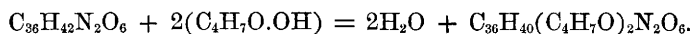


IV.—*Action of the Organic Acids and their Anhydrides on the Natural Alkaloids.* Part II. *Butyryl and Benzoyl derivatives of Morphine and Codeine.*

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§ 1. *Action of Butyric Acid on Codeine.*

When anhydrous codeine and twice its weight of butyric acid are gently boiled together for five or six hours, *dibutyryl-codeine* is formed in virtue of the reaction—



On evaporating off the excess of acid on the water-bath, dissolving the residue in water, and adding sodium carbonate, a tarry mass is precipitated, which must be dissolved in dilute hydrochloric acid and reprecipitated by sodium carbonate to remove any traces of unaltered codeine mechanically carried down. The ethereal solution of the purified base does not crystallise by spontaneous evaporation, even when a crystal of some analogously constituted body (*e.g.*, diacetyl-codeine), is added to the saturated solution, the dibutyryl-codeine only making its appearance as a varnish-like mass; even when the base was regenerated from a specimen of hydrochloride purified by several recrystallisations, it was found impracticable to obtain it in a crystalline condition by any means whatever. On adding hydrochloric acid to the varnish-like base, or to its ethereal solution, a well-crystallised hydrochloride is produced; of this 1.545 gram dried in blotting-paper lost at 100° 0.183 gram = 11.84 per cent.

The formula, $\text{C}_{36}\text{H}_{40}(\text{C}_4\text{H}_7\text{O})_2\text{N}_2\text{O}_6.2\text{HCl}.6\text{H}_2\text{O}$, requires 11.75 per cent.

0.2730 gram of hydrochloride dried at 100° gave 0.6535 CO_2 and 0.177 H_2O .

0.4280 gram of hydrochloride dried at 100° gave 0.1510 AgCl .

	Calculated.		Found.
C ₄₄	528	65·11	65·28
H ₅₆	56	6·91	7·20
Cl ₂	71	8·75	8·73
N ₂	28	3·45	—
O ₆	128	15·78	—
<hr/> C ₃₆ H ₄₀ (C ₄ H ₇ O) ₂ N ₂ O ₆ .2HCl <hr/>	<hr/> 811 <hr/>	<hr/> 100·00 <hr/>	<hr/> — <hr/>

The platinum salt gave the following numbers:—

0·5370 gram gave 0·0920 Pt = 17·13 per cent.

The formula, C₃₆H₄₀(C₄H₇O)₂N₂O₆.2HCl.PtCl₄, requires 17·18 per cent.

Dibutyryl-codeine differs from diacetyl-codeine, not only in being non-crystalline (the latter base being most readily crystallised from ether), but also in the amount of water of crystallisation taken up by the hydrochloride, the former base yielding a salt containing six proportions of water, while the latter contains only four.

§ 2. Action of Butyric Anhydride on Codeine.

From the former results obtained with acetic acid and anhydride, it would appear, *a priori*, probable that butyric anhydride would yield the same dibutyryl-codeine as that obtained by the action of butyric acid; and in point of fact this is the case: by heating codeine to 140° with excess of butyric anhydride, the dibutyryl-codeine above described is produced. The hydrochloride obtained as above described gave the following numbers:—

1·144 gram, dried in blotting-paper, lost at 100°, 0·1480 gram = 12·94 per cent.

The formula, C₃₆H₄₀(C₄H₇O)₂N₂O₆.2HCl.6H₂O, requires 11·75 per cent.

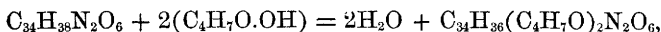
0·3185 gram of platinum-salt gave 0·0550 Pt = 17·26 per cent.

Calculated percentage = 17·18 per cent.

All attempts to obtain the free base in the crystalline state proved fruitless.

§ 3. Action of Butyric Acid on Morphine.

When anhydrous morphine is heated to 130° or higher for 5—6 hours with twice its weight of butyric acid, a reaction occurs precisely similar to that produced by the action of acetic acid (Part I), viz.:—



the only difference observable being that the hydrochloride of the resulting dibutyryl-morphine is far more soluble and crystallises less readily than that of the corresponding α -diacetyl-morphine.

On treating the product of the reaction with ammonia or sodium carbonate and ether, an ethereal solution is obtained which, if evaporated quickly, dries up to a varnish-like mass; by slow spontaneous evaporation, however, crystals are sometimes formed, and on bringing a crystal so produced into contact with the sticky resinous product formed in other cases, the whole becomes crystalline. The crystals thus produced appear to be anhydrous when air-dry. They lose in weight slightly, at 100° , however, apparently from decomposition. In three experiments, 0.22, 0.44, and 0.51 per cent. was thus lost, whilst the dried substances gave on analysis numbers slightly in excess of the calculated values.

After several recrystallisations from ether, dibutyl-morphine gives no coloration with ferric chloride; it is, however, difficult to arrive at this state of purity, as a small quantity either of some decomposition-product formed on standing, or of some substance formed simultaneously with the dibutyl morphine (β -dibutyl morphine?), pertinaciously adheres to the crystals, and communicates to them the power of striking a faint blue with ferric chloride.

The following numbers were obtained after drying at 100° :—

Specimen A. 0.3030 gram gave 0.7935 CO_2 and 0.2020 H_2O .

„ B. 0.3240 gram gave 0.8530 CO_2 and 0.2230 H_2O .

	Calculated.		Found.	
			(A.)	(B.)
C_{42}	504	71.00	71.43	71.80
H_{50}	50	7.04	7.41	7.64
N_2	28	3.94	—	—
O_8	128	18.02	—	—
<hr/> $\text{C}_{34}\text{H}_{36}(\text{C}_4\text{H}_7\text{O})_2\text{N}_2\text{O}_6$ <hr/>	<hr/> 710 <hr/>	<hr/> 100.00 <hr/>		

When exactly neutralised with dilute hydrochloric acid, this dibutyl-morphine forms a syrupy liquid, which sometimes dries up to a gummy mass without crystallising, and sometimes solidifies to a mass of radiating crystals very soluble in water. The same behaviour has also been noticed in the case of tetracetyl-morphine hydrochloride.

After drying at 100° , the following numbers were obtained; the slight excess of carbon found denoting a minute amount of decomposition, just as with the free base :—

0.6020 gram gave 0.2190 AgCl .

0.6390 „ 0.2330 „

0.4490 „ 1.0645 CO_2 and 0.2725 H_2O .

	Calculated.		Found.	
C ₄₂	504	64.37	64.65	
H ₅₂	52	6.64	6.74	
Cl ₂	71	9.07	8.99	9.02
N ₂	28	3.57		
O ₈	128	16.35		
<hr/> C ₃₄ H ₃₆ (C ₄ H ₇ O) ₂ N ₂ O ₆ .2HCl		<hr/> 783	<hr/> 100.00	

The platinum salt gave the following numbers:—

0.5970 gram gave 0.1055 Pt = 17.67 per cent.

The formula, C₃₄H₃₆(C₄H₇O)₂N₂O₆.2HCl.PtCl₄ requires 17.60 per cent.

The ethereal mother-liquors from which the dibutryl-morphine has separated, contain a small quantity of a non-crystalline base, which gives a blue coloration with ferric chloride: probably this is the butryl correlative of the analogous product formed together with α -diacetyl morphine by the action of acetic acid on morphine (Part I.).

Separated as far as possible from the crystalline base by spontaneous evaporation almost to dryness, rubbing up with a few drops of absolute alcohol (which only dissolves the crystalline base slowly) and quick filtration, a viscid liquid was obtained which utterly refused to crystallise; converted into platinum salt, it gave the following numbers:—

0.6545 gram gave 0.1130 Pt = 17.27 per cent.

Calculated for C₃₄H₃₆(C₄H₇O)₂N₂O₆, 2HCl, PtCl₄ = 17.60 „

Hence it appears that this non-crystalline base is isomeric with the crystalline one: in all probability the two are the butryl correlatives α - and β -diacetyl morphine respectively.

§ 4. Action of Butyric Anhydride on Morphine.

Anhydrous morphine was heated to 140° for three hours with twice its weight of butyric anhydride; the product was dissolved in warm water, filtered from a little tarry decomposition-product, and precipitated by sodium carbonate: the precipitate on treatment with ether, yielded an ethereal solution from which no crystals could be obtained by evaporation, a varnish-like mass only resulting, like dibutryl codeine; unlike this product, however, the base, *tetrabutryl-morphine*, refused to yield a crystalline hydrochloride; the *neutral* solution of the hydrochloride drying up to a gummy mass differing from the hydrochlorides of β -diacetyl-morphine only in that it gave no blue coloration with ferric chloride. The following numbers were obtained:

0·3270 gram gave 0·7745 CO₂ and 0·2120 H₂O.

0·3940 gram treated volumetrically gave 0·0301 Cl.

0·5430 gram of a different specimen treated volumetrically gave 0·0422.

	Calculated.		Found.
C ₅₀	600	65·01	64·60
H ₆₄	64	6·93	7·20
Cl ₂	71	7·69	7·64 7·77
N ₂	28	3·03	—
O ₁₀	160	17·34	—
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C ₃₄ H ₃₄ (C ₄ H ₇ O) ₄ N ₂ O ₆ ·2HCl	923	100·00	

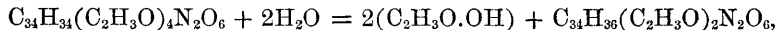
Converted into platinum salt, the following numbers were obtained:—

0·7295 gram gave 0·1150 gram Pt = 15·76 per cent.

The formula, C₃₄H₃₄(C₄H₇O)₄N₂O₆·2HCl·PtCl₄, requires 15·65 per cent.

§ 5. *Action of Water on Tetrabutryl-morphine.*

It has been shown in Part I that tetracetyl-morphine, on boiling with water, breaks up thus:—



forming the same diacetyl morphine (the α -modification) that is produced by the action of acetic acid on morphine. Precisely the same result is produced in the case of tetrabutryl-morphine, with this difference, that the action is very much slower, and that in order to facilitate it, it is necessary to use a mixture of alcohol and water (about equal bulks) so as to retain the base in solution. Even then 12 hours', or more, incessant boiling (with an inverted condenser attached), is required before any considerable amount of dibutryl-morphine is formed. On distilling off the alcohol, an aqueous liquor is obtained, containing the butyrates of dibutryl-morphine and morphine (the latter generated by the further splitting up of the dibutryl-morphine), and a tarry precipitate of unaltered tetrabutryl-morphine: this is filtered off and treated over again. On treating the aqueous solution with sodium carbonate and ether, an ethereal solution is obtained, from which dibutryl-morphine may be obtained in crystals by slow spontaneous evaporation. This base appears to be in all respects identical with that formed by the action of butyric acid on morphine; the base when sufficiently purified, gives no coloration to ferric chloride. By spontaneous evaporation its ethereal solution deposits crystals which appear to be anhydrous, but which lose a small amount on heating to 100°, just as

the product from the action of butyric acid on morphine, probably from incipient decomposition: after drying at 100° —

0.3370 gram gave 0.8850 CO_2 and 0.2290 H_2O .

	Calculated.		Found.
C_{42}	504	71.00	71.62
H_{50}	50	7.04	7.55
N_2	28	3.94	—
O_8	128	18.02	—
<hr/>			
$\text{C}_{34}\text{H}_{36}(\text{C}_4\text{H}_7\text{O})_2\text{N}_2\text{O}_6$	710	100.00	

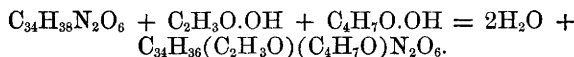
The hydrochloride, in one experiment, dried up to a non-crystalline gum, in another, to a mass of radiating crystals very soluble in water; the platinum salt gave these numbers—

0.7700 gram gave 0.1350 Pt = 17.53 per cent.

The formula, $\text{C}_{34}\text{H}_{36}(\text{C}_4\text{H}_7\text{O})_2\text{N}_2\text{O}_6 \cdot 2\text{HCl} \cdot \text{PtCl}_4$, requires 17.60 per cent.

§ 6. *Acetyl-butryl-morphine.*

When anhydrous morphine is boiled for several hours with twice its weight of a mixture of equivalent quantities of acetic and butyric acids, acetyl-butryl-morphine is generated in virtue of the reaction—



On treating the product with sodium carbonate and ether, and agitating the ethereal solution of the base with enough hydrochloric acid to form a neutral liquid, a copious supply of crystals was obtained notably more soluble in water than α -diacetyl morphine hydrochloride; after drying at 110° , they gave the following numbers:—

0.5695 gram gave 0.2185 AgCl: chlorine = 9.49 per cent.

The formula, $\text{C}_{34}\text{H}_{36}(\text{C}_2\text{H}_3\text{O})(\text{C}_4\text{H}_7\text{O})\text{N}_2\text{O}_6 \cdot 2\text{HCl}$, requires 9.40 per cent.

These crystals were recrystallised from boiling water; but unfortunately it was found that they were decomposed by the treatment; crystals were deposited on cooling, consisting chiefly of α -diacetyl-morphine hydrochloride, whilst the mother-liquors contained much of a very soluble butyrylated morphine: after three successive recrystallisations from hot water, the crystals finally obtained were nothing but α -diacetyl-morphine hydrochloride; they lost, at 120° , 13.35 per cent., the calculated amount (for $6\text{H}_2\text{O}$) being 12.93; and on saponification by potash and distillation with enough sulphuric acid to liberate just *half*

the acid thus formed, a distillate was obtained from which a barium salt was formed containing

Barium	53.5 per cent.
Calculated for acetate	53.7 „

Had any acetyl-butryl-morphine been present in the crystals, this barium salt would have contained all the butyric acid formed on saponification.

In another experiment, where a mixture of acids in which butyric acid greatly predominated was employed, a product was formed from which a crystalline hydrochloride was isolated as before; this gave the following numbers after one recrystallisation from warm (not boiling) water:—

0.9995 gram of air-dry salt lost, at 100°, 0.1590 = 15.91 per cent.

The formula, $C_{34}H_{36}(C_2H_3O)(C_4H_7O)N_2O_6 \cdot 2HCl \cdot 8H_2O$, requires 16.02 per cent.

0.3145 gram of dried substance gave 0.7280 CO_2 and 0.1885 H_2O .

0.4615 „ „ „ „ 0.1765 AgCl.

0.3775 „ „ „ „ 0.1445 „

0.4730 „ substance dried at 120° gave 0.1795 AgCl.

	Calculated.				Found.	
C_{40}	480	63.58	—	63.13	—	
H_{48}	48	6.36	—	6.66	—	
Cl_2	71	9.40	9.46	9.47	9.39	
N_2	28	3.71	—	—	—	
O_8	128	16.95	—	—	—	
$C_{34}H_{36}(C_2H_3O)(C_4H_7O)N_2O_6 \cdot 2HCl$	755	100.00				

The neutral liquid from which these crystals separated in the first instance, dried up to a gum-like mass which gave a blue coloration with ferric chloride, and contained—

Carbon, 63.75; chlorine, 9.16 per cent.

Dibutryl morphine requires carbon, 64.37; chlorine, 9.07 per cent., from which it appears that, as might be expected, the excess of butyric acid present gave rise also to dibutryl-morphine, or a mixture of isomeric dibutryl-morphine.

§ 7. Action of Benzoic Anhydride on Codeine.

Codeine was heated to 130° for four hours with rather more than its own weight of benzoic anhydride: the product dissolved sparingly in hot water, somewhat more readily in hot very dilute hydrochloric acid. The warm opalescent solution was precipitated by carbonate of soda; the precipitate was dissolved in warm dilute hydrochloric acid,

and again precipitated with sodium carbonate; and this precipitate was dissolved in ether. The ethereal solution gave, on evaporation, a copious crop of anhydrous crystals which yielded the following numbers on combustion:—

0.3110 gram gave 0.8525 CO₂ and 0.1780 H₂O.

	Calculated.		Found.
C ₅₀	600	74.44	74.76
H ₅₀	50	6.20	6.36
N ₂	28	3.48	—
O ₈	128	15.88	—
<hr/>		<hr/>	
C ₃₆ H ₄₀ (C ₇ H ₅ O) ₂ N ₂ O ₆	806	100.00	

This base, *dibenzoyl-codeine*, is very sparingly soluble in water both cold and hot; from a large bulk of boiling water it can be crystallised unchanged; when it is dissolved in very dilute warm hydrochloric acid, a clear solution is obtained; on cooling, this salt does not deposit crystals, but becomes an opalescent gelatinous mass, much resembling starch-paste or gelatinous silica; from a strong solution the hydrochloride separates as an amorphous tarry mass: it is, however, possible to obtain the hydrochloride in crystalline form by dissolving it in dilute slightly warm alcohol, and leaving the solution to cool slowly with constant stirring and rubbing: the crystals thus produced gave rise to nothing but a gelatinous mass when dissolved in warm water and allowed to cool. Dried in blotting-paper and exposed to the air until a constant weight was attained, they gave the following numbers:—

1.027 gram of air-dried substance lost 0.043 gram = 4.18 per cent

The formula, C₃₆H₄₀(C₇H₃O)₂N₂O₆.2HCl.2H₂O, requires 3.93 per cent.

The anhydrous salt gave the following numbers:—

0.3420 gram gave 0.8530 CO₂ and 0.1990 H₂O.

0.2800 gram estimated volumetrically gave 0.0225 Cl.

0.2990 gram gave 0.0970 AgCl.

	Calculated.		Found.	
C ₅₀	600	68.26	68.02	—
H ₅₂	52	5.92	6.47	—
Cl ₂	71	8.08	8.03	8.03
N ₂	28	3.18	—	—
O ₈	128	14.56	—	—
<hr/>		<hr/>		
C ₃₆ H ₄₀ (C ₇ H ₅ O) ₂ N ₂ O ₆ .2HCl	879	100.00		

The platinum salt gave the following numbers:—

0.3080 gram gave 0.0500 Pt = 16.23 per cent.

The formula, $C_{36}H_{40}(C_7H_5O)_2N_2O_6 \cdot 2HCl \cdot PtCl_4$, requires 16.21 per cent.

This platinum salt, like the benzoylated morphine products described in the next sections, differs from the acetylated platinum salts and most platinum salts of morphine and codeine derivatives, in being much more readily soluble in alcohol than in water, the converse being usually the case.

§ 8. Action of Benzoic Anhydride on Morphine.

Morphine was heated to about 130° for three or four hours with twice its weight of benzoic anhydride; the product dissolved in hot dilute hydrochloric acid, was precipitated by sodium carbonate, and treated with ether; on evaporation, anhydrous crystals of *tetrabenzoylmorphine* separated: these gave no colour reaction with ferric chloride.

0.2960 gram gave 0.8220 CO_2 and 0.1530 H_2O .

	Calculated.		Found.
C_{62}	744	75.46	75.73
H_{54}	54	5.47	5.74
N_2	28	2.84	—
O_{10}	160	16.23	—
<hr/>			
$C_{34}H_{34}(C_7H_5O)_4N_2O_6$	986	100.00	

The hydrochloride of this base is very sparingly soluble in cold water; it possesses properties precisely similar to those of dibenzoyl-codeine, saving that no artifice has hitherto been successful in obtaining it in a crystallised condition.

0.4775 gram gave 0.0312 gram Cl (volumetric).

0.3810 „ „ 0.9845 CO_2 and 0.2000 H_2O .

	Calculated.		Found.
C_{62}	744	70.26	70.47
H_{56}	56	5.29	5.83
Cl_2	71	6.70	6.53
N_2	28	2.64	—
O_{10}	160	15.11	—
<hr/>			
$C_{34}H_{34}(C_7H_5O)_4N_2O_6 \cdot 2HCl$	1059	100.00	

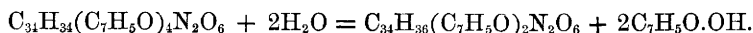
The platinum salt, made by adding platonic chloride to a warm aqueous solution of the salt, gave these numbers:—

0.2440 gram gave 0.0345 Pt. = 14.14 per cent.

The formula $C_{34}H_{34}(C_7H_5O)_4N_2O_6 \cdot 2HCl \cdot PtCl_4$ requires 14.13 „

§ 9. *Action of Water on Tetrabenzoyl-morphine.*

Tetrabenzoyl morphine is somewhat less readily acted on by boiling water than tetrabutyl-morphine (which as above shown is less readily attacked than tetracetyl-morphine); when boiled with a mixture of about equal volumes of alcohol and water, as described in § 5, for 48 hours consecutively, it partially undergoes the following reaction, whereby dibenzoyl-morphine is generated apparently identical with that formed by the direct action of benzoic acid on morphine (§ 10).



The production of benzoic acid in this way was verified by treating the resulting liquid (after distillation of alcohol) with hydrochloric acid and ether, when benzoic acid was dissolved out giving the ordinary qualitative tests. Carbonate of soda threw down from the acidified solution a small amount of precipitate; on agitating this with ether, an ethereal solution was obtained, which yielded a mixture of the hydrochlorides of tetrabenzoyl-morphine, and dibenzoyl-morphine; the latter crystallised in minute crystals on cooling the slightly warm aqueous solution; it was, however, found difficult to obtain this free from tetrabenzoyl-morphine hydrochloride, which does not crystallise, forming a tarry mass; the platinum salt finally obtained gave the following numbers, showing that a small quantity of tetrabenzoyl-morphine platinochloride was also present.

0.8805 gram gave 0.1400 gram Pt =	15.90 per cent.
Dibenzoyl morphine platino-chloride requires	16.60 „
Tetrabenzoyl „ „ „ „	14.13 „

§ 10. *Action of Benzoic Acid on Morphine.*

Anhydrous morphine was heated for seven hours to about 160° with twice its weight of benzoic acid; the product was dissolved in warm dilute hydrochloric acid and precipitated by carbonate of soda (which only gave a very trifling precipitate, morphine being not instantaneously thrown down by this reagent, at any rate from solutions not too concentrated). On treating the mass with ether a minute portion was dissolved; the ethereal solution yielded a tarry mass on agitation with a few drops of hydrochloric acid, and this, when dissolved in hot water, gave white crystals on cooling, very sparingly soluble and apparently identical with those described in the previous section. The quantity of these being too small for experiment, they were converted into platinum salt, of which

0.4005 gram gave 0.0670 Pt	= 16.73 per cent.
The formula $\text{C}_{34}\text{H}_{36}(\text{C}_7\text{H}_5\text{O})_2\text{N}_2\text{O}_6.2\text{HCl.PtCl}_4$ requires	16.60 „

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The product of the action of benzoic anhydride on tetracetyl morphine was precipitated by carbonate of soda and treated with ether; by spontaneous evaporation crystals were formed. A portion of these crystals and the last few drops of mother-liquor (representing about one-twentieth of the whole) were converted into platinum salts and examined with the following results:—

0.3585 gram of salt from crystals gave	0.0620 Pt = 17.29 p.c.
0.5040 " " mother-liquors gave	0.0830 16.46 "
Tetracetyl-morphine platinochloride requires	17.17 "
Diacetyl-dibenzoyl-morphine " "	15.50 "
Tetrabenzoyl-morphine " "	14.13 "

In the same way the product of the action of acetic anhydride on tetrabenzoyl morphine was converted into the free base; the ethereal solution of this, however, did not crystallise spontaneously; it was therefore converted into hydrochloride by treatment with warm dilute hydrochloric acid. Most of the base became converted into an almost insoluble tarry hydrochloride, resembling in all respects tetrabenzoyl morphine hydrochloride; a minute portion, however, dissolved. These two portions were converted into platinum salts and examined with the following results:—

0.6800 gram of salt from insoluble hydrochloride gave
0.1015 Pt = 14.92 per cent.
0.0760 gram of salt from soluble hydrochloride gave
0.0110 Pt = 14.47 per cent.

Tetrabenzoyl-morphine	requires platinum = 14.13 per cent.
Diacetyl-dibenzoyl-morphine " "	15.50 "
Tetracetyl-morphine " "	17.17 "

The physical characters of the resulting hydrochloride show that only a very minute amount of the readily soluble tetracetyl morphine or diacetyl-dibenzoyl-morphine hydrochlorides could have been present.

Hence it may be concluded that there is no marked tendency towards the replacement of benzoyl by acetyl, or *vice versa*, on heating benzoylated morphine with acetic anhydride or acetylated morphine with benzoic anhydride.

In conclusion, we beg to tender our sincere thanks to Messrs. Macfarlan and Co. (Edinburgh) for further supplies of pure alkaloids, presented for the purpose of making these experiments.