

CCXVII.—*Synthesis of Cotarnic Acid.*

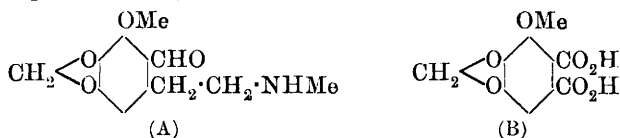
By WILLIAM HENRY PERKIN, jun., ROBERT ROBINSON, and FREDERICK THOMAS.

DURING the course of an investigation on narcotin and its degradation products, on which we have been engaged for a considerable time, we have carried out a series of experiments which have resulted in a synthesis of cotarnic acid, and have thus definitely established the constitution of this important acid.

Wöhler (*Annalen*, 1844, **50**, 19) first obtained cotarnine,  $C_{12}H_{15}O_4N$ , from narcotin,  $C_{22}H_{23}O_7N$ , by oxidation with manganese dioxide and dilute sulphuric acid, and the careful investigation of this important substance has shown that it is probably an aldehyde of the constitution :



Furthermore, the experiments of Freund and Becker (*Ber.*, 1903, **36**, 1521) have made it probable that the methoxy-group in cotarnine is adjacent to the aldehyde group, and the above formula may therefore be expanded to (A) :



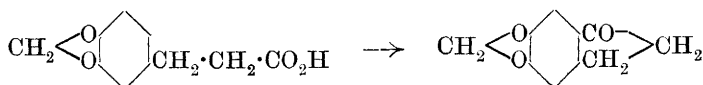
When cotarnine is oxidised with permanganate, it yields cotarnic acid,  $C_{10}H_9O_7$ , and if the constitution for cotarnine just given is accepted as correct, the constitution of cotarnic acid will be represented by the formula (B), and this acid is therefore methoxyhydrastic acid.

The highly ingenious method which Freund and Becker have employed to show that cotarnine is a derivative both of piperonal and

of salicylaldehyde methyl ether, as indicated in the formula just mentioned, does not appear to us to be quite conclusive, and we have therefore confirmed this formula by synthesising cotarnic acid by a method which leaves no room for doubt as to its constitution.

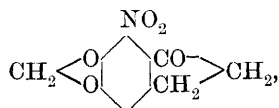
The synthesis proved to be a difficult one, but after many unsuccessful attempts in other directions, we ultimately succeeded in solving the problem by a process which is briefly as follows :

The starting point was 5 : 6-methylenedioxy-1-hydrindone, which we prepared in quantity from 3 : 4-methylenedioxyphenylpropionic acid by the action of phosphoric oxide :



(compare Perkin and Robinson, *Trans.*, 1907, **91**, 1084).

When this substance is treated with concentrated nitric acid, it is readily converted into 7-nitro-5 : 6-methylenedioxy-1-hydrindone (m. p. 164—165°),



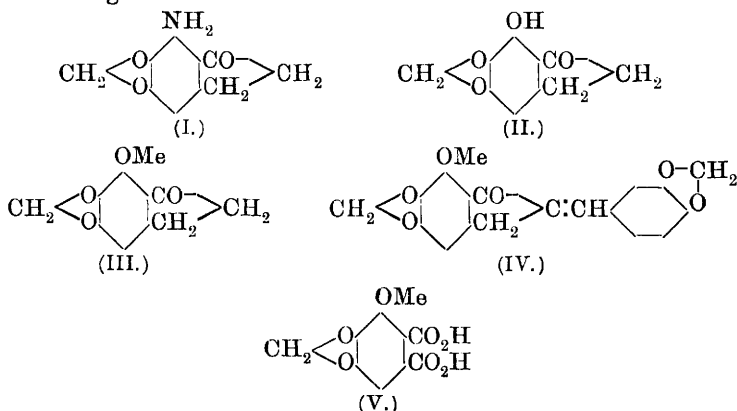
and this is reduced by tin and hydrochloric acid with formation of the corresponding amino-derivative, m. p. 175° (I). The next step was to convert the amino-derivative into 7-hydroxy-5 : 6-methylenedioxy-1-hydrindone (II) by diazotisation, and although, owing to the formation of brown by-products, the yield of the hydroxy-derivative was very small, we succeeded in obtaining sufficient for our purpose.

This hydroxy-derivative yields an intense violet coloration on the addition of ferric chloride to the alcoholic solution, and the hydroxy-group is therefore most probably adjacent to the carbonyl group. It was for this reason that we assign the position 7 to the nitro-group in 7-nitro-5 : 6-methylenedioxy-1-hydrindone.

By treatment in alkaline solution with methyl sulphate, the hydroxy-derivative was next converted into the corresponding methoxy-derivative (III), and this, when condensed with piperonal and dilute aqueous potassium hydroxide, yielded 7-methoxy-5 : 6-methylenedioxy-2-piperonylidene-1-hydrindone (m. p. 225—230°, IV).

This piperonylidene derivative was oxidised by permanganate, and the acid produced was recognised as cotarnic acid (V) by conversion into the characteristic methylimide, which melted at 205°, and had the same properties as a specimen of the methylimide of cotarnic acid which we prepared from cotarnic acid obtained by the oxidation of

cotarnine. The steps in this synthesis of cotarnic acid are therefore the following :



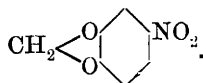
The yield of cotarnic acid obtained in this way is, unfortunately, very small, and we are engaged in an attempt to discover a more satisfactory method of synthesis.

#### *Nitration of the Methylene Ether of Catechol.*

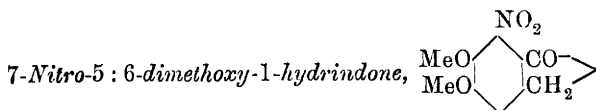
The methylene ether of catechol has been prepared by Moureu (*Bull. Soc. chim.*, 1896, [iii], **15**, 654) by the action of methylene iodide on the sodium derivative of catechol. Since we wished to investigate the constitution of its mononitro-derivative, we have endeavoured to use the cheaper methylene chloride in its preparation, and we find that the methylene ether can be so produced, but the yield is very unsatisfactory. Catechol (66 grams) was dissolved in absolute alcohol and mixed with a solution of sodium (27.6 grams) in alcohol and methylene chloride (50 grams). After boiling for sixteen hours in a reflux apparatus, the bulk of the alcohol was distilled off, water was then added, the oil extracted with ether, and the ethereal solution dried and evaporated. The residue consisted almost entirely of an oil which distilled at 170—175° under the ordinary pressure, whereas the boiling point of the methylene ether of catechol is stated by Moureu (*loc. cit.*) to be 172—173°. A small quantity of this substance was dissolved in glacial acetic acid and treated with a little nitric acid, when the nitro-derivative separated and, after crystallisation from alcohol, had the correct melting point, 147°. Its constitution was proved as follows: The nitro-compound was readily reduced by tin and hydrochloric acid, and the resulting base was obtained by rendering the solution alkaline with potassium hydroxide and extracting with ether. The base was converted, by warming with acetic anhydride,

into the acetylamino-compound, which crystallised from water in colourless needles and melted at 135°.

Since the melting point was unaltered by admixture with the acetyl-amino-derivative of the methylene ether of catechol, which is obtained by the successive action of potassium hypobromite and acetic anhydride on the amide of piperonylic acid, it is clear that the nitro-compound produced by the nitration of the methylene ether of catechol is 4-nitro-1:2-methylenedioxybenzene,



Salway (this vol., 1155) has already shown that one of the products of the nitration of piperonal has the same constitution.



In order to prepare this substance, 5:6-dimethoxyhydrindone (Perkin and Robinson, *Trans.*, 1907, **92**, 1092, 2 grams) was stirred vigorously with nitric acid (D 1.42, 10 c.c.), when the whole dissolved, and, if the hydrindone was quite pure, no oxidation occurred.

After adding water, the sticky mass which separated gradually became hard, and was collected and washed with water.

This nitro-compound crystallises from a mixture of ethyl acetate and light petroleum in pale yellow prisms, or from methyl alcohol, in which it is very sparingly soluble in the cold, in almost colourless, prismatic needles. If the hot saturated solution in methyl alcohol is rapidly cooled, needles separate, and after some time these change into prisms :

0.1681 gave 8.4 c.c. N<sub>2</sub> at 15° and 771 mm. N = 6.0.

C<sub>11</sub>H<sub>11</sub>O<sub>5</sub>N requires N = 5.9 per cent.

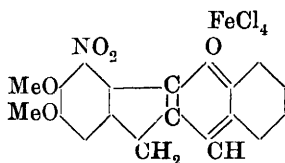
7-Nitro-5:6-dimethoxy-1-hydrindone melts at 149—150°, and, as the following experiments show, exhibits the characteristic properties of a derivative of hydrindone. (I) The solution in hot methyl alcohol was treated with piperonal and a little potassium hydroxide, when a yellow colour was immediately produced and a canary-yellow, crystalline precipitate of the piperonylidene derivative quickly separated. This substance may be recrystallised by adding methyl alcohol to its solution in hot pyridine, and the pale yellow prisms thus obtained melt at 260° with slight previous darkening. The colour of its solution in concentrated sulphuric acid is intense reddish-purple, and becomes yellow on dilution with water.

(II) Approximately equal weights of the nitro-hydrindone and of salicylaldehyde were dissolved in methyl alcohol, and a rapid stream of hydrogen chloride passed through the solution for a minute.

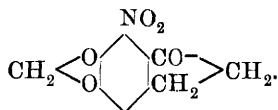
On cooling, brick-red crystals of the oxonium anhydro-hydrochloride separated from the solution. This salt dissolves in water or concentrated sulphuric acid to yellow solutions which do not fluoresce.

The double salt with platinum chloride crystallises in orange, microscopic needles. The anhydro-ferrichloride melts at 188°, and is a brick-red precipitate, which crystallises from glacial acetic acid in orange-brown needles with characteristic prismatic edges.

This ferrichloride has analogous properties to the similarly constituted substances already described by Perkin, Robinson and Turner (Trans., 1908, 93, 1085), and there can be little doubt that it has the constitution



*7-Nitro-5:6-methylenedioxy-1-hydrindone,*



This substance may be prepared by adding nitric acid (D 1.42, 15 c.c.), previously boiled to remove nitrous acid, to 5:6-methylenedioxy-1-hydrindone (Trans., 1907, 91, 1084). The hydrindone dissolves and, after two minutes, water is added, and the precipitated nitro-compound, which rapidly hardens, is collected, washed, dried, and then purified by repeated extraction with boiling light petroleum (b. p. 60—70°):

0.1507 gave 8.5 c.c.  $N_2$  at 10° and 749 mm.  $N = 6.6$ .

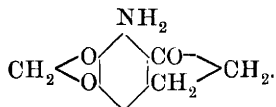
$C_{10}H_7O_5N$  requires  $N = 6.3$  per cent.

*7-Nitro-5:6-methylenedioxy-1-hydrindone* melts at 164—165°, and, if pure hydrindone was employed in its preparation, it may be readily crystallised from methyl alcohol, from which it separates in very pale elongated prisms. The colour of the solution in sulphuric acid is only pale yellow, which is rather remarkable in view of the fact that 5:6-methylenedioxyhydrindone itself dissolves in sulphuric acid with an intense red coloration.

The piperonylidene derivative, prepared in the usual way, separates in lemon-yellow, microscopic needles, which are very sparingly soluble in alcohol and melt at 290° with decomposition. It is soluble in boil-

ing glacial acetic acid, and, on the addition of hydrochloric acid, a red colour is produced, which disappears as the substance crystallises from the solution. The colour of the solution of the piperonylidene derivative in sulphuric acid is purple.

*7-Amino-5 : 6-methylenedioxy-1-hydrindone,*

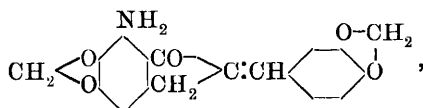


The reduction of 7-nitro-5 : 6-methylenedioxy-1-hydrindone to the corresponding amino-derivative may be carried out by gently boiling its alcoholic solution for two hours with alcohol (200 c.c.) and hydrochloric acid (22.5 c.c.) with excess of tin. The product is then poured into dilute hydrochloric acid, filtered hot from insoluble matter, and the tin eliminated by treatment with hydrogen sulphide. As soon as the liquid smells strongly, it is filtered, and the clear solution rendered alkaline with sodium hydroxide, when a finely divided precipitate separates, which is collected, dried on porous porcelain, and crystallised from methyl alcohol. Owing to the various by-products, the yield was, unfortunately, only about 10 per cent. of that theoretically possible :

0.1612 gave 10.4 c.c.  $N_2$  at  $13^\circ$  and 746 mm.  $N = 7.5$ .

$C_{10}H_9O_3N$  requires  $N = 7.3$  per cent.

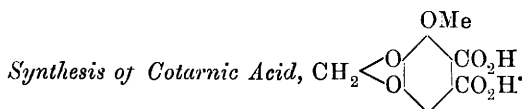
*7-Amino-5 : 6-methylenedioxy-1-hydrindone* separates from methyl alcohol in colourless needles, and melts at  $175^\circ$ . It yields, with piperonal and alcoholic potassium hydroxide, a bright yellow, crystalline piperonylidene derivative, which doubtless has the constitution



since, on treatment with sodium nitrite and hydrochloric acid in excess of alcohol, a solution is obtained which gives a red coloration with alkaline  $\beta$ -naphthol. Aminomethylenedioxyhydrindone dissolves slowly in dilute hydrochloric acid, and the colourless solution becomes yellow on the addition of sodium nitrite.

On adding this to an alkaline solution of  $\beta$ -naphthol, a crimson solution is obtained, from which a scarlet azo-compound separates.

This azo-compound dissolves in concentrated sulphuric acid with an intense indigo-blue colour.



The conversion of 7-amino-5:6-methylenedioxy-1-hydrindone into cotarnic acid proved to be a much more difficult operation than was expected, owing principally to the formation, even under the best conditions, of large quantities of other substances and consequent small yield of the acid. After several comparative experiments, the synthesis was ultimately accomplished in the following way.

Aminomethylenedioxyhydrindone (10 grams) was dissolved in the least possible quantity of warm dilute hydrochloric acid and cooled with ice, when some of the hydrochloride of the base separated.

Sodium nitrite (3.5 grams), dissolved in a little water, was then added, the solution vigorously boiled for ten minutes, filtered, saturated with ammonium sulphate, and repeatedly extracted with ether.

The solution, mixed with alcohol, gave an intense violet coloration\* on the addition of ferric chloride, indicating that the hydroxy-methylenedioxyhydrindone produced probably contains a hydroxy-group in the ortho-position with respect to the carbonyl group (compare p. 1978). Unfortunately, the conversion of the amino- into the hydroxy-group is always accompanied by the formation of an insoluble, brown substance, which could not be crystallised, and greatly affects the yield of the hydroxy-derivative. The ethereal solution of the hydroxy-derivative was extracted with small quantities of dilute potassium hydroxide, and the alkaline solutions agitated in the cold with methyl sulphate in excess. When all the methyl sulphate had been decomposed, the solution was extracted with ether and the ethereal solution evaporated. The residue showed a tendency to crystallise, but, as the whole of the material was required for the synthesis, the product was not directly investigated, but, at once, dissolved in alcohol and treated with piperonal and some dilute potassium hydroxide. The yellow precipitate so obtained undoubtedly consists of 7-methoxy-5:6-methylenedioxy-2-piperonylidene-1-hydrindone (IV, p. 1979).

It may be crystallised from a mixture of pyridine and alcohol, melts at 225—230°, and dissolves in sulphuric acid, yielding an intense carmine solution. The substance obtained from five of the above operations was oxidised, at as low a temperature as possible, with

\* On one occasion, the reaction, for some unknown reason, proceeded in another direction, and the ether extract contained a substance which yielded a green coloration with ferric chloride.

potassium permanganate containing a small quantity of potassium carbonate, but oxidation proceeded, especially at first, with difficulty, owing largely to the insolubility of the substance. After a considerable amount of permanganate had been reduced, the solution was boiled, filtered, the manganese precipitate treated with hot water and sulphur dioxide, and the unchanged piperonylidene derivative collected and again oxidised with permanganate, the operation being repeated until only a negligible amount remained unoxidised.

The alkaline filtrates from the manganese precipitates were combined, evaporated to a small bulk, the solution was then rendered acid to Congo-paper, and the small quantity of piperonylic acid which separated removed by filtration. The filtrate was evaporated to dryness, extracted with pure dry ether in a Soxhlet apparatus, and, after distilling off the ether, a small quantity of a syrupy acid remained, which quickly crystallised, apparently in plates. The quantity was so small that an analysis was not attempted, and as the melting point of cotarnic acid is not sufficiently decisive, the whole was converted into the methylimide which we had previously prepared from a specimen of cotarnic acid from cotarnine and found to be highly characteristic. In this experiment, the crude acid was dissolved in a little hot water, when it was noticed that the solution, on cooling, deposited crystals exactly resembling those of cotarnic acid. Excess of methylamine was now added, the solution evaporated to dryness on the water-bath, and the methylamine salt heated in a test-tube, when a sublimate of needles was obtained and an oil distilled which soon solidified. The distillate and sublimate were dissolved in a little boiling methyl alcohol, when the filtered solution deposited a crop of almost colourless needles, which melted at  $205^{\circ}$ , and had all the properties of the methylimide of cotarnic acid, the identity with which was further confirmed by the fact that an intimate mixture of the two preparations melted sharply at  $205^{\circ}$ . There can thus be no doubt that the substance synthesised in the experiments described above was cotarnic acid.

THE UNIVERSITY,  
MANCHESTER.

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