The Brominative Decarboxylation of Optically Active Silver *trans*-1,2-Cyclohexanedicarboxylate

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The brominative decarboxylation (Hunsdiecker reaction) of the title compound has been found to yield optically active *trans*-1,2-dibromocyclohexane, with net inversion of configuration. The amount of optical activity varied over a wide range, but was always of the same sign. The *cis*-dibromide was not formed and was shown to be stable under the reaction conditions. A mechanistic scheme is proposed involving competitive intramolecular bromine atom transfer in a 2-bromocarboxycyclohexyl radical and some nonstereospecific mechanism, probably with a cyclohexene intermediate. The absolute configurations of the diacid and dibromide have been assigned.

Preliminary work in this laboratory[1] showed that the Hunsdiecker reaction of optically active silver *trans*-cyclobutane-1,2-dicarboxylate gave an optically active *trans*-dibromide product. This result was considered interesting in terms of its possible bearing upon the intermediacy of an olefin or bridged-bromine radical, but no information was then available on the optical purity of the product, the preferred stereochemistry (retention or inversion), or the possibility of an asymmetric induction of optical activity in the product by a path unrelated to the Hunsdiecker reaction. The present research considers these matters in some detail. The cyclobutane system was abandoned in favor of the more accessible silver cyclohexane–1,2-dicarboxylate, which has been shown by Abell[2] and confirmed by us to give only *trans*-1,2-dibromocyclohexane, with no detectable amount of *cis* product.

trans-Cyclohexane-1,2-dicarboxylic acid was prepared in 64% over-all yield by ethanolysis-esterification of commercial *cis*-hexahydrophthalic anhydride, followed by base-catalyzed epimerization to the *trans* form and saponification.[3] The acid was resolved with quinine by the method of Werner and Conrad[4] to give the dextrorotatory form in higher optical purity than has been previously obtained. Conversion of the optically active acid to its disilver salt was essentially quantitative.

Brominative decarboxylations were carried out at 0° and at 31.3° in the inverse manner (addition of silver salt to a solution of bromine in carbon tetrachloride). The specific experimental conditions, yields, and optical results for thirteen runs are summarized in Table I. The most important features of these data are the following: (1) Although the optical purities of the products varied erratically, the lower temperature clearly favored a higher optical purity. (2) The optical purity of the product was not detectably affected by a threefold increase in initial bromine concentration. (Compare especially runs 11 and 13 with runs 3–5.) (3) The rotations of products approached zero, but were always negative. (4) The yields of dibromide product were increased from 14–19% at 0° in ambient laboratory light to 39 41% by irradiation, to 36–58% by use of excess bromine, and to 26–29% by an increase in the temperature to 31.3°.

TABLE I

SUMMARY OF THE RESULTS OF THE BROMINATIVE DECARBOXYLATIONS OF OPTICALLY ACTIVE SILVER *trans*-1,2-CYCLOHEXANEDICARBOXYLATE

Run	Temp., °C.[a]	Specific rotation (neat) of dibromide, degrees	% yield of dibromide	Specific rotation of diacid, degrees
1	31.3	− 1.77	26	+21.8
2	31.3[b]	− 4.87	29	+21.8
3	0 ± 1	−18.9	14	+21.8
4	0 ± 1	−27.0	14	+21.8
5	0 ± 1	−25.4	16.5	+21.8
6	0 ± 1[c]	−19.8	39	+20.5
7	0 ± 1[c,d]	−21.4	41	+20.5
8	0 ± 1[e]	− 8.38	19	+20.5
9	0 ± 1[e]	−10.2	14	+20.5
10	0 ± 1	−11.7	19	+20.5
11	0 ± 1[f]	−25.3	58	+21.9
12	0 ± 1[g]	−17.5	36	+21.9
13	0 ± 1[h]	−24.5	51	+21.9

[a] The reactions at 0 ± 1° were carried out for a total time of eight hours, while those at 31.3° were carried out for a total time of one hour. The additions required one hour and fifteen minutes, respectively. [b] A flashing light was the heat source in the constant temperature bath. [c] The reaction mixture was illuminated by a sun lamp at a distance of nine inches from the flask. [d] Thirty-two per cent of the starting diacid was recovered, m.p. 178–182° (original m.p. 179–182°). [e] The reaction mixture was shielded from light. [f] The reaction was carried out with three times the theoretical amount of bromine for a total of nine hours. [g] Twice the theoretical amount of bromine was added fifteen minutes before the end of the reaction; the reaction was carried out for a total of nine hours. [h] The reaction was carried out with three times the theoretical amount of bromine.

The other reaction products were esters and probably a β-lactone (infrared absorption at 1820 cm.$^{-1}$), but these were not identified or investigated beyond learning how to remove them from the dibromide.

Before any interpretation of the data in Table I is presented, it would be well to consider some controls to determine whether the data can properly be interpreted solely in terms of the mechanism of the Hunsdiecker reaction. First, the optical activity of the product was shown to be activity of the dibromide and not of some impurity by identity of the infrared spectra, indices of refraction, and vapor chromatographic thermal cracking patterns of product and authentic *trans*-1,2-dibromocyclohexane; and especially by the constancy of the optical rotations in successive distillation fractions of the product. Second, it was shown that optical activity was not induced in racemic dibromide by reaction with optically active silver salt under the conditions of the Hunsdiecker reactions. Third, it was shown that the optically active dibromide

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(1) D. E. Applequist and A. S. Fox, *J. Org. Chem.*, **22**, 1751 (1957).

(2) P. I. Abell, *ibid.*, **22**, 769 (1957).

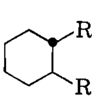
(3) (a) C. C. Price and M. Schwarcz, *J. Am. Chem. Soc.*, **62**, 2891 (1940); (b) J. L. Fedrick, Ph.D. thesis, University of Illinois, 1959.

(4) A. Werner and H. E. Conrad, *Ber.*, **32**, 3046 (1899).

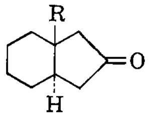
was not racemized at all by bromine in carbon tetrachloride at 31.3°, and in a Hunsdiecker reaction system (silver acetate) it was racemized to the extent of only 8.1% at 0° and 42% at 31.3°. Fourth, it was shown that *cis*-1,2-dibromocyclohexane was not isomerized to the *trans* isomer to a detectable extent under the conditions of a Hunsdiecker reaction (silver acetate), so the *trans* isomer is indeed the initial product of the reactions reported here. Fifth, it was shown that the *trans*-diacid recovered from a Hunsdiecker reaction of the active silver salt had not lost any optical activity in preparation of the silver salt or during the Hunsdiecker reaction.

A final question to be considered before specific mechanisms are proposed is that of the predominant stereochemistry (net inversion or net retention) of the reaction. Some efforts were made to determine the relative configurations of starting material and product directly by displacements on the dibromide with ammonia, azide, and cyanide, any of which might have given an inverted *trans* product which could easily be related to the diacid. The reaction with ammonia in *t*-butyl alcohol gave 3-aminocyclohexene as the only basic product.[5] Azide gave a similar result. The reaction with cyanide ion in acetonitrile or acetone gave no *trans*-1,2-cyclohexanedinitrile, which was hardly a surprising result.[6,7] However, the reaction of *trans*-dibromide with cyanide in dimethyl sulfoxide[8] gave a mixture of *cis*- and *trans*-1,2-cyclohexanedinitrile, which were separated by distillation and hydrolyzed to the corresponding acids. Unfortunately, the *trans*-diacid from optically active dibromide was racemic, possibly due to racemization in the reaction mixture after the displacement.

In view of the failure to obtain the relative configurations of diacid and dibromide directly, efforts were next directed toward the assignment of absolute configurations of both substances. The absolute configuration of (+)-*trans*-1,2-cyclohexanedicarboxylate was found to be as shown in formula Ia. This assignment was accomplished by conversion of the diacid Ia ($[\alpha]^{27}_D$ +21.9°) by lithium aluminum hydride reduction[9] to the glycol Ib ($[\alpha]^{27}_D$ −20.2°), formation of the tosylate Ic ($[\alpha]^{28}_D$ +25.0°, m.p. 109–109.7°),[10] conversion of Ic to the dinitrile Id ($[\alpha]^{25}_D$ +64.7°),[11] and hydrolysis to the diacid Ie ($[\alpha]^{27}_D$ +49.4°).[12] Ie had been converted to levorotatory *trans*-hexahydroindan-2-one[13] (IIa), whose absolute configuration was known from the identity of its optical rotatory dispersion curve with that of (−)-*trans*-8-methylhexahydroindan-2-one (IIb), which had been synthesized from compounds of known absolute configuration.[14]

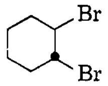


Ia. R = CO_2H
b. R = CH_2OH
c. R = CH_2OTs
d. R = CH_2CN
e. R = CH_2CO_2H



IIa. R = H
b. R = CH_3

The absolute configuration of (−)-1,2-dibromocyclohexane was assigned by comparison of its optical rotatory dispersion curve in cyclohexane with those of suitable dibromocholestanes. It was found that whereas cholestane gave a plain positive dispersion of moderate slope ($[\Phi]_{650}$ +81.4°, $[\Phi]_{300}$ +517°), both (−)-1,2-dibromocyclohexane and 2α,3β-dibromocholestane (diequatorial) gave plain negative dispersions of steeper slopes ($[\Phi]_{650}$ −28.3°, $[\Phi]_{300}$ −306° for the former, and $[\Phi]_{650}$ −118°, $[\Phi]_{300}$ −1390° for the latter). These facts by themselves suggest the configuration shown in formula III for (−)-1,2-dibromocyclohexane. In further confirmation of this assignment, the dispersion of 1α,2β-dibromocholestane (diaxial) was found to be a plain positive curve of moderate slope ($[\Phi]_{650}$ +166°, $[\Phi]_{300}$ +760°), suggesting that the fraction of III in the diaxial conformation would not have a rotation such as to reverse the assignment, a conclusion which is further confirmed by experiments described below. One unexpected observation was that 2β,3α-dibromocholestane (diaxial, opposite configuration from III) gave a plain positive dispersion ($[\Phi]_{650}$ +314°, $[\Phi]_{300}$ + 2840°) with much larger rotations and a steeper slope than either cholestane or the 1α,2β derivative, suggesting that diaxial bromines can under some conditions contribute to the rotation. The direction of that contribution in this case is, however, still in agreement with the configuration III for (−)-*trans*-1,2-dibromocyclohexane, whose rotation would then be the sum of negative contributions from both diaxial and diequatorial conformations.



III

Of particular significance is the fact that the dispersion curve of 2α,3β-dibromocholestane (diequatorial) from 300 mμ to 650 mμ is very nearly the sum of the curves for cholestane and III, provided that a weighting factor be applied to the latter curve. The weighting factor should be directly related to the optical purity of III and to the conformational equilibrium of III. Thus, a sample of III whose neat specific rotation was −21.4° was employed (next paragraph) to determine the specific rotation of the diequatorial conformer to be −41.2°. A sample whose neat rotation at 27.5° was −25.1° had a specific rotation in 2% cyclohexane solution at 27.5° of −24.4°. Since the rotatory dispersion curves were run under nearly the latter conditions (1% solutions of the neat −21.4° material in cyclohexane at 31°), molecular rotations of III at the seven wave lengths shown in the Experimental were multiplied by (41.2)(25.1)/(24.4)(21.4) = 1.98 to obtain molecular rotations of the diequatorial form. The resulting numbers were equal to 0.302 times the

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[5] F. Hofmann and P. Damm, *Mitt. schles. Kohlenforschungsinst.*, **2**, 97 (1925); *Chem. Zentr.*, **I**, 2342 (1926).

[6] H. B. Hass and J. R. Marshall, *Ind. Eng. Chem.*, **23**, 352 (1931).

[7] P. J. C. Fierens and P. Verschelden, *Bull. soc. chim. Belges*, **61**, 427 (1952).

[8] R. A. Smiley and C. Arnold, *J Org. Chem.*, **25**, 257 (1960).

[9] D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **72**, 5743 (1950).

[10] G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953), had previously prepared the enantiomeric ditosylate, $[\alpha]^{21.5}_D$ −24.8°, m.p. 109–110°.

[11] M. E. Ali and L. N. Owen, *ibid.*, 2111 (1958).

[12] W. Hückel, M. Sachs, J. Yantschulewitsch, and F. Nerdel, *Ann.*, **518**, 155 (1935).

[13] J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 1069 (1935).

[14] (a) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956); (b) P. M. Bourn and W. Klyne, *J. Chem. Soc.*, 2044 (1960).

difference between the molecular rotations of $2\alpha,3\beta$-dibromocholestane and cholestane at each wave length, with an average deviation of 6.2% and a maximum deviation of 9.6%. Such additivity of the curves could be expected only if the diaxial form has very little rotation or if its rotation is directly proportional to that of the diequatorial form as wave length is varied. The optical purity of the sample of III was then approximately 30%, and the maximum optical purity obtained from a Hunsdiecker reaction (Table I) was about 38%. Similar additivity of the dispersion curves was not observed for the other two dibromocholestanes, but this is perhaps not surprising in view of the possibilities for general distortion of the carbon skeleton by 1,3-diaxial interactions in these cases. The optical purities obtained by this procedure are unlikely to have more than qualitative significance, even when additivity is observed.

The conformational equilibrium of *trans*-1,2-dibromocyclohexane in solution has been studied with dipole moment measurements by Kwestroo, Meijer, and Havinga,[15] who found the substance to be 68% diaxial in carbon tetrachloride at 30° and 52% diaxial in benzene at 30°. From our observed rotations of one sample of III ($[\alpha]^{30}\mathrm{D}$ $-21.0°$ in CCl_4) in these solvents, one can calculate the specific rotations of the two conformers (assuming these rotations to be solvent independent) as $[\alpha]^{30}\mathrm{D}$, axial $-11.5°$, and $[\alpha]^{30}\mathrm{D}$, equatorial $-41.2°$. These observations and those on the dibromocholestanes (except the $2\beta,3\alpha$ derivative) are in qualitative agreement with the empirical theory of Brewster,[16] which predicts the conformations Ia for the (+)-diacid and III for the (−)-dibromide, though the simple theory predicts no rotation for the diaxial conformer in the latter case.

Taken together, the foregoing evidence appears to provide sufficient basis for the assignment of III for the configuration of the Hunsdiecker product, which means that the reaction proceeds with net inversion of configuration.

Mechanistic Conclusions.—A considerable body of evidence may now be cited[17] in support of a mechanism for the simple Hunsdiecker reaction which consists of a free-radical chain decomposition of an intermediate acyl hypobromite. The following are probable propagation steps:

$$RCO_2\cdot \longrightarrow R\cdot + CO_2 \qquad (1)$$

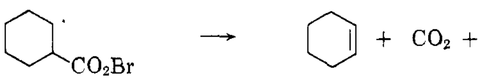
$$R\cdot + RCO_2Br \longrightarrow RBr + RCO_2\cdot \qquad (2)$$

In the presence of excess bromine, the following steps probably are also involved:

$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot \qquad (3)$$

$$Br\cdot + RCO_2Br \longrightarrow RCO_2\cdot + Br_2 \qquad (4)$$

The particular interest of the vicinal dicarboxylate system is that it could shed light upon the interactions of the neighboring functional groups and radicals involved in the mechanism, thereby confirming the mechanism shown above and/or revealing new properties of these functional groups and radicals. Several possible neighboring group involvements are shown in equations 5–8.



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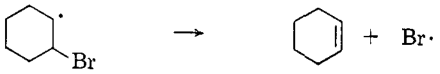

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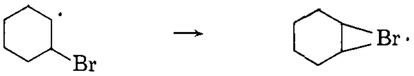

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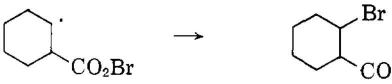

(8)

In order to accommodate the data of Table I and the controls described above, it is necessary to have a mechanistic scheme which includes an inversion pathway and either a retention pathway or a pathway leading to racemic product. In Chart I is presented a scheme of possibilities based upon reactions 1–8 and assuming (for the immediate discussion only) that the bishypobromite IV is an intermediate in all pathways. Decomposition of IV by reactions 9, 13, and 14, involving an intramolecular bromine atom transfer of type 8, appears to be the most reasonable mechanism for formation of inverted product III. Reactions 9–12, with steric control of entering bromine in steps 10 and 12, represent the classical Hunsdiecker mechanism (reactions 1–4) without specific neighboring group involvements, and could be expected to lead to dextrorotatory dibromide. It is felt that this pathway makes little if any contribution, since reaction 10 should be favored over 13 by increased bromine concentration, whereas a three-fold increase in initial bromine concentration (resulting in a larger ratio as the reaction proceeds) did not decrease the optical activity of the product (Table I). Furthermore, it will be noted that whereas under some conditions the activity of the product became almost nil, it always remained negative. The evidence then suggests most strongly that there is a racemate-producing mechanism in competition with 9, 13, and 14.

The most likely racemate-producing mechanisms are those which involve a cyclohexene intermediate (which would add bromine ionically under the reaction conditions) and those which involve a bridged-bromine radical, V, as an intermediate or as a transition state for racemization of the 2-bromocyclohexyl radical (VI). A strong argument against the participation of V is that its formation from VI in competition with reaction 14 would be favored by low bromine concentration, so that the failure of a threefold increase in bromine concentration to change the optical activity of product (Table I) argues against reaction 15 in the same way that it argues against 10. This result is a little surprising in view of recent demonstrations of rapid 1,2 shifts of bromine atoms and/or bridged bromine radicals by Skell, Allen, and Gilmour[18] and by Abell and Piette.[19] Particularly pertinent is the latter work, which showed by an elegant e.p.r. method that the radical from addition of bromine atom to cyclohexene in a glass at 77° K. is either the bridged

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[15] W. Kwestroo, F. A. Meijer, and E. Havinga, *Rec. trav. chim.*, **73**, 717 (1954).

[16] J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475, 5483 (1959).

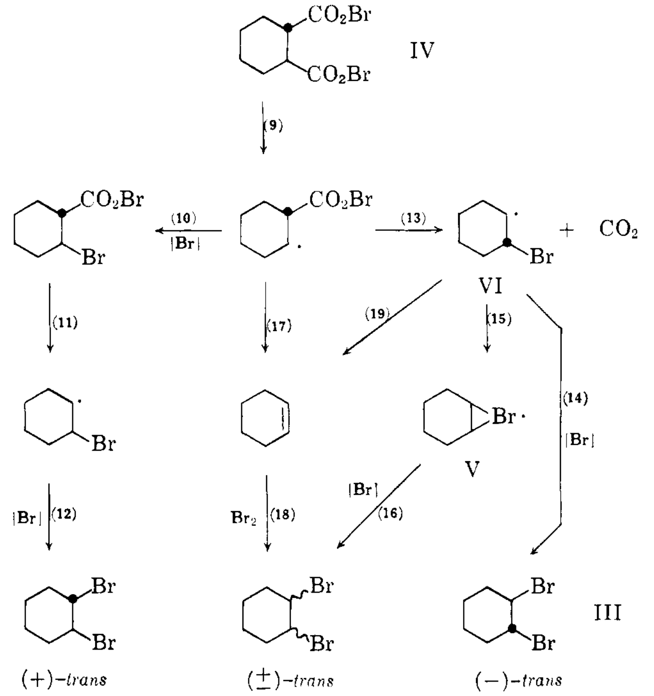
[17] C. V. Wilson, *Org. Reactions*, **IX**, 332 (1957).

[18] P. S. Skell, R. G. Allen, and N. D. Gilmour, *J. Am. Chem. Soc.*, **83**, 504 (1961).

[19] P. I. Abell and L. H. Piette, *ibid.*, **84**, 916 (1962).

CHART I

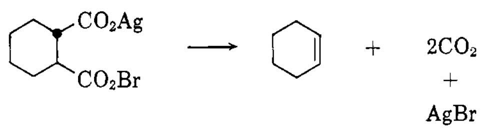
HOMOGENEOUS FREE-RADICAL MECHANISMS



radical V or a classical 2-bromocyclohexyl radical (VI) which is racemizing by bromine migration at a rate of at least 10^7 sec.$^{-1}$ The present results certainly argue in favor of the oscillating classical structure rather than the bridged structure, a distinction which the e.p.r. studies could not make. The failure of radical VI to racemize in the present work is not inconsistent with the e.p.r. studies, since if one assumes a normal bimolecular frequency factor[20] (10^{11}) for reaction of VI with bromine (or acyl hypobromite) and a low activation energy[21] (<3 kcal.) for this process, then the lifetime of VI under the Hunsdiecker conditions would be substantially less than 10^{-7} seconds.

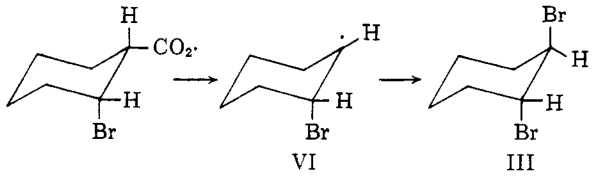
If we grant that V is not responsible for the racemic product, then we are left with paths through cyclohexene as the only obvious racemate-producing mechanisms.[22] Loss of a bromine atom from VI, though a known reaction type,[23] is ruled out in the present work again by the insensitivity of the optical yield to bromine concentration. Reaction 17 might form cyclohexene in a path whose competition with the inversion mechanism (reaction 13) would be independent of bromine concentration.

Left unsettled by the above discussion is the cause of the erratic optical yields (Table I) which while reproducible enough to establish independence of bromine concentration, were nevertheless scattered considerably more than one would expect from a simple competition of reactions 13 and 17, which should lead only to small variations in optical yield, due to slight temperature variations. A possible explanation is the formation of cyclohexene by a heterogeneous reaction, 20, which would be affected by a number of difficultly-controlled variables in experimental conditions. Although the case is good for a homogeneous decomposition of a hypobromite in most Hunsdiecker reactions[17] (the usual lack of stereospecificity and the demonstrations of metastable, silver-free solutions of acyl hypobromites being especially significant evidence), such a homogeneous pathway is not independently supported by the evidence presented here, and since nothing comparable to reaction 20 can be expected in simpler systems, the previous knowledge cannot be used to argue against it.



(20)

Although we have argued that reaction 14 must be responsible for the inverted product and that there is no significant amount of *cis*-dibromide formed, it is not possible to conclude that reaction 14 gives the *trans* product stereospecifically, unless we know the optical yield of the reaction. This was proposed to be as high as 38% by analogy with the observed molecular rotations of cholestane and $2\alpha,3\beta$-dibromocholestane (above). If this number is valid and since the infrared method will detect as little as 5% of the *cis*-dibromide in the *trans* product, then we can conclude that reaction 14 must be at least 85% stereospecific to give *trans* product. Such specificity is comparable with that observed in the reaction of the 1,2-dibromocyclohexyl radical with hydrogen bromide, which has been discussed by others.[24] Of the explanations which have been offered in that case, the only one which appears applicable to reaction 14 is a conformational control,[25] as shown in reaction 21. It is possible that the diaxial arrangement is the preferred transition state for the conversion of VI to III, or that this reaction takes place by preferential axial attack before conformational equilibration of VI (which may have an energy barrier as high as 10 kcal.[26]) takes place.



(21)

Experimental[27]

***trans*-1,2-Cyclohexanedicarboxylic Acid.**[3]—A mixture of 100 g. (0.65 mole) of *cis*-1,2-cyclohexanedicarboxylic anhydride (Matheson, Coleman and Bell), 100 ml. of absolute ethanol, 300 ml. of benzene, and 1 ml. of sulfuric acid was heated under

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[20] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 130.

[21] C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 374.

[22] Exotic possibilities, such as bromine oxidation of VI to a cyclic bromonium ion, may be written and cannot be ruled out with the evidence available, but are not discussed in detail simply because they seem not to have close analogies.

[23] Ref. 21, p. 302.

[24] Ref. 19 and papers cited therein.

[25] H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **77**, 3465 (1955).

[26] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 205.

[27] All melting points and boiling points are uncorrected unless otherwise specified. The infrared spectra were obtained with a Perkin–Elmer Infracord or a Perkin–Elmer spectrophotometer, Model 21B, both with sodium chloride optics. The nuclear magnetic resonance spectra were measured at 60 Mc. on a Varian nuclear magnetic spectrophotometer, Model V-4300 B. The optical rotatory dispersions were determined on a Rudolph recording spectropolarimeter, Model 260/655/850/810-614. Thanks are due to Dr. Max Marsh of the Eli Lilly Co. for assistance in determining the dispersions and for the use of its instrument. Experimental details not given here are to be found in the Ph.D. thesis of N. D. Werner, University of Illinois, 1962.

reflux with continuous removal of the water–benzene–ethanol azeotrope for 10 hr. The solution was then washed with 5% aqueous sodium bicarbonate and water. The solvent was removed under reduced pressure to give 122 g. (79%) of crude diethyl ester, which was added to an ethanolic solution of sodium ethoxide prepared from 5.0 g. (0.22 g.-atom) of sodium and 1.3 l. of absolute ethanol. The solution was heated at reflux overnight. An aqueous solution of 150 g. (2.68 moles) of potassium hydroxide in 1.3 l. of water was added to the cloudy yellow reaction mixture. The reaction mixture was then heated at reflux for 4 hr. The ethanol was distilled while the solution was kept at constant volume by the continuous addition of water. After most of the ethanol had been removed, the solution was filtered to remove solid impurities. The pH of the solution was adjusted to a value of approximately 2 with concentrated hydrochloric acid. The white solid was collected on a filter and washed with ice–water. The solid was dried in an oven (130°) for 3 hr. The yield of the *trans*-diacid was 71 g. (81% based upon ester), m.p. 227–229° (lit.,[3] m.p. 227–229°).

Resolution of (±)-*trans*-1,2-Cyclohexanedicarboxylic Acid.—A solution of 43 g. (0.25 mole) of (±)-*trans*-1,2-cyclohexanedicarboxylic acid in 370 ml. of 95% ethanol was heated to boiling and then added slowly (heat was evolved) to a hot solution of 162 g. (0.50 mole) of quinine in 950 ml. of 95% ethanol. The combined solution was heated to boiling and then filtered. The filter was washed with 195 ml. of hot 95% ethanol. The solution was cooled overnight and the solid was then removed by filtration to give 117 g. (95%) of a white crystalline material. After three more recrystallizations from 95% ethanol, the diastereomer was sufficiently pure to give (+)-*trans*-1,2-cyclohexanedicarboxylic acid with high optical purity. The yield of pure quinine salt was 55 g. (45% based upon isolation of one diastereomer). Fifty grams (0.089 mole) of the quinine salt was added in portions to 500 ml. of a sulfuric acid–water solution (1:4) in an ice bath. The solution was then continuously extracted with ether for 2 days. The ether was removed on a steam bath and 10.3 g. (100%) of (+)-*trans*-1,2-cyclohexanedicarboxylic acid was obtained, m.p. 183.5–185.0° (lit.,[4] m.p. 179–183°); $[\alpha]^{30}$D in acetone +22.3° (c = 5.3) (lit.,[4] $[\alpha]^{20}$D +18.2°).

Silver *trans*-1,2-Cyclohexanedicarboxylate.—A mixture of 20.0 g. (0.116 mole) of *trans*-1,2-cyclohexanedicarboxylic acid in 200 ml. of water was titrated with 1 *M* aqueous sodium hydroxide to a phenolphthalein end point. The solution was filtered. A solution of 40.0 g. (0.235 mole) of reagent grade silver nitrate in 200 ml. of water was added over a 25-min. period to the neutralized solution of the *trans*-diacid. The addition of the silver nitrate solution was carried out in diffuse light and the reaction mixture was stirred continuously during the addition. The white precipitate was collected on a filter and washed with water, ethanol, and ether. The silver salt was dried in a vacuum desiccator over phosphorus pentoxide for several days at room temperature. The yield was 43.6 g. (97.8%).

***trans*-1,2-Dibromocyclohexane** was prepared in the manner described by Snyder and Brooks.[28] The product boiled at 76–78° at 4.5 mm., n^{25}D 1.5483 (lit.,[28] b. p. 99–103° at 16 mm., n^{25}D 1.5510[2]).

Brominative Decarboxylation of Optically Active Silver *trans*-1,2-Cyclohexanedicarboxylate.—To an ice-cooled solution of 8.3 g. (0.052 mole) of bromine (dried over phosphorus pentoxide) in 200 ml. of dry carbon tetrachloride was added over a 1-hr. period 10.0 g. (0.026 mole) of dry optically active silver *trans*-1,2-cyclohexanedicarboxylate. After the addition of silver salt was completed the suspension was stirred for seven more hours at 0°. The solid was then collected on a filter and washed with carbon tetrachloride. The combined carbon tetrachloride solutions were washed with 10% aqueous sodium bisulfite solution, 10% aqueous sodium bicarbonate solution, and water. The carbon tetrachloride solution was dried over anhydrous magnesium sulfate and distilled under reduced pressure to obtain 1.30 g. of colorless distillate and 0.3 g. of a nonvolatile, gummy residue. The distillate was taken up in 10 ml. of hexane (distilled over sodium) and chromatographed on 25 g. of neutral alumina. Hexane was used as an eluent to remove the expected *trans*-1,2-dibromocyclohexane from the column. The hexane was distilled on the steam bath and the residual liquid was distilled through a modified Holzman semimicro column.[29] The distillation yielded 0.90 g. (14%) of a colorless liquid boiling at 53–55° (1.4 mm.). The infrared spectrum of this liquid was identical to that of an authentic sample of *trans*-1,2-dibromocyclohexane, n^{21}D 1.5511 (lit.[2] n^{25}D 1.5510); $[\alpha]^{22}$D (neat) −27.0°. In a similar Hunsdiecker reaction the specific rotations of two consecutive distillation fractions were the same within experimental error of the polarimetric measurement. The distillation residue from one run showed intense infrared absorption at 1740 cm.$^{-1}$ and 1820 cm.$^{-1}$. A sample of the dibromide decomposed in the injection port of a gas chromatograph (at 180–250°), but the pattern of peaks thus produced was identical to that obtained from an authentic sample of *trans*-1,2-dibromocyclohexane.

A very similar procedure was used for reactions at 31.3°, the addition time being 15 min. and the total reaction time being 60 min. (see Table I).

The following analysis was obtained from a sample of (−)-*trans*-1,2-dibromocyclohexane prepared by a Hunsdiecker reaction.

Anal. Calcd. for $C_6H_{10}Br_2$: C, 29.77; H, 4.17. Found: C, 30.09; H, 4.12.

It was shown by iodimetric titration in one run at 0° that after 8.3 hr., only 40% of the theoretical bromine (or hypobromite) had been consumed. It was further found that a 38% yield of recovered diacid, with undiminished optical rotation, could be isolated from such a reaction mixture by ether extraction of the acidified aqueous washings.

Silver Acetate.—The preparation was carried out in diffuse light. A solution of 15.0 g. (0.183 mole) of reagent grade sodium acetate in 50 ml. of water was prepared. A solution of 31.0 g. (0.183 mole) of reagent grade silver nitrate in 50 ml. of water was added dropwise to the aqueous sodium acetate solution. The white precipitate was collected on a filter, washed with water, ethanol, and reagent grade ether. The silver acetate was dried in a vacuum desiccator over phosphorus pentoxide for several days at room temperature. The yield was 22.0 g. (72%).

Stability of (−)-*trans*-1,2-Dibromocyclohexane.—In an apparatus similar to that used for the above Hunsdiecker reactions, 7.8 g. (0.047 mole) of silver acetate was added over a period of 1 hr. to an ice-cooled solution of 11.2 g. (0.070 mole) of bromine (dried over phosphorus pentoxide) and 0.63 g. (0.0026 mole) of (−)-*trans*-1,2-dibromocyclohexane ($[\alpha]^{22}$D (neat) −27.0°) in 200 ml. of dry carbon tetrachloride. The reaction mixture was stirred for an additional 7 hr., and then treated in the same manner as described for the Hunsdiecker reactions above. The yield of recovered *trans*-1,2-dibromocyclohexane was 0.35 g., n^{22}D 1.5524, $[\alpha]^{22}$D (neat) −24.8°, corresponding to 8.1% racemization. The infrared spectrum was identical with that of an authentic sample.

When the same experiment was performed at 31.3° (1 hr.) instead of 0°, a sample of dibromide with $[\alpha]^{26}$D −6.12° gave recovered dibromide with $[\alpha]^{26}$D −3.55° (42% racemized).

When a similar experiment was done at 31.3° (1 hr.) but without any silver acetate present, the dibromide was recovered in 82% yield with undiminished rotation.

Stability of (±)-*trans*-1,2-Dibromocyclohexane.—To 6.3 g. (0.039 mole) of (±)-*trans*-1,2-dibromocyclohexane in 200 ml. of dry carbon tetrachloride at 0° was added 5.0 g. (0.013 mole) of optically active silver *trans*-1,2-cyclohexanedicarboxylate in portions. The mixture was stirred for 8 hr. at 0° and the silver salt then collected on a filter and washed with carbon tetrachloride. The carbon tetrachloride was distilled under reduced pressure and distillation of the residual liquid through a modified Holzman semimicro column gave 5.9 g. (94%) of *trans*-1,2-dibromocyclohexane boiling at 50–52° (1.0 mm.), n^{26}D 1.5489. The infrared spectrum was identical to that of an authentic sample. The recovered *trans*-1,2-dibromocyclohexane exhibited no optical rotation within experimental error.

A similar experiment conducted at 31.3° for 1 hr. gave the same result.

Stability of *cis*-1,2-Dibromocyclohexane under Conditions of the Hunsdiecker Reaction.—*cis*-1,2-Dibromocyclohexane was prepared according to a published procedure.[30] The material obtained boiled at 54–56° (0.3 mm.), $n^{28.5}$D 1.5490 (lit.,[30b] n^{25}D 1.5509).

In an apparatus similar to that used for the Hunsdiecker reactions, immersed in a constant temperature bath at 31.3°, was placed a solution of 5.5 g. (0.034 mole) of bromine (dried

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over phosphorus pentoxide) in 127 ml. of dry carbon tetrachloride. The solution was stirred for 0.5 hr. and then 1.0 g. (0.0041 mole) of *cis*-1,2-dibromocyclohexane was added over a 15-min. period. The reaction mixture was stirred for an additional 45 min. The silver bromide was collected on a filter and washed with carbon tetrachloride. The carbon tetrachloride solution was washed with 10% aqueous sodium bisulfite, 10% aqueous sodium bicarbonate, and water. The carbon tetrachloride solution was dried over sodium sulfate and distilled at reduced pressure. Distillation of the residual liquid through a modified Holzman semimicro column gave 0.92 g. of a colorless liquid, b.p. 50–60° (1.6 mm.); n^{25}D 1.5635. A bromine analysis indicated that this liquid contained 69.75% bromine. A comparison of the infrared spectrum of this liquid with those of authentic *cis*-1,2-dibromocyclohexane and authentic *trans*-1,2-dibromocyclohexane showed that the spectrum of the liquid contained all the absorption maxima characteristic of the *cis*-dibromide, but none that could be ascribed definitely to the *trans*-dibromide. It was estimated that the liquid contained not more than 5% of the *trans*-dibromide, if any at all.

The Reaction of Optically Active *trans*-1,2-Dibromocyclohexane and Sodium Cyanide in Dimethyl Sulfoxide.—To a mixture of 2.4 g. (0.049 mole) of sodium cyanide (vacuum dried) and 40 ml. of dimethyl sulfoxide (passed through a column of molecular sieves, Linde Co., Type 4A, and then distilled) was added dropwise 5.0 g. (0.022 mole) of (−)-*trans*-1,2-dibromocyclohexane ($[\alpha]^{23.5}$D neat −11.0°). The reaction mixture was heated at 85° for 10.5 hr., then poured into a saturated aqueous sodium chloride solution, and this mixture was extracted with four portions of chloroform. The chloroform solution was dried over sodium sulfate, the chloroform was removed under reduced pressure, and the residue was taken up in ether except for a small amount of brown solid which did not dissolve. The ether was removed on a steam bath and the residual liquid was distilled to give 0.96 g. of material, b.p. 105–110° (0.4 mm.). A portion of this material (0.84 g.) was chromatographed on neutral alumina, and elution with 30% benzene–hexane gave a fraction, which after evaporation of the solvent contained 0.36 g. of solid. Further elution with 30% benzene–hexane gave two more fractions which contained 0.21 g. and 0.10 g. of material, respectively. The first fraction was recrystallized from low boiling petroleum ether to give 0.21 g. of dinitrile, m.p. 47–48.5° (cor.). An infrared spectrum had an absorption maximum at 2240 cm.$^{-1}$. A 30% solution of this material in benzene exhibited no optical activity within experimental error. A suspension of 97 mg. (0.00074 mole) and 4 ml. of 2 *N* nitric acid was heated at reflux for 24 hr. After the solution had cooled, 95 mg. (76%) of *trans*-1,2-cyclohexanedicarboxylic acid precipitated, m.p. 227.9–228.7° (cor.) (lit.,[31] m.p. 227–229°). An optical rotatory dispersion curve obtained on a 2% solution in absolute ethanol indicated that the diacid possessed no optical activity within experimental error.

A reaction run in the same way on 5 g. of optically inactive dibromide was examined more carefully, and was found to yield 0.16 g. of *cis*-1,2-cyclohexanedinitrile, m.p. 62–64° (lit.,[32] m.p. 63–65°), hydrolyzable with 2 *N* nitric acid to *cis*-diacid (compared with an authentic sample) and 0.68 g. of a more volatile, lower melting, impure *trans*-dinitrile, which was hydrolyzable to nearly pure *trans*-diacid.

Reaction of Ammonia with *trans*-1,2-Dibromocyclohexane.—A solution of 3 g. (0.18 mole) of anhydrous ammonia and 7.5 g. (0.031 mole) of *trans*-1,2-dibromocyclohexane in 50 ml. of dry *t*-butyl alcohol was heated in a sealed tube for 64 hr. at 91–112°. The *t*-butyl alcohol was distilled through a packed 12-in. Vigreux column and the residual liquid was then taken up in 2 *N* hydrochloric acid and extracted with ether. The acidic aqueous solution was then made basic (pH >11) with sodium hydroxide and continuously extracted with ether for 1 week. An Ascarite drying tube protected the extraction system from carbon dioxide in the atmosphere. The ether was distilled through a packed 12-in. Vigreux column and the residual liquid was distilled through a modified Holzman semimicro column. Two colorless liquid fractions were obtained. The first fraction weighed 0.98 g., b.p. 50° (2 mm.), and the second fraction weighed 0.23 g. Vapor phase chromatography indicated that the first fraction was a pure compound while the second fraction consisted mainly (>95%) of the compound present in the first fraction. This compound, which was obtained in 40% yield, was 3-aminocyclohexene as characterized by the formation of the 2,4-dinitrophenyl derivative, which was prepared in the usual manner,[33] m.p. 107–108°.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.84; H, 4.88; N, 16.14.

A similar displacement was attempted with sodium azide in dimethyl sulfoxide solvent at 85° for 7.5 hr. The resulting organic azide was reduced without careful purification by lithium aluminum hydride in ether to obtain a small yield of amine which yielded the same 2,4-dinitrophenyl derivative, m.p. 107.5–108.5°, though satisfactory elemental analyses could not be obtained in this case.

Anal. Found: C, 55 29; H, 4.90; N, 16.59.

(−)-*trans*-1,2-Bis(hydroxymethyl)cyclohexane.—A solution of 10.0 g. (0.058 mole) of (+)-*trans*-1,2-cyclohexanedicarboxylic acid ($[\alpha]^{27}$D +21.9°) in 220 ml. of dry ether was added to a stirred refluxing suspension of 8.8 g. (0.23 mole) of lithium aluminum hydride in 300 ml. of ether at such a rate as to maintain gentle reflux. After the addition was completed the reaction mixture was heated at reflux for 8 hr. The excess lithium aluminum hydride was then decomposed with 8.8 ml. of water (carefully), 8.8 ml. of aqueous 15% sodium hydroxide solution, and 25.4 ml. of water. The suspension was stirred for 25 min. and the solid was collected on a filter and washed with ether. The ether was evaporated on a steam bath and a clear, slightly yellow oil was obtained which crystallized slowly. The white solid was dissolved in benzene and hexane was added until the solution became slightly cloudy. The solution was placed in a −20° freezer overnight and the solid was collected on a filter and washed with hexane–benzene. The solid was air dried and 6.9 g. (82%) of (−)-*trans*-1,2-bis(hydroxymethyl)cyclohexane was obtained, m.p. 63–64°; $[\alpha]^{24}$D (in benzene) −20.2° (c = 4.0) [lit.,[10] m.p. 61–62°; $[\alpha]^{24}$D +21.4° (enantiomer)].

(+)-*trans*-1,2-Bis(hydroxymethyl)cyclohexane Di-*p*-toluenesulfonate.—The ditosylate was prepared in a manner similar to that described by Ali and Owen.[11] Six grams (0.039 mole) of (−)-*trans*-1,2-bis(hydroxymethyl)cyclohexane in 21.8 ml. of dry pyridine was added dropwise over 30 min. to a vigorously stirred solution of 18.0 g. (0.094 mole) of *p*-toluenesulfonyl chloride in 38 ml. of dry pyridine in an ice bath. The reaction mixture was then stirred at room temperature for 0.5 hr. and poured into an ice–water mixture. A viscous oil formed which soon crystallized. The solid was collected on a filter, washed with ice–water, and recrystallized from methanol to give 11.1 g. (65%) of the ditosylate, m.p. 109–109.7°; $[\alpha]^{28}$D (in benzene) (+25.0° (c = 5.0) [lit.,[10] m.p. 109–110°; $[\alpha]^{21.5}$D −24.8° (enantiomer)].

(+)-*trans*-1,2-Cyclohexanediacetonitrile was prepared in a manner similar to that described by Ali and Owen[11] for the racemic dinitrile. To a mixture of 4.6 g. (0.071 mole) of reagent grade potassium cyanide and 73 ml. of 90% ethanol was added 11.0 g. (0.0243 mole) of (+)-*trans*-1,2-bis(hydroxymethyl)-cyclohexanedi-*p*-toluenesulfonate. The mixture was heated to boiling and a clear solution was obtained. This solution was heated at reflux for 67 hr. and then concentrated at reduced pressure. The residue was taken up in saturated aqueous sodium chloride solution and extracted four times with ether. The ether solution was washed twice with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The ether was removed on a steam bath and a viscous oil which crystallized slowly was obtained. A recrystallization from benzene–hexane gave 1.8 g. of a yellow crystalline solid, m.p. 57–63°. A small amount of this solid was sublimed at 54° (0.2 mm.) to give a white solid, m.p. 62–63° (cor.) which was analyzed.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.30; H, 8.77; N, 16.94.

The benzene–hexane mother liquor was evaporated to dryness and the solid was recrystallized from ether to give 0.49 g. of a white solid, m.p. 62–63°; $[\alpha]^{25}$D (in benzene) +64.7° (c=5.0). The total yield of (+)-*trans*-1,2-cyclohexanediacetonitrile was 58% of theoretical.

(+)-*trans*-1,2-Cyclohexanediacetic Acid.—The procedure used was similar to that described by Ali and Owen[11] for the preparation of the racemic diacid. A solution of 1.7 g. (0.011 mole)

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of (+)-*trans*-1,2-cyclohexanediacetonitrile and 30 ml. of 50% aqueous sulfuric acid solution was heated at reflux for 4 hr. When the solution cooled, solid precipitated and was collected on a funnel and washed with cold water. The solid was recrystallized from methanol to give 1.28 g. (61%) of (+)-*trans*-1,2-cyclohexanediacetic acid, m.p. 149–150°; $[\alpha]^{27}\mathrm{D}$ (absolute ethanol) +49.4° ($c = 5.0$) (lit.,[12,13] m.p. 152°; $[\alpha]^{19.5}\mathrm{D}$ +48.28°).

Measurement of the Dependence of the Optical Activity of *trans*-1,2-Dibromocyclohexane on Solvent.—The measurements were made in a 1-dm. polarimeter tube which was maintained at 30.0°. The measurements were made on solutions which were prepared in the following manner: Approximately 0.2 g. of (−)-*trans*-1,2-dibromocyclohexane (weighed to four significant figures) was placed in a 2-ml. volumetric flask and diluted to the mark with the appropriate solvent. The values listed for benzene and carbon tetrachloride solutions are the results of duplicate determinations, while those listed for dioxane and absolute ethanol solutions are the results of single determinations. The benzene used was reagent grade benzene which had been distilled from sodium and the dioxane was purified by the method of Hess and Frahm.[34] The carbon tetrachloride and the absolute ethanol used were reagent grade solvents which were not purified further. The values obtained for the specific rotations in various solvents are listed in Table II.

TABLE II

SPECIFIC ROTATION OF *trans*-1,2-DIBROMOCYCLOHEXANE IN VARIOUS SOLVENTS AT 30.0°

Solvent	$[\alpha]^{30.0}\mathrm{D}$
Benzene	−25.8°
Dioxane	−23.7
Absolute ethanol	−22.5
Carbon tetrachloride	−21.0

2-Bromocholestan-3-one was prepared from cholestanone[35] (m.p. 129.0–129.6°) by a modification of the procedure of Butenandt and Wolff.[36] Six drops of a 40% aqueous hydrogen bromide solution were added to a solution of 12.0 g. (0.031 mole) of cholestanone in 360 ml. of glacial acetic acid. A solution of 5.4 g. (0.034 mole) of bromine in 12 ml. of glacial acetic acid was added in a dropwise manner to this solution and the total solution concentrated under reduced pressure. The solid residue was recrystallized from ethanol–acetone to give 10.0 g. (69%) of 2-bromocholestan-3-one, m.p. 167–169° (lit.,[36] m.p. 169–170°).

2β,3α-Dibromocholestane was prepared from 2-bromocholestan-3-one by the method of Alt and Barton[37] in 18% over-all yield, m.p. 123.7–124.7° (lit.,[37] m.p. 123–124°). The n.m.r. spectrum had broad, overlapping low-field signals at about 274 and 283 c.p.s. from tetramethylsilane.

2α,3β-Dibromocholestane was prepared by thermal isomerization[37] of the 2β,3α isomer at 180–190°, m.p. 145–146° (lit.,[37] m.p. 144–145°). The n.m.r. spectrum had broad overlapping low-field signals at about 239 and 248 c.p.s. from tetramethylsilane.

Cholestane.—A suspension of 300 mg. (0.0008 mole) of Δ^2-cholestene dissolved in 70 ml. of reagent grade ethyl acetate and 82 mg. of platinum oxide catalyst was subjected to a hydrogen atmosphere of 35 lbs./sq. in. on a Parr shaker for 73 hr. at room temperature. The catalyst was collected on a filter and the solvent was removed under reduced pressure. The residue was chromatographed on neutral alumina and eluted with hexane. The hexane was distilled and the solid residue was recrystallized from ether–ethanol to give 212 mg. (70%) of cholestane, m.p. 79.5–80.5° (lit.,[38] m.p. 79.5–80°).

Δ^1-Cholestene.—2-Bromocholestan-3-one was converted to Δ^1-cholestenone semicarbazone by the method of Djerassi,[39] and the semicarbazone was converted to the ketone by the method of Hershberg.[40] The ketone was in turn reduced to Δ^1-cholesten-3-ol by the method of Bergmann, Kita, and Giancola,[41] and the alcohol converted to Δ^1-cholestene as described by Henbest and Wilson.[42] The over-all yield from 2-bromocholestan-3-one was 13%, m.p. 66–67° (lit.,[42] m.p. 69°).

1α,2β-Dibromocholestane was prepared by bromination of Δ^1-cholestene both by the method of Henbest and Wilson[42] (36% yield, m.p. 133–134°) and by the method of Grob and Winstein[43] (30% yield, m.p. 130–131°, no depression of mixed melting point with the former sample). The n.m.r. spectrum showed broad but clearly separated signals at 273 and 293 c.p.s. from tetramethylsilane.

Attempts to isomerize the 1α,2β-dibromide to the 1β,2α isomer by heating it to 180–190° for 7 hr. or by treatment with anhydrous zinc bromide in refluxing cyclohexane gave no isolable isomerization product, but only recovered starting material (35% and 64% yields, respectively).

Optical Rotatory Dispersion Studies.—The measurements were carried out with a Rudolph recording spectropolarimeter, and a 1-dm. polarimeter tube with quartz end plates was used for all determinations. A scanning speed of 25 min. was used except for the solvent blank, when a scanning speed of 12.5 min. was used. Duplicate determinations were made in all cases except for *trans*-1,2-dibromocyclohexane. Eastman spectro grade cyclohexane was the solvent used in all determinations and the concentrations of all solutions were approximately 1%. The determinations were carried out at a temperature range between 30 and 31°. The values listed are molecular rotations, $[\Phi]$:

Cholestane; plain positive curve (650 mμ) +81.4; (600) +95.5; (589) +103; (500) +149; (400) +248; (350) +346; (300) +517.

2β,3α-Dibromocholestane; plain positive curve (650 mμ) +314; (600) +380; (589) +401; (500) +624; (400) $+1.10 \times 10^3$; (350) $+1.64 \times 10^3$; (300) $+2.84 \times 10^3$.

2α,3β-Dibromocholestane; plain negative curve (650 mμ) −118; (600) −138; (589) −143; (500) −246; (400) −458; (350) −749; (300) -1.39×10^3.

1α,2β-Dibromocholestane; plain positive curve (650 mμ) +166; (600) +198; (589) +206; (500) +306; (400) +477; (350) +621; (300) +760.

(−)-*trans*-1,2-Dibromocyclohexane; plain negative curve (650 mμ) −28.3; (600) −32.8; (589) −35.0; (500) −61.3; (400) −118; (350) −176; (300) −306.

The sample of (−)-*trans*-1,2-dibromocyclohexane used had a neat rotation (polarimeter) $[\alpha]^{26.5}\mathrm{D}$ −21.4°. Another sample whose neat rotation was $[\alpha]^{27.5}\mathrm{D}$ −25.1° gave a specific rotation $[\alpha]^{26.5}\mathrm{D}$ −24.4° as a 2% solution in cyclohexane.[44]

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