XXVIII.—*On the Action of the Organic Acids and their Anhydrides on the Natural Alkaloïds.* Part V.

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§ 1. *Action of Acetic Anhydride on Opium Bases.*

Codeine and morphine appear to possess a structure different from that of the other opium alkaloïds, in so far as the actions of organic acids and anhydrides are concerned. As shown in the previous portions of these researches, these two bases readily yield acetyl-, &c., derivatives; only negative results, however, have been obtained as regards the formation of acetylated bases by the action of acetic anhydride on *narcotine* (and its derivatives, *hydrocotarnine* and *cotarnine*), *narceine*, *papaverine*, and *thebaine*. Narceine thus treated, appears to lose the elements of water (this Journal, 1875, 699), whilst thebaine becomes almost wholly converted in a non-crystalline base in no way resembling acetyl-codeine or morphine. The thebaine employed was kindly presented to us by Wm. D. Howard, Esq., by whom it had been extracted from opium; it gave the following numbers on combustion:—

0·3090 gram. gave 0·8295 CO_2 and 0·298 H_2O.

	Calculated.		Found.
C_{19}	228	73·31	73·21
H_{21}	21	6·75	7·12
N	14	4·50	—
O_3	48	15·44	—
$C_{19}H_{21}NO_3$	311	100·00	

The resinous base formed by heating thebaine with excess of acetic anhydride at 100° for one hour, was dissolved out by means of sodium carbonate and ether; it gave no crystalline hydrochloride, but yielded an amorphous platinum salt containing 9·56 per cent. Pt: thebaine platinochloride requires 19·09 per cent.: hence it would seem as though the thebaine were polymerised by the action, forming a substance (like acetylated tetracodeine) deficient in acid-saturating power.

Papaverine was considered by Merck, its discoverer, to be indicated by the formula $C_{20}H_{21}NO_4$, and this result was corroborated by the analyses of Anderson; Hesse, on the other hand, has found that papaverine, purified by conversion into the acid oxalate, and regenerated from the recrystallised salt, is indicated by the formula $C_{21}H_{21}NO_4$. Again, Anderson regarded the base as being capable of retaining ammonia when precipitated therewith, so as to yield an abnormally high percentage of nitrogen, whilst it has been supposed that the base prepared by Hesse's purification process might retain oxalic acid. Our own results seem to show that Hesse's formula is the correct one, and that the base purified by oxalic acid retains none of that substance after precipitation by potash or ammonia and crystallisation from benzene, whilst no ammonia is retained by the substance precipitated by that reagent.

Two samples of material were received from Messrs. Macfarlan, one almost snow-white, and believed to be absolutely pure papaverine, the other a crude impure product containing much dark colouring matter, and other substances. The first specimen gave these numbers after crystallisation from boiling benzene:—

(A.) 0·3145 gram gave 0·8280 CO_2 and 0·1840 H_2O.

Three parts of the latter substance and one of oxalic acid were dissolved together in hot water; on cooling and standing, with occasional stirring, the acid oxalate of papaverine separated out in crystals; these were pressed and recrystallised from hot water four or five times; finally, the hot solution of the nearly colourless salt was poured into excess of ammonia, and the precipitate collected, washed, dried, and crystallised four times from boiling benzene.

(B.) 0·3220 gram gave 0·8470 CO_2 and 0·1865 H_2O.

After another crystallisation from benzene—

(C.) 0·3285 gram gave 0·8615 CO_2 and 0·1920 H_2O.
0·6740 gram burnt with soda lime gave 0·1815 Pt.

Another specimen was prepared from the purified oxalate as (B), potash being substituted for ammonia as precipitant.

(D.) 0·3295 gram gave 0·8630 CO_2 and 0·1940 H_2O.
0·7000 „ burnt with soda-lime gave 0·1970 Pt.

In order to see if, by any possibility, oxalic acid was retained by these samples, a quantity of the purified oxalate was dissolved in hot water, and to the solution acetate of ammonia and chloride of calcium were added; the filtrate containing papaverine hydrochloride was precipitated by potash, and the precipitate crystallised from benzene.

(E.) 0·3470 gram gave 0·9080 CO_2 and 0·2055 H_2O.

All these numbers agree closely together, and with those calculate for Hesse's formula, $C_{21}H_{21}NO_4$, whereas they do not agree so well with Anderson's formula, $C_{20}H_{21}NO_4$; thus—

	Calculated		Found.				
	For $C_{20}H_{21}NO_4$.	For $C_{21}H_{21}NO_4$.	A.	B.	C.	D.	E.
Carbon	70·80	71·79	71·80	71·74	71·52	71·43	71·37
Hydrogen ..	6·19	5·99	6·50	6·43	6·49	6·54	6·58
Nitrogen....	4·13	3·99	—	—	3·82	3·99	—
Oxygen	18·88	18·23					
	100·00	100·00					

The following numbers represent the mean values obtained by Merck, Anderson, Hesse, and ourselves:—

	Merck.	Anderson.	Hesse.	B. & W.
Carbon	70·59	70·63	71·78	71·57
Hydrogen ..	6·54	6·40	6·02	6·51
Nitrogen ..	4·75	4·18	4·26	3·90

The impurity of the products examined by Merck and Anderson is probably occasioned by the great difficulty experienced in completely freeing papaverine by crystallisation from another substance which is precipitated along with it and persistently adheres to it; Hesse's oxalate process, however, effects the separation completely; thus the crude papaverine employed was crystallised four times from benzene, whereby perfectly colourless crystals were obtained : of these—

(F.) 0·3315 gram gave 0·8515 CO_2 and 0·1890 H_2O.

Even after two more crystallisations, the percentage of carbon still fell considerably below that required for Hesse's formula.

(G.) 0·3210 gram gave 0·8355 CO_2 and 0·1835 H_2O.

	Calculated.	Found.	
		(F.)	(G.)
Carbon............	71·79	70·06	70·98
Hydrogen	5·99	6·34	6·35

§ 2. *Action of Acetic Anhydride on Strychnine.*

Strychnine was treated for varying periods and at different temperatures with excess of acetic anhydride, without causing the formation of any crystallisable acetylated base; the products of the action evaporated on the water-bath yielded to water a salt from which nothing but unaltered strychnine could be obtained: after boiling strychnine for 20 hours with the anhydride, an inverted condenser being attached, the evaporated liquid refused to dissolve wholly in water; the insoluble residue dissolved in alcohol and was precipitated from the solution by addition of water in amorphous flakes. After drying at 100°, these contained : Carbon, 71·22 ; hydrogen, 6·22 (diacetylstrychnine, $C_{21}H_{20}(C_2H_3O)_2N_2O_2$, would require carbon, 71·77; hydrogen, 6·22); they much resembled acetylated tetracodeine, and refused to form a hydrochloride on addition of hydrochloric acid ; the small quantity of substance obtained, however, and its want of crystalline character, rendered further experiments on its nature unprofitable.

By boiling strychnine with glacial acetic acid, no new base appears to be formed, nothing but unaltered strychnine being obtainable from the product by solution in water and cautious addition of ammonia. Hence, apparently, either strychnine does not give rise to acetyl-derivatives, or they immediately become saponified in contact with aqueous solutions.

§ 3. *Action of Acetic Anhydride on the Cinchona Alkaloïds.*

Schützenberger has shown (*Jahresbericht*, 1858, 369), that benzoyl chloride acts on quinine and cinchonine with formation of monobenzoyl-quinine and monobenzoyl-cinchonine respectively, and that resinous bases of apparently analogous composition are similarly formed by the action of acetyl chloride; these latter substances, however, were not fully examined by Schützenberger.

On heating quinine and cinchonine with twice their weight of acetic anhydride to 130° for three hours, acetylated bases are formed, corresponding in physical properties with those obtained by Schützenberger; apparently, however, these substances are not the acetyl-derivatives of quinine and cinchonine, but of their isomerides, quinicine and cinchonicine, as on saponification they give rise to these substances, and as precisely the same bodies are also derivable from their respective isomerides, quinidine and cinchonidine [termed by some chemists conchinine and quinidine respectively; Hesse (*Annalen der Chemie*, clxvi, 217) applies the term quinidine to an alkaloïd different from either of those described by Körner (*Jahresbericht*, 1862, 619), and calls the former one conchinine, the latter cinchonidine]. The bases used were kindly presented to us by David Howard, Esq., to whom we are further indebted for the polariscopic observations made. The quinidine and cinchonidine gave the following numbers on combustion after drying at 100°:—

0·2705 gram of quinidine gave 0·7345 CO_2 and 0·1840 H_2O.

	Calculated.		Found.
C_{20}	240	74·08	74·05
H_{24}	24	7·41	7·56
N_2	28	8·64	—
O_2	32	9·87	—
$C_{20}H_{24}N_2O_2$	324	100·00	

0·2280 gram of cinchonidine gave 0·6520 CO_2 and 0·1710 H_2O.

	Calculated.		Found
C_{20}	240	77·92	77·99
H_{24}	24	7·79	8·33
N_2	28	9·09	—
O	16	5·20	—
$C_{20}H_{24}N_2O$	308	100·00	

This substance did not give the faintest trace of thalliochin reaction.

According to Leers (*Annalen der Chemie*, lxxii, 147), cinchonidine has the formula $C_{18}H_{22}N_2O$; Pasteur, and more recently Howard (this Journal, 1872, 101), also Hesse (*Annalen der Chemie*, clxxviii, 244), have, however, shown that the same isomeride, cinchonicine, is obtainable from both cinchonine and cinchonidine; on the other hand, Schützenberger (*Jahresbericht*, 1858, 372), found that so-called cinchonine has not always a definite composition, one specimen giving numbers agreeing with the formula $C_{18}H_{22}N_2O_2$; Stahlschmidt has described (*Annalen der Chemie*, xc, 218), a methiodide of cinchonidine of composition $C_{18}H_{22}N_2O,CH_3I$; D. Howard, however (this

Journal, 1873, 1177), found that cinchonidine ethiodide is expressed by the formula $C_{20}H_{24}N_2O,C_2H_5I$; the above analysis and the following percentages show that the body examined by us was veritably an isomeride of cinchonine, $C_{20}H_{24}N_2O$.

0·9290 gram of platinum salt, dried at 100°, gave 0·2555 Pt.
Pt = 27·50 per cent.
Calculated for $C_{20}H_{24}N_2O.2HCl.PtCl_4$ = 27·42 ,,

0·5110 gram of the diethiodide formed by heating cinchonidine with excess of ethyl iodide, in a sealed tube at 100° for one hour, and crystallising from 90 per cent. spirit, lost at 100°, after becoming constant in the air, 0·0100 gram, and gave 0·3835 AgI.

	Calculated for $C_{22}H_{24}N_2O,2C_2H_5I,\frac{1}{2}H_2O$.	Found.
Water of crystallisation	1·43	1·95
Iodine	40·38	40·56

[The formation of diethiodides by heating cinchona alkaloïds with excess of ethyl iodide, has been already pointed out by D. Howard, *loc. cit.*]

(A.) *Acetylated Base from Quinine.*

The product of the heating of one part of quinine dried at 130° with two of acetic anhydride to gentle boiling for three hours, was evaporated on the water-bath, and the residue dissolved in warm water was fractionally precipitated by potash. The second fraction was readily soluble in ether, from which the base was obtained as a clear varnish by evaporation; no crystallisation could be provoked in this, nor could any crystallised salts be obtained from it.

0·3290 gram dried at 110° gave 0·8630 CO_2 and 0·2250 H_2O.

	Calculated.		Found.
C_{22}	264	72·13	71·54
H_{26}	26	7·10	7·60
N_2	28	7·65	—
O_3	48	13·12	—
$C_{20}H_{23}(C_2H_3O)N_2O_2$	366	100·00	

With chlorine-water and ammonia it readily gave the thalleiochin reaction.

On saponification by heating with alcohol and rather more of a soda-solution of known strength than was required to neutralise the acetic acid generated, evaporation to dryness of the product, and taking up the sodium acetate and unneutralised soda with water, numbers were obtained agreeing with those required for the above formula.

1·106 gram neutralised 5·80 c.c. of soda-solution, of which 1 c.c. = 0·0314 gram acetic acid; hence there was formed 0·1821 gram of acetic acid .... = 16·46 per cent.

Calculated .... = 16·40 „

Hence the acetylated product was formed by the reaction—

$$C_{20}H_{24}N_2O_2 + (C_2H_3O)_2O = C_2H_3O.OH + C_{20}H_{23}(C_2H_3O)N_2O_2.$$

This acetyl-derivative appeared to be deficient in acid-combining power; on dissolving in a slight excess of hydrochloric acid and precipitating with platinic chloride, flocculent non-crystalline flakes were obtained, two samples of which contained respectively 21·16 and 18·28 per cent. of platinum: the normal salt $C_{20}H_{23}(C_2H_3O)N_2O_2,2HCl,PtCl_4$ would require 25·38, and the monoacid salt $(C_{20}H_{23}(C_2H_3O)N_2O_2,HCl)_2PtCl_4$ would require 17·44 per cent. of platinum; similarly on shaking up an ethereal solution of the base with hydrochloric acid, so as to obtain a just feebly acid aqueous solution, and evaporating this to dryness, a gum-like residue was obtained containing carbon = 65·9, hydrogen = 6·9, chlorine = 6·9; the formula $5[C_{20}H_{23}(C_2H_3O)N_2O_2] + 4HCl$ requires carbon, 66·7; hydrogen, 6·7; chlorine, 7·2.

The base produced by the saponification of this acetylated product appeared to be simply *quinicine*, somewhat altered by the high temperature employed in the acetylation process; it gave numbers on analysis indicating that it was a quinine isomeride, and was found by D. Howard to give the same molecular rotation as ordinary quinicine; nevertheless it was found excessively difficult to obtain any crystalline salts, the oxalate only becoming indistinctly crystalline to a small extent on long standing; moreover, the platinum salt precipitated from a solution containing an excess of hydrochloric acid was found to contain less platinum than normal quinine platinochloride; thus one sample contained only 18·35 per cent. of platinum after drying at 100°, whilst another precipitated from a very acid solution contained 26·15; the formulæ $(C_{20}H_{24}N_2O_2.HCl)_2PtCl_4$ and $C_{20}H_{24}N_2O_2,2HCl,PtCl_4$ require respectively 18·63 and 26·82 per cent., the latter representing ordinary quinine platinochloride.

Hesse has already pointed out (*Annalen der Chemie*, 178, 244) that quinicine when heated to 130°—140° yields a crystalline oxalate only with great difficulty, and that cinchonicine platinochloride thrown down from a solution not strongly acid, contains less platinum than the normal salt.

(B.) *Acetylated Base from Quinidine.*

On repeating the above experiments with quinidine, products were obtained undistinguishable from those from quinine; the acetylated base gave these numbers:

	Calculated.	Found.	
Carbon	72·13	71·66	
Hydrogen..............	7·10	7·38	
Acetic acid generated on saponification	16·46	17·57	17·88

The base formed on saponification possessed the same rotatory power as that from quinine (*i.e.*, the same molecular rotation as quinicine), and gave numbers indicating that it was somewhat impure quinicine; a platinum salt made from a slightly acid solution contained 22·76 per cent. of platinum; both the saponification product and the acetylated base readily gave the thalleiochin reaction.

(C.) *Acetylated bases from Cinchonine and Cinchonidine.*

In the same way, *monoacetyl cinchonicine* was obtained from cinchonine and cinchonidine: the base is obtainable only as a varnish, and yields no crystalline salts: on combustion numbers were obtained with each sample agreeing with the formula $C_{20}H_{23}(C_2H_3O)N_2O$, and on saponification with soda 17·0 per cent. of acetic acid was formed from the product from cinchonine, and 17·7 and 16·2 per cent. from that from cinchonidine, the theoretical number being 17·14 per cent. The base produced on saponification appeared to be somewhat impure cinchonicine, giving numbers agreeing with the formula $C_{20}H_{24}N_2O$, forming a crystalline oxalate with considerable difficulty and possessing the rotatory powers (D. Howard) of ordinary cinchonicine; hence the product was formed by the reaction—

$$C_{20}H_{24}N_2O + (C_2H_3O)_2O = C_2H_3O.OH + C_{20}H_{23}(C_2H_3O)N_2O.$$

When the platinum salt was precipitated from slightly acid solutions 19·97 and 18·61 per cent. of platinum was found in the products (dried at 100°) from cinchonine and cinchonidine respectively, the normal salt $C_{20}H_{24}N_2O,2HCl,PtCl_4$ requiring 27·42 per cent., and the mono acid salt $(C_{20}H_{24}N_2O,HCl)_2PtCl_4$, requiring 19·20 per cent.