infrared analysis, based on the intensity of the N–H band at 2.9 μ.

Irradiation of N-Methyl-N-vinylbenzenesulfonamide.—Crystalline N-methyl-N-vinylbenzenesulfonamide (40 g.) was placed in a crystallizing dish 117 cm.^{2} in cross section. The dish was covered with 0.25 mil. Mylar polyester film and set in an ice-bath. It was passed through a beam of 2-Mev. electrons 60 times, the incident irradiation amounting to about 11 watt-sec./cm.^{2}/pass. The total absorbed dose amounted to 7.7×10^4 watt-sec. The product, a mixture of gum and crystals, was crystallized from 40 ml. of ethyl acetate to give 15.8 g. (40% conversion, $G = 24$) of N-methyl-2-phenylsulfonylvinylamine (m.p. 130–131°).

Irradiation of *cis*- and *trans*-N-Methyl-N-β-styryl-*p*-toluenesulfonamide.—Thin samples of each isomer were exposed to 440 watt-sec./cm.^{2} of 2-Mev. electrons. There was no evidence of isomerization to a sulfonylvinylamine in either case, the infrared spectra of the irradiated samples showing no absorption band in the N–H region. However, the irradiation isomerized about 20% of the low-melting isomer to the high-melting isomer, which was isolated by fractional crystallization.

Irradiation of N-Butyl-N-vinyl-*p*-toluenesulfonamide.—A sample of N-butyl-N-vinyl-*p*-toluenesulfonamide (1.0 g.) was placed in a Beckman cup 3.14 cm.^{2} in cross section. The cup was set in an aluminum dish that was covered with 0.25 mil Mylar film and swept out with nitrogen. The dish was placed in an ice-bath and exposed to 660 watt-sec./cm.^{2} of 2-Mev. electrons. The product, a brown viscous oil, was taken up in ethyl acetate. It did not crystallize on standing in the cold for several days. Attempts to isolate the product by vacuum distillation or sublimation were unsuccessful due to its instability at high temperatures. Infrared and ultraviolet spectra of the crude product indicated the presence of N-butyl-2-*p*-tolylsulfonylvinylamine. Alkaline hydrolysis showed that the product contained about 70% of the vinylamine. A sample of the crude reaction mixture (0.2 g.) was dissolved in 10 ml. of ethyl alcohol with 2,4-dinitrophenylhydrazine (0.16 g.). The solution was heated to reflux, 0.2 ml. of hydrochloric acid was added and refluxing continued for 3–4 minutes. The orange-red dinitrophenylhydrazine, which separated on cooling, was filtered off, dried and recrystallized from 20 ml. of benzene. The product (0.16 g., 55% yield) melted at 182–184°. A mixture with an authentic sample of *p*-tolylsulfonylacetaldehyde 2,4-dinitrophenylhydrazone (m.p. 183–185°) melted at 182–184°.

Anal. Calcd. for $C_{15}H_{14}N_4O_6S$: C, 47.62; H, 3.73; N, 14.81. Found: C, 47.80; H, 3.70; N, 14.34.

On standing in air, the crude reaction mixture slowly crystallized. Recrystallization from ethyl acetate gave a white crystalline product (m.p. 190.5°–191°) which was found to be N-[2,4-bis-(*p*-tolylsulfonyl)-1-butadienyl]-*n*-butylamine (VI), λ_{max}^{EtOH} 226 (ϵ 22,500), 325 mμ (ϵ 27,000).

Anal. Calcd. for $C_{22}H_{27}NO_4S_2$: C, 60.96; H, 6.28; N, 3.23; S, 14.77. Found: C, 61.01; H, 6.40; N, 3.42; S, 15.30.

Azo-initiated Isomerization of N-Methyl-N-vinyl-*p*-toluenesulfonamide.—A solution of 50 mg. of α,α'-azodiisobutyronitrile in 1.00 g. of N-methyl-N-vinyl-*p*-toluenesulfonamide was heated for 3 hours in an oil-bath at 90°. Crystallization of the reaction mixture from 1.5 ml. of ethyl acetate gave 0.50 g. (50% yield) of N-methyl-2-*p*-tolylsulfonylvinylamine (m.p. 122–123°). In like manner the other sulfonamides studied (Table III) all underwent azo-catalyzed isomerization. Yields were in the range 30–70%.

WILMINGTON 98, DEL.

[CONTRIBUTION FROM THE BIOCHEMISTRY DEPARTMENT, UNIVERSITY OF PITTSBURGH, SCHOOL OF MEDICINE]

A Synthesis of Cyclopropane-*cis*-1,2-diacetic Acid[1–3]

BY KLAUS HOFMANN, SALVADOR F. OROCHENA, SYLVAN M. SAX AND (IN PART) GEORGE A. JEFFREY

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A synthesis of cyclopropane-*cis*-1,2-diacetic acid of unequivocal stereostructure is described. Cyclohexa-1,4-diene was treated with dibromocarbene to give 7,7-dibromonorcar-3-ene which was oxidized to 3,3-dibromocyclopropane-*cis*-1,2-diacetic acid. The replacement of the bromine atoms by hydrogens was effected by hydrogenolysis over Raney nickel in methanolic potassium hydroxide. The reaction between cyclohexa-1,4-diene and methyl diazoacetate was shown to afford a mixture composed of at least three compounds, namely, a methyl norcarene-7-carboxylate, a methyl cycloheptadienecarboxylate and a doubly unsaturated derivative of methyl cyclohexaneacetate. Single crystal data for 7,7-dibromonorcar-3-ene for cyclopropane-*cis*-1,2-diacetic acid and some related cyclopropane derivatives are presented.

The results of chemical, physical and microbiological studies[3–5] left little doubt regarding the *cis* configuration of the cyclopropane fatty acids, lactobacillic and dihydrosterculic acids, but final proof for the assigned structures will depend on a comparison of these natural materials with synthetic specimens of unequivocal constitution. Procedures for the preparation of cyclopropane fatty acids of established *trans* configuration have been recorded,[4] but routes to the corresponding *cis* isomers remained to be developed. The present investigation was undertaken with the aim of devising such procedures.

Our studies of long-chain cyclopropane fatty acids have shown that *cis–trans* isomers in this series differ little in the very physical properties which are useful for purification purposes. Thus, in order to have assurance regarding stereochemical homogeneity of the final products, methods of synthesis had to be devised which precluded the presence of mixtures of stereoisomers in the final products. Taking into account this reasoning, it seemed desirable to prepare an intermediate of unquestionable *cis* configuration which could be converted into long-chain *cis*-cyclopropane fatty acids without the risk of *cis–trans* inversion during the process. Cyclopropane-*cis*-1,2-diacetic acid (I) seemed ideally suited for this purpose since methods are available for its conversion into acids of the general structure II, and since the separation of the carboxyl groups from the centers of asymmetry could be expected to eliminate the possibility of *cis–trans* inversions during these transformations.

(1) This study is dedicated to the memory of my former collaborator, Salvador F. Orochena, who died unexpectedly on January 23, 1958. K. H.

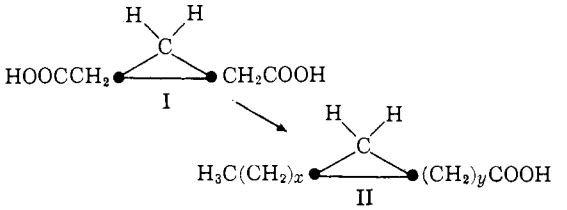
(2) Supported by Grants from the American Cancer Society, upon recommendation of the Committee on Growth of the National Research Council, and by the U. S. Public Health Service.

(3) A preliminary communication describing some of the results of this investigation has appeared in THIS JOURNAL, **79**, 3608 (1957).

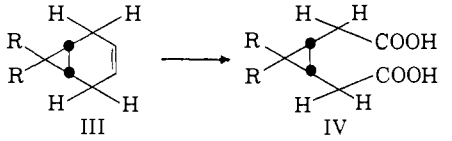
(4) K. Hofmann, O. Jucker, W. R. Miller, A. C. Young, Jr., and F. Tausig, *ibid.*, **76**, 1799 (1954).

(5) T. Brotherton and G. A. Jeffrey, *ibid.*, **79**, 5132 (1957).

Thus, we developed a route to cyclopropane-*cis*-1,2-diacetic acid.



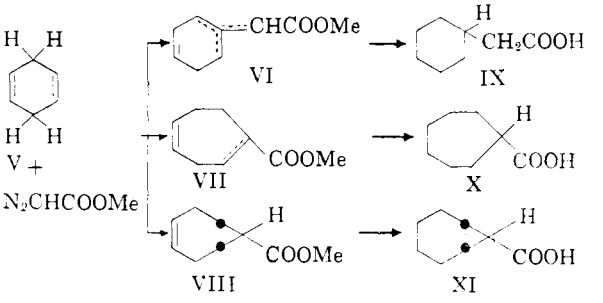
Although a number of procedures have been described for the synthesis of cyclopropane derivatives, limited information is available regarding the exact stereostructure of the final products. It seemed to us that oxidation of suitably substituted derivatives of norcar-3-ene (III) could provide an unambiguous route to substituted cyclopropane-*cis*-1,2-diacetic acids (IV) since the fusion between the cyclohexene and cyclopropane rings must be *cis* on sterical grounds. In view of the well documented differential stability on oxidation between the cyclopropane ring and an olefinic linkage, oxidative fission was expected to occur at the site of the double bond.



The facility with which cyclohexene is converted into ethyl norcarane-7-carboxylate prompted attempts to produce ethyl norcar-3-ene-7-carboxylate by treating cyclohexa-1,4-diene (V) with ethyl diazoacetate. In an initial experiment we carried out a reaction in the presence of a copper catalyst essentially according to the procedure of Ebel and collaborators.[6] Distillation of the reaction products afforded a main fraction (b.p. 71–72° at 0.2 mm.), which was saponified to give an acidic material of melting point 91.5–93.0°. The analytical data for this substance were in good agreement to those expected for the desired norcar-3-ene-7-carboxylic acid, but the material absorbed 1.85 mole equivalents of hydrogen when subjected to catalytic hydrogenation, and gave a liquid product. Norcarane-7-carboxylic acid (XI) melts at 96.0–97.0°, and fails to absorb hydrogen under identical conditions of hydrogenation. These results pointed to the presence of two double bonds in our product. A sample of the liquid hydrogenation product was converted into the amide (m.p. 169–170°) which was identified as cyclohexane acetamide by mixed melting point determination with an authentical sample. It follows from these observations that under our experimental conditions the reaction of cyclohexa-1,4-diene with ethyl diazoacetate had not followed the desired course, but had afforded a doubly unsaturated compound possessing the carbon skeleton of cyclohexaneacetic acid. The location of the double bonds has not been explored, but it seems highly plausible that the second double bond is located in one of the three positions marked by dotted lines in formula VI.

(6) F. Ebel, R. Brunner and P. Mangelli, *Helv. Chim. Acta*, **12**, 19 (1929).

Since it was suspected that the presence of copper may have favored the formation of rearrangement products rather than of the desired ethyl norcar-3-ene-7-carboxylate, a second experiment was conducted using experimental conditions (essentially those described by Grundmann and Ottmann[7]) in which contact of the reactants with metals was largely eliminated. Methyl diazoacetate was mixed with a large excess of cyclohexa-1,4-diene, and the mixture heated at 105±5° for 2.5 hours in a glass lined autoclave. Distillation of the reaction products afforded a main fraction (b.p. 60.0–63.5° at 0.1 mm.) which absorbed 1.5 mole equivalents of hydrogen on catalytic hydrogenation. Careful distillation of the hydrogenation products afforded three distinct fractions, I, II and III, representing 32, 20 and 31%, respectively, of the material. Each fraction was saponified, and the resulting acid identified by comparison with an authentical sample. Fraction I afforded cyclohexaneacetic acid (IX), whereas fractions II and III gave cycloheptanecarboxylic acid (X) and norcarane-7-carboxylic acid (XI), respectively. Thus, the hydrogenation mixture was composed of methyl cyclohexane acetate, methyl cycloheptanecarboxylate and methyl norcarane-7-carboxylate. These results demonstrate that the interaction of methyl diazoacetate with cyclohexa-1,4-diene in the absence of metal afforded a mixture of at least three compounds (VI, VII and VIII), and thus failed to provide a productive route to the desired ethyl norcar-3-ene-7-carboxylate. Plausible locations for one of the double bonds in compounds VI and VII are indicated by dotted lines. The possibility of migration of the other double bond has not been excluded.



At this stage of our investigation we became acquainted with a study by Doering and Hoffmann[8] who demonstrated that dihalogenocarbenes react with cyclohexene to form 7,7-dihalogenonorcaranes in excellent yield. It seemed logical to extend this reaction to cyclohexa-1,4-diene (V) with the aim of obtaining 7,7-dihalogenonorcar-3-enes. These substances could be expected to undergo oxidation at the double bond with formation of 3,3-dihalogenocyclopropane-*cis*-1,2-diacetic acids. Replacement of the halogen atoms by hydrogen should give the desired cyclopropane-*cis*-1,2-diacetic acid (I).

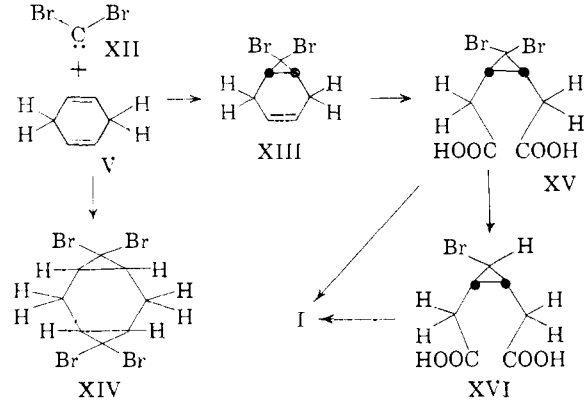
Equimolar proportions of cyclohexa-1,4-diene (V) and bromoform were brought into reaction in the presence of potassium *t*-butoxide (dibromocar-

(7) C. Grundmann and G. Ottmann, *Ann.*, **582**, 163 (1953).

(8) W. von E. Doering and A. K. Hoffmann, THIS JOURNAL, **76**, 6162 (1954).

bene (XII)) to give a beautifully crystalline material of melting point 36.8–37.0° in a 70% yield. This substance decolorized a solution of potassium permanganate in acetone, and its elemental analysis and iodine number agreed closely to those expected for 7,7-dibromonorcar-3-ene (XIII). The molecular weight, determined by the X-ray technique, was found to be 254, in agreement within experimental error with the theoretical value of 252. The infrared absorption spectrum exhibiting bands at 3.4, 6.1, 9.5 and 13.6 μ provided additional support for the assigned structure. The maxima at 3.4 and 6.1 μ are characteristic features of the olefinic double bond, whereas the 9.5μ absorption has been attributed to the cyclopropane ring. The 13.6 μ maximum may reflect the presence of carbon–bromine bonds; the same maximum is seen in the infrared absorption spectrum of 7,7-dibromonorcarane.[8]

The crystals are orthorhombic and the systematic X-ray extinctions are $(0kl)$ absent when $(k+l)$ is odd, $(hk0)$ absent when h is odd. The space group is $Pn2_1a$ or Pnma. If the space group is $Pn2_1a$, the general positions are fourfold and the molecules may be asymmetric. If the space group is Pnma, the molecules lie on special positions with molecular symmetry m. This mirror plane passes through carbon 7, the midpoint between carbons 3, 4 and 1, 6 and is normal to the plane of the cyclohexene ring (see formula XIII). Any other position of the double bond in the ring is incompatible with this symmetry and this space group. Since the bromine atoms would then lie on the mirror plane, it was possible to investigate this possibility further from a comparatively cursory examination of the X-ray intensities. The $(0k0)$ intensities were strong and decreased uniformly. From the intensities of the $(h0l)$ reflections a Patterson F^2 Fourier synthesis was computed. Although the Harker peaks on the projection are indistinguishable for both space groups, the intramolecular Br–Br vector should reveal the molecular orientation. For the space group Pnma, this vector peak must correspond to the unprojected bromine–bromine distance and be about $\sqrt{3} \times 1.9$Å. = 3.3 Å. from the origin. The most prominent peak on the Patterson synthesis was at 3.4 Å. from the origin. Assigning this to the Br–Br intramolecular vector, it was confirmed that the corresponding molecular orientation gave a very reasonable molecular packing model for the unit cell. Only a complete crystal structure determination could be conclusive, but this preliminary examination gives no reason to suspect that the molecule does not possess the mirror plane of symmetry, and that the configuration is not as represented in formula XIII.



In addition to 7,7-dibromonorcar-3-ene, a second minor product was isolated from the reaction mixture. This material melted at 205–207°, and failed to decolorize potassium permanganate in acetone. The analytical data pointed to one of the isomers of 2,2,6,6-tetrabromotricyclo[1.0.0.1]octane (XIV) as a likely structure for this compound. The infrared absorption spectrum which lacked the olefinic bands at 3.4 and 6.1μ but exhibited a very pronounced maximum at 13.6 μ (carbon–bromine bonds) is compatible with this formulation.

Oxidation with potassium permanganate in acetone solution converted 7,7-dibromonorcar-3-ene into 3,3-dibromocyclopropane-*cis*-1,2-diacetic acid (XV) (m.p. 179–181°). The elemental composition and the fact that this acid afforded cyclopropane-*cis*-1,2-diacetic acid when the bromine atoms were exchanged for hydrogens establish the structure. In addition to the typical bands for carboxylic acid groups, *i.e.*, the hydrogen-bonded hydroxyl band at 3.8μ and the carbonyl band at 5.9μ, the infrared absorption spectrum exhibited a pronounced maximum at 9.2μ and a weak band at 9.9μ. It seems likely that one of these bands is attributable to the cyclopropane ring. A pronounced band at 13.4μ has been assigned to the carbon–bromine bonds.

The conversion of 3,3-dibromocyclopropane-*cis*-1,2-diacetic acid (XV) into the halogen-free compound I was investigated under a variety of experimental conditions. Treatment of the dibromo acid with zinc dust in glacial acetic acid afforded a crystalline acid (m.p. 149.5–150.5°) which contained one bromine atom less than the starting material. This same compound was also obtained when the dibromo acid was subjected to catalytic hydrogenation over platinum in methanol containing potassium hydroxide. Hydrogenation over a Raney nickel catalyst in methanol containing potassium hydroxide converted this monobromo acid into a mixture of cyclopropane-*cis*-1,2-diacetic and pimelic acids. We conclude from these findings that the monobromo acid must be one of the stereoisomeric 3-bromocyclopropane-*cis*-1,2-diacetic acids (XVI), or, less likely, a mixture of both isomers.

Hydrogenation over a Raney nickel catalyst in methanol containing potassium hydroxide provided the best experimental conditions for conversion of the dibromo acid XV into cyclopropane-*cis*-1,2-diacetic acid (I). An average yield of at least 80% was realized in a series of hydrogenation experiments. The halogen-free acid was purified by recrystallization from ethyl acetate (m.p. 131–133°). The analytical data were in excellent agreement with theory. The typical carboxyl bands were present in the infrared absorption spectrum of this compound; a sharp band at 9.7 μ seems to be due to the presence of the cyclopropane ring. Three additional maxima at 10.9, 11.8 and 12.8 μ were present also. Small amounts of pimelic acid were isolated from the mother liquors.

Drastic oxidation of cyclopropane-*cis*-1,2-diacetic acid afforded a small quantity of cyclopropane-*cis*-1,2-dicarboxylic acid. The method of synthesis, coupled with the finding that cyclopropane-*cis*-1,2-dicarboxylic acid was formed upon oxidation, left little doubt regarding the structure of our cyclopropane-*cis*-1,2-diacetic acid. Recently this structure has received confirmation by an independent synthesis involving reduction of the anhydride of cyclopropane-*cis*-1,2-dicarboxylic acid with lithium aluminum hydride, and conversion of the ensuing *cis*-diol into cyclopropane-*cis*-1,2-diacetic acid *via* the ditosylate, bisiodomethyl derivative and dinitrile.[9] A direct comparison between the acids obtained by both routes was carried out in these laboratories. The compounds had the same melting point, and both the infrared absorption spectrum and the X-ray powder diffraction patterns matched identically. No depression of the melting point was observed with a 1:1 mixture of the specimens.

Finally we wish to record our inability to cleave the cyclopropane ring of cyclopropane-*cis*-1,2-diacetic acid by catalytic hydrogenation. We had previously shown that a number of long-chain cyclopropane fatty acids undergo ring fission when hydrogenated in glacial acetic acid over a platinum oxide catalyst.[4] Many attempts were made to cleave the cyclopropane ring of cyclopropane-*cis*-1,2-diacetic acid under similar conditions. The results were entirely negative. The reason for this behavior of the acid is not too clear, but the possibility exists that the shape of the molecule is such that it is incapable of orienting itself favorably on the surface of the catalyst.

Experimental[10]

Preparation of Reference Compounds.—Cyclohexaneacetic acid was prepared from phenylacetic acid by catalytic hydrogenation.[11] The amide (m.p. 169.0–171.0°) and the *p*-bromophenacyl ester (m.p. 91.0–91.5°) were prepared and recrystallized from water and 95% ethanol, respectively. Suberone[12] was reduced with lithium aluminum hydride to suberol and the latter converted into cycloheptyl bromide.[13] Cycloheptanecarboxylic acid was synthesized from cycloheptyl bromide as described by Ruzicka, *et al.*[14] The *p*-bromophenacyl ester was prepared in the usual manner, and recrystallized from 95% ethanol (m.p. 97.0–97.5°). Norcarane-7-carboxylic acid was prepared according to the procedure of Ebel, *et al.*,[5] and was recrystallized from aqueous methanol (m.p. 95.8–97.2°). Cyclopropane-*trans*-1,2-dicarboxylic acid[15] (m.p. 176–178°) was converted into the anhydride of the *cis* isomer[16] (m.p. 59–60°). For preparation of the *cis*-dicarboxylic acid (m.p. 138–139°) the *cis*-anhydride was refluxed with water.

Reaction of Cyclohexa-1,4-diene with Ethyl Diazoacetate. a. In the Presence of Copper Catalyst.—A mixture of cyclohexa-1,4-diene[17] (8.0 g.), di-*n*-butyl ether (20 ml.) and a copper catalyst (0.5 g.) was heated at 90–95°, and a solution of ethyl diazoacetate (6 g.) in di-*n*-butyl ether (10 ml.) was added over a period of 40 minutes with rapid stirring. The mixture was cooled to room temperature and the catalyst was removed by filtration. The filtrate was washed with three 6-ml. portions of 10% sulfuric acid, one 10-ml. portion of water, one 10-ml. portion of saturated sodium bicarbonate and finally with saturated sodium chloride and was dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was distilled giving a main fraction boiling at 71–72° at 0.2 mm.; yield 5.1 g. This material was dissolved in 5% ethanolic potassium hydroxide (90 ml.) and the mixture was allowed to stand at room temperature for 16 hours. Potassium maleate which had precipitated was removed by filtration, and the ethanol was evaporated. Water (40 ml.) was added and the solution was washed with two 10-ml. portions of ether. The aqueous layer was acidified to congo red with 50% sulfuric acid, the acid was isolated in the usual manner and recrystallized from 50% aqueous methanol; yield 4.5 g. (m.p. 91.0–93.0°).

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.5; H, 7.3; neut. equiv., 138.0. Found: C, 69.3; H, 7.4; neut. equiv., 140.0.

A sample of this acid (2.0 g.) was hydrogenated in ethanol (200 ml.) using a 5% palladium-on-charcoal catalyst (0.5 g.). The hydrogen uptake was rapid, and the hydrogenation came to a standstill when 1.85 mole equivalents of hydrogen had been absorbed. The hydrogenated material was distilled (b.p. 91–93° at 0.1 mm.) and was converted into the amide. Following two recrystallizations from water, the amide melted at 169–170°. No melting point depression was observed when this material was admixed with an authentical sample (m.p. 169–171°) of cyclohexane acetamide.

b. In Absence of Copper Catalyst.—A mixture of cyclohexa-1,4-diene (500 ml.) and methyl diazoacetate[18] (25 g.) was placed in a glass-lined Aminco autoclave of the rocker type, and the pressure was raised to 26 atm. with nitrogen. The autoclave was heated slowly (2.5 hours) until the temperature reached 105 ± 5°. At this point the pressure had risen to 39 atm. Heating was discontinued, and the autoclave was left to cool overnight. The excess of cyclohexa-1,4-diene was evaporated, and the residue distilled to give a main fraction (31.5 g.) which boiled at 60.5–63.0° at 0.1 mm. A sample of the distillate (4.2 g.) was hydrogenated in ethyl acetate (200 ml.) over a 5% palladium-on-charcoal catalyst (1.0 g.). The hydrogen uptake was rapid and came to a standstill when 1.52 mole equivalents of hydrogen had been absorbed. Two additional samples were similarly reduced, and the pooled hydrogenation products (11.8 g.) were distilled in a Piros–Glover spinning-band type still (at 3 ± 0.1 mm. pressure) to give three fractions, I, II and III, which boiled at 55.5°, 60–61° and 69–70°, respectively. These represented 32, 20 and 31% of the hydrogenation products. Fraction I, $n^{25}D$ 1.4456, on saponification afforded a liquid acid which was converted into the *p*-bromophenacyl ester. Following recrystallization from 95% ethanol the ester melted at 91.0–91.5°, and gave no melting point depression when admixed with the *p*-bromophenacyl ester (m.p. 91.0–91.6°) of cyclohexane acetic acid. Fraction II, $n^{25}D$ 1.4716, on saponification afforded a liquid acid which was converted into the *p*-bromophenacyl ester. Following recrystallization from 95% ethanol the ester melted at 95.5–97.5°; and gave no depression of the melting point when admixed with the *p*-bromophenacyl ester (m.p. 97.0-97.5°) of cycloheptanecarboxylic acid. Fraction III, $n^{25}D$ 1.4740, on saponification afforded a solid acid (m.p. 95.0–96.5°) which gave no depression of the melting point when admixed with norcarane-7-carboxylic acid (m.p. 95.0–96.5°).

7,7-Dibromonorcar-3-ene.—Potassium *t*-butoxide was prepared by adding 15 g. of potassium in small portions under anhydrous conditions to 450 ml. of *t*-butyl alcohol. The solvent was evaporated and the residue was dried at 150° *in vacuo*. The resulting cake of potassium *t*-butoxide was powdered and suspended in 250 ml. of *n*-pentane. The suspension was cooled at 0° and cyclohexa-1,4-diene (230 ml.) was added. The mixture was stirred and bromoform (114 g.) was introduced at such a rate that the temperature remained between 0 and 5°. Following the addition of the bromoform (which required 1.5 hours), the mixture was stirred for an additional 20 minutes when water

(9) We wish to thank Dr. E. Vogel of the Institut für Organische Chemie der Technischen Hochschule in Karlsruhe, Germany, for advanced notice of his synthesis of cyclopropane-*cis*-1,2-diacetic acid and for a sample of his substance.

(10) The melting points are uncorrected.

(11) R. Adams and J. R. Marshal, THIS JOURNAL, **50**, 1970 (1928).

(12) I. Vogel, *J. Chem. Soc.*, 2032 (1928).

(13) O. Grummitt, *Org. Syntheses*, **19**, 88 (1939).

(14) L. Ruzicka, P. Barman and V. Prelog, *Helv. Chim. Acta*, **34**, 401 (1951).

(15) E. Buchner, *Ber.*, **23**, 701 (1890).

(16) T. W. B. Gregory and W. H. Perkin, Jr., *J. Chem. Soc.*, **83**, 780 (1903).

(17) T. B. Tom and K. W. Greenlee, *Am. Petroleum Inst. Rep.*, **45**, 4 (1948).

(18) F. B. LaForge, W. A. Gersdorff, N. Green and M. S. Schechter, *J. Org. Chem.*, **17**, 381 (1952).

(300 ml.) was added. The organic layer was separated, the aqueous layer was reëxtracted with two 150-ml. portions of *n*-pentane and the combined extracts were dried over anhydrous calcium chloride. The solvent was evaporated and the residue distilled *in vacuo*. A main fraction (82 g., b.p. 84.5–93.0° at 8 mm. pressure) was obtained. A solid residue (approximately 1 g.) remained in the distilling flask. The main fraction solidified on standing in a refrigerator, and was contaminated with a lachrymatory material which was not investigated. After six recrystallizations from *n*-pentane at −30° (25 ml. per crystallization) a substance melting at 36.8–37.0° was obtained; yield 68 g. (70%); orthorhombic needles with unit cell dimensions, a = 10.38 Å., b = 9.35 Å., c = 8.87 Å., space group $Pn2_1a$ or $Pnma$. The needle axis is b. The density measured by flotation is 1.96 g./ml. With 4 molecules per unit cell the molecular weight is 254, in agreement within experimental error with the theoretical value of 252.

Anal. Calcd. for $C_7H_8Br_2$: C, 33.4; H, 3.2; Br, 63.4; iodine no., 100. Found: C, 33.0; H, 3.5; Br, 63.0; iodine no., 97.5.

The distillation residue after recrystallization from methylene chloride afforded a colorless material (m.p. 205.2–207.0°).

Anal. Calcd. for $C_8H_8Br_4$: C, 22.7; H, 1.9; Br, 75.4; iodine no., 0.0. Found: C, 22.8; H, 1.8; Br, 74.8; iodine no., 0.7.

3,3-Dibromocyclopropane-*cis*-1,2-diacetic Acid.—Powdered potassium permanganate (116 g.) was added in small portions with stirring over a period of 24 hours to a solution of 7,7-dibromonorcar-3-ene (63 g.) and sodium bicarbonate (8 g.) in acetone (2.52 l.). The temperature was maintained at 0° throughout the addition, and the mixture was stirred for an additional 72 hours at 0°. The mixture was filtered and the filtercake (manganese dioxide plus the potassium salt of the desired acid) was added slowly to cracked ice with stirring. The manganese dioxide was removed by filtration, and washed with several portions of water at room temperature. The combined filtrate and washings were concentrated *in vacuo* to a volume of 500 ml., the residue was acidified to congo red with 50% (v./v.) sulfuric acid and saturated with sodium chloride. This solution was extracted with three 250-ml. portions of ether, and the combined ethereal solutions were extracted with three 75-ml. portions of 10% sodium carbonate and two 75-ml. portions of water. The extracts were combined, acidified to congo red with 50% sulfuric acid, saturated with sodium chloride and extracted with three 250-ml. portions of ethyl acetate. The ethyl acetate extracts were washed with three 50-ml. portions of saturated sodium chloride, decolorized with Norit A, dried over sodium sulfate and concentrated to a small volume when crystallization occurred. The crystals were collected and recrystallized from ethyl acetate; yield 25 g. (32%), m.p. 179.4–181.2°.

Anal. Calcd. for $C_7H_8O_4Br_2$: C, 26.6; H, 2.6; Br, 50.6; neut. equiv., 158.0. Found: C, 26.5; H, 2.2; Br, 50.5; neut. equiv., 158.7.

3-Bromocyclopropane-*cis*-1,2-diacetic Acid. a. **By Partial Dehalogenation of 3,3-Dibromocyclopropane-*cis*-1,2-diacetic Acid with Zinc Dust.**—A solution of 3,3-dibromocyclopropane-*cis*-1,2-diacetic acid (6.3 g.) in glacial acetic acid (160 ml.) was maintained at 50° and zinc dust (26 g.) was added in small portions with stirring over a period of 2 hours. Stirring at 50° was continued for 40 hours when the mixture was filtered. The filtercake was washed with three 20 ml. portions of glacial acetic acid and three 30-ml. portions of water, and the combined filtrate and washings were evaporated to a small volume *in vacuo*. The concentrate was acidified to congo red with 10% (v./v.) sulfuric acid, the solution was saturated with sodium chloride and was extracted with three 100-ml. portions of ethyl acetate. The organic extracts were washed with three portions of saturated sodium chloride, the solution was decolorized with Norit and dried over sodium sulfate. The ethyl acetate was evaporated and the residue recrystallized from benzene-ethyl acetate (1:1); yield 2.4 g. (50%), m.p. 149.5–150.5°.

Anal. Calcd. for $C_7H_9O_4Br$: C, 35.5; H, 3.8; Br, 33.7; neut. equiv., 118.5. Found: C, 35.6; H, 3.6; Br, 33.0; neut. equiv., 119.1.

b. **By Catalytic Reduction of 3,3-Dibromocyclopropane-*cis*-1,2-diacetic Acid.**—A sample of 3,3-dibromocyclopropane-*cis*-1,2-diacetic acid (3.2 g.) was hydrogenated over a platinum oxide catalyst (0.2 g.) in methanol (300 ml.) containing potassium hydroxide (4 g.). The sample absorbed 1.4 mole equivalents of hydrogen over a period of 24 hours. The catalyst was removed by filtration, the solvent evaporated, the residue dissolved in a small quantity of water, and the solution acidified to congo red with 10% sulfuric acid. The monobromo acid was isolated in the manner described above and was recrystallized twice from ether–benzene (1:1) and six times from benzene; yield 1.22 g. (51%), m.p. 149.5–150.5°. No melting point depression was observed when this material was admixed with the product from the zinc dust experiment. Similar results were obtained when the reduction was carried out in the presence of palladium-on-charcoal or palladium-on-barium sulfate catalysts.

Cyclopropane-*cis*-1,2-diacetic Acid. a. **By Hydrogenation of 3,3-Dibromocyclopropane-*cis*-1,2-diacetic Acid.**—To a solution of 3,3-dibromocyclopropane-*cis*-1,2-diacetic acid (15.3 g.) in methanol (200 ml.) was added a solution of potassium hydroxide (12.8 g.) in water (50 ml.) and Raney nickel (approximately two teaspoons) and the mixture was shaken in an atmosphere of hydrogen for 24 hours when approximately 80% of the expected quantity of hydrogen had been absorbed. The mixture was filtered and the filtrate evaporated to a small volume *in vacuo*. The residue was acidified to congo red with 10% sulfuric acid, the solution was saturated with sodium chloride and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated sodium chloride, decolorized with Norit, dried over sodium sulfate and evaporated. The resulting solid material was recrystallized from ethyl acetate; yield 6.4 g. (84%), m.p. 131–133°; colorless monoclinic prisms with cell dimensions, a = 15.15, b = 6.61, c = 7.57 Å., β = 101.8°, V = 742 Å.^{3}; density observed 1.38 g./ml., density calculated 1.41 g./ml. with 4 molecules per unit cell. The space group is $P2_1/a$ with molecular symmetry 1.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.2; H, 6.4; neut. equiv., 79.1. Found: C, 53.0; H, 6.2; neut. equiv., 79.6.

Pimelic acid (m.p. 103–104°) was isolated from the mother liquors in a yield of 10%.

b. **By Hydrogenation of 3-Bromocyclopropane-*cis*-1,2-diacetic Acid.**—A sample of the monobromo acid (m.p. 149.5–150.5°, 0.193 g.) was hydrogenated over Raney nickel in methanol (30 ml.) containing potassium hydroxide (0.3 g.) and water (5 ml.). An amount of hydrogen corresponding to 1.1 mole equivalents was absorbed within two hours. The catalyst was removed by filtration, the methanol was evaporated and the residue acidified to congo red with 10% sulfuric acid. The bromine-free acid was isolated in the manner described above and recrystallized once from a mixture of ethyl acetate and benzene (1:1) and once from benzene; yield 0.11 g. (85%), m.p. 130.2–132.0°. No depression of the melting point was observed when this compound was admixed with the acid prepared according to procedure a. Pimelic acid (m.p. 103–104°) was isolated from the mother liquors.

Oxidation of Cyclopropane-*cis*-1,2-diacetic Acid.—A solution of cyclopropane-*cis*-1,2-diacetic acid (0.953 g.) in water (30 ml.) was heated at 80° and powdered potassium permanganate (2 g.) was added slowly with stirring. After the purple color had disappeared additional permanganate (2 g.) was added and the mixture was stirred at 80° for 1 hour. The manganese dioxide was removed by filtration, and the filtrate concentrated to a volume of approximately 10 ml. The solution was acidified with dilute hydrochloric acid and was then concentrated to a volume of 5 ml. Acetone (40 ml.) was added; the resulting precipitate was removed by filtration, and the filtrate was evaporated to dryness. The residue was extracted with acetone, and the filtered extract was evaporated. Recrystallization from a mixture of benzene and ethyl acetate gave 0.75 g. of starting material, m.p. 130–132°. From the mother liquors crystals were obtained which melted at 138–139°, yield 40 mg. This material did not depress the melting point of an authentical sample of cyclopropane-*cis*-1,2-dicarboxylic acid, and the infrared absorption spectrum matched that of the reference compound.

Single Crystal Data on Related Cyclopropane Derivatives.—During the course of the X-ray studies, the following crystal data were obtained on related compounds.

Cyclopropane-*trans*-1,2-dicarboxylic Acid.—Recrystallization from water gave colorless crystals (m.p. 176–178°) tabular on (100). These are monoclinic with cell dimensions, $a = 12.71$, $b = 5.07$, $c = 9.44$ Å., $\beta = 98°$; density measured 1.46 g./ml., density calculated 1.45 g./ml. with 4 molecules per unit cell. The space group is A2/a with molecular symmetry 1.

Anhydride of Cyclopropane-*cis*-1,2-dicarboxylic Acid.—Recrystallization from ethyl ether gave colorless needles (m.p. 59–60°), elongated about the *c*-axis with a tendency to lath formation. The solid had a high vapor pressure and the crystals had to be sealed in gelatin capsules or thin-walled glass capillaries for X-ray examination. The crystals are monoclinic with $a = 6.13$, $b = 8.43$, $c = 5.35$ Å., $\beta = 116°$; density measured 1.50 g./ml., density calculated 1.49 g./ml. with two molecules per unit cell. The space group is $P2_1/m$ with molecular symmetry m, or $P2_1$ with molecular symmetry 1.

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[CONTRIBUTION OF THE CHEMISTRY DEPARTMENT OF OHIO UNIVERSITY]

The Role of Hydrogen in the Pinacol Rearrangement of 2-Methyl-2,3-butanediol

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The rates of rearrangement of 2-methyl-2,3-butanediol and 2-methyl-2,3-butanediol-3-*d* in aqueous perchloric acid at various temperatures and acidities have been measured. Isotope effects of 1.5–1.8 have been observed. The internal migration of deuterium during the course of the rearrangement was determined through an infrared spectral analysis of the reaction product, methyl isopropyl ketone. The synthesis and rearrangement of 2-methyl-2,3-butanediol-4-C^{14} has been carried out. The iodoform degradation of the reaction product indicated that no reversible methyl migration or secondary hydroxyl removal had occurred during the formation of the ketone. Consideration of the kinetic expression supports the belief that the isotope effect arises due to differences in hydrogen participation during the rate-determining step.

In recent years much evidence has been amassed to support the view that atoms or groups of atoms located adjacent to the reaction site may directly participate in organic solvolysis and rearrangement reactions.[2] The question of whether or not hydrogen is capable of such participation has not been completely answered.

Winstein and co-workers have studied several systems which shed some light on this problem.[3] Thus, neomenthyl *p*-toluenesulfonate undergoes acetolysis about one hundred and seventy times more rapidly than the corresponding menthyl compound. While the rate increase here may be due to the contribution which the favorably located hydrogen makes to the rate-determining ionization, the situation is complicated by the fact that steric strain relief is greater for the departure of the axial tosyl group from the neomenthyl compound than for the equatorial tosyl group from the menthyl tosylate.

Winstein and Marshall[4] found that the acetolysis of 3-methyl-2-butyl *p*-bromobenzenesulfonate was about twice as fast as that of 3,3-dimethyl-2-butyl *p*-bromobenzenesulfonate. Again proper assessment of the role of the hydrogen is difficult due to the possible operation of such diverse factors as steric inhibition to solvation of the transition state, hyperconjugation and the inductive effect of the methyl groups at C_β.

A particularly useful approach to this problem is suggested by the effect which the substitution of deuterium for hydrogen may have on the reaction rates and products of organic reactions. Melander[5] has shown that when an isotopic bond is broken in the rate-determining step a significant kinetic isotope effect will be observed. This principle was first applied to reaction mechanism studies by Melander[6] and Westheimer.[7]

When the deuterium for hydrogen substitution is made at some point more remote from the reaction site, secondary kinetic isotope effects may be observed. Such effects as have been observed are smaller in magnitude than those which actually involve the breaking of isotopic bonds. Shiner[8] has carried out an extensive study of S_N1, S_N2, E_1 and E_2 reactions by observing the effect of replacing hydrogen by deuterium at a position near the reaction site in a number of different molecules. Lewis and co-workers[9] have also carried out a similar series of experiments. Recently, Streitwieser, *et al.*,[10] have discussed in detail the source of the secondary isotope effects found in the solvolysis reactions of the deuterated cyclopentyl tosylates. In each of the studies carried out by these workers the isotope effects observed were small (1.1–1.3). However, none of these reactions provide any additional information regarding the possibility of hydrogen participation as no examples of an internal 1,2-shift of hydrogen were observed in any of the above.

Of a more pertinent nature is the recent report by Winstein and Takahashi[11] that the formolysis and acetolysis of 3-methyl-2-butyl *p*-toluenesulfonate and 3-methyl-2-butyl *p*-toluenesulfonate-3-*d* proceed with isotope effects of 1.7–2.1. Evidence from the reaction products and rate effects was interpreted as indicating appreciable hydrogen participation (anchimeric assistance) during the course of the rearrangement.

(1) Taken in part from the M.S. dissertations of Richard E. Bowman and Thomas J. Kmet, Ohio University, 1958.

(2) S. Winstein and L. L. Ingraham, THIS JOURNAL, **77**, 1738 (1955), and references therein.

(3) S. Winstein, *et al.*, *ibid.*, **74**, 1131 (1952).

(4) S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).

(5) L. Melander *Arkiv Kemi*, **2**, 211 (1950).

(6) L. Melander, *Acta Chem. Scand.*, **3**, 95 (1949).

(7) F. H. Westheimer and N. Nicolaides, THIS JOURNAL, **71**, 25 (1949); M. Cohen and F. H. Westheimer, *ibid.*, **74**, 4387 (1952).

(8) V. J. Shiner, (a) *ibid.*, **74**, 5285 (1952); (b) **75**, 2925 (1953); (c) **76**, 1603 (1954); (d) **78**, 2653 (1956).

(9) E. S. Lewis and C. E. Boozer, (a) *ibid.*, **74**, 6307 (1952); (b) **76**, 791 (1954); (c) **76**, 794 (1954).

(10) A. Streitwieser, R. H. Jagow, R. C. Fahey and S. Suzuki, *ibid.*, **80**, 2326 (1958).

(11) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).