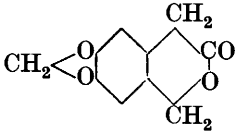
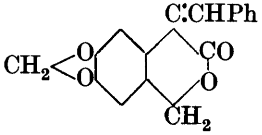
CCCLXXII.—*A New Synthesis of Hydrastic Acid.*

By Thomas Stevens Stevens and Mary Carrick Robertson.

In the course of recent synthetic work, the lactone (I) was obtained by the action of formaldehyde on homopiperonylic acid, and its structure confirmed by oxidising it to 4 : 5-methylenedioxyhomophthalic acid (Stevens, this vol., p. 178). It was further considered desirable to attempt the conversion of (I) into hydrastic acid, both on account of the interest attaching to a synthesis of that important substance, and also because the homophthalic acid is not readily characterised.

(I.)



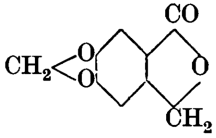


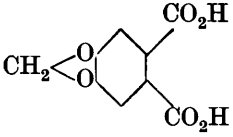
(II.)

The compound (I) was condensed with benzaldehyde in presence of piperidine to form the lactone (II) of α-(6-*hydroxymethylpiperonyl*)-*cinnamic acid.* Oxidation with neutral permanganate converted this into 4 : 5-*methylenedioxyphthalide* (III), which was further oxidised in alkaline solution to hydrastic acid (IV). The substances

(III) and (IV) are clearly the " methylenedioxy-analogues " of *m*-meconin and *m*-hemipinic acid, and it was hoped that it would be possible to complete the series by oxidising (III) to the aldehydo-acid (V), analogous to *m*-opianic acid, but this could not be accomplished.

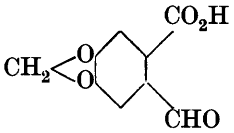
(III.)

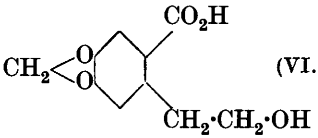




(IV.)

(V.)





(VI.)

The hydroxy-acid derived from the lactone (I) lactonises spontaneously when liberated from its salts, whereas that derived from (III), like many derivatives of *o*-hydroxymethylbenzoic acid, is comparatively stable. This greater stability of the γ-hydroxy-acids relatively to the δ-, as compared with the opposite behaviour of simple aliphatic compounds, is significant in view of von Braun's suggestion that in the formation of cyclic structures two carbon atoms of a benzene ring are sterically more nearly equivalent to one methylene group than to two (*Ber.*, 1925, **58**, 2765; 1927, **60**, 1257). On the other hand, 6-β-hydroxyethylpiperonylic acid (VI) (Perkin, J., 1890, **57**, 1020) and β-*o*-hydroxyphenylpropionic acid are fairly stable. The relative stabilities of these three δ-hydroxy-acids are in striking contrast to those of the δ-amino-acids prepared by von Braun and Reich (*Annalen*, 1925, **445**, 225), who observed that the lactam of *o*-aminomethylphenylacetic acid, analogous to (I), was *less* readily formed than those of the isomeric β-*o*-aminophenylpropionic and *o*-β-aminoethylbenzoic acids.

EXPERIMENTAL.

α-(6-Hydroxymethylpiperonyl)cinnamolactone (II).—The lactone (I) (10 g.) is dissolved in hot benzaldehyde (15 c.c.), piperidine (8—10 drops) added, and the mixture heated at 120° for 2 hours. The melt is dissolved in boiling acetic acid, and the solid (12 g.), which separates on cooling, recrystallised from alcohol or acetic acid. It forms pale yellow needles, m. p. 190—192°, fairly soluble in hot acetic acid and sparingly soluble in alcohol, and gives an intensely orange solution in concentrated sulphuric acid (Found: C, 72·9; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%). It dissolves slowly in boiling aqueous alkali to a colourless solution: on acidification a colourless acid separates, which passes back into the lactone on being heated with dilute acids.

4 : 5-*Methylenedioxyphthalide* (III).—A solution of the lactone (II) (10 g.) in warm acetone (230—300 c.c.) is cooled (any crystallisation being disregarded), and stirred during the gradual addition of potassium permanganate (13 g.) and magnesium sulphate (13 g.) in warm concentrated aqueous solution. The mixture is boiled and filtered; much of the product then separates on cooling, and more may be obtained from the manganese sludge (5 g. in all). Methylenedioxyphthalide is soluble in about 100 parts of boiling water, and crystallises in white needles, m. p. 188—189°, which sublime readily without decomposition at about 150—160°. The sublimate consists principally of stout, short prisms which show the same m. p. as the original material and are reconverted into the needles on crystallisation from water (Found: C, 60·6; H, 3·7. $C_9H_6O_4$ requires C, 60·6; H, 3·4%). Attempts to oxidise the substance to the aldehydo-acid (V) with manganese or lead dioxide and sulphuric or acetic acid, or with chromic anhydride in acetic anhydride, were not successful.

6-*Hydroxymethylpiperonylic Acid*.—The phthalide (III) is not attacked by cold carbonates, but rapidly dissolves in hot sodium hydroxide solution, and the hydroxy-acid is precipitated in minute crystals when the cold solution is acidified. It melts indefinitely at about 140—150°, quickly resolidifies, and then melts at the m. p. of the lactone (Found: M, by titration, 193. $C_9H_8O_5$ requires M, 196). The acid is readily soluble in hot water and crystallises unchanged on rapid cooling; boiling dilute mineral acids reconvert it at once into the lactone. The *silver* salt forms colourless, microscopic prisms which are sparingly soluble in boiling water (Found: Ag, 35·8. $C_9H_7O_5Ag$ requires Ag, 35·6%).

Hydrastic Acid (IV).—The phthalide (III) was dissolved in dilute alkali solution and oxidised in the cold with a moderate excess of aqueous potassium permanganate. On acidification of the filtrate from the manganese dioxide, hydrastic acid, m. p. 175° (decomp.), crystallised in a yield of more than 50% of the theoretical. It was characterised by conversion into the methylimide, m. p. 228°, and by analysis of the silver salt (Found: Ag, 51·0. Calc., Ag, 50·9%).

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