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No. 109

SYNTHESIS OF COTARNINE

BY

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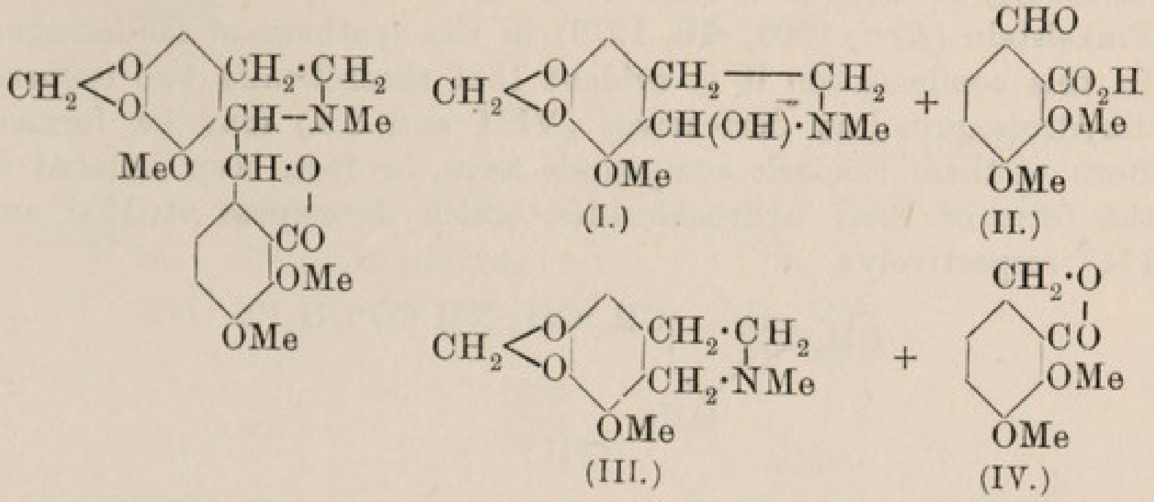
CVI.—*Synthesis of Cotarnine.*

By ARTHUR HENRY SALWAY.

THE alkaloid narcotine, as is well known, is converted by oxidising agents into cotarnine (I) and opianic acid (II), but when the degradation is effected by reducing agents, hydrocotarnine (III) and meconine (IV) are obtained:



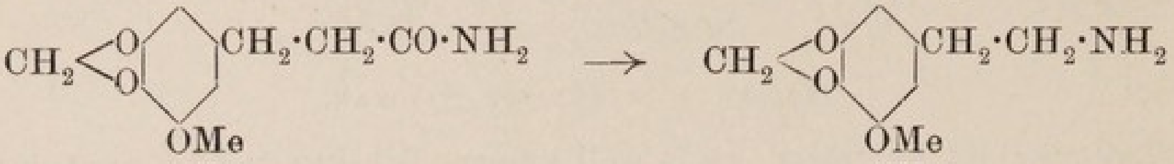
It is therefore evident that the problem of the complete synthesis of narcotine depends for its solution on the following three factors: (1) the synthesis of the degradation products, cotarnine or hydrocotarnine, and opianic acid or meconine; (2) the recombination of these substances to form racemic narcotine; and (3) the resolution of the latter into its enantiomorphous components. The first step in this direction was the synthesis of meconine from guaiacol, which was accomplished by Fritsch (*Annalen*, 1898, **301**, 351), whilst Perkin and Robinson (Proc., 1910, **26**, 46 and 131) have not only succeeded in recombining cotarnine and meconine with the production of *dl*-narcotine, but have also resolved the latter into its optically active components. In order, therefore, to complete the synthesis of the natural alkaloid, the synthesis of cotarnine alone remained to be accomplished. The present author has for some time been engaged on this task, which has now been brought to a successful conclusion.

The steps by which the synthesis of cotarnine has now been attained may be briefly described as follows. Myristicin, $CH_2{:}O_2{:}C_6H_2(OMe){\cdot}CH_2{\cdot}CH{:}CH_2$ (compare Power and Salway, Trans., 1907, **91**, 2054), was first converted into β-3-methoxy-4 : 5-methylenedioxyphenylpropionic acid,

$$CH_2{:}O_2{:}C_6H_2(OMe){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H,$$

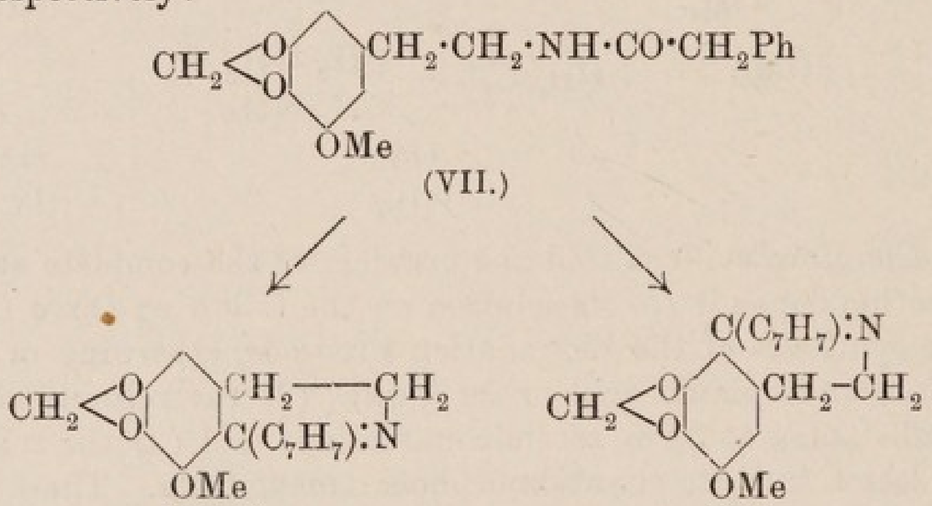
by a series of reactions which has previously been described (Trans., 1909, **95**, 1204). This acid was next transformed into its *amide*

(V), and the latter converted by means of Hofmann's reaction into *β-3-methoxy-4 : 5-methylenedioxyphenylethylamine* (VI):



(V.) (VI.)

The *phenylacetyl* derivative of this base (VII) was then condensed by heating with phosphoric oxide in the presence of xylene, according to a method similar to that employed by Pictet and Finkelstein (*Ber.*, 1909, **42**, 1979) in the synthesis of laudanosine. In this condensation it is evident that theoretically two isomeric dihydro*iso*quinoline derivatives (VIII and IX) may be formed. Both of these isomeric compounds have, in fact, been isolated in the form of their hydrochlorides, which decompose at 192° and 174° respectively:



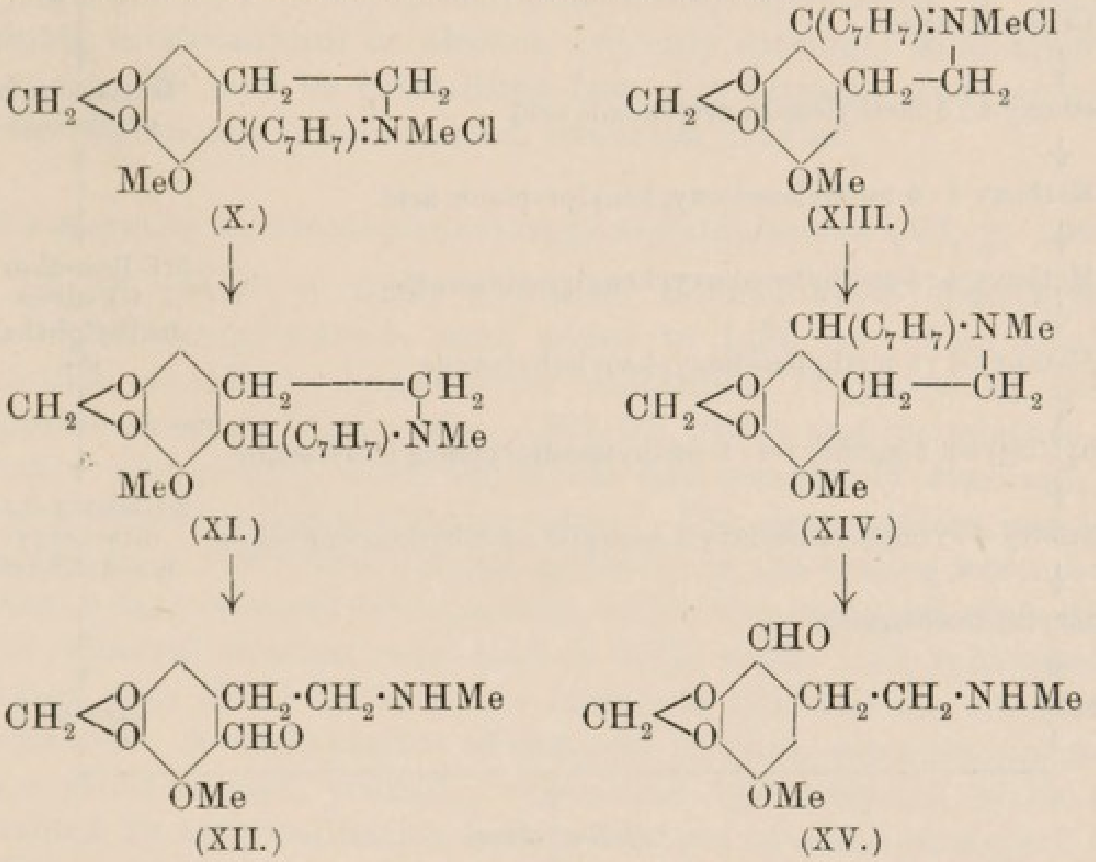
(VII.)

(VIII.) (IX.)

It has, furthermore, been possible to assign to the above-mentioned isomerides their respective formulæ (VIII and IX), since the compound decomposing at 192°, when treated as indicated below, yielded cotarnine, and must therefore be represented by (VIII), whilst the substance decomposing at 174° gave an isomeride of cotarnine, and consequently possesses the formula (IX).

For the preparation of cotarnine from *8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro*iso*quinoline* (VIII), the latter was first converted into its methochloride (X), and this reduced with tin and hydrochloric acid. The product, 1-benzylhydrocotarnine (XI), was then oxidised by manganese dioxide in the presence of sulphuric acid (compare Pyman, Trans., 1909, **95**, 1751), when it yielded a substance which was identical in all respects with cotarnine (XII). The identity was established by means of analyses and by a comparison of its derivatives with the corresponding derivatives of a specimen of cotarnine which had been obtained by the oxidation of narcotine.

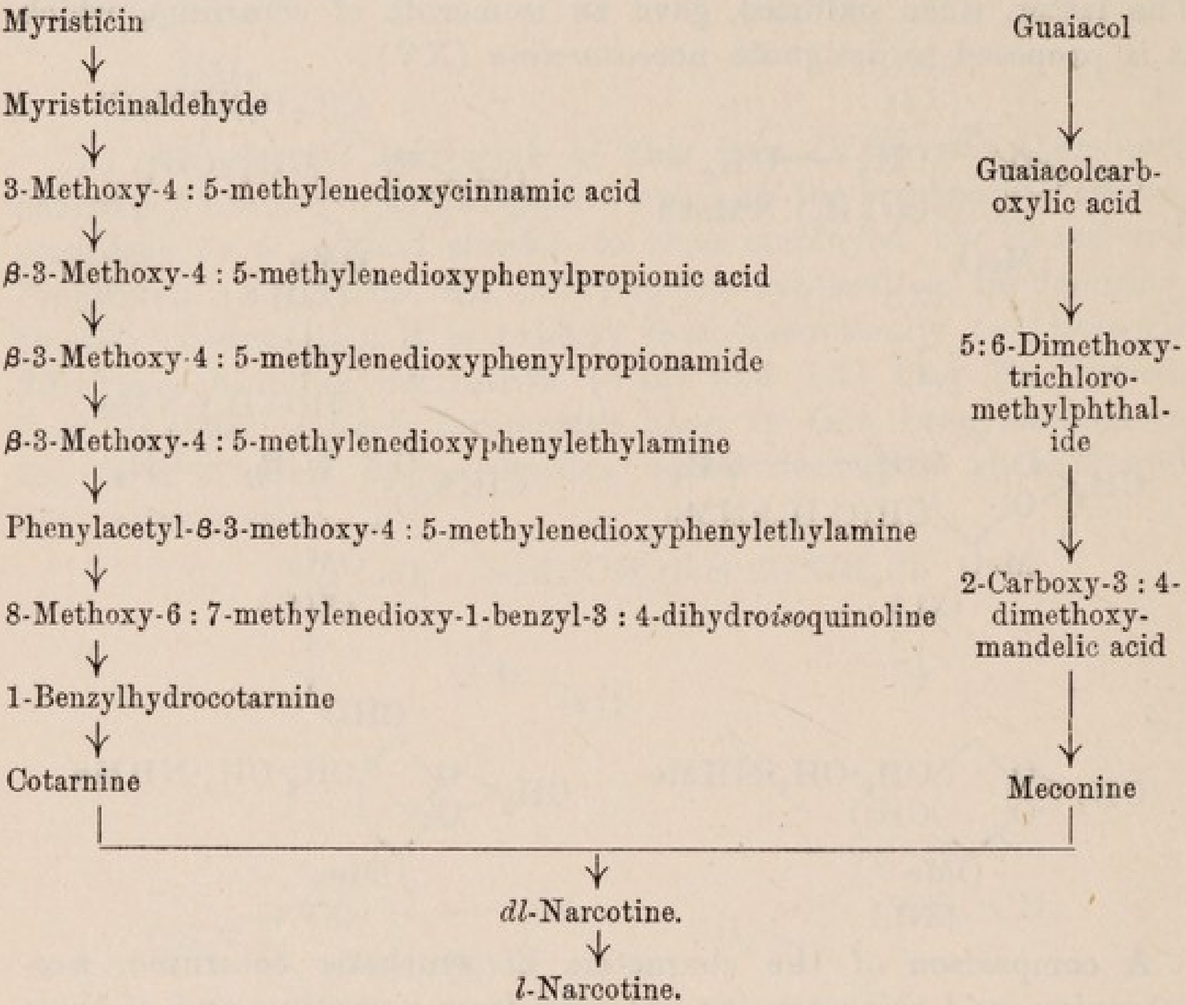
The hydrochloride of 6-*methoxy*-7 : 8-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline* (IX) was also converted into its methochloride (XIII), and then reduced to 6-*methoxy*-7 : 8-*methylenedioxy*-1-*benzyl*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline* (XIV). The latter, when oxidised, gave an isomeride of cotarnine, which it is proposed to designate neo*cotarnine* (XV):



A comparison of the characters of synthetic cotarnine, *neo*-cotarnine, and the cotarnine obtained from narcotine, and of their respective derivatives, is presented in the following table:

	Free base.	Hydrochloride.	Aurichloride.	Picrate.
1. Synthetic cotarnine.	Colourless needles, decompose at 130°	Colourless needles, decompose at 197°	Golden-yellow plates, melt at 136—137°	Yellow needles, melt at 143°
2. Cotarnine from narcotine.	Colourless needles, decompose at 131°	,, ,,	,, ,,	,, ,,
3. Mixture of synthetic cotarnine with cotarnine from narcotine.	Decompose at 129°	,, ,,	,, ,,	,, ,,
4. *neo*Cotarnine.	Colourless prisms, decompose at 124°	Yellow or red needles (two modifications), decompose at 185°	Chocolate-brown prisms, melt at 127°	Yellow needles, sinter at 90°, melt at 100°

The synthesis of cotarnine having now been accomplished, that of the alkaloid narcotine has become complete. The stages by which these syntheses have been effected may be represented by the following scheme:



Experimental.

β-3-*Methoxy*-4 : 5-*methylenedioxyphenylpropionamide* (V, p. 1209).

For the preparation of this compound, 100 grams of β-3-methoxy-4 : 5-methylenedioxyphenylpropionic acid,* which had been obtained from myristicin by a series of reactions described in a previous investigation (Trans., 1909, **95**, 1208—1210), were dissolved in benzene, and the solution gently warmed with 1 molecule of phosphorus pentachloride until the reaction was complete. The mixture was then heated on the water-bath under diminished pressure for some time, whereby the solvent, and the phosphoryl chloride which had been formed, were completely removed. The residual crude acid chloride, dissolved in benzene, was gradually added, with vigorous agitation, to an excess of concentrated aqueous ammonia. The

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* The melting point of β-3-methoxy-4 : 5-methylenedioxyphenylpropionic acid was erroneously given as 124—125° in the previous paper (*loc. cit.*). The correct melting point of this compound is 99—100°.

precipitate of acid amide thus formed was collected and recrystallised from alcohol, when it separated in long, colourless needles, melting at 129—130°:

0·1246 gave 0·2706 CO_2 and 0·0672 H_2O. C=59·2; H=6·0.

$C_{11}H_{13}O_4N$ requires C=59·2; H=5·8 per cent.

β-3-*Methoxy*-4: 5-*methylenedioxyphenylpropionamide* is readily soluble in chloroform or alcohol, but only sparingly so in ether or benzene. It may be crystallised from hot benzene, and separates from this solvent in well-formed, colourless needles.

β-3-*Methoxy*-4: 5-*methylenedioxyphenylethylamine* (VI, p. 1209).

Ninety grams of finely powdered β-3-methoxy-4: 5-methylenedioxyphenylpropionamide were added to 1400 c.c. of an alkaline solution of sodium hypochlorite containing 77 grams of active chlorine (compare Graebe, *Ber.*, 1902, **35**, 2753), and the mixture was shaken continuously until the amide had completely dissolved, for which about two hours were necessary. The clear solution was then heated for a short time (fifteen minutes) on the boiling-water bath, when a dark-coloured oil separated, which was extracted with ether. The ethereal solution was washed with water, and subsequently shaken with dilute hydrochloric acid until the base was completely extracted. A small portion of this acid solution, when concentrated to a small volume, yielded a crystalline *hydrochloride*, which was purified by recrystallisation from a mixture of absolute alcohol and ethyl acetate. It separated from this solvent in colourless needles, melting at 165°:

0·1496 gave 0·2826 CO_2 and 0·0850 H_2O. C=51·5; H=6·3.

$C_{10}H_{14}O_3NCl$ requires C=51·8; H=6·0 per cent.

β-3-*Methoxy*-4: 5-*methylenedioxyphenylethylamine*, as obtained from its hydrochloride, was a light brown oil, which did not solidify on keeping. Its *benzoyl* derivative crystallises from a mixture of benzene and light petroleum in shining, colourless, flat prisms, melting at 90—91°.

Phenylacetyl-β-3-*methoxy*-4: 5-*methylenedioxyphenylethylamine* (VII, p. 1209).

The solution of β-3-methoxy-4: 5-methylenedioxyphenylethylamine hydrochloride obtained in the above reaction was directly converted into the phenylacetyl derivative by shaking with an excess of phenylacetyl chloride in the presence of alkali. After a short time the desired compound separated as a light brown solid; this was collected, and crystallised from alcohol, from which it separated in well-formed, colourless needles, melting at 103—104°:

0·1206 gave 0·3066 CO_2 and 0·0669 H_2O. C = 69·3; H = 6·2.

$C_{18}H_{19}O_4N$ requires C = 69·0; H = 6·1 per cent.

Phenylacetyl-β-3-methoxy-4 : 5-methylenedioxyphenylethylamine is readily soluble in chloroform or alcohol, but only moderately so in water or cold benzene.

Condensation of Phenylacetyl β-3-Methoxy-4 : 5-methylenedioxyphenylethylamine.

The condensation of this substance to the corresponding dihydro*iso*quinoline was conducted according to a method first proposed by Bischler and Napieralski, and recently modified by Pictet and Kay (*Ber.*, 1909, **42**, 1973). Sixty-five grams of phenylacetyl β-3-methoxy-4 : 5-methylenedioxyphenylethylamine were dissolved in 500 c.c. of xylene, and 100 grams of phosphoric oxide then added. After heating the mixture for about fifteen minutes a further 80 grams of phosphoric oxide were added, and the heating continued until a small portion of the xylene gave no precipitate of unchanged substance on the addition of light petroleum. The xylene was then decanted from the yellow mass of phosphorus compound, and the latter extracted with hot water until only an insoluble resin remained undissolved. The aqueous extract was shaken with ether to remove adhering xylene, then rendered alkaline with sodium hydroxide, and the oil, which was thus precipitated, extracted with ether. After the ethereal solution had been washed, dried, and the solvent removed, there remained a viscid, brown oil, which did not solidify, and amounted to 40 grams.

*Separation of Two Isomeric Methoxymethylenedioxybenzyldihydro*iso*quinolines* (VIII and IX, p. 1209).

Since the condensation of phenylacetyl β-3-methoxy-4 : 5-methylenedioxyphenylethylamine can proceed in two directions, it was to be expected that the above brown, oily condensation product would consist of a mixture of two isomeric bases. In order to effect a separation of these compounds, the oil was dissolved in dry ether and a current of dry hydrogen chloride passed into the solution, when the hydrochlorides were precipitated as a light brown solid. This mixture of crude hydrochlorides was then fractionally crystallised from a mixture of absolute alcohol and ethyl acetate. After considerable fractionation, two distinct hydrochlorides were isolated, one of which crystallised in colourless prisms, melting and decomposing at 192°, whilst the other separated in pale yellow, slender needles, which melted and decomposed at 174°. These compounds were analysed:

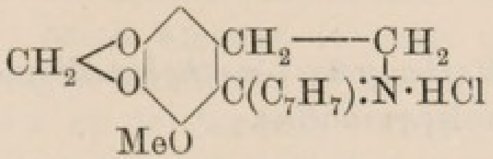
Substance melting and decomposing at 192°.

0·1020 * gave 0·2427 CO_2 and 0·0505 H_2O. C = 64·9; H = 5·5.
0·5061 * ,, 0·2181 AgCl. Cl = 10·7.
$C_{18}H_{18}O_3NCl$ requires C = 65·2; H = 5·4; Cl = 10·7 per cent.

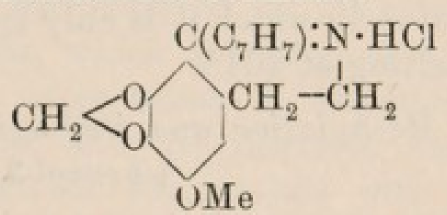
Substance melting and decomposing at 174°.

0·0936 * gave 0·2220 CO_2 and 0·0475 H_2O. C = 64·7; H = 5·6.
0·3986 * ,, 0·1707 AgCl. Cl = 10·6.
$C_{18}H_{18}O_3NCl$ requires C = 65·2; H = 5·4; Cl = 10·7 per cent.

From a consideration of these results, and the method of preparation of the two compounds, it is evident that they are isomeric and are represented by the following constitutional formulæ:


(A.)

and


(B.)

It has been possible to assign to the above-mentioned hydrochlorides their respective constitutional formulæ, since a substance of formula (A), on successive methylation, reduction, and oxidation, will yield cotarnine, whilst a compound having the formula (B) will yield, under similar treatment, an isomeride of cotarnine. The hydrochloride melting and decomposing at 192°, when subjected to the series of operations described below, has been found to give cotarnine, and must therefore possess the formula (A). It consequently follows that the hydrochloride melting and decomposing at 174° is represented by formula (B).

8-*Methoxy*-6:7-*methylenedioxy*-1-*benzyl*-3:4-*dihydro*iso*quinoline hydrochloride* (A), when crystallised from a mixture of absolute alcohol and ethyl acetate, forms colourless prisms, which are anhydrous and possess an intensely bitter taste. It is very soluble in alcohol or water, and crystallises from a concentrated aqueous solution in pale yellow leaflets, containing two molecules of water of crystallisation. When the hydrated salt is heated it partly melts at 85° with loss of water of crystallisation and becomes colourless, whilst the anhydrous substance then melts and decomposes at 192° with the formation of a deep red liquid:

0·7074 lost at 100° 0·0686 H_2O. H_2O = 9·7.
$C_{18}H_{18}O_3NCl,2H_2O$ requires H_2O = 9·8 per cent.

The free base, 8-*methoxy*-6:7-*methylenedioxy*-1-*benzyl*-3:4-*dihydro*iso*quinoline*, as obtained from its hydrochloride by the addi-

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* Dried at 110°.

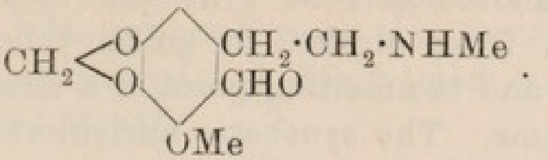
tion of sodium carbonate, is a viscid, colourless oil, which does not solidify. It yields a *picrate*, which is only sparingly soluble in hot water, but readily so in alcohol, from which it separates in glistening, yellow laminæ, melting at 154°.

6-*Methoxy*-7 : 8-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline hydrochloride* (B) crystallises from a mixture of absolute alcohol and ethyl acetate in pale yellow needles, which melt and decompose at 174°. It is readily soluble in alcohol or water, and from the latter it separates in long needles of a deep yellow colour. Unlike its isomeride, it does not possess a bitter taste. The free base, 6-*methoxy*-7 : 8-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline*, is precipitated from a solution of the hydrochloride as a pale yellow, viscid oil, which does not solidify. The *picrate* crystallises from water, in which it is only sparingly soluble, in small, yellow needles, melting at 204°.

Methylation and Reduction of 8-*Methoxy*-6 : 7-*methylenedioxy*-1-*benzyl*-3 : 4-*dihydro*iso*quinoline.*

The base regenerated from 7 grams of 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro*iso*quinoline hydrochloride was dissolved in methyl alcohol, an excess of methyl iodide added, and the mixture heated at 100° for an hour in a sealed tube. The methyl alcohol and excess of methyl iodide were removed by distillation, the residual crude methiodide dissolved in warm water, and then converted into the methochloride by shaking the solution for a short time with freshly precipitated silver chloride. After removing the silver chloride and iodide, the deep yellow filtrate was concentrated to dryness under diminished pressure, when the crude 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro*iso*quinoline methochloride was obtained as a reddish-yellow, gummy mass. Without further examination, the latter was reduced by heating for forty-eight hours with tin and concentrated hydrochloric acid in the presence of alcohol. The hot liquid was then decanted from undissolved tin, water added, and the double salt of tin, which was precipitated, collected and decomposed by heating with aqueous sodium hydroxide. The base thus liberated was extracted with ether, the ethereal solution being washed, dried, and the solvent removed, when a brown, viscid oil was obtained. From the above method of preparation, this product should consist of 1-benzylhydrocotarnine, which has already been described by Freund and Reitz (*Ber.*, 1906, **39**, 2231) as a colourless, crystalline solid, melting at 70°. The synthetic product, however, did not solidify on keeping, and as the quantity of material was not large, it was deemed advisable to proceed to the final stage of the synthesis without its further purification.

Cotarnine,



The crude 1-benzylhydrocotarnine, amounting to 5·2 grams, was accordingly dissolved in 50 c.c. of a 10 per cent. aqueous solution of sulphuric acid, and oxidised (compare Pyman, Trans., 1909, **95**, 1751) by heating for a short time on the boiling-water bath with 4 grams of pyrolusite (81 per cent. MnO_2). After cooling the mixture, it was extracted with benzene, which removed the non-basic oxidation product, consisting chiefly of benzaldehyde, and then rendered alkaline by means of sodium carbonate. The manganese carbonate thus precipitated was removed by filtration, and the filtrate first shaken with benzene, which extracted only a very small amount of basic substance, after which it was made strongly alkaline with sodium hydroxide, and the liberated base taken up in benzene. This benzene extract was washed with a little water and then shaken with small quantities of dilute hydrochloric acid until the basic substance was completely removed. On evaporating the acid liquid, a yellow, crystalline solid, amounting to 1·1 grams, was obtained, which was purified by recrystallisation from a mixture of absolute alcohol and ethyl acetate. It separated from this solvent in long, colourless needles, melting and decomposing at about 197° with the formation of a deep red liquid. On comparing this compound with a specimen of cotarnine hydrochloride prepared from the naturally-occurring alkaloid narcotine, the two were found to be identical in every respect:

0·3267,[*] on heating at 110°, lost 0·0378 H_2O. $H_2O = 11·6$.

$C_{12}H_{14}O_3NCl,2H_2O$ requires $H_2O = 12·35$ per cent.

0·1162 [†] gave 0·2396 CO_2 and 0·0598 H_2O. $C = 56·2$; $H = 5·7$.

0·3075 [†] „ 0·1742 AgCl. $Cl = 14·0$.

$C_{12}H_{14}O_3NCl$ requires $C = 56·4$; $H = 5·5$; $Cl = 13·9$ per cent.

Additional evidence of the identity of the synthetic cotarnine with that obtained from narcotine was afforded by a comparison of the respective aurichlorides and picrates, which do not appear to have hitherto been described.

Cotarnine Aurichloride.—This compound was first prepared from a specimen of cotarnine hydrochloride as derived from narcotine, when it was obtained as a voluminous, reddish-yellow precipitate, which was very sparingly soluble in water, but readily so in hot alcohol. It crystallised from the latter in golden-yellow laminæ, which melted at 136—137°, and were anhydrous. The aurichloride

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[*] Air-dried.

[†] Dried at 110°.

from the above-described synthetic cotarnine hydrochloride also crystallised from alcohol in golden-yellow laminæ, melting at 136—137°, and the melting point of a mixture of the two specimens was the same. The synthetic aurichloride was ignited, with the following result:

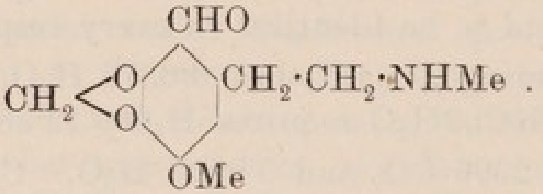
0·1342 gave 0·0475 Au. Au = 35·4.

$C_{12}H_{14}O_3NCl_4Au$ requires Au = 35·3 per cent.

Cotarnine Picrate.—When aqueous picric acid is added to a solution of cotarnine hydrochloride, an oily precipitate is formed, which soon becomes solid. It is moderately soluble in hot water, from which it crystallises in slender, yellow, silky needles. These sinter at 133°, and melt at 143°. The picrate from the synthetic hydrochloride was prepared in a similar manner, and found to possess the same properties. The melting point of a mixture of the two specimens was 143°.

The identification of the above-described synthetic product was finally completed by the preparation of the free base itself, which was obtained as a colourless, crystalline solid when an aqueous solution of sodium hydroxide was cautiously added to a solution of synthetic cotarnine hydrochloride. The base was purified by recrystallisation from benzene, when it was deposited in stellar clusters of prismatic needles, which melted and decomposed at 130°. It was identical in all respects with a specimen of cotarnine prepared from narcotine.

neo*Cotarnine, an Isomeride of Cotarnine,*



For the synthesis of this substance, 6-methoxy-7 : 8-methylenedioxy-1-benzyl-3 : 4-dihydro*iso*quinoline hydrochloride (B) (p. 1214) was subjected to the same series of operations as those which have already been described in connexion with the conversion of 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro*iso*quinoline into cotarnine. Accordingly, the base regenerated from 3 grams of the pure hydrochloride was successively converted into its methiodide and methochloride, and the latter reduced with tin and hydrochloric acid in the presence of alcohol. The reduction product, 1-benzyl*neo*cotarnine (XIV, p. 1210), was obtained as a brown oil, which was not further investigated, but directly oxidised by means of manganese dioxide and sulphuric acid. On examining the products of oxidation, a crystalline hydrochloride was isolated, which was purified by crystallisation from a mixture of absolute alcohol and ethyl acetate. It separated from this solvent in long, bright yellow needles, which melted and decomposed at 185° with the formation of a deep red liquid:

0·1486 * gave 0·3070 CO_2 and 0·0782 H_2O. $C=56·3$; $H=5·8$.
0·2968 * „ 0·1620 AgCl. $Cl=13·5$.
$C_{12}H_{14}O_3NCl$ requires $C=56·4$; $H=5·5$; $Cl=13·9$ per cent.

Since a mixture of the above substance and cotarnine hydrochloride decomposes at about 170°, the two cannot be identical, and must therefore be isomeric. It is proposed to designate the new base neo*cotarnine*.

neo*Cotarnine hydrochloride* is readily soluble in water or alcohol, but insoluble in ether or ethyl acetate. It is best crystallised from a mixture of absolute alcohol and ethyl acetate, from which it separates in long, yellow needles containing 1½ molecules of water of crystallisation:

0·4665, when heated at 110°, lost 0·0438 H_2O. $H_2O=9·4$.
$C_{12}H_{14}O_3NCl,1\frac{1}{2}H_2O$ requires $H_2O=9·6$ per cent.

In losing its water of crystallisation, the bright yellow hydrochloride changes in colour to dark red. This change is not due to decomposition, since, on the one hand, the red hydrochloride re-absorbs 1½ molecules of water and becomes yellow again on exposure to air, whilst, on the other hand, the yellow hydrochloride, when dried in a vacuum over sulphuric acid, loses its water of crystallisation without any change of colour. The yellow, anhydrous substance so obtained then becomes red, without loss in weight, by prolonged heating at 110°:

0·3538 anhydrous substance absorbed 0·0378 H_2O on exposure to air. $H_2O=9·7$.
$C_{12}H_{14}O_3NCl,1\frac{1}{2}H_2O$ requires $H_2O=9·6$ per cent.

neo*Cotarnine*.—The free base differs from its isomeride, cotarnine, in not being precipitated from an aqueous solution of its hydrochloride by the addition of dilute alkali hydroxides. It may, however, be obtained from such an alkaline solution by extracting with benzene and removing the solvent in a vacuum. The base then remains as a hard, crystalline mass, which, on recrystallisation from benzene, is deposited in colourless prisms, melting and decomposing at 124°.

*neo*Cotarnine is readily soluble in alcohol, chloroform, or ethyl acetate, but only sparingly soluble in ether. It dissolves in hot water, giving a yellow solution, from which it does not readily separate. The *aurichloride* is precipitated as a dark brown solid

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* Dried at 110°.

on the addition of gold chloride to an aqueous solution of *neo*cotarnine hydrochloride. It is only sparingly soluble in water, but readily so in hot methyl alcohol, from which it crystallises in chocolate-brown prisms. These are anhydrous, and melt and decompose at 127°:

0·1398 gave 0·0489 Au. Au = 35·0.

$C_{12}H_{14}O_3NCl_4Au$ requires Au = 35·3 per cent.

neo*Cotarnine picrate* is obtained as an oily precipitate, which soon solidifies, when an aqueous solution of picric acid is added to *neo*cotarnine hydrochloride. It is readily soluble in alcohol, but only moderately so in hot water, from which it is deposited in long, yellow needles, sintering at 90° and melting at 100°.

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