XI —*Narcotine, Cotarnine, and Hydrocotarnine.* (Part II.)

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§ 1. *Action of Water on Narcotine Hydrochloride.*

WHEN narcotine is dissolved in 50 parts of boiling water containing as little hydrochloric acid as is necessary for complete solution (about two or three equivalents), and the liquid is allowed to cool, filamentous silky crystals separate, quite unlike those of normal narcotine hydrochloride, and containing a smaller percentage of chlorine; if these crystals be recrystallised, or if the normal hydrochloride be dissolved in hot water and the solution allowed to cool, still more basic crystals separate, approximating in composition to $7\bar{N}$, HCl (N stand-

ing for narcotine, $C_{22}H_{23}NO_7$). Although readily dissolved by boiling water, these crystals are but little altered by further recrystallisations, the product after several crystallisations having approximately the composition $8\bar{N},HCl$.

Thus, narcotine was dissolved in boiling water containing 2 equivalents of HCl , and of this five-sixths was neutralised by means of standard soda-solution; by the slow addition of this, amorphous flakes were thrown down which mostly dissolved on agitation and boiling, leaving, however, some crystalline narcotine undissolved. From the filtered liquid filamentous crystals separated, of which 0.3820 gram gave—

0.0260 $AgCl$ (after drying at 100°).... $Cl = 1.68$ per cent.

Calculated for $5\bar{N},HCl$ $Cl = 1.69$ „

On dissolving these in hot water, and leaving the solution to cool, similar crystals separated; of these 0.5600 gave—

0.0285 $AgCl$ $Cl = 1.26$ per cent.

Calculated for $7\bar{N},HCl$.. $Cl = 1.21$ „

Again, crystallised normal hydrochloride of narcotine was dissolved in 50 parts of boiling water; on cooling crystals formed, of which, after drying at 200° ,

0.2980 gram gave 0.016 $AgCl$ $Cl = 1.32$ per cent.

After recrystallisation from 50 parts of boiling water,

0.7490 gram gave 0.0345 $AgCl$ $Cl = 1.14$ per cent.

After another crystallisation,

0.2460 gram gave 0.010 $AgCl$ $Cl = 1.01$ per cent.

Calculated for $8\bar{N},HCl$ = 1.06 „

Hence it results that narcotine hydrochloride is, like narceine hydrochloride, split up into basic salts and hydrochloric acid by the action of hot water; whilst a portion of chlorine is retained with comparatively considerable force.

§ 2. Action of Ethyl-iodide on Hydrocotarnine.

When hydrocotarnine was heated to 100° with excess of ethyl iodide and absolute alcohol, a product is obtained which, on cooling, becomes a crystalline mass. The crystals were recrystallised from 80 per cent. alcohol, and formed snow-white micaceous plates, becoming yellowish by exposure to air; when dry, they were apparently anhydrous, as they only lost a few tenths per cent. at 100° ; the dried mass gave the following numbers :—

0.3340 gram gave 0.5480 CO₂ and 0.1690 H₂O.

0.5230 „ „ 0.3235 AgI.

	Calculated.		Found.
C ₁₄	168	44.56	44.74
H ₂₀	20	5.31	5.62
I.....	127	33.69	33.43
N.....	14	3.71	—
O ₃	48	12.73	—
C ₁₂ H ₁₅ NO ₃ .C ₂ H ₅ I..	377	100.00	

These crystals were but sparingly soluble in cold water, but dissolved more readily in alcohol, especially when hot. On agitation with water and freshly prepared silver hydrate, a strongly alkaline aqueous solution was obtained which precipitated heavy metals (*e.g.*, lead and mercury salts) and absorbed carbon dioxide from the air, giving on spontaneous evaporation, crystals readily soluble in water and alcohol, but precipitated from the latter solution by ether: these crystals were apparently the carbonate, as they effervesced strongly with hydrochloric acid, precipitated barium nitrate on boiling, and gave the following numbers after drying over sulphuric acid:—

0.3185 gram gave 0.6355 CO₂ and 0.2130 H₂O.

	Calculated.		Found.
C ₂₉	348	55.07	54.42
H ₄₈	48	7.59	7.43
N ₂	28	4.43	—
O ₁₃	208	32.91	—
(C ₁₂ H ₁₅ NO ₃ .C ₂ H ₅) ₂ CO ₃ .4H ₂ O..	632	100.00	

On agitation with water and silver chloride (freshly precipitated) the ethiodide formed the ethyl-chloride, separating on spontaneous evaporation as feathery crystals which, after drying over sulphuric acid, fused at 100° to a glassy mass, becoming crystalline on cooling and standing. Of this

0.2905 gram gave 0.0365 Cl (volumetric) = 12.53 per cent.

Calculated for C₁₂H₁₅NO₃.C₂H₅Cl = 12.44 „

The platinum salt made from it gave these numbers—

0.4370 gram gave 0.0945 Pt = 21.62 per cent.

Calculated for (C₁₂H₁₅NO₃.C₂H₅Cl)₂PtCl₄ = 21.69 „

In order to see if the crystals formed by the action of ethyl iodide on hydrocotarnine are really the ethiodide of a nitril-base, or a com-

pound analogous to hydriodide of ethylamine, they were dissolved in hot absolute alcohol and shaken with freshly precipitated silver hydrate previously well washed with alcohol; the alcoholic filtrate was sealed up in a tube with a large excess of ethyl iodide, and the whole heated to 100° for 20 minutes; on cooling, the product deposited crystals which were found to be simply the original ethiodide, and not the ethiodide of ethyl-hydrocotarnine.

0.6300 gram gave 0.3920 AgI. Iodine = 33.63 per cent.

The formula $C_{12}H_{15}NO_3, C_2H_5I$ requires 33.69 „

Whilst the formula $C_{12}H_{14}(C_2H_5)NO_3, C_2H_5I$ requires 31.36 „

Hence it results that hydrocotarnine is a nitril base, and therefore that by addition of H_2 the conversion of cotarnine into hydrocotarnine is a reaction parallel with that whereby acetylene is converted into ethylene, and not with that whereby hydrocyanic acid becomes methylamine: in other words hydrocotarnine does not contain in its formula the group NH_2 , nor the group NH .

§ 3. Action of Ethyl Iodide on Narcotine.

How has already found (*Annalen der Chemie*, xcii, 336) that when narcotine and cotarnine are treated with ethyl iodide, non-crystallisable iodised compounds are produced, from which platinum salts are obtainable by the action of silver nitrate, hydrochloric acid, and platinic chloride, having approximately the composition of narcotine and cotarnine platino-chloride respectively; and hence How concluded that the ethiodides of narcotine and cotarnine are not thus formed, but that only the hydriodide is produced by the decomposition of the ethyl iodide employed. On repeating How's experiments, however, we have been led to entirely different conclusions.

Narcotine when heated to 100° for half an hour with absolute alcohol and a slight excess of ethyl iodide yields, as stated by How, a clear fluid from which, on cooling and standing, crystals of unchanged narcotine separate; if, however, a large excess of ethyl iodide is used (3 or 4 times the theoretical quantity) and the action is prolonged for 2 hours at 100° in a sealed tube, perfect conversion of all the narcotine into ethiodide occurs, nothing whatever separating on cooling and standing. On exposure to air, the liquid dries up to a varnish-like mass. A portion of the alcoholic solution was fractionally precipitated by addition of water; colourless tarry masses were thus obtained which, after drying over sulphuric acid and finally at 100° , gave the following numbers:—

1st. Precipitate	0.5650 gram	gave 0.2285 AgI ..	I = 21.86 per cent.
2nd. „	0.5360 „	0.2215 „ ..	= 22.23 „
The formula	$C_{22}H_{23}NO_7 \cdot C_7H_5I$	requires	= 22.32 „
whilst	$C_{22}H_{23}NO_7 \cdot HI$	would require	= 23.47 „

On shaking up this non-crystalline ethiodide with water and freshly precipitated silver hydrate, a strongly alkaline aqueous solution was obtained necessarily free from narcotine, since that base is practically insoluble in water; the silver iodide formed, however, was found to contain some narcotine separable by boiling with alcohol and filtering hot: hence it would seem that narcotine ethyl-hydrate is very unstable, readily splitting up into alcohol and narcotine; that this is the case is shown by the fact that on allowing the aqueous solution of the ethyl-hydrate to stand over sulphuric acid it dries up, sometimes to a varnish, sometimes to a mass of crystals; but in each case, on addition of water, a portion refuses to dissolve, this portion being made up of minute crystals of narcotine.

With hydrochloric acid and platinic chloride, the fresh aqueous solution of ethyl hydrate of narcotine gave non-crystalline flakes, somewhat soluble in alcohol; after drying over sulphuric acid for some days, and finally at 100° , one specimen gave these numbers:—

0.2085 gram	gave 0.0315 Pt	= 15.11 per cent.
Calculated for	$(C_{22}H_{23}NO_7, C_2H_5Cl)_2PtCl_4$	= 15.26 „
Narcotine hydrochloride	$(C_{22}H_{23}NO_7, HCl)PtCl_4$	requires 15.95 per cent.

Other specimens, especially if heated to 100° before complete drying over sulphuric acid, gave slightly higher percentages of platinum. Thus one specimen thus treated contained Pt = 15.56 per cent.

Unlike most organic ethiodides, narcotine ethiodide is partially decomposed by caustic potash; on adding to an alcoholic solution of the ethiodide, alcoholic caustic potash and then water, a tarry precipitate falls, consisting of bases free from iodine, apparently ordinary narcotine mixed with the ethyl hydrate, as on treating this precipitate with alcohol, part dissolves, leaving crystalline narcotine insoluble: the alcoholic solution dries up to a varnish, which on standing becomes a mass of crystals, precisely resembling the product obtained by the evaporation of the aqueous solution of the ethyl-hydrate over sulphuric acid; the platinum salt made from this crystalline mass gave the following numbers:—

0.3350 gram	gave 0.0505 Pt	= 15.07 per cent.
Calculated for	$(C_{22}H_{23}NO_7, C_2H_5Cl)_2PtCl_4$	= 15.26 „

From these results, it follows that the action of ethyl iodide on nar-

cotine is like that on most other bases, viz., combination and formation of an ethiodide: narcotine, however, is not wholly transformed into ethiodide unless some considerable excess of ethyl iodide is present, and the ethiodide and its derivatives have a great tendency to split up, losing ethyl and forming narcotine or compounds thereof. In these respects, as in the analogous action of water on the hydrochloride, narcotine closely resembles narceine (this Journal [2], xii, 109). Moreover, these two bases are not merely alike in these properties; they are capable, as will be shown in a future paper, of giving rise to the same oxidation-product, and accordingly have at least a considerable portion of their "structures" identical.

§ 4. Action of Ethyl-iodide on Cotarnine.

When cotarnine is heated to 100° in a sealed tube with excess of ethyl iodide and a little absolute alcohol, a liquid results, which dries up on evaporation, to a varnish-like, very hygroscopic mass; on rubbing this up with water and freshly-precipitated silver hydrate, a very alkaline filtrate is obtained, which does not crystallise by spontaneous evaporation; on addition of hydrochloric acid till just neutral, and spontaneous evaporation over sulphuric acid, a jelly-like, non-crystalline ethyl chloride is left; this yields a flocculent, non-crystalline platinum salt, from which the following numbers were obtained:—

0.4675 gram gave 0.1015 Pt	= 21.71 per cent.
0.3895 " " 0.084 "	= 21.56 "
Calculated for $(C_{12}H_{13}NO_3, C_2H_5Cl)_2PtCl_4$	= 21.78 "

Cotarnine platinochloride $(C_{12}H_{13}NO_3, HCl)_2PtCl_4$ requires 23.23 per cent.

By the action of silver nitrate, hydrochloric acid and platinic chloride on the product of the reaction of ethyl iodide on cotarnine, How obtained (*loc. cit. supra*) a platinum salt containing 22.38 per cent. of platinum, whence he concluded that this was cotarnine platinochloride, and not cotarnine ethyloplatinochloride, as the formula of cotarnine was then considered to be $C_{13}H_{13}NO_3$, whence the platinum salt required 22.58 per cent. of platinum. The results of Matthiessen and Foster, however, have proved that cotarnine is really represented by the formula $C_{12}H_{13}NO_3$, a result quite corroborated by the numbers obtained by us in Part I: hence it is manifest that the platinum salt obtained by How really was slightly impure cotarnine ethyloplatinochloride, the slightly high value of the platinum being probably due to a partial decomposition whilst drying: we have found that if the platinum salt be heated to 100° before almost perfect desiccation by standing over sulphuric acid for several days, it gives

much higher percentages of platinum; two specimens thus treated gave 22.41 and 23.14 per cent. respectively: after thorough drying over sulphuric acid, however, no appreciable decomposition is brought about by heating to 100° for two or three hours.

From the above results, it may be inferred that narcotine, cotarnine, and hydrocotarnine yield definite ethiodides and other ethyl compounds like most other alkaloïds; and that they are nitril bases.

§ 5. *Action of Acetic Anhydride on Narcotine, Cotarnine and Hydrocotarnine.*

Nothing but the original bases could be obtained from the products of several experiments in which narcotine, cotarnine, and hydrocotarnine were severally treated with acetic anhydride under various conditions, in the hope of producing acetyl derivatives; it thence results that these alkaloïds are not hydroxylated bases, *i.e.*, the group OH is not contained in their formulæ.

APPENDIX A.

Physiological Action of Hydrocotarnine Ethylchloride as compared with that of the Hydrochloride. By F. PIERCE, M.D., L.R.C.P. (Lond.), Associate of The Owens' College.

THE effect of ethylation of hydrocotarnine is somewhat analogous to that produced by uniting methyl iodide to strychnine; a most marked diminution in toxic properties results, the general action of the ethylchloride being analogous to that of the hydrochloride, though of a much less marked character; doses of 4 decigrams of the ethylchloride were subcutaneously administered to rabbits, kittens, and cats, with but slight effects in the first instances, and little or none in the last; whilst the same doses of hydrochloride produced death in nearly all cases.

APPENDIX B.

On the "Structural" Formulæ of Narcotine and its Derivatives. By C. R. ALDER WRIGHT.

THE experiments made by Matthiessen and Foster (this Journal, 1863, 342), led to them assigning to narcotine the "structural" formula—

cotarnine being represented by these chemists as—

the evidence in support of these formulæ being that cotarnine can give rise to methylamine and cotarnic acid (bibasic) $\text{C}_{11}\text{H}_{12}\text{O}_5$, and to cotarnamic acid, $\text{C}_{11}\text{H}_{13}\text{NO}_4$; whilst narcotine forms by oxidation cotarnine and opianic acid, which latter gives rise, by further oxidation, to hemipinic acid (bibasic), from which, again, methyl iodide (2 equivalents) and a monobasic acid, *hypogallic acid*, can be formed by the reaction,

an intermediate monobasic acid, *methyl-hypogallic acid*, being also obtainable by the action of hydrochloric acid, thus—

Moreover, narcotine, when treated with hydriodic acid, gives rise to three equivalents of methyl iodide, of which the first two eliminated are derived from the opianic acid radical, the last being from the cotarnine radical (Matthiessen and Wright, *Phil. Trans.*, 1869, 667).

On the other hand, Liechti has found, on examining the action of hydriodic acid on hemipinic acid (*Annalen der Chemie, Suppl.*, vii, 129), that instead of hypogallic acid, $\text{C}_7\text{H}_6\text{O}_4$, two isomeric acids are formed, termed by him *opinic* and *isopinic* acids, each expressed by the formula $\text{C}_{14}\text{H}_{10}\text{O}_8$, his analytical figures for each acid mainly differing from Matthiessen and Foster's, in that they show a lesser amount of hydrogen; isopinic acid was considered by Liechti to be identical with the hypogallic acid of Matthiessen and Foster, notwithstanding that the analytical figures did not agree sharply, and that a difference of upwards of 30° in the melting point was observed.

Some doubt being thus cast on the validity of the evidence on which the formula of Matthiessen and Foster is based, it appears to be desirable that these points should be submitted to revision, and that additional evidence should be obtained, if possible, as to the relationships of the narcotine derivatives to other classes of bodies; and this appears to be the more desirable, since we have recently succeeded in

obtaining from narceine an oxidation-product identical with the hemipinic acid, derived from narcotine, whence it results that these two alkaloids have structures alike to some portion of their extent. We have, accordingly, as will be described in a future paper, investigated anew the mutual relationships of meconin, opianic acid and hemipinic acid, and the nature of some of their reactions and decompositions, and have been led, accordingly, to views in some respects different from those hitherto held on the subject.

As regards the formula for narcotine proposed by Matthiessen and Foster, it is to be noticed in the first place that some modifications must be made before the action of aqueous liquids on narcotine can be expressed by the structure adopted; as shown in Part I of their researches (this Journal [2], xiii, 573). This action is such as to give rise to opianic acid and hydrocotarnine, the elements of water being taken up in so doing. Secondly, that formula indicates the possibility of obtaining from narcotine an acetyl-derivative, since the group OH is contained in the formula (as it also is in their cotarnine formula). We have, however, as shown above, completely failed in obtaining from either narcotine, cotarnine, or hydrocotarnine, any acetylated derivatives by subjecting them to the action of acetic anhydride under various conditions, nothing but the original bases being obtainable from the products of the reaction. Thirdly, the mere production of methylamine from cotarnine by oxidation, most of the product being altogether destroyed, is scarcely sufficient to warrant the introduction of the methylamine residue, $N-CH_3$, into the formula of cotarnine, and consequently into that of narcotine; the facts that methyl chloride or iodide can be obtained from cotarnine, and that *three* equivalents of methyl iodide can be formed from narcotine, tend rather to indicate that the group $O.CH_3$ should be written, instead of $N.CH_3$. It is known that *trimethylamine* is obtainable from narcotine, by the action of potash; and hence it is clear that the number of methyl groups originally associated with the N symbol, cannot be inferred from the nature of the decomposition-products of the alkaloid.

The experiments above described show that narcotine, as well as cotarnine and hydrocotarnine, is a nitrile-base. From these various reasons, the following formula appears to be more in accordance with the present state of our knowledge of narcotine and its decomposition products than that of Matthiessen and Foster.

while it is not specified whether the O.CH_3 , or N.CH_3 group is present in the cotarnine radicle; the formula renders account of all reactions of narcotine known at present. The action of water is represented by the equation:—

As regards the structure of the trivalent radicle, $\text{C}_7\text{H}_3\text{O}$, it has already been pointed out by Matthiessen and Foster that, from the results which they obtained by acting on hemipinic acid with hydriodic acid, the former may be regarded as the dimethylised derivative of a dioxyterephthalic acid:—

From the formation of an anhydride from hemipinic acid, however, by simply heating to about 180° (Matthiessen and Wright, *Phil. Trans.*, 1869, 667), it seems more probable that hemipinic acid is dimethyl-dioxyphthalic acid, since phthalic acid can yield an anhydride by heating, whilst the isomeric terephthalic acid does not do so.

This being the structure of hemipinic acid, opianic acid is probably indicated, as Liebermann and Chojnacki have pointed out (*Jahresb.*,

1871, 638) by the aldehydic formula, $\text{C}_6\text{H}_2 \left\{ \begin{array}{c} \text{COH} \\ \text{CO.OH} \\ \text{O.CH}_3 \\ \text{O.CH}_3 \end{array} \right.$, from which it results that the structural formula of narcotine is

If, however, the action of hydriodic acid on hemipinic acid be not that represented by the equation—

as would seem to be indicated by the results of Liechti, it results that this structure is purely hypothetical. On examining this point we have come to conclusions in some respects different from those arrived at by Matthiessen and Foster, and also opposed to those of Liechti, but we have found that hydriodic acid does produce a product, $C_7H_6O_4$, in virtue of the above reaction, this product being simply protocatechuic acid, the supposed isomeric "hypogallic acid" of Matthiessen and Foster being probably a mixture of protocatechuic acid with other intermediate products of the reaction. We have obtained a number of other proofs that the true structure of hemipinic

acid is $C_6H_2 \begin{Bmatrix} CO.OH \\ CO.OH \\ O.CH_3 \\ O.CH \end{Bmatrix}$, and that, moreover, it is a carboxylated dime-

thyl protocatechuic acid, opianic acid being a carboxylated dimethyl-protocatechuic aldehyde, whilst the lateral chains, COH and OCH_3 , in the narcotine formula are in the same relative positions as these same radicals in dimethylprotocatechuic aldehyde.

As regards the constitution of meconin, this body may be regarded

either as a double aldehyde, $C_6H_2 \begin{Bmatrix} COH \\ COH \\ O.CH_3 \\ O.CH_3 \end{Bmatrix}$; or as the anhydride of

an alcoholo-acid analogous to salicylic acid, viz., $C_6H_2 \begin{Bmatrix} CO \\ CH_2 \\ O.CH_3 \\ O.CH_3 \end{Bmatrix} O$;

of these the latter is far the more probable, inasmuch as meconin can be obtained from opianic acid by the action of nascent hydrogen, but cannot be again oxidised to opianic acid; whilst the action of heated potash breaks up opianic acid into meconin and hemipinic acid, just as many aromatic aldehydes break up into alcohols and acids when thus treated. Thus:—