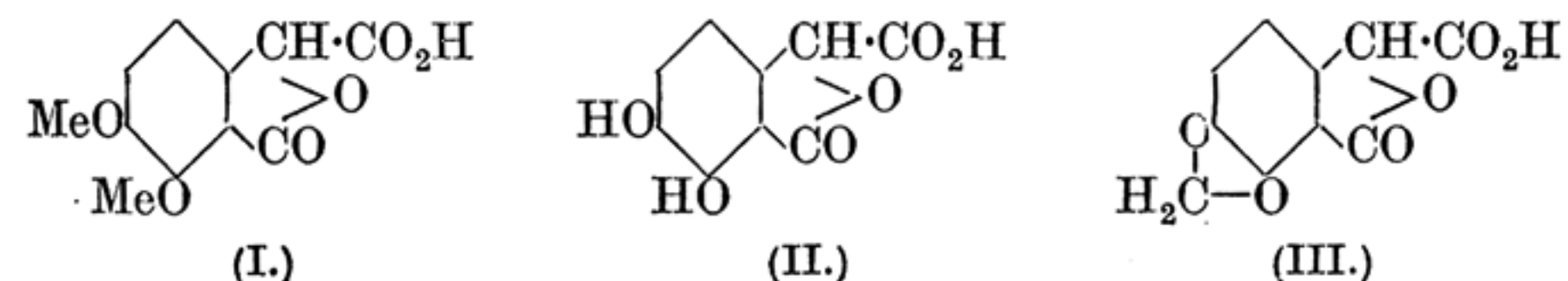


CCCLXXXIX.—*Synthesis of Some Derivatives of Methylenedioxybenzene.*

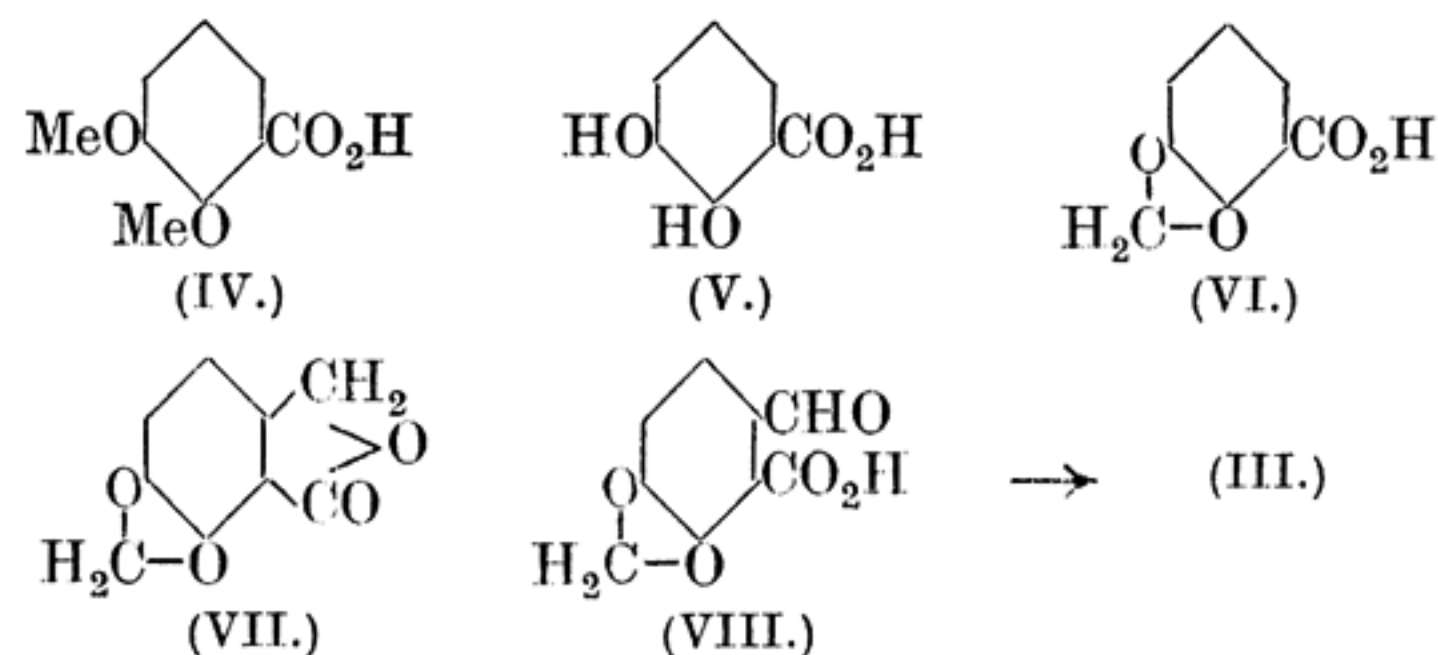
By WILLIAM HENRY PERKIN, jun., and VICTOR MARTIN TRIKOJUS.

DURING the course of the experiments on the synthesis of cryptopine and protopine which have recently been brought to a successful conclusion (Haworth and Perkin, this vol., p. 1770), it seemed possible that the synthesis of oxyepiberberine—an essential step in the synthesis of cryptopine—might be achieved by employing methods similar to those which had been successful in the synthesis of oxyberberine (Perkin, Ray, and Robinson, J., 1925, **127**, 740). The remaining stages would then be (i) reduction to tetrahydroepiberberine and (ii) the conversion of this substance into anhydro-dihydrocryptopine followed by the oxidation of the latter to the amino-oxide by perbenzoic acid and treatment of this with acetic-hydrochloric acid (compare Haworth and Perkin, *loc. cit.*, p. 1773). In the synthesis of oxyepiberberine following the method of Perkin, Ray, and Robinson, the essential starting point is 3 : 4-methylenedioxyphthalidecarboxylic acid (III), and the present investigation was undertaken primarily with the object of preparing this important unknown acid. Starting with meconinecarboxylic acid (I), the idea was to convert this into 3 : 4-dihydroxyphthalidecarboxylic acid (II) by the action of hydriodic acid and then to introduce the methylene group by treating the acid or its ester with potassium hydroxide and methylene iodide.



It was recognised at the time that the chance of success was a remote one and we were surprised to find that the acid (I), when treated with hydriodic acid under the conditions detailed on p. 2927, was converted without elimination of carbon dioxide quite smoothly into 3 : 4-dihydroxyphthalidecarboxylic acid (m. p. 215°), the intermediate stage being a monomethyl derivative (m. p. 203°), which is probably 3-hydroxy-4-methoxyphthalidecarboxylic acid. Unfortunately, however, in spite of a large number of experiments carried out under a variety of conditions, the final stage, namely, the conversion of (II) into (III), could not be accomplished, and therefore this route to the synthesis of cryptopine had to be abandoned.

The next process we attempted will be clear from the following formula sketch :



o-Veratric acid (IV) is readily demethylated by heating with hydriodic acid and gives a good yield of 2:3-dihydroxybenzoic acid (*o*-protocatechuic acid, m. p. 204°), which had previously been obtained in small quantities by Miller (*Annalen*, 1883, 220, 116, 126) by heating pyrocatechol with ammonium carbonate or by fusing 3-iodosalicylic acid with potassium hydroxide and recently by Kawai (*Sci. Papers Inst. Phys. Chem. Res.*, 3, 279—281, Tokio) in good yield by heating pyrocatechol with potassium carbonate and glycerol. This acid, now readily available, is converted (yield 45%) into 2:3-methylenedioxybenzoic acid (*o*-piperonylic acid, VI) when its solution in aqueous-alcoholic potassium hydroxide is vigorously stirred and heated with methylene iodide. *o*-Piperonylic acid condenses readily with formaldehyde in the presence of acetic-hydrochloric acid to yield 3:4-methylenedioxyphthalide (VII), a synthesis which, in view of the fact that ordinary piperonylic acid does not condense with formaldehyde under these conditions (Edwards, Perkin, and Stoye, J., 1925, 127, 196), was scarcely to be expected. Meconine (3:4-dimethoxyphthalide), on oxidation with manganese dioxide and sulphuric acid, is readily converted into opianic acid, and it therefore seemed probable that the analogously constituted 3:4-methylenedioxyphthalide (VII) would, without difficulty, yield the corresponding 3:4-methylenedioxyphthalaldehydic acid (VIII), from which it was hoped, by condensation with potassium cyanide followed by hydrolysis, to synthesise the substance (III). Unfortunately, however, the substance (VII) is so resistant to oxidation that no trace of the aldehydo-acid (VIII) could be isolated and therefore the process sketched above also had to be abandoned. The successful synthesis of oxyepiberberine and cryptopine by Haworth and Perkin (*loc. cit.*), using 3:4-methylenedioxy-2-carboxyphenylacetic acid instead of (III), has, in the meantime, rendered it unnecessary to continue the experiments on the synthesis of the acid (VIII).

The opportunity has been taken, during this investigation, to prepare and characterise several derivatives, such as the ethyl ester, amide and nitrile, of the hitherto undescribed *o*-piperonylic acid—an acid which, in many of its properties, resembles ordinary piperonylic acid.

2:3-Methylenedioxybenzaldehyde (*o*-piperonal, IX), the hitherto unknown isomeride of ordinary piperonal (X), was obtained by



reducing *o*-piperonylonitrile with stannous chloride in the presence of an ethereal solution of hydrogen chloride according to the valuable method for the conversion of nitriles into aldehydes devised by Stephen (J., 1925, 127, 1874). It melts at 34° and has an odour reminiscent of, but much fainter than, that of piperonal (m. p. 37°). Like piperonal, the oxime of which exists in two modifications (m. p. 112° and 146°), readily convertible into each other, *o*-piperonal gives at first an oxime, m. p. 127°, which, on standing, passes into the second modification, m. p. 138—139°, and when the latter is melted it reverts to the modification of m. p. 127°. *o*-Piperonal condenses readily with malonic acid to yield 2:3-methylenedioxy-cinnamic acid, CH₂O₂:C₆H₃:CH:CH:CO₂H, m. p. 194°, and other derivatives of methylenedioxybenzene are described in the experimental part of this communication.

EXPERIMENTAL.

3:4-Dihydroxyphthalidecarboxylic Acid (*Normeconinecarboxylic Acid*, II).—Meconinecarboxylic acid (I; 20 g.) (Perkin, Ray, and Robinson, *loc. cit.*) was heated with five times its weight of freshly-distilled hydriodic acid (b. p. 126°), the temperature being gradually raised so as to permit of a uniform evolution of methyl iodide and being finally maintained at 130° for an hour; almost the theoretical quantity of methyl iodide collected in the receiver. After 12 hours, the crystalline acid was washed with a little very dilute sulphurous acid and crystallised from ethyl acetate-petroleum or from concentrated hydrochloric acid, separating in elongated prisms (13 g.), m. p. 215° with previous softening. A small quantity of cruder acid was obtained by concentrating the mother-liquor (Found: C, 51.1; H, 2.9. C₉H₆O₆ requires C, 51.4; H, 2.9%).

This acid is soluble in water, alcohol, or ethyl acetate and sparingly soluble in petroleum. The aqueous solution, which does not darken rapidly on addition of alkali, gives, with ferric chloride, an

intense green coloration which changes to crimson on the addition of sodium carbonate.

The *methyl* ester, obtained in the usual way by saturating a methyl-alcoholic solution of the acid with hydrogen chloride, crystallises from dilute methyl alcohol in needles. The air-dried substance melts at 104° and contains 1H₂O (Found: loss at 90°, 7.1. C₁₀H₈O₆·H₂O requires H₂O, 7.4%). After drying at 100°, the methyl ester is anhydrous and melts at 150° (Found: C, 53.6; H, 3.9. C₁₀H₈O₆ requires C, 53.6; H, 3.6%). The substance is very soluble in alcohol and to some extent in water and the solution gives with ferric chloride a brilliant green colour changing to red on addition of sodium carbonate.

Attempts were made to methylenate normeconinecarboxylic acid under different conditions: (i) by using potassium hydroxide (3 mols.) and methylene iodide in aqueous alcohol; (ii) as (i), but using 4 mols. of potassium hydroxide so as to allow for the opening of the phthalide ring by hydrolysis; (iii) by heating the methyl ester in a sealed tube with potassium methoxide, methylene iodide, and methyl alcohol; (iv) as (iii), but substituting potassium amyl-oxide and amyl alcohol; (v) by heating the methyl ester in acetone solution with methylene iodide and anhydrous potassium carbonate. In each case the result was a negative one, but it is interesting that when pyrocatechol was employed under the conditions in (v) a 30–40% yield of pyrocatechol methylene ether resulted.

3-Hydroxy-4-methoxyphthalidecarboxylic Acid.—In a preliminary experiment on the demethylation of meconinecarboxylic acid the process was incomplete, since the product melted indefinitely at about 180°. Fractional crystallisation from ethyl acetate yielded as the less soluble portion an *acid* crystallising in colourless, glistening plates, m. p. 203° (Found: C, 53.6; H, 3.7. C₁₀H₈O₆ requires C, 53.6; H, 3.6%). It is appreciably soluble in water or alcohol and the solutions give with ferric chloride a blue coloration changed by sodium carbonate to brownish-pink.

2:3-Dihydroxybenzoic Acid (o-Protocatechuic Acid, V).—*o*-Vanillin (CHO:OH:OMe = 1:2:3) was converted into *o*-veratraldehyde by treatment, in methyl-alcoholic solution, with potassium hydroxide and methyl sulphate (compare the preparation of veratraldehyde from vanillin; Perkin and Robinson, J., 1907, 91, 1079), and this was oxidised in hot dilute acetone solution with an equal weight of permanganate in 10% aqueous solution, sufficient acetone being added from time to time to keep the aldehyde in solution. After filtration, distillation of the acetone, and extraction with ether to remove traces of *o*-veratraldehyde, the alkaline solution was acidified; the precipitate, after being washed, was employed directly

for the demethylation. For this purpose, the acid (50 g.) was heated with freshly-distilled hydriodic acid (b. p. 126°; 300 g.) for about 2 hours, the temperature of the bath being finally raised to 135°. When the solution was cooled, *o*-protocatechuic acid rapidly separated; the crystals were collected after some time and washed with a little water. The dry, nearly pure, crystalline acid melted at 200° and was employed in this condition in the subsequent methylenation experiments. The hydriodic acid mother-liquor yielded, on evaporation, a small quantity of an acid which, after crystallisation from water, had a red tinge and contained iodine.

2:3-Methylenedioxybenzoic Acid (o-Piperonylic Acid, VI).—As the result of a number of comparative experiments, the following process was adopted for the preparation of this new acid. Finely-powdered *o*-protocatechuic acid (95 g.) was suspended in water (180 c.c.) in a flask fitted with a very rapidly working mechanical stirrer (closed by a mercury seal), an inlet tube for hydrogen, and a reflux condenser. After the air had been expelled by a stream of hydrogen, a solution of potassium hydroxide (103 g.) in water (400 c.c.) was added slowly, followed by methylene iodide (170 g.) dissolved in alcohol (250 c.c.). The whole was gently boiled by means of an oil-bath, with vigorous stirring to prevent the methylene iodide settling on the bottom of the flask and with continuous passage of hydrogen. The unchanged methylene iodide was then distilled in steam and the solution, after cooling in a stream of hydrogen, was acidified with concentrated hydrochloric acid. The crude *o*-piperonylic acid (65 g.), which separated as a light brown powder, was crystallised from alcohol, from which the acid separated in small, thick prisms (46 g.), m. p. 227°. A further quantity was obtained by working up the mother-liquor (Found: C, 58.1; H, 3.7. C₈H₆O₄ requires C, 57.8; H, 3.6%). The acid is very sparingly soluble in water but crystallises well from alcohol, ethyl acetate, or dilute acetic acid.

The *ethyl* ester, obtained by warming an alcoholic solution of the acid, saturated with hydrogen chloride, for a short time on the steam-bath, pouring the cooled mixture into sodium bicarbonate solution, and extracting this with ether, was a pleasant-smelling oil which distilled at about 272° and then crystallised in a freezing mixture. It separated from ether in elongated prisms, m. p. 35.5° (Found: C, 61.6; H, 5.4. C₁₀H₁₀O₄ requires C, 61.8; H, 5.1%).

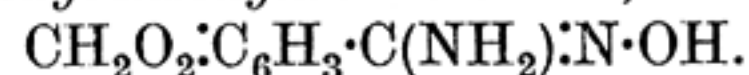
2:3-Methylenedioxybenzoyl chloride. The acid (6 g.) was gently heated on the steam-bath for ½ hour with freshly-distilled thionyl chloride (18 c.c.). The excess of thionyl chloride having been distilled off, the acid chloride solidified and was sufficiently pure for conversion into the amide. It distilled readily under reduced

pressure and separated from benzene-petroleum in long, colourless needles, m. p. 116° (Found: Cl, 19.3. $C_8H_5O_3Cl$ requires Cl, 19.2%). When decomposed by water, it yielded *o*-piperonylic acid; this separated from alcohol in glistening, colourless prisms, whereas the acid prepared as described on p. 2929 is always brown, even after repeated crystallisation.

The *amide*, prepared by saturating a solution of the acid chloride in dry benzene with ammonia or by carefully pouring the benzene solution into excess of concentrated aqueous ammonia, separated from alcohol in colourless prisms, m. p. 176° (Found: C, 58.3; H, 4.4. $C_8H_7O_3N$ requires C, 58.2; H, 4.2%).

2 : 3-Methylenedioxybenzonitrile (*o*-Piperonylonitrile). The amide (4 g.) was heated on the steam-bath with thionyl chloride (20 c.c.) for 6 hours, and the product kept over-night. After the excess of thionyl chloride had been removed under reduced pressure, the substance remaining solidified when rubbed. Sodium carbonate was added until the product was neutral and the *nitrile*, obtained in almost quantitative yield, was washed with water and crystallised from dilute alcohol with the aid of animal charcoal (Found: C, 65.1; H, 3.6. $C_8H_5O_3N$ requires C, 65.3; H, 3.4%). This nitrile is readily soluble in alcohol, ether, or chloroform and separates in colourless needles, m. p. 80°. It is volatile in steam and the vapour has an odour reminiscent of that of benzonitrile.

2 : 3-Methylenedioxybenzenylamino-oxime,



The nitrile (0.5 g.) was warmed for about 12 hours with an alcoholic solution of hydroxylamine (from 0.36 g. of hydroxylamine hydrochloride and the equivalent quantity of sodium ethoxide), the alcohol removed, and the product mixed with ice; the *amino-oxime* then solidified. It separates from aqueous alcohol in colourless, flat prisms, m. p. 139°, and is soluble in acids and alkalis (Found: C, 53.6; H, 4.6. $C_8H_8O_3N_2$ requires C, 53.3; H, 4.4%).

3 : 4-Methylenedioxyphthalide (VII).^{*}—*o*-Piperonylic acid (2 g.), dissolved in hot glacial acetic acid (10 c.c.), was mixed with concentrated hydrochloric acid (8 c.c.) and 40% formaldehyde (3 c.c.), and the mixture boiled for about ½ hour, until all had dissolved. The solution was diluted with water, mixed with excess of sodium bicarbonate, and extracted several times with chloroform. The solid (1 g.) remaining after the solvent had been dried and removed separated from glacial acetic acid in colourless, elongated prisms, m. p. 226°. These were sparingly soluble in hot water, but soluble in boiling dilute sodium hydroxide solution and were reprecipitated

^{*} We are indebted to Dr. R. D. Haworth for carrying out this experiment.

by hydrochloric acid (Found: C, 60.5; H, 3.4. $C_9H_6O_4$ requires C, 60.7; H, 3.3%).

In attempts to convert this substance into 3 : 4-methylenedioxyphthalaldehydic acid, the following oxidising agents were tried without success, the meconine being either recovered unchanged or completely destroyed: (i) manganese dioxide and dilute sulphuric acid; (ii) as (i), but with the addition of glacial acetic acid to increase the solubility of the meconine; (iii) chromic anhydride and dilute sulphuric acid; (iv) potassium permanganate in acetone solution; (v) alkaline hydrogen peroxide.

2 : 3-Methylenedioxybenzaldehyde (*o*-Piperonal, IX).—Anhydrous stannous chloride (25 g.), prepared from the pyridine derivative by the method recommended by Stephen (J., 1925, 127, 1874), was finely powdered, sieved, suspended in dry ether (150 c.c.), and saturated with dry hydrogen chloride until it had dissolved and the mixture had separated into two layers. *o*-Piperonylonitrile (8 g.), dissolved in chloroform (20 c.c.), was then added with rapid shaking in a flask fitted with a calcium chloride tube. A yellow solid soon began to separate and, after standing for 2 days with occasional shaking, this was collected and washed with chloroform. The solid, suspended in water, was heated for 3 hours on the steam-bath and the product was cooled and extracted several times with ether. The ethereal solution was concentrated and repeatedly extracted with aqueous sodium hydrogen sulphite, and the unchanged nitrile recovered by evaporating the ethereal solution. The aqueous extract was decomposed by sodium carbonate, the aldehyde extracted with ether, the ether evaporated, and the residue, which partly solidified, distilled in steam. The distillate deposited the solid aldehyde (2 g.), and a further quantity (0.6 g.) was obtained from the aqueous portion by extraction with ether. The substance crystallised from a very little alcohol or ether in colourless prisms, m. p. 34° (Found: C, 64.1; H, 4.1. $C_8H_6O_3$ requires C, 64.0; H, 4.0%).

The α- and β-oximes. When the aldehyde was rapidly treated with hydroxylamine hydrochloride and potassium carbonate in aqueous solution, and the product immediately crystallised from dilute methyl alcohol, the *α-oxime* was obtained in long, thin prisms, m. p. 127° (Found: C, 58.1; H, 4.4. $C_8H_7O_2N$ requires C, 58.2; H, 4.2%). When this oxime was kept, the melting point gradually rose to 138—139°, complete transformation into the *β*-modification having taken place. The *β-oxime* was obtained directly when the aldehyde was heated with hydroxylamine hydrochloride and potassium acetate for 2 hours (Found: C, 58.0; H, 4.5%). When the *β-oxime* was melted, it changed into the *α*-modi-

fication, the solidified mass melting at 127° . In time, however, the m. p. gradually rose to $138-139^{\circ}$.

The *p*-nitrophenylhydrazone separated immediately when the aldehyde, dissolved in acetic acid, was mixed with *p*-nitrophenylhydrazine in acetic acid and crystallised from acetic acid as a flocculent mass of minute, orange-red prisms, m. p. 258° (Found : N, 14.6. $C_{14}H_{11}O_4N_3$ requires N, 14.7%). Its colour is not so intensely scarlet as that of the corresponding derivative of ordinary piperonal.

2 : 3-Methylenedioxcinnamic Acid, $CH_2O_2 \cdot C_6H_3 \cdot CH : CH \cdot CO_2H$.—This acid was readily obtained when *o*-piperonal (0.22 g.), malonic acid (0.31 g.), pyridine (1.5 c.c.), and piperidine (2 drops) were heated on the steam-bath for 90 minutes, and the product poured into dilute hydrochloric acid. It is sparingly soluble in water and separates from dilute methyl alcohol or ethyl acetate in small, faintly yellow prisms, m. p. 194° (Found : C, 62.7; H, 4.3. $C_{10}H_8O_4$ requires C, 62.5; H, 4.2%). The corresponding dihydrocinnamic acid will be described in a future communication.

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