SYNTHESIS OF \textit{m}-HEMIPINIC ACID.

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\textit{m}-HEMIPINIC acid has been obtained as a degradation product of many alkaloids such as corydaline, berberine, papavarine and narcotine and is important as it serves to establish the constitution of alkaloids.

Gilbody, Perkin and Yates\textsuperscript{1} obtained \textit{m}-hemipinic acid from brasiliin-trimethylether; Perkin and Weizmann obtained it\textsuperscript{2} from 4-5-dimethoxy-2-methyl benzaldehyde by oxidation with potassium permanganate (20 p.c.).

It has now been synthesised by a useful method from veratric acid.

Veratric acid (I) when condensed with chloral in presence of sulphuric acid yields 3-4-dimethoxy-6-\textit{a}-trichloromethyl phthalide (II). This is reduced to 3-4-dimethoxy-6-\textit{\beta}-dichloroethyl benzoic acid (III) with zinc and acetic acid. This is oxidised to \textit{m}-hemipinic acid (IV) with alkaline potassium permanganate solutions. The acid obtained had m.p. \(174^\circ\text{-}176^\circ\).

The m.p. alone does not establish its identity as different m.p.'s are recorded for the same acid by different workers.

For identification, therefore, the characteristic ethylimide and anhydride were prepared.

The ethylimide from (IV) melts at \(229^\circ\text{-}230^\circ\) and the anhydride melts at \(175^\circ\). This proves the acid (IV) to be \textit{m}-hemipinic acid. The linking of the chloral group in (II) therefore is at the \textit{p}-position to the 3-methoxy group.

\textsuperscript{1} \textit{J.} 79, 1465.

\textsuperscript{2} \textit{J.} 89, 1851.
3-4-dimethoxy-6-α-trichloromethyl phthalide (II).—Veratric acid (I) (15 g.), chloral (40 g.) and sulphuric acid (40 c.c. 96–98%) when mixed together dissolved to a clear solution. After 3 days the reaction mixture was poured over pounded ice when a solid substance separated. This was found to be a mixture of acid and its condensation product. The mixture was treated with dilute sodium hydroxide solution to remove the veratric acid from the condensation product. This crystallised from acetone in hexagonal prisms, m.p. 146°. (Found: Cl, 34.09; C₁₁H₉O₄Cl₂ requires 34.19%). The substance is soluble in methyl and ethyl alcohol, acetone, ether, acetic acid, insoluble in petrol-ether, benzene, chloroform and water.

3-4-dimethoxy-6-α-carboxy phthalide (IIa).—(II) (4 g.) and sodium hydroxide 50 c.c. of 20% solution were mixed and heated on the water-bath when the substance slowly goes into solution. After heating for four hours the mixture was neutralised with hydrochloric acid when the sodium salt of the acid was obtained. This was crystallised from hot water. The free acid was obtained from the salt by heating with sulphuric acid (40%) till the salt went into solution. On cooling the acid separated. This was crystallised from acetone m.p. 212°. (Found: Equiv., 236.1; C, 55.33; H, 4.33; C₁₁H₁₀O₈ requires Equiv., 238.1; C, 55.47; H, 4.23%). The substance is soluble in alcohol, ether, acetone, acetic acid and hot water, insoluble in petrol-ether, chloroform, toluene and carbon tetrachloride.

The sodium salt crystallised with 3H₂O which are removed on heating at 110°. (Found: Na, 7.01; C₁₁H₉O₆Na, 3H₂O requires Na, 7.32%). After heating at 110° to constant weight (Found: Na, 8.57; C₁₁H₉O₆ Na requires Na, 8.84%).

3-4-dimethoxy-6-β-dichloroethyl benzoic acid (III).—(II) (10 g.) was reduced with zinc 5 g. and acetic acid (40 c.c.). The product crystallised from benzene in slender silky needles, m.p. 201°. (Found: Equiv., 277.9; Cl, 25.23; C₁₁H₁₂O₄Cl₂ requires Equiv., 279; Cl, 25.45%). The substance is soluble in alcohol, acetone, chloroform, hot benzene, ether, acetic acid, toluene; insoluble in petrol-ether, carbon disulphide and water.

Calcium salt crystallised from water in needles with 4H₂O. (Found: Ca, 5.89; (C₁₁H₁₁O₄Cl₂)₂ Ca, 4H₂O requires 5.98%). After heating to
m-Hemipinic acid (IV).—(III) (5 g.) was dissolved in potassium hydroxide solution (5 g. in 25 c.c.) and to the hot solution potassium permanganate (10 g. in 110 c.c.) was added in small quantities at a time. The reaction mixture was heated on the water-bath for one hour. The oxidation was rapid in the beginning. After keeping for 24 hours the manganese dioxide was filtered off and the bluish green colour of the filtrate was removed with sulphur dioxide. The solution was evaporated to a small bulk, treated with dilute sulphuric acid and extracted 15 times with ether. The yellowish white mass was crystallised from water in needles.

The ethylimide was prepared by dissolving m-hemipinic acid in an aqueous solution of ethylamine, evaporating to dryness on the water-bath, distilling the residue from a retort, and crystallising the distillate from methyl alcohol in yellowish needles, m.p. 92°–230°.

The anhydride was prepared by digesting the acid with acetic anhydride and heating on the water-bath for two hours. On cooling, m-hemipinic anhydride separated, m.p. 175°.