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

By G. H. Beckett and C. R. Alder Wright, D.Sc. (Lond.), Lecturer on Chemistry in St. Mary's Hospital Medical School.

§ 1. Action of Acetic Anhydride on the Polymerides of Codeine and Morphine.

A. *Action of Acetic Anhydride on Dicodeine.*

In a former paper (*Proc. Roy. Soc.*, xx, 278), it has been stated by one of us that dicodeine is obtained as an *amorphous* precipitate by adding sodium carbonate to the solution of its hydrochloride, which salt, however, crystallises well. Whilst preparing dicodeine for the under-mentioned experiments, it was found that carbonate of sodium throws down, from a solution of dicodeine hydrochloride purified by several successive crystallisations, a precipitate consisting wholly of very fine needles, soluble in ether, and crystallising therefrom also in very fine needles, readily visible under a low power, though not large enough to be clearly distinguishable by the naked eye. After drying in blotting paper, the crystals gave the following numbers :—

1·068 gram lost at 100° 0·065 gram = 6·08 per cent.
The formula $C_{72}H_{84}N_4O_{12}.4H_2O$ requires 5·68   ,,

When the anhydrous base was boiled for four hours with twice its weight of acetic anhydride, a product was formed consisting of the acetate of *tetracetyl-dicodeine*, produced in virtue of the reaction

$$C_{72}H_{84}N_4O_{12} + 4(C_2H_3O)_2O = C_{72}H_{80}(C_2H_3O)_4N_4O_{12} + 4(C_2H_3O.OH).$$
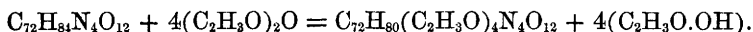
On solution in water, and addition of sodium carbonate, a tarry non-crystalline precipitate was thrown down, readily soluble in ether ; on agitating the ethereal solution with a little hydrochloric acid, crystals were obtained, excessively soluble in water, and consisting of the hydrochloride of the new base ; after recrystallisation, these gave the following numbers :—

1·432 gram, dried in blotting-paper, lost at 100° 0·1640 gram = 11·45 per cent.
The formula $C_{72}H_{80}(C_2H_3O)_4N_4O_{12}.4HCl.10H_2O$ requires 10·65 per cent.

After drying at 100° 0·3640 gram gave 0·8470 CO_2 and 0·2250 H_2O.
   ,,   ,,   0·4180   ,,   0·1590 AgCl.

	Calculated.		Found.
C_{80}	960	63·58	63·46
H_{96}	96	6·36	6·87
Cl_4	142	9·40	9·41
N_4	56	3·71	—
O_{16}	256	16·95	—
$C_{72}H_{80}(C_2H_3O)_4N_4O_{12}.4HCl$	1510	100·00	

The platinum salt was indistinctly crystalline, and gave the following numbers :—

0·5215 gram gave 0·0945 gram Pt   = 18·12 per cent.
The formula $C_{72}H_{80}(C_2H_3O)_4N_4O_{12}.4HCl.2PtCl_4$ requires 18·05   ,,

Hence it results that the product of the action of acetic anhydride on dicodeine is polymeric with diacetyl-codeine, from which it differs in that the hydrochloride of the former is more soluble in water than that of the latter, whilst tetracetyl-dicodeine in the free state is not readily crystallisable from ether, whereas diacetyl-codeine crystallises most readily from that solvent.

B. *Action of Acetic Anhydride on Tetracodeine.*

Tetracodeine was heated to about 120° for three hours with excess of acetic anhydride : the product refused to dissolve in water after evaporation to dryness on the water-bath, and was also insoluble in dilute hydrochloric acid; in alcohol and alcoholic hydrochloric acid, however, it dissolved readily, being precipitated from both solvents unchanged on addition of water (the precipitate being wholly free from chlorine in the latter case). By fractional precipitation with water, a nearly colourless product was ultimately obtained in amorphous flakes, which darkened slightly on drying over sulphuric acid; these gave the following numbers, agreeing with those required for *octacetyl-tetracodeine,* a compound polymeric both with diacetyl-codeine and with tetracetyl-dicodeine :—

0·3110 gram gave 0·7965 CO_2 and 0·188 H_2O.

	Calculated.		Found.
C_{60}	1920	70·38	69·85
H_{184}	184	6·74	6·72
N_8	112	4·11	—
O_{32}	512	18·77	—
$C_{144}H_{160}(C_2H_3O)_8N_8O_{24}$	2728	100·00	

An attempt was made to prepare a platinum salt of octacetyl-tetra-

codeine by adding excess of alcoholic platinic chloride to its alcoholic solution (also containing hydrochloric acid), and then precipitating with water; the precipitate thus obtained gave these numbers:—

0·4205 gram gave 0·0275 Pt = 6·54 per cent.

The calculated percentage for the normal salt would be 18·05 per cent., whilst the basic salt, $C_{144}H_{160}(C_2H_3O)_8N_8O_{24}.2HCl.PtCl_4$ would require 6·29 per cent.

It hence results that in the conversion of codeine successively into dicodeine and tetracodeine, no change is produced of the kind that would be denoted by an alteration of the number of OH groups in the formula relatively to the number of N symbols, the ratio being 1 to 1 throughout; but the polymerisation does bring about a considerable change in the basic character of the alkaloïd; whilst dicodeine and tetracodeine can saturate acids forming neutral salts (e.g., the hydrochlorides and platinum salts), their acetyl derivatives differ in that the acetyl derivative of tetracodeine is almost wholly deprived of antacid characters, refusing to form a hydrochloride at all, and only giving rise to an abnormally basic platinum salt. Tetramorphine and also strychnine appear to be similarly affected.

C. *Action of Acetic Anhydride on Tetramorphine.*

Tetramorphine is difficult to obtain even approximately pure in the free state, as its salts yield with carbonate of soda a precipitate which rapidly takes up oxygen on exposure to air. A portion dried as rapidly as possible was heated to 120° for three hours with a large excess of acetic anhydride, and the product evaporated to dryness on the water-bath. The resulting mass much resembled the corresponding product obtained with tetracodeine; it was, however, less readily precipitated from alcoholic solution by water, being more soluble in dilute alcohol than the tetracodeine product; moreover, it oxidised by exposure to air like tetramorphine itself, from which, however, it differed in basicity, the precipitate thrown down by water from alcoholic solution containing hydrochloric acid being free from chlorine. It was not found practicable to obtain the product in a fit state for analysis, but its characters and mode of production indicate that it consisted of the tetrapoly-meride of tetracetyl-morphine, and hence that with morphine, as with codeine, polymerisation renders the substance of a less antacid character.

D. *Action of Iodide of Ethyl on Tetracodeine and Octacetyl-tetracodeine.*

With a view to ascertaining whether the power of uniting with the alcoholic iodides is altered by polymerisation, tetracodeine was heated

with its own weight of ethyl iodide and a little absolute alcohol in a sealed tube to 100° for twenty minutes; on cooling, a tarry mass separated; this dissolved in boiling alcohol, separating on cooling in flakes much resembling tetracodeine, and simulating a crystalline character, but consisting only of coalesced globules visible under the microscope. Of these flakes,—

0·5920 gram gave 0·2960 AgI   Iodine $= 27·02$ per cent.
Calculated for $C_{144}H_{168}N_8O_{24}.8C_2H_5I$ . . . . 27·91   ,,

The product dissolved readily in hot water, separating again in flakes on cooling. Hence it results that tetracodeine, like codeine, unites with ethyl iodide in the proportion of one equivalent of iodine, as iodide, for one of nitrogen in the base.

When, however, octacetyl-tetracodeine is similarly treated, a body results excessively soluble in alcohol, and precipitated from this solution by addition of water, just like octacetyl-tetracodeine itself; this product was found to contain 12·72 per cent. of iodine; the amount calculated for $C_{144}H_{160}(C_2H_3O)_8N_8C_{24}.8C_2H_5I$ would be 25·55 per cent., whilst $C_{144}H_{160}(C_2H_3O)_8N_8O_{24}.4C_2H_5I$ would require 15·15 per cent.: hence it is evident that the acetylation of tetracodeine prevents its ready combination with ethyl iodide, just as it does with hydrochloric acid, and with platinum chloride, &c., to form a normal platinum salt.

§ 2. ISOMERIC DIACETYL-MORPHINES.

It has been shown in Part I that at least two isomeric products exhibiting the composition of diacetylated morphine are obtainable from morphine, two substances of this composition having been obtained, differing in that one of them (α-diacetyl-morphine) forms a sparingly soluble crystalline hydrochloride, whilst the second (previously designated β-diacetyl-morphine) forms a very soluble hydrochloride, which dries up to a varnish without crystallising. At the time that paper was written, all attempts to obtain either free base in the crystallised state had proved abortive; since then, however, it has been found that if the ethereal solution of α-diacetyl morphine (regenerated from the hydrochloride purified by several successive recrystallisations) be allowed to evaporate spontaneously, crystals are sometimes deposited, which are sometimes hydrated and sometimes anhydrous, even though the ether be saturated with water: thus, one crop of crystals had the composition $C_{34}H_{36}(C_2H_3O)_2N_2O_6,2H_2O$. When air-dry, 0·3885 gram of crystals gave 0·9380 CO_2, and 0·2410 H_2O.

	Calculated.		Found.
C_{38}	456	66·09	65·85
H_{46}	46	6·66	6·89
N_2	28	4·06	—
O_{10}	160	23·19	—
$C_{34}H_{36}(C_2H_3O)_2N_2O_6.2H_2O$	690	100·00	

On drying at 100°, 1·685 gram lost 0·0870 gram = 5·16 per cent.

 ,, ,, 0·6755 ,, 0·0345 ,, = 5·11 ,,

 The above formula requires .... 5·22 ,,

Other crops of crystals lost only a few tenths per cent. at 100°: one specimen gave these numbers :—

After drying at 100°, 0·3210 gram gave 0·8255 CO_2, and 0·1985 H_2O.

	Calculated.		Found.
C_{38}	456	69·73	70·13
H_{42}	42	6·42	6·87
N_2	28	4·28	—
O_8	128	19·57	—
$C_{34}H_{36}(C_2H_3O)_2N_2O_6$	654	100·00	

When the product described in Part I as hydrochloride of β-diacetyl morphine is precipitated by carbonate of sodium, and the base dissolved in ether, an ethereal solution is obtained, which on slow spontaneous evaporation dries up to a syrupy liquid, in which more or less small crystals are disseminated; by washing this syrup quickly with a little ether or absolute alcohol, and recrystallising from ether the crystals thus left, a diacetyl morphine is obtained, differing from α-diacetyl-morphine in that its hydrochloride is excessively soluble in water, and crystallises only with great difficulty, its solutions often drying up to a varnish without crystallising, but sometimes becoming a crystalline mass over sulphuric acid.

The crystals of the base gave the following numbers; they were anhydrous :—

  0·3045 gram gave 0·7775 CO_2 and 0·1860 H_2O.

  0·1520 ,, 0·3855 ,, 0·0940 ,,

	Calculated.			
C_{38}	456	69·73	69·63	69·17
H_{42}	42	6·42	6·78	6·87
N_2	28	4·28	—	—
O_8	128	19·57	—	—
$C_{34}H_{36}(C_2H_3O)_2N_2O_6$	654	100·00		

The platinum salt gave these numbers :—

0·5515 gram gave 0·1020 Pt = 18·49 per cent.
Calculated percentage ..... = 18·52   ,,

This diacetyl-morphine gives no coloration with ferric chloride, and is provisionally distinguished as γ-*diacetyl-morphine.*

When the ethereal or alcoholic mother liquors of γ-diacetyl-morphine are allowed to evaporate spontaneously, a syrup is again obtained containing few crystals (or none at all). This is thinned with a little ether and quickly filtered. The filtrate dries up to a varnish, exhibiting no tendency whatever to crystallisation. This varnish usually strikes a pale blue tint with ferric chloride, but on one occasion it was obtained in a condition in which it gave no coloration with this reagent, from which, together with the easy decomposibility of this isomeride, it appears probable that the pure base gives no colour, and the coloration observed in the other samples and in the crude product described in Part I is due to the presence of a small quantity of some decomposition-product (morphine or monoacetyl-morphine). That this non-crystalline base is really an isomeride of the α- and γ-diacetyl-morphines above described is evident from the circumstance that the mixture of hydrochlorides of this base and the γ variety described in Part I gave numbers agreeing with this view on analysis, and which is of more importance, gave the theoretical amount of acetic acid on saponification, which would not have been the case had not this substance (which constitutes much more than half of the crude product) been actually a diacetyl-morphine. Moreover, as shown in the next section, this non-crystalline base yields with ethyl iodide a compound isomeric with the analogous products obtained from α- and γ-diacetyl-morphines. It is therefore proposed to restrict to this base the term β-*diacetyl morphine,* which in Part I was used to indicate the mixture of this base and γ-diacetyl-morphine.

The hydrochloride of β-diacetyl-morphine is less stable than that of either α- or γ-diacetyl-morphine ; its aqueous solution soon decomposes, setting acetic acid free, and forming morphine hydrochloride, readily recognised by the much deeper blue tint struck by the solution with ferric chloride after standing. The platinum salt also is readily decomposible on standing whilst moist. The following numbers were obtained, the slight excess of platinum being evidently due to this decomposition :—

0·3110 gram gave 0·0595 gram Pt = 19·13 per cent.
0·0555   ,,   0·0105   ,,   = 18·92   ,,
Calculated for diacetyl-morphine
platinochloride............. = 18·52   ,,

Hence it results on the whole that when acetic anhydride in quantity just sufficient for the reaction—

$$C_{34}H_{38}N_2O_6 + 2(C_2H_3O)_2O = 2(C_2H_3O.OH) + C_{34}H_{36}(C_2H_3O)_2N_2O_6,$$
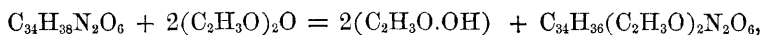
is allowed to act on anhydrous morphine, three isomeric diacetyl morphines are produced, the properties of which may be thus contrasted :—

	Relative quantity.	Free base.	Hydrochloride.	Ethyiodide (§ 3).
α-diacetyl-morphine.	Formed only in very small quantity, say 2 or 3 per cent. of the whole.	Crystallisable from ether by spontaneous evaporation, sometimes anhydrous, sometimes with $2H_2O$.	Comparatively sparingly soluble in cold water : crystals contain $6H_2O$.	Crystallises from 85 per cent. alcohol with H_2O.
β-diacetyl-morphine.	Formed in largest quantity.	Apparently quite uncrystallisable.	Very soluble ; non-crystallisable : more unstable in aqueous solution than its isomerides.	Refuses to crystallise from absolute or from 85 per cent. alcohol.
γ-diacetyl-morphine.	Constitutes about 25 per cent. of the whole.	Crystallisable anhydrous from ether with ease when free from β-diacetyl morphine.	Very soluble in water ; crystallisable, but with difficulty.	Crystallises from 85 per cent. alcohol with $3H_2O$.

§ 3. ACTION OF ETHYL IODIDE ON ACETYLATED MORPHINE AND CODEINE DERIVATIVES AND ANALOGOUS PRODUCTS.

The bases examined were sealed up in tubes with twice their weight of absolute alcohol and about their own weight of ethyl iodide (a large excess), and were then heated to 100° for a quarter of an hour. On cooling, the mass frequently solidified to a crystalline magma. The contents of the tubes were dissolved in a hot mixture of alcohol and a little water (making about 80 to 85 per cent. alcohol) and allowed to crystallise by cooling the solution.

A. *Diacetyl-codeine Ethiodide.*

Diacetyl codeine unites with ethyl iodide when treated as above described, forming the compound $C_{36}H_{40}(C_2H_3O)_2N_2O_6 . 2C_2H_5I . H_2O$

(after crystallisation from 85 per cent. alcohol). At 100° this compound loses the water of crystallisation, slightly decomposing at the same time.

1·0320 gram lost at 100° 0·0260 gram = 2·52 per cent.

0·7270   ,,   ,,   0·0170 ,, = 2·34   ,,

Calculated .... 1·78   ,,

0·3250 gram dried at 100° gave 0·6380 CO_2 and 0·1770 H_2O.

0·5110   ,,   ,,   0·2425 AgI.

	Calculated.		Found.
C_{44}	528	53·12	53·52
H_{56}	56	5·63	6·05
I_2	254	25·55	25·64
N_2	28	2·82	—
O_8	128	12·88	—
$C_{36}H_{40}(C_2H_3O)_2N_2O_6.2C_2H_5I$	994	100·00	

Diacetyl-codeine ethiodide forms snow-white crystals very sparingly soluble in cold absolute alcohol or 90 per cent. spirit, but more soluble in water and in hot not absolute alcohol. When agitated with a little water and well washed freshly precipitated silver chloride, it forms silver iodide and a solution of *diacetyl-codeine ethylochloride.* This is much more soluble in water than the ethyl iodide, forming only as crystalline crusts as the solution evaporates almost to dryness over sulphuric acid. These crystals after drying at 100° contain $C_{36}H_{40}(C_2H_3O)_2N_2O_6 . 2C_2H_5Cl . H_2O$.

0·2140 gram gave 0·7755 CO_2 and 0·3325 H_2O.

0·5900   ,,   0·2030 AgCl.

0·8740   ,,   0·2980 ,,

	Calculated.		Found.	
C_{44}	528	63·69	63·61	
H_{58}	58	7·00	7·15	
Cl_2	71	8·56	8·52	8·44
N_2	28	3·38		
O_9	144	17·37		
$C_{36}H_{40}(C_2H_3O)_2N_2O_6.2C_2H_5Cl.H_2O$	829	100·00		

The platinum salt of this compound decomposes on drying. Two specimens were found to contain 17·91 and 18·66 per cent., whilst the calculated value is 17·17 (for the formula $C_{36}H_{40}(C_2H_3O)_2N_2O_6$, $2C_2H_5Cl,PtCl_4$).

B. *Tetracetyl-morphine Ethiodide.*

This product much resembles diacetyl-codeine ethiodide, but is somewhat less stable, a considerable portion becoming altered by boil-

ing for a few minutes with 85 per cent. alcohol. The crystals deposited from this solvent contain $C_{34}H_{34}(C_2H_3O)_4N_2O_6 . 2C_2H_5I . H_2O$, whilst the mother-liquor contains products probably formed by the removal of acetyl by the action of the alcohol.

1·518 gram lost at 100° 0·0300 gram = 1·97 per cent.
Calculated...................... 1·69   „

Continued heating at 100° causes some amount of decomposition, a much greater loss being experienced, and the product becoming coloured.

0·3090 gram of dried product gave 0·5980 CO_2 and 0·1630 H_{20}.
0·5750   „   „   0·2580 AgI.

	Calculated.		Found.
C_{46}	552	52·57	52·77
H_{56}	56	5·33	5·86
I_2	254	24·19	24·24
N_2	28	2·67	—
O_{10}	160	15·24	—
$C_{34}H_{34}(C_2H_3O)_4N_2O_6.2C_2H_5I$	1050	100·00	

Silver chloride converts tetracetyl-morphine ethiodide into the corresponding ethylochloride. This is readily soluble in water, but cannot be obtained pure in the solid state, inasmuch as the aqueous solution decomposes partially on heating or on standing over sulphuric acid. The crystalline crusts thus obtained were found to contain (after drying at 100°) 8·78 per cent. of chlorine, the calculated amount being 8·19 per cent.

C. α-Diacetyl-morphine Ethiodide.

This product much resembles the ethiodide of tetracetyl-morphine. After crystallisation from 85 per cent. alcohol it gave the following numbers, agreeing with the formula $C_{34}H_{36}(C_2H_3O)_2N_2O_6 . 2C_2H_5I . H_2O$:—

0·8035 gram of air-dry crystals lost at 100° 0·0195 gram = 2·42 per cent.

Calculated............................ 1·83 per cent.
0·4110 gram dried at 100° gave 0·7870 CO_2 and 0·2110 H_2O.
0·3240   „   „   0·1575 AgI.

	Calculated.		Found.
C_{42}	504	52·18	52·22
H_{52}	52	5·39	5·70
I_2	254	26·29	26·27
N_2	28	2·89	
O_8	128	13·25	
$C_{34}H_{36}(C_2H_3O)_2N_2O_6.2C_2H_5I$	966		

D. β-*Diacetyl-morphine Ethiodide.*

β-diacetyl-morphine purified from γ-diacetyl-morphine as far as practicable by the process above described, yielded a product which refused to crystallise either from absolute or 85 per cent. alcohol on cooling or by spontaneous evaporation; a tarry mass separated which gave the following numbers after drying over sulphuric acid:—

0·6590 gram gave 0·3170 AgI, Iodine = 26·00 per cent.
Calculated for diacetyl-morphine ethiodide 26·29   „

E. γ-*Diacetyl-morphine Ethiodide.*

This product was crystalline, and much resembled the isomeric product from α-diacetyl-morphine, from which, however, it differed in that the crystals formed from 85 per cent. alcohol contained more water of crystallisation.

0·2760 gram of air-dry salt lost at 100° 0·0160 gram = 5·80 per cent.
The formula $C_{34}H_{36}(C_2H_3O)_2N_2O_6$. $2C_2H_5I$. $3H_2O$ requires 5·29 per cent.
0·2570 gram dried at 100° gave 0·1235 gram, Iodine = 25·96 per cent.
Calculated .... Iodine = 26·29 per cent.

Notwithstanding the marked difference between the hydrochlorides of α- and γ-diacetyl-morphine in solubility, the ethyl iodides do not differ much in this respect.

F. *Dibutyryl-codeine Ethiodide.*

This product much resembled diacetyl-codeine ethiodide, crystallising readily from 85 per cent. alcohol.

0·4710 gram of crystals lost at 100° 0·0155 gram = 3·29 per cent.
The formula $C_{36}H_{40}(C_4H_7O)_2N_2O_6$. $2C_2H_5I$. H_2O requires 1·70 per cent.
0·4175 gram of dried product gave 0·1840 AgI, Iodine = 23·81 per cent.
Calculated .... Iodine = 24·19 per cent.

Continued heating at 100° causes decomposition, the odour of butyric acid being clearly distinguishable.

G. *Tetrabutyryl-morphine Ethiodide.*

Like the hydrochloride, this product utterly refused to crystallise. It could only be obtained as a soft, tarry, slightly coloured mass, which exhaled a fœtid odour on heating to 100°. Of this product—

0·5450 gram gave 0·2330 AgI, Iodine = 23·11 per cent.
The formula $C_{34}H_{34}(C_4H_7O)_4N_2O_6$. $2C_2H_5I$ requires 21·86 per cent.
And $C_{34}H_{36}(C_4H_7O)_2N_2O_6$. $2C_2H_5I$ requires 24·85 per cent.

Hence the first product was tetrabutyryl-morphine ethiodide, which became somewhat decomposed on standing and heating.

H. *Dibutyryl-morphine Ethiodide.*

This product resembled tetrabutyryl ethiodide in physical character, utterly refusing to crystallise, and in this respect quite differing from dibutyryl-codeine ethiodide.   It does not decompose so readily at 100° as tetrabutyryl-morphine ethiodide.

0·4890 gram gave 0·2185 AgI. Iodine = 24·15 per cent.
Calculated for $C_{34}H_{36}(C_4H_7O)_2N_2O_6$. $2C_2H_5I$ = 24·85 per cent.

I. *Dibenzoyl-codeine Ethiodide.*

This product crystallised well from 85 per cent. alcohol, the crystals being represented by the formula $C_{36}H_{40}(C_7H_5O)_2N_2O_6$. $2C_2H_5I$. H_2O.

0·772 gram of crystals lost at 100° 0·0135 = 1·75 per cent.
Calculated .... = 1·59   ,,
0·4115 gram of dried substance gave 0·1725 AgI. Iodine = 22·65 per cent.
Calculated. .... 22·72 per cent.

J. *Tetrabenzoyl-morphine Ethiodide.*

This compound also crystallises well from 85 per cent. alcohol, the crystals containing H_2O.

0·2710 gram lost at 100° 0·0050 = 1·84 per cent.
Calculated.................. = 1·37   ,,

0·4080 gram of dried substance gave 0·1460 AgI. Iodine = 19·34 per cent.
Calculated for $C_{34}H_{34}(C_7H_5O)_4N_2O_6$. $2C_2H_5I$ = 19·57 per cent.

K. α-*Diacetyl-dibenzoyl-morphine Ethiodide*.

This product was obtained from α-diacetyl-dibenzoyl morphine by the above-described process. It crystallised well from 85 per cent. alcohol, the crystals containing $C_{34}H_{34}(C_2H_3O)_2(C_7H_5O)_2N_2O_6 . 2C_2H_5I . H_2O$.

0·2190 gram lost at 100° 0·0040 = 1·83 per cent.
Calculated .... = 1·51   ,,

0·2045 gram of dried product gave 0·0830 AgI. Iodine = 21·94 per cent.
Calculated..................... Iodine = 21·64 per cent.

It hence appears that those ethiodides of acetylated, butyrylated, and benzoylated codeines and morphines which can be obtained in a crystalline form crystallise with H_2O from 85 per cent. alcohol, just as the ethiodides of morphine and codeine (How); the only exception to this rule being γ-diacetyl morphine, which appears to crystallise with $3H_2O$: also, as a rule, those bases which yield readily crystallisable hydrochlorides also form readily crystallisable ethiodides, and *vice versâ*. This rule, however, is not invariably observed. Thus dibutyryl-morphine hydrochloride is crystallisable, though only with difficulty, whilst the ethiodide is wholly non-crystalline. On the other hand, tetrabenzoyl-morphine forms a hydrochloride which has not hitherto been obtained crystallised, whilst the ethiodide crystallises readily. In each of these two cases the free base is crystalline. It seems extremely probable that all the bases and salts of non-polymerised morphine and codeine derivatives are really crystalline in character, the difficulty observed in obtaining some of them in a crystallised state being mainly due to the very strongly marked tendency to form supersaturated solutions, which either gradually dry up to varnishes, or allow the substance to separate at times so quickly that it has not time to assume the crystalline form. The presence of minute quantities of colouring matters and other analogous bye-products very greatly enhances the difficulty in crystallising, which difficulty is indeed more or less marked in certain cases with nearly all the opium alkaloïds or their salts.

§ 4. ACTION OF ETHYLATE OF SODIUM ON ACETYLATED CODEINE AND MORPHINE.

A priori, the occurrence of the following reaction and analogous ones would seem probable, whereby ethylated codeine and similar products would result :—

$$C_{36}H_{40}(C_2H_3O)_2N_2O_6 + 2(NaO.C_2H_5) = 2(NaO.C_2H_3O) + C_{36}H_{40}(C_2H_5)_2N_2O_6.$$
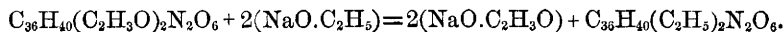
On trying the experiment, however, nothing of the kind appears to take place. Whether a solution of ethylate of sodium in absolute alcohol were used, or the solid substance (prepared by dissolving sodium in absolute alcohol and driving off the excess of alcohol by a stream of dry air, the whole being kept at temperatures varying from 90° to 140° in different experiments), in no case could any ethylated base be isolated from the product of the reaction. Codeine was simply reproduced, and more or less polymerised to tetra-codeine. Thus numbers were obtained from the products of the action of boiling alcoholic sodium ethylate on codeine, of the fusion together of diacetyl-codeine (melting-point about 135°) and solid sodium ethylate, and of the action of a boiling anhydrous benzene solution of diacetyl-codeine on solid sodium ethylate, agreeing in each instance with those required for ordinary codeine; whilst the following numbers were obtained from one of the specimens of tetra-codeine simultaneously produced :—

(A.) 0·3100 gram gave 0·8200 CO_2 and 0·1930 H_2O.

The production of the tetracodeine was traced to the action of the sodium ethylate on the codeine first formed, and hence the following process for preparing tetracodeine was finally arrived at, the chief advantage of which is that the resulting product is considerably purer than that obtained by the action of acids, as in that case traces of bye-products are apt to be formed which absorb oxygen from the air during drying and colour the mass of a more or less dark brownish tint. Anhydrous codeine is dissolved in boiling benzene, and the solution boiled with powdered ethylate of sodium for three or four hours, an inverted condenser being attached. The benzene liquor is then cooled and agitated with dilute hydrochloric acid. From the acid aqueous liquid the tetracodeine is finally precipitated by carbonate of soda, and purified by solution in hydrochloric acid and fractional pre-cipitation by carbonate of soda. Finally it is washed and dried, and dissolved in boiling benzene, from which it separates on cooling in almost white flakes which simulate a crystalline character, but are seen under the microscope to consist of masses of coalesced minute globules. Instead of ethylate of sodium, powdered caustic potash can be used, but the production of colouring matter seems to be somewhat greater in this case; one part of ethylate or caustic potash suffices to poly-merise the majority of ten parts of codeine in four or five hours when treated in this way. A specimen of tetracodeine thus prepared gave the following numbers :—

(B.) 0·2980 gram gave 0·7920 CO_2 and 0·1900 H_2O.

	Calculated.		Found.	
			(A.)	(B.)
C_{144}	1728	72·24	72·14	72·48
H_{168}	168	7·02	6·91	7·09
N_8	112	4·68	—	—
O_{24}	384	16·06	—	—
$C_{144}H_{168}N_8O_{24}$	2392	100·00		

When tetracetyl-morphine in benzene solution is similarly boiled with dry sodium ethylate, morphine is regenerated, and to a considerable extent polymerised to tetramorphine. The tetramorphine thus produced is somewhat purer than that formed by the action of sulphuric acid on morphine. By dissolving it in a very slight excess of dilute hydrochloric acid and precipitating fractionally by concentrated acid, almost white flakes of tetramorphine hydrochloride are readily obtained.