THE REACTIONS OF N-BROMOSUCCINIMIDE, N,N-DIBROMOBENZENESULFONAMIDE AND BENZENESULFONYL AZIDE WITH BICYCLO-[2.2.1]-5-HEPTENE-2,3-DICARBOXYLIC ANHYDRIDE. N-ALKYL CLEAVAGE OF γ-LACTAMS BY ACID HYDROLYSIS. STEREOCHEMICAL DETERMINATIONS IN THE BICYCLO[2.2.1]-HEPTANE SYSTEM VIA NUCLEAR MAGNETIC RESONANCE.

By

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1959

Submitted to the Faculty of the Graduate School
of the Oklahoma State University
in partial fulfillment of the requirements
for the degree of
DOCTOR OF PHILOSOPHY
May, 1963

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ACKNOWLEDGMENT

I wish to express my gratitude to Dr. Leon Zalkow for his invaluable guidance and counsel during the course of my graduate work and preparation of this thesis.

I want to express my thanks to Dr. O. C. Dermer for helpful criticism especially during preparation of this thesis.

I thank my wife, Janis, for her patience, encouragement and assistance in helping me toward my goals.

Thanks also are rendered to the National Department of Health, Education and Welfare for a three-year (1959-1962) National Defense Education Act Fellowship, and for funds administered through the Research Foundation of Oklahoma State University for support during the summer of 1962. Finally, I wish to thank Continental Oil Company for allowing preparation of this thesis while being employed by them.

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GENERAL INTRODUCTION

Bicyclo[2.2.1]heptane derivatives are particularly advantageous systems for studying the stereochemical path of chemical reactions because of their rigid nuclei. The four chapters of this dissertation deal with chemical and physical studies in these bicyclic systems. The research problems described in the four chapters are not directly related and thus each chapter has its corresponding historical and introduction, results and discussion, and experimental sections.

CHAPTER I

THE REACTIONS OF N-BROMOSUCCINIMIDE AND N,N-DIBROMOBENZENESULFONAMIDE WITH BICYCLO[2.2.1]-5-HEPTENE-*endo*-*cis*-2,3-DICARBOXYLIC ANHYDRIDE

Historical and Introduction

The reaction of N-bromoacetamide with alkenes such as 2,3-dimethyl-2-butene to yield allylic bromides was first described by Wohl[1] in 1919, but reactions of this sort received little attention until Ziegler[2] in 1942 published the results of an intensive investigation with a variety of N-haloamides, selecting N-bromosuccinimide (NBS) as a particularly convenient and effective reagent for allylic brominations. Since the introduction of bromine into an allylic position is a highly desirable operation in many fields of organic chemistry the reaction has been avidly applied by a large number of organic chemists; thus a large amount of literature dealing with the use of NBS has arisen. Djerassi[3] wrote a very elegant review on the subject in 1948, and in 1951, a book by Waugh[4] on the reactions of NBS was published. The field was reviewed more recently by Horner and Winkelmann.[5]

Bloomfield[6] and Hey[7] first suggested that NBS reacts via a radical chain mechanism. This was further supported by Schmid and Karrer.[8] Recently, Dauben and McCoy[9,10] reported a very thorough investigation of the reaction of NBS with cyclohexene in carbon tetrachloride. The mechanism proposed by these workers in its simplest and most general form is shown below:

Initiation: $In - In \longrightarrow 2\ In\cdot$ $\quad In\cdot$ = initiator radical

$In\cdot + (CH_2CO_2)NBr \longrightarrow In - Br + (CH_2CO_2)N\cdot$

$In\cdot + -C=C-C-H \longrightarrow In - H + -C=C-C\cdot$

Propagation: $(CH_2CO)_2N\cdot + -C=C-C-H \longrightarrow (CH_2CO)_2NH + -C=C-C\cdot$

$-C=C-C\cdot + (CH_2CO)_2NBr \longrightarrow -C=C-C-Br + (CH_2CO)_2N\cdot$

Termination: $2(CH_2CO)_2N\cdot \longrightarrow\ ?$

Although the above mechanism has been widely accepted, another mechanism has been proposed which does not involve succinimidyl radicals.[11,12,13] In this second mechanism, first suggested by Goldfinger,[11] it is suggested that the function of NBS is to provide a constant low concentration of molecular bromine which leads to allylic bromination. Very strong evidence supporting the Goldfinger mechanism in benzylic brominations with NBS was reported very recently.[14,15] The Goldfinger mechanism is illustrated as follows:

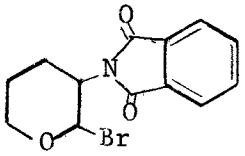
$$(CH_2CO)_2NBr + HBr \longrightarrow (CH_2CO)_2NH + Br_2$$

$$Br_2 \longrightarrow 2Br\cdot$$

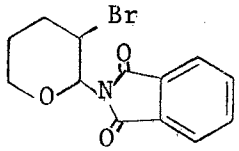
$$Br\cdot + \text{-C=C-C-H} \longrightarrow \text{-C=C-C}\cdot + HBr$$

$$Br_2 + \text{-C=C-C}\cdot \longrightarrow \text{-C=C-C-Br} + Br\cdot$$

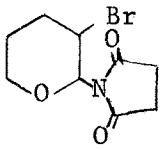
Assuming the former mechanism is correct, Walling[16] has explained the abstraction of hydrogen atoms by the succinimidyl radical in preference to addition to the double bond as being due to the greater bond energy of the N-H bond in the succinimide produced as compared to the N-C bond which would result from the addition of the succinimidyl radical to the alkene. However, there have been examples reported in the literature in which NBS and other N-haloimides and N-haloamides have been shown to give stable 1:1 adducts with unsaturated compounds. For example, dihydropyran has been reported to add N-bromophthalimide[17] and NBS[18] in refluxing carbon tetrachloride. Hurd[17] and co-workers assigned structure I to the former adduct. Structure I would be expected if the addition occurred by a radical mechanism, whereas structure II would result from an ionic addition. Shelton[18] has recently shown that the adduct with NBS has the structure III and suggested that the addition occurs by an ionic mechanism explaining



I



II



III

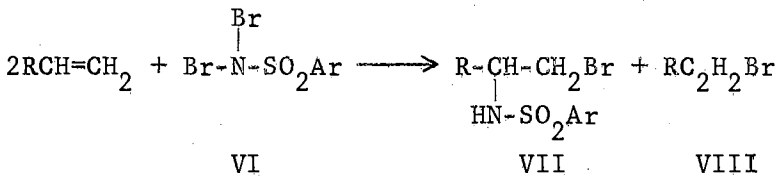
it as follows: "The polarizing effect of the oxygen alpha to the double bond is considered to increase the nucleophilic character and thus favor a polar mechnism." It is interesting to note that a small acceleration in the formation of III was observed in the presence of oxygen or peroxide and both geometrical isomers of III were formed. With substituted dihydropyrans it appears that the position of the substituent influences the type of product obtained.[19] N-Bromotrifluoroacetamide and N-bromotrichloroacetamide have been shown to add to cyclohexene.[20] Under identical conditions N-bromotrifluoroacetamide gave predominantly ring bromination of toluene, whereas N-bromotrichloroacetamide gave mainly side chain bromination.[20] Thus, in these cases, there appears to be a change from an ionic to a free radical mechanism as one changes the nature of the N-haloamide.

Kharasch and Priestley[21] observed the addition of N-halosulfonamides to alkenes. N-Bromo-N-methyl aromatic sulfonamides IV were found to add to propene, 2-methylpropene, vinyl chloride and styrene to yield adduct V. The direction of addition observed would be expected in a

$$\underset{\text{IV}}{RCH{=}CH_2 + Br\text{-}\overset{\overset{CH_3}{|}}{N}\text{-}SO_2Ar} \longrightarrow \underset{\text{V}}{R\text{-}\overset{\overset{Br}{|}}{CH}\text{-}CH_2\text{-}\overset{\overset{CH_3}{|}}{N}\text{-}SO_2Ar}$$

radical process. N,N-Dibromosulfonamides VI, on the other hand, were

found to add to alkenes to yield products possessing structure VII in which the bromine atom takes the position expected in an ionic reaction.[21] Others[22] have observed the addition of the sulfonamido



VI VII VIII

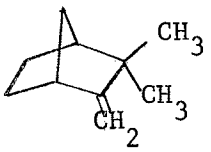
group to olefins in the presence of alcohols and phenols; these undoubtedly occur by an ionic process.

Methylenecyclobutane has been reported to form an adduct with NBS.[23] The yield of this adduct was very low and it was obtained only under non-radical conditions.[23] The oily product was isolated by distillation, which however did not effectively free it from succinimide. This might have been due to decomposition of the adduct to yield succinimide during the distillation. The elimination of succinimide from a compound which was suggested to be an NBS-alkene adduct, when a mixture containing the compound was allowed to stand for several days, was reported recently.[24] In another case[25] NBS reacted with vinylacetonitrile to yield 2% of 3-bromo-4-succinimido-butyronitrile. This adduct was obtained in addition to other brominated products and the mechanism of the addition reaction was not established.

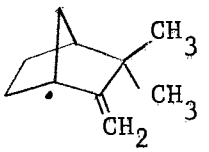
Several investigators have reported isolations of succinimidyl derivatives from the products of the reaction of NBS with various unsaturated compounds. It is possible that these compounds arise by addition of NBS followed by loss of the bromine atom. N-Phenylsuccinimide was obtained in the reaction of methylenecyclobutane with NBS in benzene solution.[23] N-Phenylsuccinimide was also obtained, although only in 1% yeild, when cyclohexene was treated with NBS in benzene

solution.[26] Other workers have reported the formation of N-(cyclohepta-2,4,6-trienyl)succinimide in high yield from NBS and cycloheptatriene.[27] Markees[28] has observed the formation of dl-N-α-methoxy-p-nitrobenzyl-succinimide from NBS and p-nitrobenzyl methyl ether. Braun and Looker[29] more recently reported a similar reaction of NBS with p-bromophenyl benzyl ether to yield dl-N-α-(p-bromophenoxy)benzylsuccinimide. A free radical chain mechanism which accounts for the formation of the latter three succinimidyl compounds has been proposed.[28]

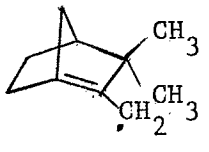
The only hydrogen atom allylic to the double bond in camphene (IX) is at a bridgehead position. Roberts and Trumbull[30] were interested in testing the scope of the reaction of NBS with alkenes by reacting NBS with camphene (IX) under the normal free-radical conditions. If resonance stabilization of an intermediate radical was an essential



IX



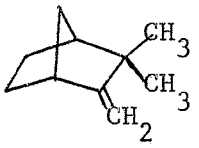
X



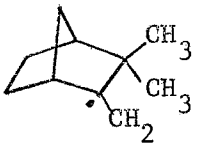
XI

feature of the NBS reaction, the allylic bromination of IX by this method should have been difficult or impossible, since X, the free radical intermediate, would not be expected to be stabilized by resonance contributions of forms involving a bridgehead double bond such as XI.[30] Under free radical conditions NBS reacted with camphene (IX) to give 8-bromocamphene (XII).[30] The free-radical nature of the reaction was established and the reaction mechanism for the bromination in the 8-position was formulated as involving the attack of a bromine atom or a species capable of donating a bromine atom at the 8-position to

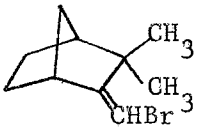
give XIII, followed by removal of a hydrogen atom by a hydrogen acceptor, which in this case would be the succinimidyl radical, to yield 8-bromocamphene (XII).[30]



IV

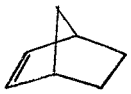


XIII



XII

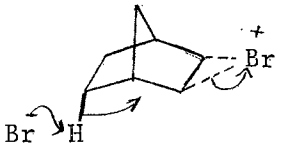
In an extension of this problem, Roberts and co-workers[31] treated bicyclo[2.2.1]-2-heptene (XIV), another compound which has bridgehead hydrogen atoms as the only allylic hydrogens, with NBS. The product isolated was 3-bromonortricyclene (XV). Although XV was formed under



XIV

XV

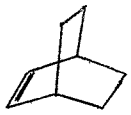
radical conditions, the addition of hydrogen bromide markedly accelerated the reaction. The bromine thus formed from the reaction of hydrogen bromide with NBS could react with XIV to give the intermediate XVI. The



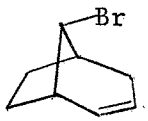
XVI

objection, however, to a free-radical pathway is not as serious as first believed since the findings of Dauben and McCoy[9,10] have shown that bromine, in very small concentrations, acts as an accelerator in allylic brominations.

Bridgehead radicals are known in norbornyl compounds though they have not been produced by abstraction of bridgehead hydrogen atoms.[32] However, the bridgehead hydrogen atom in bicyclo[2.2.2]octane has been shown to be easily abstracted by chlorine atoms.[33] In view of this, one might expect allylic bromination of bicyclo[2.2.2]octene (XVII).



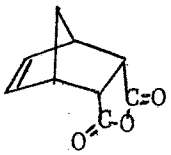
XVII



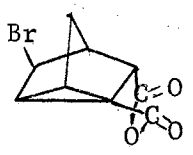
XVIII

However, when XVII was treated with NBS under radical conditions, endo-8-bromobicyclo[3.2.1]-2-octene (XVIII) was produced as the major product.[24]

In view of the unexpected products produced in the reaction of NBS with alkenes containing bridgehead hydrogen atoms as the only allylic hydrogen, it was decided to investigate the reaction of NBS with bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride (XIX). The endo-anhydride group in XIX should make formation of a nortricyclene type product, as was the case with XIV, more difficult owing to the steric strain that would be introduced into the semi-trans fused anhydride ring as depicted in XX. A resonance-stabilized intermediate

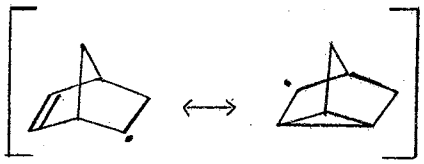


XIX

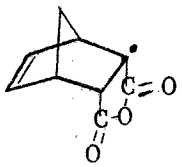


XX

XXI was suggested as an intermediate in the formation of 3-bromonortricyclene (XV) in the reaction of NBS with XIV.[31] The free-radical intermediate XXII would not be expected to be highly stabilized by such



XXI



XXII

a resonance contribution owing to steric inhibition resulting from the additional fused anhydride ring.

Because of the results obtained in the investigation of the reaction of NBS with XIX, described below, and previously reported work,[21,22] the reaction of N,N-dibromobenzenesulfonamide with XIX was thought to be of significance since the NBS reaction was found to go via a free-radical mechanism and the latter reaction was expected to proceed via an ionic mechanism.

Results and Discussion

The reaction of bicyclo[2.2.1]-5-heptene-*endo*-*cis*-2,3-dicarboxylic anhydride (XIX) with an equimolar quantity of NBS was carried out in carbon tetrachloride employing benzoyl peroxide as the radical initiator. Identical results were obtained whether the reaction was carried out in the presence or absence of light. However, light alone would not catalyze the reaction. No reaction occurred when the reaction was run without the benzoyl peroxide catalyst. The intially heterogeneous reaction mixture became homogeneous after about 20 min. of refluxing. Duplicate reaction mixtures were worked up by three different methods after the 2.5-hr. reflux period.

The first work-up procedure involved the direct addition of water to cooled reaction product mixture. Addition of water to the carbon tetrachloride solution caused a vigorous evolution of carbon dioxide which came from hydrolysis of the β-bromopropionyl isocyanate (XXIII) produced during the reaction via rearrangement of some of the NBS. Pure β-bromopropionyl isocyanate (XXIII) could be obtained by distillation of the reaction product mixture prior to hydrolysis. This same ixocyanate XXIII has been previously shown to be formed in good yields when NBS was refluxed in the presence of a free-radical initiator, in an inert solvent, such as carbon tetrachloride, with a catalytic amount of any one of a number of alkenes containing an unreactive allylic position.[34,35,36] The isolation of the methyl carbamate XXIV of XXIII is described below. Extensive washing of the water-treated organic layer (a viscous oil) with ether gave the crystalline diacid of the NBS-alkene adduct, *exo*-5-bromo-*exo*-6-succinimido-bicyclo[2.2.1]-heptane-*endo*-*cis*-2,3-dicarboxylic acid (XXV). This adduct diacid XXV

was obtained as either one of two or a mixture of different crystalline modifications which will henceforth be referred to as adducts "A" and "B". The two gave different infrared spectra in potassium bromide pellets but gave the same infrared spectra in dioxane solution. The two gave the same melting points and admixture did not cause melting point depression. Neither adduct could be converted to the other on heating in vacuo at 144° for prolonged periods; therefore, the two adducts are not considered to be hydrate polymorphs.

The methyl carbamate XXIV corresponding to XXIII was obtained directly from the reaction product mixture by the addition of methanol rather than water, to the reaction mixture. On cooling the carbamate crystallized from the carbon tetrachloride solution in 51% yield (based on starting NBS). The mother liquor remaining after removal of the carbamate XXIV was hydrolyzed by prolonged treatment with acetone and water. The dimethyl ester XXVI* corresponding to the NBS adduct XXVII was obtained in 84% yield (based on reacted alkene), by treatment of the acetone-water hydrolyzed solution with ethereal diazomethane. Column chromatography of the ether solution remaining after removal of most of XXVI by crystallization yielded 76% of unreacted XIX as the dimethyl ester XXVIII. Thin layer chromatography of the above ether solution, prior to column chromatography, gave two unidentified spots in the region of the spot corresponding to the adduct diester XXVI. It was considered possible that an adduct of carbon tetrachloride with XIX could have been formed under the conditions of the NBS-alkene reaction and its resulting dimethyl ester XXIX might correspond to

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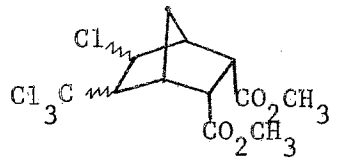
*The same ester was obtained from either adduct "A" or adduct "B" by treatment with ethereal diazomethane.

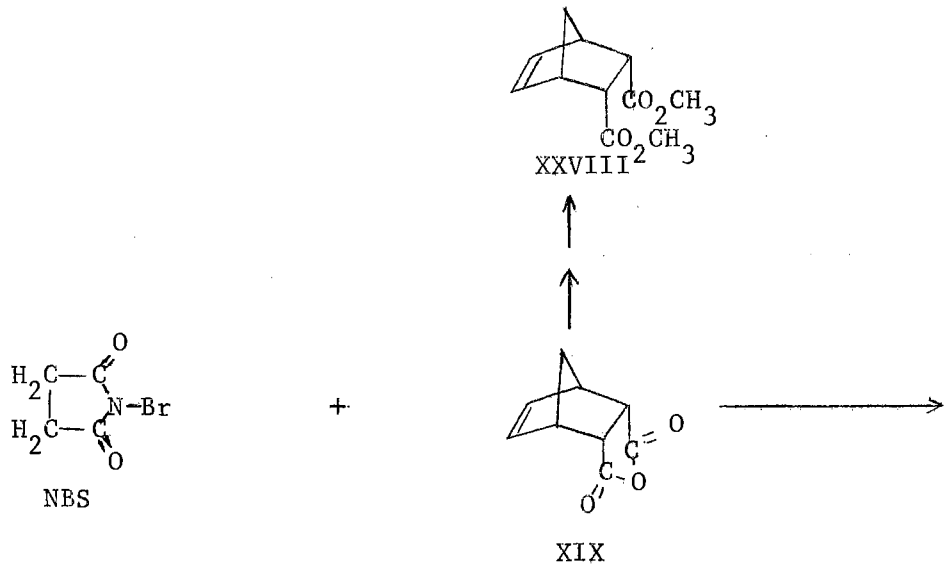


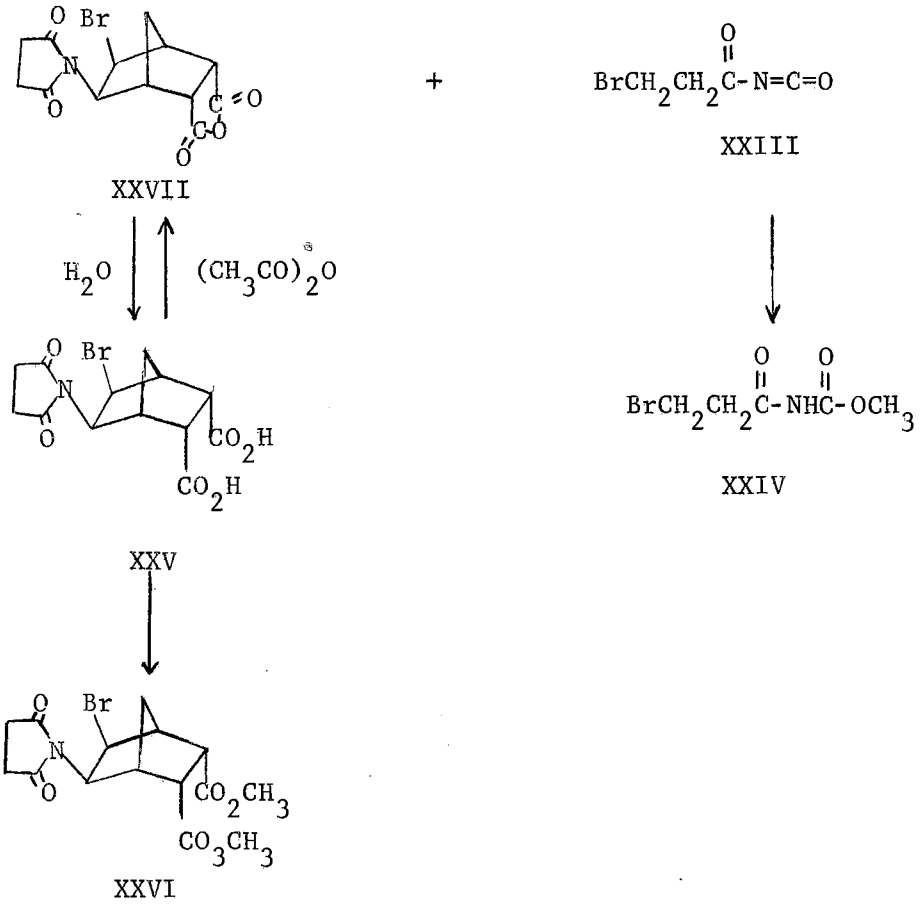
XXIX

one of the two unidentified spots. However, when XIX was subjected to the NBS-alkene reaction conditions in the absence of NBS followed by hydrolysis and esterification, the product gave an Rf value which was the same as the Rf of XXVIII. The use of benzoyl peroxide in higher concentrations than those employed in the NBS-alkene reaction, similar to those employed by Huyser[37] for inducing addition of carbon tetrachloride to alkenes, was tested, but again, on esterification, the product gave the same Rf value as that of XXVIII. Quantitative thin layer chromatography showed these two unidentified spots to represent at most a weight of about 1.6% of the weight of starting materials excluding solvent.

Treatment of either adduct "A" or "B", XXV, with acetic anhydride readily yielded the anhydride XXVII, which in turn was easily hydrolyzed back to a mixture of the diacid adducts, "A" and "B" XXV.

Since the rearrangement of NBS to the isocyanate XXIII has been reported to require a catalytic amount of an alkene with an unreactive allylic position,[34,35,36] it was considered possible that the isocyanate XXIII was the product of an initial addition of NBS to the double bond of XIX followed by an elimination reaction which included a rearrangement of the succinimido group. However, when XXVII was subjected to the original NBS-alkene reaction conditions, no isocyanate was formed and no decomposition of the adduct occurred. The fact that


NBS
XIX
XXVIII

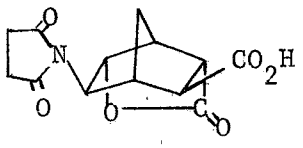

XXVII
XXIII
XXIV
XXV
XXVI

the isocyanate XXIII was not formed via the adduct XXVII does not eliminate the possibility of an NBS-alkene type adduct as an intermediate in the formation of XXIII; it only eliminates this particular cis adduct XXVII as the intermediate.

Hydrolysis of the adduct diacid XXV with concentrated hydrochloric acid gave succinic acid (XXX) and an amino acid hydrochloride salt XXXI. The infrared spectrum of XXXI showed no lactone carbonyl absorption. When XXXI was treated with nitrous acid the known bromolactone acid[38] XXXII was obtained in 18% yield. It is probable that the epimer XXXIII of XXXII was also formed, although not isolated, since an aqueous solution of XXXI passed through a weakly basic ion exchange column gave the lactone zwitterion XXXIV in 50% yield. Treatment of this lactone zwitterion XXXIV with nitrous acid gave the previously reported[39] dilactone XXXV. The isomerization of cis-endo carboxyl groups to trans carboxyl groups with concentrated hydrochloric acid, as above, is well known in such systems.[38] The isolation of XXXII of known stereochemistry showed that the bromine atom in adduct XXVII is exo.

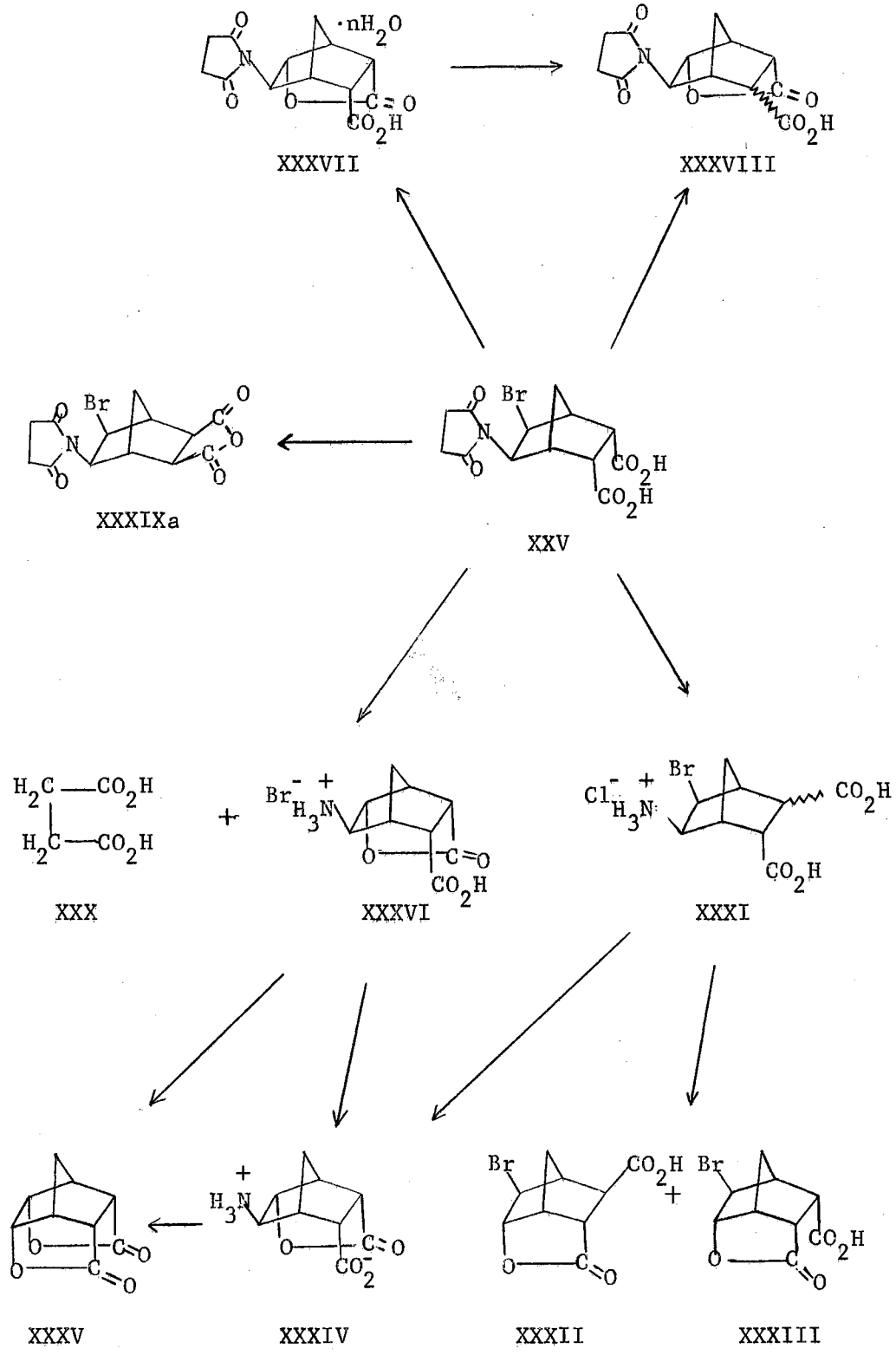
Simple water hydrolysis of the adduct diacid XXV yielded succinic acid quantitatively. The hydrolysis solution from which the succinic acid had previously been extracted gave a positive silver nitrate test for bromine. When this aqueous solution was treated with sodium nitrite, the dilactone XXXV was obtained, whereas passage through a weak basic ion exchange resin as above gave the lactone zwitterion XXXIV in 86% yield. These results showed that lactonization as well as hydrolysis of the succinimido group occurred during water hydrolysis to yield XXXVI, the hydrogen bromide salt adduct of XXXIV. The high yield of the lactone zwitterion XXXIV via hydrolysis of the adduct

diacid XXV and its subsequent conversion to the known dilactone XXXV showed that no rearrangement of the bicyclo[2.2.1]heptane nucleus occurred during the addition of NBS to XIX. Rearrangement was unlikely in view of the free-radical nature of the reaction. The adduct diacid XXV was monolactonized with refluxing pyridine, and the product crystallized from water to yield the succinimidolactone acid hydrate XXXVII. On heating a few degrees above its melting point XXXVII was converted into a new succinimidolactone acid XXXVIII. The hydrate XXXVII was also converted to XXXVIII by sublimation, which occurred a few degrees below its melting point. The infrared spectra of the sublimate and the pyrolysis product were identical; these spectra were significantly different from the spectrum of XXXVII. The pyrolysis product XXXVIII might possess structure XXXVIIIa, since epimerization of one of two cis-endo-carboxy groups to the less hindered exo position in a very similar case has been reported.[38]



XXXVIIIa

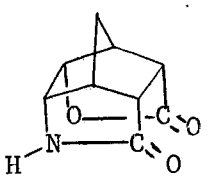
When the adduct diacid XXV was melted and heated to 235° in vacuo in a sublimation apparatus a compound XXXIX sublimed. The infrared spectrum of XXXIX gave carbonyl absorption similar to that of XXVII, but the finger print regions showed few similarities. The melting point (111°) of XXXIX was much lower than that of XXVII (197-197.5°) and the melting point of XXXIX was depressed on admixture with XXVII. Elemental analysis of XXXIX showed it to have the same empirical formula as the anhydride XXVII of XXV. The anhydride XXXIX must therefore be


XXXVII
XXXVIII
XXXIXa
XXV
XXX
XXXVI
XXXI
XXXV
XXXIV
XXXII
XXXIII

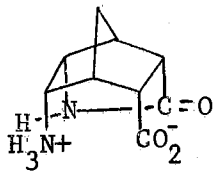
an epimer of XXVII, possibly the one depicted by structure XXXIXa. By raising the temperature of the melt of XXV to about 280°, after the evolution of XXXIX appeared complete, a second compound sublimed, which proved to be the same as XXXVIII. The formation of a γ-lactone in a bicyclo[2.2.1]heptane system by the elimination of hydrogen bromide on pyrolysis has been previously observed.[38]

The lactonization reactions described above, which necessarily involved back-side displacement of bromine, support the assigned exo configuration of the bromine atom in XXV previously shown by stereospecific degradation of XXV to its derivative XXXII of known configuration.

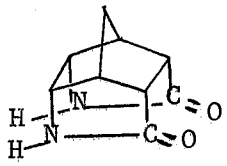
The succinimido group in XXV was shown to be exo as follows. If the nitrogen were endo in XXXIV the lactone-lactam XL would be expected to form on heating XXXIV, by the elimination of water, since the lactam zwitterion XLI yields the dilactam XLII on pyrolysis.[41]



XL

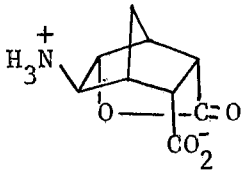


XLI

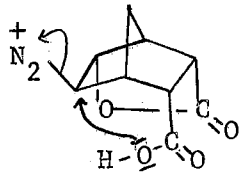


XLII

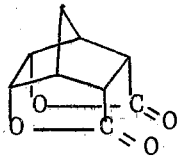
However, the lactone zwitterion XXXIV remained unchanged up to about 310°. The exo configuration of the amino group of XXXIV was also shown by treatment of the lactone zwitterion XXXIV with nitrous acid to obtain the dilactone XXXV. The dilactone results from a back-side



XXXIV

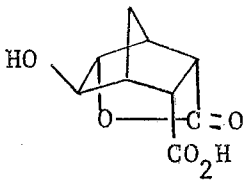


XLIII

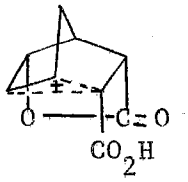


XXXV

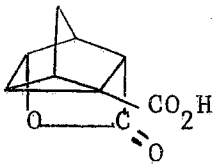
displacement of the exo-diazonium group by the endo-carboxy group of the intermediate XLIII since if the diazonium group of XLIII was endo, either one of two products, XLIV or XLV, would be expected. The known hydroxylactone acid XLIV[42] would result if the hypothetical endo-diazonium was displaced by a molecule of water from the exo side



XLIV

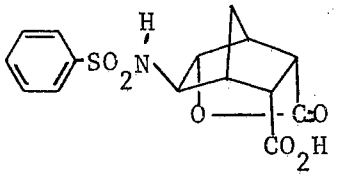


XLVI

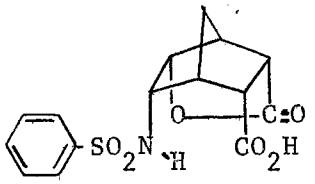


XLV

whereas if the diazonium group split off as nitrogen to give the stable non-classical carbonium ion XLVI, the lactone acid XLV could be expected (see Chapter II, p. 48).[40] The benzenesulfonamide derivative XLVII of XXXIII was shown to have the depicted stereochemistry by



XLVII



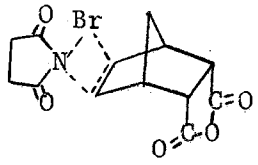
XLVIII

comparison of XLVII with the isomeric sulfonamide XLVIII which was synthesized by an independent route[43] (see Chapter III, p. 60).

Evidence for the assigned configuration of the sulfonamido group of XLVII and both the succinimido and bromo groups of XXVI has also been obtained by nuclear magnetic resonance[44] (see Chapter IV).

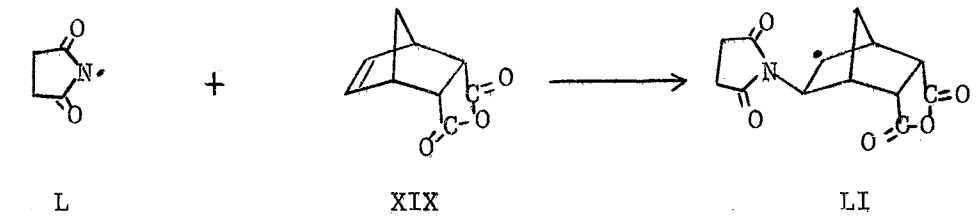
Recently controversy has arisen concerning the mechanism involved in allylic brominations with NBS. The Goldfinger[11] mechanism, which does not involve succinimido radicals, has been shown to be the mechanism involved in benzylic brominations with NBS.[14,15] However, the more widely accepted mechanism suggested by Bloomfield[6] for allylic brominations

in general, requires the succinimido radical as the chain carrier in a chain reaction mechanism. The previously described reaction of NBS with the bicyclic alkene XIX under radical conditions to give the cis-exo adduct XXVII necessitates the presence of succinimido radicals. A radical-induced four-center type mechanism involving the intermediate depicted by XLIX is disfavored because no change in the yield

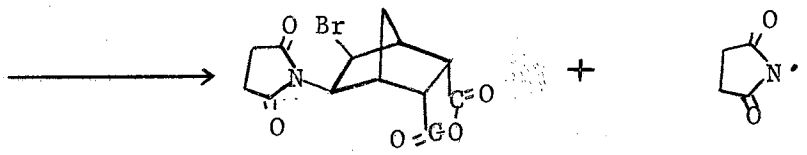


XLIX

of XXVII was observed when the concentrations of the radical initiator was double or triple the normal amount used* as would be expected if XLIX was an intermediate since the mechanism would not involve a chain process. A mechanism involving the succinimido radical L as a chain carrier must then account for the formation of XXVII. The formation of the adduct XXVII by a chain mechanism may be explained by the primary addition of a succinimido radical L from the least hindered exo side of XIX to give the intermediate LI which then abstracts a bromine atom



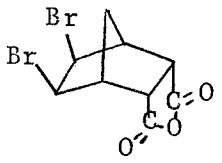
L XIX LI



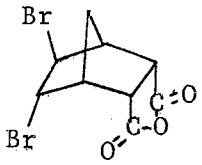
XXVII L

*See p. 27 for normal amount of radical initiator.

from NBS to give the adduct XXVII and another succinimido radical, thus completing the propagation cycle. The fact that the bromo and succinimido groups both add exo and cis indicates that the endo-anhydride of XIX offers more steric hindrance to a trans addition of the second radical than the adjacent exo group offers to a cis addition. Steric hindrance of this type has previously been observed in the formation of the cis dibromide LII by the addition of bromine to XIX.[45] Neglecting steric factors the trans dibromide LIII would be

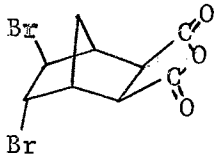


LII

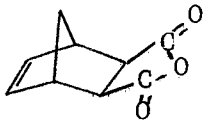


LIII

expected.[46] The expected trans dibromide LIV was obtained on bromination



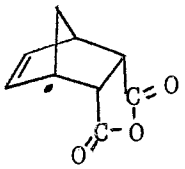
LIV



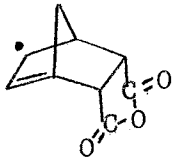
LV

of the corresponding bicyclic alkene LV,[46] in which the anhydride offers no steric interference.

The failure of the succinimido radical L to abstract a hydrogen atom from the allylic position is not surprising since the bridgehead



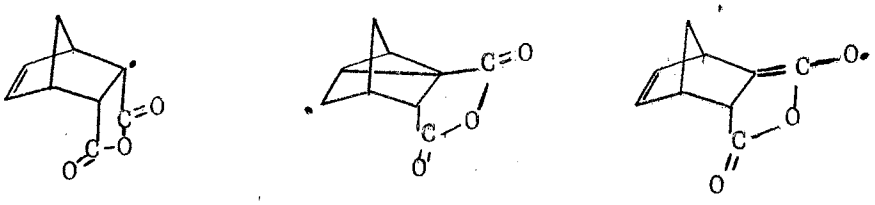
LVI



LVII

radical LVI cannot be stabilized by a resonance contributing form such as LVII,[47] and thus the energy required for such an abstraction would

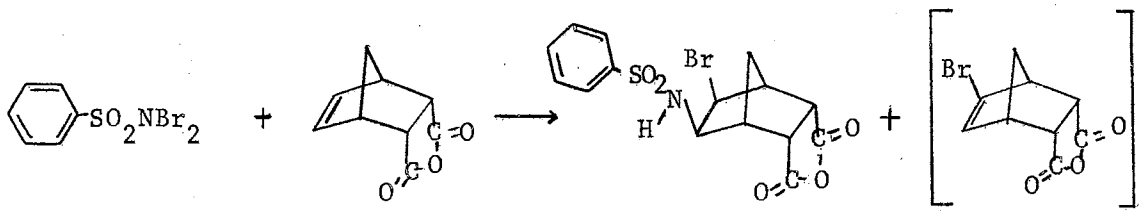
be expected to be very high. Likewise, the hydrogen atom alpha to one of the carbonyls would be expected to be removed with difficulty owing



XXII LVIII LIX

to steric inhibition of stabilization of intermediate XXII by contributing resonance forms such as LVIII and LIX.

The reaction of N,N-dibromobenzenesulfonamide (LX) with the bicyclic alkene XIX was carried out in carbon tetrachloride employing no catalysts. Once the reaction mixture was heated to reflux, the exothermic reaction evolved sufficient heat to cause the reaction mixture to continue refluxing for about ten minutes. As the reaction proceeded, a light tan viscous oil precipitated. Evaporation of the solvent after the exothermic reaction subsided and extraction of the residue with chloroform yielded crystalline adduct LXI in 21% yield (based on starting LX).



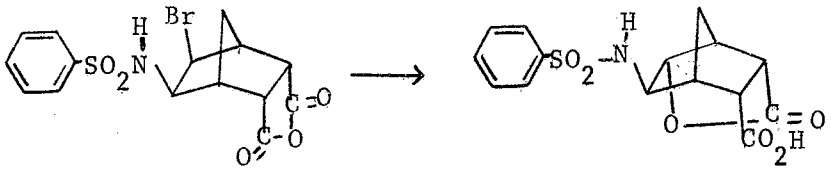
LX XIX LXI LXII

The vinylic bromide LXII may have been formed in the above reaction but attempts to isolate LXII or a derivative of LXII were unsuccessful. The formation of LXII would correspond to the formation of the vinylic bromide VIII mentioned above (see p. 6) in a similar reaction.[21] Lower than 21% yields of LXI were obtained when the ratio of XIX to LX was

less than two. This apparent requirement for a second mole of XIX indicates probable formation of LXII at some stage in the above reaction.

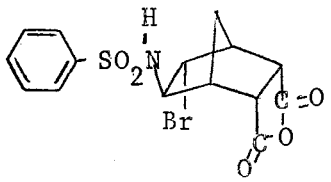
When the reaction of LX with XIX was carried out in the presence of various free-radical retarders, a slightly higher yield of the adduct LXI was obtained than when no radical retarder was present. The formation of the adduct LXI from LX and XIX was also accomplished in the dark, the yield being essentially the same as if the reaction were run in the light. Therefore, it was concluded that the addition of LX to XIX occurred via an ionic mechanism.

The configuration of the benzenesulfonamido group was shown to be exo by converting the adduct LXI to the lactone XLVII which was previously obtained from the NBS adduct XXVII. Treatment of LXI with aqueous sodium carbonate solution yielded the lactone XLVII in 66%

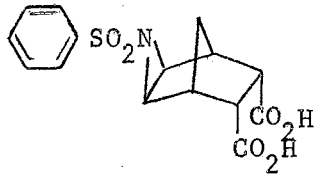


LXI XLVII

yield. The fact that XLVII was obtained from LXI showed that no skeletal rearrangement occurred during the addition reaction. The configuration of the bromine in LXI was also shown to be exo as depicted, by the formation of the lactone XLVII by back-side displacement of the bromine atom by the carboxylate ion in the above reaction. When the dimethyl ester LXIII corresponding to LXI was treated with refluxing aqueous sodium carbonate solution it was quantitatively recovered unchanged. This is strong evidence that the lactone XLVII could not have been derived via the aziridine LXIV under these conditions. Under somewhat more severe conditions the aziridine LXIV conceivably

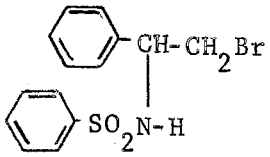


LXV



LXIV

could arise from the hypothetical endo-bromo compound depicted by LXV, since formation of the N-p-toluenesulfonylaziridine LXVI was accomplished

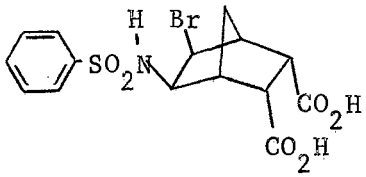


LXVII

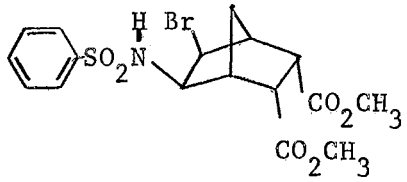
LXVI

by Kharasch[21] by treatment of LXVII with potassium hydroxide in absolute ethanol. However, the fact that LXIII was unaffected by the sodium carbonate solution shows that LXIV could not be formed from LXI under the conditions employed to convert LXI to XLVII.

The dimethyl ester LXIII was obtained by acetone-water hydrolysis of the anhydride LXI to yield the diacid LXVIII which was then esterified



LXVIII



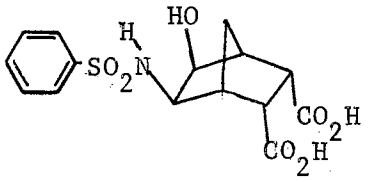
LXIII

by treatment with ethereal diazomethane.

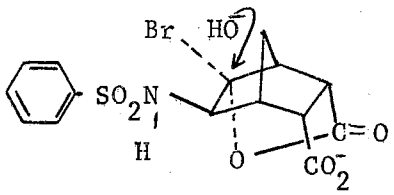
The bromo and sulfonamido groups of LXIII were also shown to be cis-exo, as depicted, by nuclear magnetic resonance[44] (see Chapter IV).

When the adduct LXI was treated with refluxing 20% sodium hydroxide solution a compound assigned the structure depicted by LXIX was obtained,

The infrared spectrum, neutralization equivalent and elemental analysis of LXIX showed it to have the empirical formula $C_{15}H_{17}O_7NS$, and to contain one hydroxy, one benzenesulfonamido and two carboxy groups. Since no skeletal rearrangement would be expected to occur under basic conditions and LXIX could not be lactonized on pyrolysis or treatment with acid, the hydroxy group must have <u>exo</u> stereochemistry. The diacid LXIX



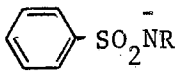
LXIX



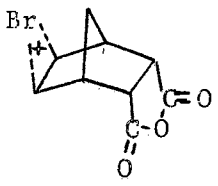
LXX

could arise via an intermediate such as LXX in which neighboring group participation by the carboxylate ion has lengthened the bond length of the carbon-bromine bond to such an extent that attack by a hydroxyl ion from the <u>exo</u> side could occur to yield LXIX.

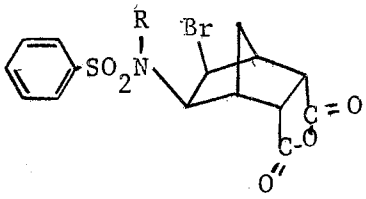
The formation of the adduct LXI by an ionic mechanism can be explained by an initial heterogeneous cleavage of one of the two nitrogen-bromine bonds of LX to yield a bromonium ion and the anion LXXI. Assuming an initial attack by the bromonium ion on XIX to give



LXXI



LXXII



LXXIII

the intermediate LXXII, the anion then would be expected to attack the intermediate LXXII to yield the <u>exo-cis</u> adduct LXXIII. An analogy[45] to this <u>cis</u> ionic addition reaction is the ionic addition of bromine to XIX to yield the <u>exo-cis</u> dibromide LII described above (see p. 21). In both addition reactions to form LXXIII and LII, the anhydride group

apparently offers more steric hindrance to the normal trans-addition[46,48] than does the bromine to cis addition (see p. 21). The substituent on the sulfonamido nitrogen of the anion LXXI is represented by R since it is not known at what stage in the formation of LXI hydrogen is substituted for one of the bromine atoms of LX.

Experimental

The reaction of N-bromosuccinimide (NBS) with bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride (XIX) --

N-Bromosuccinimide (8.90 g.(50 mmole), Eastman reagent grade), the bicyclic alkene XIX (8.20 g. (50 mmole), Fisher reagent grade), benzoyl peroxide (0.1 g.), and carbon tetrachloride (35 ml., Fisher reagent grade), were refluxed for 2.5 hr. in a 50-ml. round bottom flask fitted with a condenser which had been thoroughly dried and fitted with a drying tube. The initially heterogeneous mixture became homogeneous after refluxing 0.5 hr. and eventually became turbid after about 1.0 hr. of refluxing. The light brown colored solution A was cooled after the 2.5 hr. reflux period. The solution A was worked up either by the addition of water, by the addition of methanol or by distillation as described below.

1. Water (20 ml.) was added dropwise with stirring to cooled solution A, whereupon there was a vigorous evolution of gas. This gas was identified as carbon dioxide by the formation of a precipitate on bubbling the gas through a saturated solution of $Ba(OH)_2$. The stirring was stopped after no further evolution of gas could be detected and the mixture separated into three layers, an aqueous layer (top), a carbon tetrachloride layer (bottom) and a viscous oily layer (middle) in which, on standing 24 hrs., crystalline solid formed. After 48 hr. the aqueous layer was decanted off and the carbon tetrachloride layer was removed using a pipette. The remaining viscous oil layer was extensively extracted with ten portions (20 ml. each) of ether, with vigorous stirring, for about 15 min. The remaining ether-insoluble

solid was leached twice with 10-ml. portions of acetone. The undissolved adduct diacid XXV, 0.58 g., gave m.p. 225-227°, ν_{max}^{KBr} 1772, 1728, and 1688 cm^{-1} (adduct "A"*) or 1750, 1700, and 1662 cm^{-1} (adduct "B"*).

The ether and acetone solutions from the above extractions were combined and evaporated on a steam bath to an oily solid and the above extraction procedure was repeated on this material to yield an additional 0.70 g. of XXV, m.p. 224-227°. An additional repetition of this procedure yielded 0.33 g. more of XXV, m.p. 223-225°. The combined yield of XXV was 1.61 g. (4.5 mmole). Both adducts "A" and "B" gave $\nu_{max}^{dioxane\ soln.}$ 1746, 1738, and 1710 cm^{-1}. Evaporation of the dioxane solutions of adducts "A" and "B" both yielded adduct "B". An analytical sample of adduct "B", m.p. 227-228°, was prepared by recrystallization from a 1:1 (v/v) ethanol-water solution. The infrared spectra of adduct "B" did not change on recrystallization.

Anal. Calcd. for $C_{13}H_{14}O_6NBr$: C, 43.31; H, 3.89; N, 3.89; Br, 22.23. Found: C, 43.49; H, 3.97; N, 4.10; Br, 22.00.

The same dimethyl ester XXVI was obtained from adducts "A" and "B" by treatment of the adducts with an excess of ethereal diazomethane until the yellow color of the diazomethane persisted. The ether was allowed to evaporate in air to a viscous oil which crystallized on addition of a small amount of 95% ethanol. The white crystalline solid gave m.p. 140°. An analytical sample, m.p. 140°, was prepared by recrystallization of the diester XXVI from 95% ethanol and drying

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*Two adducts, "A" and "B", which were shown to be crystalline modifications of each other, might both be obtained as a mixture or either one might be obtained separate from the other, unpredictably, under presumably identical conditions as described above. Both adducts "A" and "B" gave the same melting point and the melting point was not depressed on admixture. They differed only in their infrared spectra.

at 100° and 1 mm pressure for 5 hr. ν_{max}^{KBr} (weak) 1775, 1734, and 1707 cm^{-1}.

Anal. Calcd. for $C_{15}H_{18}O_6NBr$: C, 46.39; H, 4.68. Found: C, 46.57; H, 4.67.

2. Methanol (20 ml.) was added slowly, with stirring, to cooled solution A. Methyl β-bromopropionylcarbamate (XXIV) crystallized when the solution was cooled in an ice bath. After allowing the solution to stand at room temperature for 6 hr., filtration yielded the carbamate XXIV, 4.75 g., m.p. 133-135°. On partial evaporation of the filtrate from the above, additional carbamate crystallized, 0.77 g., m.p. 134-136°. A total of 5.52 g. (25.3 mmole) of XXIV was obtained. More solid which was probably the carbamate crystallized from the filtrate on further evaporation, but it was not collected. Recrystallization of the carbamate XXIV from methanol gave m.p. 138-138.5° (reported[34,35,36] 138-139°). ν_{max}^{KBr} 3250, 3130, 1795, 1755, and 1693 cm^{-1}. An authentic sample prepared as previously described[36] gave m.p. 136-137° and an identical infrared spectrum.

The filtrate from above was evaporated to a viscous oil with a stream of air. The oil, in an open beaker, was stirred with water (20 ml.) and enough acetone to keep the mixture homogeneous. The solution was then allowed to evaporate in air to give a viscous oil after four days. This hydrolyzed oil was treated with 6 g. of diazomethane in ether solution (approx. 100 ml.) in which complete solution was evaporated off on a steam bath the remaining ether solution was dried over anhydrous magnesium sulfate for 2 hr. One eighth of this dried ether solution was allowed to stand at 0° for 2 months. During this time a fraction of the dimethyl ester XXVI corresponding to the

adduct XXVII crystallized, 0.140 g. (0.36 mmole), m.p. 140°. υ_{max}^{KBr} (weak) 1775, 1734, and 1707 cm^{-1}. The mother liquor was concentrated in vacuo at room temperature to a small volume (approx. 2 ml.) and chromatographed on Merck acid-washed alumina (175 g. in a column 2.5 x 45 cm.) using chloroform as the eluent. The dimethyl ester XXVIII of bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic acid was eluted with 400 ml. of chloroform. Evaporation of the chloroform yielded the diester XXVIII, 0.995 g. (4.75 mmole). υ_{max}^{film} 1737, 1438, 1367, and 1345 cm^{-1}. The infrared spectrum of a sample of XXVIII prepared by a previously described[49] procedure was identical. The diester XXVIII from the above chromatography gave only one spot with thin layer chromatography* on silica gel using ether (Rf 0.8) or ethanol (Rf 0.6) as a solvent. Authentic[49] XXVIII gave the same Rf values under corresponding conditions and combined samples gave only one spot when thin layer chromatographed together.

A second fraction was eluted from the above column chromatograph by an additional 125 ml. of chloroform. Evaporation of the chloroform yielded an oil, B, 0.378 g. Thin layer chromatography of oil B on silica gel with ether as eluent gave one major spot (Rf 0.35) and two minor spots** (Rf 0.45). Quantitative thin layer chromatography of oil B showed that 92% of oil B, based on recovered material from the preparative thin layer chromatograph, was the adduct diester XXVI, 0.348 g. (0.90 mmole). The infrared spectrum and Rf of the adduct

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*I_2 vapor was used to develop the compounds on all thin layer chromatographs described.

**These two spots could be resolved only by allowing the solvent front to move 20 cm.

diester XXVI from thin layer chromatography agreed identically with those of pure adduct diester XXVI.

Further elution of the above column chromatograph with chloroform yielded no additional material.

The quantities of materials obtained from the column chromatograph, multiplied by a factor of eight, represent a total of 7.92 g. (38.0 mmole) of the diester XXVIII and 3.9 g. (10.1 mmole) of the adduct diester XXVI that were recovered by the above sequences from 50 mmole each of NBS and the alkene XIX.

3. The carbon tetrachloride was removed from cooled solution A in vacuo (38 mm) at room temperature. The residue was filtered to remove the precipitated solid and the filtrate was distilled at 25 mm pressure, to yield β-bromopropionyl isocyanate (XXIII), approx. 1.25 g. (using estimated density of 1 g./ml.) (7.0 mmole), b.p. approx. 69°. υ_{max}^{film} 2450, 1725, and 1410 cm^{-1}. An authentic sample of the isocyanate XXIII prepared as previously described[36] gave an identical infrared spectrum. The residue remaining after distillation of the isocyanate was estracted with 4 portions (50 ml. each) of ether, dissolved in acetone (100 ml.) containing a small amount of conc. sulfuric acid (2 ml.), and left open to the atmosphere for 6 days during which time the adduct diacid XXV crystallized, 0.83 g. (2.3 mmole), m.p. 226-227°. υ_{max}^{KBr} 1750, 1700, and 1662 cm^{-1}.

Reaction of NBS with bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride (XIX) with no radical initiator present

1. N-Bromosuccinimide (17.8 g. (100 mmole), Eastman reagent grade), the bicyclic alkene XIX (16.4 g. (100 mmole), Fisher reagent

grade), and carbon tetrachloride (65 ml.) were refluxed, open to the atmosphere, for 3 hr. The resulting mixture was heated to boiling in an open beaker with carbon tetrachloride. The undissolved solid was allowed to settle and the clear liquid was decanted off. This washing procedure was repeated 5 times using 50-ml. portions of carbon tetrachloride. The solid which was insoluble in hot carbon tetrachloride was unreacted NBS, 13.2 g. (74.5 mmole), m.p. 170-173° (m.p. of starting NBS, 171-173°). An admixture with the NBS used as starting material did not depress the melting point. The recovered NBS gave υ_{max}^{KBr} 1815, 1785, and 1705 cm^{-1} -- the same as for authentic NBS. The combined hot carbon tetrachloride extracts were evaporated to dryness to give the starting alkene XIX, 14.4 g. (88 mmole), m.p. 165-167° (m.p. of starting alkene XIX 170°). Admixture with starting alkene gave m.p. 165-169°.

2. N-Bromosuccinimide (17.8 g. (100 mmole), same source as above), the bicyclic alkene XIX (16.4 g. (100 mmole), same source as above), and carbon tetrachloride (65 ml.) were refluxed for 3 hr. The reaction mixture was allowed to cool and the unreacted starting material* was removed by filtration. Water (50 ml.) was added to the filtrate. No reaction occurred on the addition of water and no reaction products could be isolated. The above reaction mixture remained clear, except for undissolved starting material, for the duration of the reaction period as contrasted to the marked brown color attained when radical initiator was present**. A duplicate of the

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*Identified as above.

**As described on p. 27.

above (no radical initiator present) was refluxed for 12 hr. with no color change.

Attempted elimination of the bromo and succinimido groups from XXVII as a rearrangement product, β-bromopropionyl isocyanate (XXIII)

A mixture of the NBS adduct XXVII (2.0 g. (5.85 mmole), m.p. 197-197.5° [dried at 144° and 1 mm pressure for 2 hr.]), benzoyl peroxide (0.05 g.) and 3.7 ml. of carbon tetrachloride were refluxed together in a dry 25-ml. flask, fitted with a condenser and drying tube, for 24 hr. The reaction mixture remained heterogeneous during the reflux period, after which the hot mixture was filtered. The starting anhydride was recovered in quantitative yield unchanged, the melting point and infrared spectrum of the recovered material being the same as those of the starting anhydride XXVII. When water was added to the hot filtrate there was no visible evolution of a gas.

The reaction of bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride (XIX) with carbon tetrachloride under free-radical conditions

A mixture of the bicyclic alkene XIX (4.1 g. (25.0 mmole), Eastman reagent grade), benzoyl peroxide (0.262 g. (1.0 mmole), Fisher reagent grade) and carbon tetrachloride (30.8 g. (200 mmole), Fisher reagent grade) were heated at reflux for 18 hr. The mixture was homogeneous after only a few minutes of refluxing; however, at the end of the 18-hr. reflux period a viscous brown oil precipitate had formed. The mixture was cooled and 15 ml. of water was added along with enough acetone to keep the mixture homogeneous. The mixture was stirred, open to the atmosphere, for 6 days during which time all of the solvent

evaporated. The resulting product was treated with an excess of ethereal diazomethane until the yellow color of the diazomethane persisted. The ether solution was dried over anhydrous sodium sulfate and evaporated on a steam bath to yield an oil; a sample of this oil was thin layer chromatographed on silica gel using ether as the eluent. Only one spot* was detected, Rf 0.8. The same Rf was obtained under identical conditions for authentic** dimethyl bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylate (XXVIII).

Duplicates of the following were run. A mixture of the alkene XIX (4.1 g. (25.0 mmole), same source as above), benzoyl peroxide (0.050 g. (0.19 mmole), same source as above) and 17 ml. of carbon tetrachloride were heated to reflux for 3 hr. This solution was cooled, hydrolyzed and treated with diazomethane as above. The diazomethane solution was dried over anhydrous sodium sulfate and evaporated to yield an oil which gave only one spot, Rf 0.8, when thin layer chromatographed as above.

exo-5-Bromo-exo-6-succinimidobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic anhydride (XXVII)

The same anhydride XXVII was obtained from either adduct "A" or "B" by the following procedure. The diacid XXV, either adduct "A" or "B", (4.00 g. (11.12 mmole), m.p. 225-226°) and acetic anhydride (40 ml., Fisher reagent grade) were heated to reflux, then the mixture was distilled at 45 mm pressure (approximately 10 ml. remained undistilled). The undistilled residue was cooled and 100 ml. of carbon tetrachloride

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*Developed with iodine vapor.
**See p. 30.

was added. At first, oily crystals separated out and stuck to the sides of the flask. The remainder of the solution was decanted and cooled in an ice bath. White needle-like crystals of the anhydride XXVII formed in the decanted solution. After air drying, the anhydride XXVII, 2.23 g. (6.5 mmole), gave m.p. 197-197.5°. υ_{max}^{KBr} 1850, 1785, and 1707 cm^{-1}. An additional recrystallization from acetic anhydride and carbon tetrachloride did not raise the melting point.

The anhydride XXVII (0.25 g.) was hydrolyzed back to the diacid XXV by heating on a steam bath in a mixture of carbon tetrachloride (30 ml.), water (30 ml.) and acetone (5 ml.) until a volume of approximately 30 ml. remained. On cooling, white crystals of the diacid XXV formed. After air drying, the diacid XXV gave m.p. 224-226°, υ_{max}^{KBr} 1772, 1750, 1728, shoulder at approx. 1700, 1688, and a shoulder at approx. 1662 cm^{-1}. This was apparently a mixture of adducts "A" and "B". Admixture of the diacid obtained by hydrolysis of the anhydride with either pure adduct "A" or adduct "B" did not depress the melting point.

Concentrated hydrochloric acid hydrolysis of exo-5-bromo-exo-6-succinimidobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic acid (XXV)

A mixture of the adduct diacid* XXV (5.000 g. (13.9 mmole), m.p. 225-227°) and conc. hydrochloric acid (150 ml.) in a 300-ml. flask equipped with an efficient condenser was refluxed for 17.5 hr.; this solution was then continuously extracted with ether for 24 hr. Evaporation of the ether solution yielded succinic acid (XXX), 1.0 g. (8.3 mmole) m.p. 188.5° (reported[50] 189-190°). $\upsilon_{max}^{Nujol\ mull}$ 1730, 1710,

*Either adduct "A" or adduct "B" gave the same results.

and 1695 cm^{-1}. Admixture with an authentic sample (Matheson, Coleman and Bell) of succinic acid did not depress the melting point. The commercially available succinic acid gave an identical spectrum.

Evaporation of the aqueous solution on a rotary evaporator gave XXXI, 3.91 g., υ_{max}^{KBr} 2700-3000, 1720, 1590, 1507, and 1400 cm^{-1}. The salt XXXI (1.00 g.) dissolved in water (100 ml.) was passed through Amberlite IR-4B (45 g. (wet wt.) in a column 3 cm. in diameter) in a manner analogous to that described by Meyers and Miller.[51] The column was eluted with 1.0 l. of doubly distilled water. Evaporation of the effluent on a rotary evaporator gave the lactone zwitterion XXXIV, 0.305 g. (1.6 mmole); the compound starts decomposing above 310° but sublimes unchanged at 300° and 38 mm pressure. υ_{max}^{KBr} 3550, 2700-3000, 1775, 1590, and 1407 cm^{-1}. Sodium nitrite (0.5 g.) was added slowly to XXXI (0.500 g.) dissolved in 20% hydrochloric acid (10 ml.), and the solution heated on a steam bath for 20 min. On standing the known[38] bromolactone acid XXXII crystallized, 0.072 g. (0.28 mmole) m.p. 183.5-184.5° (reported[39] 186°). Admixture with an authentic sample prepared as previously reported[38] did not depress the melting point. υ_{max}^{KBr} 1750 and 1735 cm^{-1} after drying 8 hr. at 144° and 1 mm pressure.

Anal. Calcd. for $C_9H_9O_4Br$: C, 41.40; H, 3.47; Br 30.61. Found: C, 41.22; H, 3.49; Br 31.50.

Water hydrolysis of exo-5-bromo-exo-6-succinimidobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic acid (XXV)

Either adduct "A" or "B" XXV (1.00 g. (2.78 mmole) m.p. 225-227°) in 50 ml. of distilled water was heated over a steam bath for 3 days.

The aqueous solution was evaporated to a volume of 10 ml. at the end of the 3-day hydrolysis period and extracted with ether by continuous extraction for 48 hr. Evaporation of the ether extract yielded succinic acid (XXX), 0.330 g. (2.78 mmole), m.p. 186°. Admixture of the succinic acid obtained from the ether extract with an authentic sample (see above) did not depress the melting point. The extracted aqueous hydrolysis solution, which gave a positive silver nitrate test for free halogen, was passed through Amberlite IR-4B(OH) as previously described[51] (25 g. (wet wt.) in a column 1.5 cm. in diameter). The column was eluted with 1.0 l. of water and the effluent was evaporated on a rotary evaporator to yield the lactone zwitterion* XXXIV, 0.455 g. (2.38 mmole), turns slightly brown above 310°. υ_{max}^{KBr} 3550, 2700-3000, 1775, 1590, and 1407 cm^{-1}. The lactone zwitterion XXXIV was recrystallized by dissolving it in a minimum amount of hot water and adding four times that volume of an equal mixture of ethanol and ether. Essentially 100% of the lactone zwitterion recrystallized on cooling the water-ethanol-ether mixture in an ice bath. No change in the infrared spectra occurred on recrystallization.

When sodium nitrite (0.670 g.) was added to the ether-extracted aqueous hydrolysis solution or to the lactone zwitterion XXIV (0.455 g., dissolved in 10 ml. of 5% hydrochloric acid) the dilactone XXXV formed and crystallized from solution, 0.25 g. (1.39 mmole), m.p. 268°. υ_{max}^{KBr} 1795 and 1770 cm^{-1}. An authentic sample prepared as previously described[52] gave identical infrared absorption.

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*The same lactone zwitterion XXXIV was obtained from either adduct "A" or "B" in essentially the same yield.

Pyrolysis of exo-5-bromo-exo-6-succinimidobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic acid (XXV)

The adduct diacid XXV (1.0 g. (2.78 mmole), m.p. 225-227°) was heated at 230° for 2 hr. in an open beaker using a heating bath made of potassium nitrate (80 g.) and sodium nitrate (65 g.). The melted adduct diacid XXV resolidified after 5 to 10 min. at 230°. The anhydride XXXIX sublimed on heating this solid at 235° and 35 mm pressure. Sublimation at these conditions for 5 hr. yielded 0.095 g. (0.284 mmole) of the anhydride XXXIX, m.p. 110-111°, ν_{max}^{KBr} 1862, 1780, and 1705 cm^{-1}. Resublimation did not raise the melting point.

Anal. Calcd. for $C_{13}H_{12}O_5NBr$: C, 45.63; H, 3.54, Found: C, 45.13; H, 3.93.

The anhydride XXXIX gave a positive Beilstein test, a neutralization equivalent of 176 when titrated with sodium hydroxide (phenolphthalein end point) and a neutralization equivalent of 334 when titrated with sodium ethoxide in absolute ethanol (phenolphthalein end point). Calcd. mol. wt. 342.17.

After the sublimation of the anhydride XXXIX appeared complete, the bath temperature was raised to 280° (35 mm pressure) and the lactone XXXVIII sublimed, 0.070 g. (0.252 mmole), m.p. approx. 338° with decomposition, ν_{max}^{KBr} 1775, 1728, and 1670 cm^{-1}. The lactone XXXVIII gave a negative Beilstein test.

Anal. Calcd. for $C_{13}H_{13}O_6N$: C, 55.91; H, 4.69. Found: C, 56.34; H, 4.96.

endo-5-Hydroxy-exo-6-succinimidobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic acid γ-lactone hydrate (XXXVII) and its pyrolysis product XXXVIII

The adduct diacid* XXV (1.00 g. (2.78 mmole), m.p. 225-227°) and dry pyridine (10 ml., Eastman reagent grade -- freshly distilled from potassium hydroxide) were refluxed together for 2 hr., in a 25-ml. flask fitted with a condenser and drying tube. The pyridine was then evaporated on a rotary evaporator and the residue oil was dissolved in 5 ml. of water. The aqueous solution was filtered and acidified with 5 ml. of conc. hydrochloric acid. On standing at room temperature for 6 hr. light amber-colored crystals of the lactone hydrate XXXVII formed, 0.475 g., m.p. 265-270° (by raising the temp. 15°/min.). Recrystallization from a one-to-one mixture of acetone and water did not raise the melting point nor change the color of the crystals. ν_{max}^{KBr} 1767, 1712, and 1697 cm^{-1}. When the lactone hydrate XXXVII was heated slowly, water of hydration appeared to be given off starting at about 252°. By raising the temperature slowly the lactone hydrate XXXVII melted at about 252-257°, then resolidified at about 275° after the water was given off. After the melt reached a temperature of approximately 270°, it started to sublime. The sublimate and the pyrolysis product were both identical to the lactone XXXVIII obtained from pyrolysis** of XXV, m.p. above 330°. ν_{max}^{KBr} 1775, 1728 and 1670 cm^{-1}.

The same lactone hydrate XXXVII was obtained in lower yield by refluxing the adduct diacid XXV, 1.55 g. (4.3 mmole), and aqueous 5%

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*Either adduct, "A" or "B".

**Described on p. 38.

sodium carbonate (30 ml.) for 3 hr. The product was isolated by acidification with excess conc. HCl and continuous extraction of the aqueous solution with ether for 10 days. The ether was evaporated from the extract and water (100 ml.) was added to the solid product. The water-insoluble compound was the lactone hydrate XXXVII, m.p. 250-255°, 0.1 g. (estimated). υ_{max}^{KBr} 1767, 1712, and 1697 cm^{-1}. It is noted that this yield probably could be increased by using less sodium carbonate solution (approx. 5 ml.) for the lactonization, from which the lactone hydrate XXXVII would probably crystallize on acidification with conc. hydrochloric acid.

Benzenesulfonation of endo-5-hydroxy-exo-6-aminobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic acid-γ-lactone (XXXIV)

The lactone zwitterion XXXIV (0.204 g. (1.07 mmole), prepared as described above) and benzenesulfonyl chloride (0.183 g. (107 mmole), Eastman reagent grade) were stirred in 5% aqueous sodium hydroxide (20 ml.) for 12 hrs. at room temperature. The solution was then made acidic with conc. hydrochloric acid and extracted with one 100-ml. portion of ether. After drying the ether solution over anhydrous sodium sulfate and evaporation to approximately 5 ml., the benzenesulfonamide XLVII crystallized, 0.050 g. (0.152 mmole), m.p. 188-190°. Recrystallization of an analytical sample of XLVII from ether gave m.p. 194.5-195.5°. υ_{max}^{KBr} 3240, 1780, and 1703 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}O_6NS$: C, 53.40; H, 4.48; N, 4.15. Found: C, 53.52; H, 4.49; N, 3.95. It is noted that only one ether extraction of the aqueous solution containing the benzenesulfonamide XLVII was made. Continuous ether extraction undoubtedly would have

given a higher yield of XLVII since it is only slightly soluble in ether.

The addition of N,N-dibromobenzenesulfonamide (LX) to bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride (XIX)

A mixture of N,N-dibromobenzenesulfonamide (LX) (4.53 g. (14.5 mmole), m.p. 114°, prepared as previously described[53]), the bicyclic alkene XIX (5.86 g. (35.7 mmole), Eastman reagent grade) and carbon tetrachloride (100 ml.) were stirred together at room temperature for 5 min. in a flask equipped with a heating mantle, magnetic stirrer and a condenser fitted with a drying tube. The mixture was then heated, with stirring, to reflux; the heat was then removed, but the reaction mixture continued to reflux, owing to the heat of reaction, for several minutes. As the reaction proceeded during the reflux period a light tan colored viscous oil precipitated. More of this viscous oil precipitated as the reaction mixture cooled to room temperature. The mixture was then evaporated on a rotary evaporator until the residue began to foam. Chloroform (50 ml.) was added to the residue and the solution was again evaporated until the residue began to foam. The procedure was repeated twice more to remove as much of the carbon tetrachloride as possible, then the residue was dissolved in 50 ml. of chloroform and allowed to stand at room temperature, open to the atmosphere, for 12-18 hr. The adduct LXI crystallized during this period (1.301 g. (3.07 mmole), m.p. 228-230°). Extraction of the adduct LXI with hot acetyl chloride raised the melting point to 230-233°. An analytical sample was prepared by drying the extracted adduct at 144° and 1 mm pressure for 5 hr. υ_{max}^{KBr} 3250, 1760, and 1778 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}O_5NSBr$: C, 45.01; H, 3.53; Br, 19.97. Found: C, 45.16; H, 3.66; Br, 20.42.

When the above procedure was repeated using as a free radical trap, either anthracene (0.25 g.), p-dinitrobenzene (0.25 g.), chloranil (0.75 g.) or a stream of oxygen (bubbled through the reaction mixture) in the reaction mixture, which was otherwise the same as described above, the adduct LXI was obtained in yields greater than when no radical inhibitor was present, the highest of which was from the reaction using anthracene as a radical trap, (1.589 g. (3.70 mmole), m.p. 224-226°). The infrared spectrum of the adduct isolated from each of the reactions employing the above radical retarders was identical to that of the adduct from the unretarded reaction as described above. The use of chloranil as a radical retarder is inconvenient because of its low solubility in chloroform. It is difficult to separate the chloranil from the adduct; however, the other radical retarders mentioned above did not require alteration of the adduct isolation procedure described above.

When the above reaction, with no free radical retarder, was repeated in the dark, the reaction was again exothermic after the reaction mixture was heated to reflux. The same adduct LXI was obtained from the reaction in the dark as was obtained when the reaction was run in the light and in essentially the same yield.

The same adduct LXI was also formed when the bicyclic alkene XIX and the N,N-dibromoamide LX were stirred together in carbon tetrachloride (same quantities as above) at room temperature for seven days.

The diacid LXVIII was prepared by heating the anhydride LXI (0.50 g.) in an open beaker with water (10 ml.) and acetone (10 ml.)

until the compound dissolved. On cooling, the diacid LXVIII precipitated, 0.33 g., m.p. 198-200°, ν_{max}^{KBr} 3250 and 1720 cm^{-1}. The diacid gave a positive Beilstein test for halogen.

Anal. Calcd. for $C_{15}H_{16}O_6NSBr$: N, 3.14. Found: N, 305.

The dimethyl ester LXIII of the diacid LXVIII was prepared by treating the diacid with excess etheral diazomethane until the yellow color of the diazomethane persisted. By allowing the ether solution to slowly evaporate in air, the dimethyl ester crystallized from solution as large clear crystals, m.p. 130-130.5°. Recrystallization from ether did not raise the melting point. An analytical sample was prepared by drying the dimethyl ester for 5 hr. at 100° and 1 mm pressure. ν_{max}^{KBr} 3220, 1738, and (shoulder) 1723 cm^{-1}.

Anal. Calcd. for $C_{17}H_{20}O_6NSBr$: C, 45.74; H, 4.51; N, 3.13. Found: C, 45.97; H, 4.94; N, 3.05.

endo-5-Hydroxy-exo-6-benzenesulfonamidobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic acid-γ-lactone (XLVII) from the anhydride LXI

The anhydride LXI (0.5 g. (1.25 mmole), prepared as described above), and aqueous 5% sodium carbonate (20 ml.) were refluxed for 45 min. The hydrolysis solution was then made acidic with excess conc. hydrochloric acid (approx. 5 ml.) and continuously extracted with ether for 12 hr. Evaporation of the ether extract to a small volume (approx. 5 ml.) yielded white crystals, (0.27 g. (0.82 mmole), m.p. 188-190°), ν_{max}^{KBr} 3240, 1780, and 1703 cm^{-1}. The melting point of the benzenesulfonamide XLVII was raised to 193.5-194.5° by washing the crystals with a small amount of ether (5 ml.). Admixture of the benzenesulfonamide obtained by this procedure and the one obtained by benzenesulfonylation

of the lactone zwitterion XXXIV did not depress the melting point. The infrared spectra of the two were identical.

Strong base hydrolysis of exo-5-bromo-exo-6-benzenesulfonamidobicyclo-[2.2.1]heptane-endo-cis-2,3-dicarboxylic anhydride (LXI)

The anhydride LXI (0.50 g. (1.25 mmole), prepared as described above) and aqueous 20% sodium hydroxide (25 ml.) were refluxed 2 hr. The hydrolysis solution was acidified with excess conc. hydrochloric acid. Continuous extraction of the acidic solution with ether for 12 hr. yielded LXIX as white plate-like crystals, (0.31 g. (0.86 mmole), m.p. 235-235.5°), υ_{max}^{KBr} 3380, 3220, 2500-3000, and 1700 cm^{-1}. The compound LXIX gave a negative Beilstein test and a neutralization equivalent of 179.6 (calcd. for two carboxyls and $C_{15}H_{17}O_7SN$, 177.7).

Anal. Calcd. for $C_{15}H_{17}O_7SN$: C, 50.70; H, 4.68; N, 9.01. Found: C, 50.71; H, 4.68; N, 9.05.

CHAPTER II

N-ALKYL CLEAVAGE OF BICYCLIC γ-LACTAMS BY ACID HYDROLYSIS

Historical and Introduction

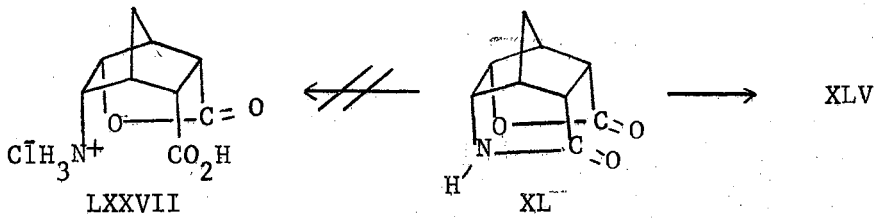
Previously N-alkyl amides of the type RCONR'R" (R and R' = alkyl, aryl or hydrogen; R" = alkyl) have been assumed to hydrolyze under acidic conditions only via N-acyl cleavage.[54] In fact it has been stated that the hydrolysis of N-substituted amides necessarily involves N-acyl, rather than N-alkyl, bond breakage and if this were not so, alcohols, rather than amines, would be formed in such solvolyses.[54]

Usually N-alkyl sulfonamides are cleaved at the sulfur-nitrogen bond by acid hydrolysis, but when the nitrogen atom is substituted by an alkyl group that forms a stable carbonium ion, N-alkyl cleavage takes place and dealkylated sulfonamides are obtained.[55] For example N-t-butyl-p-toluenesulfonamide (LXXIV) gave t-butyl chloride (LXXV) and

$$\underset{\text{LXXIV}}{p\text{-}CH_3C_6H_4SO_2NHC(CH_3)_3} \longrightarrow \underset{\text{LXXVI}}{p\text{-}CH_3C_6H_4SO_2NH_2} + \underset{\text{LXXV}}{(CH_3)_3CCl}$$

p-toluenesulfonamide (LXXVI) on hydrolysis with hydrochloric acid whereas N-isopropyl-p-toluenesulfonamide remained unchanged under the same conditions.[56]

In an attempt to obtain the lactone amino acid salt LXXVII by acid hydrolysis of the lactone-lactam XL, a lactone acid XLV containing no nitrogen was isolated.[57] This observation led to an investigation

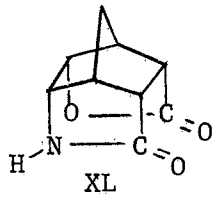


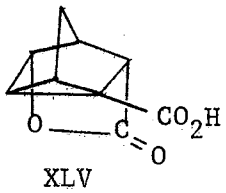
LXXVII XL

of the acid hydrolysis of XL and other bicyclic γ-lactams.

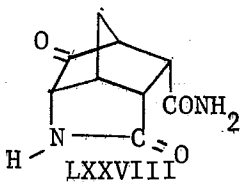
Results and Discussion

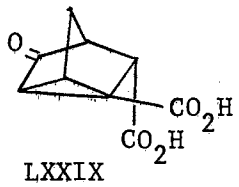
When the lactone-lactam XL was subjected to refluxing 5% hydrochloric acid, N-alkyl cleavage occurred and the previously described[52,58] tricyclo lactone acid XLV was isolated in 85% yield.[40] By making the hydrolysis solution basic, 99% of the theoretical nitrogen content resulting from N-alkyl cleavage was obtained as ammonia. In a similar


XL


XLV

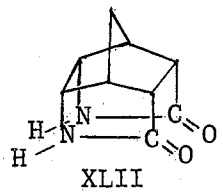
manner the keto carbamoyl lactam LXXVIII gave N-alkyl cleavage of the lactam to yield LXXIX which was converted into XLV by reduction with

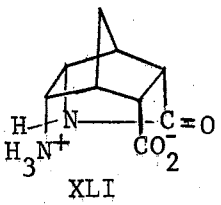

LXXVIII


LXXIX

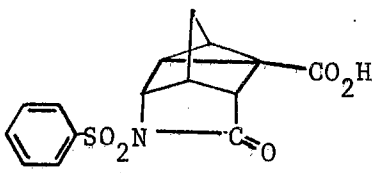
sodium borohydride.[40] The nitrogen content of LXXVIII was also obtained quantitatively as ammonia when the acidic hydrolysis solution containing LXXIX was made basic. The tricyclo ketone LXXIX has been previously prepared by oxidation of XLV.[52]

The dilactam XLII had been previously shown to yield the lactam zwitterion XLI by mild acid hydrolysis at room temperature for seven days followed by passage through an ion exchange column.[41] However, when XLII was refluxed in 5% hydrochloric acid mono-N-alkyl cleavage

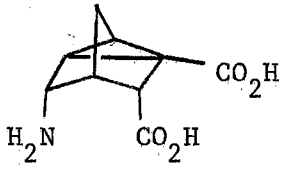

XLII


XLI

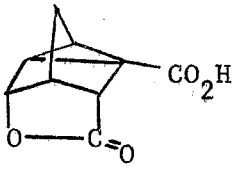
occurred to yield the tricyclo amino diacid LXXX. In this case, 49% of the nitrogen content of XLII was liberated as ammonia when the acidic hydrolysis solution containing LXXX was made basic. The amino diacid LXXX was converted to XLV by treatment of the acidic hydrolysis solution with sodium nitrite. Treatment of the acidic solution of LXXX with benzenesulfonyl chloride and excess sodium hydroxide for



LXXXI



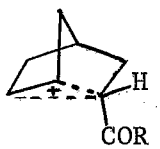
LXXX



XLV

several hours followed by acidification, ether extraction of the acidic solution and evaporation of the ether extract gave a residue which when heated <u>in vacuo</u> yielded the crystalline N-benzenesulfonyl lactam LXXXI. The structure of LXXXI is based on its elemental analysis, infrared spectrum, the ammonia recovered from acid hydrolysis of the dilactam XLII (which corresponded to one N-alkyl cleavage) and the subsequent isolation of the known[52,58] derivative XLV.

Each of the above N-alkyl cleavages occurs in a molecule which can form a stable non-classical carbonium ion intermediate such as the one depicted by LXXXII. This in turn can lose a proton alpha to the carbonyl group to yield a cyclopropane derivative. The quantitative



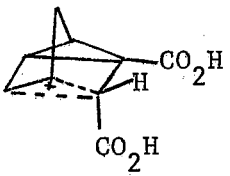
R = NH_2 or OH

LXXXII

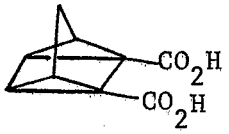
evolution of theoretical yields of ammonia in each case, as described above, indicates that hydrolysis of the γ-lactams occurs only by N-alkyl

cleavage with the exception of one of the lactam groups in the dilactam XLII. The conversion of the lactone zwitterion XXXIV to its hydrochloride LXXXIII under the conditions employed above for N-alkyl cleavages indicates that N-alkyl cleavage does not occur via the amino acid. Also, the fact that LXXX is stable under these conditions bears this out.

The mono-N-alkyl cleavage of the dilactam may be explained by the fact that once the first N-alkyl cleavage has occurred to yield a cyclopropane derivative, a second N-alkyl cleavage in the same bicyclic system may not be stabilized by an intermediate non-classical carbonium ion depicted by LXXXIV. The known dicyclopropane LXXXV is



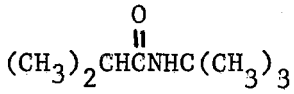
LXXXIV



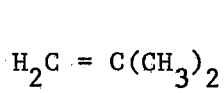
LXXXV

so unstable that it reacts with water and ethanol at room temperature.[59]

Thus, the major requirement for N-alkyl cleavage appeared to be the formation of a stable carbonium ion intermediate. This hypotehsis was supported by the observation that acid hydrolysis of N-t-butylisobutyramide LXXXVI gave 75% of the theoretical yield of isobutylene LXXXVII.[40]



LXXXVI



LXXXVII

Experimental

endo-5-Hydroxytricyclo[2.2.1^{2,6}]heptane-2-carboxy-endo-3-carboxy-γ-lactone (XLV)

The lactone-lactam XL (0.75 g., m.p. 191-192.5°) prepared as previously described[41] was refluxed for 6 hr. in 5% hydrochloric acid (20 ml.). The product was isolated as long white needles by concentrating the solution to a small volume and cooling. Recrystallization from water gave XLV, 0.61 g., m.p. 207-207.5°. Admixture with an authentic sample* of XLV did not depress the melting point. The lactone acid gave ν_{max}^{KBr} 3090, 1780, and 1722 cm^{-1}, as did the authentic sample* of XLV.

The aqueous solution left after removal of the lactone acid XLV was made basic and steam distilled. The ammonia liberated was collected in a buffer solution** and titrated with standard acid using a modified** micro-Kjeldahl procedure[60] and 99% of the theoretical nitrogen content resulting from N-alkyl cleavage was detected as ammonia.

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*Kindly supplied by Dr. P. Wilder, Jr.

**The buffer solution (100 ml.) was made up of a 2% solution of boric acid (adjusted to Ph 5 using 0.2N NaOH) containing 1 ml. of indicator made by dissolving brom-cresol green (83 mg.) and methyl red (17 mg.) in 95% ethanol (100 ml.).

Acid hydrolysis of 5-keto-endo-6-aminobicyclo[2.2.1]heptane-endo-3-carbamoyl-endo-2-carboxy-γ-lactam (LXXVIII)

The lactam LXXVIII (0.1 g., p.m. 235-236°) prepared as previously described by Worral[41] was refluxed for 6 hr. in 10% hydrochloric acid (20 ml.). The product was isolated as white crystals by concentrating the solution to a small volume and cooling. The keto diacid LXXIX obtained (0.071 g.) gave m.p. 238-238.5° (reported[58] 239°). ν_{max}^{KBr} 1778, 1718, and 1693 cm^{-1}. Recrystallization twice from water did not raise the melting point.

The aqueous solution left after removal of the keto diacid LXXIX was made basic and steam distilled. The ammonia liberated was determined as before; 100% of the theoretical amount was found.

Conversion of LXXIX to XLV.

The ketone LXXIX (0.048 g.) was added to a solution of 0.056 g. of sodium borohydride in one ml. of 50% ethanol. After standing at room temperature for 2 hr. the solution was made acidic with dilute hydrochloric acid and continuously extracted with ether for 10 hr. Evaporation of the ether left a solid which was heated in a sublimation tube at 170° and 44 mm for 3 hr. The residue (0.010 g.) was identical in melting point and infrared spectrum with an authentic sample of XLV.

Mono N-alkyl cleavage of endo-cis-5,6-diaminobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxy-γ-dilactam (XLII)

The dilactam XLII (0.10 g. (5.62 mmole), m.p. 207-210°) synthesized as previously described,[41] and 5% hydrochloric acid (10 ml.)

were refluxed together for 11 hr. This hydrolysis solution was treated with sodium nitrite (0.150 g.) and heated on a steam bath for 15 min. There was a vigorous evolution of gas when the solution was first heated. The solution was then evaporated to dryness in a rotary evaporator, redissolved in 20 ml. of water and continuously extracted with ether for 10 hr. The ether solution was evaporated on a rotary evaporator to a viscous oil. The addition of dry ether (5 ml.) caused the lactone acid XLV to crystallize, 0.056 g. (3.12 mmole), m.p. 205-206°, ν_{max}^{KBr} 3090, 1780, and 1722 cm^{-1}.

When the above hydrolysis solution, prior to the addition of sodium nitrite, was made basic and steam distilled, the liberated ammonia was determined as above to show 49% of theoretical yield.

N-Benzenesulfonyl-endo-5-aminotricyclo[2.2.1$^{2.6}$]heptane-2-carboxy-endo-3-carboxy-γ-lactam (LXXXI)

The dilactam XLII (0.150 g. (0.84 mmole), m.p. 207-210°) and 5% hydrochloric acid (15 ml.) were refluxed together for 6.5 hr. The solution was then cooled and made basic with solid sodium hydroxide (3 g.). Benzenesulfonyl chloride (1.51 g. (8.5 mmole), Eastman reagent grade) was added to the alkaline solution, which was stirred at room temperature for 12 hr. The solution was made acidic with conc. hydrochloric acid (15 ml.) and continuously extracted with ether for 12 hr. The ether extract solution was evaporated in a rotary evaporator and the residue was heated at 70-75° and 35 mm pressure for about 30 min. The addition of dry ether (approximately 30 ml.) to the dried residue caused the N-benzenesulfonyl lactam LXXXI to crystallize, 0.153 g. (0.48 mmole), m.p. 233-236°. An analytical sample was prepared by

recrystallization from absolute ethanol, m.p. 242-243°. Further recrystallizations did not raise the melting point. The analytical sample was dried for 3 hr. at 144° and 1 mm pressure and gave, ν_{max}^{KBr} 1753 and 1694 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}O_5NS$: C, 56.43; H, 4.08. Found: C, 56.54; H, 4.33.

endo-5-Hydroxy-exo-6-aminobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic acid-γ-lactone hydrogen chloride salt (LXXXIII)

The lactone zwitterion XXXIV (0.1 g.) was dissolved in conc. hydrochloric acid (5 ml.) and evaporated to dryness with heating in a rotary evaporator. The resulting hygroscopic salt LXXXIII was dried in vacuo over P_2O_5 for 4 days. The salt LXXXIII did not melt below 300°. ν_{max}^{KBr} 3400, 3200-2750, 1700, 1724, and 1410 cm^{-1}.

Anal. Calcd. for $C_9H_{12}O_4NCl$: C, 46.05; H, 5.54; N, 5.97. Found: C, 45.45; H, 5.40; N, 5.84.

N-Alkyl cleavage of N-t-butylisobutyramide (LXXXVI)

N-t-Butylisobutyramide* (0.800 g. (6.27 mmole), m.p. 115-117°) was added to a refluxing solution of 20% hydrochloric acid in a closed system containing a gas burette. After one hr., 94 ml. (4.2 mmole**) of gas was evolved. The gas was identical in its infrared spectrum with isobutylene. $\nu_{max}^{10\ cm.\ gas\ cell}$ 3060, 2925, 2730, 1775, 1650, 903, 887, and 870 cm^{-1}.

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*Kindly supplied by Dr. R. C. Freeman, Monsanto Chemical Co., St. Louis, Mo.

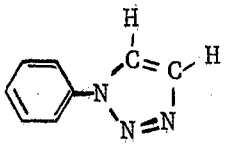
**Not corrected to standard conditions.

CHAPTER III

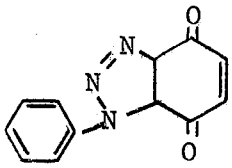
THE REACTIONS OF BENZENESULFONYL AZIDE WITH BICYCLO[2.2.1]-5-HEPTENE-*endo*-*cis*-2,3-DICARBOXYLIC ANHYDRIDE AND BICYCLO[2.2.1]-5-HEPTENE-*exo*-*cis*-2,3-DICARBOXYLIC ANHYDRIDE

Historical and Introduction

The reaction of an organic azide with an unsaturated compound was first reported in 1910. Dimroth and Fester[61] reported the reaction of phenyl azide with acetylene to give the 1,2,3 triazole LXXXVIII. Two years later Wolff[62] reported the reaction of phenyl azide with p-benzoquinone to give LXXXIX. Of greater mechanistic interest is the reaction

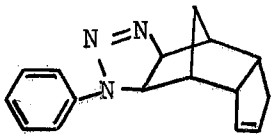


LXXXVIII



LXXXIX

of phenyl azide with bicyclo[2.2.1]-2-heptene (XIV) and its derivatives described by Alder and co-workers[63] in 1931. Recently, Huisgen and his associates[64] have found that this reaction is only one member of a large group of reactions which they refer to as "1,3-dipolar cycloadditions." In the reaction with dicyclopentadiene, addition occurs only to the double bond in the bicyclic system, forming a triazoline ring as depicted by XC. The heat of hydrogenation[65] of XIV exceeds



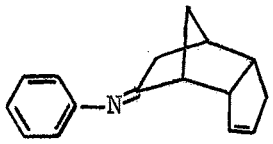
XC

that of common cycloalkenes by 6-7 kcal. mole^{-1} and indicates angular strain in the bicyclic system. Capacity to add phenyl azide is regarded as diagnostic of angular strain in double bonds.

Recently increasing activity in the chemistry of azides has reawakened interest in the reaction of azides with unsaturated compounds.

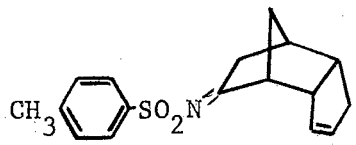
Since the addition products are generally solids which are often easily purified, they are useful as derivatives for identifying or characterizing azides. For example, Clegg and Smith[66] have used acetylenedicarboxylic acid to characterize azides.

When triazoles such as XC are heated, usually to a temperature of 150° or above, they lose nitrogen and produce what has been reported as imino compounds such as XCI.[67]

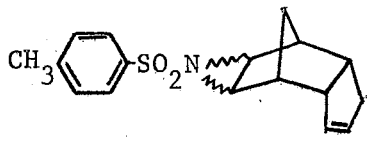


XCI

Bruner[68] first reported the reaction of p-toluenesulfonyl azide with dicyclopentadiene. This reaction occurred at room temperature with the evolution of nitrogen. The imido structure XCII was suggested for the product although the aziridine XCIII was mentioned as another



XCII



XCIII

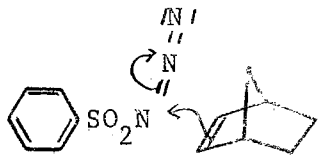
possibility. Bruner[68] also prepared adducts of p-toluenesulfonyl azide with indene, bicyclo[2.2.1]-2-heptene (XIV), bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride (XIX) and bicyclo[2.2.1]-5-heptene-exo-cis-2,3-dicarboxylic anhydride (LV).

The decomposition of benzenesulfonyl azide (XCV) in aromatic solvents was investigated by Dermer and Edmison[69] and later by Heacock and Edmison.[70] A short-lived diradical, XCVI, was suggested as being the decomposition intermediate. The final products, when the azide XCV was

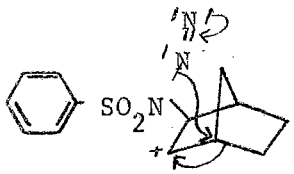
decomposed in various aromatic solvents, were the ones that would be expected from ionic electrophilic substitution.

Very recently Tilney-Bassett[71] reported a study of the reaction of benzenesulfonyl azide (XCV) with anthracene, which produced various anthracenemonosulfonamides. The anthracenesulfonamides obtained were the 1-, 2- and 9-sulfonamidyl anthracenes in 55, 15 and 5-15% yields respectively. The reaction was carried out in chlorobenzene and as was observed earlier[69,70] the aromatic solvent was attacked also to produce both o- and p-chlorobenzenesulfonamides. This work further indicates the existence of an attacking species such as the benzenesulfonimido nitrene radical XCVI.

Bruner reported that certain bicyclic alkenes such as dicyclopentadiene and bicyclo[2.2.1]-2-heptene reacted at room temperature, whereas the bicyclic anhydrides, XIX and LV, formed adducts at higher temperatures. Concurrently with the investigation reported in this chapter an investigation was made concerning the reaction of benzenesulfonyl azide with bicyclic alkenes which react at room temperature, a part of which has recently been reported.[72] Zalkow and Oehlschlager[72] found that benzenesulfonyl azide (XCV) reacted with bicyclo[2.2.1]-2-heptene (XIV) at room temperature to yield the azetidine XCVIII. The ionic mechanism proposed for this reaction involves the attachment of the nitrogen bonded to sulfur at C_2 from the less hindered exo side of the bicyclic ring with simultaneous skeletal rearrangement and loss of nitrogen as depicted by XCIX.



XCV



XIV

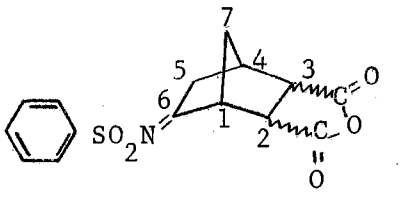
XCIX

XCVIII

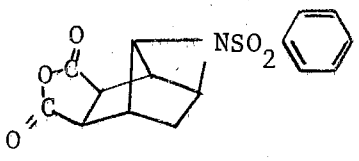
This chapter deals with the reaction of benzensulfonyl azide (XCV) with both bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride and bicyclo[2.2.1]-5-heptene-exo-cis-2,3-dicarboxylic anhydride, XIX and LV respectively. Both of the above reactions occur only at temperatures significantly higher than those required for the reactions with dicyclopentadiene and bicyclo[2.2.1]-2-heptene discussed above.

Results and Discussion

Under conditions where benzenesulfonyl azide reacts with XIV in a vigorous exothermic reaction with the evolution of nitrogen,[72] no detectable evolution of nitrogen could be observed with alkenes XIX and LV. However, both XIX and LV reacted slowly with benzenesulfonyl azide in refluxing carbon tetrachloride to give products with elemental analyses ($C_{15}H_{15}O_5NS$) indicating that the benzenesulfonimido group ($C_6H_5SO_2N$) had become attached to the alkene in each case. The infrared spectrum of each of these products showed the presence of anhydride and benzenesulfonamido groups but the absence of double bonds. Of particular interest was the absence of N-H absorption in the spectra of the products. Both products were converted into dimethyl esters with diazomethane in ether-methanol. The n.m.r. spectra of the two dimethyl esters were very similar and showed the presence of only one methylene group ($\geq CH_2$) in each compound, all other protons appearing further downfield. These data indicate that the products do not have the sulfonimide structure C, since such structures would be expected to show the presence of four protons at high field (two on C_5 and two on C_7). The sulfonimide structure had been suggested for the



C



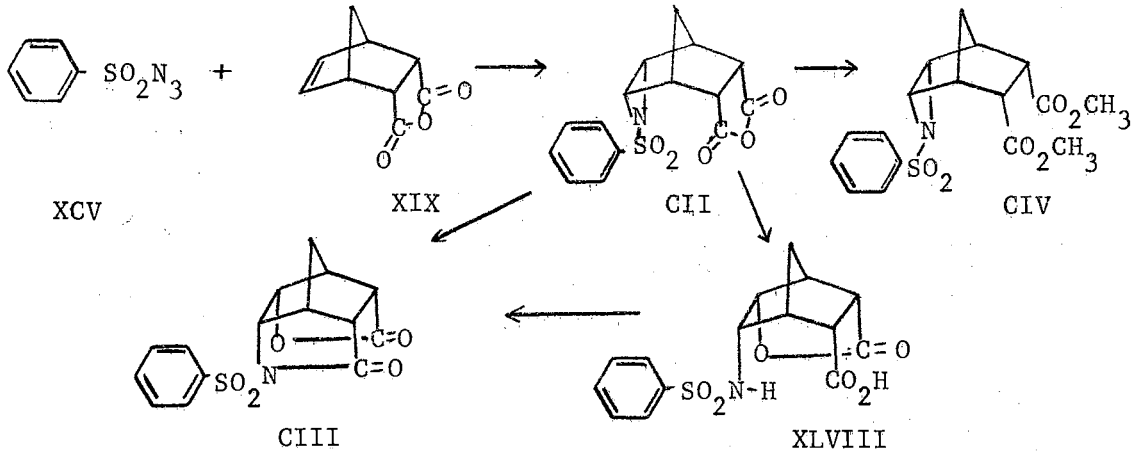
CI

products of the reaction of XIX and LV with p-toluenesulfonyl azide by Bruner.[68]

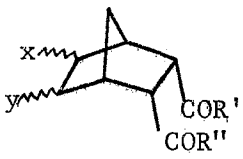
When the product from the reaction of XIX with benzenesulfonyl azide was refluxed in a 10% sodium carbonate solution and the solution

then acidified, A ($C_{15}H_{15}O_6NS$) was obtained. The infrared spectrum of A showed the presence of an N-H bond (3250 cm^{-1}), a carboxyl group (3200-2800 and 1727 cm^{-1}) and a γ-lactone (1755 cm^{-1}). Heating of A at 260° and 35 mm resulted in the loss of water and the formation of B ($C_{15}H_{13}O_5NS$). The infrared spectrum of B no longer showed the presence of an N-H bond and the characteristic absorptions of the carboxyl group were absent. In the carbonyl region, two sharp bands appeared at 1790 cm^{-1} and 1748 cm^{-1}. One of these bands (see below) must arise from the carbonyl of the N-benzenesulfonyl γ-lactam. The formation of B eliminates structure CI for the product of the reaction of XIX with benzenesulfonyl azide, since lactam formation is clearly not possible in this case. Structure CI was to be expected if the reaction had proceeded in an analogous manner to that observed in the reaction of bicyclo[2.2.1]-2-heptene with benzenesulfonyl azide to yield XCVIII.

Structure CII is suggested for the product of the reaction XIX with benzenesulfonyl azide and <u>ipso facto</u> the structures XLVIII and CIII are assigned to A and B, respectively. The n.m.r. spectrum of CIV (in $CDCl_3$, δ = 0 for TMS), the dimethyl ester corresponding to CII, supports the assigned structures. The two C_7 protons appeared as



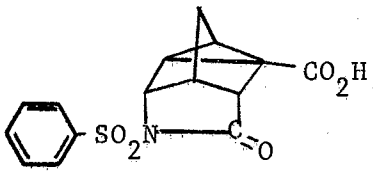
a pair of doublets (J = 10 cps) centered at δ 1.53 and δ 2.00; the two protons at C_2 and C_3 were located at δ 2.82 and the two protons on the bridgeheads C_1 and C_4, showed a doublet (J = 1.5 cps) centered at δ 2.92. The two protons at C_5 and C_6 gave an ill-defined multiplet centered at δ 3.63. The six protons of the methyl ester groups appeared as a single sharp signal at δ 3.53, and the five aromatic protons gave multiplets in the region 440-480 cps downfield from TMS. The n.m.r. spectra of XLVIII and CIII (in CF_3CO_2H) showed the C_7 protons as singlets centered at δ 1.80 and δ 2.00, respectively. An extensive study[44] (see Chapter IV, p. 74) of compounds possessing structure CV where x and y are nitrogen, oxygen or halogen, has shown that only when both x and y (but not x ≡ y) are <u>endo</u> do the C_7 protons appear as a singlet.



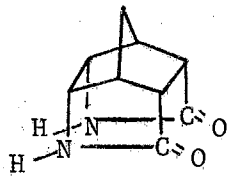
CV

When x or y or both x and y are <u>exo</u>, then the two C_7 protons appear non-equivalent and show a pair of doublets with J = 11 to 13 cps.

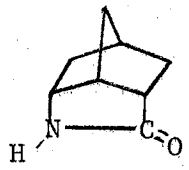
The carbonyl bands in the infrared spectrum of CIII are of particular interest. Momose et al.[73] found that the amide-I band of N-acetyl-sulfonamides was shifted to higher frequencies as compared to that of unsulfonated amides. We likewise have observed that the amide-I band of LXXXI (see Chapter II), appears at 1753 cm^{-1} whereas the amide-I band of XLII[41] and CVI[74] appear at 1675 cm^{-1} and 1690 cm^{-1}, respectively. The infrared spectrum of XXXIII[75] shows the lactone carbonyl band at 1764 cm^{-1} and the lactone-lactam XV[41] shows carbonyl bands at 1660 cm^{-1} and 1761 cm^{-1}. The lower frequency band (1660 cm^{-1}) in XL, by analogy,



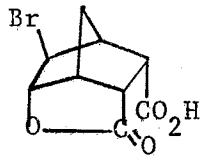
LXXXI



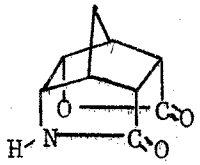
XLII



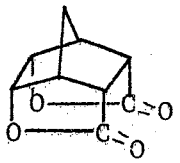
CVI



XXXIII



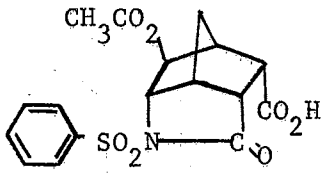
XL



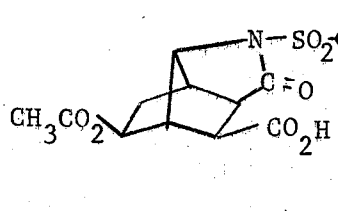
XXXV

can be assigned to the lactam carbonyl band and the higher frequency band (1761 cm^{-1}) can be assigned to the lactone carbonyl band. It is interesting that in the dilactone[52] the two lactone carbonyl bonds give distinct and separate bands at 1795 cm^{-1} and 1770 cm^{-1}. Therefore, the 1790 cm^{-1} band in CIII is assigned to the lactone carbonyl and the 1748 cm^{-1} band to the lactam carbonyl group.

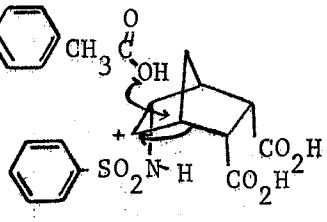
When CII was refluxed in glacial acetic acid, CIII was again obtained and, in addition, a second product was isolated for which structure CVII has been assigned. The elemental analysis, neutralization equivalent and infrared and n.m.r. spectra were consistent with structure



CVII



CVIII

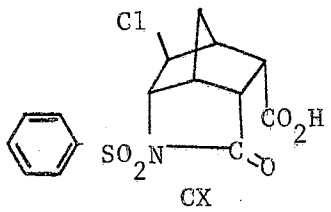


CIX

CVII. Structure CVIII must also be considered on mechanistic grounds for the product of the reaction of CII with acetic acid. Structure CVIII could arise by protonation of the nitrogen atom in CII to give the carbonium ion CIX which rearranges to yield the product. The n.m.r.

spectrum of the product, however, is in agreement with CVII and not with CVIII. The spectrum showed two protons as doublets at high field (δ 1.78 and δ 2.25) each with a coupling constant of 13 cps, analogous to that observed in compounds of the same type (see Chapter IV). Thus, these protons behave as a typical AB case and this is consistent with structure CVII, these signals arising from the C_7 protons. If structure CVIII had been correct we should observe an ABC-type spectrum and the C_5 *endo* proton should give more than two lines, since it should be split by the C_6 proton in addition to the C_5 *exo* proton. In addition the proton on the carbon carrying the acetoxy group (C_5 in CVII, C_6 in CVIII) appeared as a sharp singlet at δ 5.35. This again is consistent with structure CVII ($J_{45} = 0$; $J_{56} = 0$) but not with structure CVIII ($J_{5\underline{endo}\text{-}6} \neq 0$).[76]

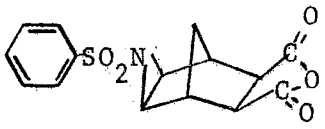
In a similar manner treatment of CII with concentrated hydrochloric acid in acetone gave CX. Structure CX is again consistent with the observed n.m.r. spectrum. The C_7 protons appeared as a pair of doublets



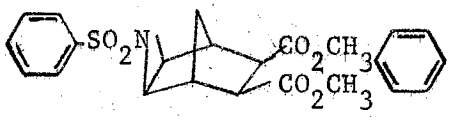
CX

at δ 1.81 and δ 2.47, with a coupling constant of 13 cps. The C_5 proton appeared as a sharp singlet at δ 4.27.

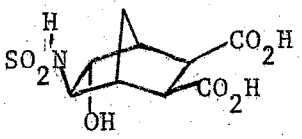
Structure CXI is suggested for the product of the reaction of bicyclo[2.2.1]-5-heptene-*exo*-*cis*-2,3-dicarboxylic anhydride (LV) with benzenesulfonyl azide. The aziridine structure CXI rather than an azetidine type structure such as XCVIII is proposed for CXI because of the similarity of the n.m.r. spectrum of its corresponding dimethyl



CXI



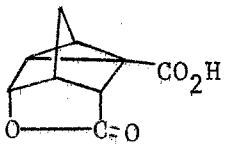
CXII



CXIII

ester CXII to that of CIV. The exo configuration is assigned to the aziridine ring of CXI since the reactive benzenesulfonamido intermediate XCVI would be expected to react with the alkene LV from the less hindered exo side in the absence of electronic effects. When CXI was refluxed in water a hydroxy dicarboxylic acid was obtained. Structure CXIII is suggested for this product.

All attempts to syntehsize CIII from the previously reported[41] lactone-lactam XL were unsuccessful. When XL was treated with aqueous sodium hydroxide and benzenesulfonyl chloride under various conditions the benzenesulfonyl group did not become attached to the nitrogen atom, presumably because of interference of the opened lactone group. During the workup of the above reaction mixture, the alkaline solution was acidified with hydrochloric acid at room temperature and this resulted



XLV

in the formation of the nortricyclene derivative XLV. This reaction has recently been reported to occur under more drastic conditions (see Chapter II).[40]

The mechanism involved in the formation of CII is of particular interest since the benzenesulfonimido group becomes attached to the

alkene XIX from the more hindered endo side. The sluggishness of the reaction of XIX and LV as compared to norbornylene[72] with benzenesulfonyl azide and the formation of aziridines in the former case as compared to an azetidine in the latter case strongly suggests that different mechanisms are involved in the two cases. Under the conditions in which CII and CXI were formed, benzenesulfonyl azide probably decomposes to yield the benzenesulfonyl nitrene, XCVI, which adds to the double bond. This nitrene is known to be strongly electrophilic[69,70] and it is therefore probably attracted to the endo side of XIX by the electron-rich oxygen atoms of the anhydride group. In the formation of CXI only steric factors would be involved and thus the exo aziridine is formed. The opening of the aziridine ring of CII to yield the lactone XLVIII under alkaline conditions is somewhat surprising since a front-side displacement is involved.

Experimental

Preparation of 8-aza-N-benzenesulfonyltricyclo[2.2.1.$1^{2.3\text{-endo}}$]octane-endo-5,6-dicarboxylic anhydride (CII) and its corresponding dimethyl ester CIV

A mixture of bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride* (XIX) (16.4 g. (100 mmole), Eastman reagent grade), benzenesulfonyl azide (XCV) (18.3 g. (approx. 75 mmole), prepared as previously described[72]), and carbon tetrachloride (125 ml.) were heated at reflux for 34 hr. during which time a gummy solid precipitated. The precipitate was collected by filtration and washed thoroughly with two portions (25 ml. each) of chloroform. The chloroform-insoluble material was the endo-aziridine CII, 13.4 g. (42 mmole), m.p. 207-210°. Recrystallization of CII from acetone, followed by drying for 8 hr. at 144° and 1 mm pressure, gave an analytical sample having m.p. 215-216.5° and υ_{max}^{KBr} 1865, 1822, 1780, 1327, and 1163 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}O_5NS$: C, 56.43; H, 4.08; N, 4.39. Found: C, 56.85; H, 4.34; N, 4.38.

The endo-aziridine CII was also formed by heating the bicyclic alkene XIX (32.8 g. (200 mmole), same source as above) and benzenesulfonazide (XCV) (47 g. (196 mmole), prepared as previously described[72]), together in a rotary evaporator at 60° and 35 mm pressure for 8 hr. There was a steady evolution of gas after the mixture had been heated

---

*Both XIX and LV were shown to be homegeneous and uncontaminated with each other by gas chromatographic analysis using a ¼" diameter x 10' long column of 5% SE-30 on acid washed chromasorb ω and a helium flow rate of 80 ml./min. Under these conditions the retention times were as follows: XIX 6.42 min., LV 5.25 min.

for about 10 min.; the mixture became homogeneous at about the same time. After about 30 min. of heating a solid started precipitating. After 8 hr. of heating, 30 ml. of chloroform was added and the reaction mixture was stirred for 30 min. at room temperature. The crystalline precipitate was collected by filtration and thoroughly washed with four portions (30 ml. each) of chloroform to yield the chloroform-insoluble endo-aziridine CII, 24 g. (131 mmole), m.p. 207-210°. Recrystallization from acetone gave m.p. 215-216.5°.

The dimethyl ester CIV was prepared by treating the solid anhydride CII with an excess of 1:1 absolute methanol-ethereal diazomethane until the yellow color of diazomethane persisted. The methanol-ether solution containing the diester was allowed to slowly evaporate in the air. The dimethyl ester CIV crystallized and gave m.p. 130-131°. Recrystallization of CIV from methanol-ether gave no change in melting point and υ_{max}^{KBr} 1733 cm^{-1}; n.m.r. (in $CDCl_3$) δ 1.53 (J = 10 cps one proton at C_7), δ 2.00 (J = 10 cps one proton at C_7), δ 2.82 and δ 2.92 (4 protons at C_1, C_4, C_2 and C_3), δ 3.53 (6 protons of methyl ester), δ 3.63 (2 protons at C_2 and C_5), 440-480 cps (5 aromatic protons).

endo-5-Hydroxy-endo-6-benzenesulfonamidobicyclo[2.2.1]-endo-cis-2,3-dicarboxy-γ-lactone (XLVIII)

A mixture of the endo-aziridine CII (0.500 g. (1.56 mmole), m.p. 207-210°) and aqueous 10% sodium carbonate solution (25 ml.) were refluxed together for 12 hr. The hydrolysis solution was then cooled and acidified with conc. hydrochloric acid and the crude lactone acid XLVIII precipitated, 0.26 g. (0.77 mmole), m.p. 228-234°. Recrystallization from 1:1, acetone-water followed by drying at 144° and 1 mm

pressure for 5 hr. gave the analytical sample, m.p. 242-245°. ν_{max}^{KBr} 3250, (broad) 3200-2800, 1755, 1727, 1360, 1340, 1170 cm^{-1}; n.m.r. (CF_3CO_2H): δ 1.80 (2 C_7 protons).

Anal. Calcd. for $C_{15}H_{15}O_6NS$: C, 53.41; H, 4.41. Found: C, 53.17; H, 4.31.

The same lactone acid XLVIII was obtained from the endo-aziridine CII by heating a mixture of CII (0.5 g. (1.56 mmole), m.p. 207-210°) and aqueous 10% sodium hydroxide on a steam bath for 4 hr. On cooling and acidification of the reaction mixture as above the same lactone acid XLVIII precipitated, however, in lower yield (0.1 g. (0.3 mmole), m.p. 237-242°).

Pyrolysis of XLVIII; Preparation of CIII

The lactone acid XLVIII (0.050 g. (0.148 mmole), m.p. 242-245°) was heated at 260° and 35 mm pressure in a sublimation apparatus. The lactone lactam CIII thus formed sublimed very rapidly. The sublimate lactone lactam after drying at 200° for 10 min., 0.042 g. (0.132 mmole), gave m.p. 244.5-245°. An analytical sample was prepared by resublimation of the dried lactone lactam, m.p. 248-248.5°. ν_{max}^{KBr} 1790, 1748, 1355, 1347 and 1155 cm^{-1}; n.m.r. (CF_3CO_2H): δ 2.05 (2 C_7 protons).

Anal. Calcd. for $C_{15}H_{13}O_5NS$: C, 56.43; H, 4.08; N, 4.39. Found: C, 56.15; H, 4.04; N, 4.49.

The reaction of the endo-aziridine CII with acetic acid; Preparation of CVII and CIII

The endo-aziridine CII (4.6 g. (14.4 mmole), m.p. 215-216.5°) was

dissolved in hot glacial acetic acid* (30 ml.) and the mixture was refluxed for 6 hr. and then allowed to cool slowly. The lactone lactam CIII crystallized as clear needles and crystallization seemed complete after 12 hr. The crystals were then collected by filtration, washed with three portions (1.5 ml. each) of glacial acetic acid, and dried for 9 hr. at 144° and 1 mm pressure, 1.32 g. (4.14 mmole), m.p. 245-247°. ν_{max}^{KBr} 1790, 1748, 1355, 1347, and 1155 cm^{-1}.

Admixture of this lactone lactam with the one obtained above from pyrolysis of the lactone acid XLVIII showed no depression of melting point and their infrared spectra were identical. Thin layer chromatography of the lactone lactam CIII, obtained above, on silica gel using an eight to one (v/v) mixture of absolute ethanol and glacial acetic acid respectively, as eluent, gave only one spot**, Rf 0.5.

The filtrate remaining after removal of CIII was evaporated to approximately 20 ml. and allowed to cool slowly as described above. The acetate lactam acid CVII crystallized as white plates. The crystalline acetate lactam acid CVII was collected by filtration and dried at 144° and 1 mm pressure for 5 hr., 1.52 g. (4.02 mmole), m.p. 209-211°. On standing open to the atmosphere for several days the mother liquor deposited additional acetate lactam acid CVII, 0.86 g. (2.28 mmole), m.p. 209-212°. Further evaporation of the mother liquor in the air yielded more crystals. An analytical sample of CVII was prepared by recrystallization from 1:1 ethanol-water and drying at 144° and 1 mm pressure for 8 hr. which raised the melting point to 214-215°

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*This volume is not critical for reaction to occur but is critical in the isolation of the products since they are separated by fractional crystallization.

**I_2 vapor was used as developer.

and gave υ_{max}^{KBr} (broad) 3100-2800, 1765, 1700, 1362, and 1140 cm^{-1} and n.m.r. (CF_3CO_2H): δ 1.78 (doublet J = 13 cps one C_7 proton), δ 2.25 (doublet J = 13 cps one C_7 proton. The lower field signal of this doublet is buried under the strong signal of the methyl ketone protons), δ 4.69 (doublet J = 5 cps C_6 proton), δ 5.35 (C_5 proton).

Anal. Calcd. for $C_{17}H_{17}O_7NS$: C, 53.81; H, 4.51. Found: C, 53.90; H, 4.38.

The above acetate lactam acid CVII prior to recrystallization gave only one spot*, Rf 0.63, on a thin layer chromatogram made on silica gel using the same eluent as above. It also gave a neutralization equivalent of 370 (calc. 379.37). Thin layer chromatography on silica gel of a mixture of the above lactone lactam CIII and acetate lactam acid CVII using the same eluent as described above gave two spots, Rf 0.5 and 0.63. In another experiment, the lactone lactam was removed by filtration as described above, but the filtrate was not then evaporated to a smaller volume. On slow air evaporation the acetate lactam acid CVII eventually crystallized from the filtrate to give a yield comparable to that obtained as described above.

The reaction of the endo-aziridine with concentrated hydrochloric acid in acetone; Preparation of CX

The endo-aziridine CII (0.50 g. (1.57 mmole), m.p. 213-216°), conc. hydrochloric acid (10 ml.) and acetone (10 ml.) in an open 50-ml. beaker were heated together on a steam bath for about 15 min. The solution was then allowed to stand open to the atmosphere at room

*I_2 vapor was used as developer.

temperature for 12 hr. The product CX crystallized as long clear needles which were collected by filtration, washed with 5 ml. of ethanol and dried at 144° and 1 mm pressure for 5 hr., 0.3 g. (0.84 mmole), m.p. 214-215°. ν_{max}^{KBr} (broad) 3050-2800, 1747, 1715, 1370, 1340, 1175, and 1129 cm^{-1}; n.m.r. (CF_3CO_2H): δ 1.81 (doublet J = 13 cps one C_7 proton), δ 2.47 (doublet J = 13 cps one C_7 proton), δ 4.27 (C_5 proton), δ 4.78 (doublet J = 5 cps C_6 proton).

Anal. Calcd. for $C_{15}H_{14}O_5NS$: C, 50.63; H, 3.94; N, 3.94. Found: C, 50.76; H, 4.15; N, 3.92.

Preparation of CXI and its corresponding dimethyl ester CXII

A mixture of bicyclo[2.2.1]-5-heptene-exo-cis-2,3-dicarboxylic anhydride (LV) (6.36 g. (36 mmole), p.m. 141-142, prepared as previously described[46]) benzenesulfonyl azide (XCV) (5.95 g. (approx 27 mmole), prepared as previously described[72]) and carbon tetrachloride (62.5 ml.) were heated at reflux for 24 hr. during which time a gummy solid precipitated. The carbon tetrachloride was decanted from the precipitate and the precipitate was washed thoroughly with benzene (40 ml.) at room temperature to yield a white solid; this solid was then recrystallized from hot benzene and dried at 144° and 1 mm pressure for 5 hr. to give the exo-aziridine CXI, 3.6 g. (11.3 mmole), m.p. 168-168.5°. ν_{max}^{KBr} 1863, 1830, 1775, 1345, 1320, and 1163 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}O_5NS$: C, 56.43; H, 4.08; N, 4.39. Found: C, 56.59; H, 4.13; N, 4.40.

The dimethyl ester CXII was made by treating the anhydride CXI (0.56 g.) with an excess of ethereal diazomethane and 10 ml. of methanol. The solution containing the dimethyl ester CXII was evaporated in vacuo

at room temperature, leaving a semi-crystalline material, which when washed with 5 ml. of n-hexane yielded crystalline dimethyl ester CXII, m.p. 99-100°. Recrystallization of CXII from hot n-hexane raised the melting point to 102° and gave υ_{max}^{KBr} 1740, 1327, and 1160 cm^{-1}; n.m.r. ($DCCl_3$): δ 1.92 (J = 11 cps one proton at C_7) δ 2.32 (J = 11 cps one proton at C_7), δ 2.78 and δ 2.92 (4 protons at C_1, C_4, C_2 and C_3), δ 3.50 (2 protons at C_2 and C_5), δ 3.66 (6 protons of methyl ester), 435-380 cps (5 aromatic protons).

Reaction of the exo-aziridine CXI with water

The exo-aziridine CXI (1.0 g. (3.14 mmole), m.p. 168-168.5°) and water (20 ml.) were refluxed together for 10 hr. The solution was homogeneous after one hr. of refluxing. After a 10-hr. reflux period, the solution was evaporated to dryness in a rotary evaporator to yield the hydroxy diacid CXIII, 1.11 g. (3.12 mmole), m.p. 214-215°. An analytical sample of the hydroxy diacid CXIII was prepared by recrystallization from water followed by drying at 144° and 1 mm pressure for 5 hr. and gave m.p. 214-215°. υ_{max}^{KBr} 3400, 3260, (broad) 3000-2500, 1723, 1705, and 1155 cm^{-1}.

Anal. Calcd. for $C_{15}H_{17}O_7NS$: C, 50.69; H, 4.82. Found C, 50.84; H, 5.02.

The dimethyl ester CXIV of CXIII was prepared by treating the hydroxy diacid CXIII with an excess of ethereal diazomethane until the yellow color of the diazomethane persisted. The ether was evaporated to yield the dimethyl ester as a viscous oil. All attempts to crystallize the dimethyl ester CXIV failed. υ_{max}^{film} 3440, 3260, 1738, and 1160 cm^{-1}.

The attempted synthesis of CIII from XL

The lactone-lactam XL (1.00 g. (5.58 mmole), prepared as previously described[41]) was heated in 20 ml. of refluxing 10% aqueous sodium hydroxide solution for 12 hr. The mixture was then evaporated to a solid in a rotary evaporator. The solid obtained was dissolved in 20 ml. of water containing benzenesulfonyl chloride (0.95 g. (5.58 mmole), Matheson, Coleman and Bell reagent grade) and stirred at room temperature for 4 hr. The basic solution was then made acidic with excess concentrated hydrochloric acid and continuously extracted with ethyl ether for 72 hr. The lactone acid XLV crystallized from the ether solution, 0.895 g. (4.97 mmole), m.p. 202-204°. ν_{max}^{KBr} 3140, 1777, and 1722 cm^{-1}.

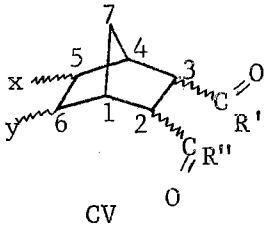
Other attempts to synthesize CIII directly from XL also failed. The attempts were as follows: (1) Benzenesulfonyl chloride and XL, in equimolar amounts, were heated together in an open flask at 100° for several hours with no reaction occurring. (2) Benzensulfonyl chloride and XL in equimolar amounts were heated in refluxing dioxane solution for several hours. No reaction occurred and XL was recovered unchanged. (3) An equimolar amount of benzenesulfonyl chloride, pyridine and XL in dioxane solution yielded none of the desired product. (4) Benzenesulfonyl chloride and XL in equimolar quantities were heated together in a sealed tube at approximately 200° for thirty minutes. No identifiable product was obtained. (5) The reaction of benzenesulfonyl chloride with XL in equimolar quantities in dry pyridine solution failed to yield CIII.

CHAPTER IV

STEREOCHEMICAL DETERMINATIONS IN THE BICYCLO[2.2.1]HEPTANE SYSTEM VIA NUCLEAR MAGNETIC RESONANCE

Historical and Introduction

During the course of the investigations reported in the first three chapters of this dissertation, a need was found for an instrumental method useful in determining the configuration of substituents on derivatives of the bicyclo[2.2.1]heptane-2,3-dicarbonyl system depicted by CV. Of course, chemical methods such as lactonization,[77]



CV

x and y = electron-withdrawing groups

iodolactonization[78] and titrimetric analysis[79] may be used for this purpose; however, they are limited in usefulness by restricted applicability as well as possible occurrence of rearrangements under the reaction conditions. Certain stereospecific degradative procedures such as those employed for the chemical proofs of structures in the preceding three chapters are generally unambiguous but exceedingly arduous. For these reasons the applicability of nuclear magnetic resonance as a tool for determination of substituent configuration on derivatives of CV was investigated.

It has already been found that in the camphane-2,3-diols,[76] in α- and α'-chlorocamphor,[80] and in 3,8-cyclocamphor[81] the magnitude of the coupling of an <u>exo</u> proton with the adjacent bridgehead proton is larger (4-5 cps) than when the proton is endo (0-1 cps). Thus when such a proton is well separated from the rest of the absorption pattern, the magnitude of the spin-spin interaction with the bridgehead proton should establish the configuration of the compound.[82] The

larger coupling constants (4-5 cps) should be expected in the case of an exo proton coupling with the bridgehead proton since the dihedral angle between these protons is closer to 0^{o} and further from 90^{o} than is the endo proton-bridgehead proton dihedral angle. A minimum coupling constant is expected when the dihedral angle is 90^{o} and a maximum at 0^{o} and 180^{o}.[83]

As a result of chemical structure elucidations both by this author (see Chapters I, II and III) and others a significant number of derivatives of CV with established configurations was available for study. The investigation described in this chapter was begun with hopes of finding a more explicit nuclear magnetic resonance effect for determining the configuration of the C_5 and C_6 substituents on derivatives of CV than the use of the coupling constants between the C_5 and C_6 protons and the adjacent bridgehead protons described above.

Results and Discussion

When the nuclear magnetic resonance (n.m.r.) spectra of the compounds listed in Tables 1 and 2 were examined it was found that when the electron-withdrawing groups (represented in CV by x and y) were trans or cis-exo, the C_7 protons showed up in the expected methylene proton region as a quartet (see Plate I) with a coupling constant of 11-13 cps. A coupling constant of this magnitude is indicative of spin-spin splitting of the AB type where protons A and B are both on the same carbon atom.[84] The nonequivalence of the C_7 protons, which causes them to split one another, is attributed to the proximity of one of the protons to the exo electron withdrawing substituent(s) on C_6 and/or C_5.

Normally (with no effective environmental electronic effects) the C_7 protons are expected to appear as a singlet in the methylene proton region as shown in Plate II. The compounds listed in Table 3 all give a single line in the methylene region which corresponds to their two C_7 protons. This is expected since no environmental electronic effects of sufficient magnitude to make the C_7 protons appear nonequivalent in the n.m.r. spectra are present.

The compounds selected for this investigation are particularly good models for studying effects of electron-withdrawing substituents on the C_7 protons. In every case the protons other than the C_7 protons are downfield from the regular methylene proton region. The protons on C_1, C_2, C_3 and C_4 of the compounds in the tables generally appear in the region δ 3.0 to δ 3.7 in trifluoroacetic acid and δ 2.5 to δ 3.4 in either carbon tetrachloride or deuterochloroform (δ TMS = 0).

In general the protons of the system depicted by CV appear further downfield in trifluoroacetic acid than in either carbon tetrachloride or deuterochloroform.

A comparison of two cis-carbonyl bromolactones, XXXIII and CXV, with the two bromolactones having trans-carbonyls, XXXII and CXVII, shows the lines assigned to the C_6 protons to be fairly consistant at approximately δ 5.14 with trifluoroacetic acid as solvent, whereas the lines assigned to the C_5 protons of XXXIII and CXV are about 0.5 ppm further downfield from TMS than the lines assigned to the C_5 protons of XXXII and CXVII. This is attributed to a deshielding effect on the C_5 protons by the endo-3-carbonyl groups of XXXIII and CXV. The C_5 protons of XXXII and CXVII are not subject to deshielding by the exo-3-carbonyls owing to the stereochemistry involved. The doublet at δ 4.85 of XLIV is assigned to the C_6 proton because it is closer to the position of the lines assigned to the C_6 proton of the four bromolactones in Table 1 than is the line at δ 4.57, which is thus assigned to the C_5 proton. It follows then that the assignments for the C_5 and C_6 protons of CXVI should be as shown in Table 1 since the entire spectrum appeared to be shifted, relative to XLIV, by solvent effects. Lines centered at δ 3.88 and δ 4.83 are assigned to the C_5 and C_6 protons of XLVII respectively because the line at δ 3.88 is much further upfield than would be expected for the C_6 proton as a result of examination of the spectra of the compounds appearing above XLVII in Table 1. The line at δ 5.97 is assigned to the C_6 proton of XXXVII rather than the C_5 proton because steric effects could conceivably cause the plane of the succinimido group to be approximately parallel with the C_1-C_2-C_3-C_4 plane, thus allowing one of the carbonyls

of the succinimido group of XXXVII to be in a position to deshield the C_6 proton; therefore, by analogy with other compounds in Table 1 the C_6 proton would be expected to give a line further downfield than δ 4.75. The line at δ 4.75 is thus assigned to the C_5 proton of XXXVII. The lines corresponding to the C_5 and C_6 protons of CX and CVII are assigned as shown in Table 1 since the lines for the C_6 protons of both CX and CVII should have approximately the same chemical shift; also δ 5.35 corresponds closely to the value that could be expected for a proton on C_5 of CVII since the electronegativity of the acetoxy group should not be significantly different from that of γ-lactones such as described above. The C_5 proton of CVII is subject to deshielding by the endo-3-carboxyl group which could be expected to result in a downfield shift as compared to the line of an α-alkyl hydrogen on a γ-lactone. A proton on carbon attached to chlorine is not expected to show up as far downfield as a proton on carbon attached to an acetate.[85]

The above assignments of lines corresponding to C_5 and C_6 protons have been made without employing the coupling constant method (with the bridgehead protons) for differentiation between exo and endo hydrogens previously described*; however, the above assignments are in complete agreement with this method also. Assignment of lines corresponding to the C_5 and C_6 protons of XXXIV would be difficult on the basis of the coupling constant method alone since both give two lines with $J \approx 5$ cps. The assignments for the C_5 and C_6 protons of XXXIV given in Table 1 are based on the observation that the line at δ 5.18 is in closer

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*See p. 75.

proximity than the line at δ 4.32 to the values for the C_6 protons of the above discussed bromo- and hydroxylactones.

The number of exo-electronegative substituents (one or two) in compounds of the type CV cannot be determined by observation of the C_7 splitting pattern alone; however, when x and y are different and both exo, the C_5 and C_6 protons split each other to give AB type spin-spin splitting expected of nonequivalent protons on adjacent carbon atoms.[84] The coupling constants (6-7 cps) shown in Table 2 are in agreement with the expected values for this type of splitting.[84] The trans hydrogens on carbon atoms C_5 and C_6 of the compounds listed in Table 1 apparently did not split each other because the dihedral bond angle was close to 90°. The assignments of lines corresponding to protons on C_5 and C_6 of the first six compounds listed in Table 2 are the results of correlations made from assignments given in Table 1. However, in some cases they may quite conceivably be switched as indicated by the alternate assignments appearing in brackets. The C_5 and C_6 protons of LV are identical and give a single line at δ 6.39. The lines corresponding to the C_5 and C_6 protons of CXII show up as a triplet centered at δ 3.50.

The chemical shift of the C_7 protons of XXVI, XXVII and XXV (Table 2) is worth noting. The doublet corresponding to one of the C_7 protons in these compounds is so highly deshielded that its lines are under the broad lines corresponding the either C_1 and C_4 or C_2 and C_3 protons. An explanation for this phenomenon may be offered which involves both steric and electronic factors. The bromine atom may force the plane of the succinimido group closer to being parallel with the C_6-C_1-C_2 plane than the C_1-C_2-C_3-C_4 plane as was suggested

for XXXVII, thus subjecting one of the C_7 protons to very close environmental electronic (apparently deshielding) factors.

The assignments given in Table 3 are fairly obvious except for lines corresponding to the protons on C_5 and C_6 of CIII and XLVIII. The C_5 and C_6 protons of CIII appeared as a sextet whereas the C_5 and C_6 protons of XLVIII gave a quartet with the doublets centered at δ 3.66 and δ 3.79 with a coupling constant of 4 cps. The AB type spin-spin splitting of the nonequivalent protons of XLVIII is in agreement with this type splitting by cis hydrogens discussed above; however, CIII showed the protons on C_5 and C_6 coupled with other protons as well as with each other.

Listed in Table 4 are two compounds which at first appeared to be an exception to the rule that if no electron-withdrawing groups (represented by x and y in CV) are exo, the C_7 protons will give a single n.m.r. line, however, an explanation for the results observed may be offered. The π orbital of the double bond in XIX provides an electronic effect sufficient to make the C_7 protons nonequivalent and thus splitting results. The three-membered ring of the aziridine CIV apparently is similar enough to a double bond to cause the C_7 protons to be nonequivalent and show up as a quartet. This ability of the endo aziridine to affect the C_7 protons may be related to the strain involved in the aziridine ring of CIV as well as distortion resulting from the close proximity of the endo-cis diester groups to the endo aziridine ring.

The following conclusions can be made with regard to stereochemical determinations in compounds of the CV type:

1. When x and y (but not x ≡ y) are neither <u>exo</u>, the C_7 protons appear equivalent as exemplified by Plate II.

2. When x and y are <u>cis</u>, <u>endo</u> or <u>exo</u>, the protons at C_5 and C_6 will give AB or possibly and ABX_n type spin-spin splitting.

3. When either x or y or both x and y are <u>exo</u>, the C_7 protons will show up as a quartet with a coupling constant of 11-13 cps, an example of which is shown in Plate I.

TABLE 1

THE CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J) OF THE C_5, C_6 AND C_7 PROTONS OF COMPOUNDS WITH <u>trans</u> C_5 AND C_6 SUBSTITUENTS SHOWING AB TYPE C_7 PROTON SPIN-SPIN SPLITTING

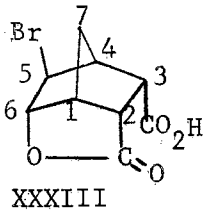
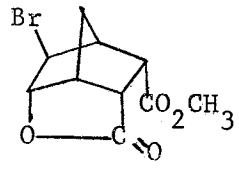
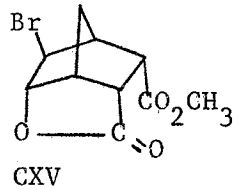
Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 XXXIII	1.93	(12)	4.44	(2)	5.16	(5)	CF_3CO_2H
	2.58	(12)					
 CXV	1.92	(12)	4.40	(2)	5.16	(5)	CF_3CO_2H
	2.57	(12)					
 CXV	1.80	(12)	4.57	(2.5)	4.95	(5)	$DCCl_3$
	2.42	(12)					

TABLE 1 (Continued)

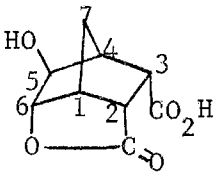
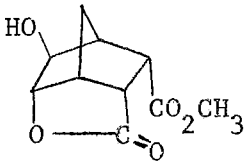
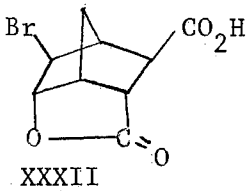
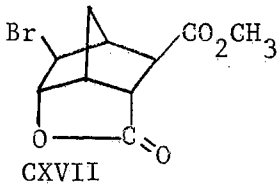
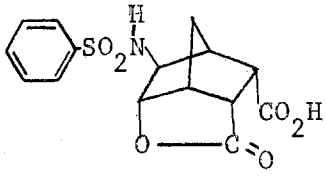
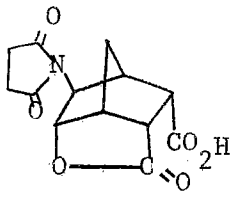
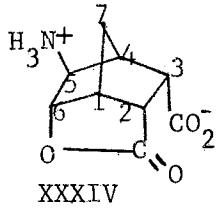
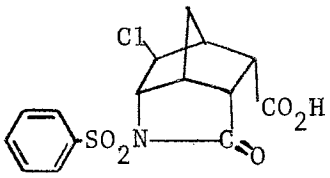
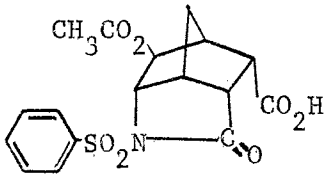
Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 XLIV	1.93 2.30	(12) (12)	4.57	(0)	4.85	(5)	CF_3CO_2H
 CXVI	1.59 2.23	(12) (12)	4.28	(0)	4.49	(5)	$DCCl_3$
 XXXII	2.00 2.52	(13) (13)	3.97	(2)	5.13	(4)	CF_3CO_2H
 CXVII	1.92 2.45	(12) (12)	3.92	(?)*	5.09	(5)	CF_3CO_2H
 XLVII	1.84 2.18	(12) (12)	3.88	(0)	4.83	(5)	CF_3CO_2H
 XXXVII	1.92 2.52	(12.5) (12.5)	4.75	(0)	5.97	(5)	CF_3CO_2H

TABLE 1 (Continued)

Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 XXXIV	2.05 2.38	(13) (13)	4.32	(5.5)	5.18	(4.5)	CF_3CO_2H
 CX	1.81 2.47	(13) (13)	4.27	(0)	4.78	(5)	CF_3CO_2H
 CVII	1.78 2.25	(13) (13)	5.35	(0)	4.69	(5)	CF_3CO_2H

*One line of this doublet is under the methyl ester protons.

TABLE 2

THE CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J) OF THE C_5, C_6 AND C_7 PROTONS OF COMPOUNDS WITH <u>cis</u> C_5 AND C_6 SUBSTITUENTS SHOWING AB TYPE C_7 PROTON SPIN-SPIN SPLITTING

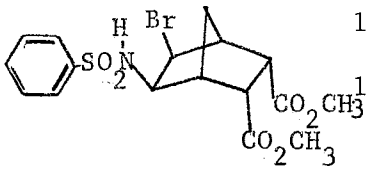
Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 LXIII	1.39 1.99	(11) (11)	5.30 [4.73	(6) (6)]	4.75 [5.30	(6) (6)]	$DCCl_3$

TABLE 2 (Continued)

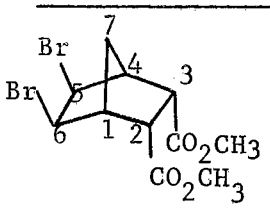
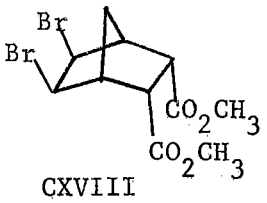
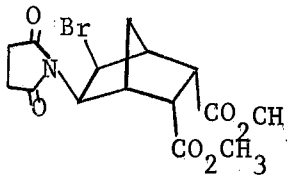
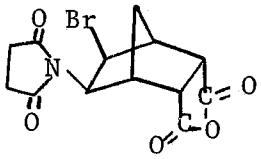
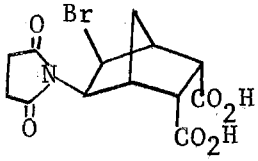
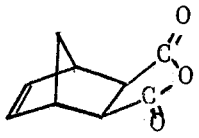
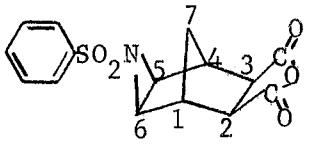
Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 CXVIII	1.60 2.59	(12) (12)	4.80	(0)	4.766	(0)	CF_3CO_2H
 CXVIII	1.50 2.43	(12) (12)	4.72	(0)	4.75	(0)	CCl_4
 XXVI	1.63 ≅ 2.69*	(11) (11)	4.59 [4.88	(6.5) (6.5)]	4.88 [4.59	(6.5) (6.5)]	$DCCl_3$
 XXVII	2.04 ≅ 3.10*	(11) (11)	4.16 [4.58	(7) (7)]	4.58 [4.16	(7) (7)]	CF_3CO_2H
 XXV	2.04 ≅ 3.10*	(12) (12)	4.15 [4.57	(7) (7)]	4.57 [4.15	(7) (7)]	CF_3CO_2H
 LV	1.46 1.79	(11) (11)	6.39	(0)	6.39	(0)	CF_3CO_2H

TABLE 2 (Continued)

Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 CXII	1.92 2.32	(11) (11)	3.50**		3.50**		$DCCl_3$

*Calculated by a previously described method.[86]
**The two protons showed up as a triplet centered at δ 3.5.

TABLE 3

THE CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J) OF THE C_5, C_6 AND C_7 PROTONS OF COMPOUNDS SHOWING NO C_7 PROTON SPIN-SPIN SPLITTING

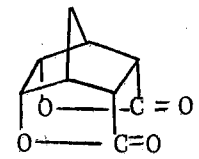
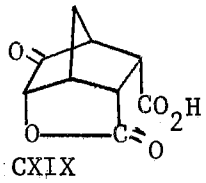
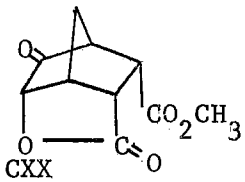
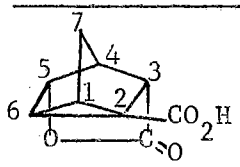
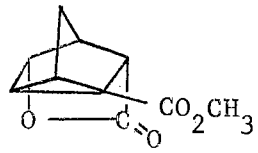
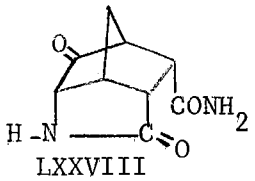
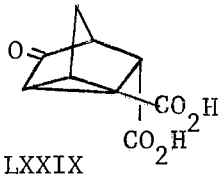
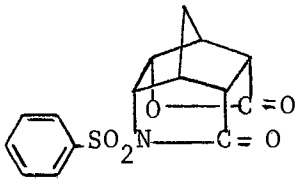
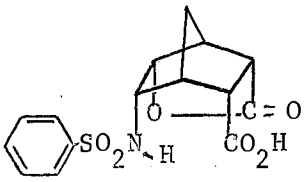
Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 XXXV	2.08	(0)	4.89	(0)	4.89	(0)	CF_3CO_2H
 CXIX	2.19	(0)	---		4.73	(5)	CF_3CO_2H
 CXX	2.17	(0)	---		4.73	(4)	CF_3CO_2H

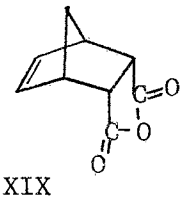
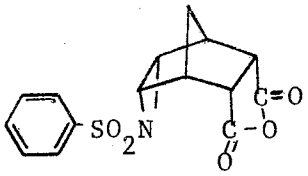
TABLE 3 (Continued)

Compound	C_7 δ	C_7 (J cps)	C_5 δ	C_5 (J cps)	C_6 δ	C_6 (J cps)	Solvent
 XLV	2.07	(0)	5.03	(0)	---		CF_3CO_2H
 CXXI	1.90	(0)	4.82*		---		$DCCl_3$
 LXXVIII	2.30	(0)	---		3.54	(0)	CF_3CO_2H
 LXXIX	2.32	(0)	---		3.47		CF_3CO_2H
 CIII	2.00	(0)	5.1 4.97 > (7) 4.90 > (4) [4.8 4.73 > (4) 4.62 > (7)]		4.8 4.73 > (4) 4.62 > (7) [5.1 4.97 > (7) 4.90 > (4)]		CF_3CO_2H
 XLVIII	1.80	(0)	3.66 [3.79	(4) (4)]	3.79 [3.66	(4) (4)]	CF_3CO_2H

*A triplet centered at δ 4.82.

TABLE 4

THE CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J) OF THE C_5, C_6 AND C_7 PROTONS OF COMPOUNDS OF THE CV TYPE IN WHICH x ≡ y

Compound	C_7 (J cps)	C_5 (J cps)	C_6 (J cps)	Solvent
 XIX	1.66 (9) 1.91 (9)	6.33 (0)	6.33 (0)	CF_3CO_2H
 CIV	1.53 (10) 2.00 (10)	3.63*	3.63*	$DCCl_3$

*A triplet centered at δ 3.63.

Plate I

Nuclear Magnetic Resonance Spectrum of exo-5-Hydroxy-endo-6-hydroxybicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxy-γ-lactone (XLIV)

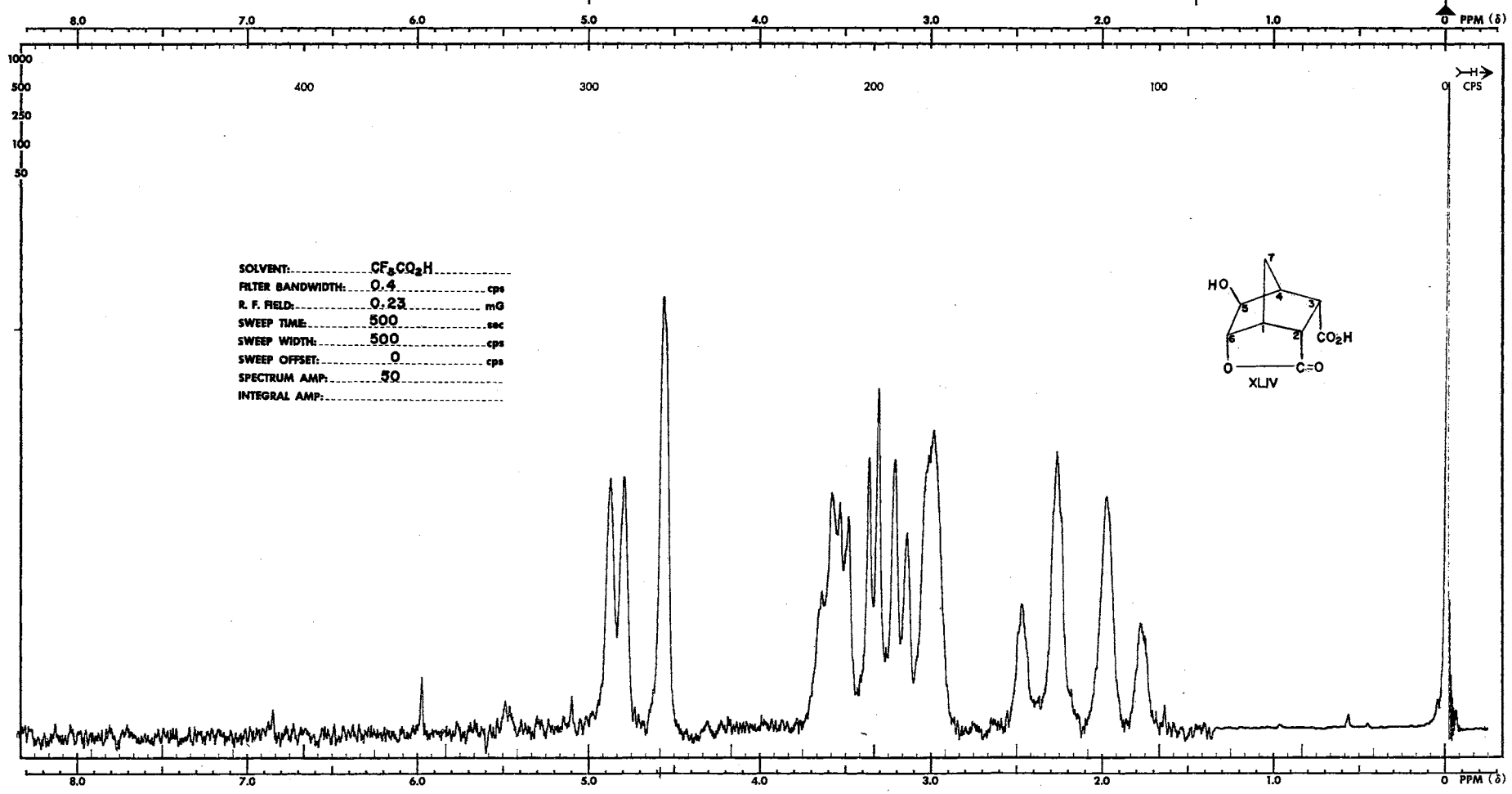
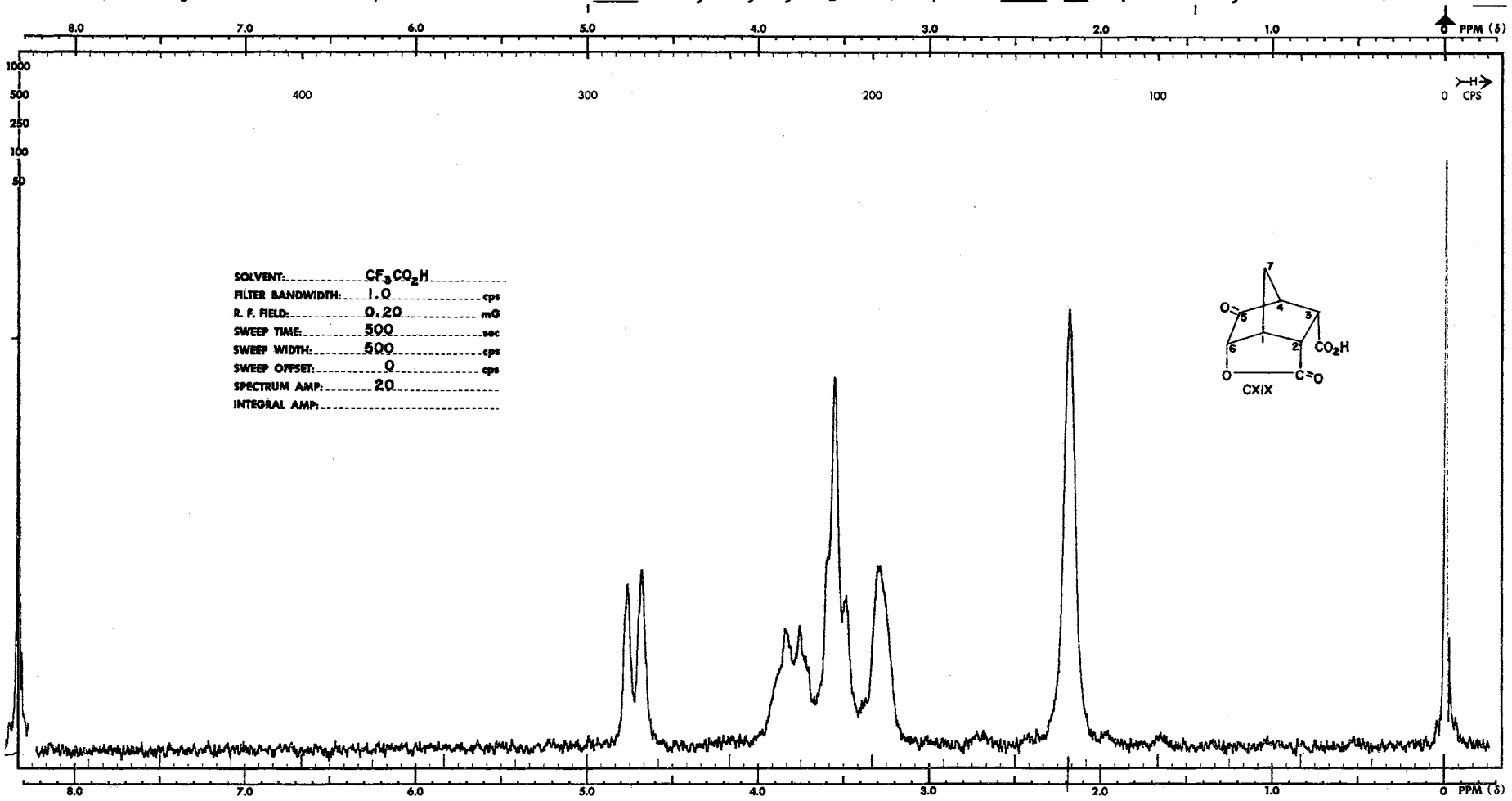


Plate II

Nuclear Magnetic Resonance Spectrum of 5-Keto-endo-6-hydroxybicyclo [2.2.1] heptane-endo-cis-2,3-dicarboxy-γ-lactone (CXIX)



Experimental

All spectra were recorded on a Varian model A-60 NMR Spectrometer. The samples were approximately 20% (w/v) solutions in trifluoroacetic aicd, carbon tetrachloride, or deuterochloroform with tetramethylsilane (TMS) as an internal standard ($\delta = 0$). No noticeable transformations occurred in the samples dissolved in trifluoroacetic acid, as detected by running repeat n.m.r.'s on the dissolved samples after standing several hours, or by melting point determination of the recovered samples.

XXXIII and CXV

The bromolactone acid XXXIII was synthesized by the procedure of Kwart and Kaplan,[75] starting with commercially available (Eastman reagent grade) bicyclo[2.2.1]-5-heptene-endo-cis-2,3-dicarboxylic anhydride. The bromolactone acid hydrate gave m.p. 113-116° (reported[87] 116°) and υ_{max}^{KBr} 1760 and 1707 cm^{-1} (reported[87] υ_{max}^{KBr} 1757 and 1707 cm^{-1}). The bromolactone acid after being dried 3 hr. at 1 mm and 100° gave m.p. 157-158° and υ_{max}^{KBr} 1768, 1745 and 1712 cm^{-1}, the same as previously reported.[87]

The methyl ester CXV was prepared by the method of Alder and Stein[38] using ethereal diazomethane and gave m.p. 76° (reported[38] 77°). υ_{max}^{KBr} 1790, 1775 and 1739 cm^{-1} (reported[87] υ_{max}^{KBr} 1785 and 1740 cm^{-1}).

XLIV and CXVI

The hydroxylactone acid XLIV prepared by the method described by Berson[42] gave m.p. 204-205° (reported[42] 204-206°) and υ_{max}^{KBr} 3400, 1760, and 1725 cm^{-1}.

The methyl ester CXVI was prepared as previously described.[42] The ester hydrate gave m.p. 58° (reported[42] 61°), which after drying (in vacuo for 30 hr. at 55°) gave m.p. 90-90.5° (reported[42] 90-90.8°). The ester hydrate gave ν_{max}^{KBr} 3500, 1770, and 1728 cm^{-1} (reported[42] $\nu_{max}^{HCCl_3}$ soln. 3605, 1778, and 1737 cm^{-1}).

XXXII and CXVII

The bromolactone acid XXXII was synthesized by the procedure of Alder.[38] The bromolactone acid XXXII gave m.p. 184-185° (reported[38] 187°). ν_{max}^{KBr} 1770 and 1730 cm^{-1}. After drying the bromolactone acid XXXII for 8 hr. at 1 mm and 144°, it gave m.p. 184-185° and ν_{max}^{KBr} 1750 and 1735 cm^{-1}.

The methyl ester CXVII was prepared by treatment of the acid with an excess of ethereal diazomethane until the yellow color persisted. Needle-like crystals formed on air evaporation of the ether solution, and gave m.p. 115-116°. Recrystallization from methanol gave m.p. 115.5-116° and ν_{max}^{KBr} 1788, 1775 and 1735 cm^{-1}.

CXVIII

An excess of diazomethane (≈ 2 g.), dissolved in ether (70 ml.), was added to a mixture of exo-cis-5,6-dibromobicyclo[2.2.1]heptane-endo-cis-2,3-dicarboxylic anhydride (5 g., m.p. 210-211°, prepared as previously described[88]) and allowed to stand overnight. The solution was then evaporated to a viscous oil in a rotary evaporator. On cooling, the oil crystallized. Recrystallization of the diester from methanol (20 ml.) yielded 4 g. of needle-like crystals which gave m.p. 80-80.5° (reported[48] 80.5-81.5°) and ν_{max}^{KBr} 1737 and 1715 cm^{-1}.

XXXV

The dilactone XXXV was syntehsized by the method of Winston and Wilder.[52] The dilactone gave m.p. 274.5-275.5° (reported[52] 274-275°) and υ_{max}^{KBr} 1795 and 1770 cm^{-1} (reported[52] $\upsilon_{max}^{Nujol\ mull}$ 1805 and 1785 cm^{-1}).

CXIX and CXX

The ketolactone acid CXIX was prepared by the procedure of Alder.[89] The ketolactone acid gave m.p. 218-221° (reported[89] 218-219°) and υ_{max}^{KBr} 1780, 1757 and 1705 cm^{-1}.

The methyl ester CXX was prepared by treating the acid CXIX with an excess of ethereal diazomethane until the yellow color persisted. Evaporation of the ether yielded the exter CXX which gave m.p. 167-168°. The ester gave m.p. 170.5-171° and υ_{max}^{KBr} 1780, 1757 and 1722 cm^{-1} after one recrystallization from methanol. Further recrystallizations from methanol did not raise the melting point.

CXXI

The methyl ester CXXI was prepared as previously described[58] by treatment of XLV with excess ethereal diazomethane. The prepared ester gave m.p. 73-74° (reported[58] 75°).

LXXVIII

The ketocarbamoyl lactam LXXVIII was prepared as previously described by Worral.[41] The lactam gave m.p. 238-239° (reported[41] 234-235.5°). υ_{max}^{KBr} 3300, 3175, 1775, 1750, 1660, 1625, and 1600 cm^{-1} (reported[41] $\upsilon_{max}^{Nujol\ mull}$ 1755 and 1725 cm^{-1}).

LV

The exo-anhydride LV was syntehsized by a previously described method[46] and shown to be pure by gas chromatography (see p. 66).

XIX

Commercially available XIX (Eastman reagent grade) was used. The endo-anhydride XIX was shown to be pure by gas chromatography (see p.

The preparations of the bicyclic compounds appearing in Tables 1, 2, 3 and 4 which are not given in this chapter are described in the experimental sections of the preceding three chapters.

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Doctor of Philosophy

Thesis: THE REACTIONS OF N-BROMOSUCCINIMIDE, N,N-DIBROMOBENZENE-SULFONAMIDE AND BENZENESULFONYL AZIDE WITH BICYCLO[2.2.1]-5-HEPTENE-2,3-DICARBOXYLIC ANHYDRIDE. N-ALKYL CLEAVAGE OF γ-LACTAMS BY ACID HYDROLYSIS. STEREOCHEMICAL DETERMINATIONS IN THE BICYCLO[2.2.1]HEPTANE SYSTEM VIA NUCLEAR MAGNETIC RESONANCE.

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