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Proximity Effects. XXXVIII. Solvolytic and Elimination Reactions of Cyclooctane and Cyclodecane Derivatives[1]

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The following reactions have been investigated: cyclooctyl and cyclodecyl bromides with silver acetate in acetic acid, with sodium amide, and with lithium di-sec-butylamide; base-catalyzed decomposition of cyclooctanone and cyclodecanone p-toluenesulfonylhydrazones in protonic and aprotic solvents; cyclodecanol and hydrogen bromide in acetic acid; cyclodecylamine and nitrous acid. Certain of these reactions gave appreciable amounts of bicyclic hydrocarbons in addition to the expected cyclic olefins. Mechanistic pathways are discussed.

Prior to initiation of this work several cases of formation of a new ring system by transannular elimination had been reported. Treatment of 2-bromocyclodecanone, 2,2-dibromocyclodecanone, and 2,2-dibromocyclononanone with base gave trans-1-decalone, bicyclo[4.4.0]-1(6)-decen-2-one, and bicyclo[4.3.0]-1(6)-nonen-2-one, respectively.[4] Similarly, nortricyclene derivatives had been obtained from 1,4-endo-methylene-2-bromocyclohexane-2,3-dicarboxylic acid anhydride.[5] We have observed the formation of small amounts of cis- and trans-decalin under the conditions of acid-catalyzed equilibration of cyclodecenes.[6] Decalins have also been formed from the spontaneous decomposition of cyclodecyl p-toluenesulfonate.[7] Pyrolysis of cyclooctyl and cyclodecyl acid phthalates gave small amounts of bicyclic hydrocarbons in addition to the expected cyclic olefins.[8] We now report a study undertaken to determine the extent and generality of bicyclic product formation in elimination reactions of cyclooctane and cyclodecane derivatives.

The reaction of cyclooctyl bromide with sodamide gave only cis-cyclooctene, while cyclodecyl bromide and sodamide gave a mixture of cis- and trans-cyclodecene (predominantly trans). No bicyclic hydrocarbons were detected in either case. With the bulkier base lithium di-sec-butylamide a trace of trans-cyclooctene was found as well, and the ratio of trans-/cis-

cyclodecene increased, but still no transannular products were formed.[9]

In an isotopic investigation of the diazotization of cyclodecylamine it was reported that the cyclodecene formed absorbed only 87.5% of the theoretical amount of hydrogen.[10] This led us to repeat the deamination but we found no bicyclic hydrocarbons.

Preparation of cyclodecyl bromide by bubbling hydrogen bromide into a refluxing solution of cyclodecanol in acetic acid had also given a low-boiling fraction which resembled cis-cyclodecene in its infrared spectrum but absorbed only 70% of the theoretical amount of hydrogen.[11] The saturated material was stated to be cyclodecane. Reinvestigation of this hydrocarbon fraction by gas chromatography revealed substantial amounts of cis- and trans-decalin. On the other hand, analysis of the hydrocarbons from the reaction of cyclodecyl bromide with silver acetate in acetic acid showed the presence of only cis- and trans-cyclodecene. Cyclooctyl bromide treated with silver acetate under the same conditions did, however, yield small amounts of cis-bicyclo[3.3.0]octane, bicyclo[5.1.0]octane, and 1-methylcycloheptene.

Formation of cis- and trans-decalin in the reaction of cyclodecanol and hydrogen bromide and formation of cis-bicyclo[3.3.0]octane and bicyclo[5.1.0]octane can be explained by elimination of a transannular proton from a classical carbonium ion or from a bridged non-classical carbonium ion with the transannular hydrogen atom as the bridging species. 1-Methylcycloheptene

(9) Traces of cyclooctane and cyclodecane were found among the products of the reaction with lithium di-sec-butylamide. That this should result from exchange of the bromides with small amounts of unchanged n-butyllithium is improbable because di-sec-butylamine was present in excess. Evidence obtained from a study of the reactions of a number of alkyl and cycloalkyl bromides with n-butyllithium [J. F. Eastham and G. W. Gibson, J. Org. Chem., 28, 280 (1963)], prompts us to suggest a hydride transfer mechanism similar to that presented by Eastham and Gibson for the formation of the saturated cycloalkanes.

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(4) K. Shenker and V. Prelog, Helv. Chim. Acta, 36, 896 (1953).

(5) K. Alder and F. Brockhagen, Ber., 87, 167 (1954).

(6) A. C. Cope, D. C. McLean, and N. A. Nelson, J. Am. Chem. Soc., 77, 1628 (1955).

(7) V. Prelog, W. Küng, and T. Tomljenović, Helv. Chim. Acta, 45, 1352 (1962).

(8) A. C. Cope and M. J. Youngquist, J. Am. Chem. Soc., 84, 2411 (1962).

(10) V. Prelog, H. J. Urech, A. A. Bothner-By, and J. Würsch, Helv. Chim. Acta, 38, 1095 (1955).

(11) A. T. Blomquist, R. E. Burge, Jr., and A. C. Sucsy, J. Am. Chem. Soc., 74, 3636 (1952).

Table I. Elimination Reactions of Cyclooctane Derivatives

Cyclooctane derivative	Reaction conditions	Products, %[a]					
		cis-Cyclo-octene	trans-Cyclo-octene	cis-Bicyclo-[3.3.0]-octane	Bicyclo-[5.1.0]-octane	1-Methyl-cyclo-heptene	Others
Bromide	HOAc + AgOAc	97.9	0	0.3	0.4	1.4	0
Bromide	NaNH₂	100	0	0	0	0	0
Bromide	CH₃ | (CH₃CH₂CH—)₂NLi	97.7	0.8	0	0	0	1.0 cyclo-octane, 0.5
p-Toluenesulfonyl-hydrazone	Na in HOCH₂CH₂OH	83.3	0	6.4	10.3	0	<0.05
p-Toluenesulfonyl-hydrazone	NaOCH₃ in Diethyl Carbitol	43.5	0	50	6.5	0	<00.5

[a] Identified by comparison of infrared spectra and retention times with those of authentic samples.

Table II. Elimination Reactions of Cyclodecane Derivatives

Cyclodecane derivative	Reaction conditions	Products, %[a]					
		trans-Cyclo-decene	cis-Cyclo-decene	cis-Decalin	trans-Decalin	Bicyclo-[5.3.0]-decane	Others
Bromide	AgOAc + HOAc	13	87	0	0	0	0
Bromide	NaNH₂	85	15	0	0	0	0
Bromide	CH₃ | (CH₃CH₂CH—)₂NLi	94	6	0	0	0	0.05 cyclo-decane
Cyclodecanol	HBr + HOAc	8.7	71.0	7.8	12.5	0	0
Cyclodecylamine	HNO₂	0.4	99.6	0	0	0	0
p-Toluenesulfonyl-hydrazone	Na in HOCH₂CH₂OH	30.6	69.8	0.05[b]	0	0.2	0
p-Toluenesulfonyl-hydrazone	NaOCH₃ in Diethyl Carbitol	3.5	15.4	18	0	63.0	0

[a] Identified by comparison of infrared spectra and retention times with those of authentic samples. [b] Identified by retention time only.

could be formed either by acid-catalyzed opening of bicyclo[5.1.0]octane followed by elimination or by ring contraction of the cyclooctylcarbonium ion.

The widely different percentages of cis- and trans-cyclodecenes formed in these elimination reactions (Table II) are worthy of note; prominent among a number of possible reasons for this may be differences in ionizing power of the reaction media.

Recent investigations[12a-e] of the base-catalyzed decomposition of tosylhydrazones of ketones originally discovered by Bamford and Stevens[13] have shown that the distribution of products is highly dependent on the nature of the solvent.[14] Decomposition of camphor tosylhydrazone in aprotic solvents led almost exclusively to tricyclene, while camphene was the principal product in protonic solvents.[12a,c] Originally Bamford and Stevens represented the reaction carried out in ethylene glycol as proceeding through an intermediate diazoalkane which decomposes to nitrogen and a carbene; subsequent shift of a hydrogen atom from an adjacent carbon would yield the olefinic products. Later studies on the decomposition of tosylhydrazones in protonic solvents have suggested polar intermediates.[12a,c-e] A carbene intermediate has been proposed for the decomposition of tosylhydrazones in aprotic solvents.[12a-c]

The hydrocarbon mixtures isolated from the decomposition of cyclooctanone and cyclodecanone tosylhydrazones in Diethyl Carbitol were found to contain more bicyclic products than olefins,[15] while the reverse was true when decompositions were run in ethylene glycol (Tables I and II). The bicyclic hydrocarbons formed in these reactions all possessed the cis configuration, regardless of thermodynamic stability relative to the trans isomers.[16] This high degree of stereospecificity can best be accommodated by a carbene mechanism involving a concerted 1,3-, 1,5-, or 1,6-transannular hydrogen migration and intramolecular insertion. The formation of olefins is explained simply by a 1,2-hydride shift. Occurrence of the less stable trans-cyclodecene[17] may be attributed to conformational effects in the cyclodecyl carbene intermediate. It should be pointed out that, although this mechanism is analogous to the one established[18] for the reaction of medium-ring oxides with bases, the carbenes generated in the two different cases may

(12) (a) L. Friedman and H. Shechter, J. Am. Chem. Soc., 81, 5512 (1959); (b) L. Friedman and H. Shechter, ibid., 82, 1002 (1960); (c) J. W. Powell and M. C. Whiting, Tetrahedron, 7, 305 (1959); (d) E. J. Corey and R. A. Sneen, J. Am. Chem. Soc., 78, 6269 (1956); (e) C. H. dePuy and D. H. Froemsdorf, ibid., 82, 634 (1960).

(13) W. R. Bamford and T. S. Stevens, J. Chem. Soc., 4735 (1952).

(14) However, the distribution of products from the carbenoid decomposition of diazirines has been reported to be unaffected by the nature of the solvent: E. Schmitz, Angew. Chem., 75, 723 (1963).

(15) Essentially identical results were obtained independently by L. Friedman and H. Shechter, J. Am. Chem. Soc., 83, 3159 (1961).

(16) The more stable form in each case is: cis-bicyclo[3.3.0]octane, R. P. Linstead and E. M. Meade, J. Chem. Soc., 935 (1934); A. H. Cook and R. P. Linstead, ibid., 946 (1934); J. W. Barrett and R. P. Linstead, ibid., 436 (1935); trans-decalin, N. L. Allinger and J. L. Coke, J. Am. Chem. Soc., 81, 4080 (1959); and trans-bicyclo[5.3.0]decane, N. L. Allinger and V. B. Zalkow, ibid., 83, 1144 (1961).

(17) A. C. Cope, P. T. Moore, and W. R. Moore, ibid., 82, 1744 (1960).

(18) A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, ibid., 82, 6370 (1960).

not have the same energy and conformational properties. This would account for the reversed order of the relative amounts of 1,5- and 1,6-hydride shifts observed in the C_{10} series in the two cases.

Decomposition of cyclooctanone and cyclodecanone tosylhydrazones in ethylene glycol also gave bicyclic hydrocarbons but in much smaller total amounts than did the decompositions in Diethyl Carbitol (Tables I and II). The extent of transannular reaction in the C_{10} case in ethylene glycol is insignificant. The decomposition in ethylene glycol probably proceeds by the earlier proposed cationic path[12a,c-e] involving elimination of a β-proton to form olefins or of a transannular proton to give bicyclic compounds.

Experimental[19]

Cyclooctanone p-toluenesulfonylhydrazone was prepared by heating under reflux for 1 hr. a solution of 3 g. of cyclooctanone and 1 equiv. of p-toluenesulfonylhydrazide in 15 ml. of ethanol. The solution was refrigerated overnight and the product, 6.36 g. (91%), m.p. 132.5–137.5° dec., was recrystallized three times from ethanol to give an analytical sample, m.p. 135.5–138.0° dec.[20]

Anal. Calcd. for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7.53; N, 9.52. Found: C, 60.94; H, 7.46; N, 9.46.

Cyclodecanone p-toluenesulfonylhydrazone was prepared similarly and recrystallized from ethanol, m.p. 130.0–132.5° dec. Another sample had m.p. 137.2–141.4°.

Anal. Calcd. for $C_{17}H_{26}N_2O_2S$: C, 63.38; H, 8.13; N, 8.69. Found: C, 63.42; H, 7.92; N, 8.56.

Decomposition of Cyclooctanone p-Toluenesulfonylhydrazone in Diethyl Carbitol. A stirred suspension of 2.62 g. of sodium methoxide and 2.94 g. of the tosylhydrazone in 35 ml. of Diethyl Carbitol (distilled from lithium aluminum hydride, b.p. 74.5° at 12 mm.) was heated at 165–170° for 2 hr. The mixture was then slowly distilled and the distillate was taken up in 100 ml. of pentane. The pentane solution was washed eight times with water to remove Diethyl Carbitol and dried over magnesium sulfate. Distillation afforded a mixture of hydrocarbons, 0.58 g. (52.5%), b.p. 70–74° (63 mm.).

Decomposition of Cyclodecanone p-Toluenesulfonylhydrazone in Diethyl Carbitol. A mixture of 1.128 g. of the tosylhydrazone and 1.126 g. of sodium methoxide in 20 ml. of Diethyl Carbitol was decomposed as described above. The cooled mixture was filtered and the residue was washed with pentane. The filtrate was diluted with 100 ml. of pentane and then extracted four times with cold 48% sulfuric acid to remove Diethyl Carbitol.[21] The organic layer was washed with 50 ml. of water and 50 ml. of 10% sodium carbonate solution and dried over magnesium sulfate. Distillation in a short-path still under reduced pressure af-

forded 0.358 g. (74%) of a liquid, which was separated into cyclodecanone (23%) and a mixture of hydrocarbons (77%) by gas chromatography (silicone grease, 175°).

Decomposition of Cyclooctanone p-Toluenesulfonylhydrazone in Ethylene Glycol. Cyclooctanone p-toluenesulfonylhydrazone (5 g.) was heated under reflux for 2 hr. with a solution prepared from 1.8 g. of sodium and 50 ml. of ethylene glycol. The solution was cooled and diluted with 250 ml. of pentane and 100 ml. of water, and the aqueous layer was extracted with 50 ml. of pentane. The combined pentane extracts were washed three times with water and dried over magnesium sulfate. Distillation afforded a hydrocarbon fraction, b.p. 73–74° (93 mm.), 0.75 g. (40%), and an alcohol fraction, b.p. 92–96° (1 mm.), 0.70 g. (24%), $n^{25}D$ 1.4766.

Analysis of the alcohol fraction by mass spectrometry (mol. wt. 172) and by n.m.r. spectroscopy indicated that it consisted of cyclooctyl 2-hydroxyethyl ether.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.86; H, 11.97.

Decomposition of Cyclodecanone p-Toluenesulfonylhydrazone in Ethylene Glycol. Cyclodecanone p-toluenesulfonylhydrazone (2.65 g.), in a solution prepared from 1.5 g. of sodium and 50 ml. of ethylene glycol, was decomposed as described above. Distillation afforded 0.59 g. (36%) of a hydrocarbon fraction, b.p. 95–99° (39 mm.). The viscous residue was not investigated.

Cyclodecyl Bromide. A. Dry pyridine (5.0 g.) was added dropwise with cooling to a solution of 6.6 g. of phosphorus tribromide in 5 ml. of benzene. The solution was cooled to −5° and a solution of 10 g. of cyclodecanol in 15 ml. of benzene was added during 15 min. The mixture was stirred at room temperature for 2 hr. and at 100° for 1 hr. It was poured into 100 ml. of cold 10% hydrochloric acid and extracted with three 60-ml. portions of ether. The extracts were washed with cold 10% hydrochloric acid and saturated sodium bicarbonate solution, dried, concentrated, and distilled, giving 8.65 g. (62%) of cyclodecyl bromide, b.p. 74–76° (1.5 mm.), $n^{25}D$ 1.5122.

B. Cyclodecanol (16.3 g.) was treated with hydrogen bromide in refluxing acetic acid by a procedure previously described.[11] Distillation gave a C_{10} hydrocarbon fraction, 1.56 g. (11%), b.p. 85–91° (21 mm.), $n^{25}D$ 1.4799, and cyclodecyl bromide, 13.77 g. (62%), b.p. 102.5–103.5° (2.5 mm.), $n^{25}D$ 1.5116 (lit.[11] b.p. 119–121° at 11 mm., $n^{20}D$ 1.5125), with an infrared spectrum identical with that of the bromide prepared by method A.

Reactions of Cyclodecyl Bromide. A. Solvolysis in Acetic Acid Containing Silver Acetate. A stirred suspension of 6.4 g. of silver acetate in 1.7 ml. of acetic anhydride and 32 ml. of acetic acid was heated for 2 hr. at 100–110°. Cyclodecyl bromide (3.02 g.) was added dropwise and the mixture was stirred and heated for 5 hr., then cooled, diluted with 250 ml. of ether, and filtered. The filtrate was washed with several portions of water and saturated sodium bicarbonate solution and dried over magnesium sulfate. The hydrocarbons collected weighed 1.71 g. (89%), b.p. 90–95° (21 mm.).

(19) Melting points are corrected and boiling points are uncorrected. Conditions and equipment used for gas chromatography are described in footnote 23 of A. C. Cope and G. L. Woo, *J. Am. Chem. Soc.*, **85**, 3601 (1963).

(20) The melting point was strongly dependent on the rate of heating. The sample was introduced when the heating bath was 10° below the expected melting point and the bath temperature raised 2°/min. Another sample had m.p. 139.0–143.2°.

(21) This was necessary because the hydrocarbons and Diethyl Carbitol have similar boiling points. Authentic cis- and trans-cyclodecenes were found to be stable under the extraction conditions.

B. *With Sodamide.* A mixture of 3.8 g. of cyclo-decyl bromide and sodamide prepared from 2.05 g. of sodium was refluxed in 50 ml. of dry benzene under nitrogen for 10 hr. The mixture was cooled, diluted with ether, and filtered. The filtrate was washed with water and dried over magnesium sulfate. The hydro-carbon fraction (1.08 g., 45%), had b.p. 74–77° (9.5 mm.). A viscous pot residue was not investigated.

C. *With Lithium Di-sec-butylamide.* Lithium di-sec-butylamide was prepared from 7.1 g. of di-sec-butylamine and 40 ml. of 1.26 M n-butyllithium in ether. The ether was replaced by 55 ml. of dry benzene and then 4.78 g. of cyclodecyl bromide was added. The mixture was heated under reflux in a nitrogen atmosphere for 24 hr., cooled to 0°, and diluted with 50 ml. of ether. The solution was washed successively with several portions of cold 12% hydrochloric acid and with saturated sodium bicarbonate solution, and dried over magnesium sulfate. The hydrocarbon fraction, 2.57 g. (85%), had b.p. 96–99° (35 mm.).

Reactions of Cyclooctyl Bromide. A. Solvolysis in Acetic Acid Containing Silver Acetate. Cyclooctyl bromide prepared in nearly quantitative yield from cis-cyclooctene and hydrogen bromide in acetic acid[22] had an infrared spectrum showing the presence of cyclooctyl acetate. Washing with 85% sulfuric acid at 5° removed this impurity and gave the pure bromide, b.p. 71.0–72.5° (2.5 mm.), n^{25}D 1.5078.

Cyclooctyl bromide (9.0 g.) was treated with 9.3 g. of silver acetate in 2.5 ml. of acetic anhydride and 48 ml. of glacial acetic acid in the manner described for cyclo-decyl bromide. Distillation gave a hydrocarbon frac-tion, 1.12 g. (22%), b.p. 78–79° (89 mm.), and cyclo-octyl acetate, 2.50 g. (32%), b.p. 92–94° (5 mm.), n^{25}D 1.4580.

B. *With Sodamide.* Cyclooctyl bromide (10.2 g.) was treated with sodamide (prepared from 2.15 g. of sodium) in refluxing benzene exactly as described for cyclodecyl bromide. The hydrocarbon fraction, 0.50 g. (8.5%), had b.p. 57–60° (ca. 35 mm.), and unchanged cyclooctyl bromide, 4.85 g. (48%), had b.p. 120–122° (35 mm.), n^{25}D 1.5090.

C. *With Lithium Di-sec-butylamide.* Cyclooctyl bromide (5.31 g.) was treated with lithium di-sec-butylamide (from 40 ml. of 1.26 M n-butyllithium in ether and 7.1 g. of di-sec-butylamine) in refluxing benzene exactly as described for cyclodecyl bromide. The hydrocarbon fraction, 1.30 g. (43%), had b.p. 69–71° (65 mm.). A viscous pot residue was not in-vestigated.

Standard Hydrocarbons. cis-Decalin was an API standard (99.89% purity), n^{25}D 1.4797. trans-Decalin was prepared by the method of Zelinsky,[23] n^{25}D 1.4711. Gas chromatography showed a composition of 93/7 trans-cis-decalin. cis-Bicyclo[3.3.0]octane was pre-pared by a previously described procedure,[24] n^{25}D 1.4589. A sample of trans-bicyclo[3.3.0]octane, n^{25}D 1.4568, was kindly supplied by Professor John D. Roberts.[25] cis- and trans-cyclodecene were samples prepared previously,[6] as were bicyclo[5.1.0]octane[8] and 1-methylcycloheptene.[8] cis-Bicyclo[5.3.0]decane was prepared as follows. cis-Bicyclo[5.3.0]decan-8-one[26] was reduced with lithium aluminum hydride in refluxing ether to a mixture of the endo and exo alcohols in 89% yield, b.p. 93–96° (4 mm.), n^{25}D 1.4935. Com-parison of the infrared spectrum of the product with the spectra of the isomeric alcohols[26] showed that it was a mixture of the two. The mixture was treated with thionyl chloride in pyridine to give a mixture of the corresponding chlorides, b.p. 83–86° (9 mm.), n^{25}D 1.4919–1.4942. Hydrogenation of the chlorides in the presence of Adams catalyst in glacial acetic acid at 1 atm. and room temperature gave cis-bicyclo[5.3.0]-decane, n^{25}D 1.4728 (lit.[26] n^{20}D 1.4736). Its infrared spectrum was identical with the published spectrum.[26]

(22) R. Willstätter and E. Waser, *Ber.*, 43, 1181 (1910).

(23) N. Zelinsky and M. Turowa-Pollak, *ibid.*, 65, 1299 (1932).
(24) A. C. Cope and W. R. Schmitz, *J. Am. Chem. Soc.*, 72, 3056 (1950).
(25) J. D. Roberts and W. F. Gorham, *ibid.*, 74, 2278 (1952).
(26) E. Kovats, A. Furst, and H. H. Gunthard, *Helv. Chim. Acta*, 37, 534 (1954).