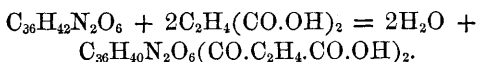


XXXIV.—*On the Action of the Organic Acids and their Anhydrides on the Natural Alkaloids.* PART IV.

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Action of Polybasic Acids on Morphine and Codeine.

Action of Succinic Acid on Codeine.—When codeine and twice its weight of succinic acid are heated together to 180°, the whole fuses to a viscid liquid, which does not solidify on cooling to 160°—170°; if it be kept at this temperature for several hours, water is slowly given off, and a new product formed in accordance with the reaction



This new substance, to which the name *codeine-succinic acid* might be applied, were it not that it exhibits the characters of a base much more distinctly than those of an acid, can be readily obtained pure by dissolving the product of the action in water, and cautiously adding either ammonia or sodium carbonate until a precipitate just begins to appear. The liquid is then filtered, whereby a nearly colourless solution is obtained, from which a very cautious further addition of alkali throws down the new product in flakes readily soluble in excess of any alkali; by this fractional precipitation the colouring matters formed by the decomposition of the codeine at the high temperature employed are almost wholly removed. The precipitate is drained, slightly washed with cold water, and dissolved in boiling 80 per cent. alcohol, from which it crystallises on cooling in small white crystals containing 10H₂O. These crystals are permanent in the air, insoluble in water, ether, and benzene, sparingly soluble in cold alcohol, but readily dissolved by boiling alcohol; they dissolve readily in either acids or alkalis, apparently forming salts in each case, but the alkaline salts are of such slight permanence that they cannot be isolated; a solution of the body in barium hydrate is wholly decomposed by carbon dioxide gas, no barium salt being thus obtainable; whilst an ammoniacal solution, if cautiously evaporated over sulphuric acid at the ordinary temperature, yields only large thin micaceous crystals of the body itself, and none of its ammonia salt. The salts formed with acids are, however, well-defined crystallisable bodies.

The following numbers were obtained:—

- (A) 1.069 grams of crystals exposed to the air till constant in weight, lost at 100° 0.1960
 (B) 1.615 grams of crystals exposed to the air till constant in weight, lost at 100°..... 0.3130

Calculated for $C_{36}H_{40}(CO.C_2H_4.CO.OH)_2N_2O_6, 10H_2O$.	Found.	
	A.	B.
18.4	18.3	19.3

0.3475 gram of air-dry crystals gave 0.6830 CO_2 and 0.2330 H_2O .

Calculated.		Found.	
C_{44}	528	53.99	53.60
H_{70}	70	7.16	7.45
N_2	28	2.86	—
O_{22}	352	35.99	—
<hr/> $C_{36}H_{40}(CO.C_2H_4.CO.OH)_2N_2O_6, 10H_2O$	<hr/> 978	<hr/> 100.00	

0.3745 gram of substance dried at 100° gave 0.9030 CO_2 and 0.2230 H_2O .

0.3135 gram of substance dried at 100° gave 0.7565 CO_2 and 0.1840 H_2O .

Calculated.		Found.	
C_{44}	528	66.17	65.75 65.82
H_{50}	50	6.26	6.62 6.52
N_2	28	3.51	— —
O_{12}	192	24.06	— —
<hr/> $C_{36}H_{40}(CO.C_2H_4.CO.OH)_2N_2O_6$	<hr/> 798	<hr/> 100.00	

When it is dissolved in a very slight excess of dilute hydrochloric acid, a liquid is obtained from which crystals moderately soluble in water, are deposited on standing over sulphuric acid; when air-dry, contain $C_{44}H_{50}N_2O_{12} \cdot 2HCl \cdot 2H_2O$.

0.9110 gram lost at 100° 0.0415 = 4.55 per cent.
 Calculated 3.97 „

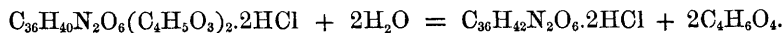
0.8190 gram of dry substance gave 0.2700 $AgCl$ $Cl=8.16$ per cent.
 Calculated for $C_{44}H_{50}N_2O_6 \cdot 2HCl$... = 8.15 „
 With platinic chloride this hydrochloride throws down heavy flakes of a platinum salt; of this

0.6350 gram gave 0.1035 Pt = 16.29 per cent.
 Calculated for $C_{44}H_{50}N_2O_6 \cdot 2HCl \cdot PtCl_4$ = 16.32 „

All attempts to prepare metallic salts of this substance proved failures; an ammoniacal solution mixed with silver nitrate, and evaporated over

sulphuric acid, gave rise to the partial reduction of the silver, but no silver salt could be obtained; an alcoholic solution of the substance yielded no precipitate with barium, iron, lead, or other metallic salts.

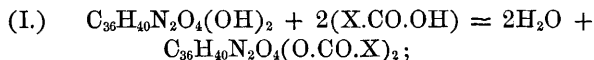
Yet further to fix the composition of this product, the anhydrous hydrochloride was heated with water, and slightly more of a standard potash-solution than would be required to neutralise the succinic acid formed in virtue of the reaction



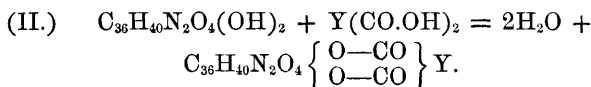
0.981 gram of hydrochloride thus generated enough succinic acid to saturate 8.15 c.c. of standard solution, of which 1 c.c. = 0.03185 gram of succinic acid, *i.e.*, generated 0.2596 gram of acid = 26.46 per cent.

Calculated for above equation, 27.09 per cent.

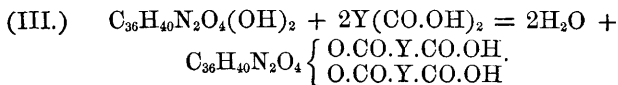
It is hence manifest that the action of succinic acid on codeine is not that which would be anticipated from the results hitherto obtained with monobasic organic acids, indicated by the formula $\text{X} \cdot \text{CO} \cdot \text{OH}$; these acids (*e.g.*, acetic, butyric, benzoic) give rise to the following reaction,



whence it might be anticipated that a dibasic acid, $\text{Y}(\text{CO} \cdot \text{OH})_2$, would give rise to the reaction,

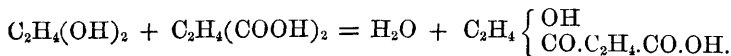


The above results, however, show that the action of succinic acid is of the form



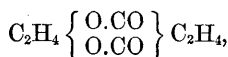
whilst the experiments described below seem to indicate that this, and not (II) is the general form of such reaction.

It is noteworthy that the product thus formed is analogous to the ethylene-succinic acid or glycol-succinic acid of Lourenço (*Ann. Chem. Pharm.*, cxv, 358), formed by the parallel reaction



Lourenço's product, however, is a glycol-derivative in which only

half the hydroxyl is substituted, whilst in the codeine product the whole is thus exchanged: Lourenço's product, moreover, readily formed a silver salt, and of course exhibited no tendency to combine with acids, these differences being due to the absence of nitrogen. At a higher temperature (near 300°) Lourenço obtained the body



corresponding with the hypothetically probable substance formed by equation (II); the inability of codeine to withstand such a temperature precludes the attempt to form such a codeine product, or the allied body, $\text{C}_{36}\text{H}_{40}\text{N}_2\text{O}_2 \left\{ \begin{array}{c} \text{O.CO.C}_2\text{H}_4.\text{CO} \\ \text{C.CO.C}_2\text{H}_4.\text{CO} \end{array} \right\} \text{O}$.

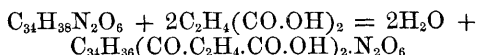
Action of Succinic Acid on Morphine.

Morphine was treated with succinic acid in the way above described with a precisely similar result: rather more colouring matter is formed than with codeine, so that the yield of pure product is less through the greater loss by fractional precipitation; the final fraction just precipitated by ammonia or by sodium carbonate should be filtered off quickly, otherwise it may be contaminated with unchanged morphine, which is not instantaneously precipitated in the liquor, especially if stirring with a glass rod be avoided as far as practicable. After crystallisation from boiling 80 per cent. alcohol, crystals are formed, much resembling the codeine product; they are insoluble in water, ether, and benzene, and give no blue colour with ferric chloride; they contain $\text{C}_{34}\text{H}_{36}\text{N}_2\text{O}_4(\text{C}_4\text{H}_5\text{O}_3)_2 \cdot 8\text{H}_2\text{O}$.

1.4960 gram of a dry substance lost at 100° 0.2360 = 15.77 p. c.
 Calculated. 15.75 ,,
 0.3240 gram of dry substance gave 0.7770 CO₂, and 0.1815 H₂O.

	Calculated.		Found.
C ₄₂	504	65.45	65.39
H ₄₆	46	5.97	6.23
N ₂	28	3.64	—
O ₁₂	192	24.94	—
<hr/>	<hr/>	<hr/>	
C ₃₄ H ₃₆ (CO.C ₂ H ₄ .CO.OH) ₂ N ₂ O ₆	770	100.00	

Hence this product is formed by the reaction



With hydrochloric acid this body forms a crystallisable salt readily soluble in water; from this the platinum salt was made.

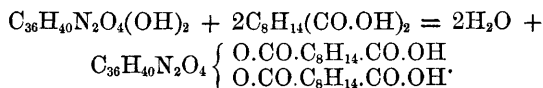
0.5500 gram gave 0.0905 Pt. = 16.45 per cent.

Calculated for $C_{34}H_{36}(C_4H_5O_3)_2N_2O_6 \cdot 2HCl \cdot PtCl_4$ 16.71 ,,

It was not found practicable to form metallic salts; an ammoniacal solution of the substance reduces silver salts quickly, but forms no ammonia salt by evaporation over sulphuric acid; alkalis dissolve the substance with great facility, but it was not found practicable to isolate the salts thus formed.

Action of Camphoric Acid on Codeine.

When codeine and twice its weight of camphoric acid are heated together to 180° for 3—4 hours, a reaction is produced parallel with that above described, viz.,



The resulting product is best isolated in the following way: the cooled and perfectly hard mass is powdered, and added in small portions at a time, to boiling very dilute hydrochloric acid, and the solution filtered hot; on cooling, a mixture of crystals of camphoric acid, and gelatinous masses of the hydrochloride of the new product, separate; these are drained and washed, and dissolved in dilute ammonia, preferably alcoholic; on long standing over sulphuric acid, crystals of the new product separate as the ammonia passes off. The crude product may also be dissolved at first in hot dilute ammonia, and the filtered liquid left over sulphuric acid for a few days; the mass then becomes a thick jelly, bearing an absurd resemblance to glue; on heating, however, the gelatinous mass becomes crystalline, and can be filtered, drained, and crystallised from boiling alcohol; or a little alcohol can be added to the gelatinous mass, and the whole heated till a clear solution is obtained; on cooling, nearly white crystals separate. After recrystallisation from alcohol, and standing in the air till constant in weight, these gave the following numbers. Specimen crystallised from dilute alcohol—

0.6140 gram lost 0.0810 gram at 100° .. = 13.19 per cent.

Calculated for $C_{36}H_{40}(C_{10}H_{15}O_3)_2N_2O_6 \cdot 8H_2O$ = 13.02 ,,

Another specimen crystallised from 80 per cent. alcohol—

1.5920 grams lost 0.1545 gram at 100° .. = 9.71 per cent.

Calculated for $C_{36}H_{40}(C_{10}H_{15}O_3)_2N_2O_6 \cdot 6H_2O$ = 10.09 ,,

0.2975 gram of dried substance gave 0.7625 CO_2 , and 0.2090 H_2O .

	Calculated.		Found.
C ₃₆	672	69·85	69·89
H ₇₀	70	7·28	7·80
N ₂	28	2·91	—
O ₁₂	192	19·96	—
<hr/>	<hr/>	<hr/>	
C ₃₆ H ₄₀ (C ₁₀ H ₁₅ O ₃) ₂ N ₂ O ₆	962	100·00	

When treated with dilute hydrochloric acid, these crystals form a non-crystalline mass, very sparingly soluble in cold water; on boiling with water a solution is obtained, from which gelatinous flakes separate on cooling; from hot dilute alcohol (about 50 per cent.) crystals form on cooling and standing; after draining and washing slightly with water, and standing in the air till constant in weight, these gave the following numbers:—

0·3965 gram lost at 100° 0·0365 gram = 9·21 per cent.

Calculated for C₃₆H₄₀N₂O₆(C₁₀H₁₅O₃)₂·2HCl·6H₂O = 9·41 ,,

0·3600 gram of anhydrous substance burnt with quicklime gave—

0·0975 AgCl Cl = 6·70 per cent.

Calculated..... = 6·86 ,,

From this hydrochloride a gelatinous platinum salt was made; after drying over sulphuric acid, and finally at 100°,

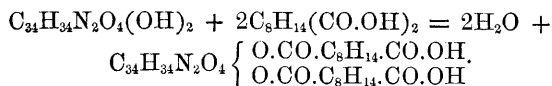
0·7640 gram gave 0·1090 Pt = 14·29 per cent.

Calculated for C₃₆H₄₀N₂O₆(C₁₀H₁₅O₃)₂·2HCl·PtCl₄ = 14·37 ,,

The yield of camphoric codeine-derivative obtained is much smaller than that of the succinic codeine-product above described; the greater part of the codeine employed remains wholly unaltered.

Action of Camphoric Acid on Morphine.

On treating morphine in the way above described, a dark-coloured mass results, containing only a minute quantity of the morphine derivative corresponding with the camphoric-codeine product, and formed by the reaction



This substance was formed in too small quantity for complete examination; by dissolving the product of the action in ammonia, and leaving it to stand over sulphuric acid, nothing separates save a little ordinary morphine; on adding to the filtrate a slight excess of

hydrochloric acid, non-crystalline flakes of the hydrochloride of the new product separate; these are soluble in alcohol and in cold alkalis, but only very sparingly in cold water, and not much more so in boiling water. This hydrochloride can also be obtained by treating the pulverised product of the heating together of morphine and twice its weight of camphoric acid with ether, so as to dissolve out most of the camphoric acid and anhydride formed, and then treating again with dilute hydrochloric acid so as to dissolve out morphine.

From the hydrochloride a platinum salt was made by fractional precipitation to remove colouring matters; the second precipitate was gelatinous, and gave the following numbers after drying over sulphuric acid, and finally at 100°:—

0.4490 gram gave 0.0645 Pt = 14.37 per cent.
 Calculated for $C_{34}H_{34}(C_{10}H_{15}O_3)_2N_2O_6 \cdot 2HCl \cdot PtCl_4$ = 14.67 ,,

Action of Tartaric Acid on Codeine.

Codeine was heated for 3—4 hours with twice its weight of tartaric acid dried at 150° to 180°—190°. Water was given off during the heating, and the mass, which was readily fused at first, became viscid and almost solid.

On treating the product with water, the greater part dissolved; the only base present in the solution, however, was unaltered codeine; a small quantity of insoluble substance was left, which, with hydrochloric acid alone, refused to dissolve, but with alcoholic hydrochloric acid gave a clear brownish solution. All attempts to obtain anything crystalline from this liquid failed; addition of water precipitated flakes possessing a structure closely resembling that of tetracodeine under the microscope, consisting of coalesced globules; addition of carbonate of soda in slight excess, and then of water, also precipitated flakes, destitute in this case of chlorine, whereas the flakes precipitated from the hydrochloric acid solution in alcohol contained chlorine.

One specimen of the chlorinated flakes gave the following numbers, agreeing approximately with those calculated for a basic hydrochloride of a body formed from codeine and tartaric acid, with elimination of water.

Calculated for $(4C_{36}H_{42}N_2O_6 + 4C_4H_6O_6 - 8H_2O) \cdot 3HCl$.	Found.	
Carbon.....	64.89	65.12
Hydrogen.....	6.05	6.16
Chlorine.....	3.60	3.58

This basic hydrochloride dissolved readily in ammonia and alkalis, just as the camphoric codeine-product; addition of hydrochloric acid reprecipitated chlorinated flakes.

On adding excess of alcoholic platonic chloride to the alcoholic solution of this hydrochloride (also containing excess of hydrochloric acid) no precipitate was formed; but on further adding water, a platinum salt was thrown down, containing 9.05 per cent. of platinum.

The normal tetracodeine derivative, $(\bar{C}_4 + 4C_4H_6O_6 - 8H_2O).8HCl$. $4PtCl_4$, would require 17.56 per cent. From these results, and the physical characters of the body and its salts, it is evident that it is a tartaric tetracodeine-derivative; and that, like acetyl-tetracodeine (p. 313 of this volume), this derivative is deficient in acid-combining powers.

The marked difference in the action on codeine between succinic acid (which does not appreciably polymerise the codeine, and converts a large portion into succinic codeine-product) and tartaric acid (which partially polymerises, and gives no tartaric derivative of non-polymerised codeine) is noteworthy.

Action of Oxalic Acid on Codeine.

Codeine and twice its weight of oxalic acid dried at 110° were intimately mixed and heated in a paraffin bath to 140° — 150° for three hours; the mass fused to a clear liquid, which gave off, with great rapidity, bubbles of a mixture of about equal volumes of carbon oxide and carbon dioxide, together with steam and acid vapours; the residue gradually acquired the property of yielding an amorphous precipitate with carbonate of soda after solution in water, and thickened somewhat towards the end. The product of the action was dissolved in water, and exactly precipitated by carbonate of soda; the precipitate mostly dissolved in ether, a small amount of an amorphous coloured mass being left insoluble; the ethereal solution, on spontaneous evaporation, deposited white crystals, which on examination proved to be nothing but *dicodeine*, identical with that obtained by the action of dilute sulphuric or phosphoric acid on codeine; the mother-liquors of these crystals contained a non-crystalline base, agreeing in properties with *tricodeine*, whence the substance insoluble in ether probably consisted of *tetracodeine*; no appreciable amount of any oxalic derivative analogous to the bodies formed with succinic and camphoric acids could be isolated.

The dicodeine thus obtained gave the following numbers:—

0.2615 gram lost 0.0155 gram at $100^\circ = 5.93$ per cent.

Calculated for $C_{72}H_{84}N_4O_{12}.4H_2O = 5.68$ per cent.

0.2330 gram of dried product gave 0.6140 CO_2 , and 0.1560 H_2O .

	Calculated.		Found.
C ₇₂	864	72·24	71·86
H ₈₄	84	7·02	7·44
N ₄	56	4·68	—
O ₁₂	192	16·06	—
<hr/>	<hr/>	<hr/>	<hr/>
C ₇₂ H ₈₄ N ₄ O ₁₂	1196	100·00	

The hydrochloride crystallised readily, exactly resembling that prepared by means of sulphuric and phosphoric acids.

0·3780 gram of substance dried at 100° gave 0·03952 Cl (volumetric).

Cl = 10·45 per cent.

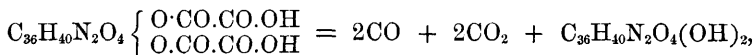
Calculated 10·58 „ „

The syrupy mother-liquors of this hydrochloride utterly refused to crystallise, and exactly resembled the tricodeine hydrochloride obtainable by the action of dilute sulphuric acid or of zinc chloride on codeine; and notably this product gave the reaction characteristic of tricodeine with ferric chloride, viz., no coloration just at first, but development of a dark dirty purple on standing; with nitric acid it gave a deep blood-red colour; converted into platinum salt it gave the following numbers:—

0·5625 gram dried at 100° gave 0·1110 Pt = 19·73 per cent.

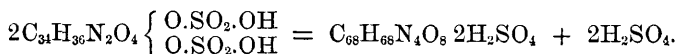
Calculated 19·55 „ „

It thus results that oxalic acid acts on codeine quite differently from its higher homologue, succinic acid, polymerisation of the codeine being the only noticeable end-result. It is extremely probable that an oxalic derivative is actually first formed, and that this immediately splits up into carbon oxide and dioxide, and codeine, thus:—



the codeine polymerising whilst in the nascent state; probably, also, similar reactions occur with the inorganic acids, *e.g.*, sulphuric and phosphoric acids, *i.e.*, with sulphuric acid for example, probably a body,

$\text{C}_{36}\text{H}_{40}\text{N}_2\text{O}_4 \left\{ \begin{array}{l} \text{O} \cdot \text{SO}_2 \cdot \text{OH} \\ \text{O} \cdot \text{SO}_2 \cdot \text{OH} \end{array} \right.$ is temporarily formed, and this, in presence of water, forms sulphuric acid and codeine, which polymerises whilst nascent. When sulphuric acid acts on morphine a similar action in all probability takes place; a portion, however, of the sulphuric derivative thus formed rearranges itself, producing “apomorphine” sulphate, and sulphuric acid.



It has not, however, been found practicable to isolate these probable intermediate compounds.

It is noticeable that with oxalic acid and codeine the yield of the two higher polymerides is comparatively small, so that dicodeine can be directly crystallised from the ethereal solution of the crude bases; much more tricodeine is formed by the action of sulphuric acid, so that the crude ethereal solution will not deposit crystals, a circumstance which led both Armstrong (who first obtained dicodeine, though, probably, in an impure state—this Journal [2], ix, 56) and Wright to regard the base as non-crystalline, an error pointed out by us in a former paper (*ibid.* [2], xiii, 312).

Action of Oxalic Acid on Morphine.

In the hope that this action might lead to the isolation of the missing morphine polymeride, *dimorphine*, morphine was heated to 140°—150°, for 3 hours, with three times its weight of oxalic acid dried at 110°; much carbon oxide and dioxide were liberated, and a considerable amount of higher morphine polymerides were formed; the desired body, however, could not be isolated from the products of the action. On adding sodium carbonate to the aqueous solution of the resulting mass, an amorphous white precipitate was thrown down, becoming green on standing; this was partially soluble in ether, the greater part being insoluble in that menstruum; the ethereal extract refused to crystallise by spontaneous evaporation, and yielded a hydrochloride which dried up to a varnish without depositing any crystals: hence “apomorphine” was not a product of the action. This varnish-like hydrochloride corresponded in all respects with the trimorphine hydrochloride obtained by Mayer and Wright by the action of dilute sulphuric acid on morphine.

With ferric chloride it yielded a coloration of a bluish purple at first, changing to reddish-purple in a few seconds, and speedily becoming dirty purplish-red; with nitric acid it gave a blood-red coloration.

The following numbers were obtained:—

0.2785 gram gave 0.6390 CO₂, and 0.1655 H₂O.

0.5125 „ „ 0.2320 AgCl.

	Calculated.		Found.
C ₁₀₂	1224	63.46	62.57
H ₁₂₀	120	6.22	6.60
N ₆	84	4.35	—
O ₁₈	288	14.93	—
Cl ₃	213	11.04	11.18
C ₁₀₂ H ₁₁₄ N ₆ O ₁₈ .6HCl	1929	100.00	

If the solution of the hydrochloride obtained by shaking up the ethereal solution of the base with hydrochloric acid, and leaving it over sulphuric acid, be strongly acid, the excess of hydrochloric acid present acts on the trimorphine, producing a considerable amount of the chlorinated derivative, $C_{102}H_{112}Cl_2N_6O_{16}.6HCl$, described in a former paper (this Journal, 1873, p. 226); to obtain trimorphine hydrochloride in a pure state, therefore, it is essential to shake up the ethereal solution with slightly less hydrochloric acid than is equivalent to the base in solution, and then to render the aqueous liquid exactly neutral by cautious addition of much-diluted hydrochloric acid.

Simultaneously with trimorphine, much tetramorphine is formed, being left undissolved by ether; this was recognised by its physical properties, and by the precipitation of the hydrochloride from an aqueous solution containing but little free acid by addition of strong hydrochloric acid. A specimen thus prepared by fractional precipitation gave the following numbers:—

0.3250 gram gave 0.1445 AgCl.	Chlorine = 11.01 per cent.
	Calculated 11.04 „ „
