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

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

IN a former paper (*Proc. Roy. Soc.*, 1872, p. 278), it was stated that attempts to form codeine derivatives by the action of glacial acetic acid at $100°$ met with only an extremely small degree of success; when, however, codeine dried at $140°$ is heated to boiling with twice its weight of glacial acetic acid for eight hours (an inverted condenser being attached to retain the acid volatilised), a large quantity of a new base, *diacetyl-codeine*, is formed, in virtue of the reaction,

$$C_{36}H_{42}N_2O_6 + 2C_2H_3O.OH = 2H_2O + C_{36}H_{40}(C_2H_3O)_2N_2O_6.$$
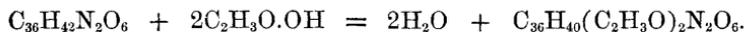
On evaporating the resulting liquid to dryness on the water-bath, dissolving the residue in water, and adding sodium carbonate, an immediate white precipitate is thrown down, flocculent at first but soon becoming crystalline on standing; by rapid filtration this is separated from unaltered codeine, which is not immediately precipitated in this manner, save in very concentrated solutions. By dissolving the precipitate in dilute hydrochloric acid, and repeating the precipitation by sodium carbonate three or four times, a product is obtained quite free from codeine; the last precipitate is dissolved in ether or hot dilute alcohol, from either of which solvents the new base crystallises in bold, well-defined anhydrous crystals; it can also be recrystallised from benzene, chloroform, and boiling water without change, being readily soluble in all these solvents except water, in which it is only sparingly soluble even when boiling.

0·3500 gram gave 0·8940 Co_2 and 0·2105 H_2O.
0·3120　,,　　,,　0·7975 ,,　　,,　0·1895　,,

	Calculated.		Found.	
C_{40}	480	70·38	69·66	69·71
H_{46}	46	6·74	6·68	6·75
N_2	38	4·11		
O_8	128	18·77		
$C_{36}H_{40}(C_2H_3O)_2N_2O_6$	682	100·00		

Diacetyl-codeine forms a well crystallised hydrochloride somewhat

4 A 2

more soluble in water than codeine hydrochloride; when air-dry, the crystals contain $C_{40}H_{46}N_2O_6.2HCl.4H_2O$.

0·6695 gram lost at 100° 0·0595 gram = 8·88 per cent.
        The above formula requires 8·71   ,,
0·6090 gram dried at 100° gave 0·2285 AgCl.
0·2860   ,,   ,,   ,,   0·661 CO_2 and 0·174 H_2O.

	Calculated.		Found.
C_{40}	480	63·58	63·03
H_{48}	48	6 36	6·76
N_2	28	3·71	—
O_8	128	16·95	—
Cl_2	71	9·40	9·28
$C_{36}H_{40}(C_2H_3O)_2N_2O_6.2HCl$	755	100·00	

When it is precipitated by platinic chloride, a yellow non-crystalline precipitate is formed; this gave the following numbers after drying over sulphuric acid for a fortnight:—

0·5090 gram gave 0·0925 pt.   = 18·17 per cent.
0·4465   ,,   ,, 0·0810 ,,   = 18·14   ,,
The formula, $C_{36}H_{40}(C_2H_3O)_2N_2O_6,2HCl,PtCl_4$ requires 18·05   ,,

Diacetyl-codeine salts give no coloration with ferric chloride; the pre-cipitated base is but little soluble in ammonia or carbonate of soda, but is more readily dissolved by caustic potash.

Attempts to prepare *monoacetyl-codeine*, $C_{36}H_{41}(C_2H_3O)N_2O_6$, or to isolate it from the products of the action of acetic acid on codeine did not meet with success; it was, however, noticed that a larger portion of the first precipitate thrown down by carbonate of soda was soluble in excess of the precipitant than was the case in subsequent precipi-tations, whence it is probable that the monoacetylated base is formed together with diacetyl-codeine; hitherto, however, no means of sepa-rating it from unaltered codeine have been devised; as mentioned in § 5, monoacetyl-morphine has been obtained; this, however, is readily separated from unaltered morphine, being soluble in ether, whilst morphine is virtually insoluble in that menstruum.

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

In order to see if higher acetyl derivatives are obtainable by the action of acetic anhydride, codeine was treated with a large excess of that substance in various ways; in every case, however, nothing but diacetyl-codeine resulted, whether the actions were allowed to take

place at the ordinary temperature (by standing some weeks), at 100° for several hours, or at 130° for six hours; thus the resulting base, isolated as above described, gave the following numbers in each of the above instances:—

A at the ordinary temperature, three weeks—
    0·4020 gram gave 1·0315 CO_2 and 0·243 H_2O.

B at 100°, one hour—
    0·2290 gram gave 0·5845 CO_2 and 0·1415 H_2O.

C at 130°, six hours—
    0·2965 gram gave 0·7650 CO_2 and 0·1845 H_2O.

	Calculated.	Found.		
		(A)	(B)	(C)
Carbon..........	70·38	69·98	69·61	70·37
Hydrogen	6·74	6·72	6·87	6·91

The hydrochlorides of these three preparations gave the following numbers after drying at 100° :—

(A) 0·4210 gram gave 0·1620 AgCl
(B) 0·5095 ,,   ,,   0·1945 ,,
(C) 0·4460 ,,   ,,   0·1670 ,,
    0·2675 ,,   ,,   0·6260 CO_2 and 0·1675 H_2O.

	Calculated.	Found.		
		(A)	(B)	(C)
Carbon...........	63·58	—	—	63·82
Hydrogen	6·36	—	—	6·95
Chlorine	9·40	9·52	9·45	9·26

An attempt to prepare monoacetyl-codeine from the theoretical quantities of anhydrous codeine and acetic anhydride led to no result, much of the codeine being wholly unaltered, and a small portion being converted into diacetyl-codeine, the formation of which renders the isolation of monoacetyl-codeine extremely difficult if not impossible.

§ 3. *Action of Acetic Acid on Morphine.*

When morphine is boiled for several hours with twice its weight of glacial acetic acid, an inverted condenser being attached, a large amount is converted into a substance related to morphine in the same manner as diacetyl-codeine is to codeine; by dissolving the product in water, adding ammonia, and shaking up with ether, an ethereal solution is obtained which yields a copious crystalline hydrochloride on shaking with hydrochloric acid; this hydrochloride is but sparingly soluble in

cold water, but can be recrystallised from that menstruum when hot without change.   The crystals contain $C_{34}H_{36}(C_2H_3O)_2N_2O_6.2HCl.6H_2O$.

0·7535 gram dried at 120° lost 0·0985 gram = 13·07 p.c.

The above formula requires   12·93 ,,

The dried substance gave these numbers –

0·2686 gram gave 0·6185 CO_2 and 0·1570 H_2O.

0·3840 ,,   ,,   0·1535 AgCl.

	Calculated.		Found.
C_{38}	456	62·72	62·82
H_{44}	44	6·05	6·49
N_2	28	3·85	—
O_8	128	17·61	—
Cl_2	71	9·77	9·89
$C_{34}H_{36}(C_2H_3O)_2N_2O_6.2HCl$	727	100·00	

A warm aqueous solution of the salt yields with ammonia a flocculent non-crystalline precipitate, readily soluble in ammonia, sodium carbonate, caustic potash, ether, alcohol, and benzene ; from the latter three solutions it separates on spontaneous evaporation as a gummy film, wholly destitute of crystalline characters ;* on bringing dilute nitric or hydrochloric acid in contact with the amorphous base, a well-crystallised sparingly soluble salt is in each case formed,

The free base precipitated by ammonia and dried over sulphuric acid gave these numbers—

0·2960 gram gave 0·7495 CO_2 and 0·1745 H_2O.

	Calculated.		Found.
C_{38}	456	69·73	69·06
H_{42}	42	6·42	6·55
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 was amorphous, and gave the following numbers—

0·3355 gram dried over sulphuric acid gave 0·0615 Pt = 18·33 p.c.

0·4310 ,,   dried at 100°   ,,   0·0805 ,, = 18·67 ,,

The formula $C_{34}H_{36}(C_2H_3O)_2N_2O_6,2HCl,PtCl_4$ requires 18·53 ,,

When pure, neither the free base nor its salts give any coloration with ferric chloride; simultaneously with this base, however, there is formed a small quantity of a substance which does colour ferric chloride

* Since the above was written, it has been found practicable to obtain the base in crystals, containing $C_{34}H_{36}(C_2H_3O)_2N_2O_6.2H_2O$.

blue like morphine, but differs therefrom in being soluble in ether and in being precipitated by carbonate of soda in white amorphous flakes, soluble in excess of the precipitant; this substance does not seem to give a crystalline hydrochloride, and is apparently identical with the *β-diacetyl-morphine* described in § 5, *i.e.*, is isomeric with the above base, yielding a sparingly soluble crystalline hydrochloride, which is accordingly designated *α-diacetyl morphine.*

§ 4. *Action of Acetic Anhydride in excess on Morphine.*

When morphine is brought into contact with excess of acetic anhydride, the following reaction takes place, *tetracetyl-morphine* being produced :—

$$C_{34}H_{38}N_2O_6 \ + \ 4(C_2H_3O)_2O \ = \ C_{34}H_{34}(C_2H_3O)_4N_2O_6 \ + \ 4C_2H_3O.OH.$$

The same result is brought about whether the materials are allowed to remain in contact at the ordinary temperature for several days, or are heated to 100° or to 140° for some hours; on adding sodium carbonate to the product dissolved in water, a precipitate is obtained flocculent at first, but soon becoming crystalline; this dissolves readily in ether (morphine is virtually insoluble in that menstruum), and is obtained in fine anhydrous crystals by evaporation; it can also be recrystallised without change from hot alcohol or benzene, and from chloroform; long-continued boiling with alcohol partially decomposes it, whilst boiling with water quickly alters it.

(A.) At the ordinary temperature, 0·3305 gram gave 0·824 CO_2 and 0·189 H_2O.

(B.) At 100° for an hour, 0·2955 gram gave 0·737 CO_2 and 0·171 H_2O. 0·2565 gram gave 0·6425 CO_2 (H_2O lost).

(C.) At 140° for six hours, 0·3715 gram gave 0·931 CO_2 and 0·211 H_2O.

	Calculated.		Found.			
			(A.)	(B.)		(C.)
C_{42}	504	68·29	68·00	68·02	68·31	68·34
H_{46}	46	6·24	6·35	6·43	—	6·31
N_2	28	3·79				
O_{10}	160	21·68				
$C_{34}H_{34}(C_2H_3O)_4N_2O_6$	738	100·00				

Tetracetyl-morphine gives no colour reaction with ferric chloride; like morphine, it is but very sparingly soluble in ammonia and sodium carbonate, but in caustic potash it is readily soluble. When it is *exactly* neutralised with dilute hydrochloric acid, a solution is obtained which

deposits crystals on standing over sulphuric acid; these are extremely soluble in water, so that they only form just before the whole mass has evaporated to dryness ; if any excess of hydrochloric acid be present, partial decomposition takes place during the evaporation, acetic acid being evolved. When dried at 100° the crystals gave the following numbers :—

Specimen A. 0·2575 gram gave 0·5845 CO_2 and 0·148 H_2O.
            0·3990   ,,   ,,   0·1405 AgCl.
Specimen B. 0·2455   ,,   ,,   0·5575 CO_2 and 0·1440 H_2O.
            0·5425   ,,   ,,   0·1915 AgCl.

	Calculated.		Found.	
			(A.)	(B.)
C_{42}	504	62·14	61·91	61·93
H_{48}	48	5·92	6·38	6·52
N_2	28	3·45	—	—
O_{10}	160	19·73	—	—
Cl_2	71	8·76	8·71	8·73
$C_{34}H_{34}(C_2H_3O)_4N_2O_6,2HCl$	811	100·00		

The platinum salt was amorphous, and gave these numbers—

Specimen A. 0·5235 gram gave 0·0895 Pt   = 17·10 p.c.
  ,,   B. 0·2795   ,,   ,,   0·0480   = 17·17 ,,
  ,,   C. 0·6985   ,,   ,,   0·1195   = 17·11 ,,
The formula $C_{34}H_{34}(C_2H_3O)_4N_2O_6.2HCl.PtCl_4$ requires 17·17 ,,

The syrupy ethereal mother-liquors from which tetracetyl-morphine has mostly crystallised, contain more or less α-diacetyl morphine, which may readily be extracted by shaking up the ethereal liquor with hydrochloric acid, when the sparingly soluble hydrochloride of the α base crystallises out. After recrystallisation from water, a specimen gave these numbers—

0·7705 gram lost at 120°, 0·098 gram = 12·72 per cent.
           Calculated   = 12·93   ,,

0·2700 gram gave 0·6190 CO_2 and 0·156 H_2O.
0·4425   ,,   ,,   0·1740 AgCl.

|	Calculated.	Found.
Carbon	62·72	62·52
Hydrogen	6·05	6·42
Chlorine................	9·77	9·73

Probably this base is formed by the action of the trace of water taken up by the ether on the tetracetyl base (§ 6) during the evaporation of the ether.

§ 5. *Action of Acetic Anhydride not in excess on Morphine.*

When anhydrous morphine is heated with a quantity of acetic anhydride less than that requisite to form tetracetyl-morphine, various intermediate products appear to be formed according to circumstances; thus, when the requisite quantities are taken for the following equation:—

<div align="center">Diacetyl-morphine.</div>

$$C_{34}H_{38}N_2O_6 + 2(C_2H_3O)_2O = C_{34}H_{36}(C_2H_3O)_2N_2O_6 + 2C_2H_3O.OH,$$

and the whole is heated to 100° for an hour, the chief product is that expressed by the above equation; but the diacetyl-morphine thus produced is not identical with the α-diacetyl-morphine above described; it yields a hydrochloride excessively soluble in water and incapable of crystallising, but drying up to a varnish, and it strikes a blue colour with ferric chloride; the free base is readily soluble in ether and is precipitated from its salts in amorphous flakes by alkalis; it is readily dissolved by ammonia, sodium carbonate, and caustic potash; it is much less stable than α-diacetyl morphine, ordinary morphine soon crystallising out from an ammoniacal solution of the base, which is decomposed in virtue of the reaction—

$$C_{34}H_{36}(C_2H_3O)_2N_2O_6 + 2NH_3 + 2H_2O = C_{34}H_{38}N_2O_6$$
$$+ 2NH_4.O.C_2H_3O.$$
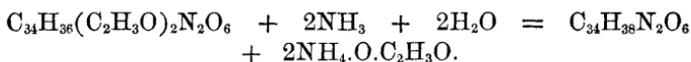
When in contact with excess of hydrochloric acid, the hydrochloride decomposes in a similar manner, morphine hydrochloride crystallising out and acetic acid being set free.

To obtain the hydrochloride of the base, the crude acetate obtained as above is dissolved in water and precipitated with carbonate of soda; on agitation with ether, the base is dissolved, and on shaking the ethereal solution with a little hydrochloric acid, insufficient to neutralize the whole, a neutral solution of hydrochloride is formed which is allowed to stand: in a few hours a minute quantity of α-diacetyl hydrochlorides crystallises out; the viscid mother-liquor is again treated with sodium carbonate, ether, and hydrochloric acid, and the *neutral* hydrochloride solution obtained is evaporated over sulphuric acid. The gummy residue will bear heating to 100° without change if perfectly dry, but if moist, it gives off acetic acid; it is most excessively hygroscopic.

The following numbers were obtained:—

Specimen A. 0·3995 gram gave 0·9210 CO_2 and 0·2325 H_2O
0·6790 „   „   0·2660 AgCl.
Specimen B. 0·3770 „   „   0·218 H_2O and 0·866 CO_2.
0·4410 „   „   0·1730 AgCl.

	Calculated.	Found.	
		(A.)	(B.)
Carbon	62·73	62·88	62·65
Hydrogen	6·05	6·47	6·43
Chlorine	9·77	9·69	9·71

Converted into platinum salts—

Specimen A. 0·6540 gram gave 0·1220 platinum = 18·65 per cent.
,,   B. 0·7030 ,,   ,,   0·1290   ,,   = 18·35 ,,
,,   D. 0·6355 ,,   ,,   0·1165   ,,   = 18·33 ,,
,,   C. 0·6720 ,,   ,,   0·1240   ,,   = 18·45 ,,

Calculated = 18·53   ,,

This base is for the present designated as β-diacetyl-morphine. It is manifest that several diacetyl-morphines may be predicted from the formula—

$$C_{34}H_{34}N_2O_2(OH)_4 \; [vide \; \S \; 7]$$

if the OH group be different in function, and that the non-crystalline hydrochloride may possibly be a mixture of two, or even more, of them.

When a considerably smaller quantity of acetic anhydride is taken and the whole heated to 100° for an hour, a product is formed which resembles β-diacetyl-morphine in every particular, save that it yields different numbers on analysis. The hydrochloride obtained as above described gave the following numbers :—

Specimen A. 0·4005 gram gave 0·9285 CO_2 and 0·233 H_2O
           0·4440 ,,   ,,   0·1835 AgCl.
Specimen B. 0·2745 ,,   ,,   0·639 CO_2 and 0·167 H_2O
           0·4350 ,,   ,,   0·186 AgCl.

	Calculated.		Found.	
			(A.)	(B.)
C_{36}	432	63·07	63·22	63·47
H_{42}	42	6·13	6·46	6·75
N_2	28	4·09	—	—
O_7	112	16·35	—	—
Cl_2	71	10·36	10·23	10·58
$C_{34}H_{37}(C_2H_3O)N_2O_6.2HCl$	685	100·00		

That this substance is truly a *monoacetyl-morphine* (or a mixture of isomeric monoacetyl derivatives) and not a mixture of morphine and diacetyl derivatives, is shown by the fact that the base itself is soluble

in ether, whereas morphine is practically not soluble in that menstruum ; moreover, a mixture of β-diacetyl-morphine hydrochloride and morphine hydrochloride in equal quantities dissolved in a little water allows almost the whole of the latter salt to crystallise out, and does not dry up to a varnish over sulphuric acid but to a crystalline mass wetted by a syrup, which finally dries up to a glaze over the crystals. Moreover, the platinum salt prepared with the neutral liquids obtained by shaking up the ethereal solutions with hydrochloric acid before the liquids had stood over sulphuric acid to dry up, gave the following numbers :—

A. 0·3540 gram gave 0·0690 Pt .... = 19·49 per cent.

B. 0·4980 „ „ 0·0950 „ .... = 19·41 „

Calculated for $C_{34}H_{37}(C_2H_3O)N_2O_6,2HCl,PtCl_4 = 19\cdot29$ „

No morphine could have been present in these preparations.

§ *6. Action of Water and Diluted Alkaline Solutions on Acetylated Codeine and Morphine.*

A. As diacetyl codeine can be crystallised without change from boiling water, the action of water alone on the base is not marked ; however, by long continued boiling with water a partial decomposition is brought about, acetic acid and codeine being formed. This change takes place readily if the base be heated in a sealed tube to 150° for three hours with water containing just sufficient of caustic potash to combine with the acetic acid generated; by using standard solutions any excess of potash and the codeine produced can readily be titrated, and hence the acetic acid generated can be found.

1·3420 gram of diacetyl-codeine yielded 0·2360 ⎱
   acetic acid............................ ⎰ = 17·6 per cent.
               Calculated . ... = 17·6 „

B. Tetracetyl-morphine in the free state when boiled with water gradually dissolves ; if the process be interrupted just as the last portions are on the point of solution (at the end of an hour or two) the liquid consists almost wholly of acetate of α-diacetyl-morphine, formed thus :—

$$C_{34}H_{34}(C_2H_3O)_4N_2O_6 + 2H_2O = C_{34}H_{36}(C_2H_3O)_2N_2O_6 + 2C_2H_3O.OH$$

if the action be prolonged, morphine acetate and free acetic acid are formed.

$$C_{34}H_{34}(C_2H_3O)_4N_2O_6 + 4H_2O = C_{34}H_{38}N_2O_6,2C_2H_3O.OH + 2C_2H_3O.OH.$$

The former base is readily extracted by adding carbonate of soda, shaking with ether, and agitating the ether with hydrochloric acid ; the

recrystallised sparingly soluble hydrochloride gave the following numbers after drying at 120° :—

$$0·2875 \text{ gram gave } 0·6610 \ CO_2 \text{ and } 0·170 \ H_2O$$
$$0·3685 \quad ,, \quad ,, \quad 0·1455 \ AgCl.$$

	Calculated.	Found.
Carbon..............	62·72	62·70
Hydrogen	6·05	6·57
Chlorine............	9·77	9·77

It is somewhat remarkable that α-diacetyl morphine chiefly results when morphine is treated with acetic acid, and when morphine is treated with excess of acetic anhydride, and half the acetyl thus removed by the action of water; whereas, when acetic anhydride not in excess is made to act on morphine, β-diacetyl-morphine is produced with only a minute quantity of the α-base.

The total acetic acid generated in the second reaction was estimated by titration as above, 1·103 gram being heated to 150° for eight hours with about 50 c.c. of water in a sealed tube (the action was only imperfect in a shorter time).

Acetic acid generated 0·3540 gram = 32·1 per cent.
Calculated............ = 32·5   ,,

C. α-Diacetyl-morphine in the free state is pretty readily decomposed by boiling water, producing morphine acetate; the hydrochloride, however, is much more stable. Thus, when the anhydrous hydrochloride was heated with water to 150° for five hours, the acetic acid generated was only—

Acetic acid .... = 10·5 per cent.
Calculated .... = 16·5   ,,

whereas when 1·086 gram of hydrochloride (deprived of water of crystallisation) was heated with water and just enough potash to liberate the base, the acid generated was—

0·1775 gram.......... = 16·35 per cent.
Calculated ...... = 16·50   ,,

D. β-Diacetyl-morphine hydrochloride is decomposed by water even more readily, boiling being sufficient to produce complete decomposition rapidly.

0·7965 gram of hydrochloride gave 0·1225 gram acetic acid = 15·4 p. c.
0·3140   ,,   ,,   0·0535   ,,   ,,   = 17·0 ,,

Calculated .... = 16·5 ,,

The morphine thus reproduced from the acetylated morphines ex-

hibited all the properties of ordinary morphine, and when precipitated by ammonia contained $C_{34}H_{38}N_2O_6, 2H_2O$.

Thus, 0·3225 gram from experiment C lost at 120° 0·0205 gram.

Loss .... $= 6·36$ per cent.
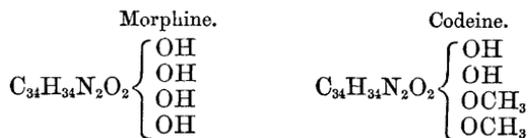
Calculated for $C_{34}H_{38}N_2O_6$ $2H_2O = 5·94$,,

After drying at 125°, the following numbers were obtained :—

B. From tetracetyl-morphine, 0·3005 gram gave 0·7865 CO_2 and 0·1815 H_2O.

C. From α-diacetyl-morphine, 0·2625 gram gave 0·6920 CO_2 and 0·1585 H_2O.

D. From β-diacetyl-morphine, 0·3025 gram gave 0·7930 CO_2 and 0·1820 H_2O.

	Calculated.		Found.		
			(B.)	(C.)	(D.)
C_{34}	408	71·58	71·38	71·89	71·49
H_{38}	38	6·67	6·71	6·71	6·69
N_2	28	4·91			
O_6	96	16·84			
$C_{34}H_{38}N_2O_6$	570	100·00			

§ 7. *Discussion of the foregoing Results.*

From the foregoing results it may be concluded (in accordance with the usual conventions as to symbolic formulæ) that the dissected rational formula of codeine contains *two* hydroxyl groups, and that of morphine *four;* and combining this with the results formerly obtained as to the mutual relationships of morphine and codeine, the following expressions are arrived at as the partially dissected formulæ of these alkaloïds respectively :—

Morphine.

$$C_{34}H_{34}N_2O_2 \begin{cases} OH \\ OH \\ OH \\ OH \end{cases}$$

Codeine.

$$C_{34}H_{34}N_2O_2 \begin{cases} OH \\ OH \\ OCH_3 \\ OCH_3 \end{cases}$$

The production of a substance having the composition of monoacetyl-morphine affords another proof that the formula of morphine must be written as the *double of the empirical formula,* $C_{17}H_{19}NO_3$.

The acetyl-derivatives described appear to be the first members of a new class of bodies related to the natural alkaloids as acetic ether, ethylene diacetate, triacetin, &c., are to alcohol, glycol, glycerin, &c. (and *not* related as acetamide to ammonia) : it is evident that in com-

position they are closely related to the bodies "chlorocodide," "bromocodide," and the unnamed bases previously described as Q and R. (This Journal, 1873, page 215.)

$$\left.\begin{array}{c} \text{Bromocodide.} \\ (\overline{C} + 2HBr - 2H_2O) \\ \text{Chlorocodide.} \\ (\overline{C} + 2HCl - 2H_2O) \end{array}\right\} \qquad \begin{array}{c} \text{Diacetyl-codeine.} \\ (\overline{C} + 2(H.C_2H_3O_2) - 2H_2O) \end{array}$$

$$\begin{array}{c} \text{Base Q.} \\ (\overline{M} + HCl - H_2O) \end{array} \qquad \begin{array}{c} \text{Monacetyl-morphine.} \\ (\overline{M} + H.C_2H_3O_2 - H_2O) \end{array}$$

$$\begin{array}{c} \text{Base R.} \\ (\overline{M} + 2HCl - 2H_2O) \end{array} \qquad \begin{array}{c} \text{Diacetyl-morphine.} \\ (\overline{M} + 2(H.C_2H_3O_2) - 2H_2O \end{array}$$

$$\begin{array}{c} \text{Tetracetyl-morphine.} \\ (\overline{M} + 4(H.C_2H_3O_2) - 4H_2O) \end{array}$$

Writing HX for any one of the monobasic acids, hydrochloric acid, hydrobromic acid, acetic acid, all these substances are included in the general formulæ.

$$\overline{M} + nHX - nH_2O : \text{where n is not greater than 4.}$$
$$\overline{C} + nHX - nH_2O : \qquad \text{,,} \qquad \text{,,} \qquad 2.$$

It is especially noteworthy that the brominated and chlorinated products hitherto obtained correspond physically with β-diacetyl morphine and the monoacetyl-morphine above described, and not with α-diacetyl morphine, and the (probably α) diacetyl-codeine. Taking the physical condition as an index, the following table may be constructed:—

α Series.	β Series.
	Chlorocodide and bromocodide.
Diacetyl-codeine.	
	Monoacetyl-morphine.
α diacetyl-morphine.	β-diacetyl-morphine.
Tetracetyl-morphine.	
	Base Q.
	Base R.

In connection with this it is noteworthy that Zorn has recently obtained from cinchonine, cinchonidine, quinine, and quinidine (*J. pr. Chem.* [2], viii, 279; abstract, p. 482 of this volume), chlorinated products bearing to these bases relations precisely analogous to those of "chlorocodide" to codeine; these, however, are capable of yielding well crystallised salts.

The above described results suggest a large number of experiments of various kinds, several of which are now being carried out in conjunction with Mr. G. H. Beckett; thus, butyric acid appears to act on

morphine, giving a dibutyryl-morphine; an α-benzoyl-morphine is apparently obtainable in small quantities by the action of benzoic acid on morphine; whilst benzoic anhydride forms dibenzoyl-codeine and tetrabenzoyl-morphine.

§ 8. *On the Physiological Action of the above Morphine and Codeine Derivatives.* By F. M. PIERCE, M.D., L.R.C.P. (Lond.), Associate of The Owens College.

Doses of the anhydrous hydrochloride of α- and β-diacetyl-morphine, tetracetyl-morphine, and diacetyl-codeine were subcutaneously injected into young dogs and rabbits, the quantities used in each instance being equivalent to 0·050 gram of anhydrous morphine hydrochloride. *i.e.,* the doses being—

α-diacetyl-morphine hydrochloride	......	0·0565 gram.		
β ,, ,, ,,	.....	0·0565 ,,		
Tetracetyl ,, ,,	.....	0·0630 ,,		
Diacetyl-codeine ,,	.....	0·0585 ,,		

with the following general results. No great amount of difference between the effects of the first three substances was noticeable, great prostration, fear, and sleepiness speedily following the administration, the eyes being sensitive, and pupils dilated, considerable salivation being produced in dogs, and slight tendency to vomiting in some cases, but no actual emesis. Respiration was as first quickened, but subsequently reduced, and the heart's action was diminished, and rendered irregular. Marked want of co-ordinating power over the muscular movements, and loss of power in the pelvis and hind limbs, together with a diminution of temperature in the rectum of about 4°, were the most noticeable effects, the action on rabbits being less marked than that on dogs, and salivation and defæcation not being produced in their case.

In the case of β-diacetyl-morphine, the moderate excitement produced after the first injection, and the diminution of temperature in the rectum were somewhat more marked than with the others, tetracetyl-morphine apparently producing the least excitement.

Diacetyl-codeine produced results of precisely the same character, but somewhat less marked; the want of muscular co-ordination was less noticeable, whilst salivation was most profusely caused with dogs; moreover, whilst in the case of the morphine derivatives, the animals only fully recovered in about 24 hours, about 8 hours sufficed for recovery in the case of diacetyl-codeine.

Other experiments are in progress; from these first results it seems that the physiological action of these acetylated bases is nearly the same as that of deoxymorphine and deoxycodeine, the codeine derivative being somewhat less potent than an equivalent quantity of the corresponding morphine derivative.