methylcycloheptanone (22.6 min., 12%), and cyclooctanone (28.6 min., 2%). An unidentified peak (4%) appeared at a retention time of 16.9 min. The major ketone was isolated by gas chromatography and its infrared spectrum was identical with the spectrum of 2-methylcycloheptanone with the exception that the spectrum of the trapped ketone showed absorption in the region of 2.9–3.0 μ. 4-Methylcycloheptanone was also separated from the mixture of ketones by gas chromatography and its spectrum was identical to the spectrum of authentic material.

Acknowledgment.—This work was supported in part by a grant from the Research Corporation, New York, New York.

Fused Small-Ring Compounds. I. Synthesis of Some *trans*-Bicyclo[3.2.0]heptanes and *trans*-Bicyclo[4.2.0]octanes[1]

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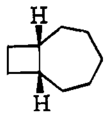
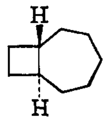
Received March 24, 1964

A nonphotochemical reaction sequence leading to several *trans*-fused bicyclo[3.2.0]heptanes and bicyclo-[4.2.0]octanes is described. The chief compounds of interest include *trans*-bicyclo[3.2.0]heptan-3-ol (**21**), *trans*-bicyclo[3.2.0]heptan-3-one (**22**), *trans*-bicyclo[4.2.0]octan-3-one (**27**), and the equatorial and axial forms of *trans*-bicyclo[4.2.0]octan-3-ol (**28** and **31**).

The study of highly strained, *trans*-fused bicyclic compounds has aroused considerable interest in recent years.[3–9] In particular, much attention has been devoted to those structures which incorporate a *trans*-fused cyclobutane moiety. It had been presumed[3] until quite recently that a seven-membered ring is the smallest cycle that can span a cyclobutane ring in a *trans* manner. Indeed, the two possible 7–4 hydrocarbons are known[4] (*i.e.*, *cis*- and *trans*-bicyclo[5.2.0]-nonane, **1** and **2**), but it is interesting to note that their physical properties suggest that their heat contents are comparable, if the conformational rule is applicable.[4]

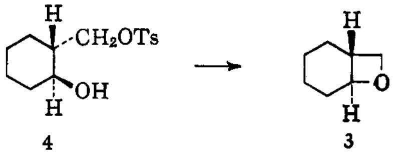


1

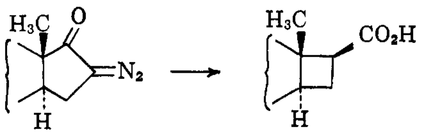


2

In 1961, *trans*-7-oxabicyclo[4.2.0]octane (**3**), an example of a *trans*-fused 6–4 system containing a hetero atom, was prepared[5] in 14% yield by treatment of the hydroxy tosylate **4** with concentrated alkali. Shortly thereafter, four reports[6] appeared outlining the synthesis of several D-norsteroids, substances incorporating a 6–4 *trans* fusion within a steroidal framework. The D-norsteroids (**6**) were made by the irradiation of diazo ketones (**5**), which were readily derived from the appropriate 17-keto steroids.

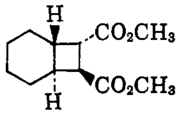


4 **3**

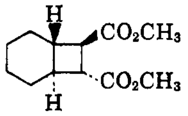


5 **6**

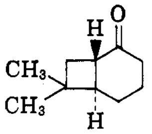
In 1963, the photochemically induced addition of dimethyl maleate to cyclohexene was reported[7] to give a mixture of four diesters, two of which (*i.e.*, **7a** and **7b**) were shown to have a *trans* ring fusion. This remarkable *trans* addition of an olefin to an excited ethylenic system has also been encountered[8] in the preparation of an intermediate utilized in the synthesis of *dl*-caryophyllene. In this case, addition, by photochemical means, of 2-cyclohexenone to isobutylene afforded a mixture of *cis*- and *trans*-7,7-dimethylbicyclo-[4.2.0]octan-2-one, with the *trans* isomer **8** comprising *ca.* 80% of the mixture.



7a

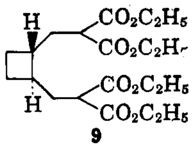


7b



8

There has been only a single report[4] of a *trans*-fused 5–4 system. Alkylation of diethyl malonate with *trans*-1,2-bis(bromomethyl)cyclobutane (**14**, see Chart I), designed to produce the tetra ester **9**, gave as a byproduct (*ca.* 16% yield) a substance assigned the *trans* structure **16**.



9

It was our purpose to explore the possibilities of preparing simple derivatives of 5–4 and 6–4 *trans*-fused carbocyclic systems. These systems are of interest in that the *trans* fusion of the five- and six-

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[1] This work was supported in part by a research grant (no. GM 10090) provided by the National Institutes of Health.

[2] National Institutes of Health Postdoctoral Fellow, 1962–1963.

[3] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 273.

[4] N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Am. Chem. Soc.*, **81**, 4074 (1959).

[5] O. Kovacs, Z. Tuba, I. Weisz, and G. Schneider, *Chem. Ind.* (London), 1222 (1961).

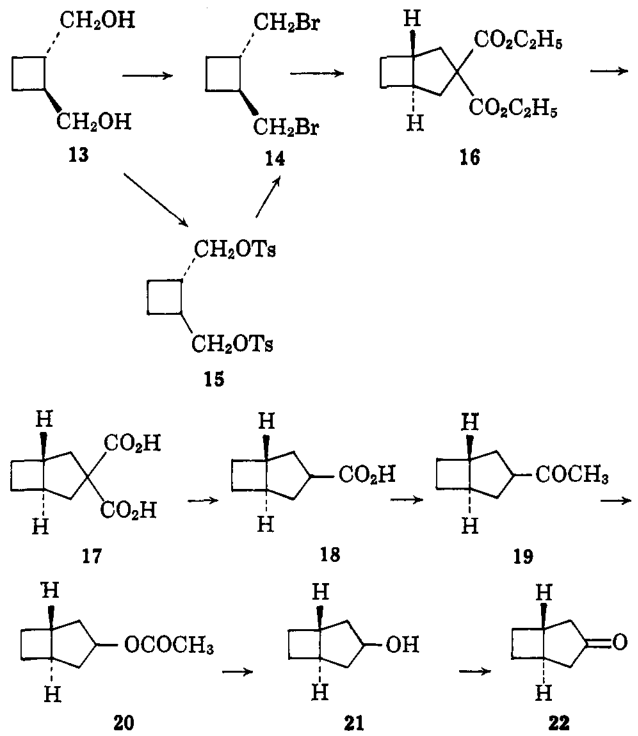
[6] M. P. Cava and E. Moroz, *J. Am. Chem. Soc.*, **84**, 115 (1962); J. Meinwald, G. G. Curtis, and P. Gassman, *ibid.*, **84**, 116 (1962); J. L. Mateos, O. Chao, and H. Flores R, *Tetrahedron*, **19**, 1051 (1963); G. Muller, C. Huynh, and J. Matheiu, *Bull. soc. chim. France*, 296 (1962).

[7] P. de Mayo, R. W. Yip, and S. T. Reid, *Proc. Chem. Soc.*, 54 (1963).

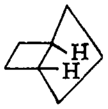
[8] E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **85**, 362 (1963).

[9] A. C. Cope and J. K. Hecht, *ibid.*, **85**, 1780 (1963).

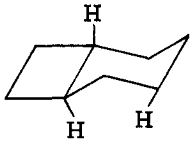
CHART I



membered rings to the cyclobutane ring would seem, from a consideration of Dreiding molecular models, to make special demands on the adjoining ring. Thus, *trans*-bicyclo[3.2.1]heptane (A) would appear to require an exaggerated half-chair conformation,[10] while *trans*-bicyclo[4.2.0]octane (B) should adopt a somewhat folded-chair conformation in which the axial bonds tend to converge.



A



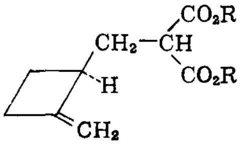
B

The *trans* fusion to a smaller ring should hold the 5- and 6-membered rings in A and B relatively rigid, and substituted derivatives should permit studies which would relate their conformations to reactivity.

Toward this end, it appeared to us that the previously reported 5–4 *trans* diester **16**[4] might be an excellent point of departure for our synthetic goals. We sought, therefore, to obtain quantities of **16** sufficient to permit a confirmation of its structure and, also to serve as the starting material in our synthetic scheme.

For the preparation of *trans*-1,2-bis(bromomethyl)-cyclobutane (**14**), modified versions of the previously reported methods[4,11] were used (*cf.* Chart I). Cyclobutane-1-2-dicarboxylic acid (**11**), prepared by the acid hydrolysis of a mixture of *cis*- and *trans*-1,2-dicyanocyclobutane,[12] was converted into its diethyl ester and subjected to epimerizing conditions by treatment with sodium ethoxide, to give chiefly the *trans* isomer (**12**).[13] The *trans* diol **13**, obtained from **12** by lithium aluminum hydride reduction, exhibited a two-proton singlet at τ 4.94 (hydroxyl protons) and a four-proton multiplet centered at 6.50 (side-chain methylene protons) in its n.m.r. spectrum at 60 Mc. Phosphorus tribromide treatment of the diol produced the dibromide **14**.[4,11] Since it was considered possible that a ring expansion might accompany this transformation,[14,15] the dibromide was also prepared by the action of lithium bromide in acetone upon the ditosylate **15**. The same material was obtained from both syntheses, and its n.m.r. spectrum was in accord with expectations.

The alkylation of diethyl malonate with **14** was carried out using potassium *t*-butoxide in *t*-butyl alcohol under conditions expected to favor the formation of the bicyclic diester **16**. A material whose physical properties corresponded to those reported for the substance assigned structure **16** was isolated in 43% yield. Since the evidence upon which this structure was based was not extensive, and since this compound was to play a key role in the remainder of our synthetic work, we took special care to consider alternative possibilities. Among these, we entertained the isomeric methylene cyclobutane structure **24**. The n.m.r. spectrum of this product, however, indicated the absence of olefinic protons, and appeared completely consistent with the previous structural assignment. Proof that this diester contains a five-membered ring is provided by its ultimate conversion to a cyclopentanone (**22**) (*vide infra*). The surprising success of this Perkin ring closure, in spite of the apparently great distance between the reacting centers in the monoalkylated intermediate, requires that cyclobutane rings be either considerably more flexible or less planar than indicated by Dreiding models.[13b]



24

Our early attempts to synthesize bicyclo[3.2.0]-heptan-3-one (**22**) focused upon the possibility of a direct degradation of the diacid **17**. In the course of studies on the conversion of malonic acids into ketones, we found that di-*n*-butylmalonic acid could be converted directly into 5-nonanone by treatment with lead tetraacetate in acetonitrile, conditions similar to those employed in the preparation of olefins from 1,2-

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[10] K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959).

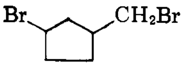
[11] A. T. Blomquist and J. A. Verdol, *ibid.*, **77**, 1806 (1955).

[12] E. C. Coyner and W. S. Hillman, *ibid.*, **71**, 324 (1949).

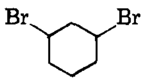
[13] (a) Vapor phase chromatographic analysis of the diester which had been subjected to the epimerization conditions indicated 5–10% of a second component, presumed to be the *cis* diester **23**, even after prolonged ethoxide treatment. (b) This observation fits in well with equilibration studies of 1,2-disubstituted cycloalkanes reported recently by G. J. Fonken and S. Shiengthong [*J. Org. Chem.*, **28**, 3435 (1963)].

[14] J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).

[15] Such processes might result in the formation of dibromides of the type i or ii. These structures were subsequently ruled out by an examination of the n.m.r. spectrum of **14**, showing a four-hydrogen multiplet centered at τ 6.51 (side-chain methylene protons). In that region, a three-hydrogen multiplet is to be expected for i, and a two-hydrogen multiplet for ii.



i

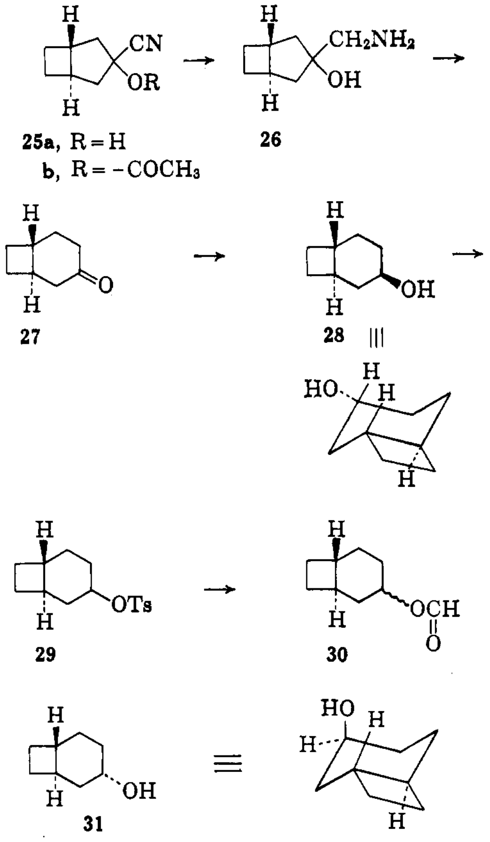


ii

diacids.[16] Treatment of **17** in a similar fashion afforded a small quantity of **22**, as evidenced by gas chromatographic and spectral examination (*e.g.*, infrared absorption at 5.71 μ typical of a strained cyclopentanone). This ketone (*i.e.*, **22**) could also be generated by sodium bismutate cleavage[17] of *trans*-3-carboxybicyclo[3.2.0]heptan-3-ol, formed from the corresponding monocarboxylic acid (**18**) by oxidation with alkaline permanganate.[18] The modified Curtius procedure, by which malonic acids can be converted into ketones,[19] when applied to **17**, also gave a low yield of **22**. The method finally chosen, however, was the more lengthy but more efficient five-step sequence outlined in Chart I. *trans*-3-Carboxybicyclo[3.2.0]-heptane (**18**), prepared by decarboxylation of **17**,[4] was converted into the corresponding methyl ketone **19** in 84% over-all yield by treatment with methyllithium. The acetate **20** was prepared from **19** in 91% yield in a Baeyer–Villiger reaction using *m*-chloroperbenzoic acid in chloroform. The alcohol **21**, obtained by lithium aluminum hydride reduction of **20** was oxidized to the desired ketone[20] (**22**) in 52% yield with 6 *N* chromic acid.

Extensive attempts to prepare the *trans* 6–4 system directly by utilizing the ring contraction reactions previously used in the steroid work were relatively unfruitful. However, the bicyclic ketone **22** proved to be a useful intermediate for the synthesis of its homolog (*cf.* Chart II). Thus, by means of the Tiffeneau–Demjanov ring expansion,[21] we were able to effect the transformation of **22** into the 6–4 *trans* ketone, **27**. For this purpose, the cyanohydrin **25a** was prepared and converted into its acetate (**25b**) by the method of Roberts and Gorham.[22] Lithium aluminum hydride reduction of **25b** gave the amino alcohol **26**, which was converted into *trans*-bicyclo[4.2.0]octan-3-one (**27**) in 33% yield by treatment with nitrous acid. Partial dissociation of the cyanohydrin to **22**, followed by reduction with lithium aluminum hydride, led to a small amount of **21** as a by-product in this reaction sequence. Reduction of **27** with lithium aluminum hydride or sodium and ethanol produced a single product, designated as the equatorial epimer **28**, since sodium–alcohol reductions of ketones are known[23] to give the more stable epimer preferentially.

CHART II



25a, R = H
b, R = -COCH₃
26
27
28
29
30
31

In order to obtain the axial alcohol **31**, the equatorial tosylate **29**, prepared from **28** in the usual manner, was converted into a mixture of formates (**30**) by refluxing in dimethylformamide.[24] This mixture was treated with lithium aluminum hydride to give the desired axial alcohol, **31**, as the major product, along with a smaller amount of **28**. The separation of these alcohols was accomplished by preparative gas chromatography, and the infrared spectra of the two isomers were strikingly different. Proof of the structure of **31** was provided by its oxidation with 6 *N* chromic acid to give **27**. Analogous oxidation of **28** also gave **27**.

Now that synthetic routes to these simple, *trans*-fused bicyclo[3.2.0]heptanes and bicyclo[4.2.0]octanes have been developed, we hope to study reactions which will reflect conformational effects in these compounds.

Experimental[25,26]

Cyclobutane-1,2-dicarbocyclic Acid (11).[4,12]—A mixture of 200 g. of 1,2-dicyanocyclobutane (**10**),[25] 1 l. of concentrated hydrochloric acid, and 1 l. of water was heated under reflux for 13 hr. After this time the homogeneous solution was continuously extracted with ether for 4 days. The extract was dried over an-

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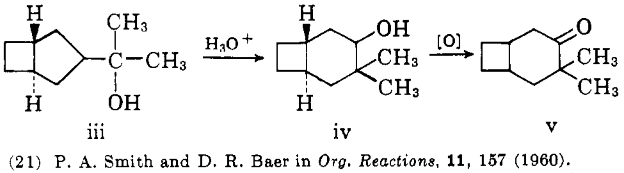
(16) C. A. Grob and A. Weiss, *Helv. Chim. Acta*, **43**, 1390 (1960); C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *ibid.*, **41**, 1191 (1958).

(17) W. Rigby, *J. Chem. Soc.*, 1907 (1950).

(18) G. Büchi and I. M. Goldman, *J. Am. Chem. Soc.*, **79**, 4741 (1957); J. Meinwald and P. G. Gassman, *ibid.*, **82**, 2857 (1961).

(19) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961); C. Beard and A. Burger, *ibid.*, **27**, 1647 (1962); **26**, 2335 (1961).

(20) (a) The final fractions from the ketone distillation contained a substance which appeared to be a six-membered ring ketone (infrared absorption at 5.85 μ). It was suspected that this might have been derived from the tertiary alcohol iii, since alcohols are frequently observed by-products in the reaction of methyllithium with acids. (b) Indeed, v.p.c. examination of the alcohol **21** indicated *ca.* 8–10% of an alcohol, separated by preparative v.p.c., whose n.m.r. spectrum shows no proton adjacent to hydroxyl and the area of whose hydroxyl proton peak was 1/18 of the combined peak areas, a requirement for structure iii. (c) J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960).



iii
iv
v

(21) P. A. Smith and D. R. Baer in *Org. Reactions*, **11**, 157 (1960).

(22) J. D. Roberts and W. F. Gorham, *J. Am. Chem. Soc.*, **74**, 2278 (1952).

(23) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(24) The reaction of dimethylformamide with tosylates to produce the corresponding configurationally inverted formates has been described by F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

(25) We wish to thank the Food Machinery Corp. for a gift of *m*-chloroperbenzoic acid and the Knapsack-Griesheim Corp. for a generous supply of 1,2-dicyanocyclobutane.

(26) Infrared spectra were taken of pure liquids on a Perkin-Elmer Model 137 B spectrophotometer, unless otherwise noted. N.m.r. spectra were taken in carbon tetrachloride on a Varian Model A60 spectrophotometer. Melting points were determined in open capillaries and are uncorrected. V.p.c. analyses were carried out on an Aerograph Model 600 HyFl unit; preparative separations were carried out on a Beckman Model GC-2 vapor fractometer.

hydrous magnesium sulfate and evaporated to give 280 g. of crude **11**.

trans-**Diethyl Cyclobutane-1,2-dicarboxylate** (**12**).[4]—Crude **11** (*ca.* 280 g.) was dissolved in a mixture of benzene (300 ml.) and absolute ethanol (380 ml.), and *p*-toluenesulfonic acid (1.2 g.) was added. The mixture was refluxed for 8 hr. with the removal of water (Dean–Stark separator) at intervals. An equal volume of benzene was added each time water was removed. After 8 hr., 100 ml. of absolute alcohol was added and the refluxing was continued for another 3 hr. The benzene solution was then washed with saturated sodium bicarbonate solution and with water, and dried over anhydrous magnesium sulfate. The solvent was evaporated to give crude **12**. Analytical v.p.c. (NGS column, 139°) showed the presence of 75% of **12** (retention time 6.8 min.) and 25% of the *cis* diester (retention time 8.7 min.). Distillation at this stage gave the ester mixture (b.p. 83–85° at 1.3 mm.) in 80% yield.

The crude ester was equilibrated by refluxing with a solution prepared from 5 g. of sodium in 750 ml. of magnesium-dried ethanol. After 3 hr., v.p.c. analysis (as above) indicated the presence of 5–10% of *cis* diester, and this proportion did not diminish with longer refluxing. Most of the ethanol was evaporated, the residue was cooled in ice, and ether was added. The cold ethereal solution was washed with water, dilute sulfuric acid, and water, then dried over anhydrous magnesium sulfate. This dried ethereal solution was used directly in the next step.

trans-**1,2-Bis(hydroxymethyl)cyclobutane** (**13**).[4,11]—The dried ethereal solution containing *ca.* 350 g. of **12** was divided into two portions and each was reduced in turn as follows. Lithium aluminum hydride (40 g.) in anhydrous ether (2800 ml.) was placed in a 5-l., 3-neck flask fitted with a dropping funnel, stirrer, and condenser. One-half of the ethereal solution of the diester (*vide supra*) was added dropwise with stirring to maintain steady refluxing (1–2 hr.). The mixture was stirred for a further 2 hr., and then water (160 ml.) was cautiously added to decompose excess hydride. The reaction mixture was filtered and dried over anhydrous magnesium sulfate. The ether was removed, leaving a viscous residue. The residues from two such experiments were distilled to give 152 g. (67% from **10**) of **13**, b.p. 102–104° at 0.6 mm. (lit.[4] b.p. 111–114° at 3 mm.). The n.m.r. spectrum indicated a two-proton singlet at τ 4.94 (–OH) and a four-proton multiplet at 6.50 ($-CH_2O-$).

trans-**1,2-Bis(bromomethyl)cyclobutane** (**14**).[4,11] **Method A.**—To phosphorus tribromide (120 g., 0.44 mole), cooled to −10°, was added dropwise with stirring 51.4 g. (0.44 mole) of distilled **13**. The addition took place over a 2-hr. period. The mixture was then heated overnight in an oil bath t 80–85°. The reaction mixture was cooled in ice, 100 ml. of water was added, and the lower layer was separated. The aqueous layer was extracted several times with methylene chloride, and the combined organic layers were washed with dilute sodium carbonate and water. Removal of the solvent from the dried extract gave crude **14**, which upon distillation gave 96.2 g. (90%) of pure material, b.p. 54–56° at 0.45 mm. (lit.[11] b.p. 71° at 1.8 mm.).

Method B.—Diol **13** (12.2 g., 0.10 mole) was dissolved in 70 ml. of pyridine (freshly distilled from barium oxide). *p*-Toluenesulfonyl chloride (38.0 g., 0.20 mole) was added over 20 min. to the cooled solution (−8°), and the reaction mixture was stirred for 5 hr. at −8 to −2°. Pyridine hydrochloride began to separate after 15 min. The reaction mixture was poured into ice–water, and 3 *N* hydrochloric acid was added to *ca.* pH 3. The aqueous solution was extracted with ether and the extract was washed with 3 *N* hydrochloric acid, water, dilute sodium carbonate solution, and water. The ethereal solution was dried and then evaporated, leaving a viscous oil (34 g., 80%) exhibiting typical tosylate absorption in the 7.4- and 8.4-μ regions of the infrared spectrum.

The crude *trans*-1,2-bis(tosyloxymethyl)cyclobutane (**15**, 10 g., 0.024 mole) was dissolved in 40 ml. of anhydrous acetone. Lithium bromide (20.0 g., 0.23 mole) was added, and the mixture was stirred and refluxed for 90 min. A precipitate separated at once. The acetone was evaporated and the residue was diluted with water. The organic layer was separated and the aqueous layer was extracted twice with petroleum ether (b.p. 30–60°). The combined organic layers were dried (magnesium sulfate) and the solvents were removed under reduced pressure. The dibromide (4.7 g., 85%) was twice distilled, b.p. 76–79° at 3 mm.

Infrared spectra and v.p.c. analysis (10% Carbowax, 200°) indicated that the dibromides prepared *via* both routes were identical (retention time 8.7 min. with a small peak at 10.3 min. corresponding to the *cis* isomer). The n.m.r. spectrum shows a four-proton multiplet at τ 6.51 ($-CH_2Br$).

trans-**3,3-Dicarboethoxybicyclo[3.2.0]heptane** (**16**).[4]—An improved yield of **16** was obtained by using a modification of the method of Allinger, Nakazaki, and Zalkow,[4] who obtained it as a by-product in the preparation of *trans*-1,2-bis(β,β-dicarboethoxyethyl)cyclobutane (**9**).

In a 2-l., 3-neck flask, fitted with stirrer, condenser, and dropping funnel, was placed a mixture of 96.2 g. of **14**, 62 g. of diethyl malonate and 350 ml. of dry *t*-butyl alcohol. The mixture was refluxed under nitrogen and a solution of potassium *t*-butoxide (94.4 g.) in dry *t*-butyl alcohol (450 ml.) was added dropwise over a 6-hr. period. After refluxing and stirring for a further 8 hr., an equal volume of water was added to the cooled reaction mixture; the solution was extracted with ether several times. The combined extracts were washed with 3 *N* hydrochloric acid and dilute sodium bicarbonate solution, and dried with magnesium sulfate. The reside, after removal of solvent, was distilled. Analysis of the distillate by v.p.c. (10% Carboxwax, 200°) indicated that a fraction b.p. 104–106° at 1.3 mm. (lit.[2] b.p. 100–105° at 0.8 mm.), 37.9 g., was the pure malonic ester **16** (retention time 17.2 min.) while earlier fractions contained some diethyl malonate. The early fractions were combined and redistilled to give a further 3.5 g. of **16**, bringing the yield to 41.4 g. (43%).

The infrared spectrum showed a strong band at 5.78 μ (ester carbonyl) and the n.m.r. spectrum, which indicated no unsaturation, showed a four-proton quadruplet at τ 5.94 ($-OCH_2-$) and a two-proton multiplet at 7.62 (tertiary hydrogens).

trans-**3,3-Dicarboxybicyclo[3.2.0]heptane** (**17**).[4]—The malonic ester **16** was hydrolyzed with a 50% methanolic potassium hydroxide solution as previously described. Recrystallized **17**, m.p. 183–185° dec. (lit. m.p. 182° dec.), was obtained in 70% yield.

trans-**3-Carboxybicyclo[3.2.0]heptane** (**18**).[4]—Recrystallized **17** was decarboxylated by heating at 190° for 1 hr. The resulting pale yellow liquid (*i.e.*, **18**) was dissolved in anhydrous ether, and used directly for the preparation of **19**.

trans-**3-Acetylbicyclo[3.2.0]heptane** (**19**).—Methyllithium was prepared by the addition of methyl iodide (5.7 g., 0.04 mole) in anhydrous ether (20 ml.) to a stirred suspension of lithium (0.7 g., 0.1 mole) in anhydrous ether (25 ml.) at a rate sufficient to maintain steady refluxing.

The resultant methyllithium solution was added dropwise to a stirred solution of **18** (obtained from 1.84 g., 0.01 mole, of **17** by decarboxylation) in anhydrous ether (50 ml.) under a nitrogen atmosphere. After being stirred for 2 hr., the reaction mixture was poured into 70 g. of crushed ice. The ether layer was separated and the aqueous layer was re-extracted with ether. Evaporation of the dried (magnesium sulfate) extracts afforded the sweet-smelling methyl ketone, **19** (infrared absorption at 5.85 μ). The crude product was distilled to give pure **19** (1.16 g., 84% from **17**), b.p. 86–87° at 15 mm.; v.p.c. (Carbowax, 134°) indicated that this fraction consisted of a single, pure compound (retention time 6.2 min.).

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.94; H, 10.23.

trans-**3-Acetoxy[3.2.0]heptane** (**20**).—A solution of 1.0 g. of **19** in 3 ml. of chloroform was added to a stirred solution of 1.89 g. of chloroperbenzoic acid[25] in 10 ml. of chloroform, and the progress of the reaction followed by v.p.c. analysis (Carbowax, 140°) of aliquots. The peak at 6.4 min. characteristic of **19** was completely replaced by a peak at 5.3 min. corresponding to **20** after the reaction mixture had been stored for 20 hr. in the dark at room temperature. At this time, crystals of *m*-chloroperbenzoic acid had crystallized from the reaction mixture. The chloroform solution was washed with aqueous sodium carbonate solution and dried (magnesium sulfate); the chloroform was distilled through a short column. The residual acetate gave upon distillation (bath temperature 105–110° at 20 mm.) 1.0 g. (91%) of analytically pure material. The infrared spectrum (neat) exhibited absorption bands at 5.76 and 8.1–8.2 μ.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.92; H, 9.32.

trans-**Bicyclo[3.2.0]heptan-3-ol** (**21**).—To 0.25 g. of lithium aluminum hydride in 10 ml. of anhydrous ether was added with stirring a solution of 1.06 g. of distilled **20** in 10 ml. of anhydrous ether. The reaction mixture was stirred for 2 hr. and 1 ml. of water was cautiously added. The inorganic salts were dissolved by the addition of dilute sulfuric acid. The ether layer was separated and washed with sodium bicarbonate solution, then dried (magnesium sulfate). Removal of the solvent and fractional distillation of the residue gave pure **21** (0.70 g., 91%), b.p. 91–92° at 20 mm. The infrared spectrum (neat) shows absorption in the 3.0–3.1-μ region (–OH stretch) and v.p.c. analysis (Carbowax, 152°) indicated that the distilled alcohol was homogeneous (retention time 5.3 min.).

Anal. Calcd. for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.93; H, 10.89.

***trans*-Bicyclo[3.2.0]heptan-3-one (22). Method A.**—Alcohol **21** (9.9 g.) was dissolved in acetone (45 ml.) and 6 *N* chromic acid (45 ml.) was added dropwise over a 20-min. period. After being stirred for a further hour, the reaction mixture was diluted with water (40 ml.) and extracted with petroleum ether (b.p. 30–60°). The combined extracts were then washed with water and sodium bicarbonate solution, and dried (magnesium sulfate). The solvent was distilled through a short column and the residue was then fractionally distilled to give 5.05 g. of **22** (52%), b.p. 85–87° at 50 mm. The infrared spectrum (carbon tetrachloride solution) showed absorption at 5.71 μ (five-ring ketone).

Anal. Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.17; H, 9.27.

Method B.—The diacid **17** (0.01 mole, 1.84 g.) was placed in 15 ml. of anhydrous acetonitrile to which had been added 3.2 ml. of dry pyridine. Lead tetraacetate (0.022 mole, 9.4 g.), dried by suction on a sintered-glass funnel to remove acetic acid, was added at once to the above solution. The mixture was stirred and heated to 50–55°, whereupon evolution of carbon dioxide commenced. After 30 min. at this temperature, the reaction mixture was cooled and added to 30 ml. of 3 *N* nitric acid. The aqueous solution was extracted with ether and the ether solution was then extracted with dilute sodium bicarbonate solution. The ethereal solution was dried over magnesium sulfate and the ether was removed by distillation. The residue was treated on the steam bath for 10 min. with a solution of methanol (2 ml.) in water (5 ml.) containing 1 g. of potassium hydroxide. Water (10 ml.) was added and the solution was extracted with ether. The ether was distilled from the dried organic extracts to leave a residue from which **22** was isolated by preparative-scale vapor phase chromatography (10 ft., Carbowax, 105°).

Method C.—The diacid **17** (0.01 mole, 1.84 g.) was placed in a 50-ml. flask protected with a drying tube and heated to 185–195° for 45 min. The resulting **18** was added to a solution of 7.3 g. potassium hydroxide in 23 ml. of water. Potassium permanganate (2.8 g.) and 20 ml. of petroleum ether (b.p. 60–70°) were added and the mixture heated to 50–55° for 20 hr. Sulfur dioxide was passed through this solution for 1 min. The solution was filtered, and 27 ml. of water and 20 ml. of petroleum ether (b.p. 30–60°) were added. The immiscible layers were separated and the petroleum ether solution was dried over magnesium sulfate. The organic solvents were removed by distillation to leave 1.1 g. of a residue which was placed in 15 ml. of water. Sodium bismuthate (7 mmoles, 2.31 g., 85% purity) was added to the above solution. A solution of 2.25 g. of 85% phosphoric acid in 0.6 ml. of water was added over a 10-min. period with stirring. The temperature was raised to 45° over 60 min. and kept at 45–48° for 16 hr. The reaction mixture was cooled and extracted with ether. The ether solution was washed with dilute sodium bicarbonate, and dried (magnesium sulfate), and the ether was removed by distillation. The desired ketone was isolated from the residue as described in method B.

Method D.—The diacid **17** (0.01 mole, 1.84 g.) was dissolved in 4 ml. of acetone to which had been added 4.5 ml. water. The solution was cooled to −5 to 0° in an ice–salt mixture. Triethylamine (24 mmoles, 2.4 g.) was added in one portion. Slowly, ethyl chloroformate (24 mmoles, 2.6 g.) in 5 ml. of acetone was added and the solution was stirred for 45 min. at 0°. Sodium azide (0.03 mole, 1.96 g.) in 6 ml. of water was added dropwise. The solution was stirred at 0° for 1 hr. The reaction mixture was poured into ice–water and extracted with ether. The ether extract was dried (magnesium sulfate), absolute ethanol (50 ml.) was added, and the ether was removed by distillation. The ethanol was refluxed for 2 hr., cooled, then evaporated under diminished pressure. The residue, after standing overnight, was treated with 50 ml. of 2% sulfuric acid and steam distilled. The 150 ml. of steam distillate was saturated with salt and extracted with ether. The dried ether extract was distilled through a short Vigreux column and the desired **22** was isolated as described in method B.

***trans*-3-Acetoxy-3-cyanobicyclo[3.2.0]heptane (25b).**—The cyanohydrin acetate was prepared according to the method of Roberts and Gorham.[22] A mixture of 2.2 g. of **22** and 2 ml. of anhydrous hydrogen cyanide was cooled to 0°. Two drops of piperidine and a crystal of potassium cyanide were added. The mixture was allowed to stand in an ice bath for 2 days. The piperidine was neutralized by the addition of 2 drops of concentrated sulfuric acid, and then the crude **25a** was acetylated with an ethereal solution of acetic anhydride (4 ml.) and acetyl chloride (0.16 ml.). The acetylation mixture was kept at 0° for 24 hr. and then allowed to stand at room temperature for 5 days. The excess hydrogen cyanide and ether were removed by distillation at atmospheric pressure. The residue was taken up in ether, washed with water and dilute sodium bicarbonate solution, then dried (magnesium sulfate). Removal of solvent and distillation (bath temp. 125° at 2.7 mm.) of the residue gave 2.54 g. (71%) of **25b**. The infrared spectrum of **25b** indicated absorption at 4.50, 5.70, and 8.1 μ.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.13; H, 7.49; N, 7.92.

***trans*-3-Aminomethyl-3-hydroxybicyclo[3.2.0]heptane (26).**—Cyanohydrin acetate **25b** (0.6 g.) in anhydrous ether (40 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (1.0 g.) in ether (40 ml.). The mixture was refluxed for 3.5 hr., then cooled. Water (5 ml.) was cautiously added. After being stirred for a further 30 min., the reaction mixture was filtered. The ethereal solution was dried (magnesium sulfate) and evaporated to yield amino alcohol **16** (0.453 g., 96%) as a viscous colorless oil. The infrared spectrum showed absorption at 3.1 and 6.26 μ.

***trans*-Bicyclo[4.2.0]octan-3-one (27).**—The crude **26** (0.29 g.) was dissolved in water (3 ml.) containing acetic acid (0.15 ml.). The solution was cooled in an ice bath and a solution of sodium nitrite (0.18 g.) in water (3 ml.) was added slowly with swirling. The mixture was kept in an ice bath for 1 hr., then heated under reflux on a steam bath for 1 hr. The mixture was extracted with methylene chloride and the extract was washed with dilute sodium carbonate solution, then water. The solvent was removed from the dried (magnesium sulfate) extract. The residue was separated by preparative v.p.c. (Carbowax, 118°). The major component (**27**) (retention time 16.5 min.) was collected and separated from *ca.* 5% of an impurity (retention time 22.5 min.). This impurity was shown to be **21** by infrared comparison (*cf.* Discussion). This preparative procedure resulted in the isolation of pure **27** in 33% yield. The infrared spectrum (neat) showed a strong band at 5.87 μ (six-ring ketone) and v.p.c. analysis (Carbowax, 106°) showed a single peak (retention time 14.2 min.). The n.m.r. spectrum was consistent with the proposed structure (*i.e.*, a complex multiplet is apparent centered at *ca.* τ 8.0; no olefinic proton resonance was observed).

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 76.97; H, 9.81.

Equatorial *trans*-Bicyclo[4.2.0]octan-3-ol (28).—A sample of crude **27** obtained from 2.0 g. of **26** was reduced with lithium aluminum hydride in the usual manner (*vide supra*). The crude product was purified by preparative v.p.c. (Carbowax, 152°). Pure **28** (retention time 15 min.) (0.60 g.) was collected and shown to be homogeneous on several v.p.c. columns (LAC 446, 156°, 4.4 min.; TCEP, 122°, 44 min.; Carbowax, as above). Thin layer chromatographic techniques also indicated the alcohol to be pure.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.16; H, 11.25.

A small amount of **27** was reduced with sodium in ethanol. The alcohol obtained appeared by infrared and v.p.c. examination (see above) to be identical with the alcohol from the lithium aluminum hydride reduction of **27**.

Axial *trans*-Bicyclo[4.2.0]octan-3-ol (31).—The equatorial alcohol (**28**, 0.39 g.) was converted into **29** by treatment with *p*-toluenesulfonyl chloride (0.6 g.) in pyridine (4 ml.) for 24 hr. at 0°. The reaction mixture was poured into 60 ml. of ice–water containing 4 ml. of concentrated hydrochloric acid. The resulting solution was extracted with ether. The combined extracts were washed with water, aqueous sodium bicarbonate solution, and water, then dried (magnesium sulfate). Removal of solvents afforded a pale yellow oil (0.64 g.) with displayed infrared bands at 6.25, 7.37, 8.4, 8.5, and 10.7 μ, indicative of a tosylate (also apparent was a weak band in the hydroxyl region probably due to the presence of some unreacted **28**).

The crude **29** (0.55 g.) was heated under reflux for 20 hr. with dimethylformamide (60 ml.) containing sodium acetate (5 g.).

The reaction mixture was cooled and diluted with water (70 ml.). The product was extracted with petroleum ether (b.p. 30–60°) and the extract was washed with dilute hydrochloric acid, then water. The dried extract (magnesium sulfate) was evaporated to give an oil whose infrared spectrum (neat) shows absorption at 3.1, 5.8, and 8.42 μ, indicating the product to be a mixture of alcohol and formate (**30**).[24]

The crude product was reduced with lithium aluminum hydride in anhydrous ether in the usual way. The resulting product was analyzed by v.p.c. (TCEP, 128°) and showed to be a mixture of two components (retention times 31.5 and 39.8 min.), the minor of which was the original **28**. The two alcohols were separated by preparative v.p.c. (combined 5-ft. TCEP and 5-ft. Carbowax column). The new alcohol (retention time 23 min.) (*i.e.*, the axial alcohol **31**) had an infrared spectrum very different from that of **28** (retention time, 28 min.).

Oxidation of each alcohol (10 mg.) with 6 *N* chromic acid (0.1 ml.) in acetone (0.2 ml.) gave ketone **27**, identified by infrared and v.p.c. comparisons with authentic material (Carbowax, 111°, single peak at 11.5 min.).

Preparation and Properties of 2- and 3-Bromo-1-methylcyclohexanes

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Received April 1, 1964

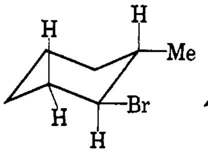
Samples of 2- and 3-bromo-1-methylcyclohexanes have been prepared by the Hunsdiecker method. Spectral methods showed these to be free of other position isomers, but to be mixtures of geometric isomers. Some attempts to prepare pure *cis* or *trans* isomers proved unsuccessful. The nature of the products obtained from a variety of methods of preparing such cycloalkyl bromides has been surveyed.

The considerable difficulties associated with the preparation of pure secondary bromides are well known.[2] Secondary cycloalkyl bromides, with their possibilities for geometric isomerism, provide a more complex problem than do aliphatic bromides. Recently Jensen and Gale[3] showed that cleavage of cycloalkylmercuric bromides under proper conditions can be achieved with complete retention of configuration, thereby providing an elegant mode of synthesis for geometrically uniform cycloalkyl bromides. The Hunsdiecker reaction has also been shown[3,4] to be useful for the preparation of unrearranged cycloalkyl bromides. Having need for pure samples of 2- and 3-bromo-1-methylcyclohexanes, we have studied the preparation of these substances in some detail. The results of this work are reported here.

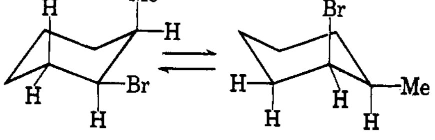
Identity and Purity.—Both 2-bromo-1-methylcyclohexane (I) and 3-bromo-1-methylcyclohexane (II) have been reported previously in the literature.[5] In no case, however, has unequivocal evidence been provided for identity and purity of these. Samples of I and II have been prepared now from the corresponding methylcyclohexanecarboxylic acids *via* the Hunsdiecker reaction. Satisfactory evidence for identity of I and II was provided in each case by (a) their mode of preparation, (b) their conversion *via* a Grignard reagent to 2- and 3-methylcyclohexanol, respectively, and thence to the relevant ketones which were identified by gas chromatography, and (c) the spectroscopic data discussed below. Both I and II were obtained as mixtures of *cis* and *trans* isomers when prepared in this way. A sample of I prepared from a nearly pure (m.p. 48–51°) *trans*-2-methylcyclohexanecarboxylic acid[6] was indistinguishable from a sample prepared from a liquid mixture of *cis* and *trans* isomers. The result parallels the observations of Eliel and Archarya.[4]

The n.m.r. spectrum of I is characterized by a very sharp doublet (J = 6.0 c.p.s.) at τ 8.90, and two low-field multiplets, one a clean sextet (doublets of a triplet, J = 10.5, 4.0 c.p.s.) centered at τ 6.32, the second an unresolved multiplet at τ 5.65. The ratio of the area under the 6.32 and 5.65 peaks to the rest of the spectrum is almost exactly 1:12. These data show that the product is a secondary bromide with one methyl group attached to a carbon bearing one hydrogen, and the chemical shift for the methyl group means the bromine atom must be attached to a carbon at least two carbons from the methyl. Excluded by this result alone are such rearrangement products as 1-bromo-1-methylcyclohexane, α-bromoethylcyclopentane, and 2-bromomethyl-1-methylcyclopentane. The presence of two peaks for the CHBr proton means that this is a mixture. Thus, the n.m.r. spectrum does not immediately eliminate II or mixtures of I and II as possibilities. Comparison of the spectrum with that of a sample ultimately identified as II shows (see below) that II cannot be present in I.

I is expected to be a mixture of *cis* and *trans* forms. The *trans* form (Ia) is conformationally uniform and its low-field CHBr proton is axial. From first-order analysis it should give rise to a sextet (doublets of a triplet) with $J_{a,a} > J_{a,e}$. Though nonuniform conformationally, the *cis* form Ib should have predominantly[7] an equatorial CHBr proton. Since $J_{a,e} \simeq$



Ia



Ib

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[7] Assuming the conformational equilibrium constant for Ib is similar to that of *cis*-4-bromo-1-methylcyclohexane,[8] the ratio of H_e to H_a should be near 9:1.

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