Proximity Effects. XLI. Solvolysis of Methyl 5-Tosyloxycyclooctanecarboxylates^{1,2}

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cis- and trans-methyl-5-hydroxycyclooctanecarboxylate were prepared by stereospecific syntheses and their tosylates were solvolyzed in formic acid. The normal elimination product (methyl 4-cyclooctenecarboxylate) and substitution products (methyl cis- and trans-5formyloxycyclooctanecarboxylate) were formed. In addition, the lactone of cis-5-hydroxycyclooctanecarboxylic acid was formed on solvolysis of the trans tosylate. There was no evidence for 1,5-hydride migration in either case.

A number of reactions of cyclooctyl derivatives of the type commonly formulated as proceeding through carbonium ions leads predominantly to products formed by transannular hydride migration. Both 1,5and 1,3-hydride migrations have been demonstrated.⁴⁻⁶ Studies of the solvolysis of 1,2,2,8,8-pentadeuteriocyclooctyl tosylate⁷ have shown that in the absence of ring substituents 1,5-hydride shift constitutes the major path of the reaction (48-56%), and that the extent of 1,3-hydride shift is small (0-3%). The effect of a *cis*-5-methyl substituent in this reaction⁸ is to increase greatly the proportion of 1,5-hydride shift products (90%), and that of a trans-5-methyl substituent⁸ is to favor the formation of unrearranged products (90%). In a continuation of these studies, the effect of a carbomethoxy group was investigated in the solvolysis of the tosylates of methyl cis- and trans-5hydroxycyclooctanecarboxylate. Unlike a 5-methyl substituent, which stabilizes the (tertiary) carbonium ion formed by 1,5-hydride migration, the 5-carbomethoxy substituent would destabilize the carbonium ion formed by 1,5-migration, so the solvolysis would be expected to take another course. The stereospecific synthesis of these isomeric tosylates is formulated below.

The lactone 1, prepared by oxidation of bicyclo-[3.3.1]nonan-9-one as described previously,8 was hydrolyzed at room temperature to the cis acid 2, which was converted with diazomethane to the methyl ester 3. The crystalline tosylate 4, m.p. 68–69°, was inverted by treatment with tetraethylammonium acetate, and hydrolysis of the resulting acetate afforded the trans acid 5, which was converted to ester 6 and tosylate 7, m.p. 55–56°, respectively.

- (1) Supported in part by a research grant (NSF-GP-1587) from the National Science Foundation.
- (2) Paper XL: A. C. Cope, M. Gordon, S. Moon, and C. H. Park, J. Am. Chem. Soc., 87, 3119 (1965).
- (3) National Science Foundation Postdoctoral Fellow, 1963-1964.
- (4) A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, J. Am. Chem. Soc., 82, 6366 (1960).
 - (5) N. L. Allinger and S. Greenberg, *ibid.*, **84**, 2394 (1962).
 (6) A. C. Cope and G. L. Woo, *ibid.*, **85**, 3601 (1963).
 (7) A. C. Cope and D. M. Gale, *ibid.*, **85**, 3747 (1963).

 - (8) A. C. Cope and D. M. Gale, ibid., 85, 3743 (1963).



Each of the isomeric tosylates was solvolyzed in anhydrous formic acid containing sodium formate. The products were separated by gas chromatography and identified by comparison of their retention times and infrared spectra with those of authentic samples. In both cases the main product was the normal elimination product, methyl 4-cyclooctenecarboxylate (8). The products from the cis-tosylate 4 were 8 (91%), a mixture of cis- and trans-5-formyloxycyclooctanecarboxylate 9 (8.5%), and a poorly resolved mixture of at least two minor components (0.2%). The products from the trans-tosylate 7 were the unsaturated ester 8 (78%), the mixture of formates 9 (18\%), and the 1,5lactone 1 (4.4%), as shown below.



In both cases the mixture of formates 9 contained predominantly the cis isomer, in larger proportion from the

solvolysis of *trans*-tosylate 7, corresponding to inversion at the reaction center. Product compositions were not changed significantly by varying reaction time or sodium formate concentration.

To determine whether appreciable amounts of rearrangement products could have escaped detection by the analytical method employed, control experiments were carried out to verify the homogeneity of the major products in each case. The presence of appreciable contamination of **8** with the isomeric 1,5-hydride shift product, methyl 1-cyclooctenecarboxylate (10), was excluded by showing that authentic 10 was separated from **8** by the gas chromatographic procedure used, and that ultraviolet absorption at 220 m μ due to 10 was absent in the crude solvolysis product. In addition, the unsaturated solvolysis product **8** was converted by lithium aluminum hydride reduction to a single alcohol (homogeneous by gas chromatography) which was identical with authentic 4-cyclooctene-1-methanol.⁶

Hydrolysis of the substitution products 9, followed by chromic acid oxidation and reesterification with diazomethane, led to the formation of only lactone 1 and methyl 5-oxocyclooctanecarboxylate. These same products were obtained from identical oxidation and esterification of the *cis* acid 2. These experiments show that structural isomers are not present in the formate ester product 9.

In addition to the expected effect of the 5-carbomethoxy group of preventing or retarding a 1,5hydride shift because of its electron-withdrawing properties, a transannular effect of the ester group itself is indicated by formation of lactone 1 from the *trans*-tosylate 7. Neighboring group participation during the solvolysis, as illustrated below, is possible in a concerted manner only in the case of the *trans* isomer.



From approximate kinetic studies of the solvolyses, no evidence was found for a rate acceleration associated with anchimeric assistance in 7.9

Experimental¹⁰

cis-5-Hydroxycyclooctanecarboxylic Acid (2). A mixture of 54.0 g. of 9-oxabicyclo[3.3.2]decan-10-one,⁸ 30 ml. of ether, and 240 ml. of 10% aqueous sodium hydroxide was stirred at 25-35° for 3 hr. with slow evaporation of the ether. The resulting clear, aqueous solution was extracted with 50 ml. of ether, cooled in an ice bath, and slowly acidified with 75 ml. of concentrated hydrochloric acid with stirring and cooling. The white precipitate was collected by filtration and washed with three 50-ml. portions of water. The crude solid was dried to a constant weight of 53.5 g. (89%) after 48 hr. in a vacuum desiccator over phosphorus pentoxide. The infrared spectrum of this solid, m.p. 109-110°, showing strong absorption (KBr disk) at 3270 and 1675 cm.⁻¹, was identical with that of the same compound, m.p. 109–110°, prepared previously.¹¹

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.37. Found¹¹: C, 62.82; H, 9.29.

Methyl cis-5-Hydroxycyclooctanecarboxylate (3). To a mixture of 10.7 g. of the solid cis acid 2 and 60 ml. of ether was added cautiously an excess of an ethereal solution of diazomethane. When gas evolution ceased, the solution was boiled gently until colorless, washed with 10% aqueous sodium carbonate, and dried, and the ether was removed, leaving 9.6 g. of a liquid residue. An analytical sample was obtained by elution of a portion of the crude product from a silicic acid column with carbon tetrachloride containing increasing amounts of chloroform. The major fraction, $n^{25}D$ 1.4833, eluted with 25% chloroform, showed an infrared spectrum identical with that of the crude product, including strong absorption at 3400 and 1715 cm.⁻¹ (neat).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.50; H, 9.74. Found: C, 64.69; H, 9.81.

Methyl cis-5-p-Toluenesulfonyloxycyclooctanecarboxylate (4). To a cold solution of 19.0 g. of the cis-hydroxy ester 3 in 40 ml. of dry pyridine was added a cold solution of 35.0 g. of p-toluenesulfonyl chloride in 95 ml. of dry pyridine. The mixture was kept at 5° for 20 hr. and then poured into 500 g. of a mixture of ice and water. The resulting white suspension was stirred for 30 min. and filtered. The air-dried solid was dissolved in 470 ml. of ether and dried, the ether was replaced gradually by hexane by heating, and the hexane solution was cooled, giving 30.9 g. of colorless crystals, m.p. 68.1-68.9° (89%).

Anal. Calcd. for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11; S, 9.42. Found: C, 60.12; H, 7.19; S, 9.32.

trans-5-Hydroxycyclooctanecarboxylic Acid (5). To a solution of 9.0 g. of the cis-tosylate 4 in 200 ml. of dry acetone was transferred quickly 18 ml. of tetraethylammonium acetate monohydrate.¹² The resulting solution was refluxed for 25 hr. and the acetone was distilled. The residue was diluted with 100 ml. of pentane and 25 ml. of water. The phases were separated, the aqueous layer was washed with 50 ml. of pentane and 25 ml. of ether, and the combined organic extracts were dried with magnesium sulfate and evap-The fragrant liquid residue showed strong orated. infrared absorption at 1734 and 1240 cm.⁻¹. The crude product was refluxed with 4.0 g. of potassium hydroxide in 25 ml. of water, 5 ml. of methanol, and 115 ml. of dioxane for 5 hr., cooled, evaporated to a volume of 30 ml., diluted with 20 ml. of water, and washed with two 50-ml. portions of ether. The aqueous solution was cooled in an ice bath and acidified slowly with 15 ml. of concentrated hydrochloric acid with stirring and cooling. The mixture was stirred for 15 min. more at 0° and filtered. The solid was washed with two 10-ml. portions of cold water and dried in a desiccator over phosphorus pentoxide, affording 3.4 g. of the acid (75% yield from the tosylate), m.p. 123-124.5°. A sample was recrystallized from pentanechloroform, m.p. 124.5-125.1°.

(11) A. C. Cope and P. Scheiner, unpublished results.

⁽⁹⁾ The ratio of first-order rate constants, k_{trans}/k_{cis} , was about 0.7 at 25°.

⁽¹⁰⁾ Melting points are corrected and boiling points are uncorrected. An F & M Model 720 instrument was used for gas chromatographic analyses. A silicone nitrile identified as XF-1150 was used as the liquid phase.

⁽¹²⁾ J. Steigman and L. P. Hammett, J. Am. Chem. Soc. 59, 2536 (1937).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 62.77; H, 9.37. Found: C, 62.72; H, 9.32.

This compound absorbed strongly (KBr pellet) at 3420 and 1705 cm.⁻¹. A mixture melting point with cis-5-hydroxycyclooctanecarboxylic acid (2) was 107-111°.

Methyl trans-5-Hydroxycyclooctanecarboxylate (6). The trans acid 5 was esterified with diazomethane and purified by the procedure described above for the cis isomer. The desired product, $n^{25}D$ 1.4814, was eluted from a silicic acid column by 25% chloroform in carbon tetrachloride.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.50; H, 9.74. Found: C, 64.21; H, 9.57.

An infrared spectrum of this compound (neat liquid) showed absorption at 3450 and 1730 cm.⁻¹, and was different from that of the *cis* isomer **3**.

Methyl trans-5-p-Toluenesulfonyloxycyclooctanecarboxylate (7). Cold solutions of 3.5 g. of methyl trans-5-hydroxycyclooctanecarboxylate in 7 ml. of pyridine and of 7.0 g. of p-toluenesulfonyl chloride in 20 ml. of pyridine were mixed and kept at 5° for 20 hr., and then poured into 125 g. of an ice-water mixture. On stirring, no crystallization was effected, and the mixture was extracted with three 50-ml. portions of ether. From the ether extracts, after drying and evaporation, was obtained 4.5 g. of crystals, m.p. $54-55^{\circ}$ (70%). Recrystallization from ether-hexane to constant melting point afforded an analytical sample of 7, m.p. $55.5-56.1^{\circ}$.

Anal. Calcd. for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11; S, 9.42. Found: C, 60.17; H, 7.17; S, 9.47.

Solvolysis of Methyl cis-5-p-Toluenesulfonyloxycyclooctanecarboxylate (4). A solution of 22.0 g. of 4 in 500 ml. of anhydrous formic $acid^{13}$ 0.50 N in sodium formate¹⁴ was kept at room temperature for 4 hr., diluted with 600 ml. of ether, extracted with two 500-ml. portions of water and with 5% aqueous sodium carbonate solution until the aqueous extracts were alkaline. The ether solution was dried and evaporated under reduced pressure, leaving 10.4 g. of liquid residue, shown by gas chromatography on XF-1150 (linear programming from 110 to 190° at 2°/min.) to consist of 8 (91%), a mixture of unidentified components (0.2%), and cis and trans 9 (8.5%), in order of increasing retention time. These products were identified by comparison of their infrared spectra and retention times with those of authentic samples, described below. Although *cis* and *trans* 9 were incompletely resolved on all of the gas chromatography columns tried, it could be estimated that the isomeric composition was 55-70% cis and 30-45% trans. No significant change in product composition was observed in repeated reactions with a fivefold increase in reaction time or with a tenfold decrease in concentration of 4 and of sodium formate.

The crude solvolysis product was separated by partial distillation into 8.44 g. of 8 (77.7% yield from tosylate 4), b.p. 74–75° (2.1 mm.), and 1.66 g. of residue which was separated by gas chromatography as above into 40% of 8, 1.5% of the minor components (an n.m.r. spectrum indicated a mixture of compounds), and 58% of 9.

(13) S. Winstein and H. Marshall, J. Am. Chem. Soc., 74, 1120 (1952).
(14) S. Winstein and R. Heck, *ibid.*, 78, 4801 (1956).

A sample of the distilled ester 8 showed no appreciable shoulder in its end absorption in the ultraviolet spectrum at 220 m μ . The value of ϵ at this wave length was 50 \pm 10.

A sample of the distillate (2.10 g.) was reduced with lithium aluminum hydride in refluxing ether during a period of 2 hr. After cooling and cautious addition of 1.0 ml. of water and enough 3 N hydrochloric acid to dissolve the precipitate, the two phases were separated and the aqueous phase was extracted with two 50-ml. portions of ether. The combined ether extracts were dried and evaporated, leaving 1.58 g. (90.4%) of an alcohol, which was shown to be 98% pure by gas chromatography. The only detected impurity (2%) was found to be unreduced ester 8. A collected sample of the alcohol, n^{25} D 1.4929, showed an infrared spectrum identical with that of authentic 4-cyclooctene-1-methanol.⁵

The formate products 9 collected by gas chromatography were saponified in a refluxing solution of potassium hydroxide in dioxane-water-methanol, and the crude acid product was oxidized and reesterified as described below in the preparation of methyl 5-oxocyclooctanecarboxylate. The only products detectable by gas chromatography were the lactone 1 (40%) and methyl 5-oxocyclooctanecarboxylate (60%).

Solvolysis of Methyl trans-5-p-Toluenesulfonyloxycyclooctanecarboxylate (7). The trans-tosylate 7 (3.30 g.) was solvolyzed in 85 ml. of dry formic acid 0.5 N in sodium formate by the same procedure used for the cis isomer 4. The crude product mixture (1.54 g.) was separated by gas chromatography (XF-1150, linear programming from 110 to 190° at 2°/min.) into 8 (78%), cis and trans 9 (18%), and lactone 1 (4.4%). The partially resolved isomeric mixture 9 was estimated to contain 80–95% of the cis isomer. The product composition was not changed by increasing the reaction time or decreasing the concentrations of 7 and sodium formate. The experiments used to check the homogeneity of solvolysis products from 4 yielded the same results when applied to the products 8 and 9 from 7.

Methyl cis- and trans-5-Formyloxycyclooctanecarboxylate. To cold solutions of methyl cis- and trans-5hydroxycyclooctanecarboxylate in 10 ml. of dry pyridine were added 1.5-ml. portions of formic acidacetic anhydride reagent.¹⁵ After 1 hr. at room temperature, 1.0 ml. of methanol was added, and each solution was diluted with cold water and pentane. The organic phases were separated, washed with 3 N hydrochloric acid, dried, and evaporated. In each case, the crude formate was purified by gas chromatography (XF-1150 at 180°). Both cis-methyl 5-formyloxycyclooctanecarboxylate, $n^{25}D$ 1.4718, and the *trans* isomer, n^{25} D 1.4711, showed broad infrared absorption at 1710-1740 cm.⁻¹ and no absorption in the hydroxyl region, but the spectra of the two isomers differed significantly in the 650-1500-cm.⁻¹ region.

Methyl 4-Cyclooctenecarboxylate. An ethereal solution of 4-cyclooctenecarboxylic acid⁶ was treated with diazomethane solution. After removal of ether, the residue was purified by gas chromatography, n^{25} D 1.4729. The ester showed infrared absorption at 1730 and 1635 cm.⁻¹.

(15) F. Reber, A. Lardon, and T. Reichstein, Helv. Chim. Acta, 37, 45 (1954).

Methyl 1-Cyclooctenecarboxylate. This ester was prepared as described previously^{16,17} and purified by gas chromatography. The purified ester, $n^{25}D$ 1.4858, showed ultraviolet absorption at λ_{max} 220 m μ (ϵ 10,800) and strong infrared absorption at 1715 and 1640 cm.⁻¹.

Methyl 5-Oxocyclooctanecarboxylate. To a cold solution of 0.80 g. of *cis*-5-hydroxycyclooctanecarboxylic acid in 20 ml. of acetone was added 4.0 ml. of chromic acid-sulfuric acid solution¹⁸ with cooling in an ice bath. The mixture was stirred for 10 min. at room temperature, diluted with 20 ml. of cold water, and

(16) A. C. Cope and M. Brown, J. Am. Chem. Soc. 80, 2859 (1958).

(17) A. C. Cope, M. Burg, and S. W. Fenton, *ibid.*, 74, 173 (1952).
 (18) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, J. Chem. Soc. 20 (1946)

J. Chem. Soc., 39 (1946).

extracted with four 25-ml. portions of ether. The reddish ether extracts were washed with aqueous sodium thiosulfate until colorless, dried, and evaporated to a volume of 25 ml. This solution was treated with ethereal diazomethane until color persisted, then was evaporated, leaving 0.85 g. of a crude product, which was separated by gas chromatography into 45% of 5-hydroxycyclooctanecarboxylic acid lactone and 55% of the keto ester as a liquid, $n^{25}D$ 1.4792, which showed infrared absorption maxima at 1705 and 1740 cm.⁻¹.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.13; H, 8.75.

A 2,4-dinitrophenylhydrazone of the keto ester recrystallized from aqueous ethanol melted at $151.0-151.5^{\circ}$.

Proximity Effects. XLII. The Reaction of Lithium Diethylamide with *cis*- and *trans*-4-Octene Oxide¹

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Treatment of cis- and trans-4-octene oxides with lithium diethylamide gave trans-5-octen-4-ol as the major product in each case. Among the minor products no cis-5-octen-4-ol was detected, nor were there any products attributable to proximity effects. The formation of trans-5-octen-4-ol was shown to proceed largely by removal of a proton from a position α to the oxirane ring rather than by removal of a proton on the ring followed by generation of a carbene intermediate.

Treatment of *cis*-cyclooctene and *cis*-cyclodecene oxides with strong bases gave products of transannular reactions.^{2,3} Because a straight-chain olefin of sufficient length could assume a conformation approximating that of a medium-sized ring, it was of interest to determine whether such an olefin oxide on treatment with a strong base would give any products that could be ascribed to proximity effects. Accordingly the reactions of lithium diethylamide with *cis*- and *trans*-4-octene oxides were studied. The symmetrical olefin oxides were chosen in order to simplify the separation and identification of products. Neither *cis*-4-octene oxide nor *trans*-4-octene oxide was found to yield any products which could be attributed to a proximity effect.

The results of five separate reactions run under identical conditions except for reaction time are summarized in Table I. The major product in each case was an alcohol ($C_8H_{16}O$) which consumed 1 molar equiv. of hydrogen on catalytic reduction forming 4-

(1) Supported in part by a research grant (NSF-GP-1587) of the National Science Foundation. Paper XLI: A. C. Cope and D. L. Nealy, J. Am. Chem. Soc., 87, 3122 (1965).

(3) A. C. Cope, H. H. Lee, and H. E. Petree, *ibid.*, 80, 2849 (1958).

 Table I. Products of the Reaction of Lithium Diethylamide with cis- and trans-4-Octene Oxides^e

4- Octene oxide	Time, hr.	Recov- ered oxide, %	Allylic alco- hol, %	Amino alco- hol, %	Gly- col, ^o %	Alde- hyde, %
trans	7	67	16		16	Trace
trans	24	33	45		9	Trace
trans	72	12	75			3
cis	7	41	32	7		
cis	72	16	55	14	· •	••

^a Compositions of mixtures were determined by combinations of chromatography on alumina and gas chromatography on 1,2,3-tris(2-cyanoethoxy)propane (TCEP) or silicone oil columns. ^b Identified as *meso*-4,5-octanediol, presumably formed during the isolation of products by attack of lithium hydroxide on unchanged epoxide.

octanol (characterized as the 3,5-dinitrobenzoate). Treatment of the unsaturated alcohol with active manganese dioxide⁴ resulted in partial oxidation to an α,β -unsaturated ketone, as shown by ultraviolet and infrared spectra. The infrared spectrum of the unsaturated alcohol itself had a strong band at 975 cm.⁻¹ (*trans* double bond). The alcohol was identified as *trans*-5-octen-4-ol by comparison with an authentic specimen prepared by treatment of *n*-butyraldehyde with the lithium salt of 1-butyne followed by lithium aluminum hydride reduction of the resulting 5-octyn-4-ol. *cis*-5-Octen-4-ol over Lindlar catalyst, and was shown to be absent (in amounts detectable by gas

⁽²⁾ A. C. Cope, M. Brown, and H. H. Lee, *ibid.*, 80, 2855 (1958).

⁽⁴⁾ J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, J. Chem. Soc., 1094 (1952).