12. *Experiments on the Synthesis of Brazilin and Hæmatoxylin. Part IV. Synthesis of O-Diethylenehæmatoxylone.*

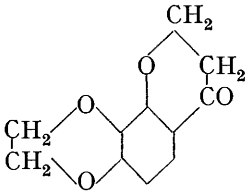
By (the late) W. H. Perkin, jun., A. Pollard, and Robert Robinson.

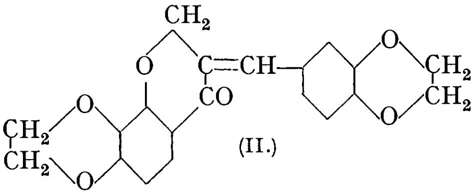
In 1928 (J., 1504, footnote) we mentioned that the investigation herein described had been completed, but we reserved publication in the hope of further developments. As, however, the hoped-for conversion of deoxytrimethylbrazilone into trimethylbrazilin or analogous transformations in the hæmatoxylin series have not been realised, the present account is submitted in order to complete the record.

The method of synthesis is that of Perkin and Robinson (*Proc.*, 1912, **28**, 7) and Perkin, Rây, and Robinson (J., 1926, 94; 1927, 2094; 1928, 1504) contemporaneously developed by Pfeiffer and his collaborators (Pfeiffer and Emmer, *Ber.*, 1920, **53**, 945; Pfeiffer, Angern, Haack, and Willems, *Ber.*, 1928, **61**, 839).

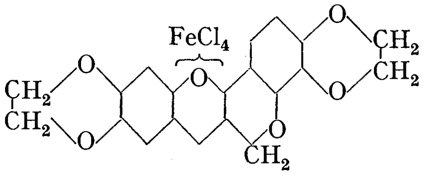
2 : 3-*Ethylenedioxy-β-phenoxypropionic acid*, $C_2H_4O_2{:}C_6H_3{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, has been dehydrated by means of phosphoric oxide to 7 : 8-*ethylenedioxychromanone* (I), which was condensed in the usual manner with 3 : 4-ethylenedioxybenzaldehyde. The resulting *bisethylenedioxybenzylidenechromanone* (II) yields the *ferrichloride* (III) when it is treated with anhydrous ferric chloride in acetic anhydride solution. (For a proof of the constitution in an analogous case, cf. Keller and Robinson, J., 1934, 1533.)

(I.)



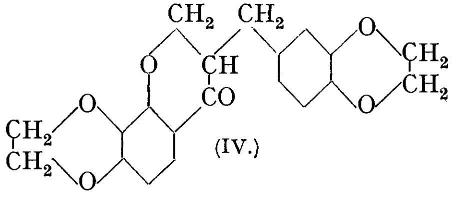


(II.)

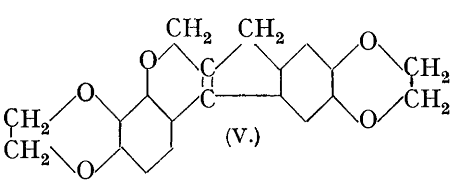


(III.)

Catalytic reduction of (II) furnishes the *dihydro*-derivative (IV), which is dehydrated by phosphoric oxide with formation of O-*diethylenedeoxyhæmatoxylone* (V). This proved to be an unsatisfactory substance, but it had the same properties as the specimen made from hæmatoxylin by a series of processes.

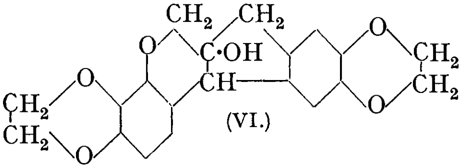


(IV.)

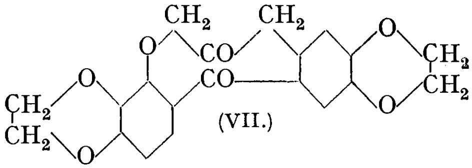


(V.)

O-*Diethylenehæmatoxylin* (VI) affords the characteristic O-*diethylenehæmatoxylone* (VII) on oxidation with chromic acid. The latter is reduced by phenylhydrazine to a product tallying with the synthetic (V).



(VI.)



(VII.)

Finally the synthetic (V) was catalytically reduced and then oxidised to diethylenehæmatoxylone identical with (VII) from hæmatoxylin.

EXPERIMENTAL.

2 : 3-*Ethylenedioxyphenol*.—Sodium ethoxide (sodium, 19 g.) in alcohol (275 c.c.) was added during 3½ hours with stirring under hydrogen to a mixture of pyrogallol (50 g.), alcohol (20 c.c.), and ethylene dibromide (75 g.) which was heated on the steam-bath under a reflux condenser. After boiling for a further ½ hour the alcohol was distilled, hot water was added to the residue, and after acidification the mixture was extracted with benzene. The benzene solution, after washing with water to remove unchanged pyrogallol, was dried and after removal of the solvent the residue was distilled, giving 19 g. of an almost colourless oil, b. p. 166°/25 mm., and then a bright red resin, b. p. > 300°/20 mm. The phenol was identified with that described by Magatti (*Ber.*, 1879, **12**, 1860) by preparation of the bromo-derivative.

2 : 3-*Ethylenedioxy-β-phenoxypropionic Acid*.—A solution of β-chloropropionic acid (25 g.) and sodium bicarbonate (18 g.) in water (100 c.c.) was added gradually during 1 hour to 2 : 3-ethylenedioxyphenol (30 g.) in aqueous potassium hydroxide (40 c.c. of 30%) heated on the steam-bath. After heating during 2 more hours, the solution was cooled and acidified with hydrochloric acid, and the precipitate collected and washed with water and then several times with ether. The first aqueous filtrate was extracted with ether and the combined ethereal solutions were extracted with aqueous sodium bicarbonate; acidification of these aqueous solutions afforded a further quantity of the acid. After crystallisation from alcohol, 17 g. of the *acid* were obtained and unchanged phenol was recovered from the ethereal solutions. Recrystallised from alcohol and from benzene, the acid had m. p. 156·5—158° (Found: C, 59·2; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·3%).

7 : 8-*Ethylenedioxychromanone* (I).—This ketone was first prepared by heating ethylenedioxyphenoxypropionic acid with 80% sulphuric acid (cf. J., 1927, 2097), but as the yield was unsatisfactory the following method was employed.

Phosphoric oxide (50 g.) was added to a solution of the acid (15 g.) in dry benzene (350 c.c.), and the solution refluxed for 4 hours. The benzene was decanted from the dark phosphoric complex, which was decomposed by the addition of ice and the mixture was warmed and extracted with benzene. The *chromanone* was isolated as a reddish solid (11 g.), which became colourless on crystallisation from alcohol (charcoal), m. p. after recrystallisation from alcohol, 120—121° (Found: C, 64·0; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·8%).

3 : 4-*Ethylenedioxybenzaldehyde*.—This compound was prepared by ethylenating protocatechualdehyde by means of sodium ethoxide and ethylene dibromide. As, however, the

yield obtained was only 20% of the theoretical, this method was abandoned and we followed Vorländer (*Annalen*, 1894, **280**, 205), Moureu (*Compt. rend.*, 1898, **126**, 1427), and Gattermann (*Annalen*, 1907, **357**, 373) with some modifications.

A mixture of pyrocatechol (100 g.) and ethylene dibromide (174 g.) was heated on the steam-bath under hydrogen, and a solution of sodium ethoxide (44 g. of sodium) in alcohol (700 c.c.) added during 3½ hours with stirring. After refluxing for a further ½ hour, the product was isolated in the known manner (67 g. of a pale yellow oil, b. p. 105°/15 mm.). The yield in the Gattermann reaction was 30%. The aldehyde forms long, silky, white needles, m. p. 51·5°.

7 : 8 : 3′ : 4′-*Bisethylenedioxy*-3-*benzylidenechromanone* (II).—7 : 8-Ethylenedioxychromanone (3·7 g.) and 3 : 4-ethylenedioxybenzaldehyde (4 g.) were dissolved in glacial acetic acid (30 c.c.), and the solution saturated with hydrogen chloride at 0°. After keeping at the room temperature for some hours, the solution became filled with crimson crystals, which were collected, washed with a little acetic acid, and triturated with water at about 40°; the salt then decomposed, giving the unsaturated *ketone* as a buff-coloured powder. This crystallised from ethyl acetate in pale yellow needles, m. p. 200—202° (yield, 75%) (Found: C, 68·1; H, 4·8. $C_{20}H_{16}O_6$ requires C, 68·1; H, 4·5%).

When treated in acetic anhydride solution with anhydrous ferric chloride, this substance gives an oxonium ferrichloride analogous to the one described by Perkin, Rây, and Robinson (J, 1926, 950).

Anhydrous ferric chloride (5 g.) was added to a solution of the chromanone derivative (1 g.) in acetic anhydride (25 c.c.) and after the reaction had subsided a further amount (3 g.) was added. After 10 minutes the solution was poured into water (250 c.c.) and the dark red solid was collected. On addition of a solution of ferric chloride in concentrated hydrochloric acid to the aqueous solution a further amount was obtained. Recrystallised from acetic anhydride, the ferrichloride formed garnet-red needles with a green sheen, m. p. 232—233° after softening at 229° (Found: C, 43·8; H, 2·8; Fe_2O_3, 14·5. $C_{20}H_{15}O_6Cl_4Fe$ requires C, 43·7; H, 2·8; Fe_2O_3, 14·6%).

This salt is 6 : 7 : 7′ : 8′-*bisethylenedioxychromeno*(4′ : 3′ : 2 : 3)*benzopyrylium ferrichloride* (III).

7 : 8 : 3′ : 4′-*Bisethylenedioxy*-3-*benzylchromanone* (IV).—An aqueous solution of palladous chloride (50 c.c. of 0·5%) with alcohol (40 c.c.) and norit (5 g., previously heated to redness) was stirred in hydrogen until no further absorption occurred. The unsaturated ketone (5 g.) in fine suspension in a mixture of ethyl acetate and alcohol (300 c.c.) was then introduced, and the solution stirred till the absorption of hydrogen slackened considerably and nearly the theoretical amount had been taken up. The solution was then filtered, concentrated to about 50 c.c., and added to water, and the white flocculent precipitate collected (80% of the theoretical). The crude *product* was dissolved in alcohol, ether added, and the solution repeatedly washed with water and then dried and concentrated; white needles separated, m. p. 130—132° (Found: C, 67·6; H, 5·2. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

Synthesis of O-*Diethylenedeoxyhæmatoxylone* (V).—After carrying out the reaction under various conditions, we found that the following gave the best results. A solution of the benzylchromanone derivative (4 g.) in dry toluene (100 c.c.) was refluxed for 2½ hours, during which time phosphoric oxide (60 g.) was added at intervals of ½ hour. The toluene solution was decanted, the residue washed several times with toluene, and crushed ice added. The phosphoric acid was neutralised with ammonia, and the toluene removed in a current of steam. After the cold mixture had been kept for some hours, a dark brown solid was collected, washed with water and with warm alcohol, and dissolved in ethyl acetate. Precipitation with light petroleum gave a flocculent brown precipitate, which was taken up in chloroform, and a solution of bromine in light petroleum added, causing the separation of a crimson solid bromide of the deoxy-compound. This was collected and shaken with zinc dust and acetic acid; the regenerated deoxy-compound was isolated as a pale yellowish-brown precipitate by pouring the acid solution into water.

A specimen which had been twice purified by conversion into the bromide and reduction by zinc dust and by aluminium amalgam separated from alcohol in pale ochreous crystals, m. p. 157° with slight previous softening, and exhibiting the same behaviour on admixture with *O*-diethylenedeoxyhæmatoxylone. The crystalline form was not characteristic, but the synthetic and the hæmatoxylin-derived specimen gave identical purple-red bromides and identical magenta colorations in benzene solution when treated with nitric acid. Their behaviour with solvents was identical in each case, both being readily soluble in chloroform, ethyl acetate, benzene and acetic acid, slightly soluble in alcohol and in hot water, and insoluble in light petroleum.

O-*Diethylenehæmatoxylin* (VI).—This *compound* was obtained by treating hæmatoxylin with an excess of ethylene dibromide and sodium ethoxide under the conditions employed in the preparation of 2 : 3-ethylenedioxyphenol, but the yield was only 10%. The following method gave better results. An intimate mixture of hæmatoxylin (10 g.) and finely powdered potassium carbonate (15 g.) with ethylene dibromide (20 g.) and acetone (10 c.c.) was heated in a sealed tube at 90° for 7 days. The reddish-brown mass was extracted with acetone, the solution filtered, and the acetone removed. The small amount of ethylene dibromide present was steam-distilled, leaving the hæmatoxylin ether as a brown amorphous solid (10·5 g.). The substance could not be crystallised, but it was purified by thorough washing in ethereal solution with aqueous sodium hydroxide and after recovery by repeated precipitation from benzene solution by light petroleum. The colourless flocks, freely soluble in most organic solvents, resinified on collection (Found : C, 68·0; H, 5·2. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

O-*Diethylenehæmatoxylone.*—*O*-Diethylenehæmatoxylin (10 g.) was dissolved in warm glacial acetic acid (60 c.c.), cooled, and a solution of chromic anhydride (5·8 g.) in a little water added gradually below 15°. A red precipitate first separated and this passed into solution as more chromic acid was added. After keeping for 2 hours, a pink solid separated, which was collected, washed with water and alcohol, and the solutions combined and diluted with water (500 c.c.), giving a further amount of materials. In the best experiments a yield of nearly 90% of the crude *diethylenehæmatoxylone* was obtained. Recrystallised from glacial acetic acid, the substance was obtained as almost colourless prisms, m. p. 198—200° (decomp.) (Found : C, 65·1; H, 4·6. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·3%).

O-*Diethylenedeoxyhæmatoxylone* (V).—Diethylenehæmatoxylone (4·4 g.) was added gradually to a mixture of acetic acid (20 c.c.) and phenylhydrazine (9·2 c.c.) at about 70°. After standing over-night, a certain amount of acetphenylhydrazide which had separated was collected, and the solution added to warm water. The orange-coloured precipitate was washed with warm water and cold alcohol to remove phenylhydrazine derivatives, and then dissolved in ethyl acetate. Addition of ligroin to the solution caused the separation of the *deoxy*-compound as a pale brown, flocculent mass, which was further purified by conversion into the bromide and then reduction by zinc and acetic acid. A crude specimen darkened and began to melt at 153°; when purified by separation from alcohol, it melted at 157° with slight previous softening (Found : C, 71·1; H, 4·9. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%). The substance resembles deoxytrimethylbrazilone and deoxytetramethylhæmatoxylone in general behaviour and some of its properties have been mentioned above.

Synthesis of O-*Diethylenehæmatoxylone.*—Synthetic diethylenedeoxyhæmatoxylone, purified only once through the bromide, was treated in boiling alcoholic solution with amalgamated aluminium foil for 4 hours and then recovered, the object of the treatment being the removal of traces of nuclear-substituting bromine. The colourless amorphous substance (2·1 g.) was dissolved in ethyl acetate (75 c.c.), platinum-black (0·2 g.) added, and reduction effected by shaking with pure hydrogen for 3 hours, absorption of the gas then being very slow. The product was isolated and distilled at $<$ 0·1 mm. pressure (it was impossible to observe the b. p.). The distillate (1·6 g.) was dissolved in acetic acid (30 c.c.), and chromic anhydride (2·0 g.) in a little water gradually added at about 25°; after keeping for a few hours in the ice-chest a crystalline deposit had formed and this was collected, washed with acetic acid, and crystallised from the same solvent. The colourless prismatic needles had m. p. 198—200° (decomp.) alone or mixed with diethylenehæmatoxylone prepared from hæmatoxylin (Found : C, 65·3; H, 4·5%). The specimens were identical in every respect and the characteristic reactions with alcoholic potash, sulphuric acid and nitric acid were carefully compared.

It may be noted that in earlier experiments the products of catalytic hydrogenation of natural and synthetic diethylenedeoxyhæmatoxylone (in various ways) were examined and found to be similar (m. p., *ca.* 144—146° or 154—158°, after softening at 123—126°), but the substance was never obtained in a perfectly homogeneous condition and it may be a mixture of stereoisomerides.

Other Experiments.—No pinacol could be obtained by the reduction of diethylenehæmatoxylone under various conditions.

O-Acetyldiethylenehæmatoxylin crystallised from benzene–light petroleum as elongated, colourless tablets, m. p. 132—134°.

O-Tetra-acetylhæmatoxylone crystallised from alcohol as colourless needles, m. p. 125—127°. The amorphous *O*-tetrabenzylhæmatoxylin gave an acetyl derivative from benzene–light petroleum, m. p. 112°.

O-Tetrabenzylhæmatoxylone did not crystallise, but by the action of acetic anhydride furnished acetylanhydrotetrabenzylhæmatoxylone, needles from benzene–light petroleum, m. p. 164° after sintering at 160°.

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