REACTIONS OF BRIDGED BICYCLIC COMPOUNDS

By
Allan Cameron Oehlschlager
Bachelor of Science
Oklahoma State University
Stillwater, Oklahoma
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Thesis Approved:

Leon H. Zalkow
Thesis Adviser

Louis P. Varga

Norman D. Heindel

O. C. Dermer

J. J. Boggs
Dean of the Graduate School

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CHAPTER I

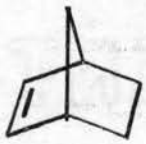
THE REACTION OF BENZENESULFONYL AZIDE WITH BRIDGED BICYCLIC ALKENES

A. Historical and Introduction

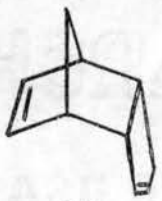
Over fifty years ago phenyl azide was reported to react with acetylene to give 1-phenyltriazole, on heating the reactants in an acetone solution in a sealed tube at 100° for 20 hr.[1] Later it was found that bicyclo(2.2.1)-2-heptene (I) and its derivatives reacted with phenyl azide in the cold to form triazolines which usually crystallized from the solution after only a few minutes.[2] Since only strained alkenes were found to react readily with phenyl azide, the reaction soon became a diagnostic test for angular strain in double bonds. A classic example of this is the preferential reaction of phenyl azide with the double bond in the bicyclic ring of dicyclopentadiene (II) to give triazoline III. Recently, Huisgen and his associates[3] have found that the azide-alkene reaction is only one member of a large group of reactions which they refer to as "1,3-dipolar cycloadditions." The addition of the 1,3-dipole to the alkene occurs by a simultaneous multicenter process[3] which usually involves only slight charge imbalance in the transition state.[3,4]

The azide-alkene reaction has received considerable attention from a number of investigators. This interest stems, in part, from the potential use of the triazoline products in the synthesis of

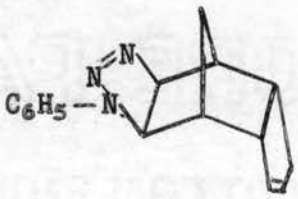
substituted aziridines via loss of molecular nitrogen.[5] Under the conditions necessary for the addition of alkyl and aryl azides to alkenes possessing a high degree of angular strain, the triazoline adduct is usually isolated. However, as has recently become apparent, when azides containing strong electron-withdrawing groups such as picryl,[6] benzoyl,[7] or p-toluenesulfonyl[8] react with bicyclic alkenes the products obtained at room temperature or below are usually not triazolines but rather correspond to 1:1 adducts minus molecular nitrogen. At the inception of this work the only report of the reaction of an azide containing a strong electron-withdrawing group with bicyclic alkenes was that of Bruner.[8] He found that p-toluenesulfonyl azide reacted at room temperature with both I and II and with the bicyclic anhydrides IV and V at higher temperatures to give products which in each case gave analyses corresponding to the addition of a mole of the azide to one mole of the alkene followed by the loss of a mole of nitrogen from the adduct. He, however, provided no chemical evidence to support structures for any of the aforementioned products, but suggested that the dicyclopentadiene derivative possessed the sulfonimide ($C_6H_5SO_2N{=}C$) structure.



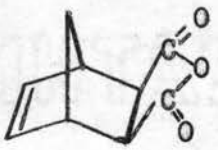
I



II



III

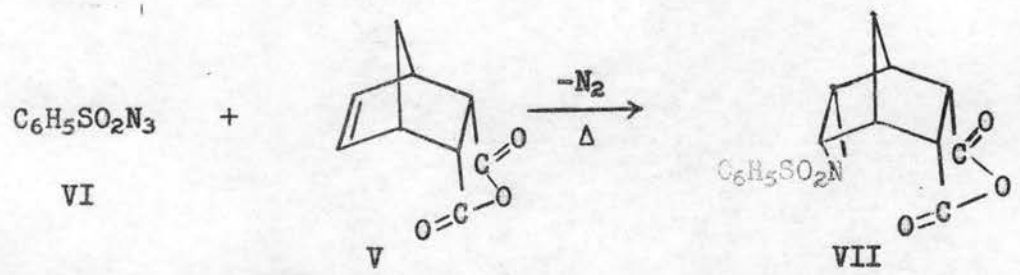


IV

During the course of work in our laboratory, Huisgen[7] reported that the reaction of benzoyl azide and p-toluenesulfonyl azide with I led to products possessing the aziridine structure, but he provided

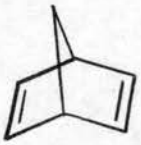
no supporting chemical evidence.

In conjunction with the present investigation, other work in this laboratory has shown that benzenesulfonyl azide reacts with bicyclo(2.2.1)-5-heptene-endo-cis-2,3-dicarboxylic anhydride (V) in refluxing carbon tetrachloride to give predominantly the endo aziridine VII.[9]

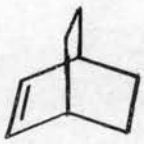


The present investigation was undertaken in order to: 1) study the course of the reaction of benzenesulfonyl azide (VI) with bicyclic alkenes; 2) establish the structure of the addition products; 3) study the reactions of the addition products.

The alkenes chosen for this study were bicyclo(2.2.1)-2-heptene (I), bicyclo(2.2.1)-2,5-heptadiene (VIII), dicyclopentadiene (II), bicyclo(2.2.2)-2-octene (IX), bicyclo(2.2.1)-5-heptene-exo-cis-2,3--dicarboxylic anhydride (IV), and its endo isomer V. Each of these (except IX) possesses the bicyclo(2.2.1)heptane nucleus and they vary only in the electronic and steric factors surrounding positions 5 and 6 of the carbon skeleton. Because of the rigid geometry of the bicyclo(2.2.1)heptane ring system, each olefinic linkage possesses very nearly the same amount of angular strain and one is afforded an opportunity to study the directive effects of 5,6 substitution on the course of the azide addition reaction without the serious complication of conformational effects.



VIII

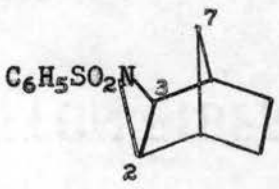


IX

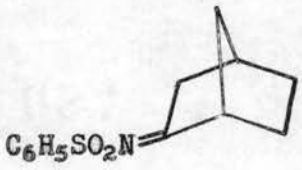
B. Results and Discussion

1. The Structure and Reactions of the 1:1 Adduct of Benzenesulfonyl Azide and Bicyclo(2.2.1)-2-heptene

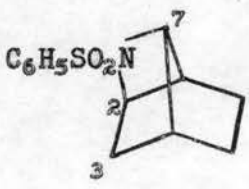
When benzenesulfonyl azide was added to bicyclo(2.2.1)-2-heptene (I) in benzene or petroleum ether at room temperature, an exothermic reaction occurred with evolution of nitrogen, and the product, which could be isolated in quantitative yield, began to crystallize from the solution almost immediately. The infrared and n.m.r. spectra of the product of the reaction, X, showed that it contained the benzenesulfonamido group, but no N-H band appeared to be present. The three structures XI, XII, and XIII are consistent with the elemental and spectral data and may be expected on mechanistic and steric grounds. Structure XII, however, could be eliminated by examination of the n.m.r.



XI



XII

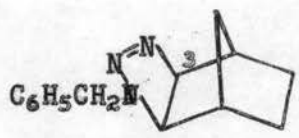


XIII

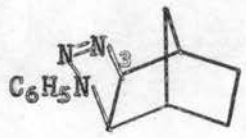
spectrum of the product, X, which showed two protons on carbon attached to the nitrogen of the benzenesulfonamido group.

In order to determine which of the remaining structures (XI or XIII) was correct, a model compound was synthesized for direct n.m.r.

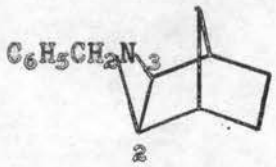
comparison. The triazoline adduct (XIV) of I and benzyl azide was prepared by the usual method and its n.m.r. spectrum was essentially identical to that of the known phenyl azide adduct of I (XV). In XIV the C_2 and C_3 protons appeared as a pair of doublets (J = 9.8 c.p.s.) at δ 2.98 and δ 4.25 respectively. The n.m.r. spectrum of XV gave a similar AB quartet (J = 9.5 c.p.s.) with the C_2 proton centered at δ 3.54 and the C_3 proton at δ 4.42. Such large AB coupling constants are expected for a 2,3-attachment of the triazoline rings in XIV and XV but are clearly not consistent with the alternative 2,7-arrangement.[10] Additional support for the structure of XIV was provided by its conversion (by G. A. Cabat) to cis-1,3-cyclopentanedicarboxylic acid by hydrogenation in the presence of Raney nickel followed by basic permanganate oxidation. Ultraviolet photolysis of XIV at room temperature in hexane gave XVI.[5] No molecular rearrangement would be expected in the conversion of XIV to XVI because of the known resist-



XIV



XV



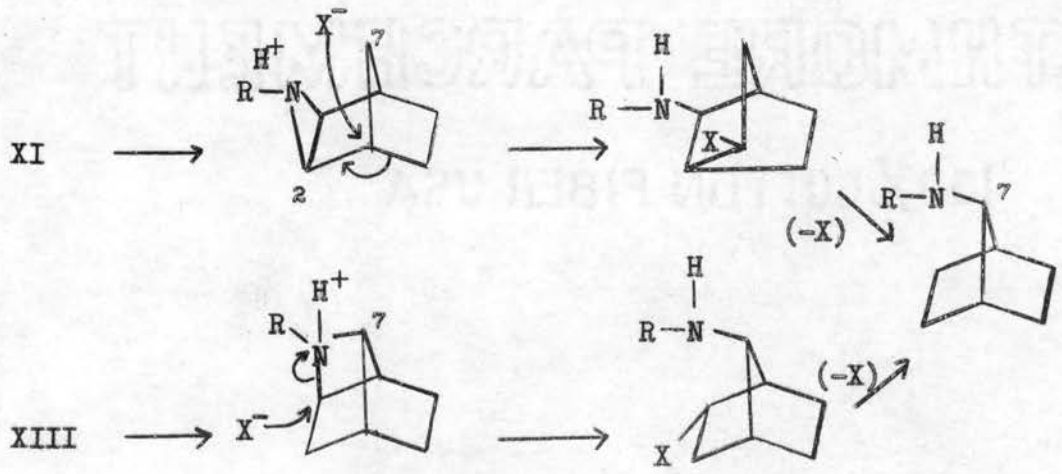
XVI

ance of 3-norbornyl free radicals to rearrangement.[11] The n.m.r. spectrum of the bicyclic aziridine XVI showed a sharp singlet for the protons on carbon attached to nitrogen at δ 1.40, whereas in X the corresponding signals appeared as a sharp singlet at δ 2.84. If the correct structure of X were XIII, then it would be suprising that the C_2 and C_7 protons were equivalent and that the endo C_2 proton was not split by the endo C_3 proton. In XVI the C_7 protons appeared as a pair

of doublets ($J = 9$ c.p.s.) centered at δ 0.63 and 1.63. An examination of the n.m.r. spectrum of X did indeed reveal a possibility of an AB type splitting similar to that observed above for the C_7 protons of XVI and this was the following: a doublet ($J = 10$ c.p.s.) centered at δ 0.70 could be assumed to arise from one of the protons at C_7 of XI, and the second doublet arising from the other C_7 proton, since it was not obvious, could be assumed to be hidden in the complex group of peaks at δ 1.2-1.6. The signal at δ 0.70 in the spectrum of X may arise from one of the C_3 protons of XIII; however, this possibility would be expected to lead to a more complex pattern. Although the n.m.r. spectrum of X did not allow an unambiguous decision between structures XI and XIII,[12-14] the similarity of the n.m.r. spectrum of X and XVI strongly favored the assignment of structure XI to X.

In order to distinguish chemically between structures XI and XIII, cleavage of the nitrogen-containing ring to give a benzenesulfonamido derivative seemed appropiate. Structure XI would lead to a 2-amido derivative, whereas the 7-amido derivative would be expected from XIII, since displacement would occur at C_2 rather than at C_7.[15] Bruner[8] reported that the adduct formed between dicyclopentadiene and p-toluenesulfonyl azide was unchanged by alcoholic potassium hydroxide and hot glacial acetic acid, whereas strong mineral acids gave unidentifiable products. The nitrogen-containing ring of X was readily opened with hydrogen bromide and hydrogen chloride in carbon tetrachloride, with acetic acid and with neutral, acidic, and alkaline aqueous solutions. Opening of the nitrogen-containing ring of X under acidic conditions does not provide suitable evidence for use in

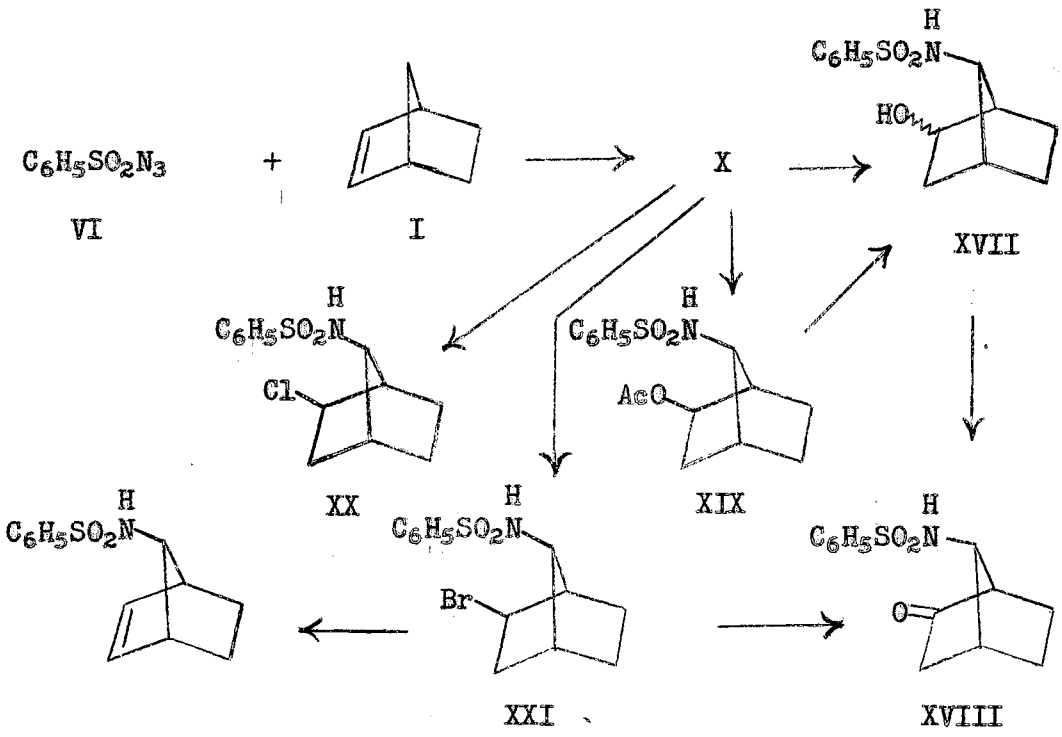
distinguishing between structures XI and XIII, since under carbonium-ion conditions both structures could lead to the same 7-amido derivatives, as shown below.



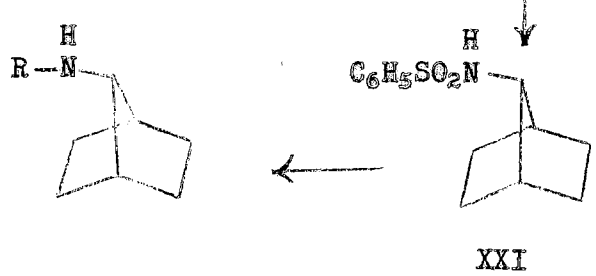
When the nitrogen-containing ring of X was opened by neutral and alkaline aqueous solution, the major product was the same alcohol XVII β, m.p. 142-144°, as isolated in the acid-catalyzed ring opening. This alcohol was also obtained by treating X with acetic acid followed by saponification. In addition, a second alcohol (XVIIα) was obtained in the neutral, acid, and alkaline hydrolysis but only to a minor extent, except in the acid hydrolysis. Both N-H and O-H bands were clearly visible in the infrared spectrum of XVII β. Oxidation of XVII β with chromic anhydride in acetic acid gave ketone XVIII. The latter ketone was also obtained from the bromide XXI, itself obtained by treating X with hydrogen bromide, by hydrolysis in aqueous lithium carbonate solution followed by oxidation with chromic anhydride. Compound XVIII showed an N-H band at 3130 $cm.^{-1}$ and a carbonyl band at 1725 $cm.^{-1}$ in its infrared spectrum indicating that the carbonyl function

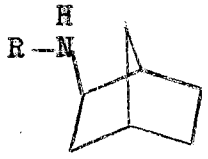
was in a six-membered ring. Wolff-Kishner reduction of ketone XVIII gave 7-benzenesulfonamidobicyclo(2.2.1)heptane (XXII). That the benzenesulfonamido group was attached at C_7 was shown as follows. Both 2-*exo* and 2-*endo*-aminobicyclo(2.2.1)heptane were prepared by known procedures and converted into their *N*-benzenesulfonyl derivatives. Melting point comparisons of the *N*-benzenesulfonyl derivatives were not found useful. However, thin layer chromatography showed that XXII was not identical with either 2-*endo*-benzenesulfonamidobicyclo(2.2.1)-heptane (XXXIII) or 2-*exo*-benzenesulfonamidobicyclo(2.2.1)heptane (XXIX) and was less polar than either of these two isomers. Sulfonamide XXII was hydrolyzed with aqueous hydrochloric acid by heating at 150 -175° in a sealed tube for 12 hr. The amine XXIII thus obtained was converted into its *N*-acetyl derivative XXII, which was compared with 2-*exo*-acetamidobicyclo(2.2.1)heptane (XXVII) and 2-*endo*-acetamidobicyclo(2.2.1)heptane (XXXI) by melting point and gas chromatography. Again melting point comparisons were not conclusive, but gas chromatographic analysis showed that XXIV was less polar than either the 2-*exo* or 2-*endo* isomer.

The *N*-chloroacetyl derivatives of 2-*exo*-, 2-*endo*-, and 7-aminobicyclo(2.2.1)heptane had been reported to have significantly different melting points; therefore this derivative was also prepared in each case. The melting point of the *N*-chloroacetyl derivative of XXIII (XXV) checked closely with that reported for the 7-amino derivative. Mixture melting points with the 2-*exo* and 2-*endo* isomers again, although slightly depressed, were not conclusive. Thin layer chromatography showed that XXV was not identical with *exo*-(XXVIII) or *endo*-*N*-2-

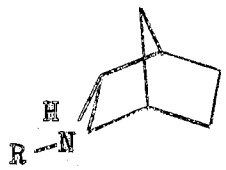


XXIII, R = H
XXIV, R = CH_3CO
XXV, R = $ClCH_2CO$



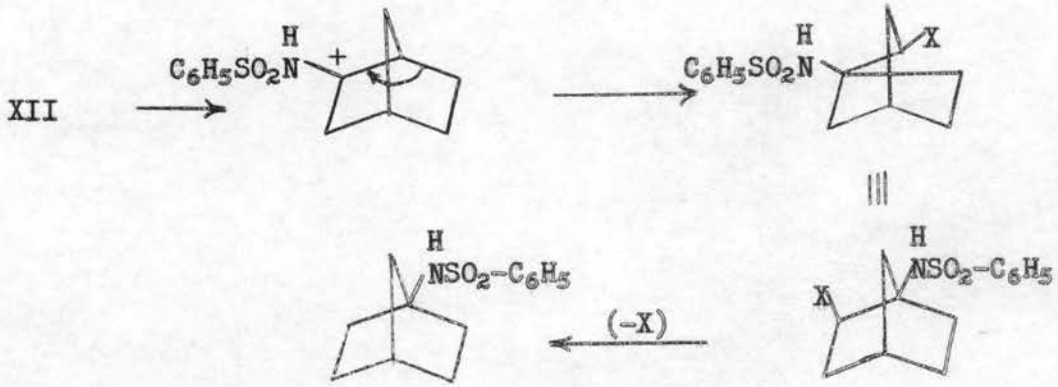


XXVI, R = H
XXVII, R = CH_3CO
XXVIII, R = $ClCH_2CO$
XXIX, R = $C_6H_5SO_2$



XXX, R = H
XXXI, R = CH_3CO
XXXII, R = $ClCH_2CO$
XXXIII, R = $C_6H_5SO_2$

-chloroacetylaminobicyclo(2.2.1)heptane (XXXII). This evidence conclusively established that the nitrogen-containing moiety of XXII and its derivatives was not attached at positions 2, 3, 5, or 6 of the bicyclo(2.2.1)heptane nucleus; this leaves only positions 7 and the bridgehead positions as possibilities. Mechanistically, attachment at the bridgehead position seems unlikely although one can visualize a 1--aminobicyclo(2.2.1)heptane derivative arising from structure XII as follows.



XXXIV

That XXII was not represented by structure XXXIV was shown by its n.m.r. spectrum which clearly indicated that the nitrogen-containing moiety was attached to a carbon bearing one proton. This proton appeared as a doublet (J = 5 c.p.s.) centered at δ 3.01, splitting arising from the hydrogen attached to nitrogen which itself appeared as a doublet (J = 5 c.p.s.) at δ 5.93. Upon the addition of deuterium oxide the former signal collapsed to a singlet and the latter disappeared from the spectrum.

These data can be interpreted in two ways. First, one can assume that the correct structure of X is XI and that in neutral and even in

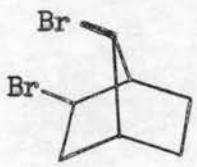
alkaline solution the aziridine ring slowly opens in an S_N1 reaction with skeletal rearrangement to give XVII. In such a case the hydroxyl group of XVII may be either exo or endo. If the correct structure of X is XI, the ring opening to yield XVII should not be base catalyzed (S_N2) since this would lead not to XVII, but to 2-exo-benzenesulfonamido--3-endo-hydroxybicyclo(2.2.1)heptane. The second interpretation is that the correct structure of X is XIII, and the azetidine ring is opened either by S_N1 or S_N2 solvolysis to yield XVII. In an S_N1 solvolysis the hydroxyl group in XVII might be either exo or endo, but in an S_N2 solvolysis it would be endo.

In order to test these two possibilities it was necessary first to examine carefully product XVII obtained in the hydrolytic ring opening of X. The alcoholic products obtained in the neutral, acidic, and alkaline hydrolyses were compared by thin layer chromatography. In each case mixtures were obtained, but in neutral and alkaline solutions one product. XVII β, was by far predominant. As mentioned earlier, basic hydrolysis of XIX gave XVII β. The n.m.r. spectrum of XIX showed the hydrogen at C_2 as a triplet (J = 5 c.p.s.) at δ 4.70. A similar triplet (J = 6 c.p.s.) is observed for the 2-endo proton of XXXV, strongly suggesting the acetoxy group in XIX possesses the exo configuration; therefore XVII β must possess a 2-exo-hydroxyl group. A second isomeric alcohol, XVII α, obtained to only a minor extent in the neutral and alkaline solvolyses, was present in somewhat larger amounts in the acid hydrolysis product. Oxidation of XVII α likewise gave XVIII. The structures of XVII β and XVII α must, therefore, be 2-exo- and 2-endo--hydroxy-7-syn-benzenesulfonamidobicyclo(2.2.1)heptane, respectively.

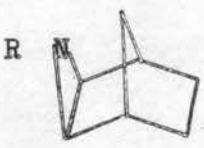
Base catalysis was indicated in the ring opening reaction by measuring the extinction of the N-H peak in product XVII by infrared spectroscopy, using various base concentrations and water. The ring opening was found to be faster in more concentrated base, but the concomitant formation of XVII β suggested slow S_N1 ring opening of XI accelerated in more concentrated base owing to the increased ionic strength of the solvolytic medium (salt effect). Although these data do not allow an unambiguous assignment the total weight of evidence strongly suggests that the correct structure of X is the aziridine XI.

Conclusive proof that X is represented by structure XI has recently been obtained in this laboratory by chemical correlation of X with XVI. Thus, reduction of XXXVI, prepared as previously described,[7] with lithium aluminum hydride, using inverse addition of the latter, afforded XXXVII which was converted into XI, XVI, and XXXVI by treatment with the appropriate chloride in pyridine.[13]

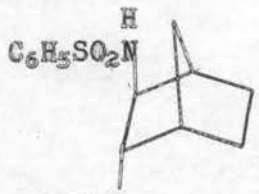
More recently, additional chemical evidence for the aziridine structure has been obtained by S_N2 cleavage of the nitrogen-containing ring by potassium thiophenoxide to yield 2-endo-thiophenoxy-3-exo--benzenesulfonamidobicyclo(2.2.1)heptane (XXXVIII).[14]



XXXV



XXXVI, R = C_6H_5CO
XXXVII, R = H

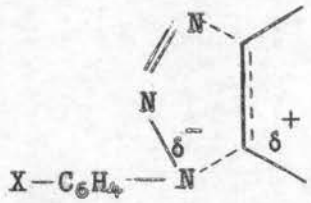


XXXVIII

A second product, formed in small amounts when the reaction of benzenesulfonyl azide (VI) and I was conducted at slightly higher temperatures (ca. 40°), was identified as XII by its ready hydrolysis

to bicyclo(2.2.1)-2-heptanone and benzenesulfonamide.[13]

A recent kinetic study of substituent effects by Scheiner and coworkers[4] has shown that the addition of substituted phenyl azides to bicyclo(2.2.1)-2-heptene proceeds by a multicenter mechanism involving a transition state (XXXIX) in which considerable negative charge may reside on the α-azido nitrogen. In this respect it is noteworthy that

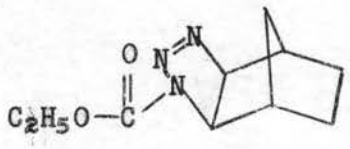


XXXIX

the addition of p-nitrophenyl azide proceeds much faster than expected from a simple Hammett treatment, suggesting that this substituent stablizes the transition state in an exceptional manner. In a similar manner, the strongly electron-withdrawing picryl, benzoyl, and benzenesulfonyl groups would be expected to stabilize such a transition state. One is then faced with the fact that azides containing these strong electron-withdrawing groups react with I without giving the expected triazoline even at room temperature.

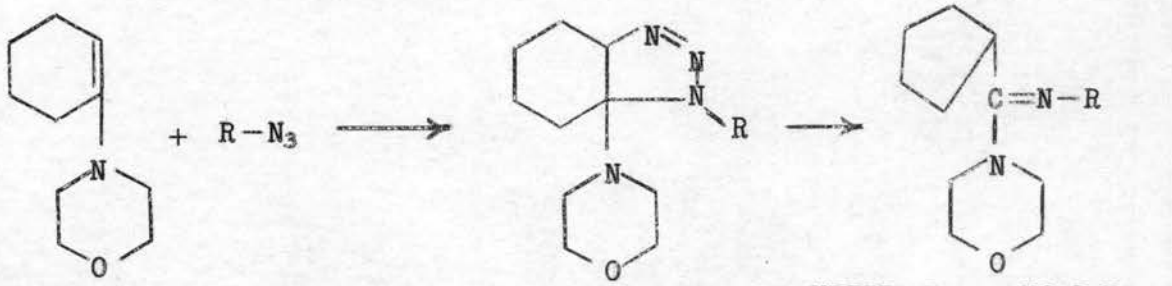
It has been postulated[14] that the addition of benzenesulfonyl azide to I does not proceed by a 1,3-dipolar addition (i.e., a triazoline intermediate) but rather involves an epoxide-type transition state. The recent report[5] of the detection of XL in the reaction of ethyl azidoformate with I, coupled with its reported thermal instability (it decomposes at 70°C) compared to aryl-substituted triazoline adducts of I (which decompose in excess of 150°C), points strongly to a decrease in stability of 1-substituted Δ^2-1,2,3-triazoline as the 1-substituent

becomes more electronegative.



XLI

A similar decrease in stability of 1-substituted Δ^2-1,2,3-triazoline is seen in the reaction of substituted aryl azides with enamines.[16] Thus while XLI, formed upon addition of p-nitrophenyl azide to XLII, must be heated above 150° to give XLIII, the addition of 2,4-dinitrophenyl azide or p-toluenesulfonyl azide to XLII at room temperature gave XLIV and XLV directly.[16]



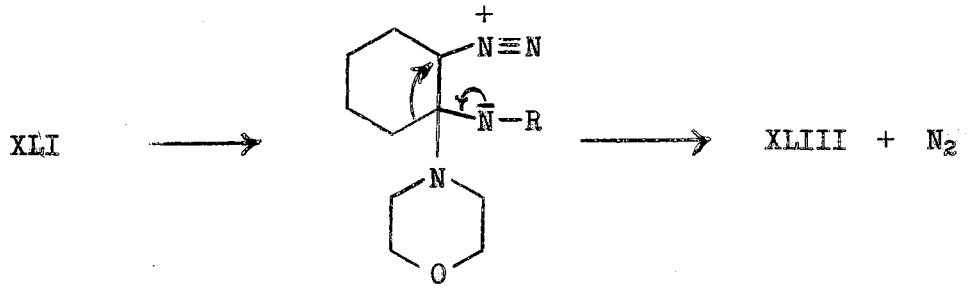
XLII

XLI, R = p-$NO_2C_6H_4$

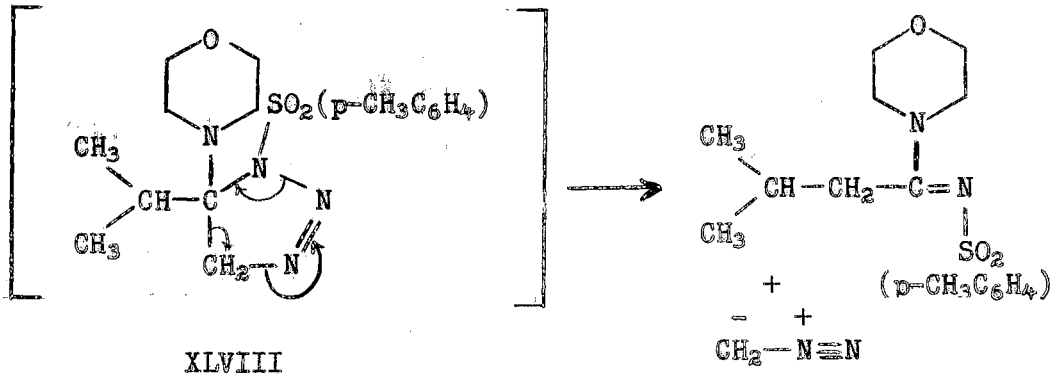
XLIII, R = p-$NO_2C_6H_4$
XLIV, R = 2,4-$(NO_2)_2C_6H_3$
XLV, R = p-$CH_3C_6H_4SO_2$

These data indicate that nitrogen evolution, upon the addition of azides possessing strong electron-withdrawing groups to I, is not due to a change in the mechanism of addition but to instability of the intermediate 1-substituted triazoline. A clue to the reason for this instability may lie in the mode of rearrangement of XLI to XLIII. This rearrangement has been postulated[16] to proceed through the diazonium betaine XLVI. Support for this mode of rearrangement comes from the isolation (via esterification of benzoic acid) of the diazomethane arising from the decomposition of the triazoline intermediate XLVII formed upon the

addition of p-toluenesulfonyl azide to 2-morpholino-3-methyl-1-butene.[16]



XLVI



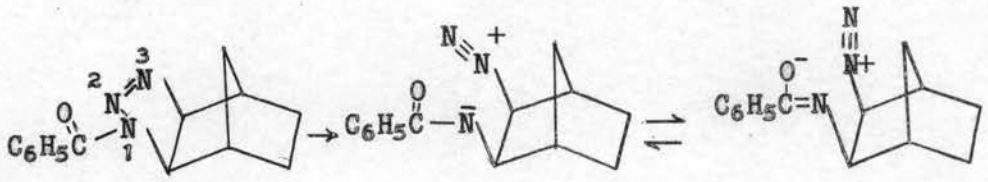
XLVIII

The decomposition of olefinic azides containing unsaturation 2, 3, 4, and 5 bonds away from the azide group has been recently reported.[17] In these cases the azide function adds intramolecularly to the double bond to give a triazoline which opens in the rate determining step, presumably[17] via a diazonium betaine intermediate to give evolution of nitrogen and imine and azfiridine products.

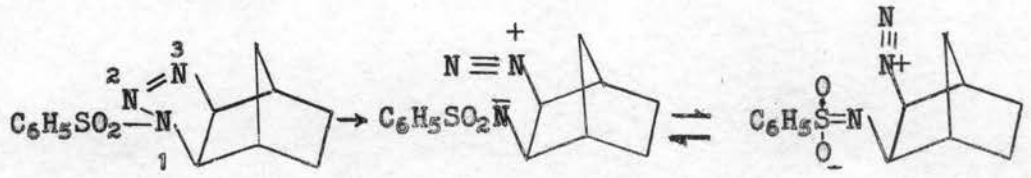
It appears (see above) that although azides containing strong electron-withdrawing groups may react with I at enhanced rates owing to delocalization of the negative charge on the α-azido nitrogen in the transition state, the ability of a substituent to extensively de-

localize such a charge at N-1 of the incipient triazoline may also result in its decomposition with simultaneous loss of nitrogen.

A priori, it would seem that formation of a diazonium betaine in the case of the 1-benzoyl-(XLVIII) and 1-benzenesulfonyl-(XLIX) triazolines of I would be favored by the delocalization of the electronic charge on N-1 by these electronegative groups as shown below. The betaine

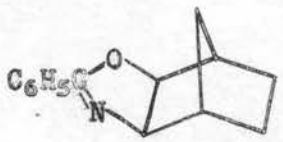


XLVIII L LI



XLIX LII LIII

L would be expected to give aziridine XXXVI, while oxazoline LIV can be visualized as arising from resonance form LI. Indeed both XXXVI and



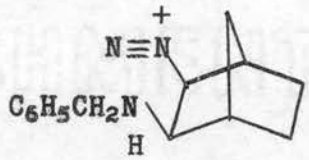
LIV

LIV are formed during the addition of benzoyl azide to I at room temperature, conditions which preclude the thermally induced rearrangement of XXXVI to LIV.[7] The absence of rearranged products such as azetidines (e.g. XIII) is, ipso facto, indication that no participation of the C_4, C_5 bonds of L -LIII is involved in the decomposition process. Studies of

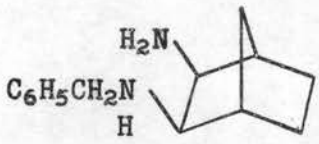
the decomposition of aliphatic diazonium ions[19] and closely related diazo esters[18] show that neither solvent nor neighboring group participation play much role in the breaking of $C-N_2^+$ bonds. The fate of the "high-energy" carbonium ions developed during these reactions is determined by the relative proximity of the various neighboring groups and solvent molecules.[19] In the betaines in question the residual nitrogen is ideally suited both electronically and sterically for closure to XXXVI and XI respectively.

The formation of XII from LII requires a 2,3 hydride shift. The fact that a hydride shift occurs under such mild conditions is also reason to suspect a highly reactive cationic type intermediate during the reaction. This is apparently analogous to the formation of XLIV upon treatment of XLII with 2,4-dinitrophenyl azide under similar conditions.[16]

Acid-catalyzed decomposition of aryltriazolines derived from I to amino alcohol derivatives[20] probably involves an intermediate similar to those discussed above. The acid-catalyzed decomposition of XIV would be particularly suitable for study in that the proposed intermediate LV could be generated by diazotization of LVI, which has been prepared[13]



LV



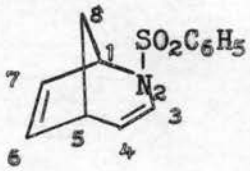
LVI

from XIV by hydrogenation in the presence of Raney nickel catalyst. Since both the acid-catalyzed decomposition of XIV and the diazotization of LVI could be done under similar conditions a correlation of the

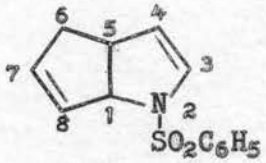
products obtained in each case would provide information useful in the evaluation of LV as an intermediate in the acid decomposition of XIV.

2. The Structure and Rearrangement of the 1:1 Adduct of Benzenesulfonyl Azide and Bicyclo(2.2.1)-2,5-heptadiene

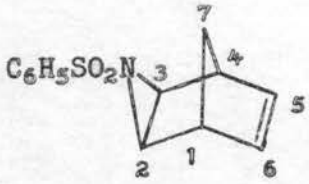
The reaction of benzenesulfonyl azide with bicyclo(2.2.1)-2,5-heptadiene (VIII) was recently reported by Franz and Osuch.[21] On the basis of the infrared and n.m.r. spectra of the product LVII, they suggested structures LVIII and LIX but provided no definitive chemical evidence to support either structure.



LVIII



LIX



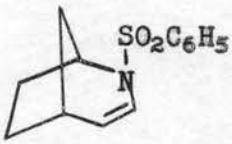
LX

The present investigation[22] has shown that benzenesulfonyl azide reacts with excess VIII to yield initially the aziridine, LX. The nitrogen insertion product (LVII) of Franz and Osuch has been shown to arise by rearrangement of LX and the structure of LVII has been established.

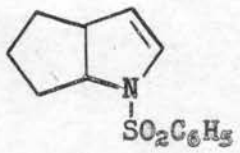
When a solution of benzenesulfonyl azide (VI) and bicyclo(2.2.1)-2,5-heptadiene (VIII) in deuterochloroform (1% tetramethylsilane) was allowed to stand at room temperature, nitrogen was immediately evolved. Periodic analysis of the reaction mixture by n.m.r. showed that LX was formed initially and as time progressed increasing amounts of LVII appeared as LX decreased. The n.m.r. spectrum showed the following signals arising from LX: an AB quartet ($J = 8.5$ c.p.s.) at δ 1.07 and 1.66 arising from the C_7 protons, a broad multiplet centered at

δ 2.96 due to the bridgehead protons, a sharp singlet at δ 3.18 for the C_2 and C_3 protons, and a triplet (J = 1.5 c.p.s.) centered at δ 6.35 arising from the C_5 and C_6 protons. After three days, rearrangement to LVII was complete and the infrared and n.m.r. spectra were identical to those reported[21] for this product.

Hydrogenation of the reaction mixture after the rearrangement was approximately 50% complete afforded a 1:1 mixture of aziridine XI and a second product LXI (formulated by others[21] as either LXII or LXIII) which were separated by chromatography on alumina. Hydrogenation of LVII also gave LXI.



LXII



LXIII

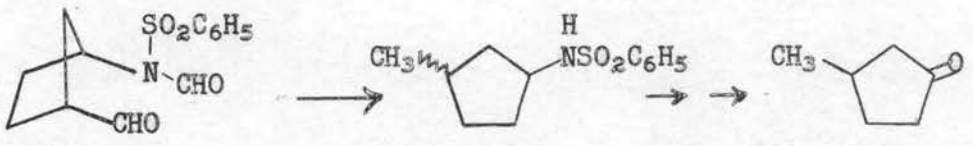
The n.m.r. spectrum of the rearrangement product LVII indicated the presence of four nonequivalent olefinic protons and two nonequivalent bridgehead protons. Although both structures LVIII and LIX satisfy these requirements, the remaining features of the n.m.r. spectrum support the assignment of structure LVIII to the molecule. The n.m.r. spectrum of LVII (reproduced in Plate I) revealed only two protons at high field and these appeared as an AB quartet. One proton of the quartet gave a simple doublet (J = 10 c.p.s.); however, the other proton gave a pair of triplets (J = 4 c.p.s.) having center signals 10 c.p.s. apart, i. e., the second proton is coupled in an equivalent manner with two vicinal protons. These signals could arise either from the protons attached to C_8 of LVIII or C_6 of LXIX. Molecular models (warped Dreiding models)

indicate that in LXIX the dihedral angles between both protons on C_6 and the adjacent protons on C_5 and C_7 are essentially the same (*ca.* 55-60°). On the basis of the dependence of the coupling constant vicinal protons on the dihedral angle[23] one would expect both protons at C_6 of LXIX to couple with protons at C_5 and C_7 in a similar manner. Models of LVIII indicate the dihedral angle between the *syn* C_8 proton (*syn* to nitrogen) and the bridgehead protons to be *ca.* 80°, so that coupling of the *syn* C_8 proton with the bridgehead protons would be small. However, the *anti* C_8 proton shows an angle of *ca.* 55-60° with the bridgehead protons and a coupling constant of 4 c.p.s. is therefore compatible with this orientation. Thus the high-field doublet and sextet of LVII probably arise from the *syn* and *anti* C_8 protons of LVIII respectively.

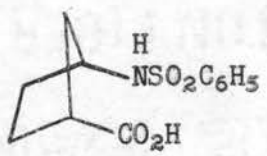
The infrared spectrum of dihydro-LVII (LXI) showed, in addition to the usual benzenesulfonamido absorptions, a band at 1625 cm^{-1} suggestive of an enamine-type structure. The n.m.r. spectrum of LXI (reproduced in Plate II) indicated two nonequivalent olefinic protons with a splitting pattern that could be interpreted equally well in terms of either LXII or LXIII and the remaining portion of the spectrum provided no basis of distinction between these two structures.

Chemical proof that LVII is correctly represented by structure LVIII was provided by the degradation of LXI to 3-methylcyclopentanone. Ozonolysis of LXI gave LXIV which decarboxylated upon Tollens oxidation to give LXV. Hydrolytic removal of the *N*-formyl group of LXIV during reduction under Wolff-Kishner conditions gave a mixture of *cis* and *trans*-*N*-(3-methylcyclopentyl)benzenesulfonamide (LXVI). Reduction of

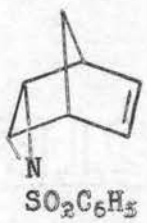
LXVI with sodium in alcohol gave cis and trans-3-methylcyclopentylamine which on nitrous acid deamination gave a mixture of 3-methylcyclopentanol (62%) and olefins (29%). Chromic acid oxidation of the deamination mixture gave as the only ketonic product 3-methylcyclopentanone (LXVII) which was identified by gas chromatography and mixed melting point of its dibenzylidene derivative with an authentic sample.[24] Rearrangement in the deamination reaction to yield 3-methylcyclopentanol is ruled out since both cis and trans-2-methylcyclopentylamine are known not to yield 3-methylcyclopentanol on deamination under identical conditions.[25] The nitrogen-containing moiety in LXIV must therefore be γ to the aldehyde group as required by structure LVIII. These results are clearly not compatible with structure LIX.



LXIV LXVI LXVII



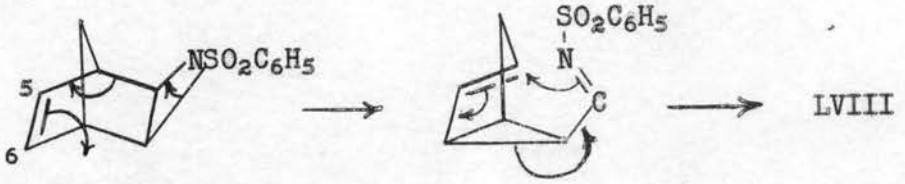
LXV



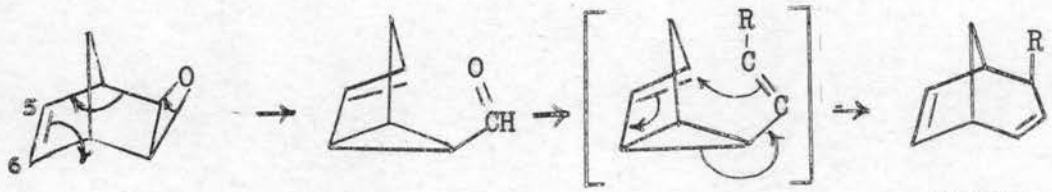
LXVIII

As mentioned earlier, it has been suggested[14] that the mechanism of aziridine formation in the reaction of benzenesulfonyl azide with bicyclo(2.2.1)-2-heptene (I) parallels that of epoxidation. In this

regard it is noteworthy that no detectable amount of LXVIII was formed during the reaction of benzenesulfonyl azide with bicyclo(2.2.1)-2,5--heptadiene (VIII), whereas the epoxidation[26a] of VIII gives an appreciable quantity of the corresponding <u>endo</u> monoepoxide. It is also interesting to note that LXVIII is quite stable, as is the corresponding <u>endo</u> epoxide, suggesting that the rearrangement of LX is facilitated by <u>back-side</u> participation of the 5,6-double bond as in the recently reported rearrangement of LXIX to LXX during the epoxidation of VIII.[26a,b]



LX LXXI



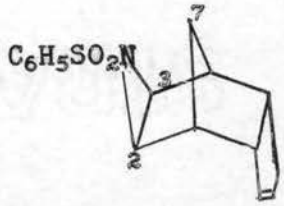
LXIX LXX LXXII

The formation of LVIII from an intermediate such as LXXI is analogous to the formation of bicyclo(3.2.1)-2,6-octadiene (LXXII) during the Wittig reaction of LXX.[27]

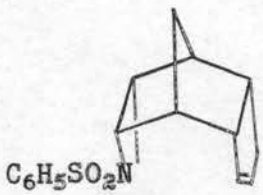
3. <u>The Structure of the 1:1 Adduct of Benzenesulfonyl Azide and Dicyclopentadiene</u>

Dicyclopentadiene (II) reacted smoothly with benzenesulfonyl azide (VI) in chloroform solution at room temperature to give a crystalline product which gave an elemental analysis ($C_{16}H_{17}NO_2S$) indicating that one mole of azide had reacted with one mole of the diene. The infrared and

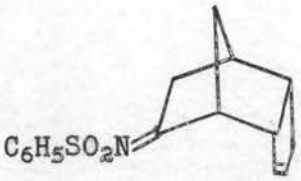
n.m.r. spectra of the product showed the presence of a double bond and a benzenesulfonamido group but the absence of N-H absorption. The structures LXXIII, LXXIV, LXXV, and LXXVI are consistent with the



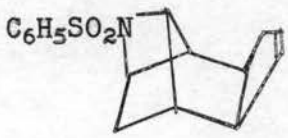
LXXIII



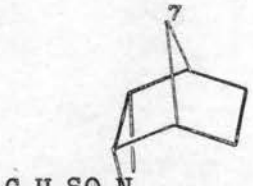
LXXIV



LXXV



LXXVI



LXXVIII

elemental and spectral data and may be expected on mechanistic and/or steric grounds. The n.m.r. spectrum of the product showed two protons on carbon bearing the nitrogen of the benzenesulfonamido group. This observation eliminates the sulfonimide structure LXXV which had been suggested for the product of the reaction of dicyclopentadiene and p-toluenesulfonyl azide by earlier workers.[8] The signals arising from the protons on carbon attached to nitrogen appeared as an AB quartet ($J = 5.5$ c.p.s.) centered at δ 2.62 and 2.88. Catalytic hydrogenation of the reaction product gave a dihydro derivative (LXXVII), the n.m.r. spectrum of which showed that the protons on carbon attached to nitrogen were now equivalent and appeared as a sharp singlet at δ 2.90. These observations are clearly not consistent with structure LXXVI but may be interpreted in terms of LXXIII or LXXIV.

Although structure LXXIV might be eliminated on the basis of steric

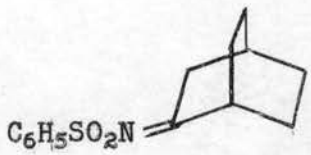
arguments, the n.m.r. spectra of the product and its dihydro derivative provide a clear basis for distinction between LXXIII and LXXIV. The n.m.r. spectrum of the addition product showed an AB quartet at high field ($J = 9.5$ c.p.s.) centered at δ 0.88 and 1.55 due to the protons at C_7. An examination of the n.m.r. spectrum of the dihydro product (LXXVII) also revealed an AB splitting of the C_7 protons; a doublet ($J = 9.5$ c.p.s.) centered at δ 0.92 constituted half of the quartet, while the second doublet, since it is not obvious, may be buried in the methylene envelope. An examination of Table I reveals that the n.m.r. spectra of bicyclo(2.2.1)heptane derivatives possessing aziridine or epoxide rings exhibit an AB splitting pattern for the C_7 protons. It is of particular interest that the n.m.r. spectra of compounds containing an exo aziridine ring (e.g. XI, XIV, and XCII) show the doublet signal for the anti C_7 proton at very high field ($\delta < 1$) whereas the corresponding signal in the spectra of compounds containing an endo aziridine ring (e.g. LXXVIII, LXXXVII, and the dimethyl ester from XCVI) appears at much lower field ($\delta > 1.5$). This observation clearly indicates LXXIII and not LXXIV as the correct structure of the addition product. The nonequivalence of the C_2 and C_3 protons in LXXIII is due to the shielding effect of the 8,9-double bond of the endo cyclopentene ring on the endo proton at C_2.

4. The Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.2)-2-octene

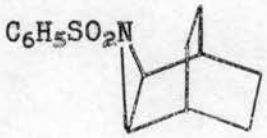
In order to study the effect of decreasing angular strain in the olefinic linkage on the course of the azide reaction with bicylic alkenes, bicyclo(2.2.2)-2-octene (IX) was treated with benzenesulfonyl

azide (VI).

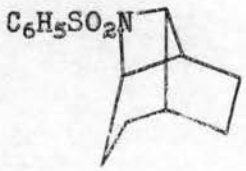
Under conditions where benzenesulfonyl azide reacts with I, II, and VIII in a vigorous exothermic reaction with evolution of nitrogen, no detectable reaction of evolution of nitrogen could be observed with IX. In refluxing benzene, however, benzenesulfonyl azide reacted with bicyclo(2.2.2)-2-octene to give a mixture of two compounds. The presence of (ca. 30%) LXXIX was established by the appearance in the infrared



LXXIX



LXXX

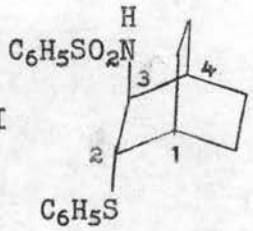


LXXXI

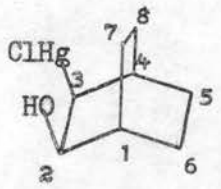
spectrum of the reaction mixture of an intense absorption band at 1612 $cm.^{-1}$ (-C = N-) and by the facile hydrolysis of LXXIX to bicyclo-(2.2.2)-2-octanone and benzenesulfonamide. The infrared spectrum of the second product (ca. 50%) showed the presence of a benzenesulfonamido group and the absence of N-H absorption. The n.m.r. spectrum of this product revealed signals arising from two protons on carbon attached to nitrogen of the benzenesulfonamido group as a multiplet centered at δ 2.88. These data are consistent with both the expected aziridine LXXX and the azetidine LXXXI.

When the nitrogen-containing ring of the second product was cleaved under S_N2 conditions in refluxing tert-butyl alcohol containing potassium thiophenoxide, LXXXII was obtained. Chemical confirmation of the skeletal structure of LXXXII was provided by its reduction to 2-benzene-sulfonamidobicyclo(2.2.2)octane, which was synthesized by an independent route.

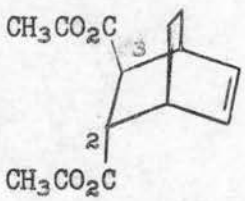
LXXXIII



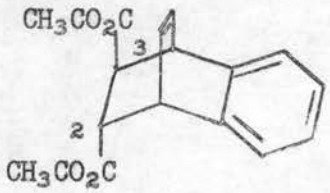
Structure LXXXI is incompatible with the above observation and additional evidence was provided to show that LXXXII possessed the trans stereochemistry expected of an S_N2 cleavage of the nitrogen-containing ring of LXXX. This evidence was obtained by examination of the n.m.r. spectrum of LXXXII in dilute trifluoroacetic acid solution. Under these conditions the C_2, C_3 protons were coupled to give a quartet with a coupling of 6.5 c.p.s. That this coupling reflects a trans relationship of the C_2, C_3 protons may be seen from the following examples.[28,29]



$J_{2,3}$ = 10 c.p.s.



$J_{2,3}$ = 6 c.p.s.



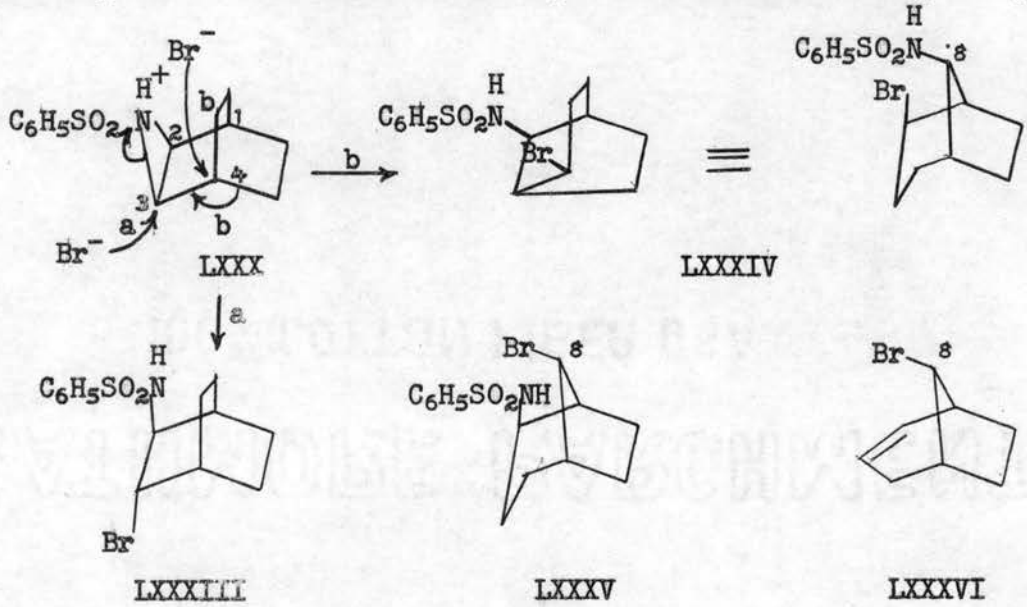
$J_{2,3}$ = 5 c.p.s.

These data clearly eliminate structure LXXXI and indicate the correctness of the assignment of structure LXXX.

Cleavage of the nitrogen-containing ring of LXXX by hydrogen bromide in carbon tetrachloride solution gave a separable mixture of LXXXIII and LXXXIV. The n.m.r. spectrum of LXXXIII in dilute trifluoroacetic acid solution was very similar to that of LXXXII in the methylene envelope region and revealed a quartet splitting for the C_2, C_3 protons with a

coupling of 5 c.p.s. Comparison of this value with the above examples again indicates that the substituents in LXXXIII on C_2 and C_3 are trans.

Structure LXXXIV is assigned to the other cleavage product on the basis of mechanistic considerations and its n.m.r. spectrum. Assuming protonation of the nitrogen of the benzenesulfonamido group to be the initial step in the cleavage process, one could envision the formation of LXXXIII from LXXX by direct attack at C_3. The formation of LXXXIV would involve a Wagner-Meerwein shift with displacement by bromide at C_4. That the benzenesulfonamido group of the second cleavage product is syn at C_8 of a bicyclo(3.2.1)octane ring system is substantiated by the following n.m.r. spectral comparisons. The n.m.r. spectrum, in dilute trifluoroacetic acid solution, of the compound in question revealed the proton attached to carbon bearing the nitrogen of the benzenesulfonamido group as a triplet ($J = 4$ c.p.s.) and the proton attached to carbon bearing the bromine atom as a more complicated multiplet. The n.m.r. spectrum, under identical conditions, of the isomeric LXXXV, the pre-



paration of which is described later in this thesis, revealed the proton at C_2 as a similar multiplet to that described above and the anti proton at C_8 as a triplet ($J = 4$ c.p.s.). A similar triplet ($J = 4$ c.p.s.) has been reported[30] for the anti C_8 proton in endo-8-bromobicyclo(3.2.1)--2-octene (LXXXVI).

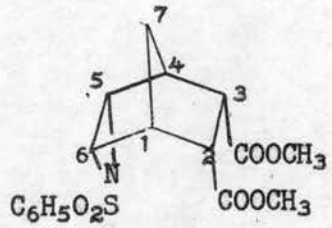
5. The Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.1)-5--heptene-endo-cis-2,3-dicarboxylic Anhydride and Bicyclo(2.2.1)-5-heptene-exo-cis-dicarboxylic Anhydride

Recent work from this laboratory has shown that benzenesulfonyl azide reacts with bicyclo(2.2.1)-5-heptene-endo-cis-2,3-dicarboxylic anhydride (V) in refluxing carbon tetrachloride to give predominantly the endo aziridine, VII.[9] The present reinvestigation has revealed that smaller amounts of a second aziridine are also formed in this reaction.

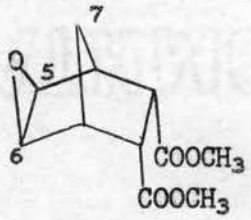
When a solution of benzenesulfonyl azide and V in carbon tetrachloride solution was refluxed for 48 hrs. a gummy solid precipitated from the solution. Crystallization of this gum from benzene-acetone yielded (ca. 30%) VII. Esterification of the mother liquors with methanolic diazomethane followed by chromatography on alumina gave (ca. 30%) LXXXVII and (ca. 19%) another isomer (LXXXVIII) along with minor amounts of unreacted starting materials.

The infrared spectrum of the second product (LXXXVIII) showed the presence of ester and benzenesulfonamido functions but the absence of N-H and $\rangle C = N$ absorptions. The n.m.r. spectrum of LXXXVIII confirmed the absence of a sulfonimide linkage ($C_6H_5SO_2N = C\langle$) in that it showed two protons on carbon attached to the nitrogen of the benzenesulfonamido group. The endo aziridine LXXXVII showed signals for the protons at C_5

and C_6 as a triplet (J = 2 c.p.s.) centered at δ 2.63, whereas in LXXXVIII the corresponding signal appeared as a sharp singlet at δ 3.13. An examination of the n.m.r. spectrum of LXXXIX also revealed the protons attached to carbon at C_5 and C_6 as a sharp singlet. The equivalence of the protons at C_5 and C_6 of LXXXVIII clearly eliminates structures such as

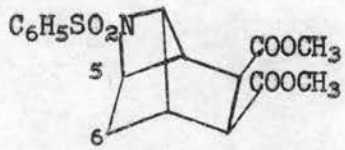


LXXXVII

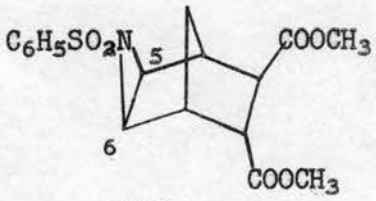


LXXXIX

XC and XCI which might be expected on mechanistic and steric grounds. It is noteworthy that in the n.m.r. spectrum of LXXXVII the C_7 protons appeared as an AB quartet with one doublet at δ 1.54 and the other at



XC

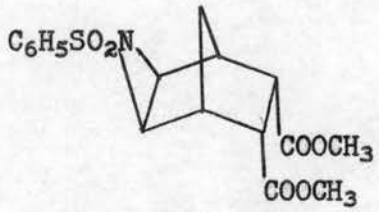


XCI

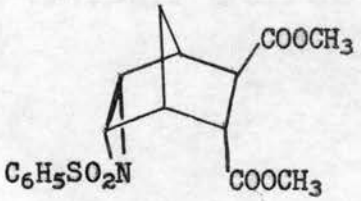
1.98; a similar situation was observed in the n.m.r. spectra of LXXXIX and the isomer in question (LXXXVIII). However, in the latter two cases a larger difference in chemical shift was observed for the C_7 protons. Thus, the n.m.r. spectrum of LXXXIX showed a pair of doublets for the C_7 protons at δ 0.80 and 1.50 and the n.m.r. spectrum of LXXXVIII showed similar signals at δ 0.90 and 1.70. The larger difference in chemical shift of the C_7 protons in the n.m.r. spectrum of LXXXIX compared with that observed in the n.m.r. spectrum of LXXXVII, is due, <u>vide infra</u>, to

the proximity of the exo oxygen to the C_7 protons. The similarly large difference in chemical shifts exhibited by the C_7 protons in LXXXVIII clearly indicates that LXXXVIII possesses an exo moiety which is in close proximity to the C_7 protons.

The aziridine structure XCII rather than XCIII is suggested for LXXXVIII because of the similarity of its n.m.r. spectrum to that of



XCII



XCIII

LXXXIX. The endo-cis configuration is assigned to the diester function since the mild conditions under which this product was isolated would preclude the observed difficult isomerization of the ester groups of LXXXVII and similar compounds. In support of this conclusion is the observation that the n.m.r. spectrum of LXXXVIII shows a single signal for the two methyl ester protons. The assignment of the exo configuration to the aziridine ring follows from the above and the assumption that a certain amount of the benzenesulfonamido intermediate would be expected to react from the less hindered exo side of the double bond of V.

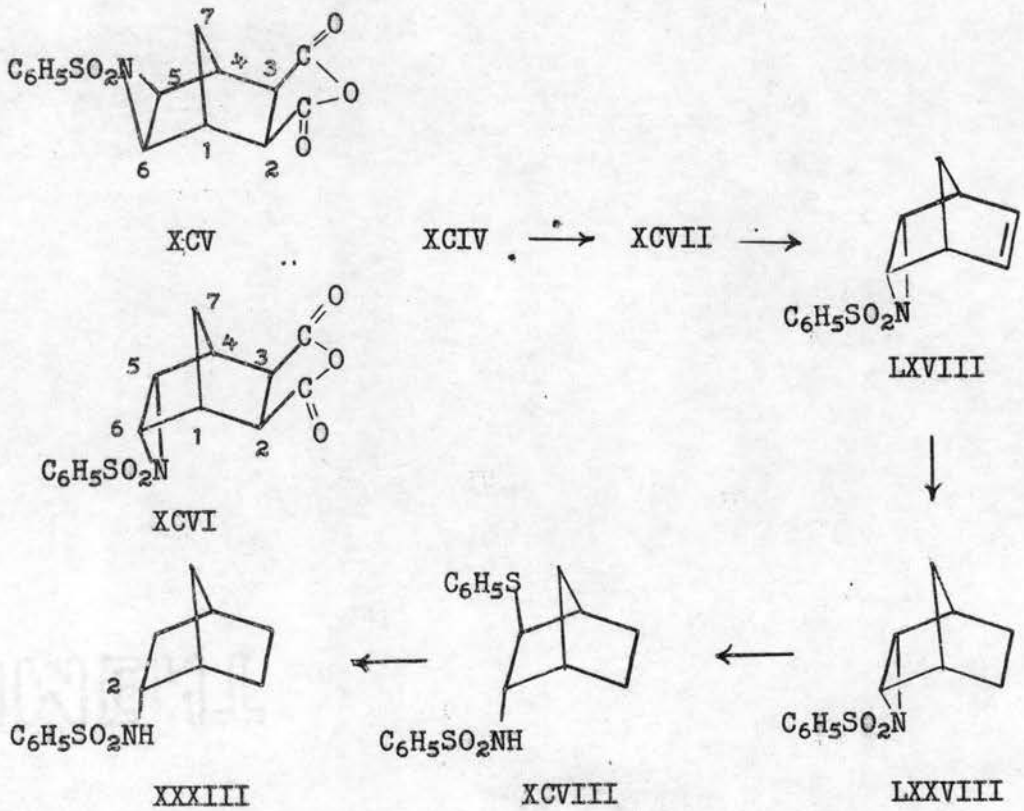
If the correct structure of LXXXVIII were XC, XCI, or XCIII then it would be surprising that the n.m.r. spectrum of this compound revealed both protons at C_2 and C_3 as equivalent, both protons at C_1 and C_4 as equivalent, and both protons at C_5 and C_6 as equivalent and as a sharp singlet. A similar equivalence of corresponding protons was exhibited in the n.m.r. spectrum of LXXXIX.

The reaction of benzenesulfonyl azide with bicyclo(2.2.1)-5-heptene exo-cis-2,3-dicarboxylic anhydride (IV) in refluxing carbon tetrachloride also led to the formation of two isomeric products which could be isolated in a manner similar to that described above for VII and XCII. The predominant isomer (XCIV, ca. 74%), which crystallized from the reaction mixture in benzene, is that for which structure XCV had been suggested.[9] The exo configuration was assigned to the aziridine ring since the electrophilic benzenesulfonamido intermediate would be expected to react with IV from the less hindered exo side in the absence of electronic effects of the endo anhydride ring which is present in the isomer V.

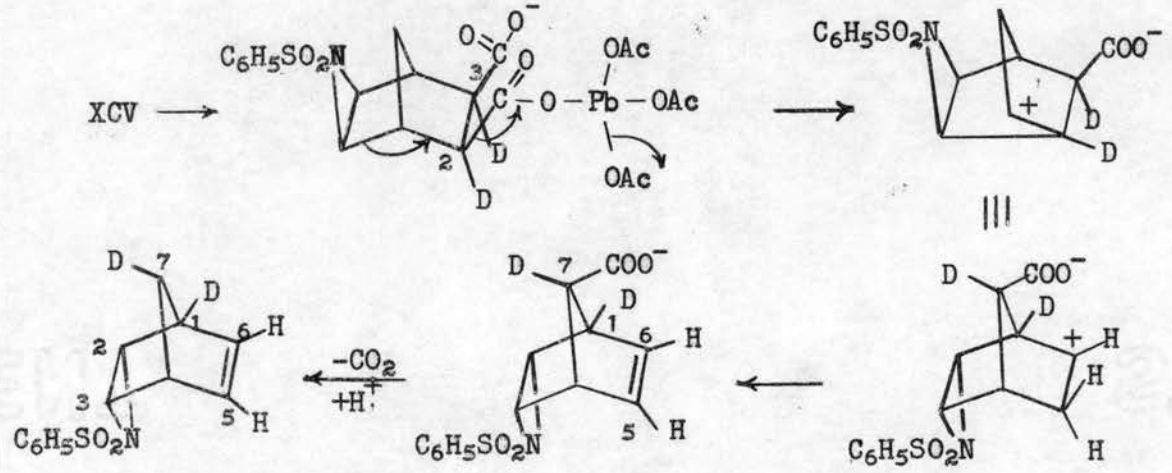
The n.m.r. spectrum of the dimethyl ester from XCIV showed striking similarity to that of LXXXVII. The n.m.r. spectrum of each isomer showed an AB quartet for the C_7 protons, a narrow multiplet for the bridgehead protons, and a similar multiplet for the protons on carbon at C_2 and C_3. The signals arising from the protons on carbon attached to the nitrogen atom of the benzenesulfonamido group in both isomers appeared as a triplet ($J = 2$ c.p.s.), whereas in the exo aziridines XCII, XI, and XVI the corresponding signal appeared as a sharp singlet. If XCV is the correct structure of XCIV then it is surprising that the C_5 and C_6 protons in the dimethyl ester from XCIV appear as triplet instead of a singlet, in its n.m.r. spectrum. The multiplet structure of the signals arising from the protons at C_5 and C_6 in the dimethyl ester from XCIV strongly indicates that the aziridine ring in XCIV possesses the endo configuration and thus is correctly represented in structure XCVI.

In order to distinguish chemically between structures XCV and XCVI

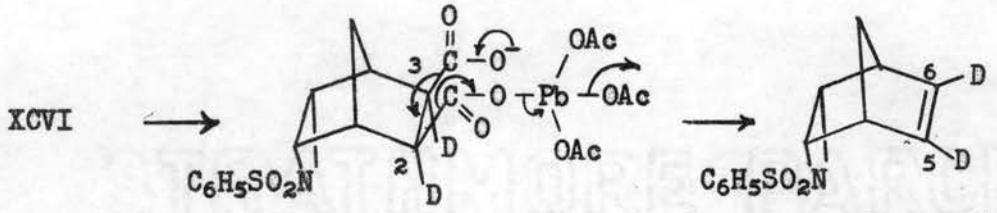
elimination of the carboxylic anhydride moiety of XCIV seemed appropriate. Structure XCV would lead to the known <u>exo</u> aziridine XI whereas the <u>endo</u> aziridine LXXVIII would be expected from XCVI. The anhydride group of XCIV was readily opened in boiling water to give the <u>cis</u> dicarboxylic acid XCVII the dimethyl ester of which was identical with that obtained by treatment of XCIV with methanolic diazomethane. Oxidative bisdecarboxylation of XCVII with lead tetraacetate in pyridine gave the unsaturated aziridine LXVIII which upon catalytic hydrogenation gave LXXVIII. Chemical confirmation of the structure of LXXVIII was provided by cleavage of the nitrogen-containing ring by potassium thiophenoxide to give XCVIII followed by reductive removal of the thiophenoxy group to give 2-<u>endo</u>-benzenesulfonamidobicyclo(2.2.1)heptane (XXXIII).



These data can be interpreted in two ways. First, one can assume that the correct structure of XCIV is XCVI and that degradation to XXXIII involves no skeletal rearrangement. If such is the case, the carbons in positions 2 and 3 of XCVI will be in positions 5 and 6 of LXVIII (see below). The second interpretation is that the correct structure is XCV and that degradation to XXXIII involves a molecular rearrangement. Since rearrangement during the conversion of LXVIII to XXXIII is excluded (S_N2 reaction), skeletal rearrangement, if it occurs at all, must occur during the decarboxylation of XCVII. In this respect, it should be pointed out that recent investigations by a number of workers[31] have demonstrated that cationic intermediates are generated during oxidative bisdecarboxylations using lead tetraacetate. The ability of the bicyclo(2.2.1)heptane ring system to rearrange during reactions in which a nuclear cationic charge is generated is well known.[32] If skeletal rearrangement should occur during the decarboxylation the carbons at positions 2 and 3 of XCV might be expected to be found at positions 1 and 7 of LXVIII as shown below.

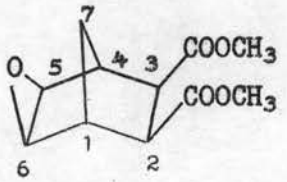


LXVIII - 1,7-d

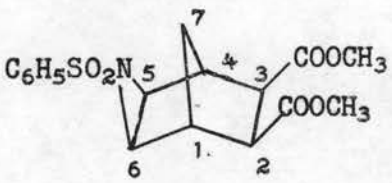


LXVIII - 5,6-d

In order to test these two possibilities it was necessary to label the 2 and 3 positions of XCIV. This was done by synthesizing XCIV with deuterium (ca. 70%) in the C_2, C_3 positions. Hydrolysis of XCIV-2,3-$d_{1.4}$ to XCVII-2,3-$d_{1.4}$ was carried out in 80% deuterium oxide, so as to preclude any loss of deuterium due to exchange on the carbons attached to the carboxyl moieties of XCIV-2,3-$d_{1.4}$. Lead tetraacetate bisdecarboxylation of XCVII-2,3-$d_{1.4}$ gave LXVIII which, by n.m.r. analysis, was found to contain deuterium (ca. 70%) at the 5 and 6 positions. Thus no skeletal rearrangement occurred during the decarboxylation and XCVI must be the correct structure of XCIV.



XCIX



C

The n.m.r. spectrum of the dimethyl ester of the minor isomer (ca. 22%) from reaction of benzenesulfonyl azide with IV revealed the presence of only one methylene group and this appeared as an AB quartet (J = 11 c.p.s.) with doublets centered at δ 1.47 and 1.75; the remaining protons were much further downfield. The protons at C_1, C_2, C_3, and C_4 appeared as a narrow signal at δ 2.82 and the two protons on carbon attached to the nitrogen of the benzenesulfonamido group

appeared as a sharp singlet at δ 3.03. An examination of the n.m.r. spectrum of XCIX revealed a nearly identical situation; thus, the spectrum of XCIX showed an AB quartet for the C_7 protons (J = 10.5 c.p.s.) with doublets centered at δ 1.33 and δ 1.64, a single multiplet at δ 2.80 for the protons at C_1, C_2, C_3, and C_4 and a sharp singlet for the protons at C_5 and C_6. On the basis of this spectral correspondence and since some of the benzenesulfonamido intermediate would be expected to attack IV from the exo side structure C is suggested for this compound.

Under conditions in which I, II, and VIII reacted readily with benzenesulfonyl azide no appreciable reaction with IV or V occurred. It has been suggested[9] that under the conditions necessary for benzenesulfonyl azide to react with IV and V the azide slowly decomposes to yield the benzenesulfonylnitrene which then adds to the double bonds of IV and V. The explanation offered for the predominance of endo attack in the case of V was based on the reported electrophilic behavior of this nitrene in aromatic substitution reactions.[33] It was postulated[9] that the "electron-rich" oxygen atoms of the endo anhydride group attract the "electron-deficient" nitrene to the endo side of the double bond of V.

The electronic effects of the exo 2,3-anhydride group of IV can be considered to have a negligible effect on the electronic environment in the endo portion of the molecule. Addition of the benzenesulfonylnitrene from the exo side (presumably the least hindered) would then be expected since other electrophilic reagents invariably add from this side.[34,35] If one assumes that a nitrene intermediate is involved and that it behaves in the manner proposed for singlet carbenes,[36,37]

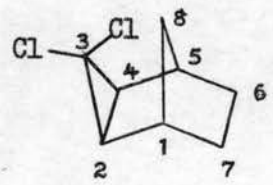
bonding in the transition state would originate from simultaneous overlap of both p orbitals on the carbon atoms of the double bond with the sp^2 orbital of the nitrene. Such overlap should be maximized if the nitrene lies over the olefin in a plane parallel to the plane of the double bond. In order for this criterion to be fulfilled a nitrene approaching from the exo side would encounter nonbonded repulsions between the lone-pair on nitrogen and the syn-7-hydrogen. As the transition state passes on to the aziridine the repulsions between the lone-pair on nitrogen and the syn-7-hydrogen should decrease slightly owing to the change in hydridization at C_5 and C_6 from sp^2 to sp^3; on the other hand, the bond-tightening process would have an opposite effect. The syn-7-hydrogen and the lone-pair on nitrogen in N-substituted exo aziridines occupy the flagpole positions of what amounts to a rigidly fused boat-form piperidine ring. Although conformational studies reveal the lone-pair on piperidines is small compared to hydrogen,[38] the close proximity of the nitrogen to the syn-7-hydrogen in exo aziridines is revealed by the deshielding effect exerted by the aziridine ring on the proton in question in the n.m.r. spectra of these compounds (See Table I, and compare e.g., bicyclo(2.2.1)heptane with XI or XVI).

Attack of the nitrene from the endo side should also occur in a plane parallel to that of the π orbital of the double bond. Approach from this direction would product strong nonbonded interactions between the endo-2,3-hydrogens and the lone-pair on nitrogen. As in the case of exo attack, rehybridization of the C_5 and C_6 carbons during the latter stages of bond formation would relieve these repulsions and the resultant bond tightening would have an opposite effect. In the case of the

endo aziridines the lone-pair on the nitrogen appears from molecular models to occupy a somewhat less crowded position in space than its *exo* counterpart. This is substantiated (see below) by the fact that the *endo*-5,6-hydrogens of LXXVIII are not deshielded by the *endo* nitrogen moiety. The predominance of *endo* aziridine would therefore imply that the repulsions present in the *exo* aziridine more than compensate for the bond-tightening process and that although the initial transition state arising from *endo* attack may be more hindered the bond-tightening process is more than sufficient to overcome any nonbonded repulsions remaining in the *endo* aziridine. Thus a valid question arises: why should I, II, and VIII yield *exo* addition products with benzenesulfonyl azide (and for that matter epoxidizing agents) if a more strained product results?

The formation of XI from I and benzenesulfonyl azide most likely involves decomposition of an unstable triazoline intermediate. Examination of the molecular models of triazolines XIV and XV reveals no interactions between the *syn*-7-hydrogen and any nitrogen of the triazoline moieties. This is confirmed (see below) by the fact that in the n.m.r. spectra of these compounds the signals arising from the C_7 protons appear in the usual methylene region. It is readily apparent from the course of additions to the double bond of I[32] that *exo* substituents at C_2 and C_3 are considerably less hindered than their *endo* counterpart. This is also true in the case of *exo* (vs *endo*) C_2, C_3 bonded triazolines. However, the decomposition of an *exo* triazoline intermediate would give rise to a sterically more hindered *exo* aziridine. Similar reasoning may be extended to other *exo* additions in this

ring system. Thus, if a group approaches the π-orbital of the double bond closer to one olefinic carbon than to the other, the sterically more favorable approach parallel to the π-cloud is from the exo side. The formation of an exo epoxide, for example, would by this reasoning arise from a transition state in which one bond is formed to an appreciable extent before the other one is. The exo attack of dichlorocarbene on I to give the highly strained dichlorocyclopropane CI has been



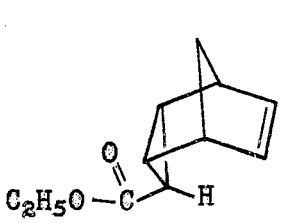
CI

attributed[39] to such an unsymmetrical addition process.

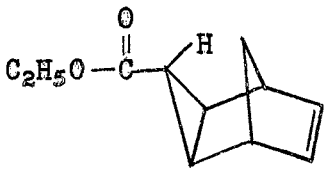
As has been inferred above and elsewhere,[14] the n.m.r. spectra of exo epoxides and exo aziridines of bicyclo(2.2.1)heptane and its derivatives possess common distinctive characteristics. The most apparent of these is the divergence of the chemical shifts of the C_7 protons of these derivatives as compared to those observed in the parent compound.[14,40a] Tori, et. al.[40a] have recently reported that the introduction of an exo epoxy group into the norbornane system caused marked shielding of the anti C_7 proton but slight deshielding of the syn C_7 proton. The shielding effect was ascribed to an epoxide ring current, while the deshielding of the syn C_7 proton was attributed to a nonbonded interaction between the oxygen lone-pair electrons and this proton. The assignments of the syn and anti protons at C_7 in Table I are by analogy with this work. This explanation differs somewhat from that offered by Moore and coworkers[39] to account for

similar shielding of the anti C_8 proton and the deshielding of the syn C_8 proton in CI. Moore reasoned that the severe repulsions of the syn C_3 chlorine atom and the syn C_8 proton would cause bond distortion in such a manner that the C_8 bridge would be bent toward C_6 and C_7. This would have the effect of pushing the anti C_8 proton into the molecule and thus this proton would become more highly shielded. The deshielding of the syn C_8 proton of CI was attributed to interaction of this proton with the chlorine atom. However, both of these interpretations point to the close proximity of the syn methylene bridge proton to an exo substituent bonded simultaneously to C_2 and C_3 of the bicyclo(2.2.1)heptane nucleus. The fact that the n.m.r. spectra of exo aziridines of bicyclo(2.2.1)heptane and its derivatives in Table I show the anti C_7 proton to be highly shielded while the syn C_7 proton is slightly deshielded indicates some nonbonded interaction exists between the nitrogen lone-pair and the syn proton.

At this time the exact origin of the shielding of the C_7 anti proton in the above cases is open to question; however, similar diamagnetic shifts in closely related systems are most easily interpreted in terms of the ring current effect. Of particular interest is the diamagnetic shift (0.49 p.p.m.) exhibited by the vinyl protons of LXVIII with respect to LX (Table I). Since the vinylic protons of LXVIII lie in the cone circumscribed by the nitrogen-containing ring and perpendicular to this ring it appears this effect may be attributed to a ring current effect. The diamagnetic shift of the vinylic protons of CII with respect to CIII (0.60 p.p.m.) and of CIV with respect to I (0.30 p.p.m.) have been explained by others in terms of a ring current



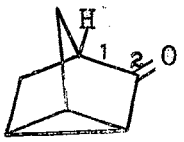
CII



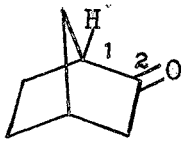
CIII

CIV

effect.[41] Of greater interest is the diamagnetic shift (ca. 0.69 p.p.m.) of the C_1 proton of tricyclo(2.2.1.$0^{3,5}$)-2-heptanone (CV) with respect to CVI. This has also been explained[41] in terms of a ring current effect. The position of the C_1 proton with respect to the cyclopropane ring in CV parallels that of the anti C_7 proton in the exo aziridines in question

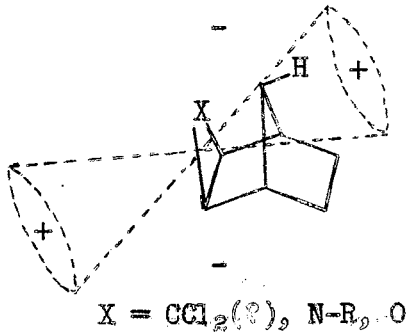


CV



CVI

to the nitrogen-containing ring. In both cases the relevant proton is in the cone circumscribed by the three-membered ring and perpendicular to the plane of the ring as shown below.



X = CCl_2(?), N-R_2, O

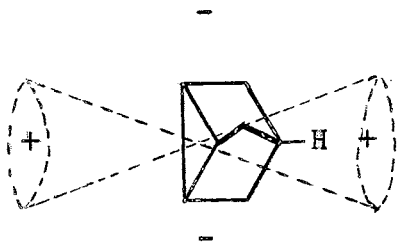


TABLE I

THE CHEMICAL SHIFTS OF C_7 AND VINYLIC PROTONS OF COMPOUNDS CONTAINING EPOXIDE OR AZIRIDINE RINGS

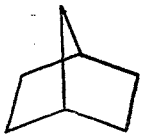
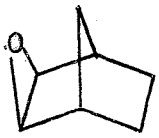
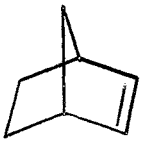
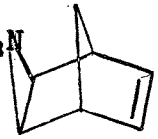
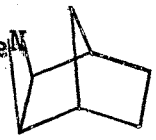
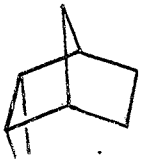
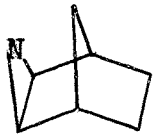
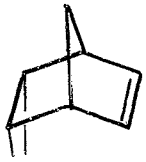
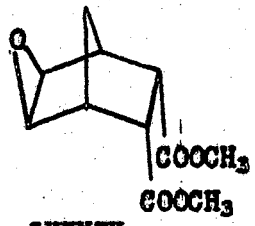
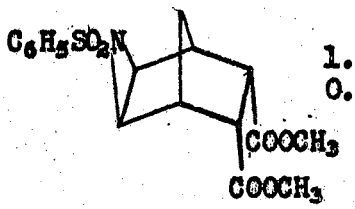
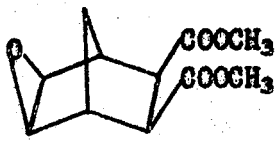
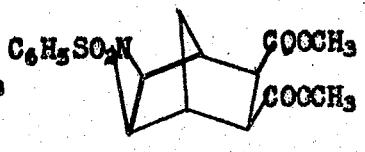
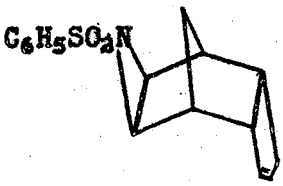
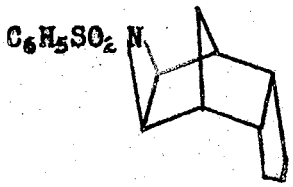
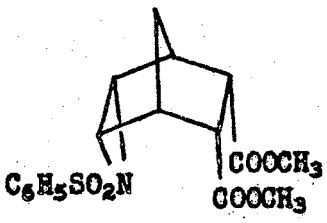
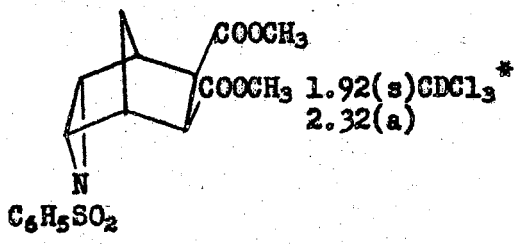
Compound	δ[a]	Solvent	Compound	δ[a]	Solvent
	1.20(s) 1.20(a)	$CDCl_3$[40b]		1.44(s) 0.43(a)	C_6H_6[14]
				1.35(s) 0.70(a)	$CDCl_3$[40a]
	1.18(s) 1.33(a) 5.98(v)	$CDCl_3$[40b]	$C_6H_5SO_2N$ 	1.66(s) 1.07(a) 6.35(v)	$CDCl_3$
I			LX		
$C_6H_5SO_2N$ 	1.38(s) 0.43(a)	C_6H_6[14]		1.25(s) 1.25(a)	CS_2
	1.2- 1.6(s) 0.70(a)	$CDCl_3$			
XI			$C_6H_5SO_2$ N LXXVIII		
$C_6H_5CH_2$ N 	1.63(s) 0.63(a)	CS_2		1.76(s) 1.76(a) 5.86(v)	$CDCl_3$
XVI			$C_6H_5SO_2$ N LXVIII		

TABLE I (Continued)

Compound	δ[a]	Solvent	Compound	δ[a]	Solvent
 LXXXIX	1.50(s) 0.80(a)	$CHCl_3$	 XCII	1.70(s) 0.90(a)	$CDCl_3$
 XCIX	1.64(s) 1.33(a)	$CDCl_3$	 C	1.75(s) 1.47(a)	$CDCl_3$
 LXXIII	1.46(s) 0.87(a)	CCl_4	 LXXVII	1.3-1.7(s) 0.92(a)	CS_2
 LXXVII	1.53(s) 2.00(a)	$CDCl_3$ [9]*	 dimethyl ester from XCVI	1.92(s) 2.32(a)	$CDCl_3$*

[a] In molecules containing epoxide or aziridine rings syn (s) and anti (a) refer to these rings and v = vinylic protons. *The assignment of signals to syn and anti protons in these cases is based on the observed long range splitting of the δ 1.92 signal in the dimethyl ester from XCVI which is assumed to arise by coupling with the endo C_2 and C_3 protons as observed by others[40] in similar cases.

C. Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded with a Beckman IR-5 spectrophotometer; n.m.r. spectra were obtained with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane (TMS) as an internal standard (δ 0). Carbon and hydrogen analyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind., and nitrogen analyses were performed by a previously described procedure.[42] All thin layer chromatograms were developed in iodine vapor unless otherwise stated.

1. The Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.1)-2-heptene:

Preparation of N-Benzenesulfonyl-8-azatricyclo(2.2.1.$1^{2,3\text{-exo}}$)-octane (X≡XI)

Benzenesulfonyl azide (VI) was prepared as previously described, but with the modification that the liquid benzenesulfonyl chloride was added directly to the ethanolic sodium azide solution. When the benzenesulfonyl chloride was dissolved in ethanol before addition to the ethanolic sodium azide solution, as done by previous workers,[33b] appreciable amounts (up to 25%) of ethyl benzenesulfonate were formed as shown by the presence of the characteristic ethyl group signals in the n.m.r. spectrum.

Bicyclo(2.2.1)-2-heptene (I) was prepared by a well established procedure.[43]

Benzenesulfonyl azide (VI, 4.7 g.) was added to a solution of 5 g. of I in benzene or petroleum ether at room temperature with stirring. The evolution of nitrogen, which began immediately, ceased

after 1.5 hr. The crystalline product, which precipitated in quantitative yield as the exothermic reaction proceeded, was filtered out and recrystallized three times from 95% ethanol to give 5.3 g. (79%) of X, m.p. 105°; ν_{max}^{KBr} 1310, 1155, 1090, 975, 910, 720, and 690 $cm.^{-1}$; n.m.r. (in CCl_4), δ 2.42 (protons at C_1 and C_4), 2.84 (protons at C_2 and C_3), 7.3-8.0 (5 aromatic protons).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.96; H, 6.05; N, 5.41.

Preparation of XIV and XV

A solution of 2.6 g. of benzyl azide and 1.9 g. I were stirred in 15 cc. of petroleum ether at 50° for 12 hr. Removal of the solvent *in vacuo* gave 91% of IV, m.p. 70-71°. The analytical sample, prepared by recrystallization from petroleum ether, had m.p. 72-73°; ν_{max}^{KBr} 1455, 1352, 1091, 948, 742 and 700 $cm.^{-1}$; n.m.r. (in CCl_4) δ 0.9-1.5 (6 protons), 2.08 (proton at C_4), 2.57 (proton at C_1), 2.98 (proton at C_2, doublet, J = 9.8 c.p.s.). 4.25 (proton at C_3, doublet J = 9.8 c.p.s.), 4.72 (benzylic protons, doublet, J = 4 c.p.s.) and 7.30 (5 aromatic protons).

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54. Found: C, 74.29; H, 7.70.

The preparation of XV was carried out using the same procedure. After recrystallization from petroleum ether XV had m.p. 103-105° (lit.[4] m.p. 101-102°).

The n.m.r. spectrum of XV in CS_2 showed the following signals: δ 1-1.6 (6 protons), 2.57 (protons at C_1 and C_4, broad multiplet), 3.54 (proton at C_3, doublet, J = 9.5 c.p.s.), 4.42 (proton at C_2,

doublet, J = 9.5 c.p.s.), and 6.83-7.34 (5 aromatic protons).

Preparation of N-benzyl-8-azatricyclo(2.2.1.$1^{2,3\text{-exo}}$)octane (XVI)

A solution of 3.45 g. of XIV in 350 cc. of hexane was irradiated for 5 hrs. at 25-40° with a 200-watt Hanovia mercury lamp using a quartz filter. Evaporation of the solvent gave an oil which was fractionally distilled under reduced pressure to give 1.29 g. of XVI (b.p.$_{0.3\text{ mm.}}$ 115-120°) and 0.610 g. of an unidentified oil (b.p.$_{0.1\text{ mm.}}$ 150-160°).

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.37; H, 8.60. Found: C, 84.95; H, 8.61.

The n.m.r. spectrum of XVI in CS_2 revealed the following signals: δ 0.63 (anti proton at C_7, doublet, J = 10 c.p.s.), 1.0-1.2 (4 protons), 1.40 (protons at C_2 and C_3), 1.63 (syn proton at C_7, doublet, J = 9 c.p.s.), 2.25 (protons at C_1 and C_4), 3.19 (benzylic protons), and 7.23 (5 aromatic protons).

Preparation of 2-exo-Hydroxy-7-syn-benzenesulfonamidobicyclo-(2.2.1)heptane (XVII)

A. Acid-Catalyzed Hydrolysis of X

A solution prepared by adding 0.92 g. of X to 10 cc. of water containing 10 drops of concentrated hydrochloric acid was refluxed for 15 min. The solution was evaporated to yield an oil which was taken up in ether. After drying over anhydrous magnesium sulfate, the ether was evaporated to yield 0.92 g. of oil (XVII) which partially crystallized after two distillations (b.p.$_{0.07\text{ mm.}}$ 160°) and standing in the refrigerator for 2 weeks. Three recrystallizations from ethanol gave

XVII β, m.p. 142-144°; ν_{max}^{KBr} 3450 (OH), 3116 (NH), 1310, 1163, 767, 721, and 691 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{17}NO_3S$: N, 5.24. Found: N, 5.22.

Preparative thin layer chromatography on Silica Gel-G in chloroform-ethyl acetate (3:1) was used to separate a small amount of the oily acid-catalyzed hydrolysis product into alcohols XVII α and XVII β. Oxidation of these alcohols with chromic anhydride in acetic acid gave the same ketone XVIII, as detected by thin layer chromatography (detection by 2,4-dinitrophenylhydrazone).

B. Hydration of X

A suspension of 3 g. of X in 25 cc. of water was refluxed for 24 hr. and the solution was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, decolorized with Norit and evaporated to give 2.8 g. of an oil, identical in infrared spectrum with the product obtained by the acid-catalyzed hydrolysis of X. This sample of alcohol, on oxidation, gave the same crystalline ketone XVIII as obtained by the oxidation of alcohol prepared by procedure A.

C. Alkaline Hydrolysis of X

To a solution of 3.94 g. of XI in 10 cc. of 50% aqueous potassium hydroxide was added 10 cc. of ethanol and the entire solution was refluxed for 2 days. After extraction with ether, the remaining aqueous solution was acidified with dilute hydrochloric acid, then extracted again with ether. This latter ether extract was washed with an aqueous sodium carbonate solution, dried over anhydrous magnesium sulfate, and evaporated to yield 0.81 g. of an oil which after oxidation gave crystalline ketone XVIII identical in all respects with ketone XVIII

prepared from the alcohol as obtained by procedure A. On evaporation, the ether extract of the alkaline solution gave 2.35 g. of unchanged X.

Basic catalysis in the conversion of X to XVII was demonstrated as follows. Four 20-cc. ethanolic solutions each containing 0.8132 g. of X were prepared. To one was added 10 cc. of 1.0 N sodium hydroxide, to a second was added 10 cc. of 0.10 N sodium hydroxide, to a third was added 10 cc. of 0.01 N sodium hydroxide, and to the fourth 10 cc. of water was added. The four solutions were refluxed under identical conditions for 4 days and at intervals of 6 to 12 hours, 1 cc. aliquots were removed from each solution, diluted to 4 cc. with water, and carefully neutralized, in the cold, with dilute hydrochloric acid. The aqueous solutions were extracted twice with 5 cc. portions of benzene; the benzene solutions were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield an oily residue of 25 ± 5 mg. in each case. After drying overnight under reduced pressure, each sample was weighed and diluted to 0.20 cc. with dry chloroform. The infrared spectrum was then obtained in a 0.96-cm. cell in the region 2.5-3.5 μ. Using weighed reference samples of X and XVII β, the extinction of the N-H absorption in the various samples was determined, and the percent conversion in each sample was determined. A plot of concentration in moles/liter of X vs. hours of reaction time gave the following times for 50% conversion of X: 0.3 N sodium hydroxide, disregarded because of precipitate formation during reaction; 0.03 N sodium hydroxide, 27 hr.; 0.003 N sodium hydroxide, 32 hr.; water, 45 hr.

The various samples from the kinetic runs were compared by thin layer chromatography, and all showed the same spots but increasing

amounts of XVII were present with increasing reflux time and with increasing basic strength. The unused solutions from the kinetic runs were combined and after working up as described previously, the residues were chromatographed on Merck acid-washed alumina. Crystalline XVII β (m.p. 143-144°) was obtained from the eluent.

Thin layer chromatographic comparisons of the acid, alkaline, and neutral hydrolysis products gave the comparisons shown in Table II.

TABLE II

DISTRIBUTION OF PRODUCTS FROM HYDROLYSIS OF X

Products	R_f [a]	Relative intensities and conditions A [b]	B [b]	C [b]
Benzenesulfonamide	0.10			1
Unknown	.20	1	1	1
Unknown	.22	1	1	1
XVII β	.40	4	4	4
XVII α	.57	1	1	3
X	.63	2	1	3

[a] All thin layer chromatograms were run on Silica Gel-G in 3:1 chloroform-ethyl acetate, allowing the solvent front to advance 15 cm.
[b] A, 96 hr. refluxing water; B, 96 hr. refluxing 0.03 N sodium hydroxide; C, 30 min. refluxing dilute hydrochloric acid. Intensities were determined by visually estimating the darkness of the iodine-developed spots: darkest spot, 4; lightest, 1.

Preparation of 2-Keto-7-*syn*-benzenesulfonamidobicyclo(2.2.1)-heptane (XVIII)

To a solution containing 0.63 g. of oily XVII in 31 cc. of glacial acetic acid was added a mixture of 0.17 g. of chromic anhydride, 5 cc. of acetic acid, and 2 cc. of water. After stirring at room temperature for 48 hr., methanol was added to destroy excess chromic anhydride and the solution was diluted with 200 cc. of water. The aqueous solution was extracted with ether, and the extract washed with sodium carbonate solution, dried over anhydrous magnesium sulfate, and evaporated to yield 0.54 g. of ketone XVIII as an oil which crystallized from ether to give m.p. 147-148°; ν_{max}^{KBr} 3130 (N-H), 1725 (C=O), 1335, 1163, 1090, 887, 773, 761, 719, and 691 $cm.^{-1}$.

Anal. Calcd. for $C_{13}H_{17}NO_3S$: C, 58.85; H, 5.70. Found: C, 58.80; H, 5.62.

The 2,4-dinitrophenylhydrazone readily formed upon the addition of acidified, methanolic 2,4-dinitrophenylhydrazine solution to the ketone. Recrystallization from 95% ethanol gave m.p. 240-242°.

Anal. Calcd. for $C_{19}H_{19}N_5O_6S$: C, 51.25; H, 4.27. Found: C, 51.12; H, 4.73.

Alcoholic mixture XVII was also oxidized as follows. To a solution containing 0.36 g. of XVII in 10 cc. of acetone was added 2 cc. of Jones reagent[44] (1 cc. ≡ 0.004 mole of alcohol) After standing at room temperature for 1 hr., the solution was diluted with excess 10% sodium carbonate solution and extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to yield 0.34 g. of oil which after crystallization from ether gave 0.19 g. of XVIII,

m.p. 146-147° (2,4-dinitrophenylhydrazone, m.p. 242°), identical in all respects with XVIII prepared as previously described.

Preparation of 2-exo-Acetoxy-7-syn-benzenesulfonamidobicyclo-(2.2.1)heptane (XIX)

A solution containing 2.16 g. of X in 10 cc. of glacial acetic acid was heated on a steam bath for 0.5 hr. The solution was then poured on ice and extracted with ether. The ether extract was washed with aqueous sodium carbonate solution, dried over anhydrous magnesium sulfate, and evaporated to give 2.37 g. of an oil which distilled at 134-135° at 0.07 mm. The distilled oil was crystallized from ethanol-water and had m.p. 135-136° ; ν_{max}^{KBr} 3200 (N-H), 1700 (C=O), 1260, 1160, 1088, 1052, 900, 853, 760, 723, and 689 $cm.^{-1}$; n.m.r. (in $CHCl_3$) δ 0.9-2.2 (8 protons), 2.04 (acetate methyl protons), 3.44 (proton at C_7, doublet, J = 8 c.p.s.), 4.74 (proton at C_2, triplet, J = 5 c.p.s.), 5.42 (N-H, doublet, J = 8 c.p.s.), and 7.5-8.1 (5 aromatic protons).

Anal. Calcd. for $C_{15}H_{19}O_4NS$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.15; H, 6.30; N, 4.56.

Hydrolysis of XIX

A solution of 4.42 g. of XIX in 30 cc. of ethanol and 10 cc. of 20% aqueous potassium hydroxide was heated on the steam bath for 2 hr. After cooling to room temperature, the solution was diluted with 50 cc. of water and carefully neutralized with 5% hydrochloric acid. The neutral aqueous solution was extracted with ether, which after drying over anhydrous magnesium sulfate was evaporated to yield 3.42 g. of crude alcohol from which crystalline XVII β, m.p. 142-143°, was obtained as previously described.

Preparation of 2-Chloro-7-syn-benzenesulfonamidobicyclo(2.2.1)-heptane (XX)

Dry hydrogen chloride gas was passed through a refluxing solution of 0.46 g. of X in 25 cc. of dry carbon tetrachloride for 1.5 hr. The solvent was removed under reduced pressure and the residue distilled to give 0.48 g. of oil, b.p.$_{0.07\ mm.}$ 160°. Crystallization of the oil from ethanol at 0° gave 0.37 g. (70%) of XX, m.p. 114-115°; ν_{max}^{film} 3300 (N-H), 1450, 1320, 1162, 890, 758, 720, 690, and 1092 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{16}ClNO_2S$: C, 54.63; H, 5.64; N, 4.90. Found: C, 54.45; H, 5.83; N, 4.96.

Preparation of 2-Bromo-7-syn-benzenesulfonamidobicyclo(2.2.1)-heptane (XXI)

Dry hydrogen bromide was passed through a solution of 2.2 g. of X in 15 cc. of carbon tetrachloride at room temperature for 1.5 hr. The solution was then swept with nitrogen and the solvent evaporated to yield 2.3 g. of oil from which 1.2 g. of crystalline material precipitated after standing at 0° for 1 week. The analytical sample XXI was prepared by recrystallization from ethanol, m.p. 99-100°; ν_{max}^{KBr} 3200 (N-H), 1485, 1445, 1325, 1160, 1100, 918, 760, 720, and 691 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{16}BrNO_2S$: C, 47.28; H, 4.88. Found: C, 47.50; H, 4.82.

Conversion of XXI to XVII

A solution prepared by adding 2.3 g. of XXI and 1 g. of lithium carbonate to 5 cc. of methanol and 25 cc. of water was refluxed for 3 days. The aqueous solution was extracted with ether. The ether

extract was dried over anhydrous magnesium sulfate and evaporated to yield an oily residue. Distillation of the residue gave 0.98 g. of a liquid, b.p.$_{0.05\ mm.}$ 160°, the infrared spectrum of which showed the presence of N-H (3300 cm.$^{-1}$) and O-H (3520 cm.$^{-1}$).

Jones oxidation[44] of 371 mg. of this alcohol gave 220 mg. of XVIII, m.p. 146-147°, identical in all respects with ketone XVIII prepared as previously described.

Treatment of XXI with Pyridine

A solution containing 0.18 g. of XXI in 2 cc. of dry pyridine was refluxed for 48 hr. After the pyridine was removed *in vacuo* the residue was analyzed by thin layer chromatography (Silica Gel-G, chloroform) and found to contain starting material (R_f 0.50), benzenesulfonamide (R_f 0.06), and a new product (R_f 0.43). Chromatography on alumina gave the new product as an oil the n.m.r. spectrum of which indicated the presence of an alkene, the product is presumably 7-*syn*-benzenesulfonamidobicyclo(2.2.1)-2-heptene; n.m.r. (in CS_2) δ 5.85 (triplet with J = 2 c.p.s., two protons). Under similar conditions the olefinic protons of bicyclo(2.2.1)-2-heptene appeared at δ 5.85 (triplet with J = 2 c.p.s.).

Preparation of 7-Benzenesulfonamidobicyclo(2.2.1)heptane (XXII)

Ketone XVIII (1.77 g.) was added to a solution of 3.5 g. of potassium hydroxide in 2.6 g. of 95+% hydrazine and 15 cc. of ethylene glycol, and the reaction mixture was refluxed for 3 hr. The excess hydrazine and water were removed by distillation until the pot temperature reached 185°, and the solution was then refluxed an additional 17 hr. After cooling to room temperature, 50 cc. of water was added and

the solution neutralized with 5% hydrochloric acid. The neutral solution was extracted with ether, and the extract dried over anhydrous magnesium sulfate and evaporated to yield 1.16 g. of XXII, which, after recrystallization from ethanol-water, had m.p. 104-105°; ν_{max}^{KBr} 3028 (N-H), 1450, 1438, 1341, 1325, 1160, 1095, 905, 751, 719, and 688 cm.$^{-1}$; n.m.r. (in CS_2), δ 0.8-1.8 (10 protons), 3.10 (proton at C_7, doublet, J = 5 c.p.s.), 5.93 (N-H, doublet, J = 5 c.p.s.), and 7.2-8.0 (5 aromatic protons).

Anal. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82. Found: C, 62.53; H, 7.13.

Preparation of 7-Aminobicyclo(2.2.1)heptane (XXIII) and Derivatives

A suspension of 0.59 g. of XXII in 2 cc. of 10% hydrochloric acid was heated in a sealed tube at 150-175° for 12 hr. Concentrated hydrochloric acid (10 cc.) was added to the solution after the tube was opened, and the solution was extracted with ether. The remaining aqueous solution was made basic with 20% sodium hydroxide and extracted with ether. The latter ether extract was dried and evaporated to yield 0.12 g. of 7-aminobicyclo(2.2.1)heptane which was converted into the N-acetyl derivative by heating a few minutes with excess acetic anhydride. The excess acetic anhydride and acetic acid were removed by distillation under reduced pressure. The residue was crystallized from hexane three times to give 7-acetamidobicyclo(2.2.1)-heptane (XXIV), m.p. 130-131°; ν_{max}^{KBr} 3280, 2925, 1620, 1540, 1315, 1300, and 1290 cm.$^{-1}$. The crystalline derivative and the hexane-free mother liquor from which it was obtained were found to give a single identical peak when analyzed by gas chromatography

and to differ from the corresponding 2-*endo* and 2-*exo* isomers by gas chromatography.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.49; H, 9.98.

The *N*-chloroacetyl derivative (XXV) was prepared by heating the amine with chloroacetyl chloride in pyridine-benzene and had m.p. 80° after recrystallization from petroleum ether (lit.[45] m.p. 84-85°).

Preparation of 2-*endo*-Aminobicyclo(2.2.1)heptane (XXX)

A suspension of 30 g. of I in 75 cc. of cold 60% sulfuric acid was shaken with occasional cooling until the solution became homogeneous. After neutralization, the aqueous solution was extracted with ether which in turn was dried and evaporated to yield 18 g. of bicyclo(2.2.1)-2-heptanol.[46]

The bicyclo(2.2.1)-2-heptanol was oxidized to give bicyclo(2.2.1)--2-heptanone (CVI) as previously described.[47] The bicyclo(2.2.1)-2--heptanone (CVI) was converted into 2-*endo* aminobicyclo(2.2.1)heptane by preparation of the oxime and subsequent catalytic reduction as described by Alder and Stein.[48] The *N*-acetyl derivative which had m.p. 130-132° (lit.[49] m.p. 131-132°) was prepared by the usual method and was found by gas chromatography (see later section) to be uncontaminated by the *exo* isomer.

When bicyclo(2.2.1)-2-heptanone oxime was reduced with sodium in ethanol, the resulting amine was the *endo* amine contaminated with *exo* isomer, as shown by gas chromatographic analysis of the acetylated amine.

The benzenesulfonyl derivative of 2-*endo*-aminobicyclo(2.2.1)-

heptane was prepared using benzenesulfonyl chloride in pyridine. The analytical sample was obtained by three recrystallizations from methanol and had m.p. 105-106°.

Anal. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82. Found: C, 62.63; H, 6.76.

The chloroacetyl derivative was prepared as previously described and had m.p. 104-105° (lit.[45] 105-106°).

Preparation of 2-exo-Aminobicyclo(2.2.1)heptane (XXVI)

A mixture of endo- and exo-2-cyanbicyclo(2.2.1)-5-heptene was prepared by the Diels-Alder reaction of acrylonitrile and cyclopentadiene as previously described.[50] exo-2-Carbamylbicyclo(2.2.1)-5-heptene was prepared from the mixture of cyanides by the action of sodium amide in liquid ammonia as described by Boehme, et al.[51] Hydrogenation of the unsaturated amide with platinum oxide catalyst in ethanol gave the previously reported[51] saturated amide, m.p. 192° (lit.[51] m.p. 192.5-193.5°), which was converted into 2-exo-aminobicyclo(2.2.1)heptane by the Hofmann reaction according to the procedure of Berson and Ben-Efriam.[49] The N-acetyl derivative, prepared with acetic anhydride, had m.p. 132-133° (lit.[49] m.p. 140-143°). The gas chromatogram of this derivative indicated a slight contamination with the endo isomer.

The benzenesulfonyl derivative of the exo amine was prepared by treating the amine in pyridine with benzenesulfonyl chloride. The analytical sample was obtained after four recrystallizations from aqueous methanol and had m.p. 89-91°.

Anal. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82. Found: C, 62.54; H, 7.20.

The N-chloroacetyl derivative, prepared as described previously, had m.p. 120-121° (lit.[45] m.p. 126-127°).

Gas Chromatographic Comparisons of Acetylated Amines, XXIV, XXVII, and XXXI.

All gas chromatographic analyses were performed on a 0.25-in. x 10-ft. Craig polyester column at 210° using a helium flow rate of 59 cc. per min. The following retention times were observed: 7--acetamidobicyclo(2.2.1)heptane (XXIV), 12 min.; 2-endo-acetamidobicyclo-(2.2.1)heptane (XXXI), 13.3 min.; 2-exo-acetamidobicyclo(2.2.1)heptane (XXVII), 14.0 min.

Thin Layer Chromatographic Comparisons of Amine Derivatives

Thin layer chromatograms were obtained by ascending (15 cm.) chromatography on glass plates coated with a 50 μ thick layer of Silica Gel G. The reported R_f values shown in Table III are for leading edges.

TABLE III

THIN LAYER CHROMATOGRAPHIC COMPARISONS OF AMINOBICYCLO(2.2.1)HEPTANE DERIVATIVES

Solvent	R_f					
	N-Benzenesulfonamido			N-Chloroacetamido		
	2-endo XVIII	2-exo XIX	7 VIII	2-endo XVII	2-exo XIV	7 XI
Chloroform	0.25	0.20	0.32	0.16	0.14	0.24
1:1 Chloroform-benzene	.29	.23	.32			

Infrared Spectral Comparisons of N-Chloroacetyl Derivatives of Isomeric Amines

In the 1500-4000 cm.$^{-1}$ region of the infrared spectrum all three N-chloroacetyl derivatives (XXV, XXVIII, and XXXII) exhibited essentially identical bands at 3330, 2790, 1800, and 1600 cm.$^{-1}$.

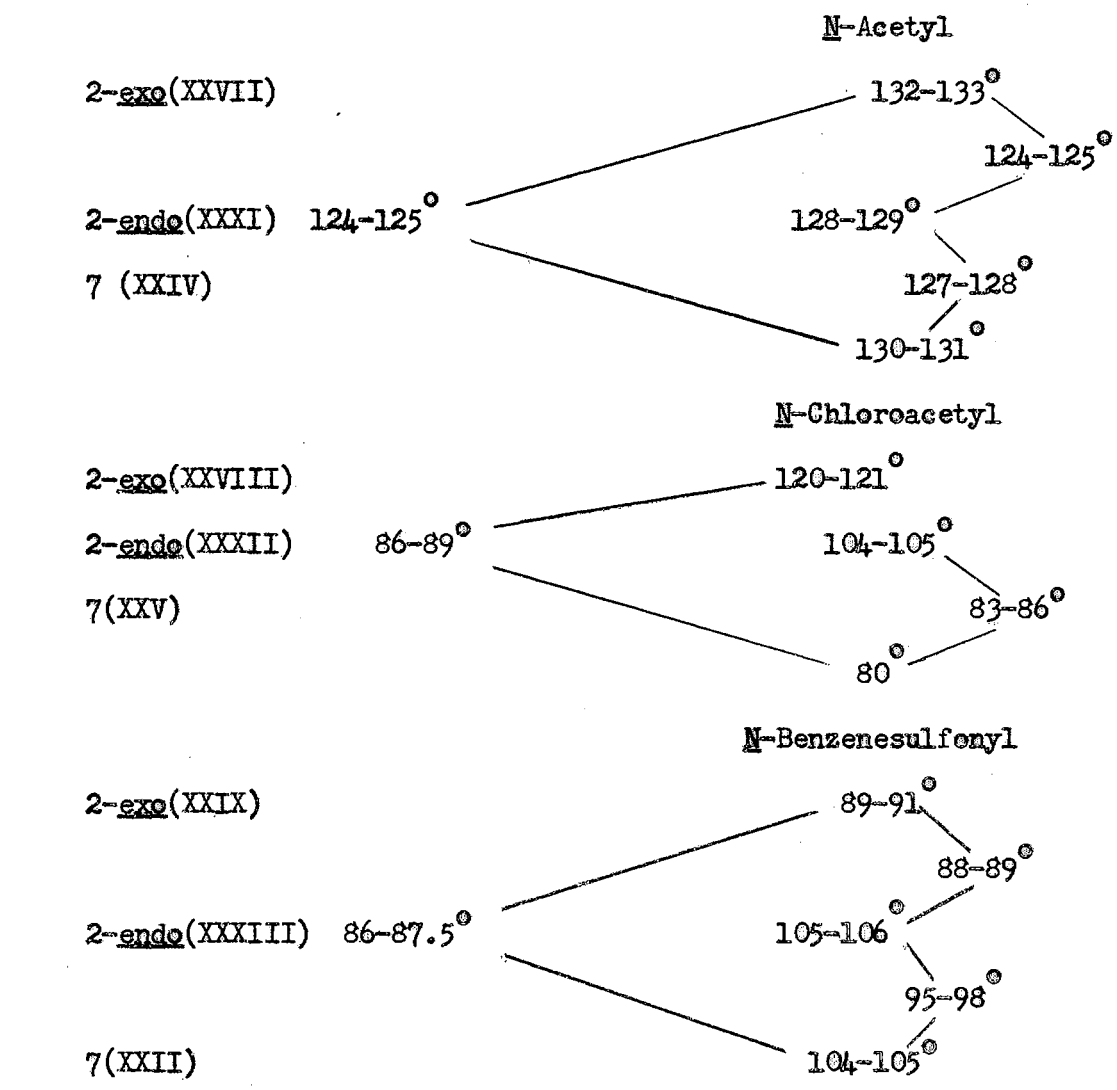
The following differences were noticed in the infrared spectra of the three isomers. In the 900-1500 cm.$^{-1}$ region, the 2-exo isomer showed a moderately strong band at 1107 cm.$^{-1}$ which was shifted to 1320 and 1235 cm.$^{-1}$ in the 7-isomer; a moderately intense band at 1200 cm.$^{-1}$ in the spectrum of the 7-isomer was not present in the spectra of the 2-exo and 2-endo isomers. In the 750-900 cm.$^{-1}$ region a moderately intense band at 878 cm.$^{-1}$ in the 2-exo isomer was shifted to 888 cm.$^{-1}$ in the 2-endo isomer, and the 7-isomer showed a weak doublet at 873 and 890 cm.$^{-1}$; the 7-isomer showed a moderately intense doublet at 805 and 788 cm.$^{-1}$, whereas in the 2-exo isomer, a single band appeared at 788 cm.$^{-1}$ with a very weak band at 813 cm.$^{-1}$.

Melting Point Comparisons of Amine Derivatives

All mixture melting points, indicated by numbers at points of lines joining two melting points as shown below, were determined after mixing, melting, and allowing the solid mixture to resolidify.

TABLE IV

MELTING POINT COMPARISONS OF AMINOBICYCLO(2.2.1)HEPTANE DERIVATIVES



2. Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.1)-2,5--heptadiene:

Preparation of N-Benzenesulfonyl-2-azabicyclo(3.2.1)-3,6-octadiene (LVII≡LVIII)

A solution of 22 g. of benzenesulfonyl azide (VI) and 32 g. VIII in 200 cc. of benzene was stirred overnight at room temperature. The benzene was removed in vacuo and the residue chromatographed on 750 g. of Merck acid-washed alumina. Elution with 2 l. of benzene gave 18.3 g. of LVII as an oil which decomposed on standing. Elution with 2 l. of ethyl ether gave 5.7 g. of a mixture of several unidentified polar components which showed N-H, O-H, and carbonyl absorption in the infrared spectrum. An analytical sample of LVII, was prepared by distillation at 100° and 0.03 mm.; n.m.r. (in $CHCl_3$) δ 1.23 (syn C_8 proton, doublet, J = 10 c.p.s.), 1.70 (anti C_8 proton, sextet, $J_{8\text{-anti},\ 8\text{-syn}} = 10$ c.p.s., $J_{8\text{-anti},\ 1,4} = 4$ c.p.s.), 2.65 (proton at C_5, quintet) 4.80 (proton at C_1), 5.27 (protons at C_4 and C_6), 6.15 (proton at C_7, quartet, $J_{7,1} = 2.9$ c.p.s., $J_{7,6} = 5.7$ c.p.s.), 6.35 (proton at C_3, quartet, $J_{3,4} = 7.5$ c.p.s., $J_{3,5} = 1.5$ c.p.s.), and 7.46-8.03 (5 aromatic protons). See Plate I.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.64; H, 5.53.

N.M.R. Study of the Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.1)-2,5-heptadiene

A solution of 0.244 g. VIII and 0.240 g. benzenesulfonyl azide (VI) in 1 cc. deuterochloroform (1% tetramethylsilane) was placed in an n.m.r. tube at 26° and the spectrum recorded periodically. Based

on the integration of total aromatic protons in the mixture and selected non-aromatic protons in LX and LVII, the percentage ($\pm$ 2%) of each component at a given time after mixing is shown in Table V

TABLE V

REARRANGEMENT OF LX TO LVIII

Time (hrs.)	LX	LVIII
2	53%	13%
4.5	50%	25%
8.5	54%	31%
19	43%	45%
48	21%	60%
72	<1%	81%

The following signals in the n.m.r. spectrum at 2 hr. were attributed to LX: An AB quartet (J = 8.5 c.p.s.) at δ 1.07 and 1.66 arising from the C_7 protons, a broad multiplet centered at δ 2.96 due to the bridgehead protons, a sharp singlet at δ 3.18 for the C_2 and C_3 protons and a triplet (J = 1.5 c.p.s.) centered at δ 6.35 arising from the C_5 and C_6 protons.

Preparation of N-Benzenesulfonyl-8-azatricyclo(3.2.1.$1^{2,3}$exo)-octane (XI) from LX

A solution of 32 g. of VIII and 21.4 g. of benzenesulfonyl azide (VI) in 300 cc. of benzene was stirred overnight. Removal of the benzene in vacuo left 28.7 g. of an oil which n.m.r. analysis showed to contain 33$\pm$ 2% LX and 40$\pm$ 2% LVII. A solution of 5.8 g. of this mixture in 50 cc. of ethyl acetate was hydrogenated in the presence of 0.7 g. platinum oxide. After the uptake of hydrogen ceased, the catalyst was removed by filtration and the solvent evaporated to give 5.9 g. of an oil. Analysis of the hydrogenated mixture by n.m.r. showed the

presence of 33± 2% XI and 42± 2% LXI. The hydrogenated mixture was chromatographed directly on 700 g. Merck acid-washed alumina. Elution with 1 l. of benzene gave 1.232 g. of LXI, m.p. 47-51°. Mixture melting point with an authentic sample of XI (m.p. 104-105°) was undepressed.

Preparation of N-Benzenesulfonyl-2-azabicyclo(3.2.1)-3-octene (LXI≡LXII) from LVII

A solution of 18 g. of LVII in 250 cc. methanol was stirred for 24 hr. under hydrogen at atmospheric pressure in the presence of 2 g. of 5% palladium on charcoal. After hydrogen uptake ceased, the reaction mixture was filtered and the methanol was removed from the filtrate *in vacuo*. The hydrogenated product was chromatographed on 750 g. of Merck acid-washed alumina. Elution with 2 l. of benzene gave 15.3 g. of LXI which crystallized and had m.p. 47-51°. This material showed only one spot (R_f 0.45) upon thin layer chromatography on Silica Gel-G (20 cm.) in chloroform. The analytical sample was prepared by sublimation thrice at 50° at 0.03 mm. and had m.p. 51-52° (lit.[21] m.p. 50-53°); ν_{max}^{melt} 1625, 1318, 1165, 1100, 968, and 726 $cm.^{-1}$; n.m.r. (in $CHCl_3$) δ 0.93-2.0 (6 protons), 2.29 (proton at C_5), 4.48 (proton at C_1), 5.25 (proton at C_4, sextet, $J_{4,3}$ = 7.2 c.p.s., $J_{4,5}$ =1.5 c.p.s.), 6.47 (proton at C_3, quartet, $J_{3,4}$ = 7.2 c.p.s., $J_{3,5}$ = 1.5 c.p.s.), and 7.49-7.99 (5 aromatic protons). See Plate II.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06. Found: C, 63.01; H, 6.30.

Ozonolysis of LXI (LXI≡LXII)

A stream of oxygen containing ozone was passed through a solution

of 15 g. of LXI in 50 cc. of methylene chloride maintained at -70°. After the uptake of ozone ceased (ca.2 hr.), the solution was poured into 50 cc. of 50% acetic acid containing approximately 2 g. of zinc dust and the slurry stirred overnight. The acidic aqueous layer was neutralized with sodium carbonate and the organic layer was decanted. The aqueous layer was extracted with additional methylene chloride. The methylene chloride extracts were combined, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography of the concentrate on 500 g. Merck acid-washed alumina yielded 7.1 g. of LXIV as an oil eluted with benzene-ether (9:1). ν_{max}^{film} 2775, 1725, 1365, 1230, 1177, and 1100 $cm.^{-1}$; n.m.r. (in $CDCl_3$) δ 1.40-2.74 (7 protons), 4.34 (proton at C_3), 7.59-8.09 (5 aromatic protons), 9.22 (N-formyl proton), and 9.71 (aldehydic proton, doublet, J = 1.5 c.p.s.).

Preparation of 3-Benzenesulfonamidocyclopentanecarboxylic Acid (LXV) and its Methyl Ester from LXI (LXI ≡ LXII)

A stream of oxygen containing ozone was passed through a solution of 9.7 g. LXI in 20 cc. of methylene chloride maintained at -70°. After the uptake of ozone ceased (ca.1 hr.) the solution was treated with 25 cc. of 30% hydrogen peroxide and stirred for 4 hr. The excess peroxide was than destroyed by the addition of platinum oxide and the methylene chloride solution was treated directly with excess Tollens reagent (16 g. $AgNO_3$ in 320 cc. of water mixed with 160 cc. of 10% NaOH and 160 cc. dilute NH_4OH just before use). After 24 hr. the excess Tollens reagent was destroyed by addition of formaldehyde. The aqueous basic solution was washed with ether and acidified. The acidic aqueous solution was extracted with ether which, after drying over anhydrous

magnesium sulfate, was evaporated to give 8.2 g. of LXV as an oil. Crystallization of LXV from ether in the cold gave m.p. 117-119°; ν_{max}^{KBr} 3280 (N-H) and 1715 (C = O) cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.31; H, 5.97. Found: C, 53.20; H, 5.56.

The methyl ester was prepared by treatment of LXV with excess ethereal diazomethane. Thin layer chromatography of the methyl ester prepared from unpurified LXV, on Silica Gel-G (15 cm.) in chloroform-acetone (9:1) showed a major component (R_f 0.45). ν_{max}^{KBr} 3250, 1730, 1320, and 1160 cm.$^{-1}$; n.m.r. (in $CHCl_3$) δ 1.47-2.15 (6 protons), 2.45-3.12 (proton at C_1), 3.65 (4 protons, methyl ester protons superimposed on proton at C_3), 5.95 (N-H, doublet, J = 8 c.p.s.), and 7.55-8.10 (5 aromatic protons).

Conversion of LXIV to N-3-(methylcyclopentyl)-benzenesulfonamide (LXVI)

To a solution of 3.9 g. of LXIV in 45 cc. of ethylene glycol were added 10.5 g. potassium hydroxide and 5 cc. of 95+ % hydrazine. The reaction mixture was refluxed for 4 hr., then the temperature was raised to 210° by distillation of water and excess hydrazine. More hydrazine (5 cc.) was added and the solution refluxed at 190° for an additional 18 hr. The reaction mixture was cooled, poured onto 100 cc. water, neutralized with dilute sulfuric acid, and extracted with ether. The ether extract was washed twice with 100-cc. portions of water and then dried over anhydrous magnesium sulfate. Evaporation of the ether gave an oil which was chromatographed on 250 g. of Merck acid-washed alumina. Elution with 1 l. of benzene-ether (9:1) gave

2.0 g. of LXVI as an oil. Thin layer chromatography of the eluate on Silica Gel-G (15 cm.) in chloroform showed that successive chromatographic fractions contained two poorly resolved components (R_f 0.40, 0.42). An analytical sample of LXVI was prepared by distillation of the eluate at 150-160° and 0.05 mm.; n.m.r. (in $CDCl_3$) δ 0.78-1.0 (3 protons, methyl protons as 2 overlapping doublets), 1.0-2.0 (7 protons), 3.64 (proton at C_1, sextet), 6.01 (N-H, doublet, $J = 7.5$ c.p.s.), and 7.44-8.17 (5 aromatic protons).

Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 60.31; H, 7.13.

Conversion of LXVI to 3-Methylcyclopentylamine

To a solution of 1.5 g. of LXVI in 20 cc. of sec-butyl alcohol was added 2 g. of metallic sodium over a period of 15 min. The solution was refluxed overnight, cooled, diluted with water, and acidified with dilute hydrochloric acid. The reaction mixture was then concentrated in vacuo to remove the alcohol and then extracted several times with chloroform. The aqueous portion was rendered basic and extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was slowly evaporated through a Vigreux column to give 450 mg. of the amine as a foul-smelling oil. The amine was converted into its HCl salt by the addition of excess dilute hydrochloric acid followed by evaporation in vacuo of the excess hydrogen chloride and water. The HCl salt thus prepared was used without further purification.

Nitrous Acid Deamination of 3-Methylcyclopentylamine

A solution of 405 mg. of the HCl salt of the amine prepared above in 2 cc. of water was heated at 60° for 4 hr. with 0.32 g. of sodium

nitrite and seven drops of glacial acetic acid. After this time the solution was neutralized with aqueous sodium carbonate solution and steam distilled. The steam distillate was extracted with ether which, after drying over anhydrous magnesium sulfate, was slowly evaporated through a Vigreux column leaving 200 mg. of a mixture of 3-methylcyclopentanol and olefins. Gas chromatography of the mixture on a 0.25-in. x 10-ft. DEGS column at 120° using a helium flow-rate of 115 cc. per min. showed the following peaks: 0.5 min. (29%, olefins), 1.75 min. (6%), 4 min. (3%), and 6.5 min. (62%, 3-methylcyclopentanol). Cyclopentanol had a retention time of 5.5 min. under these conditions.

Preparation of 3-Methylcyclopentanone (LXVII)

A portion (160 mg.) of the deamination mixture from above was stirred for 24 hr. with 300 mg. of chromic anhydride in 3 cc. of 90% acetic acid. The reaction mixture was diluted with 5 cc. of water and neutralized with sodium carbonate. The neutral solution was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated slowly through a Vigreux column to give 102 mg. of LXVII. Gas chromatography of the oxidation mixture using the same conditions described above except for a flow rate of 86 cc./min. showed LXVII as the major component (T_r = 6.5 min.), identical with an authentic sample of LXVII,[24] which under these conditions had a retention time of 5.5 min. The dibenzylidene derivative of LXVII had m.p. 156-157°. after recrystallization from methanol and showed no depression upon mixture melting point with an authentic sample[24] which had m.p. 156-157°.

3. Reaction of Benzenesulfonyl Azide with Dicyclopentadiene: Preparation of LXXIII

A solution of 4.3 g. of dicyclopentadiene (II) and 7.0 g. benzenesulfonyl azide (VI) in 10 cc. of chloroform was stirred at room temperature for 3 hrs. During this time nitrogen was smoothly evolved and a white solid precipitated from the reaction solution. The solid was recrystallized from benzene-petroleum ether (1:1) to give 9.49 g. of LXXIII, m.p. 138°; ν_{max}^{KBr} 1310, 1160, 1090, 885, and 750 cm.$^{-1}$; n.m.r. (in CCl_4) δ 0.88 (anti C_7 proton, doublet, J = 9.5 c.p.s.), 1.55 (syn C_7 proton, doublet, J = 9.5 c.p.s.), 2.62 (proton at C_2, doublet, J = 5.5 c.p.s.), 2.88 (proton at C_3, doublet, J = 5.5 c.p.s.), 2.2-3.2 (6 protons, broad multiplet), 5.4-5.9 (2 vinylic protons), and 7.4-7.9 (5 aromatic protons).

Anal. Calcd. for $C_{16}H_{17}NO_2S$: C, 67.37; H, 5.96; N, 4.91. Found: C, 67.27; H, 5.92; N, 4.68.

Hydrogenation of LXXIII

A solution of 0.560 g. of LXXIII in 20 cc. of 95% ethanol was hydrogenated in a Parr hydrogenation apparatus with 0.5 g. of Raney Ni (wet weight) under an initial pressure of 40 p.s.i.g. After 48 hr. the solution was filtered and the hydrogenated product was precipitated (0.526 g.) from the alcoholic filtrate by the adding of water. The product, LXXVII, had m.p. 144-145°; ν_{max}^{KBr} 1310, 1160, and 878 cm.$^{-1}$; n.m.r. (in CS_2) δ 0.92 (anti C_7 proton, doublet, J = 9.5 c.p.s.), 1.35-1.72 (9 protons), 2.21-2.40 (protons at C_1, C_4, C_5, and C_6), 2.90 (protons at C_2 and C_3) and 7.23-7.82 (5 aromatic protons).

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62. Found: C, 66.54; H, 6.66.

4. Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.2)-2-octene:

Preparation of LXXIX and LXXX

A solution of 12.4 g. of benzenesulfonyl azide (VI) and 7.3 g. of bicyclo(2.2.2)-2-octene (IX) in 30 cc. benzene was heated on a steam bath for 3 days. Analysis of the reaction mixture by infrared spectroscopy at 24 hr. intervals showed an increase in absorption at 1612 $cm.^{-1}$ as the azide absorption at 2108 $cm.^{-1}$ decreased in intensity (no absorption for N-H was observed). Removal of the benzene under vacuum left 18.5 g. of semisolid residue.

The infrared spectrum of a portion of the reaction residue exposed to moist air overnight showed N-H absorption in the 3300 $cm.^{-1}$ region and a carbonyl absorption at 1730 $cm.^{-1}$ but no absorption at 1612 $cm.^{-1}$.

A 2.05 g. portion of the reaction mixture was finely ground and exposed to moist air overnight. Chromatography of this portion on 100 g. of silica gel gave 1.41 g. of solid upon elution with 0.8 l. of benzene-petroleum ether (1:1). Thin layer chromatography of the solid on Silica Gel-G (10 cm) in benzene-petroleum ether (1:1) showed this eluate to be a mixture of LXXX and bicyclo(2.2.2)-2-octanone. These two components were separated by addition of excess acidic, ethanolic, 2,4-dinitrophenylhydrazine followed by fractional recrystallization. The 2,4-dinitrophenylhydrazone derivative and LXXX were separated by repeatedly adding water to ethanolic solutions of the mixture; the hydrazone precipitated immediately and the aziridine only upon standing. In this manner 0.685 g. of bicyclo(2.2.2)-2-octanone 2,4-dinitrophenylhydrazone, m.p. 165-166° (lit.[30] m.p. 165-166°), and 1.102 g. (54%) of LXXX, m.p. 88-90°, were obtained. The analytical sample of LXXX gave ν_{max}^{KBr} 1308, 1160, 1092, and 990 $cm.^{-1}$; n.m.r.

(in CS_2) δ 1.13 (2 protons at C_7 and C_8, doublet, J = 9.5 c.p.s.), 1.53 (6 protons as broad multiplet), 1.82-2.05 (protons at C_1 and C_4), 2.88 (protons at C_2 and C_3, multiplet), and 7.47-7.84 (5 aromatic protons).

Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.89; H, 6.51. Found: C, 63.95; H, 6.90.

Elution of the silica gel column with 150 cc. of 95% ethanol gave 0.8 g. of brown solid from which 0.4 g. (33%) of benzenesulfonamide, m.p. 150-152°, was sublimed; mixture melting point with an authentic sample was undepressed.

Preparation of trans-2-Thiophenoxy-3-benzenesulfonamidobicyclo-(2.2.2)octane (LXXXII)

A solution of 1.7 g. of LXXX and 1.3 g. of thiophenol in 13 g. of tert-butyl alcohol (0.1 N in potassium tert-butoxide) was refluxed for 12 hr. The reaction mixture was diluted with water and carefully neutralized with dilute hydrochloric acid. The mixture was extracted with ether which was then dried over anhydrous magnesium sulfate and evaporated to give 2.17 g. (89%) of LXXXII, m.p. 135-136°; n.m.r. (in $CHCl_3$) δ 1.29-1.82 (10 protons), 3.10 (2 protons, multiplet; sharpened to AB quartet upon addition of CF_3COOH with doublets centered at δ 2.82 and 3.02, $J_{2,3}$ = 6.5 c.p.s.), and 6.08 (N-H, doublet, J = 5.5 c.p.s.; disappears upon addition of CF_3COOH). An analytical sample was prepared by recrystallization from ether and had m.p. 135-136°.

Anal. Calcd. for $C_{20}H_{23}NO_2S_2$: C, 64.31; H, 6.21. Found: C, 64.11; H, 6.35.

Conversion of LXXXII to 2-Benzenesulfonamidobicyclo(2.2.2)octane

A suspension of 12 g. of Raney nickel in 25 cc. of isopropyl alcohol containing 1.7 g. of LXXXII was refluxed for 12 hr.[14] The reaction mixture was then filtered and the nickel washed several times with isopropyl alcohol. Evaporation of the filtrate gave 1 g. of 2-benzenesulfonamidobicyclo(2.2.2)octane, m.p. 95-96°. An analytical sample was prepared by recrystallization from ether and had m.p. 97-98°; ν_{max}^{KBr} 3282, 1330, and 1165 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22. Found: C, 63.72; H, 7.37.

An authentic sample of 2-benzenesulfonamidobicyclo(2.2.2)octane was prepared from bicyclo(2.2.2)-2-octanone oxime, m.p. 113-116°, (lit.[52] m.p. 114-118°) by catalytic reduction with Raney nickel in methanol to the amine and subsequent treatment of the amine with benzenesulfonyl chloride. The sample prepared in this manner had m.p. of 96-97° and mixture melting point with that prepared from LXXXII was undepressed.

Treatment of LXXX with Hydrogen Bromide

Dry hydrogen bromide was passed through a solution of 4.7 g. of LXXX dissolved in 25 cc. of carbon tetrachloride at room temperature for 1 hr. The solution was allowed to stir overnight and then swept with nitrogen and washed with aqueous sodium carbonate solution. The carbon tetrachloride solution was dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed directly on 300 g. of Merck acid-washed alumina. Elution with benzene-chloroform mixtures gave initial eluate (1.6 g.) containing two components (thin layer chromatography) from which LXXXIV crystallized from petroleum ether-

ether solution, m.p. 129-130°; ν_{max}^{KBr} 3300, 1318, 1170 and 1097 cm.$^{-1}$; n.m.r. (in $CHCl_3$) δ 1.10-2.31 (10 protons), 3.49 (proton at C_8 multiplet; sharpened to a triplet, J = 4 c.p.s., upon addition of CF_3COOH), 4.28 (proton at C_2, multiplet), and 6.09 (N-H, doublet, J = 9 c.p.s.; disappeared upon addition of CF_3COOH).

Continued elution with benzene-chloroform mixtures of increasing polarity gave 2.3 g. of LXXXIII, m.p. 136-137°; ν_{max}^{KBr} 3230, 1310, 1160, and 1080 cm.$^{-1}$; n.m.r. (in $CHCl_3$-CF_3COOH) δ 1.27-2.0 (10 protons), 3.70 (proton at C_2, doublet, J = 5 c.p.s.), 3.96 (proton at C_3, doublet, J = 5 c.p.s.), and 7.50-8.15 (5 aromatic protons).

Anal. Calcd. for $C_{14}H_{18}BrNO_2S$: C, 48.84; H, 5.27. Found: C, 49.18; H, 5.35.

5. Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.1)-5-heptene--endo-cis-2,3-dicarboxylic Anhydride

Preparation of VII and LXXXVIII (LXXXVIII ≡ XCII)

A solution of V (4.4 g., 26.8 mmole) and benzenesulfonyl azide (V) (6.0 g., 32.8 mmole) in 65 cc. carbon tetrachloride was refluxed for 48 hr. The solvent was removed in vacuo and VII (4.132 g., 13.0 mmole) crystallized from benzene-acetone to give m.p. 206-210°. The crystalline product had m.p. 215-216° (lit.[9] m.p. 215-216.5°) after recrystallization from acetone. The mother liquors were combined and concentrated. The concentrate was treated with excess diazomethane in ether-methanol. The esterified mixture was concentrated and chromatographed directly on 250 g. of Merck acid-washed alumina. Elution with 0.5 l. of benzene gave 0.714 g. of benzenesulfonyl azide. Elution with 1 l. of benzene-chloroform (9:1) gave the dimethyl ester from V (0.252 g.,

1.2 mmole). Elution with 1 l. (8:2), 0.5 l. (7:3), and 0.7 l. benzene-chloroform (6:4) gave LXXXVIII (1.76 g., 4.8 mmole). The analytical sample, prepared by crystallization from methanol, had m.p. 113-114°; ν_{max}^{KBr} 1740, 1325, 1200, 1160, and 880 cm.$^{-1}$; n.m.r. (in $CDCl_3$) δ 0.90 (anti C_7 proton, doublet, J = 10.5 c.p.s.), 1.70 (syn C_7 proton, doublet, J = 10.5 c.p.s.), 2.83 (protons at C_1 and C_4), 3.13 (protons at C_2 and C_3), 3.53 (protons at C_5 and C_6), 3.67 (6 protons of dimethyl ester), and 7.5-8.1 (5 aromatic protons).

Anal. Calcd. for $C_{17}H_{19}O_6NS$: C, 55.88; H, 5.24. Found: C, 56.22; H, 5.45.

Continued elution with 0.4 l. of benzene-chloroform (6:4) gave LXXXVII (0.858 g., 2.4 mmole) which had m.p. 129-130° after recrystallization from ether (lit.[9] m.p. 130-131°). Elution with 2 l. of chloroform gave 0.771 g. of an unidentified oil containing N-H absorption in the infrared and whose n.m.r. spectrum showed several methoxyl signals. Thin layer chromatographic analysis showed this material to be a mixture of several very polar components.

6. Reaction of Benzenesulfonyl Azide with Bicyclo(2.2.1)-5-heptene-exo-cis-2,3-dicarboxylic Anhydride:

Preparation of XCIV (XCIV≡XCVI) and C

A solution of IV (4.77 g., 29 mmole) and benzenesulfonyl azide (5.95 g.) in 62 cc. of carbon tetrachloride was refluxed for 48 hr. during which time a gummy solid precipitated. The solvent was stripped in vacuo and the precipitate partially crystallized from benzene to give XCIV (4.18 g., 13.1 mmole), m.p. 167-8°, (lit.[9] 168-168.5°). The mother liquors were concentrated and treated with excess diazomethane

in ether-methanol. The esterified mixture was chromatographed on 500 g. of Merck acid-washed alumina. Elution with 0.5 l. benzene gave 0.69 g. of benzenesulfonyl azide. Continued elution with 1.5 l. of benzene gave 0.65 g. (3.1 mmole) of the dimethyl ester from IV. Elution with 1 l. (9:1), 1 l. (8:2), and 1 l. (7:3) benzene-chloroform gave 0.245 g. of a mixture which was shown by n.m.r. analysis to contain 1.51 mmole of the dimethyl ester from IV and 0.6 mmole of the dimethyl ester from XCIV. Elution with 1 l. (6:4) benzene-chloroform gave 2.937 g. of a mixture of 4.3 mmole of the dimethyl ester from XCIV and 3.7 mmole of C. Elution with 1 l. (1:1) benzene-chloroform gave 1.12 g. of a mixture of 1.05 mmole XCIV dimethyl ester and 2.05 mmole C. Crystallization of the last mentioned eluate from ether gave 0.347 g. of C, m.p. 148-149°; ν_{max}^{KBr} 1740, 1365, 1322, 1220, and 1160 cm.$^{-1}$; n.m.r. (in $CDCl_3$) δ 1.47 (anti C_7 proton, doublet, J = 11 c.p.s.), 1.75 (syn C_7 proton, doublet, J = 11 c.p.s.), 2.82 (protons at C_1, C_2, C_3 and C_4), 3.03 (protons at C_5 and C_6), 3.68 (6 protons of dimethyl ester), and 7.5-8.0 (5 aromatic protons).

Anal. Calcd. for $C_{17}H_{19}O_6NS$: C, 55.88; H, 5.24. Found: C, 56.11; H, 5.07.

Elution with 1 l. (1:9) benzene-chloroform gave 0.347 g. of an unidentified oil which showed N-H absorption in the infrared and several methoxyl signals in the n.m.r. spectrum. Thin layer chromatographic analysis showed this to be a mixture of several polar components.

Decarboxylation of XCVII: Preparation of N-Benzenesulfonyl-8-azatricyclo(2.2.1.1$^{2,3\ endo}$)-5-octene (LXVIII)

Aziridine XCIV (2.37 g.) was dissolved in 100 cc. of hot water over

a period of 20 min. Upon cooling 2.08 g. of aziridine diacid XCVII precipitated and had m.p. 180-182°. The dimethyl ester of XCVII was prepared using diazomethane and after crystallization from petroleum ether had m.p. 102-103° (lit.[9] m.p. 102-103°).

The aziridine diacid XCVII (1.487 g.) was dissolved in 50 cc. dry pyridine at 50° under nitrogen. Lead tetraacetate (4.33 g.) was added and the temperature was raised to 80° over a period of 20 min. The reaction mixture was cooled and the pyridine evaporated under vacuum. The residue remaining was taken up in 50 cc. of chloroform which was washed with 30 cc. of dilute hydrochloric acid and filtered. The chloroform portion was decanted, dried over anhydrous magnesium sulfate, and evaporated to give ca. 0.9 g. of a dark oil. Thin layer chromatography on Silica Gel-G (15 cm.) in chloroform gave three small spots below R_f 0.25 and one large spot at R_f 0.60. Chromatography of this residue on 29 g. of Merck acid-washed alumina gave 0.667 g. (58%) of LXVIII, m.p. 90-92°, eluted in benzene. The analytical sample of LXVIII was prepared by recrystallization from ethanol and had m.p. 92-93.5°; ν_{max}^{KBr} 1305, 1155, and 715 cm.$^{-1}$; n.m.r. (in $CDCl_3$) δ 1.76 (2 protons at C_7), 2.87 (protons at C_1 and C_4), 3.55 (protons at C_2 and C_3, triplet, J = 1.8 c.p.s.), 5.86 (protons at C_5 and C_6, triplet, J = 1.5 c.p.s.), and 7.3-8.1 (5 aromatic protons).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.04; H, 5.29.

Preparation of N-Benzenesulfonyl-8-azatricyclo(2.2.1.$1^{2,3}$ endo)-octane (LXXVIII)

The unsaturated aziridine LXVIII (0.227 g.) was hydrogenated in

the presence of 0.2 g. of 10% palladium-on-charcoal catalyst in 50 cc. of methanol under hydrogen at atmospheric pressure. The theoretical volume of hydrogen was absorbed in 15 min. Removal of the catalyst by filtration followed by evaporation of the methanol gave 0.21 g. of LXXVIII, b.p.$_{0.03\ mm.}$ 150±5°; ν_{max}^{film} 1310, 1160, and 910 cm.$^{-1}$; n.m.r. (in CS_2) δ 1.2-1.5 (5 protons), 1.83 (1 proton, doublet, J = 9.5 c.p.s.), 2.31 (protons at C_1 and C_4), 3.29 (protons at C_2 and C_3, triplet, J = 2 c.p.s.) and 7.4-8.0 (5 aromatic protons).

Preparation of 2-*exo*-Thiophenoxy-3-*endo*-benzenesulfonamidobicyclo-(2.2.1)heptane (XCVIII)

A solution of 0.83 g. of LXXVIII and thiophenol (0.70 g.) in 7 cc. of 0.1 N potassium *tert*-butoxide in *tert*-butyl alcohol was refluxed overnight. The reaction mixture was poured onto water and neutralized with 5% hydrochloric acid. The aqueous solution was extracted with ether which was then dried over anhydrous magnesium sulfate. Evaporation of the ether extract gave 1.15 g. of XCVIII which, after washing with petroleum ether, had m.p. 114-115°; n.m.r. (in nitrobenzene containing CF_3COOH); δ 1.1-1.9 (6 protons), 2.08 (proton at C_1, broad multiplet), 2.25 (proton at C_4, broad multiplet), 2.98 (proton at C_2, quartet, $J_{2,3}$ = 4 c.p.s., $J_{2,7\text{-}anti}$ = 2 c.p.s.), and 3.54 (proton at C_3, triplet, $J_{2,3} = J_{3,4}$ = 4 c.p.s.).

Anal. Calcd. for $C_{19}H_{21}NO_2S_2$: C, 63.48; H, 5.89. Found: C, 63.37; H, 6.05.

Conversion of XCVIII to 2-*endo*-Benzenesulfonamidobicyclo(2.2.1)-heptane (XXXIII)

The thiophenol addition product XCVIII (0.705 g.) was refluxed

for 15 hr. with a slurry of 6 g. of Raney nickel (W-2) in 15 cc. of isopropyl alcohol. The solution was filtered and the catalyst was washed several times with ethanol. Evaporation of the alcohol filtrate gave 0.175 g. of XXXIII, m.p. 104-105°. Mixture melting point with authentic XXXIII which had m.p. 104-105°, prepared as described previously, was undepressed. Mixture melting point with 7-benzenesulfonamidobicyclo-(2.2.1)heptane (XXII), m.p. 103-104°, prepared as described earlier, gave m.p. 90-93°. Authentic 2-exo-benzenesulfonamidobicyclo(2.2.1)-heptane (XXIX) gave m.p. 89-91°, well below that of the isomer prepared from XCVIII.

Preparation of N-Benzenesulfonyl-8-azatricyclo(2.2.1.$1^{2,3}$ endo)-octane-5,6-endo-dideuterio-5,6-exo-dicarboxylic Anhydride (XCIV-2,3-$d_{1.4}$ ≡ XCVI-2,3-$d_{1.4}$)

A mixture (3.9 g.) of 2,3-exo-dideuterio-2,3-endo-dicarboxybicyclo-(2.2.1)-5-heptene anhydride and the protio species V were prepared by the reaction of maleic anhydride-maleic anhydride-d_2 and cyclopentadiene according to the procedure of Van Sickle and Rodin.[53] Analysis of the mixture by n.m.r. showed 70±5% deuterium in the 2,3 positions.

Heating 3.3 g. V-2,3-$d_{1.4}$ in an open flask at 200° for 2 hr. gave a mixture of V-2,3-$d_{1.4}$ and IV-2,3-$d_{1.4}$ from which 0.715 g. of IV-2,-3-$d_{1.4}$ crystallized in benzene.[54] Gas chromatography using a 0.25-in. x 10-ft. column of 5% SE-30 on acid-washed Chromosorb W at 180° with helium flow rate of 80 cc. per min. showed IV-2,3-$d_{1.4}$ to be uncontaminated with V. Analysis by n.m.r. showed IV-2,3-$d_{1.4}$ to contain 71±2% deuterium in the 2,3 positions.

A solution of 0.648 g. IV-2,3-$d_{1.4}$ and 0.59 g. benzenesulfonyl azide in 10 cc. of carbon tetrachloride was refluxed 36 hr. The carbon tetrachloride was decanted and the residue was crystallized thrice from benzene to give 0.4 g. of XCIV-2,3-$d_{1.4}$, m.p. 167-168°. Analysis by n.m.r. showed 71±2% deuterium at C_5 and C_6.

Preparation of N-Benzenesulfonyl-8-azatricyclo(2.2.1.$1^{2,3}$ endo)-5,6--dideuterio-5-octene (LXVIII-5,6-$d_{1.4}$)

Aziridine XCIV-2,3-$d_{1.4}$ (0.4 g.) was dissolved in 15 cc. of hot 80% D_2O over a period of 30 min. Evaporation of the aqueous portion *in vacuo* gave 0.406 g. of XCVII-2,3-$d_{1.4}$. After drying over phosphorus pentoxide for 12 hr. XCVII-2,3-$d_{1.4}$ had m.p. 181-183°; ν_{max}^{KBr} 1750 $cm.^{-1}$.

The aziridine diacid XCVII-2,3-$d_{1.4}$ (0.406 g.) was dissolved in 13 cc. dry pyridine under nitrogen at 50° and 1.19 g. of lead tetra-acetate was added. The reaction mixture was stirred at 75° for 20 min. and then worked up by the usual procedure. Chromatography of the reaction mixture directly on Merck acid-washed alumina gave 35 mg. of LXVIII-5,6-$d_{1.4}$, m.p. 90-91°, eluted in benzene. Analysis of LXVIII-5,6--$d_{1.4}$ by n.m.r. showed 72±2% deuterium on C_5 and C_6;

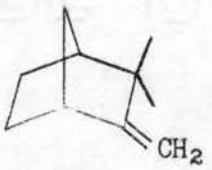
CHAPTER II

THE REACTION OF N,N-DIBROMOBENZENESULFONAMIDE WITH BRIDGED BICYCLIC ALKENES

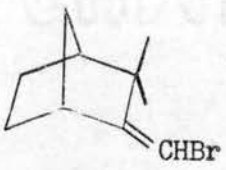
A. Historical and Introduction

The reaction of N-halo imides and N-halo amides with alkenes to produce allylic substitution and addition of halogen is well known.[55] Likewise the use of N-halo compounds as a source of positive halogen in polar solvents is well documented.[56] Although the literature contains a number of examples in which addition of N-halo imides and N-halo amides to alkenes has been observed, this reaction has not been extensively studied. The extent to which addition competes with halogenation and the direction of addition vary with seemingly subtle changes in the structure of the N-halo compound and the alkene. For example, both N-bromotrichloroacetamide and N-bromotrifluoroacetamide are reported to give addition products with cyclohexene, but the unsubstituted, monochloro, and dichloro N-bromoacetamides give only allylic substitution and addition of bromine. This was attributed to the increased positive character of the N-bromine in the trichloro and trifluoroacetamides.[57] Dihydropyran has been reported to add N--bromophthalimide in carbon tetrachloride solvent but in a reverse direction to that observed with N-bromosuccinimide (NBS).[58] In substituted dihydropyrans, the position of the substituent appears to influence the type of products produced with NBS. Although NBS has

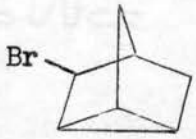
been used extensively as an allylic brominating agent under free-radical conditions it reacts abnormally with bicyclo(2.2.1)heptene and its derivatives in which the only allylic hydrogen atoms are at bridgehead positions. This was first reported by Roberts and coworkers, who studied the reaction of NBS with camphene (CVII)[60] and bicyclo(2.2.1)--2-heptene (I).[61] Under free radical conditions, 8-bromocamphene



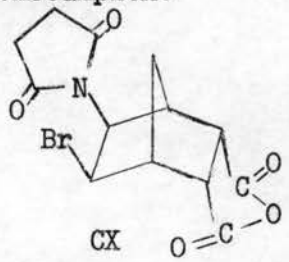
CVII



CVIII



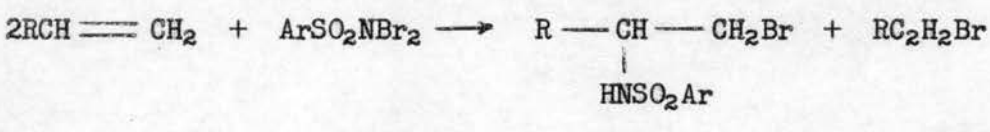
CIX



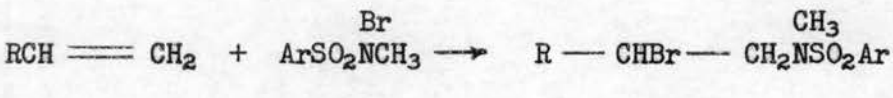
CX

(CVIII) was formed from CII and 2-bromotricyclo(2.2.1.$0^{3,5}$)heptane (CIX) was formed from I. Recently bicyclo(2.2.2)-2-octene (IX) was found to react with NBS to give <u>endo</u>-8-bromobicyclo(3.2.1)-2-octene (LXXXVI).[30] All of the bromo compounds CVIII, CIX, and LXXXVI were produced under conditions identical with those used in normal allylic brominations with NBS. More recent work in this laboratory has shown that under free-radical conditions NBS adds to V to give the <u>cis</u> adduct CX.[62] In view of the unusual results obtained in the reaction of NBS with bicyclic alkenes under free-radical conditions, the present investigation was undertaken to study the course of ionic additions of <u>N</u>-bromo compounds to bicyclo(2.2.1)-2-heptene (I) and bicyclo(2.2.2)--2-octene (IX). Kharasch and Priestly[63] found that <u>N</u>,<u>N</u>-dibromoarenesulfonamides (CXI) gave addition products (CXII) with unsymetrical alkenes such as styrene, in which the bromine atom assumed the position expected in an ionic process. The second active bromine atom of the <u>N</u>,<u>N</u>-dibromoarenesulfonamide simultaneously brominated a second mole of

the alkene giving a vinyl bromide (CXIII). In contrast, N-bromo-N--methylarenesulfonamides (CXIV) gave addition products (CXV) in which the bromine atom assumed the position expected for a radical process. Because of the reported ionic mode of addition of N,N-dibromoarenesulfonamides (CXI) to alkenes it was decided to investigate the reaction of N N-dibromobenzenesulfonamide with I and IX.

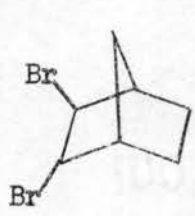


CXI CXII CXIII

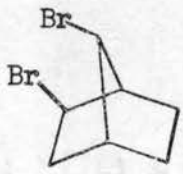


CXIV CXV

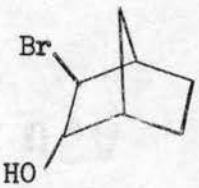
The course of ionic additions to I is well known.[64] The ionic addition of N,N-dibromobenzenesulfonamide to I is seemingly analogous to the addition of bromine to this alkene which yields CIX, CXVI, and XXXV.[65] Likewise the addition of hypobromous acid to I yields CIX, CXVII, and CXVIII.[66]



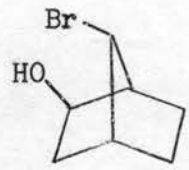
CXVI



XXXV



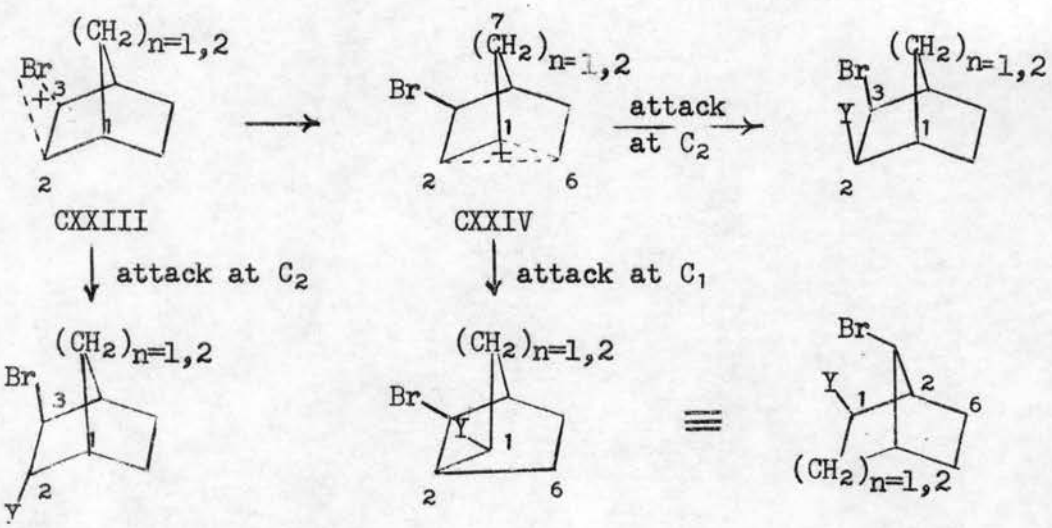
CXVII



CXVIII

The ionic addition of bromine to bicyclo(2.2.2)-2-octene (IX) also gives rearranged products. In this case the principal monobromide formed is LXXXVI, and the dibromides formed are CXIX and CXX.[30] The aforementioned ionic additions to I and IX all involve initial formation

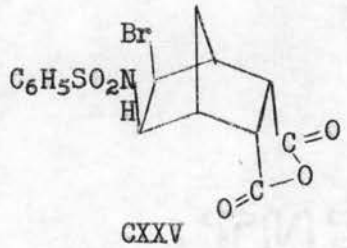
CXIX CXX



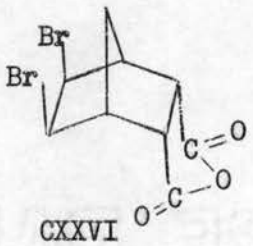
of a bromonium ion (CXXIII) which under the conditions of the reaction may be cleaved by displacement at C_2 or C_3 to give trans C_2, C_3 products or rearrange to the carbon-bridged ion (CXXIV) which itself can undergo displacement at C_2 to give cis C_2, C_3 products or at C_1 to give rearranged products as shown. The formation of the monobromo products CIX and LXXXVI arise from loss of C_6 and a C_7 proton from CXXIV respectively.[64]

Concurrently with the investigations reported in this chapter an investigation was made concerning the reaction of N,N-dibromobenzenesulfonamide with V. The addition of N,N-dibromobenzenesulfonamide to V in refluxing carbon tetrachloride solution leads to the formation of CXXV.[67] This is analogous to the formation of CXXVI in the bromina-

tion of V[68] and may involve front-side cleavage of the exo C_5, C_6 bromonium ion initially formed.



CXXV



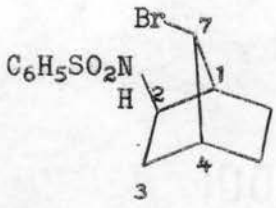
CXXVI

B. Results and Discussion

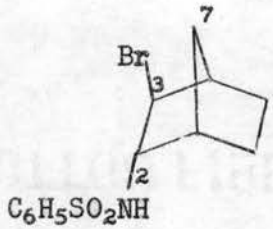
The Reaction of N,N-Dibromobenzenesulfonamide with Bicyclo(2.2.1)-2-heptene

When N,N-dibromobenzenesulfonamide was added to I in benzene at room temperature, an exothermic reaction occurred and benzenesulfonamide began to precipitate from the solution almost immediately.[69] Chromatography of the benzene-soluble portion of the reaction mixture on alumina yielded three major fractions. The first fraction (65% based on I consumed), eluted in petroleum ether, consisted of 86±3% CIX and the remainder dibromobicyclo(2.2.1)heptane, (probably CXVI and XXXV). The second fraction (19.5%) eluted in benzene-chloroform yielded a crystalline product (CXXVII) the infrared and n.m.r. spectra of which indicated the presence of a secondary bromine and a secondary benzenesulfonamido group. The third fraction (8.5%) eluted in chloroform yielded a second crystalline product (CXXVIII) having infrared and n.m.r. spectra very similar to those of CXXVII.

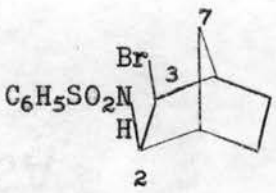
By analogy with the addition of bromine[66] and hypobromous acid[67] to I, structures CXXIX, CXXX, and possibly CXXXI would be expected and are consistent with the elemental and spectral data.



CXXIX



CXXX



CXXXI

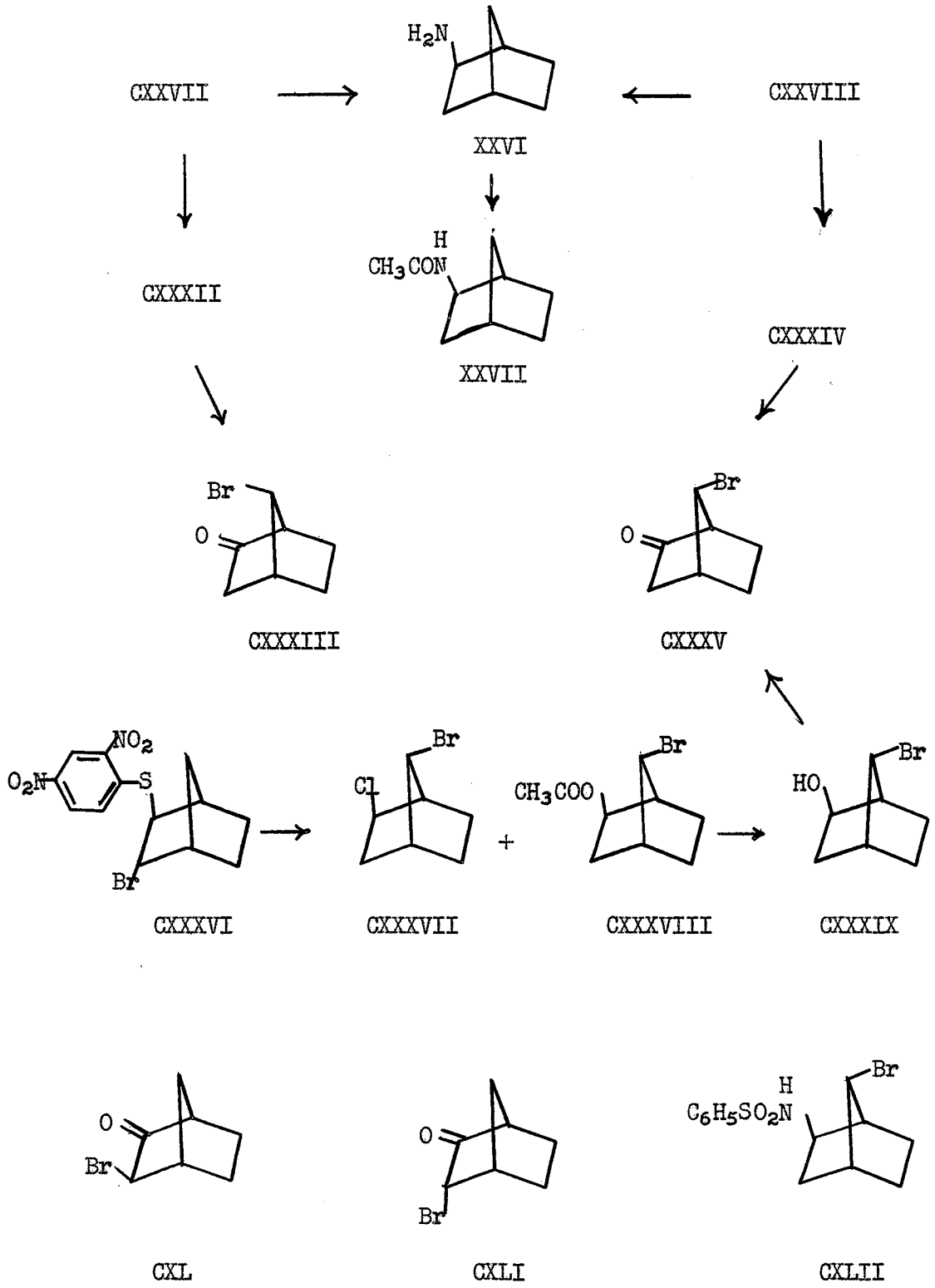
The n.m.r. spectrum of CXXVII showed a proton on carbon attached to the nitrogen atom of the benzenesulfonamido group as a multiplet. Upon addition of trifluoroacetic acid the multiplet sharpened to a triplet ($J = 6.7$ c.p.s.) indicating that the benzenesulfonamido group was located on one of the ethyleneic carbons. The n.m.r. spectrum of XXXV showed a similar triplet ($J = 6.0$ c.p.s.) at δ 3.92 for the 2-endo proton. The n.m.r. spectrum of CXXVII also revealed unresolved coupling in the signal due to the proton on carbon attached to the bromine atom. It is noteworthy that the width of this signal is only 4.0 c.p.s. at half-height. On the basis of known vicinal coupling constants in bicyclo(2.2.1)heptane systems[10] and the similarity in width ($W_{1/2}$ = 4.0 c.p.s.) to the signal of the anti C_7 proton in XXXV, this signal was considered indicative of the presence of C_7 bromine atom.

The position and stereochemistry of the benzenesulfonamido group in CXXVII were shown by reduction with sodium in alcohol to a known aminobicyclo(2.2.1)heptane. The amine thus obtained was converted into its N-acetyl derivative, which was shown to be identical with 2-exo-acetamidobicyclo(2.2.1)heptane (XXVII) and different from 2-endo-acetamidobicyclo(2.2.1)heptane (XXXI) by melting point comparisons

and gas chromatography. The possibility that CXXVII originally contained a 2-*endo*-benzenesulfonamido group, which underwent epimerization during the sodium-alcohol reduction to the thermodynamically more stable *exo* isomer, was excluded in the following manner. Reduction of 2-*endo*--benzenesulfonamidobicyclo(2.2.1)heptane (XXXIII) with sodium in alcohol under conditions identical to those used for the reduction of CXXVII yielded a single amine. This amine was shown to be 2-*endo*-aminobicyclo-(2.2.1)heptane (XXX) by gas chromatographic analysis and melting point of its N-acetyl derivative (XXXI). In order to establish the position and stereochemistry of the bromine atom in CXXVII hydrolysis of the benzenesulfonamido group seemed appropriate. The sulfonamide linkage was hydrolyzed by heating CXXVII with aqueous hydrochloric acid in a sealed tube at 175° for 24 hr. The bromo amine (CXXXII) thus obtained was oxidized by a known procedure[70] to 7-*syn*-bromobicyclo(2.2.1)-2--heptanone (CXXXIII).[66,71] This establishes the structure of CXXVII as CXXIX.

The n.m.r. spectrum of CXXVIII also showed a proton on carbon attached to the nitrogen of the benzenesulfonamido group as a multiplet. Upon addition of trifluoroacetic acid the multiplet sharpened to a quartet (J_1 = 3.9 c.p.s., J_2 = 8.1 c.p.s.) indicating that the benzene-sulfonamido group in CXXVIII was also at C_2. The proton on carbon attached to the bromine atom showed unresolved couplings and $W_{1/2\ h}$ = 4.0 c.p.s., again indicative of a C_7 bromine atom.

Reduction of CXXVIII with sodium in alcohol gave an amine which gave an N-acetyl derivative identical to XXVII and different from XXXI by melting point and gas chromatography. This establishes the position

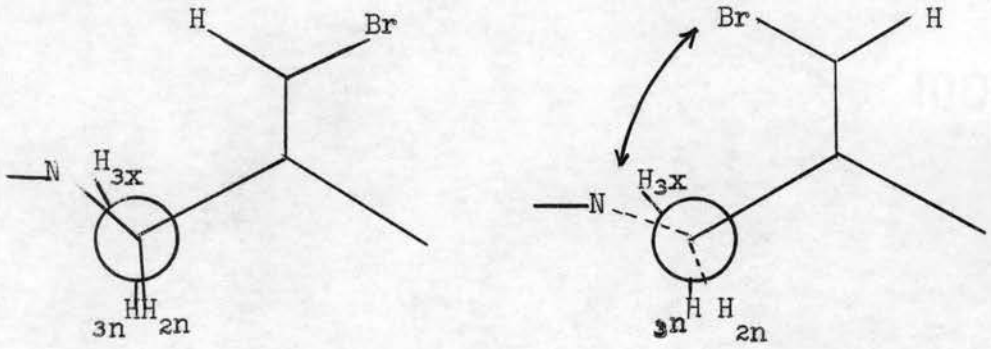

CXXVII
XXVI
CXXVIII
CXXXII
XXVII
CXXXIV
CXXXIII
CXXXV
CXXXVI
CXXXVII
CXXXVIII
CXXXIX
CXL
CXLI
CXLII

and stereochemistry of the benzenesulfonamido group as 2-*exo* and allows assignment of J_1 as the coupling of the 2,3-*trans* protons and J_2 as the coupling of the 2,3-*cis* protons.[10] Hydrolysis of the sulfonamido linkage of CXXVIII was accomplished by heating in an aqueous hydrochloric acid solution in a sealed tube at 175° for 48 hr. The resulting bromo amine, CXXXIV, was oxidized to 7-*anti*-bromobicyclo(2.2.1)-2-heptanone (CXXXV) which was synthesized by an unambiguous procedure as described below.

Kwart and Miller have reported the reaction of 2,4-dinitrosulfenyl bromide and I to yield CXXXVI.[72] Treatment of an acetic acid slurry of CXXXVI with gaseous chlorine led to a mixture of CIX, CXXXVII, and CXXXVIII, which were separated by fractional distillation at reduced pressure.[72] Reduction of CXXXVIII with lithium aluminum hydride afforded 2-*exo*-hydroxy-7-*anti*-bromobicyclo(2.2.1)heptane (CXXXIX). Jones oxidation of CXXXIX gave CXXXV identical in all respects with that obtained by oxidation of CXXVIII and different from CXXXIII, CXL, and CXLI by gas chromatography. These data establish the structure of CXXVIII as CXLII.

It is interesting that the 2-*endo* proton in CXXIX gives rise to a triplet in the n.m.r. spectrum, whereas the corresponding signal in CXLII gives a quartet. As pointed out in Chapter I nonbonded repulsions between 2(3)-*exo* substituents and 7-*syn* hydrogens in bicyclo(2.2.1)-heptanes appears to be neglible. This evidently is not the case for a 2(3)-*exo* substituent and a 7-*syn* bromine atom. The fact that the 2-*endo* proton in CXXIX gives rise to a triplet points strongly to a nonbonded repulsion between the 2-*exo*-benzenesulfonamido group and the

7-syn bromine atom. Such a repulsion would be relieved by rocking of C_2 about the C_2, C_3 bond as shown. This would have the effect of increasing the dihedral angle between the 2,3-trans protons. On the



basis of the dependence of vicinal coupling constants on dihedral angles one would expect this type of distortion to result in a decrease in the coupling constant between the 2,3-cis protons and an increase in coupling constant betweeen the 2,3-trans protons.[10] The n.m.r. spectrum of CXLII reveals a 2,3-cis coupling of 8.1 c.p.s. and a 2,3--trans coupling of 3.9 c.p.s. whereas in the n.m.r. spectrum of CXXIX both couplings are 6.0 c.p.s. This type of deformation also accounts for the triplet signal given by the 2-endo proton in XIX and XXXV.

The formation of CXLII and the apparent* absence of any appreciable amount of 2,3-trans product of structure CXXX in the reaction of

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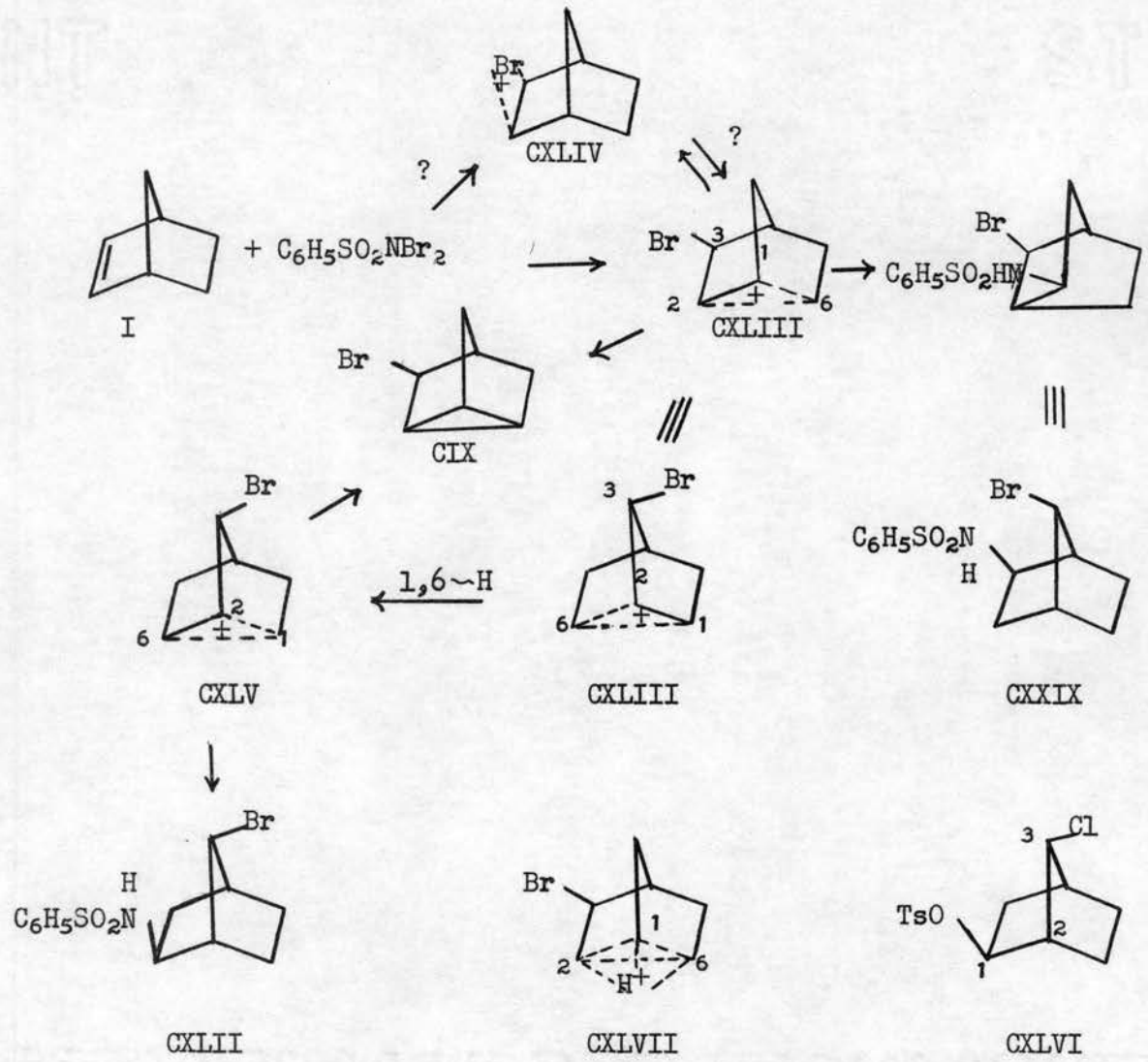
*Thin layer chromatography of the crude reaction mixture did reveal a third addition product in the reaction. This isomer and CXLII were poorly resolved (TLC) and it was not isolated. The amount of this third isomer could not have exceeded 6% since 94% of I consumed was accounted for.

N,N-dibromobenzenesulfonamide with I is of particular interest. Mechanistically, the formation of CXXIX and CXLII can be visualized as occurring as outlined below:



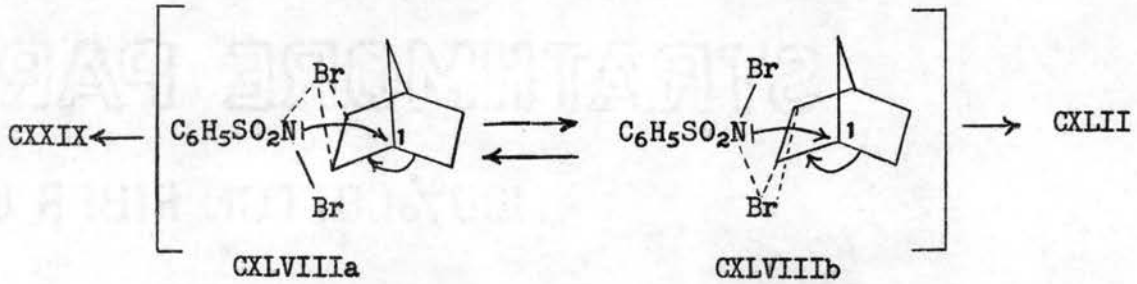
It is postulated that the carbon-bridged cation CXLIII is the reactive intermediate formed rather than the halogen-bridged cation CXLIV since the latter would be expected to lead to product CXXX. Attack of CXLIII at C_1 would lead to CXXIX and 1,6-hydride shift of CXLIII would lead to intermediate CXLV which by attack at C_6 would give

CXLII. The lack of reactivity of CXLIII and CXLV at C_2 would arise from the unfavorable influence of the adjacent C_3 halogen dipole. The apparently inconsequential formation of C_2, C_3 substituted products from the corresponding chlorine-substituted cations generated during the solvolysis of CXLVI has been rationalized on the basis that nucleophilic attack would occur preferentially at C_1 since the C_2 position would have but slight cationic character because of the proximity of the adjacent carbon-halogen dipole at C_3.[73] Intermediate CXLVII would likewise satisfactorily account for products CXXIX and CXLII, but if it were the sole product-forming intermediate it would be difficult to explain the almost 2:1 yield ratio of CXXIX to CXLII.[73] Although 1,6-hydride shifts, as required in the formation of CXLII, are well established in solvolysis reactions they are virtually unknown during addition reactions of I, especially under the non-polar conditions used in this reaction.[32] (For an example of how reactions conditions affect the course of additions to CVII see Ref. 74). An explanation for the 1,6-hydride shift may be found in the relative sluggishness of the nucleophile ($C_6H_5SO_2\overset{R}{N}^-$) involved which would allow the slow[73] hydride shift to occur before attack on the cation.

As pointed out earlier the addition of reagents containing positive halogen (i.e. Br_2) to I is believed to proceed via the halogen-bridged ion CXLIV. That both CXVI and XXXV are formed in appreciable amounts during the bromination of I has been construed by others to indicate that CXLIII and CXLIV are of comparable stability. More specifically they have proposed that an equilibrium exists between these two ions.[64] An equally attractive explanation would be that the relative amounts

of C_2, C_3 and C_2, C_7 products formed from these intermediates is a function, not of the equilibrium concentrations of CXLIII and CXLIV (as is implied above), but of the rate of attack of the nucleophile (Br^-, OH^-, $\overset{R}{N}SO_2C_6H_5$ etc.) at C_3 on CXLIV compared to its conversion into CXLIII. At this time there appears to be no data available which would permit a differentiation of these two explanations. In any event, the cation CXLIV does not appear to be a major product-forming intermediate in the present instance.

The possibility of <u>endo</u> attack by a bromonium species should not be overlooked, especially since it is possible that both bromine atoms are attached to the benzenesulfonamido moiety when addition occurs. This situation could presumably allow electrophilic attack from both sides as shown below in CXLVIII. The formation of CXXIX and CXLII would then occur by attack of the benzenesulfonamido group at C_1 of CXLVIIIa and CXLVIIIb respectively with concomitant skeletal rearrangement. Because the nitrogen function must attack C_1 through the <u>exo</u> bromonium ion in CXLVIII a and because the formation of CXLII from CXLVIIIb involves front-side cleavage of the <u>endo</u> bromonium ion, this mechanism is presently considered the less likely of the two to represent the true sequence of events.

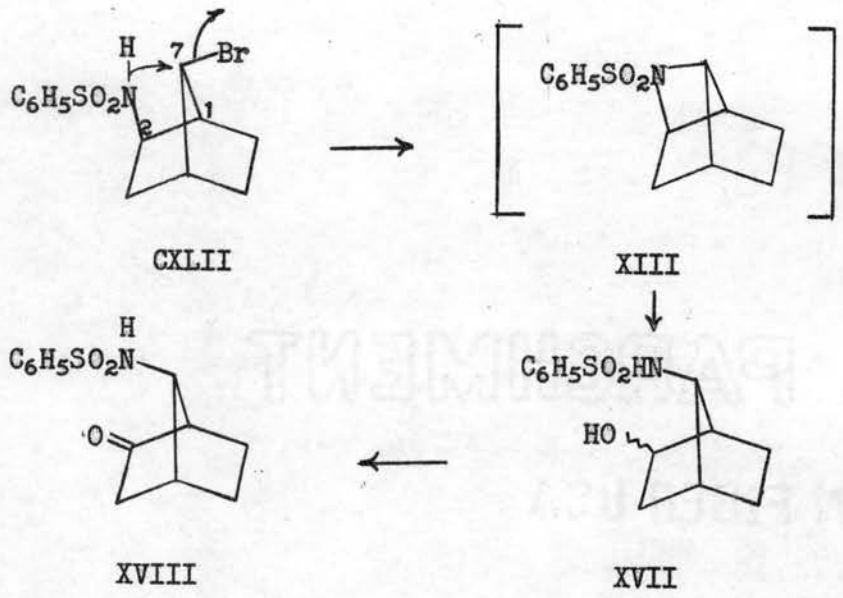


The point at which the second bromine atom in N,N-dibromobenzenesulfonamide is lost is not clear at present. Kharasch and Priestley[63] first pointed out that N,N-dibromobenzenesulfonamide reacted with two moles of an alkene in an ionic manner to give the vicinal bromo-benzenesulfonamido derivative and a vinyl bromide in relatively equal amounts. In the present case CIX is formed rather than an unsaturated bromide and its much larger yield as compared to that of the addition products (CXXIX and CXLII) indicates that it is formed, at least partly, independently of CXXIX and CXLII presumably via intermediates CXLIII and CXLV.

When CXLII was refluxed for 25 hr. in an aqueous methanolic solution containing excess sodium carbonate, there was obtained 2-hydroxy-7--syn-benzenesulfonamidobicyclo(2.2.1)heptane (XVII) as the minor product and 3-cyclopentenylacetaldehyde (CXLIX) as the major product.[75]

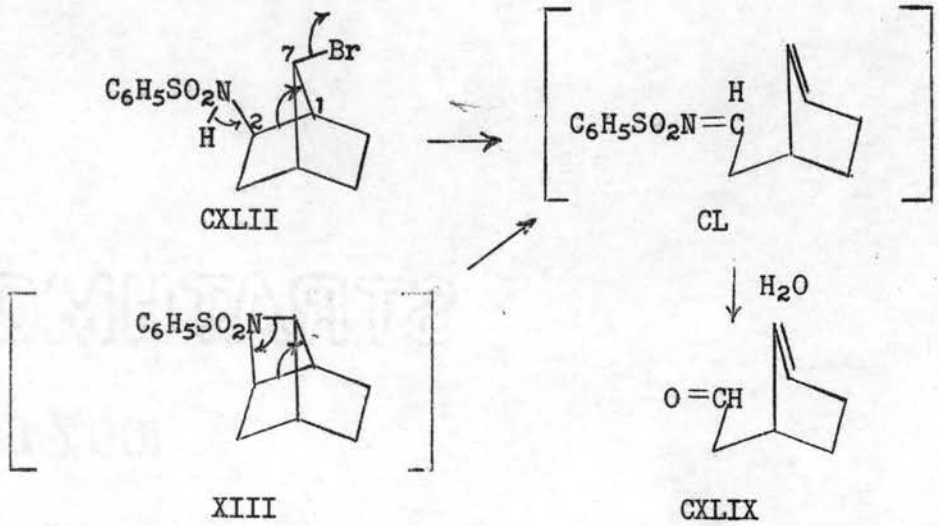
The formation of XVII can be visualized as occurring by back-side displacement of the 7-anti bromine by the 2-exo-benzenesulfonamido group to give the intermediate azetidine (XIII) which under the reaction conditions is ring-opened by hydroxide ion to give XVII. Participation of a suitable 2-exo group in the solvolysis of 7-anti substituents might be expected in view of the known pronounced acceleration of solvolysis shown in 7-anti-bicyclo(2.2.1)heptenyl systems.[32] However, the 2-methylene substituent was ineffective in this regard.[76] Chemical confirmation of the structure of XVII was provided by its conversion to the known XVIII upon Jones oxidation.[44]

The major product CXLIX undoubtedly arises by hydrolysis of CL, the latter presumably being formed by cleavage of the C_1, C_2 bond as depicted, or from intermediate XIII, which may suffer collapse of the



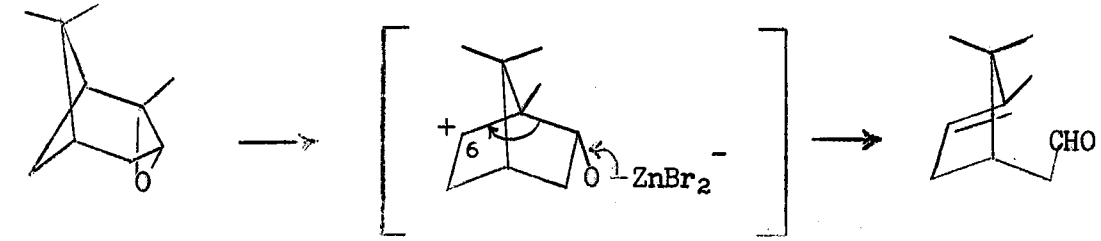
CXLII XIII XVII XVIII

strained azetidine ring under the reaction conditions. The former path is analogous to solvolytic fragmentation reactions of β-bromo amines recently studied by Grob.[77] Aldehyde CXLIX was identified by melting point[78] and elemental analysis of its 2,3-dinitrophenylhydrazone derivative. The n.m.r. spectrum of this derivative showed six methylene protons (δ 1.2-2.6), one methine proton (δ 3.0), two olefinic protons (δ 5.75), and one aldehydic proton (δ 8.84).

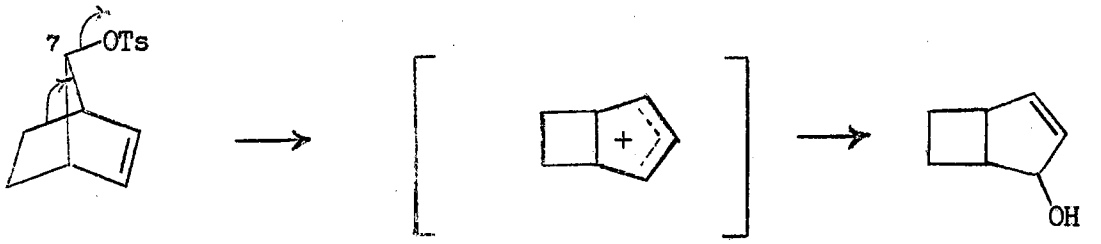


CXLII CL XIII CXLIX

Formal cleavage of a bicyclo(2.2.1)heptane has been reported in only a few cases[32,79] and this is believed to be the first example in which cleavage occurs by displacement at C_7 giving a double bond at the C_1, C_7 position of the original skeleton. The reported conversion[80] of α-pinene oxide (CLI) to campholenic aldehyde (CLII) is somewhat analogous, but involves displacement at C_6. Internal displacement at C_7 has been observed in the hydrolysis of CLIII to yield CLIV.[81] In the latter case, the formation of a stabilized intermediate allylic carbonium ion provides a strong driving force for the ring cleavage.



CLI CLII



CLIII CLIV

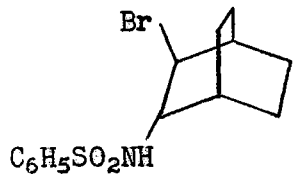
In contrast to the solvolysis of CXLII, as described above, the isomeric CXXIX was quantitatively recovered unchanged after refluxing in 5% aqueous alcoholic sodium hydroxide for 60 hr.; thus it is apparent that participation by the benzenesulfonamido group must occur in the cleavage of the C-Br bond in CXLII.

2. The Reaction of N,N-Dibromobenzenesulfonamide with Bicyclo-(2.2.2)-2-octene

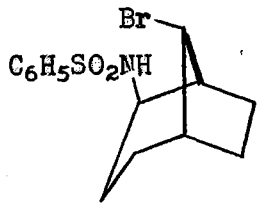
The reaction of N,N-dibromobenzenesulfonamide with IX in benzene

at room temperature also led to the formation of bromination and addition products. The bromination products consisted primarily of LXXXVI, although minor amounts of dibromobicyclooctanes (probably CXIX and CXX) were detected by gas chromatography. Thin layer chromatography of the crude reaction mixture revealed the presence of four addition products, three of which were isolated by repeated chromatography of the reaction mixture on alumina. The infrared and n.m.r. spectra of the three addition products isolated indicated that they each possessed a secondary bromine and a secondary benzenesulfonamido group.

By analogy with the addition of bromine to IX,[30] structures LXXXIII and LXXXV would be expected and are consistent with the elemental and spectral data.



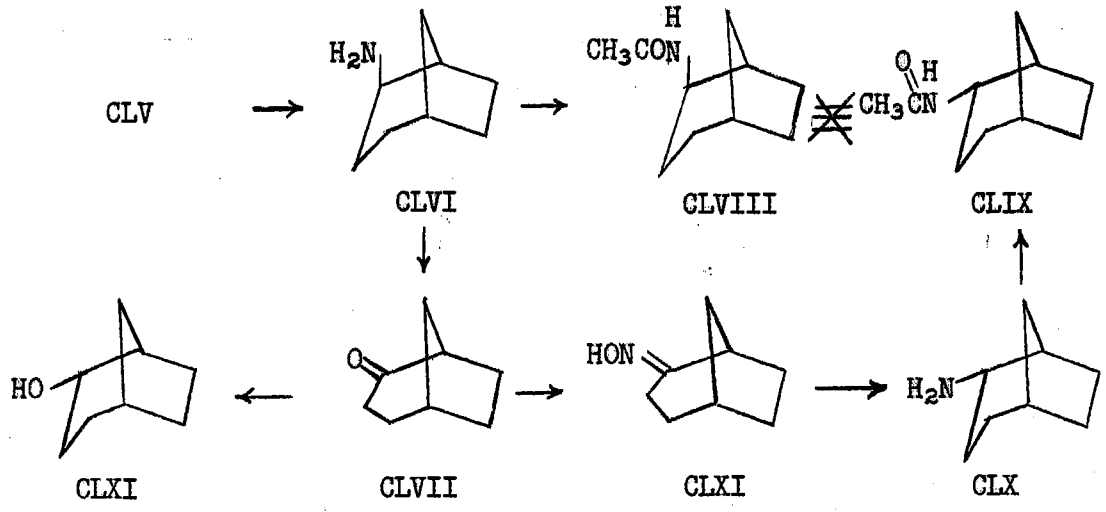
LXXXIII



LXXXV

The n.m.r. spectrum of the least polar addition product (CLV) showed a triplet (J = 4 c.p.s.) for the proton on carbon bearing the bromine atom, suggestive of an 8-<u>syn</u>-bromobicyclo(3.2.1)octane derivative (See Chapter I). The skeletal structure of CLV was established by its reduction with sodium in alcohol to a 2-aminobicyclo(3.2.1)octane (CLVI) which upon oxidation gave the known[82] bicyclo(3.2.1)-2-octanone (CLVII). The stereochemistry of the nitrogen function in CLVI was deduced in the following manner. Acetylation of CLVI gave CLVIII which was different from the 2-acetamidobicyclo(3.2.1)octane (CLIX) obtained upon acetylation of the amine (CLX) derived from lithium

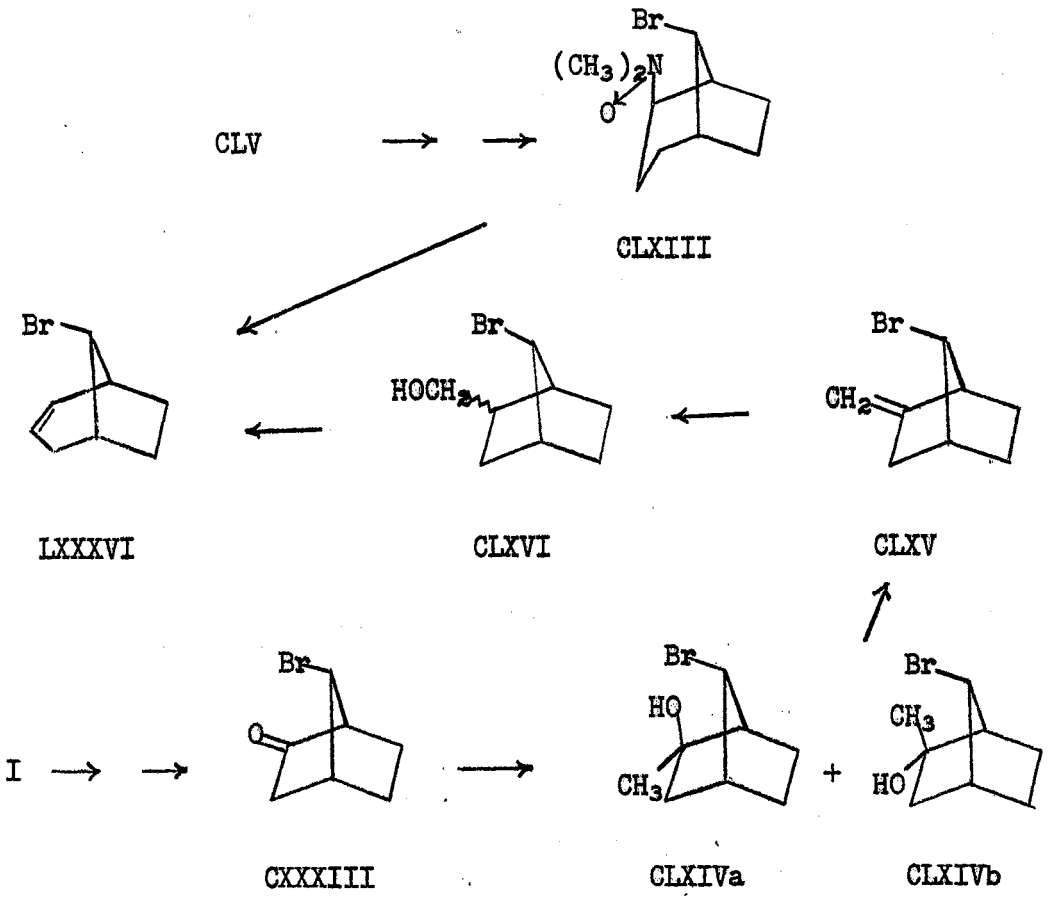
aluminum hydride reduction of CLXI. Since reduction of CLVII with lithium aluminum hydride yields the <u>equatorial</u> alcohol CLXII,[82] the 2-acetamidobicyclo(3.2.1)octane (CLIX) derived from CLXI can be assumed to be the <u>equatorial</u> isomer. This requires CLVIII to be the <u>axial</u> isomer.



That the bromine atom in CLV was indeed at C_8 and <u>syn</u> to the trimethylene bridge was shown as follows. Treatment of CLV with aqueous hydrochloric acid in a sealed tube at 175° for 24 hr. gave a bromo amine which was converted into the dimethylamine oxide, CLXIII. Pyrolysis of the latter at 135° under partial vacuum gave the previously reported LXXXVI.[30] Earlier workers[30] had established the skeleton of LXXXVI by chemical means, but the position of the bromine atom in LXXXVI was determined indirectly by n.m.r. and dipole moment studies. In order to firmly establish the position of the bromine atom in LXXXVI its synthesis from I was undertaken.[66]

Treatment of I with hypobromous acid gave CXVIII as the major product. Roberts, Johnson, and Carboni[83] had previously shown that

hypochlorous acid adds to I to give the corresponding chloro analog of CXVIII and more recently Sauers and Hawthorne[71] have confirmed the correctness of the structure of CXVIII. Jones[44] oxidation of CXVIII



gave ketone CXXXIII which on treatment with methylmagnesium iodide gave a mixture of CLXIVa and its C_2 isomer CLXIVb. The n.m.r. spectrum of CLXIVa showed a signal at δ 1.23 for the C_2 methyl group, whereas in the n.m.r. spectrum of CLXIVb the corresponding signal appeared at δ 1.55. The mixture of alcohols CLXIV was distilled in the presence of iodine to give the bromoolefin CLXV which on hydroboration[84] gave a mixture of 7-syn-bromobicyclo(2.2.1)heptane-2-methanols, CLXVI. Heating of mixture CLXVI in the presence of phosphorous acid gave

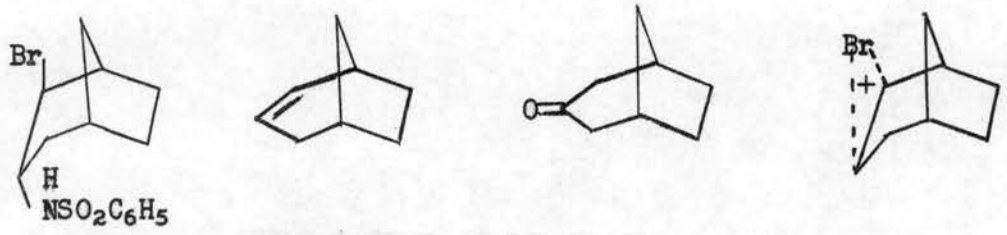
LXXXVI, identical in all respects with that previously reported[30] and that derived from CLV. This firmly establishes the position of the bromine atom in CLV and the correct structure of this compound must therefore be LXXXV.

A second addition product formed upon the reaction of N,N-dibromobenzenesulfonamide with IX was identified as LXXXIII by comparison to that obtained from the cleavage of the aziridine LXXX with hydrogen bromide. Chemical confirmation of the skeletal structure of LXXXIII was provided by its reduction with sodium in alcohol to 2-aminobicyclo-(2.2.2)octane, which was identified by gas chromatography of its N-acetyl derivative.

Structure CLXVII is suggested for the third addition product isolated from the reaction of N,N-dibromobenzenesulfonamide with IX. This product undoubtedly arises from the reaction of N,N-dibromobenzenesulfonamide with bicyclo(3.2.1)-2-octene (CLXVIII) which is formed from IX under the Diels-Alder conditions necessary to produce IX from ethylene and 1,3-cyclohexadiene.[30]

Repeated attempts to analyze the starting alkene IX for CLXVIII contaminant by gas chromatography failed, but it is estimated (See ref. 30) that CLXVIII does not account for more than 5-10% of the olefinic starting material. Since CLXVII was not a major product, it may safely be assumed to arise from CLXVIII.

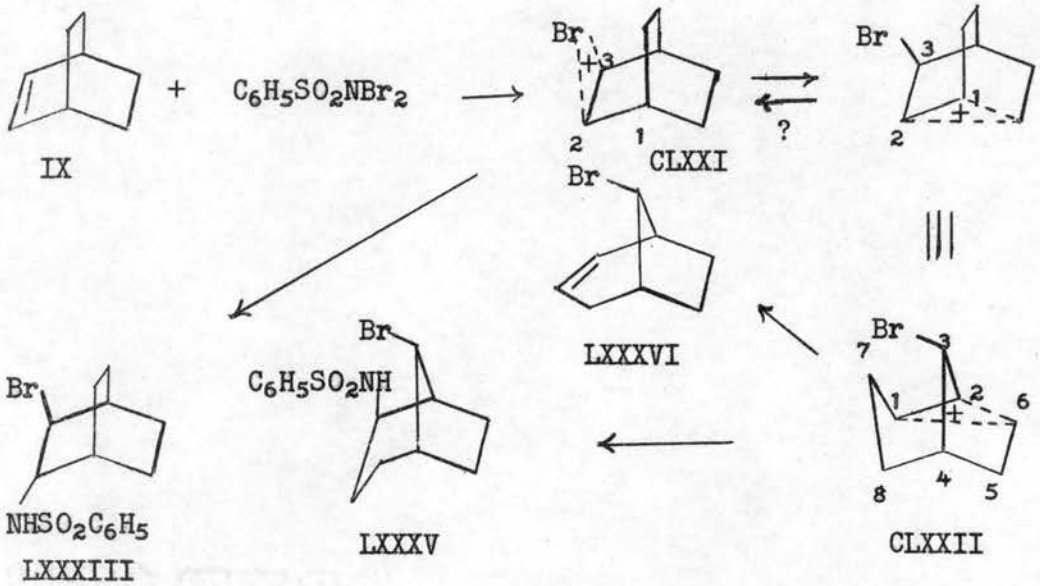
Reduction of CLXVII with sodium in alcohol gave an amine which upon oxidation gave a ketone. The ketone thus obtained was identified as bicyclo(3.2.1)-3-octanone (CLXIX) by gas chromatography comparison and by melting point of its 2,4-dinitrophenylhydrazone derivative.[39]



CLXVII CLXVIII CLXIX CLXX

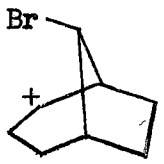
The stereochemistry of the benzenesulfonamido group and the position of the bromine atom in CLXVII are assigned on the assumption that initial attack of CLXVIII occurs from the less hindered exo side to give CLXX; attack of CLXX at C_3 would give the trans bromo sulfonamide CLXVII.

The formation of LXXXIII and LXXXV is postulated occurring through ionic intermediates CLXXI and CLXXII as shown below.



Attack of CLXXI at C_2 would lead to LXXXIII and attack of CLXXII at C_1 would give LXXXV. Loss of a C_7 proton from CLXXII would produce LXXXVI. The formation of LXXXIII, LXXXV, and LXXXVI in the reaction of N,N-dibromobenzenesulfonamide with IX is exactly analogous to the formation

of CXIX, CXX, and LXXXVI upon the addition of bromine to IX. The observation that LXXXV possesses an axial benzenesulfonamido group at C_2 is evidence against CLXXIII as a product-forming intermediate since this would be expected to be attacked from the less hindered equatorial side.



CLXXIII

C. Experimental

1. Reaction of N,N-Dibromobenzenesulfonamide with Bicyclo(2.2.1)-=2-heptene

Preparation of CIX, CXXVII (CXXVII ≡ CXXIX) and CXXVIII (CXXVIII ≡ CXLII)

To a solution of 20 g. (0.213 mole) of I in 80 cc. of dry benzene was slowly added 39.2 g. (0.124 mole) of N,N-dibromobenzenesulfonamide.[85] The addition of the N,N-dibromo compound was continued until aliquots withdrawn from the reaction did not decolorize bromine in carbon tetrachloride. After the exothermic reaction subsided (15 min.) the benzenesulfonamide which had precipitated was removed by filtration and washed with benzene (9:1 g., 0.058 m., m.p. 151-152°). The combined benzene filtrate and wash was removed through a Vigreux column and the residue chromatographed on 500 g. of Merck acid-washed alumina.

Elution with 700 cc. of petroleum ether (b.p. 50-70°) gave 25 g. of bromobicyclo(2.2.1)heptanes. The mixture of bromides was analyzed

by gas chromatography with a 0.25-in. x 9-ft. column containing 10% Silicone 550 on acid-washed firebrick at 150° using a helium flow rate of 63 cc. per min. The mixture contained 86±3% CIX (0.124±0.004 mole), identified by mixed injection, and 15±3% dibromobicyclo(2.2.1)-heptanes (0.014±0.003 mole). The benzene removed from the reaction contained another 1-2 g. of CIX as detected by gas chromatography.

Elution with 2 l. of benzene and 0.3 l. (19:1), 0.9 l. (9:1), and 0.6 l. (1:1) benzene-chloroform gave 13.4 g. (0.041 mole) of CXXVII which crystallized from ethanol and had m.p. 92-93°; ν_{max}^{KBr} 3225, 1315, 1160, and 1090 cm.$^{-1}$; n.m.r. (in $CDCl_3$) δ 1.0-2.0 (4 protons), 2.11 (proton at C_4), 2.30 (proton at C_1), 3.42 (proton at C_2, multiplet; sharpened to a triplet, J = 6.7 c.p.s, upon addition of CF_3COOH), 3.80 (proton at C_7), 5.38 (N-H, doublet, J = 10.5 c.p.s.; vanished upon addition of CF_3COOH), and 7.6-8.1 (5 aromatic protons).

Anal. Calcd. for $C_{13}H_{16}BrNO_2S$: C, 47.28; H, 4.88. Found: C, 47.33; H, 5.44.

Elution with 0.6 l. of chloroform gave 2.29 g. (0.007 mole) of an oil which thin layer chromatography (10 cm. on Silica Gel-G in chloroform) showed to be a mixture of CXXVII and CXXVIII. Continued elution with 0.4 l. of chloroform gave 6.1 g. (0.018 mole) of CXXVIII as an oil which crystallized from aqueous methanol and had m.p. 90-91°; ν_{max}^{KBr} 3300, 1332, 1160, and 1090 cm.$^{-1}$; n.m.r. (in $CHCl_3$) δ 1.0-2.5 (6 protons), δ 3.22 (proton at C_2, multiplet; sharpened to a quartet, $J_{2,3\ \underline{cis}}$ = 8.1 c.p.s., $J_{2,3\ \underline{trans}}$ = 3.9 c.p.s.), 4.16 (proton at C_7), and 5.96 (N-H, doublet, J = 7 c.p.s.; vanished upon addition of CF_3COOH.).

Anal. Calcd. for $C_{13}H_{16}BrNO_2S$: C, 47.28; H, 4.88. Found: C,

47.52; H, 5.02.

The mixture melting point of CXXVII (m.p. 92-93°) and CXXVIII (m.p. 90-91°) was 75-80°.

Conversion of CXXVII to 2-exo-Acetamidobicyclo(2.2.1)heptane (XXVII)

A solution of 1.376 g. of CXXVII in 25 cc. of dry sec-butyl alcohol was treated with 2 g. of metallic sodium over a period of 15 min. The reaction mixture was heated to 110° over a period of 2 hr. and then stirred at 110° for 6 hr. The solution was then cooled, acidified with 10% hydrochloric acid, and washed with ether. The acidic aqueous solution was then rendered basic by addition of sodium hydroxide solution and extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give 0.21 g. (45%) of XXVI. The N-acetyl derivative (XXVII) was prepared by treatment of the amine with acetyl chloride in pyridine and had m.p. 138-140° after crystallization from hexane.

Analysis of the acetyl derivative by gas chromatography was performed on a 0.25-in. x 10-ft. Craig polyester column at 200° using a helium flow rate of 56 cc. per min. The mixed injection of the 2-exo--acetamidobicyclo(2.2.1)heptane obtained from CXXVII and the 2-exo--acetamidobicyclo(2.2.1)heptane prepared by known procedures (See Experimental section of Chapter I) gave a single peak. Mixed injection of 2-endo-acetamidobicyclo(2.2.1)heptane (XXXI) and the 2-exo acetyl derivative obtained from CXXVII gave two peaks at 18.0 min. and 18.75 min. respectively.

Preparation of 2-endo-Acetamidobicyclo(2.2.1)heptane (XXXI) from 2-endo-Benzenesulfonamidobicyclo(2.2.1)heptane (XXXIII)

Sulfonamide XXXIII was refluxed 6 hr. in 25 cc. of dry sec-butyl alcohol containing 1.4 g. of metallic sodium. The amine was isolated by the procedure described above and the N-acetyl derivative was prepared with acetic anhydride. The crude acetamidobicyclo(2.2.1)heptane thus prepared was shown to be the 2-endo isomer, XXXI, and to be free of 2-exo-acetamidobicyclo(2.2.1)heptane (XXVII) by gas chromatography. Crystallization of XXXI prepared from XXXIII from hexane gave m.p. 129-130°.

Conversion of CXXVII to 7-syn-Bromo-2-exo-aminobicyclo(2.2.1)-heptane (CXXXII)

A suspension of 2.010 g. of CXXVII in 15 cc. of 10% hydrochloric acid was heated in a sealed tube at 175° for 24 hr. The reaction mixture was cooled and washed with ether. The ether extract was decolorized with charcoal, dried over anhydrous magnesium sulfate, and evaporated to give 1.127 g. of CXXVII. Evaporation of the acidic aqueous reaction solution gave an oil which crystallized in methanol-ether to give a 46% yield of the hydrochloride of CXXXII. The amine CXXXII was liberated by addition of dilute aqueous sodium hydroxide to an aqueous solution of the hydrochloride. The basic solution was extracted with ether which, after drying over anhydrous magnesium sulfate, was evaporated to give CXXXII as an oil.

Preparation of 7-syn-Bromobicyclo(2.2.1)-2-heptanone (CXXXIII) from CXXXII

To 215 mg. (1.14 mmole) of CXXXII and 11 mg. (0.04 mmole) of $Na_2MoO_4 \cdot 2H_2O$ in 1 cc. of water and 1 cc. of 30% hydrogen peroxide was added enough methanol to make the mixture homogeneous.[70] The

solution was stirred overnight, acidified, diluted with 15 cc. of water, and extracted with ether. Addition of acidic, methanolic, 2,4-dinitrophenylhydrazine solution to the ether extract gave a fine crystalline precipitate upon standing. After recrystallization of the derivative thrice from petroleum ether it had m.p. 203-203.5°. Mixture melting point with the 2,4-dinitrophenylhydrazone of authentic[66,71] (see below) 7-syn-bromobicyclo(2.2.1)-2-heptanone (CXXXIII) was undepressed and the two derivatives gave identical infrared spectra. The two bromobicyclo(2.2.1)heptanones were also identical by gas chromatography.

Conversion of CXXVIII to 2-exo-Acetamidobicyclo(2.2.1)heptane (XXVII)

The reduction of CXXVIII with sodium in alcohol was carried out in 50% yield in the manner described above for the reduction of CXXVII. The amine prepared in this manner from CXXVIII gave an N-acetyl derivative (m.p. 138-140°) which was shown by gas chromatography, as described above, to be identical to the 2-exo isomer, XXVII, and different from the 2-endo isomer, XXXI.

Conversion of CXXVIII to 7-anti-Bromo-2-exo-aminobicyclo(2.2.1)-heptane (CXXXIV)

A suspension of 2.009 g. of CXXVIII in 15 cc. of 10% hydrochloric acid was heated at 175° for 48 hr. in a sealed tube. The reaction was worked up by the procedure described above for the hydrolysis of CXXVII. No CXXVIII was recovered and the yield of CXXXIV hydrochloride was 12.6% after recrystallization from aqueous methanol (m.p. 235-245° with dec.). The amine CXXXIV was liberated by addition of dilute aqueous

base to an aqueous solution of the hydrochloride. The aqueous basic solution was extracted with ether which, after drying over anhydrous magnesium sulfate, was evaporated to give CXXXIV as an oil.

Preparation of 7-anti-Bromobicyclo(2.2.1)-2-heptanone from CXXXIV

Oxidation of 745 mg. of CXXXIV by the procedure described above for CXXXII gave about 50 mg. of crude bromo ketone. A portion of the crude product was treated with excess acidic methanolic 2,4-dinitrophenylhydrazine solution. The 2,4-dinitrophenylhydrazone prepared in this manner was purified by chromatography on Merck acid-washed alumina using benzene as the eluent followed by preparative thin layer chromatography on Silica Gel-G (19 cm.) in benzene. Finally, the derivative was crystallized from petroleum ether to give a solid which melted at 116.5-117.5° which solidified and remelted again at 151.5-152.5°. Mixture melting point with the 2,4-dinitrophenylhydrazone of authentic 7-anti--bromobicyclo(2.2.1)-2-heptanone, prepared as described below, was 151.5-152.5°. The bromobicyclo(2.2.1)heptanones prepared by these two procedures were also identical by gas chromatography.

Preparation of CXXXVII and CXXXVIII from CXXXVI

The reaction of 2,4-dinitrobenzenesulfenyl bromide with I to give CXXXVI (m.p. 171-173°, lit.[72] m.p. 173.8-174.8°) was carried out in 87% yield according to the procedure of Kwart and Miller.[72] The n.m.r. spectrum of CXXXVI in nitrobenzene showed the proton on carbon bearing the bromine at δ 4.14 as a triplet (J = 4.1 c.p.s.) and the proton on carbon bearing the sulfur at δ 3.42 as a quartet ($J_{2,3\ trans}$ = 4.1 c.p.s.; $J_{2\ endo,\ 7\ anti}$ = 2.0 c.p.s.).

Chlorine gas was passed through a slurry of 80 g. of CXXXVI in

261 cc. of 96% acetic acid for 1 hr.[72] The mixture was stirred overnight and unreacted CXXXVI (about 15 g.) was removed by filtration. The filtrate was diluted with 250 cc. of ice water and extracted with petroleum ether. The petroleum ether extract was washed with aqueous sodium carbonate solution, dried over anhydrous magnesium sulfate, and evaporated. The residue was fractionally distilled under vacuum to give 2.1 g. CIX (b.p.$_{0.7\text{-}0.6 \text{ mm.}}$ 35-40°), 10.5 g. CXXXVII (b.p.$_{0.7 \text{ mm.}}$ 50-52°, lit.[72] b.p.$_{0.55 \text{ mm.}}$ 40-42°), 10.2 g. of a mixture of CXXXVII and CXXXVIII (b.p.$_{0.7 \text{ mm.}}$ 52-70°), and 4.8 g. of CXXXVIII (b.p.$_{0.7 \text{ mm.}}$ 70-72°, lit.[72] b.p.$_{0.6 \text{ mm.}}$ 61-67°). The n.m.r. spectrum of CXXXVII in CS_2 showed the signal for the 2-endo proton at δ 3.86 as a quartet ($J_{2,3\ \underline{trans}}$ = 4.3 c.p.s., $J_{2,3\ \underline{cis}}$ = 7.5 c.p.s.) and the 7-syn proton appeared as a tall narrow multiplet. The n.m.r. spectrum of CXXXVIII in CS_2 showed the signal for 2-endo proton at δ4.15 as a quartet ($J_{2,3\ \underline{trans}}$ = 3.0 c.p.s., $J_{2,3\ \underline{cis}}$ = 7.5 c.p.s.) and the 7-syn proton appeared as a tall narrow multiplet.

Preparation of 2-exo-Hydroxy-7-anti-bromobicyclo(2.2.1)heptane (CXXXIX) from CXXXVIII

A solution of 1.5 g. of CXXXVIII and 0.15 g. of lithium aluminum hydride in 25 cc. of dry ether was refluxed for 4 hr. The solution was diluted with wet ether, acidified with aqueous 10% hydrochloric acid, and finally extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give an oil. The oil was distilled under vacuum to give 1.1 g. of CXXXIX, b.p.$_{0.7 \text{ mm.}}$ 75-80°; n.m.r. (in CS_2) δ 3.68 (proton at C_2, quartet, $J_{2,3\ \underline{trans}}$ = 2.9 c.p.s., $J_{2,3\ \underline{cis}}$ = 7.1 c.p.s.), 3.76 (O-H, vanished upon addition of D_2O), and

4.14 (proton at C_7, triplet, $J_{7,\ 1\text{-}4}$ = 1.4 c.p.s.).

Preparation of 7-anti-Bromobicyclo(2.2.1)-2-heptanone (CXXXV) from CXXXIX

A solution of 806 mg. of CXXXIX in 8 cc. of dry acetone was treated with a 0.5 molar excess of Jones reagent.[44] The solution was allowed to stir 4 hr. after which time it was diluted with 40 cc. of water and extracted several times with petroleum ether. The petroleum ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give 450 mg. of CXXXV; n.m.r. (in CS_2) δ 4.19 (proton at C_7, triplet, $J_{7,\ 1\text{-}4}$ = 1.4 c.p.s.). The 2,4-dinitrophenylhydrazone was prepared by addition of excess acidic, methanolic 2,4-dinitrophenylhydrazine solution to CXXXV. The derivative was purified by chromatography on Merck acid-washed alumina using benzene as the eluent followed by preparative thin layer chromatography (19 cm. on Silica Gel-G in benzene). The 2,4--dinitrophenylhydrazone of CXXXV prepared in this manner crystallized from petroleum ether and had m.p. 116.5-117.5°. The analytical sample was prepared by crystallization from ether and had m.p. 152-153°.

Anal. Calcd. for $C_{13}H_{13}N_4O_4Br$: C, 42.29; H, 3.55. Found: C, 42.96, 43.31; H, 3.91, 3.72.

Preparation of CXL and CXLI

Bicyclo(2.2.1)-2-heptanone (CVI) was brominated according to the procedure of Woods and Roberts.[86] The bromo ketones obtained were fractionally distilled under vacuum using a 0.25-in. x 10-in. tantalum spiral column to give pure 3-exo-bromobicyclo(2.2.1)-2-heptanone (CXL), m.p. 25°, b.p.$_{1\ mm.}$ 80-82° (lit.[86] m.p. 30°, b.p.$_{23\ mm.}$ 126.5-128.5°); n.m.r.[87] (neat) δ 3.86 (proton at C_3, doublet, $J_{3,7\ anti}$ = 3 c.p.s.).

Heating CXL with 10 g. of glacial acetic acid containing 10 g. of potassium acetate for 24 hr. according to the procedure of Krieger[88] gave a 1:1 mixture of CXL and CXLI.

Gas Chromatographic Comparisons of Bromobicyclo(2.2.1)heptanones CXXXIII, CXXXV, CXL, and CXLI

All gas chromatographic analyses were performed on a 0.25-in. x 10-ft. Silicone 550 column at 165° using a helium flow-rate of 120 cc. per min. The following retention times were observed: 7-anti-bromobicyclo(2.2.1)-2-heptanone (CXXXV), 15.0 min.; 7-syn-bromobicyclo(2.2.1)--2-heptanone (CXXXIII) and 3-endo-bromobicyclo(2.2.1)-2-heptanone (CXLI), 20.8 min.; and 3-exo-bromobicyclo(2.2.1)-2-heptanone (CXI), 18.5 min.

Hydrolysis of CXLII

A solution of 603 mg. of CXLII in 12 cc. of aqueous 80% methanol, containing an excess of sodium carbonate, was refluxed for 25 hr. The solution was diluted with 15 cc. of water and extracted with chloroform. The chloroform extract was evaporated under vacuum into a dry ice trap to which acidic, methanolic 2,4-dinitrophenylhydrazine solution was added.

The residue left by evaporation of the chloroform contained a precipitate of 24 mg. of benzenesulfonamide (m.p. 151-152°), which was collected by filtration. The precipitate was washed with benzene and the latter was returned to the residue. The residue was concentrated and analyzed by thin layer chromatography on Silica Gel-G (15 cm.) in chloroform. Major spots were found at R_f's of 0.053 (benzenesulfonamide), 0.30, 0.53, and 0.60. The above mixture was oxidized by the Jones procedure[44] without further purification. The oxidized mixture was chromatographed by preparative thin layer chromatography on Silica

Gel-G (15 cm.) in 3:1 chloroform-ethyl acetate. Spots were evident at R_f's 0.10, 0.30, and 0.60.

The major spot (R_f 0.20-0.35) was removed and the Silica Gel-G eluted with chloroform. Evaporation of the chloroform eluent and recrystallization of the eluate from ether gave 51 mg. of 2-keto-7--syn-benzenesulfonamidobicyclo(2.2.1)heptane (XVIII), m.p. 146-147°. Mixture melting point with an authentic sample (See Chapter I) was undepressed.

The contents of the dry ice trap were concentrated and the concentrate chromatographed directly on Merck acid-washed alumina. Elution with benzene gave the 2,4-dinitrophenylhydrazone of CXLIX. Crystallization of the eluate from hexane gave 215 mg. of the 2,4-DNP, m.p. 100-101° (lit.[78] 98-99°); n.m.r. (in CS_2) δ 1.17-2.13 (2 protons), 2.13-2.58 (4 protons), 2.83-3.22 (1 proton), 4.05 (2 protons), 7.42-8.33 (3 protons), 8.88 (1 proton, doublet, J = 2 c.p.s.), and 10.97 (1 proton).

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86. Found: C, 53.94; H, 5.34.

Attempted Alkaline Hydrolysis of CXXIX

A solution of 2.103 g. of CXXIX in 20 cc. of 5% NaOH and 5 cc. of 95% ethanol was refluxed for 60 hr. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give back 2.010 g. of CXXIX (m.p. 90-91°).

2. Reaction of N,N-Dibromobenzenesulfonamide with Bicyclo(2.2.2)--2-octene

Preparation of LXXXVI, CLV (CLV≡LXXXV), LXXXIII, and CLXVII

To 30 g. of IX in 300 cc. of dry benzene were slowly added 44 g. of N,N-dibromobenzenesulfonamide. The solution was stirred overnight and the benzene carefully removed through a Vigreux column. The reaction mixture was chromatographed directly on 750 g. of Merck acid-washed alumina. Elution with benzene-petroleum ether (1:1) gave 21 g. of endo-8-bromobicyclo(3.2.1)-2-octene (LXXXVI) b.p.$_{5\ mm.}$ 65-70° (about 95% pure by gas chromatography). Elution with benzene and benzene-chloroform mixtures gave 47 g. of a mixture of adducts. Thin layer chromatography of this mixture on Silica Gel-G in chloroform showed spots at R_f 0.40, 0.30, 0.27, and 0.17. Elution with 9:1 chloroform-methanol gave 7.1 g. benzenesulfonamide (m.p. 151-152°). The crude mixture of adducts obtained above was chromatographed repeatedly on alumina varying the polarity of the eluent from petroleum ether to benzene to chloroform. The benzene eluates were oils from which CLV (R_f 0.40) crystallized from cold ether and had m.p. 99-100°; ν_{max}^{KBr} 3230, 1325, 1160, 753, 721, and 792 cm.$^{-1}$; n.m.r. (in $CHCl_3$) δ 3.45 (proton at C_2, multiplet), 4.08 (proton at C_8, triplet J = 4 c.p.s.) and 6.32 (N-H, doublet, J = 5.4 c.p.s.).

Anal. Calcd. for $C_{14}H_{18}BrNO_2S$: C, 48.84; H, 5.27. Found: C, 49.14; H, 5.67.

Thin layer chromatography of the benzene-chloroform eluates on Silica Gel-G in chloroform showed LXXXIII (R_f 0.30) and CLXVII (R_f 0.27) poorly resolved. Fractions consisting mostly of LXXXIII were combined and upon standing in the cold LXXXIII crystallized from ethanol. After several recrystallizations LXXXIII had m.p. 135-136° and mixed melting point with a sample of trans-2-bromo-3-benzenesulfonamidobicyclo(2.2.2)-

octane (m.p. 136-137°) prepared as described earlier (See Chapter I) was undepressed. The third isomer CLXVII (R_f 0.27) crystallized from fractions rich in CLXVII upon standing in the cold in ethanol. Recrystallization thrice from ethanol gave CLXVII, m.p. 189-190°; ν_{max}^{KBr} 3270, 1310, 1160, 1080, 970, 753, 725, and 688 cm.$^{-1}$; n.m.r. (in $CHCl_3$) δ 1.42-2.50 (10 protons), 3.25 (proton at C_3, multiplet; sharpened to triplet, J = 6.5 c.p.s., upon addition of CF_3COOH), 3.98 (proton at C_2, multiplet) and 5.62 (N-H, doublet, J = 5 c.p.s., disappeared upon addition of CF_3COOH).

Anal. Calcd. for $C_{14}H_{18}BrNO_2S$: C, 48.84; H, 5.27. Found: C, 49.29; H, 5.39.

The chloroform eluates gave mixtures of LXXXIII, CLXVII, and a third minor component (R_f 0.17) which could not be separated by chromatography or crystallization.

Conversion of CLV to axial-2-Acetamidobicyclo(3.2.1)octane (CLVIII)

A solution of 1.42 g. CLV in 30 cc. of dry sec-butyl alcohol was treated with 3 g. of metallic sodium over a period of 0.5 hr. The reaction mixture was refluxed for 4 hr. and worked up in the usual manner to yield 452 mg. of axial-2-aminobicyclo(3.2.1)octane (CLVI) as a waxy solid. The N-acetyl derivative, CLVIII, was prepared with acetic anhydride and after crystallization from ether-petroleum ether had m.p. 122-123°. Repeated recrystallizations did not raise the melting point; ν_{max}^{KBr} 3280, 1645, 1565, 1195, and 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.24. Found: C, 71.64; H, 10.43.

Preparation of equatorial-2-Acetamidobicyclo(3.2.1)octane (CLIX)

A suspension of 0.4 g. of lithium aluminum hydride in 40 cc. of ether containing 0.8 g. of bicyclo(3.2.1)-2-octanone oxime (CLXI), prepared by a known procedure,[52] was stirred overnight. After the excess hydride was destroyed, the solution was made acidic with dilute hydrochloric acid. The acidic aqueous solution was washed with ether, then made basic and extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give 271 mg. of equatorial-2-aminobicyclo(3.2.1)octane (CLX) as a waxy solid. The N-acetyl derivative, prepared with acetic anhydride, after crystallization from ether-hexane CLIX had m.p. 137-138°. Repeated recrystallizations did not raise the melting point; ν_{max}^{KBr} 3280, 1646, 1550, 1122, 1085, 944, and 910 cm.$^{-1}$. The infrared spectra of CLVIII and CLIX were different. The mixture melting point of CLVIII and CLIX was 128-131°.

Gas chromatography of CLVIII and CLIX on an ECNSS-S, 0.02-in. x 150-ft. column and a 0.25-in. x 10-ft. Craig polyester column showed single peaks for both CLVIII and CLIX but failed to resolve a mixture of the two.

Preparation of Bicyclo(3.2.1)-2-octanone (CLVII) from CLVI

Oxidation of 104 mg. of CLVI by the procedure described earlier gave a low yield of crude ketone. A portion of the crude product was treated with excess acidic, methanolic 2,4-dinitrophenylhydrazine solution. The derivative was purified by chromatography on Merck acid-washed alumina using benzene as the eluent. The hydrazone crystallized from ether and had m.p. 137-138°. Mixture melting point with the 2,4-dinitrophenylhydrazone of authentic CLVII (m.p. 139-140°, lit.[89] 137.5-139°), prepared by an established procedure,[89] was 138-139°.

Degradation of CLV to endo-8-Bromobicyclo(3.2.1)-2-octene (LXXXVI)

A suspension of 2.05 g. of CLV in 15 cc. of 10% hydrochloric acid was heated at 175° in a sealed tube for 24 hr. The reaction mixture was cooled and the acidic solution washed twice with chloroform. Evaporation of the acidic aqueous solution gave 125 mg. of bromo amine hydrochloride. The bromo amine was isolated by treatment of the hydrochloride salt with dilute aqueous base followed by ether extraction of the basic aqueous solution. The ether extract, after drying over anhydrous magnesium sulfate, was carefully evaporated to give 105 mg. of bromo amine which was used without further purification. The bromo amine (105 mg.) was stirred with 120 mg. 90% formic acid and 90 mg. of 40% formaldehyde for 24 hr. at room temperature and then for 2 hr. on a steam bath.[90] Dilute hydrochloric acid was added to the solution and the excess formic acid and formaldehyde were removed by distillation. The concentrate was diluted with 5 cc. of water and washed with several portions of chloroform. The acidic aqueous solution was made basic and the aqueous sodium hydroxide solution was extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give 53 mg. of N,N-dimethyl bromoamine as a light brown oil. The crude N,N-dimethyl bromoamine was treated with 1 cc. of 30% hydrogen peroxide in 1 cc. of methanol for 12 hr. at room temperature. The excess peroxide was destroyed by treatment of the alcoholic solution with a small amount of 5% platinum on charcoal. The catalyst was removed by filtration and evaporation of the filtrate in vacuo gave 39 mg. of CLXIII as a viscous oil.

The N,N-dimethylamine oxide, CLXIII, (39 mg.) was heated over a

period of 0.75 hr. to 135° and maintained at that temperature for 0.5 hr. under 30-40 mm. pressure, during which time 12 mg. of an oil distilled. Gas chromatographic analysis of the distillate on a 0.25-in. x 10-ft. Craig polyester column at 135° using a helium flow rate of 74 cc. per min. showed endo-8-bromobicyclo(3.2.1)-2-octene (LXXXVI) as the major component (95%), identified by mixed injection with an authentic sample.[30] Analysis on a 0.125-in. x 10-ft. Silicone Rubber column at 80° using a nitrogen flow-rate of 40 cc. per min. also showed LXXXVI as the major component by mixed injection.

Preparation of CXVIII

N-Bromosuccinimide (140 g.) was added to 60 g. of I dissolved in 1.2 l. of 1 N sulfuric acid and 800 cc. of tert-butyl alcohol. After stirring at room temperature overnight, the solution was diluted with 5 l. of water and exhaustively extracted with petroleum ether. The extract was washed with sodium carbonate solution, dried over anhydrous magnesium sulfate, and concentrated. Fractionation of the residue gave 18.1 g. of CIX (b.p.$_{0.7\ mm.}$ 45-55°) and 55.8 g. of the bromonorborneol fraction which solidified on standing. Gas chromatographic analysis of the latter fraction on a 0.25-in. x 10-ft. 10% Silicone 550 on firebrick column at 190° with a helium flow-rate of 55 cc. per min. showed that it contained two components in a ratio of 3:1. The component in larger amount was identified as CXVIII and the minor component as CXVII by n.m.r. The bromonorborneol fraction had m.p. 40-43° after two sublimations and was used without further separation for the next step.

Preparation of 7-syn-Bromobicyclo(2.2.1)-2-heptanone (CXXXIII) from CXVIII

The above mentioned bromonorborneol fraction was oxidized in dry acetone using a molar equivalent of Jones reagent.[44] The reaction mixture was diluted with water, then extracted with n-hexane. The hexane extract, after washing with sodium carbonate solution, was dried over anhydrous magnesium sulfate and concentrated. The residue was fractionally distilled to yield 72% of CXXXIII, b.p.$_{8.4\ mm.}$ 68-70°; ν_{max}^{film} 1750 cm.$^{-1}$, n.m.r. (in CS_2) δ 4.4 (C_7 proton, quartet, J = 1 c.p.s.). The gas chromatogram (same conditions as above) showed 5% impurities. The 2,4--dinitrophenylhydrazone was prepared by the addition of an acidic, methanolic 2,4-dinitrophenylhydrazine solution and after chromatography on alumina and recrystallization from petroleum ether had m.p. 201.5-202.5°.

Preparation of CLXIV

A solution of ketone CXXXIII (0.185 mole) in ether was slowly added to 0.190 mole of methylmagnesium iodide in 250 cc. dry ether. After stirring for 3 hr., aqueous ammonium sulfate was added, and the solution was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated to yield 37 g. of residue the n.m.r. spectrum of which indicated the presence of about 30% of unreacted CXXXIII about 50% CLXIVa and about 20% CLXIVb. A pure sample of CIXIVb was obtained after chromatography on Merck acid-washed alumina and had m.p. 74-75° after three recrystallizations from petroleum ether; ν_{max}^{KBr} 3320, 1188, and 930 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{13}OBr$: C, 46.85; H, 6.39. Found: C, 47.07; H, 6.62.

Preparation of 7-syn-Bromo-2-methylenebicyclo(2.2.1)heptane (CLXV)

The crude product (24 g.) from the above mentioned Grignard reaction

was slowly distilled at 85-110° (20-55 mm.) in the presence of a few crystals of iodine. The distillate was fractionally distilled to give 11.4 g. of 7-syn-bromo-2-methylenebicyclo(2.2.1)heptane (detected by n.m.r.) and 9.23 g. of a fraction containing ketone CXXXIII (unreacted from Grignard reaction) and olefin CLXV. The latter fraction was separated into 2.8 g. of CLXV and 4.8 g. of CXXXIII by use of Girard's T reagent. The analytical sample of CLXV was obtained by preparative gas chromatography on a 3/8-in. x 20-ft. Silicone nitrile column. ν_{max}^{film} 3090, 1630, and 882 cm.$^{-1}$; n.m.r. (in CS_2) δ 3.87 (C_7 proton, doublet, J = 1.5 c.p.s.), and 4.85 (vinylic protons, doublet, J = 10 c.p.s.).

Anal. Calcd. for $C_8H_{11}Br$: C, 51.36; H, 5.93. Found: C, 51.29; H, 5.96.

Conversion of CLXV into endo-8-Bromobicyclo(3.2.1)-2-octene (LXXXVI)

A solution of sodium borohydride (0.37 g.) and boron trifluoride-etherate (2.5 cc.) in 10 cc. of tetrahydrofuran was added to 2.3 g. of CLXV in 20 cc. dry tetrahydrofuran and the solution stirred at 60° for 3.5 hr.[84] After destroying the excess borohydride, 1.3 cc. of 3 N sodium hydroxide and 1.3 cc. of 30% hydrogen peroxide were cautiously added and after stirring at 50° for 1 hr. the solution was diluted with 150 cc. of water. Extraction with ether and removal of the ether gave an oily residue which on distillation gave 1.3 g. of the isomeric 7-syn-bromobicyclo(2.2.1)heptane-2-methanols (CLXVI) in a ratio of 3:1 (gas chromatography on Silicone 550 column). The isomeric mixture (1.3 g.) was heated at 160° with 85% phosphoric acid[90] (0.5 g.) for 30 min. at 50 mm., during which period water and a dark-colored organic liquid distilled from the reaction mixture. The residue and distillate were combined, diluted with

water, and extracted with petroleum ether. After washing and drying the extract was concentrated to give 352 mg. of residue. Gas chromatographic analysis (Silicone 550 column) indicated that this residue contained 25% of the desired bromo olefin LXXXVI. A sample of LXXXVI was obtained by preparative gas chromatography (Silicone 550 column) and the sample so obtained was identical in infrared and nuclear magnetic resonance spectra with a sample of LXXXVI prepared as previously described [30] and that which was prepared from CLV.

Reduction of LXXXIII with Sodium in Alcohol

A solution of 2.1 g. of LXXXIII in 42 cc. dry sec-butyl alcohol was slowly treated with 3.4 g. of metallic sodium. The reaction mixture was heated to 110° and refluxed for 6 hr. After cooling, the reaction mixture was acidified with 10% hydrochloric acid and washed with ether. The acidic aqueous solution was made basic and the product extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give a mixture of amines. The amine mixture was treated with acetic anhydride and the amine acetates (mixture) isolated in the usual manner. The n.m.r. spectrum of the crude acetylated mixture showed that $>90\%$ of the acetylated product possessed a secondary halogen function. Gas chromatography of the crude acetylated mixture on a 0.25-in. x 10-ft. Silicone nitrile column at 220° using a helium flow-rate of 100 cc. per min. showed only a single peak with a retention time less than 25 min. Under these conditions 2-acetamidobicyclo(2.2.2)octane (See Chapter I for preparation of the corresponding amine) had a retention time identical to the acetyl compound derived from LXXXIII. Neither CLVIII nor CLIX were separated from 2-acetamidobicyclo(2.2.2)octane or the acetyl

compound derived from LXXXIII under these conditions. The 3-acetamidobicyclo(3.2.1)octane derived from CLXVII and the 8-acetamidobicyclo(3.2.1)-octane derived from LXXXIV were separated from 2-acetamidobicyclo(2.2.2)-octane and the acetyl derivative derived from LXXXIII under the above conditions. A number of different polyester and Silicone columns under varied conditions failed to separate the acetyl compound derived from LXXXIII from 2-acetamidobicyclo(2.2.2)octane, CLVIII or CLIX.

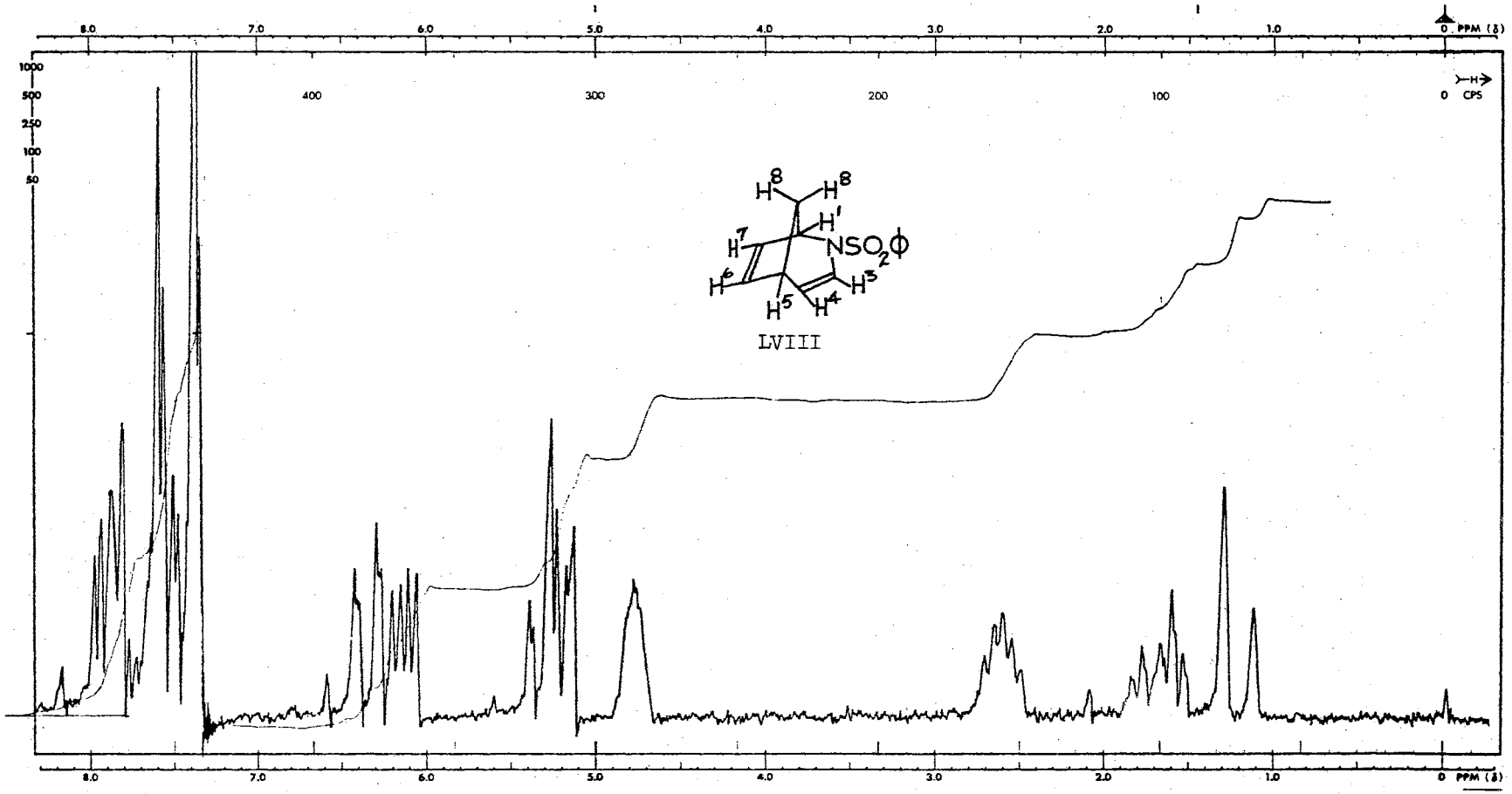
Conversion of CLXVII to Bicyclo(3.2.1)-3-octanone (CLXIX)

Reduction of 430 mg. of CLXVII with sodium in alcohol by the usual procedure gave 102 mg. of amine as a waxy solid. The amine thus obtained was oxidized with 30% hydrogen peroxide in the presence of $Na_2MoO_4 \cdot 2H_2O$ in aqueous methanol. After acidification of the oxidation reaction solution with dilute hydrochloric acid the aqueous solution was extracted with ether. The ether extract, after drying over anhydrous magnesium sulfate, was evaporated to give 15 mg. of CLXIX. Gas chromatographic analysis of the crude ketone on a 0.02-in. x 150-ft. ENSS-S column showed one major component (about 95%). Mixed injection of a mixture of CLVII and CLXIX prepared by hydroboration of CLXVIII[92] showed the ketone derived from CLXVII to be identical with CLXIX and different from CLVII. The ketone derived from CLXVII was also identical to CLXIX and different from bicyclo(2.2.2)-2-octanone by mixed injection on a 0.25-in. x 10-ft. Silicone nitrile column at 220° using a helium flow-rate of 115 cc. per min.

The 2,4-dinitrophenylhydrazone of CLXIX derived from CLXVII had m.p. 163-164° (lit.[39] 165-166.2°).

Plate I

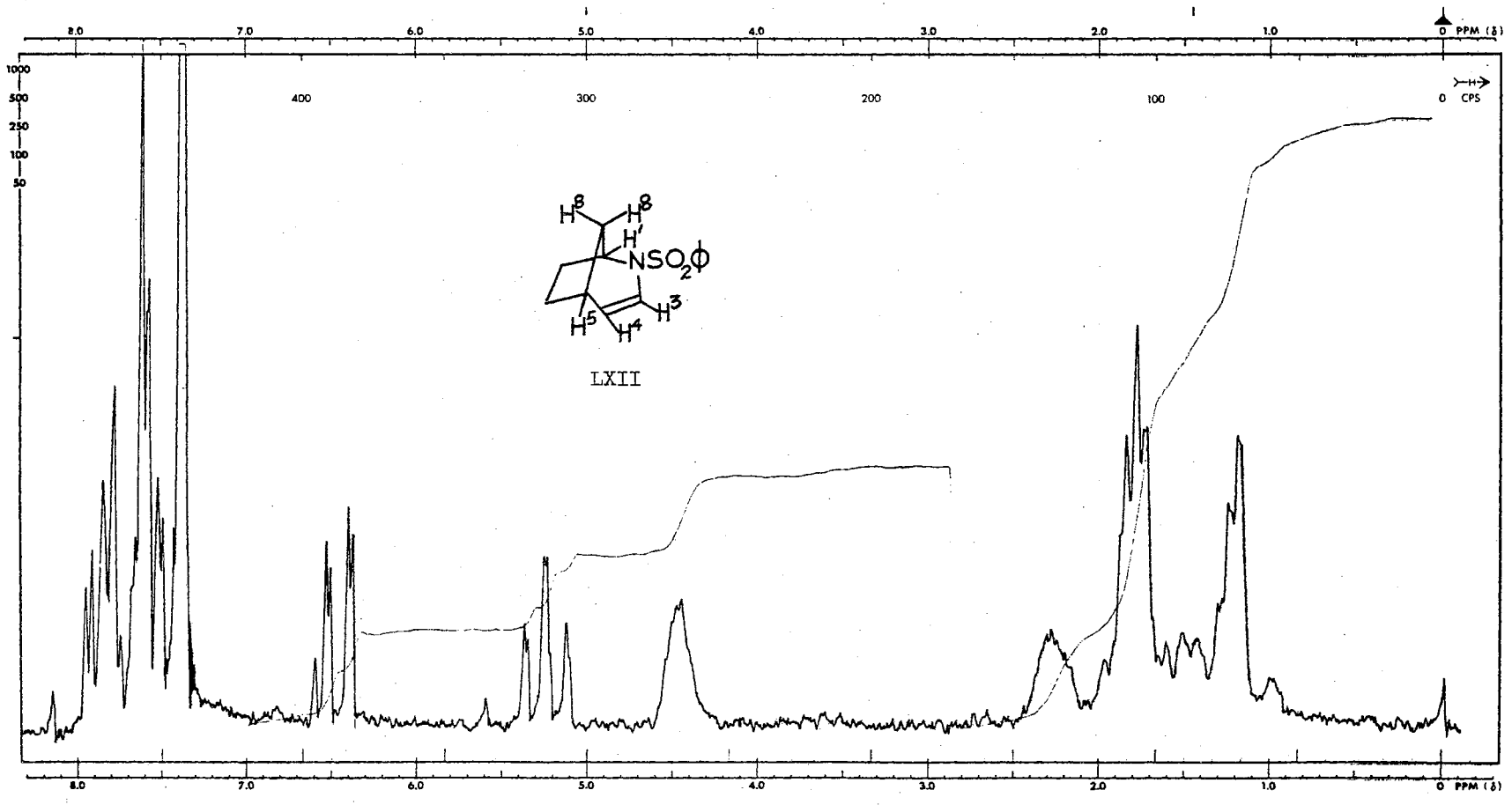
Nuclear Magnetic Resonance Spectrum of N-Benzenesulfonyl-2-azabicyclo(3.2.1)-3,6-octadiene (LVIII)



LVIII

Plate II

Nuclear Magnetic Resonance Spectrum of N-Benzenesulfonyl-2-azabicyclo(3.2.1)-3-octene (LXII)



LXII

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VITA

ALLAN CAMERON OEHLSCHLAGER

Candidate for the Degree of

Doctor of Philosophy

Thesis: REACTIONS OF BRIDGED BICYCLIC COMPOUNDS.

Major Field: Organic Chemistry

Biographical:

Personal Data: Born in Hartford, Connecticut, September 8, 1940, the son of Henry Allan and Kathryn Oehlschlager. Married Roberta June Weldon, January 27, 1961. Two children, Cameron Kelly, born September 30, 1961, and Stephen Lynn, born July 5, 1963.

Education: Graduated from Yale High School, Yale, Oklahoma in 1958. Received the Bachelor of Science degree from Oklahoma State University with a major in Chemistry in August 1962; completed the requirements for the Doctor of Philosophy degree, with a major in Organic Chemistry, in May, 1965.

Professional Experience: Undergraduate Teaching Assistant and Lew Wentz Service Scholar in Chemistry, Oklahoma State University, 1961-1962; National Science Foundation Summer Research Participant, Oklahoma State University, 1962; National Defense Education Act Fellow at Oklahoma State University, 1962-1965.

Membership in Professional Societies: Sigma Xi, Phi Lambda Upsilon, American Chemical Society, The Chemical Society (London).