Small Ring Compounds. VII. The Syntheses of 3-Oxabicyclo-[3. 1. 0]hexane and Its Derivatives

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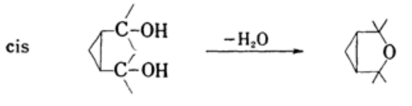
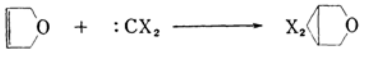
The cyclopropane ring has been reasonably considered to be different from other alicyclic rings in its electronic structure and to show characteristic chemical and physical properties. In order to clarify these points, the authors have reported in the preceding paper[1] of this series on the syntheses of cyclopropane derivatives and on some of their characteristic reactions. In the present paper the syntheses and properties of some cyclic ethers, which include the cyclopropane ring, that is, 3-oxabicyclo-[3. 1. 0] hexane (I) derivatives, will be reported.

Two methods are available for the syntheses of these bicyclic ethers. One of them is the dehydration of *cis*-1, 2-dimethylolcyclopropane and its derivatives (Eq. 1), while the other is the addition of some carbenes to 2, 5-dihydrofuran (Eq. 2):

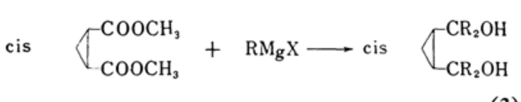


(1)



(2)

The synthesis of *cis*-1, 2-dimethylolcyclopropane was reported in the previous paper,[1] and $\alpha, \alpha, \alpha', \alpha'$-tetrasubstituted homologs were prepared from the corresponding *cis*-diester by Grignard reaction (Eq. 3):



(3)

For the dehydrating ring closure of these glycols, four methods were examined: The use of potassium bisulfate, phosphoric acid and

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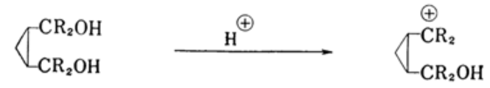
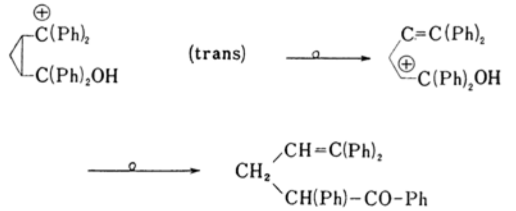
[1] Small Ring Compounds. VI. T. Shono, T. Morikawa, R. Okayama and R. Oda, *Makromol. Chem.*, in press.

dimethyl sulfoxide as dehydrating agents, and the alkaline fusion of the tosylate of the glycols. Among these methods, that employing potassium bisulfate gave the best result; by the alkaline fusion of tosylate, the ether was not obtained at all. It is of interest that the dehydration of the glycols in acidic media was affected by the substituents and that sometimes rearranged products were formed. In acidic dehydration, the first-formed cation (see Eq. 4) would be the so-called "cyclopropyl carbinyl"-type cation, which is known to exhibit a complicated behavior in the course of reaction.[2]



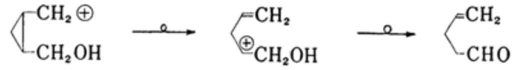
(4)

The cyclopropylcarbinyl cation may be considered to belong to a nonclassical carbonium ion; hence, ring-opening and rearrangement should occur. When the cation has some substituents at appropriate positions, the substituents have a great effect on its character; that is, the substituents determine whether it is a nonclassical or a localized cation. In our results, bicyclic ether was obtained almost quantitatively in the case of $R=CH_3$ (cf. Eq. 4), whereas in the case of $R=H$ or C_6H_5, some ring-opened products were obtained besides bicyclic ether. For example, *cis*-1, 2-di(α, α-diphenyl)methylolcyclopropane was rearranged through dehydration to give 1, 1, 4-triphenyl-4-benzoylbutene-1 (80%), which is the same as the product obtained in the acidic dehydration of the trans isomer[3] (Eq. 5):



(5)

The yield of the normally dehydrated product, bicyclic ether, was only 20%. These results show that two competing reactions, i. e., cyclization and rearrangement, occurred. In addition, the dehydrated products from a glycol, where $R=H$, had a very complicated composition. The yield of the expected product, 3-oxabicyclo [3. 1. 0] hexane, was only 35%, and the formation of an aldehyde (abt. 4%) and a large amount of oligomer containing a carbonyl group was observed. The mechanism of the formation of this aldehyde seems similar to that where $R=C_6H_5$ (Eq. 6):

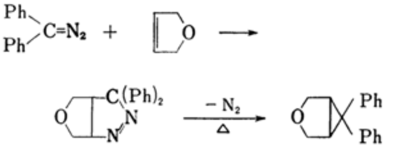


(6)

The 2, 4-dinitrophenylhydrazone of this aldehyde gave the same elementary analysis data and melting point as did an authentic sample.

On the other hand, it has been reported that, when methyl group is present at an appropriate position of the cyclopropyl carbinyl cation, this methyl group effects the localization of the cation and diminishes the contribution of the non-classical character.[2] This fact agrees with our finding that no rearrangement was observed in the dehydration of the glycol where $R=CH_3$. The courses of dehydration of these glycols, both cis- and trans-, are now under investigation and will be reported on elsewhere.

The methods of the syntheses of bicyclic ethers through carbene addition to 2, 5-dihydrofuran differed according to the character of the carbene. For example, dichlorocarbene was generated by two methods, (1) $CHCl_3+t\text{-}C_4H_9OK$ and (2) $Cl_3CCOOCH_3+CH_3ONa$. Method 2 gave a better result, but in both cases the products were a mixture of two isomeric compounds, which could be separated only by vapor-phase chromatography. One of them was 6, 6-dichloro-3-oxabicyclo [3. 1. 0]-hexane; the structure of the other isomeric product could not be elucidated, though it can be considered to be an insertion product. On the other hand, fluorenyl carbene was generated from the corresponding diazo compound in a solution of 2, 5-dihydrofuran with a copper catalyst. Under similar conditions, however, diphenyldiazomethane was directly added to 2, 5-dihydrofuran to form a pyrazoline derivative, which lost its nitrogen easily upon heating and afforded the bicyclic ether (Eq. 7):



(7)

In addition, the Simmons-Smith[4] method was adopted as a modified procedure for the synthesis of 3-oxabicyclo [3. 1. 0] hexane, instead of using diazomethane as a carbene source. A zinc-copper couple was prepared by the wet method. The yield was only 5%, though it

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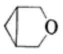
[2] P. de Mayo, "Molecular Rearrangements," Interscience Publishers, N. Y. (1963), p. 233.

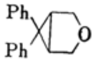
[3] R. A. Darby and R. E. Luty, *J. Org. Chem.*, **22**, 1353 (1957).

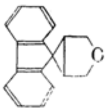
[4] R. D. Smith and H. E. Simmons, "Organic Syntheses," **41**, 72 (1961).

TABLE I. STRUCTURES OF 3-OXABICYCLO[3.1.0]HEXANE DERIVATIVES AND THEIR PREPARATION

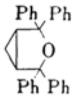

(I)


(II)


(III)


(IV)

(V)

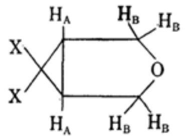


(VI)

(I) 3-Oxabicyclo[3.1.0]hexane
(II) 6, 6-Dichloro-3-oxabicyclo[3.1.0]hexane
(III) 6, 6-Diphenyl-3-oxabicyclo[3.1.0]hexane
(IV) 3, 4-(9, 9-Fluorenylidene) tetrahydrofuran
(V) 2, 2, 4, 4-Tetramethyl-3-oxabicyclo[3.1.0]hexane
(IV) 2, 2, 4, 4-Tetraphenyl-3-oxabicyclo[3.1.0]hexane

Compound	Method	Yield, %	M. p. °C (or b. p. °C/mmHg)
I	Dehydration		
	a $KHSO_4$	35	(85—90/760)
	b H_3PO_4	5	—
	c DMSO	2	—
	Simmons-Smith method	3—5	—
II	Dichlorocarbene		
	a $CHCl_3$	7	—
	b $Cl_3CCOOCH_3$	37	(88—89/35)
III	Diazo compd.	19	86.5—87.5
IV	Diazo compd.	5	169—170.5
V	Dehydration ($KHSO_4$)	77	(91—91.5/164)
VI	Dehydration ($KHSO_4$)	21	166—167

TABLE II. CHEMICAL SHIFTS RELATIVE TO TMS AS INTERNAL STANDARD (60 Mc.)



Compound	X	Solvent	Chemical shift, c. p. s. (τ value)		
			H_A	H_B	
II	Cl	CCl_4	137.0(7.55)	227.6(5.92)	
III	C_6H_5	CCl_4	120.1(7.85)	215.8(6.13)	
IV	$\frac{1}{2}(C_{12}H_8)$	CCl_4	130.7(7.65)	223.4(6.00)	
I	H	CCl_4	78.2(8.60)	H_B 199.3(6.46)	$H_{B'}$ 191.7(6.59)

Coupling constant $J_{BB'}$ (compound I) 8.4 c. p. s.

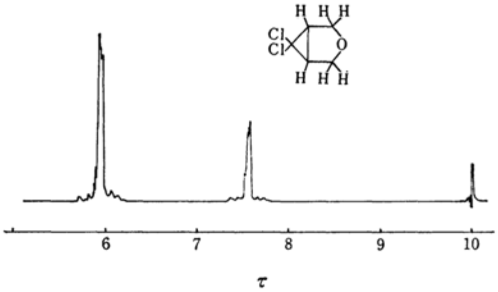


Fig. 1. NMR spectrum of II using TMS as internal standard.

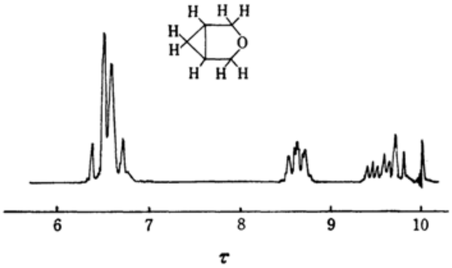
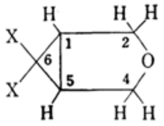


Fig. 2. NMR spectrum of I, using TMS as internal standard.

has been reported that in the case of dihydropyran the yield reached up to 65%.

The NMR spectra of compounds II, III and IV had only two peaks, near $\tau=7.7$ and 6.0 (see Table II) (Fig. 1). These peaks correspond to the bridge-head protons and to the methylene protons adjacent to oxygen respectively. Further, each peak showed a negligibly small fine-structure, indicating that the spin-spin coupling between $H_{(1)}$ and $H_{(2)}$ (or $H_{(5)}$ and $H_{(4)}$) is negligibly small in these bicyclic compounds. In these compounds the three-membered ring and the five-membered ring do not lie on the same plane; hence, the two hydrogens at position 2 or 4 would not be equivalent, and the spectrum of these hydrogens would be of the type AB. In the spectra of 6, 6-disubstituted bicyclic ethers, however, the chemical shifts of the two hydrogens of position 2 or 4 were nearly equal, and hence the AB-type spectrum was not confirmed. However, in the case of compound I (X=H), the spectrum of $H_{(2)}$ (or $H_{(4)}$) was clearly of the AB type, and still the coupling between $H_{(1)}$ and $H_{(2)}$ (or $H_{(5)}$ and $H_{(4)}$) (Fig. 2) was negligibly small.



The infrared spectra of these bicyclic ethers showed the presence of a characteristic band near 1090 cm⁻¹ (Fig. 3).

Attempts to polymerize these bicyclic ethers (particularly I and II) with phosphorous pentafluoride, antimony pentachloride or a thionyl chloride - ferric chloride complex were unsuccessful. The reason why they could not be polymerized is uncertain. Moreover, neither I nor II copolymerized with 3, 3-bischloromethyloxethane in the presence of a modified catalyst of triethyl aluminum ($AlEt_3+H_2O+$ Epichlorohydrin).

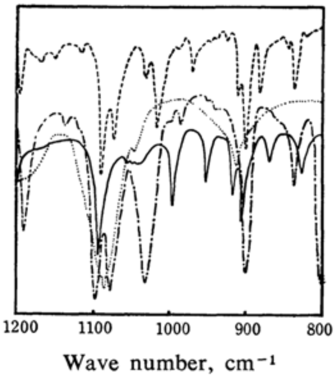


Fig. 3. Infrared spectra of bicyclic ethers.

——: X=H, ------: X=C_6H_5
—-—: X=Cl, (······: THF)

Experimental

3-Oxabicyclo[3. 1. 0]hexane (I).—*a) By Dehydration using Potassium Bisulfate.*—In a 50 ml. distilling flask 2.6 g. (3/160 mol.) of calcined potassium bisulfate was placed. The flask was then heated at 150—160°C, and 7.6 g. (3/40 mol.) of *cis*-1, 2-dimethylolcyclopropane was added drop by drop over a 15-min. period. The distillate separated in two layers, and the organic layer was dried successively over sodium bicarbonate and Drierite (raw yield; 43%). By fractional distillation I was obtained in a 35% yield, b. p. 85—90°C, it contained a slight amount of an aldehyde.

Found (for I): C, 70.78; H, 9.67. Calcd. for C_5H_8O: C, 71.39; H, 9.58%.

b) By Dehydration using Phosphoric Acid.—Into a flask heated to 260°C, a mixture of 23 g. (0.23 mol.) of *cis*-1, 2-dimethylolcyclopropane and 0.25 ml. of 80% phosphoric acid was added drop by drop. The distillate was dried over anhydrous magnesium sulfate and distilled. A fraction with the boiling range of 70—80°C was proved to be pure I by gas chromatography (yield, 5%).

c) By Dehydration using Dimethyl Sulfoxide (DMSO).—A mixture of 16 g. (0.16 mol.) of *cis*-1, 2-dimethylolcyclopropane and 150 g. of DMSO was heated at 160—170°C under refluxing for 18 hr. Then the mixture was distilled below the boiling point of DMSO, the distillate was extracted with petroleum ether, and the organic layer was dried over anhydrous magnesium sulfate. After fractional distillation, a fraction with the boiling range of 60—106°C was obtained; in this fraction I was detected by gas chromatography and infrared absorption (yield, 2%).

d) By the Simmons-Smith Reaction.—The procedure was almost analogous to that of the synthesis of norcarane. The yield was only 3—5% (by gas chromatography).

6, 6-Dichloro-3-oxabicyclo[3. 1. 0]hexane (II).—*a) Using Chloroform as the Source of Carbene.*—Dichlorocarbene was generated by the usual method⁵⁾ from chloroform and potassium *t*-butoxide in an ether solution of 2, 5-dihydrofuran. The reaction mixture was then treated with aqueous phosphoric acid and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate and distilled to give a fraction with the boiling range of 80—94°C/60 mmHg; from this fraction II was separated by preparative gas chromatography (yield, 7%).

b) Using Methyl Trichloroacetate as the Carbene Source.—The procedure was almost analogous to that of ethyl trichloroacetate.⁶⁾ The yield of II was 37% (b. p. 81—85°C/25 mmHg) after it had been purified by gas chromatography.

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5) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

6) J. C. Anderson and C. B. Reese, *Chem. & Ind.*, **1963**, 575.

6, 6-Diphenyl-3-oxabicyclo[3. 1. 0]hexane (III).—Diphenyldiazomethane was prepared according to the usual method.[7] To a solution of 8 g. (0.04 mol.) of diphenyldiazomethane in 27 g. (0.4 mol.) of 2,5-dihydrofuran, a catalytic amount of copper powder was added; then the mixture was heated under refluxing for 10 hr. After the excess dihydrofuran, had been removed, the remaining solid was recrystallized from ligroin and proved to be a pyrazoline derivative. Yield, 2.2 g. (21%). M. p. 119.5 —121°C.

Found: C, 77.12; H, 6.21. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10%.

When this pyrazoline derivative was heated, a rapid evolution of nitrogen occurred. The recrystallization of the residue gave 1.8 g. (92%) of III. M. p. 86.5—87.5°C.

Found: C, 86.40; H, 6.82. Calcd. for $C_{17}H_{16}O$: C, 86.72; H. 6.83%.

3, 4-(9, 9-Fluorenylidene) tetrahydrofuran (IV).—Diazofluorene,[8] prepared from 3 g. of the corresponding hydrazone, was dissolved in 5 g. of dihydrofuran and refluxed for 3 days in the presence of a copper catalyst. After dihydrofuran had been evaporated, the residue was recrystallized from benzene and ether successively to afford 0.2 g. (5%) of IV. M. p. 169—170.5°C.

Found: C, 87.42; H, 5.95. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02%.

2, 2, 4, 4-Tetramethyl-3-oxabicyclo [3. 1. 0] hexane (V).—*cis*-1, 2-Di(α, α-dimethyl) methylolcyclopropane (V′) was prepared by the usual method from methylmagnesium iodide and *cis*-dimethyl 1,2-cyclopropane dicarboxylate. Yield, 44%. M. p. 85.5—87°C.

Found (for V′): C, 68.33; H, 11.76. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47%.

A mixture of 11 g. (0.07 mol.) of V′ and 5 g. (0.035 mol.) of calcined potassium bisulfate was heated in a distilling flask; then the distillate was collected and dried over calcium chloride. Distillation gave 7.5 g. of V (77%). B. p. 91—91.5°C/164 mmHg.

Found (for V): C, 76.83; H, 11.34. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50%.

2, 2, 4, 4-Tetraphenyl-3-oxabicyclo[3. 1. 0] hexane (VI).—To a Grignard solution prepared from 24 g. (0.15 mol.) of bromobenzene and 3.7 g. (0.15 mol.) of magnesium, 5.0 g. (0.031 mol.) of *cis*-dimethyl 1,2-cyclopropane dicarboxylate in 10 ml. of ether was added drop by drop while the mixture was being refluxed and stirred. After vigorous stirring for two hours, the reaction mixture was hydrolyzed with a saturated aqueous ammonium chloride solution and extracted with ether. After the ether had been evaporated off, 7.5 g. (61%) of *cis*-1,2-di(α, α-diphenyl) methylolcyclopropane (VI′) was obtained. M. p. 198—201°C, recrystallized from ethanol.

Found: C, 86.20; H, 6.64. Calcd. for $C_{29}H_{26}O_2$: C, 85.68; H, 6.45%.

A mixture of 1 g. of VI′ and 0.3 g. of calcined potassium bisulfate was melted at 130°C under reduced pressure for 5 min. After the gas evolution had ceased, the reaction mixture was crushed and extracted with petroleum ether. The extract was recrystallized from the same solvent, and two kinds of crystals, white block and fine grain, were obtained. The latter was picked up and recrystallized to give 0.2 g. (21%) of VI. M. p. 166—167°C.

Found (for VI): C, 89.60; H, 6.69. Calcd. for $C_{29}H_{24}O$: C, 89.65; H, 6.23%.

The former was 1,1,4-triphenyl-4-benzoylbutene-1. Yield, 0.75 g. (76%). M. p. 129—131°C. No depression in melting point was observed when it was admixed with an authentic sample.

Summary

Some bicyclic ethers containing a cyclopropane ring, i. e., 3-oxabicyclo [3. 1. 0] hexane derivatives, have been synthesized. Two methods have been used in the syntheses of these compounds. One of them has been the dehydration of *cis*-1, 2-dimethylolcyclopropane derivatives, and the other, the addition of some carbenes to 2, 5-dihydrofuran. The Simmons-Smith method has also been adopted. The NMR spectra of these bicyclic ethers have been examined. The types of their spectra are fairly simple. The chemical shifts and the coupling constant of some protons have also been measured. Attempts to polymerize these bicyclic ethers, unfortunately, have been unsuccessful.

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[7] L. I. Smith and K. L. Howard, "Organic Syntheses," Coll. Vol. III, 351 (1956).

[8] C. N. Nenitzescu and E. Solomonica, ibid., Coll. Vol. II, 496 (1948).