CCXXXIV.—*The Preparation of* 3 : 4-*Methylenedioxyhomophthalic Acid.*

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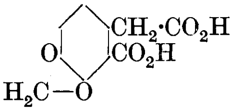
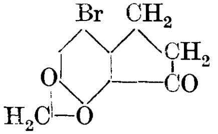
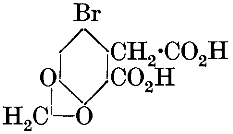
It has been shown previously (Haworth, Perkin, and Pink, J., 1925, **127**, 1709) that homophthalic acid and its derivatives can be employed for the synthesis of substances allied to oxyberberine, but in order to make this method generally useful in the synthesis of natural products it became necessary to prepare 3 : 4-methylenedioxyhomophthalic acid (I) and 3 : 4-dimethoxyhomophthalic acid, the former to serve as a basis for the synthesis of compounds related to cryptopine and protopine, and the latter for the synthesis of derivatives of berberine and palmatine. The present communication contains an account of the preparation of 3 : 4-methylenedioxyhomophthalic acid. The extension of the method to 3 : 4-dimethoxyhomophthalic acid is in progress.



(I.)



(II.)



(III.)

When β-piperonylpropionic acid is treated with phosphorus pentoxide in boiling benzene solution, it is converted into 5 : 6-methylenedioxy-1-hydrindone, ring formation taking place in the para-position to the methylenedioxy-group. The hydrindone may then be converted into 4 : 5-methylenedioxyhomophthalic acid by the method described by Perkin and Robinson (J., 1907, **91**, 1082). In order to obtain 3 : 4-methylenedioxyhomophthalic acid by a similar process, it was therefore necessary to protect the 6-position of the β-piperonylpropionic acid with a group capable of subsequent removal, and for this purpose a bromine atom was introduced into this position. When β-piperonylpropionic acid is treated with bromine in acetic acid solution, it is converted into β-6-bromopiperonylpropionic acid, the constitution of which was indicated by the observation of Weinstein (*Annalen*, 1885, **227**, 43) that the acid is formed along with 6-bromopiperonal by the oxidation of the acid $CH_2O_2:C_6H_2Br\cdot CH_2\cdot CH_2\cdot CH:CH\cdot CO_2H$. This result was confirmed by preparing the same acid from 6-bromopiperonal of known constitution (compare Mameli, *Atti R. Accad. Lincei*, 1905, **14**, ii, 424, 510; Rilliet and Krittmann, *Helv. Chim. Acta*, 1921, **4**, 588). The aldehyde is condensed with malonic acid to give 6-*bromo*-3 : 4-*methylenedioxycinnamic acid* and this is reduced to β-6-bromopiperonylpropionic acid by addition of hydrogen bromide followed by treatment with zinc dust and acetic acid.

When β-6-bromopiperonylpropionic acid is treated with phosphorus pentoxide in boiling benzene solution, a mixture of products is obtained from which a 20% yield of 4-*bromo*-6 : 7-*methylenedioxy*-1-*hydrindone* (II) can be isolated. This ketone, which gives a characteristic *piperonylidene* derivative, m. p. 280°, is converted into 4-*bromo*-6 : 7-*methylenedioxy*-2-iso*nitroso*-1-*hydrindone* by the action of methyl nitrite and concentrated hydrochloric acid, and this undergoes the Beckmann rearrangement under the influence of phosphorus pentachloride (compare Perkin and Robinson, *loc. cit.*; Haworth and Pink, J., 1925, **127**, 1368) with the production of the corresponding *o*-carboxyphenylacetonitrile. The latter, which was not isolated in the pure condition, is readily hydrolysed to 6-*bromo*-3 : 4-*methylenedioxyhomophthalic acid* (III), and this is then dehalogenated in hot alkaline solution by means of sodium amalgam with the production of 3 : 4-*methylenedioxyhomophthalic acid* (I).

EXPERIMENTAL.

6-*Bromo*-3 : 4-*methylenedioxycinnamic Acid.*—6-Bromopiperonal (5 g.), malonic acid (7·5 g.), pyridine (20 c.c.), and piperidine (0·5 c.c.) are mixed, heated on the steam-bath for 1 hour, boiled under reflux for 5 minutes, and the product is poured into an excess of dilute hydrochloric acid. The white precipitate of the cinnamic acid is collected and crystallised from glacial acetic acid, in which it is rather sparingly soluble, but from which it separates in small, colourless prisms which soften at 235° and melt at 249—251° (Found: C, 43·9; H, 2·8. $C_{10}H_7O_4Br$ requires C, 44·3; H, 2·6%).

The *methyl* ester is obtained by boiling the acid for 2 hours with methyl-alcoholic hydrogen chloride (150 parts of 3%) and crystallises from methyl alcohol, in which it is sparingly soluble, in colourless needles, m. p. 159—162° (Found: C, 46·3; H, 3·2. $C_{11}H_9O_4Br$ requires C, 46·3; H, 3·2%).

When a solution of bromine (1 mol.) in sodium hydroxide is added to an alkaline solution of the acid (1 mol.), and the mixture acidified by the gradual addition of acetic acid, a milky precipitate is formed which soon solidifies and then separates from dilute alcohol in colourless needles, m. p. 73—75° (Found: C, 35·1; H, 2·1. $C_9H_6O_2Br_2$ requires C, 35·3; H, 2·0%). This substance is non-acidic and appears to be 6 : ω-*dibromo*-3 : 4-*methylenedioxystyrene.*

β-6-*Bromopiperonylpropionic Acid.*—(*a*) 6-Bromo-3 : 4-methylenedioxycinnamic acid (0·6 g.) was mixed with a solution of hydrogen bromide in acetic acid (45 c.c.; *d* 1·34), heated to 60—70°, and stirred until it dissolved. After 2 hours, the mixture was cooled somewhat and reduced by the gradual addition of a large excess of zinc dust while the temperature was raised to 80°. The mixture was filtered, the filtrate diluted with water, and the acid extracted with chloroform and crystallised from benzene.

(*b*) Pure * β-piperonylpropionic acid, m. p. 87—89°, dissolved in

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* Unless very pure β-piperonylpropionic acid is used, the bromo-acid melts over the range 125—140° and is unaltered in m. p. by repeated crystallisation and even by conversion into the sharply melting methyl ester or amide and subsequent hydrolysis.

glacial acetic acid (2 parts), was treated with bromine (2 parts) dissolved in the same solvent, when the bromo-acid rapidly separated. After 3 hours the mixture was poured into water, and the solid collected and crystallised from benzene.

The bromo-acid prepared by either method (*a*) or (*b*) separated from benzene or aqueous alcohol in long, well-defined prisms which softened very slightly at 130° and melted at 138—140° (Found : C, 44·2; H, 3·5; Br, 29·2. Calc. : C, 44·0; H, 3·3; Br, 29·3%). The *methyl* ester, obtained in the usual manner, crystallised from methyl alcohol in long, colourless needles, m. p. 44—45° (Found : Br, 27·8. $C_{11}H_{11}O_4Br$ requires Br, 27·9%). When the acid was dissolved in chloroform and boiled for $1\frac{1}{2}$ hours with a moderate excess of thionyl chloride, it was apparently converted into a mixture of anhydride and acid chloride. After most of the chloroform had been evaporated and light petroleum added, the *anhydride* separated as pale yellow nodules, m. p. 140°. When the filtrate from the anhydride was treated with concentrated ammonia, the amide separated; it crystallised from aqueous alcohol in long, colourless needles, m. p. 151—152° (compare Baker, this vol., p. 1075).

4-*Bromo*-6 : 7-*methylenedioxy*-1-*hydrindone* (II).—β-6-Bromopiperonylpropionic acid (40 g.) was dissolved in boiling benzene (300 c.c.), and phosphorus pentoxide (150 g.) gradually added. After boiling for 2—3 hours with occasional shaking, the mixture was poured into ice and extracted three times with benzene (800 c.c. in all); much flocculent material then remained which produced very objectionable emulsions. The extract was washed with 5% sodium hydroxide; the alkaline layer then assumed a dark brown colour and gradually deposited a brown solid which contained some impure sodium β-6-bromopiperonylpropionate. The benzene layer (A) was dried over sodium sulphate, concentrated, cooled, and the hydrindone collected, and further crops were obtained by concentrating the mother-liquors.

As the isolation of the hydrindone from a mixture such as the above is usually troublesome, the following procedure should be adopted in cases where the hydrindone does not separate in the crystalline condition from the benzene solution. The benzene layer (A) is evaporated to dryness, the residual viscid mass extracted several times with much boiling alcohol, the extract treated with charcoal and concentrated; the hydrindone then separates in yellow nodules.

The crude hydrindone, obtained by either of the methods described above, recrystallised from benzene in pale yellow prisms, m. p. 197—199° (yield about 20%) (Found : C, 47·2; H, 2·8;

Br, 31·5. $C_{10}H_7O_3Br$ requires C, 47·1; H, 2·7; Br, 31·4%). This bromo-hydrindone is sparingly soluble in ether, methyl or ethyl alcohol, moderately easily soluble in hot benzene, chloroform, or acetone, and more soluble in ethyl acetate or glacial acetic acid.

The *piperonylidene* derivative was obtained by the addition of a few drops of strong aqueous potassium hydroxide to a solution of equivalent quantities of the hydrindone and piperonal in hot alcohol; a yellow, gelatinous precipitate then immediately separated. This was washed with alcohol and crystallised from much glacial acetic acid in aggregates of microscopic, yellow needles, m. p. 278—281° (Found: C, 55·8; H, 2·8. $C_{18}H_{11}O_5Br$ requires C, 55·8; H, 2·7%). It is sparingly soluble in acetic acid and almost insoluble in alcohol, acetone or xylene, and dissolves in concentrated sulphuric acid with an intense purplish-red colour which slowly changes to brown on addition of a drop of nitric acid.

4 - *Bromo* - 6 : 7 - *methylenedioxy* - 2 - iso*nitroso* - 1 - *hydrindone*.—4-Bromo-6 : 7-methylenedioxy-1-hydrindone (8 g.) was dissolved in boiling glacial acetic acid (100 c.c.), concentrated hydrochloric acid (5 c.c.) added, the solution cooled to 60° and saturated with methyl nitrite gas. After a few minutes the iso*nitroso*-derivative separated in yellow plates. Benzene (200 c.c.) was added in order to complete the precipitation, and after 12 hours the solid was collected, washed with methyl alcohol, and dried (Found: N, 5·1. $C_{10}H_6O_4NBr$ requires N, 4·9%). The *iso*nitroso-compound is sparingly soluble in the usual organic solvents and melts at about 240° (decomp.). It dissolves readily in dilute sodium hydroxide to a deep orange-coloured solution, from which it separates on saturation with carbon dioxide. In many experiments, crude bromohydrindone (II), *i.e.*, the residue after removal of benzene from extract A mentioned in the preceding experiment, was employed as above for conversion into the *iso*nitroso-derivative.

4-*Bromo*-6 : 7-*methylenedioxyhomophthalic Acid* (III).—Heat was evolved and the mixture became semi-liquid when the *iso*nitroso-derivative (8 g.) was triturated with phosphorus pentachloride (24 g.), and to prevent decomposition of the products the mass was covered with ether as soon as violent reaction commenced. After ½ hour, the mixture was poured into ice, thoroughly extracted with ether, dried, the solvent removed, and the solid residue boiled with 10% sodium hydroxide until the evolution of ammonia was complete. The solution was diluted with water, treated with charcoal, filtered, and the filtrate acidified with concentrated hydrochloric acid; the homophthalic acid (6 g.) was collected, and a further small crop obtained by extracting the filtrate with ether. The acid (III) was crystallised by dissolving it in a little methyl alcohol, adding water, boiling off the methyl alcohol, and allowing the solution to cool; it then separated in colourless, stout prisms, m. p. 215° (decomp.) (Found: C, 39·7; H, 2·5. $C_{10}H_7O_6Br$ requires C, 39·6; H, 2·3%).

3 : 4-*Methylenedioxyhomophthalic Acid* (I).—A solution of 6-bromo-3 : 4-methylenedioxyhomophthalic acid (6 g.) in 1% sodium hydroxide solution (200 c.c.) was heated on the water-bath for 12 hours with 3% sodium amalgam (200 g.). The mixture was filtered, concentrated to half its bulk, cooled, acidified with concentrated hydrochloric acid, and the 3 : 4-methylenedioxyhomophthalic acid (3 g.) collected. The filtrate was saturated with ammonium sulphate and extracted six times with ether, the extract dried over sodium sulphate and evaporated; a further crop (1·1 g.) of the acid was then obtained.

3 : 4-*Methylenedioxyhomophthalic acid* (I) differs from the isomeric 4 : 5-methylenedioxyhomophthalic acid in its ready solubility in boiling water, from which it separates, on cooling, in colourless plates, m. p. 203—204° (decomp.) (Found: C, 53·9; H, 3·8. $C_{10}H_8O_6$ requires C, 53·6; H, 3·6%). The *anhydride* was obtained by heating the acid (I) for 2 hours with an excess of acetyl chloride, removing the excess of the latter in a vacuum, and recrystallising the anhydride from much benzene; colourless plates, m.p. 195°, were then obtained (Found: C, 58·1; H, 3·0. $C_{10}H_6O_5$ requires C, 58·2; H, 2·9%).

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