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Title The Synthesis and Spectral Properties of Some 2, 4-  
dioxabicyclo [3. 3. 1] nonanes

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3-Methyl-2, 4-dioxabicyclo [3. 3. 1] nonane and 7-hydroxy-3-methyl-2, 4-dioxabicyclo [3. 3. 1] nonane were synthesized by the method of Croxall, Glavis and Neher, although in low yields.

The structure of both compounds was proven by analytical methods and analysis of their spectral properties.

Tentative configuration of C-3 in both compounds was assigned on the assumption that the ring closing step is kinetically controlled. Both configurations were shown to be present at C-7 in 7-hydroxy-3-methyl-2, 4-dioxabicyclo [3. 3. 1] nonane.

The conformation of both compounds was tentatively assigned to the chair-boat form.

THE SYNTHESIS AND SPECTRAL PROPERTIES OF SOME  
2, 4-DIOXABICYCLO [3. 3. 1] NONANES

by

STEPHEN GLENN PROVANT

A THESIS

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Professor of Chemistry

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Dean of Graduate School

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Typed by Penny A. Self

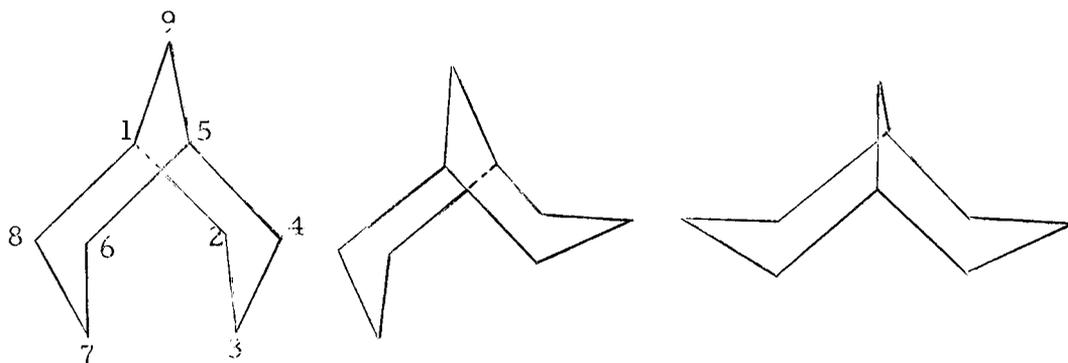
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THE SYNTHESIS AND SPECTRAL PROPERTIES OF SOME  
2,4 DIOXABICYCLO [3.3.1] NONANES

INTRODUCTION

The possible conformations of bicyclo[3.3.1]nonane provide an interesting problem in molecular geometry. Of the three conformations of this system, the double boat form can confidently be predicted to be of considerably less stability than



the other two forms and can therefore be ignored. The relative energies of the other two conformations cannot be predicted with confidence. The double chair form has a serious non-bonded interaction between the two internal hydrogens on carbons 3 and 7. By appropriate bond angle distortions in this molecule, the energy due to this interaction could be reduced, perhaps below the ca. 6 kcal/mole, which is the energy requirement necessary for adoption of the

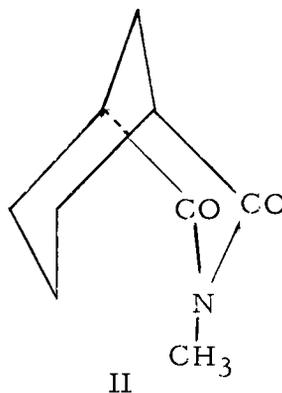
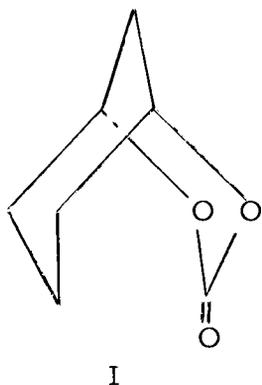
chair-boat form. However, whether or not this can occur is a question which has not been answered. To date no experimental test of this point has been made.

At present, studies are underway in our laboratory on derivatives of the bicyclo[3.3.1]nonanes. The difficulties associated with the preparation of the desired all carbon ring systems led us to attempt to find a more easily accessible route to an alternate heterocyclic system. Once this system was obtained we hoped to measure the physical properties of a selected series of derivatives of this system in an effort to obtain a satisfactory answer to the question posed above. The 2,4-dioxabicyclo[3.3.1]nonane ring seemed a suitable choice, and the preparation and properties of two examples of this ring system are described in this thesis.

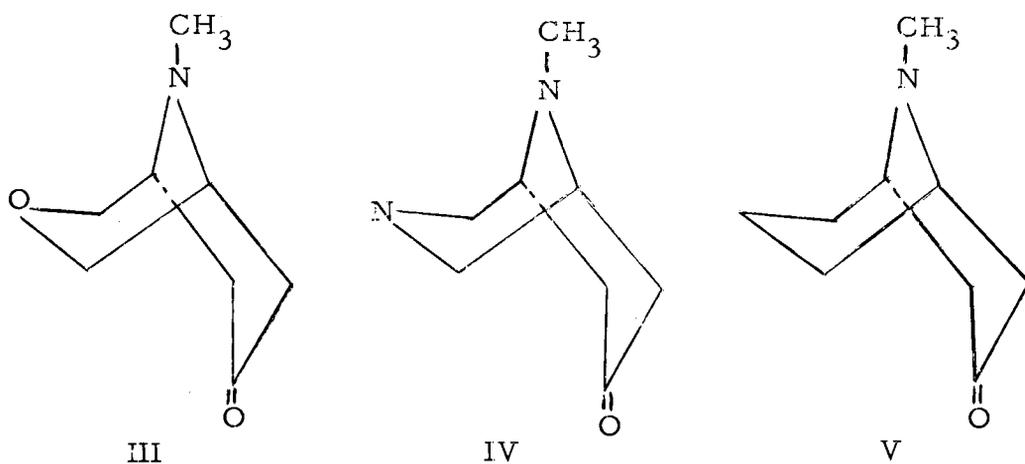
## HISTORICAL

Examples of the bicyclo[3.3.1]nonane system have been reported in the literature for many years. An encyclopedia of organic chemistry has been published (8, p. 1057) which contains a collection of the derivatives reported in the literature up to 1948. Rabe (12) and Knoevenagel (10), working independently, first reported synthesizing this system in 1903. Bicyclo[3.3.1]nonane itself was not synthesized until 1922 when Meerwein (11) reported this compound.

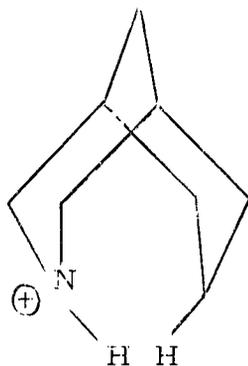
Although a number of derivatives of this ring system have been reported, the only instances of conformational assignments found in the literature have been tentative. Thus, 2,4-dioxabicyclo[3.3.1]nonan-3-one (I) and 3-methyl-3-azabicyclo[3.3.1]nonane-2,4-dione (II) are reported to exist as two fused chairs (6, p. 6416).



Although 2,4-dioxabicyclo[3.3.1]nonan-3-one appears to be similar to the compounds discussed in this thesis, it is actually a cyclic carbonate and lacks the acetal grouping. For these reasons we felt that this compound would be of no aid in our study. Also reported is a series of analogs (15), 9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (III), 9-methyl-3-thia-9-azabicyclo[3.3.1]nonan-7-one (IV), 9-methyl-9-azabicyclo[3.3.1]nonan-7-one (V), and the respective alcohols. The studies carried out with these compounds indicate that a boat-chair conformation may be more favored, but a firm conclusion concerning the more favored conformation of these compounds was not reached (15, p.398).



In a private communication<sup>1</sup>, the molecule below was reported to have a double chair conformation, the carbon-7,



nitrogen-3 distance being measured as 3.0 Å. The distance between the internal hydrogens on these atoms was measured as 2.0 Å.

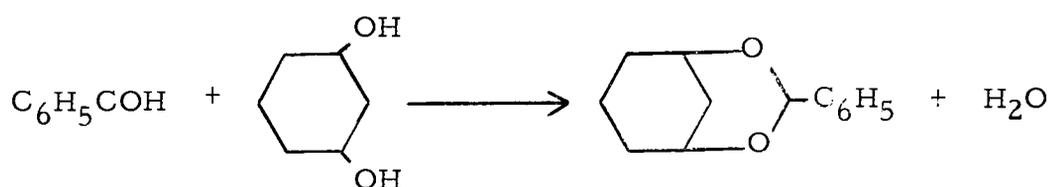
<sup>1</sup> J. Dunitz, Eidg. Technische Hochschule, Zurich, Switzerland.

## DISCUSSION

In this research, an attempt was made to develop a convenient synthesis for some substituted 2,4-dioxabicyclo[3.3.1]nonane derivatives. Although two examples of the ring system were obtained, no satisfactory synthesis was achieved.

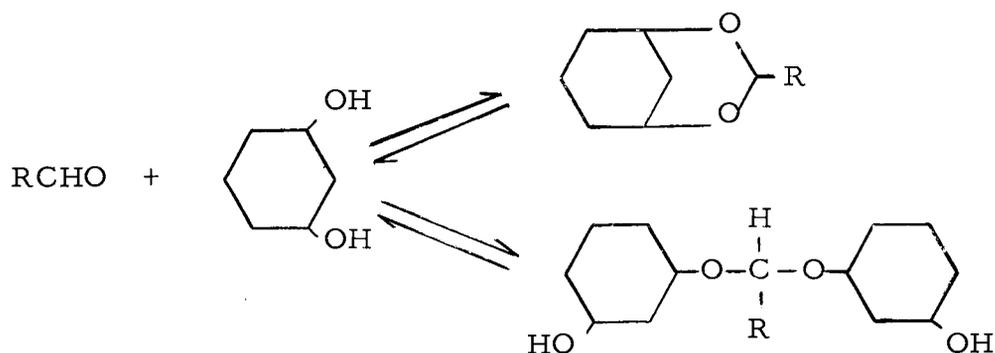
Synthesis

Since cyclic acetals and ketals are usually available by simple synthesis processes, the synthesis of the 2,4-dioxabicyclo[3.3.1]nonane ring system was not expected to present many difficulties. Synthesis of 3-phenyl-2,4-dioxabicyclo[3.3.1]nonane was attempted several times by acid catalyzed acetal formation between



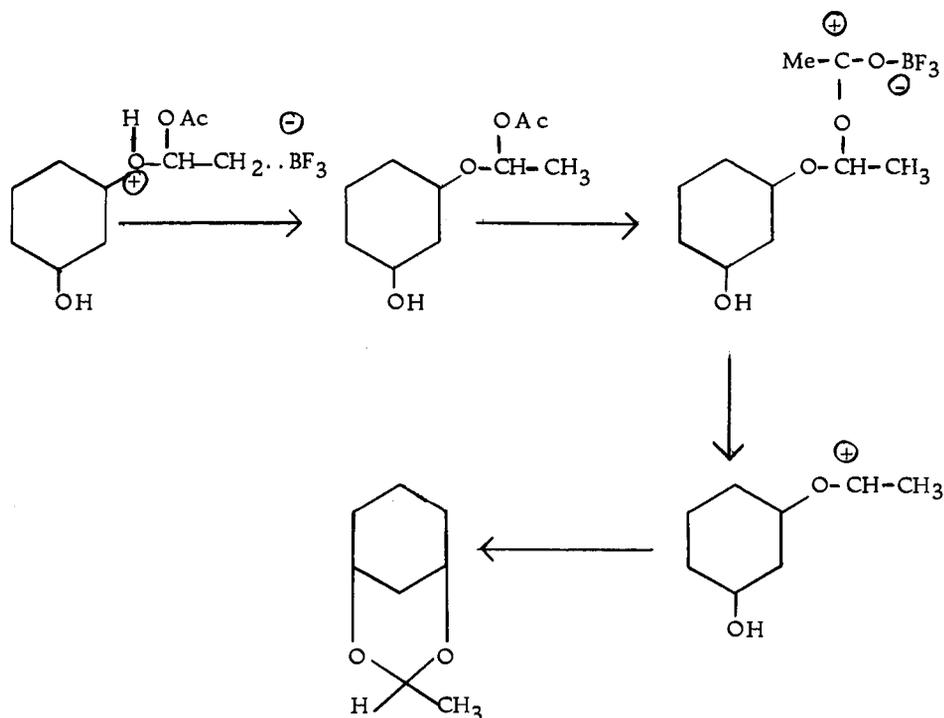
benzaldehyde and cis-1,3-cyclohexanediol. The desired product was not obtained. Reaction conditions must be carefully chosen for preparation of this bicyclic acetal system, since an alternate course can lead to the formation of polymeric acetal. Thus, if the

cyclic acetal formation is slow or subject to an unfavorable equilibrium constant, the reaction will proceed via the competing



process, which in most cases of cyclic acetal formation is less favorable.

On the assumption that formation of the bicyclic acetal was subject to an unfavorable equilibrium constant, reaction conditions were sought by which acetal formation would be more likely to occur under kinetic control. The method of Croxall, Glavis and Neher (5) was used with better results. This procedure uses vinyl acetate as a source of the aldehyde, and boron trifluoride as the catalyst. Their conditions were modified slightly by using a molar excess of vinyl acetate and a much more dilute solution to favor the ring closure. The reaction was performed a number of times, the desired 3-methyl-2, 4-dioxabicyclo[3.3.1]nonane being



obtained, however, always in low yield. The reaction invariably produced a considerable amount of polymer from which it was difficult to separate the acetal.

An attempt to form the bicyclic acetal of 1, 3, 5-cyclohexanetriol by this procedure was unsuccessful, the major product being polymer. An acetal interchange reaction employing acetaldehyde diethyl acetal met with a similar lack of success. Once again the Croxall process was used, however, this time we tried a greater dilution and a lower ratio of vinyl acetate to triol. The major product of this reaction was polymer. However, a small amount of liquid with the properties expected of 7-hydroxy-3-methyl-2,4-dioxabicyclo [3.3.1] nonane was isolated in crude form. This

substance proved so susceptible to acid catalyzed polymerization that we were unable to isolate it in pure form.

### Structure Proof

The structure of 3-methyl-2,4-dioxabicyclo[3.3.1]nonane was proven as follows. Analysis and molecular weight determination agree closely with the molecular formula  $C_8H_{14}O_2$ . On acid hydrolysis, acetaldehyde was recovered, strongly indicating that the molecule is an acetal. Its infrared spectrum shows the absence of any absorption due to hydroxyl groups and the presence of a doublet at  $1155-1100\text{ cm}^{-1}$  which is characteristic of acetals (1, p. 119). This data, plus the fact that no carbonyl absorption was found, rules out the possibility of any dimeric acetals, acetate esters of the diol, or ethers of the 1,3 diol.

The proton magnetic resonance spectrum is in complete accord with the assigned structure. It shows a doublet (3H) at  $8.87\tau$ , a triplet (2H) at  $5.79\tau$ , a quartet (1H) at  $4.75\tau$  and some complex multiplets in the region  $7.1-8.8\tau$ . The chemical shift of the doublet ( $J = 4.7\text{ cps}$ ) is in good agreement for a  $CH_3-C\begin{matrix} \nearrow O \\ \searrow O \end{matrix}$  group and is therefore assigned to the 3-methyl group (2, spectrum 143; 7, p. 55). The methyl group is spin coupled to a single proton

( $J = 4.7$  cps), which in turn is coupled only to the methyl group. This proton therefore appears as a quartet which is shifted to a  $\tau$  value of 4.75 due to the deshielding effect of the two neighboring oxygen atoms. There are two equivalent methine groups in the molecule, each attached to an oxygen atom. The protons on these groups appear as an apparent triplet ( $J = 4.0$  cps) at  $\tau = 5.79$ . The triplet could be a disguised quintuplet which would be expected due to the near equivalence of the four protons on adjacent carbon atoms.

Because of the small quantity of 7-hydroxy-3-methyl-2, 4-dioxabicyclo[3.3.1]nonane obtained, and the difficulties experienced in handling this substance, its structural assignment is based mainly on analogy with 3-methyl-2, 4-dioxabicyclo[3.3.1]nonane. The infrared and nmr spectra of the two compounds show great similarities. Its infrared spectrum shows the presence of the expected bands associated with the hydroxyl function. The nmr spectrum confirms the presence of the hydroxy and  $\text{CH}_3\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{H}$  groups.

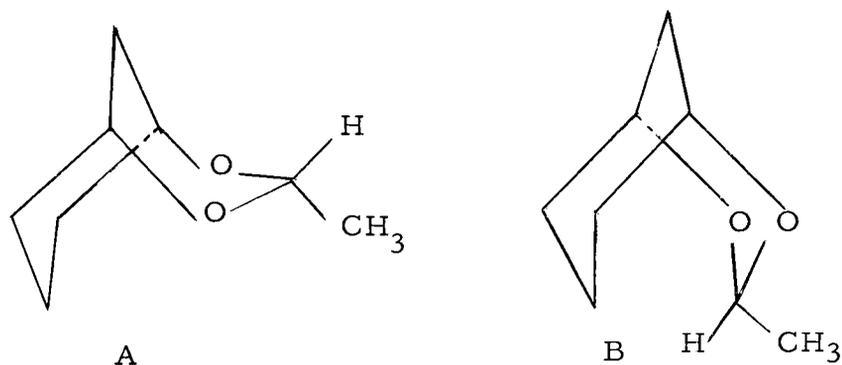
### Configuration and Conformation

Originally, we had hoped to assign the configuration at C-3 in both 2, 4-dioxabicyclo[3.3.1]nonane derivatives and also

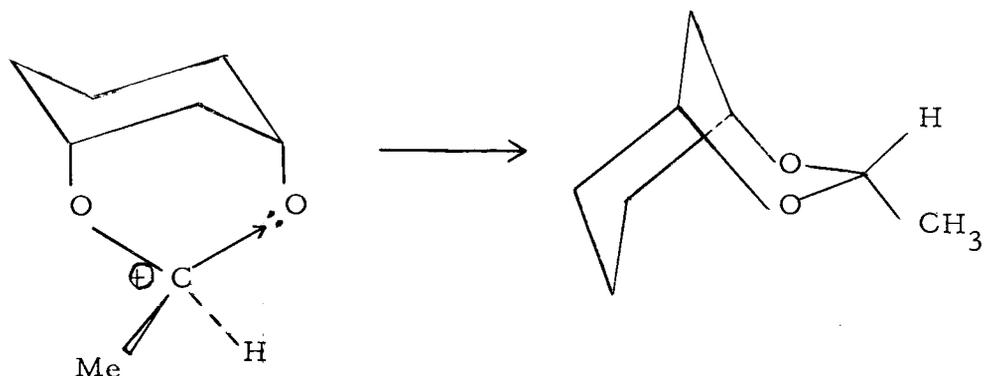
that at C-7 in 7-hydroxy-3-methyl-2, 4-dioxabicyclo[3. 3. 1]nonane as well as the conformation of the molecule in each case. However, a complete solution of this problem was not realized since we were unable to prepare the necessary derivatives of the bicyclo[3. 3. 1]nonane system. Certain tentative conclusions can be reached on the basis of the physical measurements made on the two compounds isolated. However, neither the configurations of C-3 and C-7 nor the conformation can be determined unambiguously.

Let us consider first the 3-methyl-2, 4-dioxabicyclo[3. 3. 1]nonane. In the nmr spectrum of this acetal, the band, due to the proton on C-3, appears as a sharply defined, symmetrical quartet. Since only one quartet appears and it is sharply defined and symmetrical, then this must mean that there is only one configuration present for this carbon. If both configurations were present, more than one set of bands would be observed for the C-3 proton since axial and equatorial proton bands appear at different fields. It can also be stated with confidence that only a single conformation is present. It seems very unlikely that both configurations at C-3 would be present with one having conformation (A), the other with conformation (B), and that both C-3 protons would coincidentally absorb at exactly the same field. This would be the only possible

exception to there being more than one configuration and conformation present.

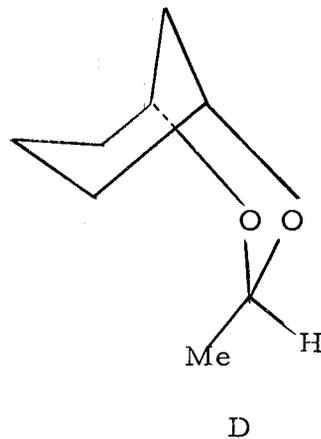
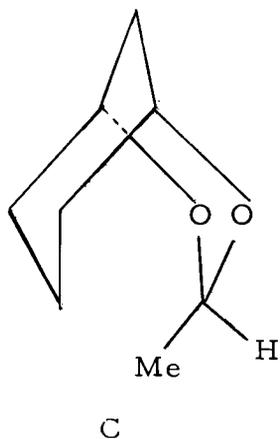


The presence of only one configuration must occur either because the product is kinetically controlled and the reaction stereospecific or because the product is equilibrium controlled and one form is thermodynamically much more stable than any other. Theoretical calculations of thermodynamic stability for the different possible configurations and conformations of this system would be prohibitably difficult and, therefore, the thermodynamically more stable product cannot be predicted by this method. If we assume the product is kinetically controlled, then the step which determines the configuration of C-3 is the ring closure step, and inspection of models indicates that the configuration shown below is heavily favored over the alternate possibility. Although we cannot be certain



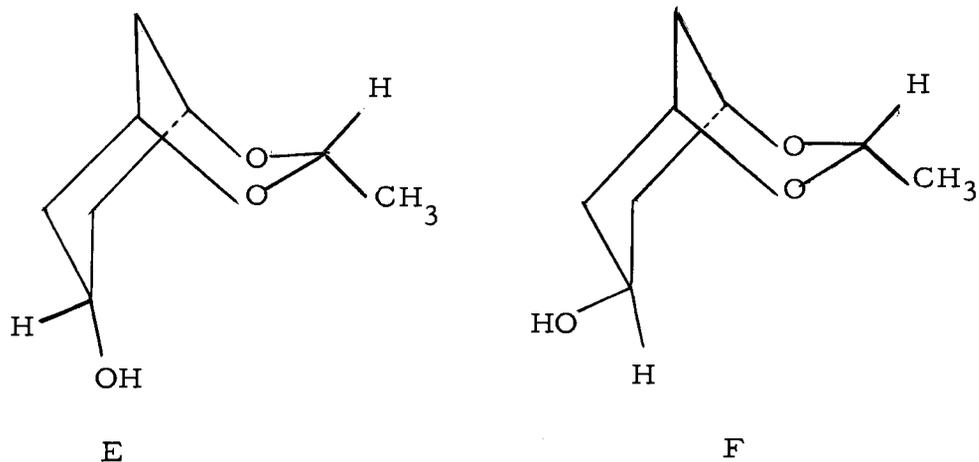
that this reaction is kinetically controlled, there is one piece of evidence which indicates that this is the case. The 7-hydroxy-3-methyl-2,4-dioxabicyclo[3.3.1]nonane polymerizes very rapidly, even in reasonably dilute solutions in the presence of a trace of acid. Thus, if the reaction is kinetically controlled, then equilibration through ring opening would be expected to yield the more stable product, in this case polymer.

There are three conformations to be considered if we assume the cyclic acetal has this configuration due to kinetic control. These are (A), (C), and (D). Of these, (D) is less stable than (A) by a considerable factor since it has three bulky groups axial to the acetal ring. (C) also has the same three bulky groups axial to the acetal ring and adds a methyl interaction with C-7. However, it has one less boat form than either (A) or (D). If (C) were the

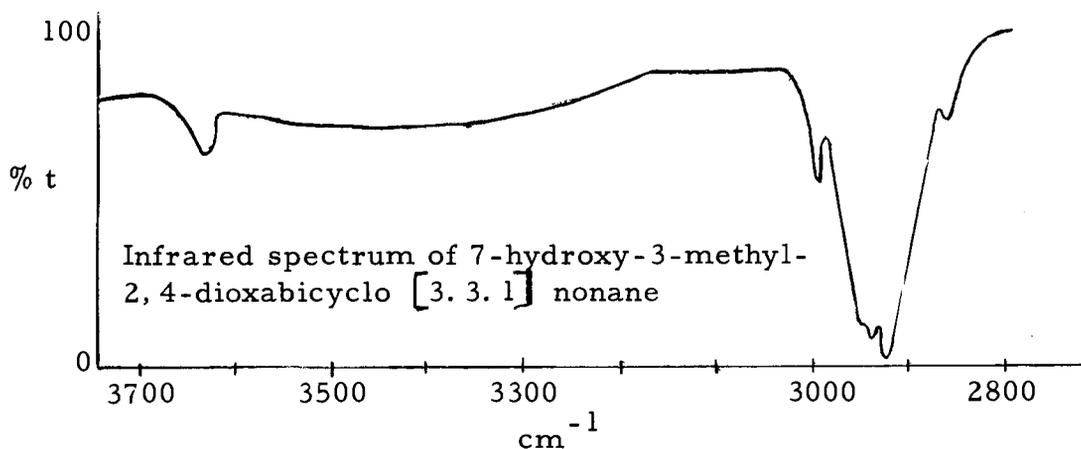


preferred conformation, then there should be evidence of a very energetic interaction between the methyl group and C-7. We can eliminate (D) due to its lower stability and (C) due to the lack of an observed methyl group, C-7 interaction. Thus, we assume (A) is the preferred conformation. On these bases then, we tentatively assign the configuration and conformation of (A) to the 3-methyl-2,4-dioxabicyclo [3. 3. 1] nonane isolated in this work.

Added confirmation for this assignment is obtained from an examination of the infrared spectra of dilute solutions of 7-hydroxy-3-methyl-2,4-dioxabicyclo [3. 3. 1] nonane. We have assumed both configurations (E) and (F) at C-7 to be present since the starting material apparently was a mixture of cis- and trans-1,3,5-cyclohexanetriol and since the reaction conditions did not seem



likely to be selective for one particular form. In (E) the hydroxyl group may be expected to be intramolecularly hydrogen bonded to the acetal oxygen. The infrared spectra shows that dilution does not completely remove the bonded hydroxyl frequencies.



The appearance of a carbon-hydrogen stretching frequency at  $2996\text{ cm}^{-1}$  in the infrared spectra of both cyclic acetals was studied with interest in an effort to provide further evidence

for this configurational and conformational assignment. Kivelson and Winstein (9) have provided evidence for an asymmetrical methylene stretching frequency which appears near  $3000\text{ cm}^{-1}$ . This band is due to interaction of one hydrogen of a methylene group with another hydrogen bonded to carbon when they are forced into close proximity (less than the van der Waal's radius). It appeared that the hydrogen atoms on C-9 and C-3 might be sufficiently close to cause this same effect, causing the observed carbon-hydrogen stretching frequency at  $2996\text{ cm}^{-1}$ . However, examination of a series of model acetals suggests that the C-3 methyl group is responsible for this band. We therefore conclude that in our molecules there are no hydrogen-hydrogen interactions of the type found by Kivelson and Winstein.

## EXPERIMENTAL

1, 3-Cyclohexanediol

1, 3-Cyclohexanediol was prepared, b. p.  $95-105^{\circ}\text{C}$  (1.0 mm),  $n_{\text{D}}^{22.6}$  1.4990,  $\nu = 3307, 2937, 2866, 1459, 1365, 1127, 1060, 1032, 1012, 980\text{ cm}^{-1}$ , according to the method of Clarke and Owen (4) using commercially available resorcinol, m. p.  $109-111^{\circ}\text{C}$ . The physical constants reported by the authors are: b. p.  $130-140^{\circ}\text{C}$  (6 mm),  $n_{\text{D}}^{19}$  1.5015.

3-Methyl-2, 4-dioxabicyclo [3. 3. 1] nonane

A solution containing 50 g (0.43 mole) of 1, 3-cyclohexanediol, 0.53 g of mercuric oxide and 0.5 ml of boron trifluoride-etherate in 200 ml of anhydrous tetrahydrofuran was cooled in an ice bath. To this 111 g (1.29 moles) of freshly distilled vinyl acetate was slowly added. The temperature was held below  $25^{\circ}\text{C}$  until the vinyl acetate had reacted, and the mixture was then stirred for 12 hours at room temperature. It was then poured into an aqueous solution containing 66.7 g (0.64 mole) of sodium carbonate. More sodium carbonate was added until gas evolution ceased. The organic layer was separated and dried over anhydrous potassium

carbonate. After the solvent had been removed, the product was distilled, b. p. 77-78° (17 mm),  $n_D^{20}$  1.4630,  $\nu$  = 3002, 2945, 2915, 1404, 1310, 1256, 1228, 1151, 1108, 1096, 967, 921, 892, 870  $\text{cm}^{-1}$ . The nmr spectrum showed a quartet (1H) at 4.75 $\tau$ , a triplet (2H) at 5.79 $\tau$ , a doublet (3H) at 8.87 $\tau$  and a multiplet centered at 7.96 $\tau$ .

Analytical:

Calculated for  $\text{C}_8\text{H}_{14}\text{O}_2$ : C, 67.57%; H, 9.92%; M. W. 142

Found: C, 67.8%; H, 9.99%; M. W. (commercial osmometer) 142.9

Acid hydrolysis of 3-methyl-2,4-dioxabicyclo[3.3.1]nonane

To an ethanol solution of 1 g (7 mmole) of 3-methyl-2,4-dioxabicyclo[3.3.1]nonane was added four drops of 6N hydrochloric acid and five ml of a 2,4-dinitrophenylhydrazine in diglyme solution (14). The mixture was refluxed until the 2,4-dinitrophenylhydrazone of acetaldehyde formed, m. p. 148° C. Reported value: m. p. 148-150° C (3, p. 582).

1,3,5-Cyclohexanetriol (Phloroglucitol)

A solution of 56 g (0.44 mole) of phloroglucitol in 340 ml

of absolute ethanol was hydrogenated over 4 g of Raney nickel at 125° C and 130 atm. for 48 hours. The solution was filtered and concentrated to half its original volume and then crystallized. The 1, 3, 5-cyclohexanetriol obtained was dried for several days over phosphous pentoxide; m. p. 130-131° C,  $\nu = 3260, 2915, 2870, 1478, 1363, 1311, 1235, 1136, 1080, 1025, 990, 850, 835 \text{ cm}^{-1}$ . Reported: m. p. cis 184° C, trans 145° C (13).

3-Methyl-7-hydroxy-2, 4-dioxabicyclo[3. 3. 1]nonane

A solution containing 16.1 g (0.122 mole) of 1, 3, 5-cyclohexanetriol, 0.4 g of mercuric oxide and 0.3 ml of boron trifluoride-etherate was added to 1500 ml of anhydrous tetrahydrofuran and heated to reflux. To this 12.9 g (0.15 mole) of freshly distilled vinyl acetate was slowly added. The mixture was refluxed until all the phloroglucitol had gone into solution, and then for an additional two hours. An aqueous solution containing 7.9 g (0.075 mole) of sodium carbonate was then added. More sodium carbonate was added until gas evolution ceased. The organic layer was separated and dried over anhydrous potassium carbonate. After the solvent had been removed, the product was extracted with chloroform, and then with anhydrous ether until no more polymer formed on addition of the ether. The product was distilled, pot temperature 110° C

(0.05 mm)  $\nu = 3425, 2948, 1740, 1720, 1471, 1409, 1319, 1245, 1141, 1108, 1093, 973, 935, 913 \text{ cm}^{-1}$ . The nmr spectrum showed a quartet (1H) at  $4.88\tau$ , a triplet (2H) at  $5.68\tau$ , a quartet at  $8.88\tau$ , a singlet in the region of  $6.0-6.6\tau$ , and a multiplet centered at  $7.99\tau$ .

#### 2-Methyl-1, 3-dioxolane

2-Methyl-1, 3-dioxolane, b. p.  $80-82^{\circ} \text{C}$ ;  $n_D^{20} 1.3966$ , was prepared according to the procedure of Croxall, Glavis and Neher (5). Infrared spectrum:  $2993, 2959, 2941, 2886 \text{ cm}^{-1}$ .

#### 1, 1-Diethoxy ethane (Acetal)

Commercially available 1, 1-diethoxy ethane was carefully fractionated, b. p.  $100.6^{\circ} \text{C}$ . Infrared spectrum:  $2978, 2973, 2935, 2901, 2885 \text{ cm}^{-1}$ .

#### trans 1, 3 Di-t-butyl cyclohexane

trans 1, 3 Di-t-butyl cyclohexane was kindly supplied by Dr. N. Allinger at Wayne State University. Infrared spectrum:  $2966, 2952, 2909, 2867 \text{ cm}^{-1}$ .

### Infrared Spectra

The complete spectra in the region from 4000-650  $\text{cm}^{-1}$  were taken with a Perkin-Elmer Model 21 Infrared Spectrophotometer using a sodium chloride prism. The spectra were taken either in a sandwich cell or as a 5-7% solution in  $\text{CCl}_4$  in a .05 mm fixed cell.

A high resolution study in the region from 3200-2800  $\text{cm}^{-1}$ , using a Beckman IR-7, was made of a series of compounds. The spectra were taken as a 5-7% solution in  $\text{CCl}_4$  in a .05 mm fixed cell. The author is indebted to Dr. J. C. Decius for assistance in this study.

### NMR Spectra

All nmr spectra were taken with a Varian-60 High Resolution Spectrophotometer. In all cases, the compounds were dissolved in carbon tetrachloride with tetramethylsilane as an internal standard.

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