

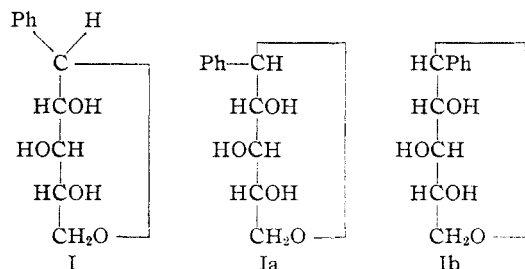
[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF STANFORD UNIVERSITY AND NORTHWESTERN UNIVERSITY]

The Stereochemical Configuration of the Number One Carbon Atom in β -D-Xylopyranosylbenzene

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A simplification in the method of preparing triacetyl- β -D-xylopyranosylbenzene is described. This substance has been deacetylated to give crystalline β -D-xylopyranosylbenzene which, along with its crystalline tripropionate and tribenzoate, is described for the first time. The question of the stereochemical configuration of the anomeric center in β -D-xylopyranosylbenzene has been answered experimentally in the following way. The action of periodate on β -D-xylopyranosylbenzene led to sirupy phenyldiglycolaldehyde. This in turn was oxidized to phenyldiglycolic acid, which was esterified and converted to its crystalline amide. The latter proved identical with an authentic sample of D-(+)-2-phenyldiglycolamide prepared synthetically from L-(+)-mandelic acid. The identity of the two samples establishes the anomeric center of β -D-xylopyranosylbenzene as possessing the 1,2-*trans* or β -configuration, a fact presumably capable of generalization to other low-rotating d-glycopyranosylaromatic hydrocarbons formerly designated β - in view of their low specific rotations.

Glycosylated aromatic hydrocarbons, as typified by β -D-xylopyranosylbenzene (I) are available by several synthetic routes, namely, (a) the catalytic alkylation of aromatic hydrocarbons with polyacetyl- α -D-glycopyranosyl halides¹ or fully ac-



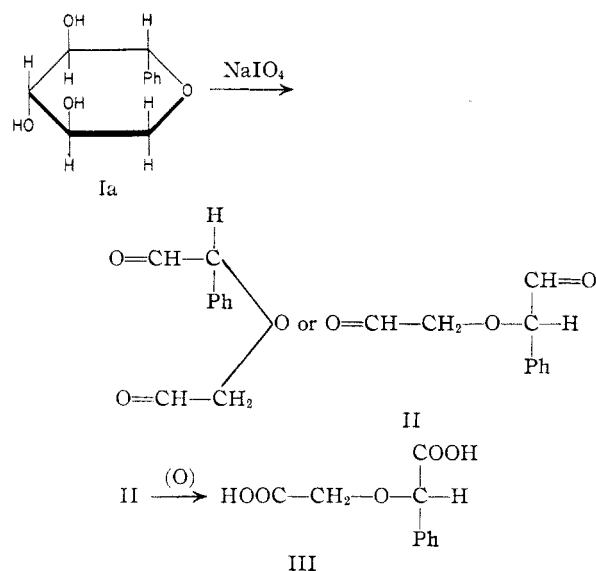
tylated D-aldoses,² (b) the metathetical reaction of the halogen atom of a polyacetyl- α -D-glycopyranosyl halide with a Grignard reagent^{3,4,5} and (c) the reaction of a polyacetyl- α -D-glycopyranosyl halide with certain other organometallic reagents.⁶ Preparation of such glycopyranosylbenzenes by the Grignard method gave good yields of crystalline, low-rotating β -anomers, as well as substantial amounts of sirupy, high-rotating products previously designated as the " α -anomers." With glucopyranosylbenzene, the sirupy product was recently⁷ shown to be a mixture of the two anomers and from the mixture pure, crystalline α -D-glucopyranosylbenzene was obtained. Crystalline α - and β -D-mannopyranosylbenzenes and their tetraacetates have also been described.⁵

The nomenclature of the anomeric glycosylaromatic hydrocarbons has been based on optical rotations according to Hudson's convention,⁸ not on the actual stereochemical configurations at the anomeric centers. There has been no information as to whether the rotationally designated β -anomer, I, for example, actually possesses the configurational β -structure (*trans*), typified by Ia, or the configurational α -structure (*cis*), typified by Ib. The present investigation provides information on this point, and shows that indeed it is Ia.

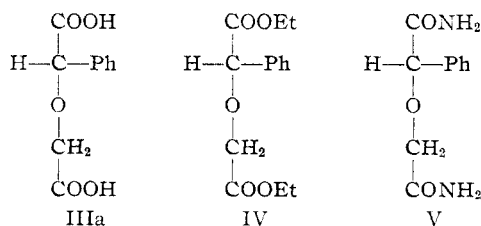
This proof of structure rests on the fact that the configuration of the carbon atom holding the

phenyl group in I can be correlated with the structure of L-(+)-mandelic acid.⁹ Structure Ia, but not Ib, would permit this relationship.

Periodate oxidation of Ia would lead to the dialdehyde, II, whose oxidation would in turn produce the acid III.



III might be named L-(O-carboxymethyl)-mandelic acid to emphasize its structural relationship to L-(+)-mandelic acid. The diglycolic acid skeleton in III is better suited for naming, however, since it treats both carboxyl groups alike. From this viewpoint structure III would be oriented as IIIa, and named D-2-phenyldiglycolic acid.



Conversion of III to ethyl-D-2-phenyldiglycolate (IV) and reaction of the latter with ammonia would produce D-2-phenyldiglycolamide (V). Independent synthesis of V from L-mandelic acid would establish its identity, especially as regards the con-

- (1) C. D. Hurd and W. A. Bonner, *THIS JOURNAL*, **67**, 1664 (1945).
- (2) C. D. Hurd and W. A. Bonner, *ibid.*, **67**, 1759 (1945).
- (3) C. D. Hurd and W. A. Bonner, *ibid.*, **67**, 1972 (1945).
- (4) W. A. Bonner, *ibid.*, **68**, 1711 (1946).
- (5) C. D. Hurd and R. P. Holysz, *ibid.*, **72**, 1732 (1950).
- (6) C. D. Hurd and R. P. Holysz, *ibid.*, **72**, 1735, 2005 (1950).
- (7) W. A. Bonner and J. M. Craig, *ibid.*, **72**, 3480 (1950).
- (8) C. S. Hudson, *ibid.*, **31**, 66 (1909).

- (9) K. Freudenberg, F. Brauns and H. Siegel, *Ber.*, **56**, 193 (1923); K. Freudenberg and L. Markert, *ibid.*, **58**, 1753 (1925).

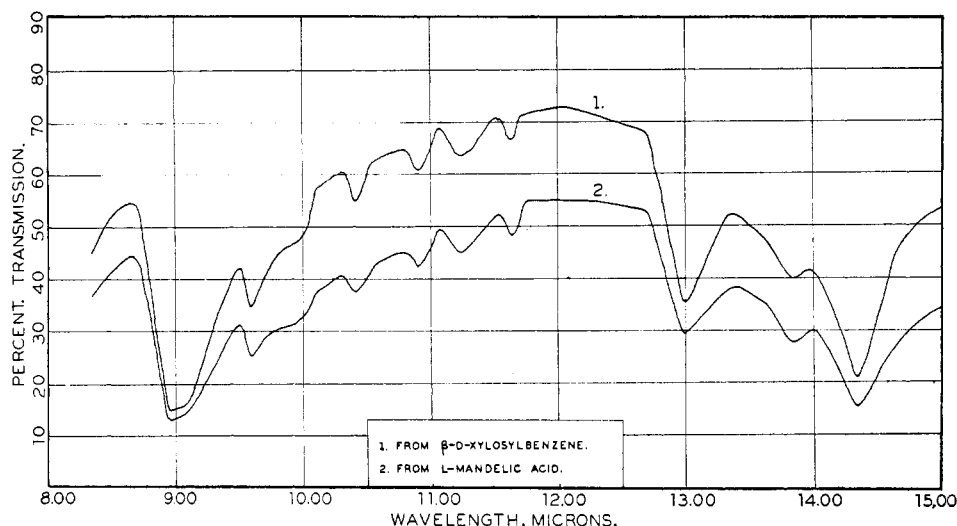
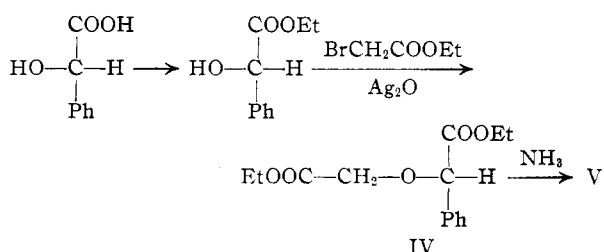


Fig. 1.—Infrared absorption spectra of D(+)-2-phenyl diglycolamide samples.

figuration at the asymmetric carbon. The following sequence illustrates the steps contemplated in the synthesis of V.



An improved method for the preparation of triacetyl- β -D-xylopyranosylbenzene was developed wherein it was unnecessary to isolate triacetyl- α -D-xylopyranosyl chloride in purified form as the starting material. The crude sirup obtained on treatment of β -D-xylose tetraacetate with titanium tetrachloride gave acceptable yields of triacetyl- β -D-xylopyranosylbenzene on treatment with excess phenylmagnesium bromide. The product was readily deacetylated to produce I, which, along with its tripropionate and tribenzoate are here reported for the first time.

Determination of the ring size of I by the usual procedure¹⁰ with periodic acid confirmed the pyranose ring, in agreement with previous results on compounds of the same type.^{5,6,7} Isolation of the product after such a reaction, or after oxidation with sodium periodate, resulted in a glassy sirup, the dialdehyde, II. This sirup could not be readily purified, and its rotation varied widely depending on its method of isolation. The sirupy nature of II makes the rotational discrepancies not too surprising. It was found that I itself could be readily extracted from water into ether, and any remaining unoxidized or partially oxidized material could account for the randomness in the rotations of various samples of II. No well defined solid derivative was found for II.

When II was oxidized with potassium hypoiodite the acid III, ester IV and amide V subsequently ob-

tained were found substantially racemic. Presumably the alkaline conditions prevailing during the oxidation permitted racemization of II or III through the accepted enolization mechanism.¹¹ When silver oxide was used as oxidant in the reaction II \rightarrow III, however, the crude acid and its derivatives were only partially racemized. Purification of the final amide, V, gave D(+)-2-phenyldiglycolamide, m.p. 172–172.5°, $[\alpha]_D^{25}$ 102.2° (ethanol). This sample had a comparable rotation and showed no mixed m.p. depression and identical infrared absorption spectrum (Fig. 1) with the authentic D(+)-2-phenyldiglycolamide described below.

For comparative purposes the enantiomorphous phenyldiglycolamides were prepared synthetically. The synthesis was first attempted by the action of ethyl bromoacetate on the sodium salt of carefully resolved ethyl mandelate, after Godchot's method¹² for preparing D,L-phenyldiglycolamide. The resulting ethyl phenyldiglycolate, however, proved to be racemic, indicating that the anion of sodium ethyl mandelate was optically unstable. This interpretation was supported by the fact that when ethyl L(+)-mandelate was converted to its sodium derivative and the latter retained for five hours at room temperature, the ethyl mandelate regenerated on treatment with water was 96% racemized.

The use of silver oxide or silver carbonate as condensing agent, however, permitted the enantiomorphous ethyl phenyldiglycolates to be synthesized in good yield from ethyl bromoacetate and the active ethyl mandelates. It should be emphasized that inversion could not attend this process, since the bond between oxygen and the asymmetric centers in the latter esters remains undisturbed. The enantiomorphous ethyl phenyldiglycolates, in turn, gave good yields of the corresponding phenyldiglycolamides on ammonolysis.

Although the enantiomorphous amides were prepared identically, have practically opposite rotations, and both analyze correctly, the melting point of the D(–)-2-phenyldiglycolamide was not raised to that of the L(+)-enantiomorph even after sev-

(10) E. L. Jackson in Chap. 8, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944.

(11) A. McKenzie and H. Wren, *J. Chem. Soc.*, **115**, 602 (1919).

(12) M. Godchot, *Compt. rend.*, **177**, 1226 (1923).

eral recrystallizations. This is perhaps due to the presence of small amounts of some impurity not removed by recrystallization, or to crystallization as a polymorphic modification. When equal amounts of the enantiomorphous amides were ground together, the m.p. of the mixture was 160–161°, identical with and not depressing the m.p. of racemic 2-phenyldiglycolamide. When a small quantity of one of the active amides was mixed with an excess of the racemic modification, the m.p. of the latter was depressed, suggesting the racemic form to be an actual racemic compound.¹³

When either racemic or active ethyl phenyldiglycolates were prepared by the silver oxide or silver carbonate method, the formation of a low-boiling by-product was invariably noted. This was identified as ethyl diglycolate, formed apparently by action of the condensing agent upon the excess of ethyl bromoacetate. Heintz¹⁴ has noted the formation of ethyl diglycolate by action of sodium carbonate on ethyl chloroacetate, and apparently a similar type of reaction occurs in the present experiments.

An interesting point arises in connection with the periodate oxidation of I to II. When the rotations of the *crude* ester IV and the *crude* amide V are compared with the rotations of the pure enantiomorphs IV and V, it is found that the *crude* degradation products contain about 20% of the enantiomorphous structure. Since racemization during the silver oxide oxidation of II to III is unlikely, it appears possible that the periodate oxidation of I to II is accompanied by slight racemization. Partial racemizations attending periodate oxidations of structures containing an aromatic ring have previously been noted in configurational studies in the 1-C-phenyl-D-pentitol series.¹⁵

Isolation of D(+)-2-phenyldiglycolamide on degradation of I clearly indicates that the D-xylopyranosylbenzene rotationally designated as β -actually possess the β -configuration (*trans*). Since anomeric designations based on optical rotations generally accord with designations based on actual configuration, there is little reason to doubt that other rotationally designated β -anomers in the glycosylaromatic hydrocarbon series also possess the β -configuration. We may, therefore, tentatively conclude that the question of anomeric configuration in this series has been answered.

Experimental

Triacetyl- β -D-xylopyranosylbenzene.— β -D-Xylose tetraacetate¹⁶ (50 g., m.p. 126–127°) was dissolved in chloroform (240 ml., distilled from phosphoric anhydride), and the solution treated with a mixture of titanium tetrachloride (15 ml.) in dry chloroform (125 ml.).¹⁷ The mixture was refluxed for four hours, cooled, and washed four times with water, breaking the emulsion when necessary by filtration through Celite. The solution was dried over magnesium sulfate, filtered, and the solvent distilled from the filtrate *in vacuo* at 50–60°. The residue was dissolved in dry ether (400 ml.), and the solution slowly added to a Grignard solution made from bromobenzene (296 g.) and magnesium (46 g.) in dry ether (600 ml.). The mixture was stirred under reflux for several hours after completion of the addition,

allowed to stand overnight, and cautiously decomposed by pouring into ice-water acidified with acetic acid. The water layer was washed with ether, then concentrated to dryness *in vacuo* at 100°. The residue, oven-dried for several days, was acetylated at 100° with acetic anhydride (800 ml.) and sodium acetate (50 g.), adding the anhydride in small portions at the outset. The mixture, stirred for five hours at 100°, was cooled, poured onto ice, diluted with water to 3800 ml., and allowed to stand at 5° overnight. The product was extracted with ether, and the ether extract processed in the usual way³ to produce 20.1 g. (37.2%) of triacetyl- β -D-xylopyranosylbenzene, m.p. 170.5°. When the above Grignard reaction was conducted four times and the combined aqueous layer residues (1800 g.) acetylated as above with acetic anhydride (4300 ml.) and sodium acetate (1000 g.), the yield of final product was 108 g. (50%).

β -D-Xylopyranosylbenzene.—Triacetyl- β -D-xylopyranosylbenzene (125.4 g.) was treated with methanol (1300 ml.) and two freshly cut chips of sodium.¹⁸ Solution of the acetate was complete within thirty minutes, and deacetylation was allowed to continue overnight. The solution was partially decolorized by filtration through Norit, and the solvent removed from the filtrate at 100° *in vacuo*. The white residue was dissolved in boiling ethyl acetate (800 ml.) and the solution clarified by filtration through Norit. On cooling, 47.7 g. of white needles resulted, m.p. 149.5–150°. Concentration of the mother liquors to 150 ml. led to an additional 13.5 g., m.p. 149.5–150°, total yield 78%. Recrystallization from ethyl acetate gave a product of m.p. 150–151°, $[\alpha]_D^{25} -14.4^\circ$ (*c* 7.28, water).

Anal. Calcd. for $C_{11}H_{11}O_4$: C, 62.84; H, 6.72. Found: C, 62.81; H, 6.60.

Acetylation of β -D-Xylopyranosylbenzene.— β -D-Xylopyranosylbenzene (1.00 g.) was dissolved in pyridine (10 ml.) and acetic anhydride (10 ml.) added. After three days the solution was poured into water (60 ml.), and the mixture allowed to stand for 90 minutes. Ether extraction followed by the usual processing led to a quantitative yield of triacetyl- β -D-xylopyranosylbenzene, m.p. after one recrystallization from 2-propanol, and mixed m.p. with an authentic sample 170°.

Tripropionyl- β -D-xylopyranosylbenzene.— β -D-Xylopyranosylbenzene (2.00 g.) was caused to react with propionic anhydride (20 ml.) in pyridine (20 ml.) as above. The crude product, m.p. 118.5–119.5°, weighed 3.52 g. (98%). After two recrystallizations from 2-propanol (20 ml.) containing water (3 ml.), the product had m.p. 121°, $[\alpha]_D^{25} -48.8^\circ$ (*c* 3.63, chloroform).

Anal. Calcd. for $C_{20}H_{26}O_7$: C, 63.95; H, 6.94. Found: C, 63.98; H, 7.39.

Tribenzoyl- β -D-xylopyranosylbenzene.— β -D-Xylopyranosylbenzene (2.00 g.) in pyridine (30 ml.) reacted with benzoyl chloride (20 ml.). After three days the mixture was poured into water and the product (4.21 g. [85%]) isolated as before. After two recrystallizations from 2-propanol the substance showed m.p. 175–175.5°, $[\alpha]_D^{25} -60.5^\circ$ (*c* 5.03, chloroform).

Anal. Calcd. for $C_{32}H_{26}O_7$: C, 73.63; H, 5.02. Found: C, 73.69; H, 4.97.

Periodic Acid Oxidation of β -D-Xylopyranosylbenzene.—A solution of β -D-xylopyranosylbenzene (2.1020 g.) in 0.2655 *M* periodic acid (82.83 ml.) was allowed to stand overnight, then analyzed for excess periodic acid in the usual way.¹⁰ Five ml. of the oxidation solution with 0.1077 *N* sodium arsenite (25.00 ml.) and 20% potassium iodide (1 ml.) required 24.42 ml. of 0.1002 *N* iodine in the final titration. Moles HCOOH/moles compound: calcd., 2.000; found, 1.995.

The remainder of the oxidation solution was neutralized to the phenolphthalein end-point with hot strontium hydroxide solution, and the solid filtered. The filtrate was concentrated *in vacuo* to ca. 20 ml., and refiltered. Vacuum concentration was continued to dryness at 40–50°. The residue was extracted with four 25-ml. and four 10-ml. portions of absolute ethanol, and then 5 ml. of acetone. The combined extract was filtered through Norit, and the filtrate concentrated to dryness *in vacuo* at 50°, producing 1.86 g. (110%) of phenyldiglycolaldehyde, a thick glass, $[\alpha]_D^{25} 10^\circ$ (*c* 5.00, methanol). In other experiments the rotation of the final product varied from the present value to

(13) H. W. B. Roozeboom, *Z. physik. Chem.*, **28**, 494 (1899).

(14) W. Heintz, *Ann.*, **144**, 95 (1868).

(15) W. A. Bonner, *This Journal*, **73**, 3126 (1951).

(16) C. S. Hudson and J. M. Johnson, *ibid.*, **37**, 2748 (1915).

(17) E. Pacsu, *Ber.*, **61**, 1508 (1928).

(18) G. Zemplén, *ibid.*, **59**, 1258 (1926).

20°, and in one experiment, where the product was isolated by ether extraction, the sirup had $[\alpha]^{25}_D -11^\circ$. One sample, $[\alpha]^{25}_D 20^\circ$ (c 2.52, methanol) was dried and analyzed.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.48; H, 5.66. Found: C, 67.42; H, 5.85.

Sodium Periodate Oxidation of β -D-Xylopyranosylbenzene.— β -D-Xylopyranosylbenzene (6.30 g.) was dissolved in water (50 ml.) and the solution cooled in ice. Sodium metaperiodate* (14.1 g., 10% excess) was dissolved in hot water (175 ml.), and the solution cooled in ice. The latter solution was poured into the former over a five-minute period, and the mixture allowed to stand in ice for 90 minutes. It was then saturated with sodium chloride, extracted thrice with ether, and finally extracted continuously with ether for 24 hours. The extracts were dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated *in vacuo* at 40° to give 6.60 g. (123%) of crude sirup, $[\alpha]^{25}_D -12.4^\circ$ (c 3.32 methanol).

Extractibility of β -D-Xylopyranosylbenzene.— β -D-Xylopyranosylbenzene (0.50 g.) was dissolved in water (20 ml.). The solution was saturated with sodium chloride and extracted eight times with 10-ml. portions of ether. The extract was dried over sodium sulfate, filtered, and the solvent distilled to give 0.18 g. of solid, $[\alpha]^{25}_D -11.1^\circ$ (c 1.80, water). These results give a plausible explanation for the haphazard rotations observed on the periodate cleavage products above.

Oxidation of Phenylidiglycolaldehyde. With Potassium Hypoiodite.—A sample (1.00 g.) of phenylidiglycolaldehyde ($[\alpha]^{25}_D 17.5^\circ$ (methanol)) prepared by the periodic acid procedure above was dissolved in methanol (100 ml.), and iodine (5.72 g., twofold excess) added. The solution was warmed to 45° and treated while stirring with a solution of potassium hydroxide (5.00 g.) in methanol (150 ml.). Addition of the first 85 ml. was made over 45 minutes, and the remainder all at once. Stirring was continued for two hours at 40°, after which the methanol was distilled *in vacuo* at 40–50°. The residue was dissolved in water (65 ml.), and the solution acidified with sulfuric acid, saturated with sodium chloride, and extracted four times with 35-ml. portions of ether. The extracts were washed with saturated aqueous sodium thiosulfate, then with water, and finally with 10% aqueous potassium hydroxide. The ether layer was discarded. The aqueous layer was acidified, saturated with sodium chloride, and extracted three times with ether. Drying of the extract, filtration through Norit, and solvent removal left 0.52 g. (44%) of practically racemic phenylidiglycolic acid, a thick sirup having $[\alpha]^{25}_D 5.5^\circ$ (c 8.91, ethanol). In a duplicate experiment a product of $[\alpha]^{25}_D 14.2^\circ$ (c 6.92, ethanol) was obtained in 71% yield.

With Silver Oxide.¹⁵—Phenylidiglycolaldehyde (6.59 g.) from the above sodium periodate oxidation was dissolved in acetone (60 ml.), and water (40 ml.) was added. Silver oxide (50 g.) and glass beads (25 g.) were added, and the mixture stirred for 48 hours. The mixture was then chilled and slowly treated while stirring with a solution of concd. hydrochloric acid (50 ml.) in water (50 ml.). Stirring was continued for 45 minutes. The mixture was filtered, and the cake washed by restirring with chloroform for 45 minutes. The layers were separated, and the aqueous layer re-extracted with chloroform after saturation with sodium chloride. The combined chloroform solution was extracted twice with 10% aqueous sodium carbonate, and once with water. Solvent removal after drying left 1.16 g. of amber sirup, presumably unreacted starting material, since it was strongly reducing toward Fehling solution. The sodium carbonate extract was acidified with sulfuric acid, saturated with sodium chloride, and extracted four times with chloroform. Drying and solvent removal left 0.84 g. of sirupy acid, $[\alpha]^{25}_D 64.4^\circ$ (c 4.32, ethanol). Neither this nor the above acid sample was analyzed due to their sirupy nature and the small quantities at hand.

Esterification of Phenylidiglycolic Acid. From Hypoiodite Oxidation.—The sirupy acid from the first oxidation above was treated with absolute ethanol saturated with hydrogen chloride (16 ml.) and the mixture diluted to 25 ml. with absolute ethanol. After five hours of reflux the solution was cooled, poured into water, and extracted with ether. The extracts were washed to neutrality with aqueous bicarbonate, dried, and the solvent removed to give 0.47 g. (71%) of crude, substantially racemic ethyl 2-phenylidiglycolate, $[\alpha]^{25}_D 4.56^\circ$ (c 4.72, ethanol).

From Silver Oxide Oxidation.—The sirupy acid (0.84 g.) from the second oxidation above was dissolved in absolute ethanol (25 ml.) containing sulfuric acid (1 ml.), the solution refluxed for five hours, and the ester isolated as described above. The crude product weighed 0.70 g. (86%) and had $[\alpha]^{25}_D 63.0^\circ$ (c 3.49, ethanol). This contrasts to $[\alpha]^{25}_D 92.2^\circ$ for the ethyl D(+)-2-phenylidiglycolate described below. If one assumes the present low rotation due to the presence of the enantiomorph, the above product has the approximate composition 83% ethyl D(+) and 17% ethyl L(–)-2-phenylidiglycolate.

Ammonolysis of Ethyl Phenylidiglycolate. From Hypoiodite Oxidation.—The ester (0.47 g.) from the first esterification above was dissolved in absolute ethanol (13 ml.) and liquid ammonia (*ca.* 8 ml.) added. The solution was stoppered lightly and allowed to stand over Dry Ice in a Dewar flask for five days, after which the solvent was allowed to evaporate in an air stream. The white residue was crystallized from a mixture of acetone and pentane to give 0.10 g. of solid, m.p. 157–160°, $[\alpha]^{25}_D 13.9^\circ$ (c 0.655, ethanol). Another recrystallization gave a sample of m.p. 161.5–162°, $[\alpha]^{25}_D 21.0^\circ$ (c 0.860, ethanol). This showed a m.p. of 162–162.5° when mixed with authentic D,L-2-phenylidiglycolamide.

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: N, 13.46. Found: N, 13.22.

In another run 0.74 g. of ester led to 0.29 g. of amide, m.p. 160.5–161.5°, $[\alpha]^{25}_D 15.7^\circ$ (c 1.20, ethanol) after one recrystallization.

From Silver Oxide Oxidation.—The ester (0.70 g.) from the second esterification above was allowed to react with ammonia in ethanol in the same fashion. There resulted 0.45 g. (82%) of crude amide, $[\alpha]^{25}_D 69.4^\circ$ (c 0.447, ethanol). This rotation corresponds to a composition of about 80% D(+) and 20% L(–)-2-phenylidiglycolamide. The product was recrystallized four times from a mixture of acetone and pentane, using Norit during the first recrystallization. The final product had m.p. 172–172.5° and $[\alpha]^{25}_D 102.2^\circ$ (c 0.450, ethanol). It showed no mixed m.p. depression (173–174°) and an identical infrared absorption spectrum (Fig. 1) with the authentic D(+)–2-phenylidiglycolamide prepared below.

D(–) and L(+)-Mandelic Acids.—D,L-Mandelic acid was resolved by the convenient method of Smith¹⁹ using the enantiomorphous α -phenylethylamines.²⁰ The D(–)-acid had m.p. 133°, $[\alpha]^{25}_D -158.0^\circ$ (c 1.49, water), while the L(+)-acid had m.p. 133°, $[\alpha]^{25}_D 157.0^\circ$ (c 1.55, water).

Ethyl D(–) and L(+)-Mandelates.—The resolved acids above were esterified with absolute ethanol containing sulfuric acid²¹ in approximately 95% yield. The D(–)-ester had b.p. 103–105° (2 mm.) and $[\alpha]^{25}_D -136.6^\circ$ (c 3.55, chloroform), while the L(+)-ester had b.p. 106–107° (4 mm.) and $[\alpha]^{25}_D 136.6^\circ$ (c 3.74, chloroform).

Ethyl D,L-2-Phenylidiglycolate by Racemization.—When an attempt was made to prepare ethyl D-2-phenylidiglycolate from one of the above esters by a modification of the procedure of Godchot,¹² the product was racemic. Ethyl L(+)-mandelate (8.00 g.) was dissolved in dry ether (20 ml.). Sodium (1.03 g.) was finely divided by rapid stirring in refluxing toluene (25 ml.). On cooling the toluene was decanted, and dry ether (50 ml.) added, along with glass beads (25 g.). The above ester solution was added to the sodium mixture with vigorous stirring over a 15-minute period, and stirring was continued for 90 minutes. A solution of ethyl bromoacetate (15 g., two moles) in dry ether (25 ml.) was then added with stirring over five minutes, and the mixture stirred under reflux for 14 hours, after which it was cooled, filtered, and washed with water. The solvent was distilled and the residue steam distilled (75 ml.) until the excess ethyl bromoacetate was removed. Customary processing after ether extraction of the residue gave the crude product, 9.1 g. of amber oil, which was subjected to vacuum fractionation. The fraction of b.p. 148–149° (1 mm.) weighed 3.95 g., had $n^{25}_D 1.4918$, and $[\alpha]^{25}_D 0.40^\circ$ (c 8.68, ethanol).

This fraction was dissolved in absolute ethanol (70 ml.) and the solution treated with liquid ammonia as in previous conversions to the amide. The final phenylidiglycolamide

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

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

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

weighed 2.20 g. (74%) after one recrystallization from acetone, had m.p. 163–164°, and was optically inactive.

Racemization of Ethyl D(-)-Mandelate.—Sodium (0.13 g.) was finely divided in toluene (25 ml.) as before. The toluene was decanted and dry ether (15 ml.) added. A solution of ethyl D(-)-mandelate (1.00 g.) in dry ether (15 ml.) was added with stirring, which was continued at room temperature for five hours. Water was cautiously added, the ether layer separated, dried, and the solvent removed to give 0.44 g. of 96% racemized ethyl mandelate, $[\alpha]^{25}_D -5.98^\circ$ (*c* 7.53, chloroform).

Ethyl L(-)- and D(+)-2-Phenyldiglycolates.—Ethyl D(-)-mandelate (5.0 g.), ethyl bromoacetate (50 ml.), silver carbonate (15 g.), Drierite (15 g.) and glass beads were stirred with a Hershberg stirrer at 55–60° for 24 hours under protection from moisture and light. The filtered mixture was freed of ethyl bromoacetate by steam distillation, the residue extracted with ether, and the crude product isolated as in the case of D,L-ester above. The crude material (10.4 g.) was fractionated into three fractions as follows: (1) 3.54 g., b.p. 96–103° (1 mm.), $[\alpha]^{25}_D -6^\circ$ (*c* 7.25, chloroform); (2) 0.73 g., b.p. 103–136° (1 mm.), and (3) 4.43 g., b.p. 136–140° (1 mm.); $[\alpha]^{25}_D -96^\circ$ (*c* 7.30, chloroform). Fraction (3) was redistilled to give a product of b.p. 145–148° (0.5 mm.) and $[\alpha]^{25}_D -95^\circ$ (*c* 4.96, chloroform). In a similar experiment the final ester had n^{25}_D 1.4818 and $[\alpha]^{25}_D -90^\circ$ (*c* 4.30, chloroform). The product analyzed poorly, presumably due to the unavoidable contamination of the desired product with the low-boiling forerun in the quantities at hand.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.2; H, 6.81. Found: C, 61.9; H, 6.71.

Ethyl D(+)-2-phenyldiglycolate was prepared in exactly the same way, and with corresponding results, from ethyl L(+)-mandelate. The desired fraction, on redistillation, had b.p. 137–140° (1 mm.), n^{25}_D 1.4827, and $[\alpha]^{25}_D$ 92° (*c* 5.25, chloroform). Its analysis was also low.

Anal. Found: C, 59.6; H, 6.82.

The Low-Boiling Forerun.—The low-rotating, low-boiling foreruns obtained in the previous syntheses of ethyl D- and L-2-phenyldiglycolates were combined and redistilled. The middle cut, comprising 60% of the total, had b.p. 93–95° (1 mm.), n^{25}_D 1.4383, and d^{25}_D 1.146. Its analyses proved slightly high, presumably due to residual contamination by higher boiling material.

Anal. Calcd. for $C_8H_{10}O_3$: C, 50.5; H, 7.38; sapn.

equiv., 95.1. Found: C, 51.6, 51.7; H, 6.97, 6.90; sapn. equiv., 99.6.

The material proved to be ethyl diglycolate on ammonolysis. A sample of the redistilled product (0.50 g.) was dissolved in ethanol (3 ml.) and saturated with ammonia. After 15 hours 0.18 g. of solid was filtered, m.p. 182.5–183°. Resaturation of the mother liquors with ammonia produced an additional 0.15 g. (total 95%) of solid after several days. On recrystallization from ethanol the product had m.p. 183.5–184.5°, unchanged on admixture with an authentic sample of diglycolamide (m.p. 184–184.5°).

Anal. Calcd. for $C_8H_{10}O_3N_2$: C, 36.64; H, 6.10. Found: C, 36.48, 36.59; H, 6.13, 6.19.

The authentic sample was prepared by esterification of diglycolic acid followed by similar ammonolysis.

L(-)- and D(+)-2-Phenyldiglycolamides.—The above redistilled ethyl L(-)-2-phenyldiglycolate (2.0 g.) was dissolved in absolute ethanol (20 ml.) and treated with liquid ammonia (*ca.* 8 ml.) as before. The crude product, isolated as usual, weighed 0.96 g. (61%) and had m.p. 162.5–164.5°. This was recrystallized thrice from acetone to give a product having m.p. 170° and $[\alpha]^{25}_D -111.3^\circ$ (*c* 3.50, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.75; H, 5.81. Found: C, 57.99; H, 5.77.

D(+)-2-Phenyldiglycolamide was prepared in an identical fashion with similar results from ethyl D(+)-2-phenyldiglycolate of $[\alpha]^{25}_D$ 92.2°. The crude amide had m.p. 168–170.5° and was obtained in 74% yield. Two recrystallizations from acetone gave a product of m.p. 174–174.5° and $[\alpha]^{25}_D$ 106.2° (*c* 0.570, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.75; H, 5.81. Found: C, 57.62; H, 5.79.

A mixed m.p. of this material with D,L-2-phenyldiglycolamide, m.p. 160–161°, was 158.5–160.5°. The ratio of active to racemic amide in the mixture was about 1/10.

Infrared Spectra.—The infrared spectra (Fig. 1) of the two D-2-phenyldiglycolamides from L-mandelic acid and from β-D-glucosylbenzene were determined in mineral oil suspension using a Perkin-Elmer Infrared Spectrometer for the region 8–15 μ. The authors are indebted to Professor John H. Wise of Stanford University for his kindness in determining these spectra. The vertical displacements of the two curves in Fig. 1 arise as a result of the differing sample thicknesses in the two measurements.

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Action of Pyridine and Iodine upon Two *o*-Phenolic-1,4-diketones: 4,6,7-Trimethylcoumarandione and its 5-Hydroxy Derivative

BY LEE IRVIN SMITH AND RICHARD REMSEN HOLMES¹

The two phenolic 1,4-diketones, Ia and Ib, have been subjected to the action of pyridine and iodine, followed by action of alkali. In this manner, Ia is converted into the coumarandione II, the structure of which has been proved by two independent syntheses. The chemistry of II has been explored, and in particular it has been converted into its 5-hydroxy derivative III, and the structure of the latter has also been confirmed by an independent synthesis. It was not possible to convert 5-hydroxy-4,6,7-trimethylcoumarandione III into the related quinone IX, nor could the lactone ring of III be opened by action of ethanol. Conversion of II into III—a derivative of a hydroquinone—via a sequence of reactions ordinarily leading to a quinone illustrates the peculiar properties of these highly methylated compounds. In contrast to the behavior of Ia, the diketone Ib was not converted into a pyridinium iodide by action of pyridine and iodine. Instead the product of this reaction was the oxindigo XII.

In a previous paper² the preparation, and certain aspects of the chemistry of the two phenolic 1,4-diketones, Ia and Ib have been discussed. Another paper³ has dealt with the reduction of Ia and the behavior of the isomeric diols so obtained. The

present paper constitutes a report of the behavior of the diketones Ia and Ib, when subjected to the action of iodine and pyridine, followed by action of alkali, a sequence found by King, McWhirter and Barton⁴ to be effective for degradation of *o*-hydroxyketones to salicylic acids.

The product produced from Ia by this sequence of reactions, 4,6,7-trimethylcoumarandione (II), as

(1) Abstracted from a thesis by Richard Remsen Holmes, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1950. American Chemical Society Predoctoral Fellow, 1946–1950.

(2) L. I. Smith and R. R. Holmes, *THIS JOURNAL*, **73**, 3847 (1951).

(3) L. I. Smith and R. R. Holmes, *ibid.*, **73**, 3851 (1951).

(4) L. C. King, M. McWhirter and D. M. Barton, *ibid.*, **67**, 2089 (1945).