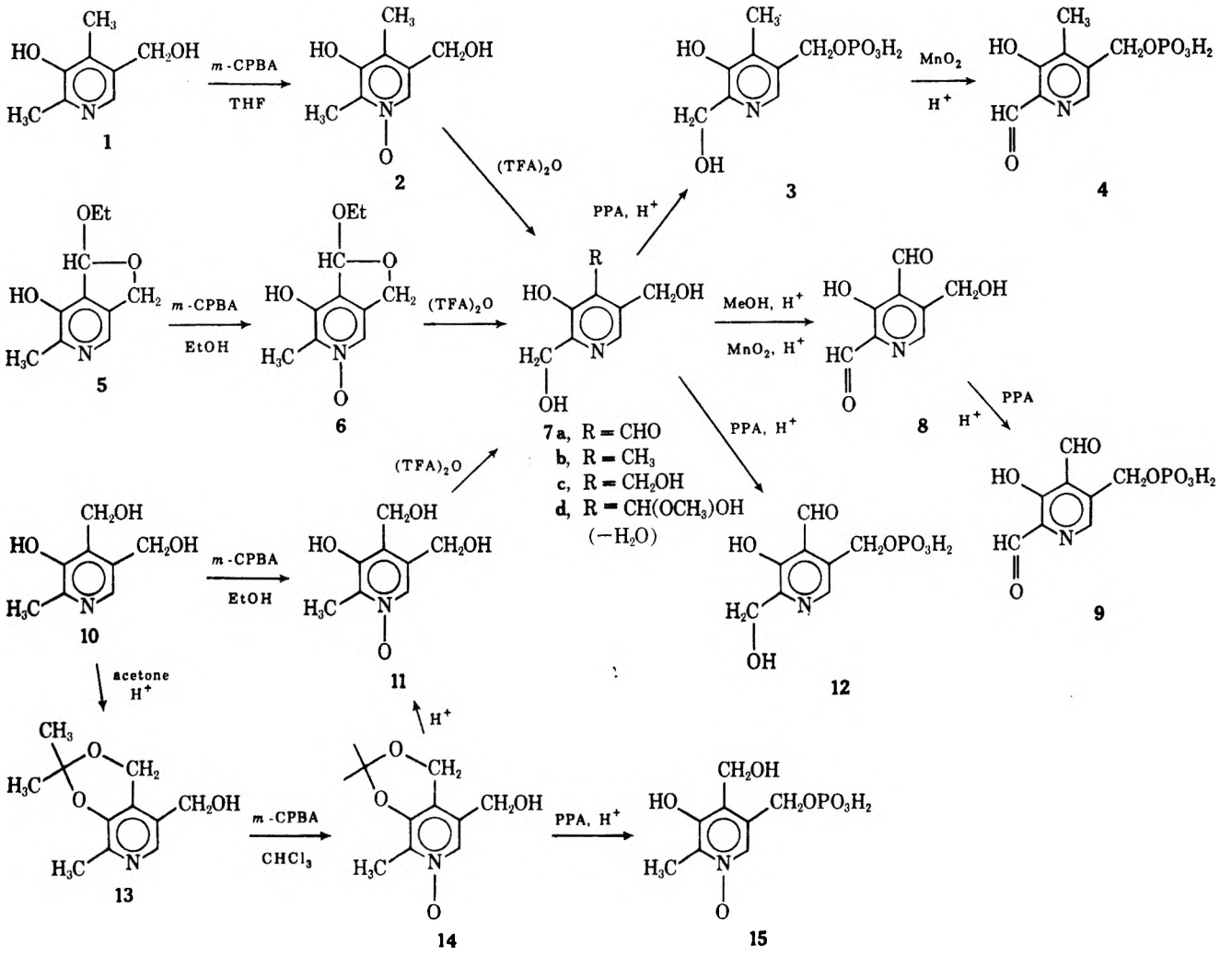
(6) T. Sakuragi and F. A. Kummerow, *J. Org. Chem.*, **24**, 1032 (1959).

(7) G. R. Bedford, A. R. Katritzky, and H. M. Wuest, *J. Chem. Soc.*, 4601 (1963).

(8) S. Oae, *Tetrahedron*, **20**, 2677 (1966).

(9) Trifluoroacetic anhydride was previously employed on a preparative scale in a Beckmann rearrangement [see W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 6522 (1957)] and in mechanistic studies of N–O bond cleavage of amine oxides [T. Koenig, *ibid.*, **88**, 4045 (1966)].

SCHEME I



aldehyde. Consequently, **8** was obtained by the selective oxidation of ω-hydroxypyridoxal methyl hemiacetal (**7d**) followed by acid hydrolysis. Phosphorylation of the 5-hydroxymethyl function was effected with polyphosphoric acid by well-established procedures[10,11] to afford **9**.

A similar synthesis gave 2-nor-2-formyl-4-deoxypyridoxol 5′-phosphate **4**, a cofactor analog possessing a divergent orientation of reactive groups around the pyridine ring. Likewise, the preparation of ω-hydroxypyridoxal 5′-phosphate (**12**), previously obtained *via* an elaborate procedure,[12] is readily accomplished starting from **7a** (unpublished results). This approach constitutes a general route for the conversion of 2-methylpyridoxol analogs to their 2-formyl derivatives and opens the way to further modifications of this position.

Verification of the structure of the new compounds proceeded in a number of ways. Whereas 3-pyridinols display in general only one absorption band at acid pH, the amine oxides consistently show two strong bands, as illustrated in Table I. Therefore, ultraviolet spectra served as a diagnostic tool to differentiate the amine oxides from their precursors as well as from their 2-carbinol derivatives. Moreover, the course of N-oxidation can be conveniently monitored by following the marked hypsochromic shift (*ca.* 20 nm) of the $\pi-\pi^*$ transition which occurs in ethanolic solution; the contribution of the reagent *m*-CPBA is minimal. Aromatic amine oxides are known to possess low acidic dissociation constants and are consequently singled out from all other intermediates by migration in an electrical field and on cationic exchangers.

Furthermore, the conversion of the bases to the 2-carbinol derivatives was established employing nmr spectroscopy by following the disappearance of the 2-methyl proton signals in the cationic species and the appearance of the 2-methylene signals, the latter being clearly distinct from both the 4- or 5-methylene peaks as reported in Table II.[13] The presence of the ring proton signal coupled with a positive Gibbs reaction given by all the intermediates ruled out a pyridone structure. It has been established that both hydration and hemiacetal formation in pyridoxal derivatives increases with the acidity of the solution. Consequently, the aldehydic C-4 proton signal is shifted to a higher field and appears as a doublet, the result of coupling to one of the 5-methylene protons. The nonequivalence of the latter is apparent only at higher pH.

(10) E. A. Peterson, H. A. Sober, and A. Meister, *Biochem. Prep.*, **3**, 29 (1953).

(11) M. Iwanani, T. Numata, and M. Murakami, *Bull. Chem. Soc. Jap.*, **41**, 161 (1968).

(12) Y. Nakai, F. Nasugi, N. Ohishi, and S. Fukui, *Vitamins (Kyoto)*, **38**, 189 (1968).

(13) W. Korytnyk and R. P. Singh, *J. Amer. Chem. Soc.*, **85**, 2813 (1963), and references cited therein.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF INTERMEDIATES AND FINAL PRODUCTS

Compd	0.1 N HCl		Phosphate buffer pH 7		0.1 N NaOH	
	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}
Pyridoxal *N*-oxide	291	4970	310	5600	312[a]	6200
	258	7900	393	2400	387	1800
4-Deoxypyridoxol *N*-oxide (2)	285	6500	317	5900	317[a]	7200
	258	4100				
Pyridoxol 5′-phosphate *N*-Oxide (15)	293	5100	325	4800	325[a]	6700
	260	4800	258 sh	7950	255 sh	7000
ω-Hydroxypyridoxol *N*-oxide	300	5300	331	5700	331[a]	7500
	262	9100				
ω-Hydroxypyridoxal (7a)	288	8000	315	7300	305	5400
			390	100	390	700
ω-Hydroxy-4-deoxypyridoxol (7b)	282	8300	313	7400	303	6600
			252	3900	244	6900
ω-Hydroxy-4-deoxypyridoxol 5′-phosphate (3)	282	9200	313	8500	303	6900
			252	4000	244	6900
2-Nor-2-formylpyridoxal (8)	315 sh	100	368	8300	368	8900
	285	7800	255 sh	6800	255 sh	6500
2-Nor-2-formylpyridoxal 5′-phosphate (9)	325 sh	2300	415[b]	5500	410	5900
	295	6100	255 sh	5200	255 sh	5400
2-Nor-2-formyl-4-deoxypyridoxol 5′-phosphate (4)[c]	310 sh	3200	378	5200	378	6400
	285	7000	303	3800	308	3100
			237	9100	237	11500

[a] Insignificant shifts occurring in the alkaline range indicate that no additional proton dissociation takes place above pH 7. [b] In 50 m*M* glycerophosphate buffer (pH 7) containing 30 m*M* mercaptoethanol, the standard buffer for phosphorylase assay, a considerable blue shift to 385 nm occurs. The shift was not observed with glycerophosphate buffer alone. It is tentatively attributed to a selective thioacetal formation at the 2-carbonyl position, since none of the 4-carbonyl derivatives thus far investigated have displayed a shift of this magnitude. [c] Uncorrected for water content.

TABLE II

NMR SPECTRA OF THE SYNTHETIC INTERMEDIATES AS COMPARED WITH THEIR PARENT COMPOUNDS[a]

Compd	Proton shifts at position			
	C-2	C-4	C-5	C-6
Pyridoxol	−156	−298	−286	−498
ω-Hydroxypyridoxol (7c)	−302	−299	−289	−497
4-Deoxypyridoxol	−156	−141	−285	−487
ω-Hydroxy-4-deoxypyridoxol (7b)	−298	−143	−287	−494
Pyridoxal	−158	−406	−316	−495
		−405		
ω-Hydroxypyridoxal (7a)	−302	−408	−319	−503
		−407		
2-Nor-2-formylpyridoxal (8)	−606[b]	−401	−312	−495
		−399		

[a] Solutions of the hydrochlorides (10% in D_2O) were employed for all determinations. Shifts are reported in hertz units at 60 MHz downfield from tetramethylsilane with 1,4-dioxane as internal standard. Assignment of peaks is in good agreement with published data (see ref 13). [b] Tentative assignment.

The low-field signal at −606 Hz observed in **8** is therefore tentatively assigned to the 2-formyl proton. This peak, however, disappears altogether in the cationic species of **9**, indicating complete hydration of both carbonyl groups, while the protons of the dihydrate show as a multiplet centered at −384 Hz. A detailed analysis of the nmr signals of the zwitterionic and anionic species is now in progress. Interestingly, the infrared spectra of all the carboxaldehydes as determined in Nujol mulls did not display the anticipated carbonyl stretching vibration. Apparently this function is masked either as a hemiacetal or a hydrate in the solid state.

Preliminary studies with rabbit muscle glycogen apophosphorylase indicate that **9** restores activity to the extent of 30%, suggesting that binding to a unique ε-aminolysine group at the PLP pocket occurs.[3] However, **4** does not markedly reactivate the apoenzyme (<1%), presumably as a consequence of an unfavorable orientation of substituent groups, although binding does occur as verified by characteristic spectral shifts. Work now in progress attempts to delineate the biochemical significance of these experiments and to identify the peptide loop joining the 2- and 4-carboxyaldehydes in **9**. These findings will be published elsewhere.

Experimental Section

All chemicals employed were of reagent grade or the highest grade available commercially. *m*-Chloroperbenzoic acid (*m*-CPBA) of 94% purity was kindly provided by the Norac Company Inc., Azusa, Calif. The Amberlite CG-50 ion exchanger was purchased from Mallinckrodt, whereas Dowex 50-X8 (200–400 mesh) was obtained from Bio-Rad. Unless otherwise specified, 2.5 × 50 or 100 cm columns in the hydrogen ion form were employed as required, using water as eluent. Activated manganese dioxide was prepared according to Harfenist.[14] Paper electropherograms (on Whatman 3MM) were run in pyridine–acetate buffer (pH 3.6) for 30 min at 2000 V; distance of migration is reported relative to the migration of pyridoxal 5′-phosphate and expressed as R_{PLP}. Spots were detected by the Gibbs test;[15] aldehydes were visualized by the phenylhydrazine reagent[16] and phosphate esters by the Hanes–Isherwood molybdate stain.[17]

Ultraviolet spectra were recorded on a Beckman DK-1 spectrophotometer, infrared spectra were obtained with a Perkin-Elmer 21 spectrophotometer, and nuclear magnetic resonance spectra were determined on a Varian A-60 instrument. Melting points were taken in a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental microanalyses were performed by Alfred Bernhard, Elbach über Engelskirchen, West Germany, and by Galbraith Laboratories, Inc., Knoxville, Tenn.

A Facile Preparation of ω-Hydroxypyridoxal Methyl Hemiacetal Hydrochloride (7d).—Pyridoxal hydrochloride (0.05 mol)

(14) M. Harfenist, A. Baverley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).
(15) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927).
(16) H. Wada and E. E. Snell, *J. Biol. Chem.*, **236**, 2089 (1961).
(17) C. S. Hanes and F. A. Isherwood, *Nature (London)*, **164**, 1107 (1949).

was converted to the ethyl hemiacetal in the usual manner[18] and the acid was neutralized with 1 equiv of sodium bicarbonate in the cold. Salts were removed by filtration and the ethanolic solution was chilled to −10° and used without further purification. A solution of *m*-CPBA (0.08 mol) in 50 ml of ethanol was then added dropwise with stirring and the reaction mixture was left in the freezer overnight, when the amine oxide **6** crystallized out. A small amount of contaminating starting material was removed by recrystallization from ethanol. The yield (8.9 g, 85%) can be increased by submitting the pooled residues from the recrystallization steps to one passage through Amberlite CG-50 cationic exchanger and one additional crystallization from ethanol. This product, which does not melt but decomposes on heating above 150°, was indistinguishable from a sample obtained by the oxidation of pyridoxol *N*-oxide with activated manganese dioxide, as established by uv spectroscopy and preparation of the known *p*-toluidine Schiff base.[19]

Pyridoxal *N*-oxide ethyl hemiacetal (**6**, 0.01 mol) was then suspended in 50 ml of dry chloroform and chilled to −10°. Trifluoroacetic anhydride (20 ml, 0.07 mol) was added dropwise with stirring over a period of 30 min, and the solution was held under gentle reflux for 6 hr and left to stand overnight. Following this, all solvents were flash evaporated, and the residual brownish oil was hydrolyzed by warming in hydrochloric acid and decolorized with Darco. On evaporation and drying the crude hydrochloride thus obtained was immediately converted into the methyl hemiacetal hydrochloride (**7d**) by a short reflux period in absolute methanol. One crystallization from methanol–THF gave 2.05 g (88%) of the pure compound which, like its precursor, did not melt but decomposed above 150°.

Anal. Calcd for $C_9H_{11}NO_4 \cdot HCl$: C, 46.26; H, 5.18; N, 6.00; Cl, 14.95. Found: C, 46.05; H, 5.15; N, 6.20; Cl, 15.18.

2-Nor-2-formylpyridoxal (8).—ω-Hydroxypyridoxal methyl hemiacetal hydrochloride (**7d**, 1 g) was dissolved in a mixture of 10 ml of methanol and 50 ml of tetrahydrofuran. Manganese dioxide "A" (5 g) was added and the reaction was allowed to proceed with stirring at room temperature for 24 hr. The catalyst was then filtered off and washed thoroughly with methanol. The combined filtrate and washings were evaporated and fractionated on an Amberlite CG-50 column and the product was recrystallized from water to afford 0.41 g (51%) of **8** as the white monohydrate, mp 167–168° dec. A yellow form is obtained by column chromatography on silica gel employing ethanol–chloroform (1:1) mixture as eluent. On recrystallization from water the yellow crystals revert to the white habit. Reduction of both forms with sodium borohydride in aqueous solution afforded a compound indistinguishable in its spectral and chromatographic properties from ω-hydroxypyridoxol (**7c**). The compound can be detected on paper by the slow change in color of its phenylhydrazone from yellow to amber and finally to maroon, quite distinct from the stable yellow color obtained with 3-pyridinol monocarboxaldehydes. It is fairly acidic, as is demonstrated by its migration on paper electropherograms (R_{PLP} −0.2) and on ion exchangers.

Anal. Calcd for $C_8H_7NO_4 \cdot H_2O$: C, 48.24; H, 4.55; N, 7.03. Found: C, 48.45; H, 4.64; N, 7.19.

Azomethine formation proceeds readily with a number of amines, such as *p*-toluidine, 1-adamantamine, and *p*-aminobenzoic acid. The bis-*p*-toluidine Schiff base crystallized out from methanol–water in orange needles, mp 148° dec, as the dihydrate.

Anal. Calcd for $C_{22}H_{21}N_3O_2 \cdot 2H_2O$: C, 66.82; H, 5.35; N, 10.63. Found: C, 66.99; H, 5.10; N, 9.89.

2-Nor-2-formylpyridoxal 5′-Phosphate (9).—The bis-*p*-toluidine Schiff base of **8** (0.4 g) was submitted to phosphorylation with polyphosphoric acid. After one passage through a Dowex 50-8X column the fractions containing **9** were pooled and reapplied to the recycled column. This treatment removed unidentified contaminants which coeluted in the first purification. Only 40 mg (14%) of pure product was obtained. The low yield appears to be due to interference by condensation reactions. The phosphate ester (R_{PLP} 1.7), like the parent compound, is distinguishable from all other PLP analogs by the maroon-colored stain obtained on paper with phenylhydrazine reagent. Moreover, the electronic spectra as shown in Table I are consistent with an extended π-electron system.

Anal. Calcd for $C_8H_8NO_7P \cdot {}^1/_2H_2O$: C, 35.56; H, 3.36; N, 5.12; P, 11.48. Found: C, 35.18; H, 3.62; N, 4.93; P, 10.88.

ω-Hydroxy-4-deoxypyridoxol 5′-Phosphate (3).—4-Deoxypyridoxol base (0.02 mol) was dissolved in 150 ml of tetrahydrofuran and treated with *m*-CPBA (0.03 mol) in the cold. The product was collected by filtration and purified by one passage through Amberlite CG-50 and crystallization from ethanol–tetrahydrofuran mixture; the amine oxide (2.8 g, 84%) separates as the monohydrate, mp 185° dec.

Anal. Calcd for $C_8H_{11}NO_3 \cdot H_2O$: C, 51.33; H, 6.99; N, 7.48. Found: C, 50.97; H, 6.93; N, 7.96.

The rearrangement of 4-deoxypyridoxol *N*-oxide (2 0.03 mol) was effected essentially as described under ω-hydroxypyridoxal. After treatment with Darco and flash evaporation an almost pure product (2.9 g 78%) crystallized out, which required only one recrystallization from ethanol–ethyl acetate mixture mp 184° dec.

Anal. Calcd for $C_8H_{11}NO_3 \cdot HCl$: C 46.72; H 5.88; N 6.81; Cl, 17.24. Found: C, 46.95; H, 5.45; N, 6.75; Cl, 17.23.

The synthesis was completed by phosphorylation of **7b** (0.03 g) as described above. The pure compound (0.29 g, 79%) was obtained following passage through an Amberlite CG-50 column and crystallization from water–ethanol mixture, from which it separates as slender white needles. On paper electropherograms at pH 3.6 or 6.5 the migration of **3** is almost identical with that of its isomer pyridoxol 5′-phosphate. However, a good separation can be accomplished by tlc on polyamide sheets in *n*-butyl alcohol–acetone–acetic acid–ammonia–water mixture (3.5:2.5:1.5:1.5:1.0) with R_f's of 0.52 and 0.13, respectively.

Anal. Calcd for $C_8H_{12}NO_6P$: C, 38.56; H, 4.86; N, 5.62; P, 12.43. Found: C, 38.30; H, 4.79; N, 5.74; P, 12.42.

2-Nor-2-formyl-4-deoxypyridoxol 5′-Phosphate (4).—ω-Hydroxypyridoxol 5′-phosphate (**3**, 0.2 g) was dissolved in 5 ml of 4 *N* H_2SO_4 and chilled to −15°. Manganese dioxide "A" (0.8 g) was added and the mixture was kept in the freezer with stirring for 35 hr, when the catalyst was filtered off and washed with a small amount of ice-cold water. The filtrate was neutralized in the cold with 50% sodium hydroxide and chromatographed on an Amberlite CG-50 column in the dark. Fractions containing the carboxaldehyde were pooled and evaporated, then rechromatographed to remove a small amount of contaminating starting material. Compound **4** (78 mg, 39%) was obtained as a yellow, glassy solid containing variable amounts of water and defied crystallization. The spectral properties of this compound (Table I) are consistent with a 3-hydroxy-2-pyridine aldehyde structure and are markedly different from that of PLP. On paper electropherograms **4** migrates as a single spot (R_{PLP} 1.5), gives a strong greenish color with Gibbs reagent and a bright yellow color with phenylhydrazine, and displays a green fluorescence when exposed to ammonia vapor.

Pyridoxol *N*-Oxide 5′-Phosphate (15).—α^4,3-*O*-Isopropylidene pyridoxol base[20] (**13**, 0.01 mol) was dissolved in 50 ml of dry chloroform and *m*-CPBA (0.015 mol) was added dropwise with cooling. After standing overnight in the cold, 2.2 g (98%) of the product was isolated by chromatography on basic alumina[5] and purified by one crystallization from tetrahydrofuran, mp 173°. Hydrolysis of the acetonide afforded a substance identical in melting point and uv absorption with that obtained by the direct oxidation of pyridoxol with *m*-CPBA or with peracetic acid.[6]

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.66; H, 6.77; N, 6.15.

α^4,3-*O*-Isopropylidenepyridoxol *N*-oxide (1 g) was phosphorylated with polyphosphoric acid in the usual manner. On acid hydrolysis and one passage through an Amberlite CG-50 column, 0.76 g (66%) of pure pyridoxol *N*-oxide-5′-phosphate (**15**) was obtained. The structure of the final compound was verified by mobility on paper electropherograms (R_{PLP} 2.2) and spectral analysis (see Table I). Attempts to effect the rearrangement of the phosphorylated amine oxide resulted in a number of unidentified side products.

Anal. Calcd for $C_8H_{12}NO_7P \cdot 2.5H_2O$: C, 30.97; H, 5.52. Found: C, 31.36; H, 5.37.

(18) D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, **73**, 3430 (1951).

(19) J. Vidgoff, Ph.D. Thesis, University of Washington, Seattle, Washington, 1970.

(20) W. Korytnyk and W. Wiedeman, *J. Chem. Soc.*, 2351 (1962).

ω-Hydroxypyridoxol N-Oxide.—Oxidation of ω-hydroxypyridoxol with *m*-CPBA in ethanol as described above afforded the title compound, mp 160° dec, in 75% yield.

Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.80; H, 5.44; N, 7.02.

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Registry No.—**1**, 61-67-6; **2**, 42253-78-1; **3**, 42253-79-2; **4**, 42253-80-5; **6**, 42253-81-6; **7a**, 20885-15-8; **7b** hydrochloride, 42253-82-7; **7c**, 29712-70-7; **7c** *N*-oxide, 42253-83-8; **7d** hydrochloride, 42253-84-9; **8**, 42253-85-0; **8** bis(*p*-toluidine) Schiff base, 42253-86-1; **9**, 42253-87-2; **13**, 1136-52-3; **14**, 42253-89-4; **15**, 42253-90-7; pyridoxal hydrochloride, 65-22-5.

Nucleotide Synthesis. IV.[1] Phosphorylated 3′-Amino-3′-deoxythymidine and 5′-Amino-5′-deoxythymidine and Derivatives[2,3]

RONALD P. GLINSKI,* M. SAMI KHAN, AND RICHARD L. KALAMAS

Ash Stevens Inc., Detroit, Michigan 48202

MICHAEL B. SPORN

The Lung Cancer Unit, National Cancer Institute, Bethesda, Maryland 20014

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3′-Amino-3′-deoxythymidine 5′-phosphate (**10**) and 5′-amino-5′-deoxythymidine 3′-phosphate (**18**) were prepared. Compounds **10** and **18** are analogs of deoxythymidine 5′- and 3′-phosphates in which the 3′- and 5′-hydroxyl groups are replaced by amino groups. The synthetic sequence leading to **10** and **18** involved the synthesis of 3′-azido-3′-deoxythymidine (**5**) and 5′-azido-5′-deoxythymidine (**15**) by different multistep pathways. Phosphorylation of **5** and **15**, followed by removal of the protecting groups, gave nucleotides **9** and **17** which contained azide groups in the 3′ and 5′ positions, respectively. The azide group was unaffected by these transformations. Catalytic reduction of the azide groups of **9** and **17** gave the title compounds **10** and **18** in good yield. Moreover, **10** and **18** formed crystalline inner salts, **11** and **19**, respectively, which facilitated purification and characterization. In addition, **10** was converted into 3′-chloroacetamido-, 3′-*N*-(*O*-ethylcarbamoyl)-, and 3′-heptafluorobutyramido-3′-deoxythymidine 5′-phosphates (**12**, **13**, and **14**, respectively) and **18** was converted into 5′-acetamido-, 5′-chloroacetamido-, and 5′-*N*-(*O*-ethylcarbamoyl)-5′-deoxythymidine 3′-phosphates (**20**, **21**, and **22**, respectively); these derivatives were candidate active-site-directed inhibitors of a nuclear exoribonuclease isolated from nuclei of mammalian cells.

The presence of 3′-amino-3′-deoxy-β-D-ribofuranose moiety in the antibiotic puromycin[4] has stimulated considerable interest in other amino sugar nucleosides and nucleotides as pharmacological agents. Furthermore, several types of 3′-deoxy or 3′-amino-3′-deoxy nucleoside and nucleotide analogs have been reported to inhibit the synthesis of nucleic acid and, at least in some cases, the inhibition is due to incorporation of a nucleoside which cannot support further chain elongation. Thus, 3′-deoxyadenosine has been shown to inhibit the synthesis of both DNA and RNA in Ehrlich ascites tumor cells.[5,6] Other studies[6,7] have demonstrated *in vitro* inhibition of RNA synthesis by 3′-deoxyadenosine 5′-triphosphate, catalyzed by RNA polymerase. Also described was inhibition due to incorporation of 3′-deoxyadenosine at the 3′ terminus of the growing RNA molecule. The absence of 3′-hydroxyl function in this position prohibits further chain elongation. 3′-Amino-3′-deoxyadenosine[8] and 3′-deoxyguanosine[9] appear to function in a similar manner.

The synthesis of 3′-amino-3′-deoxythymidine 5′-phosphate (**10**), 5′-amino-5′-deoxythymidine 3′-phosphate (**18**), and derivatives containing a haloacetamido inactivating group was undertaken in these laboratories as part of a program devoted to the design of candidate active-site-directed inhibitors of a nuclear exoribonuclease. The exoribonuclease, isolated from the nuclei of mammalian cells, selectively degrades single-stranded, newly synthesized *m*-RNA from the 3′ end, liberating nucleotides with a 5′ phosphate group.[10] The enzyme has affinity for mononucleotides and oligonucleotides, but not for uncharged nucleosides. In addition, the enzyme is present in relatively large amounts in neoplastic tissues, relative to most normal tissues,[11] thus enhancing the importance of the acquisition of selective inhibitors of nuclear exoribonuclease in studying normal and abnormal nucleic acid metabolism. This paper describes the synthesis, purification, and characterization of these novel nucleotides; detailed biochemical results will be described elsewhere.

The key concept underlying the successful preparation of compounds **10** and **18** was the use of stable

(1) Paper III: R. P. Glinski and M. B. Sporn, *Biochemistry*, **11**, 405 (1972).

(2) A preliminary account of a portion of this work has appeared: R. P. Glinski, M. S. Khan, R. L. Kalamas, C. L. Stevens, and M. B. Sporn, *Chem. Commun.*, 915 (1970).

(3) This investigation was supported by NIH Contract PH 43-66-929.

(4) J. J. Fox, K. A. Watanabe, and A. Block, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 251 (1966).

(5) H. Klenow, *Biochem. Biophys. Acta.*, **76**, 347, 354 (1963).

(6) H. T. Shigeura and C. N. Gordon, *J. Biol. Chem.*, **240**, 806 (1965).

(7) H. T. Shigeura and G. E. Boxer, *Biochem. Biophys. Res. Commun.*, **17**, 758 (1964).

(8) H. T. Shigeura, G. E. Boxer, M. L. Meloni, and S. D. Sampson, *Biochemistry*, **5**, 994 (1966).

(9) C. O. Gitterman, R. W. Burg, G. E. Boxer, D. Meltz, and J. Hitt, *J. Med. Chem.*, **8**, 664 (1965).

(10) M. B. Sporn, D. M. Berkowitz, R. P. Glinski, A. B. Ash, and C. L. Stevens, *Science*, **164**, 1408 (1969).

(11) M. B. Sporn, H. M. Lazarus, J. M. Smith, and W. R. Henderson, *Biochemistry*, **8**, 1698 (1969).

azidodeoxy nucleosides, instead of amino or protected aminodeoxy nucleosides, in the phosphorylation reaction. This approach had been used first in the synthesis of D-ribofuranosylamine 5′-phosphate.[12] Since the appearance of our preliminary communication[2] describing the synthesis of nucleotides **10** and **11**, other groups[13] have used this approach successfully to synthesize derivatives of phosphorylated 2′-amino-2′-deoxyuridine and poly(2′-amino-2′-deoxyuridylic acid). Another recent report[14] describes the synthesis of poly(2′-azido-2′-deoxyuridylic acid). Finally, Letsinger and Mungall[15] have prepared short oligonucleotides containing phosphoramidate linkages derived from 5′-amino-5′-deoxythymidine; this synthesis, however, did not require the use of an azido nucleoside in the phosphorylation reaction. Briefly, in the present case, the azido nucleosides were converted into azido nucleotides, which, in turn were deblocked and reduced catalytically to afford the desired amino nucleotides. The azido group was stable to the phosphorylating conditions employed, and the basic (1 *N* sodium hydroxide at 100°) and the mild acidic conditions used for the removal of the protecting groups.

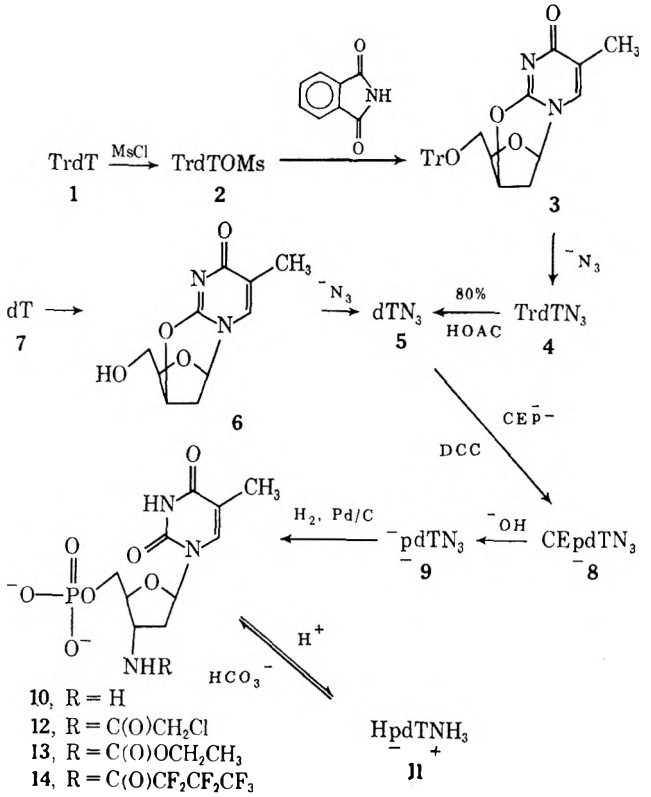
The key intermediate, 5′-*O*-trityl-2,3′-anhydrothymidine (**3**, Scheme I), in the synthesis of 3′-amino-3′-deoxythymidine 5′-phosphate (**10**) is available from thymidine *via* a three-step reaction sequence.[16] In our hands, however, the literature procedure proved to be unsuitable for large-scale synthesis and was modified. Thus, 5′-*O*-trityl-3′-*O*-mesylthymidine (**2**), prepared from 5′-*O*-tritylthymidine (**1**),[17] was allowed to react with potassium phthalimide in dimethylformamide–water mixtures at 90° to give **3** in 77% yield. Treatment of **3** with sodium azide in a mixture of dimethylformamide–water under reflux for 11 hr gave crude 3′-azido-3′-deoxy-5′-*O*-tritylthymidine (**4**). Crude **4** could be used as such for the preparation of **5**. A sample, however, was obtained in crystalline form for analysis after purification by column chromatography over silica gel. The 5′-*O*-trityl group of **4** was removed with 80% acetic acid at 100° in 1.75 hr. Crystallization from 2-propanol gave pure 3′-azido-3′-deoxythymidine (**5**) in 71% yield. Compound **5** had been prepared earlier by a similar route[18] without isolation or characterization of various intermediates. While this work was in progress, a brief communication appeared[19] reporting the synthesis of 2,3′-anhydrothymidine (**6**) directly from thymidine using 2-chloro-1,1,2-trifluorotriethylamine reagent.[20] The direct synthesis of **6** from thymidine provided a better alternate route for the preparation of **5**. The conversion of **6** into **5** was performed in a similar manner to the conversion of **3** into **5** in yields of 40–60%. Samples of **5** prepared by both routes were identical in all respects.

Phosphorylation of **5** in anhydrous pyridine containing *N*,*N*′-dicyclohexylcarbodiimide using β-cyanoethyl phosphate reagent[21] gave 3′-azido-3′-deoxythymidine 5′-(β-cyanoethyl phosphate) sodium salt (**8**) in essentially quantitative yield. This product was sufficiently pure for further transformations. For characterization, however, a small sample was purified by preparative paper chromatography and fractional precipitation. The β-cyanoethyl group of **8** was removed in 1 *N* NaOH at 100° for 1.5 hr to give 3′-azido-3′-deoxythymidine 5′-phosphate disodium salt (**9**). Crude **9** was purified by large-scale preparative paper chromatography and fractional precipitation from methanol–2-propanol mixtures. Catalytic reduction of the azide group of compound **9** in the presence of 10% Pd/C in water solution gave 3′-amino-3′-deoxythymidine 5′-phosphate disodium salt (**10**). Crude **10** was readily purified by conversion into the crystalline inner salt **11** with trifluoroacetic acid. Treatment of **11** with mild base regenerated pure **10**.

Compound **10**, interesting in itself as an analog of deoxythymidine 5′-phosphate, served as a starting material for the synthesis of various candidate active-site-directed inhibitors of the nuclear exoribonuclease. A number of inactivating groups were incorporated into the 3′ position of **10** for evaluation of biological activity. Thus, **10**, on reaction with chloroacetic anhydride in methanol–water mixtures gave 3′-chloro-

SCHEME I

SYNTHETIC PATHWAY TO 3′-AMINO-3′-DEOXYTHYMIDINE 5′-PHOSPHATE 10 AND DERIVATIVES[a]



10, R = H
12, R = C(O)CH_2Cl
13, R = C(O)OCH_2CH_3
14, R = C(O)$CF_2CF_2CF_3$

[a] Abbreviated formulas are as follow: dT is thymidine; Tr to the left of dT in TrdT refers to a 5′-*O*-trityl group; OMs to the right of dT as in TrdTOMs refers to 3′-*O*-mesylate substitution; CEp refers to 2-cyanoethyl phosphate.

(12) R. Carrington, G. Shaw, and D. V. Wilson, *J. Chem. Soc.*, 6854 (1965).

(13) J. Hobbs, H. Sternbach, and F. Eckstein, *Biochem. Biophys. Res. Commun.*, **46**, 1509 (1972); D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **37**, 1876 (1972).

(14) P. F. Torrence, J. A. Waters, and B. Witkop, *J. Amer. Chem. Soc.*, **94**, 3638 (1972).

(15) R. L. Letsinger and W. S. Mungall, *J. Org. Chem.*, **35**, 3800 (1970).

(16) N. Miller and J. J. Fox, *J. Org. Chem.*, **29**, 1972 (1964); J. J. Fox and N. Miller, *ibid.*, **28**, 936 (1963).

(17) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955).

(18) J. P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, **29**, 2076 (1964).

(19) E. Kowollik, K. Gaertner, and P. Langen, *Tetrahedron Lett.*, 3863 (1969).

(20) N. N. Yarovenko and M. A. Raksha, *Zh. Obskch. Khim.*, **29**, 2159 *Chem. Abstr.*, **54**, 9724*h* (1960); L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

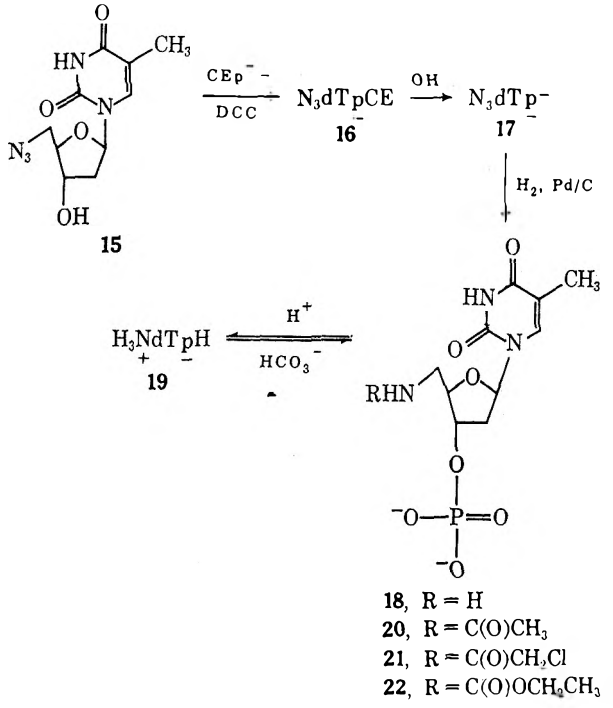
(21) G. M. Tener, *J. Amer. Chem. Soc.*, **83**, 159 (1961).

acetamido-3′-deoxythymidine 5′-phosphate disodium salt (**12**). In a similar manner, 3′-*N*-(*O*-ethylcarbamoyl)-3′-deoxythymidine 5′-phosphate disodium salt (**13**) was prepared from **10** on reaction with ethyl chloroformate. Finally, reaction of **10** with heptafluorobutyryl–imidazole reagent in pyridine gave 3′-heptafluorobutyramido-3′-deoxythymidine 5′-phosphate (**14**). For these reactions, isolated **10** (prepared from crystalline inner salt **11**) or compound **10** generated *in situ* from **11** was utilized. Compounds **12**, **13**, and **14** were purified for characterization and analysis by preparative paper chromatography and fractional precipitation.

The experience accumulated during the preparation of derivatives of **10** prompted us to direct our attention to the companion syntheses of the corresponding 5′-substituted derivatives (Scheme II). The starting

SCHEME II

SYNTHETIC PATHWAY TO 5′-AMINO-5′-DEOXYTHYMIDINE 3′-PHOSPHATE (**18**) AND DERIVATIVES



material for these syntheses, 5′-azido-5′-deoxythymidine (**15**), available *via* a six-step reaction sequence from thymidine,[22] was phosphorylated, as was described earlier for the 3′-substituted isomer, with β-cyanoethyl phosphate reagent[21] in pyridine in the presence of *N*,*N*′-dicyclohexylcarbodiimide to give 5′-azido-5′-deoxythymidine 3′-(β-cyanoethyl phosphate) pyridinium salt (**16**). Compound **16** was not purified, but was used as such in the next reaction. Compound **16** was allowed to stand in 1 *N* NaOH at room temperature for 45 min to cleave the β-cyanoethyl ester group to give 5′-azido-5′-deoxythymidine 3′-phosphate (**17**). Compound **17** was purified for analysis and characterization by preparative paper chromatography and fractional precipitation. Hydrogenation of **17** in water solution in the presence of 10% Pd/C gave 5′-amino-5′-deoxythymidine 3′-phosphate dilithium salt (**18**). As was the case for the corresponding 3′-amino analog, **18** afforded a crystalline inner salt (**19**) on treatment with trifluoroacetic acid, facilitating purification and characterization. Compound **19** regenerated **18** on treatment with mild base. Treatment of **18**, or **18** generated *in situ* from inner salt **19**, with the appropriate reagents in a manner similar to that described earlier for the corresponding 3′ isomers gave 5′-acetamido-5′-deoxythymidine 3′-phosphate (**20**), 5′-chloroacetamido-5′-deoxythymidine 3′-phosphate (**21**), and 5′-*N*-(*O*-ethylcarbamoyl)-5′-deoxythymidine 3′-phosphate (**22**). Compounds **20**, **21**, and **22** were purified by preparative paper chromatography and fractional precipitation for characterization purposes.

(22) J. P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, **29**, 2076 (1964).

Experimental Section

Paper chromatography (Table I) was by the descending technique using the following solvent systems: A, 1-butanol–acetic acid–water (5:2:3, v/v); B, 2-propanol–water–concentrated NH_4OH (7:2:1, v/v); C, 2-propanol–aqueous 1% ammonium sulfate (5:2, v/v); and D, ethanol–aqueous 1% ammonium acetate (5:2, v/v). The nucleotides were detected with ultraviolet light. Analytical pc[23] was performed using Whatman No. 1 paper. Whatman 3 MM paper and solvent system A were used for the large-scale ppc (1–2 g of compound per 20 sheets) as outlined earlier.[24]

TABLE I

PAPER CHROMATOGRAPHY OF NUCLEOTIDE DERIVATIVES

Compd	R_f's in systems A	B	C	D
8	0.49	0.47	0.54	0.70
9	0.42	0.24	0.38	0.53
10 and **11**	0.22	0.08	0.13	0.30
12	0.38	0.09[a]	0.37	0.50
13	0.41	0.21	0.34	0.53
14	0.71	0.61	0.65	0.73
17	0.41	0.16	0.36	0.54
18 and **19**	0.20	0.08	0.15	0.27
20	0.31	0.18	0.38	0.45
21	0.32	0.16	0.31	0.47
22	0.43	0.23	0.41	0.51

[a] Streaking in this system due to decomposition.

Thin layer chromatography (tlc) was performed using Eastman chromatogram sheets 6060 (silica gel) impregnated with a fluorescent indicator unless stated otherwise. Other tlc plastic sheets used were Eastman chromatogram sheets 6064 (cellulose) impregnated with a fluorescent indicator. The spots were visualized with uv light and compounds containing a trityl group were detected by spraying with aqueous 5% $HClO_4$ acid and heating at 80° for 5 min. The following tlc systems were used: A, diethyl ether; B, ethyl acetate–EtOH–tetrahydrofuran (1:1:1-v/v); C ethyl acetate; D, $CHCl_3$–1% NH_4OH in CH_3OH (3:2, v/v); E, 2-propanol–water–concentrated NH_4OH (7:2:1, v/v).

Fractions from the fractional precipitations were collected by centrifugation. The residual pellets were washed with anhydrous diethyl ether and dried in a gentle anhydrous N_2 stream and *in vacuo* at room temperature.

Uv spectra (distilled water) were recorded using a Hitachi-Coleman 124 spectrophotometer. Ir spectra were recorded using a KBr disk on a Perkin-Elmer Model 237B spectrophotometer. Nmr spectra were recorded using a Varian T-60 spectrometer. Determinations of pK_a and molecular weight were performed according to procedures outlined earlier,[24] unless

(23) The abbreviations used are ppc, pc, and tlc for preparative paper chromatography, paper chromatography, and thin layer chromatography, respectively. The ion exchange resin AGC-244H$^+$ (strong acid) was purchased from J. T. Baker Chemical Company, Phillipsburg, N. J.

(24) R. P. Glinski, A. B. Ash, C. L. Stevens, and M. B. Sporn, *J. Org. Chem.* **36**, 245 (1971).

indicated otherwise. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Pyridine was distilled and stored over Linde molecular sieves (type 4A).

5′-*O*-Trityl-2,3′-anhydrothymidine (3).—The starting material, 5′-*O*-trityl-3′-*O*-mesylthymidine (2), was prepared according to the literature procedure (Michelson and Todd, 1955)[17] without modification from thymidine by a two-step reaction sequence. Compound 2 (27 g) was added to a solution of potassium phthalimide (45 g) in dimethylformamide (410 ml) and water (120 ml). The mixture was heated to 95° with stirring over a period of 20 min. The reaction mixture was cooled to room temperature and the course of the reaction was monitored by tlc using tlc system A. Tlc indicated that the reaction was complete. The solution was poured onto an ice–water mixture (4 l.) and the resulting heterogeneous mixture was stirred for 30 min. The product was removed by filtration and washed well with water. The wet precipitate was dissolved in hot 2-propanol (1 l.) and the solution was seeded. After standing at room temperature for 5 days, the resulting crystalline product was removed by filtration and dried to give 4.4 g of 3 with mp 224–227° (softening at 150°). An additional 16.1 g of 3 with mp 229–232° (softening at 150°) was obtained by concentrating the 2-propanol mother liquor to dryness *in vacuo* and stirring the resulting residue under anhydrous diethyl ether overnight. Thus, the total yield was 20.5 g (91.4%). Tlc (tlc system A) indicated the presence of a trace amount of phthalimide. The solid was heated under reflux on a steam bath in 2-propanol for 2 hr. The heterogeneous mixture was allowed to cool. The solid was removed by filtration, yield 12.26 g of 3 with mp 228–233° (no softening at 150°). The mother liquor was concentrated *in vacuo* to *ca.* 200-ml volume. Additional 3 which resulted was removed by filtration, yield 5.68 g of pure 3 with mp 231–233° (no softening at 150°). The previous 12.26-g crop was dissolved in $CHCl_3$ (700 ml) and the solution was filtered, yield 830 mg of impurity with mp <300°. The $CHCl_3$ mother liquor was concentrated *in vacuo* to *ca.* 100-ml volume, diethyl ether was added to the point of turbidity, and seeds of 3 were added, yield 11.46 g of pure 3 with mp 230–233° (no softening at 150°). The total yield of pure 3, therefore, was 17.14 g (77%). The physical constants of 3 were in agreement with the literature values.[16]

2,3′-Anhydrothymidine (6).—Thymidine (55 g), dissolved in dimethylformamide (280 ml, which had been purified by passage through acid-washed alumina), was added to 75 g of 2-chloro-1,-1,2-trifluorotriethylamine.[20] The mixture was heated at 70° (oil bath temperature) for 30 min. The reaction mixture was poured into acetone (700 ml) and the resulting crude crystalline product (24 g) was removed by filtration and air dried. The crude product was recrystallized from a mixture of dimethylformamide–acetone to give 20.5 g (40%) of product 6 with mp 242–243°. The physical properties of compound 6 were in agreement with those recorded in the literature.[19]

3′-Azido-3′-deoxy-5′-*O*-tritylthymidine (4).—5′-*O*-Trityl-2,-3′-anhydrothymidine (3, 22 g) was dissolved in dimethylformamide (220 ml). Sodium azide (11 g) and water (30 ml) were added with stirring. The resulting homogeneous solution was heated under reflux for 11 hr. The course of the reaction was followed by tlc using tlc system C. The reaction was essentially complete after 11 hr and only a very faint trace of starting material remained. The dimethylformamide was removed *in vacuo* at room temperature. Water (2 l.) was added and the heterogeneous mixture was stirred in room temperature for 3 hr. The solid was removed by filtration and washed well with water. The solid was dried *in vacuo* over P_2O_5 for 16 hr to give 23.2 g (97%) of crude 4. Compound 4 was purified by column chromatography using silica gel (600 g). The column was eluted with benzene (3 l.) to remove a minor yellow impurity. A second minor yellow impurity was eluted from the column with 8 l. of 50% chloroform–benzene. Elution of the column with 8 l. of chloroform and 1 l. of 50% chloroform–diethyl ether gave 13.5 g of relatively pure product (71%). Tlc (tlc system C) indicated that the solid was one spot. Tlc (tlc system A) indicated the presence of two minor impurities. A small sample was purified for analysis by crystallization and recrystallization from chloroform–*n*-pentane mixtures and dried at 60° (5×10^{-3} mm) over P_2O_5: mp 104–105°; uv max (ethanol) 265 mμ (ε 8800), 250/260 (0.55), 260/270 (1.00), 270/280 (1.76).

Anal. Calcd for $C_{29}H_{27}N_5O_4 \cdot 1.25H_2O$: C, 65.46; H, 5.59; N, 13.16. Found: C, 65.48; H, 5.13; N, 12.92.

The analysis was repeated after block drying at the melting point by the analyst.

Anal. Calcd for $C_{29}H_{27}N_5O_4$: C, 68.36; H 5.34; N 13.74; O, 12.56. Found: C, 67.70; H 5.35; N 13.53; O 12.34.

3′-Azido-3′-deoxythymidine (5). A.—5′-*O*-Trityl-2,3′-anhydrothymidine (3, 146 g) was dissolved in dimethylformamide (1500 ml) containing sodium azide (75 g) and water (225 ml). The mixture was refluxed for 13 hr and was allowed to stand at room temperature for 10 hr after cooling. Tlc (tlc system A) showed only trace amounts of starting material remaining and a major faster migrating spot corresponding to product. The reaction mixture was poured into ice–water (6 l.) with stirring. The resulting precipitate was collected by filtration. The wet solid was dissolved in chloroform (1.5 l.), and the aqueous layer was separated. The chloroform was dried (Na_2SO_4) and removed *in vacuo* to afford 220 g of brown syrup which, by tlc, was mostly 3′-azido-3′-deoxy-5′-*O*-tritylthymidine (4). Compound 4 was dissolved in aqueous 80% acetic acid (1500 ml) and the mixture was heated for 1.75 hr on a steam bath with stirring. Tlc (tlc system A) showed that no starting material remained. The mixture (heterogenous owing to the presence of trityl alcohol) was poured into cold water (1.5 l.) and the insoluble trityl alcohol was removed by filtration. The filtrate was concentrated *in vacuo* to *ca.* 750-ml volume. The solution was extracted twice with *n*-pentane (250 ml). The aqueous layer was lyophilized and the residue was dissolved in water (250 ml). The solution was seeded with crystalline 3′-azido-3′-deoxythymidine (5) prepared earlier and the solution was allowed to stand at room temperature for 1 day, followed by 2 days at 1°. The resulting crystalline product (35 g) was removed by filtration. The mother liquor was extracted ten times with ether (200 ml). The ether extracts were combined and concentrated *in vacuo* to a syrup. The syrup was dissolved in a minimum amount of 2-propanol and the solution was seeded. More crystalline product (6 g) resulted. The combined 41 g of crystalline product was recrystallized from a minimum amount of hot 2-propanol to give 25 g (30% for two steps) of product 5 with mp 118–120°. The mother liquor of the 2-propanol recrystallization was concentrated *in vacuo* to a syrup. The syrup was dissolved in water (125 ml) and the solution was seeded to give an additional 2.4 g (3%), mp 115–120°, of 5. A small sample was recrystallized twice from water for analysis: mp 120–122°; uv max 266 mμ (ε 10,200), uv min 234 mμ (ε 2600), 250/260 (0.66), 260/270 (0.96), 270/280 (1.55).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.91; H, 4.90; N, 26.20. Found: C, 44.92; H, 4.82; N, 26.50.

In several earlier experiments, 5 with mp 105–106° (bubbling and softening at 100°) was obtained by crystallization from dilute, hot diethyl ether solution. A mixture melting point of this material with 5 (mp 120–122°) was 120–122° and the uv spectra were identical. A sample of the lower melting form was dried at 110° (5×10^{-3} mm) for 30 min for analysis, mp 105–106° (no softening at 100°).

Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.91; H, 4.90; N, 26.20; O, 23.95. Found: C, 44.83; H, 4.96; N, 25.98; O 23.94.

B.—2,3′-Anhydrothymidine (6, 5 g), lithium azide (2.2 g), and NH_4Cl (300 mg) were heated in dimethylformamide at 123–129° (oil bath temperature) for 17 hr. Tlc (tlc system D) showed no starting material (6) and a major spot corresponding to product 5, contaminated with a minor amount of slower migrating impurities. The reaction mixture was poured into water (300 ml) and the aqueous solution was allowed to cool. Product 5 was extracted from the aqueous solution with ethyl acetate (12 × 150 ml) to give, after removal of the ethyl acetate *in vacuo*, 5.57 g of brown syrup. The syrup was dissolved in a minimum amount of acetone and the acetone solution was applied to a silica gel (60–200 mesh, 100 g, 250 ml) column (40 × 300 mm) which had been preequilibrated in diethyl ether. The column was eluted with diethyl ether and 250-ml fractions were collected. Fractions 3–6 were combined and concentrated *in vacuo* to give 4.55 g of 5 as a semisolid. Crystallization of the semisolid from a mixture of acetone, diethyl ether, and *n*-pentane gave 3.02 g of pure 5 with mp 121–122°. The mother liquor was purified again by column chromatography to give additional 5 (780 mg) as a syrup, which, on crystallization gave 245 mg of 5 with mp 119–121°. The total yield was 3.27 g (55%). Compound 5, prepared from 6, was identical in all respects with 5 prepared from 3.

3′-Azido-3′-deoxythymidine 5′-(β-Cyanoethyl Phosphate) Sodium Salt (8).—3′-Azido-3′-deoxythymidine (5, 5 g, 18.7 (mequiv) was dissolved in pyridine (100 ml) and *N*,*N*′-dicyclohexylcarbodiimide (38.5 g, 187 mequiv in 77 ml of pyridine) was added with stirring. β-Cyanoethyl phosphate pyridinium

salt[21] (23.4 mequiv in 140 ml of pyridine) was added dropwise over a period of 1 hr. The course of the reaction was monitored by pc (system A) after 16 hr. Starting material, or an impurity migrating the same as starting material, was evident in addition to product. The reaction mixture was concentrated *in vacuo* to *ca.* 150-ml volume and additional *N,N'*-dicyclohexylcarbodiimide (38.5 g, 187 mequiv in 77 ml of pyridine) was added. Additional β-cyanoethyl phosphate pyridinium salt (17.5 mequiv in 105 ml of pyridine) was added dropwise over a period of 90 min. The solution was allowed to stand at room temperature overnight. Again, a spot migrating the same as starting material was evident by pc in addition to product. The paper strips were sprayed with molybdate reagent to detect the presence of phosphorus. The spot with a R_f corresponding to starting material (5) gave a positive test for phosphorus, indicating that this material was not 5. The solution was diluted with water (200 ml), frozen, and lyophilized. Water (1 l.) was added to the residue and the heterogeneous mixture was stirred for 3 days at room temperature. The precipitate (*N,N'*-dicyclohexylurea) was removed by filtration and washed well with water. Tlc (tlc system C) indicated that the *N,N'*-dicyclohexylurea contained a small amount of product in addition to the spot which had an R_f corresponding to starting material (5). The filtrate was concentrated *in vacuo* to a small volume and lyophilized to afford 9.2 g of crude 8, contaminated with a small amount of *N,N'*-dicyclohexylurea. A sample of 8 (1 g) was purified by ppc using pc system A to give 640 mg of homogeneous 8. A sample of this material (240 mg) was purified further by fractional precipitation from methanol–ethanol and methanol–ethanol–2-propanol mixtures for analysis. Seven fractions were collected. Fraction 5 (45 mg) was dissolved in a minimum amount of water and the solution was passed through a Dowex 50 (Na^+) column (3 ml). The column was eluted with water (20 ml). The eluate was concentrated *in vacuo* and the residue was azeotroped with water. The residue was redissolved in water and lyophilized to give *ca.* 25 mg of a hygroscopic solid: ir (KBr) 4.0 (C≡N), 4.72 μ (N_3); uv max 267 mμ (ε 10,200), uv min 234 mμ (ε 2600), 250/260 (0.66), 260/270 (0.96), 270/280 (1.57).

Anal. Calcd for $C_{13}H_{16}N_6O_7P\cdot Na\cdot 1.5H_2O$: C, 34.75; H, 4.26; N, 18.71; P, 6.89. Found: C, 35.17; H, 4.09; N, 18.55; P, 6.37.

3'-Azido-3'-deoxythymidine 5'-Phosphate Disodium Salt (9).—Crude 8 (1 g) was dissolved in 1 *N* sodium hydroxide (33 ml). The solution was heated in an oil bath with stirring at 100° (bath temperature) for 1.5 hr. Tlc (tlc system D) indicated that the reaction was complete. The reaction mixture was cooled to room temperature and applied to a Dowex 50 (Li^+) column (180 ml). The column was eluted with water (300 ml). The eluate was lyophilized to afford 997 mg of compound 9 (dilithium salt). The product was purified by ppc (20 sheets of 3 MM paper) using pc system A. The product was eluted off the paper with 10% acetic acid (2 l.). The last traces of acetic acid were removed by repetitive lyophilization. The extremely hygroscopic residue was dissolved in a minimum amount of water, the solution was applied to a Dowex 50 (H^+) column (30 ml), and the column was eluted with water (200 ml). The eluate was lyophilized to give 337 mg (45%) of 9 (free acid) as a nonhygroscopic solid, uv max 267 mμ (ε 9200 as a dihydrate), uv min 234 mμ (ε 2470). Free acid 9 was converted into disodium salt by neutralization (pH 7–7.5) of an aqueous solution of 8 with 1 *N* NaOH: yield 300 mg (81%) after lyophilization; uv max 267 mμ (ε 9800 as a dihydrate), uv min 234 mμ (ε 2600). Compound 9 was purified by fractional precipitation from methanol–2-propanol solutions. Three fractions were collected. Fraction 1 was insoluble in methanol while fractions 2 and 3 were insoluble in methanol–2-propanol mixtures and appeared to be crystalline. A sample of fractions 2 and 3 (187 mg after azeotroping with water and lyophilization) was sent for analysis: uv max 267 mμ (ε 10,200 as a dihydrate), uv min 234 mμ (ε 2600), 250/260 (0.66), 260/270 (0.98), 270/280 (1.59).

Anal. Calcd for $C_{10}H_{12}N_5O_7P\cdot 2Na\cdot 2H_2O$: C, 28.11; H, 3.78; N, 16.39; P, 7.25. Found: C, 28.34; H, 3.87; N, 16.33; P, 7.02.

3'-Amino-3'-deoxythymidine 5'-Phosphate Disodium Salt (10).—3'-Azido-3'-deoxythymidine 5'-phosphate (9, 100 mg, analytically pure) was hydrogenated in the presence of 10% Pd/C (30 mg) in water solution (1 ml) for 3 hr at room temperature. Processing of the reaction mixture in the usual manner afforded a hygroscopic white solid. Attempts to purify the solid by fractional precipitation failed because of the formation of oils. A glass resulted on combination and evaporation of the various solutions from the fractional precipitation. The glass was dissolved in a minimum amount of water, and 2-propanol was added to the point of turbidity. The mixture was centrifuged and a small amount of oil deposited. The supernatant was concentrated *in vacuo* to afford a gum. The gum was dissolved in water and the solution was lyophilized to afford a hygroscopic solid: uv max 267 mμ (ε 9400) uv min 234 mμ (ε 2500), 250/260 (0.68), 260/270 (1.00), 270/280 (1.65).

Anal. Calcd for $C_{10}N_{14}N_3O_7PNa_2\cdot 3H_2O$: C, 28.65; H, 4.80; N, 10.02; P, 7.39. Found: C, 29.13; H, 4.79; N, 9.63; P, 7.13.

Anal. Calcd for $C_{10}H_{14}N_3O_7PNa_2\cdot 1H_2O$: C, 31.34; H, 4.21. Found (after block drying by the analyst at 160°): C, 31.48; H, 4.13.

3'-Amino-3'-deoxythymidine 5'-Phosphate Inner Salt (11).—3'-Azido-3'-deoxythymidine 5'-phosphate disodium salt dihydrate (9, 1.05 g, ε 8000 as a dihydrate, purified by ppc only) was dissolved in water (15 ml) containing 10% Pd/C (300 mg) and the mixture was stirred under hydrogen at atmospheric pressure for *ca.* 4 hr. Tlc (cellulose sheets, pc system B) showed the absence of starting material (9) and one spot corresponding to 3'-amino-3'-deoxythymidine 5'-phosphate disodium salt (10). The catalyst was removed by filtration using a Celite bed and was washed thoroughly with water. The combined filtrate and washings were lyophilized to afford 880 mg (86%) of extremely hygroscopic product 10. Compound 10 was dissolved in water (3 ml) and trifluoroacetic acid (0.47 ml) was added. 2-Propanol was added to the point of turbidity and the solution was seeded with crystalline inner salt 11. After standing at room temperature for several hours and at 1° for 16 hr, the crystalline material which resulted was removed by filtration and air dried to afford 400 mg of 11 with mp 219–220° dec. A sample was dried at room temperature (5×10^{-3} mm) and 110° (5×10^{-3} mm) for 16 and 3 hr, respectively, for analysis: uv max 265 mμ (ε 10,800, calcd per mol wt 359.3 based on first analysis), uv min 233 mμ (ε 2700), 250/260 (0.82), 260/270 (1.00), 270/280 (1.69).

Anal. Calcd for $C_{10}H_{16}N_3O_7P\cdot H_2O\cdot 0.33\ (CH_3)_2CHOH$: C, 36.77; H, 5.83; N, 11.70; P, 8.62. Found: C, 36.51; H, 5.68; N, 11.84; P, 8.56.

Anal. Calcd for $C_{10}H_{16}N_3O_7P$: C, 37.39; H, 5.02; N, 13.08; P 9.64. Found (after block drying by the analyst at 170°): C, 37.14; H, 5.47; N, 12.86; P, 9.10.

3'-Chloroacetamido-3'-deoxythymidine 5'-Phosphate Disodium Salt (12).—3'-Amino-3'-deoxythymidine 5'-phosphate disodium salt (10, 200 mg) was dissolved in water (1 ml), and methanol (2 ml) was added. The mixture was stirred at 0° and chloroacetic anhydride (100 mg) was added portionwise as a solid. After stirring at 0° for 10 min, all of the chloroacetic anhydride dissolved. The course of the reaction was monitored by tlc (pc system A, cellulose tlc plates); tlc showed that the reaction was essentially complete. The reaction mixture was diluted with water and streaked directly on six sheets of 3 MM paper and 12 was purified by ppc (pc system A). Processing in the usual manner yielded 173 mg of homogeneous 12. The product was combined with an earlier preparation of 12 (total wt 269 mg) and the solid was dissolved in a minimum amount of water. The solution was applied to a Dowex 50 (Na^+) column (15 ml). The column was eluted with water and the effluent was lyophilized to afford 174 mg of compound 12. An analytically pure sample was obtained by fractional precipitation from water–methanol–2-propanol mixtures. Four fractions were collected. The fourth fraction, a gum, was solidified by trituration under 2-propanol. The solid was removed by centrifugation and was washed with diethyl ether to give 90 mg of 12. The solid was dissolved in water (5 ml) and the solution was concentrated *in vacuo* three times. Finally, the residue was dissolved in water and the solution was lyophilized to afford 80 mg of analytically pure 12: uv max 267 mμ (ε 9700), uv min 237 mμ (ε 2500), 250/260 (0.65), 260/270 (0.95), 270/280 (1.51).

Anal. Calcd for $C_{12}H_{15}ClN_3O_8PNa_2\cdot 2.5H_2O$: C, 29.61; H, 4.14; Cl, 7.28; N, 8.63; P, 6.36. Found: C, 29.90; H, 4.16; Cl, 6.95; N, 8.91; P, 6.35.

3'-*N*-(*O*-Ethylcarbamoyl)-3'-deoxythymidine 5'-Phosphate Disodium Salt (13).—3'-Amino-3'-deoxythymidine 5'-phosphate inner salt (11, 300 mg) was dissolved in a mixture of methanol (2 ml) and water (2 ml) containing Na_2CO_3 (290 mg). The mixture was stirred at 0° and ethyl chloroformate (130 mg, 1.2 mmol) was added dropwise. The reaction mixture was stirred at 0° for 10 min and the course of the reaction was monitored by tlc (pc

system A, cellulose tlc sheets). Tlc indicated that the reaction was complete. The solution was neutralized (pH 7) with 0.1 *N* HCl and was streaked directly onto five sheets of 3 MM paper for purification by ppc (pc system A): yield, 299 mg; uv max 267 mμ (ε 8200), as a dihydrate), uv min 234 mμ (ε 1400), 250/260 (0.66), 260/270 (0.95), 270/280 (1.51). The solid was purified by fractional precipitation for analysis using water–methanol–ethanol–2-propanol mixtures. The fractions were collected on the addition of 2-propanol. Fraction 4 (120 mg) was dissolved in water and the solution was concentrated *in vacuo*. This procedure was repeated five times using 5-ml portions of water. The residue was dissolved in a small amount of water and lyophilized to afford 100 mg of analytically pure **13**: uv max 267 mμ (ε 9900), uv min 234 mμ (ε 2600), 250/260 (0.66), 260/270 (0.94), 270/280 (1.49); nmr (D_2O) δ 1.14 [t, 3, J = 3.5 Hz, C-(O)OCH_2CH_3], 1.84 (s, 3, C-3 CH_3), 2.33 (t, 2, J = 3.0 Hz, C-2′ H_2), 3.95 [m, 6, C(O)OCH_2CH_3, C-3′ H, C-4′ H, C-5′ H_2], *ca.* 4.75 (broad s, 1, OH), 6.18 (t, 1, J = 3.0 Hz, C-1′ H), 7.67 (s, 1, C-2 H).

Anal. Calcd for $C_{13}H_{18}N_3O_9PNa_2 \cdot 3.5H_2O$: C, 31.21; H, 5.04; N, 8.40; P, 6.19. Found: C, 31.53; H, 5.38; N, 8.46; P, 5.92.

Anal. Calcd for $C_{13}H_{18}N_3O_9PNa_2$: C, 35.71; H, 4.15; N, 9.61; P, 7.08. Found (after block drying by the analyst at 150°): C, 36.11; H, 4.60; N, 8.99; P, 7.04; weight loss, 10.71%.

3′-Heptafluorobutyramido-3′-deoxythymidine 5′-Phosphate (14).—3′-Amino-3′-deoxythymidine 5′-phosphate inner salt (11, 300 mg) was suspended in anhydrous pyridine (3 ml), and heptafluorobutyrylimidazole (1.18 g) was added in portions [210 (177 μl), 210 (177 μl), 450 (400 μl), and 340 mg (300 μl)] over a period of several hours with magnetic stirring. The solution was still heterogeneous at the end of this time. The course of the reaction was monitored after each addition by tlc. After the last addition, tlc (cellulose tlc sheets, pc system D) indicated that the reaction was essentially complete. Water (20 ml) was added and the solution was lyophilized to yield a semisolid. The semisolid was dissolved in water. The water solution was applied to an AGC-244 (H^+)[23] column (*ca.* 10 ml, *ca.* 40 mequiv) and the column was eluted with water (*ca.* 200 ml) until the effluent no longer absorbed uv light at 254 mμ. The effluent was lyophilized to give 710 mg of crude **14** (free acid) as a solid. The solid was dissolved in water (2 ml), and methanol (1 ml) was added. The solution was clarified by centrifugation. The supernatant was lyophilized to afford a solid. The solid was purified by ppc in pc system A on 12 sheets to give 550 mg of homogeneous **14**. The product was dissolved in water and the water solution was passed through a Dowex 50 (H^+) column (10 ml), eluting with water. The effluent was lyophilized. The resulting solid (*ca.* 400 mg) was dissolved in minimum water and the solution was clarified by centrifugation. The pellet was discarded and the supernatant was diluted with methanol (2 ml). The solution was clarified by centrifugation and the pellet was discarded. The supernatant was diluted with water and the solution was lyophilized to afford 290 mg (62%) of pure **14**: uv max 267 mμ (ε 9500), uv min 234 mμ (ε 3100), 250/270 (0.69), 260/270 (0.97), 270/280 (1.57).

Anal. Calcd for $C_{14}H_{15}F_7N_3O_8P \cdot 2H_2O$: C, 30.39; H, 3.46; N, 7.59; P, 5.60. Found: C, 30.36; H, 2.98; N, 7.02; P, 5.26.

5′-Azido-5′-deoxythymidine 3′-Phosphate Dilithium Salt (17).—*N*,*N*′-Dicyclohexylcarbodiimide (6.3 g, 24 mmol) in 42 ml of pyridine and β-cyanoethyl phosphate[21] (1.30 g, 8 mmol) in 35 ml of pyridine were added to a solution of 5′-azido-5′-deoxythymidine (**15**, 1.056 g, 5 mmol) in anhydrous pyridine (10 ml). The solution was stirred at room temperature for 2 days. Tlc (tlc solvent system D) indicated that the reaction was complete. The product (**16**) migrated slower than starting material (**15**). Water (3 ml) was added and the mixture was allowed to stand at room temperature for 1 hr. Additional water (100 ml) was added. The resulting precipitate was removed by filtration and washed well with water. The washings and filtrate were combined and lyophilized to afford a solid. The solid was dissolved in water (50 ml) and the solution was clarified by filtration. The filtrate was lyophilized to give 1.8 g of intermediate **16** as an amorphous solid. The solid was dissolved in 1 *N* NaOH (50 ml) and the solution was allowed to stand at room temperature for 45 min. Tlc indicated that intermediate **16** had been converted into the product (**17**). The reaction mixture was applied to a Dowex 50 (H^+) column (175 ml) and the column was eluted with water until the eluate was neutral. The pH of the eluate was adjusted to 7.5 by the dropwise addition of 1 *N* LiOH solution. The solution was lyophilized to give 2.1 g of crude **17**. The ir (KBr) of crude **17** showed a strong azide absorption at 4.8 μ. Pc indicated that the product was relatively pure. Compound **17** was purified by ppc using 20 3 MM sheets and pc system D to give 720 mg of homogeneous **17**. The product was purified further by fractional precipitation from methanol–water mixtures. Ten fractions were collected. Fraction 9 was dissolved in water (4 ml) and lyophilized to give 100 mg. A portion of fraction 9 was dried at room temperature for 16 hr, and at 110° for 1 hr for analysis: uv max 266 mμ (ε 10,200), uv min 234 mμ (ε 2,600), 250/260 (0.67), 260/270 (0.96), 270/280 (1.55).

Anal. Calcd for $C_{10}H_{12}N_5O_7PLi_2 \cdot 2H_2O$: C, 30.40; H, 4.08; N, 17.72; P, 7.85. Found: C, 30.35; H, 4.00; N, 17.68; P, 8.01.

5′-Amino-5′-deoxythymidine 3′-Phosphate Dilithium Salt (18).—Compound **17** (200 mg), dissolved in water (15 ml), was stirred magnetically under hydrogen at atmospheric pressure at room temperature in the presence of 10% Pd/C (100 mg) for 2.5 hr. Tlc (tlc system E) indicated that the reduction was complete. The product (**18**) migrated slower than starting material (**17**). The catalyst was removed by filtration using a Celite bed and was washed thoroughly with water. The filtrate and washings were combined and lyophilized to yield 170 mg of **18**. The ir spectra (KBr) of the product showed the absence of an azide band at 4.8 μ which had been present in the starting material (**17**). The product was purified by fractional precipitation from water–ethanol mixtures. Five fractions were collected. Fraction 4 was dissolved in water (3 ml) and the solution was lyophilized to yield 50 mg of pure **18**. A sample was dried at room temperature (5×10^{-3} mm) for 12 hr for analysis: uv max 266 mμ (ε 9600), uv min 234 mμ (ε 2600) 250/260 (0.69), 260/270 (1.03), 270/280 (1.68).

Anal. Calcd for $C_{10}H_{14}N_3O_7PLi_2 \cdot 2H_2O$: C, 32.54; H, 4.92; N, 11.38; P, 8.38. Found: C, 32.32; H, 5.16; N, 11.14; P, 8.10.

5′-Amino-5′-deoxythymidine 3′-Phosphate Inner Salt (19).—5′-Amino-5′-deoxythymidine 3′-phosphate dilithium salt (**18**, 100 mg) was dissolved in water (3 ml), and trifluoroacetic acid (89 mg) was added with stirring. When the addition was complete, 2-propanol was added dropwise to the point of turbidity. A small amount of water was added, dropwise, to obtain a clear solution. The solution was allowed to stand at room temperature for 24 hr. The resulting crystalline product (**19**, 80 mg) was removed by filtration and air dried. Two recrystallizations from water–2-propanol mixtures afforded 70 mg of **19** with mp 213–215° dec. A sample was dried at room temperature (5×10^{-3} mm) for 14 hr for analysis: uv max 265 mμ (ε 10,300), uv min 234 mμ (ε 2600), 250/260 (0.68), 260/270 (1.02), 270/280 (1.75).

Anal. Calcd for $C_{10}H_{16}N_3O_7P \cdot 2H_2O$: C, 33.62; H, 5.64; N, 11.76; P, 8.67. Found: C, 33.65; H, 5.49; N, 11.89; P, 8.69.

5′-Acetamido-5′-deoxythymidine 3′-Phosphate Dilithium Salt (20).—5′-Amino-5′-deoxythymidine 3′-phosphate dilithium salt (**18**, 444 mg) was dissolved in a mixture of methanol (5 ml) and water (5 ml) and the solution was cooled to 0°. Acetic anhydride (140 mg) was added dropwise, with magnetic stirring, over a period of 10 min. After the addition was complete, the reaction mixture was stirred for an additional 20 min at 0°. The course of the reaction was followed by tlc (cellulose tlc sheets, pc system A). The reaction mixture migrated as a single spot (R_f 0.65), different from starting material (R_f 0.42). The solution was concentrated *in vacuo* to a small volume. Water (5 ml) was added and the solution was lyophilized to give 520 mg of crude **20**. Crude **20** was purified by ppc (11 sheets of 3 MM paper, pc system A) to afford 360 mg of homogeneous solid. The solid was dissolved in water (2 ml) and the solution was applied to a Dowex 50 (H^+) column (10 ml). The column was eluted with water. The course of the elution was monitored by uv at 254 mμ. The pH of the eluate was adjusted to 7.5 (pH paper) by the dropwise addition of LiOH solution. The effluent was lyophilized to yield 310 mg of **20** as a dilithium salt. Compound **20** was purified further by fractional precipitation from water–ethanol–2-propanol mixtures. Five fractions were collected. Fraction 4 was dissolved in water (15 ml) and the solution was concentrated *in vacuo* (repeated three times). The residue was dissolved in water again and the solution was lyophilized to afford 130 mg of pure **20**: uv max 266 mμ (ε 10,100), uv min 234 mμ (ε 2500), 250/260 (0.67), 260/270 (0.98), 270/280 (1.53).

Anal. Calcd for $C_{12}H_{16}N_3O_8PLi_2 \cdot 2H_2O$: C, 35.05; H, 4.90; N, 10.22; P, 7.53. Found: C, 35.11; H, 4.87; N, 10.15; P, 7.37.

5'-Chloroacetamido-5'-deoxythymidine 3'-Phosphate Disodium Salt (21).—5'-Amino-5'-deoxythymidine 3'-phosphate inner salt (19, 385 mg) and Na_2CO_3 (297 mg) were dissolved in a mixture of methanol (5 ml) and water (5 ml) and the solution was stirred at 0°. Chloroacetic anhydride (342 mg) was added. As the reaction progressed, the chloroacetic anhydride dissolved in the reaction media. After stirring at 0° for 20 min, tlc (cellulose sheets, pc system A) indicated that the reaction was complete (product R_f 0.47, starting material R_f 0.26). The solution was concentrated *in vacuo* to a small volume. Water was added and the solution was lyophilized to give 920 mg of crude 21. Compound 21 was purified by ppc (18 sheets of 3 MM paper, pc system A) to afford 580 mg of homogeneous solid with a low ϵ value: uv max 267 mμ (ϵ 5600) as a dihydrate, uv min 234 mμ (ϵ 2300). The solid was extracted with three portions of 2-propanol (10 ml). The 2-propanol extracts were discarded. The residue (560 mg, ϵ 5800) was extracted with three portions of ethanol (10 ml). The ethanol extract had no significant uv absorption and was discarded. The residue (300 mg, ϵ 8100) was purified for analysis by fractional precipitation from water–ethanol mixtures. Five fractions were collected. All five fractions were contaminated with a slower migrating impurity by tlc (cellulose tlc sheets, pc system A). The supernatants from the five fractions were combined and concentrated *in vacuo*. The residue (100 mg, ϵ 9200) was homogeneous by tlc. The solid was fractionally precipitated from water–2-propanol mixtures. Two fractions were collected. Fraction 2 (55 mg) was dissolved in water (10 ml) and the solution was concentrated *in vacuo* (repeated four times). The residue was dissolved in water again and the solution was lyophilized to give 50 mg of pure 21: uv max 267 mμ (ϵ 9700), uv min 234 mμ (ϵ 2500), 250/260 (0.66), 260/270 (0.97), 270/280 (1.53).

Anal. Calcd for $C_{12}H_{15}ClN_3O_8PNa_2 \cdot 2H_2O$: C, 30.17; H, 4.00; N, 8.79; P, 6.48; Cl, 7.42. Found: C, 30.18; H, 3.83; N, 8.44; P, 6.45; Cl, 6.78.

5'-*N*-(*O*-Ethylcarbamoyl)-5'-deoxythymidine 3'-Phosphate Disodium Salt (22).—5'-Amino-5'-deoxythymidine 3'-phosphate inner salt (19, 300 mg) and Na_2CO_3 (310 mg) were dissolved in a mixture of methanol (4 ml) and water (4 ml) and the solution was stirred at 0°. Ethyl chloroformate (135 mg) was added dropwise over a period of 5 min. The reaction mixture was stirred for an additional 10 min at 0°. The course of the reaction was monitored by tlc (cellulose tlc sheets, pc system A) and showed one spot (R_f 0.70), different from starting material (R_f 0.47). The reaction mixture was neutralized with 0.3 *N* HCl solution and concentrated *in vacuo* to a small volume. Water was added and the solution was lyophilized to give 500 mg of crude 22. The product was purified by ppc (pc system A, 12 sheets of 3 MM paper) to afford 250 mg of homogeneous 22. Compound 22 was purified further by fractional precipitation from water–2-propanol mixtures. Five fractions were collected. Fraction 2 was dissolved in water (10 ml) and the solution was concentrated *in vacuo* (repeated three times). The residue was dissolved in water again and lyophilized to give 40 mg of pure 22: uv max 267 mμ (ϵ 9700), uv min 234 mμ (ϵ 2500), 250/260 (0.67/270 (0.98), 270/280 (1.62).

Anal. Calcd for $C_{13}H_{18}N_3O_9PNa_2 \cdot 2H_2O$: C, 32.98; H, 4.69; N, 8.88; P, 6.55. Found: C, 33.27; H, 4.91; N, 9.04; P, 6.33.

Registry No.—2, 42214-24-4; 3, 25442-42-6; 4, 29706-84-1; 5, 30516-87-1; 6, 15981-92-7; 8, 30516-88-2; 9, 29706-87-4; 10, 29706-88-5; 11, 42214-32-4; 12, 42214-33-5; 13, 42214-34-6; 14, 42214-35-7; 15, 19316-85-9; 16, 29912-68-3; 17, 42214-38-0; 18, 29706-89-6; 19, 42319-49-3; 20, 42214-40-4; 21, 42214-41-5; 22, 42214-42-6.

General Methods of Synthesis of Indole Alkaloids. XII. Syntheses of *dl*-18,19-Dihydroantirhine and Methyl Demethylilludinate[1,2]

ERNEST WENKERT,* P. W. SPRAGUE, AND R. L. WEBB

Department of Chemistry, Indiana University, Bloomington, Indiana 47401

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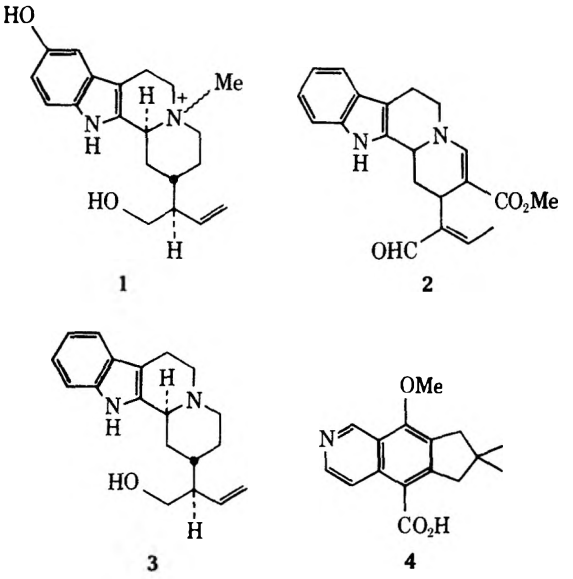
Methyl 4-carbomethoxymethylnicotinate was prepared from 4-methylnicotinic acid and condensed with acetaldehyde and with 3,3-dimethylcyclopentanone. Esterification, reduction, and oxidation of the first condensation product led to 4-(1-hydroxy-2-butyl)nicotinic lactone and thence in three steps to a derivative of antirhine, while esterification and cyclization of the second condensation product afforded an illudinine derivative.

The two-reaction sequence of partial hydrogenation of 1-alkyl-3-acylpyridinium salts and cyclization of the resultant 2-piperideines has constituted the backbone of alkaloid synthesis of a large variety of structure types.[3] This scheme of synthesis now has been exploited for the construction of a base structurally representative of the hunterburnine α- and β-metho salts (**1**),[4] vallesiachotamine (**2**),[5] and antirhine (**3**),[6] while intermediates on route to this base have been utilized for the synthesis of a derivative of illudinine (**4**).[7]



(1) Dedicated to Professor Edgar Lederer on the occasion of his 65th birthday.

(2) (a) This investigation was supported by the U. S. Public Health Service. (b) Part XI: E. Wenkert and G. D. Reynolds, *Syn. Commun.*, **3**, 241 (1973).

(3) E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).

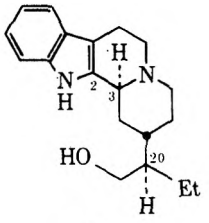
(4) J. D. M. Asher, J. M. Robertson, G. A. Sim, M. F. Bartlett, R. Sklar, and W. I. Taylor, *Proc. Chem. Soc., London*, 72 (1962); C. C. Scott, G. A. Sim, and J. M. Robertson, *ibid.*, 355 (1962); M. F. Bartlett, B. Korzun, R. Sklar, A. F. Smith, and W. I. Taylor, *J. Org. Chem.*, **28**, 1445 (1963); J. D. M. Asher, J. M. Robertson, and G. A. Sim, *J. Chem. Soc.*, 6355 (1965).

(5) C. Djerassi, H. J. Monteiro, A. Walser, and L. J. Durham, *J. Amer. Chem. Soc.*, **88**, 1972 (1966).

(6) S. R. Johns and J. A. Lamberton, *Chem. Commun.*, 229 (1967); S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Aust. J. Chem.*, **20**, 1463 (1967); *cf.* also Y. K. Sawa and H. Matsumura, *Tetrahedron*, **25**, 5319 (1969).

(7) M. S. R. Nair, H. Takeshita, T. C. McMorris, and M. Anchel, *J. Org. Chem.*, **34**, 240 (1969).

18,19-Dihydroantirhine (5).—Under the challenge of three chiral centers in its structure, the total, stereospecific synthesis of dihydroantirhine (**5**) *via* the route first perfected for the synthesis of corynanthediol[8] was undertaken. While the proper 3,15-trans relationship was expected to arise in the cyclization step creating the C(2)–C(3) bond,[8] special attention had to be paid to the stereochemistry of C(20) on the rotationally unrestricted hydroxybutyl side chain. Hence, a scheme of synthesis was designed to maintain full stereochemical control by incorporation of part of the side chain into a ring system and introduction of the proper C(20) configuration onto the thus restrained side chain. Lactone **6** became the first important synthesis goal.



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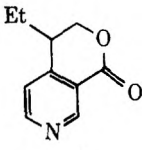

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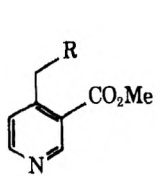
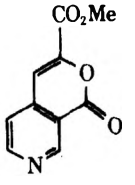
Base-catalyzed condensation of methyl oxalate with methyl 4-methylnicotinate (**7a**)[9] yielded the enolate salt of the keto diester **7b**, whose neutralization gave lactone **8**. Alkaline hydrolysis of the salt, decarboxylation of the resultant keto diacid by oxidation with alkaline hydrogen peroxide, and esterification with methanolic acid led to methyl 4-carbomethoxymethylnicotinate (**7c**). Base-induced condensation of the latter with acetaldehyde and reesterification of the product[10] afforded diester **9a**,[12] whose hydrogenation produced the nicotinic ester derivative **10**.



7a, R = H
b, R = $COCO_2Me$
c, R = CO_2Me



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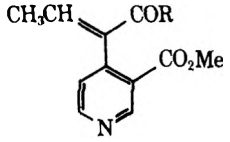
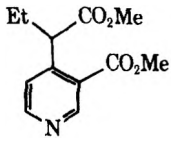


9a, R = OMe
b, R = CO_2Me

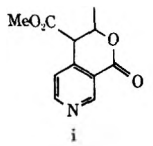


10

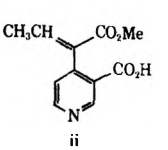
(8) E. Wenkert, K. G. Dave, and F. Haglid, *J. Amer. Chem. Soc.*, **87**, 5461 (1965).

(9) J. L. Webb and A. H. Corwin, *J. Amer. Chem. Soc.*, **66**, 1456 (1944).

(10) In analogy with the Stobbe condensation,[11] a lactone (i) is the initial intermediate and the β-elimination product ii its successor. Hence, a subsequent esterification is necessary.



i



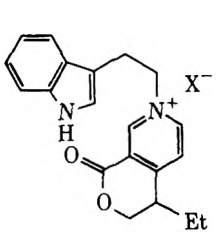
ii

(11) W. S. Johnson and G. H. Daub, "Organic Reactions," Vol. VI, Wiley, New York, N. Y., p 1.

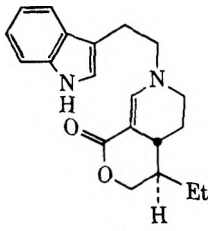
(12) Similar condensation of **7b** with acetaldehyde yielded **9b** (see Experimental Section).

Lithium aluminum hydride reduction thereof and oxidation of the diol product with manganese dioxide yielded the desired lactone **6**.

Alkylation of lactone **6** with tryptophyl bromide gave a pyridinium salt (**11a**) whose hydrogenation[3] led to a tetrahydropyridine. The latter was assigned stereostructure **12** on the assumption of the hydrogenation occurring under thermodynamic control in the absence of overriding steric factors and the 15,20-trans stereochemistry being the energetically more favorable one. Alkaline hydrolysis (followed by decarboxylation and cyclization[8]) of **12** afforded *dl*-18,19-dihydroantirhine (**5**) spectrally identical with a sample derived from the natural product.[13,14]



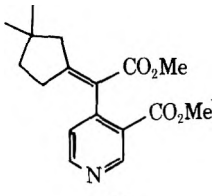
11a, X = Br
b, X = ClO_4



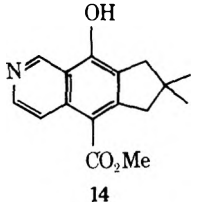
12

Methyl Demethylilludininate (14).—In view of the availability of diester **7c** and the favorable experience of its condensation with a carbonyl compound (**7c** → **9a**), it was decided to synthesize the illudinine (**4**) ring system from **7c** by a related reaction sequence.

Base-catalyzed condensation of methyl 4-carbomethoxymethylnicotinate (**7c**) with 3,3-dimethylcyclopentanone,[15] followed by esterification of the resultant acid esters (*cf.* ref 10), yielded a mixture of diester **13** and its stereoisomer. Their further base treatment under equilibrium conditions was expected to induce the aromatic ester moiety to condense into the less sterically encumbered allylic site of the cyclopentane unit. On exposure of the diester mixture to potassium *tert*-butoxide in *tert*-butyl alcohol, a single product was obtained whose spectral properties revealed it to be the illudinine derivative **14**.



13



14

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Proton magnetic resonance spectra of solutions with tetramethylsilane acting as internal standard were recorded on Varian Associates A-60 and HA-100 spectrometers.

Methyl 4-Carbomethoxymethylnicotinate (7c).—Freshly cut potassium, 5 g, was dissolved in 60 ml of *dry tert*-butyl alcohol (refluxed and distilled over calcium hydride) under dry nitrogen. Dry, peroxide-free 1,2-dimethoxyethane (refluxed, distilled, and

(13) The authors are indebted to Dr. S. Johns for a gift of a sample of *l*-antirhine.

(14) For other syntheses of dihydroantirhine, see T. Kimara and Y. Ban, *Chem. Pharm. Bull.*, **17**, 296 (1969); H.-P. Husson, L. Chevolot, Y. Langlois, C. Thal, and P. Potier, *Chem. Commun.*, 930 (1972).

(15) T. Henshall, *J. Soc. Chem. Ind., London*, **62**, 127 (1943); H. Pines, F. J. Pavlik, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **73**, 5738 (1951).

stored over sodium wire), 200 ml, was added and the mixture was cooled to 10°. Methyl 4-methylnicotinate (**7a**),[9] 12.8 g, was added and the mixture was stirred for 5 min. Thereupon 12.8 g of dimethyl oxalate was added in one portion and the mixture was stirred under dry nitrogen for 18 hr. The resultant solid paste was poured into 600 ml of dry ether and the flocculent, yellow precipitate was filtered onto a sintered glass funnel under a stream of dry nitrogen and washed with 50 ml of dry ether. The dry enolate salt was dissolved in 100 ml of water. After a few minutes lactone **8** began to precipitate, whereupon a solution of 13 g of potassium hydroxide in 65 ml of water was added and the orange-red solution was stirred at room temperature for 2 hr. (Absence of lactone precipitation generally reflected failure of the initial condensation.) Next, eight 2.4-ml portions of 30% hydrogen peroxide were added to the stirring solution at 0–5° in a cold room over a period of 24 hr. (Both peroxide concentration and temperature were critical for maintaining a reasonable yield of final product.) The mixture was stirred at 0–5° for another 12 hr, whereupon water was removed from the light yellow solution by freeze-drying up to 50° (preferably below room temperature). Further drying at 0.2–0.5 Torr for 12 hr left a yellow-green solid. (Insufficient drying led to failure of the subsequent esterification.) The latter was stirred in 500 ml of dry methanol at −70° for 2 hr. Methanol, 200 ml, saturated with hydrogen chloride gas and precooled to −70° was added and the mixture was stirred and allowed to come to room temperature. (Neutralization of the dicarboxylate salt and passage through the isoelectric point at temperatures above −70° resulted in extensive decarboxylation.) It then was stirred, protected by a drying tube, at room temperature for 4 days. The pale orange mixture was poured slowly onto 800 ml of a methylene chloride suspension of an excess of sodium bicarbonate, the inorganic material was filtered, and the filtrate was dried over anhydrous sodium carbonate. Evaporation of the filtrate under vacuum at 35° yielded a viscous, orange oil whose pmr spectrum revealed it to contain *ca.* 5% of starting ester (**7a**). Chromatography of the oil on alumina, activity IV, and elution with benzene gave 12.3 g of a low-melting solid. (Distillation thereof led to its total destruction.) Crystallization from hexane afforded colorless plates of diester **7c**: mp 51.5–52°; ir (KBr) C=O 5.73 (s), 5.82 (s), C=C 6.28 (m), 6.42 μ (m); pmr (CCl_4) δ 3.64 (s, 3, OMe of aliphatic ester), 3.87 (s, 3, OMe of aromatic ester), 3.98 (s, 2, methylene), 7.10 [d, 1, J = 5.0 Hz, C(5) H], 8.53 [d, 1, J = 5.0 Hz, C(6) H], 9.07 [s, 1, C(2) H].

Anal. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70: Found: C, 57.70; H, 5.36; N, 6.65.

Lactone 8.—A solution of 2.0 g of the enolate salt of **7b** in 10 ml of water was brought to pH 6 with 2 *M* hydrochloric acid and the resultant precipitate was filtered, dried, and sublimed at 150° (15 Torr). Crystallization of the sublimate from methanol gave 0.9 g of colorless prisms of lactone **8**: mp 187–188°; ir (KBr) C=O 5.70 (s), 5.81 (s), C=C 6.12 (m), 6.29 μ (s); uv (MeOH) λ_{max} 221 nm (ε 5100), 242 (3500), 250 (3200), 272 (2300), 291 (2400), 381 (1000); pmr ($CDCl_3$) δ 3.99 (s, 3, OMe), 7.45 (s, 1, enol methine), 7.48 (d, 1, J = 5.0 Hz, pyridine β′ H), 8.95 (d, 1, J = 5.0 Hz, pyridine α′ H), 9.52 (s, 1, pyridine α H).

Anal. Calcd for $C_{10}H_7O_4N$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.57; H, 3.61; N, 6.85.

Methyl 4-(α-Carbomethoxypropenyl)nicotinate (9a).—Diester **7c**, 2.90 g, was added to a solution of potassium *tert*-butoxide, prepared from 0.63 g of freshly cut potassium in 5 ml of *tert*-butyl alcohol, in 200 ml of dry 1,2-dimethoxyethane and the mixture was stirred under nitrogen at room temperature for 10 min. It then was cooled to 0° and a solution of 3 ml of freshly distilled acetaldehyde in 100 ml of dry 1,2-dimethoxyethane was added dropwise over a period of 45 min. The mixture was stirred under nitrogen for 18 hr and then evaporated. The residue was dissolved in 200 ml of methanol saturated with hydrogen chloride gas and the mixture was left at room temperature for 4 days. It then was poured onto a methylene chloride suspension of an excess of sodium bicarbonate and filtered. The filtrate was dried over anhydrous sodium carbonate and evaporated. Chromatography of the residue on alumina, activity IV, and elution with cyclohexane gave a pale yellow oil whose distillation [150° (0.05 Torr)] yielded 1.80 g of colorless liquid diester **9a**: ir (neat) C=O 5.81 (s), C=C 6.11 (w), 6.31 (m), 6.50 μ (m); pmr (CCl_4) δ 1.68 [d, 3, J = 7.0 Hz, Me of major (88%) isomer], 2.25 [d, 3, J = 7.0 Hz, Me of minor (12%) isomer], 3.62, 3.82 (s, 3 each, methoxyls), 7.05 [d, 1, J = 5.0 Hz, C(5) H], 7.07 (q, 1, J = 7.0 Hz, olefinic H), 8.65 [d, 1, J = 5.0 Hz, C(6) H], 9.10 [s, 1, C(2) H]. (The liquid turned yellow and its purity decreased on storage.)

Anal. Calcd for $C_{12}H_{13}O_4N$: N, 5.95. Found: N, 5.86.

Keto Diester 9b.—A solution of 1.0 g of methyl 4-methylnicotinate (**7a**) and 0.90 g of potassium *tert*-butoxide in 30 ml of 1:1 *tert*-butyl alcohol and 1,2-dimethoxyethane was kept under nitrogen at 0° for 10 min. Dimethyl oxalate, 1.0 g, was added and the mixture was stirred at room temperature for 5 hr. It was cooled to 0° and a solution of 1.0 g of acetaldehyde in 10 ml of 1,2-dimethoxyethane was added dropwise over a period of 30 min. The mixture was stirred at room temperature for 18 hr and then evaporated under reduced pressure. The residue was dissolved in 50 ml of dry methanol, saturated with hydrogen chloride gas, and the solution was kept for 3 days. It then was neutralized with sodium bicarbonate and filtered. The filtrate was evaporated, the residue was extracted with chloroform, and the extract was washed with water, dried, and evaporated under vacuum. The residual, viscous, yellow oil, 1.5 g, solidified slowly. Crystallization from chloroform afforded 0.90 g of colorless needles of ester **7b**: mp 159–160°; ir (KBr) C=O 5.69 (s), 5.80 (s), C=C 6.24 μ (m); pmr (deuterioacetone) δ 1.38 (d, 3, J = 7.0 Hz, Me), 3.90, 4.28 (s, 3 each, methoxyls), 5.61 (q, 1, J = 7.0 Hz, olefinic H), 7.54 [d, 1, J = 5.0 Hz, C(5) H], 8.80 [d, 1, J = 5.0 Hz, C(6) H], 9.02 [s, 1, C(2) H].

Anal. Calcd for $C_{13}H_{13}O_5N$: N, 5.32. Found: N, 5.54.

Methyl 4-(α-Carbomethoxypropyl)nicotinate (10).—A mixture of 2.0 g of **9a** and 40 mg of platinum oxide in 80 ml of dry methanol was hydrogenated at atmospheric pressure and room temperature. After 24 hr, the mixture was filtered, the filtrate was evaporated, and the residual oil was chromatographed on alumina, activity IV. Elution with benzene yielded 1.7 g of colorless, liquid diester **10**: ir (neat) C=O 5.80 (s), C=C 6.30 (m), 6.46 μ (w); pmr (CCl_4) δ 0.91 (t, 3, J = 7.0 Hz, Me), 1.0–2.2 (m, 2, methylene), 3.61, 3.88 (s, 3 each, methoxyls), 4.58 (t, 1, J = 7.0 Hz, methine), 7.25 [d, 1, J = 5.0 Hz, C(5) H], 8.49 [d, 1, J = 5.0 Hz, C(6) H], 9.00 [s, 1, C(2) H].

Anal. Calcd for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.68; H, 6.63; N, 5.97.

Lactone 6.—A solution of 2.00 g of the diester **10** in 50 ml of ether was added dropwise to a suspension of 1.00 g of lithium aluminum hydride in 150 ml of ether over a period of 15 min and the mixture then was refluxed for 18 hr. Moist sodium sulfate was added and the suspension was shaken for 30 min. It then was filtered and the precipitate was washed with hot ethyl acetate. The combined filtrate and washings were dried over magnesium sulfate and evaporated. A mixture of the residual, colorless, viscous, liquid diol, 1.40 g, and 10.0 g of activated manganese dioxide[16] in 350 ml of dry ether was stirred at room temperature for 46 hr. It was filtered through Celite and the solid was washed with hot ethyl acetate. The combined filtrate and washings were dried and evaporated. Chromatography of the residual yellow oil on alumina, activity IV, and elution with benzene yielded 950 mg of colorless, liquid lactone **6**: ir (neat) C=O 5.79 (s), C=C 6.24 μ (s); pmr (CCl_4) δ 1.01 (t, 3, J = 7.0 Hz, Me), 1.2–2.0 (m, 2, methylene), 2.82 (m, 1, methine), 4.2–4.7 (m, 2, oxymethylene), 7.25 [d, 1, J = 5.0 Hz, C(5) H], 8.59 [d, 1, J = 5 Hz, C(6) H], 8.95 [s, 1, C(2) H]; yellow plates of its picrate, crystallized from methanol, had mp 153–154°.

Anal. Calcd for $C_{16}H_{14}O_9N_4$: C, 47.30; H, 3.47; N, 13.79. Found: C, 47.43; H, 3.73; N, 13.63.

Pyridinium Salt 11b.—A solution of 80 mg of lactone **6** and 101 mg of tryptophyl bromide in 30 ml of ether was stirred at room temperature under nitrogen for 36 hr. The mixture was evaporated and the residue was washed with dry ether. Since the resultant salt could not be induced to crystallize, it was treated with a saturated, aqueous solution of sodium perchlorate. Crystallization of the new salt from methanol yielded 100 mg of **11b**: mp 150–153°; ir (KBr) NH 2.90 (s), 2.98 (s), 3.13 (s), C=O 5.90 (s), C=C 6.15 μ (m).

Anal. Calcd for $C_{20}H_{21}O_6N_2Cl$: C, 55.60; H, 4.87; N, 6.50. Found: C, 55.84; H, 5.14; N, 6.65.

***dl*-18,19-Dihydroantirhine (5).**—A mixture of 20 mg of 10% palladium on charcoal and 1.2 ml of triethylamine in 15 ml of methanol was saturated with hydrogen and a solution of 100 mg of salt **11b** in 15 ml of methanol was then added. The mixture was hydrogenated at atmospheric pressure. After an uptake of 2 equiv of hydrogen, it was filtered and the filtrate was evaporated.

(16) J. Attenborrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

Chromatography of the residue on alumina, activity IV, and elution with benzene gave 40 mg of oily **12**: ir (CCl_4) NH 3.18 (m), C=O 6.00 (s), C=C 6.32 μ (s). In view of its instability, it was used for the next reaction without further purification.

A solution of 40 mg of **12** in 10 ml of 10% methanolic potassium hydroxide was stirred at room temperature under nitrogen for 30 hr. It was neutralized with 10% hydrochloric acid and evaporated. Extraction of the residue with ethanol and evaporation of the extract gave 10 mg of a viscous oil which crystallized slowly. Crystallization from ethyl acetate–ethanol yielded 4 mg of prisms of *dl*-18,19-dihydroantirhine (**5**): mp 95–97.5°; infrared, ultraviolet, mass spectral, and tlc characteristics identical with those of an authentic sample;[6,13] *m/e* 298.204516 (calcd 298.204503).

Methyl Demethylilludinate (14).—A solution of dry potassium *tert*-butoxide (from 620 mg of potassium) and 3.24 g of diester **7c** in 25 ml of 1,2-dimethoxyethane was added dropwise to 1.75 g of 3,3-dimethylcyclopentanone[15] over a 1-hr period and the mixture was stirred at room temperature under nitrogen for 15 hr. Hydrochloric acid (50 ml of 3 *N*) was added and the mixture was evaporated at 50° to dryness. The residue was dried further in a vacuum desiccator for 12 hr and then dissolved in 50 ml of methanol saturated with hydrogen chloride gas. After 2 hr, the mixture was worked up in a previously described manner[17] and the crude product was chromatographed on alumina (activity III) and eluted with a 3:2 mixture of cyclohexane–benzene. Crystallization of the product from pentane gave 2.98 g of colorless crystals, mp 38–45°, whose sublimation afforded the diesters **13** and its stereoisomer: mp 45–55°; ir (KBr) C=O 5.78 (s), 5.81 (s), C=C 6.12 (m), 6.31 (m), 6.48 (m); uv (MeOH) λ_{max} 224 nm (log ϵ 4.36); pmr ($CDCl_3$) δ 0.93 (s, 3, Me), 1.08 (s, 3, Me), 1.62 (t, 2, J = 8 Hz, CH_2 of major isomer), 1.88 (broad s, 2,allyl CH_2 of major isomer), 2.18 (t, 2, J = 8 Hz, CH_2 of minor isomer), 2.83 (broad s, 2, allyl CH_2 of minor isomer), 3.10 (t, 2, J = 8 Hz, allyl CH_2 of major isomer), 3.61 (s, 3, OMe), 3.82 (s, 3, OMe), 7.12 [t, 1, J = 4 Hz, C(5) H], 8.68 [d, 1, J = 4 Hz, C(6) H], 9.13 [broad s, 1, C(2) H].

Anal. Calcd for $C_{17}H_{21}O_4N$: C, 67.29; H, 6.98; N, 4.62. Found: C, 67.13; H, 7.08; N, 4.63.

A solution of 733 mg of diester **13** and its stereoisomer in 5 ml of dry 1,2-dimethoxyethane was added to a solution of potassium *tert*-butoxide (from 104 mg of potassium) in 25 ml of 1,2-dimethoxyethane and the intensely red solution was stirred under nitrogen for 0.5 hr. The color had disappeared and the mixture was evaporated to dryness. The residue was treated with 10 ml of water and the mixture was brought to pH 6 with 5% hydrochloric acid and extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethyl acetate yielded 525 mg of yellow, crystalline ester **14**: mp 220° dec; ir (Nujol) C=O 5.87 (s), C=C 6.14 (s), 6.27 (w), 6.38 (s); uv (MeOH) λ_{max} 242 nm (log 4.63), 285 (4.03), 307 (4.01), 333 (3.98), 385 (3.66); $\lambda_{shoulder}$ 260 nm (log ϵ 4.33), 348 (3.93); pmr (DMSO-d_6) δ 2.85 (s, 2, CH_2), 3.08 (s, 2, CH_2), 3.92 (s, 3, OMe), 8.23 (d, 1, J = 6 Hz, pyridine β H), 8.45 (d, 1, J = 6 Hz, pyridine α H), 9.50 (s, 1, pyridine α' H).

Anal. Calcd for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.10; H, 6.47; N, 5.33.

Registry No.—**5**, 42289-79-2; **6**, 42253-62-3; **6** picrate, 42289-80-5; **7a**, 33402-75-4; **7b** enolate, 42253-64-5; **7c**, 33402-74-3; **8**, 33402-73-2; **9a**, 42253-67-8; **9b**, 42253-68-9; **10**, 42253-69-0; **11b**, 42253-70-3; **12**, 42253-71-4; **13**, 42253-72-5; **13** stereoisomer, 42253-73-6; **14**, 42253-74-7; dimethyl oxalate, 553-90-2.

(17) E. Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague, *J. Amer. Chem. Soc.*, **90**, 5251 (1968).

Steroids Derived from Bile Acids. A Novel Side-Chain Degradation Scheme

MARCEL FETIZON,* FREDERIC J. KAKIS, AND VALENTINE IGNATIADOU-RAGOUSSIS

Department of Synthetic Organic Chemistry, Ecole Polytechnique, Paris, France

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A four-step degradative sequence of methyl cholanate (**1**) and methyl lithocholate (**13**) is described with a 35 and 27% overall yield, respectively. The method involves conversion of the esters to the rearranged phenyl ketones (**4** and **16**) which are in turn subjected to a Norrish type II photoelimination. Ozonolysis of the final products leads to physiologically important steroid compounds.

In a recent publication[1] we have described a novel method for the degradation of the carbon chain of organic acids and their derivatives. The key substance in the sequence we have described is a phenyl ketone which is easily obtainable by an established[2] rearrangement procedure. In view of the intensive recent interest[3-7] in the photolysis of such compounds by Norrish type II processes, we have decided to utilize this reaction, combine it with a part of our previous scheme, and apply it to the degradation of the side chain of steroidal substrates. Thus a convenient modification of the original degradative sequence has resulted, the individual steps of which are outlined in Scheme I.

Results and Discussion

Samples of esters **1** and **13** were converted to the corresponding tertiary alcohols **2** and **14** by means of a standard Grignard reaction with phenylmagnesium bromide in nearly quantitative yields. Dehydration of the alcohols in acetic anhydride afforded the corresponding olefins **3** and **15**. The yields for this step were 85%. The olefins **3** and **15** were easily and quantitatively converted to the corresponding ketones **4** and **16** by means of the Kakis reaction.[2] This reaction in the present system generates a pair of diastereomers, epimeric around the C_{23} asymmetric carbon. Although not directly related to the degradative scheme, which utilizes the mixture, we thought it would be of theoretical as well as practical interest to separate the stereoisomers and to obtain the spectra and their physical constants. This seemed to be particularly appropriate since these compounds have never been prepared before and their physiological properties are not known. Separation was achieved by laborious thin-layer chromatography. The pure isomers were isolated and their melting points, optical rotations, and nmr spectra were obtained.

(1) M. Fetizon, F. J. Kakis, and V. Ignatiadou-Ragoussis, *J. Org. Chem.*, **38**, 1732 (1973).

(2) F. J. Kakis, D. Brase, and A. Oshima, *J. Org. Chem.*, **36**, 4117 (1971).

(3) J. D. Coyle and H. A. J. Carless, *Chem. Soc. Rev.*, **1**, 465 (1972).

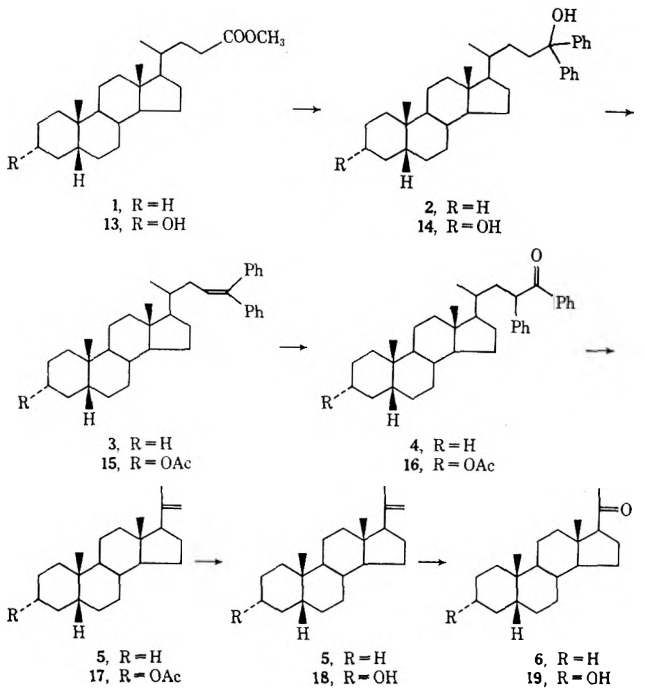
(4) P. J. Wagner, P. A. Kelso, and R. G. Zepp, *J. Amer. Chem. Soc.*, **94**, 7480 (1972).

(5) P. J. Wagner, I. E. Kochevar, and A. E. Kemppainen, *J. Amer. Chem. Soc.*, **94**, 7489 (1972).

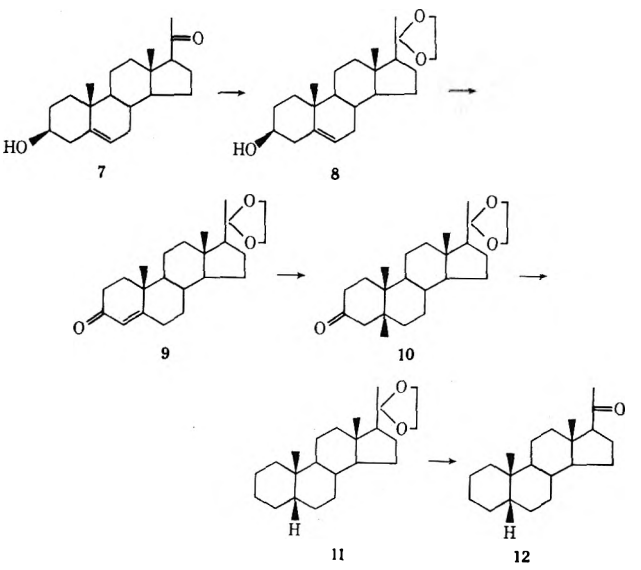
(6) P. J. Wagner, P. A. Kelso, A. E. Kemppainen, and R. G. Zepp, *J. Amer. Chem. Soc.*, **94**, 7500 (1972).

(7) P. J. Wagner, P. A. Kelso, A. E. Kemppainen, J. M. McGrath, H. N. Schott, and R. G. Zepp, *J. Amer. Chem. Soc.*, **94**, 7506 (1972).

SCHEME I



SCHEME II



The mixtures of ketones **4** and **16** were subjected to the conditions of the Norrish type II photoelimination, which resulted in a complex mixture of products. Separation of the mixtures by thin-layer chromatography afforded the degradation products **5** and **17** in 45 and 35% yields, respectively. No attempt was made to isolate or identify the other photolysis products.

We have found by means of repeated trials that a small increase in the yields occurs when the photolysis is carried out in *tert*-butyl alcohol instead of benzene.

Identification of structure was obtained by infrared and nuclear magnetic resonance spectroscopy and by elemental analysis. To obtain final confirmation, samples of compounds **5** and **18** were subjected to standard ozonolysis and the corresponding ketones **6** and **19** were compared and found to be identical with authentic samples. An authentic sample of compound **19** was obtained commercially.[8] The other authentic sample, compound **6**, was synthesized from pregnenolone (**7**) *via* a five-step synthesis, the details of which are shown in Scheme II.

The degradative scheme (I) described above afforded a 35 and 27% overall yield for the four-step degradation of methyl cholanate and methyl lithocholate, respectively. These yields are significantly higher than those obtained by many other published pathways.[9-14] We are currently investigating its application to the degradation of the lanosterol side chain and other steroidal substrates. Finally, it is noteworthy that the terminal products of our pathway are useful precursors of physiologically important compounds.[15]

(8) Ikapharm Chemical Co., Ramat-Gan, Israel.
(9) (a) P. Barbier and R. Locquin, *C. R. Acad. Sci.*, **156**, 1443 (1913).
(10) H. Wieland, *Z. Physiol. Chem.*, **161**, 80 (1926).
(11) Ch. Meystre, H. Frey, A. Wettstein, and K. Miescher, *Helv. Chim. Acta*, **27**, 1815 (1944).
(12) Y. Yanuka, R. Katz, and S. Sarel, *Tetrahedron Lett.*, 1725 (1968).
(13) Y. Yanuka, R. Katz, and S. Sarel, *Chem. Commun.*, 849, 851 (1968).
(14) L. H. Briggs, J. P. Bartley, and P. S. Rutledge, *Tetrahedron Lett.*, 1237 (1970).
(15) L. Gyermek, J. Iriarte, and P. Crabbé, *J. Med. Chem.*, **11**, 117 (1968).

Experimental Section

General.—Melting points were taken on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined on a Joel Model C60H spectrometer using tetramethylsilane as internal standard and are reported in parts per million. Optical rotations were measured with the aid of a Perkin-Elmer Model 141 polarimeter. Irradiations were performed with a Hanau TQ 150-W medium-pressure mercury lamp contained in a quartz immersion well. The 3130-Å line was isolated with a 1-cm path of 0.002 *M* potassium chromate in a 5% aqueous solution of potassium carbonate. The required cooling was achieved by circulation of this solution. Microanalysis were performed by the microanalysis service of CNRS at the Gif Sur Yvette Laboratories in France.

24,24-Diphenyl-24-hydroxy-5β-cholane (2).—This compound was prepared from a sample (17 g, 0.0227 mol) of pure (mp 87–88°) methyl cholanate (**1**) by the standard addition of phenylmagnesium bromide (57.8 g, 0.227 mol) in anhydrous ether. After hydrolysis of the reaction mixture and decomposition with a saturated solution of ammonium chloride, a viscous yellow oil (27 g) was obtained. After purification by column chromatography over silica (Merck 0.05–0.2 mm) using a pentane–ether mixture as the eluent (10:1), 21.9 g of alcohol **2** were obtained. The crystallization from hexane (−10°) afforded a pure (mp 95–96°) product in 96% yield: ir (CCl_2CCl_2) 3610, 3080, 3060, 3030, and 700 cm^{-1}; nmr ($CDCl_3$) 0.62, 0.89 (3 H, singlet, C_{18} and C_{19} protons), 7.1–7.6 (10 H, multiplet, aromatic protons).

Anal. Calcd for $C_{36}H_{50}O$: C, 86.69; H, 10.11; O, 3.21. Found: C, 86.47; H, 9.97; O, 3.28.

24,24-Diphenyl-5β-chol-23-ene (3).—This compound was prepared by dehydrating a sample of alcohol **2** (8.8 g) in refluxing acetic anhydride for a period of 12 hr. After removal of the solvents by rotatory evaporation and one recrystallization from methanol–ether, a crystalline sample (8.2 g) was obtained. Further purification was achieved by column chromatography over silica (Merck, 0.05–0.2 mm) using pentane as the eluent. Thus a pure (mp 120–122°) sample (7.1 g, 84%) of olefin **3** was obtained: ir (CCl_2CCl_2) 3080, 3060, 3020, 1600, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.61, 0.9 (singlet, C_{18} and C_{19} protons), 6.1 (1 H, triplet, ethylenic, J = 7.5 Hz), 7–7.6 (10 H, multiplet, aromatic protons).

Anal. Calcd for $C_{36}H_{48}$: C, 89.94; H, 10.06. Found: C, 89.77; H, 10.03.

23,24-Diphenyl-5β-cholan-24-one (4).—A sample (1.3 g) of olefin **3** was converted to ketone **4** by the Kakis method.[2] The reaction afforded 1.27 g (94%) of sufficiently pure ketone **4**: ir (CCl_2CCl_2) 3090, 3060, 3030, 1690, 1600, 1450, and 700 cm^{-1}.

Anal. Calcd for $C_{36}H_{48}O$: C, 87.04; H, 9.74; O, 3.22. Found: C, 86.74; H, 9.45; O, 3.24.

This reaction results in a mixture of two (**4a** and **4b**) diastereomers, epimeric around the C_{23} asymmetric carbon. The stereoisomers were separated by thin-layer chromatography on fluores-

cent silica using several successive elutions with pentane–ether (50:1). Subsequently, each isomer was recrystallized from methanol. The least polar substance (**4a**) melted sharply at 146–146.5°. The other isomer (**4b**) melted sharply at 158–159°: nmr (**4a**) ($CDCl_3$) δ 0.6, 0.9 (singlets, C_{18} and C_{19} protons), 4.77 (multiplet, 1 H, proton α to the carbonyl), 7.05–8.2 (10 H, multiplet, aromatic protons); nmr (**4b**) 0.47, 0.87 (singlets, C_{18} and C_{19} protons), 4.65 (multiplet, 1 H, proton α to the carbonyl), 7.1–8.2 (10 H, multiplet, aromatic protons); $[\alpha]_D$ ($CHCl_3$) (**4a**) −73°, $[\alpha]_D$ ($CHCl_3$) (**4b**) +96.5°.

20-Methylene-5β-pregnane (5).—A sample (1 g) of the diastereomeric mixture of ketones (**4**) was dissolved in anhydrous *tert*-butyl alcohol (70 ml) and irradiated for a period of 3 hr. On evaporation of the solvents under vacuum, a sample (1.03 g) of crude (yellow oil) product was obtained. Purification was achieved by thin-layer chromatography on silica containing 8% silver nitrate. After three elutions with pentane–ether (40:1) a pure sample (275 mg; *ca.* 45%; R_f 0.7) of olefin **5** was obtained which crystallized spontaneously. Recrystallization was achieved with some difficulty from methanol–ether producing the analytical sample (mp 72–74°): ir (CS_2) 3080 and 885 cm^{-1}; nmr ($CDCl_3$) δ 0.57, 0.95, 1.77 (singlets, C_{18}, C_{19}, and C_{21} protons), 4.7, 4.85 (2 H, two adjacent singlets, exocyclic methylene protons); $[\alpha]_D$ ($CHCl_3$) +12.5°.

Anal. Calcd for $C_{22}H_{36}$: C, 87.92; H, 12.08. Found: C, 87.53; H, 12.02.

The above irradiation was repeated many times. The yields in *tert*-butyl alcohol ranged from 45 to 48% and in benzene from 35 to 40%.

Pregnenolone Ethylene Ketal (8).—A commercial sample (29 g, 0.091 mol) of pregnenolone (**7**) was converted to the ethylene ketal (**8**) by a standard method.[16] Thus 31 g (95%) of crude product was obtained. After recrystallization from methanol containing a few drops of pyridine a pure sample of ketal **8** was obtained which melted at 164–166° in agreement with the literature:[16] ir (CS_2) 3610, 1070, 1050, 1025, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.81 (3 H, singlet, C_{18} protons), 1.05 (3 H, singlet, C_{19} protons), 1.33 (3 H, singlet, C_{21} protons), 3.5 (1 H, C_3 proton), 3.93 (4 H, multiplet, $-OCH_2CH_2O-$), 5.37 (1 H, multiplet, ethylenic proton).

Progesterone 20-Ethylene Ketal (9).—A sample of pregnenolone ethylene ketal (**8**) above (15.6 g, 0.044 mol) was converted by a standard Oppenauer oxidation to progesterone ethylene ketal (**9**). The yield of the crude product (13.9 g) was 89%. Recrystallization from methanol containing a few drops of pyridine afforded a pure product (mp 189–191°) whose melting point was in agreement with the literature value:[16] ir (CS_2) 1680, 1070, 1050, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.71 (3 H, singlet, C_{18} protons), 1.2 (3 H, singlet, C_{19} protons), 1.3 (3 H, singlet, C_{21} protons), 3.9 (4 H, multiplet, $-CH_2CH_2O-$), 5.7 (1 H, singlet, C_4 proton).

20-Ethylenedioxy-5β-pregnane-3-one (10).—This compound was prepared by an adaptation of a previously reported method.[17] Thus a sample of progesterone ethylene ketal (**9**) (5 g, *ca.* 0.014 mol) in freshly distilled *N*-methylpyrrolidine (250 ml) was treated with a commercial sample[18] (2.5 g, 5% Pd on $CaCO_3$) of the catalyst and hydrogenated. At the end of the reaction a white crystalline product (5.1 g) was isolated which consisted of a mixture of the two stereoisomers with the 5β isomer predominating. On recrystallization from acetone containing a few drops of pyridine a pure sample (2.7 g, mp 172–174°) of the 5β isomer was obtained. Column chromatography of the mother liquors over silica (Merck 0.05–0.2 mm) with pentane–ether (1:1) afforded an additional sample (1.55 g) of the pure 5β isomer (total yield ~80%): ir (CS_2) 1715, 1070, 1050, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.77 (3 H, singlet, C_{19} protons), 0.9 (3 H, singlet, C_{18} protons), 1.32 (3 H, singlet, C_{21} protons), 3.57 (4 H, multiplet, $-OCH_2CH_2O-$). Final confirmation of the structure of **10** was obtained by hydrolysis of a small sample which afforded 5β-pregnane-3,20-dione whose melting point (123–124°) and spectra were in agreement with previously reported values.[19]

20-Ethylenedioxy-5β-pregnane (11).—This compound was prepared by a standard Wolff–Kishner reduction of a sample (2.8 g, *ca.* 0.008 mol) of compound **10**. Thus a white crystalline product (2.6 g, 95%) was obtained, and recrystallized from acetone containing a few drops of pyridine. The pure sample melted at 110–112°: ir (CS_2) 1070, 1050, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.72 (3 H, singlet, C_{19} protons), 0.9 (3 H, singlet, C_{18} protons), 2.3 (broad band, methylenes, and C_{21} methyl protons), 3.9 (4 H, multiplet, $-OCH_2CH_2O-$).

5β-Pregnan-20-one (12). **A.**—A sample of ethylene ketal **11** (2.6 g) was hydrolyzed in acetic acid–water (1:1, 100 ml) for a period of 3 hr. To increase the solubility it was necessary to add some methylene chloride. At the end of the reaction the mixture was neutralized with concentrated ammonium hydroxide, diluted with water, and extracted with methylene chloride. On drying the extracts and evaporation of the solvent, a crude crystalline product (2.5 g) was obtained. After recrystallization in ethanol a pure sample (mp 114–116°) of ketone **12** was obtained: ir (CS_2) 1705 cm^{-1}; nmr ($CDCl_3$) δ 0.6 (3 H, singlet, C_{18} protons), 0.92 (3 H, singlet, C_{19} protons), 2.1 (3 H, singlet, C_{21} protons). The above physical constants were in complete agreement with previously reported values.[15]

B.—To obtain final confirmation of compound **5** a small sample was subjected to ozonolysis in the usual way. This afforded a keto steroid whose melting point and ir and nmr spectra were identical with those of the authentic sample of 5β-pregnan-20-one (**12**) independently prepared above. When mixture melting points were taken there was no temperature depression.

3α,24-Dihydroxy-24,24-diphenyl-5β-cholane (14).—This compound was prepared by a standard Grignard reaction in tetrahydrofuran. The procedure was identical with that reported above for compound **2**. Thus starting with a sample (25 g) of methyl lithocholate (**13**) we have obtained 31.15 g (95%) of pure (mp 146–147°) diol **14**: ir (CS_2) 3610, 3090, 3060, 3040, and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.6, 0.9 (singlets, C_{18} and C_{19} protons), 3.52 (1 H, multiplet, 3β H), 7.1–7.6 (10 H, multiplet, olefinic protons).

3α-Acetoxy-24,24-diphenyl-5β-chol-23-ene (15).—Simultaneous acetylation of the 3-hydroxy and dehydration of the Grignard product **14** was achieved by refluxing a sample (24 g) of diol **14** with acetic anhydride–acetic acid (145 ml, 5:1) for a period of 5 hr. Upon the usual work-up and recrystallization from methanol–methylene chloride a pure sample (mp 161–163°, 85%) of compound **15** was obtained. The observed melting point was in agreement with that reported in the literature:[20] ir (CS_2) 3080, 3060, 3020, 1740, 1240 and 700 cm^{-1}; nmr ($CDCl_3$) δ 0.62, 0.93 (singlets, C_{18} and C_{19} protons), 2.0 (singlet, acetoxy protons), 4.72 (1 H, multiplet, 3β proton), 6.1 (1 H, triplet, ethylenic proton, J = 7.5 Hz), 7–7.5 (10 H, multiplet, aromatic protons).

3α-Acetoxy-23,24-diphenyl-5β-cholan-24-one (16).—This product was obtained from a sample of olefin **15** (5 g) by means of the Kakis method.[2] The reaction afforded 4.9 g (95%) of sufficiently pure ketone **16**: ir (CS_2) 3080, 3060, 3030, 1735, 1685, 1240, and 700 cm^{-1}.

Anal. Calcd for $C_{38}H_{50}O_3$: C, 82.26; H, 9.08; O, 8.65. Found: C, 82.41; H, 9.19; O, 8.69.

This reaction results in a mixture of two (**16a** and **16b**) diastereoisomers, epimeric around the C_{23} asymmetric carbon. Separation of these isomers proved to be difficult; nevertheless, we were able to obtain a pure sample of each by thin layer chromatography on fluorescent silica involving at least 12 successive elutions with pentane–ether (10:1). Subsequently, each isomer was recrystallized from methanol–ether. The least polar substance (**16a**) melted at 145–147° and the other (**16b**) at 146–148°. Owing to the closeness of the melting points, nmr spectra and optical rotations of the two isomers were also taken: nmr (**16a**) ($CDCl_3$) δ 0.65, 0.95 (singlets, C_{18} and C_{19} protons), 2.05 (singlet, acetoxy protons), 4.8 (multiplet, 2 H, proton α to carbonyl and 3β proton), 7.1–8.2 (10 H, multiplet, aromatic protons); nmr (**16b**) 0.5, 0.9 (singlet, C_{18} and C_{19} protons), 2.0 (singlet, acetoxy protons), 4.7 (2 H, multiplet, proton α to carbonyl and 3β proton), 7.1–8.2 (10 H, multiplet, aromatic proton); $[\alpha]_D$ ($CHCl_3$) (**16a**), −33.5°; $[\alpha]_D$ ($CHCl_3$) (**16b**), +76°.

3α-Acetoxy-20-methylene-5β-pregnane (17).—This compound was obtained by irradiation of a sample (1.8 g) of the ketone mixture **16**. A procedure identical with that described for the photolysis of compound **5** was followed, except that in the chromatography of the products a 10:1 pentane–ether mixture was used. Thus 450 mg (38%) of pure product were obtained which

(16) K. R. Bharucha, G. C. Buckley, C. K. Cross, L. J. Rubin, and P. Ziegler, *Can. J. Chem.*, **34**, 982 (1956).

(17) M. G. Combe, H. B. Henbest, and W. R. Jackson, *J. Chem. Soc.*, 2467 (1967).

(18) Fluka Chemical Co. Basel, Switzerland.

(19) G. Slomp, Jr., Y. F. Shealy, J. L. Johnson, R. A. Donia, B. A. Johnson, R. P. Holysz, R. L. Pederson, A. O. Jensen, and A. C. Ott, *J. Amer. Chem. Soc.*, **77**, 1216 (1955).

(20) S. Sarel and Y. Yanuka, *J. Org. Chem.*, **24**, 2018 (1959).

crystallized spontaneously. Recrystallization from methanol–ether at −10° afforded an analytical sample (mp 85–86.5°): ir (CS_2) 3080, 1740, 1240, and 885 cm^{-1}; nmr ($CDCl_3$) δ 0.55, 0.95, and 1.77 (singlets, C_{18}, C_{19}, and C_{21} protons), 2.05 (singlet, acetoxy protons), 4.62 and 4.75 (two adjacent singlets, exocyclic methylene and 3β protons); $[\alpha]D$ ($CHCl_3$) +41°.

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68; O, 8.92. Found: C, 80.56; H, 10.52; O, 8.75.

The above irradiation was repeated many times. The yields in *tert*-butyl alcohol ranged from 35 to 38% and in benzene from 33 to 35%.

Final confirmation was obtained by lithium aluminum hydride reduction of the acetoxy compound **17** followed by standard ozonolysis of the resulting alcohol **18**. Thus a sample of 3α-hydroxy-5β-pregnan-20-one (**19**) was obtained whose physical constants and spectra were identical with those of an authentic sample.[8]

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Registry No.—**1**, 2204-14-0; **2**, 42151-39-3; **3**, 42151-40-6; **4a**, 42151-41-7; **4b**, 42151-42-8; **5**, 42151-43-9; **7**, 145-13-1; **8**, 2415-36-3; **9**, 978-98-3; **10**, 18000-86-7; **11**, 42151-47-3; **12**, 4729-67-3; **13**, 1249-75-8; **14**, 42151-48-4; **15**, 4144-29-0; **16a**, 42151-50-8; **16b**, 42151-51-9; **17**, 42151-52-0.

Synthesis of 4-Amino-4,6-dideoxy-D-allose Derivatives[1,2]

CALVIN L. STEVENS,* K. K. BALASUBRAMANIAN, CHARLES P. BRYANT,[3] JEAN B. FILIPPI, AND P. MADHAVAN PILLAI

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

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Base-catalyzed isomerization of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose (**2**) gave methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexopyranosid-4-ulose (**3**) by inversion at C-5. Conversion of **3** to its oxime **6** followed by reduction with lithium aluminum hydride yielded methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (**7**). Acetylation of **7** with acetic anhydride in pyridine followed by hydrolysis of the isopropylidene group gave methyl 4-acetamido-4,6-dideoxy-β-D-allopyranoside (**8**), which was then deacetylated to give methyl 4-amino-4,6-dideoxy-β-D-allopyranoside (**9**). Conversion of **7** to several derivatives including the free sugar, 4-*N*,*N*-dimethylamino-4,6-dideoxy-D-allose (**12**), is discussed. Also, synthesis of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*ribo*-hexopyranosid-4-ulose (**18**) and its conversion into methyl 4-amino-4,6-dideoxy-α-D-allopyranoside (**32**) and the *N*-acetate **33** are reported. Compound **33** was also obtained from 4-acetamido-4,6-dideoxy-2,3-di-*O*-methanesulfonyl-α-D-glucopyranoside (**35**) by internal displacement of the sulfonate ester at C-3 by the neighboring *N*-acetate followed by desulfonylation with sodium naphthalene reagent. The D-erythro stereochemistry at C-4 and C-5 of both **8** and **33** was confirmed by their degradation to D-allothreoninol.

The occurrence of several 4-amino-4,6-dideoxy sugar derivatives in biologically important natural sources[4] prompted us to undertake a comprehensive investigation on the synthesis and chemistry of this new class of carbohydrates. So far, the syntheses of the derivatives of seven of a possible total of eight of these hexoses (D series) have been recorded.[1,5] We now report the isomerization of an L-hexos-4-ulose into a D-keto sugar by base-catalyzed inversion at C-5 and the conversion of the new ketone into 4-amino-4,6-dideoxy-D-allose derivatives. A derivative of this amino sugar was also obtained from a 4-amino-4,6-dideoxy-D-glucose derivative by the internal displacement of a sulfonate ester at C-3 by the neighboring *N*-acetyl group.

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose[6,7] (**2**) was prepared from methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside[8] (**1**) by oxidation with either a mixture of dimethyl sulfoxide and phosphorus pentoxide in pyridine[1a] or with a catalytic amount of ruthenium tetroxide in the presence of sodium hypochlorite.[9,10] When a solution of **2** in 80% aqueous pyridine was heated at 100°, a small proportion of a new product was formed as shown by

(1) Synthesis and Chemistry of 4-Amino-4,6-dideoxy Sugars. V. (a) Part III: C. L. Stevens, R. P. Glinski, and K. G. Taylor, *J. Org. Chem.*, **33**, 1586 (1968). (b) Part IV: C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and S. K. Gupta, *J. Amer. Chem. Soc.*, **92**, 3160 (1970).

(2) Preliminary accounts of parts of this work have appeared. See (a) C. L. Stevens and K. K. Balasubramanian, *Carbohyd. Res.*, **21**, 166 (1972); (b) C. L. Stevens and K. K. Balasubramanian, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, CARB 20; (c) C. L. Stevens and C. P. Bryant in "Methods in Carbohydrate Chemistry," Vol. 6, R. N. Whistler and J. N. BeMiller, Ed., Academic Press, New York, N. Y., 1972, p 235; (d) C. L. Stevens and C. P. Bryant, *ibid.*, p 337; (e) C. L. Stevens, C. P. Bryant, J. B. Filippi, and B. Gross, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, CARB 7.

(3) Taken in part from the Ph.D. Dissertation of C. P. Bryant, Wayne State University, 1969.

(4) (a) C. L. Stevens, R. J. Gasser, T. K. Mukherjee, and T. H. Haskell, *J. Amer. Chem. Soc.*, **78**, 6212 (1956); (b) C. L. Stevens, K. Nagarajan, and T. H. Haskell, *J. Org. Chem.*, **27**, 2991 (1962); (c) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Amer. Chem. Soc.*, **85**, 1552 (1963); (d) R. W. Wheat, E. L. Rollins, and J. M. Leatherwood, *Biochem. Biophys. Res. Commun.*, **9**, 120 (1962); (e) C. L. Stevens, P. Blumbergs, F. A. Daniher, R. W. Wheat, A. Kiyomoto, and E. L. Rollins, *J. Amer. Chem. Soc.*, **85**, 3061 (1963); (f) C. L. Stevens, P. Blumbergs, D. H. Otterbach, J. L. Strominger, M. Matsuhashi, and D. N. Dietzler, *ibid.*, **86**, 2937 (1964); (g) C. L. Stevens, P. Blumbergs, F. A. Daniher, J. L. Strominger, M. Matsuhashi, and D. N. Dietzler, *ibid.*, **86**, 2939 (1964); (h) B. Jann and K. Jann, *Eur. J. Biochem.*, **2**, 26 (1967); (i) C. H. Lee and C. P. Schaffner, *Tetrahedron Lett.*, 5837 (1966); (j) C. L. Stevens, S. K. Gupta, R. P. Glinski, K. G. Taylor, P. Blumbergs, C. P. Schaffner, and C. H. Lee, *Carbohyd. Res.*, **7**, 502 (1968).

(5) (a) C. L. Stevens, P. Blumbergs, and D. H. Otterbach, *J. Org. Chem.*, **31**, 2817 (1966); (b) C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. G. Taylor, *ibid.*, **31**, 2822 (1966); (c) C. L. Stevens, P. Blumbergs, J. P. Dickerson, and D. Chitharanjam, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 5C; (d) C. L. Stevens, J. P. Dickerson, and K. G. Taylor, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 17C; (e) J. S. Brimacombe, O. A. Ching, and M. Stacey, *Carbohyd. Res.*, **8**, 498 (1968); (f) J. Jary, P. Novak, Z. Ksandr, and Z. Samek, *Chem. Ind. (London)*, 1490 (1967); (g) J. Jary and P. Novak, *Collect. Czech. Chem. Commun.*, **33**, 1744 (1968); (h) S. W. Gunner, W. G. Overend, and N. R. Williams, *Carbohyd. Res.*, **4**, 498 (1967).

(6) P. M. Collins and W. G. Overend, *Chem. Ind. (London)*, 374 (1963); *J. Chem. Soc.*, 1912 (1965); P. M. Collins, *J. Chem. Soc. C*, 1960 (1971).

(7) U. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, **43**, 3452 (1965).

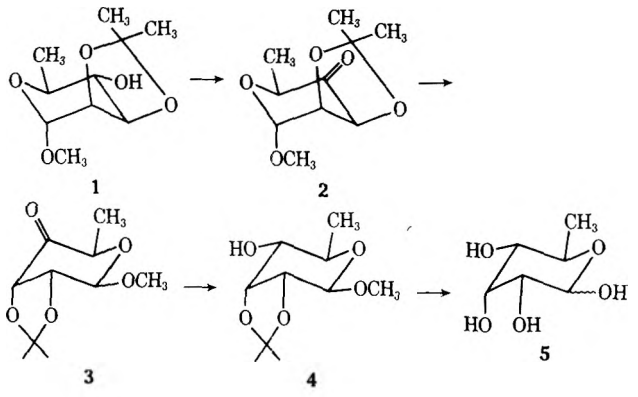
(8) P. A. Irvine and I. E. Muskat, *J. Biol. Chem.*, **105**, 431 (1934).

(9) M. B. Perry, National Research Council, Ottawa, Canada, personal communication, 1968.

(10) This method is similar to oxidation with ruthenium tetraoxide in the presence of sodium periodate. See, for example, (a) B. T. Lawton, W. A. Szarek, and J. K. N. Jones, *Carbohyd. Res.*, **10**, 456 (1969); (b) D. C. Baker, D. Horton, and C. G. Tindall, Jr., *ibid.*, **24**, 192 (1972).

gas chromatography. A detailed examination of this reaction indicated that equilibrium was reached after 2.5 hr and the mixture contained 82% of **2** and 18% of the new compound, subsequently shown to be methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexopyranosid-4-ulose (**3**). Bases like triethylamine[11] and potassium hydroxide can also be used to effect this isomerization. When potassium hydroxide was used as the catalyst, ketone **3** was formed in higher proportions, but the recovery of the mixture of ketones was lower owing to the formation of undesirable side products.

Compound **3** was separated from **2** by preparative gas chromatography and was crystallized from pentane. An elemental analysis indicated **3** to be isomeric with **2**. The infrared spectrum had absorptions at 1730 (C=O) and 1375 cm^{-1} (*gem*-dimethyl) and nmr spectrum was consistent with structure **3**. The ORD curve of **3** exhibited a positive Cotton effect with a peak at 325 nm and a trough at 290 nm, whereas the starting ketone **2** had a negative Cotton effect with a trough at 330 nm and a peak at 290 nm. An investigation of the optical rotation of **3** showed that the rotation changed rapidly when **3** was dissolved in aqueous pyridine or methanol while the rotation remained constant in anhydrous pyridine and chloroform solutions. The change in rotation, however, was not due to isomerization but resulted from the addition of water or methanol to the carbonyl group, as ketone **3** was shown to remain unchanged by gas chromatography.[12]



Chemical proof for the structure of **3** was obtained as follows. Reduction of **3** with sodium borohydride in methanol gave methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allopyranoside[13] (**4**) as a colorless liquid in 90% yield. The crude reduction product consisted of at least 95% of one material as shown by gas chromatography. The stereoselectivity of this reaction is due to the attack by the hydride ion from the less hindered side of the carbonyl group and is in accordance with previous findings.[1a,10b] Hydrolysis of **4** with 1.0 *N* hot sulfuric acid gave 60% of 6-deoxy-D-allose[14] (**5**) identical with an authentic sample. The fact that an allose derivative was obtained by base-catalyzed isomerization indicates that inversion took place only at C-5. Although enolization at C-3 is also possible under the reaction conditions, the configuration at C-3 remained unchanged because a 2,3-cis stereochemistry is favored for the isopropylidene group as observed in similar isomerizations.[15]

As 4-keto sugars have been used for the synthesis of 4-amino hexoses,[1a,16] a valuable intermediate for the preparation of 4-amino-4,6-dideoxy-D-allose derivatives was found in compound **3**. Accordingly, treatment of **3** with hydroxylamine hydrochloride in a mixture of pyridine and ethanol at room temperature gave the oxime **6** as a mixture of isomers. The mixture was separated by preparative thin layer chromatography on silica gel to yield 62% of the major isomer as a crystalline material and 16% of the minor isomer as a gum. Reduction of **6** either as a pure isomer or as a mixture with lithium aluminum hydride in tetrahydrofuran at room temperature gave methyl 4-amino-4,6-dideoxy-β-D-allopyranoside (**7**) in 86% yield as a colorless liquid, isolated and characterized as the crystalline hydrogen *p*-toluenesulfonate. That it was possible to reduce each isomer separately to the same amine showed that the two oximes were in fact syn and anti isomers and not oximes of the isomeric ketones, **2** and **3**. The reduction product in each case, before any purification, was at least 95% of one material as shown by gas chromatography, indicating that the reduction of the oxime, as in the case of its ketone analog, **3**, proceeded by attack of the hydride ion almost exclusively from the less hindered side.[1a,10b]

Acetylation of **7** with acetic anhydride in pyridine followed by hydrolysis with 0.05 *N* hydrochloric acid gave methyl 4-acetamido-4,6-dideoxy-β-D-allopyranoside (**8**) in 52% yield. Degradation of this *N*-acetate **8** to D-allothreoninol by a previously described method[1b,17] confirmed the D-erythro stereochemistry at C-4 and C-5 as required for a D-allose derivative. Methyl 4-amino-4,6-dideoxy-β-D-allopyranoside (**9**) was obtained in 56% yield by the hydrolysis of **8** with a 9% solution of barium hydroxide in water under refluxing conditions. Hydrogenation of the amine **7** with formaldehyde in methanol in the presence of palladium on carbon as a catalyst gave methyl 4-*N*,*N*-dimethylamino-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (**10**), characterized as its hydrochloride. Removal of the isopropylidene group was accomplished by heating **10** with 0.1 *N* hydrochloric acid at 95° for 6 hr. Methyl 4-*N*,*N*-dimethylamino-4,6-dideoxy-β-D-allopyranoside (**11**) thus obtained was characterized as its hydrogen *p*-toluenesulfonate. Hydrolysis of **11** with 1.0 *N* hydrochloric acid under refluxing conditions for 24 hr provided the free sugar, 4-*N*,*N*-dimethylamino-4,6-dideoxy-D-allose (**12**), isolated and characterized as its crystalline hydrochloride salt.

The *N*-methyl derivative of **7** was prepared by two methods. Treatment of **7** with ethyl chloroformate in a mixture of pyridine and chloroform gave the *N*-carbethoxy derivative as an oil, which on reduction with lithium aluminum hydride in tetrahydrofuran yielded methyl 4-*N*-methylamino-4,6-dideoxy-2,3-*O*-

(11) P. M. Collins and P. Gupta, *J. Chem. Soc. C*, 1695 (1971), obtained a 3:1 mixture of **2** and **3** by treatment of **2** with triethylamine in aqueous ethanol.

(12) Certain keto sugar derivatives are known to form stable hydrates. See, for example, K. Antanakis and F. Leclercq, *Bull. Soc. Chim. Fr.*, 2142 (1971), and *ref 10b*.

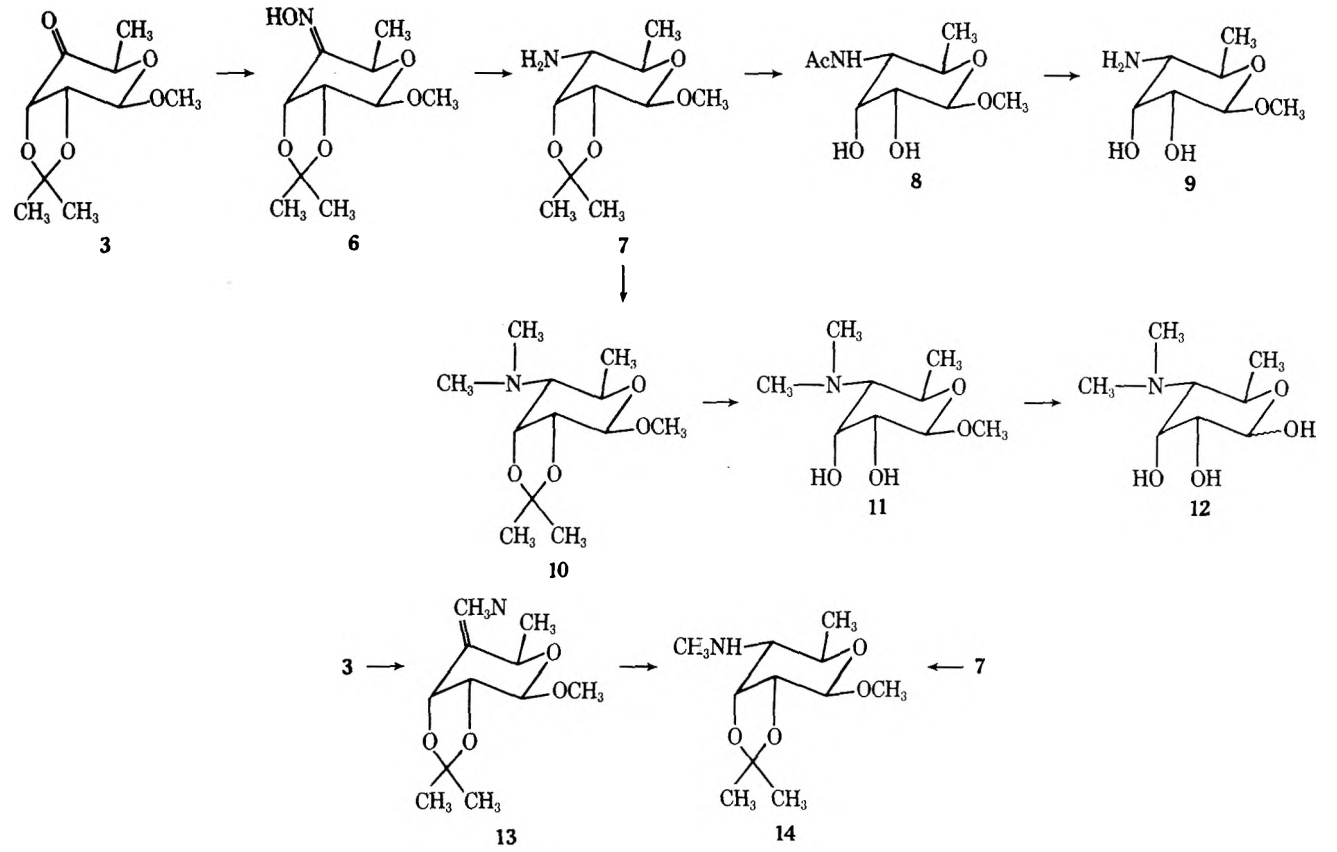
(13) St. Hoímann, Ek. Weiss, and T. Reichstein, *Helv. Chim. Acta*, **49**, 2209 (1966).

(14) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936); H. Kaufmann, P. Muhlradt, and T. Reichstein, *Helv. Chim. Acta*, **50**, 2287 (1967).

(15) D. Horton, J. S. Jewell, E. K. Just, and J. D. Wander, *Carbohyd. Res.*, **18**, 49 (1971).

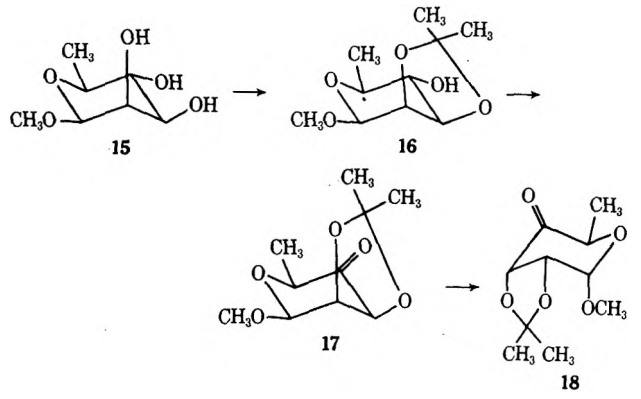
(16) E. L. Albano and D. Horton, *Carbohyd. Res.*, **11**, 485 (1969).

(17) C. L. Stevens, S. K. Gupta, R. P. Glinski, G. E. Gutowski, and C. P. Bryant, *Tetrahedron Lett.*, 1817 (1968).



isopropylidene-β-D-allopyranoside (14) characterized as its hydrochloride. Compound 14 was also obtained from ketone 3 by converting it to the imine 13 by treatment with methylamine in the presence of anhydrous sodium bisulfate followed by reduction with sodium borohydride in methanol. The identity of the two samples was established by superimposable ir spectra and a mixture melting point determination of the crystalline hydrochlorides.

As only the α-methyl glycosides of the other 4-amino-4,6-dideoxy hexoses were known in most cases,[1,5] the synthesis of methyl 4-amino-4,6-dideoxy-α-D-allopyranoside was necessary for comparative studies. This was accomplished by two methods as given below. Conversion of methyl 6-deoxy-β-L-mannopyranoside[18] (15) into the 2,3-*O*-isopropylidene derivative (16)



followed by oxidation with a mixture of phosphorous pentoxide and dimethyl sulfoxide in pyridine gave methyl 6-deoxy-2,3-*O*-isopropylidene-β-L-*lyxo*-hexopyranosid-4-ulose (17) as an oil. Isomerization of 17 to methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*ribo*-hexopyranosid-4-ulose (18) was achieved by base-catalyzed inversion at C-5 as in the conversion of 2 to 3. Thus, when a solution of 17 in 80% aqueous pyridine was heated on a steam bath for 2.5 hr, a mixture consisting of 64% of 18 and 36% of 17 was formed which was separated by preparative thin layer chromatography.

Ketone 18 was also obtained by an entirely different series of reactions as described here. Reductive debenzylation of methyl 6-deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-glucopyranoside[5a] (19) by hydrogenation in the presence of palladium on carbon and hydrochloric acid as catalysts gave methyl 6-deoxy-4-*O*-methylsulfonyl-α-D-glucopyranoside (20) as a gum which was characterized as its diacetyl derivative 21 and di-*p*-nitrobenzoyl derivative, 22. Treatment of 20 with sodium methoxide in a mixture of chloroform and methanol as solvent gave a 60% yield of the epoxide 23.[19] Although an acid opening of this epoxide (23) is expected to give a gulose derivative, its 6-hydroxy analog has been reported to yield a mixture of products on treatment with dilute acid.[20] However, methyl 2-*O*-acetyl-3,4-anhydro-α-D-galactopyranoside or its 6-triphenylmethyl derivative gave mostly methyl 3-*O*-acetyl-α-D-gulopyranoside under mild acid hydrolysis.[20,21] Compound 23 was therefore converted to methyl 6-deoxy-2-*O*-acetyl-3,4-anhydro-α-D-galactopyranoside[19] (24) by treatment with acetic anhydride and pyridine. Hydrolysis of 24 in acetone–water with a trace of sulfuric acid gave a single crystalline mono-

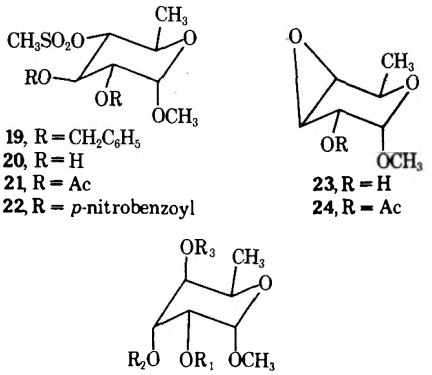
(18) E. Fischer, M. Bergmann, and R. Babe, *Ber. Deut. Chem. Ges. B*, **53**, 2362 (1920); L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 1702 (1950).

(19) J. Jary and K. Capek, *Collect. Czech. Chem. Commun.*, **31**, 315 (1966).

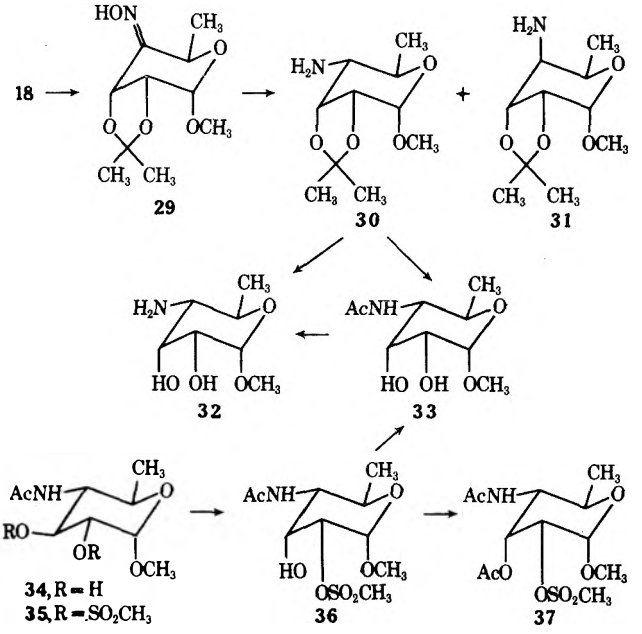
(20) J. G. Buchanan, *J. Chem. Soc.*, 2511 (1958).

(21) J. G. Buchanan and R. Fletcher, *J. Chem. Soc.*, 6316 (1965); J. G. Buchanan in "Methods in Carbohydrate Chemistry," Vol. 6, R. L. Whistler and J. N. BeMiller, Ed., Academic Press, New York, N. Y., 1972, p 135.

acetate, **25**, in excellent yield. An examination of the nmr spectrum of **25** in acetone-d_6–D_2O showed that the proton on the acetate bearing carbon (the most deshielded hydrogen in the molecule) appeared as an unsymmetrical triplet at 306 Hz and the anomeric proton as a doublet (J = 4 Hz) at 270 Hz. As decoupling of either of these protons did not affect the appearance of the other, it was shown that the acetate group was not attached to C-2. As acyloxy groups are known to participate in the epoxide opening,[22] the acetate group could migrate to C-3 as found in a similar reaction.[21] That compound **25** was indeed the 3-*O*-acetate was shown by a spin-decoupling irradiation of the C-2 proton (which appeared as part of a multiplet at 240 Hz together with the C-5 hydrogen) when the anomeric proton collapsed into a singlet and the C-3 proton into a doublet (J = 4 Hz). Deacetylation of **25** with catalytic amounts of sodium methoxide in methanol yielded methyl 6-deoxy-α-D-gulopyranoside (**26**) as a clear, colorless gum, which was characterized as its crystalline triacetyl derivative, **27**. Compound **27** was also obtained by the acetylation of **25** with acetic anhydride in pyridine. Treatment of **26** with diethoxypropane in acetone in the presence of *p*-toluenesulfonic acid as a catalyst gave methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-gulopyranoside (**28**) in 80% yield. Compound **28** was oxidized to ketone **18** with catalytic amounts of ruthenium tetroxide in the presence of sodium hypochlorite.[9,10] The two samples of **18** obtained by the different methods were identical in all respects. Also, when either **17** or **18** was subjected to the isomerization conditions, the same mixture of the two compounds was formed as shown by gas chromatography.



Treatment of **18** with hydroxylamine hydrochloride in a mixture of pyridine and ethanol gave 80% of the oxime **29** as a mixture of syn and anti isomers. The mixture was separated by preparative thin layer chromatography to give the major component as a crystalline material and the minor isomer as a gum. Reduction of either the crystalline oxime or the mixture with lithium aluminum hydride in tetrahydrofuran at room temperature gave methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-allopyranoside (**30**). Although **30** was isolated as its crystalline hydrogen *p*-toluenesulfonate in only 56% yield, a gas chromatographic analysis of the reduction mixture before any purification showed that over 95% of **30** was formed in the reaction. The minor component (less than 5%) was identified as methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-gulopyranoside (**31**) by gas chromatography. Reduction of **29** with lithium aluminum hydride in refluxing tetrahydrofuran produced **30** and **31** in a ratio of 85:15. The higher temperature has apparently decreased the stereoselectivity of this reaction, as was found previously in the reduction of certain ketones with lithium aluminum hydride.[23] Hydrolysis of **30** as its hydrogen *p*-toluenesulfonate in water on a steam bath for 30 min gave 89% of methyl 4-amino-4,6-dideoxy-α-D-allopyranoside (**32**) isolated and characterized as its hydrogen *p*-toluenesulfonate. The *N*-acetyl derivative **33** was obtained from **30** by acetylation with acetic anhydride in pyridine followed by hydrolysis of the isopropylidene group with an acid resin in methanol.



Methyl 4-acetamido-4,6-dideoxy-α-D-allopyranoside (**33**) was alternately synthesized by inversion of the hydroxyl group at C-3 of a glucose derivative.[24] Treatment of methyl 4-acetamido-4,6-dideoxy-α-D-glucopyranoside[5b] (**34**) with methanesulfonyl chloride in pyridine gave the 2,3-di-*O*-methylsulfonate **35** in 90% yield. When a solution of **35** in ethylene glycol monomethyl ether containing 2 equiv of sodium acetate was refluxed for 28 hr, 95% of methyl 4-acetamido-4,6-dideoxy-2-*O*-methylsulfonyl-α-D-allopyranoside (**36**) was obtained as a crystalline material. Compound **36** was further characterized as its *O*-acetyl derivative, **37**. Cleavage of the methylsulfonate group from compound **36** by sodium naphthalene reagent[25] yielded 57% of **33** identical in all respects with the previously prepared sample. Further, hydrolysis of **33** with a solution of barium hydroxide in water under refluxing conditions gave methyl 4-amino-4,6-dideoxy-α-D-allopyranoside (**32**) in 70% yield.

(22) For reviews, see (a) B. Capon, *Chem. Rev.*, **69**, 407 (1969); (b) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967).

(23) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).

(24) For reviews on internal displacements of sulfonyloxy groups by neighboring *N*-acetates, see ref 22a and b.

(25) W. D. Closson, P. Wriede, and S. Bank, *J. Amer. Chem. Soc.*, **88**, 158 (1966); J. R. Ganson, S. Schulenberg, and W. D. Closson, *Tetrahedron Lett.*, 4397 (1970).

The D-erythro stereochemistry at C-4 and C-5 of **33** was confirmed as in the case of **8** by degradation to allothreoninol.[1b,17] Also, the structures of **8** and **33** were correlated by the following method. Methanolysis of **8** in the presence of hydrogen chloride gave a mixture of **8** and **33** by equilibration at the anomeric center. Treatment of this mixture with hexamethyldisilazane and trimethylchlorosilane in pyridine followed by gas chromatographic analysis of the trimethylsilyl derivatives showed the presence of two compounds corresponding to **8** and **33**. The identities of the peaks in the chromatogram were established by mixed injections with authentic samples.

Experimental Section[26]

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose[6,7] (**2**).—A 5.5% solution of NaOCl in water[27] was added dropwise to a rapidly stirred mixture of a solution of 1.0 g (4.6 mmol) of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside[8] (**1**) in 10 ml of $CHCl_3$ (freed from EtOH by passing over a column of Woelm grade I alumina), 20 mg of active[2d] RuO_2, and 2 ml of water. Addition was continued until a permanent pale yellow color was obtained for the $CHCl_3$ layer, marking the presence of an excess of RuO_4 in solution. A gc analysis at this point showed that the oxidation was complete. The $CHCl_3$ layer was separated and the aqueous layer was extracted twice with $CHCl_3$. The combined organic solution was washed with $Na_2S_2O_3$ solution followed by water, dried (Na_2SO_4), and evaporated to dryness to yield 0.68 g (68%) of **2** as an oil, $[\alpha]^{26}D$ −105.83° (c 1.0 $CHCl_3$), ORD ($CHCl_3$) peak at 290 nm, trough at 330 nm (negative Cotton effect). This material was identical (ir, gc, tlc) with a sample of **2** obtained by the oxidation of **1** by DMSO–P_2O_5 in pyridine by a previously described procedure.[1a]

Methyl 6-Deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexopyranosid-4-ulose (**3**).—A solution of 10 g (46.3 mmol) of **2** in 50 ml of 80% aqueous pyridine was heated at 100° for 3 hr. An analysis of the mixture by gc showed that it consisted of 82% of **2** and 18% of **3**. The solvents were removed *in vacuo*, and the residue was dissolved in ether, washed with a saturated solution of NaCl, dried (Na_2SO_4), and evaporated to dryness. The residual oil was distilled under reduced pressure to give 9.01 g (90.1%) of the mixture of ketones. Separation by preparative gc using a 8 ft × 2.5 in. 3% ethylene glycol succinate on Chromosorb W column at 120° gave 5.54 g of **2** (90% pure by gc), 593 mg of **3** (92% pure), and 1.3 g of a mixture of **2** and **3** for a total recovery of 8.43 g (93%). Compound **3** solidified and was recrystallized from cold pentane: mp 42–43°; ir ($CHCl_3$) 1730 (C=O), 1375 cm^{-1} (*gem*-dimethyl); nmr ($CDCl_3$) τ 8.55 (d, J = 8 Hz, 3, C-6 H), 6.4 (s, 3, OCH_3), 5.55 (q, J = 8 Hz, 1, C-5 H); ORD ($CHCl_3$) peak at 325 nm, trough at 290 nm (positive Cotton effect).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.56; H, 7.44. Found: C, 55.48; H, 7.44.

For specific rotation of **3** in different solvents, see Table I.

In subsequent experiments for the preparation of **3**, ketone **2** was isomerized using KOH as described below.

Isomerization Studies of 2 Using KOH as a Catalyst.—A solution of 6.0 g (27.8 mmol) of **2** in 60 ml of CH_3OH was stirred with 30 ml of 0.5 *M* KOH in CH_3OH for 15 min at room temperature. The solution was neutralized with Dowex-50 (H^+), filtered, and evaporated to dryness. The residue on extraction with pentane followed by removal of the solvent gave 4.9 g (81.7%) of an oil containing 45% of **2** and 55% of **3** as shown by gc. The pentane-insoluble material was identified as 2-methyl-3-hydroxy-4-pyrone[28] (maltol), mp 160–162°.

Further studies showed that the proportion of **3** increased when the reaction was conducted for a longer time. However, the recovery of the mixture of ketones was poor as increasing amounts of maltol were formed.

TABLE I

SPECIFIC ROTATION OF 3 IN DIFFERENT SOLVENT SYSTEMS AT 26°

Solvent system	Concn, g/100 ml	Initial value,[a] deg	Equilibrium value,[b] deg
Chloroform	0.4	+36.18	+36.18
Pyridine	0.3	+33.2	+33.2
Pyridine–water (99:1)	0.3	+33.7	−15.1
Pyridine–water (96:4)[c]	0.3	+30.0	−16.0
Pyridine–water (94:6)[c]	0.3	+21.6	−33.3
Pyridine–water (80:20)[c]	0.3	−62.2	−62.2
2-Propanol	0.3	+27.18	+26.1
Ethanol	0.3	+25.9	+8.0
Methanol[c]	0.3	+26.8	−25.0
Methanol–water (80:20)[c]	0.3	−4.0	−39.0
Water	0.3	−60.6	−60.6

[a] Specific rotation immediately after preparing the solution. [b] All the solutions on analysis by gc after reaching equilibrium showed the presence of only one ketone, **3**. [c] An ORD curve of this solution after reaching equilibrium did not exhibit any peaks. Only a plane curve was obtained.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (**4**).—A solution of 84 mg (0.4 mmol) of **3** in 5 ml of CH_3OH was treated with 37 mg of $NaBH_4$ at 0°. Analysis by gc and tlc after 30 min indicated that the reduction was complete. The solvent was removed *in vacuo* and the residue was heated on a steam bath with 1 ml of water for 5 min. The mixture was extracted with ether, dried (Na_2SO_4), and evaporated to dryness to give 80 mg (95%) of **4** as a liquid. Gc analysis of this material on three different columns indicated that it consisted of only one compound. A small portion of this material was evaporatively distilled for analysis, $[\alpha]^{26}D$ −50.0° (*c* 0.45, $CHCl_3$) [lit.[13] $[\alpha]D$ −47.4 ± 2° (*c* 2.22, acetone)].

Anal.[29] Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.23; H, 8.46.

6-Deoxy-D-allose (**5**).—A mixture of 80 mg of **4** and 3 ml of 1 *N* H_2SO_4 was heated on a steam bath for 1 hr. The solution was neutralized with solid $BaCO_3$ and filtered. The $BaSO_4$ was washed with water and the combined aqueous solution was evaporated to dryness. The residue was extracted with anhydrous EtOH and concentrated, ether was added, and the residue was cooled to give 45 mg (75%) of **5**, mp 143–145°, $[\alpha]^{26}D$ −4.2° (*c* 1.0, H_2O). A mixture melting point of this material with an authentic sample of 6-deoxy-D-allose[14] was undepressed.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexopyranosid-4-ulose Oxime (**6**).—A mixture of 2.0 g (9.26 mmol) of **3** and 2.0 g of hydroxylamine hydrochloride in 20 ml of 1:1 pyridine–ethanol was heated on a steam bath for 45 min. The solvents were removed *in vacuo*, and the residue was mixed with water and extracted several times with ether. The ether solution was dried (Na_2SO_4) and evaporated to dryness to give 2.0 g (93%) of **6** as a gum which showed two spots on tlc. Trituration of this material with 25 ml of pentane yielded 1.2 g (57%) of a crystalline oxime (one spot on tlc) which was recrystallized from ether–pentane, mp 133–134.5°, $[\alpha]^{26}D$ + 42.5° (*c* 0.63, $CHCl_3$).

Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.36; N, 6.06. Found: C, 52.14; H, 7.40; N, 6.21.

The pentane-soluble portion, which showed two spots on tlc, was separated by preparative tlc to give 126 mg more of the

(26) Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography, both analytical and preparative, was carried out using silica gel G from Brinkmann Instruments. An ether–pentane (1:1) solvent system was used unless otherwise stated. Compounds were detected by spraying with 6 *N* H_2SO_4 followed by baking at 110°. Gas chromatographic analyses were performed on an F & M Model 810 instrument equipped with dual flame ionization detectors. A 3 ft × 0.25 in. 6% ethylene glycol succinate on Chromosorb W column was used unless mentioned otherwise. For separation of compounds by gc, an F & M Model 775 preparative gas chromatograph was used. The nmr spectra were taken on a Varian A-60 or T-60 spectrometer using tetramethylsilane as an internal standard. The infrared spectra were recorded on a Perkin-Elmer 237 B grating spectrophotometer. Specific rotations were measured on a Perkin-Elmer Model 141 polarimeter at 1-dm path lengths. Optical rotatory dispersion curves were obtained using a Cary 60 instrument. The pK_a's were determined in 50% aqueous methanol. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

(27) A solution of Roman Cleanser Bleach can be used instead of the sodium hypochlorite solution.

(28) J. R. Schenck and M. A. Spielman, *J. Amer. Chem. Soc.*, **67**, 2276 (1945).

(29) The authors thank Mr. Harold Hauser for preparing this analytical sample.

crystalline oxime, mp 133–134°, for a total yield of 1.326 g (62%). The slower moving band on extraction gave 342 mg (16.2%) of a gum (one spot on tlc), $[\alpha]^{26}D$ +9.14° (*c* 0.72, $CHCl_3$), ir ($CHCl_3$) and nmr ($CDCl_3$) similar to but not identical with those of the crystalline material.

Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.36; N, 6.06. Found: C, 52.09; H, 7.55; N, 5.92.

When $CHCl_3$ solutions of the two pure isomers were left overnight at room temperature, mixtures of the two oximes were formed as shown by tlc and nmr.

Methyl 4-Amino-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (7).—A solution of 700 mg (2.1 mmol) of the crystalline oxime in 20 ml of dry tetrahydrofuran was stirred with 300 mg of $LiAlH_4$ at room temperature for 12 hr. The excess $LiAlH_4$ was destroyed by the careful addition of wet ether followed by water and the white, gelatinous precipitate was filtered off and washed with ether. The ether solution was dried (K_2CO_3) and evaporated to dryness to give 572 mg (86%) of **7** as an oil, more than 95% pure by gc. This material was dissolved in ether and treated with *p*-toluenesulfonic acid to give 557 mg (68%) of methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (**7**) hydrogen *p*-toluenesulfonate, mp 184–189°. Recrystallization from $CHCl_3$–ether gave an analytical sample, mp 191–193°, $[\alpha]^{26}D$ −28.5° (*c* 0.67, $CHCl_3$).

Anal. Calcd for $C_{17}H_{27}NO_7S$: C, 52.42; H, 7.03; N, 3.59. Found: C, 52.48; H, 7.16; N, 3.66.

Reduction of the minor isomer and the mixture of oximes separately under the above conditions gave essentially the same results.

Methyl 4-Acetamido-4,6-dideoxy-β-D-allopyranoside (8).—A solution of 365 mg (1.68 mmol) of **7** (free base) in 1 ml of pyridine was treated with 1 ml of acetic anhydride at room temperature for 12 hr. The solvents were removed *in vacuo*, and the residue was dissolved in $CHCl_3$, washed with water, dried (K_2CO_3), and evaporated to dryness to give 300 mg (68.5%) of methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside as a gum, ir ($CHCl_3$) 1650 cm^{-1} (amide). This material was hydrolyzed with 0.05 *N* hydrochloric acid at 100° for 40 min. The solution was evaporated to dryness under reduced pressure followed by azeotroping with ethanol and benzene. The residue was triturated with ether to give 192 mg (75.6%) of **8** which was recrystallized from ethanol–ether, mp 224–225°, $[\alpha]^{26}D$ + 3.9° (*c* 0.4, CH_3OH).

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.41; H, 7.75; N, 6.53.

Degradation of 80 mg (0.36 mmol) of **8** according to a previously reported procedure[1b,17] gave 18 mg (25.7% for four steps) of D-allothreoninol hydrogen oxalate, mp 172–173° dec. A mixture melting point with an authentic sample was unchanged.

Methyl 4-Amino-4,6-dideoxy-β-D-allopyranoside (9).—A mixture of 190 mg (0.868 mmol) of **8** and 3.0 ml of 9% $Ba(OH)_2$ in water was heated on a steam bath for 12 hr. The solution, after cooling, was carefully neutralized with 1 *N* H_2SO_4 and the $BaSO_4$ was removed by filtration. The filtrate was evaporated to dryness under vacuum followed by azeotroping with ethanol. The residue was extracted with hot $CHCl_3$. Removal of $CHCl_3$ yielded 86 mg (56%) of **9**, mp 168–172°. An analytical sample was prepared by recrystallization from ethanol–ether, mp 174–176°, $[\alpha]^{26}D$ −50.6° (*c* 0.75, CH_3OH), pK_a 7.20.

Anal. Calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.5; N, 7.82. Found: C, 47.77; H, 8.66; N, 8.06.

Methyl 4-*N*,*N*-Dimethylamino-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (10).—A solution of 600 mg (2.76 mmol) of **7** (free base) and 1.5 ml of 40% aqueous formaldehyde in 10 ml of CH_3OH was hydrogenated at atmospheric pressure in the presence of 100 mg of 5% Pd/C. After removal of the catalyst, the solution was evaporated to dryness to give 572 mg (88%) of **10** as a gum which was converted to the hydrochloride salt, 467 mg (70%), mp 199–201° dec. Recrystallization from ethanol–ether gave an analytical sample, mp 203–204° dec, $[\alpha]^{26}D$ −16.8° (*c* 0.5, CH_3OH), pK_a 6.32.

Anal. Calcd for $C_{12}H_{24}ClNO_4$: C, 51.14; H, 8.58; Cl, 12.60; N, 4.97. Found: C, 50.98; H, 8.63; Cl, 12.86; N, 5.07.

Methyl 4-*N*,*N*-Dimethylamino-4,6-dideoxy-β-D-allopyranoside (11).—A solution of 75 mg (0.3 mmol) of **10** in 2 ml of 0.1 *N* hydrochloric acid was heated at 95° under a nitrogen atmosphere for 6 hr. The solution was evaporated to dryness under vacuum and the residue was redissolved in ethanol and neutralized with solid K_2CO_3. The inorganic materials were filtered and the filtrate was evaporated to dryness. The residue was extracted with methanol and the methanol was removed *in vacuo* to give **11** as a gum. It was converted to the hydrogen *p*-toluenesulfonate salt, 70 mg (62%), mp 168–169° after recrystallization from ethanol–ether, $[\alpha]^{26}D$ −12.8° (*c* 0.5, CH_3OH), pK_a 6.80.

Anal. Calcd for $C_{16}H_{27}NO_7S \cdot {}^1/_2\ H_2O$: C, 49.73; H, 7.30; N, 3.62. Found: C, 49.37; H, 7.05; N, 3.63.

4-*N*,*N*-Dimethylamino-4,6-dideoxy-D-allose (12).—A solution of 95 mg (0.46 mmol) of **11** (free base) in 2 ml of 1.0 *N* hydrochloric acid was heated at 100° under a nitrogen atmosphere for 24 hr. The solution was evaporated to dryness under vacuum and repeatedly azeotroped with ethanol. The white, foamy solid was recrystallized from ethanol–ether to give 19 mg (17.1%) of 4-*N*,*N*-dimethylamino-4,6-dideoxy-D-allose (**12**) hydrochloride, mp 166–168°, $[\alpha]^{26}D$ +38.09° (initial) and +33.2° (equilibrium) (*c* 1.52, CH_3OH).

Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 42.16; H, 7.83; N, 5.90.

Methyl 4-*N*-Methylamino-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (14). A. From Amine 7.—A solution of 384 mg (1.77 mmol) of **7** in 1 ml of pyridine and 2 ml of $CHCl_3$ was stirred with 300 mg of ethyl chloroformate at 0° for 2 hr. The mixture was diluted with $CHCl_3$ and washed with $NaHCO_3$ solution followed by water. The $CHCl_3$ solution was dried and evaporated to dryness to give 480 mg (100%) of the *N*-carbethoxy derivative as an oil. This material without further purification was dissolved in 15 ml of tetrahydrofuran, treated with 250 mg of $LiAlH_4$ overnight at room temperature, and then heated under reflux for 3 hr. The mixture was cooled and the excess $LiAlH_4$ was decomposed with wet ether. Filtration and evaporation of the solvents gave 380 mg (92.5%) of **14** as a pale brown liquid which was converted to the hydrochloride salt, mp 216–217° dec after recrystallization from ethanol–ether, $[\alpha]^{26}D$ −12.63° (*c* 0.5, CH_3OH), pK_a 7.05.

Anal. Calcd for $C_{11}H_{22}ClNO_4$: C, 49.33; H, 8.28; N, 5.23. Found: C, 49.20; H, 8.42; N, 5.21.

B. From Ketone 3.—A mixture of 240 mg (1.1 mmol) of **3** in 20 ml of $CHCl_3$, 3 g of freshly fused $NaHSO_4$, and 2 ml of methylamine was stirred at room temperature for 12 hr. The solvents were removed under vacuum and the residue was extracted with ether. Removal of ether gave 200 mg (74.5%) of the imine **13** as a brown liquid, ir 1670 cm^{-1} (C=N). A solution of this material in 2 ml of CH_3OH at 0° was stirred with 180 mg of $NaBH_4$ for 30 min and then at room temperature for 30 min. The solvent was evaporated *in vacuo* and the residue was treated with water. The mixture was extracted with ether and dried (K_2CO_3), and the solvent was removed to give 148 mg (73.5%) of **14** as an oil which contained a small amount of another basic compound as shown by tlc. This material was converted to its HCl salt (52 mg) and recrystallized from ethanol–ether, mp 212–214° dec. A mixture melting point of the two samples prepared by methods A and B was 212–215° dec and they had superimposable ir spectra.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-β-L-mannopyranoside (16).—A mixture of 356 mg (2.0 mmol) of methyl 6-deoxy-β-L-mannopyranoside[18,30] (**15**), 3 ml of 2,2-diethoxypropane, and 10 mg of *p*-toluenesulfonic acid was stirred at room temperature for 20 min. The solution was diluted with ether, washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness to give 385 mg (88%) of **16** as a viscous liquid, more than 90% pure by gc: nmr ($CDCl_3$) τ 8.64 (d, $J_{5,6}$ = 8 Hz, 3, CCH_3), 8.6 and 8.43 (both s, 3, *gem*-dimethyl), 5.3 (d, $J_{1,2}$ = 2.5 Hz, 1, C-1 H), 6.4 (s, 3, OCH_3); ir ($CHCl_3$) 1375 cm^{-1} (*gem*-dimethyl).

Methyl 6-Deoxy-2,3-*O*-isopropylidene-β-L-*lyxo*-hexopyranosid-4-ulose (17).—Phosphorus pentoxide (1 g) was added in small portions to a solution of 750 mg (3.44 mmol) of **16** in 10 ml of DMSO and 0.6 ml of pyridine at room temperature. The solution was heated at 65° for 14 hr and cooled, and the excess P_2O_5 was decomposed by the addition of ice. The mixture was extracted with ether washed with NaCl solution, dried [Na_2SO_4), and evaporated *in vacuo* to dryness and then azeotroped with toluene to remove the last traces of DMSO and pyridine. The liquid residue (510 mg, 74%) was purified by preparative tlc: ir ($CHCl_3$) 1730 (C=O) and 1375 cm^{-1} (*gem*-dimethyl); nmr ($CDCl_3$) τ 8.52 (d, $J_{5,6}$ = 7 Hz, 3, CCH_3), 5.2 (d, $J_{1,2}$ = 3 Hz, 1, C-1 H), 5.9 (q, $J_{6,5}$ = 7 Hz, 1, C-5 H); $[\alpha]^{26}D$ +45.09° (*c* 0.51, $CHCl_3$).

(30) Compound **15**, mp 137–138°, $[\alpha]^{26}D$ +93.2° (*c* 0.53, H_2O), was obtained in 3% yield from the mother liquors of the preparation of methyl 6-deoxy-α-L-mannopyranoside from L-rhamnose.

Anal. Calcd for $C_{10}H_{16}O_6$: C, 55.56; H, 7.40. Found: C, 55.99; H, 7.71.

Methyl 6-Deoxy-2,3-di-*O*-acetyl-4-*O*-methylsulfonyl-α-D-glucopyranoside (21).—A solution of 40 g (92 mmol) of methyl 6-deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-glucopyranoside[5a] (19) in 160 ml of tetrahydrofuran and 640 ml of CH_3OH was hydrogenated in the presence of 2.5 g of 10% Pd/C and 3 ml of concentrated HCl at atmospheric pressure. When the hydrogen uptake was complete (4.13 l.), the mixture was neutralized with Dowex-1 X_2 (OH^-), Pd/C was removed by filtration, and the filtrate was evaporated to dryness to give 23 g (98%) of methyl 6-deoxy-4-*O*-methylsulfonyl-α-D-glucopyranoside (20) as a gum. This material (11.26 g, 44 mmol) was treated with 20 ml of pyridine and 20 ml of acetic anhydride at room temperature for 16 hr. The solution was poured into ice water, filtered, and dried to give 13.6 g (91%) of 21, mp 93–95°. An analytical sample was prepared by recrystallization from benzene–ether–pentane, mp 94–95°, $[\alpha]^{26}D$ +120.9° (*c* 1.0, CH_3OH).

Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.34; H, 5.92; S, 9.42. Found: C, 42.51; H, 5.93; S, 9.20.

Methyl 6-Deoxy-2,3-di-*O*-(*p*-nitrobenzoyl)-4-*O*-methylsulfonyl-α-D-glucopyranoside (22).—A solution of 5.12 g (20 mmol) of 20 in 30 ml of pyridine was treated with 14.8 g (80 mmol) of *p*-nitrobenzoyl chloride at room temperature for 48 hr. The mixture was poured into ice water, filtered, dried, and recrystallized from $CHCl_3$–pentane to give 10.5 g (95%) of 22, mp 178–179°, $[\alpha]^{26}D$ +194.6° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{22}H_{22}N_2O_{13}S$: C, 47.65; H, 4.00; N, 5.05; S, 5.78. Found: C, 47.50; H, 3.89; N, 4.88; S, 5.56.

Methyl 6-Deoxy-3,4-anhydro-α-D-galactopyranoside (23).—A solution of 23 g (90 mmol) of 20 in 200 ml of CH_3OH and 200 ml of $CHCl_3$ was treated with sodium methoxide (130 mmol, obtained by dissolving 3.0 g of sodium in methanol) at 0° for 48 hr. The solution was neutralized with solid CO_2, the inorganics were filtered off, and the filtrate was evaporated to dryness. Extraction of the residue with ethyl acetate followed by removal of the solvent gave 11.75 g (80%) of 23 as a solid which was recrystallized from ether–pentane, mp 69.5–70°, $[\alpha]^{26}D$ +100° (*c* 0.92, $CHCl_3$) [lit.[19] mp 65.5–66.5°, $[\alpha]^{26}D$ +70.0° (*c* 0.5, H_2O)].

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.73; H, 7.59.

Methyl 6-Deoxy-2-*O*-acetyl-3,4-anhydro-α-D-galactopyranoside (24).—A solution of 33.0 g (20.6 mmol) of 23 in 300 ml of pyridine was stirred with 41 ml of acetic anhydride at 0° for 8 hr. The solvents were removed *in vacuo*, and the residue was dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated to dryness. The resulting solid was recrystallized from ether to give 38 g (94%) of 24, mp 113.5–114.5°, $[\alpha]^{23}D$ +128° (*c* 0.9, $CHCl_3$) [lit.[19] mp 112.5–114°, $[\alpha]^{23}D$ +131.5° (*c* 0.54, $CHCl_3$)].

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.68; H, 6.96.

Methyl 6-Deoxy-3-*O*-acetyl-α-D-gulopyranoside (25).—A solution of 468 mg (2.32 mmol) of 24 in 20 ml of acetone was mixed with 0.6 ml of 2 *N* H_2SO_4 and heated under reflux for 2 hr. The cooled solution was neutralized with $BaCO_3$ and the barium salts were removed by filtration. The filtrate on evaporation under vacuum gave a solid which was recrystallized from ether to give 410 mg (80%) of 25: mp 144–145°; $[\alpha]^{26}D$ +133.9° (*c* 1.32, CH_3OH); nmr (acetone-d_6–D_2O) τ 8.8 (d, $J_{5,6}$ = 7 Hz, 3, CCH_3), 7.9 (s, 3, $COCH_3$), 6.6 (s, 3, OCH_3), 6.4 (broad d, 1, C-4 H), 6.0 (m, 2, C-2 and C-5 H), 5.3 (d, $J_{1,2}$ = 4 Hz, 1, C-1 H), 4.9 (t, 1, C-3 H).

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.21; H, 7.16.

Methyl 6-Deoxy-2,3,4-tri-*O*-acetyl-α-D-gulopyranoside (27).—A solution of 354 mg (1.6 mmol) of 25 in 3 ml of pyridine and 600 mg of acetic anhydride was stirred at room temperature for 18 hr. The mixture was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ solution was successively washed with 2 *N* HCl, Na_2CO_3 solution, and water, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized from ether–hexane to give 332 mg (67.6%) of 27, mp 81–82°, $[\alpha]^{26}D$ +112° (*c* 1.24, $CHCl_3$).

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.30; H, 6.62. Found: C, 51.57; H, 6.63.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-gulopyranoside (28).—A solution of 16.3 g (74 mmol) of 25 in 225 ml of CH_3OH was treated with a catalytic amount of sodium methoxide at room temperature. When the deacetylation was complete as shown by tlc, the solution was neutralized with solid CO_2 and then evaporated to dryness. The residue was extracted with boiling ethyl acetate. Removal of the solvent *in vacuo* gave methyl 6-deoxy-α-D-gulopyranoside (26) as a gum. This material was dissolved in 225 ml of acetone and the solution was stirred with 37.5 ml of 2,2-diethoxypropane and 225 mg of *p*-toluenesulfonic acid at room temperature for 1 hr, at which point tlc indicated completion of the reaction. The solution was neutralized with $BaCO_3$, the barium salts were filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from ethyl ether to give 13.25 g (82%) of 28, mp 48–50°, $[\alpha]^{26}D$ +67.7° (*c* 0.77, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.08; H, 8.31. Found: C, 55.29; H, 8.38.

Acetylation of 890 mg (5 mmol) of 26 with acetic anhydride in pyridine gave 1.2 g (80%) of the triacetate, 27, mp 81–82°; a mixture melting point with an analyzed sample was undepressed.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-*ribo*-hexopyranosid-4-ulose (18). A. By the Oxidation of 28.—Treatment of 10 g (46 mmol) of 28 in 100 ml of ethanol-free $CHCl_3$ with catalytic amounts of RuO_2 and bleach solution as described for the preparation of 2 from 1 gave 7.1 g (71%) of 18 as a gum which crystallized on standing, mp 48°, $[\alpha]^{26}D$ +176.2° (*c* 1.07, $CHCl_3$).[31]

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.56; H, 7.46. Found: C, 55.70; H, 7.37.

B. By the Isomerization of 17.—A solution of 180 mg (0.83 mmol) of 17 in 2 ml of 80% aqueous pyridine was left overnight at room temperature. A gc analysis indicated that partial isomerization had taken place and the solution consisted of 76% 17 and 24% 18. The mixture was then heated on a steam bath and the reaction was monitored by gc. Equilibrium consisting of 34% 17 and 66% 18 was reached after 2.5 hr. The solvents were removed *in vacuo* and the residue was separated by preparative tlc to give 48 mg of 17 and 56 mg (31%) of 18 as a gum, $[\alpha]^{26}D$ +173.4° (*c* 0.5, $CHCl_3$). This material was identical (ir, gc, tlc) with an analyzed sample of 18 before it crystallized. Also, a solution of 18 (crystalline material) in 80% aqueous pyridine when heated on a steam bath produced an equilibrium mixture consisting of 66% of 18 and 34% of 17 as shown by gc.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-*ribo*-hexopyranosid-4-ulose Oxime (29).—Ketone 18 (7 g, 32.4 mmol) was converted to 6.1 g (82%) of 29 as described for the conversion of 3 to 6. This gummy material was shown to be a mixture of two oximes by tlc. A portion of the mixture was separated by preparative tlc to give the major isomer as a crystalline material which was recrystallized from ether, mp 117–118°, $[\alpha]^{25}D$ +260° (c 1.12, $CHCl_3$).

Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.95; H, 7.35; N, 6.06. Found: C, 52.03; H, 7.41; N, 6.18.

Methyl 4-Amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-allopyranoside (30).—A solution of 6.0 g (26 mmol) of 29 (gum, mixture of isomers) in 100 ml of tetrahydrofuran was reduced with 3.0 g of $LiAlH_4$, taking special care to keep the temperature below 30°. After 2 hr, a tlc indicated that the reaction was complete. The excess $LiAlH_4$ was decomposed by adding 3 ml of water, 3 ml of 15% NaOH, and 9 ml of water in that order. The inorganic materials were removed by filtration and the filtrate was evaporated to dryness and azeotroped with benzene under reduced pressure to give a gum. A gc analysis of this material using a 6 ft × 0.125 in., 3% SE-52 on a dichlorodimethylsilane-treated, acid-washed Chromosorb W column at 100° showed that it consisted of over 95% of 30 and less than 5% of 31.[32] A solution of this mixture in ether was treated with an ethereal solution of *p*-toluenesulfonic acid and the salt was recrystallized from $CHCl_3$–ether to give 30 as its hydrogen *p*-toluenesulfonate (5.6 g, 56%), mp 198–200°, $[\alpha]^{25}D$ +56.8° (*c* 0.89, CH_3OH), pK_a 6.35.

Anal. Calcd for $C_{17}H_{27}NO_7S$: C, 52.42; H, 7.00; N, 3.59; S, 8.23. Found: C, 52.47; H, 6.95; N, 3.60; S, 7.98.

(31) The specific rotation previously reported[2d] for compound 18 was that of a hydrated sample and therefore should be corrected.

(32) The two peaks on the gas chromatogram were identified as follows. A small portion of the gum when treated with acetic anhydride in pyridine followed by hydrolysis with Dowex-50 X_2 (H^+) in CH_3OH gave a mixture of *N*-acetates which was then treated with pyridine, hexamethyldisilazane, and trimethylchlorosilane according to C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963). Analysis of this mixture by gc using the SE-52 column at 160° gave two peaks which corresponded to the di-*O*-trimethylsilyl ethers of authentic 33 and methyl 4-acetamido-4,6-dideoxy-α-D-gulopyranoside.[5d]

Reduction of the crystalline oxime (mp 117–118°) under the above conditions gave the same results. However, when **29** was reduced with $LiAlH_4$ in refluxing tetrahydrofuran, a mixture of **30** and **31** in the ratio 85:15 was obtained as shown by gc.[32]

Methyl 4-Amino-4,6-dideoxy-α-D-allopyranoside (32).—A solution of 1.0 g (2.57 mmol) of the hydrogen *p*-toluenesulfonate salt of **30** in 15 ml of water was heated on a steam bath for 30 min. The water was removed *in vacuo* to yield a gummy solid which was recrystallized from methanol–ether to give 0.8 g (89%) of **32** as its hydrogen *p*-toluenesulfonate, mp 183–185°, $[\alpha]^{25}D$ +83.5° (*c* 0.99, CH_3OH), pK_a 7.20.

Anal. Calcd for $C_{14}H_{23}NO_7S$: C, 48.14; H, 6.59; N, 4.01; S, 9.17. Found: C, 48.21; H, 6.75; N, 4.10; S, 9.19.

Methyl 4-Acetamido-4,6-dideoxy-2,3-di-*O*-methylsulfonyl-α-D-glucopyranoside (35).—Methanesulfonyl chloride (1.1 g, 9.7 mmol) was added dropwise to a stirred solution of 1.0 g (4.57 mmol) of methyl 4-acetamido-4,6-dideoxy-α-D-glucopyranoside[5b] in 16 ml of pyridine. After 4 hr, the solution was evaporated to dryness, the residue was dissolved in 25 ml of $CHCl_3$, and the $CHCl_3$ solution was washed two times with 20 ml of water. The aqueous solution was saturated with NaCl and extracted three times with 25 ml of $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to dryness to yield 1.7 g (90%) of **35** as a clear, colorless gum which crystallized on standing. A sample was recrystallized from MeOH for analysis, mp 160–163°, $[\alpha]^{25}D$ +125° (*c* 0.95, CH_3OH).

Anal. Calcd for $C_{11}H_{21}NO_9S_2$: C, 35.19; H, 5.62; N, 3.73; S, 17.07. Found: C, 35.48; H, 5.81; N, 3.72; S, 17.34.

Methyl 4-Acetamido-4,6-dideoxy-2-*O*-methylsulfonyl-3-*O*-acetyl-α-D-allopyranoside (37).—A solution of 1.25 g (3.34 mmol) of **35** and 550 mg (6.68 mmol) of NaOAc in 95% aqueous ethylene glycol monomethyl ether was heated under reflux and the progress of the reaction was monitored by tlc ($CHCl_3$:acetone, 3:2 system). As all the starting material had disappeared in 28 hr, the solvent was removed at reduced pressure and the residue was taken up in 100 ml of $CHCl_3$ and washed three times with 10 ml of water. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to dryness and the residue was recrystallized to give 900 mg (90%) of methyl 4-acetamido-4,6-dideoxy-2-*O*-methylsulfonyl-α-D-allopyranoside (**36**): mp 134°; ir 3500 (OH), 3425 (NH), 1675 (amide), 1155 cm^{-1} (OSO_2CH_3). As a satisfactory elementary analysis could not be obtained for **36**, a portion of it (80 mg) was acetylated with acetic anhydride in pyridine and the product was recrystallized from acetone to give 80 mg (87%) of **37**, mp 157–158°, $[\alpha]^{25}D$ +146° (*c* 0.59, $CHCl_3$).

Anal. Calcd for $C_{12}H_{21}NO_8S$: C, 42.48; H, 6.19; N, 4.13; S, 9.14. Found: C, 42.41; H, 6.27; N, 4.13; S, 9.14.

Methyl 4-Acetamido-4,6-dideoxy-α-D-allopyranoside (33). A. From Compound 30.—A solution of 450 mg (2.07 mmol) of **30** (free base) in 10 ml of pyridine was mixed with 0.5 ml of acetic anhydride at 0° and then stirred at room temperature for 2 hr. The solvents were removed *in vacuo* and the residue was dissolved in $CHCl_3$ and washed with water. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to dryness to give a gum which was dissolved in CH_3OH and stirred with a small amount of Dowex-50 X2 (H^+). The resin was filtered off and the solvent was removed under reduced pressure to give 410 mg (90%) of **33** which was recrystallized from methanol–ether, mp 150–152°, $[\alpha]^{25}D$ +235° (*c* 0.75, CH_3OH).

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.76; N, 6.39. Found: C, 49.09; H, 7.88; N, 6.43.

B. From Compound 36.—A solution of sodium naphthalene reagent[26] was prepared by stirring a mixture of 512 mg (40 mmol) of naphthalene and 92 mg (40 mmol) of sodium in 13 ml of ethylene glycol dimethyl ether under a nitrogen atmosphere overnight. A slurry of 297 mg (1.0 mmol) of **36** in 5 ml of the same solvent was added to the sodium naphthalene reagent and the mixture was stirred for 20 min. Ten drops of water were added and the solvents were removed under vacuum. The yellow solid was extracted ten times with 10 ml of hot $CHCl_3$. After the $CHCl_3$ was evaporated, the residue was extracted with pentane to remove naphthalene. Recrystallization of the remaining solid from ethanol–ether gave 126 mg (57%) of **33**, mp 148–150°; a mixture melting point with a previously prepared sample was undepressed.

Hydrolysis of 100 mg (0.455 mmol) of **33** with 173 mg of $Ba(OH)_2$ in 3 ml of water followed by treatment of the product with *p*-toluenesulfonic acid gave 57 mg (36%) of methyl 4-amino-4,6-dideoxy-α-D-allopyranoside (**32**) hydrogen *p*-toluenesulfonate, mp 183–185°, identical with a sample described earlier. Also, 100 mg (0.455 mmol) of **33** was degraded to 29 mg (32.5%) of D-allothreoninol hydrogen oxalate, mp 174° dec; a mixture melting point with an authentic compound[1b,17] was unchanged and the two samples had superimposable ir spectra.

Structural Correlation of 8 and 33.—A solution of 10 mg of **8** in 1.5 ml of CH_3OH containing 1% HCl was heated under reflux for 2 hr under a nitrogen atmosphere. The solution was evaporated to dryness and repeatedly azeotroped with CH_3OH and benzene to remove the last traces of HCl. The residue was dissolved in pyridine (1.5 ml) and treated with hexamethyldisilazane (0.1 ml) and trimethylchlorosilane (0.05 ml). The product was analyzed by gc using a 6 ft × 0.125 in. 3% SE-52 on a dichlorodimethylsilane-treated, acid-wated Chromosorb W column at 160° to give two peaks which corresponded to the di-*O*-trimethylsilyl ethers of authentic **8** (major) and **33** (minor). Also compound **33** gave an identical gas chromatogram after the same series of reactions.

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Registry No.—**1**, 14133-63-2; **2**, 2592-53-2; **3**, 32848-86-5; **4**, 14685-82-6; **6** oxime A, 36031-47-7; **6** oxime B, 35954-82-6; **7**, 42213-89-8; **7** TsOH, 35941-98-1; **8**, 35941-99-2; **9**, 35942-00-8; **10**, 42213-93-4; **10** hydrochloride, 42213-94-5; **11**, 42213-95-6; **11** TsOH, 42213-96-7; **12** hydrochloride, 42213-97-8; **13**, 42213-98-9; **14** hydrochloride, 42213-99-0; **15**, 42214-00-6; **16**, 42214-01-7; **17**, 42214-02-8; **18**, 37063-23-3; **19**, 7045-38-7; **20**, 42214-06-2; **21**, 42214-04-0; **22**, 42214-07-3; **23**, 6893-94-3; **24**, 6893-96-5; **25**, 42214-10-8; **26**, 42214-11-9; **27**, 33947-13-6; **28**, 33947-10-3; **29** oxime A, 42214-14-2; **29** oxime B, 42214-15-3; **30**, 42214-16-4; **30** TsOH, 42214-17-5; **32** TsOH, 42214-18-6; **33**, 42214-19-7; **35**, 42214-20-0; **36**, 42214-21-1; **37**, 42214-22-2; methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside, 42214-23-3.

9,11-Seco Steroids[1] Derived from Estradiol 3-Methyl Ether[2]

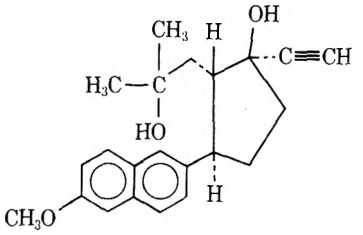
JOHN H. DYGOS* AND LELAND J. CHINN

Department of Chemical Research, Searle Laboratories, Chicago, Illinois 6068

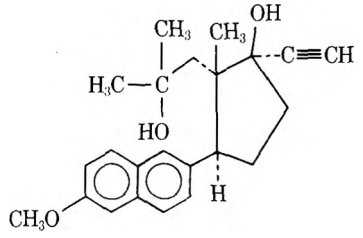
Received July 12, 1973

A series of optically active 9,11-seco steroids was prepared starting with estradiol 3-methyl ether (**3**). A key step in one of the reaction sequences involved the stereoselective addition of ethynyl Grignard reagent to the apparently more hindered side of a 2,2-disubstituted cyclopentanone derivative. Another unique feature was the stereospecific addition of ethynyl Grignard reagent to a cyclic hemiketal. Two compounds in the series exhibited biological activity. Compound **9** had weak estrogenic activity while compound **21** exhibited antifertility activity without having estrogenic activity.

Several years ago in our laboratories we[3] prepared compound **1** by total synthesis. The compound exhibited antifertility activity[4] in rats with only minimal estrogenic activity.[5] This desired separation of biological activities led us to speculate that the corresponding analog having an angular methyl group at C-13,[6] compound **2**, might also possess interesting biological properties.

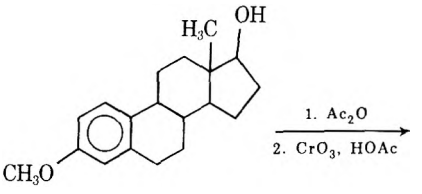


1 (*dl*)

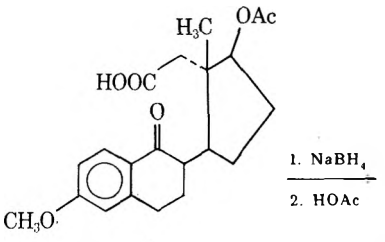


2

We were primarily interested in obtaining the optically active isomer of **2** which we envisioned could be prepared by partial degradation of a steroid of known configuration. Consequently, we chose estradiol 3-methyl ether (**3**) as our starting material. Several workers[7-9] have investigated the reaction of **3** with chromic anhydride under various reaction conditions. Cambie's[8] procedure was used to prepare 17β-hydroxy-3-methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid 17-acetate (**4**) which was a key intermediate in our synthesis of **2**. Treatment of **4** with sodium borohydride in isopropyl alcohol followed by acidification with acetic acid afforded a mixture of products which was assumed to consist of the two 9-hydroxy derivatives, **5**, along with a small amount of the seven-membered ring lactones, **6**, on the basis of their behavior on thin layer chromatography (tlc). No attempt was made to purify at this stage, however, since treatment of the crude mixture of **5** and **6** with selenous acid in refluxing ethanol afforded a mixture of **7** and **8** which was converted into pure **8** by treatment with sodium hydroxide in aqueous methanol.



3



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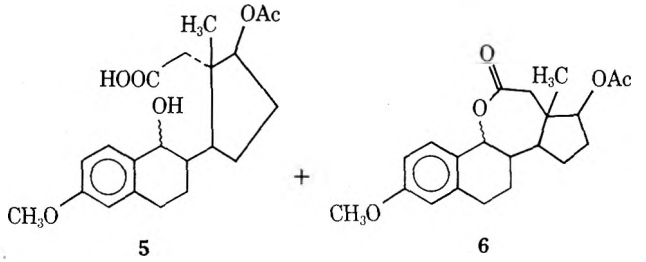

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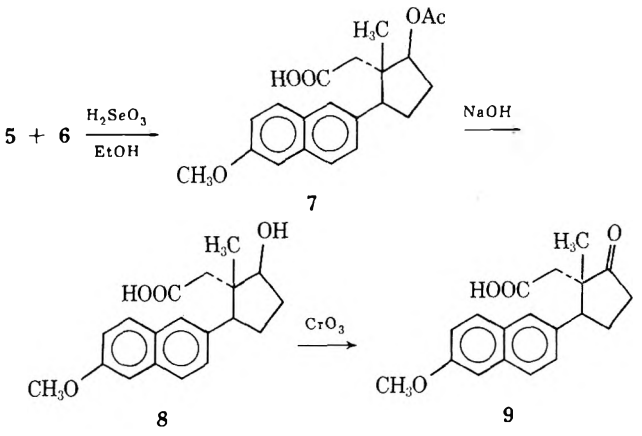


7 8 9

(1) 9,11-Seco steroids have been the subject of two recent reports: (a) N. S. Crossley and R. Dowell, *J. Chem. Soc.*, 2496 (1971); (b) E. G. Brain, F. Cassidy, M. F. Constantine, J. C. Hanson, and D. J. D. Tidy, *ibid.*, 3846 (1971).

(2) Presented in part at the 6th Regional Midwest American Chemical Society Meeting, Houghton, Mich., June 22, 1972.

(3) L. J. Chinn, unpublished results.

(4) The antifertility activity was determined by a standard procedure: R. L. Elton, E. F. Nutting, and F. J. Saunders, *Acta Endocrinol. (Copenhagen)*, **41**, 381 (1962).

(5) The estrogenic activity was determined by standard procedures: (a) B. L. Rubin, A. S. Dorfman, L. Black, and R. I. Dorfman, *Endocrinology*, **49**, 429 (1951); (b) R. A. Edgren, *Proc. Soc. Exp. Biol. Med.*, **92**, 569 (1956).

(6) The steroid numbering system has been used throughout the text of this paper for convenience.

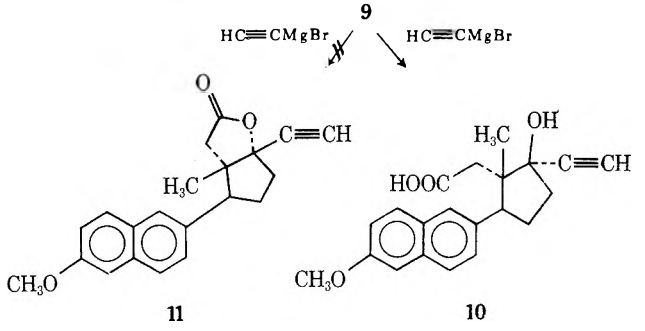
(7) Y. Suzuki, Japan Patent No. 17,831 (1964) [*Chem. Abstr.*, **62**, 5318 (1965)].

(8) R. C. Cambie, V. F. Carlisle, C. J. LeQuesne, and T. D. R. Manning, *J. Chem. Soc.*, 1234 (1969).

(9) P. D. Mainreville and B. Gastambide, *C. R. Acad. Sci., Ser. C*, **273** (7), 507 (1971).

It is not known whether partial hydrolysis of the 17-acetoxy group occurred during the borohydride reduction of **4** or during the aromatization of **5** and **6** with selenous acid. However, this is not important since the 17-hydroxy derivative, **8**, was obtained in 82% yield starting with **4**. Treatment of **8** with Jones'[10] reagent afforded the corresponding ketone, **9**, in high yield.

Based on previous results[11] with the 18-nor analog of **9**, we anticipated that reaction of **9** with a Grignard reagent would lead to a mixture of two products, **10** and **11**. The hydroxy acid, **10**, would arise *via* attack

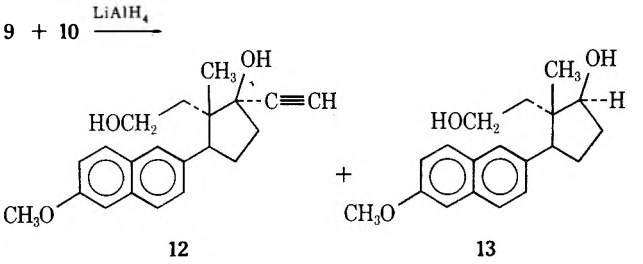


11 10

of the Grignard reagent from the α face[12] of the molecule while the lactone, **11**, would arise *via* β-face[12] attack followed by lactonization during the acid work-up.

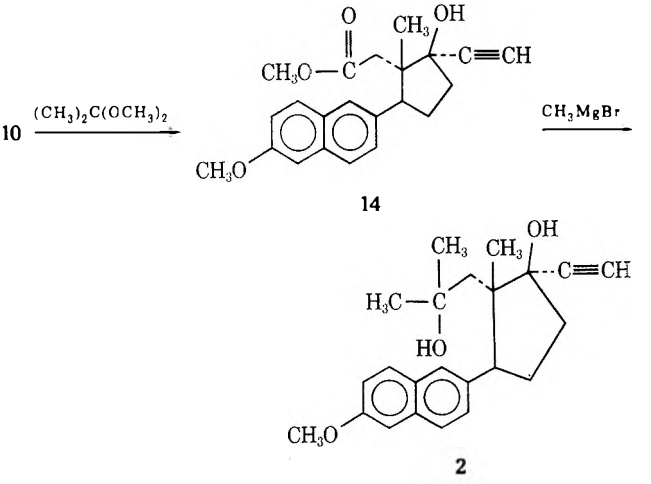
Addition of Grignard reagents to the 17-keto function of "normal" steroids usually leads to the formation of products derived from α-face attack[13] presumably due to the steric hindrance of the C-18 angular methyl group which inhibits β-face approach of the reagent. The steric environment about the 17-keto function of **9**, however, is markedly different from that in the intact steroid skeleton. Molecular models indicate that approach of a Grignard reagent from either the α or β face of **9** should be severely hindered. *A priori*, we anticipated a sluggish reaction which would give rise to a mixture of **10** and **11**. However, when **9** was treated with ethynylmagnesium bromide in tetrahydrofuran, a single addition product, **10**, was obtained in good yield along with a small amount of starting ketone, **9**, as evidenced by two distinct C-18 methyl resonances in the nmr spectrum of the crude product. No trace of any nonacidic product could be detected by thin layer chromatography.

Although a sample of **10** was obtained pure by column chromatography, a quantitative separation of **9** and **10** could not be effected. Consequently, the crude ethynylation mixture was reduced with lithium aluminum hydride to give a mixture of **12** and **13** which were readily separated by column chromatography to give **12** and **13**[14] in a molar ratio of 7:1. Thus, the ratio of **10** to **9** in the ethynylation mixture must also have been 7:1.



12 13

The conversion of **10** into **2** was accomplished in two steps. Esterification of **10** with 2,2-dimethoxypropane afforded **14** which was converted into **2** by treatment with methylmagnesium bromide.



The ethynylation product was initially assigned structure **10** on the basis of its spectral and microanalytical data as well as on its failure to lactonize even when treated with 1.8 *M* sulfuric acid in tetrahydrofuran. Conclusive proof for the assigned structure of **10** was obtained as outlined in Scheme I.

Hydrogenation of **10** over 5% Pd/C afforded the 17α-ethyl derivative **15**. When **15** was treated with 1.8 *M* sulfuric acid in tetrahydrofuran under conditions which left **10** unchanged, there was obtained a lactone whose spectral and microanalytical data were consistent with structure **16**. Treatment of **16** with methylmagnesium bromide afforded the diol **17** in which the hydroxyl group at the 17 position was α. The ethynyl group of **2** was hydrogenated over 5% Pd/C to give compound **18** in which the hydroxyl group at the 17 position was β. Compounds **17** and **18** were shown to be different by comparison of their physical and spectral properties. The fact that **17** and **18** were different indicated that the Grignard reagent added exclusively from the α face of **9** to give **10**.

As indicated earlier, this process would involve severe steric hindrance from the acetic acid side chain adjacent to the carbonyl group in **9**. Secondly, this process would appear to be electronically unfavorable due to the acetic acid anion which is generated on the α face by initial reaction of the acid function with the Grignard reagent. This anion would be expected to repulse severely the approach of a nucleophile such as ethynylmagnesium bromide from the α face of the molecule. One possible explanation of our results is that a second mole of Grignard reagent complexes with the carboxylate anion on the α face and is thus oriented for exclusive attack from the α face to give **10**. Asymmetric syntheses involving complexa-

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

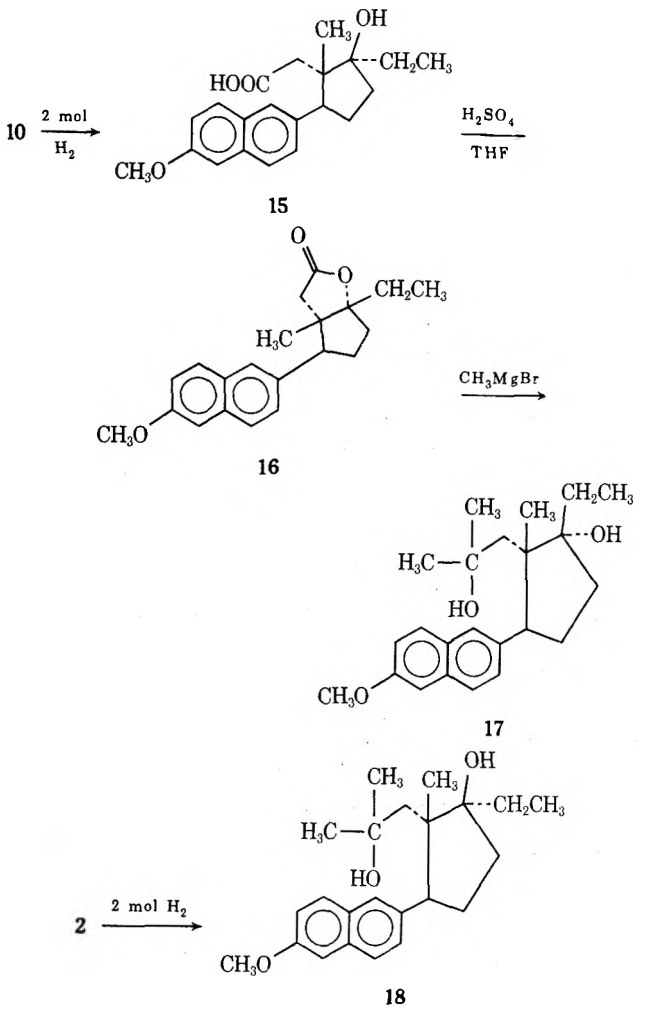
(11) L. J. Chinn, E. A. Brown, R. A. Mikulec, and R. B. Garland, *J. Org. Chem.*, **27**, 1733 (1962).

(12) The terms α and β face are borrowed from steroid nomenclature for convenience. In our case, α face refers to the side of the cyclopentanone ring in **9** on which the acetic acid side chain is located. Similarly, β face refers to the side on which the C-18 methyl group is located.

(13) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(14) An authentic sample of **13** was prepared by lithium aluminum hydride reduction of **7**.

SCHEME I



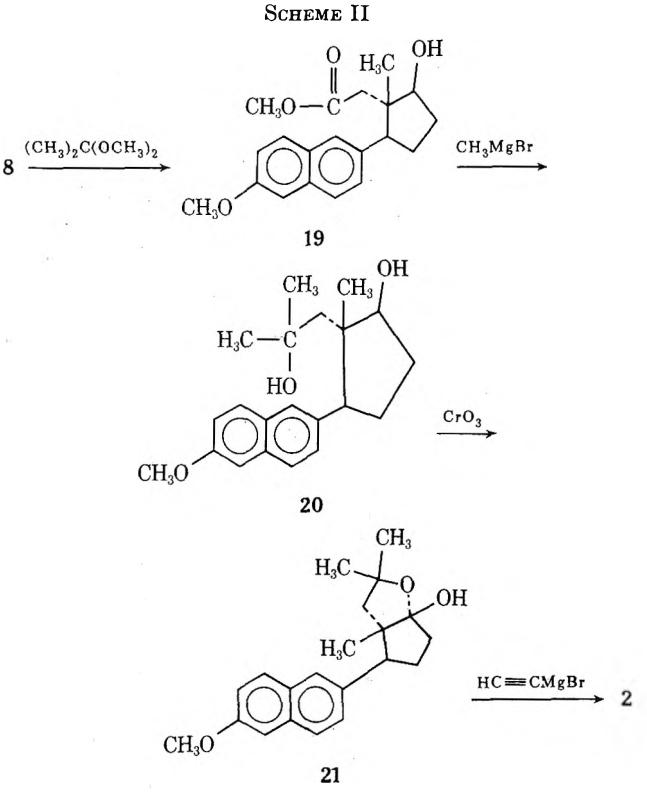
tion of Grignard reagents to groups such as hydroxy, alkoxy, or amino adjacent to a carbonyl group have been reported.[15] Asymmetric induction involving complexation of a Grignard reagent with a group which is three carbons removed from the reaction center appears to be unique.

An alternative explanation for the stereospecificity observed in the ethynylation reaction is suggested by the work of Brain and coworkers.[1b] These authors noted that the reduction of the *dl* form of **9** with sodium borohydride as well as the compound in which the methyl and acetic acid groups were interchanged occurs predominantly from the α face. They proposed that "the direction of borohydride attack must therefore be strongly influenced by the orientation of the 2-methoxynaphthyl group rather than by the two 1 substituents." Molecular models, however, indicate that the 2-methoxynaphthyl group would have to occupy a pseudoaxial rather than a pseudoequitorial configuration in order to sterically hinder the approach of a nucleophile from the β face. Our results unfortunately do not permit a clear-cut distinction between these two possible explanations.

The fact that **15** lactonized to **16** when treated with 1.8 *M* sulfuric acid in tetrahydrofuran while **10** remained unchanged under identical conditions was surprising but not totally unexpected. Although alkynyl carbonium ions have been generated from their corresponding alcohols,[16-18] the process required either very strong acids or the presence of cationic stabilizing groups on the developing carbonium ion. Our results indicate that 1.8 *M* sulfuric acid in tetrahydrofuran is incapable of generating a tertiary carbonium ion adjacent to a carbon–carbon triple bond.

Compound **2** was alternatively prepared by functionalizing the acetic acid side chain before ethynylating the 17-keto function as outlined in Scheme II. Esteri-

SCHEME II



fication of **8** with 2,2-dimethoxypropane gave **19** which was converted into the diol, **20**, with methylmagnesium bromide. Jones'[10] oxidation of **20** did not give the expected 17-keto derivative but instead gave the cyclic hemiketal, **21**, presumably *via* the intermediacy of the 17 ketone. We anticipated that the hemiketal, **21**, might exist in solution in equilibrium with the corresponding 11-hydroxy 17 ketone and that we might be able to trap this uncyclized form with a Grignard reagent and thereby establish a new equilibrium. We envisioned that such a process would eventually consume all of the hemiketal and give a mixture of the two possible Grignard addition products. However, when **21** was treated with ethynylmagnesium bromide in tetrahydrofuran, a single product was obtained which was identical with **2** in all respects. Thus, as in the case with **9**, ethynylation of **21** led exclusively to the product derived from α-face attack of the Grignard reagent.

Compound **2** exhibited no estrogenic or antifertility

(15) (a) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959); (b) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).

(16) H. G. Rickey, Jr., J. C. Philips, and L. E. Rennick, *J. Amer. Chem. Soc.*, **87**, 1381 (1965).

(17) H. G. Richey, Jr., L. E. Rennick, A. S. Kushner, J. M. Richey, and J. C. Philips, *J. Amer. Chem. Soc.*, **87**, 4017 (1965).

(18) C. U. Pittman, Jr., and G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 5632 (1965).

activity in our biology screening assays.[4,5] However, compounds **9** and **20** exhibited weak estrogenic activity and compound **21** exhibited weak antifertility activity while being devoid of estrogenic activity. None of the other compounds described in this paper showed any significant biological activity.

Experimental Section

Melting points were taken on a Fisher-Johns melting block and are uncorrected. Infrared spectra were recorded on a Beckman IR-12 grating spectrophotometer. Nmr spectra were obtained on a Varian A-60 or T-60 spectrometer using tetramethylsilane as internal standard. Specific rotations were obtained in chloroform (*c* 1.0) using a Perkin-Elmer (Model 141) polarimeter. Elemental analyses were performed by the microanalytical group at Searle Laboratories.

Sodium Borohydride Reduction of 4.—Sodium borohydride (6.10 g, 161 mmol) was added portionwise to a stirred suspension of **4** (25.3 g, 67.8 mmol) in 500 ml of isopropyl alcohol at 0°. The solution was warmed to room temperature and stirred an additional 18 hr. The solution was poured on 1.5 l. of water and acidified with hydrochloric acid. The aqueous phase was extracted with methylene chloride and the extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a brown oil which was assumed to be a mixture of **5** and **6** based on its behavior on tlc. The crude product was used without further purification.

Selenous Acid Oxidation of 5 and 6.—The crude mixture of **5** and **6** obtained *via* borohydride reduction of **4** was dissolved in 500 ml of ethanol and treated with selenous acid (35.0 g, 271 mmol). The solution was refluxed for 5 hr, cooled to room temperature, and filtered through Celite. The red-colored filtrate was concentrated *in vacuo* to give a red oil which was dissolved in methylene chloride. The solution was filtered to remove a small amount of red solid, and the filtrate was concentrated *in vacuo* to give a pink oil which was assumed to be a mixture of **7** and **8** based on its behavior on tlc. The crude product was used without further purification.

Saponification of 7.—The crude mixture of **7** and **8** obtained *via* selenous acid oxidation of **5** and **6** was dissolved in 200 ml of methanol and treated with a solution of sodium hydroxide (20.0 g, 0.500 mol) in 100 ml of water. The solution was refluxed for 18 hr, filtered through Celite, and diluted with 1 l. of water. The aqueous phase was acidified with hydrochloric acid, and the solid which formed was collected and thoroughly washed with water. Recrystallization from ethyl acetate afforded **8** (15.4 g, 49.0 mmol): mp 174–175°; $[\alpha]^{27}D$ +67°; nmr (DMSO-d_6) δ 0.67 (s, CH_3), 3.90 (s, OCH_3).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.34; H, 7.10.

An additional 2.10 g (6.70 mmol) of **8** was obtained by chromatographing the mother liquors on 420 g of SilicAR CC-4.

(1*S*,5*S*)-5-(6-Methoxy-2-naphthyl)-1-methyl-2-oxocyclopentaneacetic Acid (9).—Jones'[10] reagent was added dropwise to a stirred solution of **8** (10.0 g, 31.9 mmol) in 300 ml of acetone at room temperature until the orange color persisted for 15 min. The excess reagent was destroyed by the dropwise addition of isopropyl alcohol until the orange color disappeared. The mixture was poured on 1.5 l. of water, and the solid which formed was collected and thoroughly washed with water. The crude product was chromatographed on 800 g of SilicAR CC-4 to give **9** in the 10% ethyl acetate–90% benzene fractions. Recrystallization from benzene–Skellysolve B afforded **9** (7.42 g, 75% yield): mp 143.5–144.5°; $[\alpha]^{27}D$ −3°; ir (KBr) 1755 (C=O), 1730 cm^{-1} (COOH); nmr ($CDCl_3$) δ 0.70 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.27; H, 6.62.

Ethynylation of 9.—Acetylene[19] was bubbled through 100 ml of anhydrous tetrahydrofuran at −78° for 50 min. A 10-ml portion of 3 *M* ethylmagnesium bromide in ether was added and the solution was allowed to warm to room temperature. A solution of **9** (1.33 g, 4.26 mmol) in 25 ml of tetrahydrofuran was added dropwise, and the reaction mixture was stirred at room temperature under nitrogen for 3 days. The reaction mixture was filtered through a glass wool plug onto 1 l. of cold 5% hydrochloric acid. The solution was saturated with sodium chloride and after stirring for 20 min the product was collected, washed with water, and dried in a steam oven to give 1.30 g of a tan solid, mp 168–173°. The crude product was dissolved in 50 ml of anhydrous ether and added dropwise to a stirred suspension of lithium aluminum hydride (1.30 g, 34.3 mmol) in 50 ml of ether. After stirring for 4 hr at room temperature the mixture was hydrolyzed by the dropwise addition of 5.2 ml of 10% sodium hydroxide. The mixture was filtered and the inorganic salts were thoroughly washed with methylene chloride. The combined solvents were removed *in vacuo* to give 1.09 g of a white solid which consisted of two products as evidenced by tlc (40% ethyl acetate–60% benzene). The product was chromatographed on 100 g of SilicAR CC-7 using benzene and ethyl acetate as eluents. Compound **12** (0.804 g, 2.48 mmol) was obtained pure in the first few fractions of 50% ethyl acetate–50% benzene, while compound **13** (0.104 g, 0.347 mmol) was obtained pure in the later fractions of 50% ethyl acetate–50% benzene. Recrystallization from ethyl acetate–Skellysolve B afforded an analytical sample of **12**: mp 199–201°; $[\alpha]^{23}D$ −68°; nmr ($CDCl_3$) at δ 0.88 (s, CH_3), 2.70 (s, C≡CH), 3.90 (s, OCH_3).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.45. Found: C, 78.05; H, 7.55.

Recrystallization from benzene–Skellysolve B afforded an analytical sample of **13**: mp 188–190°, $[\alpha]^{23}D$ +29°. The spectra of this sample were virtually identical with those of an authentic sample of **13**.[14]

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05 Found: C, 76.10; H, 8.10.

In another experiment a pure sample of **10** was obtained by chromatographing the crude ethynylation mixture on SilicAR CC-4 using benzene and ethyl acetate as eluents. Recrystallization from ethyl acetate–Skellysolve B afforded an analytical sample of **10**: mp 204–206°; $[\alpha]^{24}D$ +8°; nmr ($CDCl_3$) δ 0.93 (s, CH_3), 2.67 (s, C≡CH), 3.92 (s, OCH_3); ir (KBr) 1710 (COOH); 3300 cm^{-1} (C≡CH).

Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.40; H, 6.66.

(1*S*,2*S*,5*S*)-2-Hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneethanol (13).—A solution of **7** (1.00 g, 2.71 mmol) in 20 ml of ether–5 ml of tetrahydrofuran was added dropwise to a stirred slurry of lithium aluminum hydride (0.800 g, 21.1 mmol) in 100 ml of anhydrous ether, and the mixture was stirred at room temperature for 18 hr. The mixture was hydrolyzed by the dropwise addition of 3.2 ml of 5% sodium hydroxide solution and filtered. The inorganic salts were washed with methylene chloride and the combined solvents were removed *in vacuo*. The residue was recrystallized from benzene–Skellysolve B to give **13** (0.691 g, 85% yield): mp 192–193°; $[\alpha]^{23}D$ +33°; nmr (DMSO-d_6) δ 0.63 (s, CH_3), 3.89 (s, OCH_3).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.92; H, 8.13.

Attempted Lactonization of 10.—A solution of **10** (0.760 g, 2.25 mmol) in 27 ml of tetrahydofuran with 3 ml of sulfuric acid added was stirred at room temperature for 45 min and was gently heated on a steam bath for 15 min. A tlc on the reaction mixture indicated no change. The mixture was stirred at room temperature for 24 hr at which time tlc indicated a small amount of decomposition but no lactone formation. The mixture was poured on 200 ml of ice–water and the product was collected and air-dried to give 0.707 g of a tan solid. The ir and nmr spectra of the crude product were virtually identical with those of compound **10**. No trace of the corresponding lactone **11** could be detected.

(1*S*,2*S*,5*S*)-2-Ethynyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneacetic Acid Methyl Ester (14).—A solution of **10** (1.00 g, 2.96 mmol), 4 ml of 2,2-dimethoxypropane, and 30 ml of methanol with a trace of *p*-toluenesulfonic acid added was refluxed for 18 hr. The solution was diluted with 150 ml of benzene and washed successively with water, 5% sodium bicarbonate, and saturated sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give **14** (0.889 g, 85% yield): mp 161–163°; $[\alpha]^{24}D$ −22°; ir (KBr) 3430 (OH), 1718 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.93 (s, CH_3), 2.67 (s, C≡CH), 3.64 (s, $COOCH_3$), 3.94 (s, OCH_3).

Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 75.13; H, 6.95.

(19) Acetylene gas was purified by passage through one water trap and two sulfuric acid traps.

(1*S*,2*S*,5*S*)-2-Ethynyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (2).—A 6-ml portion of 3 *M* methylmagnesium bromide in ether was added dropwise to a stirred solution of 14 (0.406 g, 1.15 mmol) in 25 ml of ether, and the mixture was stirred at room temperature for 16 hr. The reaction mixture was quenched by the dropwise addition 5% hydrochloric acid. The mixture was extracted with benzene and the extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give 2 (0.334 g, 82% yield): mp 202–205°; $[\alpha]^{27}D$ −81°; nmr ($CDCl_3$) δ 1.07 (s, CH_3), 1.18 (s, CH_3), 1.32 (s, CH_3), 2.70 (D, C≡CH), 3.92 (s, OCH_3).

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.49; H, 8.06.

(1*S*,2*S*,5*S*)-2-Ethyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneacetic Acid (15) —A solution of 10 (1.47 g, 4.35 mmol) in 200 ml of isopropyl alcohol was hydrogenated over 5% Pd/C (0.2 g) in a Paar shaker at room temperature for 24 hr. The solution was filtered and the solvent was removed *in vacuo* to give a white solid. Recrystallization from benzene–Skellysolve B afforded 15 (1.20 g, 81% yield): mp 186–190°; $[\alpha]^{24}D$ +167°; nmr ($CDCl_3$) δ 0.88 (s, CH_3), 1.05 (t, J = 7 Hz, CH_2CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.61; H, 7.50.

cis-6a-Ethylhexahydro-4-(6-methoxy-2-naphthyl)-3a-methyl-2*H*-cyclopenta[*b*]furan-2-one (16).—A solution of 15 (1.20 g, 3.52 mmol) in 41 ml of tetrahydrofuran with 4.5 ml of sulfuric acid added was stirred at room temperature for 45 min and was gently heated on a steam bath for 15 min. The solution was poured onto 300 ml of water, made basic with sodium bicarbonate, and extracted with ether and benzene. The combined extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a tan solid which was recrystallized from ether–Skellysolve B to give 16 (0.838 g, 74% yield): mp 146–148°; $[\alpha]^{27}D$ +11°; ir (KBr) 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.80 (s, CH_3), 1.10 (t, J = 7 Hz, CH_2CH_3), 3.94 (s, OCH_3).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.71; H, 7.49.

(1*S*,2*R*,5*S*)-2-Ethyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (17). A solution of 16 (0.224 g, 0.692 mmol) in 5 ml of tetrahydrofuran was added dropwise to a stirred solution of 3 ml of 3 *M* methylmagnesium bromide in 35 ml of ether, and the mixture was stirred at room temperature for 3 hr. The mixture was poured onto 75 ml of a 5% ammonium chloride solution and the layers were separated. The aqueous phase was extracted with benzene and the combined organic phases were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave an oil which solidified upon standing. The crude product was recrystallized twice from benzene–Skellysolve B to give 17 (0.124 g, 50% yield): mp 153–156°; $[\alpha]^{24}D$ −14°; nmr ($CDCl_3$) δ 0.85 (s, CH_3), 1.27 (s, CH_3), 1.32 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.44; H, 9.05.

(1*S*,2*S*,5*R*)-2-Ethyl-2-hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (18).—A solution of 2 (0.227 g, 0.645 mmol) in 200 ml of isopropyl alcohol was hydrogenated over 5% Pd/C (0.05 g) in a Paar shaker at room temperature for 18 hr. The solution was filtered and the solvent was removed *in vacuo* to give a white solid. Recrystallization from benzene–Skellysolve B afforded 18 (0.183 g, 80% yield): mp 197–198°; $[\alpha]^{27}D$ −8°; nmr ($CDCl_3$) δ 1.08 (s, CH_3), 1.13 (s, CH_3), 1.27 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.88; H, 9.25.

(1*S*,2*S*,5*S*)-2-Hydroxy-5-(6-methoxy-2-naphthyl)-1-methylcyclopentaneacetic Acid Methyl Ester (19).—A solution of 8 (5.00 g, 15.9 mmol), 25 ml of 2,2-dimethoxypropane, 150 ml of methanol, and 0.100 g of *p*-toluenesulfonic acid was refluxed for 16 hr and concentrated *in vacuo*. The residue was dissolved in 250 ml of benzene and washed with 5% sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from acetone–Skellysolve B to give 19 (5.10 g, 98% yield): mp 109–110°; $[\alpha]^{27}D$ +60°; ir (KBr) 3470 (OH), 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.80 (s, CH_3), 3.66 (s, $COOCH_3$), 3.96 (s, OCH_3).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.77; H, 7.34.

(1*S*,2*S*,5*S*)-2-Hydroxy-5-(6-methoxy-2-naphthyl)-α,α,1-trimethylcyclopentaneethanol (20) —A solution of 19 (5.11 g, 15.6 mmol) in 150 ml of ether was added dropwise to a stirred solution of 100 ml of 3 *M* methylmagnesium bromide in ether and the mixture was stirred at room temperature for 16 hr and refluxed for 6 hr The reaction was quenched by the dropwise addition of 5% hydrochloric acid The mixture was diluted with 100 ml of benzene and the layers were separated The organic phase was dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give 20 (3.84 g, 73% yield): mp 189–190°; $[\alpha]^{25}D$ −10°; nmr ($CDCl_3$) δ 0.97 (s, CH_3), 1.23 (s, CH_3), 1.27 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.76; H, 8.63.

cis-Hexahydro-4-(6-methoxy-2-naphthyl)-2,2,3a-trimethyl-2*H*-cyclopenta[*b*]furan-6a-ol (21).—Jones'[10] reagent was added dropwise to a solution of 20 (3.34 g, 10.2 mmol) in 200 ml of acetone until the orange color persisted for 15 min. The excess reagent was destroyed by adding isopropyl alcohol dropwise until the orange color disappeared The mixture was diluted with 200 ml of water and concentrated *in vacuo*. The aqueous phase was extracted with benzene and the extracts were dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was removed *in vacuo* to give 3.65 g of a red oil which was chromatographed on 300 g of silica gel. The material which was eluted in the 2% ethyl acetate–98% benzene fractions was recrystallized from benzene–Skellysolve B to give 21 (1.25 g, 38% yield): mp 150–151.5°; $[\alpha]^{27}D$ −12°; ir (KBr) 3430 (OH), no absorption between 1650 and 1800 cm^{-1}; nmr ($CDCl_3$) δ 0.85 (s, CH_3), 1.43 (s, CH_3), 1.55 (s, CH_3), 3.92 (s, OCH_3).

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.45; H, 8.04.

Ethynylation of 21.—Acetylene[19] was bubbled through 50 ml of anhydrous tetrahydrofuran at −78° for 30 min. A 30-ml portion of 3 *M* ethylmagnesium bromide in ether was added, and the solution was slowly allowed to warm to room temperature. A solution of 21 (0.468 g, 1.43 mmol) in 20 ml of tetrahydrofuran was added dropwise, and the reaction mixture was stirred at room temperature under nitrogen for 19 hr. The reaction was quenched by the careful addition of 5% hydrochloric acid and the aqueous phase was extracted with ether. The extracts were dried over anhydrous magnesium sulfate and filtered. Solvent removal gave a white solid which was recrystallized from benzene–Skellysolve B to give 2 (0.430 g, 86% yield): mp 200–203°; nmr ($CDCl_3$) δ 1.07 (s, CH_3), 1.18 (s, CH_3), 1.32 (s, CH_3), 2.70 (s, C≡CH), 3.92 (s, OCH_3). Mixture melting point with a sample of 2 prepared by treatment of 14 with methyl Grignard reagent showed no depression, mp 202–205°.

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Registry No.—2, 42151-06-4; 3, 1035-77-4; 7, 42151-07-5; 8, 42151-08-6; 9, 42151-09-7 10, 42151-10-0; 12, 42151-11-1; 13, 42151-12-2; 14, 42151-13-3; 15, 42151-14-4; 16, 42151-15-5; 17, 42151-16-6; 18, 42151-17-7; 19, 42151-18-8; 20, 42151-19-9; 21, 42151-20-2; acetylene, 74-86-2; 2,2-dimethoxypropane, 77-76-9; methyl bromide, 74-83-9.

Reactions of N-Unsubstituted Arylsulfilimines with Acylating Agents and with Activated Halobenzenes, Alkynes, and Alkenes

YASUMITSU TAMURA,* KUNIHIRO SUMOTO, HIROSHI MATSUSHIMA, HIROSHI TANIGUCHI, AND MASAZUMI IKEDA

Faculty of Pharmaceutical Sciences, Osaka University, Toneyama, Toyonaka, Osaka, Japan

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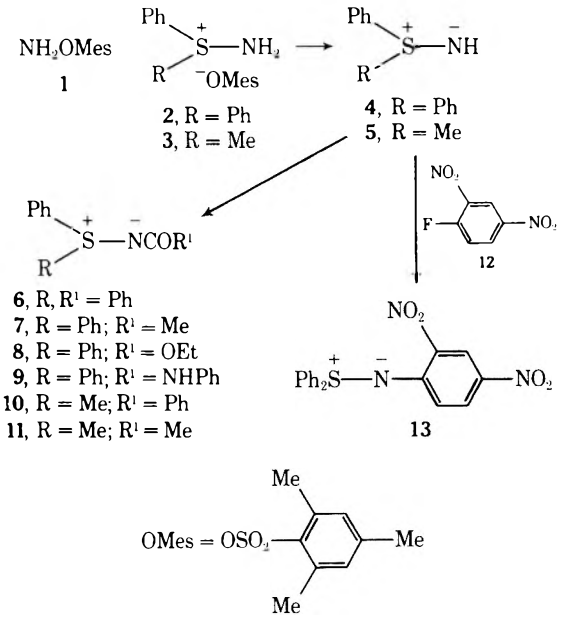
The arylsulfilimines (4 and 5) exhibit typical nucleophilicity in that they could be readily acylated with acylating agents and undergo substitution reactions with 2,4-dinitrofluorobenzene and Michael-type addition reactions with activated alkynes and alkenes under very mild conditions.

The previously investigated reactions of N-unsubstituted sulfilimines include oxidation,[1,2] hydrolysis,[1-3] thermolysis,[1-3] N-tosylation,[1-4] and reaction with carbon dioxide and carbon disulfide.[1] As our contribution to this relatively unexplored area, we have examined the nucleophilic reactions of the N-unsubstituted sulfilimine with acylating agents, 2,4-dinitrohalobenzenes, and some activated alkynes and alkenes. The present work was undertaken in part to explore the synthetic potential of sulfilimines, particularly as aminating reagents. It was also of interest to compare the physical and chemical properties of sulfilimines with those of other ylides such as sulfoximines and pyridinium *N*-imines. We chose diphenylsulfilimine (**4**) and methylphenylsulfilimine (**5**), which were conveniently synthesized by reaction of the corresponding sulfides with *O*-mesitylenesulfonylhydroxylamine (**1**) followed by anion exchange or base treatment.[4,5]

Reactions with Acylating Agents.—A simple and general method for N-acylation of sulfilimines is now reported. This procedure could be used as a route to the otherwise unavailable *N*-acylsulfilimines, for example, *N*-acylarylsulfilimines.[6] Thus, an ethanolic solution of arylsulfilimines (**4** and **5**) prepared by passing a solution of *S*-aminoarylsulfonium mesitylenesulfonates (**2** and **3**) in ethanol through anion exchange resin, was treated with acylating agents such as benzoyl chloride, acetic anhydride, ethyl chloroformate, or phenyl isocyanate to give the corresponding *N*-acylsulfilimines (**6**–**11**) in good to high yields (Scheme I).

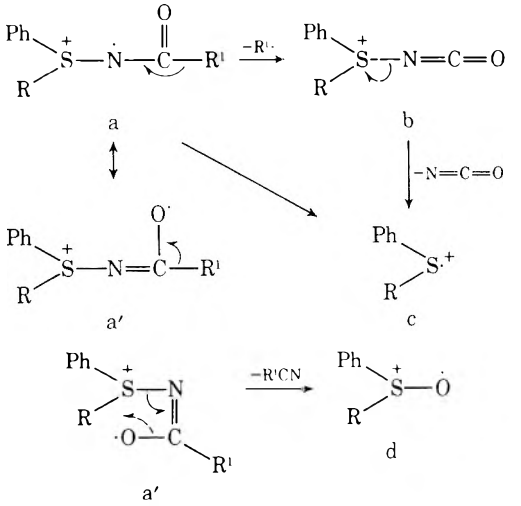
These *N*-acylsulfilimines showed ir carbonyl absorption bands characteristic of the betaine structures,[6-8] and uv absorption maxima at 217–231 nm, which were not affected by the nature of the acyl substituents, with the one exception of a phenylcarbamoyl group. Of particular interest is that the mass spectral behavior of *N*-acylarylsulfilimines (**6**–**11**) closely resembles that of *N*-acyliminopyridinium betaines.[9] Thus, the primary fragmentation process is α cleavage of the molecular

SCHEME I



ion a or a′ to give an ion b at *m/e* 228 (R = Ph) or 166 (R = Me). This ion b decomposes further by elimination of NCO to furnish a sulfide ion radical c at *m/e* 186 (R = Ph) or 124 (R = Me). The ion c may also be directly derived from the molecular ion by S–N bond fission. The other prominent peak observed in the upper mass range of *N*-benzoyl and *N*-acetyl derivatives (**6**, **7**, **10**, and **11**) is a sulfoxide ion d, which probably arises *via* a four-membered transition state (Scheme II).

SCHEME II

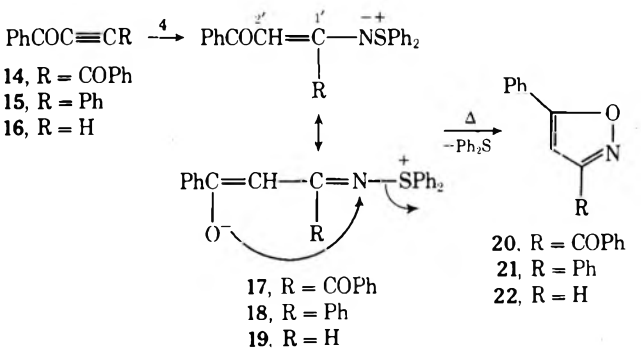


(1) R. Appel and W. Büchner, *Chem. Ber.*, **95**, 849, 855, 2220 (1962).
(2) J. B. Lambert, C. E. Mixan, and D. S. Bailey, *J. Amer. Chem. Soc.*, **94**, 208 (1972).
(3) N. Furukawa, T. Omata, T. Yoshimura, T. Aida, and S. Oae, *Tetrahedron Lett.*, 1619 (1972).
(4) Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Lett.*, 4137 (1972).
(5) Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, **38**, 1239 (1973).
(6) (a) H. Kise, G. F. Whitfield, and D. Swern, *Tetrahedron Lett.*, 1761 (1971); *J. Org. Chem.*, **37**, 1121 (1972). (b) G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, *Tetrahedron Lett.*, 3543 (1970).
(7) T. Okamoto and M. Hirobe, *J. Syn. Org. Chem.*, **26**, 746 (1968).
(8) Y. Tamura, Y. Miki, T. Honda, and M. Ikeda, *J. Heterocycl. Chem.*, **9**, 865 (1972).
(9) M. Ikeda, N. Tsujimoto, and Y. Tamura, *Org. Mass Spectrom.*, **5**, 61 (1971).

Reactions with 2,4-Dinitrohalobenzenes.—Under conditions similar to those employed for acylation, diphenylsulfilimine (**4**) failed to react with 2,4-dinitrochlorobenzene, but reacted readily with 2,4-dinitrofluorobenzene (**12**) to give *N*-(2,4-dinitrophenyl)diphenylsulfilimine (**13**) in 89% yield. This result suggests that **4** is a weaker nucleophile than pyridinium *N*-imine which undergoes a substitution reaction with 2,4-dinitrochlorobenzene.[10]

Reactions with Benzoylacetylenes.—Ylides such as sulfoxonium methylides[11] or sulfoximines[12] are known to undergo Michael addition reactions with acetylenic compounds. Diphenylsulfilimine (**4**) has now been shown to behave similarly to give 1:1 adducts. For example, when dibenzoylacetylene (**14**) was treated with **4** in chloroform at room temperature, the mixture immediately developed a yellow color. The nmr spectrum of the reaction mixture, monitored in $CDCl_3$, indicated that the reaction was complete in a few minutes. The adduct **17** was isolated as yellow crystals in 90% yield. In the same manner, benzoylphenylacetylene (**15**) or benzoylacetylene (**16**) each gave 1:1 adducts, **18** and **19**, in 68% yield (Scheme III).

SCHEME III

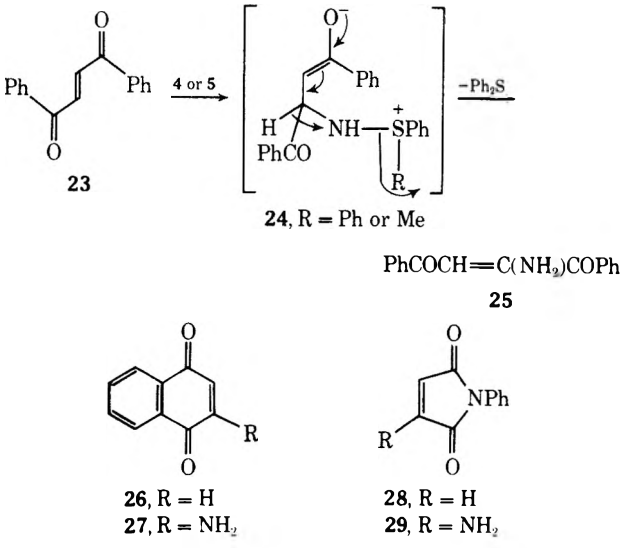


The structures of these adducts (**17–19**) were assigned on the basis of spectral data. For example, the adduct **19** exhibited two uv absorption maxima at 229 and 357 nm and has no carbonyl absorption bands above 1610 cm^{-1}, indicating that the carbonyl group is polarized. The nmr spectrum showed an AB type quartet at τ 3.6 (disappeared on treatment with D_2O) and 1.4 with a coupling constant of 13 Hz, which were assigned to $C_{2'}$ and $C_{1'}$ protons, respectively.

Confirmation of the structures of the adducts was provided by converting them into the corresponding known isoxazoles (**20–22**) in good yields by refluxing in chloroform for 1 hr. An analogous reaction is the transformation of 3-azidovinyl ketones into isoxazoles.[13]

Reactions with *trans*-1,2-Dibenzoylethylene, 1,4-Naphthoquinone, and *N*-Phenylmaleimide.—Treatment of **4** with *trans*-1,2-dibenzoylethylene (**23**) in chloroform at room temperature gave 1-amino-1,2-dibenzoylethylene (**25**) in 53% yield (Scheme IV). Similarly 1,4-naphthoquinone (**26**) and *N*-phenylmaleimide (**28**) gave the amine derivatives **27** and **29**, in 79 and 83% yields, respectively. Methylphenylsulfilimine (**5**) was also found to react with **23** in methanol to give the same product (**25**) in 90% yield. The formation of these amines (*e.g.*, **25**) presumably proceeds *via* initial addition of the sulfilimine **4** to the olefins (*e.g.*, **23**) giving an intermediate (*e.g.*, **24**), which undergoes a hydride shift to the nitrogen atom with concomitant S–N bond cleavage.

SCHEME IV



A formally analogous reaction has been reported by Sasaki and coworkers with *N*-ethoxycarbonyliminopyridinium betaine in the presence of acid.[14]

In contrast to the reaction of **4** with **23**, **26**, and **28**, the less activated olefins such as chalcone, benzylideneacetone, methyl vinyl ketone, or maleic anhydride failed to react with **4** even under refluxing conditions in chloroform; only unchanged starting material was recovered.

Reactions with Ethoxymethylene Derivatives of Malononitrile, Ethyl Cyanoacetate, Acetylacetone, and Tetracyanoethylene.—Diphenylsulfilimine (**4**) was observed to react readily with ethoxymethylene derivatives of malononitrile (**30**), ethyl cyanoacetate (**31**), and tetracyanoethylene (**32**) in chloroform at room temperature to give new stabilized diphenylsulfilimine derivatives (**33–35**) in high yields (Scheme V). Methylphenylsulfilimine (**5**) behaved analogously when a methanolic solution of **5** was treated with **30** and **31** to give the corresponding methylphenylsulfilimine derivatives (**36** and **37**). The structures of these products were evident on the basis of the elemental analyses and spectral evidence, the details of which are given in the Experimental Section. These reactions of the sulfilimines are analogous to those of the other ylides such as phosphonium ylides,[15] sulfoxonium ylides,[16] pyridinium ylides,[17] and pyridinium *N*-imines[18] and can be

(10) T. Okamoto, S. Hayashi, H. Horikiri, and M. Hirobe, *J. Pharm. Soc. Jap.*, **91**, 210 (1971).

(11) A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.*, **93**, 2471 (1971); A. G. Hortmann, *ibid.*, **87**, 4972 (1965); Y. Kishida and J. Ide, *Chem. Pharm. Bull.*, **15**, 360 (1967).

(12) T. R. Williams and D. J. Cram, *J. Amer. Chem. Soc.*, **93**, 7333 (1971); *J. Org. Chem.*, **38**, 20 (1973).

(13) U. Truck and H. Behringer, *Chem. Ber.*, **98**, 3020 (1965); F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967); K. Friederich and H. K. Thieme, *Chem. Ber.*, **103**, 1982 (1970).

(14) T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron*, **28**, 1470 (1972).

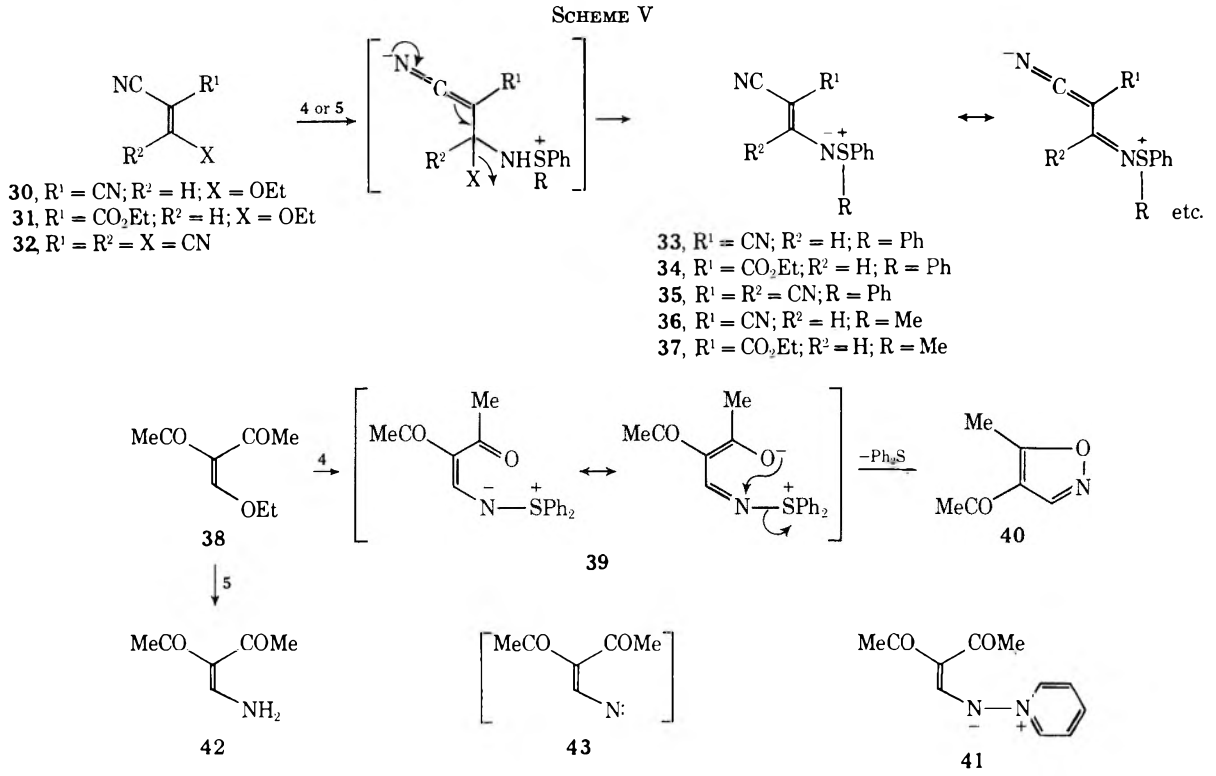
(15) S. Trippett, *J. Chem. Soc.*, 4733 (1962).

(16) G. B. Payne, *J. Org. Chem.*, **33**, 3517 (1968).

(17) Y. Tamura, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, in press.

(18) Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, in press.

SCHEME V



envisaged as proceeding by an addition–elimination mechanism.[19]

By contrast, similar treatment of **4** with 3-ethoxymethylenepentane-2,4-dione (**38**) in either chloroform or methanol gave the known 4-acetyl-5-methylisoxazole (**40**) and diphenyl sulfide. Since the related *N*-(2′,2′-diacetylvimylimino)pyridinium betaine (**41**)[18] has also been shown to undergo similar thermal reaction to form **40**, it may be assumed that the species **39** is an intermediate. This can undergo ring closure in concert with elimination of diphenyl sulfide to lead to the observed product **40**. On the other hand, when methylphenylsulfilimine (**5**) was treated with **38**, 3-aminomethylenepentane-2,4-dione (**42**) was obtained as the sole product in 78% yield. Although this is formally the product of hydrogen abstraction by a possible vinylnitrene (**43**) from solvent, we have at present no evidence to support the nitrene intermediate.

The greater stability of the cyanovinyl substituted sulfilimines (**33**–**37**) may be attributed to the enhanced charge distribution over the nitrile group.[20]

Experimental Section

Melting points are uncorrected. Nmr spectra were determined with a Hitachi R-20A spectrometer (tetramethylsilane as internal standard). Ir spectra were recorded with a Hitachi EPI-G2 spectrophotometer, and uv spectra with a Hitachi 124 spectrophotometer. Low- and high-resolution mass spectra were obtained with Hitachi RMU-6D and RMU-7M instruments, respectively, with a direct inlet system operating at 70 eV. Preparative layer chromatography (plc) was carried out on Merck alumina PF_{254}.

Diphenylsulfilimine (**4**). **A.**—A solution of 430 mg (2 mmol) of *O*-mesitylenesulfonylhydroxylamine (**1**, MSH) in 2 ml of CH_2Cl_2 was added to a solution of 372 mg (2 mmol) of diphenyl sulfide in 2 ml of CH_2Cl_2 with ice cooling. The reaction mixture was allowed to stand at room temperature for 30 min. After addition of ether, the precipitate was recrystallized from CH_2Cl_2–ether to give 720 mg (90%) of *S*-aminodiphenylsulfonium mesitylenesulfonate (**2**), mp 119–120°.

Anal. Calcd for $C_{21}H_{23}NO_3S_2$: C, 62.8; H, 5.8; N, 3.5. Found: C, 62.7; H, 5.8; N, 3.6.

A solution of the salt in methanol or ethanol was passed through a column of Amberlite IRA-410 ion-exchange resin (strong base, OH^- form) to give an alcoholic solution of **4**. Evaporation of the solvent under reduced pressure gave a white solid in quantitative yield, which was recrystallized from benzene–*n*-hexane (*ca.* 5:2): mp 69–71° (as the monohydrate) (lit.[3] mp 70°); uv max (EtOH) 226 nm (sh, log ε 4.11).

B.—A solution of 21.5 g (0.1 mol) of MSH (**1**) in 100 ml of CH_2Cl_2 was added to a solution of 18.6 g (0.1 mol) of diphenyl sulfide in 100 ml of CH_2Cl_2 dropwise with ice cooling. After standing at room temperature for 1 hr, 50 ml of 20% NaOH solution was added to the reaction mixture. The precipitated white solid was filtered off, and the organic layer was washed with water and dried over $MgSO_4$. The dried extract was concentrated to give 39.2 g (88%) of **4** which was recrystallized from benzene–*n*-hexane (*ca.* 5:2).

Methylphenylsulfilimine (**5**).—Using a similar procedure to that described in method A, *S*-aminomethylphenylsulfonium mesitylenesulfonate (**3**) was prepared from methyl phenyl sulfide and **1** in 72% yield, mp 110–111°.

Anal. Calcd for $C_{16}H_{21}NO_3S_2$: C, 56.6; H, 6.2; N, 4.1. Found: C, 56.3; H, 6.2; N, 4.3.

Treatment of **3** with ion-exchange resin gave an alcoholic solution of **5**, which was used for the further reaction, uv max (EtOH) 214 nm (sh).

General Procedure for Acylation.—An ethanolic solution of **4** or **5** prepared by treatment of 1 mmol of **2** or **3** with ion-exchange resin was added to a solution of 1 mmol of benzoyl chloride, acetic anhydride, ethyl chloroformate, or phenyl isocyanate in 3 ml of ether with stirring at room temperature. After being stirred for 1–2 hr, the reaction mixture was concentrated and the residue was purified by chromatography on alumina using $CHCl_3$ as solvent or recrystallization.

N-**Benzoyldiphenylsulfilimine** (**6**) was obtained from **4** and benzoyl chloride in 77% yield: mp 124–125° (from EtOH–ether); ir (KCl) 1595 (s), 1550 (s), 1330 cm^{-1} (s); uv max (EtOH) 231 nm (log ε 4.31), 254 (4.06); mass spectrum *m/e* (rel intensity) 305 (M^+, $C_{19}H_{15}NOS$, 3), 228 ($C_{13}H_{10}NOS$, b, 4), 212 ($C_{13}H_{10}NS$, 39), 202 ($C_{12}H_{10}OS$, d, 17), 186 ($C_{12}H_{10}S$, c, 63), 109 (C_6H_5S, 100), 105 (C_7H_5O, 35).

(19) S. Patai and S. Rappoport, "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, p 525.

(20) F. A. Cook and J. F. Moffatt, *J. Amer. Chem. Soc.*, **90**, 740 (1968).

Anal. Calcd for $C_{19}H_{15}NOS$: C, 74.7; H, 4.95; N, 4.6. Found: C, 74.7; H, 5.0; N, 4.5.

N-**Acetyldiphenylsulfilimine** (**7**) was obtained from **4** and acetic anhydride in 95% yield: mp 86–87° (from ether–AcOEt); ir (KCl) 1570 cm^{-1} (s); uv max (EtOH) 226 nm (sh, log ϵ 4.23); mass spectrum *m/e* (rel intensity) 243 (M^+, $C_{14}H_{13}NOS$ 3), 228 ($C_{13}H_{10}NOS$, b, 9), 204 ($C_{12}H_{12}OS$, 2), 202 ($C_{12}H_{10}OS$, d, 26), 186 ($C_{12}H_{11}S$, c, 100), 109 (C_6H_5S, 81).

Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.1; H, 5.4; N, 5.8. Found: C, 69.1; H, 5.4; N, 5.7.

N-**Ethoxycarbonyldiphenylsulfilimine** (**8**) was obtained from **4** and ethyl chloroformate in 44% yield: mp 88.5–89° (from EtOH–ether); ir (KCl) 1610 cm^{-1} (s); uv max (EtOH) 226 nm (sh, log ϵ 4.13); mass spectrum *m/e* (rel intensity) 273 (M^+, $C_{15}H_{15}NO_2S$, 8), 228 ($C_{13}H_{10}NOS$, b, 12), 200 ($C_{12}H_{10}NS$, 9), 186 ($C_{12}H_{10}S$, c, 100).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C 65.9; H, 5.5; N, 5.1. Found: C, 66.0; H, 5.4; N, 5.3.

N-(**Phenylcarbamoyl**)**diphenylsulfilimine** (**9**) was obtained from **4** and phenyl isocyanate in 83% yield: mp 133.5–135° (from AcOEt–*n*-hexane); ir (KCl) 3320 (m), 1610 cm^{-1} (s); uv max (EtOH) 242 nm (log ϵ 4.33); mass spectrum *m/e* (rel intensity) 320 (M^+, 4), 228 (b, 64), 200 (7), 186 (c, 100).

Anal. Calcd for $C_{19}H_{16}N_2OS$: C, 71.2; H, 5.0; N, 8.75. Found: C, 71.1; H, 5.1; N, 8.7.

N-**Benzoylmethylphenylsulfilimine** (**10**) was obtained from **5** and benzoyl chloride in 58% yield: mp 104.5–105° (from EtOH–ether); ir (KCl) 1590 cm^{-1} (s); uv max (EtOH) 229 nm (log ϵ 4.11), 253 (3.99); mass spectrum *m/e* (rel intensity) 243 (M^+, 2.2), 166 (b, 23), 150 (88), 140 (d, 63), 124 (c, 85), 109 (25), 105 (100).

Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.1; H, 5.4; N, 5.8. Found: C, 69.3; H, 5.5; N, 5.8.

N-**Acetylmethylphenylsulfilimine** (**11**) was obtained from **5** and acetic anhydride in 91% yield as an oil: ir (KCl) 1570 cm^{-1} (s); uv max (EtOH) 217 nm (sh, log ϵ 4.16); mass spectrum *m/e* (rel intensity) 181 (M^+, 2), 166 (b, 28), 140 (d, 63), 124 (c, 100), 109 (20); picrate mp 156–157.5° (from EtOH).

Anal. Calcd for $C_{15}H_{14}N_4O_8S$: C, 43.9; H, 3.4; N, 13.65. Found: C, 43.7; H, 3.5; N, 13.6.

N-(**2,4-Dinitrophenyl**)**diphenylsulfilimine** (**13**).—To an ethanolic solution of 220 mg of **4** was added 186 mg of 2,4-dinitrofluorobenzene (**12**). The reaction mixture was stirred at room temperature for 10 min and passed through a column of Amberlite IRA-410 ion-exchange resin. Evaporation of the solvent under reduced pressure gave 327 mg (89%) of a yellow solid of **13** which was recrystallized from benzene–EtOH: mp 133.5–134°; mass spectrum *m/e* (rel intensity) 367 (M^+, 2), 186 (100).

Anal. Calcd for $C_{18}H_{13}N_3O_4S$: C, 58.85; H, 3.6; N, 11.4. Found: C, 58.8; H, 3.5; N, 11.5.

N-(**1′,2′-Dibenzoylvinyl**)**diphenylsulfilimine** (**17**).—A solution of 41 mg of **4** in 1 ml of $CHCl_3$ was added to a solution of 43 mg of dibenzoylacetylene (**14**) in 1 ml of $CHCl_3$. After 5 min at room temperature, the solvent was evaporated to give 77 mg (90%) of yellow crystals, which were recrystallized from benzene: mp 131–133°; ir (KCl) 1670 (s), 1610 cm^{-1} (m); uv max (EtOH) 248 nm (log ϵ 4.13), 358 (3.96); nmr ($CDCl_3$) 1.85–2.95 (20 H, aromatic protons), 3.67 (1 H, s, olefinic proton); mass spectrum *m/e* (rel intensity), no M^+, 249 (3), 186 (47), 105 (100).

Anal. Calcd for $C_{28}H_{21}NO_2S$: C, 77.2; H, 4.9; N, 3.2. Found: C, 76.9; H, 4.8; N, 3.35.

N-(**2′-Benzoyl-1′-phenylvinyl**)**diphenysulfilimine** (**18**).—Using a procedure similar to that described for **17**, this compound was obtained from 110 mg of **4** and 103 mg of benzoylphenylacetylene (**15**) in 68% yield as hygroscopic yellow needles: mp 119–122° (from benzene); ir (KCl) 1595 cm^{-1} (m); uv max (EtOH) 248 nm (sh, log ϵ 4.37), 380 (4.11); olefinic proton signal overlaps the aromatic proton multiplets; mass spectrum *m/e* (rel intensity) 407 (M^+, 1), 221 (36), 186 (100).

Anal. Calcd for $C_{27}H_{21}NOS$: C, 79.55; H, 5.2; N, 3.4. Found: C, 79.05; H, 5.15; N, 3.4.

N-(**2′-Benzoylvinyl**)**diphenylsulfilimine** (**19**).—Using a procedure similar to that described for **17**, this compound was obtained from 219 mg of **4** and 130 mg of benzoylacetylene (**16**) in 68% yield after purification by plc using $CHCl_3$ as a yellow oil which rapidly turned brown: ir (KCl) 1605 cm^{-1} (m); uv max (EtOH) 230, 357 nm. Satisfactory elemental analysis was not obtained owing to instability.

Thermal Reaction of *N*-(**1′,2′-Dibenzoylvinyl**)**diphenylsulfilimine** (**17**).—A solution of 44 mg of **17** in 3 ml of $CHCl_3$ was refluxed for 1 hr until the starting material disappeared on tlc. After evaporation of the solvent, the residual oil was submitted to plc using benzene as solvent to give 18.7 mg (75%) of 3-benzoyl-5-phenylisoxazole (**20**) [mp 81–82° (lit.[13] mp 80–82°); ir (KCl) 1650 (s), 1595 (m), 1570 (m), 1445 cm^{-1} (s)] in addition to diphenyl sulfide (98%).

Thermal Reaction of *N*-(**2′-Benzoyl-1′-phenylvinyl**)**diphenylsulfilimine** (**18**).—Treatment of **18** as described above gave diphenyl sulfide (64%) and 3,5-diphenylisoxazole (**21**, 54%): mp 142–143° (lit.[13] mp 141–143°); ir (KCl) 1610 (m), 1590 (m), 1570 (m), 1485 (m), 1445 cm^{-1} (s).

Thermal Reaction of *N*-(**2′-Benzoylvinyl**)**diphenylsulfilimine** (**19**).—Treatment of **19** as described above gave diphenyl sulfide (87%) and 5 phenylisoxazole (72%) as an oil which was identified by uv, ir, and nmr spectra.

1-Amino-1,2-dibenzoylethylene (**25**).—A solution of 219 mg of **4** in 3 ml of $CHCl_3$ was added to a solution of 230 mg of *trans*-1,2-dibenzoylethylene (**23**) in 3 ml of $CHCl_3$. The reaction mixture was allowed to stand for 30 min at room temperature. Evaporation of the solvent under reduced pressure gave a mixture of two products, which were separated by plc using benzene–cyclohexane as solvent to give diphenyl sulfide (87%) and 1-amino-1,2-dibenzoylethylene (**25**, 53%), mp 136–137° (lit.[21] mp 137.5–138.5°). Replacing the solvent with methanol gave **25** in 90% yield.

2-Amino-1,4-naphthoquinone (**27**).—Mixing 219 mg of **4** and 158 mg of 1,4-naphthoquinone (**26**) in 3 ml of $CHCl_3$ gave a red colored solution, from which red crystals precipitated. After 30 min, the crystals were collected and recrystallized from benzene to give red needles of 2-amino-1,4-naphthoquinone (**27**) in 79% yield: mp 205–208° (lit.[22] mp 207°); ir (KCl) 3370 (m), 3200 (m), 1680 (m), 1615 (s), 1560 cm^{-1} (s).

2-Amino-*N***-phenylmaleimide** (**29**).—In a way similar to that described for **25**, 2-amino-*N*-phenylmaleimide (**29**) was obtained from 219 mg of **4** and 173 mg of *N*-phenylmaleimide (**28**) in 82% yield: mp 108° (from benzene); ir ($CHCl_3$) 3490 (m), 3380 (m), 1715 (s), 1655 cm^{-1} (s); uv max (EtOH) 233 nm (log ϵ 4.31), 258 (4.03), 360 (3.45); nmr ($CDCl_3$) τ 2.50–3.00 (5 H, m, aromatic protons), 4.70–5.00 (2 H, NH_2), 4.90 (1 H, s, olefinic proton).

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9. Found: C, 63.9; H, 4.4; N, 14.6.

General Procedure for *N*-(**2′-Cyanovinyl**)**diphenylsulfilimines** (**33–35**).—A solution of 1 mmol of **4** in 3 ml of $CHCl_3$ was added to a solution of 1 mmol of the cyano olefins **30–32** in 2 ml of $CHCl_3$ and the reaction mixture was allowed to stand at room temperature for 10 min. The solvent was evaporated and the product was purified by plc using $CHCl_3$ as solvent and recrystallization from $CHCl_3$–petroleum ether (bp 30–60°).

N-(**2,′2′-Dicyanovinyl**)**diphenylsulfilimine** (**33**) was obtained from **4** and ethoxymethylenemalononitrile[23] (**30**) in 40% yield as white needles: mp 129–131°; ir (KCl) 2150 (s), 1520 cm^{-1} (s); uv max (EtOH) 230 nm (sh, log ϵ 4.10), 295 (4.35); nmr ($CDCl_3$) τ 1.85 (1 H, s, olefinic proton), 2.20–2.60 (10 H, m, aromatic protons); mass spectrum *m/e* (rel intensity) 277 (M^+, 1), 186 (100).

Anal. Calcd for $C_{16}H_{11}N_3S$: C, 69.3; H, 4.0; N, 15.15. Found: C, 69.5; H, 4.1; N, 14.8.

N-(**2′-Cyano-2′-ethoxycarbonylvinyl**)**diphenylsulfilimine** (**34**) was obtained from **4** and ethyl 2-cyano-3-ethoxyacrylate[24] in 71% yield as white needles: mp 169–172°; ir (KCl) 2200 (s), 1680 cm^{-1} (m); uv max (EtOH) 230 nm (sh, log ϵ 4.16), 300 (4.46); nmr ($CDCl_3$) τ 1.30 (1 H, s, olefinic proton), 2.1–2.6 (10 H, m, aromatic protons), 5.79 (2 H, q, J = 7 Hz, OCH_2CH_3), 8.70 (3 H, t, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* (rel intensity) 324 (M^+, 1), 186 (69), 171 (100).

Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.7; H, 5.0; N, 8.6. Found: C, 66.7; H, 5.2; N, 8.4.

N-(**1′,2′,2′-Tricyanovinyl**)**diphenylsulfilimine** (**35**) was obtained from **4** and tetracyanoethylene (**32**) in 87% yield as yellow needles: mp 139–140°; ir (KCl) 2200 cm^{-1} (s); uv max (EtOH) 240 nm (sh, log ϵ 4.01), 342 (4.27); nmr ($CDCl_3$) τ 2.0–2.6 (m, aromatic protons); mass spectrum *m/e* (rel intensity) 302 (M^+, 3), 186 (100).

(21) R. E. Lutz, T. Amacker, S. M. King, and N. G. Shearer, *J. Org. Chem.*, **16**, 191 (1950).

(22) K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.*, 4003 (1954).

(23) T. Passalacqua, *Gazz. Chim. Ital.*, **43** (II), 566 (1913).

(24) de Bollemont, *C. R. Acad. Sci.*, **128**, 1340 (1899).

Anal. Calcd for $C_{17}H_{10}N_4S$: C, 67.5; H, 3.3; N, 18.5. Found: C, 67.4; H, 3.3; N, 18.3.

A General Procedure for *N*-(2′-Cyanovinyl)methylphenylsulfilimines (36, 37).—A methanolic solution of 1 mmol of **5** was added to a methanolic solution of 1 mmol of the cyano olefins **30** or **31** and the reaction mixture was allowed to stand at room temperature for 30 min. The solvent was evaporated and the residue was purified by plc using $CHCl_3$ as solvent and recrystallization from benzene–ether.

N-(2′,2′-Dicyanovinyl)methylphenylsulfilimine (36) was obtained from **5** and **30** in 96% yield as white plates: mp 149–150°; ir (KCl) 2150 (s), 1525 cm^{-1} (s); uv max (EtOH) 218 nm (sh, log ϵ 3.85), 292 (4.23); nmr ($CDCl_3$) τ 2.0 (1 H, s, olefinic proton), 2.1–2.6 (5 H, m, aromatic protons), 7.0 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 215 (M^+, 12) 124 (100).

Anal. Calcd for $C_{11}H_9N_3S$: C, 61.4; H, 4.2; N, 19.5. Found: C, 61.15; H, 4.3; N, 19.4.

N-(2′-Cyano-2′-ethoxycarbonylvinyl)methylphenylsulfilimine (37) was obtained from **5** and **31** in 71% yield as white needles: mp 117–118°; ir (KCl) 2180 (s), 1650 cm^{-1} (m); uv max (EtOH) 215 nm (sh, log ϵ 4.20), 296 (4.48); nmr ($CDCl_3$) τ 1.42 (1 H, s, olefinic proton), 2.1–2.6 (5 H, m, aromatic protons), 5.84 (2 H, q, J = 7 Hz, OCH_2CH_3), 6.95 (3 H, s, CH_3), 8.75 (3 H, t, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* (rel intensity) 262 (M^+, 2), 124 (100).

Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.5; H, 5.4; N, 10.7. Found: C, 59.7; H, 5.5; N, 10.4.

Reaction of 4 with 3-Ethoxymethylenepentane-2,4-dione (38). A solution of 1 mmol of **4** in 5 ml of $CHCl_3$ was added to a solution of 1 mmol of 3-ethoxymethylenepentane-2,4-dione (**38**)[25] in 5 ml of $CHCl_3$ and the reaction mixture was allowed to stand at room temperature for 10 min. The solvent was evaporated under reduced pressure and the residual oil was submitted to plc using benzene to give diphenyl sulfide (78%) and 4-acetyl-5-methylisoxazole (**40**)[18] (57%) as an oil. Replacing the solvent with methanol gave the similar result.

Reaction of 5 with 38.—Using a similar procedure described for the reaction of **4** with **38**, the reaction of **5** and **38** gave 3-aminomethylpentane-2,4-dione (**42**) in 78% yield, mp 145–145.5° (from benzene–methanol) (lit.[26] mp 142–144°), in addition to methyl phenyl sulfide.

Acknowledgment.—We thank Mr. Y. Kato of Hitachi Ltd. for determination of high-resolution mass spectra.

Registry No.—**1**, 36016-40-7; **2**, 39149-53-6; **3**, 39149-52-5; **4**, 36744-90-8; **5**, 42397-39-7; **6**, 39149-60-5; **7**, 42397-41-1; **8**, 39149-62-7; **9**, 42397-43-3; **10**, 42397-44-4; **11**, 42397-45-5; **12**, 70-34-8; **13**, 39149-63-8; **14**, 1087-09-8; **15**, 7338-94-5; **16**, 2632-15-2; **17**, 42397-48-8; **18**, 42397-49-9; **19**, 42397-50-2; **20**, 3672-49-9; **21**, 2039-49-8; **26**, 130-15-4; **27**, 2348-81-4; **28**, 941-69-5; **29**, 34314-68-6; **30**, 123-06-8; **31**, 94-05-3; **32**, 670-54-2; **33**, 42397-54-6; **34**, 42397-55-7; **35**, 42397-56-8; **36**, 42397-57-9; **37**, 42397-58-0; diphenyl sulfide, 139-66-2; methyl phenyl sulfide, 100-68-5; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7; ethyl chloroformate, 541-41-3; phenyl isocyanate, 103-71-9; ethyl 2-cyano-3-ethoxyacrylate, 94-05-3.

(25) L. Claisen, *Justus Liebigs Ann. Chem.*, **297**, 1 (1897).

(26) K. R. Huffman, F. C. Schaefer, and G. A. Peters, *J. Org. Chem.*, **27**, 551 (1962).

Synthesis and Properties of *N*-(Alkyl- and arylsulfinyl)phthalimides. A New Class of Sulfinyl-Transfer Reagents[1]

DAVID N. HARPP* AND THOMAS G. BACK

Department of Chemistry, McGill University, Montreal, Canada

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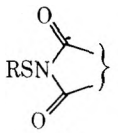
The synthesis and properties of *N*-(alkyl- and arylsulfinyl)phthalimides are described. These materials are converted in high yield to sulfinamides and sulfinate esters on treatment with amines and alcohols, respectively. The mass spectral behavior of the title compounds was also investigated in some detail.

The utility of thioimides **1** as sulfenyl-transfer reagents has been adequately demonstrated in the last few years.[2]



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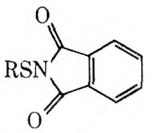

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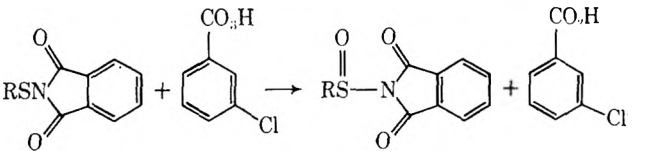
Recently we reported[3] that thiophthalimides **2** may be conveniently oxidized to the corresponding sulfinylphthalimides **3** with *m*-chloroperbenzoic acid.



2 3

Our continued investigation of sulfinylphthalimides has shown that these novel compounds possess extremely desirable properties as sulfinyl-transfer agents in much the same way as thioimides which transfer divalent sulfur. The title compounds are conveniently prepared in high yield from readily available thiophthalimides.[4] Furthermore, they are crystalline solids which are far more stable than comparable sulfinyl derivatives such as sulfinyl chlorides.[5] Also, sulfinylphthalimides react rapidly with nucleophiles, resulting in displacement of the phthalimide anion and formation of the corresponding sulfinyl derivative.

N-(Alkyl- and arylsulfinyl)phthalimides are prepared by the dropwise addition of 1 equiv of *m*-chloroper-

(1) Organic Sulfur Chemistry. XVII. For part XVI, see D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 5313 (1972).

(2) (a) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970); (b) D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig, W. F. VanHorn, and J. P. Snyder, *ibid.*, 3551 (1970); (c) D. N. Harpp and T. G. Back, *J. Org. Chem.*, **36**, 3828 (1971); (d) D. H. R. Barton, G. Page, and D. A. Widdowson, *Chem. Commun.*, 1466 (1970); (e) K. S. Boustany, *Chimia*, 396 (1970); (f) D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 4953 (1971); (g) Y. Abe and J. Tsurugi, *Chem. Lett.*, 441 (1972); (h) D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 1481 (1972); (i) T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *ibid.*, 5115 (1970); (j) T. Mukaiyama and K. Saigo, *Bull. Chem. Soc. Jap.*, **44**, 3077 (1971); (k) T. Mukaiyama, S. Kobayashi, K. Kamio, and H. Takei, *Chem. Lett.*, 237 (1972).

(3) D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 5313 (1972).

(4) Thiophthalimides may be prepared in high yield from thiols or disulfides; see (a) M. Behforouz and J. E. Kerwood, *J. Org. Chem.*, **34**, 51 (1969); (b) K. H. Buchel and A. Conte, *Chem. Ber.*, **100**, 1248 (1967).

(5) I. B. Douglass and D. A. Koop, *J. Org. Chem.*, **29**, 951 (1964).

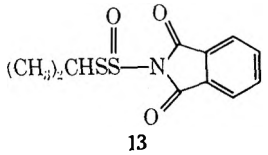
benzoic acid to a cooled (0°) solution of the thiophthalimide in chloroform. When performed at room temperature, the reaction provides slightly lower yields. The desired compounds are easily separated from the by-product *m*-chlorobenzoic acid by trituration with ether, which dissolves the highly soluble acid but not the required product. After filtering, further purification is effected by recrystallization from chloroform–petroleum ether (bp 30–60°) or chloroform–ether. In the case of hindered sulfinylphthalimides, the *m*-chlorobenzoic acid is removed by washing the chloroform solution with 5% sodium bicarbonate. However, when bulky substituent groups are not present, this purification procedure results in rapid decomposition with formation of phthalimide. All sulfinylphthalimides produced are listed in Table I along with yields and physical data.

TABLE I
PREPARATION OF *N*-(ALKYL-, ARYL-, AND THIOSULFINYL)PHTHALIMIDES

Compd	R	Method[a,b]	Yield, %	Mp, °C
4	$C_6H_5CH_2$	B	96	154–155
5	CH_3	A	91	167–170
6	C_2H_5	A	85	132–134
7	*i*-C_3H_7	B	94	125–127
8	*n*-C_4H_9	A	80	87–88
9	*t*-C_4H_9	B	100	133–136
10	C_6H_5	A	89	150–153
11	*p*-$CH_3C_6H_4$	A	92	191–194
12	CH_3OCCH_2 (O ‖)	A	87	135–136
13	*i*-C_3H_7S	A	87	93–94

[a] Method A, *m*-chlorobenzoic acid was removed by ether trituration; method B, acid was removed with 5% sodium bicarbonate solution. [b] In method A, significant second crops of product were sometimes obtained by cooling the ether filtrate.

In addition, isopropyl phthalimido disulfide[6] was similarly oxidized to the thiosulfinylphthalimide **13** in 87% yield.



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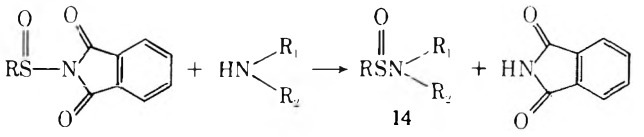
Evidence that oxidation occurs at the sulfur atom adjacent to the phthalimide group derives from nmr and mass spectral data (*vide infra*).

Preparation of Sulfinamides.—We have found that the aminolysis of sulfinylphthalimides provides a clean, rapid route for the synthesis of sulfinamides **14**. The latter compounds have traditionally been prepared by the reaction of sulfinyl chlorides with amines[7] or by the treatment of thionylamines with Grignard reagents.[8] Unfortunately, these methods often provide low yields owing to unstable precursors and concomitant side reactions. However, when sulfinylphthalimides react with primary or secondary amines in inert solvents such as carbon tetrachloride or benzene, high yields of the corresponding sulfinamides (**14**) are obtained.



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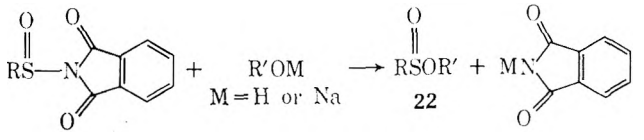
It is interesting to note that aniline, an aromatic amine, is sufficiently nucleophilic to generate sulfinanilide **21** in 88% yield. Filtration of phthalimide from the reaction mixture, followed by removal of the solvent *in vacuo*, provides the crude sulfinamide in quantitative yield. Traces of remaining phthalimide may be removed from the product by distillation or crystallization. The sulfinamides prepared by this method are listed in Table II.

Preparation of Sulfinate Esters.—The most frequently used method for preparing sulfinate esters **22** involves the alcoholysis of sulfinyl chlorides.[9] Aromatic sulfinate esters have also been prepared by the oxidation of disulfides or thiols with lead tetraacetate.[10] More recently, these compounds have been produced by the reaction of sodium sulfinates with chlorocarbonates in alcohols,[11] and by coupling sulfinic acids with alcohols using dicyclohexylcarbodiimide.[12] With the exception of the last method, these procedures all suffer from low yields and attendant side reactions.

We wish to report that sulfinylphthalimides are excellent precursors of sulfinate esters. They react with solutions of alkoxides in alcohols at room temperature to provide the products in high yield. Alternately, the alcoholysis may be accomplished by simply refluxing the sulfinylphthalimide in the appropriate alcohol. The latter method affords sulfinate esters in nearly quantitative yields and in a high state of purity.



22

In either procedure, the desired sulfinate esters are isolated by filtration of the insoluble material, evaporation of the alcohol *in vacuo*, and extraction of the product from the remaining residue with pentane. In the case of less soluble sulfinate esters (*e.g.*, **28**), it is advantageous to use 10% methylene chloride–pentane in the extraction step. The product obtained by removal of solvent under reduced pressure is generally pure as verified by tlc. Products are listed in Table III with yields and physical data.

An anomalous result was observed when *N*-(*tert*-butylsulfinyl)phthalimide (**9**) was treated with sodium isopropoxide solution. Rather than effecting displace-

(6) D. N. Harpp and D. K. Ash, *Int. J. Sulfur Chem., Part A*, **1**, 57 (1971).

(7) (a) L. C. Raiford and S. E. Hazlet, *J. Amer. Chem. Soc.*, **57**, 2172 (1935); (b) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **23**, 805 (1958).

(8) (a) H. Gilman and H. L. Morris, *J. Amer. Chem. Soc.*, **48**, 2399 (1926); (b) D. Klamann, C. Sass, and M. Zelenka, *Chem. Ber.*, **92**, 1910 (1959).

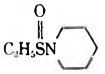
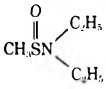
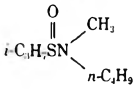
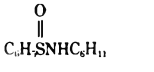
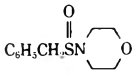
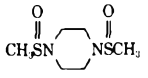
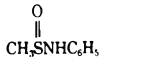
(9) (a) H. Phillips, *J. Chem. Soc.*, 2552 (1925); (b) I. B. Douglass, *J. Org. Chem.*, **30**, 633 (1965); (c) J. W. Wilt, R. G. Stein, and W. J. Wagner, *J. Org. Chem.*, **32**, 2097 (1967).

(10) L. Field, C. B. Hoelzel, and J. M. Locke, *J. Amer. Chem. Soc.*, **84**, 847 (1962).

(11) M. Kobayashi and M. Terao, *Bull. Chem. Soc. Jap.*, **39**, 1292 (1966).

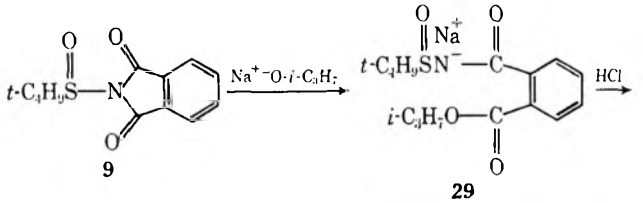
(12) Y. Miyaji, H. Minato, and M. Kobayashi, *Bull. Chem. Soc. Jap.*, **44**, 862 (1971).

TABLE II
PREPARATION OF SULFINAMIDES

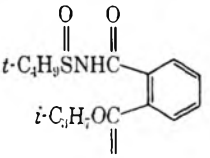
Compd	Sulfinamide	Yield, %	Solvent[a] (time, hr)	Mp or bp, °C (mm)	Lit. mp or bp, °C (mm)	n^{23}
15		77	CCl_4(1)	60–61 (0.1)		1.4964
16		80	CCl_4(1)	51–52 (0.9)	55 (1.8)[c]	1.4635
17		80	CCl_4(1)	56–57 (0.08)		1.4619
18		89	C_6H_6(0.5)[b]	114–115	116[d]	
19		94	C_6H_6(1)	83–85		
20		77	CCl_4(1)	149–154		
21		88	C_6H_6(12)	84–87	86–88[e]	

[a] Reaction of 19 was refluxed; all others were performed at room temperature. [b] The sulfinylphthalimide solution was added dropwise over 10 min to the amine solution. [c] Y. H. Chiang, J. S. Luloff, and E. Schipper, *J. Org. Chem.*, **34**, 2397 (1969). [d] Reference 8b. [e] Reference 7b.

ment of the phthalimide group, the alkoxide caused ring opening as depicted below.



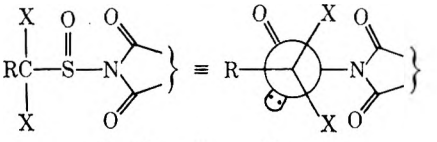
9 29



30

The sodium salt **29** was obtained in 90% yield and on acidification with HCl gave amide **30**. In addition to appropriate aliphatic signals, the latter compound showed a broad peak in the nmr spectrum at τ 1.9 (>NH) which was absent in product **29**. Furthermore, this peak disappeared on addition of D_2O. The identity of compound **30** was confirmed by a correct elemental analysis. It appears that, when the substituent group of the sulfinylphthalimide is bulky, the approaching alkoxide is diverted from the usual attack on sulfur to the less hindered carbonyl carbon atom. An analogous reaction might also explain the somewhat lower yield of sulfinate ester **25**, where isopropyl groups on both the nucleophile and the substrate create sufficient steric hindrance to allow some attack at carbon to take place. The reaction shown above is similar to the ring opening of thiophthalimides by certain primary amines.[2f,13]

Nmr Spectra of Sulfinylphthalimides, Sulfinamides, and Sulfinate Esters.—It has been well established that the sulfur atom of sulfinyl compounds constitutes a chiral center. As a result, geminal substituents in the proximity of a sulfinyl moiety possess a diastereotopic relationship which may manifest itself as observed nonequivalence in the nmr spectrum. Such effects have been previously reported in a variety of sulfinyl derivatives, including sulfoxides,[14] sulfinate esters,[15] sulfinamides,[16] and sulfinyl chlorides.[17] Our studies on the nmr spectra of sulfinylphthalimides have revealed that the three compounds shown below display complex spectra attributable to the presence of the sulfinyl group.



Compd	R	X
4	C_6H_5	H
7	H	CH_3
12	CH_3OC (O)	H

The methylene protons of the benzyl (**4**) and carbomethoxymethyl (**12**) derivatives exhibited AB quartets and the isopropyl group of product **7** showed nonequivalent methyl protons, as evidenced by the presence of two doublets in the spectrum. These doublets remained unchanged on heating to 100°. The α-methylene group in *N*-(*n*-butylsulfinyl)phthalimide (**8**) showed a crude triplet which might have shown further splitting with better resolution and the ethyl de-

(13) K. S. Boustany and J. P. VanderKooi, *Tetrahedron Lett.*, 4983 (1970).

(14) A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *J. Amer. Chem. Soc.*, **87**, 5498 (1965).

(15) (a) J. S. Waugh and F. A. Cotton, *J. Phys. Chem.*, **65**, 562 (1961); (b) M. Oki and H. Iwamura, *Bull. Chem. Soc. Jap.*, **35**, 1428 (1962); (c) J. W. Wilt and W. J. Wagner, *Chem. Ind. (London)*, 1389 (1964).

(16) R. M. Moriarty, *J. Org. Chem.*, **30**, 600 (1965).

(17) G. Canalini and G. Maccagnani, *Tetrahedron Lett.*, 3035 (1971).

TABLE III
PREPARATION OF SULFINATE ESTERS

Compd	Sulfinate ester	Yield, %	Method[a] (time, hr)	Bp, °C (mm)	Lit. bp, °C (mm)	Refractive index
23	n-$C_4H_9S(O)OCH_3$	80	A (0.5)	84–85 (12)	72–73 (10)[h]	n^{23} 1.4430[e]
24	$C_6H_5S(O)OC_2H_5$	86	A (0.5)	56–57 (0.05)	58 (0.05)[i]	n^{23} 1.5315[f]
25	i-$C_3H_7S(O)$-i-C_3H_7	63	A (0.5)	58–59 (9)	c	n^{22} 1.4325
26	$C_6H_5S(O)OCH_3$	90	A (0.5)	*b*		n^{25} 1.5432[g]
		95	B (2)	43–44 (0.07)	47.5–51 (0.2)[j]	
27	$C_6H_5CH_2S(O)OC_2H_5$	97	B (3)	69–71 (0.025)		n^{22} 1.5362
28	$CH_3OC(O)CH_2S(O)OCH_3$	93	B (2)	59–61 (0.1)	*d*	n^{22} 1.4585

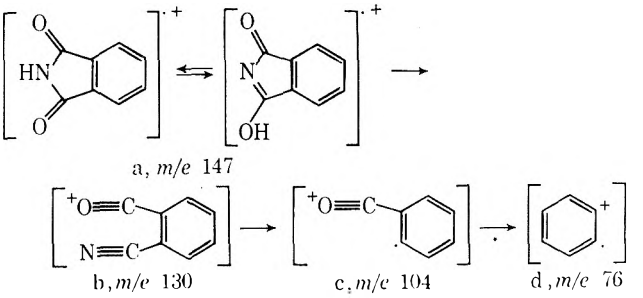
[a] Method A, the precursor was treated with alkoxide in alcohol at room temperature; method B, alcoholysis was achieved by refluxing with the alcohol. [b] The product had ir, nmr, and refractive index identical with those of samples prepared by method B and by the procedure of Douglass (ref 9b). [c] Only the nmr spectrum is reported in the literature: F. Seel, J. Bondier, and W. Gombler, *Chem. Ber.*, **102**, 443 (1969). [d] The preparation of this compound is reported in the literature but no physical data are furnished: D. O. DePree, U. S. Patent 3,014,069 (1958); *Chem. Abstr.*, **56**, 14085*b* (1962). [e] Lit.[9b] n^{25} 1.4438. [f] Lit. n^{20} 1.5308: J. Michalski, T. Modro, and J. Wieczorkowski, *J. Chem. Soc.*, 1665 (1960). [g] Lit.[9b] n^{25} 1.5437. [h] Reference 9b. [i] See Michalski, *et al.* (footnote *f*). [j] Reference 10.

rivative **6** displayed no splitting beyond a quartet for the geminal protons. Although complex spectra might be expected in the last two instances, their absence can be the result of negligible differences in the conformer populations and a low intrinsic diastereomerism.[18]

The nmr spectrum of *N*-[*S*-(isopropylthio)sulfinyl]-phthalimide (**13**) shows a single doublet attributable to the two methyl groups as well as a heptet from the methine proton at τ 6.6. The latter shift compares favorably with that of an isopropyl methine proton adjacent to divalent sulfur, but is considerably further upfield than that of a similar proton next to a sulfinyl moiety. For example, the chemical shifts of the methine protons in isopropyl phthalimido disulfide and in *N*-(isopropylsulfinyl)phthalimide are τ 6.7 and 5.5, respectively. These observations strongly support the proposed structure **13** in which the isopropyl group is adjacent to sulfenyl rather than sulfinyl sulfur.

None of the sulfinate esters in Table III show complex splitting arising from nonequivalent groups in the substituent attached to sulfur. The benzyl methylene group of **27** and the geminal protons of **28** both appear as singlets, while the methyl groups in the isopropyl moiety adjacent to sulfur in **25** display one doublet. On the other hand, groups attached to oxygen often show further splitting. For example, the methylene group of ester **24** provides a 16-line spectrum[15a] while the methyl hydrogens of the isopropyl group adjacent to oxygen in sulfinate ester **25** display two doublets revealing their diastereotopic nature. The ethyl methylene group of ester **27**, however, shows only a quartet. The nmr spectra of all other compounds listed in Tables I–III are consistent with their structures.

Mass Spectra of Sulfinylphthalimides.—Since mass spectral studies of sulfinyl compounds have rarely been reported in the literature,[19] we felt it instructive to study the electron-impact fragmentations of sulfinylphthalimides (Table IV). We observed that all products in Table I display parent peaks varying in relative intensity from <1% in the isopropyl, *n*-butyl, and *tert*-butyl derivatives (**7**, **8**, **9**) to 29% in the methyl analog **5**. All sulfinylphthalimides also show intense peaks at *m/e* 147, 130, 104, and 76 likely arising from fragments a–d. The loss of CO from c is also manifested by a metastable peak at *m/e* 55.5.



The occurrence of fragments a–d has also been reported in the mass spectra of thiophthalimides[2c,20] and alkyl phthalimido disulfides.[6]

Cleavage of the C–S bond in sulfinylphthalimides with the charge remaining on either the carbon or the

(18) M. Raban, *Tetrahedron Lett.*, 3105 (1966). It is interesting to note that, when the phthalimide moiety of sulfinylphthalimide **4** was replaced by morpholine to give sulfinamide **19**, the AB pattern of the former was observed as a singlet which remained unsplit in a variety of solvents and on cooling to −45°. Similarly, it has been reported that the methylene protons of benzylsulfinyl chloride appear as a singlet, a fact attributed by the authors to conformational equilibria and low intrinsic asymmetry.[17]

(19) (a) J. Ø. Madsen, C. Nolde, S. O. Lawesson, G. Schroll, J. H. Bowie, and D. H. Williams, *Tetrahedron Lett.*, 4377 (1965); (b) J. H. Bowie, F. C. V. Larsson, G. Schroll, S. O. Lawesson, and R. G. Cooks, *Tetrahedron*, **23**, 3743 (1967); (c) W. H. Baarschers and B. W. Krupay, *Can. J. Chem.*, **51**, 156 (1973); (d) S. Kozuka, H. Takahashi, and S. Oae, *Bull. Chem. Soc. Jap.*, **43**, 129 (1970). A detailed description of the fragmentation of sulfinamides and sulfinate esters will be reported separately.

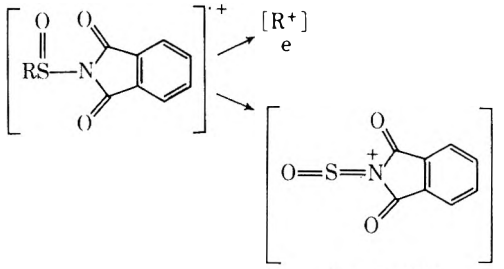
(20) B. A. Orwig, M.S. Thesis, McGill University, 1970.

TABLE IV
MASS SPECTRA OF N-(ALKYL-, ARYL-, AND THIOSULFINYL)PHTHALIMIDES (3)[a]

Compd	R	Rel intensities P+	a	b	c	d	e	f	g	h	i
4	$C_6H_5CH_2$	3	90	<1	55	58	100	8			
5	CH_3	29	16	20	18	27	6	36			
6	C_2H_5	6	15	100	29	41	19		19		
7	i-C_3H_7	<1	10	100	13	18	23		66		
8	n-C_4H_9	<1	88	92	100	88	50		42		
9	t-C_4H_9	<1	9	33	15	27	100		27		
10	C_6H_5	14	100	26	58	60	42	8		46	7
11	p-$CH_3C_6H_4$	14	100	3	57	52	34	<1		29	8
12	$CH_3O_2CCH_2$	10	100	5	78	68		37			2
13	i-C_3H_7S	2	80	38	100	96			10		

[a] Other major peaks (>10%), *m/e* (rel intensity): **4**, 148 (11), 110 (16), 103 (16), 92 (11), 83 (13), 78 (11), 77 (18), 74 (11), 66 (13), 65 (16), 51 (13), 50 (29); **5**, 160 ($P^+ - SOH$, 36), 148 (14), 63 (10), 50 (16), 46 (CH_2S, 100); **6**, 174 ($P^+ - SOH$, 17), 148 (12), 131 (10), 105 (15), 103 (15), 90 (12), 50 (19), 46 (CH_2S, 37); **7**, 46 (11), 41 (15); **8**, 149 (13), 148 (27), 131 (12), 106 (15), 105 (15), 103 (27), 90 (15), 81 (19), 77 (15), 75 (19), 74 (19), 69 (18), 63 (23), 59 (12), 56 (26), 55 (42), 50 (46), 46 (CH_2S, 23), 44 (23), 43 (92), 41 (77); **9**, 50 (15), 46 (15), 41 (45); **10**, 148 (11), 109 (18), 103 (14), 97 (12), 78 (22), 75 (11), 74 (13), 66 (18), 65 (12), 51 (36), 50 (34), 44 (16); **11**, 148 (11), 124 (15), 103 (14), 91 (34), 77 (11), 65 (11), 58 (11), 50 (25), 44 (23), 43 (25), 40 (62); **12**, 148 (17), 103 (20), 92 (13), 90 (12), 79 (18), 75 (15), 74 (13), 50 (35), 46 (52), 45 (22); **13**, 179 ($C_8H_5NO_2S$, 56), 178 (17), 151 (11), 148 (12), 105 (49), 103 (28), 91 (11), 77 (14), 75 (19), 74 (14), 50 (44), 46 (14), 41 (64).

sulfur-containing fragment is also observed. All compounds in Table I except **12** show intense peaks corresponding to the alkyl or aryl fragment e where charge is retained on the carbon atom. When this cation is exceptionally stable, it constitutes the base peak of the spectrum as in the case of the benzyl and *tert*-butyl derivatives **4** and **9**. Alternately, it is possible for the charge to reside on the sulfur-containing fragment. Hence benzyl-, methyl-, phenyl-, and carbomethoxymethylsulfinylphthalimides (**4**, **5**, **10**, and **12**, respectively) display a strong peak at *m/e* 194, attributed to fragment f. This process is confirmed by a metastable peak for the last compound only.

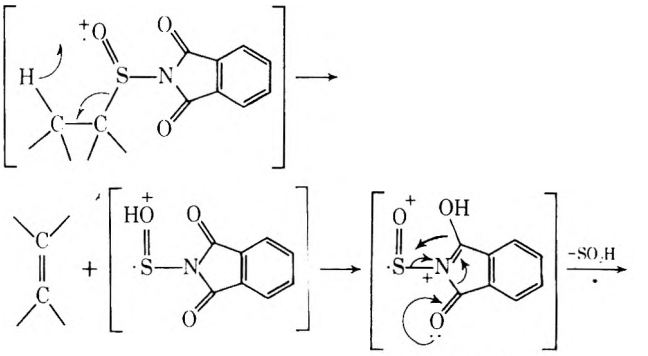


f, *m/e* 194

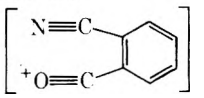
When hydrogen atoms are available β to the sulfinyl group, the fragmentation is altered. Instead of f, a strong ion is observed at *m/e* 195, suggesting a five-center McLafferty-type rearrangement[21] involving formation of g with elimination of alkene as depicted below. This transformation is observed in ethyl-, isopropyl-, *n*-butyl-, and *tert*-butylsulfinylphthalimides (**6**–**9**) and is accompanied by the corresponding metastable peak for compound **7**. Loss of SO_2H as a neutral fragment from g then results in formation of b.

(21) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1967, p 123.

The appearance of a metastable ion at *m/e* 86.7 for compounds **6**–**9** confirms this process.



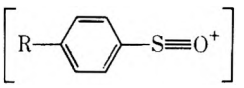
g, *m/e* 195



b

It thus appears that rupture of the C–S bond is a prominent feature in sulfinylphthalimide fragmentation resulting in abundant ions corresponding to e as well as either f or g depending on whether or not β hydrogens are present.

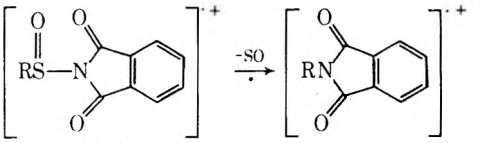
In addition, arylsulfinylphthalimides **10** and **11** produce strong ions at *m/e* 125 and 139, respectively, suggesting formation of fragment h.



h

10, R = H
11, R = CH_3

Derivatives **10**, **11**, and **12** lose SO directly from the molecular ion to produce i; the corresponding metastable ions are found at *m/e* 183.5, 197.1, and 179.6, respectively. Similar behavior has been previously reported in the case of sulfoxides.[19a]

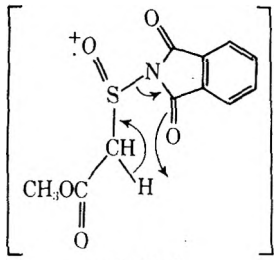


10, R = C_6H_5
11, R = p-$CH_3C_6H_4$
12, R = CH_3OCCH_2 (‖ O)

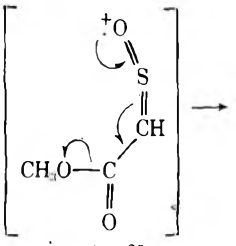
i

The mass spectrum of sulfinylphthalimide **12** is somewhat anomalous by virtue of abundant ions at *m/e* 120 and 89. These are best rationalized by loss of phthalimide from the molecular ion to generate j, followed by loss of $\cdot OCH_3$ giving the moiety k.

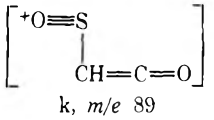
The fragmentation of the thiosulfinylphthalimide **13** resembles that of alkyl- and arylsulfinylphthalimides by the presence of intense peaks at *m/e* 147, 130, 104, 76, and 195, due to formation of a–d and g, respectively. The existence of the latter ion in the mass spectrum of **13** provides further evidence for the proposed site of oxidation during its preparation. It would be unlikely for such a fragment to be produced were not the sulfinyl group adjacent to the phthalimide



m/e 267

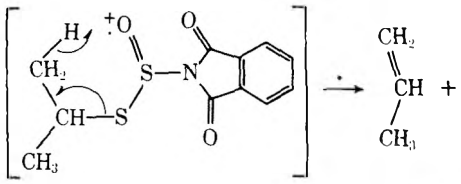


j, m/e 120

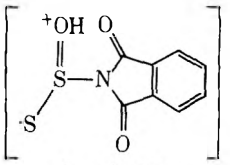


k, m/e 89

nitrogen. In addition, a strong ion at m/e 43 suggests formation of the isopropyl cation. Furthermore, loss of propene from the molecular ion is indicated by a large peak at m/e 227 (70%) and is confirmed by the presence of a metastable ion at m/e 191.6. This transformation is illustrated below.



m/e 269



l, m/e 227

Stability of Sulfinylphthalimides.—Sulfinylphthalimides **4–10** were stored in screw-top vials at room temperature with no noticeable decomposition over several weeks. After 2 months the methyl, ethyl, phenyl, and *n*-butyl derivatives showed signs of decomposition as evidenced by discoloration and lowered melting points. Less severe decomposition occurred in the benzyl and isopropyl analogs, while the *tert*-butyl compound was observed to remain unchanged. Shelf life may be prolonged considerably by storing the products at lower temperatures.

The title compounds appear to decompose rapidly in basic media to furnish phthalimide and presumably the corresponding sulfinic acid. When *N*-(*p*-tolylsulfinyl)phthalimide (**12**) was stirred with 5% sodium carbonate solution for 1.5 hr at room temperature, phthalimide was recovered in 84% yield. Stability toward base appears to be enhanced by the presence of bulky substituents. For example, it has already been mentioned that chloroform solutions of hindered sulfinylphthalimides are sufficiently stable in base to permit washing with 5% sodium bicarbonate solution.

It appears that sulfinylphthalimides are less labile in acid. When the *p*-tolyl derivative was stirred in 10% hydrochloric acid for 0.5 hr at room temperature, no decomposition whatsoever occurred and the sulfinylphthalimide was recovered unchanged in 97% yield.

Experimental Section

All melting points were obtained on a Gallenkamp block and are uncorrected. Mass spectra were obtained by Mr. W. Budd on a Model AEI-MS-902 spectrometer. High- and low-temperature nmr spectra were recorded on a Varian Model HA-100 spectrometer by Mr. R. Simenon, while a Varian Model T-60 furnished all other spectra. Elemental analyses were obtained on a Hewlett-Packard Model 185 automatic C, H, N analyzer, or alternately were performed by Organic Microanalyses (Montreal). All new compounds gave satisfactory analytical results (C, H, N) except sulfinamide **17**, which was 0.5% low in carbon.

Preparation of *N*-(Alkyl-, aryl-, and thiosulfinyl)phthalimides (4–13).—All products listed in Table I were obtained by either of two fundamental procedures. Hence, only one example of each will be described in detail.

***N*-(Ethylsulfinyl)phthalimide (6). Method A.**—A solution of 2.03 g (10 mmol) of *m*-chloroperbenzoic acid (85%) in 20 ml of chloroform was added dropwise over 0.5 hr to a solution of 2.07 g (10 mmol) of *N*-(ethylthio)phthalimide in 40 ml of chloroform at 0–5°. Stirring and cooling were continued for 0.5 hr, after which solvent was evaporated *in vacuo*. The resulting white solid was triturated with 30 ml of ether and stirred vigorously for 5–10 min. The suspended solid was then filtered and washed with cold ether to give 1.90 g (85%) of the desired product, mp 130–131°. Recrystallization from chloroform–petroleum ether gave an analytical sample, mp 132–134°.

***N*-(*tert*-Butylsulfinyl)phthalimide (9). Method B.**—The peracid (85%, 5 mmol) in 10 ml of chloroform was added to the thiophthalimide (5 mmol) in 20 ml of chloroform in the same manner as described in method A. After stirring and cooling for 1 hr, the solution was washed with 3 × 20 ml of 5% sodium bicarbonate solution and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure provided 1.26 g of product (quantitative), mp 130–131°. Recrystallization from chloroform–petroleum ether furnished an analytical sample, mp 133–136°.

Preparation of Sulfinamides 15–21.—A typical procedure involves the synthesis of *N*,*N*-diethylmethylsulfinamide (**16**) and is described below. All other sulfinamides were obtained in an analogous manner.

A solution containing 1.05 g (5 mmol) of *N*-(methylsulfinyl)-phthalimide and 0.37 g (5 mmol) of diethylamine in 20 ml of carbon tetrachloride was stirred for 1 hr at room temperature. Insoluble material was then filtered to give 0.67 g (91%) of phthalimide, mp 228–231° (lit.[22] mp 238°). Evaporation of solvent from the filtrate furnished 0.70 g (104%) of the crude product as a clear oil. Distillation gave 0.54 g (80%) of the pure sulfinamide, bp 51–52° (0.9 mm) [lit.[23] bp 55° (1.8 mm)].

Preparation of Sulfinate Esters 23–28.—All compounds in Table III were produced by one of two basic procedures.

Methyl Phenyl Sulfinate (26). Method A.—To a solution of 0.14 g (2.5 mmol) of sodium methoxide in 10 ml of methanol was added 0.68 g (2.5 mmol) of *N*-(phenylsulfinyl)phthalimide. After 0.5 hr of stirring at room temperature, the methanol was evaporated *in vacuo*. The residue was then stirred vigorously with 15 ml of pentane which was subsequently decanted. The pentane extraction was repeated several more times and the washings were combined and evaporated under reduced pressure; the resulting clear oil weighed 0.35 g (90%). Purity of this product was confirmed by its homogeneity on tlc [silica gel; benzene–ethyl acetate (5:1)]. Furthermore, the product had ir and nmr spectra as well as refractive index identical with those of genuine samples prepared by method B as well as by the method of Douglass.[9b]

Method B.—The *N*-(phenylsulfinyl)phthalimide (0.81 g, 3 mmol) was refluxed in 5 ml of methanol. The solution became clear and several minutes later a precipitate formed. After 2 hr the reaction mixture was cooled, 0.33 g of phthalimide was filtered, mp 232–236°, and the methanol was evaporated from the filtrate *in vacuo*. Extraction of the product with pentane was performed as a method A, leaving behind a residue of 0.11 g of phthalimide (total yield of phthalimide 0.44 g, quantitative). Evaporation of pentane under reduced pressure provided 0.45 g (95%) of the product as a clear oil which was homogeneous on tlc, bp 43–44° (0.07 mm) [lit.[10] bp 47.5–51° (0.2 mm)].

Preparation of *N*-(*tert*-Butylsulfinyl)phthalic Acid Monoamide Isopropyl Ester (30).—To 10 ml of a 0.25 *M* solution of sodium

(22) "Handbook of Chemistry and Physics," 47th ed, Chemical Rubber Co., Cleveland, Ohio.

(23) Y. H. Chiang, J. S. Luloff, and E. Schipper, *J. Org. Chem.*, **34**, 2397 (1969).

isopropoxide in isopropyl alcohol was added 0.63 g (2.5 mmol) of *N*-(*tert*-butylsulfinyl)phthalimide. After 0.5 hr of stirring at room temperature, the isopropyl alcohol was evaporated *in vacuo*. The resulting solid foam was taken up in 40 ml of pentane and precipitation of a white solid occurred on cooling. Filtration gave 0.75 g (90%) of the sodium salt **29**, mp 159° dec.

A portion of this material (0.33 g, 1 mmol) was then dissolved in 5 ml of water and acidified to Congo Red end point with hydrochloric acid. The resulting precipitate was filtered and washed with water to furnish 0.25 g (80% of theoretical yield based on the sodium salt **29**) of the amide **30**, mp 115–116°. The product was recrystallized from chloroform–petroleum ether to provide an analytical sample of unchanged melting point.

Acknowledgment.—We thank the National Research Council of Canada and the Defense Research Board of Canada (Grant No. 9530-97) for financial support of this work.

Registry No.—**2** (R = $C_6H_5CH_2$), 14204-26-3; **2** (R = CH_3), 40167-20-2; **2** (R = C_2H_5), 17796-70-2; **2** (R = *i*-C_3H_7), 17796-72-4; **2** (R = *n*-C_4H_9), 17796-73-5; **2** (R = *t*-C_4H_9), 17796-75-7; **2** (R = C_6H_5), 14204-27-4; **2** (R = *p*-$CH_3C_6H_4$), 15199-26-5; **2** (R = $CH_3O_2CCH_2$), 42300-49-2; **2** (R = *i*-C_3H_7S), 33704-40-4; **4**, 40167-14-4; **5**, 40167-13-3; **6**, 40167-12-2; **7**, 40739-92-2; **8**, 40318-14-7; **9**, 40167-16-6; **10**, 40167-15-5; **11**, 42300-58-3; **12**, 42300-59-4; **13**, 42300-60-7; **15**, 42300-61-8; **16**, 921-77-7; **17**, 42300-63-0; **18**, 35810-04-9; **19**, 40167-17-7; **20**, 42300-66-3; **21**, 42300-67-4; **23**, 673-80-3; **24**, 1859-03-6; **25**, 22598-57-8; **26**, 670-98-4; **27**, 42300-72-1; **28**, 42300-73-2; **29**, 42300-74-3; **30**, 42300-75-4; piperidine, 110-89-4; diethylamine, 109-89-7; *N*-methylbutylamine, 110-68-9; cyclohexylamine, 108-91-8; morpholine, 110-91-8; piperazine, 110-85-0.

Reaction of 4-Substituted Pyridines with Sulfenyl Chlorides[1]

VINCENT J. TRAYNELIS* AND JAMES N. RIECK[2]

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

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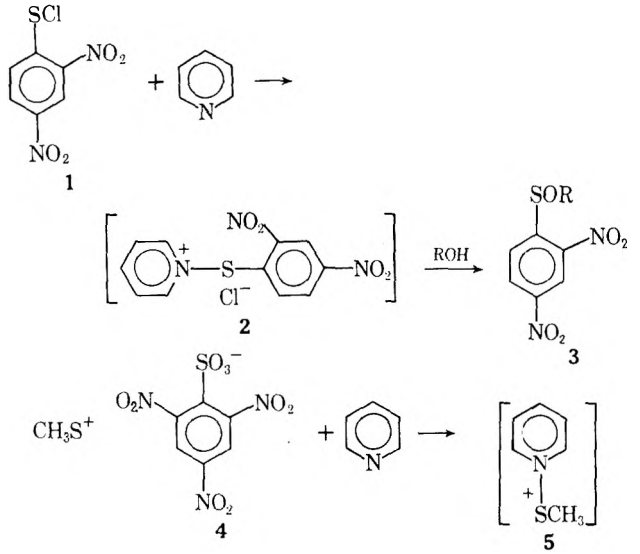
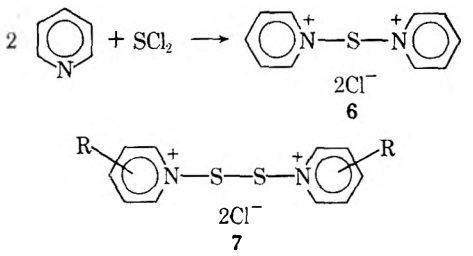
The reaction of 4-alkylpyridines with two substituents on the side-chain α carbon and arylsulfenyl chlorides gave α,α-disubstituted 4-pyridylmethyl aryl sulfides in 48–95% yield. When trichloromethanesulfenyl chloride and 4-benzhydryl- or 4-isopropylpyridine were allowed to react, diphenyl-4-pyridylmethyl or 2-(4-pyridyl)-2-propyl chloride were formed in 99 and 95% yield, respectively, while reaction of these 4-alkylpyridines with sulfur monochloride gave diphenyl-4-pyridylmethyl disulfide (~66%) or 2-(4-pyridyl)-2-propyl disulfide (82%). Analogous 3-alkyl- and 2-alkylpyridines failed to react with any of the above sulfenyl chlorides. A proposed rationalization of these reaction products entails formation of thiopyridinium ions and follows a pathway similar to the rearrangement of 4-alkylpyridine *N*-oxides and acid anhydrides.

The formation of *N*-arylthiopyridinium salts has been proposed by Kharasch[3] to explain pyridine catalysis in the conversion of 2,4-dinitrobenzenesulfenyl chloride (**1**) and alcohols to sulfenate esters **3**; however, attempts to isolate **2** were unsuccessful. More recently,



Helmkamp and coworkers[4] implied the formation of the *N*-methylthiopyridinium cation (**5**) when pyridine was added to a solution of **4** in nitrobenzene or nitromethane. The nmr upfield shift of the SCH_3 resonance supported structure **5** but no salt was isolated. However, crystalline *N*-thiopyridinium salts of structure **6** and **7** have been obtained from the reaction of pyridine



and sulfur dichloride[5] or sulfur monochloride.[6,7] In expanding our interest from *N*-oxypyridinium salts[8,9] to *N*-thiopyridinium salts we have investigated the reaction of various sulfenyl chlorides with a number of alkylpyridines and describe the results in this paper.

When a 2:1 molar solution of 4-benzhydrylpyridine (**15**) and 2,4-dinitrobenzenesulfenyl chloride (**1**), respectively, in dry ethylene chloride was stirred at room temperature for 1 hr, the reaction mixture gave a 48% yield of diphenyl-4-pyridylmethyl 2,4-dinitrophenyl sulfide (**16**) and a 38% yield of 2,4-dinitrophenyl disulfide (**9**). This reaction had been extended to other

(1) Presented in part before the Organic Division at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971.

(2) Abstracted from a portion of the Ph.D. Dissertation submitted by J. N. R. in April 1973 at West Virginia University.

(3) L. Goodman and N. Kharasch, *J. Amer. Chem. Soc.*, **77**, 6541 (1955).

(4) G. K. Helmkamp, D. C. Owsley, W. M. Barnes, and H. N. Cassey, *J. Amer. Chem. Soc.*, **90**, 1635 (1968).

(5) U. Wannagat and G. Schindler, *Angew. Chem.*, **69**, 784 (1957).

(6) H. G. Heal and J. Kane, *J. Inorg. Nucl. Chem.*, **29**, 1539 (1967).

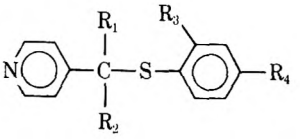
(7) R. C. Paul, K. Kishore, D. Singh, and K. C. Malhotra, *Indian J. Chem.*, **8**, 829 (1970).

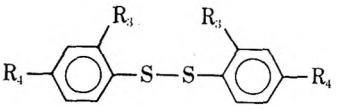
(8) V. J. Traynelis and A. I. Gallagher, *J. Org. Chem.*, **35**, 2792 (1970).

(9) V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1969, p 1.

TABLE I

REACTIONS OF 4-ALKYLPYRIDINES WITH ARYLSULFENYL HALIDES

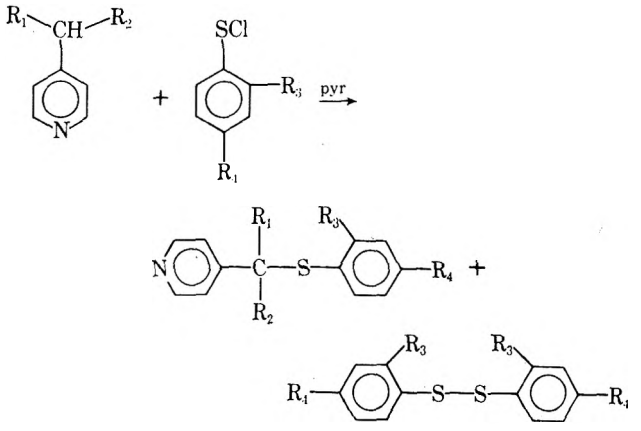




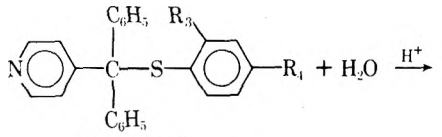
Compd	R_1	R_2	Compd	R_3	R_4	Compd	Yield, %	Compd	Yield, %
8	H	H	1	NO_2	NO_2			9	70
10	C_6H_5	H	1	NO_2	NO_2			9	67
11	CH_3	CH_3	1	NO_2	NO_2	12	95		
13	C_6H_5	CH_3	1	NO_2	NO_2	14	77	9	14
15	C_6H_5	C_6H_5	1	NO_2	NO_2	16	48	9	38
15	C_6H_5	C_6H_5	17	NO_2	H	18	88	19	12
15	C_6H_5	C_6H_5	20	H	NO_2	21	60	22	37
15	C_6H_5	C_6H_5	23	H	H	24	75[a]	25	

[a] In addition to sulfide 24, diphenyl-4-pyridylcarbinol (24% yield) was also isolated and proposed as a hydrolysis product of 24 during work-up. Thus the projected yield of 24 would approach 99%.

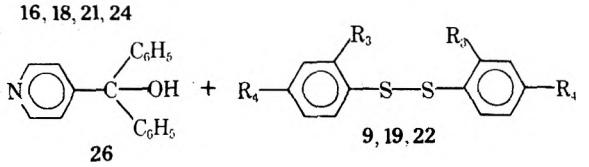
4-alkylpyridines with various arylsulfenyl chlorides as illustrated in the general equation below and summarized in Table I. Pyridine aids the overall reaction but is not essential, since the 4-alkylpyridine could serve as the base.



The disulfides **9**, **19**, and **22** are known compounds and were identified *via* melting points and spectral data. Structural assignments for the sulfide products **12**, **14**, **16**, **18**, **21**, and **24** were supported by elemental analysis and characteristic nmr and ir spectra. In addition **16**, **18**, **21**, and **24** were readily hydrolyzed to diphenyl-4-pyridylcarbinol (**26**) and the corresponding disulfide,



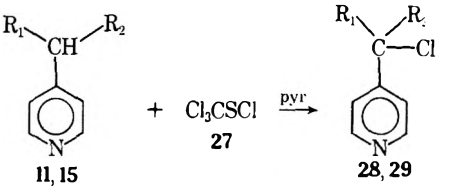
16, 18, 21, 24



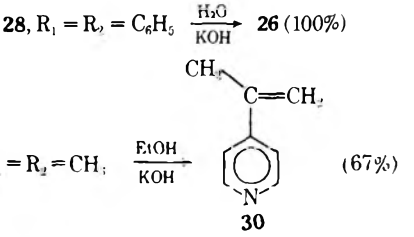
26 9, 19, 22

which probably arose by air oxidation of the corresponding arylthiol. The hydrolysis of diphenyl-4-pyridylmethyl phenyl sulfide (**24**) was particularly rapid and appears to be the source of diphenyl-4-pyridylcarbinol isolated in the reaction of 4-benzhydrylpyridine and benzenesulfenyl chloride (Table I). In contrast, sulfides **12** and **14** did not undergo hydrolysis to the corresponding carbinols even under more vigorous conditions.

The reaction of 4-benzhydrylpyridine (**15**) or 4-isopropylpyridine (**11**) with trichloromethanesulfenyl chloride (**27**) was mildly exothermic and formed a black hygroscopic precipitate and the reaction solution gave near-quantitative yields of diphenyl-4-pyridylmethyl chloride (**28**) or 2-(4-pyridyl)-2-chloropropane (**29**). Structural assignments for **28** and **29** were supported by elemental analysis, consistent nmr and ir spectra, the rapid, quantitative hydrolysis of **28** to carbinol **26**, and the base-catalyzed elimination of **29** to 4-isopropenylpyridine (**30**). The black, hygroscopic solid reacted

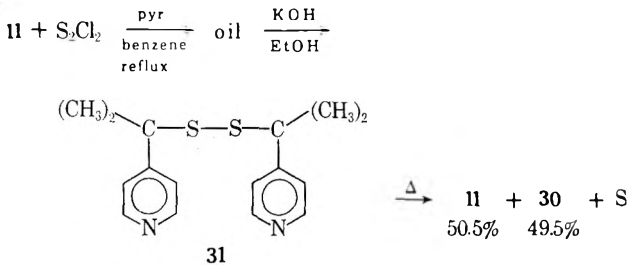


11, 15 27 28, 29



vigorously with water to produce hydrogen sulfide and colored solutions. A suggested structural possibility for the black solid involves a 2:1 complex of pyridine and thiophosgene.

A third product variation occurred in the reaction of 4-isopropylpyridine (**11**) and 4-benzhydrylpyridine (**15**) with sulfur monochloride, which produced, after alkaline treatment, 2-(4-pyridyl)-2-propyl disulfide (**31**) in 82% yield and diphenyl-4-pyridylcarbinol (**26**) in 66% yield, respectively. In the latter case an impure solid, which may be diphenyl-4-pyridylmethyl disulfide, was the precursor to **26** *via* acid or basic hydrolysis. Disulfide **31** had the proper analysis and spectral data for the assigned structure and upon thermal decomposition **31** formed sulfur along with equal amounts of 4-isopropylpyridine (**12**) and 4-iso-

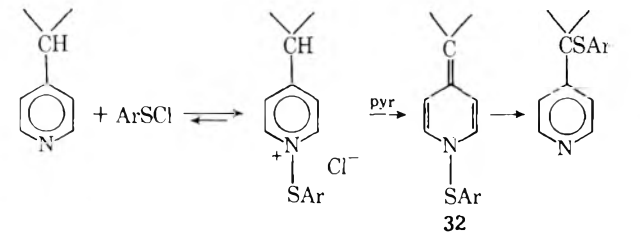


propenylpyridine (**30**). This fragmentation provides another avenue for the decomposition of aliphatic disulfides.[10]

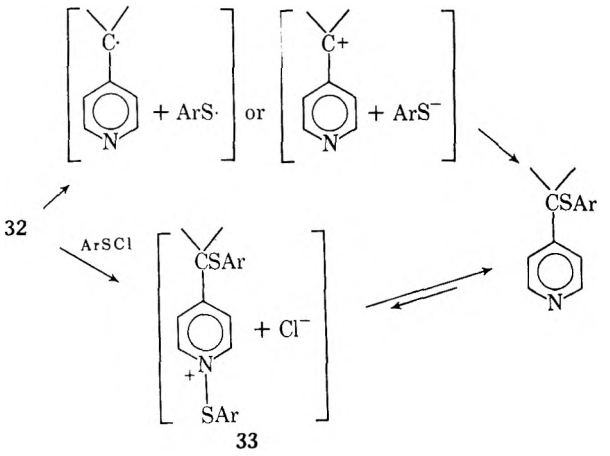
Attempts to extend these reactions to 2-alkyl- and 3-alkylpyridines were unsuccessful. Exposure to 2 benzhydryl- or 3-benzhydrylpyridine to 2,4-dinitrobenzenesulfenyl chloride, trichloromethanesulfenyl chloride, or sulfur monochloride, even under conditions more vigorous than those above, led to >90% recovery of unreacted alkylpyridines. Also no reaction occurred between triphenylmethane and 2,4-dinitrobenzenesulfenyl chloride. These observations exclude any direct attack of the sulfenyl chloride on the side-chain α carbon with substitution for the methine hydrogen and raise the question of involvement of the pyridine nitrogen.

A search for nitrogen–sulfur interaction was conducted *via* nmr measurements on equimolar solutions of pyridine and 2,4-dinitrobenzenesulfenyl chloride or trichloromethanesulfenyl chloride in deuteriochloroform. The expected downfield shift of the pyridine α hydrogens, resulting from salt formation, was absent and the position of the spectral peaks was unaffected by varying concentration. However, these observations do not preclude a low concentration (below nmr detection limits) of the *N*-arylthiopyridinium cation in equilibrium with the reactants. With this latter assumption one can explain the 4-alkylpyridine–sulfenyl halide reaction products *via* a pathway analogous to the rearrangement of 4-alkylpyridine *N*-oxide with acid anhydrides.[9]

The general reaction scheme proposed below proceeds through the key anhydro base intermediate **32**, which

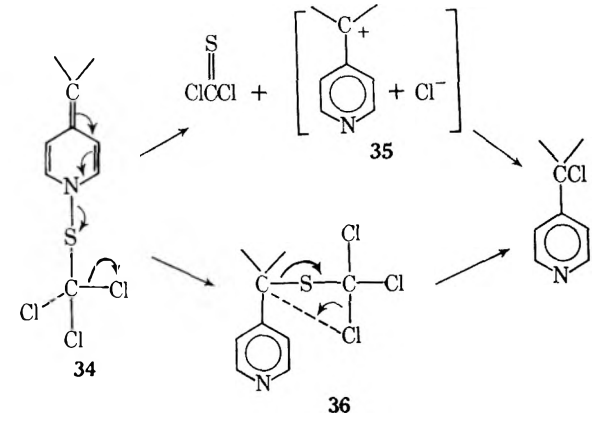


may undergo an intramolecular rearrangement or an intermolecular reaction to form the sulfide product. Fragmentation of **32** may entail homolytic cleavage of the N–S bond to form radical pairs or heterolytic cleavage to an ion pair in which either set may recombine to sulfide products. This intramolecular pathway requires a tight ion or radical pair. The intermolecular process would involve attack of **32** at the side-chain carbon by unreacted sulfenyl chloride to generate **33**, which is in favorable equilibrium with the product. Addition of arylsulfenyl chloride to anhydro



bases[11] or the structurally similar enamines[12,13] has been reported in the literature.

In the reaction of 4-alkylpyridines with sulfur monochloride the disulfide product can be rationalized by the above scheme except that two rearrangements or reactions (one in each pyridine ring) are required. Also support for the initial salt formation is available from isolation of some of these salts (**7**).[6,7] However the generation of diphenyl-4-pyridylmethyl chloride (**28**) or 2-(4-pyridyl)-2-chloropropane (**29**) from reactions using trichloromethanesulfenyl chloride requires some additional mechanistic features. The anhydro base **34** may undergo a concerted fragmentation to ion pair **35**, which recombines to give the chloro product. Alternatively, **34** may lead to **36** by the pathway outlined



above. Further decomposition of **36** analogous to the Sni decomposition of alkyl chlorosulfites or chlorocarbonates[14] should generate the chloro product and thiophosgene.

The failure of 3-benzhydrylpyridine to react with sulfenyl chlorides may be attributed to the exclusion of anhydro base formation; however, 2-benzhydryl- or 2-isopropylpyridine are capable of proceeding *via* anhydro bases according to the above pathway and thus the absence of products in these cases was surprising. Perhaps steric factors are inhibiting initial salt and/or anhydro base formation. Another puzzling point is the lack of the expected products in the reactions of 4-benzylpyridine and 4-picoline with sulfenyl

(10) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 3, Chemical Publishing Co., New York, N. Y., 1960, pp 370–372.

(11) V. I. Dénes, M. Fărcăsan, and G. Ciurdaru, *Chem. Ber.*, **96**, 174 (1963).

(12) M. E. Kuehne, *J. Org. Chem.*, **28**, 2124 (1963).

(13) G. H. Alt and A. H. Speziale, *J. Org. Chem.*, **29**, 798 (1964).

(14) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, p 268.

chlorides. These matters and the overall mechanistic scheme are under further consideration.

In conclusion, the reaction of 4-alkylpyridines which contain two substituents on the side-chain α carbon react readily with a variety of sulfenyl halides to produce high yields of sulfides, disulfides, or chlorides.

Experimental Section[15]

Alkylpyridines.—The following alkylpyridines were commercially available: 4-picoline,[16] 4-isopropylpyridine,[16] 4-benzylpyridine,[16] 4-benzhydrylpyridine,[16] 3-benzhydylpyridine, 2-benzhydrylpyridine, and 2-isopropylpyridine. The liquids were distilled prior to use and stored over KOH while the solid alkylpyridines were recrystallized from benzene or ethanol.

4-(1-Phenylethyl)pyridine.—The procedure of Villani, King, and Papa[17] was employed for the conversion of 4-benzoylpyridine (74 g, 0.39 mol) and methylmagnesium chloride (200 ml, 3 *M*, 0.60 mol) into 56 g (76%) of 1-phenyl-1-(4-pyridyl)ethanol: mp 145–146° (lit.[17] mp 146–147°); nmr ($CDCl_3$) δ 8.56–8.27 (m, 2, pyr C_2 H, C_6 H), 7.53–7.27 (m, 7, pyr C_3 H, C_5 H, and $-C_6H_5$), 4.48 (br s, 1, -OH), and 1.92 (s, 3, $-CH_3$).

To a mixture of 1-phenyl-1-(4-pyridyl)ethanol (25.9 g, 0.132 mol), zinc powder (70 g), and acetic acid (100 ml) at 110° was added with stirring concentrated HCl (90 ml) over a 10-min period followed by more concentrated HCl (60 ml) 30 min later. The reaction mixture was maintained at 110° for 2.5 hr, the residual zinc was filtered, and the filtrate was concentrated, neutralized (Na_2CO_3), and extracted with $CHCl_3$. After the extract was dried and the solvent was removed, distillation of the residue gave 5 g (21%) of 4-(1-phenylethyl)pyridine: bp 128–135° (0.1 Torr); ir (neat) 3040 (w), 2980 (w), and 1595 cm^{-1} (s); nmr ($CDCl_3$) δ 8.60–8.44 (m, 2, pyr C_2 H, C_6 H), 7.40 6.95 (m, 7, pyr C_3 H, C_5 H, and $-C_6H_5$), 4.05 [q, 1, J = 7.5 Hz, $>CH(CH_3)C_6H_5$], and 1.53 (d, 3, J = 7.5 Hz, $-CH_3$).

Benzenesulfenyl Chloride.—The reaction of phenyl disulfide (78.9 g, 0.36 mol) in CCl_4 (200 ml) and Cl_2, as described in the literature,[18] gave 57.6 g (55%) of the deep red benzenesulfenyl chloride: bp 44° (1.1 Torr) [lit.[18] bp 58° (3 Torr)]; nmr ($CDCl_3$) δ 7.70–7.54 (m, 2, C_2 H and C_6 H), 7.36–7.25 (m, 3, C_3, C_4, C_5 H's).

4-Nitrobenzenesulfenyl Chloride.—Using the above procedure,[19] 4-nitrophenyl disulfide (25.8 g, 0.084 mol) in CCl_4 (150 ml) and Cl_2 provided a quantitative conversion (31.8 g) to 4-nitrobenzenesulfenyl chloride: mp 48–49° (lit.[19] mp 52°); nmr ($CDCl_3$) δ 8.37–8.07 (m, 2, C_3 H, C_5 H), 7.57–7.23 (m, 2, C_2 H, C_6 H).

Reaction of 2,4-Dinitrobenzenesulfenyl Chloride with Various Alkylpyridines. 1. 4-Benzhydrylpyridine. Method A.—A solution of 2,4-dinitrobenzenesulfenyl chloride (5.0 g 0.021 mol) in CH_2Cl_2 (30 ml) was added to a stirred solution of 4-benzhydrylpyridine (**15**, 10.4 g, 0.0425 mol) in CH_2Cl_2 (50 ml) under N_2. The reaction mixture was stirred for 2 hr and filtered and gave 0.5 g of 2,4-dinitrophenyl disulfide (**9**), mp 310° dec (lit.[20] mp 290–300°). After CH_2Cl_2 was removed from the filtrate, the residue was treated with acetone, from which an additional 1.1 g (38% combined yield) of 2,4-dinitrophenyl disulfide was isolated. The acetone solution was diluted with water and gave 4.5 g (48%) of yellow, crystalline diphenyl-4-pyridylmethyl 2,4-dinitrophenyl sulfide (**16**), mp 160–163°. Several recrystallizations of the crude product from ethanol gave an analytical sample: mp 167–168°; ir (KBr) 3075 (w), 3040 (w), 1590 (s) 1525 (s, NO_2), and 1340 cm^{-1} (s, NO_2); nmr ($CDCl_3$) δ 8.81 (d, 1, J = 2.5 Hz, dinitrobenzene C_3 H), 8.70–8.46 (m, 2, pyr C_2 H, C_6 H), 7.82 (dd, 1, J = 9, 2.5 Hz, dinitrobenzene C_5 H), 7.33 (m, 12, pyr C_3 H, C_5 H, and C_6H_5), and 7.15 (d, 1, J = 9 Hz, dinitrobenzene C_6 H).

Anal. Calcd for $C_{24}H_{17}N_3O_4S$: C, 65.00; H, 3.86; N, 9.47. Found: C, 64.87; H, 4.13; N, 9.23.

2. 4-(1-Phenylethyl)pyridine. Method B.—After the addition of 2,4-dinitrobenzenesulfenyl chloride (3.60 g, 0.015 mol) in benzene (25 ml) to a stirred solution of 4-(1-phenylethyl)-pyridine (**13**) (2.81 g, 0.015 mol) in pyridine (25 ml) the reaction mixture was refluxed for 2 hr under N_2. The reaction mixture was cooled and filtered to give 0.42 g (14%) of 2,4-dinitrophenyl disulfide. After the filtrate was neutralized (10% Na_2CO_3) and extracted with $CHCl_3$, the $CHCl_3$ was removed and left 4.09 g (77%) of 1-phenyl-1-(4-pyridyl)ethyl 2,4-dinitrophenyl sulfide (**14**): mp 125–127° (from ethanol); ir (KBr) 3080 (w), 1590 (s), 1515 (s, NO_2), and 1350 cm^{-1} (s, NO_2); nmr ($CDCl_3$) δ 8.83 (d, 1, J = 2.5 Hz, dinitrobenzene C_3 H), 8.68 (broad s, 2, pyr C_2 H, C_6 H), 8.07 (dd, 1, J = 9, 2 Hz, dinitrobenzene C_5 H), 7.47 (m, 7, pyr C_3 H, C_5 H, and C_6H_5), 7.25 (d, 1, J = 9 Hz, dinitrobenzene C_6 H), and 2.27 (s, 3, $-CH_3$).

Anal. Calcd for $C_{19}H_{15}N_3O_4S$: C, 59.83; H, 3.96; N, 11.02; S, 8.41. Found: C, 59.56; H, 4.16; N, 10.63; S, 8.42.

3. 4-Isopropylpyridine.—Method B was used in the reaction of 4-isopropylpyridine (**11**, 3.61 g, 0.030 mol) in pyridine (25 ml) and 2,4-dinitrobenzenesulfenyl chloride (7.0 g, 0.030 mol) in benzene (25 ml) with 1 hr reflux and gave 9.03 g (95%) of 2-(4-pyridyl)-2-propyl 2,4-dinitrophenyl sulfide (**12**): mp 167–168° (from ethanol); ir (KBr) 3120 (w), 2960 (w), 1590 (s), 1510 (s, NO_2), and 1335 cm^{-1} (s, NO_2); nmr ($CDCl_3$) δ 8.84 (d, 1, J = 2.6 Hz, dinitrobenzene C_3 H), 8.74–8.50 (m, 2, pyr C_2 H, C_6 H), 8.06 (dd, 1, J = 9, 2 Hz, dinitrobenzene C_5 H), 7.64–7.40 (m, 2, pyr C_3 H and C_5 H), 7.08 (d, 1, J = 9 Hz, dinitrobenzene C_6 H), and 1.87 (s, 6, two $-CH_3$'s).

Anal. Calcd for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.10; N, 13.16; S, 10.06. Found: C, 52.86; H, 4.34; N, 12.78; S, 10.19.

4. Other Alkylpyridines.—4-Picoline, 4-benzylpyridine, 2-benzhydrylpyridine, 2-isopropylpyridine, and 3-benzhydrylpyridine were each trreated with 2,4-dinitrobenzenesulfenyl chloride and refluxed from 1 to 36 hr. Only 2,4-dinitrophenyl disulfide (70–95%) and unreacted alkylpyridines (near-quantitative yield for the last three examples) were recovered.

5. Triphenylmethane.—A solution of 2,4-dinitrobenzenesulfenyl chloride (3.00 g, 0.0128 mol) in benzene (30 ml) and triphenylmethane (3.15 g, 0.0129 mol) in pyridine (30 ml) was refluxed for 18 hr. Work-up *via* method B provided 1.38 g (54% of 2,4-dinitrophenyl disulfide and 2.95 g (95%) of triphenylmethane, identified by melting point (93.5–94°) and the absence of depression in a mixture melting point with authentic material.

Reaction of 4-Benzhydrylpyridine with Various Arylsulfenyl Chlorides. 1. Benzenesulfenyl Chloride.—A solution of 4-benzhydrylpyridine (**15**, 3.4 g, 0.014 mol) in dry pyridine (25 ml) was mixed with benzenesulfenyl chloride (**23**) (2.00 g, 0.0138 mol) in dry benzene (25 ml) in a dark vial. The vial was purged with nitrogen, sealed, shaken at room temperature for 5 min (slight exothermic reaction observed), and kept overnight. The reaction mixture was filtered and gave 0.14 g of diphenyl-4-pyridylcarbinol (**26**), mp 231–235° (lit.[17] mp 238–238.5°).

After the solvent was removed from the filtrate, the oily residue was treated with ether and gave an additional 0.72 g (23.8% total yield) of insoluble diphenyl-4-pyridylcarbinol. The ether was removed and left 3.67 g (75%) of crude diphenyl-4-pyridylmethyl phenyl sulfide (**24**), which upon crystallization from ethanol gave an analytical sample: mp 150.5–151.5°; ir (KBr) 3025–3010 (m), 1585 (s), and 1480 cm^{-1} (s); nmr ($CDCl_3$) δ 8.57–8.30 (m, 2, pyr C_2 H, C_6 H) and 7.33–7.00 (m, 17, pyr C_3 H, C_5 H and three $-C_6H_5$).

Anal. Calcd. for $C_{24}H_{19}NS$: C, 81.55; H, 5.42; N, 3.96; S, 9.07. Found: C, 81.12; H, 5.20; N, 4.06; S, 9.05.

2. 2-Nitrobenzenesulfenyl Chloride.—Using the procedure of method A the reaction mixture of 4-benzhydrylpyridine (2.59 g, 0.0106 mol) in benene (15 ml) and pyridine (15 ml) and 2-nitrobenzenesulfenyl chloride (**17**) (2.00 g, 0.0106 mol) was stirred overnight and processed to give 0.2 g (12%) of 2-nitrophenyl disulfide (**19**), mp 196–197° (lit.[21] mp 192–195°), and 3.68 g (88%) of crude diphenyl-4-pyridylmethyl 2-nitrophenyl sulfide (**18**) as a yellow oil. The oil solidified when treated with ether, and recrystallization from ethanol gave an analytical

(15) All melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Clark Microanalytical Laboratory, Urbana, Ill. Infrared spectra were determined on a Beckman IR-8 or a Beckman IR-20A spectrometer and nmr spectra were recorded on a Varian Associates Model HA-60-EL or Model A-60A spectrometer.

(16) The authors wish to thank Reilly Tar and Chemical Co., Indianapolis, Ind., for a generous supply of these alkylpyridines.

(17) F. J. Villani, M. S. King, and D. Papa, *J. Org. Chem.*, **17**, 249 (1952).

(18) H. Lecher, F. Holschneider, K. Köberle, W. Speer, and P. Stocklin, *Chem. Ber.*, **58**, 409 (1925).

(19) T. Zincke and S. Lenhardt, *Justus Liebigs Ann. Chem.*, **400**, 1 (1913).

(20) N. Kharasch, W. King, and T. C. Bruice, *J. Amer. Chem. Soc.*, **77**, 931 (1955).

(21) "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 220.

sample: mp 156–158°; ir (KBr) 3030 (w), 3015 (w), 1585 (s), 1510 (s, NO_2), and 1330 cm^{-1} (s, NO_2); nmr ($CDCl_3$) δ 8.56–8.36 (m, 2, pyr C_2 H, C_6 H) and 7.86–7.00 (m, 16, pyr C_3 H, C_5 H, $-C_6H_5$, and $C_6H_4NO_2$).

Anal. Calcd for $C_{24}H_{18}N_2O_2S$: C, 72.34; H, 4.55; N, 7.03. Found: C, 72.65; H, 4.67; N, 6.97.

3. 4-Nitrobenzenesulfenyl Chloride.—The reaction mixture of 4-nitrobenzenesulfenyl chloride (**20**, 3.0 g, 0.016 mol), 4-benzhydrylpyridine (4.5 g, 0.016 mol), CH_2Cl_2 (50 ml), and pyridine (1 ml) was stirred for 24 hr under nitrogen, and work-up according to method A gave 0.9 g (37%) of 4-nitrophenyl disulfide (**22**), mp 177–178° (lit.[19] mp 181°), and 3.79 g (60%) of diphenyl-4-pyridylmethyl 4-nitrophenyl sulfide (**21**) which was recrystallized from ethanol to give an analytical sample: mp 140–141°; ir (KBr) 3075 (w), 1580 (m), 1510 (s, NO_2), and 1340 cm^{-1} (s, NO_2); nmr ($CDCl_3$) δ 8.60–8.40 (m, 2, pyr C_2 H, C_6 H), 7.81 (d, 2, J = 9 Hz, nitrobenzene C_3 H, C_5 H), 7.40–7.22 (m, 12, pyr C_3 H, C_5 H, and two $-C_6H_5$), and 7.05 (d, 2, J = 9 Hz, nitrobenzene C_2 H, C_5 H).

Anal. Calcd for $C_{24}H_{18}N_2O_2S$: C, 72.34; H, 4.55; N, 7.03. Found: C, 72.25; H, 4.79; N, 6.84.

Hydrolysis of Diphenyl-4-pyridylmethyl Aryl Sulfides. 2,4-Dinitrophenyl Sulfide.—A solution of diphenyl-4-pyridylmethyl 2,4-dinitrophenyl sulfide (**16**) (0.6 g, 0.0014 mol) in 3 *N* HCl (10 ml) was refluxed for 1 hr and the mixture was filtered to give 0.21 g (81%) of 2,4-dinitrophenyl disulfide (**9**). The filtrate was made basic and gave 0.22 g (62%) of diphenyl-4-pyridylcarbinol (**26**), mp 237–239° (lit.[17] mp 238–238.5°). The ir spectrum was identical with that of an authentic sample.

When 1-phenyl-1-(4-pyridyl)ethyl 2,4-dinitrophenyl sulfide (**14**) or 2-(4-pyridyl)-2-propyl 2,4-dinitrophenyl sulfide (**12**) was refluxed for 1–2 hr in 3 *N* and 6 *N* HCl, only unreacted starting sulfides were recovered in near quantitative yield.

Using the preceding procedure hydrolysis of diphenyl-4-pyridylmethyl phenyl sulfide (**24**), diphenyl-4-pyridylmethyl 2-nitrophenyl sulfide (**18**) and diphenyl-4-pyridylmethyl 4-nitrophenyl sulfide (**21**) in 6 *N* HCl gave diphenyl-4-pyridylcarbinol (**26**) (quantitative, quantitative, and 88% yield, respectively) and the corresponding aryl disulfides 2-nitrophenyl disulfide (**19**) (91%) and 4-nitrophenyl disulfide (**22**) (99%).

Reaction of Trichloromethanesulfenyl Chloride with Alkylpyridines. 1. 4-Benzhydrylpyridine.—To a stirred solution of trichloromethanesulfenyl chloride (3.00 g, 0.016 mol) in dry ethylene chloride (20 ml) was added, at room temperature, a solution of 4-benzhydrylpyridine (3.96 g, 0.016 mol) in dry ethylene chloride (20 ml) and pyridine (20 ml). The reaction became warm and a solid formed while the reaction mixture was stirred at ambient temperature for 1–2 hr under N_2. Filtration of the reaction mixture gave a black, hygroscopic solid which reacted violently with H_2O and formed a purple aqueous solution with the odor of H_2S.

The solvent was distilled from the reaction mixture filtrate and the resulting dark viscous oil was extracted with hexane. After the hexane was removed, the residue was 4.45 g (99%) of diphenyl-4-pyridylmethyl chloride (**28**) as an orange oil which solidified upon scratching the flask. Either sublimation of the solid (130°, 0.05 Torr) or recrystallization from ethanol provided an analytical sample: mp 89.5–90.5°; ir (melt) 3025 (m), 3010 (m) and 1585 cm^{-1} (s); nmr ($CDCl_3$) δ 8.62–8.43 (m, 2, pyr C_2 H, C_6 H), 7.41–7.03 (m, 12, pyr C_3 H, C_5 H, and two $-C_6H_5$).

Anal. Calcd for $C_{18}H_{14}ClN$: C, 77.28; H, 5.04; N, 5.01; S, 12.67. Found: C, 77.15; H, 5.14; N, 5.35; Cl, 12.38.

2. 4-Isopropylpyridine.—The procedure of the preceding experiment was used in the reaction of trichloromethanesulfenyl chloride (6.13 g, 0.033 mol) in CH_2Cl_2 (20 ml) and 4-isopropylpyridine (4.0 g 0.033 mol) in CH_2Cl_2 (10 ml) and pyridine (10 ml) at 0°. The reaction mixture was stirred for 16–18 hr and gave a black, hygroscopic solid similar to that in the preceding experiment and 4.89 g (95%) of 2-(4-pyridyl)-2-chloropropane (**29**). Distillation of the oil provided an analytical sample: bp 44° (0.05 Torr); ir (neat) 3010 (w), 2990 (m), 2960 (w), and 1590 cm^{-1} (s); nmr ($CDCl_3$) δ 8.68–8.52 (m, 2, pyr C_2 H, C_6 H), 7.54–7.38 (m, 2, pyr C_3 H, C_5 H), and 1.93 (, 6, two $-CH_3$).

Anal. Calcd for $C_8H_{10}ClN$: C, 61.74; H, 6.48; N, 9.00. Found: C, 61.58; H, 6.35; N, 8.97.

3. Other Alkylpyridines.—The above procedure was used for the reaction of equimolar amounts of 2- and 3-benzhydrylpyridine and trichloromethanesulfenyl chloride for 3 and 5 days, respectively, at room temperature and gave 2-benzhydrylpyridine (94% recovery) and 3-benzhydrylpyridine (91% recovery), respectively.

Hydrolysis of Diphenyl-4-pyridylmethyl Chloride.—When 1 *N* ethanolic KOH (10 ml) was added to a solution of diphenyl-4-pyridylmethyl chloride (**28**, 0.46 g, 1.64 mmol) in ethanol (10 ml), an immediate precipitate formed which dissolved upon the addition of 2–5 ml of H_2O. The reaction mixture was diluted with more H_2O (20–25 ml) and filtered to give 0.43 g (100%) of diphenyl-4-pyridylcarbinol (**26**), mp 238–239°. A mixture melting point with an authentic sample was not depressed and the ir spectra of the two samples were identical.

Reaction of 2-(4-Pyridyl)-2-chloropropane with KOH.—A solution of 2-(4-pyridyl)-2-chloropropane (**29**, 0.57 g, 3.36 mmol) in 1 *N* ethanolic KOH (25 ml) was refluxed for 1 hr, cooled, and filtered, and the filtrate was diluted with an equal volume of ether. The ether was separated and dried and the solvent was removed to give 0.29 g (67%) of 4-isopropylpyridine (**30**): nmr ($CDCl_3$) δ 8.53–8.33 (m, 2, pyr C_2 H, C_6 H), 7.30–7.13 (m, 2, pyr C_3 H, C_5 H), 5.56 (broad s, 1, =CHH), 5.25–5.20 (m, 1, =CHH), 2.13 (s, 3, $-CH_3$). The ir spectrum was identical with that of a known sample.

Reaction of Alkylpyridines with Sulfur Monochloride. 1. 4-Isopropylpyridine.—A solution of sulfur monochloride (2.5 g, 0.0185 mol) in benzene (20 ml) was added to 4-isopropylpyridine (**11**, 4.49 g, 0.037 mol) in 25 ml of a 1:1 mixture of benzene–pyridine and the mixture was refluxed under N_2 for 30 min. The reaction mixture was filtered and gave 4.12 g (97%) of hygroscopic, white, crystalline pyridine hydrochloride, which had ir and nmr spectra that were identical with those of an authentic sample.

The filtrate from the reaction mixture was concentrated and refluxed for 15 min in 3 *N* ethanolic KOH (25 ml). The solution was filtered, diluted with H_2O, and extracted with ether. The extract was dried and the solvent was removed to give 4.23 g (82%) of 2-(4-pyridyl)-2-propyl disulfide (**31**). Recrystallization from ethanol provided an analytical sample: mp 70–71°; ir (melt) 3035 (s), 3010 (m), 2980 (m), 2960 (m), 2930 (w), and 1590 cm^{-1} (s); nmr ($CDCl_3$) δ 8.42 (m, 4, 2 pyr C_2 H, C_6 H), 7.15 (m, 4, 2 pyr C_3 H, C_5 H), 1.47 (s, 12, 4 $-CH_3$).

Anal. Calcd for $C_{16}H_{20}N_2S_2$ C, 63.12; H, 6.62; N, 9.20. Found: C, 63.23; H, 6.66; N, 8.94.

2. 4-Benzylhydrylpyridine.—Sulfur monochloride (1.65 g, 0.0122 mol) in benzene was added to 4-benzhydrylpyridine (6.00 g, 0.0245 mol) in 30 ml of a 1:1 mixture of benzene and pyridine and the reaction mixture was stirred overnight at room temperature under N_2. The reaction mixture was filtered and gave 2.5 g (89%) of pyridine hydrochloride.

The solvent was removed from the filtrate, the residue was treated with ether, and the ether solution was filtered. The ether was removed and left 6.54 g (97%) of crude diphenyl-4-pyridylmethyl disulfide as a yellow, sticky solid: mp 50–55°; nmr ($CDCl_3$) δ 8.50–8.44 (m, 4, 2 pyr C_2 H, C_6 H), and 7.21–7.12 (m, 24, 2 pyr C_3 H, C_5 H, and 4 C_6H_5). Attempts to purify the product by crystallization or chromatography were unsuccessful.

A solution of the yellow, sticky solid (0.99 g, 0.0018 mol) in 6 *N* HCl (15 ml) was refluxed for 1 hr, cooled, made basic with aqueous KOH, and filtered to give 0.62 g (66%) of diphenyl-4-pyridylcarbinol, mp 235–237°. The ir spectrum of this sample was identical with that of the known compound.

3. 2-Benzhydrylpyridine.—A solution of 2-benzhydrylpyridine (3.00 g, 0.0122 mol), sulfur monochloride (0.83 g, 0.0061 mol) in benzene (400 ml), and pyridine (20 ml) was refluxed for 1 hr under N_2, cooled, and quenched with H_2O (25 ml). The organic layer was separated and dried ($MgSO_4$) and the solvent was removed to provide 2.86 g (96%) of 2-benzhydrylpyridine, mp 55–57°. The nmr spectrum was identical with that of an authentic sample.

Thermal Decomposition of 2-(4-Pyridyl)-2-propyl Disulfide.—2-(4-Pyridyl)-2-propyl disulfide (**31**, 0.94 g, 3.09 mol) was placed in a microvacuum distillation apparatus and evacuated to 0.05 Torr and the still pot was heated slowly until, between 175 and 210°, a distillate collected in a receiver immersed in a Dry Ice–acetone bath. The residue (black with some yellow solid) in the distilling flask was extracted with hot CS_2 and from the cooled solution yellow crystalline sulfur, mp 119–120°, was obtained. A mixture melting point with an authentic sample of sulfur gave no depression.

The distillate, which weighed 0.56 g (76%), was analyzed by nmr and shown to contain a mixture of 4-isopropylpyridine (**11**,

50.5%) determined from the signal at δ 1.23 [-CH(CH$_3$)$_2$] and 4-isopropenylpyridine (**30**, 49.5%) determined from the signal at δ 2.13 [pyr-C(CH$_3$)=CH$_2$]. The nmr spectrum of the mixture had the following peaks: nmr (CDCl$_3$) δ 8.67–8.50 (m, 4, pyr C$_2$ H, C$_6$ H), 7.31 (m, 2, C$_3$ H, C$_5$ H, of 4-isopropenylpyridine), 7.16 (m, 2, C$_3$ H, C$_5$ H of 4-isopropylpyridine), 5.57 [s, 1, pyr-C(CH$_3$)=CH], 5.28–5.20 [m, 1, pyr-C(CH$_3$)=CH], 2.87 [septet, 1, pyr-CH(CH$_3$)$_2$], 2.13 [s, 3, pyr-C(CH$_3$)=CH$_2$], and 1.23 [d, 6, pyr-CH(CH$_3$)$_2$].

Registry No.—**11**, 69-30-0; **12**, 42362-46-9; **13**, 42362-47-0; **14**, 42362-48-1; **15**, 3678-72-6; **16**, 42362-50-5; **17**, 7669-54-7; **18**, 42362-51-6; **20**, 937-32-6; **21**, 42362-52-7; **23**, 931-59-9; **24**, 42362-53-8; **28**, 42362-54-9; **29**, 40473-14-1; **30**, 17755-30-5; **31**, 42362-57-2; 1-phenyl-1-(4-pyridyl)ethanol, 19490-94-9; phenyl disulfide, 882-33-7; Cl$_2$, 7782-50-5; 4-nitrophenyl disulfide, 100-32-3; 2,4-dinitrobenzenesulfenyl chloride, 528-76-7; trichloromethanesulfenyl chloride, 594-42-3; sulfur monochloride, 10025-67-9; diphenyl-4-pyridylmethyl disulfide, 42362-59-4.

Notes

Reaction of Tertiary Aliphatic Amines with 2,4-Dinitrobenzenesulfenyl Chloride

VINCENT J. TRAYNELIS* AND JAMES N. RIECK[1]

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

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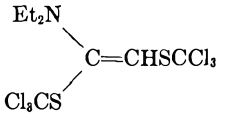
Sulfenyl chlorides react readily with primary and secondary amines to form sulfenamides;[2,3] however, tertiary amines appeared to be inert and useful as bases in the reactions of sulfenyl chlorides.[2] Some years ago Senning[4] observed a reaction between trichloromethanesulfenyl chloride and triethylamine which produced a bis(trichloromethylthio)-*N*,*N*-diethylaminoethene which was assigned structure **1**, although structure **2** could



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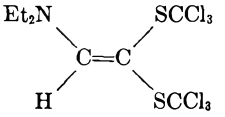

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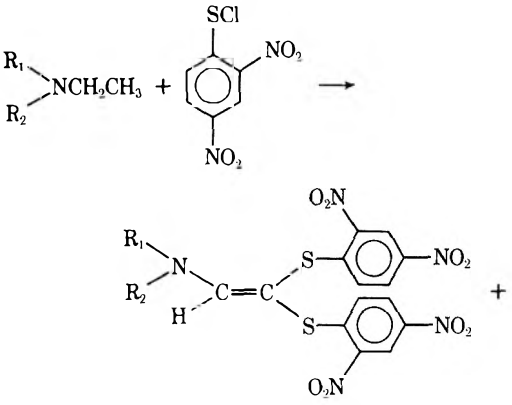
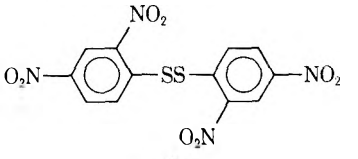
not be ruled out on the basis of spectral and chemical evidence. In a recent report Senning and Kelly[5] changed the assignment to structure **2**, which was supported by an X-ray crystallographic study.[6] In addition they reported[5] that attempts to extend this reaction to several other amines, such as tri-*n*-propylamine, tri-*n*-butylamine, diethylmethylamine, and others, with trichloromethanesulfenyl chloride were unsuccessful and the reaction of triethylamine and o-nitrobenzenesulfenyl chloride or 1,2,2,2-tetrachloroethanesulfenyl chloride failed to produce any products.

In our study of the formation of *N*-arylthiopyridinium salts[7] we had occasion to examine the mixture of triethylamine and 2,4-dinitrobenzenesulfenyl chloride and observed that reaction occurred with the formation of 1,1-bis(2,4-dinitrophenylthio)-2-*N*,*N*-diethylaminoethene (**3**). This reaction has been extended with 2,4-dinitrobenzenesulfenyl chloride and *N*,*N*-diethylcyclohexylamine or *N*,*N*-diisopropylethylamine with the formation of **4** and **5**, respectively. However, similar reactions of 2,4-dinitrobenzenesulfenyl chloride with tri-*n*-propylamine, tri-*n*-butylamine, and *N*-methylpiperidine failed to produce the corresponding enamines. The yield for each of the enaminic products **3**, **4**, and **5** was approximately 50%[8] as was the yield of bis(2,4-dinitrophenyl) disulfide (**6**) in each reaction.



3, R$_1$ = R$_2$ = CH$_3$CH$_2$
4, R$_1$ = *c*-C$_6$H$_{11}$; R$_2$ = CH$_3$CH$_2$
5, R$_1$ = R$_2$ = (CH$_3$)$_2$CH



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The accountability for the starting sulfenyl chloride was essentially quantitative in each reaction.

The assignment of structures **3**, **4**, and **5** was based on elemental analysis, on spectral data, and by analogy to compound **2** reported by Senning.[5] The infrared spectra showed the presence of the dinitrobenzene rings and the presence of the enaminic double bond (1585, 1565, 1570, and 1578 cm^{-1} [5] for **3**, **4**, **5**, and **2**, respectively) while the nmr had a characteristic olefinic peak (δ 7.43, 7.62, 7.74, and 7.55[5] for **3**, **4**, **5**, and **2**, respectively). In addition the nmr spectrum for **3** and **5** revealed the presence of two different dinitro-

(1) Abstracted from a portion of the Ph.D. Dissertation submitted by J. N. R. in April 1973 at West Virginia University.
(2) N. Kharasch, *J. Chem. Educ.*, **33**, 585 (1956).
(3) R. B. Langford and D. D. Lawson, *J. Chem. Educ.*, **34**, 510 (1957).
(4) A. Senning, *Angew. Chem., Int. Ed. Engl.*, **4**, 992 (1965).
(5) A. Senning and P. Kelly, *Acta Chem. Scand.*, **26**, 2877 (1972).
(6) See ref 5 for citation of paper, *Acta Chem. Scand.*, in press.
(7) V. J. Traynelis and J. N. Rieck, *J. Org. Chem.*, **38**, 4334 (1973).
(8) The yield of the enaminic products was based on 2,4-dinitrobenzenesulfenyl chloride.

benzene rings which overlapped but had identical coupling characteristics. Attempts to hydrolyze **3** under either acidic or basic conditions were unsuccessful, which parallel Senning's[5] observations.

The formation of these unique enamines may be rationalized by initial *N*-thioammonium salt formation and conversion to a *N*,*N*-diethylvinylamine (**7**), followed by an addition–elimination sequence of sulfenyl chloride to the enamine. The steps are detailed below. The reaction scheme proposed above resembles one offered by Senning[5] and parallels the reaction of triethylamine with trichloroacetyl chloride.[9-11] In the latter case only a single substitution occurs on the β carbon of the *N*,*N*-diethylvinylamine intermediate. Senning[5] has reported that the reaction of *N*,*N*-diethylvinylamine and trichloromethanesulfenyl chloride in the presence of trimethylamine leads to compound **2**. Further support for steps 4 and 5 can be found in the substitution of *o*-nitrobenzenesulfenyl chloride on the β carbon of enamines.[12-14] Failure to isolate the monosubstituted enamine **9** finds precedence in the reaction of heterocyclic methylene bases with *o*-nitrobenzenesulfenyl chloride, which led to the disubstituted enamine derivatives.[14]

$$Et_2NCH_2CH_3 + Cl_3CCCl \longrightarrow Et_2NCH{=}CHCCCl_3$$

The origin of the bis(2,4-dinitrophenyl) disulfide (**6**) can be explained by the reaction of 2,4-dinitrothiophenol (**8**), proposed as a by-product in the formation of *N*,*N*-diethylvinylamine (**7**), and 2,4-dinitrobenzenesulfenyl chloride. The yields of the enamine **3** and the disulfide **6** approach or are at their quantitative limits according to the proposed mechanism. The steps which require supportive evidence are steps 1 and 2, the formation of the *N*-thioammonium salt followed by elimination to an immonium ion. One also needs to consider why this reaction fails to produce the bisarylthioenamine when the tertiary amine lacks an ethyl group.

Experimental Section[15]

Reaction of 2,4-Dinitrobenzenesulfenyl Chloride with Tertiary Aliphatic Amines. Triethylamine.—A solution of 2,4-dinitrobenzenesulfenyl chloride (5.00 g, 0.0213 mol) in CH_2Cl_2 (40 ml) under N_2 was added to a stirred solution of triethylamine (3.68 g, 0.086 mol) in CH_2Cl_2 (30 ml) at 0° and the reaction mixture was stirred for 2 hr while it slowly warmed up to room temperature. The mixture was filtered and gave 2.1 g (50%) of bis(2,4-dinitrophenyl) disulfide, mp ~310° (lit.[16] mp 290–300°). The solvent was removed from the filtrate and left 2.5 g (47%)[8] of 1,1-bis(2,4-dinitrophenylthio)-2-*N*,*N*-diethylaminoethene (**3**). Recrystallization of the crude solid from CH_3CN gave an analytical sample as dark red crystals: mp 210–212°; ir (KBr) 3095 (w), 2980 (w), 2940 (w), 1585 (s, C=C), 1510 (s, NO_2), 1440 (w), 1330 (s, NO_2), 1300 (m), 1125 (w), 1074 (w), 1040 (m), 905 (m), 825 (m), and 728 cm^{-1} (m); nmr ($CDCl_3$) δ 9.13 and 9.08 (two overlapping d, 2, J = 2.5 Hz for each d, two dinitrobenzene C_3 H's), 8.55 and 8.51 (two overlapping doublet of doublets, 2, J = 2.5, 9 Hz for each d d, two dinitrobenzene C_5 H's), 7.93 and 7.90 (two overlapping d, 2, J = 9 Hz for each d, two dinitrobenzene C_6 H's), 7.43 (s, 1, -CH=C), 3.57 (q, 4, J = 7 Hz, 2 $-CH_2CH_3$), 1.27 (t, 6, J = 7 Hz, 2 $-CH_2CH_3$).

Anal. Calcd for $C_{18}H_{17}N_5O_8S_2$: C, 43.63; H, 3.46; N, 14.13; S, 12.92. Found: C, 44.09; H, 3.68; N, 14.11; S, 12.43.

***N*,*N*-Diethylcyclohexylamine.**—Using the above procedure 2,4-dinitrobenzenesulfenyl chloride (5.00 g, 0.0213 mol) in dry benzene (20 ml) and *N*,*N*-diethylcyclohexylamine (3.98 g,

(9) A. M. Platoshkin, Y. A. Cheburkov, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 112 (1969); *Chem. Abstr.*, **70**, 114541c (1969).

(10) R. R. Fraser and R. B. Swingle, *Tetrahedron*, **25**, 3469 (1969).

(11) R. Giger, R. Allain, M. Rey, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 120 (1970).

(12) M. E. Kuehne, *J. Org. Chem.*, **28**, 2124 (1963).

(13) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 798 (1964).

(14) V. I. Dénes, M. Fărcăsan, and G. Ciurdaru, *Chem. Ber.*, **96**, 174 (1963).

(15) All melting points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Clark Microanalytical Laboratory, Urbana, Ill. Infrared spectra were determined on a Beckman IR-8 or a Beckman IR-20A spectrometer, nmr spectra were recorded on a Varian Associates Model HA-60-EL or A-60A spectrometer, and the mass spectra were obtained with a Nuclide Corp. 12-90G high-resolution mass spectrometer.

(16) N. Kharasch, W. King, and T. C. Bruice, *J. Amer. Chem. Soc.*, **77**, 931 (1955).

0.0258 mol) in benzene (20 ml) were mixed and stirred overnight and upon work-up gave 2.15 g (50%) of bis(2,4-dinitrophenyl) disulfide, mp *ca.* 310°, and 2.92 g (50%)[8] of 1,1-bis(2,4-dinitrophenylthio)-2-*N*-ethylcyclohexylaminoethene (4): mp 186–188° (orange crystals from CH_3CN); ir (KBr) 3045 (w), 2960 (m), 2925 (w), 1565 (s, broad, C=C), 1510 (s, NO_2), 1420 (w), 1325 (s, NO_2), 1295 (w), 1125 (w), 1040 (m), 910 (m), 830 (m), and 730 cm^{-1} (m); nmr (DMSO-d_6) δ 8.87 (d, 2, J = 2 Hz, two nitrobenzene C_3 H's), 8.63 (dd, 2, J = 2, 8.5 Hz, two nitrobenzene C_5 H's), 8.01 (d, 2, J = 8.5 Hz, two nitrobenzene C_6 H's), 7.62 (s, 1, –CH=C), 3.93–3.28 (broad m, 3, $-CH_2CH_3$ and NCH), 2.1–1.07 (br m, 13, $-CH_2CH_3$ and five cyclohexyl CH_2's); mass spectrum (70 eV) *m/e* (rel intensity) 368 (9.9), 3.58 (20.9), 289 (13.9), 246 (10.2), 200 (13.6), 199 (18.1), 196 (11.5), 183 (22.1), 180 (22.9), 138 (10.9), 137 (11.6), 134 (18.4), 127 (28.4), 126 (15.9), 112 (13.2), 107 (14.7), 98 (15.5), 95 (21.3), 90 (13.2), 85 (13.6), 84 (100), 83 (21.7), 82 (11.6), 79 (26.0), 75 (12.2), 74 (15.5), 71 (22.2), 70 (10.0), 69 (23.8), 67 (12.7), 64 (59.6), 63 (52.7), 62 (12.5), 58 (10.8), 56 (46.9), 55 (39.2), 54 (10.9), 51 (12.40), 48 (17.7), 45 (19.2), 44 (57.3), 43 (12.1), 42 (12.9), 41 (38.8), 39 (20.6), 32 (8.1), 30 (43.3), 29 (17.5), 28 (73.6), 27 (16.3), 18 (96.7), 17 (20.0).

N,N-Diisopropylethylamine.—A mixture of 2,4-dinitrobenzenesulfenyl chloride (5.00 g, 0.0213 mol) in dry benzene (25 ml) and *N,N*-diisopropylethylamine (2.75 g, 0.0123 mol) in benzene (20 ml) was stirred for 24 hr at room temperature under N_2 and processed as above to give 2.00 g (47%) of bis(2,4-dinitrophenyl) disulfide, mp *ca.* 310°, and 2.81 g (50%)[8] of 1,1-bis(2,4-dinitrophenylthio)-2-diisopropylaminoethene (5): mp 226–228° (bright red crystals from CH_3CN); ir (KBr) 3045 (w), 2895 (w), 1590 (s), 1570 (s, C=C), 1510 (s, NO_2), 1450 (w), 1335 (s, NO_2), 1300 (m), 1180 (w), 1150 (w), 1130 (w), 1090 (w), 1042 (m), 910 (m), 830 (m), and 730 cm^{-1} (m); nmr (DMSO-d_6) δ 8.90 and 8.87 (two overlapping d, 2, J = 2 Hz for each d, two dinitrobenzene C_3 H's), 8.62 and 8.59 (two overlapping doublet of doublets, 2, J = 2, 8 Hz for each d d, two dinitrobenzene C_5 H's), 8.00 and 7.98 (two overlapping d, 2, J = 8 Hz for each d, two dinitrobenzene C_6 H's), 7.74 (s, 1, –CH=C), 4.33 [broad m, 2, two $-CH(CH_3)_2$], 1.22 [d, 12, J = 6 Hz, two $-CH(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 523 (4.9), 358 (11.1), 340 (42.2), 298 (28.3), 200 (12.5), 199 (22.5), 196 (14.0), 183 (29.7), 181 (14.7), 180 (31.8), 169 (11.1), 137 (13.7), 134 (19.3), 131 (10.0), 119 (13.1), 107 (12.4), 100 (17.6), 95 (18.2), 86 (55.1), 79 (14.9), 72 (17.5), 70 (54.2), 69 (54.9), 64 (25.9), 63 (34.5), 58 (23.6), 48 (10.5), 45 (13.5), 44 (86.0), 43 (100), 42 (23.6), 41 (37.7), 39 (19.0), 30 (19.6), 28 (15.9), 27 (16.2), 19 (12.7).

Anal. Calcd for $C_{20}H_{21}N_5O_8S$: C, 45.88; H, 4.04; N, 13.38; S, 12.25. Found: C, 45.94; H, 4.03; N, 13.32; S, 12.61.

Other Tertiary Amines.—Similar experimental conditions were applied to the reaction of 2,4-dinitrobenzenesulfenyl chloride and tri-*n*-propylamine, *N*-methylpiperidine, and tri-*n*-butylamine. In the last example the reaction mixture was refluxed for 1 hr. Each reaction gave bis(2,4-dinitrophenyl) disulfide, mp *ca.* 310° (77, 88, and 77% yield, respectively), and unreacted starting amine (85, 0, and 60% yield, respectively). The enaminic product observed in the preceding reactions was absent in these three examples.

Registry No.—**3**, 42362-43-6; **4**, 42362-44-7; **5**, 42362-45-8; **6**, 2217-55-2; 2,4-dinitrobenzenesulfenyl chloride, 528-76-7; triethylamine, 121-44-8; *N,N*-diethylcyclohexylamine, 91-65-6; *N,N*-diisopropylethylamine, 7087-68-5.

Catalysis by Tertiary Amines in the Thermolysis of Vinyl Azides to 1-Azirines

MITSUO KOMATSU,* SEIJI ICHIJIMA, YOSHIKI OHSHIRO, AND TOSHIO AGAWA

Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka, 565, Japan

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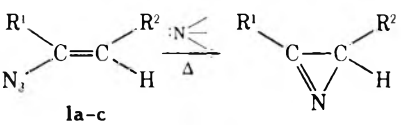
Recently, the chemistry of azirines has been widely studied and has aroused much interest. Azirines are generally prepared by pyrolysis[1] or photolysis[2] of corresponding vinyl azides. The more convenient procedure is to thermolyze the azides in aprotic solvents,[3–6] and the procedure is especially advantageous for the preparation on a large scale, although the yields are not always good. On the other hand, it has already been known that trivalent phosphines[7] and strong bases[8] catalyze the decomposition of azides and α-azido carbonyl compounds, respectively.

We have found a better method of converting vinyl azides **1a–c** to azirines **2a–c** by catalysis with tertiary



	R¹	R²
a	C_6H_5	H
b	C_6H_5	CH_3
c	*n*-C_6H_{13}	H

amines. For instance, the azide **1a** was thermolyzed into the azirine **2a** quantitatively in refluxing toluene in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco). Without catalyst, the thermolysis was slow and gave a low yield. The results of the thermolyses are shown in Table I.

TABLE I
THERMOLYSIS OF VINYL AZIDE IN THE PRESENCE OF TERTIARY AMINES

Run	Vinyl azide[a]	Solvent	Amine	Amine/azide[b]	Temp, °C	Time, min	Yield of azirine,[c] %
1	**1a**	$C_6H_5CH_3$		0.0	110	40	65
2	**1a**	$C_6H_5CH_3$	$N(C_2H_5)_3$	1.4	110	30	85
3	**1a**	C_6H_5Cl	$N(C_2H_5)_3$	1.4	110	50	45
4	**1a**	$C_6H_5CH_3$	$PhN(C_2H_5)_2$	1.0	110	45	53
5	**1a**	$C_6H_5CH_3$	Dabco[d]	1.3	110	20	95
6	**1a**	$C_6H_5CH_3$	Dabco	0.013	110	50	93
7	**1a**	C_6H_6	Dabco	1.3	80	50	24[e]
8	**1b**	$C_6H_5CH_3$	Dabco	1.3	110	20	92
9	**1c**	$C_6H_5CH_3$	Dabco	1.3	110	75	44

[a] Concentrations of azide solutions were 10 wt % in all runs. [b] Mole ratio. [c] Determined by glpc and checked frequently during reactions until no large increase in the yield was found. [d] Diazabicyclo[2.2.2]octane. [e] Unchanged azide was recovered.

It is obvious that some tertiary amines not only accelerate the reaction rate but inhibit the formation of by-products, which are reported to be ketenimines and polymers in both pyrolytic and photolytic procedures.[1,2] Though α-azidostyrene (**1a**) is known to decompose slowly into the azirine **2a** even at room temperature,[9] the rate of the thermolysis greatly depends upon the temperature. As shown in Table I, changing a refluxing solvent from toluene to benzene caused the

(1) G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).
(2) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2869 (1968); *Tetrahedron Lett.*, 1545 (1967).
(3) A. G. Hortmann, D. A. Robertson, and B. K. Gillard, *J. Org. Chem.*, **37**, 322 (1972).
(4) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **39**, 2077 (1967).
(5) K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968).
(6) F. P. Woerner and H. Reimlinger, *Chem. Ber.*, **103**, 1908 (1970).
(7) R. A. Abramovitch and E. P. Kyba in "The Chemistry of the Azido Group," S. Patai, Ed., Interscience, London, 1971, pp 294–296.
(8) J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954).
(9) J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).

remarkable retardation of the reaction. Chlorobenzene was also unsuitable for the solvent.

Among tertiary amines employed in the thermolysis, Dabco was the most effective and *N,N*-diethylaniline, which showed negative effect, was the least. With triethylamine, thermolysis gave the azirine **2a** in a high yield, but the reaction was slower than with Dabco. Hence, the order of the effectiveness is just in the order of basicity of the amines.

By measuring the rate of nitrogen evolution in the thermolyses, nitrogen release from the vinyl azide **1a** was found to obey good first-order kinetics. The rate constants are listed in Table II. The rates are equal

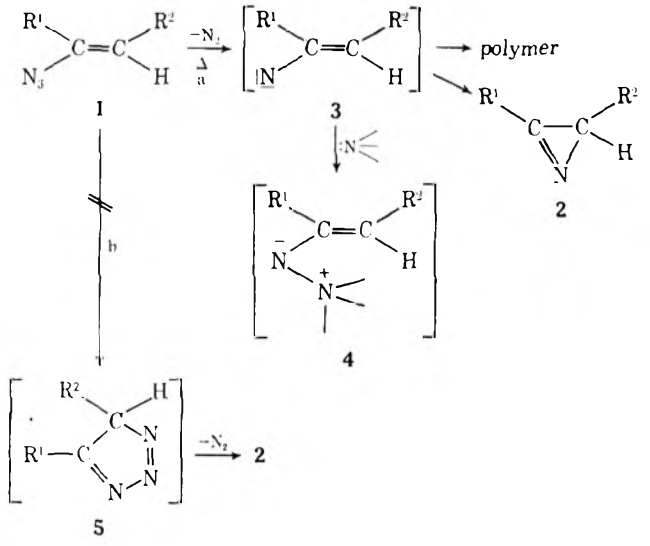
TABLE II

RATE CONSTANT FOR N_2 EVOLUTION IN THERMOLYSIS OF α-AZIDOSTYRENE (**1a**) AT 110°

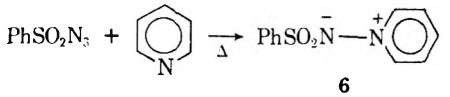
Run[a]	Solvent	Amine catalyst	$k \times 10^3$, sec^{-1}
1	Toluene		2.03
2	Toluene	NEt_3	2.03
3	Chlorobenzene	NEt_3	1.04
4	Toluene	$PhNEt_2$	1.92
5	Toluene	Dabco	2.15

[a] Run numbers correspond to those in Table I.

within an experimental error when toluene was employed as a solvent, showing that these amines do not participate in the step of nitrogen release from the azide. The low rate in chlorobenzene is due to the increase in solvent polarity, since the highly polarized vinyl azide should be more stabilized than the intermediate or the product by a polar solvent. Consequently, it is reasonable to postulate a nitrene intermediate **3** which is formed with the release of nitrogen from the azide **1** in the initial step. The intermediate **3** will convert into



an azirine **2** by intramolecular cyclization or into polymers. However, in the presence of a tertiary amine, the formation of a 1:1 adduct **4** is expected and this intermediate will give an azirine exclusively. Postulation of the adduct **4** is supported by the fact that a relatively stable adduct **6** is obtained in decomposition



6

of benzenesulfonyl azide in refluxing pyridine.[10] Such a coordination is sterically hindered in the case of *N,N*-diethylaniline, which has poor coordinating ability because of its lower basicity. In this case, the presence of the amine instead promotes the polymerization reaction.

Our runs were not successful in capturing the nitrene **3**. Similar failures in detecting nitrenes are reported in some pyrolyses and photolyses of vinyl azides.[1,11,12] However, these failures to detect any of the nitrenes do not necessarily exclude the formation of a nitrene intermediate.

As an alternative mechanism, Smolinsky proposed a triazole intermediate **5** formed by an initial cyclization.[1] This cyclization does occur in a strong basic medium, but does not take place in neutral or protic solvents, as loss of nitrogen molecule occurs much faster.[6,13] If path b to a triazole **5** in neutral solvents is promoted by an amine as a base, the rate of nitrogen evolution of the thermolysis with amines should be greater than that without amines. However, the rates are equal and, therefore, path b may be excluded.

Experimental Section

Infrared spectra of the products were obtained on a JASCO IR-E spectrophotometer and showed good agreements with those of authentic samples. Gas–liquid phase chromatographic analyses were performed on a Ohkura MS-1100 instrument using the following column: 4 mm × 2 m, 3% silicon gum SE-52 on 80–100 mesh Chromosorb W.

Materials.—α-Azidostyrene (**1a**) was prepared by Smolinsky's procedure[1] and 1-azido-1-phenylpropene (**1b**) and 2-azido-1-octene (**1c**) were obtained by the method of Fowler.[4] Authentic azirines **2a–c** were prepared by photolysis of the corresponding vinyl azides:[2] **2a**, bp 76° (10 mm), ir 1745 cm^{-1} (C=N); **2b**, bp 78° (10 mm), ir 1740 cm^{-1} (C=N); **2c**, bp 87° (40 mm), ir 1765 cm^{-1} (C=N).

Thermolysis of Vinyl Azides.—The general procedure for the thermolysis was as follows. In a 50-ml three-necked flask fitted with a dropping funnel, a magnetic stirrer, a thermometer, and a condenser whose top was connected with a gas buret, a solution of a tertiary amine was heated to the reaction temperature under nitrogen atmosphere. Then a vinyl azide was added through the funnel all at once and the rate of nitrogen evolution was measured. On a parallel run performed under the same conditions, the yield of a produced azirine was estimated by glpc.

Registry No.—**1a**, 16717-64-9; **1b**, 28022-21-1; **1c**, 42393-62-4; **2a**, 7654-06-0; **2b**, 16205-14-4; **2c**, 42393-63-5.

(10) T. Curtious and J. Rissom, *J. Prakt. Chem.*, **125**, 311 (1930).
(11) W. Lwowski, A. Hartenstein, C. de Vita, and R. L. Smick, *Tetrahedron Lett.*, 2497 (1961); W. Lwowski and T. W. Mattingly, Jr., *J. Amer. Chem. Soc.*, **87**, 1947 (1965).
(12) G. R. Harvey and K. W. Ratts, *J. Org. Chem.*, **31**, 3907 (1966).
(13) H. Reimlinger, *Chem. Ber.*, **103**, 1900 (1970).

One-Step Synthesis of 1,1-Dimethyl- and 1-Spirocycloalkano-1,2,3,4-tetrahydro-β-carbolines

N. CARRASCO, A. URZÚA, AND B. K. CASSELS*

Laboratorio Central de Química, Universidad Técnica del Estado, Santiago, Chile

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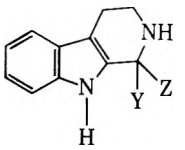
The condensation of tryptamine and substituted tryptamines with aldehydes and with α-keto acids in aqueous solution to yield 1-alkyl- and 1-alkyl-1-carboxy-

1,2,3,4-tetrahydro-β-carbolines, respectively, is a well-documented reaction.[1] 6-Hydroxy- and alkoxytryptamine derivatives also react quite readily with acetone in aqueous solution, affording the expected 1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline derivatives.[2] Tryptamine and 5-methoxytryptamine, on the other hand, do not react with simple ketones to any appreciable extent under the same conditions, and the corresponding carbolines have been prepared by cyclization of the Schiff bases using dilute sulfuric acid[3] or phosphorus oxychloride[2] as catalysts. A previous report of the cyclodehydration of tryptamine and acetone under rather unusual circumstances lacks adequate proof of the structure of the product.[4]

Using acetone as solvent, and with ethyl polyphosphate[5] as catalyst, we were able to prepare 1,1-dimethyl-1,2,3,4-tetrahydro-β-carboline (I) in one step in



I, Y = Z = Me
II, Y, Z = $(CH_2)_4$
III, Y, Z = $(CH_2)_5$

66% yield. The melting point of our product (140–141°) is practically the same as that reported by Vanderwerff,[3] and quite different from that of Hester's compound (111.5–115.5°).[2] The uv spectra, however, are similar, and our structural assignment is supported by ir and nmr spectral evidence. Also, the *N*(2)-benzoyl derivative, judging from its melting point, is the same as that described by Manske over 40 years ago.[4]

1-Spirocyclopentano- (II) and 1-spirocyclohexano-1,2,3,4-tetrahydro-β-carboline (III) were obtained similarly by cyclodehydration of tryptamine and cyclopentanone or cyclohexanone, respectively. The low solubilities of the hydrochlorides in dilute acid made their isolation and purification as such particularly easy. The uv spectra of all three compounds show that the indole chromophore is intact. The absence of ir absorption around 1665 cm^{-1} excludes the possibility of their being Schiff bases, and the absence of C(2)-H signals in the aromatic region of the nmr spectra shows that cyclization did indeed take place.

Experimental Section

Ir spectra were recorded with Perkin-Elmer 337 and 621 spectrophotometers, uv spectra with a Zeiss DMR-21, and nmr spectra with a Varian A-60 spectrometer using TMS as internal reference. Elementary analyses were performed by F. and E. Pascher, Bonn. Tlc was carried out on Merck silica gel chromatofoils, using cyclohexane–$CHCl_3$–Et_2NH (5:4:1). Melting points were determined in open capillaries, and are uncorrected.

1,1-Dimethyl-1,2,3,4-tetrahydro-β-carboline (I).—A solution of tryptamine (0.66 g) and ethyl polyphosphate (3.0 g) in acetone (80 ml) was refluxed during 36 hr. The solvent was then removed under vacuum, and the residue was diluted with water and neutralized with 4 *N* NaOH to yield a precipitate (0.54 g) which, recrystallized from cyclohexane, melted at 140–141°. The R_f values of tryptamine and of the product were 0.11 and 0.24, respectively: λ_{max}^{EtOH} (log ε) 225 (4.55), 274 (3.78), 279 (3.80), 289 nm (3.71); ν_{max}^{KBr} 1145 (C–N), 1450 cm^{-1}(*gem*-dimethyl); δ^{CDCl_3} 1.46 (s, 6 H, *gem*-dimethyl), 2.15 (s, 1 H, 2-H), 2.71 and 3.21 (2 t, *J* = 5.8 Hz, 4 H, CH_2CH_2), 7.0–7.5 (m, 4 H, 5-, 6-, 7-, and 8-H), 8.0 (br s, 1 H, 9-H); the signals at δ 2.15 and 8.0 disappear upon exchange with D_2O. *Anal.* Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.80; H, 8.25; N, 13.70.

Benzoylation of I yielded a compound which after recrystallization from acetone melted at 280–282°: λ_{max}^{EtOH} (log ε) 225 (4.60), 273 (3.72), 279 (3.69), 289 nm (3.61); ν_{max}^{KBr} 1630 cm^{-1} ($PhCONR_2$). *Anal.* Calcd for $C_{20}H_{20}N_2O \cdot {}^1/_4H_2O$: C, 77.74; H, 6.70; N, 9.07. Found: C, 77.64; H, 6.61; N, 9.13.

I, heated with an excess of methyl iodide in acetone, afforded the methiodide, which decomposed without melting at 200°: λ_{max}^{EtOH} (log ε) 225 (4.81), 272 (3.88), 278 (3.84), 288 nm (3.76). *Anal.* Calcd for $C_{15}H_{21}N_2I$: C, 50.57; H, 5.94; N, 7.86; I, 53.62. Found: C, 50.77; H, 5.89; N, 7.77; I, 35.71.

1-Spirocyclopentano-1,2,3,4-tetrahydro-β-carboline (II) Hydrochloride.—A solution of tryptamine (0.70 g) in cyclopentanone (9.0 ml), to which ethyl polyphosphate (0.45 ml) was added, was kept at 100° during 12 hr. The reaction mixture was diluted with H_2O (40 ml) and acidified with concentrated HCl (4 ml), whereupon a crystalline precipitate (0.60 g) appeared which, recrystallized from H_2O, melted at 263–264°: λ_{max}^{EtOH} (log ε) 222 (4.68), 272 (3.94), 279 (3.92), 289 nm (3.76). *Anal.* Calcd for $C_{16}H_{19}N_2Cl$: C, 68.55; H, 7.30; N, 10.66; Cl, 13.49. Found: C, 68.59; H, 7.33; N, 10.78; Cl, 13.54.

The free base, recrystallized from cyclohexane, melted at 139–140°; δ^{CDCl_3} 1.43 (s, 1 H, 2-H), 1.88 (s, 8 H, 4 CH_2), 2.71 and 3.17 (2 t, *J* = 5.5 Hz, 4 H, CH_2CH_2), 7.0–7.6 (m, 4 H, 5-, 6-, 7-, and 8-H), 7.73 (br s, 1 H, 9-H); the signals at δ 1.43 and 7.73 disappear upon exchange with D_2O.

1-Spirocyclohexano-1,2,3,4-tetrahydro-β-carboline (III) Hydrochloride.—A solution of tryptamine (0.70 g) in cyclohexanone (9.0 ml), to which ethyl polyphosphate (0.45 ml) was added, was kept at 100° during 12 hr. The reaction mixture was diluted with H_2O (40 ml) and acidified with concentrated HCl (4 ml), whereupon the product (0.62 g) crystallized: recrystallized from H_2O, mp 279–280°; λ_{max}^{EtOH} (log ε) 222 (4.62), 272 (3.92), 279 (3.91), 289 nm (3.79). *Anal.* Calcd for $C_{16}H_{21}N_2Cl \cdot {}^1/_2H_2O$: C, 67.21; H, 7.74; N, 9.78; Cl, 12.40. Found: C, 66.83; H, 7.91; N, 9.89; Cl, 12.56.

The free base, recrystallized from cyclohexane, melted at 133.5–135°: δ^{CDCl_3} 1.64 (s, 11 H, 5 CH_2 and 2-H), 2.65 and 3.09 (2 t, *J* = 5.5 Hz, 4 H, CH_2CH_2), 6.95–7.55 (m, 4 H, 5-, 6-, 7-, and 8-H), 7.69 (br s, 1 H, 9-H); upon exchange with D_2O, the signal at δ 1.64 decreased to 10 H, and the signal at δ 7.69 disappeared.

Acknowledgments.—This work was supported by a FORGE grant. We are also grateful to Mrs. A. Bau, Mr. R. Clavijo, and Mr. J. Ferrer for spectral analyses.

Registry No.—I, 6678-85-9; I benzoyl derivative, 42282-64-4; I MeI, 42282-65-5; II, 42282-67-7; II HCl, 42282-68-8; III, 6716-66-1; III HCl, 6716-70-7; tryptamine, 61-54-1; acetone, 67-64-1; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1.

(1) W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. VI, R. Adams, Ed., Wiley, New York, N. Y., 1951, p 151.
(2) J. B. Hester, *J. Org. Chem.*, **29**, 2864 (1964).
(3) W. D. Vanderwerff, *Diss. Abstr.*, **21**, 765 (1960).
(4) R. H. F. Manske, *Can. J. Res.*, **5**, 592 (1931).
(5) Y. Kanaoka, Y. Ban, K. Miyashita, K. Irie, and O. Yonemitsu, *Chem. Pharm. Bull.*, **14**, 934 (1966).

Stereochemistry of Reduction of Substituted Cyclohexanones with Lithium Triisobutyl-*n*-butylaluminate[1]

E. C. ASHBY* AND GEORGE E. HEINSOHN

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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We have recently reported the results of an investigation concerned in part with evaluation of triisobutyl-

(1) We are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and to the Ethyl Corp. for a generous sample of triisobutylaluminum.

aluminum (TIBA) as a stereoselective agent for the reduction of ketones.[2] We found that the stereochemical outcome of the reduction reaction was nominally dependent on reactant ratio, and more specifically was influenced by the ability of the aluminum alkyl to act as a Lewis acid in forming associated species and/or complexes with unreacted ketone or with reduction products. The present work is concerned with a similar evaluation of the "ate complex," lithium triisobutyl-*n*-butylaluminate (LTA). It was hoped that incorporation of tetravalent aluminum in the reducing agent would circumvent the complications arising from the complexing nature of the trivalent aluminum compound, triisobutylaluminum. Additionally, the greater steric requirement of the tetravalent "ate complex" as well as its possibly different mechanistic pathway of reduction was considered an exciting possibility for effecting stereoselective reductions. The mechanism of reaction between ketones and tetraalkylaluminum species has not been discussed in the literature.

Lithium triisobutyl-*n*-butylaluminate was prepared by mixing solutions containing equimolar quantities of triisobutylaluminum and *n*-butyllithium. The reagent was either used directly or isolated by precipitation with hexane. The results obtained for reduction of 3,3,5-trimethylcyclohexanone (1) and 4-*tert*-butylcyclohexanone (2) are presented in Table I.

TABLE I

Run	Ketone	Solvent	Ketone/LTA	% alcohols[b]	% axial alcohol
1	1	Benzene	1.0	95	97
2	1	Benzene	0.5	94	97
3	1	Benzene	2.0	83	96
4[a]	1	Benzene	1.0	89	98
5	2	Ether	1.0	100	47
6	2	Ether	0.5	73	46
7	2	Ether	2.0	86	49
8	2	Benzene	1.0	102	47
9	2	Benzene	0.5	104	47
10	2	Benzene	2.0	86	44

[a] LTA added to solution of ketone. [b] Based on millimoles of ketone converted.

Reduction was accompanied by a small amount (*ca.* 0–3%) of alkylation. Because of the minute quantities of alkylated products, no attempt was made to determine their nature or stereoisomeric composition. Clearly, the stereochemistry of reduction is independent of the nature of the solvent and of the order in which reagents are added. Quantitative conversion to alcohols was observed in several cases, indicating that formation of an aluminum enolate does not occur. In this respect, the present method is superior to reduction with TIBA, which is accompanied by 2–12% enolization.

The stereochemistry of ketone reduction with TIBA is dependent on the ratio of reactants. For example, reduction of 3,3,5-trimethylcyclohexanone with TIBA affords 63% of the axial alcohol when the TIBA to ketone ratio is 0.5, but 93% axial alcohol when the ratio is 5.0. Similarly, reduction of 4-*tert*-butylcyclohexanone with TIBA affords 14–44% axial alcohol when the ratio of TIBA to ketone is varied from 0.5 to 5.0. Reduction with lithium triisobutyl-*n*-butylaluminate is more selective, leading to isolation of 97% of the least stable (axial) alcohol in the former case and 47% in the latter. Furthermore, the isomeric composition of the product mixture is not dependent on reactant ratio, so that maximal selectivity can be attained by employing a stoichiometric quantity of reducing agent rather than (at least) a fivefold excess as in the case of TIBA. The economic consequences of this observation are obvious. Moreover, it seems that LTA might be advantageously employed in obtaining maximal selectivity in reduction of substrates with several reducible sites where use of excess reducing agent is precluded.

Experimental Section

Reagent grade ether and benzene were refluxed for 24 hr over $LiAlH_4$ and $NaAlH_4$, respectively, distilled through a 3-ft Vigreux column, and stored over sodium–lead alloy (dri-Na, J. T. Baker Chemical Co.) in a nitrogen atmosphere. Triisobutylaluminum (Ethyl Corp.) was assayed by EDTA titration and found to be satisfactory as received. Analysis of the gases evolved upon hydrolysis indicated the presence of 2.7% active hydride in the triisobutylaluminum. *n*-Butyllithium (Foote Mineral Co.) was used as received. 3,3,5-Trimethylcyclohexanone (Chemical Samples Co.) was distilled through a 2-ft glass helix packed column and the middle fraction was employed in this study. 4-*tert*-Butylcyclohexanone (Frinton Laboratories) was sublimed (10 mm) before use. Manipulation of air-sensitive compounds were performed either in a Kewaunee inert atmosphere box equipped with recirculating system[3,4] or by employing special bench top techniques.[4] Lithium was assayed with a Coleman Instruments Co. Model 21 flame photometer and aluminum by titration with EDTA. Products were analyzed by gas–liquid partition chromatography utilizing a 20-ft column packed with 5% 20M Carbowax on Chromosorb G and a Hewlett-Packard Model 700 chromatograph. Ethyl benzoate was employed as an internal standard in reductions of 3,3,5-trimethylcyclohexanone and analyses conducted at 135°. 3,3,5-Trimethylcyclohexanone was employed as an internal standard in reduction of 4-*tert*-butylcyclohexanone and analyses performed at 150°.

Lithium Triisobutyl-*n*-butylaluminate.—*n*-Butyllithium (23.6 mmol, 14.7 ml of 1.6 *M* solution in hexane) was added to a flame-dried 100-ml flask containing 30 ml of hexane. With vigorous stirring triisobutylaluminum (23.6 mmol, 21.25 ml of 1.11 *M* solution in benzene) was added affording a copious precipitate. After filtration the solid was washed with three 20-ml portions of hexane and dried (0.07 mm, 12 hr), affording white product (16.8 mmol, 71%). Analyses gave a lithium to aluminum ratio of 1.03.

General Procedure for Reduction.—A 50-ml erlenmeyer flask containing a magnetic stirring bar was flamed and allowed to cool in the entry port of an inert atmosphere box. After transfer into the box, the flask was sealed with a rubber septum, secured with an elastic band, and then connected by means of a needle to a nitrogen-filled manifold. A solution of lithium triisobutyl-*n*-butylaluminate (*ca.* 0.3 *M*) was introduced followed by sufficient solvent to bring the final volume to 10.0 ml. Stirring was initiated and the flask was immersed in a 22° water bath and allowed to come to temperature. A solution (*ca.* 1.0 *M*) of the appropriate ketone was added and allowed to react for 2.0 hr, and the reaction was quenched with 5% HCl. Internal standard was added, and the product mixture was analyzed by glc.

Registry No.—1, 873-94-9; 2, 98-53-3; LTA, 14239-17-9; TIBA, 100-99-2.

(2) G. E. Heinsohn and E. C. Ashby, *J. Org. Chem.*, in press.

(3) E. C. Ashby and R. D. Schwartz, *J. Chem. Educ.*, in press.

(4) D. F. Shriver, "The Manipulation of Air-Sensitive Compounds," McGraw-Hill, New York, N. Y., 1969.

Cyclohexenyl Intermediates in Acid-Catalyzed Cyclization of 2-Alkenyl-1-methylcyclohexanols

KENN E. HARDING* AND ROBERT C. LIGON

Department of Chemistry, Texas A & M University, College Station, Texas 77843

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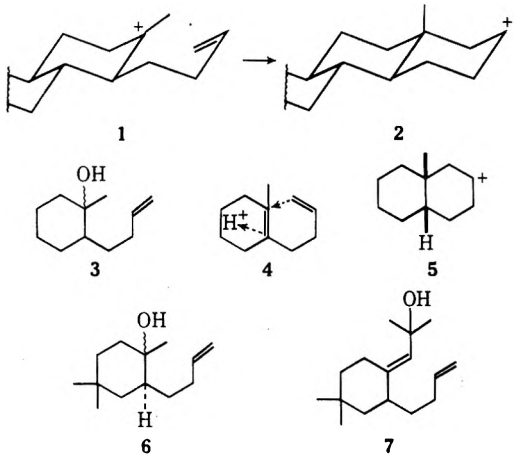
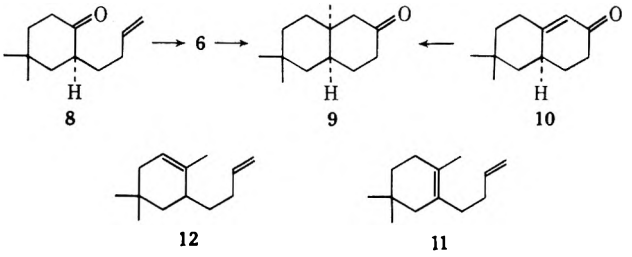
Recent results from our laboratory[1] have indicated that intramolecular attack of an olefinic double bond on a conformationally rigid cyclohexyl cation (*e.g.*, **1** → **2**) will proceed with high selectivity to give trans-fused products. This result suggested that cyclizations of alkenyl-substituted 1-methylcyclohexanols which lead to significant amounts of cis-fused products[2] may not involve cyclization through a cyclohexyl cation as the principal intermediate, since this should lead to selective formation of trans-fused products.[1] The predominant formation of cis-fused products may be rationalized, as pointed out by Stork,[3] if the cyclization involves elimination to a cyclohexene followed by concerted protonation–cyclization (**3** → **4** → **5**).

Although some evidence to support such an interpretation has been available,[2-4] previous mechanistic studies involved systems with conformationally mobile cyclohexane rings. Thus, we felt it imperative that the cyclization of alcohol **6** should be examined for comparison with previous results with alcohol **7**.[1]



Treatment of the previously prepared ketone **8**[1] with an excess of methylmagnesium iodide gave a 3:1 mixture of epimeric alcohols of structure **6**.[5] Although the two epimers could be separated by thin layer chromatography, the mixture was used in most of the cyclization studies, since cyclization of the mixture or of either of the individual isomers gave identical stereochemical results. Cyclization to bicyclic formates was readily effected in 95% yield by treatment with anhydrous formic acid at room temperature for 60 min. Reductive cleavage of the formate ester with lithium aluminum hydride followed by oxidation with Jones reagent[6] and bulb-to-bulb distillation gave bicyclic ketone **9**. The structure of this ketone was confirmed by spectral comparison with authentic material prepared by copper-catalyzed addition of methylmagnesium iodide to octalone **10**.[1,7] Close examination of the 100-MHz nmr spectrum of the cyclization ketone indicated the presence of 5–10% of the isomeric trans-fused ketone.[8]

Evidence concerning the cyclization mechanism was obtained by conducting the cyclization in deuterioformic acid. Mass spectral analysis of the ketonic products derived from this cyclization showed that 86% of the product had incorporated one or more deuterium atoms (49% d_1, 26% d_2, and 11% d_3). This result proves that cyclohexenes such as **11** and **12** must be involved in the cyclization of alcohol **6**. Concerted protonation–cyclization of either **11** or **12** by a trans-antiparallel mechanism can lead only to cis-fused products.



The above results confirm previous conclusions[4] that dehydration of 1-methylcyclohexanols is rapid relative to the cyclization reaction and that monocyclic dienes, not the monocyclic alcohols, are the primary precursors of bicyclic material. The large preponderance of cis-fused products obtained from the cyclization of alcohol **6** suggests that the major pathway for cyclization of the monocyclic dienes is by concerted protonation–cyclization rather than protonation to a cyclohexyl cation intermediate.[9]

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were obtained with Varian Associates T-60 or HA-100 spectrometers. Chemical shifts (δ) are reported in parts per million downfield with tetramethylsilane (TMS) as internal standard. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperatures of the oven during the distillation.

2-(3-Butenyl)-1,4,4-trimethylcyclohexanol (6).—To 7 ml of a solution of 1.4 *M* methylmagnesium iodide in ether, diluted with

(1) K. E. Harding, R. C. Ligon, T. Wu, and L. Rode, *J. Amer. Chem. Soc.*, **94**, 6245 (1972).

(2) Examples of this type include (a) P. T. Lansbury, P. C. Briggs, T. R. Demmin, and G. E. DuBois, *J. Amer. Chem. Soc.*, **93**, 1311 (1971); (b) P. T. Lansbury and G. E. DuBois, *Chem. Commun.*, 1107 (1971); (c) R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Amer. Chem. Soc.*, **94**, 2056 (1972).

(3) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **77**, 5068 (1955); G. Stork and H. Conroy, *ibid.*, **73**, 4748 (1951).

(4) (a) D. C. Hibbitt and R. P. Linstead, *J. Chem. Soc.*, 470 (1936). (b) Unpublished observations of W. S. Johnson and H. D. Doshan; see H. D. Doshan, Ph.D. Thesis, Stanford University, 1968.

(5) The major isomer is assumed to be the alcohol with an axial hydroxyl group resulting from preferential equatorial attack of the Grignard reagent.

(6) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(7) K. E. Harding, R. C. Ligon, and C. Tseng, *J. Org. Chem.*, in press.

(8) Ketone **9** or related ketones have potential utility as synthons for the D–E ring system of pentacyclic triterpenes. *Cf.*, *inter alia*, E. E. Van Tamelen, M. P. Seiler, and W. Wierenga, *J. Amer. Chem. Soc.*, **94**, 8229 (1973); C. H. Heathcock and J. E. Ellis, *Chem. Commun.*, 1474 (1971); J. D. Metzger, M. W. Baker, and R. J. Morris, *J. Org. Chem.*, **37**, 789 (1972).

(9) For a discussion of the relevance of this conclusion to other cyclizations of 1-methylcyclohexanols[2] see K. E. Harding, *Bioorg. Chem.*, **2**, 248 (1973).

7 ml of anhydrous ether, was added 300 mg of 2-(3-butenyl)-4,4-dimethylcyclohexanone (8) in 5 ml of anhydrous ether. The reaction was stirred at room temperature under a nitrogen atmosphere for 24 hr, then poured into a dilute, ice-cold acetic acid solution. The aqueous portion was extracted five times with ether. The combined ether fractions were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 273 mg of crude alcohol. Evaporative distillation (0.3 mm, 70°) provided 254 mg of a 3:1 mixture of axial and equatorial alcohols. The alcohols could be separated by preparative thin layer chromatography.

The major isomer had nmr (CCl_4, 100 MHz) δ 0.84 and 0.90 (s, 3 H each, geminal methyls), 1.13 (s, 3 H, C-1 methyl), 4.84–5.08 (m, 2 H, $-CH=CH_2$), and 5.52–6.00 ppm (m, 1 H, $-CH=CH_2$); ir (film) 3450, 1640, and 915 cm^{-1}.

The minor isomer had nmr (CCl_4, 100 MHz) δ 0.90 and 0.92 (s, 3 H each, geminal methyls), 0.99 (s, 3 H, C-1 methyl), 4.82–5.10 (m, 2 H, $-CH=CH_2$), and 5.57–6.00 ppm (m, 1 H, $-CH=CH_2$); ir (film) 3375, 1635, and 920 cm^{-1}.

Cyclization Studies. A. Cyclization with Formic Acid.—A 60-mg sample of the mixture of alcohols described above was dissolved in 6 ml of anhydrous formic acid and stirred at room temperature for 3 hr. The solution was poured into water and extracted four times with ether. The combined ether fractions were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 57 mg of product.

The crude material was hydrolyzed by addition to a stirred solution of lithium aluminum hydride in ether and stirring for 30 min. Then 2 ml of methanol and 2 ml of 10% sodium hydroxide solution were added carefully. The mixture was stirred for 5 min, filtered, and concentrated. The crude material was oxidized in the normal manner with Jones reagent in acetone.[6] Evaporative distillation (0.25 mm, 72°) gave 28 mg of ketonic product: nmr (CCl_4, 100 MHz) δ 0.93 (d, J = ~1 Hz, 3 H, C-9 methyl),[10] 0.96 and 0.97 ppm (s, 3 H each, geminal methyls); ir (film) 1700 cm^{-1}. Analysis by gas chromatography on SE-30 or Carbowax columns showed only one significant peak.

Careful examination of the nmr spectrum showed a small peak at δ 0.74 ppm. This peak can be attributed to the C-9 methyl of *trans*-6,6,9-trimethyl-2-decalone.[10]

Cyclization of either of the individual isomers of alcohol 6 gave results indistinguishable from cyclization of the mixture.

B. Cyclization in Deuterioformic Acid.—A 31-mg sample of alcohol 6 was dissolved in 1 ml of deuterioformic acid. The mixture was stirred for 4 hr, and the product was isolated and converted into the trimethyldecalone in the manner described above. The mass spectrum of the product showed *m/e* (rel intensity) 194 (P, 22.5), 195 (P + 1, 100), 196 (P + 2, 41.9), and 197 (P + 3, 17.3). Correction for natural isotopic abundances indicates deuterium incorporation in 86% of the product (49% d_1, 26% d_2, and 11% d_3).

cis-6,6,9-Trimethyl-2-decalone (9).—A mixture of 50 mg of cuprous bromide and 0.7 ml of 1.4 *M* methylmagnesium iodide in ether was diluted to 5 ml with anhydrous ether. Then 110 mg (0.625 mmol) of 6,6-dimethyl-$\Delta^{1,9}$-2-decalone (10) in 5 ml of ether was added. The reaction was stirred at room temperature for 2 hr and poured onto an ice–acetic acid mixture. The aqueous portion was extracted five times with ether, and the combined ether fractions were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated on a rotary evaporator to yield 96 mg of crude product. Preparative tlc and evaporative distillation (0.25 mm) gave 61 mg of authentic *cis*-6,6,9-trimethyl-2-decalone. *Anal.* Calcd for $C_{13}H_{22}O$: *m/e* 194.16719 (M^+). Found: *m/e* 194.16706. The ir and nmr spectra were identical with those obtained from material prepared by cyclization.

Acknowledgment.—We thank the Robert A. Welch Foundation and the National Institute of Arthritis and Metabolic Diseases for support of this research.

Registry No.—*cis*-6, 42271-36-3; *trans*-6, 42271-37-4; 8, 38481-13-9; 9, 42271-39-6; 10, 4044-27-3.

(10) The C-9 methyl groups of *cis*- and *trans*-9-methyl-2-decalone show absorption at δ 0.97 and 0.78 ppm, respectively.[11] The C-9 methyl of *cis*-9-methyl-2-decalone has also been observed as a doublet.[12]

(11) W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **87**, 5148 (1965).

(12) M. J. T. Robinson, *Tetrahedron Lett.*, 1685 (1965).

Lithium Dimethylcuprate Reaction with Oxygen-Substituted Epoxides[1]

BURR C. HARTMAN, THOMAS LIVINGHOUSE, AND BRUCE RICKBORN*

Department of Chemistry, University of California, Santa Barbara, California 93106

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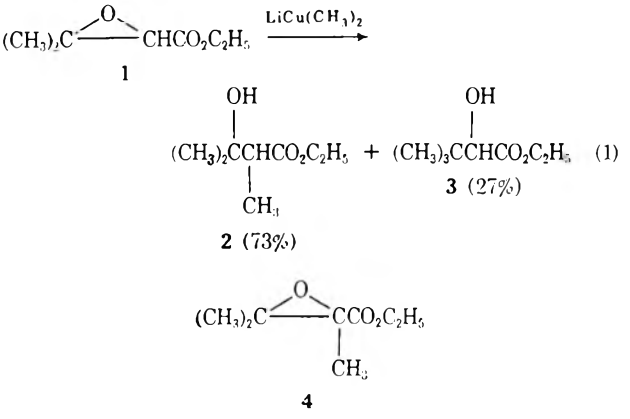
Recent work[2-4] has shown that lithium dimethylcuprate is superior to other organometallic reagents for the nucleophilic opening of epoxides. It was of interest to determine whether adjacent oxygen functions would exert a directive influence on the course of this reaction of the sort observed, *e.g.*, in the Simmons–Smith methylenation. We report here the results obtained with various substituted epoxides.

Johnson and coworkers[2] have reported that the reaction of lithium dimethylcuprate with ethyl 2,3-epoxybutyrate gives α-methylated product in good yield. We have extended this study to include the more highly substituted glycidic esters **1** and **4**. As shown in eq 1,



the reaction of **1** (overall yield 68%) shows only low regioselectivity, even though the formation of **3** formally requires substitution at a tertiary center. Interestingly, **4**, in which both epoxy centers are tertiary, failed to react at all with the organocopper reagent even under more forcing conditions. These results are difficult to interpret mechanistically, but indicate that the degree of selectivity observed in the simpler system[2] will not prove to be a generally useful feature of the reaction of glycidic esters.

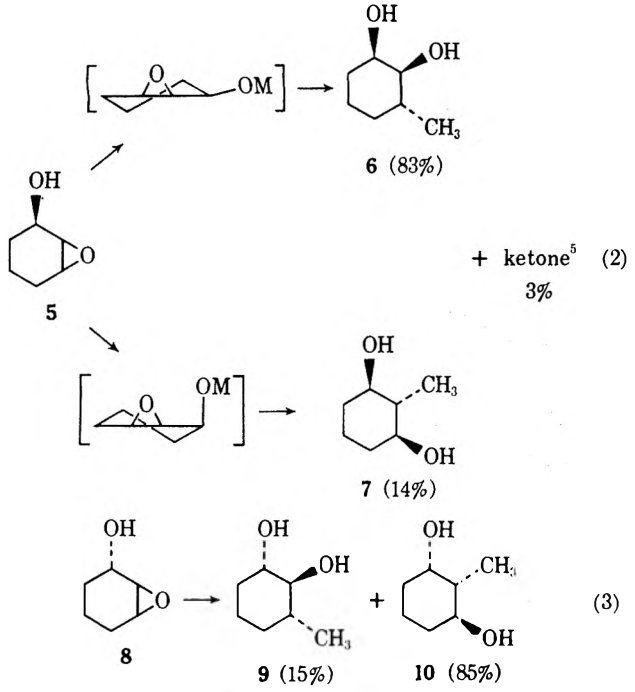
As examples of other oxygen-substituted epoxides, 3-hydroxycyclohexene oxide and its derivative methyl ether and acetate were also subjected to lithium dimethylcuprate treatment. The cis and trans alcohols (**5** and **8**) both gave rapid gas evolution (methane) followed by slower attack of the oxirane ring; the reaction must therefore involve an intermediate O-metalated species. As shown in eq 2 and 3, these reactions exhibit completely stereospecific anti opening of the oxirane ring, with moderate regioselectivity suggesting preferred diaxial opening through the half-chair con-

(1) Support in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(2) R. W. Herr, D. M. Wieland, and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 3813 (1970).

(3) R. W. Herr and C. R. Johnson, *J. Amer. Chem. Soc.*, **92**, 4979 (1970).

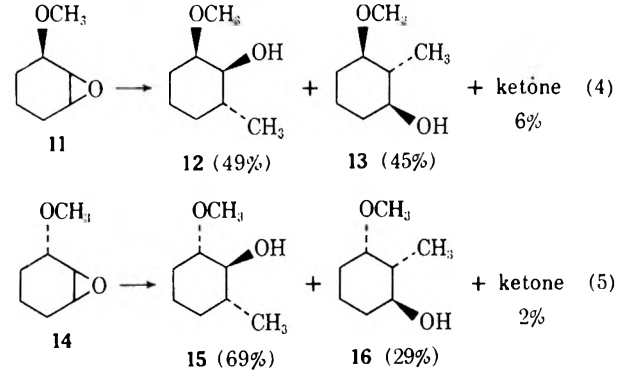
(4) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).



formers in which the 3 substituent prefers the pseudo-equatorial position.

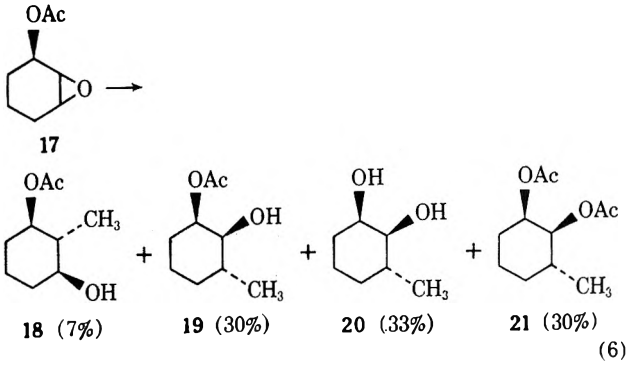
The change in preference for attack at carbons 1 and 2 in the cis,trans pair **5** and **8** suggests that neither inductive nor other specific directive influences play a major role in these reactions. However, it was noted that the trans isomer **8** reacted more slowly than the cis material **5**.

The methyl ethers **11** and **14** show even lower regioselectivity (eq 4 and 5) than the alcohols, resembling



in this respect the reactions of these materials with lithium aluminum hydride.[6] The trans ether **14** again reacted more slowly with lithium dimethylcuprate than cis **11**.

Only the cis isomer of the acetate, **17**, was examined, and this exhibited somewhat higher regioselectivity than the alcohol **5**. In this system the results were complicated by transesterification during the reaction leading to a mixture of diols and diacetates; analysis was accomplished by conversion of the mixture to the diacetate derivatives.



In summary, the results with various oxygen-substituted epoxides in the reaction with lithium dimethylcuprate suggest that no specific directive influences are to be expected, and product distribution will largely be the result of conformational control.

Experimental Section

The glycidic esters[7] **1** and **4** and epoxides[6] **5**, **8**, **11**, and **14** have all been reported previously. Compound **17** was prepared from the alcohol **5** by treatment with acetic anhydride in pyridine.

The lithium dimethylcuprate solutions were prepared by the method of Gilman,[8] using cuprous thiocyanate. The epoxides were added dropwise at −5°, and reaction progress was followed by vpc analysis of aliquots. The mixtures were quenched by adding a small amount of water and filtering. All reactions were carried out with approximately 3 mol of lithium dimethylcuprate/mol of epoxide.

The crude reaction mixtures were subjected to vpc analysis and then distilled (short path) to obtain overall yields. Further vpc analysis showed no significant fractionation; the percentages shown in the equations in the discussion section are the vpc-determined compositions of the distilled materials (*i.e.*, normalized yields.)

After 20 min, compound **1** gave an isolated 68% yield of material consisting of 73% ethyl 3-hydroxy-2,3-dimethylbutanoate[9] (**2**), nmr δ 1.1–1.5 (m, 12), 2.35 (q, J = 7 Hz, 1), 3.0 (OH), and 4.12 ppm (q, J = 7 Hz, 2), ir 870, 950, 1095, 1130–1210, 1730, 3200–3600 cm^{-1}, and 27% ethyl 2-hydroxy-3,3-dimethylbutanoate[10] (**3**), nmr δ 1.22 (s, 9), 1.27 (t, J = 7 Hz, 3), 2.37 (s, 1), 3.27 (OH), 4.11 ppm (q, J = 7 Hz, 2), ir 910, 1035, 1200, 1730, 3200–3600 cm^{-1}.

Ethyl trimethylglycidate (**4**) failed to react with the organocuprate when treated for 2 hr at −5° followed by 2 hr at 25°. Starting material was recovered in good yield.

cis-2,3-Epoxycyclohexanol (**5**) after 2 hr at −8° and subsequent conversion to the diacetate derivative[11] gave 70% of a mixture, bp 72–75° (0.7 Torr). The major product proved to be *cis*-2-hydroxy-*trans*-3-methylcyclohexanol (**6**), diacetate nmr δ 0.91 (d, J = 7 Hz, 3), 1.0–2.1 (m, 7), 1.98 and 2.03 (two s, 3 each), 4.46 (d of d, J = 1.4, 10.0 Hz, 1), and 5.19 ppm (m, 1). The minor adduct was **7**, diacetate nmr δ 0.90 (d, J = 7 Hz, 3), 0.9–2.1 (m, 7), 2.01 (s, 6), and 4.50 (t of d, J = 4.7, 11 Hz, 2).

trans-2,3-Epoxycyclohexanol (**8**) after 21.5 hr with gradual warming from −5 to 10° overnight, followed by conversion to the acetate derivative, gave 70% of a mixture, bp 92–97° (2 Torr). A significant amount (12.5%) of the acetate from unreacted starting material was obtained, with the remainder consisting of 15% of the diacetate of *trans*-2-hydroxy-*cis*-3-methylcyclohexanol (**9**), nmr δ 0.90 (d, J = 7 Hz, 3), 0.9–2.1 (m, 7), 1.99 and 2.00 (two s, 3 each), and 4.5–4.8 ppm (m, 2), and 85% of the diacetate of *trans*-3-hydroxy-*cis*-2-methylcyclohexanol (**10**), nmr δ 0.89 (d, J = 7 Hz, 3), 1.2–2.2 (m, 7), 2.01 and 2.08

(5) Epoxide–carbonyl rearrangement is a commonly observed side reaction in the lithium dimethylcuprate treatment of epoxides. For example, cyclohexene oxide gives roughly 20% of cyclohexanone.[2] In the present study these materials were not completely characterized, but appeared at short vpc retention times and exhibited carbonyl ir absorptions.

(6) B. C. Hartman and B. Rickborn, *J. Org. Chem.*, **37**, 4246 (1972).

(7) B. C. Hartman and B. Rickborn, *J. Org. Chem.*, **37**, 943 (1972).

(8) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952).

(9) S. Landa, Y. Szebenyi, O. Weisser, and J. Mastecky, *Acta Chim. Acad. Sci. Hung.*, **29**, 237 (1961).

(10) G. F. Hennion and C. F. Raley, *J. Amer. Chem. Soc.*, **70**, 865 (1948).

(11) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Amer. Chem. Soc.*, **80**, 2237 (1958); R. U. Lemieux, R. K. Kulling, H. G. Bernstein, and W. G. Schneider, *ibid.*, **80**, 6098 (1958).

(two s, 3 each), 4.72 (t of d, J = 4.5, 10.0 Hz, 1), and 5.10 ppm (m, 1).

The cis epoxy ether **11** reacted very rapidly (1 min) to give the product distribution shown in eq 4 in overall 95% yield. The acetate of **12** had nmr δ 0.85 (d, J = 7 Hz, 3), 0.9–2.1 (m, 7), 2.02 (s, 3), 3.31 (s, 3), 3.48 (m, 1), and 4.38 ppm (d of d, J = 1.4, 10.1 Hz, 1). The acetate of **13** had nmr δ 0.97 (d, J = 7 Hz, 3), 0.9–2.3 (m, 7), 1.98 (s, 3), 2.75 (t of d, J = 4.7, 11 Hz, 1), 3.31 (s, 3), and 4.38 ppm (t of d, J = 4.7, 11 Hz, 1).

The trans epoxy ether **14** after 3 hr at −5° and 2.5 hr at 25° gave 83% of a mixture having the composition shown in eq 5. The acetate of **15** had nmr δ 0.90 (d, J = 7 Hz, 3), 0.9–2.2 (m, 7), 2.00 (s, 3), 3.01 (m, 1), 3.22 (s, 3), and 4.48 (t, J = 10 Hz, 1). The acetate of **16** had δ 0.94 (d, J = 7 Hz, 3), 0.9–2.1 (m, 7), 1.96 (s, 3), 3.29 (s, 3), 3.33 (m, 1), and 4.74 ppm (t of d, J = 4.3 and 10.0 Hz, 1).

cis-2,3-Epoxycyclohexyl acetate (**17**) after 40 min at −7° gave 89% of a mixture containing 6% unreacted **17**, 29% of **6**[12] (identical with material formed in eq 2), 7% of a compound assumed to be **18** (see below), and 59% of an approximately equal mixture (by nmr, unresolved by vpc) of **19** and **21**.

This mixture was treated with acetic anhydride in pyridine, giving 93% of **6** diacetate and 7% of **7** diacetate. Combining these data allowed the determination of the product distribution shown in eq 6.

The stereospecific trans opening of the epoxide ring by lithium dimethylcuprate was evident from the mutually exclusive formation of products in, *e.g.*, eq 2 (and 6) *vs.* 3 and 4 *vs.* 5.

Registry No.—**1**, 5369-63-1; **2**, 34849-39-3; **3**, 42282-48-4; **5**, 26828-72-8; **6** diacetate, 42282-50-8; **7** diacetate, 42282-51-9; **8**, 26828-73-9; **9** diacetate, 42282-53-1; **10** diacetate, 42282-54-2; **11**, 17208-68-3; **12** acetate, 42282-56-4; **13** acetate, 42282-57-5; **14**, 2699-17-4; **15** acetate, 42282-59-7; **16** acetate, 42282-60-0; lithium dimethylcuprate, 15681-48-8.

(12) J. Klein and E. Dunkelblum, *Tetrahedron*, **24**, 5701 (1968).

Dehydrochlorination–Decarbonylation of 2-Chloro-1,3-dicarbonyl Compounds, a Method for Ring Contraction

GEORGE BÜCHI,* ULRICH HOCHSTRASSER, AND WALTRAUD PAWLAK

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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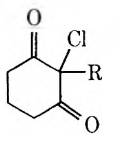
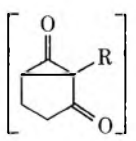
Treatment of 2-chloro-2-alkylcyclohexane-1,3-diones (**1**) with sodium carbonate in hot xylene leads to 2-alkylcyclopentenones (**3**). This new method for the



1



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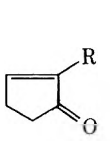


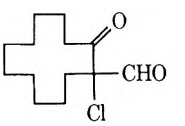
3

construction of cyclopentenones was used in efficient syntheses of methyl jasmonate and jasmone.[1] It was applied subsequently in the preparation of other cyclopentenones on the way to prostaglandins.[2,3] To survey the applicability of the new reaction, we investigated the behavior of an α-chloro-β-ketoaldehyde and two α-chloro-β-keto esters.

(1) G. Büchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971).
(2) J. Bagli and T. Bogri, *Tetrahedron Lett.*, 3815 (1972).
(3) F. Kienzle, G. Holland, J. L. Jernow, S. Kwoh, and P. Rosen, *J. Org. Chem.*, **38**, 3440 (1973).

Chlorination of 2-formylcyclododecanone with *tert*-butyl hypochlorite in chloroform solution gave the crystalline chloride **4**, whose reaction with suspended sodium carbonate in boiling xylene was slow, requiring 45 hr. The resulting cycloundecene-1-carboxaldehyde (**6**) was separated from minor amounts of 2-chlorocyclododecanone by chromatography.

tert-Butyl hypochlorite served again in the chlorination of 2-carbomethoxycyclohexanone. The resulting chloride **7** (84%) on dehydrochlorination–decarbonylation with sodium carbonate in hot xylene afforded 1-carbomethoxycyclopentene (**9**) in 71% yield.



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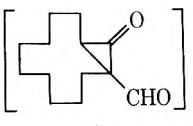

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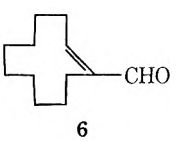

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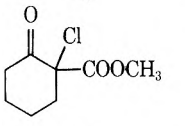

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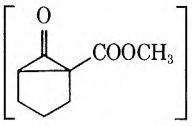

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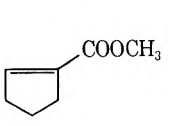


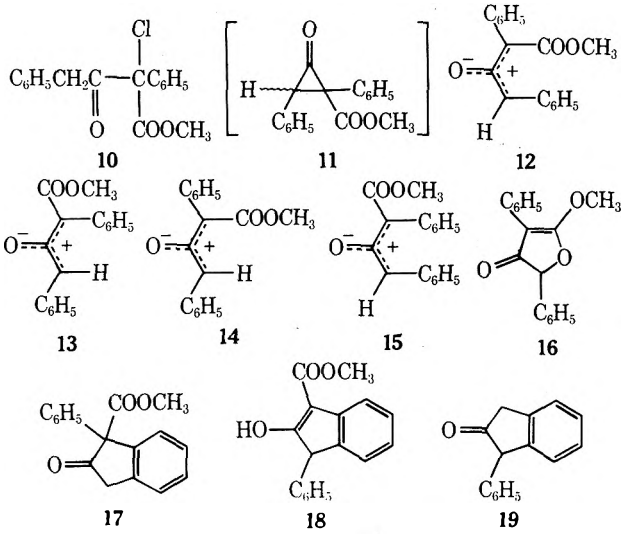
9

To study the behavior of an aliphatic α-chloro-β-keto ester, compound **10** was prepared by standard procedures. When a solution of **10** was heated in xylene over sodium carbonate, gas evolution ceased in 6 hr. Owing to the air sensitivity of some of the products, the isolation of four pure substances by chromatography was accompanied by heavy losses. The least polar, liquid material was identified as methyl (*E*)-2-phenylcinnamate (**23**, 6%) by hydrolysis to the known carboxylic acid **24**. It was followed by crystalline 1-phenyl-2-indanone (**19**, 21%). The more polar fractions contained 2-methoxy-5-oxo-3,4-diphenyl-2,5-dihydrofuran (**22**, 5%) and 2-methoxy-4-oxo-3,5-diphenyl-4,5-dihydrofuran (**16**, 14%) whose structures were deduced from spectral properties (see Experimental Section).

The products observed in the dehydrochlorination–decarbonylation of the three cyclic chlorides **1**, **4**, and **7** appear to originate from the cyclopropanones **2**, **5**, and **8** by thermal, nonconcerted elimination of carbon monoxide. Earlier work on the pyrolysis of 2-acetoxy-1,3-cyclohexanediones[4] and medium-ring 2-acetoxy ketones[5] as well as investigations on the thermolysis of 3-cyclopropyl-3-oxopropanoates[6] support this hypothesis. Thermally allowed, energetically more favorable disrotatory ring opening of these cyclopropanones to the corresponding cis–cis oxyallyl dipoles,[7] if it occurs, is nonproductive and reversible.[8] An entirely different situation prevails in the aliphatic case **10**. Two of the four phenyl-stabilized oxyallyl ions **12**–**15**, produced either directly from the enolate by ionization or, less likely, by disrotatory ring opening of the two diastereomeric cyclopropanones **11**, can cyclize to the

(4) T. A. Spencer, A. L. Hall, and C. Fordham v. Reyn, *J. Org. Chem.*, **33**, 3369 (1968).
(5) R. G. Carlson and J. H. Bateman, *J. Org. Chem.*, **32**, 1608 (1967).
(6) W. F. Berkowitz and A. A. Ozorio, *J. Org. Chem.*, **36**, 3787 (1971).
(7) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie GmbH, Weinheim/Bergstr., Germany, 1971, p 46.
(8) Compare the facile thermal racemization of optically active *trans*-2,3-di-*tert*-butylcyclopropanone with its slow decarbonylation: D. B. Sclove, J. F. Pazos, R. L. Camp, and F. D. Greene, *J. Amer. Chem. Soc.*, **92**, 7488 (1970).

ketene acetal **16** while three could cyclize to the keto esters **17** and **18**, both of which are expected to undergo decarbomethoxylation to **19** in the reaction medium.

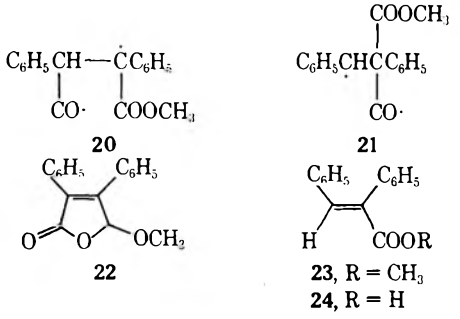


10 **11** **12**

13 **14** **15** **16**

17 **18** **19**

The cyclopropanones **11** are, however, attractive intermediates to rationalize the production of the two minor products. Methyl (*E*)-2-phenylcinnamate (**23**)

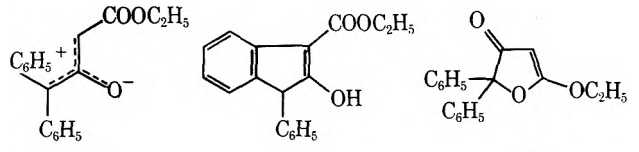


20 **21**

22 **23**, R = CH_3; **24**, R = H

results from decarbonylation of either diradical **20** or **21**. Recyclization of the former could lead to the β-butenolide and thence to the more stable α-butenolide **22** actually observed.

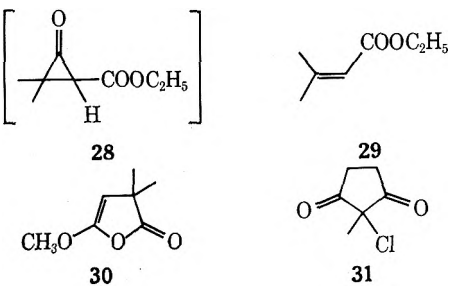
Our findings seem to be closely related to some of Kende's.[9] He found that thermal decomposition of ethyl diazoacetate in diphenylketene gave the indanone **26** and the ketene acetal **27** and hypothesized that these



25 **26** **27**

products originate from the oxyallyl intermediate **25**. Addition of ethyl diazoacetate to dimethylketene, on the other hand, yielded ethyl β,β-dimethylacrylate (**29**) and the β-butenolide **30**. The cyclopropanone **28** was postulated to be the critical intermediate and its transformation to the two products **29** and **30** is analogous to the conversion of **11** to **22** and **23**.

In summary, the dehydrochlorination–decarbonylation of 2-chloro-1,3-dicarbonyl compounds is a useful procedure for ring contraction, affording α,β-unsaturated cyclic ketones, aldehydes, and esters. It seems to be of no preparative value in the aliphatic series because reactions other than decarbonylation take place more readily. Efforts to decarbonylate the chloro diketone **31** failed and the method does not seem to serve in the synthesis of cyclobutenones.



28 **29**

30 **31**

(9) A. S. Kende, *Chem. Ind. (London)*, 1053 (1956).

Experimental Section

Microanalyses were performed in the Microanalytical Department of Firmenich SA, Geneva. Melting and boiling points are uncorrected. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian T-60 and A-60 (peaks reported in parts per million downfield from TMS as internal standard); infrared (ir), Perkin-Elmer Model 237 and A 21; mass spectrometer (mass spectrum) Atlas CH-4; ultraviolet (uv), Cary Model 14. Vapor phase chromatography (vpc) analyses were performed on F & M 720 and Varian Aerograph 1800 instruments using silicone rubber SE-30 and Carbowax 20M columns. Thin layer chromatograms (tlc) were prepared with Merck silica gel GF 254.

2-Hydroxymethylenecyclododecanone.—This substance was prepared in 73% yield according to ref 10.

2-Chloro-2-formylcyclododecanone (4).—To a stirred solution of 21.0 g (0.1 mol) of hydroxymethylenecyclododecanone in 200 ml of dry chloroform was added dropwise under nitrogen 12.8 g (0.12 mol) of *tert*-butyl hypochlorite[11] at a temperature of $-10°$ over a 30-min period. The mixture was stirred for an additional 2 hr at the same temperature and was then concentrated *in vacuo*. The residue consisted of 26 g of oily crystals, which were recrystallized from hexane to afford 20 g (80%) of 2-chloro-2-formylcyclododecanone (**4**): mp 59–61°; ir ($CHCl_3$) 1710, 1740 cm^{-1}; nmr ($CDCl_3$) δ 1.0–3.0 (20 H, m), 9.2 (1 H, s); mass spectrum (70 eV) *m/e* (rel intensity) M^+ (4.4), 209 (22), 55 (100).

Cycloundecene-1-carboxaldehyde (6).—A flask, equipped with a Dean-Stark trap, was charged with 50 g of glass beads, 11.0 g (0.105 mol) of anhydrous sodium carbonate, and 300 ml of xylene. After the contents had been heated under reflux for 1 hr, 2-chloro-2-formylcyclododecanone (**4**, 24.4 g, 0.1 mol) was added and stirring was continued at reflux under nitrogen for 45 hr. The reaction mixture was then filtered, and the filtrate was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. Distillation afforded 12.7 g (70%) of a 3:1 mixture of cycloundecene-1-carboxaldehyde (**6**) and 2-chlorocyclododecanone. These two products were separated by chromatography on a mixture of 150 g of silica gel (0.05–0.2 mm) and 50 g of silica gel GF 254, using a 1:1 mixture of benzene–chloroform as eluent. Early eluates contained 7 g of a mixture followed by 4.4 g of pure aldehyde **6**: bp 78° (0.05 mm); ir ($CHCl_3$) 1680 and 1640 cm^{-1}; nmr ($CDCl_3$) δ 9.2 (1 H, s) and 6.2 (1 H, t, J = 6 Hz); uv (EtOH) 234 nm (ϵ 14,300); mass spectrum (70 eV) *m/e* (rel intensity) 180 (10), 49 (100).

A pure sample of 2-chlorocyclododecanone was obtained by vpc collection and identified with authentic material by comparison of ir and nmr spectra.

2-Chloro-2-carbomethoxycyclohexanone (7).—To a stirred solution of 31.2 g (0.2 mol) of 2-carbomethoxycyclohexanone in 300 ml of dry methanol was added dropwise under nitrogen 23.7 g (0.22 mol) of *tert*-butyl hypochlorite at a temperature of $-10°$ over a 1-hr period. After the addition was completed, the mixture was stirred for 1 hr at the same temperature and then stored overnight in the refrigerator. The next day it was stirred

(10) V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, **30**, 1883 (1947).

(11) H. M. Teeter and E. W. Bell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 125.

for an additional 3 hr at room temperature, then concentrated *in vacuo* and distilled to give 3 g of starting material and 32 g (84%) of pure 2-chloro-2-carbomethoxycyclohexanone (**7**): bp 74° (0.1 mm); ir ($CHCl_3$) 2955, 1725, and 1440 cm^{-1}; nmr (CCl_4) δ 3.80 (3 H, s) and 1.4–3.0 (8 H, m).

Anal. Calcd for $C_8H_{11}ClO_3$: C, 50.42; H, 5.81. Found: C, 50.51; H, 5.71.

1-Carbomethoxycyclopentene (9).—Glass beads (50 g) were added to a flask containing 19.0 g (0.1 mol) of 2-chloro-2-carbomethoxycyclohexanone (**7**), 11.0 g (0.105 mol) of anhydrous sodium carbonate, and 150 ml of dry xylene. The resulting mixture was stirred at reflux for 14 hr and was then cooled, filtered, and passed through a dry column of 200 g of silica gel. After elution of the xylene with hexane, the product was washed out with chloroform. Evaporation and distillation yielded 9.0 g (71%) of 1-carbomethoxycyclopentene (**9**): bp 57° (10 mm) [lit.[12] bp 63–65° (10 mm)]; ir ($CHCl_3$) 1700 and 1620 cm^{-1}; nmr (CCl_4) δ 6.6 (1 H, s, br), 3.6 (3 H, s), and 2.7–1.7 (6 H, m); uv (EtOH) 224 nm (ϵ 9800); mass spectrum (70 eV) *m/e* (rel intensity) M^+ (32), 95 (48), 64 (100).

Methyl 2,4-diphenylacetoacetate was prepared in 78% yield according to ref 13: mp 61–63° (lit.[13] mp 59–60°); ir 1750, 1710, 1640, and 1600 cm^{-1}; nmr ($CDCl_3$) δ 3.7 (3 H, s), 3.8 (2 H, s), 4.8 (1 H, s), and 7.0–7.5 (10 H, m).

Chlorination of the Keto Ester.—To a stirred solution of 13.4 g (0.05 mol) of the above keto ester in 150 ml of dry chloroform was added dropwise under nitrogen 65 g (0.06 mol) of *tert*-butyl hypochlorite at a temperature of −10° over a 30-min period. The reaction mixture was stored for 7 days in a refrigerator and was then concentrated *in vacuo*, and the residue was diluted with an equal amount of methanol to afford 11 g (73%) of **10**, mp 50–60°. A small sample was recrystallized from methanol: mp 64–65°; ir ($CHCl_3$) 1720 and 1740 cm^{-1}; nmr (CCl_4) δ 3.7 (3 H, s), 3.8 (2 H, s), and 6.9–7.5 (10 H, m); mass spectrum *m/e* (rel intensity) M^+ (1), 184 (26), 91 (100).

Anal. Calcd for $C_{17}H_{15}O_3Cl$: C, 67.44; H, 4.99. Found: C, 67.43; H, 4.98.

"Decarbonylation" of the Chloride 10.—A flask, equipped with a Dean-Stark trap, was charged with 20 g of glass beads, 3.3 g (0.031 mol) of anhydrous sodium carbonate, and 150 ml of dry xylene. After the contents had been refluxed for 1 hr, 9.0 g (0.03 mol) of the chloride **10** was added and stirring was continued at reflux under nitrogen for 6 hr. The reaction mixture was then cooled, filtered, and concentrated *in vacuo*. The dark brown residue was chromatographed on 150 g of silica gel, using a 1:1 mixture of benzene–chloroform as eluent. Early fractions gave 2.9 g of a mixture of **23** and **19** which was rechromatographed *under argon* on silica gel (0.05–0.2 mm, 30 g) using a 4:1 mixture of hexane–ether to afford 400 mg (6%) of **23**: bp 150° (0.5 mm, Kugelrohr oven); ir ($CHCl_3$) 1720 and 1600 cm^{-1}; nmr (CCl_4) δ 3.6 (3 H, s), 6.9 (1 H, s), and 7.1–7.6 (10 H, m); uv (EtOH) 221 nm (ϵ 15,700) and 287 (22,000); mass spectrum (70 eV) *m/e* (rel intensity) M^+ (100), 177 (77), 121 (86). Hydrolysis with aqueous potassium hydroxide gave (*E*)-2-phenylcinnamic acid, mp 175° (lit.[14] mp 173°). The following fraction (1.5 g, 21% yield) consisted of a slightly yellow, exceedingly air-sensitive liquid which crystallized at −5°. Sublimation at 40° in a high vacuum gave pure **19**: mp 50° (lit.[15] mp 49–50°); ir (CCl_4) 1760 cm^{-1}; nmr (CCl_4) δ 3.5 (2 H, s), 4.6 (1 H, s), and 6.9–7.3 (9 H, m); mass spectrum (70 eV) *m/e* (rel intensity) M^+ (30), 179 (80), 178 (100), 177 (48), 165 (25), 89 (10).

Later fractions of the original chromatogram gave compound **22**, which crystallized from ether to afford 0.39 g (5%) of crystals: mp 150°; ir ($CHCl_3$) 1770 and 1650 cm^{-1}; nmr ($CDCl_3$) δ 3.7 (3 H, s), 6.2 (1 H, s), 7.2–7.6 (10 H, m); uv (EtOH) 295 nm (ϵ 10,800); mass spectrum (70 eV) *m/e* (rel intensity) M^+ (50), 238 (34), 178 (100).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 77.04; H, 5.35.

The last fraction afforded, after trituration with ether, 1.14 g (14%) of **16**: mp 111–112°; ir ($CHCl_3$) 1690, 1610, and 1590 cm^{-1}; nmr ($CDCl_3$) δ 4.2 (3 H, s), 5.6 (1 H, s), and 7.1–8.2 (10 H, m); uv (EtOH) 253 nm (ϵ 22,300) and 287 (9000); mass spectrum (70 eV) *m/e* (rel intensity) M^+ (51), 121 (100), 89 (27).

(12) S. J. Rhoads, J. K. Chattopadhyay, and E. E. Waali, *J. Org. Chem.*, **35**, 3352 (1970).

(13) J. B. Conant and A. H. Blatt, *J. Amer. Chem. Soc.*, **51**, 1227 (1929).

(14) R. Ketcham and D. Jambotkar, *J. Org. Chem.*, **28**, 1034 (1963).

(15) A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.63; H, 5.35.

Acknowledgments.—We are indebted to Firmenich SA, Geneva, for generous financial support.

Registry No.—**4**, 42367-18-0; **6**, 42367-19-1; **7**, 42367-20-4; **9**, 25662-28-6; **10**, 42367-22-6; **16**, 42367-23-7; **19**, 24017-08-1; **22**, 42367-25-9; **23**, 36854-27-0; 2-hydroxymethylenecyclododecanone, 949-07-5; 2-carbomethoxycyclohexanone, 41302-34-5; methyl 2,4-diphenylacetoacetate, 40195-49-1.

A Study of 1-Substituted Benzonorbornadienes[1]

PHILIP J. CHENIER,* STEVEN R. JENSEN, DONALD A. JESS, AND BARNETT B. ROSENBLUM

Department of Chemistry, University of Wisconsin—Eau Claire, Eau Claire, Wisconsin 54701

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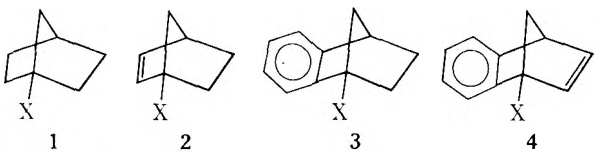
Work done on bridgehead carbinyl systems **1**,[2] **2**,[2,3] and **3**[4] has prompted us to study briefly the similar benzonorbornadiene system **4**, which has recently become available.[5–7]



1 2 3 4

a, X = Br
b, X = COOH
c, X = CH_2OH
d, X = CH_2OAc
e, X = CH_2OTs
f, X = CH_2OBs

In the solvolysis of benzonorbornenyl-1-carbinyl tosylate (**3e**) Wilt and coworkers found that π participation is precluded geometrically because of the rigid nature of the bicyclic system, preventing the twist required of the aromatic ring to achieve a phenonium ion type of geometry in the transition state for this constrained neophyl-like tosylate. They showed that tosylate **1e** solvolyzed at 50 times the rate of **3e** at 131° in acetic acid. They attributed this to the electron-withdrawing, destabilizing $-I$ effect of the aromatic ring[4] and found no phenyl migration. Bly[3] has studied brosylate **2f** and showed that acetolysis of **1f** is at least 1.3 times as rapid as that of the unsaturated tosylate **2f** at 100°, demonstrating the $-I$ effect of the double bond. They found no double-bond migration either.

(1) This investigation was supported in part by a University of Wisconsin—Eau Claire University Research Grant.

(2) J. W. Wilt, C. F. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968).

(3) (a) R. S. Bly and Q. E. Cooke, Abstracts, 148 National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1964, Paper 80-S; (b) R. S. Bly and E. K. Quinn, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Paper 91-0.

(4) J. W. Wilt, H. F. Dabek, Jr., J. P. Berliner, and C. A. Schneider, *J. Org. Chem.*, **35**, 2402 (1970).

(5) J. W. Wilt and P. J. Chenier, *J. Amer. Chem. Soc.*, **90**, 7366 (1968).

(6) J. W. Wilt and P. J. Chenier, *J. Org. Chem.*, **35**, 1562, 1571 (1970).

(7) Certain derivatives of this system have been synthesized by an entirely different route: (a) K. Wiesner and A. Philipp, *Tetrahedron Lett.*, 1467 (1966); (b) A. H. Philipp, Ph.D. Dissertation, University of New Brunswick, 1967. We thank Professor Wiesner for this information.

The present study of tosylate **4e** was undertaken for two reasons: (1) to determine if **4e**, containing both an aromatic ring and a double bond, solvolyzes slower than both **2e** and **3e** by the $-I$ effect and (2) to find if any rearrangement occurs in the absence of the easily rearranged ethano bridge of tosylates **1e**, **2e**, and **3e**.

We chose to synthesize **4e** from 1-bromobenzonorbornadiene (**4a**), previously reported.[6] Bromide **4a** was converted into benzonorbornadiene-1-carboxylic acid (**4b**) not without difficulty. Unsuccessful carbonations of organometallic reagents, including those formed from magnesium in ether, lithium in cyclohexane, and lithium in tetrahydrofuran, were followed by a successful carbonation in tetrahydrofuran of the Grignard reagent of **4a**. Reduction to benzonorbornadienyl-1-carbinol (**4c**) with lithium aluminum hydride in ether in the usual manner,[8] followed by reaction with tosyl chloride in pyridine,[9] gave tosylate **4e** in good yield. Acetate **4d** was also made from alcohol **4c**.[10]

The acetolysis of **4e** was performed at 132.5° in glacial acetic acid with 0.04 *M* sodium acetate buffer, 0.025 *M* tosylate, and 0.3% acetic anhydride. Neopentyl tosylate was solvolyzed in similar fashion at 133.5° and its solvolytic rate constant compares well with the literature value, as shown in Table I. Note

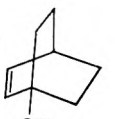
TABLE I
ACETOLYSIS STUDIES

Tosylate	Temp, °C	Ref	10^5k, sec^{-1}	k_{rel}
Neopentyl	133.5 ± 0.5		6.15	28
Neopentyl	133.0	*a*, *b*	6.8	31
Neophyl	133.0	*a*, *c*	470	2200
Norbornyl-1-carbinyl (**1e**)	133.0	*d*	27.0	120
Norbornenyl-1-carbinyl (**2e**)	132.5	*a*, *e*	7.3	34
Benzonorbornenyl-1-carbinyl (**3e**)	131.0	*d*	0.553	2.6
Benzonorbornadienyl-1-carbinyl (**4e**)	132.5 ± 0.5		0.217	1.0

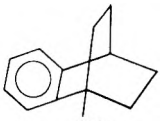
[a] Extrapolated from data at other temperatures. [b] S. Winstein and H. Marshall, *J. Amer. Chem. Soc.*, **74**, 1120 (1952). [c] S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952). [d] Reference 4. [e] Reference 3: the rate constant for the brosylate was assumed to be 2.9 times the rate of the corresponding tosylate.

that, although the temperatures for the different studies cited vary over 2°, creating an error of about 20% in k_{rel}, good qualitative conclusions can still be drawn from these values.

The benzonorbornadienyl-1-carbinyl system is an excellent example of the inductive electron-withdrawing effect of both a double bond and an aromatic ring. Tosylate **4e** solvolyzes less than $^1/_{100}$ as fast as its saturated analog **1e**, less than $^1/_{30}$ as fast as **2e** (with only the double bond), and less than $^1/_2$ as fast as **3e** (with only the aromatic ring). It is also interesting to note that tosylate **4e** behaves like norbornenyl-1-carbinyl tosylate (**2e**): a drift in rate is noticed toward the end of the acetolysis, colored side products are formed, and addition to the highly reactive double bond occurs as in the study of **2e** by Wilt. Bly[3] has shown that the drift in the rate of solvolysis of **2f** is due to the formation of the relatively unreactive brosylate **5** by methano migration and ion-pair return. He isolated **5** from the product mixture in 18% yield. Solvolysis of **3e** also gives a similar tosylate (**6**) isolated

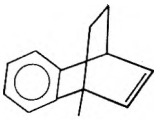


5



6

in 14% yield.[4] In our study all attempts to identify any tosylate (such as **7**) in the crude product mixture



7

failed, but it is possible that a small amount of **7** may have been missed.

Another difference between benzonorbornadienyl-1-carbinyl tosylate and the other previously studied systems is the lack of any rearrangement (with the possible exception of small amounts of **7**). Since the aromatic ring in **3e** and the double bond in **2e** do not migrate or participate, it is easily seen why neither the ring nor the double bond in **4e** undergo rearrangement. In view of the preference for ethano over methano migration in **2e** and **3e**,[3,4] it is not surprising that the methano bridge does not migrate in **4e**. Only unrearranged products were isolated from the acetolysis of tosylate **4e**. Depending on the temperature and time of solvolysis, either benzonorbornadienyl-1-carbinyl acetate (**4d**) or diacetates formed by addition to the strained double bond of **4d** were the only observed products. The diacetates were formed during a product study at 160°, whereas the rearranged monoacetate **4d** was formed in refluxing acetic acid (118°). The solvolytic rate was measured at 132.5°; so both competing reactions may be occurring at this temperature. The exact stereochemistry of the diacetates was not determined, but they are most probably *exo*-2-acetoxybenzonorbornadienyl-1-carbinyl acetate and the *exo*-3 isomer. Similar difficulties were found with tosylate **2e**.[11]

As a final proof for the strong inductive effect in the benzonorbornadienyl system, the pK_a of bridgehead acid **4b** was compared with those of the other three bicyclic structures in question. Table II summarizes the results obtained in 50% ethanol–water at 25°.

The general order of acidity is **4b** > **3b** > **2b** > **1b**; *i.e.*, as more unsaturated groups are placed on the

(8) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, pp 581–595.

(9) Reference 8, pp 1179–1185.

(10) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 247.

(11) Note also the addition of formic acid to norbornene by D. C. Kleinfelter and P. v. R. Schleyer, *Org. Syn.*, **42**, 79 (1962).

TABLE II
pK_a VALUES

Acid	Ref	pK_a
Benzoic	4	5.50
Benzoic		5.58
Norbornane-1-carboxylic (1b)	4	6.37
Norbornene-1-carboxylic (2b)	4	5.98
Benzonorbornene-1-carboxylic (3b)	4	5.88
Benzonorbornadiene-1-carboxylic (4b)		5.46

[2.2.1] skeleton, the acidity of the bridgehead acid increases because the carboxylate anion becomes more stable owing to greater electron withdrawal.

Experimental Section[12]

1-Bromobenzonorbornadiene (4a).—2-Bromobenzonorbornadiene[6] (17.5 g, 0.0800 mol) was refluxed and stirred magnetically with 48% hydrobromic acid (200 ml) for 12 hr. The mixture was diluted with water (200 ml) and extracted with petroleum ether (bp 30–60°) (4 × 50 ml). The extracts were washed with 10% sodium bicarbonate (100 ml) and water (2 × 100 ml), dried over magnesium sulfate, and rotary evaporated to a reddish-brown oil, crude 1,2-dibromobenzonorbornene (17.0 g, 0.0550 mol, 69%). The dehydrobromination with excess potassium *tert*-butoxide in *tert*-butyl alcohol was performed as described previously[6] and the product was distilled to give pure 1-bromobenzonorbornadiene (7.2 g, 0.033 mol, 41% overall from 2-bromobenzonorbornadiene) as a colorless oil, bp 90–93° (1.5 mm), identical in spectral properties with those published and free of any 2 isomer by glc.

Benzonorbornadiene-1-carboxylic Acid (4b).—Bromide **4a** (8.5 g, 0.038 mol) and magnesium (1.0 g, 0.041 g-atom) were mixed in dry tetrahydrofuran (40 ml). An iodine crystal and a few drops of dibromoethane were added and the mixture was refluxed and mechanically stirred for 5 hr. The mixture was cooled in an ice bath and dry carbon dioxide was bubbled through for 1 hr, followed by addition of Dry Ice. Sulfuric acid (10%, 300 ml) was cautiously added and the mixture was extracted with ether (3 × 75 ml). The separated ether layers were then extracted with 10% sodium hydroxide (2 × 100 ml) and the aqueous layers were acidified with 6 *N* hydrochloric acid (100 ml) to produce a white solid. The precipitate was filtered and dried to give crude benzonorbornadiene-1-carboxylic acid (4.1 g, 0.022 mol, 58%), mp 119–123°. Five recrystallizations from ligroin gave a white, crystalline solid: mp 122.2–123.0° (lit.[7b] mp 124–126°); ir (KBr) 3–4 (OH), 5.96 (C=O), 7.09, 7.72, 8.45, 10.80, 13.25, 13.90 μ; nmr ($CDCl_3$) δ 11.82 (s, 1, COOH), 6.6–7.6 (m, 6, ArH and HC=CH), 3.95 (br s, 1, CH), 2.63 (br s, 2, CH_2).

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.45; H, 5.43.

Benzonorbornadienyl-1-carbinol (4c).—Acid **4b** (4.5 g, 0.024 mol) in anhydrous ether (100 ml) was reduced with lithium aluminum hydride (2.0 g) in ether (100 ml) in normal fashion[8] to give alcohol **4c** (3.3 g, 0.019 mol, 80%), which was recrystallized once from petroleum ether: mp 54–55° (lit.[7b] mp 60°); ir (neat) 2.95 (OH), 3.24 (ArH), 3.37, 3.46 (CH), 5.80 (impurity), 6.84, 8.00, 9.5–9.9 (CO), 13.35, 13.75, 14.45 μ; nmr ($CDCl_3$) δ 6.3–7.3 (m, 6, ArH and HC=CH), 4.26 (s, 2, CH_2O), 3.26 (br s, 1, CH), 3.30 (s, 1 OH), 2.35 (d of m, 1, J = 9 Hz, anti H), 2.12 (d of m, 1, J = 9 Hz, syn H). The alcohol was used to make the tosylate and acetate.

Benzonorboranadienyl-1-carbinyl Acetate (4d).—Alcohol **4c** (1.10 g, 0.00640 mol) and acetic anhydride (4.40 g, 0.0432 mol) in pyridine (10 ml) were treated in normal fashion[10] to give acetate **4d** (1.13 g, 0.00528 mol, 83%), bp 120–140° (1 mm). The acetate was distilled twice more to obtain a pure sample: ir (neat) 3.27 (ArH), 3.4 (CH), 3.50, 5.74 (C=O), 6.90, 7.30, 8.10 (CO), 9.70 (CO), 13.35, 13.75, 14.50 μ; nmr (CCl_4) δ 6.7–7.3 (m, 5, ArH and C=CH), 6.55 (d of m, 1, C=CH, J = 6 Hz), 4.72 (s, 2, CH_2OAc), 3.7–4.0 (m, 1, CH), 2.1–2.4 (m, 2, CCH_2C), 2.03 (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.29; H, 6.76.

Benzonorbornadienyl-1-carbinyl Tosylate (4e).—Alcohol **4c** (5.74 g, 0.0334 mol) and purified tosyl chloride (12.7 g, 0.0666 mol) in pyridine (65 ml) by the usual method[9] yielded crude tosylate **4e** quantitatively. One recrystallization from petroleum ether gave mp 70–72°. Five recrystallizations gave a pure sample as white crystals: mp 71.0–71.5°; ir (melt) 3.25 (ArH), 3.35, 3.47 (CH), 6.20 (C=C), 6.80, 7.26 (S=O), 8.49 (S=O), 9.11, 10.45, 10.90, 12.40, 13.18, 13.70, 14.40 μ; nmr ($CDCl_3$) δ 7.3–8.1 (AA'BB', 4, ArH), 6.8–7.4 (m, 5, ArH and C=CH), 6.58 (d of m, 1, C=CH, J = 5 Hz), 4.71 (s, 2, CH_2OSO_2), 3.8–4.0 (m, 1, CH), 2.47 (s, 3, CH_3), 2.33 (d of m, 1, J = 8 Hz, anti H), 2.15 (d of m, 1, J = 8 Hz, syn H).

Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56. Found: C, 69.70; H, 5.65.

Kinetic Studies.—Standard procedures were followed for the acetolysis studies. Standardized 0.04 *M* sodium acetate in redistilled glacial acetic acid containing 0.3% acetic anhydride was the solvent, with a tosylate concentration of 0.025 *M*. Aliquots (2 ml) were sealed in ampoules and heated at 133 ± 0.5°. The excess sodium acetate was back-titrated in the ampoule with standard 0.014 *M* *p*-toluenesulfonic acid in acetic acid using bromophenol blue indicator (yellow to colorless end point). The first-order plot of tosylate **4e** was linear to 65% completion.

Solvolysis Products.—Two separate acetolysis product studies were performed. Tosylate **4e** (3.0 g) and sodium acetate trihydrate (1.8 g) were refluxed in acetic acid (225 ml) and acetic anhydride (3 ml) for 7 weeks. The solvent was distilled, and the solution was concentrated to 50 ml and added to solid sodium carbonate. Water was added, the products were extracted with ether, and the ether was washed with 10% sodium carbonate solution and water, dried with magnesium sulfate, and rotary evaporated to give an oil. Infrared and nmr analysis on the crude oil gave indication of only unrearranged acetate **4d**. No evidence of a tosylate was found. Glc analysis confirmed the presence of only the one acetate, **4d**.

In a second study, tosylate **4e** (2.28 g, 0.00700 mol) and anhydrous sodium acetate (1.15 g, 0.0140 mol) were dissolved in redistilled acetic acid (30 ml) containing 0.3% acetic anhydride. The mixture was heated in a pressure bottle at 160° for 10 days. The solution was diluted with water (350 ml), extracted with ether (4 × 100 ml), washed with 10% sodium bicarbonate cautiously (2 × 150 ml), water (2 × 200 ml), and brine, dried with magnesium sulfate, and rotary evaporated to a dark, viscous oil which did not resemble the acetate product above. The product was vacuum distilled to give a pale yellow oil: bp 134–138° (0.10 mm); ir (neat) 3.3–3.5 (CH), 5.81 (C=O), 6.85, 7.35, 8.20 (CO), 9.52 (CO), 10.31, 13.34 μ; nmr (CCl_4) δ 7.0–7.4 (m, 4, ArH), 4.66 (AB, 2, CH_2O, J = 20 Hz), 4.4–4.8 (m, 1, CHO), 3.3–3.5 (m, 1, CH), 2.07 (s, 3, CH_3), 2.05 (s, 3, CH_3), 1.7–2.2 (m, 4, two CH_2C). Two peaks in a ratio of 84:16 were observed by glc. They were collected together and analyzed as diacetates. Infrared, nmr, and glc data showed no indication of rearrangement.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.01; H, 6.55.

pK_a of Benzonorbornadiene-1-carboxylic Acid (4b).—The acid (0.0558 g, 0.000300 mol) was dissolved in 50% ethanol (50 ml, 1:1 absolute ethanol–distilled water by volume) and titrated with 0.0525 *N* aqueous sodium hydroxide at 24.6° while the pH was measured with a Corning Model 7 pH Meter. The pK_a was obtained from the pH at the half-neutralization point by use of a computer program designed for this purpose. Analytical reagent benzoic acid was used for a control, and its pK_a value agreed well with the literature.[4]

Registry No.—**4a**, 23537-80-6; **4b**, 5890-15-3; **4c**, 19648-23-8; **4d**, 42272-74-2; **4e**, 42272-75-3; *exo*-2-acetoxybenzonorbornadienyl-1-carbinyl acetate, 42272-76-4; *exo*-3-acetoxybenzonorbornadienyl-1-carbinyl acetate, 42272-78-6; 2-bromobenzonorbornadiene, 23537-79-3.

(12) Melting and boiling points are uncorrected. The following instruments were used: Varian T-60 nmr spectrometer, Beckman IR 8 infrared spectrophotometer, Beckman Microspec Model 1325 infrared spectrophotometer, and a Varian Aerograph Model 700 Autoprep gas chromatograph. Nmr data are given in parts per million (δ) relative to internal TMS, with the usual splitting abbreviations followed by number of protons and interpretation. Only significant ir absorptions are listed in microns (μ). Gas chromatography was performed on an SE-30 column with helium gas as carrier. Microanalyses were performed by Ilse Beetz Microanalytisches Laboratorium, West Germany, and Micro-Tech Laboratories, Skokie, Ill.

A Novel Route to 3(5)-Fluoro-1,2,4-triazoles and 8-Fluoropurines by Displacement of the Nitro Group[1]

SHAMBHU R. NAIK, JOSEPH T. WITKOWSKI,* AND ROLAND K. ROBINS

ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, California 92664

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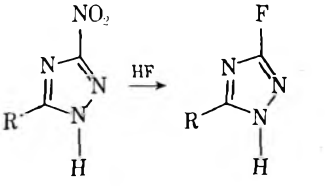
Ring-fluorinated 1,2,4-triazoles have not been previously reported and our interest in 1,2,4-triazoles has prompted us to investigate this class of heterocycles. Conventional synthetic routes to fluoro compounds are notoriously unreliable when applied to new problems. Consequently, a number of novel methods[2] have been introduced for the synthesis of fluoro compounds.

Various methods[3] for preparing fluoro derivatives starting with amino- or chloro-1,2,4-triazoles did not give encouraging results in our hands. As is the case with 7- or 9-unsubstituted purines,[2f] 3(5)-fluoro-1,2,4-triazoles with an ionizable N–H could not be obtained by displacement reactions with fluoride ion in a variety of solvents. Recently the conversion of 3(5)-nitro-1,2,4-triazoles to the corresponding halo derivatives on treatment with halogen acids has been reported.[4] The syntheses of some aromatic fluorine compounds[5] and recently certain fluoro heterocycles[6] by displacement of the nitro group with fluoride ion in high-boiling solvents have been described.

We now report that 3(5)-fluoro-1,2,4-triazoles are obtained in good yield by treatment of the corresponding nitro derivatives with hydrogen fluoride. Liquid hydrogen fluoride was utilized for this purpose to preclude the possibility of hydrolysis of the fluoro compounds at elevated temperatures. Thus, treatment of 3-nitro-1,2,4-triazole with liquid hydrogen fluoride at 150° afforded 3-fluoro-1,2,4-triazole in 80% yield. Several other examples of 3(5)-fluoro-1,2,4-triazoles prepared similarly are given in Table I.

TABLE I

SYNTHESIS OF FLUORO HETEROCYCLES[a] FROM NITRO COMPOUNDS



Registry no.	R	Temp, °C	Time, hr	Yield, %	Mp, °C (solvent of recrystn)	^{19}F nmr, δ^c	Registry no.	Ref for NO_2 compd
42297-29-0	H[b]	150	48	80	131–132 (benzene–ethyl acetate)	124.0	24807-55-4	*d–f*
42297-30-3	Br	100	36	98	113–114 (benzene)	118.3	42297-36-9	*f*
42297-31-4	$COOCH_3$	100	20	70	140–141 (benzene–ethyl acetate)	119.3	26621-28-3	*d*
42297-32-5	OH	100	36	21	125–126 (benzene–ethyl acetate)	118.3	42297-38-1	*g, h*
42297-33-6	8-Fluorotheophylline	60	16	55	245–250 dec (methanol)	106.5	2099-73-2	*i*
42297-34-7	8-Fluorocaffeine	100	20	62	162–163 (methanol)	110.5	42297-40-5	*j*

[a] Satisfactory analytical data (±0.4%) were obtained for C, H (Br), F, and N for all compounds listed in the table. [b] ^{1}H nmr (DMSO-d_6) δ 8.46 (s, 1, H-5). [c] Determined in DMSO-d_6; parts per million relative to CCl_3F as external standard. [d] Reference 4a. [e] E. J. Browne, *Aust. J. Chem.*, 22, 2251 (1969); C. F. Kroeger and R. Miethchen, *Z. Chem.*, 9, 378 (1969); L. I. Bagal, M. S. Pevzner, A. N. Frolov, and N. I. Sheludyakova, *Khim. Geterotsikl. Soedin.*, 259 (1970). [f] J. T. Witkowski and R. K. Robins, *J. Org. Chem.*, **35**, 2635 (1970). [g] Reference 4b. [h] W. Manchot and R. Noll, *Justus Liebigs Ann. Chem.*, **343**, 1 (1905); G. I. Chipen, R. P. Bokalder, and V. Ya. Grinshtein, *Khim. Geterotsikl. Soedin.*, 110 (1966). [i] B. F. Duesel, H. Berman, and R. J. Schachter, *J. Amer. Pharm. Ass.*, **43**, 619 (1954). [j] H. Schultzen, *Z. Physiol. Chem.*, 616 (1867).

These heterocycles were characterized by their ^{19}F nmr spectra (Table I).

Application of this procedure to the synthesis of some 8-fluoropurines was also successful. 8-Fluorocaffeine and 8-fluorotheophylline were obtained from the corresponding 8-nitropurines (Table I).

Analogous to 7- or 9-unsubstituted 6-fluoropurines,[2e] the 3(5)-fluoro-1,2,4-triazoles in Table I are stable to base but are hydrolyzed in acidic solution. 8-Fluorocaffeine and 8-fluorotheophylline, like 6-fluoropurines[2e]

(1) Presented in part at the Fourth International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 1973, Abstract No. B-4.

(2) (a) K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**,3060 (1971); (b) K. L. Kirk and L. A. Cohen, *ibid.*, **95**, 4619 (1973); (c) M. J. Robins and S. R. Naik, *ibid.*, **93**, 5277 (1971); (d) D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.*, **37**, 329 (1972); (e) J. Kiburis and J. H. Lister, *J. Chem. Soc. C*, 3942 (1971); (f) A. G. Beaman and R. K. Robins, *J. Org. Chem.*, **28**, 2310 (1963); (g) M. Ikehara and S. Yamada, *Chem. Pharm. Bull.*, **19**, 104 (1971).

(3) (a) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969; (b) M. Hudlicky, "Organic Fluorine Chemistry," Plenum Press, New York, N. Y., 1971.

(4) (a) L. I. Bagal, M. S. Pevzner, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin., Sb. 1: Azotsoderzhashchie Geterotsikly*, 180 (1967); *Chem. Abstr.*, **70**, 77876t (1969); (b) C. F. Kroeger, R. Miethchen, H. Frank, M. Siemer, and S. Pilz, *Chem. Ber.*, **102**, 755 (1969); (c) L. I. Bagal, M. S. Pevzner, V. Ya. Samarenko, and A. P. Egorov, *Khim. Geterotsikl. Soedin.*, 702 (1970); (d) L. I. Bagal, M. S. Pevzner, V. Ya. Samarenko, and A. P. Egorov, *ibid.*, 1701 (1970).

(5) G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, **78**, 6034 (1956).

(6) G. Bartoli, A. Latrofa, F. Naso, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1*, 2671 (1972).

and other 8-fluoropurines,[2g] are readily hydrolyzed in dilute acid.

Since both 3(5)-nitro-1,2,4-triazoles and certain 8-nitropurines[7] are readily available, this method should provide a general route to the corresponding fluoro heterocycles.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were recorded at 60 MHz for ^1H and at 56.4 MHz for ^{19}F with a Hitachi Perkin-Elmer R20A spectrometer in DMSO-d_6 solutions. Analytical data were determined by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedure.—The nitro heterocycle (20 mmol) was heated with excess (*ca.* 30 ml) liquid hydrogen fluoride in a Monel or Teflon-lined bomb under the conditions given in Table I. At the end of the reaction the bomb was cooled and volatile material was removed under a stream of nitrogen. The residue was dried in a plastic vacuum desiccator over potassium hydroxide pellets. The products were crystallized directly or in some cases were purified by chromatography over silica gel as follows. The crude product (2 g) was dissolved in methanol, and silica gel (10 g) was added to the solution. The mixture was evaporated to dryness under reduced pressure and the silica gel mixture was slurried in chloroform and applied to a small silica gel column packed in chloroform. Elution with chloroform containing 1–10% methanol provided the pure products.

Completion of the reaction and purity of the products were determined by tlc on silica gel using 9:1 chloroform–methanol. The nitro compounds and the purines were visualized under a uv light. The fluoro-1,2,4-triazoles were detected as purple spots by spraying the tlc plate first with a 1% solution of *tert*-butyl hypochlorite[8] in cyclohexane, drying the plate at room temperature, and then spraying with potassium iodide–starch solution.

(7) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **82**, 3773 (1960).

(8) Available as Unispray Aerosol Reagent from Nutritional Biochemicals Corp.; this reagent detects NH compounds.

Communications

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

Synthesis of 1-Hydroxybicyclo[*n*.1.0]alkanes from Silyl Alkenyl Ethers. A Novel Class of Cyclopropanols[1]

Summary: The reaction of trimethylsilyl cycloalkenyl ethers (**1**) with Simmons–Smith reagent gave the corresponding silyl cyclopropyl ethers (**2**), which on hydrolysis afforded 1-hydroxybicyclo[*n*.1.0]alkanes (**3**, n = 3–5) which are a novel class of cyclopropanols having the hydroxy groups at the bridgehead carbon.

Sir: Very recently Rubottom and Lopez have reported in this journal[2] the synthesis of silyl cyclopropyl ethers and cyclopropanols by the reaction of silyl alkenyl ethers with Simmons–Smith reagent. This note has prompted us to disclose our results on the synthesis of 1-hydroxybicyclo[*n*.1.0]alkanes. The synthetic method is operationally simpler and much more useful than one might evaluate it from the result of Rubottom and Lopez.

Although there has been a good deal of interest in the chemistry of cyclopropanols,[3] little has been known about 1-hydroxybicyclo[*n*.1.0]alkanes, which are a novel class of cyclopropanols having the hydroxy group at the bridgehead carbon. Aside from having intrinsic interest, this class of cyclopropanols is important as the intermediate in the Clemmensen reduction of difunctional ketones[4] and in some other rearrangements.[5] Only several isolated examples of more highly substituted, but not the parent, 1-hydroxybicyclo[*n*.1.0]alkanes have been reported in the literature,[6] except those described by Rubottom and Lopez[2] which will be mentioned later. Although a wide variety of methods have been developed for the synthesis of cyclopropanols,[3,7] most of them are not suitable or inherently not applicable for the synthesis of such cyclopropanols as 1-hydroxybicyclo[*n*.1.0]alkanes.[8]

We have now established that the transformation shown in eq 1 is an exceedingly convenient way of

(1) Synthesis *via* Silyl Alkenyl Ethers. IV. For part III see S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972). A part of this work has been presented at the Symposium on Small Ring Compounds, Oct 1972, Nagoya, Japan.

(2) G. M. Rubottom and M. I. Lopez, *J. Org. Chem.*, **38**, 2097 (1973).

(3) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968); U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **7**, 588 (1968); H. H. Wasserman, R. E. Cochoy, and M. S. Baird, *J. Amer. Chem. Soc.*, **91**, 2375 (1969); H. H. Wasserman, H. W. Adickes, and O. E. de Ochoa, *ibid.*, **93**, 5586 (1971); B. A. Howell and J. G. Jewett, *ibid.*, **93**, 798 (1971); P. v. R. Schleyer, W. F. Sliwinski, G. W. VanDine, U. Schöllkopf, J. Paust, and K. Fellenberger, *ibid.*, **94**, 125 (1972); W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *ibid.*, **94**, 133 (1972); J. R. Salaün and J. M. Conia, *Tetrahedron Lett.*, 2849 (1972); C. H. DePuy, H. L. Jones, and W. M. Moore, *J. Amer. Chem. Soc.*, **95**, 478 (1973).

(4) B. R. Davis and P. D. Woodgate, *J. Chem. Soc.*, 5943 (1965); E. Wenkert and E. Kariv, *Chem. Commun.*, 570 (1965); J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev.*, **23**, 522 (1969).

(5) R. H. Eastman and A. V. Winn, *J. Amer. Chem. Soc.*, **82**, 5908 (1960); W. von E. Doering, M. R. Willcott, III, and M. Jones, Jr., *ibid.*, **84**, 1224 (1962); W. F. Erman, R. S. Treptow, P. Bakuzis, and E. Wenkert, *ibid.*, **93**, 657 (1971); M. L. Rueppel and H. Rapoport, *ibid.*, **94**, 3877 (1972).

(6) (a) A. J. Birch and R. Keeton, *Aust. J. Chem.*, **24**, 331 (1971); (b) J. F. Templeton and W. Wie, *Tetrahedron Lett.*, 3955 (1971); (c) W. Reusch and D. P. Priddy, *J. Amer. Chem. Soc.*, **91**, 3677 (1969); (d) P. S. Venkataramani, J. E. Karoglan, and W. Reusch, *ibid.*, **93**, 269 (1971); (e) I. T. Harrison, R. J. Rawson, P. Turnbull, and J. H. Fried, *J. Org. Chem.*, **36**, 3515 (1971); (f) J. V. Paukstelis and J. Kao, *J. Amer. Chem. Soc.*, **94**, 4784 (1972).

(7) J. L. Magrane, Jr., and D. L. Cottle, *J. Amer. Chem. Soc.*, **64**, 484 (1942); J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964); H. H. Wasserman and D. C. Clagett, *Tetrahedron Lett.*, 341 (1964), and *J. Amer. Chem. Soc.*, **88**, (1966); D. T. Longone and W. D. Wright, *Tetrahedron Lett.*, 2859 (1969); H. C. Brown and S. P. Rhodes, *J. Amer. Chem. Soc.*, **91**, 4306 (1969); R. Köster, S. Arora, and P. Binger, *Angew. Chem., Int. Ed. Engl.*, **8**, 205 (1969); C. H. DePuy and R. A. Klein, *Org. Syn.*, **47**, 108 (1967); U. Schöllkopf, J. Paust, and M. R. Patsch, *ibid.*, **49**, 88 (1969).

(8) Two interesting approaches to substituted 1-hydroxybicyclo[4.1.0]-heptanes starting from alkyl enol ethers have been reported. In these studies, tetrahydropyranyl[6a] and β-chloroethyl[6b] groups were employed as the "removable" alkyl groups.

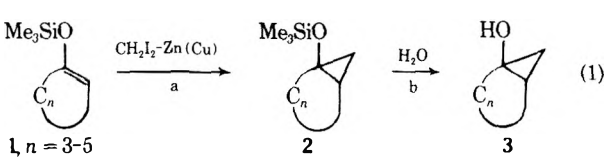
TABLE I

SYNTHESIS OF SILYL CYCLOPROPYL ETHERS AND CYCLOPROPANOLS[a]

Structure	Silyl cyclopropyl ethers (R = SiMe3)[a] Compd	Bp, °C (mm)[c]	Yield, %	Cyclopropanols (R = H)[b] Compd	Bp, °C (mm)[c] [mp, °C][c]	Ir, cm⁻¹ [d]	Nmr, δ[e]	3,5-DNB mp, °C[f]
RO	2a	66–68 (13)	76	3a	63–65 (20)	3280 3080	0.41–2.27 (9 H), 3.05 (1 H)[g]	131–132
RO	2b	84–87 (17)	71	3b	55–56 (4)	3300 3090	0.05–0.30 (1 H), 0.55–2.60 (10 H), 4.32 (1 H)[g]	113–115
RO	2c	72–75 (7)	78	3c	71–73 (8)	3300 3060	0.37 (2 H), 0.85–2.60 (11 H),[h] 3.80 (1 H)[g]	144–145
RO	2d[i]	78–85 (6)	64[j]	3d[i]	76–79 (9)	3280 3050	0.00–2.50 (13 H),[k] 3.87 (1 H)[g]	129–147[i]
RO	2e[i]	120–123 (12)	80	3e[i]	77–78 (0.5)	3300 3080	0.57–0.85 (1 H), 0.95–3.10 (18 H),[l] 4.57 (1 H)[g]	114–132[i]
RO	2f	139–143 (16)	58	3f	[106.5–107.5][m]	3350	0.90–2.92 (7 H), 2.60 (1 H),[g] 7.03–7.93 (4 H)	102–104
OR	2g	82–86 (0.2)	64[j]	3g	93–94 (0.2)	3300	0.85–1.26 (2 H), 1.56–2.73 (5 H), 4.36 (1 H),[g] 6.68–7.18 (4 H)	136–138
RO	2h	97–99 (16)	77	3h	[47–48.5][n]	3200 3100	0.03–0.37 (1 H), 0.50–2.50 (12), 3.58 (1 H)[g]	131–132

[a] Complete spectral characterization and elemental composition confirm the structural assignment. [b] Yields of the hydrolysis of 2 to 3 were quantitative. Satisfactory microanalytical data were obtained for the cyclopropanols and/or their 3,5-dinitrobenzoates. [c] Melting and boiling points were not corrected. [d] Neat liquid except for 3f and 3h (Nujol). The characteristic bands for hydroxy groups and cyclopropyl hydrogens are listed. [e] In CCl_4 except for 3f ($CDCl_3$). [f] 3,5-Dinitrobenzoates were recrystallized from a water–acetone mixture. [g] Disappeared by D_2O addition. [h] Includes a singlet at 1.18 (CH_3). [i] Mixture of ~1:1 cis and trans isomers, based on nmr. [j] For complete cyclopropanation, the reaction was repeated twice. [k] The spectra of the mixture of isomers exibited a singlet at 0.08 and two overlapping doublets at 1.02 and 1.12 (CH_3). [l] Includes two singlet at 0.81 and 0.82 [$(CH_3)_3C$]. [m] Recrystallized from benzene–hexane. [n] Sublimed at 25° (0.2 mm).

synthesizing 1-hydroxybicyclo[n.1.0]alkanes (**3**, n = 3–5). The trimethylsilyl alkenyl ethers **1** can be readily



(1)

1, n = 3-5 2 3

prepared from the corresponding ketones[9] and have electron-rich double bonds for carbenoid addition to give the silyl cyclopropyl ethers **2**, which then can be easily hydrolyzed to **3** under mild conditions without opening the acid- and base-sensitive cyclopropane ring of the products **3**.[10] Difficulty may be encountered in step a for the corresponding reaction of enol esters and in step b in the case of alkyl enol ethers.[8]

The general experimental procedure is as follows. To a suspension of zinc–copper couple[12] (0.09 mol) in anhydrous ether (110 ml) were added methylene iodide (0.08 mol) and **1** (0.05 mol). The mixture was maintained at reflux for 40 hr and worked up[13] to give **2** of

(9) (a) Yu. I. Baukov and I. F. Lutsenko, *Organometallic Chem. Rev. A*, **6**, 355 (1970); (b) H. O. House, L. J. C. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(10) Recently, the use of trimethylsilyl group in the synthesis of a cyclopropanol has been reported by Denis and Conia.[11] They prepared 1,1′-dihydroxydicyclopropyl from 2,3-bis(trimethylsiloxy)butadiene (i), which was obtained by pyrolysis of 1,2-bis(trimethylsiloxy)cyclobutene. Independently, we had obtained the same result, but were able to prepare the diene i more conveniently from biacetyl (unpublished work). See also ref 2.

(11) J. M. Denis and J. M. Conia, *Tetrahedron Lett.*, 4593 (1972).

(12) R. J. Rawson and I. T. Harrison, *J. Org. Chem.*, **35**, 2057 (1970).

(13) The solution was filtered and washed successively with cold aqueous NH_4Cl, aqueous $NaHCO_3$, and water and then dried and distilled. It is desirable to remove zinc salts by washing with NH_4Cl, while treatment with hydrochloric acid has resulted in the decomposition of **2**.

high purity (Table I). In this reaction, the amount of the solvent (*i.e.*, the reactant to ether ratio) is very important. When the Simmons–Smith reaction was carried out using the smaller amount of the solvent (*i.e.*, under higher concentration) a considerable amount of the isomer[14] of **2** was also formed. For hydrolysis to **3**, **2** (0.01 mol) was added to a mixture of methanol (30 ml) and 0.1 *N* aqueous sodium hydroxide (3 ml), and the mixture was stirred for 30 min at room temperature, evaporated under reduced pressure, taken up with ether, and dried. Removal of the ether left the practically pure **3** in quantitative yields (Table I). These cyclopropanols **3** are reasonably stable when they are pure. They remained unchanged for a few days at room temperature and can be distilled under reduced pressure. Boiling points of **3** are shown in Table I. However, they isomerize to the corresponding α-methyl ketones when heated above ~130°, dissolved in solvents, or treated with acid.[15] Therefore, it is recommended that they are best stored at the stage of stable compounds **2** and generated just before use. This is one of the principal advantages of the present method.

Rubottom and Lopez have reported very recently the similar synthesis of silyl cyclopropyl ethers **2b** and **2f** as well as cyclopropanols **3b** and **3f**.[2] However, on the work up of the Simmons–Smith reaction mixture, as well as on the hydrolysis of **2** to **3**, they treated the mixture with hydrochloric acid,[13] a reagent which, as we have observed, rapidly decomposes **2** or **3**. Consequently, they did not obtain **2** in a pure form and chromatographic separation was required. Moreover, they have described no physical constants for all compounds which they reported except the melting point of **3f**, 100–104°, whose wide range may show insufficient purity compared with that of ours, mp 106.5–107.5°. We have also synthesized 1-phenylcyclopropanol, bp 119–121° (26 mm), and 1-*tert*-butylcyclopropanol, bp 90–92° and mp 36–37°, the cyclopropanols reported in their paper[2] without any physical data.

It should be noted that the present synthesis may suggest that various types of cycloaddition reactions of **1** will provide new synthetic methods for preparing alcohols. In addition, because of high reactivity of **2** toward electrophilic reagents, **2** is also promising synthetic intermediate. For example, the reaction of **2** with bromine gave the corresponding α-bromomethyl ketones quantitatively.[16] Further study of the chemical properties of **3**, as well as those of **2**, is in progress.

Acknowledgment.—We wish to thank Emeritus Professor Shigeru Tsutsumi for his helpful discussions and encouragement. We are also grateful to Shin-Etsu Chemical Industry Co., Ltd., for providing the trimethylsilyl choloride.

(14) The isomers were found to be the trimethylsilyl ethers of 2-methylenecycloalkanols. Details will be reported in the near future.

(15) NOTE ADDED IN PROOF.—A recent report describes the conversion of silyl cyclopropyl ethers to α-methyl ketones and also to a steroidal cyclopropanol which has a 1-hydroxybicyclo[4.1.0]heptane structure; see J. M. Conia and C. Girard, *Tetrahedron Lett.*, 2767 (1973).

(16) Unpublished work.

DEPARTMENT OF PETROLEUM CHEMISTRY
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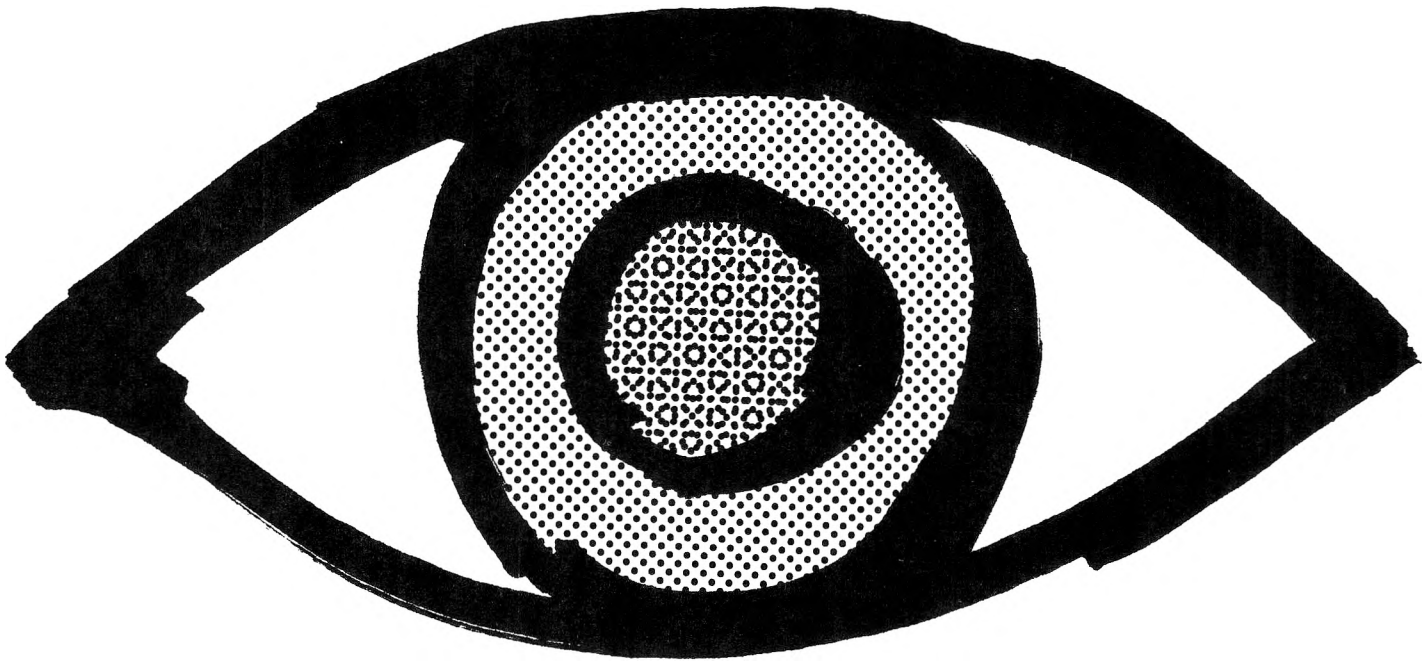

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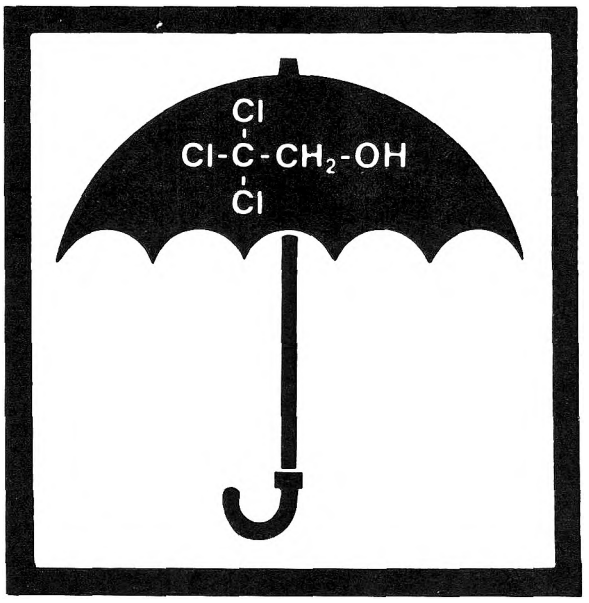
R-73

2,2,2-Trichloroethanol

Carboxylic acids are conveniently protected as their 2,2,2-trichloroethyl esters, readily formed by reacting 2,2,2-trichloroethanol with a carboxylic acid and dicyclohexylcarbodiimide. The protecting group is easily removed by stirring the esters with zinc and acetic acid at room temperature.[1] 2,2,2-Trichloroethyl esters have been used extensively in the synthesis of Cephalosphorin C[1] and oligonucleotides,[2,3] in prostaglandin work[4] and in penicillin chemistry.[5] In addition 2,2,2-trichloroethanol is used in the production of anthelmintics, herbicides, hypnotics and insecticides.



References

1) R. B. Woodward *et al.*, *J. Amer. Chem. Soc.*, **88**, 852 (1966).
2) J. Smrt, *Collection Czech. Chem. Commun.*, **37**, 1870 (1972).
3) T. Neilson and E. S. Werstiuk, *Can. J. Chem.*, **49**, 3004 (1971).
4) J. E. Pike *et al.*, *J. Org. Chem.*, **34**, 3552 (1969).
5) R. D. Cooper, Fr. Patent 1,561,048.

T5480-1 2,2,2-Trichloroethanol
100 g $5.00; 500 g $16.00; 10 kg $270.00

D8000-2 Dicyclohexylcarbodiimide
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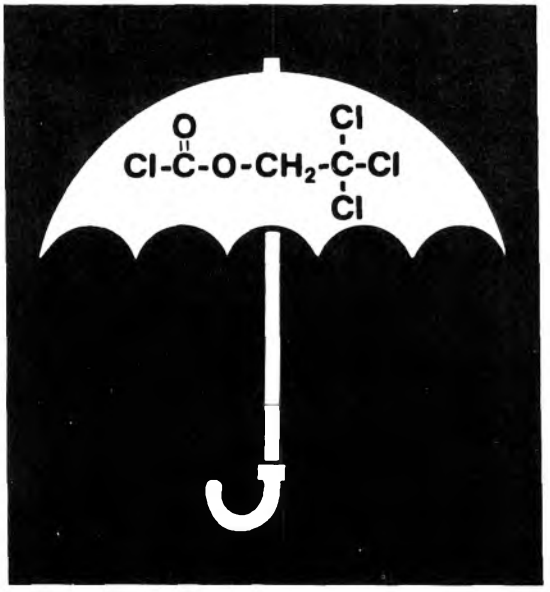

2,2,2-Trichloroethyl chloroformate

2,2,2-Trichloroethyl chloroformate is an excellent protecting agent for both aliphatic and aromatic hydroxy and amino groups.[1] The 2,2,2-trichloroethoxycarbonyl group is easily removed by stirring for 1-3 hours at room temperature with zinc and acetic acid or by brief reflux with zinc in methanol, yet is unaffected by mild hydrogenation conditions, Sarett and Jones oxidations, treatment with hydrochloric acid in dioxane or brief treatment with trifluoroacetic acid. This protecting group has been used, for example, in a convenient synthesis of unsymmetrical 1,2-diacylglycerols.[2]

References

1) T. B. Windholz and D. M. R. Johnston, *Tetrahedron Lett.*, **27**, 2555 (1967).
2) F. R. Pfeiffer *et al.*, Unchecked Procedure, *Org. Syn.*, **50**, 1970.

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† Deci-mole units

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