Solvolysis of 2-(Δ^1-Cyclobutenyl)ethyl Tosylate[1]

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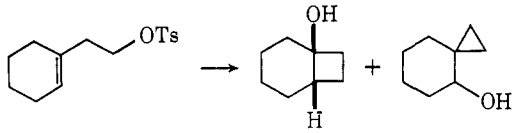
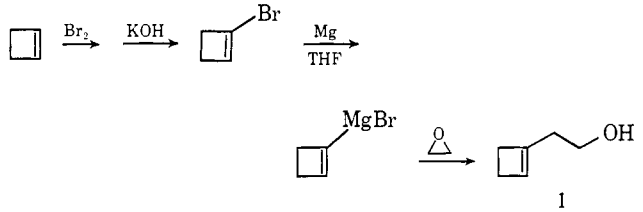
Abstract: The acetolysis of 2-(Δ^1-cyclobutenyl)ethyl tosylate gives 3-methylenecyclopentyl acetate, 2-methylenecyclopentyl acetate, 2-(Δ^1-cyclobutenyl)ethyl acetate, 1-acetoxymethylcyclopentene, and 4-acetoxy-1-methylcyclopentene as products. It appears that the bicyclo[2.1.0]pentane-1-methyl cation is an intermediate. Deuterium-labeling experiments indicate that a symmetrical spiro[2.3]hexyl-2 cation is not the intermediate. The course of the reaction is discussed.

The solvolysis of 2-(Δ^1-cyclohexenyl)ethyl tosylate has been found by Hanack and Schneider[3] to give the corresponding cyclopropylcarbinyl and cyclobutyl compounds. Similarly, Closson and Kwiatkowski



have found the 2-(Δ^1-cyclopentenyl)ethyl tosylate to give bicyclo[3.2.0]heptan-1-ol and spiro[4.2]heptan-4-ol.[4] It is not clear in these cases whether the two products are formed from a common intermediate or from two ions in equilibrium with each other. If the latter is the case, it is not known which ion is formed first.

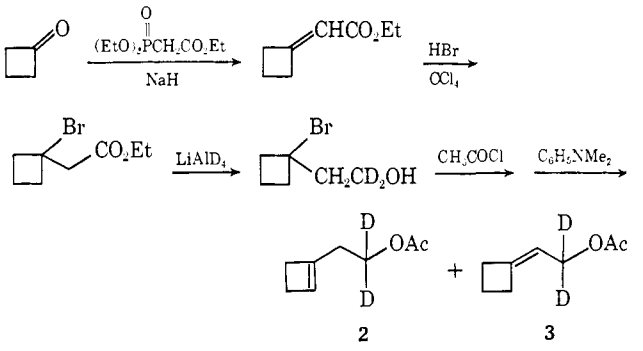
With these questions in mind, it seemed of interest to examine the solvolysis of 2-(Δ^1-cyclobutenyl)ethyl tosylate. The corresponding alcohol, **1**, was prepared.



1

As will be seen later, it was also desired to have a deuterium-labeled derivative of **1**, and this was prepared from cyclobutanone by Scheme I. The mixture

Scheme I



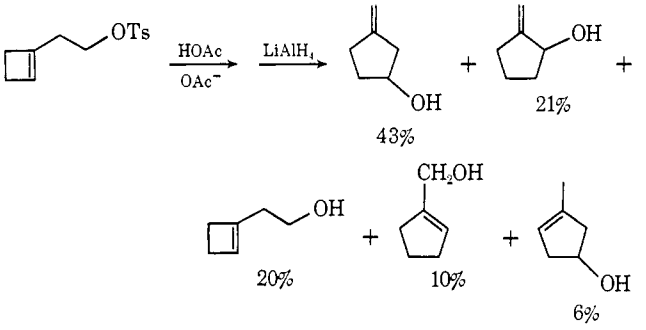
2 **3**

of **2** and **3**, formed in 1:1 ratio, could be separated by preparative vpc. Reduction with lithium aluminum hydride gave the desired alcohol.

The rates of acetolysis of the tosylate derived from **1**, as well as that of related compounds, are summarized in Table I. At 100°, the cyclobutenylethyl tosylate is seven times as reactive as ethyl tosylate. This small rate acceleration appears to be characteristic of allylcarbinyl derivatives. Thus allylcarbinyl tosylate is four times as reactive as *n*-butyl tosylate in 80% formic acid,[5] and 2-(Δ^1-cyclopentenyl)ethyl tosylate is 39 times as reactive as its saturated analog.[4]

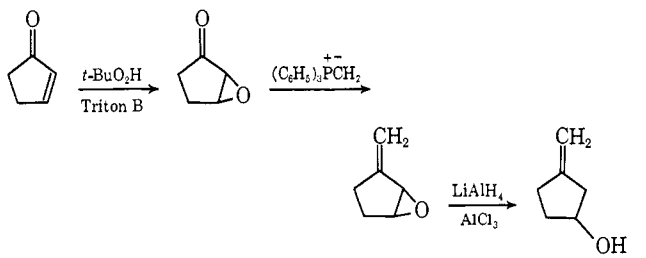
The products of the solvolysis of 2-(Δ^1-cyclobutenyl)-ethyl tosylate in buffered acetic acid are shown in Scheme II. The acetate products could not easily be

Scheme II



separated by vpc, and therefore the crude acetate mixture was reduced with lithium aluminum hydride to the corresponding alcohols. The latter could be separated, and were identified by comparison of their nmr spectra with authentic samples. 3-Methylenecyclopentanol was prepared as in Scheme III. The reduction of the

Scheme III



epoxide with lithium aluminum hydride and aluminum chloride gave only 3-methylenecyclopentanol; no 2-methylenecyclopentanol could be detected by vpc.

(1) This investigation was supported by Public Health Service Grant GM12800 from the National Institute of General Medical Science.

(2) National Institutes of Health Predoctoral Fellow, 1964–1967. This paper is taken from part of the Ph.D. thesis of J. E. H., 1968.

(3) M. Hanack and H.-J. Schneider, *Angew. Chem. Intern. Ed. Engl.*, 4, 976 (1965); **6**, 666 (1967); *Ann.*, **686**, 8 (1965).

(4) W. D. Closson and G. T. Kwiatkowski, *Tetrahedron Lett.*, 3831 (1964); *Tetrahedron*, **21**, 2779 (1965).

(5) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 3773 (1964).

Table I. Rates of Acetolysis

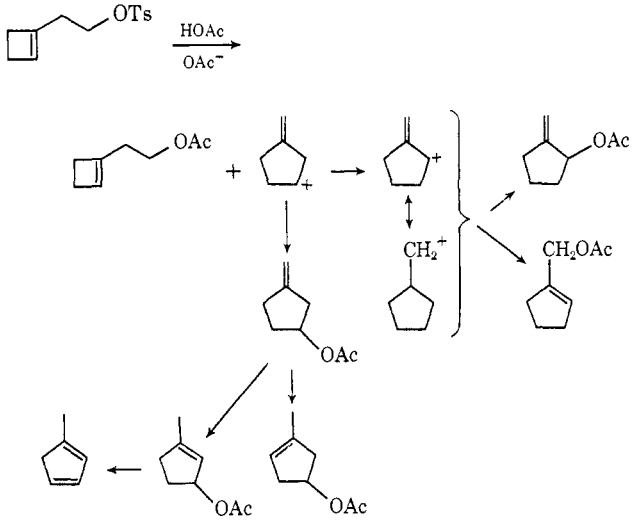
Compound	T, °C	k, sec^{-1}	Internal return, %	$\Delta H^{\pm}$	$\Delta S^{\pm}$
2-(Δ^1-Cyclobutenyl)ethyl tosylate	120.0	2.78×10^{-4}	0	21.9	−20
	100.0	5.88×10^{-5}			
	37.0	1.22×10^{-7} [a]			
Spiro[2.3]hexyl-4 tosylate	37.0	3.73×10^{-3}	41	18.4	−10
	17.0	4.42×10^{-4}			
Ethyl tosylate	100.0	8.47×10^{-6}	0	24.3	−17
	75.0	7.39×10^{-7}			
	37.0	9.33×10^{-9} [a]			

[a] Extrapolated values.

Authentic samples of 2-methylenecyclopentanol and 1-hydroxymethylenecyclopentene were prepared by the lithium aluminum hydride reduction of 2-carbethoxycyclopentanone.[6] The remaining compound could be shown by its nmr spectrum to be either 1-methyl-4-hydroxycyclopentene or 1-methyl-3-hydroxycyclopentene. The latter was prepared by the lithium aluminum hydride reduction of 3-methyl-2-cyclopentenone.[7] Its spectrum was different than the compound isolated from the solvolysis, and thus the solvolysis gave 1-methyl-4-hydroxycyclopentene.

When 3-methylenecyclopentyl acetate was subjected to the conditions used in the solvolysis of cyclobutenylethyl tosylate, it was found that isomerization to 1-methyl-4-acetoxycyclopentene occurred. It also was found that 1-methyl-3-hydroxycyclopentene was readily converted to methylcyclopentadiene. The formation and polymerization of the latter would account for the pronounced darkening of the reaction solutions. The sequence of reactions then appears to be Scheme IV.

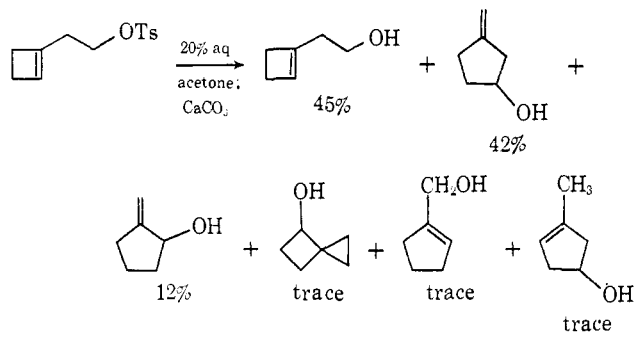
Scheme IV



Solvolysis of 3-methylenecyclopentyl tosylate in acetic acid solution gave the same products as were obtained from the solvolysis of cyclobutenylethyl tosylate, with the exception of cyclobutenylethyl acetate which probably was formed by an SN2 process.

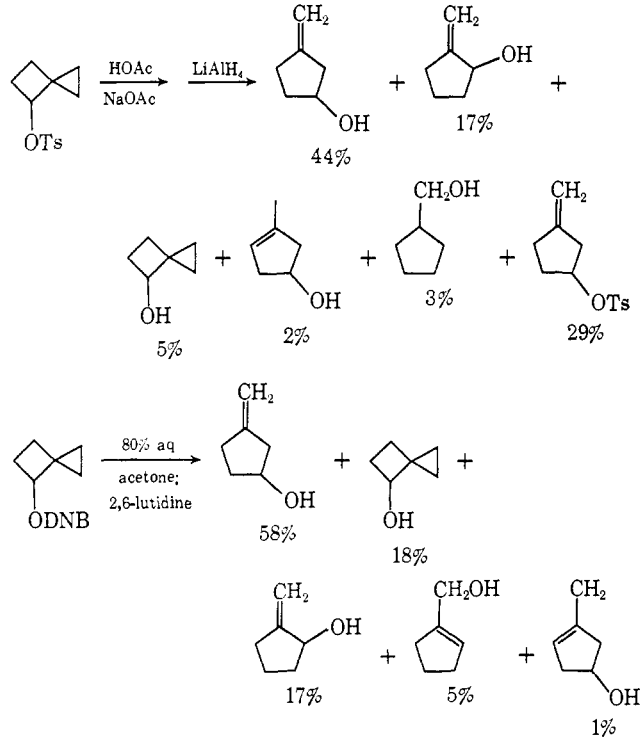
Further evidence for the course of the reaction comes from a study of the solvolysis of cyclobutenylethyl tosylate in 20% aqueous acetone (Scheme V). Here, 3-methylenecyclopentanol is the major rearranged product. It is interesting to note that some spiro[2.3]-hexanol-4 was found as a product of the reaction.

Scheme V



The acetolysis of spiro[2.3]hexyl-4 tosylate also gave the same products as cyclobutenylethyl tosylate, with the exception of cyclobutenylethyl acetate. In addition, spiro[2.3]hexyl-4 acetate was obtained. The solvolysis was also examined in 80% acetone (Scheme VI).

Scheme VI



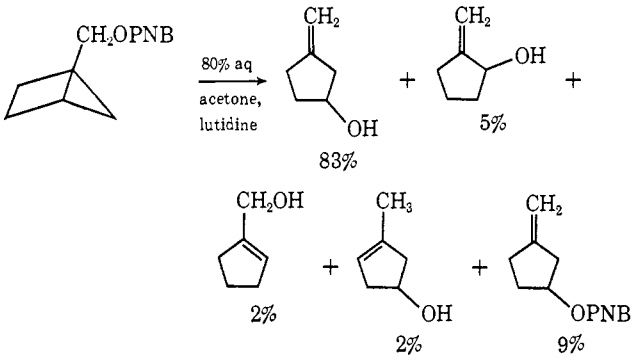
The product ratios are similar to those from cyclobutenylethyl tosylate, and it is clear that the majority of the reaction proceeds *via* similar pathways.

(6) A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, 75, 939 (1953).

(7) R. M. Acheson and R. Robinson, *J. Chem. Soc.*, 1127 (1952).

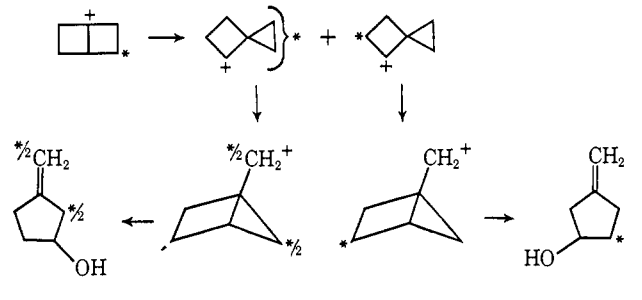
Dauben and Wiseman[8] have examined the solvolysis of bicyclo[2.1.0]pentane-1-methyl *p*-nitrobenzoate in 80% aqueous acetone at 100°, and again found a similar product distribution (Scheme VII). They did not

Scheme VII

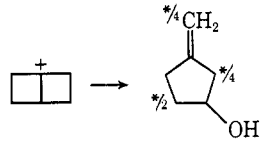


identify 1-methyl-4-hydroxycyclopentene, but from the results of the present study, and a comparison of relative vpc retention times it seems certain that this is the unidentified compound. They also demonstrated that all of the other alcohols could be derived from 3-methylenecyclopentanol by treatment with *p*-nitrobenzoic acid under the solvolysis conditions.

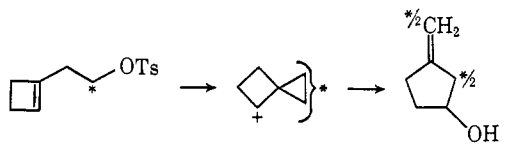
With these data in mind, we may now consider the path by which cyclobutenylethyl tosylate is converted to the 3-methylenecyclopentyl cation. By analogy with the C_7 and C_8 homologs, one might expect that the spiro[2.3]hexyl-4 and bicyclo[2.2.0]hexyl-1 cations could be intermediates. If the latter ion were formed, and one of the methylene groups in the reactant were labeled, one may expect that scrambling of the label would be found in the product. This arises because of the symmetry of the ion which makes migration of either 2-carbon bridge equally likely. Thus we might expect



or

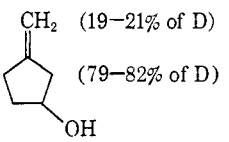


This may be contrasted with the path which proceeds *via* initial formation of the spiro[2.3]hexyl-4 cation.



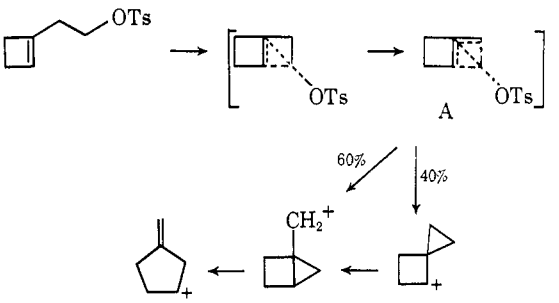
(8) W. G. Dauben and J. Wiseman, *J. Amer. Chem. Soc.*, **89**, 3545 (1967).

2-(Δ^1-Cyclobutenyl)ethyl-1,1-d_2 tosylate was prepared from the labeled alcohol and was subjected to acetolysis. The location of the deuterium in the product 3-methylenecyclopentanol was determined using the nmr spectrum and gave the results shown below.



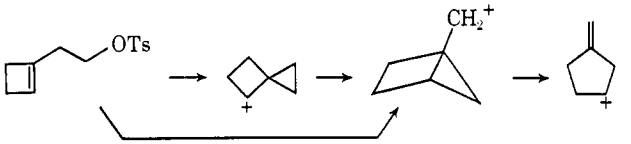
No deuterium was found in the 5 position. This eliminates a symmetrical, classical bicyclo[2.2.0]hexyl-1 cation as an intermediate. However, the distribution is not that expected from the spiro[2.3]hexyl-4 cation, since the latter should give equal amount of label at the two positions. It is clear that the bicyclo[2.1.0]-pentane-1-methyl cation is formed at least in part from a species other than the symmetrical spiro[2.3]hexyl-4 cation. The process may occur as in Scheme VIII. If

Scheme VIII



one neglects the secondary isotope effect,[9,10] the observed product distribution may be accounted for by 60% of the reactant going directly to the bicyclo[2.1.0]-pentane-1-methyl cation and 40% going to the spiro cation which then gives the other ion. The species A is of the type which is favored by our molecular orbital calculations.[11]

The postulate of the bicyclo[2.1.0]pentane-1-methyl cation as an intermediate is reasonable since it gives the same cyclopentyl products as the cyclobutenylethyl tosylate and spiro[2.3]hexyl-4 tosylate, but does not give cyclobutenylethanol and spiro[2.3]hexanol-4. The latter is formed from the other compounds, and thus it appears that the bicyclo[2.1.0]pentane-1-methyl cation is further along the reaction course than the other ions. The sequence of reactions then appear to be



It may be noted that Hanack and Schneider[3] have concluded that the solvolyses of the cyclopentenylethyl and cyclohexenylethyl tosylates proceed *via* a spiro-[2.*n*]alkyl-4 cation as the initial rearranged ion, and that the formation of the corresponding cyclobutyl

(9) Secondary isotope effects in reactions such as this are generally small[10] and certainly would not lead to a 4:1 ratio of label when a 1:1 ratio would be expected.

(10) *Cf.* E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 189 (1963).

(11) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).

derivative is a secondary process. Thus the pattern appears to continue for the present case.

Experimental Section[12]

2-(Δ^1-Cyclobutenyl)ethanol. To a 500-ml, three-necked flask equipped with a mechanical stirrer, reflux condenser with a drying tube, and a pressure-equalizing addition funnel was added 3.64 g (0.15 g-atom) of magnesium turnings. A solution of 20 g (0.15 mol) of 1-bromocyclobutene[13] in 50 ml of dry tetrahydrofuran was placed in the addition funnel and 5 ml of the solution was run into the reaction flask. An additional 10 ml of dry tetrahydrofuran, a crystal of iodine, and a few drops of ethyl bromide were added, and the mixture was warmed to reflux temperature with stirring. When the reaction commenced, external heating was reduced and the remaining solution of 1-bromocyclobutene was gradually added. After the addition was completed, 125 ml of dry tetrahydrofuran was added and the reaction mixture heated to reflux for 1 hr. At this time essentially all of the magnesium had reacted. The solution was cooled in an ice bath, the addition funnel was replaced with a Dry Ice condenser, and 15 g (0.375 mol) of ethylene oxide was condensed into the reaction flask. After the addition was completed, the reaction mixture was allowed to warm to room temperature and then heated to reflux. After about 5 min at reflux temperature the solution became too viscous for effective stirring. The mixture was cooled and enough saturated ammonium chloride solution was added to make a two-phase mixture. To the mixture was added 100 ml of ether and 200 ml of water. The ether layer was separated, washed with 100 ml of saturated ammonium chloride solution, two 100-ml portions of water, and 100 ml of saturated salt solution, and dried over anhydrous potassium carbonate. The solvent was removed by distillation, and the residue was distilled at aspirator pressure to give 18 g of crude product. This material was added to a solution of 3 g of sodium in 50 ml of methanol, and allowed to stand overnight. The solution was diluted with 200 ml of saturated salt solution and the mixture was extracted with four 50-ml portions of ether. The combined ether extract was washed with 100 ml of saturated salt solution and dried over anhydrous potassium carbonate. Distillation gave 6 g (40%) of 2-(Δ^1-cyclobutenyl)ethanol, bp 65–68° (19 mm). Further purification was effected by preparative vpc using a 6 ft × 0.75 in. Dow 710 on 50–60 mesh Anakrom U column at 130°. The nmr spectrum had bands at τ 4.28 (1 H, broadened singlet), 6.38 (2 H, triplet), 6.8 (1 H, singlet, hydroxyl), 7.5–8.0 (6 H, multiplet with major peak at 7.65).

Anal. Calcd for $C_6H_{10}O$: C, 73.5; H, 10.2. Found: C, 73.4, 73.4; H, 10.1, 10.2.

The 3,5-dinitrobenzoate was prepared, and after recrystallization from hexane had mp 78.5–79.5°.

Ethyl Cyclobutylideneacetate. To a 250-ml, three-necked flask fitted with a mechanical stirrer, a reflux condenser with a drying tube, and an addition funnel was added 1.2 g (0.05 mol) of sodium hydride and 100 ml of dry 1,2-dimethoxyethane. The resulting slurry was cooled to −20° and 11.2 g (0.05 mol) of triethylphosphonoacetate added dropwise with stirring. The mixture was stirred for 20 min after the addition was completed. A solution of 3.5 g (0.05 mol) of cyclobutanone[14] in 5 ml of dry 1,2-dimethoxyethane was then added dropwise over a 15-min period. Toward the end of the addition, the reaction mixture became opaque and within 5 min a sticky precipitate formed. The mixture was stirred for 30 min at room temperature and then worked up by adding 500 ml of water and extracting with four 75-ml portions of ether. The combined ether extract was washed with two 50-ml portions of water and dried over magnesium sulfate. The ether was removed at reduced pressure to give 10 g of a mixture of 1,2-dimethoxyethane and ethyl cyclobutylideneacetate. The nmr spectrum indicated that it contained 6.5–7.0 g of the latter (90–95%). The crude material was directly used in the following step.

Ethyl 2-Bromo-2-cyclobutylacetate. The solution of ethyl cyclobutylideneacetate prepared above was dissolved in 30 ml of carbon tetrahydrochloride and dry hydrogen bromide was bubbled in for 1 hr. The residue was distilled giving 7.5 g (72% based on cyclobutanone) of ethyl 2-bromo-2-cyclobutylacetate, bp 56–57° (0.75 mm). The nmr spectrum had bands at τ 5.83 (2 H, quartet), 7.05 (2 H, singlet), 7.10–8.25 (5 H, multiplet with major peaks at 7.28 and 7.40), 8.70 (3 H, triplet).

Anal. Calcd for $C_8H_{13}O_2Br$: C, 43.5; H, 5.9; Br, 36.1. Found: C, 43.5, 43.6; H, 5.8, 5.9; Br, 36.4, 36.4.

2-Bromo-2-cyclobutylethyl-1,1-d_2 Acetate. A slurry of 2.0 g (0.047 mol) of lithium aluminum deuteride in 100 ml of dry ether was cooled to 0° in an ice bath. A solution of 15.7 g (0.071 mol) of ethyl 2-bromo-2-cyclobutylacetate in 50 ml of dry ether was added dropwise with stirring. The solution was stirred for 15 min after the addition was completed and then 2.0 g of water, 2.0 g of 15% sodium hydroxide solution, and 6.0 g of water were added in that order. The mixture was stirred for 30 min after the last addition, the granular precipitate was separated by filtration, and washed with ether. The filtrate was dried over anhydrous potassium carbonate. Most of the ether was removed by distillation at atmospheric pressure and the last trace of ether and alcohol were removed at reduced pressure. The crude product was dissolved in 75 ml of dry pyridine, the solution was cooled to 0°, and 8.0 g (0.103 mol) of acetyl chloride was added dropwise with stirring. The reaction mixture was stirred for 15 min and 100 ml of ether was added. The ether solution was washed with 10% hydrochloric acid until the washings were acidic, then with saturated sodium bicarbonate solution and saturated salt solution, and finally dried over anhydrous sodium sulfate. The ether was removed under reduced pressure to give 11.0 g (70%) of 2-bromo-2-cyclobutylethyl-1,1-d_2 acetate. The nmr spectrum had bands at τ 7.12–8.23 (11 H, multiplet with 3 H singlet at 8.00).

In another experiment, lithium aluminum hydride was used, and the product was characterized as 2-bromo-2-cyclobutylethanol, bp 58–59° (0.5 mm). The nmr spectrum had bands at τ 5.5 (1 H, singlet, hydroxyl), 6.17 (2 H, triplet), 7.08–8.40 (8 H, multiplet with 2 H triplet centered at 7.78).

Anal. Calcd for $C_6H_{11}OBr$: C, 40.2; H, 6.2; Br, 44.6. Found: C, 40.1, 40.1; H, 6.1, 6.0; Br, 44.4, 44.5.

2-(Δ^1-Cyclobutenyl)ethyl-1,1-d_2 Acetate. A solution of 11.0 g (0.05 mol) of 2-bromo-2-(cyclobutyl)ethyl-1,1-d_2 acetate in 24.2 g (0.2 mol) of N,N-dimethylaniline was added to a 100-ml flask equipped with a magnetic stirrer and a reflux condenser. The flask was placed in an oil bath which had been preheated to 145–150° and stirred at this temperature for 50 min. The flask was cooled and the contents were diluted with 100 ml of ether. The ether solution was washed with ice-cold 10% hydrochloric acid until the washings were acidic, and then with 50 ml of saturated sodium bicarbonate solution and 50 ml of saturated salt solution, and dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue bulb-to-bulb distilled at reduced pressure, bp 30–35° (0.25 mm), to separate the product from any unreacted starting material. The crude product was purified by preparative vpc using a 6 ft × 0.75 in. 20% DEGS on 50–60 mesh Anakrom U column at 140°. The two major products (90%) were 2-(Δ^1-cyclobutenyl)ethyl-1,1-d_2 acetate and the exocyclic isomer, 2-(cyclobutylidene)ethyl-1,1-d_2 acetate, in a 1:1 ratio. The retention times were 4.3 and 6 min. The yield of vpc-purified product was 1.5 g (22%).

2-(Δ^1-Cyclobutenyl)ethan-1,1-d_2-ol. A solution of 1.5 g (0.01 mol) of 2-(Δ^1-cyclobutenyl)ethyl-1,1-d_2 acetate in 10 ml of dry ether was added to a slurry of 0.8 g (0.02 mol) of lithium aluminum hydride in 35 ml of dry ether, and the solution was stirred for 15 min at room temperature. To the reaction mixture was added 0.8 g of water, 0.8 g of 15% sodium hydroxide solution, and 2.4 g of water in that order, and the solution was stirred for 30 min. The solid was filtered off and washed with ether and the filtrate dried over anhydrous potassium carbonate. Removal of the ether gave 0.75 g (70%) of 2-(Δ^1-cyclobutenyl)ethan-1,1-d_2-ol. When the reaction sequence was carried out using unlabeled reactant, the product was found to be identical with that prepared *via* the first reaction sequence.

2-(Δ^1-Cyclobutenyl)ethyl Tosylate. A solution of 1.0 g (10.2 mmol) of 2-(Δ^1-cyclobutenyl)ethanol in 25 ml of dry pyridine was prepared, cooled to 0°, and 2.0 g (10.5 mmol) of *p*-toluenesulfonyl chloride was added. The mixture was allowed to stand in a refrigerator for 10 hr. The reaction mixture was added to a mixture of ether and ice and washed with ice-cold 10% hydrochloric acid until the washings were acidic. The ether solution was washed with 50 ml of cold saturated sodium bicarbonate solution and 50 ml of saturated salt solution and dried over anhydrous potassium carbonate at 0°. The ether was removed under reduced pressure to give a viscous oil which crystallized after standing at ice temperature for 1 hr. The material was recrystallized from an ether–pentane mixture to give 2.0 g (78%) of 2-(Δ^1-cyclobutenyl)ethyl tosyl-

(12) All nmr spectra were determined in carbon tetrachloride using TMS as the internal standard.

(13) H. Normant and P. Maitte, *Bull. Soc. Chim. Fr.*, 1424 (1960).

(14) I. V. Machinskaya, G. P. Smirnova, and V. A. Barkhash, *Zh. Obsch. Khim.*, **31**, 2390 (1961).

ate, mp 39–40°. The deuterium-labeled tosylate was also prepared, mp 39–40°.

Solvolysis of 2-(Δ^1-Cyclobutenyl)ethyl Tosylate in Acetic Acid. A solution of 3.0 g of the tosylate in 400 ml of anhydrous acetic acid which was 0.035 *M* in sodium acetate was prepared in a 500-ml flask. The flask was sealed and heated at 100° for 14 hr (3.5 half-lives). The cooled solution was poured into 600 ml of water and extracted with five 100-ml portions of pentane. The combined pentane extract was washed with 200 ml of saturated sodium bicarbonate solution and 200 ml of water and dried over anhydrous sodium sulfate. The pentane was removed by distillation and the acetate products were separated from the remaining tosylate by bulb-to-bulb distillation at 0.1 mm. The crude acetate fraction was reduced with 800 mg of lithium aluminum hydride in 35 ml of dry ether, and worked up with 0.8 g of water, 0.8 g of 15% of sodium hydroxide solution, and 2.4 g of water. The ether solution was separated and dried over anhydrous K_2CO_3. The ether was removed by distillation and the residue was separated into its components by preparative vpc on a 20 ft × 3/8 in. 20% DEGS on 70–80 mesh Anakrom U column at 140°. The products, which were collected and identified by comparison of their nmr spectra with those of authentic samples (except for 1-methyl-4-hydroxycyclopentene), were 2-methylenecyclopentanol (21.4%, 10.5 min), 1-methyl-4-hydroxycyclopentene (6%, 11.5 min), 2-(Δ^1-cyclobutenyl)ethanol (20%, 12.3 min), 3-methylenecyclopentanol (43%, 14.0 min), and 1-hydroxymethylcyclopentene (9.6%, 17.5 min).

The deuterium-labeled tosylate was solvolyzed in the same fashion and gave 2-methylenecyclopentanol (26.0%), 1-methyl-4-hydroxycyclopentene (21.4%), 2-(Δ^1-cyclobutenyl)ethanol (24%), 3-methylenecyclopentanol (19%), and 1-hydroxymethylcyclopentanol (9.6%). The mass spectrum of 3-methylenecyclopentanol indicated 99+% of two deuteriums. Using the C_1 hydrogen as a standard, the methylene position contained between 1.58 and 1.64 hydrogens and the 2 position contained between 0.36 and 0.42 hydrogens. There was no evidence of any deuterium in the 5 position.

The nmr spectrum of the 1-methyl-4-hydroxycyclopentene-d_2 indicated that no deuterium was present in the 2 position. This proton is set well apart from the rest of the spectrum.

Solvolysis of 2-(Δ^1-Cyclobutenyl)ethyl Tosylate in 20% Aqueous Acetone. A mixture of 3.0 g of powdered calcium carbonate, 3.0 g of 2-(Δ^1-cyclobutenyl)ethyl tosylate, and 150 ml of 20% aqueous acetone (by volume) was sealed in a flask and heated at 80° for 10 days. The cooled solution was saturated with sodium chloride and extracted with four 70-ml portions of ether. The combined ether extract was washed with 100 ml of water and 100 ml of saturated salt solution and dried over anhydrous potassium carbonate. The ether was removed by distillation and the residue separated into its components by preparative vpc using a 20 ft × 3/8 in. 20% DEGS on 70–80 mesh Anakrom U column at 140°. The products were spiro[2.3]hexan-4-ol (trace), 2-methylenecyclopentanol (12%), 1-methyl-4-hydroxycyclopentene (trace), 2-(Δ^1-cyclobutenyl)ethanol (45%), 3-methylenecyclopentanol (42%), and 1-hydroxymethylcyclopentene (trace). The major products were collected and identified by their nmr spectra; the trace components were identified by coinjection.

3-Methylenecyclopentanol. To a solution of 8.0 g (0.125 mol) of *n*-butyllithium in 75 ml of hexane, diluted with 200 ml of dry ether, was added with stirring 44.5 g (0.125 mol) of triphenylmethylphosphonium bromide. A solution of 12.3 g (0.125 mol) of 2,3-epoxycyclopentanone in 25 ml of ether was added dropwise with stirring, and the solution was heated to reflux overnight. After cooling, the solution was filtered and the precipitate was washed with 100 ml of ether. The ether solution was washed with 100-ml portions of water until neutral, and dried over anhydrous potassium carbonate. The ether was removed through a 35-cm vacuum-jacketed packed column. The residue was distilled through a 15-cm Vigreux column to give 2.2 g (18%) of 2,3-epoxymethylenecyclopentane, bp 55–58° (25 mm). The product was characterized by its nmr spectrum: τ 4.75 (1 H, singlet), 5.03 (1 H, singlet), 6.43 (1 H, doublet), 6.58 (1 H, doublet), 7.65–8.58 (4 H, complex multiplet).

To a slurry of 1.0 g of aluminum chloride in 25 ml of dry ether was added 1.0 g of powdered lithium aluminum hydride with ice-bath cooling. The slurry was stirred for 15 min and a solution of 2.2 g of 2,3-epoxymethylenecyclopentane in 25 ml of dry ether was added. After heating for 12 hr the reaction mixture was cooled and enough water was added to decompose the excess lithium aluminum hydride and aluminum chloride. The solution was filtered and the precipitate washed with ether. The ether solution was dried over anhydrous potassium carbonate and distilled to give a yellow oil. Distillation of the residue gave 1.65 g (74%) of 3-methylenecyclopentanol, bp 39–40° (1 mm). The nmr spectrum had bands at τ 5.18 (2 H, pentuplet), 5.75 (1 H, pentuplet), 6.8 (1 H, singlet, hydroxyl), 7.50–7.85 (4 H, complex multiplet), 7.90–8.50 (2 H, complex multiplet).

Anal. Calcd for $C_6H_{10}O$: C, 73.5; H, 10.2. Found: C, 73.3, 73.3; H, 10.2, 10.3.

Solvolysis of 3-Methylenecyclopentyl Tosylate in Acetic Acid. A solution of 3-methylenecyclopentyl tosylate (prepared from 200 mg of 3-methylenecyclopentanol) in 50 ml of glacial acetic acid which was 0.035 *M* in sodium acetate was sealed in a flask and heated at 100° for 14 hr. The cooled mixture was diluted with 100 ml of water and extracted with three 25-ml portions of pentane. The pentane solution was washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. The pentane was removed by distillation and the acetates were separated from any remaining tosylate by bulb-to-bulb distillation at 0.5 mm. The crude product was reduced with 100 mg of lithium aluminum hydride in 20 ml of dry ether and worked up in the usual fashion. After drying over potassium carbonate, the ether was removed and the residue analyzed by vpc on a 20 ft × 3/8 in. 20% DEGS on 70–80 mesh Anakrom U column at 130°. The products were 2-methylenecyclopentanol (23.4%), 1-methyl-4-hydroxycyclopentene (18.5%), 3-methylenecyclopentanol (50.5%), and 1-hydroxymethylcyclopentene (7.6%).

Isomerization of 3-Methylenecyclopentyl Acetate in Acetic Acid. A solution of 89 mg of 3-methylenecyclopentyl acetate in 5 ml of glacial acetic acid (0.035 *M*) in sodium acetate was sealed in an ampoule and heated at 100° for 14 hr. The cooled solution was diluted with 15 ml of water and extracted with three 15-ml portions of pentane. The pentane extract was washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. The pentane was removed by distillation, and the residue was treated with 25 mg of lithium aluminum hydride in 5 ml of dry ether. After work-up, the mixture was analyzed by vpc giving 2-methylenecyclopentanol (trace), 1-methyl-4-hydroxycyclopentane (15.5%), and 3-methylenecyclopentanol (84.5%).

3-Methyl-2-cyclopenten-1-ol. To a slurry of 1.0 g (0.026 mol) of lithium aluminum hydride in 30 ml of dry ether was added 1.0 g (0.01 mol) of 3-methyl-2-cyclopentenone[15] in 15 ml of dry ether, and the mixture was stirred for 30 min. To the reaction mixture was added 1 g of water, 1 g of 15% sodium hydroxide solution, and 3 g of water. The mixture was filtered and the precipitate was washed with ether. The ether solution was dried over anhydrous potassium carbonate and the ether was removed under reduced pressure. When purification was attempted by vpc, methylcyclopentadiene was obtained. Injection of pyridine prior to injection of the alcohol had no effect on the elimination of water. The nmr spectrum of the crude alcohol had bands at τ 4.60 (1 H, multiplet), 5.15–5.55 (1 H, broad), 6.2 (1 H, singlet, hydroxyl), 7.40–8.65 (7 H, multiplet, with a single peak at 8.23).

Spiro[2.3]hexan-4-ol. A slurry of 0.8 g (0.02 mol) of lithium aluminum hydride in 30 ml of dry ether was prepared, and 2.5 g (0.026 mol) of spiro[2.3]hexan-4-one[16] in 25 ml of dry ether was added with stirring. After 1 hr, 0.8 g of water, 0.8 g of 15% sodium solution, and 2.4 g of water were added. The mixture was filtered and the precipitate was washed with ether. After drying over potassium carbonate, the solution was distilled giving 2.0 g (77%) of spiro[2.3]hexan-4-ol, bp 73–74° (30 mm). The nmr spectrum had bands at τ 5.66–6.00 (1 H, distorted triplet), 6.1 (1 H, singlet, hydroxyl), 7.50–8.43 (4 H, complex multiplet), 8.98–9.95 (4 H complex multiplet).

Anal. Calcd for $C_6H_{10}O$: C, 73.5; H, 10.2. Found: C, 73.3, 73.3; H, 10.2, 10.3.

The 3,5-dinitrobenzoate was prepared and after recrystallization from aqueous acetone had mp 89–90°. The tosylate was prepared in pyridine solvent and had mp 33–35°.

Solvolysis of Spiro[2.3]hexyl-4 Tosylate in Acetic Acid. The solvolysis of the tosylate in 0.035 *M* sodium acetate in acetic acid was effected as described above. Analysis by vpc on a 30 ft × 3/8 in. 20% DEGS column showed spiro[2.3]hexan-4-ol (7.3%), 2-methylenecyclopentanol (24.4%), 1-methyl-4-hydroxycyclopentane (2.4%), 3-methylenecyclopentanol (60.7%), and 1-hydroxymethylcyclopentene (5.2%).

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Kinetics. The water content of the acetic acid used in the acetolysis studies was determined using the method of Bruckenstein.[17] Enough anhydrous sodium carbonate was added to make the solution of 0.035 *M* in sodium acetate and enough acetic anhydride was added to remove the water and leave the solution 0.01 *M* in acetic anhydride.

The rate of acetolysis of spiro[2.3]hexyl-4 tosylate was determined by preparing a 0.0300 *M* solution in acetic acid at the desired temperature. The flask was placed in a thermostat, and 3-ml aliquots were removed at appropriate intervals. The aliquots were titrated with 0.0300 *M* *p*-toluenesulfonic acid to a bromphenol blue end point. The rates of acetolysis of the other compounds were determined by preparing the solution at room temperature, placing 3.2-ml aliquots in ampoules, and sealing the ampoules. They were placed in a thermostat and removed and cooled at appropriate times. The ampoules were opened; 3.0 ml of solution was removed and titrated as above. In each case, two determinations were made and the average is reported in Table I. The average deviation was generally ±2% or less.

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Biosynthesis of Ergot Alkaloids. Evidence for Two Isomerizations in the Isoprenoid Moiety during the Formation of Tetracyclic Ergolines

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Abstract: Chanoclavine-I (**1**), but not chanoclavine-II (**5**) or isochanoclavine-I (**6**), is an efficient precursor of tetracyclic ergot alkaloids. Its cyclization to give agroclavine (**2**) is accompanied by a *cis–trans* isomerization at the double bond of the isoprenoid moiety. Experiments with mevalonic acids stereospecifically tritiated at C-4 indicate that another such *cis–trans* isomerization occurs earlier in the pathway. Thus the apparently "normal" labeling of tetracyclic ergot alkaloids from mevalonic-2-^{14}C acid in the *trans*-carbon atom of the isoprenoid moiety is an accidental result caused by two isomerizations. The cyclization of chanoclavine-I proceeds with complete retention of the hydrogen at C-10, but with only 70% retention of the hydrogen at C-9. The latter result is discussed in view of possible mechanisms of the reaction.

Ergot alkaloids are formed from L-tryptophan, mevalonic acid, and the methyl group of methionine.[2] There is evidence that 4-dimethylallyltryptophan is an early intermediate in the biosynthetic pathway, and studies on the biogenetic interrelationships of these alkaloids have established the sequence agroclavine (**2**) → elymoclavine (**3**) → lysergic acid derivatives (**4**).[3] Recently, we[4] reported that chanoclavine-I (**1**) is an efficient precursor of tetracyclic ergot alkaloids of the clavine and lysergic acid amide type, and the same observation was made independently by two other groups.[5,6] Chanoclavine-I has a methyl group in the *cis* position[7] and a hydroxymethyl group in the *trans* position at the Δ^8 double bond,[8,9] and could thus give rise to elymoclavine in two ways: by oxidative cyclization between the methyl group and the nitrogen, or by reaction between the hydroxymethyl group and the nitrogen, followed by a hydroxylation at the methyl group (Scheme I). The latter reaction would involve an isomerization at the Δ^8 double bond, and our finding[4] that chanoclavine-I was not only converted to elymoclavine but also to agroclavine suggested that this pathway is operative. The possibility of such an isomerization was also indicated by work from Arigoni's group, who found[5,10] that mevalonic-2-^{14}C acid predominantly (>90%) labels the C-methyl group of chanoclavine-I (**1**), isochanoclavine-I (**6**), and chanoclavine-II (**5**), whereas the tetracyclic ergolines are all predominantly labeled in carbon 17.[11,12]

In this paper we report on the mechanism of the conversion of chanoclavine-I into tetracyclic ergot alkaloids. Evidence will be given which indicates that two *cis–trans* isomerizations at the double bond of the isoprenoid portion take place in the course of ergot alkaloid biosynthesis. Preliminary reports of some of this work have appeared.[13,14]

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