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Spiro Compound Formation. IV.[1] Acid-catalyzed Reactions of 2-Cyclohexylidenecyclohexanone Oxide

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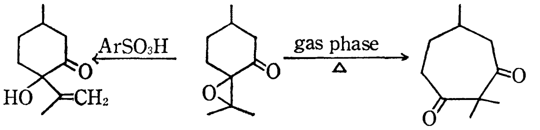
The reactions of 2-cyclohexylidenecyclohexanone oxide in the presence of (i) sulfuric acid, (ii) fluorosulfonic acid, (iii) boron trifluoride etherate, and (iv) antimony pentachloride have been studied. The products consisted of spiro[5.6]dodecane-7,12-dione, 2-(1-cyclohexenyl)-2-hydroxycyclohexanone, and 1,2,3,4,6,7,8,9-octahydrodibenzofuran. The ratio of the products was found to depend on the differences in the catalysts and solvents.

Although the reactions of α,β-epoxyketones under acidic conditions have been performed energetically from synthetic points of view,[2] only a few examinations aiming at a systematic clarification of the effects of catalysts upon the reaction mechanism have been performed.

Reusch, Anderson, and Johnson[3] recently reported that the gas-phase pyrolysis of pulegone oxide (I) at 200°C produced 2,2,5-trimethylcycloheptane-1,3-dione (II); they concluded that this reaction involved the rearrangement of I absorbed at Lewis acid sites on the Pyrex glass surface. Contrary to the above results, however, the reaction of I with *p*-toluenesulfonic acid led to the unsaturated hydroxyketone (III). These results suggest that the mechanism of the reaction of α,β-epoxyketones with Lewis acid is different from the mechanism of the reaction which is performed in the presence of Brǿnsted acid.



(III) (I) (II)

In order to investigate in more detail the dependence of the reaction pathways upon the difference in catalysts, we examined the reaction of 2-cyclohexylidenecyclohexanone oxide(IV)[4] in the presence of (i) sulfuric acid. (ii) fluorosulfonic acid, (iii) boron trifluoride etherate, and (iv) antimony pentachloride respectively. Liquid sulfur dioxide and cyclohexane were used as the solvents, and the solvent effects upon the reaction were also examined. The reactions were performed under the conditions described in Table 1.

TABLE 1. ACID-CATALYZED REACTIONS[a] OF IV AND VI

Substrate	Catalyst	Solvent	Total yield, %[b,h]		
			V[d]	VI[e]	VII[f]
IV[c]	$SbCl_5$	SO_2	93.2	0	6.8
	BF_3-Et_2O	SO_2	82.8	0	17.2
	FSO_3H	SO_2	27.7	0	72.3
	H_2SO_4	SO_2	41.8	10.6	47.6
	$SbCl_5$	Cyclohexane	30.2	44.3	25.5
	BF_3-Et_2O	Cyclohexane	41.3	35.4	23.3
	FSO_3H	Cyclohexane	6.6	49.2	44.2
	H_2SO_4[g]	Cyclohexane	8.5	0	91.5
VI	H_2SO_4	SO_2	0	13.0	87.0

a) 0.1 g Substrate, 0.1 m*l* catalyst in 10 m*l* of SO_2 at 0°C or in 10 m*l* of cyclohexane at 15°C for 1 hr.
b) Calculated from the glpc peak areas.
c) 2-Cyclohexylidenecyclohexanone oxide.
d) Spiro[5.6]dodecane-7,12-dione.
e) 2-(1-Cyclohexenyl)-2-hydroxycyclohexanone.
f) 1,2,3,4,6,7,8,9-Octahydrodibenzofuran.
g) The reaction was performed for 21 hr.
h) The total yields were almost quantitative.

Gas-liquid partition chromatography showed that the products consisted of spiro[5.6]dodecane-7,12-dione (V), 2-(1-cyclohexenyl)-2-hydroxycyclohexanone (VI), and 1,2,3,4,6,7,8,9-octahydrodibenzofuran (VII). The products were isolated by column chromatography and were characterized by physical measurements and by their chemical transformations.

The compound V was a white crystalline solid of

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1) Part III; M. Nojima and N. Tokura, This Bulletin, **42**, 1351 (1969).

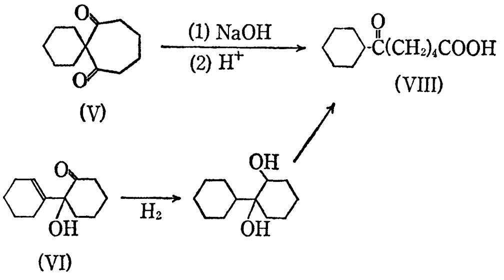
2) R. E. Parker and N. S. Issacs, *Chem. Rev.*, **59**, 737 (1959).

3) W. Reusch, D. F. Anderson and C. K. Johnson, *J. Amer. Chem. Soc.*, **90**, 4988 (1968).

4) House and Wasson examined the pyrolytic rearrangement of IV to yield spiro[5.6]dodecane-7,12-dione (V). Although the reaction of IV with BF_3 etherate was also performed in benzene or diethyl ether, they failed to obtain the same compound V; H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, **78**, 4394 (1956).

mp 69—70°C. Mass spectroscopy established a molecular formula $C_{12}H_{18}O_2$ (Calcd for $C_{12}H_{18}O_2$: 194, Found: 194). V exhibited a carbonyl absorption at 1682 cm^{-1}, forming a semicarbazone, mp 218—223°C. The treatment of V with aqueous sodium hydroxide gave 6-cyclohexyl-6-oxohexanoic acid (VIII).[4]

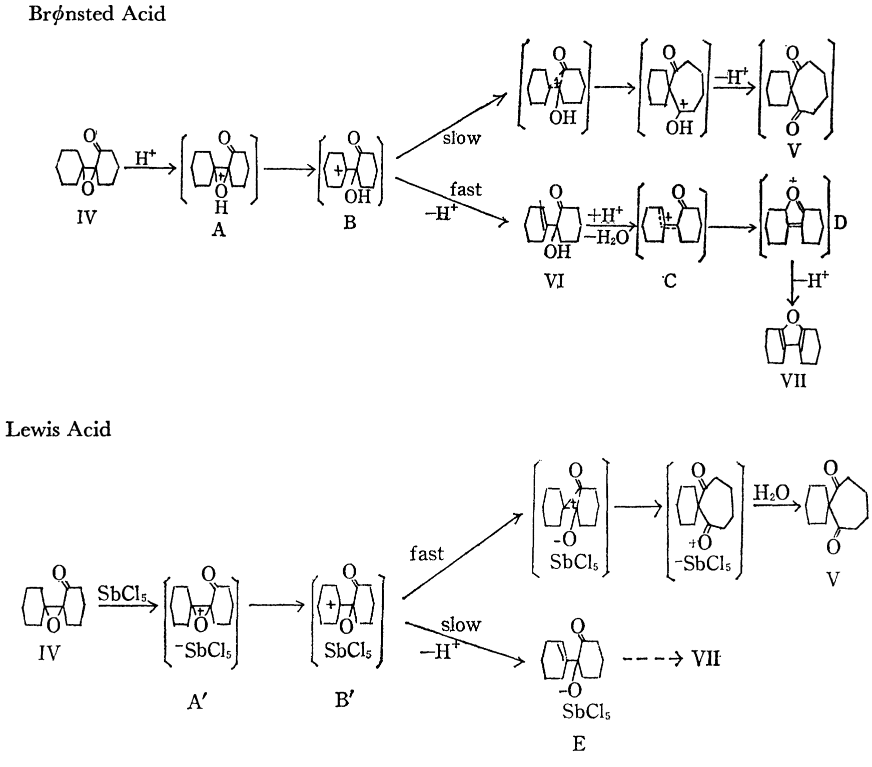
VI exhibited carbonyl and hydroxyl absorptions at 1700 and 3460 cm^{-1} respectively. The NMR spectrum displayed signals at 4.35 τ (one-proton multiplet) and 6.25 τ (one-proton singlet). Mass spectroscopy established the molecular formula of $C_{12}H_{18}O_2$ (Calcd for $C_{12}H_{18}O_2$: 194, Found: 194). When the diol obtained by the hydrogenation of VI using Raney Ni as the catalyst was oxidized by chromic acid, it gave VIII. The IR spectrum of VII (ν_{max}, 1600, 1140 cm^{-1}) indicated the presence of a furan ring, and the molecular ion in the mass spectrum was observed at *m/e* 176. Conclusive evidence for the structure assigned to VII was obtained by a comparison of the maleic anhydride adduct of VII with an authentic sample.[5]



In Table 1 the results obtained from the reactions of IV under various conditions are summarized; it is obvious that the ratio of the products varied drastically with the change in the experimental conditions. From these data, Scheme I may be considered to be the most plausible reaction scheme.

When the Brønsted acid was used as the catalyst, much VI and VII were formed. In addition to this result, we established the selective formation of VII by the reaction of VI with sulfuric acid in liquid sulfur dioxide; this seems to show that VI is the intermediate for the formation of VII. As is shown in Table 1, the spiro compound V was also obtained.

These results seem to show that the reaction of IV with Brønsted acid is very similar to the pinacol rearrangement of 1,1-dihydroxydicyclohexyl[6]; IV is attacked by a proton to form the intermediate B after the ring opening. The B intermediate then probably disappears following one of two pathways; that is, either it rearranges to form V or loses a proton to form VI. The tertiary carbonium ion is



Scheme 1

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[5] T. A. Spencer, R. W. Britton and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967).

[6] M. Qudrat-I-Kuda and A. K. Ray, *J. Indian Chem. Soc.*, **16**, 525 (1939).

well known to deprotonate very rapidly,[7] and so it may be considered that the rate of deprotonation from B to form VI is very rapid. It is reasonable to consider that the allylic alcohol VI is not stable in the presence of an acid catalyst and that VI is attacked by a proton to form the intermediate C after the dehydration. The cation cite of C may be attacked by the lone-pair electrons of oxygen to form VII with a furan ring after the deprotonation.

For the formation of the spiro compound V, Lewis acid was more effective than Brϕnsted acid; V was obtained in a 93.2% yield when the reaction was performed with antimony pentachloride in liquid sulfur dioxide. This is probably due to the instability of the intermediates B and E because of the steric hindrance of a large volume of Lewis acid. In order to diminish this steric hindrance, the ring-enlargement reaction to form V seems to be more profitable than the deprotonation to form VI.

We can not propose a good explanation of the solvent effects upon the reaction of IV, but it seems probable that the rearrangement of the intermediate B to form V is accelerated by the stabilization of the transition state due to the solvation of the liquid sulfur dioxide. When cyclohexane is used as the solvent, there is no factor to stabilize the transition state and the deprotonation to form VI seems to be an important part of this reaction.

Experimental

2-Cyclohexylidenecyclohexanone Oxide (IV) was prepared by the method of Reese.[8] From 21.0 g of 2-cyclohexylidenecyclohexanone and 21 m*l* of a 30% hydrogen peroxide solution, we obtained 10.0 g (47.6% yield based on 2-cyclohexylidenecyclohexanone) of 2-cyclohexylidenecyclohexanone oxide; mp 96.5—97°C (lit,[5] mp 96.5—97°C).

1,2,3,4,6,7,8,9-Octahydrodibenzofuran (VII) was prepared by the action of zinc dust with 2-bromocyclohexanone[5]; bp 88—89°C/2 mmHg. The adduct of VII with maleic anhydride was prepared by the following method; maleic anhydride (1 g) and 2 g of VII were dissolved in 5 m*l* of benzene, after which the mixture was allowed to react at room temperature for 24 hr. The solid obtained was recrystallized from cyclohexane; mp 166—167°C (lit,[9] 167—168°C).

The Reaction of 2-Cyclohexylidenecyclohexanone Oxide (IV) in Liquid Sulfur Dioxide. To 200 mg of IV and 10 m*l* of liquid sulfur dioxide, was added 0.1 m*l* of the acid catalyst at −68°C, after which the mixture was allowed to react at 0°C for 1 hr. The reaction mixture was then rapidly cooled, diluted with water, and extracted three times with ether. The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. The volume of the extraction solvent was kept small so that no concentration step was neccesary in vpc analysis.

The products were analyzed by a Hitachi K-53 vpc apparatus, with a flame ionization detector, on a SE 30 column operated at 130—170°C.

The Reaction of 2-Cyclohexylidenecyclohexanone Oxide (IV) in Cyclohexane. To 200 mg of IV and 10 m*l* of cyclohexane was added 0.1 m*l* of the acid catalyst, after which the mixture was allowed to react at 15°C for 1 hr. When sulfuric acid was used as the catalyst, the reaction was performed for 21 hr. The reaction mixture was treated and analyzed as has been described in the preceding experiment.

Reaction Products from 2-Cyclohexylidenecyclohexanone Oxide (IV). 2-Cyclohexylidenecyclohexanone oxide (1.0 g), 0.5 m*l* of sulfuric acid, and 20 m*l* of sulfur dioxide were maintained at 0°C for 1 hr and then extracted with ether and dried over anhydrous sodium sulfate. The residue after the removal of the solvent was chromatographed on 50 g of silica gel. Elution with ten 50-m*l* portions of petroleum ether gave 0.4 g of an oil, which was then fractionated. Vpc on a SE 30 column indicated that this product was 99% pure. The infrared and mass spectra were identical with those of authentic 1,2,3,4,6,7,8,9-octahydrodibenzofuran (VII), and a mixed melting-point determination of the maleic anhydride adduct of the isolated product with the authentic maleic anhydride adduct of VII was undepressed.

Elution with thirteen 50-m*l* portions of benzene gave 0.1 g of a solid, which was then recrystallized from petroleum ether; mp 69—70°C. The physical data were identical with those of spiro[5,6]dodecane-7,12-dione.[4] In order to clarify the structure of this solid (V), the following reaction was performed; a solution of 0.5 g of V and 2.5 m*l* of 6N aqueous sodium hydroxide in 15 m*l* of ethanol was boiled under reflux for 30 min, diluted with water, acidified with hydrochloric acid, and extracted with ether. The extract was dried over anhydrous sodium sulfate and concentrated to leave a white solid. This keto acid was crystallized from petroleum ether as colorless plates; mp 56—58°C, mixed mp 56—58°C.

2-(1-Cyclohexenyl)-2-hydroxycyclohexanone (VI) was also isolated from the reaction mixture by chromatography. Elution with ten 50-m*l* portions of methanol gave 0.4 g of an oil which was then fractionated and thus confirmed to be 99% pure by vpc; bp 104°C/4 mmHg.

VI was hydrogenated using Raney nickel and hydrogen at 40—50°C; a white crystalline solid (IX) was obtained in a quantitative yield; m/e 198; ν_{max} 3300 and 3400 cm^{-1}. By the oxidation of IX with chromic acid at 50°C, 6-cyclohexyl-6-oxohexanoic acid (VIII) was obtained; mp 56—58°C (lit,[4] 56.5—58°C).

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[7] M. Nojima, T. Nagai and N. Tokura, *J. Org. Chem.*, **33**, 1972 (1968).

[8] J. Reese, *Ber.*, **75**, 384 (1942).

[9] W. Treibs and M. Weissenfels, *Chem. Ber.*, **93**, 1374 (1960).