

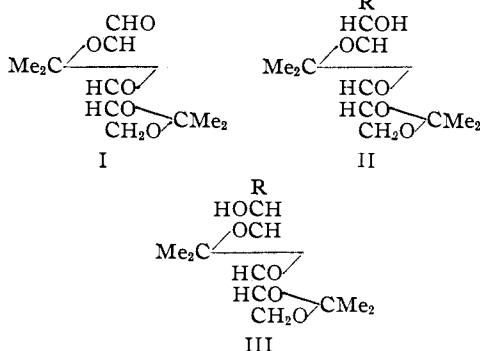
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Stereochemical Configurations of the 1-C-Phenyl-D-pentitols

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The crystalline 1-C-phenyl-2,3,4,5-diisopropylidene-D-pentitol obtained by action of phenylmagnesium bromide on 2,3,4,5-diisopropylidene-D-arabonaldehyde has been shown by protective methylation and degradation to O-methyl-L-(+)-mandelic acid to be configurationally related to D-glucose. By hydrolysis of the residue from the mother liquors remaining after crystallization of the 1-C-phenyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol, the diastereomeric 1-C-phenyl-D-*manno*-pentitol was discovered. The stereochemical configuration of this substance was established by similar degradative experiments to O-methyl-D(-)-mandelic acid. The 1-C-cyclohexyl-D-pentitol obtained by hydrolysis of the 1-C-cyclohexyl-2,3,4,5-diisopropylidene-D-pentitol resulting from interaction of cyclohexylmagnesium bromide with 2,3,4,5-diisopropylidene-D-arabonaldehyde was identical with the 1-C-cyclohexyl-D-*gluco*-pentitol produced by hydrogenation of 1-C-phenyl-D-*gluco*-pentitol, thus establishing also the stereochemical configurations of the 1-C-cyclohexyl-D-pentitols.

Three reports on the reaction of Grignard reagents with *aldehydo*-sugars are recorded in the literature. These center about the use of 2,3,4,5-diisopropylidene-D-arabonaldehyde (I), or its enantiomorph with alkyl- and arylmagnesium halides. In 1938 Gätzi and Reichstein¹ obtained the two theoretically possible diastereomeric substances 1,2,3,4-diisopropylidene-6-desoxy-L-gulitol (II, R = methyl) and 1,2,3,4-diisopropylidene-D-rhamnitol (III, R = methyl) by action of methylmagnesium iodide on I. In this instance no question



arose as to the stereochemical configurations of the newly produced centers of asymmetry, since the derivatives could be hydrolyzed to products whose configurations were known.

Later English and Griswold reported the action of phenyl-, cyclohexyl- and 1-naphthylmagnesium halides on I^{2b} and its enantiomorph.^{2a} A series of 1-C-substituted-2,3,4,5-diisopropylidene-D-pentitols (II or III, R = phenyl, cyclohexyl or 1-naphthyl) resulted, which could be hydrolyzed to the corresponding 1-C-substituted-D-pentitols. In each case, however, only one of the two possible diastereomers was isolated. In addition, since the products corresponded to none whose stereochemical structures were known, the configurations of the new asymmetric centers at carbon atom one were left undetermined, and a definitive nomenclature could not be proposed.

Our interest in this problem has been in the isolation of the other possible diastereomer in one of the cases, and in a concrete proof of the stereochemical configuration of the first asymmetric center of the two diastereomers. The general method of attack in the latter problem has been protection of the

hydroxyl group at the first asymmetric center through methylation, degradation of the resulting product to a derivative of mandelic acid, and comparison of the latter with an authentic sample.

When I reacted with phenylmagnesium bromide a mixture of the two diastereomers 1-C-phenyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (IV) and 1-C-phenyl-2,3,4,5-diisopropylidene-D-*manno*-pentitol (V) resulted. In agreement with the results of English and Griswold² only the less soluble diastereomer, m.p. 79–80.5°, was crystallizable at this point. As will be proven, this isomer possessed the *gluco*-structure IV. Hydrolysis of the sirupy residue from the mother liquors of IV readily produced the diastereomeric 1-C-phenyl-D-*manno*-pentitol (VI). Hydrolysis of IV itself yielded 1-C-phenyl-D-*gluco*-pentitol (VII) as previously observed² for the L-*gluco*-enantiomorph.

The configurations of VI and VII were related at this point to that of the 1-C-cyclohexyl-D-pentitol described by English and Griswold.² Catalytic hydrogenation of VII yielded a 1-C-cyclohexyl-D-*gluco*-pentitol (IX) identical in all respects with a sample obtained by hydrolysis of 1-C-cyclohexyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (VIII) prepared by reaction of cyclohexylmagnesium bromide with I. Thus the least soluble 1-C-substituted-2,3,4,5-diisopropylidene-D-pentitols in both the phenyl and cyclohexyl series are configurationally related.

The precise stereochemical configurations of these products were elucidated by the following degradative and synthetic experiments. Methylation of IV with methyl iodide and silver oxide produced 1-C-phenyl-1-methyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (X) which on hydrolysis yielded 1-C-phenyl-1-methyl-D-*gluco*-pentitol (XI). Oxidation of XI with sodium periodate led to L-(+)-1-methoxyphenylacetaldehyde (XII) with destruction of all of the asymmetric centers except the one whose configuration is in question. Oxidation of XII with moist silver oxide gave O-methyl-L-(+)-mandelic acid (XIII). The identity of the latter was established through analysis and by comparison with an authentic sample of XIII prepared by methylation of L-(+)-mandelic acid (XIV). The degradative sample and the synthetic sample showed similar rotations, similar melting points, no mixed melting point depression and similar infrared absorption spectra (Fig. 1). Since the configurations of the enantiomorphous mandelic

(1) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 914 (1938).(2) J. E. English, Jr., and P. H. Griswold, Jr., (a) *THIS JOURNAL*, **67**, 2039 (1945); (b) **70**, 1390 (1948).

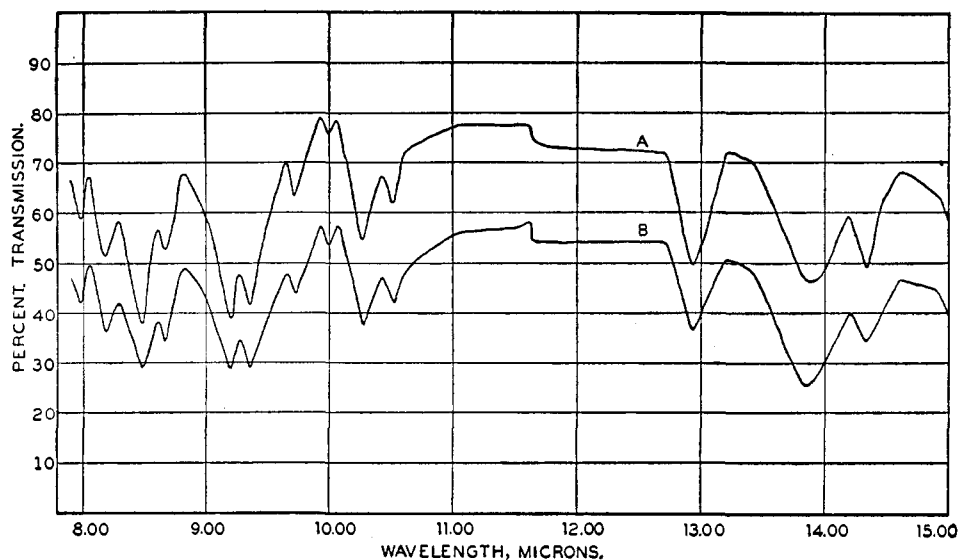


Fig. 1.—Infrared absorption spectra of O-methyl-L-(+)-mandelic acid: A, degradative sample; B, synthetic sample.

acids are known,^{3,4} and since the first carbon atom in IV has now been shown configurationally related to L-(+)-mandelic acid, it follows that IV must be assigned the *gluco*-configuration.

The stereochemical arrangement of the *manno*-derivative V, occurring in the mother liquors from IV was established in precisely the same fashion. Methylation of the residue from the mother liquors of IV led to impure, sirupy 1-C-phenyl-1-methyl-2,3,4,5-diisopropylidene-D-*manno*-pentitol (XVII). Hydrolysis of this produced crystalline 1-C-phenyl-1-methyl-D-*manno*-pentitol (XVIII). This in turn was converted *via* the aldehyde XIX to O-methyl-D-(–)-mandelic acid (XX). The identity of the latter was again established by comparison with an authentic sample prepared synthetically from D-(–)-mandelic acid (XXI).

The reactions and interrelationships of the products in this study are summarized in Fig. 2, and the physical properties of the products are given in Table I.

Knowing the specific rotations of the pure diastereomeric 1-C-phenyl-D-pentitols, VI and VII, and applying a simple scheme of rotational analysis, it is possible to obtain a rough idea of the composition of the crude Grignard reaction product with respect to IV and V. In Fig. 3 a straight line has been drawn between the rotations of pure VI and VII. The crude sirup, $[\alpha]^{25D} 36.9^\circ$ (average in pyridine), obtained by action of phenylmagnesium bromide on I was hydrolyzed and the rotation, $[\alpha]^{26D} 3.7^\circ$ (pyridine), of the crude hydrolysis product measured. Fitting this rotation value into Fig. 3 gives a composition of 65% 1-C-phenyl-D-*gluco*-pentitol and 35% 1-C-phenyl-D-*manno*-pentitol for the crude hydrolysis product, a figure presumably also applicable to the crude Grignard reaction product. Similarly, the sirup obtained from the mother liquors *after* crystallization of pure IV from the crude Grignard product had $[\alpha]^{24D} 16.9^\circ$ (pyridine). Hydrolysis of this gave a mixture of solid 1-C-phenyl-D-pentitols

having $[\alpha]^{26D} -26.3^\circ$ (pyridine). This corresponds to a composition of 75% *manno*- and 25% *gluco*-derivative in the mother liquors *after* removal of as much of the *gluco*-derivative as possible by crystallization of the crude Grignard reaction product. These values, as seen in Fig. 4, permit a rough estimate of the specific rotation of the presently unknown 1-C-phenyl-2,3,4,5-diisopropylidene-D-*manno*-pentitol (V). Extrapolating the straight line formed by the three points of known rotation and composition in Fig. 4 to the pure *manno*-derivative, one predicts a specific rotation of around 5° in chloroform for the latter.

One point in connection with Table I is noteworthy. The two supposedly enantiomorphous aldehydes, XII and XIX, have rotations in poor agreement with one another. Similarly, the rotations obtained in successive preparations of either enantiomorph were somewhat random. That these aldehydes each contained a certain amount of the undesired enantiomorph was further evident on examination of the *crude* O-methylmandelic acids obtained from them after the silver oxide oxidation. Thus the crude acid XIII had $[\alpha]^{25D} 132.0^\circ$ (ethanol) and the crude acid XX had $[\alpha]^{25D} -81.7^\circ$ (average of two values in ethanol). Applying rotational analysis similar to that described above, these figures suggest that the crude O-methyl-L-(+)-mandelic acid XIII was contaminated with about 6% of the D-(–)-enantiomorph, that the crude O-methyl-D-(–)-mandelic acid (XX) contained about 22% of the L-(+)-enantiomorph, and that the rotations of the optically pure enantiomorphous aldehydes XII and XIX should be around $\pm 95^\circ$ in chloroform. The anomalous rotations of the crude aldehydes XII and XIX strongly suggest that a certain amount of racemization attended the periodate oxidations of the 1-C-phenyl-1-methyl-D-pentitols XI and XVIII, and, furthermore, that the extent of racemization in each case was influenced by the stereochemical configurations of each of the diastereomers XI and XVIII. We know of no other instance of partial racemization attending periodate oxidation in the carbohydrate

(3) K. Freudenberg, F. Brauns and H. Siegel, *Ber.*, **56**, 193 (1923).

(4) K. Freudenberg and L. Markert, *ibid.*, **58**, 1753 (1925).

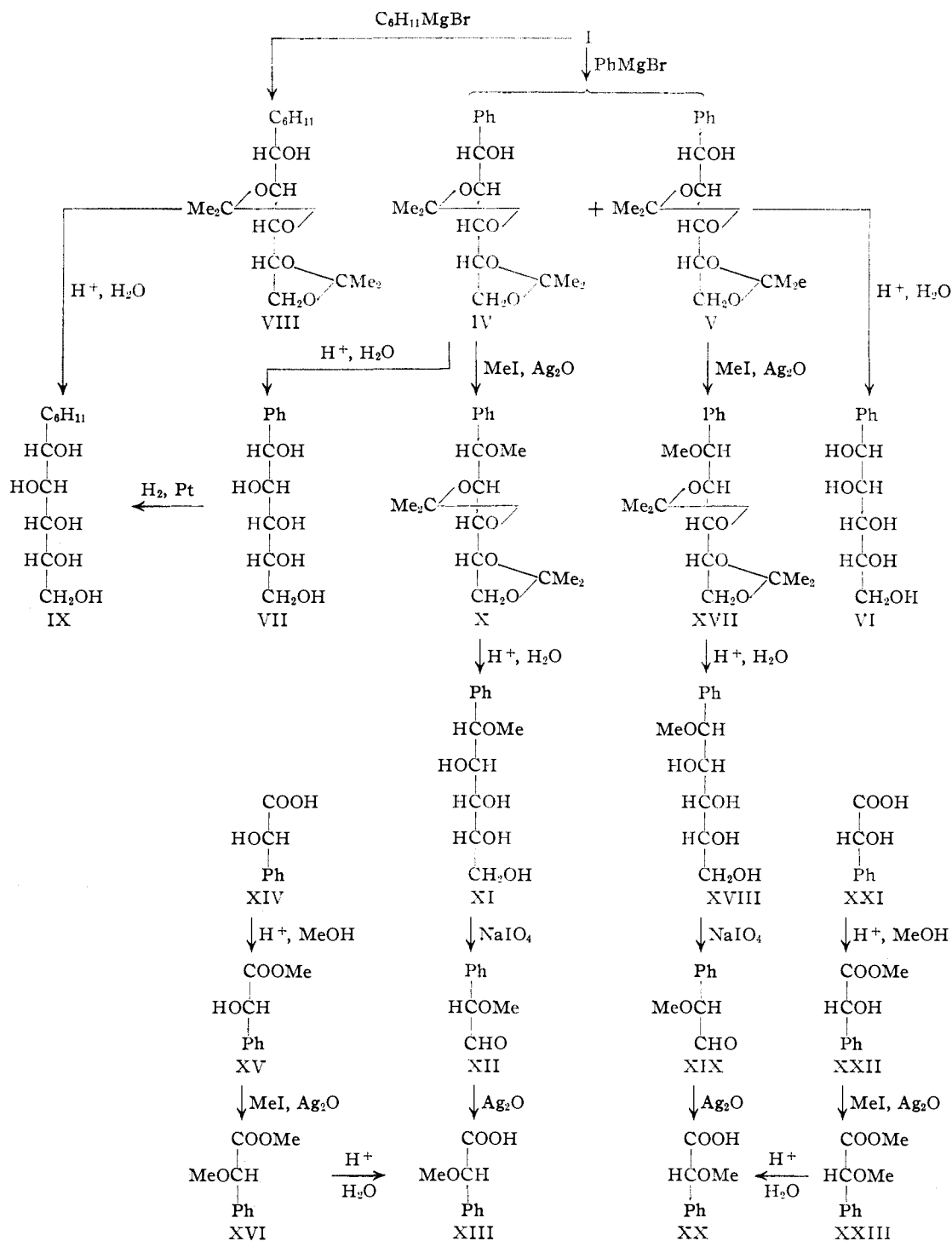


Fig. 2.—Reactions involved in configurational determinations.

series, although the recently reported⁵ isolation of D,L- α -phenyldiglycolic aldehyde on periodate oxidation of β -D-xylosylbenzene is probably interpretable in this light. The differing extent of racemization obtained on oxidation of XI and XVIII is in keeping with the well known differences in reaction rates of diastereomeric substances.

(5) W. A. Bonner and C. D. Hurd, "The Ring Size and Stereochemical Configuration of the Number One Carbon Atom in Xylosylbenzene," 110th Meeting of the American Chemical Society, Chicago, Sept., 1946.

Experimental

1,2;3,4;5,6-Triisopropylidene-D-mannitol.—This was prepared by the method of Wiggins⁶ from D-mannitol, dry acetone and sulfuric acid. The crude product, m.p. 68°, was used without further purification.

3,4;5,6-Diisopropylidene-D-mannitol.—We have been unable to obtain satisfactory results in the preparation of this compound by strictly following the method of Wiggins.⁶ With a minor modification of the work-up procedure, however, fairly reproducible results have been obtained. 1,2;3,4;5,6-Triisopropylidene-D-mannitol (60 g.) was dissolved

(6) L. F. Wiggins, *J. Chem. Soc.*, 13 (1946).

TABLE I
PHYSICAL PROPERTIES OF PRODUCTS IN FIGURE 2

| Compound | M.p., °C. | $[\alpha]_{D}^{25}$ | Solvent |
|---|-----------|---------------------|------------|
| 1-C-Phenyl-2,3,4,5-diisopropylidene-D-gluco-pentitol (IV) | 79-80.5 | 53.2 | Pyridine |
| 1-C-Cyclohexyl-2,3,4,5-diisopropylidene-D-gluco-pentitol (VIII) | 75-76 | 27.2 ^b | Pyridine |
| 1-C-Phenyl-D-gluco-pentitol (VII) | 138-138.5 | 30.5 | Pyridine |
| 1-C-Cyclohexyl-D-gluco-pentitol (IX) | 148 | -15.2 | Pyridine |
| 1-C-Phenyl-D-manno-pentitol (VI) | 172.5-173 | -44.8 | Pyridine |
| 1-C-Phenyl-1-methyl-2,3,4,5-diisopropylidene-D-gluco-pentitol (X) | Sirup | 75.6 | Pyridine |
| 1-C-Phenyl-1-methyl-D-gluco-pentitol (XI) | 172.5-173 | 39.2 | Pyridine |
| 1-C-Phenyl-1-methyl-D-manno-pentitol (XVIII) | 142-144 | -49.9 | Pyridine |
| L-(+)-1-Methoxyphenylacetaldehyde (XII) | Oil | 83.2 ^a | Chloroform |
| D-(-)-1-Methoxyphenylacetaldehyde (XIX) | Oil | -54.6 ^a | Chloroform |
| L-(+)-Mandelic acid (XIV) | 133 | 157.0 | Water |
| D-(-)-Mandelic acid (XXI) | 132.5-133 | -154.0 | Water |
| Methyl L-(+)-mandelate (XV) | 55.5 | 173.5 | Chloroform |
| Methyl D-(-)-mandelate (XXII) | 55.5 | -174.2 | Chloroform |
| Methyl O-methyl-L-(+)-mandelate (XVI) | Oil | 88.7 | Acetone |
| Methyl O-methyl-D-(-)-mandelate (XXIII) | Oil | -89.1 | Acetone |
| O-Methyl-L-(+)-mandelic acid (XIII) | 64-65 | 150.0 | Ethanol |
| O-Methyl-D-(-)-mandelic acid (XX) | 65-66 | -148.4 | Ethanol |

^a Average of several values.

in 70% ethanol (1200 ml.), the mixture heated to 40-45°, and concentrated hydrochloric acid (4 ml.) added. The solution was maintained at 40-45° for one hour, then made slightly alkaline to litmus by the addition of saturated sodium carbonate solution. The mixture was decanted through Celite from the small aqueous layer, and the filtrate distilled to dryness *in vacuo* at 100°. The residue was

slurried with hot acetone (100 ml.), filtered, and the cake rinsed with acetone. The filtrate and washings were distilled to dryness at 100° *in vacuo*. The sirupy residue was dissolved in ethanol (75 ml.) and poured into water (400 ml.), whereupon unchanged triisopropylidene-D-mannitol precipitated. This was filtered and air-dried to give 18.3 g., m.p. 68.5-69°. The filtrate was distilled *in vacuo* at 100° to a volume of 100 ml., whereupon an additional 1.6 g. of starting material was recovered. The filtrate was again distilled to dryness as before, yielding 28 g. of a mixture of 3,4;5,6-diisopropylidene-D-mannitol and 3,4-isopropylidene-D-mannitol. The corresponding crude mixture (112 g.) from several such runs involving a total of 247 g. of starting material was dissolved in benzene and chilled at 0°, producing 20 g. of crude 3,4-isopropylidene-D-mannitol, m.p. 76-78°. The benzene filtrate was taken to dryness, and the residue of impure 3,4;5,6-diisopropylidene-D-mannitol distilled in a wide-bore (24/40 joints) distilla-

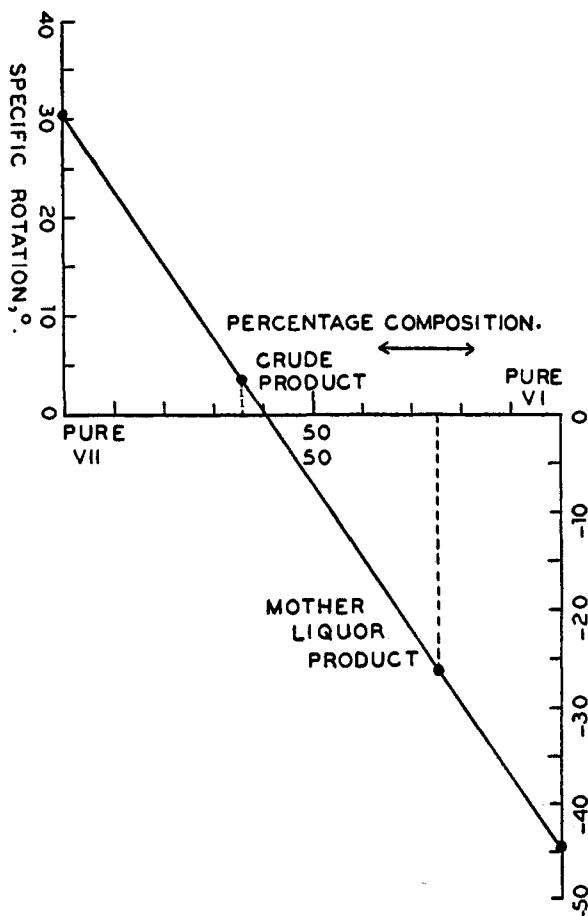


Fig. 3.—Rotation-composition diagram for 1-C-phenyl-D-pentitols.

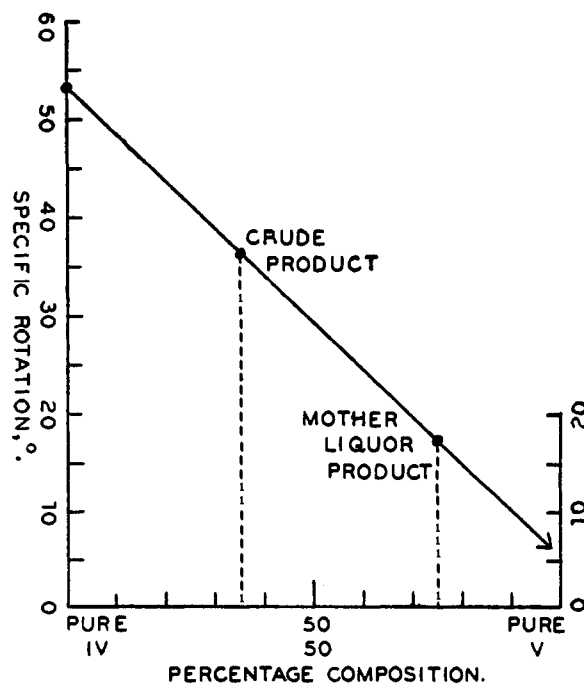


Fig. 4.—Rotation-composition diagram for 1-C-phenyl-2,3,4,5-diisopropylidene-D-pentitols.

tion apparatus. The main fraction distilled at 114–133° (0.4 mm.), weighed 59 g., and had n_D^{20} 1.4604.

2,3,4,5-Diisopropylidene-D-arabonaldehyde (I).—This substance was prepared by the sodium metaperiodate oxidation of 2,3,4,5-diisopropylidene-D-mannitol after the convenient procedure of English and Griswold.^{2b} The distilled product, b.p. 60–68° (0.3 mm. in wide-bore apparatus), from 31.4 g. of 2,3,4,5-diisopropylidene-D-mannitol weighed 24.6 g. (89%) and was used immediately in the Grignard reaction below.

Phenylmagnesium Bromide and 2,3,4,5-Diisopropylidene-D-arabonaldehyde.—The distilled 2,3,4,5-diisopropylidene-D-arabonaldehyde (24.6 g.) described above was dissolved in dry ether (100 ml.) and added over a period of 20 minutes to a solution of phenylmagnesium bromide prepared from bromobenzene (28 ml., 2.5 molecular equivalents) and magnesium (6.6 g.) in ether (100 ml.). The mixture was refluxed for 20 minutes, cooled in ice, and cautiously poured into ice-water (100 ml.) containing enough acetic acid to dissolve the magnesium salts. The layers were separated, and the aqueous layer extracted with 50 ml. of ether. The combined ether layers were washed with ice-water, dried over anhydrous sodium sulfate, and distilled to dryness *in vacuo* to give 32.4 g. of crude sirup. Similar results were obtained in another run twice this size.

The crude sirup (61.6 g.) was distilled in a wide-bore, short-path still into three fractions: Fraction 1, b.p. 65–115° (0.1 mm.), 2.7 g., rapidly solidified and proved to be mainly diphenyl (m.p. after recrystallization from a mixture of 2-propanol and water 68.5–69°; mixed m.p. with an authentic sample 68.5–69°); Fraction 2, b.p. 115–135° (0.1 mm.), 57.1 g. (92%) remained fluid while warm; Fraction 3, b.p. above 135° (0.1 mm.), 0.4 g., was discarded. Fraction 2 slowly solidified on cooling and had $[\alpha]_D^{20}$ 36.4° (*c* 2.199, pyridine). It was dissolved in 35–55° petroleum ether (100 ml.) and placed at 0° to yield 33.7 g. of crude 1-C-phenyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (IV), m.p. 77.5–78.5°. After two further recrystallizations from petroleum ether the pure product had m.p. 79–80.5° and $[\alpha]_D^{20}$ 53.2° (*c* 1.201, pyridine). English and Griswold^{2a} give m.p. 79–80°, $[\alpha]_D^{20}$ –53.0° (pyridine) for the enantiomorph 1-C-phenyl-2,3,4,5-diisopropylidene-L-*gluco*-pentitol.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.49; H, 7.82.

In another similar experiment the distilled, unseparated mixture of diastereomers had $[\alpha]_D^{20}$ 37.4° (*c* 2.677, pyridine).

1-C-Phenyl-D-*gluco*-pentitol (VII).—The above 1-C-phenyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (5.0 g.) was refluxed with 10% acetic acid (100 ml.) for four hours, then distilled to dryness *in vacuo* at 100°, giving 3.7 g. (102%) of crude, hydrolyzed product. This was dissolved in hot ethanol (15 ml.), filtered, through Celite, and the filtrate treated with acetone (15 ml.). On standing at 0° for several hours 1.9 g. of product crystallized, m.p. 138–138.5°. The mother liquors were evaporated at 100° in an air stream, dissolved in the minimum of hot ethanol, treated with acetone (15 ml.), seeded, and placed at 0° to produce an additional 1.1 g. of product, m.p. 138–138.5°. The combined crops were recrystallized twice from a mixture of ethanol and acetone, then dried for 1.5 hours at 1 mm. over phosphorus pentoxide in an Abderhalden drying pistol containing ethanol. The m.p. was unchanged at 138–138.5°, and $[\alpha]_D^{20}$ was 30.5° (*c* 1.049, pyridine).⁷

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.09. Found: C, 57.71, 57.76; H, 7.05, 7.08.

English and Griswold^{2a} report m.p. 137° and $[\alpha]_D^{20}$ –37.7° (pyridine) for the enantiomorph 1-C-phenyl-L-*gluco*-pentitol. In view of the fact that the product recovered from the mother liquors of the above recrystallizations had a specific rotation of 29.2° (*c* 0.653, pyridine), we believe the rotation value of the earlier workers to be a few degrees in error.

1-C-Phenyl-D-*manno*-pentitol (VI).—The petroleum ether mother liquors from the original crystallization of 1-C-phenyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol were concentrated *in vacuo* to give an amber oil, $[\alpha]_D^{20}$ 16.9° (*c* 1.419, pyridine). Four grams of this oil was refluxed with 10% acetic acid (60 ml.) for four hours, then concentrated to dry-

ness at 100° at the aspirator. There remained 2.6 g. (90%) of white solid, $[\alpha]_D^{20}$ –26.3° (*c* 1.178, pyridine). This was recrystallized from a mixture of ethanol (15 ml.) and acetone (15 ml.) to give 1.45 g. of product of m.p. 168.5–169.5°. After two further recrystallizations from the same solvent mixture the pure product had m.p. 172.5–173° and $[\alpha]_D^{20}$ –44.8° (*c* 0.760, pyridine).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 57.88; H, 7.09. Found: C, 57.98, 57.85; H, 7.04, 7.18.

Hydrolysis of Mixed 1-C-Phenyl-2,3,4,5-diisopropylidene-D-pentitols.—One gram of the crude, unseparated reaction product obtained by the action of phenylmagnesium bromide on 2,3,4,5-diisopropylidene-D-arabonaldehyde was hydrolyzed as above with dilute acetic acid (30 ml.). The crude product was a gummy solid. After drying at 1 mm. over phosphorus pentoxide the sample had $[\alpha]_D^{20}$ 3.7° (*c* 1.090, pyridine).

1-C-Cyclohexyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (VIII).—This product was prepared by the action of cyclohexylmagnesium bromide on 2,3,4,5-diisopropylidene-D-arabonaldehyde after the manner of English and Griswold.^{2b} The crude reaction product was crystallized without prior distillation from petroleum ether to give the desired substance of m.p. 75–76°. This was used without further purification.

1-C-Cyclohexyl-D-*gluco*-pentitol (IX).—The above product (0.70 g.) was hydrolyzed as before by refluxing for 3.5 hours with 10% acetic acid (15 ml.) and concentrating to dryness. One recrystallization from a mixture of ethanol (3 ml.) and acetone (10 ml.) gave 0.32 g. of white needles, m.p. 147.5–148.5°, $[\alpha]_D^{20}$ –15.3° (*c* 0.620, pyridine). English and Griswold^{2b} report m.p. 148° and $[\alpha]_D^{20}$ –15.0° (pyridine) for this product.

Hydrogenation of 1-C-Phenyl-D-*gluco*-pentitol.—1-C-Phenyl-D-*gluco*-pentitol (1.00 g.) was dissolved in acetic acid, placed in a 300-ml. hydrogenation bomb, treated with Adams catalyst (0.25 g.), and hydrogen run in to a pressure of 1500 p.s.i. The mixture was shaken at 60° for 1.5 hours after the method of Baker and Schuetz.⁸ After cooling, the catalyst was filtered, and the filtrate evaporated to dryness *in vacuo* at 100°. The crude, solid residue (1.12 g.) was recrystallized from a mixture of ethanol (5 ml.) and acetone (15 ml.) to give 0.65 g. of product m.p. 147°. Another recrystallization resulted in the pure product m.p. 148°, $[\alpha]_D^{20}$ –15.2° (*c* 1.085, pyridine). This sample showed no mixed melting point depression (147.5–148°) with the 1-C-cyclohexyl-D-*gluco*-pentitol prepared above.

1-C-Phenyl-1-methyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (X).—1-C-Phenyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (5.00 g.) was dissolved in methyl iodide (50 ml.) and the solution treated with silver oxide (20 g.), Drierite (20 g.) and glass beads (15 g.). The mixture was refluxed under calcium chloride tube protection for about 30 hours, stirring with a mercury-sealed Hershberg stirrer. The mixture was then filtered, and the cake rinsed by suspending several times in chloroform and refiltering. The combined filtrates were distilled to a thick sirup at 100° *in vacuo* to give 5.1 g. (98%) of clear, thin sirup. The product was distilled through a semimicro, wide-bore, short-path still and air condenser. A total of 4.73 g. of pure material, b.p. 146–147° (1.5 mm.; bath temperature 164–174°), was obtained, with a middle cut being taken for determination of the properties and analysis. The middle cut had $[\alpha]_D^{20}$ 75.6° (*c* 1.283, pyridine) and n_D^{20} 1.4899.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 67.10; H, 8.13. Found: C, 66.61, 66.65; H, 8.04, 8.07.

Impure 1-C-Phenyl-1-methyl-2,3,4,5-diisopropylidene-D-*manno*-pentitol (XVII).—20.7 grams of the sirup, $[\alpha]_D^{20}$ 16.9° (pyridine), obtained on concentration of the petroleum ether mother liquors which produced the 1-C-phenyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol were dissolved in methyl iodide (180 ml.). The solution was treated with silver oxide (100 g.), Drierite (100 g.) and glass beads (75 g.), and the reaction conducted as above. The 19.0 g. (88%) of crude, sirupy product was isolated as before, and distilled at 114–118° (0.1 mm.) to give 17.7 g. of clear sirup having $[\alpha]_D^{20}$ 6.1° (*c* 3.450, pyridine). Since this was a mixture of the two diastereomeric methyl ethers, it was not analyzed.

1-C-Phenyl-1-methyl-D-*gluco*-pentitol (XI).—1-C-Phenyl-1-methyl-2,3,4,5-diisopropylidene-D-*gluco*-pentitol (4.3 g.) was refluxed for four hours with 10% acetic acid (70 ml.),

(7) All products melting above 100° were dried in a similar manner prior to analysis. Other products were dried over phosphorus pentoxide at room temperature in a vacuum desiccator.

(8) R. H. Baker and R. D. Schuetz, *THIS JOURNAL*, **69**, 1250 (1947).

then concentrated to dryness to give 3.10 g. (96%) of white solid. This was recrystallized from a mixture of ethanol (20 ml.) and acetone (20 ml.) to give 2.50 g. of product of m.p. 172–173°. Two further recrystallizations gave the pure product, m.p. 172.5–173°, $[\alpha]_D^{25}$ 39.2° (*c* 0.843, pyridine).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.50; H, 7.49. Found: C, 59.13; H, 7.43.

1-C-Phenyl-1-methyl-D-manno-pentitol (XVIII).—The distilled, impure 1-C-phenyl-1-methyl-2,3;4,5-diisopropylidene-D-manno-pentitol described above (17.30 g.) was hydrolyzed as before with 120 ml. of 10% acetic acid. On cooling after the refluxing a small amount (1.0 g.) of residual diphenyl separated. The aqueous layer was accordingly extracted with chloroform before evaporation to dryness. Evaporation left 15.60 g. of crude product, which was recrystallized from a mixture of ethanol (35 ml.) and acetone (100 ml.) to give 5.6 g. of a first crop, m.p. 141–143°. The mother liquors were evaporated dry in an air stream at 100°, and the residue recrystallized from ethanol (10 ml.) and acetone (30 ml.) to give 5.2 g. of second crop, m.p. 115–120°. The combined crops were recrystallized twice from ethanol (20 ml.) and acetone (80 ml.) to give 9.35 g. of product, m.p. 142–144°. Another recrystallization from the same quantities of the solvent mixture gave 5.3 g. of substance of the same melting point, and having $[\alpha]_D^{25}$ –49.9° (*c* 0.942, pyridine).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.50; H, 7.49. Found: C, 59.18; H, 7.64.

L-(+)-1-Methoxyphenylacetaldehyde (XII).—1-C-Phenyl-1-methyl-D-glucos-pentitol (5.00 g.) was dissolved with heating in water (100 ml.), and the solution cooled in ice. Sodium metaperiodate (14.60 g., 10% excess) (prepared by recrystallization of Eastman Kodak Co. sodium paraperiodate from dilute nitric acid after the method of Hill⁹) was dissolved in water (225 ml.) and cooled in ice. The latter solution was poured into the former (chilled in ice) in small quantities over a period of ten minutes, and the mixture allowed to stand in ice for 30 minutes. The solution was then saturated with sodium chloride and extracted five times with 25-ml. portions of chloroform. The chloroform extracts were dried over anhydrous sodium sulfate, filtered, and the solvent removed from the filtrate *in vacuo* at 35°. There remained 2.88 g. (93%) of the crude aldehyde, $[\alpha]_D^{25}$ 81.2° (*c* 3.710, chloroform). It was oxidized directly with no attempt at purification. In a smaller scale run involving 1 g. of starting material, a 0.43 g. (70%) yield of aldehyde, $[\alpha]_D^{25}$ 85.2° (*c* 1.386, chloroform) was obtained. When 0.91 g. of the starting material was oxidized with proportional quantities of sodium metaperiodate at room temperature instead of 0°, 0.52 g. (92%) of aldehyde, $[\alpha]_D^{25}$ 74.8° (*c* 1.873, chloroform) resulted. Apparently the extent of racemization was somewhat greater at the higher temperature.

In another experiment the starting material (1.50 g.) was suspended in chloroform (15 ml.) and the solution stirred in ice with glass beads. Lead tetraacetate (9.06 g., 10% excess) dissolved in chloroform (35 ml.) was chilled and added to the former suspension over a 15-minute period. The mixture was then stirred for an hour at room temperature, glycerol (1 ml.) was added, and stirring continued another 15 minutes. The chloroform was washed twice with water, dried over anhydrous sodium sulfate, filtered, and the solvent distilled to yield 0.58 g. (62%) of the aldehyde having $[\alpha]_D^{25}$ 68.9° (*c* 1.336, chloroform). In the lead tetraacetate oxidation the extent of racemization of the aldehyde was thus apparently slightly greater. At high dilution the aldehyde obtained in each case had an odor reminiscent of roses.

L-(+)-1-Methoxyphenylacetaldehyde 2,4-Dinitrophenylhydrazone.—The aldehyde from one of the above periodate oxidations (0.45 g.) was converted to the 2,4-dinitrophenylhydrazone according to the procedure of Shriner and Fuson.¹⁰ The crude product dissolved in dilute ethanol came down as a gum. On standing, however, this reverted to an amorphous solid. This was recrystallized twice from dilute ethanol and thrice from ethanol to give the pure product, m.p. 100–101.5°.

Anal. Calcd. for $C_{15}H_{14}O_6N_4$: C, 54.50; H, 4.27; N, 16.95. Found: C, 54.86; H, 4.30; N, 17.13, 17.21.

(9) A. E. Hill, *This Journal*, **50**, 2678 (1928).

(10) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

D-(–)-1-Methoxyphenylacetaldehyde (XIX).—1-C-Phenyl-1-methyl-D-manno-pentitol (3.00 g.) was dissolved in water (80 ml.) and oxidized with sodium periodate (8.75 g.) in water (135 ml.) at 0° in the manner described for the L-(+)-derivative. The crude aldehyde obtained weighed 1.73 g. (93%) and had $[\alpha]_D^{25}$ –52.3° (*c* 3.637, chloroform).

O-Methyl-L-(+)-mandelic Acid (XIII).—L-(+)-1-Methoxyphenylacetaldehyde (2.77 g.) was dissolved in acetone (35 ml.) containing water (5 ml.). The solution was treated with silver oxide (5 g.) and glass beads (10 g.), and the mixture shaken mechanically overnight. More silver oxide (5 g.), 50% acetone (20 ml.), and more glass beads (10 g.) were added, and the shaking continued for another nine hours, whereupon 50% hydrochloric acid (14 ml.) was added and the mixture shaken for six hours. The solid was filtered and rinsed with water and chloroform. The filtrate was saturated with salt and extracted three times with chloroform. The extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate vacuum-evaporated to dryness at 100°, leaving 2.63 g. (86%) of dark oil which crystallized spontaneously and had $[\alpha]_D^{25}$ 132.0° (*c* 1.470, chloroform). After several recrystallizations, with Norit decolorization, from 55–85° petroleum ether, pure O-methyl-L-(+)-mandelic acid was obtained, m.p. 64–65°, $[\alpha]_D^{25}$ 150.0° (*c* 0.861, ethanol). This sample showed no mixed melting point depression with the authentic sample prepared synthetically below.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.00; H, 6.09. Found: C, 65.27; H, 6.13.

O-Methyl-D-(–)-mandelic Acid (XX).—The above sample of D-(–)-1-methoxyphenylacetaldehyde (1.73 g.) was dissolved in acetone (25 ml.) containing water (6 ml.). The solution was treated with silver oxide (7 g.) and glass beads (13 g.), and the mixture shaken for 15 hours. Fifty per cent hydrochloric acid (10 ml.) was added, the mixture shaken four hours, and the product isolated as described above. There resulted 1.70 g. (89%) of dark oil, $[\alpha]_D^{25}$ –86.8° (*c* 1.350, ethanol), which very slowly crystallized. This was combined with 0.55 g. of similarly obtained product, $[\alpha]_D^{25}$ –76.5° (*c* 1.177, ethanol), resulting from another run. The combined samples were dissolved in hot petroleum ether (80 ml.), decanting from a small amount of insoluble material. The product came down as two crystal types, small prisms and clumps of needles. An attempt was made to remove the latter mechanically. These weighed 0.55 g. and had m.p. 65–66°. Their recrystallization from petroleum ether (25 ml.) resulted in 0.20 g. of slightly impure O-methyl-D,L-mandelic acid, m.p. 69.5–70°, $[\alpha]_D^{25}$ –11.4° (*c* 0.700, ethanol), mixed m.p. with an authentic sample (of m.p. 69–70°) 70–71°. All of the mother liquors from the above recrystallizations were combined, rejecting any intermediately formed crystals. These were concentrated *in vacuo* to dryness giving 0.80 g. of an oil which was dissolved in petroleum ether (25 ml.) and seeded with an authentic sample of O-methyl-D-(–)-mandelic acid. On standing 0.25 g. of splendid needles resulted, m.p. 62–63.5°. Recrystallization from petroleum ether (12 ml.) resulted in a practically pure product, m.p. 63.5–64.5°, $[\alpha]_D^{25}$ –146.0° (*c* 0.747, ethanol), mixed m.p. with an authentic sample of O-methyl-D-(–)-mandelic acid (of m.p. 65–66°) 65–66°.

L-(+)-Mandelic and D-(–)-Mandelic Acids (XIV and XXI).—D,L-Mandelic acid was resolved by the elegant procedure of Smith¹¹ using the enantiomorphous α -phenylethylamines¹² to secure both acids. The L-(+)-acid had m.p. 133° and $[\alpha]_D^{25}$ 157.0° (*c* 1.070, water), while the D-(–)-acid had m.p. 132.5–133° and $[\alpha]_D^{25}$ –154.0° (*c* 2.060, water).

Methyl L-(+)- and D-(–)-Mandelates (XV and XXII).—The resolved samples of mandelic acid above were esterified by the method of Fischer and Speier¹³ by refluxing with methanol containing sulfuric acid. The methyl-D-(–)-mandelate, b.p. 100–104° (1 mm.), $[\alpha]_D^{25}$ –174.3° (*c* 1.234, chloroform) was obtained in 89% yield. One-half gram of this was recrystallized from 55–85° petroleum ether (10 ml.) to give 0.45 g. of solid, m.p. 55.5°, $[\alpha]_D^{25}$ –174.2° (*c* 0.580, chloroform). McKenzie and Wren¹² gave m.p. 54–55°,

(11) L. Smith, *J. prakt. Chem.*, [2] **84**, 743 (1911).

(12) A. W. Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

(13) E. Fischer and A. Speier, *Ber.*, **28**, 3252 (1895); A. McKenzie and H. Wren, *J. Chem. Soc.*, **93**, 312 (1908).

and Walden¹⁴ reports $[\alpha]^{18D} -167^\circ$ (chloroform) for this substance. The methyl L-(+)-mandelate, b.p. 95–97° (1 mm.), $[\alpha]^{25D} 171.4^\circ$ (*c* 1.833, chloroform), was obtained in 87% yield. One gram of this recrystallized from petroleum ether (20 ml.) gave 0.91 g. of the pure ester, m.p. 55.5°, $[\alpha]^{25D} 173.5^\circ$ (*c* 0.968, chloroform).

Anal. Calcd. for C₉H₁₀O₃: C, 65.00; H, 6.09. Found: C, 64.91; H, 5.98.

Methyl O-Methyl-L-(+)- and O-Methyl-D(-)-mandelates (XVI and XXIII).—Unrecrystallized methyl D(-)-mandelate (9.05 g.), methyl iodide (40 ml.), silver oxide (15 g.), Drierite (10 g.) and glass beads (10 g.) were stirred under reflux with calcium chloride tube protection for 24 hours. After diluting with chloroform, filtering, rinsing the cake with chloroform, and distilling the solvents *in vacuo* there remained 9.59 g. (98%) of crude product, $[\alpha]^{24D} -89.1^\circ$ (*c* 1.111, acetone). McKenzie and Wren¹⁵ give $[\alpha]^{13D} -96.3^\circ$ (acetone) for pure methyl O-methyl-D(-)-mandelate. Methyl L-(+)-mandelate was methylated by the same procedure with identical results. The crude product was distilled, b.p. 79–88° (1 mm.), and a middle cut taken for rotation and analysis; $[\alpha]^{23D}$ was 88.7° (*c* 1.070, acetone).

Anal. Calcd. for C₁₀H₁₂O₃: C, 66.70; H, 6.74. Found: C, 66.59; H, 6.76.

O-Methyl-L-(+)- and O-Methyl-D(-)-mandelic Acids (XIII and XX).—Since alkaline hydrolysis of the above methyl esters may be attended by a certain amount of racemization,¹⁶ these were hydrolyzed under acidic conditions, where the extent of racemization was found not very marked. Methyl O-methyl-D(-)-mandelate (4.00 g.) was refluxed for three hours with water (30 ml.) containing sulfuric acid (1.25 ml.). The mixture was cooled, saturated with salt, and extracted twice with chloroform. The extract was dried over anhydrous sodium sulfate, filtered, and the solvent distilled *in vacuo* to yield 3.28 g. (89%) of crude, amber oil, $[\alpha]^{22D} -144.0^\circ$ (*c* 1.174, ethanol), which crystallized spontaneously. This was dissolved in 55–85° petroleum ether (100 ml.), the solution decanted from a small amount of sludge and slowly cooled. The product crystallized as splendid long needles. Another recrystallization gave 2.10 g. of practically pure product, m.p. 65–66°, $[\alpha]^{25D} -148.4^\circ$ (*c* 1.025 ethanol). McKenzie and Wren¹⁴ give m.p. 63–64°, $[\alpha]^{17D} -150.1^\circ$ (ethanol) for O-methyl-D(-)-mandelic acid. Hydrolysis of methyl O-methyl-L-(+)-mandelate by the same procedure gave similar results. After two recrystallizations from petroleum ether the product had m.p. 64–65° and $[\alpha]^{25D} 149.4^\circ$ (*c* 0.964, ethanol).

Infrared Absorption Spectra.—The infrared absorption spectra of the O-methyl-L-(+)-mandelic acid prepared synthetically above and of the sample prepared before by degradative means were determined with a Perkin-Elmer Infrared Spectrometer in the region 8–15 μ . The samples were prepared by grinding into a mineral oil suspension as recommended by Kuhn.¹⁷ The author is indebted to his colleague, Dr. John H. Wise, for determination of these spectra.

(16) A. McKenzie and H. Wren, *ibid.*, **115**, 611 (1919).
(17) L. P. Kuhn, *Anal. Chem.*, **22**, 276 (1950).

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The Frequency of the Third Harmonic O-H Band of Methanol in Various Solvents, and the Hydrogen Bonding of Methanol with Aromatic Hydrocarbons

BY LLEWELLYN H. JONES AND RICHARD M. BADGER

The absorption spectra of dilute solutions of methanol in several solvents have been observed in the region of the third harmonic of the OH band. In non-polar solvents the OH frequency is shifted from its position in the vapor by an amount proportional to $(D - 1)/(2D + 1)$ where D is the static dielectric constant of the medium. In certain polar chlorinated solvents the frequency shift is less, but in aromatic solvents the large shift is taken as an indication of hydrogen bond formation.

Introduction

Though benzene has sometimes been regarded as an inert solvent, and has indeed been used as a medium in which to investigate the association of substances by hydrogen bonding,¹ it was some time ago pointed out that this liquid appears to exhibit an interaction with proton donor substances which may probably be described as the formation of a weak hydrogen bond.² Evidence for this interaction is the fact that phenol, for example, is much less strongly associated in benzene than in carbon tetrachloride. Furthermore, the fundamental and harmonics of the OH valence vibration of the unassociated alcohol molecules are found at considerably lower frequencies in the former solvent than in the latter.^{3,4,5}

In dilute solutions of an alcohol in an organic solvent one finds that the frequency of the OH band is in general somewhat less than in the

vapor state. If there is a simple electrostatic interaction of the oscillating dipole with its surroundings of dielectric constant D , the frequency shift will be comparatively small and Kirkwood⁶ has shown that it should be approximately proportional to $(D - 1)/(2D + 1)$.⁷ Where the shift is much larger, an interaction of a different character appears to be indicated.

It has seemed of interest to investigate further the interaction between proton donor substances and aromatic hydrocarbons and in particular to study the effect of substitution. Consequently the third harmonic of the OH band of methanol has been observed in solutions of this alcohol in benzene, toluene, *m*-xylene, mesitylene, pseudocumene and α -methyl-naphthalene. For comparison purposes several non-aromatic solvents also were employed. As will be seen later, these fall into two classes; one of these includes the non-polar substances, carbon tetrachloride, *n*-hexane and cyclohexane, and the other the halogenated hydrocarbons,

(1) E. N. Lassette and R. G. Dickinson, *THIS JOURNAL*, **61**, 54 (1939).

(2) R. M. Badger, *J. Chem. Phys.*, **8**, 288 (1940).

(3) A. Naherniac, *Ann. phys.*, **7**, 528 (1937).

(4) Kreuzer and Mecke, *Z. physik. Chem.*, **B49**, 309 (1942).

(5) See also W. Lüttke and R. Mecke, *Z. Elektrochem.*, **53**, 241 (1949).

(6) J. G. Kirkwood, private communication.

(7) The dielectric constant to be used here is the static value. In discussing shifts of frequency where an electronic transition is involved this will not be appropriate. Cases of this sort have recently been discussed by N. S. Bayliss, *J. Chem. Phys.*, **18**, 292 (1950).