

AN ABSTRACT OF THE THESIS OF

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(Name) (Degree) (Major)

Date thesis is presented July 26, 1966

Title CONFORMATION AND REACTIVITY STUDIES OF SOME
BICYCLO(3. 3. 1)NONANE DERIVATIVES

Abstract approved [REDACTED]
(Major professor)

New syntheses for 2-bicyclo(3. 3. 1)nonanone and 7-bicyclo(3. 3. 1)nonen-2-one were developed. The saturated ketone was prepared from phenol and acrylonitrile via a novel intramolecular S_N2 cyclization process. A Friedel-Crafts cyclization of 3-(3-cyclohexenyl)propanoyl chloride permitted synthesis of the unsaturated ketone from 4-cyclohexene carboxaldehyde. The formation of the bicyclo(3. 3. 1)nonane rather than a bicyclo(3. 2. 2)nonane skeleton in the Friedel-Crafts cyclization was proven by comparative mass spectrometry. An attempt to prepare 2-bicyclo(3. 3. 1)nonyl acetate by solvolysis of 3-(3-cyclohexenyl)propyl tosylate led only to monocyclic products.

The influence of the proximity of carbons 3 and 7 on the chemistry of the bicyclo(3. 3. 1)nonane ring was studied via the transannular reactions from 2-bicyclo(3. 3. 1)nonene oxide. This epoxide was shown to be the exo-2, 3-epoxide by reduction to the

known exo-2-bicyclo(3.3.1)nonanol. Solvolysis of the epoxide in trifluoroacetic acid gave almost exclusively 7-bicyclo(3.3.1)nonen-exo-2-ol. Solvolysis in acetic acid-sodium acetate gave 20% 3-bicyclo(3.3.1)nonen-exo-2-ol, 54% exo-2-exo-7-bicyclo(3.3.1)nonadiol, and about 14% exo-2-exo-3-bicyclo(3.3.1)nonadiol.

Formation of the strained 1-bicyclo(3.3.1)nonene as a transient enolate ion intermediate in the proton exchange at the bridgehead was shown by synthesis and exchange studies of 3,3-dimethyl-2-bicyclo(3.3.1)nonanone. In deuteriomethanol at 100.8° the rate of exchange equals 0.67×10^{-4} l./mole-sec.

A combination of chemical and spectral methods was used to make some conformational assignments for a number of bicyclo(3.3.1)nonane derivatives.

CONFORMATION AND REACTIVITY STUDIES OF SOME
BICYCLO(3. 3. 1)NONANE DERIVATIVES

by

DAVID MICHAEL STURMER

A THESIS

submitted to

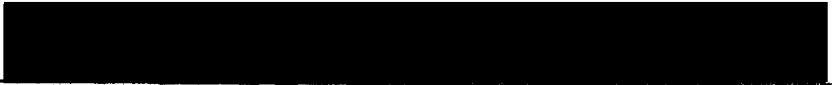
OREGON STATE UNIVERSITY

in partial fulfillment of
the requirements for the
degree of


DOCTOR OF PHILOSOPHY

June 1967


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ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Dr. E. N. Marvell for his helpful guidance and discussion during the course of this work.

The understanding and patience of the author's wife has contributed greatly to the successful completion of this study.

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CONFORMATION AND REACTIVITY STUDIES OF SOME BICYCLO(3.3.1)NONANE DERIVATIVES

INTRODUCTION

The investigation of structure-energy relationships has been a central theme for chemical endeavor. Although these relationships may arise in principle from any study of molecular structure and reactivity, the more usual approach has been to select model systems which feature certain structural aspects. The study of model systems then discerns the effect of these aspects on energy or reactivity.

The bicyclo(3.3.1)nonane model system has been selected by many workers because of unique geometric features. The bicyclic system and its three possible conformations are shown in Figure 1.

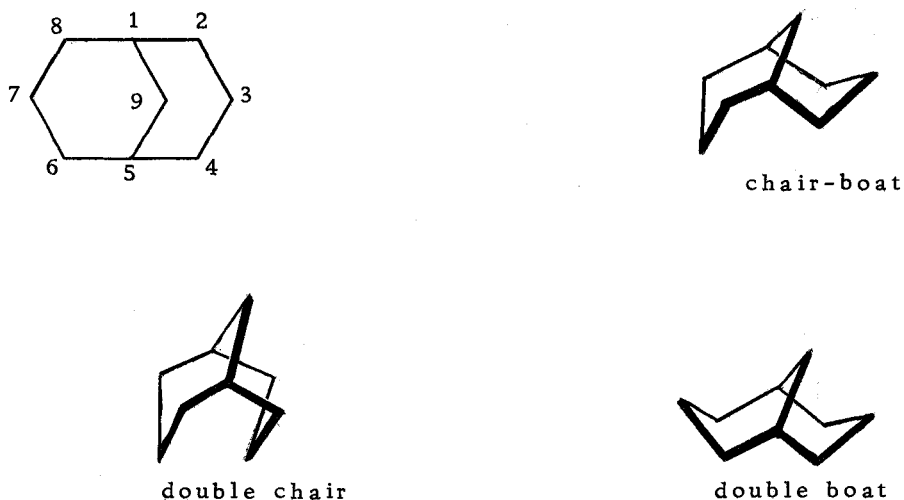


Figure 1. Conformations of Bicyclo(3.3.1)nonanes

The system consists of a cyclooctane ring which is bridged symmetrically by a single carbon (C-9). As a result chemical and physical properties peculiar to both cyclohexane and cyclooctane rings may be expected. In addition, special properties may be noted since fewer conformations are possible for this ring than for cyclooctane and since bridging may impart strain characteristics not present in either cyclohexane or cyclooctane.

The present study of this ring system was initiated to synthesize several bicyclo(3.3.1)nonanes by novel methods, to determine physical and chemical consequences of the exceptional C-3 to C-7 crowding (double chair conformation), and to study strain energies of bridgehead double bonds (C-1 to C-2). These latter areas are concerned with the most interesting characteristics which unique geometry should impart to the bicyclo(3.3.1)nonane system.

HISTORICAL

Bicyclo(3.3.1)nonane compounds were first discovered around 1900. Since then, the interest in this ring system has been sporadic. Early work centered around the study of strained olefins. Subsequently, the difficulty of synthetic approaches caused attention to turn to more readily available rigid rings. At the present time, however, there is revived interest in this system because of its unusually close C-3-C-7 hydrogens and its growing importance in the study of natural products. The following review divides the literature into two sections: one on synthetic methods and another on the chemistry of the bicyclo(3.3.1)nonanes.

Synthesis of Bicyclo(3.3.1)nonanes

Current Methods

Synthetic approaches to bicyclo(3.3.1)nonanes are made difficult by the presence of strained, six-membered rings in the bicyclic compounds. The standard synthetic routes to bicyclo(3.3.1)nonanes, listed in Table 1, find little in common with the classic approaches to carbocyclic rings (54). Historically, the most prominent syntheses of this ring system have used condensation reactions, as in methods 1, 2, 7, and 10. Frequently, activating groups alpha

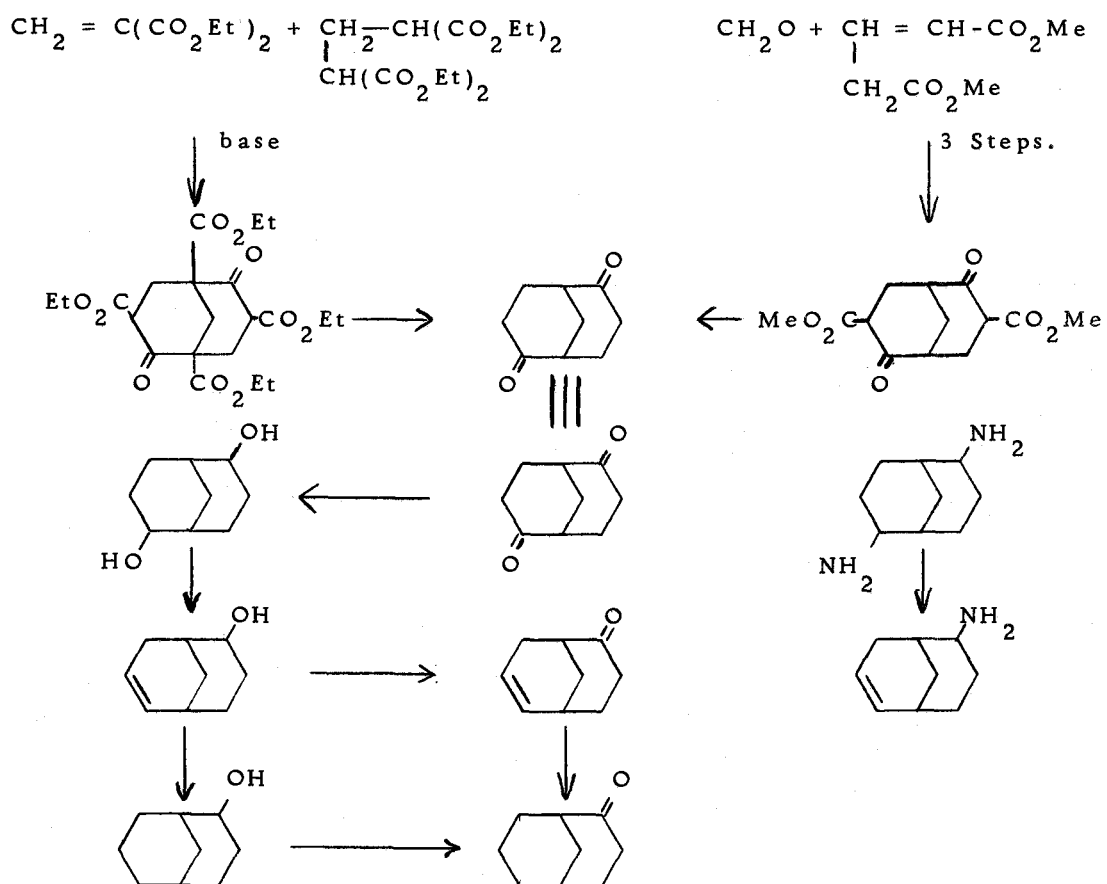
to the cyclohexanone carbonyl direct the reaction to one side of the ketone. Compounds prepared in this manner have a ketone at C-9 and at least one bridgehead substituent. The ketone can be removed by a Wolf-Kishner reaction only in the absence of base-sensitive functional groups elsewhere in the molecule. Bridgehead substituents are often difficult to displace. Attempts to remove carbethoxy groups under a variety of conditions have led to rearrangement (32, 80). As a result, condensation reactions are not general synthetic methods for simple bicyclo(3.3.1)nonane derivatives.

Probably the most promising synthetic approaches to bicyclo(3.3.1)nonanes have used Stork's enamine procedures (106). In this way Cope has modified a previous method (32) to obviate the necessity for activating groups (method 3, Table 1). Stork's synthesis of 2-pyrrolidinobicyclo(3.3.1)nonan-9-one (method 4A, Table 1) must be followed by ring opening and reclosure to remove the pyrrolidine substituent (method 4D, Table 1). A similar but direct synthesis of bicyclo(3.3.1)nonanes was developed by Woodward and Foote (method 4B, Table 1). The successful conversion of bicyclo(3.3.1)non-2-ene to alcohols and ketones has increased the usefulness of this scheme (method 4C, Table 1).

A wide variety of reactions which form carbon-carbon bonds have found minor application in syntheses of bicyclo(3.3.1)nonane ring systems. In Table 1 there are a few examples: a carbonium ion

Table I. Major Synthetic Methods

Method 1. References 78, 79, 91 and 101



Method 2. References 32, 80, and 19.

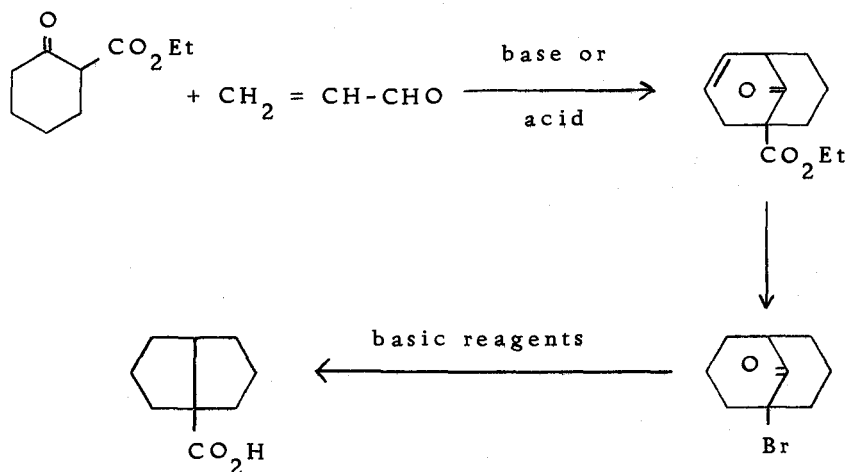
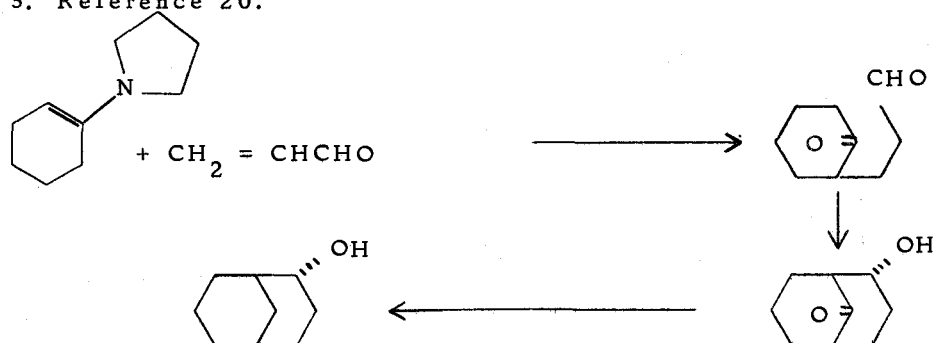


Table I. (Continued)

Method 3. Reference 20.



Method 4. Scheme A, R = Reference 107

Scheme B, R = Reference 55, p. 96-101

Scheme C, R = Reference 72

Scheme D, R = References 62, 20

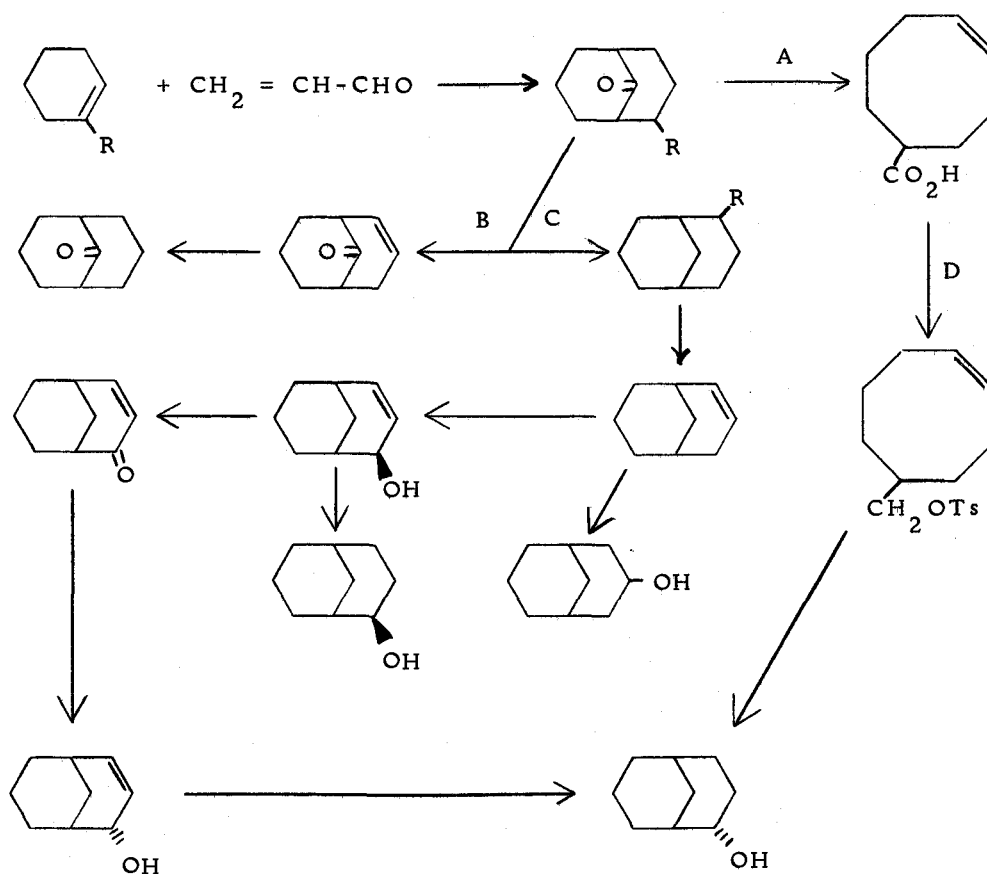
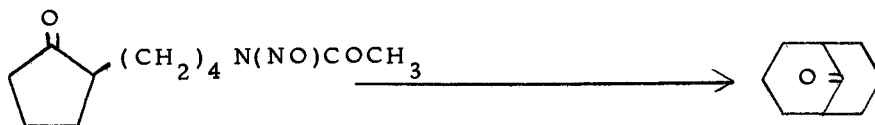


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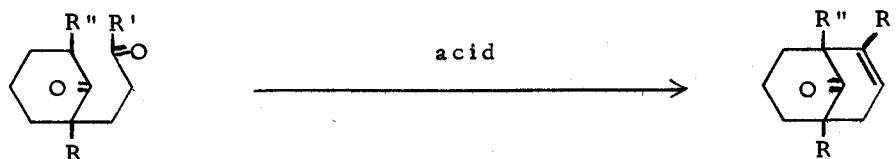
Method 5. Reference 59.



Method 6. Reference 14.



Method 7.

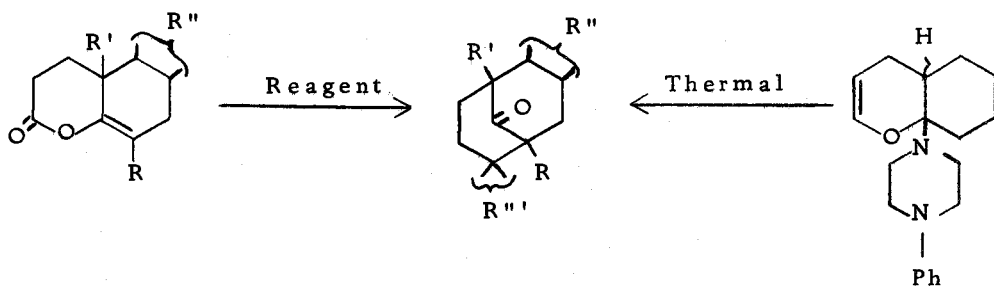


<u>Substituents</u>	<u>Reference</u>
$\text{R} = \text{CHO}, \text{R}' = \text{Me}, \text{R}'' = \text{H}$	13
$\text{R} = \text{CH}_2\text{Ph}, \text{R}' = \text{OH}, \text{R}'' = \text{H}$	58
$\text{R} = \text{CO}_2\text{Et}, \text{R}' = \text{H}, \text{R}'' = \text{Me}$	46, 81
$\text{R} = \text{CO}_2\text{Et}, \text{R}' = \text{CH}_3, \text{R}'' = \text{Me}$	43
$\text{R} = \text{Me}, \text{R}' = \text{OH}, \text{R}'' = \text{Me}$	77

no cyclization in acid or base

Table I. (Continued)

Method 8.

ConditionsReferences

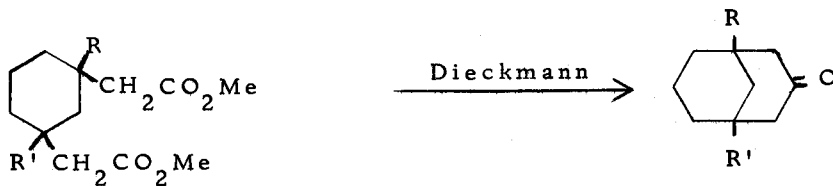
Reagent $\text{LiAlH}(\text{OtBu})_3$; $\text{R}=\text{Me}$; $\text{R}'=\text{Me}$; $\text{R}''=\text{H, H}$; $\text{R}'''=\text{epimeric H, OH}$ 77

Reagent $\text{h}\nu$; $\text{R}=\text{H}$; $\text{R}'=\text{H or CH}_3$; $\text{R}''=\text{steroid system}$, $\text{R}'''=\text{ketone}$ 115

Reagent MeMgI ; $\text{R}=\text{H}$; $\text{R}'=\text{CH}_3$; $\text{R}''=\text{steroid system}$; $\text{R}'''=\text{epimeric Me, OH}$ 57

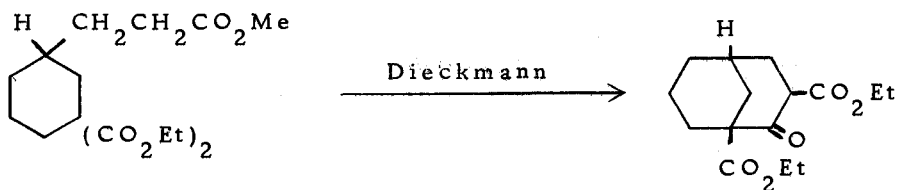
Thermal $\text{R}=\text{R}'=\text{R}''=\text{H}$, $\text{R}'''=\text{epimeric H}$, -N N-Ph 99

Method 9. References 80, 60, and 53.



$\text{R, R}'=\text{CO}_2\text{Me, Me}$ 80

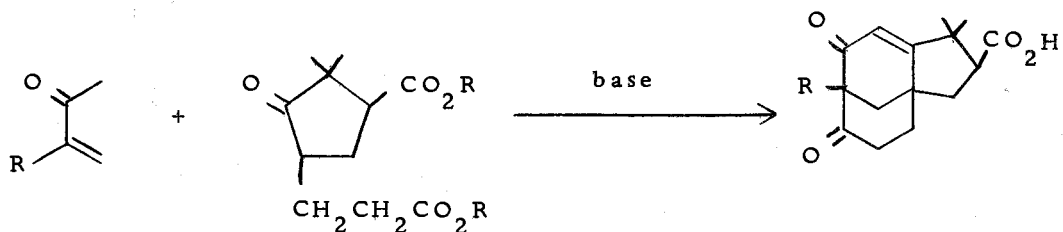
$\text{R, R}'=\text{H, H}$ 60



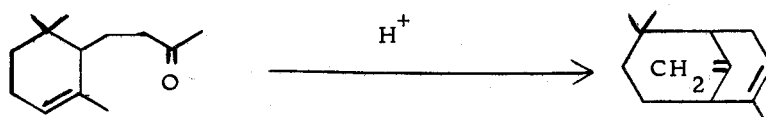
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Table I. (Continued)

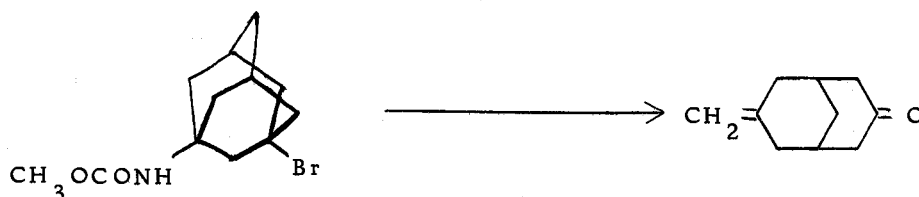
Method 10. Reference 7.



Method 11. References 105 and 17.



Method 12. Reference 102.



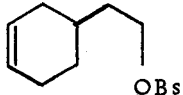
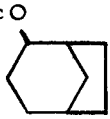
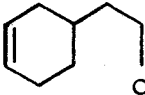
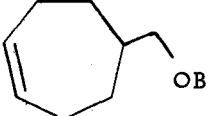
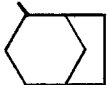
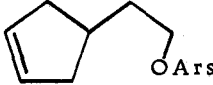
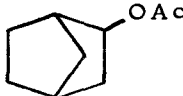
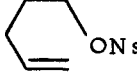
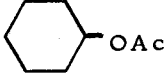
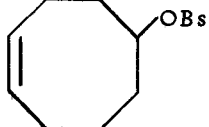
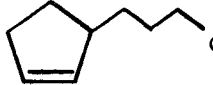
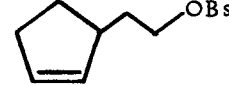
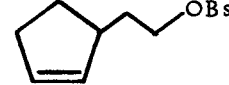
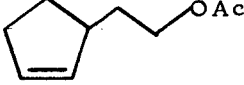
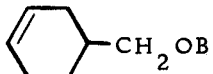
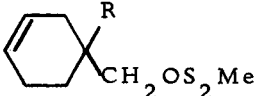


addition to a double bond (method 11); the Dieckmann reaction (61) (method 9); a carbenoid insertion (method 5); and an adamantane fragmentation (method 12). Although numerous intramolecular acylations have been catalogued by House (66, p. 282-298) and reviewers of earlier work (68, p. 114, 111), only one such reaction has been reported (64) to yield a simple bicyclo(3.3.1)nonane skeleton.

Ring enlargement reactions (67) have not been used in any general synthetic approaches to bicyclo(3.3.1)nonanes. The major obstacle to this procedure is that the compounds required for ring expansion, bicyclo(3.2.1)octanes, are difficult to prepare with the necessary substituents.

Double Bond Participation in Solvolysis

Ring closure by double bond participation in solvolytic reactions is important from both synthetic and mechanistic viewpoints. Recently, this method has been reviewed by a number of authors (5, 108, 109). Typical compounds yielding bicyclic products through participation are listed in Table II. Participation reactions show certain characteristic features. In particular, solvolytic rates are accelerated by participation. Recent publications by Bartlett and coworkers have indicated several trends: (1.) increased participation (5) occurs when the double bond can approach the site of ionization symmetrically; (2.) increased alkyl substitution (3) at the double bond accelerates the solvolysis; and (3.) increased chain length (6) leads to decreased participation. Elaboration on this latter point is particularly enlightening. The degree of participation (% bicyclic product) and the relative rates were given for three compounds (6): 2-(3-cyclopentenyl)ethyl nosylate (100%, 600); 3-(3-cyclopentenyl)propyl nosylate (0%, 1); and 3-(3,4-dimethyl-3-cyclopentenyl)propyl

Table II. Participation Reactions.

Reactant ^a	Conditions	Products	Reference
	HOAc 75°C	 	114
	HOAc		74
	HOAc, HO ₂ CH EtOH-H ₂ O		73, 4
	HOAc		5
	--	Bicyclo(3.3.0)octanols plus minor products	30
	HOAc, HO ₂ CH	100% bicyclic products	18
	HO ₂ CH	75% bicyclic products	18
	HOAc	100% 	18
	HOAc	no bicyclic products	74
	HOAc, Ac ₂ O R=H, Me; no bicyclic products		9
	HOAc	66-72% bicyclic products	108, p. 52
		CH ₂ CH(CH ₃)OSO ₂ Ar	

^aBs, Ns, Ars = *p*-bromo-, *p*-nitro-, *p*-subst.-phenylsulfonyl

nosylate (57%, --). The striking contrast between the first two compounds is caused (6) by a higher activation enthalpy for the propyl side chain. Skew butane interactions must be greatly increased to obtain participation. The larger number of unreactive conformers in a propyl (vs. ethyl) side chain is considered a minor contributor to the observed rate decrease of 600. An increased yield of bicyclic products (57%) from the third compound illustrates that methyl groups at the double bond promote participation. Consequently, the controlling factor is not primarily the frequency with which the terminal propyl carbon approaches the double bond (entropy control) but rather the increased stability of the bicyclic ion intermediate (enthalpy control).

Chemistry of Bicyclo(3.3.1)nonanes

Deuterium Exchange at Bridgehead Carbon Atoms

Bicyclic ring compounds show interesting variations in strain energy. Although the presence of strain complicates synthesis, the variations in strain can provide valuable insight into structure-energy relationships. One of the most widely studied of these relations is the stability of bridgehead double bonds in various ring systems. The more stable structures have been isolated as olefins. When these unsaturated compounds could not be isolated, enolization

to bridgehead positions has been used to estimate relative stabilities.

According to an early review, Bredt's rule is stated (50, p. 222):

In polycyclic systems having atomic bridges, the existence of a compound having a carbon-carbon or carbon-nitrogen double bond at a bridgehead position is not possible, except when the rings are large, because of the strain which would be introduced by its formation by distortion of bond angles and/or distances. As a corollary, reactions which should lead to such compounds will be hindered or will give products having other structures.

The limits on ring size for bridgehead double bonds in bicyclic systems have been investigated by Prelog and coworkers (89, 90, 94) for 1-bicyclo(x.3.1)alkenones. Unsaturated compounds were isolated for $x = 5$ to 8. More recently, Bond (10, p. 182) has shown that a stable compound with $x = 4$ can be prepared. Attempts to obtain unsaturated molecules with $x = 3$ were made by Rabe (95), but no alkenes were isolated by dehydration of 5-methyl-1-bicyclo(3.3.1)nonanol and 3,5-dimethyl-1-bicyclo(3.3.1)nonanol. Dehydration (22) of 2,4-dialkyl-2-hydroxy-9-bicyclo(3.3.1)nonanone gave the non-conjugated ketone rather than the conjugated ketone possessing a bridgehead double bond.

Double bonds to the bridgehead position in bicyclic structures have been postulated as enolic intermediates. For example, a study of the decarboxylation of beta-keto acids has been made by Ferris (53). The ease of decarboxylation is considered proportional to the stability of the six-membered transition state for the reaction and

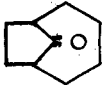

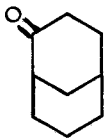
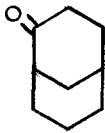

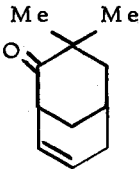
the enol form which results from this. Decarboxylations of 1-carboxybicyclo(3.3.1)nonan-2-one and 1-carboxybicyclo(3.3.1)nonan-9-one indicate that the enol between C-1 and C-2 is more stable than the enol between C-1 and C-9. More quantitative information concerning the stability of bridgehead enol forms has been obtained through deuterium exchange methods. Although a number of monocyclic ketones have been studied (42, 83, 84), more interesting examples are provided by the bicyclic ketones in Table III. Deuterium incorporation at the bridgehead does occur for all of these bicyclic structures, but the variations in experimental conditions make comparisons of enol form stabilities invalid.

Transannular Hydride Shifts and Related Reactions

Studies of transannular reactions have increased understanding of the relationship between geometry and reactivity. These efforts were most successful in their applications to monocyclic and bicyclic compounds. Although transannular shifts of various groups are noted in the literature (37), the most thorough documentation of transannular reactions has dealt with hydride shifts.

An excellent review (88) of work on transannular hydride shifts was authored recently by Prelog and Traynham. They suggested that the proximity of certain hydrogen atoms in medium-ring cycloalkanes gives rise to considerable strain and is geometrically favorable for

Table III. Deuterium Incorporation

Reactant	Conditions	Time	Extent of Reaction	Reference
	NaOMe	1 hr, R. T. 24 hrs, 65°C	0% d ₁ , 0% d ₂ 15% d ₁ , 1% d ₂	8
	NaOMe DOME	1 hr, R. T.	0% d ₁ , 100% d ₂	8
	NaOD, D ₂ O dioxane	95°C, 26 days	2.56 D/molecule	98
	NaOMe, DOME	22 hrs, R. T.	40% d ₁ , 22% d ₂ , 2% d ₃	20
	NaOEt, DOEt	24 hrs, R. T.	1% d ₁	30
	NaOMe, DOME	100.8°C	k = 1.9 × 10 ⁻⁶ l. m. sec. ⁻¹	97

transannular shifts. X-ray studies by Dunitz and coworkers (88, p. 594) give experimental proof for the suggested proximity. Transannular hydride shifts have been detected in elimination reactions of cycloalkanol (7, 9-12 membered rings) tosylates (87, 92) by either carbon-14 or deuterium labelling. Extensive rearrangement of both types of labels occurred. In deuterium-labelled trans-cyclodecene (from cyclodecyl tosylate-1-d), only 3% of the label was found alpha to the double bond while 16% of the label was on the delta and epsilon carbons. This indicates that the hydride shifts are a one step process rather than a series of 1,2-hydride shifts. More extensive transannular reaction was found in cis- and trans-cyclooctane-1,2-ditosylates (40) where the inductive effect of an adjacent tosylate group promoted reaction exclusively by 1,5-hydride shift. Prelog and Borcic (88, p. 612) have considered the general mechanism of hydride shifts. A hydrogen-bridged ionic intermediate is unlikely on the basis of the following results. During acetolyses of cyclodecyl tosylate and 5,5,6,6-tetradeuterocyclodecyl tosylate, they found only a small deuterium isotope effect and no significant change in product ratios. The isotope effect was ascribed to smaller ground state strain in the deuterium compound.

A number of transannular hydride shifts have been detected during solvolytic reactions or olefin hydroxylations by peracids. These reactions in medium rings have been reviewed by Cope,

Martin and McKerney (34). Two examples are presented in Table IV. The particularly important dependence of transannular reaction on solvent nucleophilicity is shown by cis-cyclooctene oxide solvolyses. Less transannular reaction occurs in more highly nucleophilic media. Rearrangement products from trans-cyclooctene oxide assume significant proportions and indicate that transannular reaction is perhaps less favorable here than in the cis isomer. Estimates of hydride shift types have also been made. Degradations of products from the formolysis of 5,5,6,6-tetradeutero-cis-cyclooctene oxide (24) indicate that the cis-1,4-cyclooctane diol arises by 61% 1,5-shift and 39% 1,3-shift, while the 3-cyclooctenol arises by 94% 1,5-shift and 6% 1,3-shift. Similar results were obtained in solvolyses of 1,2,2,8,8-pentadeuterocyclooctyl brosylate. Acetolysis and formolysis (21) showed rearrangement almost exclusively by 1,5-hydride shift with insignificant amounts of 1,3-shifts. Other aspects of transannular reactions are illustrated by a variety of compounds. The effect of ring size was noted in the hydroxylation of cyclohexene with performic acid. Only 0.03% of transannular product was found (26). Open chain systems also exhibit negligible transannular reaction. The oxidation of 1-octene with performic or peracetic acid gave 100% unrearranged products (31). Solvolysis of the related epoxide (31) resulted in only 0.18% of 1,3- or larger hydride shifts. In contrast to this, medium-ring

bicycloalkanes provide more interesting substrates. The solvolyses of cis-bicyclo(6.1.0)nonane (23) and trans-bicyclo(6.1.0)nonane (27) have shown the dependence of transannular reaction on stereochemistry. Products for the trans (cis) case were: transannular products, 25.2% (93%); normal products, 22.1% (--); and ring contraction products, 34.3% (--). These results are similar to the results for the oxygen analogues in Table IV.

Table IV. Solvolysis of Cyclooctene Oxides

Oxide(ref.)	Solvent	Normal Products	Transannular Products	Rearr. Products
<u>trans</u> (41)	Formic acid	1%	45%	44%
<u>cis</u> (29)	Trifluoroacetic Acid	0%	100%	0%
	Trichloroacetic Acid	6%	94%	0%
	Formic Acid	13%	87%	0%
	Acetic Acid	46%	54%	0%
	Acetic Acid-Sodium Acetate	76%	24%	0%
	Trimethylacetic Acid		no reaction	

Transannular migrations in a variety of reactions have been noted primarily by Prelog and Cope and their coworkers. Table V contains several examples. The migration of groups other than hydrogen or deuterium was discovered by Cope (37). A 1,5-phenyl

shift occurred to the extent of 1% in the solvolysis of 5,5-diphenylcyclooctyl tosylate in trifluoroacetic acid-sodium trifluoroacetate whereas no migration occurred in formic acid. Prelog and Traynham (88) ascribe this behavior to conformational mobility in medium-sized rings. The interannular positions, from which migration can most readily take place, are sterically hindered and will be occupied by hydrogens in preference to larger substituents. Thus, substitution in the 4 and 5 positions relative to the site of carbonium ion development is not sufficient to promote transannular substituent shifts.

The bicyclo(3.3.1)nonane system contains a conformationally restricted cyclooctane ring. Recently published examples of transannular reactions indicate that this system favors such processes (Table VI).

Spectroscopic Investigations

Spectroscopic examinations of ground state geometry provide uniquely reliable information. Conclusions based on chemical reactivities are fortified tremendously by such data. As in the study of medium rings and transannular reactions, a knowledge of molecular geometry for the bicyclo(3.3.1)nonane system is very important. X-ray diffraction analyses of 1-methylbrosylate-5-methyl-bicyclo(3.3.1)nonan-9-ol (15) and 3-azabicyclo(3.3.1)nonane

Table V. Miscellaneous Transannular Reactions

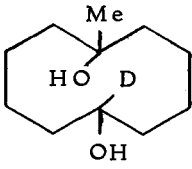
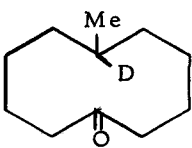
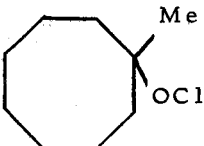
Reactant	Conditions	Transann. Prod.	Type of Migration	Reference
	acid		1, 6-deuteride	93
<u>cis-cyclodecene oxide</u>	LiNEt ₂	91%	1, 5 and 1, 6-hydride	25
4-cyclooctenyl brosylate	HOAc	94%	C = C participation	30
cyclooctanol	Pb(OAc) ₄	26%	1, 4 cyclic ether from free radical intermediate	35
cyclooctene	Pb(OAc) ₄	75%	1, 4 hydrogen	35
	hν	99%	1, 4 and 1, 5 hydrogen	39

Table V. (Continued)

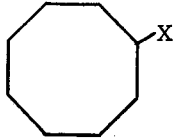
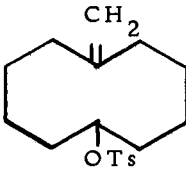
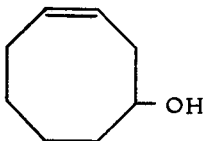
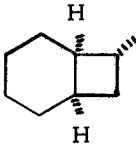
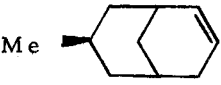
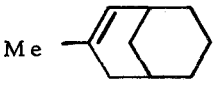
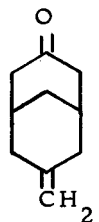

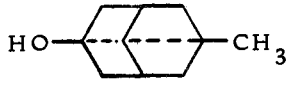
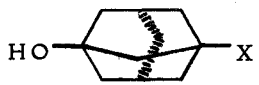
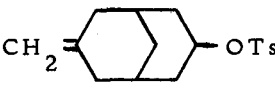
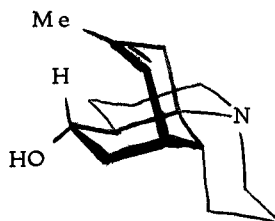
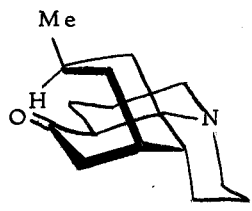
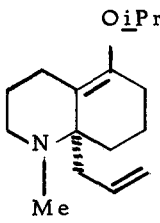
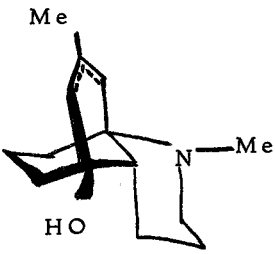


Reactant	Conditions	Transann. Prod.	Type of Migration	Reference
	X = Br, HOAc, AgOAc	0.7%	transannular elimination	36
cyclooctyl tosylhydrazone	NaOCH ₃ in diethyl carbitol	56.5%	1, 4 and 1, 5 transannular insertion	36
cyclodecylamine	HNO ₂	0%	-	56
	solvolysis	100%	C = C participation	113
cyclodecyl hydrogen phthalate	pyrolysis	small %	transannular elimination	33
	HO ₂ CH		1, 3 C = C participation	38
cyclooctanone	590°	7-octen- 2-one 12.3%	1, 5-hydride	28

Table VI. Transannular Reactions of Bicyclo(3.3.1)nonanes

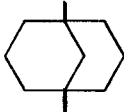
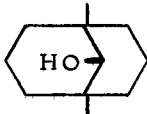
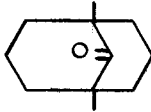
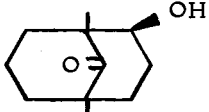
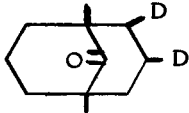
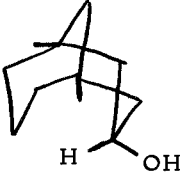
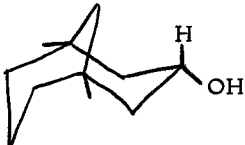
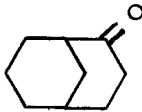
Reactant	Conditions	Products Isolated	Reference
	HO_2CH Wolf Kishner	 adamantane	1 48
	LiAlH_4 Na, moist ether HX	  	48, 102 48 103
	exo, endo $\text{Et}_2\text{O}, 6\text{NH}_2\text{SO}_4$	adamantan-1-ol	48
	75% H_2SO_4		2
	75% H_2SO_4 (cyclization followed by transannular shifts)		47
	HX		104

hydrobromide (45) show that the double chair conformation of the molecule (Figure 1) is preferred. Interaction of the C-3 and C-7 hydrogens is relieved by increasing the angles at carbons 2, 3, 4, 6, 7, and 8 to 114° . The C-3 to C-7 distance is 3.05 \AA whereas with tetrahedral angles it would be 2.52 \AA . Two planes of symmetry are retained, however, since the C-4 to C-8 and C-2 to C-6 distances are identical.

Infrared spectra of certain bicyclo(3.3.1)nonanes show enhanced C-H stretching and bending frequencies. A most thorough study of these frequencies has been published recently by Eglinton, Parker, and Sims (48). Their results, summarized in Table VII, are analogous to those of DeVries and Ryason (44) and Kivelson, et al. (70). The enhanced stretching frequencies are due to steric crowding of methylene groups. Using a relatively simple model for the interaction of the methylene groups, Kivelson (70) predicted the enhanced frequencies for molecules which are considerably more crowded than the bicyclo(3.3.1)nonanes. No such calculations have been attempted for the compounds in Table VII. It is of interest to note that no enhanced frequencies are obtained for 2-bicyclo(3.3.1)nonane in which C-2 is sp^2 hybridized.

Electronic spectra have been used to make estimates of molecular geometry. Ferguson and Nnadi (52) have recently reviewed the simple electronic interactions between unsaturated

Table VII. Enhanced Frequencies

Cmpd	ν stretch	ν bend	Ref.
	2990	1488	49
	2991	1490	49
	2992	1490	49
	2994	1488	49
	2990	1473	49
	2990	1473	76
	none	1472	76
	none	-	20

functional groups. Their discussion of the spectral characteristics of unsaturated ketones is particularly important. Direct conjugation of a ketone shifts the $\pi \rightarrow \pi^*$ band from 185 $m\mu$ ($\epsilon = 10^4$) to 220-260 $m\mu$ ($\epsilon = 10^4$). The $n \rightarrow \pi^*$ band shifts from 280 $m\mu$ ($\epsilon < 50$) to 300-350 $m\mu$ ($\epsilon = 50$). The effect of beta, gamma-unsaturation depends on the type of overlap which can occur. Generally, " π -overlap" (parallel p-orbitals) leads to strong absorption about 210-260 $m\mu$ and weak absorption around 280 $m\mu$ ($\epsilon < 50$). However, " σ -overlap" keeps the $\pi \rightarrow \pi^*$ band below 210 $m\mu$ and increases the intensity near 280 $m\mu$ ($\epsilon > 50$). Perhaps the best guide as to which type of overlap exists is the $\epsilon_{n-\pi^*}$. This value is less than 50 for " π -overlap" and greater than 50 for " σ -overlap."

A reasonably quantitative correlation of orbital overlap, electronic spectrum, and conformation has been published by MacKenzie (75). The change of the overlap integral with the geometry of a $C_4=C_3-C_2-C_1=O$ system provides a basis for conformational analysis through ϵ_{290} values. Defining the xy-plane by $C_1-C_2-C_3$, ψ is the angle of $C=O$ deviation from the xy-plane, and θ is the angle of $C_4=C_3$ deviation from the z-axis. With tabulated values of ψ , θ , and the related overlap integral $S_C^2 S_O^2$, ϵ_{290} was found to be proportional to $S_C^2 S_O^2$ by a constant $K_{n-\pi^*}$. For disubstituted beta, gamma-unsaturated ketones, $K_{n-\pi^*}$ has the value 0.30 ± 0.04 . Thus, published tables of the overlap integrals

and a measured ϵ_{290} can be used to determine the geometry of these unsaturated ketones.

DISCUSSION

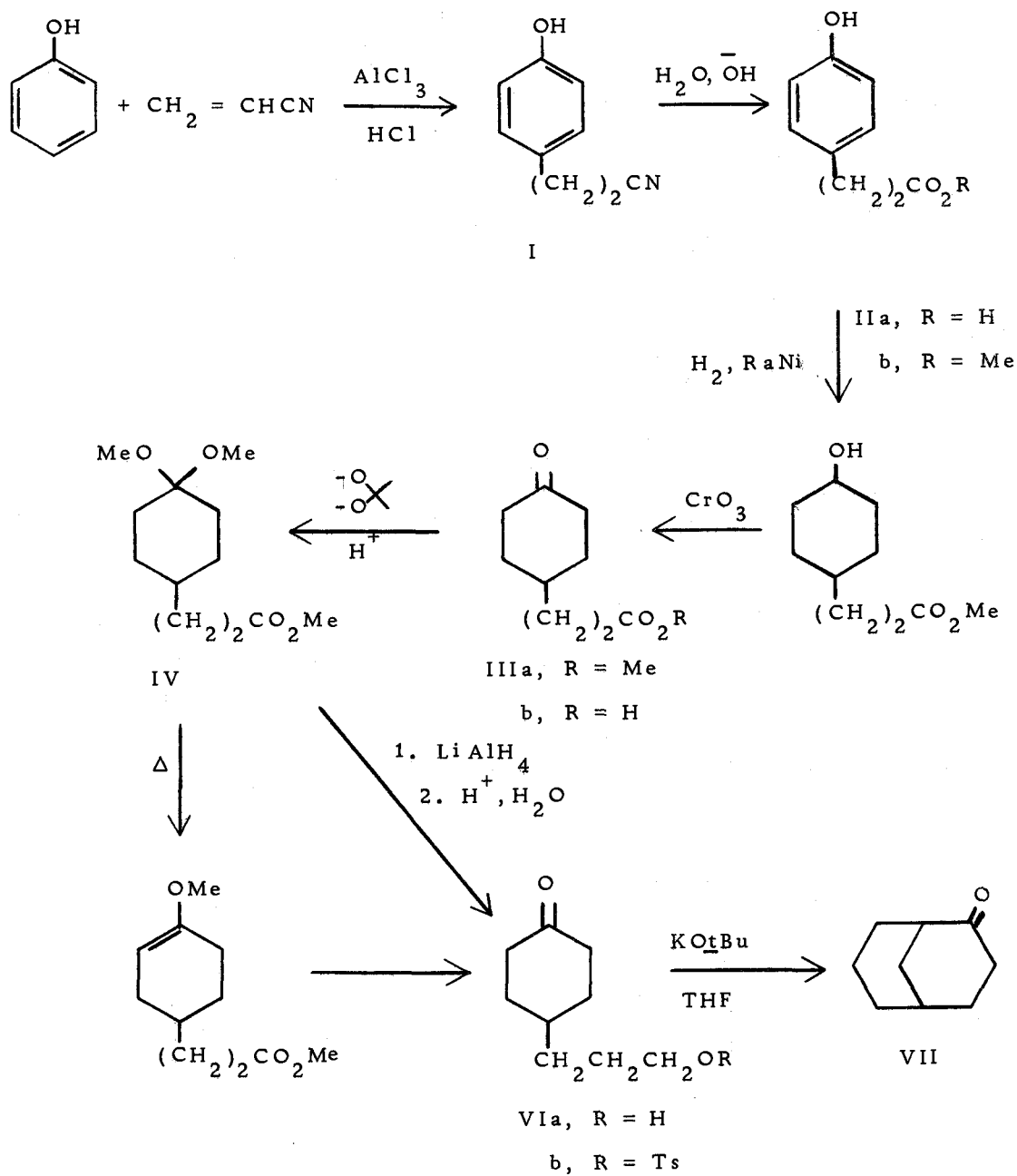
The results presented in the experimental section have two general purposes. First, a number of the reactions provide synthetic routes to the bicyclo(3.3.1)nonane system. Second, physical and chemical studies on the bicyclic compounds correlate reactivity and structure. The data pertinent to each category are discussed below.

Synthetic Approaches

Synthetic approaches to bicyclo(3.3.1)nonanes were developed as shown in Schemes I and II. In Scheme I a nucleophilic displacement was used to effect cyclization while in Scheme II an electrophilic process was used. Both approaches are well-adapted to large scale synthetic work.

Scheme I shows the unambiguous synthesis of 2-bicyclo(3.3.1)nonanone (VII). The cyanoethylation of phenol (69) yielded mainly 3-(4-hydroxyphenyl)propionitrile (I), contaminated by a small amount of the ortho isomer. Compound I was purified by fractional distillation (69). Hydrolysis of I gave the known (16) 3-(4-hydroxyphenyl)propanoic acid (IIa), which was converted to the known (63) methyl ester IIb. Nearly quantitative hydrogenation of the aromatic nucleus with W-4 Raney Nickel gave methyl

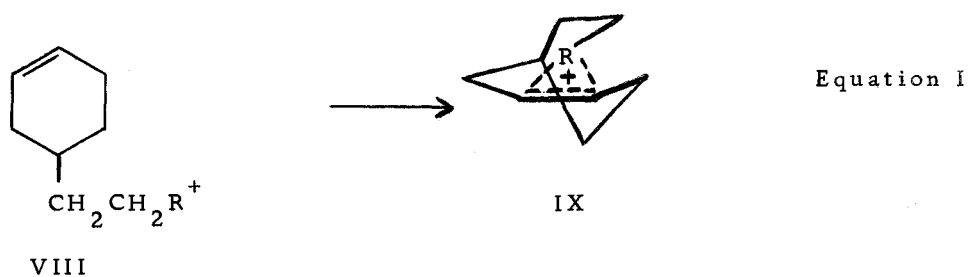
Scheme I. Bicyclo(3.3.1)nonan-2-one Synthesis.



3-(4-hydroxycyclohexyl)propanoate. This compound was oxidized in good yield to methyl 3-(4-oxocyclohexyl)propanoic acid (IIIa). A small amount of the known (11) 3-(4-oxocyclohexyl)propanoic acid (IIIb) was also isolated. The keto-ester IIIa was converted to the dimethyl ketal IV. Since IV lost methanol during distillation to give the enol ether V, both compounds IV and V were identified only by their infrared spectra. Reduction of IV (or V) with lithium aluminum hydride gave the ketal (or enol ether) of 3-(4-oxocyclohexyl)propanol (VIa). Complete reduction was evidenced by the absence of carbonyl bands in the infrared spectra. Hydrolysis of the crude reduction product in aqueous acid gave 3-(4-oxocyclohexyl)propanol (VIa), which was analysed as its 2,4-dinitrophenylhydrazone. The keto-alcohol VIa was converted to the tosylate VIb with tosyl chloride and pyridine. Temperature control at 0° in this step was quite important (110). If the pyridine solution was warmed to 10°, the product was a mixture of the tosylate VIb and 3-(4-oxocyclohexyl)propyl chloride. At room temperature only the chloride was isolated. Treatment of the tosylate VIb with potassium tert.-butoxide in tetrahydrofuran gave the known (53) 2-bicyclo(3.3.1)nonanone (VII). Presumably, this last step involves an intramolecular displacement of the tosylate group by the enolate anion. Since compound VIb has a plane of symmetry which bisects the ketone, no other bicyclic product is possible without extensive

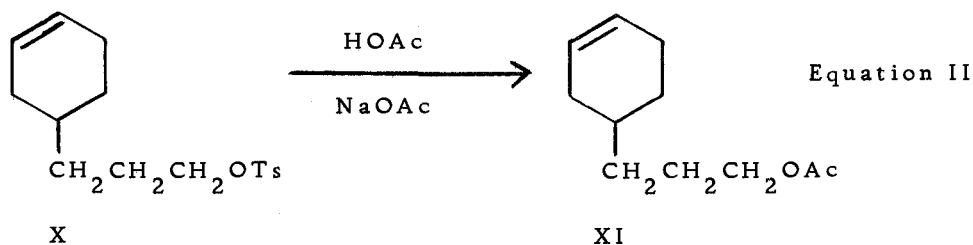
skeletal rearrangement. Only a few similar approaches have appeared in the literature, but none of these were concerned with bicyclo(3.3.1)nonanes.

More complex approaches to bicyclo(3.3.1)nonanes are based on a different mode of cyclization. Formation of a primary carbonium ion as in structure VIII (Equation I) could result in electro-



philic attack on the double bond to give structure IX. Bond formation from the bicyclic ion IX can lead to either the bicyclo(3.3.1)nonane system or the bicyclo(3.2.2)nonane system. An advantage of this method is that a bicyclic system could form with different substituents in each ring.

The solvolysis of 3-(4-cyclohexenyl)propyl tosylate (X) is shown in Equation II. Formation of the primary carbonium ion from

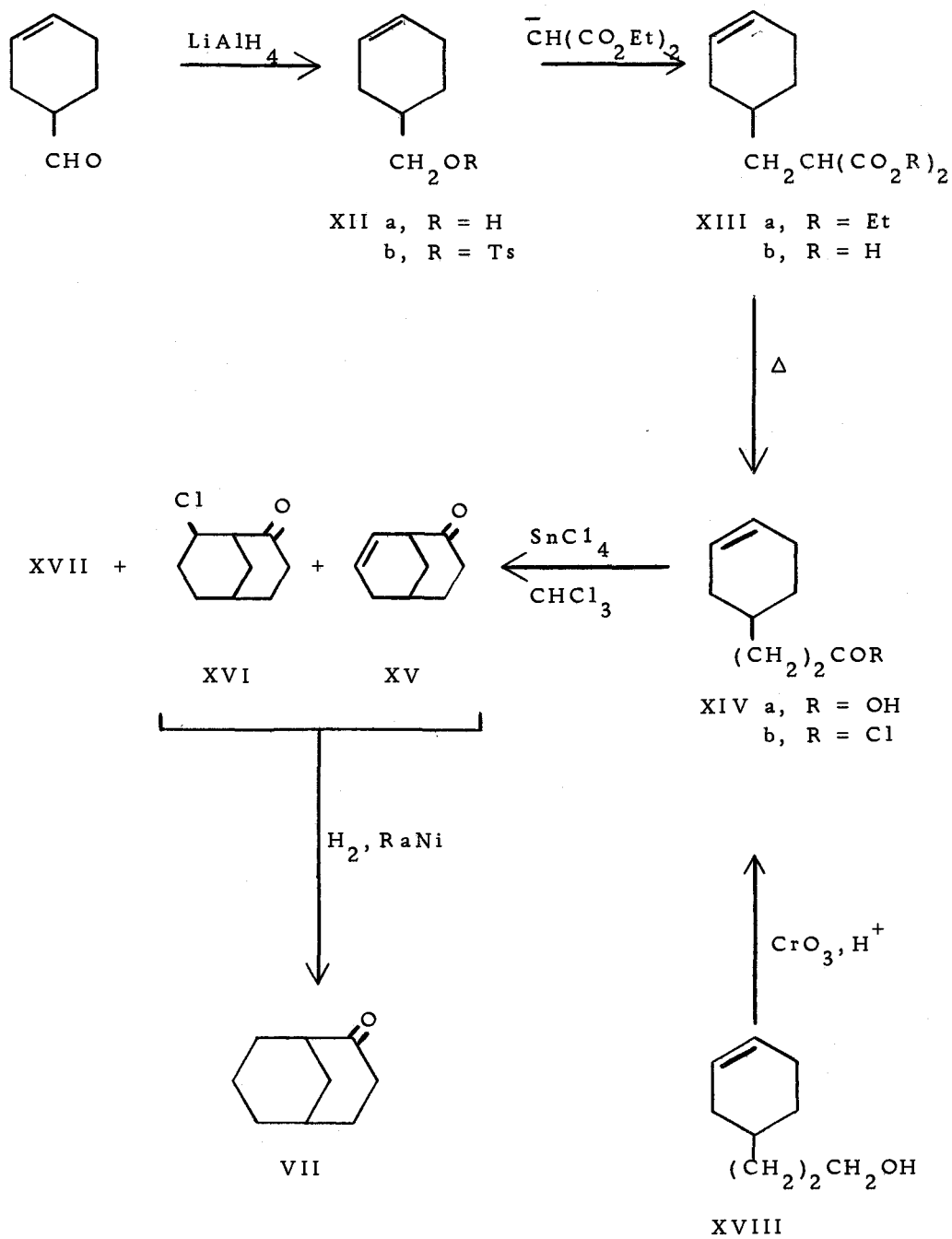


X produces the intermediate VIII (Equation I) with $R = CH_2$. In this case no cyclization through intermediate IX was detected. The only product was 3-(4-cyclohexenyl)propyl acetate (XI). The n. m. r. spectrum of XI has a $-CH_2O-$ triplet and two vinyl protons as expected. Product XI is consistent with the recent findings of Bartlett and coworkers (6) for the solvolysis of the analogous 3-(3-cyclopentenyl)propyl system. A preference for monocyclic products is attributed by Bartlett to a higher enthalpy of activation for ion IX than for the solvent-stabilized ion VIII. Less importance is given (6) to the difference in entropy of activation between ions VIII and IX. The analogy between the cyclopentene (6) and cyclohexene systems can be extended. Although the compounds above exhibit no bicyclic solvolysis products, solvolyses of 2-(3-cyclopentenyl)ethyl and 2-(4-cyclohexenyl)ethyl arylsulfonates yield large amounts of bicyclic products. These results show that conformational differences between cyclopentene and cyclohexene do not prevent cyclization. Thus, the factors preventing cyclization of X must originate in the propyl side chain as stated by Bartlett for the cyclopentene case.

It is clear that for bicyclic products to arise from VIII, formation of IX must become the only possible reaction. This restriction is not present in the solvolysis of compound X but is present in the Friedel-Crafts reaction of the acid chloride XIVb in a

non-nucleophilic solvent. Scheme II shows the synthesis of bicyclic compounds by this method. Reduction of 4-cyclohexene carboxaldehyde to 4-cyclohexenylmethanol (XIIa) was followed by conversion of the alcohol to the tosylate XIIb. Addition of the tosylate to an ethanol solution of sodium diethyl malonate gave ethyl 3-(4-cyclohexenyl)-2-carbethoxypropionate (XIIIa). After the hydrolysis of XIIIa to XIIIb in aqueous base, decarboxylation of the diacid XIIIb gave 3-(4-cyclohexenyl)propanoic acid (XIVa) in 51% overall yield from the 4-cyclohexene carboxaldehyde. The acid XIVa was also prepared by oxidation of 3-(4-cyclohexenyl)propanol (XVIII). Nearly quantitative conversion of the acid XIVa to 3-(4-cyclohexenyl)propanoyl chloride (XIVb) was obtained using oxalyl chloride and pyridine. The distilled acid chloride was treated with stannic chloride in inert solvents to give three products. These were identified as 7-bicyclo(3.3.1)nonen-2-one (XV), 8-chlorobicyclo(3.3.1)nonan-2-one (XVI), and a chloroketone (XVII) of unknown structure. The effects of solvent and of the stannic chloride/acid chloride ratio on the product ratios are noted in the experimental section. The best reaction conditions employ a 2.0 to 2.5 molar ratio of stannic chloride to acid chloride in chloroform solvent at room temperature. This gave 50% of XV, 37% of XVI, and 13% of XVII. In order to determine the carbon skeletons of the products, the mixture of XV, XVI, and XVII was hydrogenated. A single

Scheme II. Friedel Crafts Synthesis



saturated ketone was obtained from XV and XVI. Compound XVII appeared unchanged. The n. m. r. and mass spectra of the purified ketone from XV and XVI were identical with the n. m. r. and mass spectra for an authentic sample of 2-bicyclo(3.3.1)nonanone and different from the n. m. r. and mass spectra for an authentic sample of 2-bicyclo(3.2.2)nonanone. Both XV and XVI must be bicyclo(3.3.1)nonane derivatives. The structure of XVII has not been determined. However, 5-chloro-2-bicyclo(4.3.0)nonanone is consistent with the 1710 cm.^{-1} band in the infrared spectrum, the CHCl proton in the n. m. r. spectrum, the approximate molecular weight of 189 (osmometer), the long retention time of XVII on glc compared with the retention time of XVI, and the fact that XVII does not result from the rearrangement of XVI under the reaction conditions.

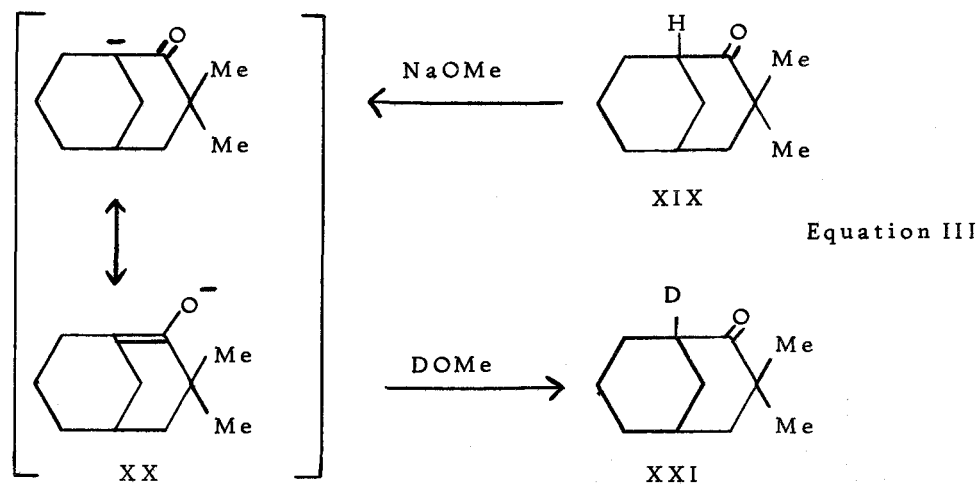
It was stated earlier that the intermediate ion IX could give either bicyclo(3.3.1)nonanes or bicyclo(3.2.2)nonanes. The exclusive experimental preference for the former system makes this synthetic procedure a particularly convenient route to bicyclo(3.3.1)nonanes. In addition to being adaptable to large scale preparations, each step provides a good yield of easily purified products. It should be noted at this point that preferential product formation in the last step is not unexpected. Bicyclo(3.3.1)nonanes are composed of two six-membered rings. Bicyclo(3.2.2)nonanes

are composed of two seven-membered rings. The directing influence in the Friedel-Crafts reaction is primarily the stability of a six-membered ring compared with that of a seven-membered ring. This preference has also been noted in classical cyclization reactions (54).

Reactivity and Structure

The structural features of the bicyclo(3.3.1)nonane system resemble those of a conformationally restricted cyclooctane ring and also those of a six-membered ring constrained to a bicyclic framework. The physical and chemical properties of this ring can be understood in terms of its structural features.

The stability of a bridgehead double bond measures part of the strain in a bicyclic system. Bicyclo(3.3.1)non-1-enes are quite strained and are unknown in the literature. The parent olefin is important since a recent synthesis of 1-bicyclo(4.3.1)decene (10, p. 182) places 1-bicyclo(3.3.1)nonenes at the present limit for unisolated bridgehead olefins. Although a bridgehead olefin was not directly available, the analogous bridgehead enol was studied by deuterium exchange. As shown in Equation III, the overlap of the C-1 anion with the π -system of the carbonyl produces a reactive enolate (XX) possessing a bridgehead double bond.



The rate of deuterium incorporation should be proportional to the stability of the double bond. Deuterium incorporation (ratio of XXI/XIX) has been determined by mass spectrometry. This method is precise to $\pm 3\%$ using fast scan methods. The second-order rate constant for deuterium incorporation at 100.8° was $k = 0.67 \times 10^{-4}$ l./m.-sec. This value may be compared to the much slower rate constant (97, p. 14) for deuterium incorporation (100.8°) in 3,3-dimethyl-7-bicyclo(3.3.1)nonen-2-one (XXII), $k' = 1.9 \times 10^{-6}$ l./m.-sec. Although the bridgehead proton in XXII is both allylic and alpha to a carbonyl group, the unsaturated ketone XXII forms a bridgehead enolate which is 2.5 kcal/mole less stable than the enolate XX. Apparently, the 6,7-double bond in XXII promotes additional strain in the bicyclo(3.3.1)nonane system. The destabilizing influence of the second double bond in XXII is consistent with Meerwein's failure (78) to obtain any bicyclo(3.3.1)nona-2,6-diene

by double dehydration of the corresponding diol. In agreement with this observation, Salisbury (97, p. 15) has found that the C-2 to C-3 enolate anion of 7-bicyclo(3.3.1)nonen-2-one (X V) is less stable than the same anion for the saturated ketone VII.

A direct comparison of the rate of deuterium exchange for XIX with that for other systems could provide an estimate of the strain of the bridgehead double bond. Two factors complicate such a comparison. First, data on analogous non-bridgehead systems in the literature could not be used due to variations in solvent and temperature or to the lack of sufficient data to estimate rate constants. Second, conformational factors are important in the rate of deuterium exchange. This can be illustrated by comparing deuterium incorporation for 2-bicyclo(3.3.1)nonanone (VII) with that for XIX. The deuterium incorporation rate for VII may be estimated from literature data (98): $k' = 4.2 \times 10^{-6}$ l./m.-sec. (dioxane-deuterium oxide, sodium deuterioxide, 95°). This value is sixteen times smaller than k for XIX and only twice as large as k' for the ketone XXII. The difference in deuterium exchange rates between VII and XIX can be explained on a conformational basis. The overlap of the C-1 anion with the C-2 carbonyl group is best when the ketone ring is in the boat form. Although 2-bicyclo(3.3.1)nonanone (VII) will probably favor a chair conformation, the rate of enolization and deuterium incorporation will be proportional to a

small equilibrium concentration of the boat conformer. For the dimethyl ketone XIX (and also XXII) the chair conformer for the ketone ring is destabilized by 1,3-diaxial interactions of the axial methyl group as well as by the interference of the methylene group at C-7. Since XIX should exist predominantly as the reactive boat conformer (Figure 2), its more rapid rate of deuterium incorporation is very reasonable.

An extension of these ideas leads to an interesting speculation about the conformations of XXII and XV (Figure 2). If these ketones have different conformations, MacKenzie's analysis (75) predicts that their ultraviolet spectra should have different ϵ_{290} values. The experimental ϵ_{290} values were 164 and 169, respectively. The striking agreement of these values indicates a similar π -overlap and thus a similar geometry. Since XXII should exist with the ketone ring in the boat form, an equivalent conformation must be postulated for XV. Although the mobility of the boat form of XV makes calculation of a theoretical ϵ_{290} difficult, the alternate chair form is rigid enough so that the angles necessary for calculation may be measured with reasonable accuracy. Based on MacKenzie's analysis (75), $\theta = 180$, $\psi = 120$, and the theoretical ϵ_{290} is calculated to be 3.0. This value is considerably lower than the experimental value of 169. The boat conformation suggested for XV is novel, however, since no large steric interactions would destabilize the

chair conformation.

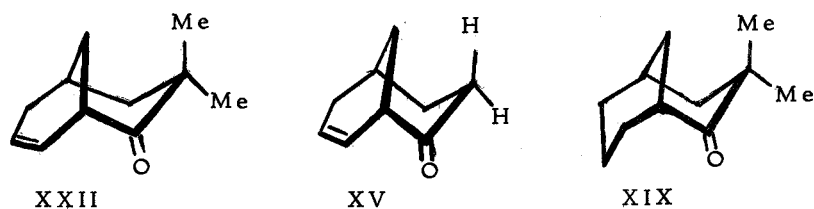


Figure 2. Preferred Conformations.

Bicyclo(3.3.1)nonanes exhibit equally unique properties because of the proximity of C-3 and C-7 in the chair-chair conformation. This form has been shown to exist for compounds like the alkane (45). Both physical and chemical methods can detect the effects of this proximity.

The infrared spectra of exo-2-bicyclo(3.3.1)nonanol (XXIX), bicyclo(3.3.1)nonane, and 3,3-dimethyl-2-bicyclo(3.3.1)nonanone (XIX) show enhanced C-H stretching and bending frequencies. These have been attributed by several groups of workers (44, 48, 70) to steric crowding of methylene groups. For the alcohol XXIX and the alkane, a reasonable source is the steric interaction of the C-3 and C-7 methylene groups. In XIX, however, the most likely interaction is between the C-9 methylene group and the axial methyl group in the boat conformation. It is interesting that 2-bicyclo(3.3.1)nonanone shows no enhanced stretching frequencies and only slightly enhanced bending frequencies. The absence of

strongly enhanced frequencies might be due to either a simple increase in the C-3 to C-7 distance or a boat form for the ketone ring. This peculiarity becomes even more interesting in light of the far-infrared spectrum for the ketone. By comparison with the far-infrared bands for the alkane, 2-bicyclo(3.3.1)nonane (VII) exhibits lower energy bands, indicating increased mobility. A very mobile twist form of this ketone can be made if both rings are placed in boat conformations. Most of the severe interactions are removed by twisting. The two possible twist forms with a low interconversion energy could explain both the low energy far-infrared bands and also the lack of enhanced infrared stretching frequencies. No evidence suggests that the double boat is the exclusive conformer for 2-bicyclo(3.3.1)nonane (VII).

The C-3 to C-7 proximity is also shown by chemical methods through the preparation and solvolysis of exo-2-bicyclo(3.3.1)nonene oxide. Bicyclo(3.3.1)non-2-ene, prepared by the method of Foote (55, p. 96-101), was oxidized by the method of Payne (86) to the epoxide. The stereochemistry of the epoxidation was established by reduction of the epoxide to a single alcohol, which has been identified as exo-2-bicyclo(3.3.1)nonanol (20). The alcohol stereochemistry was assigned (20) on the basis of infrared spectra between 1100 and 900 cm^{-1} : exo, 1045 (weak), 985 (strong); endo, 1060, 1025 (both strong) with no band at 985 cm^{-1} . The

structure of the alcohol isolated in the present work is based on an infrared spectrum identical with that for the exo (20). The structure is not based on melting point comparisons since these can have limited validity for some bicyclic compounds. In addition, the exo-epoxide is the isomer which is expected on mechanistic grounds since the endo side of the double bond would be the most hindered in a classical sense.

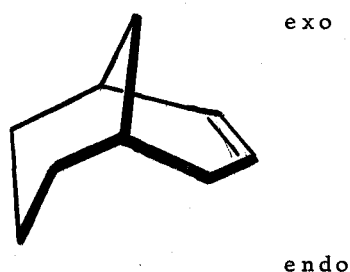
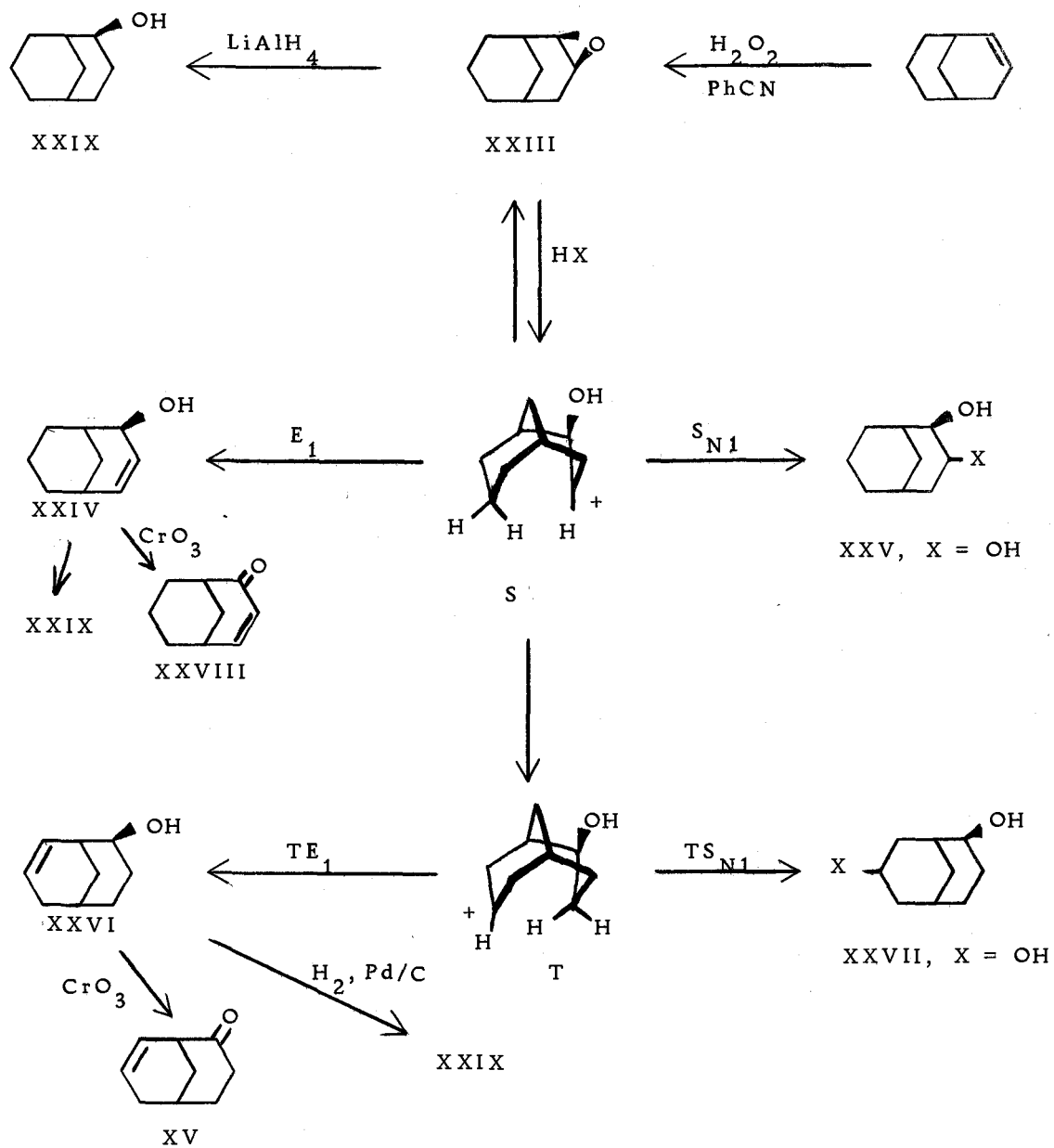


Figure 3. Bicyclo(3.3.1)non-2-ene.

The influence of geometry on reactivity is clearly illustrated by the epoxide solvolyses. Scheme III indicates that the products XXIV to XXVIII, characterized as the alcohols, can arise through the carbonium ions S and T. In trifluoroacetic acid the major solvolysis product (80%) was exo-bicyclo(3.3.1)non-7-en-2-ol (XXVI). Small amounts of exo-bicyclo(3.3.1)non-3-en-2-ol (XXIV) and diols (XXV, XXVII) were detected. The structure proof for XXVI involved hydrogenation to the known (20) alcohol XXIX, which exhibited an infrared spectrum identical to the reported spectrum (20), and oxidation to the unsaturated ketone XV. The ultraviolet spectrum of XV

Scheme III. Epoxide Solvolysis Reactions.



showed a small peak at 230 μ due to approximately 7% of XXVIII arising from XXIV. The product XXVI is formed in a kinetically controlled step, since isomerization of XXIV to XXVI does not occur under the reaction conditions. According to the mechanism proposed in Scheme III, ion T is formed by transannular hydride shift from ion S, in which a large part of the endo steric hindrance has been removed by making one carbon sp^2 hybridized. Ion T reacts predominantly by the elimination (TE_1) of a proton to give the major product XXVI. The alternate reaction pathways of elimination from ion S (E_1) and nucleophilic attack on ions S or T (S_N1 or TS_N1) are unimportant in the present trifluoroacetic acid solvolysis.

Solvolysis of the epoxide XXIII in acetic acid-sodium acetate gave a mixture of unsaturated acetates (27%) and saturated diacetates (68%). After conversion to the corresponding alcohols, the unsaturated products were identified as XXVI and XXIV. The mixture of these two compounds exhibited a broader vinyl hydrogen region in the nmr spectrum than for XXVI. The major isomer is probably XXIV, for which the vinyl hydrogens should be less equivalent than in XXVI. The mixture was oxidized to obtain the known (72) unsaturated ketone XXVIII. This product showed a clear AB vinyl hydrogen pattern (nmr), a carbonyl band at 1675 cm.^{-1} (infrared), and was separated from a small amount of the non-conjugated ketone by glc. The unsaturated alcohols were also separated directly by glc to

confirm the presence of XXIV (20%) and XXVI (7%). Hydrogenation of the unsaturated alcohol mixture gave a single saturated alcohol which was identified by infrared spectrometry to be the known (20) XXIX. The dialcohols, obtained by reduction of the diacetate products, appear to be a mixture of XXVII (approximately 54%) and XXV (approximately 14%) in spite of the fact that attempted gas chromatographic separation of either the diacetate mixture or the dialcohol mixture was not successful. Oxidation appears to give two diketones, since the infrared spectrum shows a weak band at 1750 cm.^{-1} , presumably due to the alpha-diketone from XXV, and a strong band at 1710 cm.^{-1} , due to the diketone from XXVII. The predominance of XXVII is also supported by the absence of intramolecular hydrogen bonding in the infrared spectrum of the diol mixture. Additional structural features for the diols were deduced on mechanistic grounds since equatorial nucleophilic attack by solvent would be expected on both ions S and T.

The solvolysis in acetic acid-sodium acetate has some interesting mechanistic features. Ratios of the four products indicate that preferences for the four product-forming steps (Scheme III) are as follows: $TS_N1 > E_1 > S_N1 > TE_1$. This result is surprising at first. The most effective process in acetic acid is the expected nucleophilic attack (TS_N1) of solvent on an ion such as T. In contrast to this, the ion S shows a preference for elimination (E_1)

rather than solvent attack (S_N1). If internal nucleophilic attack on S by the neighboring hydroxyl group occurs, this intramolecular reaction might predominate over external solvent attack. Such an equilibrium between the protonated epoxide and ion S would then be interrupted primarily by elimination (E_1) to give XXIV or by hydride shift to give ion T but not usually by external nucleophilic attack (S_N1) to give XXV. This would rationalize an apparent preference for elimination from S with the preference for nucleophilic attack on T. Cope (34) has concluded that cis-cyclooctene oxide solvolysis does not proceed through a completely free carbonium ion but rather through an ion which retains partial bonding with the hydroxyl group. This rate-determining partial ionization is followed by either fast hydride shift or fast attack of solvent. The degree of ionization exhibited in the present solvolytic reaction cannot be readily determined. Both a partial ionization as suggested by Cope or a rapid equilibrium as suggested above would rationalize the observed elimination-substitution preferences. In addition, partial bonding is not required to explain stereospecific substitution products since in the present reaction even a free carbonium ion would be expected to give highly stereospecific products, as explained below. The solvolysis products do, however, reflect the extent to which favorable geometry promotes hydride shift in preference to solvent attack. Although cis-cyclooctene oxide and 2-bicyclo(3.3.1)nonene oxide

give about the same amount of hydride shift in trifluoroacetic acid, the latter compound exhibits more than twice as much hydride shift (59%) in acetic acid-sodium acetate as the former (24%). The greater preference for hydride shift in the bicyclic system can be explained on a conformational basis. In contrast to the relatively flexible cyclooctene oxide ion, the intermediate S should exist in relatively few conformations. The most stable of these conformations also provides the ideal geometry for hydride shift, as shown in Scheme III, in addition to affording stereospecific attack of solvent.

This study of 2-bicyclo(3.3.1)nonene oxide solvolysis indicates the utility of this ring system for the study of transannular reactions. The observed products XXVI and XXVII show that geometric requirements for transannular reaction are admirably met. More acidic solvents also favor transannular hydride shift. In addition, the amount of transannular hydride shift is considerably greater than that for the exact monocyclic analogue, cyclooctene oxide. This demonstrates how much more effectively this system promotes transannular hydride shift.

EXPERIMENTAL

Infrared spectra were determined on either a Perkin-Elmer Model 21 or a Beckman IR-8 infrared spectrophotometer except as indicated. Gas liquid chromatography (glc) was carried out on either a Perkin-Elmer Model 154C Vapor Fractometer (PE) or an Aerograph A-700 Autoprep (Autoprep). Melting points were determined by the capillary method in a liquid bath and are corrected. Nuclear magnetic resonance (N. M. R.) spectra were determined on a Varian A-60 N. M. R. spectrometer in carbon tetrachloride solution with tetramethylsilane as an internal standard. Chemical shifts (ppm) are downfield from tetramethylsilane. Molecular weights were measured using the Mechrolab vapor pressure Osmometer Model 301 with chloroform as solvent.

Methyl 3-(4-hydroxyphenyl)propanoate(IIb). A sample, 127 g. (0.77 mole), of 3-(4-hydroxyphenyl)propanoic acid (IIa), prepared from phenol by cyanoethylation (69) and subsequent hydrolysis (16), was heated at reflux for 6 hours with 300 ml. of dry methanol, 700 ml. of ethylene chloride, and 4 ml. of concentrated sulfuric acid. The solution was washed with aqueous sodium bicarbonate and water and then dried. After the solvent had been removed, the crude product was distilled to give 123 g. (89%) of methyl 3-(4-hydroxyphenyl)propanoate, b. p. 110° (0.05 mm), m. p. 39-40.5 $^{\circ}$. This ester

has a reported m. p. 40-41°(63, p. 470).

Methyl 3-(4-hydroxycyclohexyl)propanoate. The ester IIb was hydrogenated over W-4 Raney Nickel in absolute methanol at 155-200° and 1400 psi initial hydrogen pressure. The reduced material was isolated by removal of the catalyst and solvent followed by distillation to give a colorless liquid product (98%), b. p. 80-90°(0.11 mm), $n_D^{20} = 1.4700$. Infrared spectrum: 3450, 1730, 1050 cm^{-1} , aliphatic C-H only.

Anal. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_3$: C, 64.48; H, 9.74. Found: C, 64.04; H, 9.45.

Methyl 3-(4-oxocyclohexyl)propanoate (IIIa). To a well-stirred solution of 123.9 g. (0.67 mole) of methyl 3-(4-hydroxycyclohexyl)propanoate in 1500 ml. of acetone cooled in an ice bath was added 85 g (0.85 moles) of chromium trioxide dissolved in 360 ml. of 30% aqueous sulfuric acid (12). The addition required 1.5 hours. After the solution had been stirred at 0° for 10 hours, enough potassium hydroxide was added to neutralize the acid, and some sodium bicarbonate was added to make the solution basic. The acetone was removed under reduced pressure and the residue extracted twice with ether. The ether extracts were combined, washed with saturated sodium bicarbonate (aqueous), and dried. Distillation through a short Fenske column gave 98 g. (80%) of IIIa, b. p. 75-80° (0.07-0.09 mm), $n_D^{20.2} = 1.4651$. Infrared spectrum: aliphatic

C-H, 1735, 1710 cm.^{-1}

A 2,4-dinitrophenylhydrazone prepared by the method of Shine (100) melted at 130.9-131.8 $^{\circ}$.

Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_6$: C, 52.76; H, 5.50. Found: C, 53.02; H, 5.78.

A small amount of 3-(4-oxocyclohexyl)propanoic acid (IIIb), m. p. 62-65 $^{\circ}$, was isolated from the water layer. The reported melting point for this acid is 60-65 $^{\circ}$ (11).

3-(4-Oxocyclohexyl)propanol (VIa). A mixture of 94 g (0.51 mole) of methyl 3-(4-oxocyclohexyl)propanoate (IIIa), 252 g (2.43 moles) of 2,2-dimethoxypropane, 300 ml. of methanol, and 0.375 g. of *p*-toluenesulfonic acid was allowed to stand at room temperature overnight. Solvent was removed until the distillation temperature reached 65 $^{\circ}$, at which point the residue was cooled and 15 drops of 10% aqueous potassium hydroxide and 300 ml. of ether were added. This solution was washed with 60 ml. saturated aqueous sodium sulfate. After extraction of the aqueous layer with ether, the organic layers were combined and dried. Removal of the solvent gave 117 g. (99%) of light yellow liquid (IV). Infrared spectrum: aliphatic C-H, 1735, 1110, 1052 cm.^{-1} . Attempted distillation of this ketal led to loss of methanol and formation of methyl 3-(4-methoxy-4-cyclohexenyl)propanoate (V), b. p. 87-89 $^{\circ}$ (0.07 mm), $n_D^{20.2} = 1.4699$. Infrared spectrum: 1735, 1660, 1210, 1170 cm.^{-1} .

Either the ketal IV or the enol ether V (0.5 mole) in 200 ml. of anhydrous ethyl ether was added to 0.25 moles (1 equivalent) of lithium aluminum hydride in 900 ml. of ether over a 2 hour period. The reaction mixture was heated at reflux for 9 hours. Hydrolysis with distilled water at this point yielded the reduced ketal or enol ether showing no carbonyl in the infrared spectrum. The more usual procedure was hydrolysis with excess 5% sulfuric acid followed by extraction several times with ether. The combined extracts were washed with aqueous sodium bicarbonate. Distillation of the residue from the ether solution gave 68 g. (87%) of VIa, b. p. 115-116° (0.05 mm), $n_D^{20.2} = 1.4816$. Infrared spectrum: aliphatic C-H, 3430, 1712, 1057 cm^{-1} . N.M.R. spectrum: singlet 3.69 ppm (1H), triplet 3.53 ppm ($J = 5.5$ cps, 2H), and complex pattern 1.0 to 2.5 ppm.

A 2,4-dinitrophenylhydrazone prepared by the method of Shine (100) melted at 135.5-137°.

Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_5$: C, 53.56; H, 5.99; N, 16.66.
Found: C, 53.81; H, 5.75; N, 16.82.

3-(4-Oxocyclohexyl)propyl tosylate (VIb). A solution of 5.0 g. (32 mmoles) of VIa in 15 ml. of anhydrous pyridine was added to a cold (0°) solution of 7.6 g. (40 mmoles) of p-toluenesulfonyl chloride in 20 ml. of anhydrous pyridine (110). The solution was stirred at 0° for 24 hours and then 2-3 ml. of water added. The mixture was

stirred for an additional 30 minutes, diluted with 200 ml. of ether, and washed with water, dilute sulfuric acid, and aqueous sodium bicarbonate. The ether solution was dried and the solvent was removed to give 9.3 g. (94%) of a viscous oil which would not crystallize. The crude product showed no 3400 cm.^{-1} band in the infrared spectrum, had strong infrared absorptions at 1355, 1170, and 940 cm.^{-1} , and was used without further purification.

2-Bicyclo(3.3.1)nonanone (VII). Using scrupulously dried equipment flushed with prepurified nitrogen dried over phosphorus pentoxide, a slurry of 10 g. (0.09 mole) of potassium t-butoxide was prepared in 1300 ml. of anhydrous tetrahydrofuran (distilled from sodium hydride directly into the reaction vessel). To this was added over a 1 hour period a solution of 26.4 g. (0.085 mole) of the tosylate VIb in 250 ml. of tetrahydrofuran. This mixture was stirred at $43\text{-}45^{\circ}$ for 22 hours under dry nitrogen. The reaction mixture was filtered, diluted with 150 ml of water, and placed under reduced pressure to remove most of the tetrahydrofuran. The residue was extracted several times with pentane. After the extracts were washed with aqueous sodium sulfate and dried, the pentane was removed to give 11.40 g. (97%) of a light yellow partly solid product.

Chromatography of the crude product over activity II-III alumina gave a hexane fraction and an ether fraction. Distillation of

the ether fraction gave 1.68 g. (12.7%) of recovered 3-(4-oxocyclohexyl)propanol (VIa). Sublimation of the hexane fraction gave 4.95 g. (48% based on unrecovered alcohol) of 2-bicyclo-(3.3.1)nonanone (VII), m. p. 134-137°. Infrared spectrum: 2920, 2860, 1711, 1455 cm^{-1} . N.M.R. spectrum: a series of bands between 90 and 155 cps. A semicarbazone was prepared, m. p. 176-178°. The reported properties for this compound are: ketone m. p. 135-137°; semicarbazone m. p. 179-181° (53).

3-(4-Hydroxyphenyl)propanol. A solution of 6.6 g. (0.04 mole) of 3-(4-hydroxyphenyl)propanoic acid (IIa) in 350 ml. of anhydrous ethyl ether was added to a solution of 6.7 g. (0.175 mole) of lithium aluminum hydride in anhydrous ether. The ether was refluxed for 46 hours, 1.7 g. of lithium aluminum hydride added, and refluxing continued for 10 more hours. To this mixture was added 300 ml. of 10% aqueous sulfuric acid. After all the precipitate had dissolved, the ether layer was separated and the aqueous layer extracted with four 150 ml. portions of ether. The combined ether extracts were dried, and the solvent was removed. The base-soluble product was purified from the residue and recrystallized to give 4.4 g. (72%) of 3-(4-hydroxyphenyl)propanol, m. p. 53-55°. Infrared spectrum: 3300, 3120, 1305, 1245 cm^{-1} . The dibenzoate was prepared, m. p. 70.5-71.4°. The reported properties for this compound are: dialcohol m. p. 54-55° (85); dibenzoate m. p. 72° (112).

3-(4-Hydroxyphenyl)propyl acetate. One gram (6.6 mmole) of the above alcohol, 2.5 ml. of ethyl acetate, and a trace of *p*-toluenesulfonic acid were heated at 78° for 14 hours. A dilute solution of sodium bicarbonate was added and the resulting mixture extracted three times with 15 ml. portions of ether. Evaporation of the solvent left 0.53 g. of a viscous, light yellow liquid. Chromatography on silica gel showed 34% 3-(4-hydroxyphenyl)-propyl acetate and 66% recovered starting material. The reaction was not pursued further.

4-Cyclohexenylmethanol (XIIa). To 54 g. (1.43 moles) of lithium aluminum hydride in 0.8 l. of ethyl ether was added 300 g. (2.72 moles) of 4-cyclohexene carboxaldehyde. The ether solution was refluxed overnight, and the mixture was hydrolysed with 220 ml. of ethanol followed by 2 l. of 3 N hydrochloric acid. Extraction of the aqueous layers with 3 l. of ethyl ether and distillation of the residue from the organic layer gave 256.7 g. (84%) of 4-cyclohexenylmethanol XIIa), b. p. 88-91° (5-10 mm). The reported boiling point (96, p. 59) is 99-100° (30 mm).

Ethyl 3-(4-cyclohexenyl)-2-carbethoxypropanoate (XIIIa). The tosylate of XIIa was prepared in 96% yield from 485 g. (4.34 moles) of XIIa, 900 g. (4.74 moles) of *p*-toluenesulfonyl chloride, and 1250 ml. of dry pyridine according to the method of Tipson (110). Infrared spectrum: no OH, 3030, aliphatic C-H, 1590, 1500, 1350,

1180, 975, 950, 930, 780, 663 cm^{-1} . The crude tosylate XIIb was used directly.

To a solution of sodium ethoxide (from 13.3 g of sodium) in 450 ml. of dry ethanol was added 97 g. (0.61 mole) of redistilled diethyl malonate. The crude tosylate XIIb (154 g., 0.603 mole) was added over a 5 hour period, and the solution was refluxed for 36 hours. After the mixture had been cooled, 250 ml. of water was added. Most of the ethanol was removed at reduced pressure, and then hydrochloric acid was added to acidify the water layer. The organic products were extracted with two 700 ml. portions of ethyl ether and distilled to give 102.6 g. (70%) of XIIIa, b. p. $95-102^{\circ}$ (2 mm), $n_D^{20} = 1.4620$. The reported properties for this compound (96, p. 60) are: b. p. $110-112^{\circ}$ (0.025 mm); $n_D^{20} = 1.4610$.

3-(4-Cyclohexenyl)-2-carboxypropanoic acid (XIIIb). A 10% aqueous potassium hydroxide solution (750 ml.) and 101 g. (0.40 mole) of ethyl 3-(4-cyclohexenyl)-2-carbethoxypropanoate (XIIIa) were stirred at room temperature until all of the organic material had dissolved in the aqueous layer. The aqueous layer was washed with 60 ml. of ethyl ether and acidified. Extraction of the acidic aqueous layer with three 600 ml. portions of ethyl ether and removal of the solvent from the organic extracts gave 74.5 g. (95%) of XIIIb, m. p. $121-125^{\circ}$. The reported melting point (96, p. 61) is $120-121^{\circ}$.

3-(4-Cyclohexenyl)propanoic acid (XIVa). A. By oxidation. To 29.8 g. (0.212 mole) of 3-(4-cyclohexenyl)propanol (XVIII) in 1500 ml. of acetone at 0° were added 120 ml. of Djerassi reagent (26.7 g. of chromium trioxide and 23 ml. of concentrated sulfuric acid diluted to 100 ml. with water). When the red color persisted for a few minutes, the reaction was allowed to stand overnight. After the addition of 500 ml. of water, the acetone was removed at reduced pressure. The organic product was extracted with two 1 l. portions of ethyl ether and distilled to give 25.9 g. (79%) of XIVa, m. p. 33.0-35.5°, b. p. 81-82° (0.6 mm). Infrared spectrum: 3500-2500 under C-H bands at 3024, 2910; 1710, 925, 652 cm.⁻¹ N.M.R. spectrum: broad singlet 5.60 ppm (2H) and complex multiplet 2.6 to 1.2 ppm (12H).

Anal. Calcd for C₉H₁₄O₂: C, 70.20; H, 9.15. Found: C, 70.09; H, 8.99.

B. By decarboxylation. Xylene (800 ml., b. p. 136-140°) and 74.5 g. (0.376 mole) of 3-(4-cyclohexenyl)-2-carboxypropanoic acid (XIIIb) were heated at 130-132° for 16 hours (4 hours after carbon dioxide evolution stopped). The xylene was removed at reduced pressure, and the residue was distilled to give 55.3 g. (95%) of XIVa, m. p. 34.5-36.0°, b. p. 87.0-88.5° (0.2 mm).

3-(4-Cyclohexenyl)propanoyl chloride (XIVb). A solution of 5.9 g. (0.038 mole) of 3-(4-cyclohexenyl)propanoic acid (XIVa) in

60 ml. benzene containing 4 drops of pyridine was cooled to 10-15°. To this was added 10 ml. of oxalyl chloride over a one hour period. After the solution had been stirred for two additional hours at 10-15°, the benzene and excess oxalyl chloride were removed at reduced pressure. The residue was partially dissolved in hexane, and the solution was filtered from the undissolved pyridine hydrochloride. Distillation of the residue from the hexane solution gave 6.6 g. (98%) of XIVb, b. p. 80° (1.3 mm). Infrared spectrum: 3010, 2900, 1797 cm.⁻¹

Friedel-Crafts Cyclization. The 3-(4-cyclohexenyl)propanoyl chloride (XIVb, 6.4 g., 0.037 mole) was dissolved in 150 ml. of chloroform (ethanol removed by filtration through an aluminum column), and 9.7 ml. of stannic chloride was added in one hour. The reaction mixture was stirred for 6 hours, hydrolysed with 70 ml. of 10% hydrochloric acid at 0° for 3 hours, and the organic layer was separated. The aqueous hydrochloric acid was extracted with hexane. The combined organic layers were washed with dilute base. The residue from the organic layers was a mixture of products. Bicyclo(3.3.1)non-7-en-2-one (XV) was isolated in 50% yield by vaporization (bath temperature 60° at 0.05 mm) through a six-inch, glass-helix packed column and collection in a dry ice-acetone cold trap. The remainder of the material was a mixture of 8-chlorobicyclo(3.3.1)nonan-2-one (XVI) and an unknown

chloroketone XVII.

Table VIII. Effect of Stannic Chloride on Product Composition.

Temperature	Stannic chloride to acid chloride ratio	XV	XVI	XVII
10-15°	1.55	39%	43%	17%
60°	9.01	44.6	17.4	38
25°	2.26	50	37	13
0°	2.43	51.2	22	22

% determined by glc (PE, 190°, ucon polar)

Bicyclo(3.3.1)non-7-en-2-one (XV): m. p. 66-68°. N.M.R. spectrum: multiplet 6.17-5.52 ppm (2H) and multiplet 3.0-1.70 ppm (10H). Infrared spectrum: 3020, aliphatic C-H, 1713, 670 cm.⁻¹ Ultraviolet spectrum: 297 mμ (ε = 181) and 202 mμ (ε = 2,090).

A semicarbazone was prepared, m. p. 197.3-198.9°.

Anal. Calcd for C₁₀H₁₅ON₃: C, 62.16; H, 7.82. Found: C, 62.35; H, 7.84.

8-Chlorobicyclo(3.3.1)nonan-2-one (XVI): N.M.R. spectrum: broad singlet 4.41 ppm (1H) and complex multiplet 2.75-1.30 ppm (12H). Infrared spectrum: aliphatic C-H only, 1710 cm.⁻¹

Anal. Calcd for C₉H₁₃OCl: C, 62.61; H, 7.59. Found: C, 62.86; H, 7.55.

Unknown chloroketone XVII. N.M.R. spectrum: broad singlet 4.41 ppm (1H) and complex multiplet 2.75-1.70 ppm (12H). Infrared spectrum: aliphatic C-H only, 1714 cm^{-1} . Molecular weight (osmometer), 189 ± 1 .

Anal. Calcd for $\text{C}_9\text{H}_{13}\text{OCl}$: C, 62.61; H, 7.59. Found: C, 61.83; H, 7.42.

Equilibration of XVI. Treatment of XVI (90 mg., glc pure) with 0.17 ml. of stannic chloride in 5 ml. of chloroform at room temperature for eight hours followed by hydrolysis with distilled water gave 83 mg. of organic products. The products were an equimolar mixture of XV and XVI (PE, 198° , unon polar). No conversion of XVI to the unknown chloroketone XVII was observed.

Reduction of Friedel-Crafts Products. A mixture of 4.8 g. of crude Friedel-Crafts products, 15.8 g. of potassium hydroxide, and 4.52 g. of 5% palladium on charcoal in 150 ml. of methanol was hydrogenated on a Parr hydrogenator at about 40 psi until the pressure was steady (3 hours). The solution was filtered from the catalyst, neutralized, and the methanol was evaporated at reduced pressure. The organic products were extracted from the aqueous layer with two 300 ml. portions of hexane and sublimed to give 2.14 g. (61%) of a waxy solid. The major product was coincident with the known 2-bicyclo(3.3.1)nonanone (VII) by glc, but the unknown chloroketone XVII was apparently not changed (glc). The

major product was characterized by mass spectrometry.

2-Bicyclo(3.2.2)nonanone. The 64 mg. of 6-bicyclo(3.2.2)-nonen-2-one¹ was dissolved in about 7 ml. of dry methanol. Two grams of this solution was hydrogenated using 15 mg. of 5% palladium on charcoal. This sample was concentrated to 0.37 g. of solution and used for analysis by mass spectrometry. The methanol was removed by azeotrope with carbon tetrachloride, and the remaining solution was used for analysis by n. m. r.

Mass Spectrometry. Pure samples of the reduced Friedel-Crafts product and authentic 2-bicyclo(3.3.1)nonanone were prepared by glc (Autoprep, 175^o, 14' x 3/8" 20% SF-96 column, 150 ml. helium/min., retention time 16 min.). The samples were dissolved in pentane: 28.0 mg. of reduced Friedel-Crafts product in 0.38 g. of pentane; 60.4 mg. 2-bicyclo(3.3.1)nonanone in 0.973 g. of pentane; and approximately 10-20 mg. of 2-bicyclo(3.2.2)nonanone in 0.37 g. of methanol. The samples were placed in the mass spectrometer through an 8' x 1/8" Apiezon M column at 180-190^o, retention times 40-45 minutes. The spectral data are presented on a separate page.

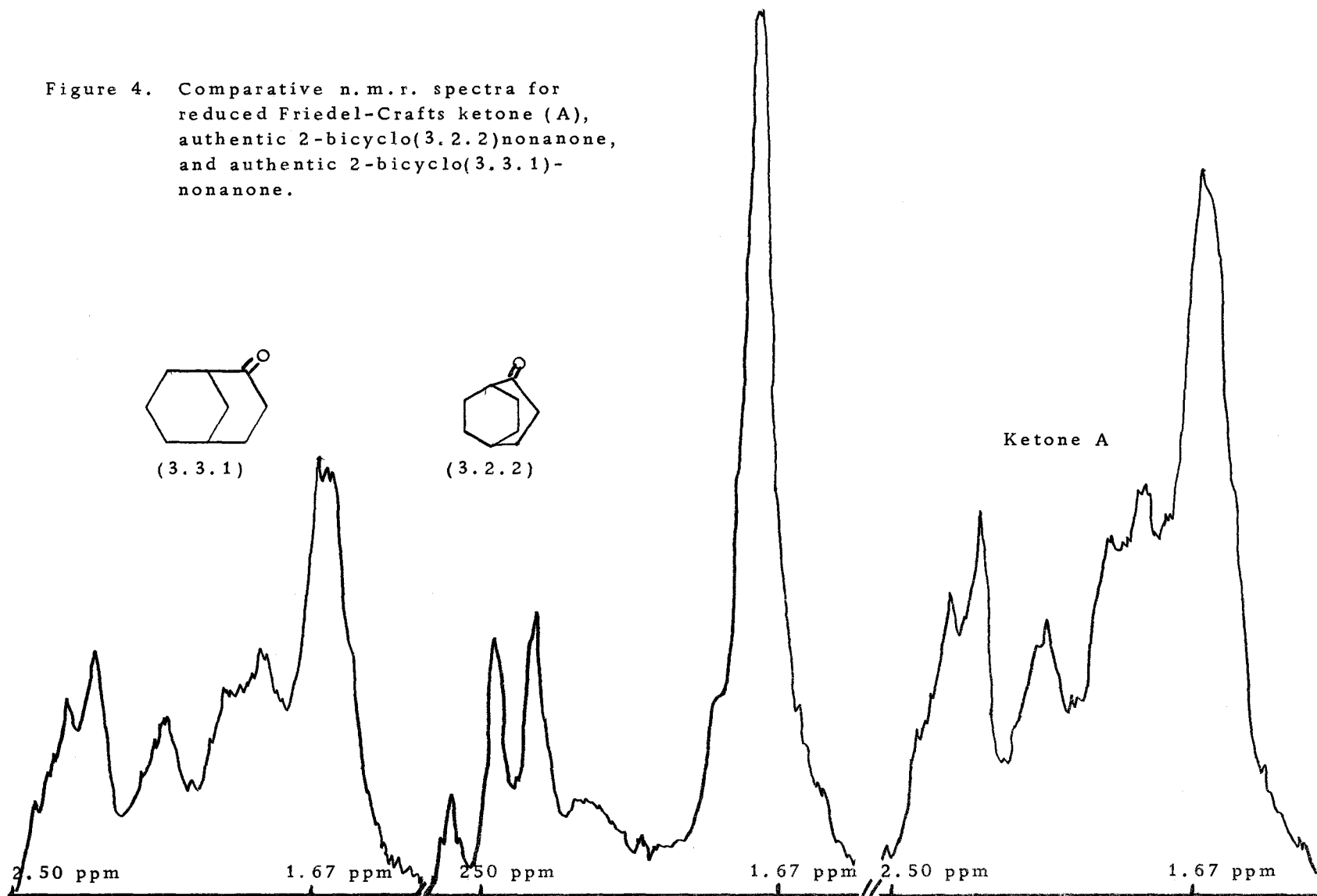
3-(4-Cyclohexenyl)propanol (XVIII). This compound was prepared by H. Sexton. A redistilled portion was characterized, $n_D^{19.2} = 1.4808$. Infrared spectrum: 3380, 1055, 3020, 652 cm.⁻¹

¹ Sample supplied by Dr. J. Berson, University of Wisconsin.

Table IX. Mass Spectral Data. 1. Saturated ketone (A) from Friedel-Crafts cyclization as compared with authentic samples of 2-bicyclo(3.3.1)nonanone (B) and 2-bicyclo(3.2.2)nonanone (C), as % of m/e 94. 2. Undeuterated 3,3-dimethyl-2-bicyclo(3.3.1)nonanone (D), as % of m/e 95.

m/e	A	B	C	m/e	D
138	22	26	37		
136	15	18	14	167	9.8
120	-	-	15	166	63
109	7.5	8.8	13	151	7.8
108	6.4	7.5	11	148	2.4
107	4.7	5.6	8.6	137	11
105	-	-	7.2	135	32
96	9.2	11	19	124	11
95	15	18	21	123	20
94	100	100	100	110	6.4
93	6.4	7.7	12	109	4.7
92	6.4	7.3	29	97	13
91	6.7	7.7	31	96	33
83	8.9	11	22	95	100
82	15	18	34	94	48
81	46	57	80	92	6.1
80	15	18	27	83	5.1
79	40	49	68	82	51
78	6.4	7.0	22	81	21
77	6.9	8.6	12	80	12
69	6.1	7.7	13	79	5.1
68	31	38	32	72	18
67	46	56	100	70	4.1
66	9.7	12	24	67	15
65	4.7	6.1	7.9	57	21
58	8.4	-	-	56	4.7
57	-	-	5.8	55	4.1
56	3.1	3.7	6.8	53	4.1
55	27	33	51		
54	25	30	57		
53	16	20	26		
42	-	-	7.9		
41	27	34	59		
39	15	20	29		
27	12	16	22		

Figure 4. Comparative n.m.r. spectra for reduced Friedel-Crafts ketone (A), authentic 2-bicyclo(3.2.2)nonanone, and authentic 2-bicyclo(3.3.1)nonanone.



N.M.R. spectrum: singlet 5.64 ppm (2H), triplet 3.60 ppm (2H, $J = 6$ cps), and complex multiplet 2.2-1.0 ppm (12H).

Anal. Calcd for $C_9H_{16}O$: C, 77.20; H, 11.40. Found: C, 77.10; H, 11.38.

3-(4-Cyclohexenyl)propyl acetate (XI). A mixture of 1.95 g. (0.014 mole) of 3-(4-cyclohexenyl)propanol (XVIII), 2.5 g. of acetic anhydride, 2 ml. of dry pyridine, and 70 ml. of dry benzene were heated at 80° for 5 hours. The benzene and excess acetic anhydride were removed under reduced pressure. The residue was distilled to give 2.20 g. (86.5%) of XI, b. p. 86° (2.2 mm), $n_D^{20} = 1.4613$. Infrared spectrum: 3020, 653, 1740, 1240, 1045 cm^{-1} . N.M.R. spectrum: broad singlet 5.60 ppm (2H), triplet 3.98 ppm (2H, $J = 6.3$ cps), and complex multiplet 2.2-1.0 ppm with methyl singlet 1.94 ppm (12H).

Anal. Calcd for $C_{11}H_{18}O$: C, 72.49; H, 9.92. Found: C, 72.51; H, 9.91.

3-(4-Cyclohexenyl)propyl tosylate (X). The tosylate X was prepared in 88% yield from 5.03 g. (0.036 mole) of XVIII, 7.5 g. (0.04 mole) of *p*-toluenesulfonyl chloride, and 42 ml. of pyridine according to the method of Tipson (110). Infrared spectrum: no OH bands, 1360, 1175, 1190, 955, 930, 902 cm^{-1} . The crude material was not purified further.

Solvolyses of 3-(4-cyclohexenyl)propyl tosylate. A. In acetic

acid-sodium acetate. A mixture of 7.16 g. (0.024 mole) of crude tosylate X, 2.1 g. (0.025 mole) of dry sodium acetate, and 500 ml. of dry acetic acid was heated at 113-114^o for 94 hours. Water and sodium sulfate were added to make the solution 25% sodium sulfate and 50% acetic acid. The organic products were extracted by three 700 ml. portions of hexane which were washed further with aqueous sodium bicarbonate to remove the acetic acid. Distillation of the residue from the hexane solution gave 3.52 g. (78%) of a clear, colorless liquid. The major product (95%) was identical with the known 3-(4-cyclohexenyl)propyl acetate (XI) by glc (PE, 156^o, K column), infrared, and n. m. r. comparisons.

B. In acetic acid. Solvolysis in unbuffered acetic acid led to considerably more decomposition, but the solvolysis products were the same as in acetic acid-sodium acetate.

C. In formic acid-sodium formate. A mixture of 2.04 g. (0.024 moles) of tosylate X, 0.50 g. of sodium formate, and 252 ml. of formic acid (98-100%) was heated at 60^o for 156 hours. The n. m. r. spectrum of the products indicated a complex mixture: 8.05 ppm (rel. area 4.1), 7.65 (1.6), 5.65 (1.5), 5.16 (1.8), 4.13 (4.6), 3.52 (0.4), 2.46 (1.6).

3,3-Dimethylbicyclo(3.3.1)nonan-2-one (XIX). Sublimed 2-bicyclo(3.3.1)nonanone (1.43 g., 10.4 mmoles), 4.4 g. (40 mmoles) of potassium t-butoxide, and 125 ml. of t-butanol were stirred for

20 minutes at room temperature. Methyl iodide (11 g., 77 mmoles) was added quickly, and the mixture was stirred for 5 hours at room temperature. Water was added, and the t-butanol was removed at reduced pressure. After the residue was acidified with sulfuric acid, the organic products were extracted with 500 ml. of hexane and distilled to give 1.23 g. (73%) of XIX, bath temperature 70-85° (0.05 mm), $n_D^{20} = 1.4869$. N.M.R. spectrum: complex multiplet 2.5-1.25 ppm (12H) and methyl singlets 1.16 and 1.08 ppm (3H). Infrared spectrum: 1375, 1355, 1712, aliphatic C-H. Molecular weight (mass spec) 166.

The oxime was prepared under forcing conditions (70° for 24 hours), m.p. 152.0-153.2°.

Anal. Calcd for $C_{11}H_{19}ON$: C, 72.88; H, 10.56. Found: C, 72.13; H, 10.46.

Methylation with one equivalent of base appears to give an equal mixture of the dimethyl ketone XIX and the starting material VII (glc analysis).

3-Methylbicyclo(3.3.1)nonan-2-one. The pyrrolidine enamine of 2-bicyclo(3.3.1)nonanone (VII) was prepared by the method of Stork (106) from 2.5 g (8 mmoles) of VII, 3.0 ml. (16 mmoles) of pyrrolidine, and 45 ml. of benzene. The distilled product was obtained in 55% yield. Infrared spectrum: no carbonyl, 1625, 1150 cm^{-1} . Alkylation of the enamine (1.9 g.) with 16 g. of methyl

iodide in refluxing benzene solution for 22 hours produced a dark red precipitate and a dark red solution. The enamine was hydrolysed with water, and the ketone was isolated by extraction into hexane. The 0.4 g. crude product contained 66% VII and 34% of a new ketone by glc (Autoprep, 140^o, SF-96). Only a small amount of product could be isolated by glc. N.M.R. spectrum: two sets of doublets centered at 1.03 ppm ($J = 6.0$ cps) and 0.97 ppm ($J = 5.5$ cps). Infrared spectrum: aliphatic C-H, 1708, 1380 cm.⁻¹

Deuterium exchange of XIX. A solution of 0.100 g. (0.60 mmole) of 3,3-dimethyl-2-bicyclo(3.3.1)nonanone (XIX), 0.7789 g. of deuteromethanol, and 0.0731 g. (1.4 mmoles active) sodium methoxide was sealed into 4 sample tubes under nitrogen. Three samples were placed into a constant temperature bath at 100.8^o and removed at various times. The fourth sample was used as a zero-point for the exchange. Each sample was quenched in dry ice-acetone after removal from the bath.

Analysis of the deuterium content (ratio of XIX to XXI) was made by mass spectrometry. An analysis by infrared was attempted but the extinction coefficient for the C-D absorption was not determined accurately, since only a single sample was used for this purpose. Mass spectra were also determined for deuterium incorporation samples of XXII which had been analysed previously by infrared (139, p. 15).

Ketone XIX, time (% C-D): 0.5 hour (13.4%), 1.6 hours (40%), 2 hours (43.8%); methoxide ion concentration, 1.25 m/l.; half-life, 2.3 hours; rate constant $k = 0.67 \times 10^{-4}$ l./m.-sec.; C^{13} correction, 12% of m/e 138.

Ketone XXII, time (% C-D): 28 hours (31%), 40 hours (34%), 72 hours (51%), 96 hours (60.5%); methoxide ion concentration, 1.65 m./l.; half-life 69 hours; rate constant $k' = 1.7 \times 10^{-6}$ l./m.-sec.; C^{13} correction, 18% of m/e 164.

Calculations: $k = (\ln 0.5)/(t \ 1/2)$ (methoxide ion concentration).

Bicyclo(3.3.1)non-2-ene oxide (XXIII). According to the method of Payne (86), 1.57 g. (12.8 mmoles) of 2-bicyclo(3.3.1)-nonene, 2 g. of potassium bicarbonate, 15 ml. of methanol, 1.4 g. (12.6 mmoles) of benzonitrile, and 1.3 ml. (11.5 mmoles) of 30% hydrogen peroxide were stirred at room temperature for 36 hours. After addition of water to the mixture, the organic products were isolated by extraction with two 200 ml. portions of hexane. The product (92%) was 1% olefin, 15% benzonitrile, and 85% epoxide by glc(PE, 134°, fluorosilicone). The epoxide was purified by glc (Autoprep, 135°, ucon polar) to give a crystalline material, m.p. 172-178° (rapid sublimation). N.M.R. spectrum: 3.0 ppm (2H, six lines) and complex multiplet 2.4-1.1 ppm (12H). The infrared spectrum showed only weak bands characteristic of epoxides.

Anal. Calcd for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C,

78.04; H, 10.98.

Exo-bicyclo(3.3.1)nonan-2-ol (XXIX). A mixture of 0.527 g. (3.81 mmoles) of epoxide XXIII, 45 ml. of tetrahydrofuran, and 1.1 g. (3 mmoles) of lithium aluminum hydride was heated to 50° for 24 hours. The excess hydride was hydrolysed with water, and the organic layer was decanted. The precipitated salts were extracted with three 150 ml. portions of ethyl ether. The crude product isolated from the combined organic layers was a solid, m.p. 150-170°. Purification of the product by glc (Autoprep, 148°, silicone SF-96) showed 16% of remaining epoxide (mixture sample) and 84% of a single alcohol XXIX, m.p. 174-176.5°. Infrared spectrum: 3600, 3425, 1440, 1455, 1048 (w), 980 (s) cm.⁻¹. The reported melting point for this compound is 180-192° (20). The reported infrared spectrum has the same 1045-985 cm.⁻¹ bands in a weak-strong pattern, while the isomeric endo-alcohol is reported to have two medium bands at 1060 and 1025 cm.⁻¹ (20).

Solvolyses of bicyclo(3.3.1)non-2-ene oxide (XXIII). A. In trifluoroacetic acid. The epoxide XXIII (3.6 g., 26 mmoles) in 50 ml. of pentane was added to 36 ml. of trifluoroacetic acid at 0°. The solution was stirred for 4 hours at 0°. A solution of 28 g. of sodium hydroxide in 125 ml. of water was added and stirring continued for 15 hours. The organic products were isolated by extracting the mixture with two 600 ml. portions of ether, washing

the ether extracts with aqueous sodium sulfate, and evaporating the solvent from the dry ether extracts. Chromatography of the 4.1 g. of crude product over 50 g. of alumina (deactivated with 1.5 g. water) gave some recovered epoxide and three fractions which were sublimed and found to be identical by n. m. r., infrared, glc (PE, 146°, fluorosilicone), and melting points: 142-148°, 141.4-147.5°, and 140-146.5°. The n. m. r. samples were combined and resublimed to give m. p. 145.5-149.5°. A portion of the material was sublimed four times and dried in the presence of phosphorous pentoxide for an analytical sample, m. p. 150.2-151.4°.

Anal. Calcd for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C, 77.89; H, 10.23.

The conversions of this product to the saturated alcohol and to the unsaturated ketone allow the following estimates of yields: exo-bicyclo(3.3.1)non-7-en-2-ol (XXVI), 32%; exo-bicyclo(3.3.1)non-3-en-2-ol (XXIV), < 3% (estimated from n. m. r. and ultraviolet data); and bicyclic diols (isolated by methanol solvent in chromatography), < 5%. The rest of the material was a dark red polymeric substance.

Exo-2-bicyclo(3.3.1)nonanol (XXIX). Hydrogenation of 53 mg. (0.38 mmole) of XXVI using 30 mg. of 5% palladium on charcoal used 7.5 ml. of hydrogen. The solution was filtered from the catalyst, and the solvent was removed. Sublimation of the product

gave 49 mg. (91%) of XXIX, m. p. 176.5-178.8°. The infrared spectrum was identical with that previously obtained for the epoxide reduction product (XXIX).

Bicyclo(3.3.1)non-7-en-2-one (XV). Jones' oxidation (12) of XXVI (36 mg., 0.26 mmole) gave 22.6 mg. (61%) product, m. p. 55-68°. Ultraviolet spectrum: 305, 297, 220, and 202 m μ ; relative intensities indicate that bicyclo(3.3.1)non-7-en-2-one (XV, m. p. 66-68°) is the major product and that bicyclo(3.3.1)non-3-en-2-one (XXVIII, m. p. 97.5-98.5°) is present in a minor amount.

Equilibration. Bicyclo(3.3.1)non-3-en-2-ol (90 mg., glc pure) in 2.5 ml. of trifluoroacetic acid and 1 ml. of pentane was stirred at 0° for 4 hours. The mixture was neutralized with excess potassium hydroxide and stirred for 10 hours. The organic product was isolated by extraction with ethyl ether followed by sublimation of the residue from the ether layer. The infrared and n. m. r. spectra of the product were identical with the spectra for the starting material XXIV and different from the spectra for the isomeric XXVI.

B. In acetic acid-sodium acetate. Pure epoxide XXIII (0.16 g., 11.6 mmoles) was dissolved at room temperature in 5.0 ml. of glacial acetic acid containing 0.25 g. (30 mmoles) of sodium acetate. The solution was heated at 100° for 72 hours, cooled, and

diluted with water. The organic products were extracted with ether. Chromatography of the products on deactivated (3% water) alumina gave a hexane fraction containing a single unsaturated acetate (57 mg., 27.2%) and an ether fraction containing a single diacetate (189 mg., 67.5%). The alcohols related to these materials were prepared by a preparative solvolysis of crude epoxide followed by lithium aluminum hydride reduction in ether.

Unsaturated alcohol XXIV or XXVI. Reduction of the 57 mg. of unsaturated acetate gave an alcohol with the same n. m. r. spectrum as the alcohol from the preparative reaction. N. M. R. spectrum: broad multiplet 5.75 ppm (2H), singlet 3.8 ppm (1H), complex multiplet 2.1-1.0 ppm (11H). Purification by glc (Autoprep 132^o, silicone SF-96) gave solid samples, m. p. 129-131^o and 130-132^o. Infrared spectrum: 3620, 3450, 1450, 1045, 3020, 2920, 985. The reported melting point for this compound is 103-103.5^o (72). The major unsaturated product is exo-bicyclo(3.3.1)non-3-en-2-ol (XXIV).

Separation of XXIV and XXVI by glc. The partial separation of the two isomeric unsaturated alcohols, XXIV and XXVI, was obtained only with a 5' x 1/4" 20% SE-30 column (Chromosorb W) at temperatures ranging from 100^o (retention times 13 and 14 minutes, respectively) to 50^o (retention times 48 and 52 minutes). At 140^o a single peak was observed. Under no conditions did the

diol portion of the chart show more than one peak (100° , 43 minutes). A sample of XXVI from the trifluoroacetic acid solvolysis contained very little XXIV, substantiating the 80% XXVI: 7% XXIV estimated from ultraviolet spectra of the corresponding ketones. The acetic acid solvolysis products were shown to be primarily XXIV (100° , 13 minutes) contaminated with XXVI (100° , 14 minutes, identified by mixture sample). Although there was considerable overlap of these two peaks at all temperatures, the relative amounts of these two products can be reasonably estimated to be 20% XXIV and 7% XXVI.

Exo-2-bicyclo(3.3.1)nonanol (XXIX). A sample of the mixture of XXIV and XXVI (20:7) was hydrogenated over Pd/C (5%) in methanol. After the solution was filtered from the catalyst and the solvent was removed, the residue was purified by gas chromatography (Autoprep, SE-30, 135°). Infrared spectrum: 3630, 3400, 2980, 2950-2850, 1480, 1450, 1445, 1040 (m), 982 (s), 963 (m), 940 (m), and 910 (m) cm^{-1} . The reported infrared spectrum for this compound has the same 1045-985 cm^{-1} bands in a weak strong pattern (20).

Oxidations to the ketones. A mixture (0.64 g., 4.1 mmoles) of the alcohol products from the solvolysis was added to 0.83 g. (8.3 mmoles) of chromium trioxide in 25 ml. of pyridine (65) and stirred at room temperature for 14 hours. The solution was diluted

with 100 ml. of ether and filtered through a deactivated (5% water) alumina column. The ketones were isolated by preparative glc (Autoprep, 114^o, SF-96-DMCS). The unsaturated product (single peak) was characterized: infrared spectrum, 1675, shoulder at 1700 cm.^{-1} ; ultraviolet spectrum, 232 $\text{m}\mu$ ($\epsilon = 4.85 \times 10^3$); m. p. 98-100^o; n. m. r. spectrum, AB vinyl protons 6.9, 6.15 ppm ($J = 10$ cps), small amount (10%) of non-AB vinyl protons. The reported melting point for this compound is 97.5-98.5^o (72). The unsaturated products from the solvolysis are considered to be 20% XXIV and 7% XXVI. The diketones were characterized similarly: infrared spectrum, 1705, shoulder at 1745, very small peak at 1800 cm.^{-1} ; n. m. r. spectrum, complex multiplet 3.0-1.5 ppm, large number of allylic hydrogens. Oxidation of pure diol from the solvolysis by Jones' reagent (12) gave essentially the same infrared spectrum for the diketones.

Saturated diol XXV or XXVII. N. M. R. spectrum: broad singlet 4.25 ppm (2H, disappear by deuterium oxide treatment), broad multiplet with superimposed broad singlet 3.42 ppm (2H), and complex multiplet 2.3-1.1 ppm (12H). Infrared studies on hydrogen bonding (5 cm. cell, Perkin Elmer 21 infrared spectrophotometer, sodium chloride prism, 0.002 moles diol/liter carbon tetrachloride): free OH absorption 3620 cm.^{-1} , no shoulder on the main peak attributable to H-bonded absorption (82, p. 42). An

analytical sample was prepared by glc (Autoprep, 150^o, silicone SF-96), m.p. 115-117^o.

Anal. Calcd for C₉H₁₆O₂: C, 69.19, H, 10.32. Found: C, 69.48; H, 10.38.

The saturated diols from the solvolysis are considered to be 54% bicyclo(3.3.1)nonane-2,7-diol(XXVII) and 14% bicyclo(3.3.1)nonane-2,3-diol (XXV).

Enhanced C-H Stretching and Bending Frequencies. Spectra were run on a Beckmann IR-7, carbon tetrachloride solutions, 0.2 or 0.5 mm cels (compensated), time constant 8, 2 x std slit, gain 400/10, 3.2 cm.⁻¹/min. scan speed. Bicyclo(3.3.1)nonan-2-one (mg. sample/gm. carbon tetrachloride = 42.2/1.14): 2934, 1416, 1443, 1452.5, 1462, 1473.5 cm.⁻¹; 3,3-dimethyl-2-bicyclo(3.3.1)nonanone (54.3/2.2): 2930, 2960, 2981, 1363, 1385, 1447, 1454, 1466, 1475.5 cm.⁻¹; bicyclo(3.3.1)nonane (18.1/1.99): 2959, 2988.5, 1447, 1456.5, 1463.5, 1485, 1489.5 cm.⁻¹; exo-2-bicyclo(3.3.1)nonanol (16.4/1.1): 2983, 1450, 1460, 1474, 1477, 1483.

Far-infrared Spectra. The spectra were run on a Beckmann IR-11 as nujol mulls with polyethylene windows (sample SSR-1362 at Beckmann Instruments, Fullerton, California). Bicyclo(3.3.1)nonane: 520, 490 (w), 380, 215 (w) cm.⁻¹ Bicyclo(3.3.1)nonan-2-one: 530, 510, 475, 450, 380, 340, 300, 245, 100 (broad) cm.⁻¹

Collected Ultraviolet Spectra. Bicyclo(3.3.1)non-7-en-2-one,

lambda max (extinction coefficient): 297 (181), 202 (2,090), $\epsilon_{290} =$
164; 3,3-dimethyl-7-bicyclo(3.3.1)nonen-2-one: 301 (198), 202
(3,910), $\epsilon_{290} = 169$; 7-methylene-3-bicyclo(3.3.1)nonanone: 280
(22.6), 209 (3,710); 6-bicyclo(3.2.2)nonen-2-one: 288 (rel. abs.
0.064), 214 (rel. abs. 0.568).

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