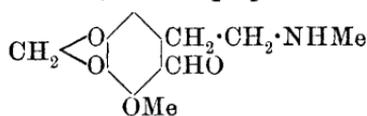


CXXXV.—*The Synthesis of Substances Allied  
to Cotarnine.*

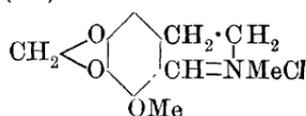
By ARTHUR HENRY SALWAY.

IN the course of a recent investigation on the constituents of the essential oil of nutmeg (Power and Salway, *Trans.*, 1907, **91**, 2037), amongst other compounds, a considerable quantity of myristicin was isolated. It seemed probable that this substance would serve as

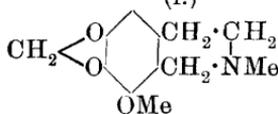
a convenient starting-point for the synthesis of cotarnine, the constitution of which has been the subject of considerable discussion. Roser (*Annalen*, 1888, **249**, 156), on the one hand, in consideration of the fact that cotarnine behaves both as an aldehyde and a secondary amine, assigns to it the formula (I), whilst its hydrochloride, which is formed with elimination of the elements of water, is given the formula (II). Decker (*J. pr. Chem.*, 1893, [ii], **47**, 222), on the other hand, draws attention to the improbability of the co-existence of an aldehydic residue and a secondary amino-group in the same molecule, and points out that Roser's formula does not explain why cotarnine is precipitated from its hydrochloride in the aldehydic form, or why hydrocotarnine (III) is converted into cotarnine on oxidation. For these reasons, Decker proposes formula (IV).



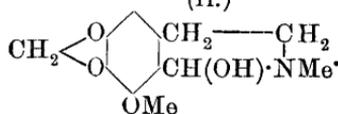
(I.)



(II.)

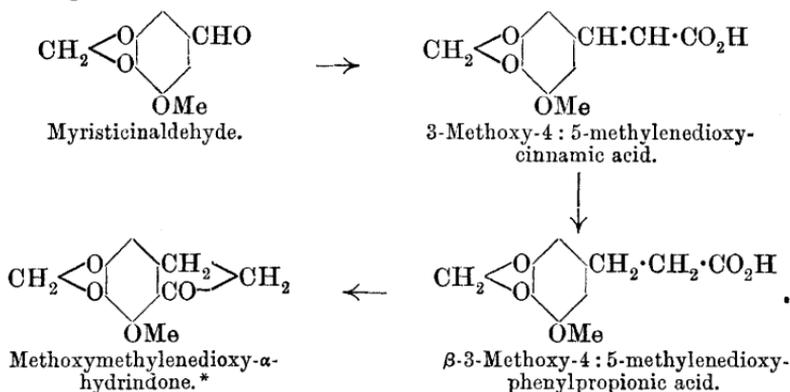


(III.)

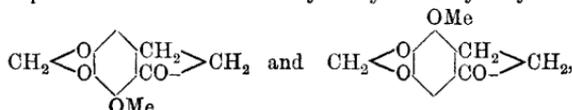


(IV.)

With the object of effecting the synthesis of cotarnine from myristicin, the first experiments consisted in preparing methoxymethylenedioxy- $\alpha$ -hydrindone, which was obtained according to the following scheme of reactions:



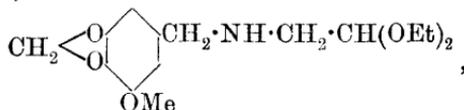
\* Of the two possible formulæ for methoxymethylenedioxy- $\alpha$ -hydrindone, namely:



the former has been adopted throughout this communication. The same applies to

Attempts to convert the oxime of methoxymethylenedioxy- $\alpha$ -hydrindone into 1-hydroxy-8(5)-methoxy-6:7-methylenedioxydihydro-*isoquinoline* by means of the Beckmann transformation were unsuccessful, so that the synthesis of cotarnine from this compound by subsequent methylation and reduction could not be effected.

A further attempt to apply the Pomeranz (*Monatsh.*, 1893, **14**, 118; 1894, **15**, 301) *isoquinoline* synthesis to myristicinaldehyde was also unsuccessful, because the condensation of myristicinyldene-aminoacetal could not be effected on account of the readiness with which the substance is reconverted into its components, myristicinaldehyde and aminoacetal. In order to obviate this disruption of the molecule, myristicinyldeneaminoacetal was first reduced to myristicinylaminoacetal,



and the latter then subjected to the action of sulphuric acid and other condensing agents under varied conditions. In this case, also, the reaction did not proceed in the desired direction, and only resinous products were formed.

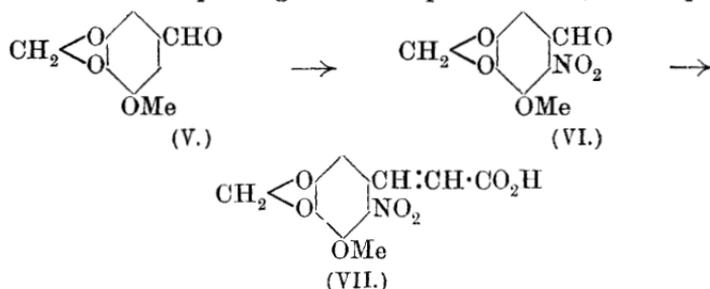
Finally, some experiments were conducted which led to the synthesis of a number of substances allied to cotarnine. It was necessary, in the first place, to prepare 2(6)-nitro-3-methoxy-4:5-methylenedioxy-cinnamic acid, and for this purpose myristicinaldehyde was converted by means of sodium and ethyl acetate into 3-methoxy-4:5-methylenedioxy-cinnamic acid; the action of nitric acid on this substance, however, leads to the displacement of the carboxyl group by a nitro-group, and at the same time a nitro-group is introduced into the nucleus:



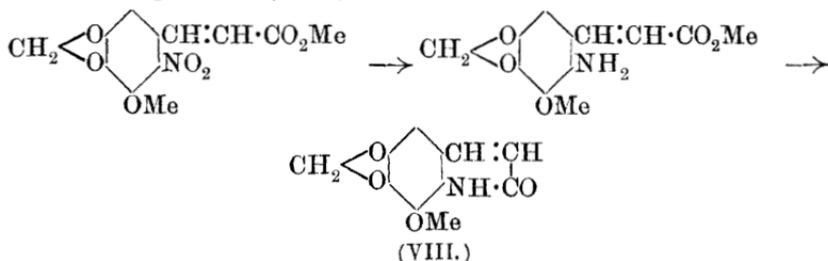
A second method for the preparation of 2(6)-nitro-3-methoxy-4:5-methylenedioxy-cinnamic acid was more successful. Myristicinaldehyde (V) on nitration yields a mixture of 5-nitro-1-methoxy-2:3-methylenedioxybenzene and nitromyristicinaldehyde (VI) (this vol., p. 1160), the latter of which readily condenses with sodium acetate and acetic anhydride with the formation of 2(6)-nitro-3-methoxy-4:5-methylenedioxy-cinnamic acid (VII).

the alternative formulæ in the case of nitromethoxymethylenedioxy-cinnamic acid, ketomethoxymethylenedioxydihydroquinoline, oxy*isocotarnine*, etc.

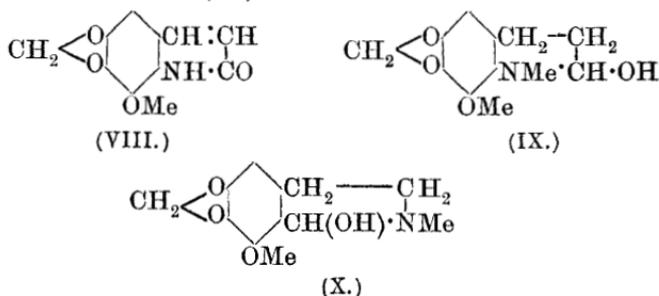
Methyl 2(6)-nitro-3-methoxy-4:5-methylenedioxybenzylideneacetate is readily reduced to the corresponding amino-compound, which, in the presence



of acids, is transformed into 2-keto-8(5)-methoxy-6:7-methylenedioxy-1:2-dihydroquinoline (VIII).

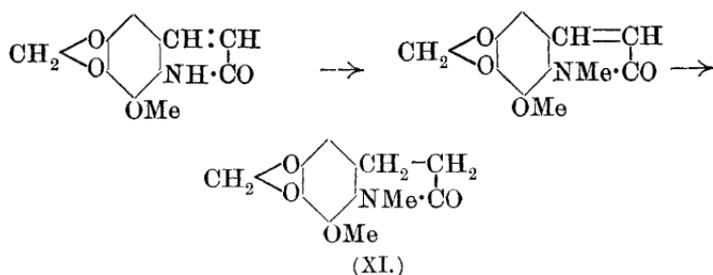


2-Keto-8(5)-methoxy-6:7-methylenedioxy-1:2-dihydroquinoline is of considerable interest on account of its relationship to cotarnine (X). If the formulæ of the two substances are compared, it would appear possible to convert the former by reduction and methylation into an isomeride of cotarnine, which might appropriately be designated *isocotarnine* (IX).



2-Keto-8(5)-methoxy-6:7-methylenedioxy-1:2-dihydroquinoline, however, polymerises so easily on reduction, either in acid or in alkaline solution, that it was found impossible to prepare the unimolecular reduction product. In this respect its behaviour is similar to that of carbostyryl itself towards reducing agents, as Friedländer and Müller (*Ber.*, 1887, 20, 2012) have shown. In order to avoid this polymerisation, 2-keto-8(5)-methoxy-6:7-methylenedioxy-1:2-dihydroquinoline

was methylated, and yielded, according to the conditions of the reaction, either an *O*- or a *N*-methyl ether. By the reduction of the latter compound, oxyisocotarnine (XI) was obtained.

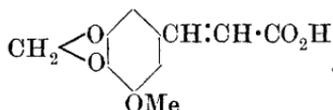


All efforts to reduce this compound to *isocotarnine* were unsuccessful. The physiological action of the above-mentioned substances is at present under investigation.

#### EXPERIMENTAL.

##### *Preparation of Myristicinaldehyde.*

Myristicin (5 parts) was heated for twenty-four hours on the water-bath with a solution of potassium hydroxide (4 parts) in 15 parts of alcohol, whereby a quantitative yield of *isomyristicin* was obtained (compare Semmler, *Ber.*, 1891, **24**, 3818; Thoms, *Ber.*, 1903, **36**, 3446). The latter substance, in portions of 10 grams at a time, was then shaken into an emulsion with water at 60°, and a solution of 20 grams of potassium permanganate in 500° c.c. of water gradually added with constant agitation, the temperature being kept at 60—65°. After all the permanganate had been added, for which about an hour was necessary, the mixture was cooled, filtered, and the manganese precipitate well washed with cold water. The precipitate, which contained the myristicinaldehyde, was dried on a porous plate, and afterwards extracted in a Soxhlet apparatus with chloroform. The chloroform extracts from several such oxidations were united, the solvent removed, and the solid residue well washed with cold ether to remove unoxidised *isomyristicin*. The yield of myristicinaldehyde was 40—45 per cent. of the *isomyristicin* employed. A quantity of myristicinic acid, varying from 15 to 20 per cent., was always formed by the oxidation, and could be obtained by acidifying the filtrate from the manganese precipitate.

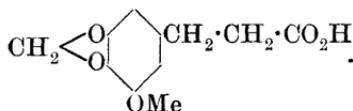
*3-Methoxy-4 : 5-methylenedioxy-cinnamic Acid,*

One hundred and fifty grams of myristinaldehyde were dissolved in 400 grams of ethyl acetate, and to this solution 37.5 grams of sodium, finely divided by vigorous agitation with boiling toluene, were added. The violent reaction which immediately ensued was moderated by cooling the mixture. When the action had subsided, the mixture was kept at the ordinary temperature for some time, after which the product was hydrolysed by heating for half an hour with an excess of alcoholic potash. The alcohol was then removed as completely as possible, water added, and the alkaline liquid extracted with chloroform to remove resinous matter. On acidifying with dilute sulphuric acid, a grey precipitate was obtained, which was crystallised from glacial acetic acid. The yield of methoxymethylenedioxy-cinnamic acid was 137 grams :

0.1342 gave 0.2914  $\text{CO}_2$  and 0.0554  $\text{H}_2\text{O}$ .  $\text{C} = 59.2$  ;  $\text{H} = 4.6$ .

$\text{C}_{11}\text{H}_{10}\text{O}_5$  requires  $\text{C} = 59.5$  ;  $\text{H} = 4.5$  per cent.

*3-Methoxy-4 : 5-methylenedioxy-cinnamic acid* is readily soluble in hot acetic acid, from which, on cooling, it crystallises in well-formed, colourless, prismatic needles, sintering at  $220^\circ$  and melting and decomposing at  $228^\circ$ . It is only moderately soluble in boiling alcohol, and is deposited from this solvent in thin, flat plates. It is practically insoluble in water and only very sparingly soluble in ether.

 *$\beta$ -3-Methoxy-4 : 5-methylenedioxypropionic Acid,*

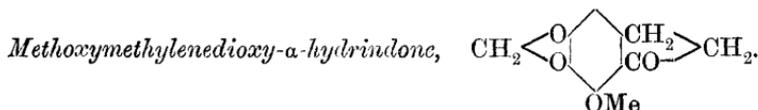
Fifty grams of 3-methoxy-4 : 5-methylenedioxy-cinnamic acid were dissolved in dilute sodium hydroxide, and reduced with 800 grams of sodium amalgam (4 per cent.) at the ordinary temperature. The liquid was mechanically stirred throughout the reduction, whilst the accumulation of alkali in the mixture was prevented by the periodic addition of hydrochloric acid. At the end of the reaction the alkaline liquid was acidified and the precipitated oil extracted with ether, when, on evaporating the solvent, a viscid, brown oil was obtained. This solidified after long keeping, and was then crystallised from benzene

and alcohol. The yield of this substance amounted to 60 per cent. of the 3-methoxy-4:5-methylenedioxcinnamic acid employed:

0.1300 gave 0.2804  $\text{CO}_2$  and 0.0672  $\text{H}_2\text{O}$ .  $\text{C} = 58.8$ ;  $\text{H} = 5.7$ .

$\text{C}_{11}\text{H}_{12}\text{O}_5$  requires  $\text{C} = 58.9$ ;  $\text{H} = 5.4$  per cent.

$\beta$ -3-Methoxy-4:5-methylenedioxypropionic acid is only sparingly soluble in benzene, light petroleum, or chloroform, but it is readily soluble in ether, ethyl acetate, or hot water, and extremely so in alcohol, acetone, or acetic acid. It crystallises with difficulty. If dissolved in hot benzene to which a few drops of alcohol have been added, it is deposited, after a long time, in hard, colourless, crystalline nodules melting at  $124\text{--}125^\circ$ .



Twenty grams of  $\beta$ -3-methoxy-4:5-methylenedioxypropionic acid were dissolved in boiling benzene (300 c.c.), and 100 grams of phosphoric oxide gradually added with constant agitation. The mixture was heated for several hours on the water-bath, after which the dark red phosphorus compound was removed by decantation and decomposed by adding ice-water. The aqueous mixture was extracted repeatedly with ether, the ethereal solution washed successively with sodium hydroxide and water, dried, and the ether removed. A pale yellow, crystalline solid remained, which separated from alcohol in slender, colourless needles, melting at  $141\text{--}142^\circ$ :

0.1256 gave 0.2967  $\text{CO}_2$  and 0.0575  $\text{H}_2\text{O}$ .  $\text{C} = 64.4$ ;  $\text{H} = 5.1$ .

$\text{C}_{11}\text{H}_{10}\text{O}_4$  requires  $\text{C} = 64.1$ ;  $\text{H} = 4.9$  per cent.

*Methoxymethylenedioxy- $\alpha$ -hydrindone* is easily soluble in ether and benzene, and crystallises from these solvents in well-formed, prismatic needles. The *oxime*, prepared in the usual way, is only very sparingly soluble in hot alcohol or ethyl acetate, and crystallises from these solvents in small, colourless needles, decomposing at about  $250^\circ$ . In benzene, ether, chloroform, or light petroleum it is practically insoluble:

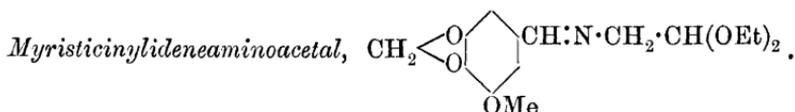
0.1057 gave 0.2320  $\text{CO}_2$  and 0.0496  $\text{H}_2\text{O}$ .  $\text{C} = 59.9$ ;  $\text{H} = 5.2$ .

$\text{C}_{11}\text{H}_{11}\text{O}_4\text{N}$  requires  $\text{C} = 59.7$ ;  $\text{H} = 5.0$  per cent.

The Beckmann transformation could not be effected in the case of this oxime; phosphorus pentachloride, in the presence of dry ether, is without any action on it, whilst with the use of benzene as solvent, on heating, a vigorous reaction ensues, with the formation of a carbonaceous mass, from which nothing definite could be isolated. Other reagents, such as sulphuric acid, phosphoric oxide, and acetyl chloride, were also

employed, but in no case was it possible to isolate any crystalline product.

The above experiments for the synthesis of cotarnine not having proved successful, a second method was tried, which has already been applied by Fritsch (*Annalen*, 1895, 286, 18) to the synthesis of hydrastinine. This consisted in the condensation of myristicinylidene-aminoacetal to the corresponding *isoquinoline* derivative; the latter, by reduction and methylation, should then be converted into hydro-cotarnine.



Twenty grams of aminoacetal and 27 grams of myristicinaldehyde were heated together at  $100^\circ$  for two hours, when the reaction was complete. The product was then dissolved in ether, the ethereal solution being washed with water, dried, and the solvent removed. The viscid, brown oil thus obtained was purified by distillation under diminished pressure:

0.1260 gave 0.2819  $\text{CO}_2$  and 0.0840  $\text{H}_2\text{O}$ . C = 61.0; H = 7.4.

$\text{C}_{15}\text{H}_{21}\text{O}_5\text{N}$  requires C = 61.0; H = 7.1 per cent.

*Myristicinylideneaminoacetal* is a colourless, viscid oil, which does not solidify at  $-20^\circ$ . It distils at  $234^\circ/15$  mm. and  $244^\circ/25$  mm. It is readily miscible with ether, alcohol, or chloroform, but only sparingly soluble in petroleum. It dissolves in dilute mineral acids, but is soon resolved into its components, myristicinaldehyde being precipitated. Owing to the readiness with which myristicinylidene-aminoacetal undergoes this change, it was found impossible to prepare from it the desired methoxymethylenedioxy*isoquinoline*. Thus, when myristicinylideneaminoacetal was added, drop by drop, to ice-cold sulphuric acid (75 per cent.), it was rapidly converted into myristicin-aldehyde, and no trace of methoxymethylenedioxy*isoquinoline* could be detected in the product. With the object of preventing this disruption of the molecule under the influence of acids, myristicinylidene-aminoacetal was reduced to myristicinylaminoacetal, but this compound, also, could not be condensed to methoxymethylenedioxydihydro-*isoquinoline*.

#### *Reduction of Myristicinylideneaminoacetal.*

Twenty grams of myristicinylideneaminoacetal were dissolved in dilute alcohol, and the solution well agitated with 4 grams of amalgamated aluminium granules. After several hours the precipitated aluminium hydroxide was removed by filtration, and the

alcoholic filtrate treated as before with a fresh portion (4 grams) of aluminium amalgam. The mixture was then filtered, and the alcohol removed as completely as possible from the filtrate, when a brown oil was precipitated. This was extracted with ether, the ethereal solution being dried, and the solvent removed. The residual oil, on agitation with light petroleum, deposited a small proportion of a solid substance, which was crystallised from a mixture of benzene and light petroleum. It separated from this solvent in slender, colourless needles, melting at 128°. The yield of this substance amounted to 10 per cent. of the material employed :

0·1205 gave 0·2672 CO<sub>2</sub> and 0·0808 H<sub>2</sub>O. C = 60·5 ; H = 7·5.

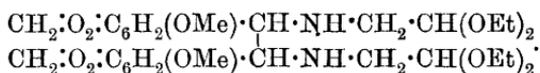
0·0767 ,, 0·1710 CO<sub>2</sub> ,, 0·0550 H<sub>2</sub>O. C = 60·8 ; H = 8·0.

0·1455 ,, 6·3 c.c. N<sub>2</sub> at 13·5° and 768 mm. N = 5·2.

0·2511, in 24·47 benzene, gave  $\Delta t$  - 0·088°. M.W. = 583.

C<sub>30</sub>H<sub>44</sub>O<sub>10</sub>N<sub>2</sub> requires C = 60·8 ; H = 7·4 ; N = 4·7 per cent. M.W. = 592.

It is evident from these results that the above compound has been formed by the association and reduction of two molecules of myristicinylideneaminoacetal. Its constitution may therefore be represented as :



The compound is extremely soluble in the usual organic solvents, with the exception of light petroleum. It dissolves also in cold dilute mineral acids without change, but on warming the solution the substance is rapidly decomposed, with the deposition of resinous matter and the production of a claret-red colour. In concentrated sulphuric acid it gives a beautiful violet coloration.

In the above reduction of myristicinylideneaminoacetal the chief product was an oil, from which the above compound melting at 128° had been removed by means of petroleum. This oil distilled at 240°/27 mm. as a colourless liquid :

0·1200 gave 0·2646 CO<sub>2</sub> and 0·0830 H<sub>2</sub>O. C = 60·1 ; H = 7·7.

0·2733 ,, 10·8 c.c. N<sub>2</sub> at 18° and 758 mm. N = 4·6.

C<sub>15</sub>H<sub>23</sub>O<sub>5</sub>N requires C = 60·6 ; H = 7·7 ; N = 4·7 per cent.

This substance, evidently myristicinylaminoacetal,



is a colourless oil, which is readily miscible with benzene, alcohol, ether, or ethyl acetate, but is only sparingly soluble in light petroleum. It dissolves unchanged in cold dilute mineral acids, but on heating the solution it decomposes, with the production of a claret-red coloration. Its *hydrochloride* may be prepared by dissolving the base in cold dilute hydrochloric acid, and allowing the solution to evaporate spontaneously over potassium hydroxide in a vacuum. The crystalline solid, which

is gradually deposited, may be recrystallised from a mixture of ethyl acetate and alcohol, when it separates in well-formed, colourless plates, melting and decomposing at  $133^{\circ}$ :

0.1672 gave 0.0704 AgCl. Cl = 10.4.

$C_{15}H_{23}O_5N$ , HCl requires Cl = 10.6 per cent.

This hydrochloride is readily soluble in water and alcohol, but insoluble in ethyl acetate.

With the object of preparing methoxymethylenedioxydihydroisoquinoline from myristicinylaminoacetal, 5 grams of the latter were added, drop by drop, to 20 c.c. of sulphuric acid (75 per cent.) at  $0^{\circ}$ . The first addition of the myristicinylaminoacetal produced an intense violet coloration, which on further addition was changed to deep red. The mixture was kept for two days at the ordinary temperature, and then neutralised by the cautious addition of alkali, when a brown, amorphous precipitate was formed. This was soluble in acids, but insoluble in the ordinary organic solvents, and constituted the sole product of the reaction, no methoxymethylenedioxydihydroisoquinoline having been produced.

Another portion of myristicinylaminoacetal was dissolved in cold concentrated hydrochloric acid, and the solution kept at the ordinary temperature for forty-eight hours. It was then diluted with water and extracted with ether, which removed a small quantity of a brown solid. On dissolving the latter in a mixture of benzene and petroleum, a few colourless needles separated, which melted at  $138^{\circ}$ , but the amount of this substance was not sufficient for further examination. The acid liquid which had been extracted with ether was rendered alkaline, when a brown, amorphous, insoluble resin separated, from which nothing definite could be isolated. It formed, with the exception of the small amount of crystalline substance mentioned above, the sole product of the reaction. This method is therefore inapplicable for the synthesis of cotarnine and allied compounds.

*The Action of Nitric Acid on 3-Methoxy-4:5-methylenedioxy-cinnamic Acid.*

Ten grams of 3-methoxy-4:5-methylenedioxy-cinnamic acid were added in small quantities at a time to 50 c.c. of nitric acid (sp. gr. 1.41) cooled in a freezing mixture. The liquid at first became yellow, but soon acquired a deep red colour, and after a short time carbon dioxide was slowly evolved. The mixture was kept in the cold for half an hour, then poured into ice-water, and the resulting yellow precipitate collected and washed. This was digested with ether, and the insoluble portion, consisting of unchanged 3-methoxy-4:5-methylenedioxy-cinnamic acid, removed by filtration. The ethereal filtrate was washed

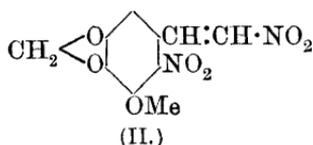
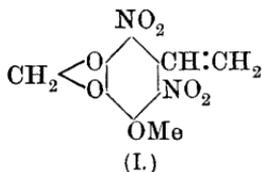
successively with aqueous sodium hydroxide and water, dried, and the solvent removed. The residual solid crystallised from alcohol in slender, lemon-yellow needles, melting at  $148^{\circ}$ :

0.1014 gave 0.1682  $\text{CO}_2$  and 0.0296  $\text{H}_2\text{O}$ .  $\text{C} = 45.2$ ;  $\text{H} = 3.2$ .

0.0777 ,, 7.4 c.c.  $\text{N}_2$  at  $23^{\circ}$  and 766 mm.  $\text{N} = 10.9$ .

$\text{C}_{10}\text{N}_3\text{O}_7\text{N}_2$  requires  $\text{C} = 44.8$ ;  $\text{H} = 3.0$ ;  $\text{N} = 10.5$  per cent.

Considering the method of preparation, it is evident that the substance must be represented by one of the two following formulæ:



It was possible to decide between these formulæ by examining the product of oxidation. A small quantity of the compound melting at  $148^{\circ}$  was oxidised with hot alkaline permanganate, and at the end of the reaction sulphur dioxide was passed into the hot mixture until the manganese precipitate had redissolved. On cooling, slender needles were deposited, which melted and decomposed at  $245^{\circ}$ . Both by analysis and by the mixed melting-point method, it was proved that this compound was identical with nitromyristicinic acid (this vol., p. 1165):

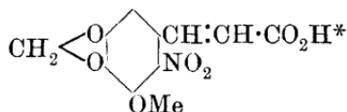
0.0714 gave 0.1170  $\text{CO}_2$  and 0.0231  $\text{H}_2\text{O}$ .  $\text{C} = 44.7$ ;  $\text{H} = 3.6$ .

$\text{C}_9\text{H}_7\text{O}_7\text{N}$  requires  $\text{C} = 44.8$ ;  $\text{H} = 2.9$  per cent.

The compound melting at  $148^{\circ}$  is therefore  $\omega$ -2(6)-dinitro-3-methoxy-4:5-methylenedioxy-styrene; its formation from 3-methoxy-4:5-methylenedioxy-cinnamic acid is evidently due to the direct displacement of the carboxyl group by a nitro-group, with the simultaneous introduction of a second nitro-group into the nucleus. The same type of reaction has recently been shown by the author (this vol., p. 1155) to be common to the ethers of aromatic hydroxyaldehydes and hydroxyacids, but the present example is of additional interest, since it shows that the reaction is not exclusively confined to those compounds in which the carboxyl group is directly attached to the benzene nucleus.

$\omega$ -2(6)-Dinitro-3-methoxy-4:5-methylenedioxy-styrene is readily soluble in the usual organic solvents. It possesses feebly acidic properties. When warmed with aqueous sodium hydroxide it dissolves with difficulty, but on the addition of a few drops of alcohol it readily passes into solution with a deep yellow colour, and is reprecipitated by hydrochloric acid.

## 2(6)-Nitro-3-methoxy-4:5-methylenedioxy-cinnamic Acid,



Fifty grams of finely powdered nitromyristicinaldehyde, prepared by the nitration of myristicinaldehyde (this vol., p. 1160), were intimately mixed with 26 grams of fused sodium acetate, and 100 c.c. of acetic anhydride added. After heating in an oil-bath at 160° for six hours, the mixture was allowed to cool, then digested with an excess of ammonia until nothing further dissolved, and the red solution extracted once with ether to remove resinous by-products. On acidifying the ammoniacal solution, 2(6)-nitro-3-methoxy-4:5-methylenedioxy-cinnamic acid was obtained as a yellow precipitate, which was washed with water and crystallised from acetic acid. The yield amounted to 84 per cent. of the aldehyde employed :

0.1231 gave 0.2240 CO<sub>2</sub> and 0.0410 H<sub>2</sub>O. C = 49.6 ; H = 3.7.

0.2168 required for neutralisation 8.05 c.c. N/10-NaOH. M.W. (for a monobasic acid) = 269.

C<sub>11</sub>H<sub>9</sub>O<sub>7</sub>N requires C = 49.4 ; H = 3.4 per cent. M.W. = 267.

2(6)-Nitro-3-methoxy-4:5-methylenedioxy-cinnamic acid crystallises from hot acetic acid in small, yellow plates, which decompose, when heated to 260°, with the formation of a carbonaceous mass. It is only moderately soluble in alcohol, from which, however, it separates in stout, deep yellow prisms.

Methyl-2(6)-nitro-3-methoxy-4:5-methylenedioxy-cinnamate was prepared by passing a current of dry hydrogen chloride for one and a-half hours into a hot mixture of methyl alcohol and the acid. It crystallises from a mixture of alcohol and ethyl acetate in long, yellow needles, melting at 192°. The ethyl ester, prepared in a similar manner, also crystallises in beautiful, yellow needles, melting at 166°.

Methyl 2(6)-amino-3-methoxy-4:5-methylenedioxy-cinnamate,



—Three grams of methyl 2(6)-nitro-3-methoxy-4:5-methylenedioxy-cinnamate were finely powdered and gently warmed on the water-bath for half-an-hour with a solution of stannous chloride (12 grams) in concentrated hydrochloric acid (36 c.c.), when the powdered nitro-compound had become changed into a crystalline hydrochloride. This was collected, washed with cold concentrated hydrochloric acid, dissolved in cold water, and the free base precipitated by the addition

\* See footnote on p. 1205.

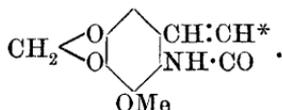
of sodium hydroxide. It crystallised from alcohol in brilliant yellow, slender needles, melting at  $153^{\circ}$  :

0.0817 gave 0.1722  $\text{CO}_2$  and 0.0432  $\text{H}_2\text{O}$ .  $\text{C} = 57.5$  ;  $\text{H} = 5.9$ .

$\text{C}_{12}\text{H}_{18}\text{O}_5\text{N}$  requires  $\text{C} = 57.4$  ;  $\text{H} = 5.2$  per cent.

Methyl 2(6)-amino-3-methoxy-4 : 5-methylenedioxcinnamate dissolves in alcohol, chloroform, or ethyl acetate with the formation of a deep yellow colour, but the solution in acids is colourless. When warmed with dilute hydrochloric acid, hydrolysis and condensation occur, and the ester is converted into ketomethoxymethylenedioxy-dihydroquinoline.

*2-Keto-8(5)-methoxy-6 : 7-methylenedioxy-1 : 2-dihydroquinoline,*



This compound is best prepared directly from methyl 2(6)-nitro-3-methoxy-4 : 5-methylenedioxcinnamate without the isolation of the intermediate amino-compound. This ester (10 grams) was dissolved in alcohol, and reduced by heating for two hours with a solution of stannous chloride (50 grams) in 150 c.c. of concentrated hydrochloric acid. The alcohol was then removed as completely as possible, and the mixture poured into water, when a crystalline solid separated, which was recrystallised from water and dried at  $105^{\circ}$  :

0.1055 gave 0.2340  $\text{CO}_2$  and 0.0420  $\text{H}_2\text{O}$ .  $\text{C} = 60.5$  ;  $\text{H} = 4.5$ .

$\text{C}_{11}\text{H}_9\text{O}_4\text{N}$  requires  $\text{C} = 60.3$  ;  $\text{H} = 4.1$  per cent.

The compound crystallises from hot water in long, silky needles, which melt at  $181$ — $182^{\circ}$  and contain half a molecule of water of crystallisation :

1.9723 lost, at  $105^{\circ}$ , 0.0826  $\text{H}_2\text{O}$ .  $\text{H}_2\text{O} = 4.2$ .

$\text{C}_{11}\text{H}_9\text{O}_4\text{N} \cdot \frac{1}{2}\text{H}_2\text{O}$  requires  $\text{H}_2\text{O} = 3.9$  per cent.

It is readily soluble in hot alcohol or chloroform, from which it separates in radiating clusters of slender needles. It exhibits both feebly acidic and basic properties. Thus it dissolves in concentrated hydrochloric acid with the formation of a *hydrochloride*, which separates in colourless leaflets decomposing at  $225^{\circ}$  ; on the addition of water the base is regenerated. It is also soluble in concentrated aqueous sodium hydroxide, but is reprecipitated by water.

\* See footnote on p. 1205.

*Reduction of 2-Keto-8(5)-methoxy-6 : 7-methylenedioxy-1 : 2-dihydroquinoline.*

Two grams of the substance were dissolved in dilute alcohol and reduced by the action of 200 grams of sodium amalgam ( $3\frac{1}{2}$  per cent.) with constant stirring. After a short time a grey precipitate separated, and the liquid gradually acquired a red colour. When the reaction was complete, the grey precipitate was removed by filtration and washed with water. It was insoluble in acids or alkalis, and practically so in ethyl acetate, chloroform, alcohol, or ether, but could be crystallised from hot acetic acid, from which it separated in small, colourless needles. These did not melt when heated to  $310^{\circ}$ :

0.0905 gave 0.1994  $\text{CO}_2$  and 0.0400  $\text{H}_2\text{O}$ . C = 60.1 ; H = 4.9.

$(\text{C}_{11}\text{H}_{10}\text{O}_4\text{N})_x$  requires C = 60.0 ; H = 4.5 per cent.

It is evident from the properties of this compound that its formation is due to polymerisation and simultaneous reduction of the ketomethoxymethylenedioxydihydroquinoline.

The alkaline filtrate from which the above compound had been separated was heated on the water-bath to remove alcohol, and then acidified with dilute hydrochloric acid, when a colourless substance was precipitated. This was collected, washed, and crystallised from dilute acetic acid, from which it was deposited in colourless needles, melting at  $290^{\circ}$ . It was very sparingly soluble in water or alcohol, but more soluble in chloroform:

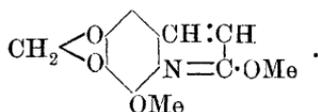
0.1051 gave 0.2307  $\text{CO}_2$  and 0.0439  $\text{H}_2\text{O}$ . C = 59.9 ; H = 4.6.

$(\text{C}_{11}\text{H}_{10}\text{O}_4\text{N})_x$  requires C = 60.0 ; H = 4.5 per cent.

The analysis and the properties of this substance show that it possesses the same empirical formula as the previously isolated compound, and is likewise a polymerised reduction product of ketomethoxymethylenedioxydihydroquinoline. No other substance could be isolated from the products of this reaction.

Ketomethoxymethylenedioxydihydroquinoline was next reduced by means of sodium amalgam in dilute acetic acid solution, but in this case, also, the chief products were the above-described polymerised compounds, melting at  $290^{\circ}$  and above  $310^{\circ}$  respectively. A small amount of substance melting at  $120^{\circ}$  was obtained, but not sufficient for its further examination.

## 8(5)-Methoxy-6 : 7-methylenedioxy carbostyryl Methyl Ether,



In order to avoid, if possible, formation of the above polymerised products, the methyl derivatives of 2-keto-8(5)-methoxy-6 : 7-methylenedioxy-1 : 2-dihydroquinoline were prepared prior to reduction.

Equal parts of ketomethoxymethylenedioxydihydroquinoline and methyl iodide were dissolved in chloroform, and the solution heated on the water-bath for several hours in the presence of dry silver oxide (1 part). The liquid was then filtered, shaken successively with sodium hydroxide and water, dried, and the solvent removed. The solid residue was crystallised from alcohol, when it separated in stellar clusters of needles, melting at  $113^{\circ}$  :

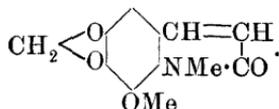
0.0706 gave 0.1600  $\text{CO}_2$  and 0.0326  $\text{H}_2\text{O}$ . C = 61.8 ; H = 5.1.

$\text{C}_{12}\text{H}_{11}\text{O}_4\text{N}$  requires C = 61.8 ; H = 4.7 per cent.

That this substance is the *O*-methyl ether is proved by its behaviour on heating with methyl iodide. Thus, when heated for three hours at  $120^{\circ}$  with an excess of methyl iodide in a sealed tube, it is quantitatively converted into the isomeric *N*-methyl ether described below (compare Knorr, *Ber.*, 1897, 30, 929).

8(5)-Methoxy-6 : 7-methylenedioxy carbostyryl methyl ether crystallises from concentrated alcoholic solution in slender needles, whilst from more dilute solutions it separates in hexagonal prisms. It is only sparingly soluble in hot water, from which it is deposited in silky needles. It possesses much stronger basic properties than the parent compound, since its hydrochloride is not dissociated in dilute aqueous solution. It is not changed by heating for several hours at  $100^{\circ}$  with 20 per cent. hydrochloric acid, but when heated with concentrated hydrochloric acid in a sealed tube it is completely decomposed, with the formation of a dark violet-coloured, resinous mass.

## 2-Keto-8(5)-methoxy-6 : 7-methylenedioxy-1-methyl-1 : 2-dihydroquinoline,



This substance, as above indicated, may be prepared from the isomeric *O*-methyl ether by heating with methyl iodide. It was also prepared directly from ketomethoxymethylenedioxydihydroquinoline by the following method. Two grams of the substance, dissolved in

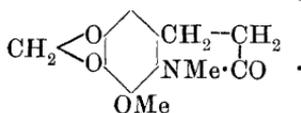
methyl alcohol, were heated for several hours with an excess of methyl iodide and sodium methoxide. The methyl alcohol was then removed, water added to the residue, and the mixture extracted with chloroform. The chloroform solution was washed, dried, and the solvent removed, when a solid residue was obtained which crystallised from alcohol in well-formed, colourless needles, melting at  $179^{\circ}$  :

0.0904 gave 0.2045  $\text{CO}_2$  and 0.0379  $\text{H}_2\text{O}$ .  $\text{C} = 61.7$  ;  $\text{H} = 4.7$ .

$\text{C}_{12}\text{H}_{11}\text{O}_4\text{N}$  requires  $\text{C} = 61.8$  ;  $\text{H} = 4.7$  per cent.

This compound possesses only feebly basic properties, and is insoluble in cold dilute hydrochloric acid.

*Oxyisocotarnine* (2-Keto-8(5)-methoxy-6 : 7-methylenedioxy-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline).



One gram of the compound just described was reduced in dilute alcoholic solution by means of 200 grams of sodium amalgam (3 per cent.). During the course of the reaction the mixture was constantly agitated, and from time to time small quantities of hydrochloric acid were added to prevent the accumulation of alkali in the solution. After a short time a small quantity of solid separated, which at the end of the reaction was collected. It was only sparingly soluble in hot alcohol, from which it crystallised in rhombohedral prisms, melting at  $280^{\circ}$ . This substance was apparently a polymerised reduction product, similar in character to the products of high molecular weight obtained on reducing ketomethoxymethylenedioxydihydroquinoline.

The filtrate from which the above compound had been separated was acidified with dilute hydrochloric acid, distilled in a current of steam to remove the alcohol, then rendered alkaline, and extracted with ether. This removed a viscid oil, which rapidly solidified, and when crystallised from dilute alcohol, separated in flat plates, melting at  $113^{\circ}$  :

0.0881 gave 0.1982  $\text{CO}_2$  and 0.0447  $\text{H}_2\text{O}$ .  $\text{C} = 61.4$  ;  $\text{H} = 5.6$ .

$\text{C}_{12}\text{H}_{13}\text{O}_4\text{N}$  requires  $\text{C} = 61.3$  ;  $\text{H} = 5.5$  per cent.

It is evident from these results that the reduction of 2-keto-8(5)-methoxy-6 : 7-methylenedioxy-1-methyl-1 : 2-dihydroquinoline by means of sodium amalgam effects the addition of two atoms of hydrogen only. The product, therefore, is isomeric with oxy-cotarnine.

*Oxyisocotarnine* possesses only feebly basic properties, since its hydrochloride dissociates in the presence of water. It is readily

soluble in alcohol, chloroform, or ether, but only sparingly so in hot water. It could not be converted by reduction into *isocotarnine*, showing in this respect great similarity to *oxycotarnine* (Freund and Wulff, *Ber.*, 1902, **35**, 1737).

THE WELLCOME CHEMICAL RESEARCH LABORATORIES,  
LONDON, E.C.

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