XXVI.—*A Synthesis of* iso*Opianic Acid.*

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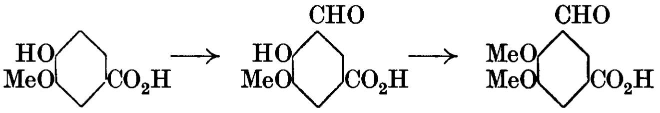
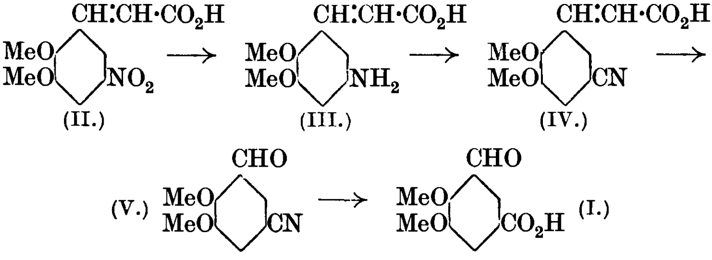
*iso*OPIANIC acid (I), m. p. 210—211°, was obtained in 1877 (*Ber.*, **10**, 397) by Tiemann and Mendelsohn by converting vanillic acid by boiling sodium hydroxide and chloroform into aldehydovanillic acid and methylating this with methyl iodide and potassium hydroxide.



(I.)

Since that date the acid does not appear to have been further investigated. During the course of experiments on the synthesis of the opianic acids we have carried out a synthesis of *iso*opianic acid which may be briefly described as follows. The starting point was 5-nitro-2 : 3-dimethoxycinnamic acid (II), which was obtained (i) by the nitration of 2 : 3-dimethoxycinnamic acid (Rubenstein, J., 1926, 651) and (ii) from 5-nitro-2 : 3-dimethoxybenzaldehyde (Davies, J., 1923, **123**, 1584; Perkin, Robinson, and Stoyle, J., 1924, **125**, 2357) by condensation with malonic acid in the presence of piperidine. The 5-nitro-acid was smoothly reduced by ferrous sulphate and ammonia to 5-*amino*-2 : 3-*dimethoxycinnamic acid* (III) and this was then converted into the corresponding 5-*cyano*-2 : 3-*dimethoxycinnamic acid* (IV) by the usual Sandmeyer process. The next step was the conversion of this acid into 5-*cyano*-2 : 3-*dimethoxybenzaldehyde* (V), which was easily effected by oxidation with permanganate in the presence of benzene, and the cyanoaldehyde was readily hydrolysed on boiling with concentrated hydrochloric acid to *iso*opianic acid (I), which was identified with the acid described by Tiemann and Mendelsohn (*loc. cit.*) by the melting point, 210—211°, and by conversion into the methyl ester, m. p.

98—99°. The various steps in this synthesis may be formulated thus :



EXPERIMENTAL.

5-*Nitro*-2 : 3-*dimethoxycinnamic Acid* (II).—Most of the acid used in this investigation was made by the nitration of 2 : 3-dimethoxycinnamic acid, the separation from the small quantity of the 6-nitro-acid, produced at the same time, being carried out essentially in the manner recommended by Rubenstein (*loc. cit.*). The second method of preparation, which is at the same time additional proof of the constitution of the acid, was carried out as follows. 5-Nitro-2 : 3-dimethoxybenzaldehyde (10 g.), malonic acid (11 g.), and piperidine (0·5 c.c.) were heated in pyridine (25 c.c.) solution for 1½ hours on the steam-bath, rapid elimination of carbon dioxide taking place ; the interaction was completed by boiling for 10 minutes. The product, when poured into excess of dilute hydrochloric acid, gave an almost quantitative yield of 5-nitro-2 : 3-dimethoxycinnamic acid ; this, after being washed and dried, crystallised from glacial acetic acid in long colourless needles, m. p. 231° (Found : N, 5·6. Calc. for $C_{11}H_{11}O_6N$: N, 5·5%).

The methyl ester. The acid (1 g.), methyl alcohol (10 c.c.), and sulphuric acid (1 c.c.) were boiled under reflux for 4 hours. The methyl alcohol was boiled off, water added, and the *methyl* ester collected, washed with dilute sodium carbonate solution, and crystallised from alcohol, separating in needles, m. p. 154—155° (Found : N, 5·1. $C_{12}H_{13}O_6N$ requires N, 5·2%). The ethyl ester, prepared by passing hydrogen chloride into a suspension of the acid in alcohol, appears to be dimorphous, separating sometimes in thin plates and sometimes, especially from concentrated solution, in rosettes of needles, m. p. 116°.

5-*Amino*-2 : 3-*dimethoxycinnamic Acid* (III).—The 5-nitro-acid (10 g.), dissolved in dilute ammonia, was gradually added to a solution of freshly crystallised ferrous sulphate (80 g.) in water (160 c.c.) which had been heated to 90° on the steam-bath. Concentrated ammonia (32 c.c.) was then gradually added with shaking, the mixture heated for ¼ hour on the steam-bath, and the precipitate washed with a little dilute ammonia. The filtrate and washings were mixed with excess of hydrochloric acid and allowed to stand; the hydrochloride of 5-amino-2 : 3-dimethoxycinnamic acid which separated was recrystallised from dilute hydrochloric acid, separating in fine needles. The hydrochloride was dissolved in hot water and decomposed by adding a saturated solution of sodium acetate; the precipitated 5-*amino*-2 : 3-*dimethoxycinnamic acid* separated from alcohol in glistening prismatic plates, m. p. 233° (decomp.) (Found : N, 6·4. $C_{11}H_{13}O_4N$ requires N, 6·3%).

5-*Cyano*-2 : 3-*dimethoxycinnamic Acid* (IV).—5-Amino-2 : 3-dimethoxycinnamic acid (4·4 g.), water (22 c.c.), and concentrated hydrochloric acid (4·6 c.c.) were mixed at 0° with a solution of sodium nitrite (1·5 g. in 10 c.c. of water) and the diazo-solution, filtered from a trace of insoluble matter, was added to a hot solution of potassium cupro-cyanide obtained by adding potassium cyanide (5·6 g. in 10 c.c. of water) to a solution of copper sulphate (5 g. in 30 c.c. of water). The mixture was heated for ¼ hour on the steam-bath, cooled, and acidified with concentrated hydrochloric acid, the precipitate was collected, washed, and dissolved in cold aqueous sodium carbonate, and this solution was filtered and acidified with hydrochloric acid. The precipitated *cyano-acid* crystallised from alcohol, with the aid of norite, in needles, m. p. 251° (Found : C, 61·5; H, 4·9. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7%). It is almost insoluble in cold water, sparingly soluble in ether or benzene, and readily soluble in boiling alcohol.

5-*Cyano*-2 : 3-*dimethoxybenzaldehyde* (V).—The cyano-acid (1 g.), dissolved in sodium carbonate solution, was covered with benzene (100 c.c.) in a separating funnel and a cold saturated solution of permanganate (1·4 g.) was gradually added with vigorous shaking. The liquids were filtered, the benzene layer was separated and dried over anhydrous sodium sulphate, and most of the benzene was distilled off; the *cyano-aldehyde* (0·6 g.) slowly separated in needles and, after recrystallisation from benzene, melted at 135° (Found : C, 63·1; H, 4·8. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·7%).

iso*Opianic Acid* (I).—5-Cyano-2 : 3-dimethoxybenzaldehyde (0·5 g.) was heated on the steam-bath with concentrated hydrochloric acid (15 c.c.) for 3 hours; on cooling, almost pure *iso*opianic acid crystallised. It was collected, dissolved in cold dilute sodium carbonate solution, filtered, reprecipitated, and crystallised from water, separating in slender needles, m. p. 210—211° (Found : C, 57·0; H, 4·7. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%). The methyl ester was prepared direct from 5-cyano-2 : 3-dimethoxybenzaldehyde by boiling with methyl alcohol and concentrated sulphuric acid under reflux for 4 hours. The product was diluted with water and extracted with ether, the ethereal solution washed with dilute aqueous sodium carbonate and dried over anhydrous sodium sulphate, the ether evaporated, and the residue crystallised from water, from which it separated in needles, m. p. 98—99° as stated by Tiemann and Mendelsohn (*loc. cit.*).

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