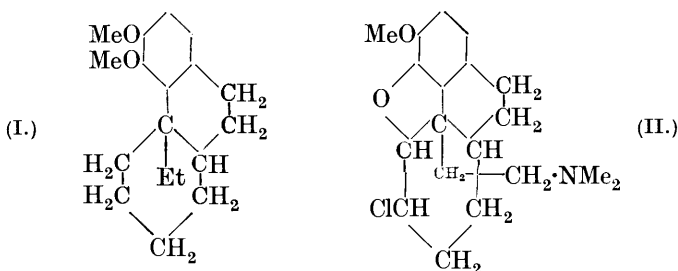# CCCXXXVII.—*Degradative Experiments in the Morphine Group.*
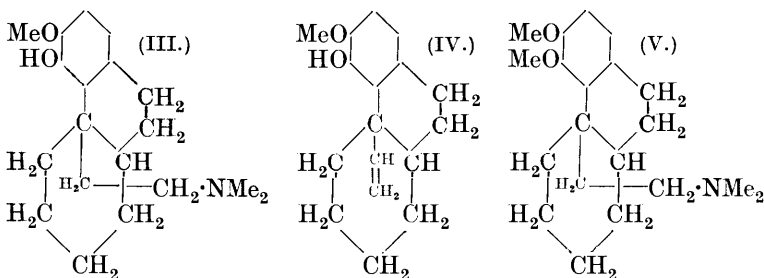
By ROBERT SIDNEY CAHN.

THE present experiments were instituted with the object of preparing degradation products of the natural alkaloids of the morphine group, which, while retaining an unmodified carbon skeleton, should yet be of as simple a character as possible. It appears that further progress in our knowledge of the structural chemistry of these bases

can only be made as a result of definite synthesis of such derivatives. With this end in view, attempts to prepare the substance having the formula (I) * were made, a study of the literature having shown that feasible routes to the compound had been indicated by other workers. For example, Speyer and Koulen (*Annalen*, 1924,

(I.)

MeO
MeO
CH$_2$
CH$_2$
C
H$_2$C Et CH
H$_2$C CH$_2$
CH$_2$

(II.)

MeO
O
CH$_2$
CH$_2$
C
CH CH
CH$_2$—CH$_2$·NMe$_2$
ClCH CH$_2$
CH$_2$

438, 34) found that tetrahydro-α-methylmorphimethine (obtained by catalytic reduction of α- or β-methylmorphimethine) on treatment with phosphorus pentachloride gave the chloro-compound (II), which was reduced by sodium and alcohol to a base, m. p. 161—163°, to which they assigned the constitution (III) (dihydrodeoxytetra-hydro-α-methylmorphimethine); the methiodide of this very readily lost trimethylamine on boiling with alkali and gave a substance, m. p. 76—78°, which they believed to be (IV), whilst by means of methyl sulphate the phenolic hydroxyl group was methylated and the dimethoxy-base (V) isolated as methiodide. If these results could be substantiated, it is clear that the substance (I) could be

(III.)

MeO
HO
CH$_2$
CH$_2$
C
H$_2$C CH
H$_2$C—CH$_2$·NMe$_2$
H$_2$C CH$_2$
CH$_2$

(IV.)

MeO
HO
CH$_2$
CH$_2$
C
H$_2$C CH CH
CH$_2$
H$_2$C CH$_2$
CH$_2$

(V.)

MeO
MeO
CH$_2$
CH$_2$
C
H$_2$C CH
H$_2$C—CH$_2$·NMe$_2$
H$_2$C CH$_2$
CH$_2$

prepared from (IV) by reduction followed by methylation, or alternatively from the methiodide of (V) by Hofmann degradation followed by reduction. On examination, however, it was found that the nitrogen-free compound, contrary to the statement of Speyer and Koulen, is insoluble in alkali, and, as it can be neither methylated

* In the formulæ in this paper the attachment of the ethanamine chain to C[13] (Gulland and Robinson, J., 1923, **123**, 980) is assumed, and the constitutions of all compounds are modified where necessary in this respect.

nor acetylated, it must contain, not a phenolic hydroxyl group as in (IV), but rather an ether linking as in thebenol, thebenone, etc. Further, the dimethoxy-methiodide on heating with amyl-alcoholic potassium hydroxide loses, not trimethylamine, but one methyl group, and gives a nearly quantitative yield of the dimethoxy-base, an oil characterised by various well-defined derivatives.

Gulland and Robinson (J., 1923, **123**, 988) treated dihydro-thebainone (VI) with diazomethane and characterised the methyl-ated product by its methiodide. The same salt was more readily obtained by methylation with methyl sulphate and on boiling with alkali gave the methine (VII). The double bond at the 9 : 10-position
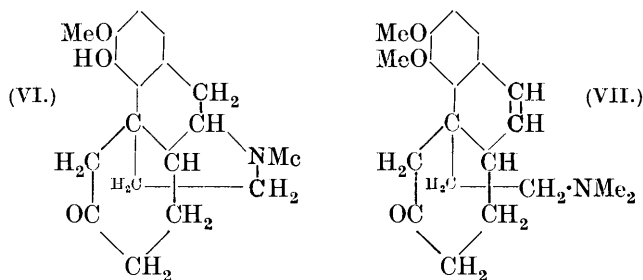

was reduced catalytically and the *dihydromethyldihydrothebainone-methine* * thus obtained yielded on reduction by Clemmensen's method an oily base to which formula (V) must be assigned, but which was *not* identical with that obtained from Speyer and Koulen's series. This difference was not due to possible *cis–trans* ring iso-merism (the explanation offered by Gulland and Robinson, *Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10, for the two tetrahydro-deoxycodeines †). Speyer and Koulen's base melting at 161—163° and the two substances derived from it all absorb one mol. of hydrogen in the presence of colloidal palladium. It follows that they are unsaturated compounds and that the formulæ assigned to them by Speyer and Koulen are incorrect. The reduction of chloro-tetrahydro-α-methylmorphimethine by sodium and alcohol leads not to (III), but to deoxytetrahydro-α-methylmorphimethine (VIII), which contains a double bond in ring III.‡ The formula of the nitrogen-free compound, m. p. 76—78°, is accordingly (IX) (a five-

* It seems preferable to extend the " methine " nomenclature to this series (compare Gulland and Robinson, J., 1923, **123**, 985) rather than to adopt the " de-*N*-methyl " method of many German chemists (see footnote, p. 2570).

† Some additional work on these compounds is reported in the experi-mental part of this paper.

‡ The position 6 : 7 chosen for the double bond seems preferable to 5 : 6, which is, however, also possible.

membered oxygen ring being adopted here in preference to the six-membered ring hitherto assigned to these compounds), and that of

MeO — (VIII.)   MeO — (IX.)   MeO — (X.)
HO   O   MeO

CH_2
CH_2
H_2C CH
H_2C—CH$_2$·NMe$_2$
HC CH_2
CH
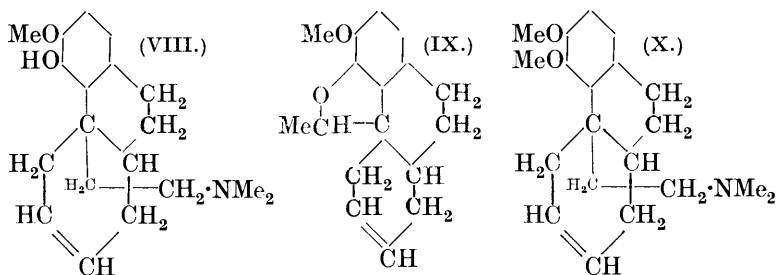
the dimethoxy-base obtained from Speyer and Koulen's methiodide is (X). The catalytic reduction of (X) did not proceed to completion owing to the impossibility of obtaining the oily substance sufficiently pure, and the nitrogen-free compound (IX) gave an oil. The base (VIII), however, yielded a crystalline substance to which formula (III) applies; the methiodide of this loses trimethylamine on heating with aqueous alkali and gives an oily nitrogen-free compound, doubtless identical with that obtained by reduction of the substance (IX); and finally, if this reduced base (III) is methylated with methyl sulphate and the quaternary salt thus obtained heated with amyl-alcoholic potassium hydroxide, one methyl group is lost and a dimethoxy-base (V) obtained, which is different from that obtained from Speyer and Koulen's methiodide and appears to be identical with that obtained from the dihydrothebainone series.

EXPERIMENTAL.

Deoxytetrahydro-α-methylmorphimethine (VIII), obtained according to Speyer and Koulen's directions (*loc. cit.*) and recrystallised from chlorobenzene, melted at 163—164°. The *perchlorate*, crystallised from water, melted at 159°. The methiodide lost trimethylamine, on heating with aqueous potassium hydroxide, with a readiness which is seldom met with in this group of compounds unless an ether linking is formed with the phenolic 4-hydroxyl group; the nitrogen-free compound (IX) thus obtained was recrystallised from a little alcohol and had m. p. 79—81°. This is the only one of these compounds which was erroneously analysed by Speyer and Koulen; in the others, the deficiency of two hydrogen atoms cannot be detected with certainty, although indications were in all cases obtained. Speyer and Koulen's figures (C, 78·2, 78·3; H, 8·1, 8·0%) agree better with the formula $C_{15}H_{18}O_2$ (C, 78·2; H, 7·9%) than with the correct formula $C_{15}H_{16}O_2$ (C, 78·9; H, 7·1%), whilst the values obtained in the present investigation (C, 79·0, 79·2; H, 8·0,

8·0%) are inconclusive. Nevertheless, the reactions now described leave no doubt as to the correct constitution (IX) and it would appear that the low-melting substance is difficult to free from adhering solvent. The substance is insoluble in dilute aqueous sodium or potassium hydroxide. Speyer and Koulen state that it is soluble in alcoholic potassium hydroxide; it is, however, fairly readily soluble in alcohol, and addition of a drop of alkali solution to a saturated alcoholic solution containing a little of the substance in suspension did not cause a further appreciable quantity to dissolve. In attempts to acetylate it by heating on the steam-bath for 1 hour with ten times its weight of acetic anhydride, or to methylate it by (a) allowing it to stand over-night with methyl sulphate in aqueous-alcoholic sodium hydroxide solution, (b) refluxing it in benzene for 2 hours with excess of methyl iodide and silver oxide, and (c) refluxing it for 2 hours in nitrobenzene with excess of methyl sulphate and potassium carbonate, the unchanged substance was in all cases isolated almost quantitatively. For the reduction of the double bond in ring III, a palladinised charcoal catalyst was prepared by stirring a suspension of norite (2 g.) in a solution of palladous chloride (0·2 g.) in water (100 c.c.) in the presence of hydrogen until absorption ceased, filtering, and washing with water and finally with alcohol. This catalyst was added to a solution of the substance (IX) (1 g.) in alcohol (35 c.c.), which then, on being stirred in an atmosphere of hydrogen, absorbed 112 c.c. (corrected to $N.T.P.$) in 25 minutes. In a blank experiment the recovered catalyst adsorbed 15 c.c.; the real absorption was thus 97 c.c. (1 mol. = 87 c.c.). After the reduction, the solution was filtered hot and evaporated to dryness, whereby a colourless oil was obtained which could not be crystallised. Seeding with the original substance was without effect.

Methyldeoxytetrahydro-α-methylmorphimethine (X).—The methiodide (2·8 g.) of this compound (Speyer and Koulen, *loc. cit.*) was refluxed in amyl alcohol (30 c.c.) with potassium hydroxide (5 g.) for 2½ hours. The alcohol was removed by steam-distillation and the oil taken up in ether and shaken with dilute acid. The ethereal solution after drying over calcium chloride gave on evaporation a minute quantity of a yellow oil. The acid solution was treated with excess of ammonia and the base was extracted by ether, dried over potassium carbonate, and obtained after evaporation as an almost colourless oil (yield 1·7 g.; 85%). It was identified as *methyl-deoxytetrahydro-α-methylmorphimethine* by its methiodide, which was readily formed on treatment with methyl iodide and could be recrystallised from water or from acetone–ether; it melted at 209— 211° after sintering at 208° and at the same temperature when mixed with the original methiodide used for the degradation. The

hydriodide separates from water, in which it is very sparingly soluble in the cold, in felted needles and short columns, m. p. 170—171° (Found, in material dried at 100° in a vacuum : C, 54·25; H, 6·85; I, 28·3; MeO, 13·5. $C_{20}H_{30}O_2NI$ requires C, 54·15; H, 6·8; I, 28·6; 2MeO, 14·0%). The *perchlorate* separates from water in needles, m. p. 206—208°. The base dissolves in concentrated sulphuric acid with a not very intense reddish-orange coloration which soon disappears on dilution.

Dihydrodeoxytetrahydro-α-methylmorphimethine (III).—A solution of deoxytetrahydro-α-methylmorphimethine (3·5 g.; m. p. 163—164°) in 1% acetic acid solution (100 c.c.), on being stirred with hydrogen in the presence of the colloidal palladium derived from 20 c.c. of standard catalyst solution,* absorbed 272 c.c. (corrected to *N.T.P.*) in 70 minutes (1 mol. = 258 c.c.). After flocculation of the colloid and filtration, *dihydrodeoxytetrahydro-α-methylmorphimethine* (3·2 g.) was precipitated by ammonia as a colourless, microcrystalline powder, which separated from chlorobenzene in rods, m. p. 152·5—154° (Found, in material dried at 100° : C, 75·2; H, 9·7. $C_{19}H_{29}O_2N$ requires C, 75·2; H, 9·6%). It is somewhat more soluble in chlorobenzene than the unreduced compound. A satisfactory depression of m. p. could not be obtained after mixing it with the unreduced base ; when approximately equal quantities were either mixed on a porous plate or melted together on a watch-glass and allowed to resolidify, the m. p. was 148—151° after slight previous sintering. The *hydriodide* of the new base separates from water in rectangular columns and irregular plates, m. p. 219—220°, whereas that of the unreduced base could not be crystallised and is also not recorded by Speyer and Koulen. The *perchlorate* separates from water in rods, m. p. 150—153°. The *methiodide* was gradually precipitated as a crystalline powder on warming a solution of the base in ethyl acetate with methyl iodide, m. p. 230° (Found, in material dried at 100° in a vacuum : I, 28·5. $C_{20}H_{32}O_2NI$ requires I, 28·5%). To a solution of this methiodide (0·7 g.) in boiling water (2·5 c.c.) was added 50% potassium hydroxide solution (5 c.c.), whereupon precipitation of an oil and rapid evolution of trimethylamine took place. The reaction was completed by boiling the solution for 5 minutes; the oil was purified but could not be crystallised. Seeding with Speyer and Koulen's substance (IX) was without effect and it is highly probable that this oil is identical with that obtained by reduction of the substance (IX).

Methyldihydrodeoxytetrahydro - α - methylmorphimethine (V). — *Method A.* Dihydrodeoxytetrahydro-α-methylmorphimethine (2·3

* This solution contained 0·5% of palladous chloride and 0·5% of gum arabic in water.

g.) was shaken with 8% sodium hydroxide solution (in which this phenolic base does not dissolve), and methyl sulphate (7·5 c.c.) gradually added with cooling, shaking being continued until the whole was homogeneous. Addition of potassium iodide solution to a portion of this solution precipitated an oily methiodide, which could not be induced to crystallise, and seeding with the methiodide of dihydrodeoxytetrahydro-α-methylmorphimethine and with that of methyldeoxytetrahydro-α-methylmorphimethine was without effect (the former to indicate whether methylation had taken place, the latter to confirm the reduction). To the bulk of the solution was added 50% potassium hydroxide solution (75 c.c.) and the whole refluxed for 2 hours, whereupon a dark oil rapidly separated ; this consisted of the methosulphate, which was stable to boiling aqueous alkali, for at the end of this time ether extracted only a negligible quantity of material, either neutral or basic. The solution was then treated with solid potassium hydroxide, and the supernatant oil dissolved in amyl alcohol (15 c.c.). Potassium hydroxide (5 g.) was added to the alcoholic solution, which was refluxed for 2 hours ; the amyl alcohol was then removed by distillation in steam and the residual solution extracted with ether. The extract was shaken with dilute acid and then retained only a negligible amount of neutral material. *Methyldihydrodeoxytetrahydro-α-methylmorphimethine* was extracted by ether from the acid solution after addition of ammonia, dried over potassium carbonate, and obtained on removal of the solvent as a nearly colourless oil (yield 1·8 g. ; 78%). The *hydriodide*, after two recrystallisations from water, melted at 174— 176° ; mixed with that of methyldeoxytetrahydro-α-methyl-morphimethine (m. p. 170—171°), it sintered at 153° and melted unsharply at *ca.* 155—158°. The *methiodide* could not be crystallised. The *perchlorate* after recrystallisation from water melted at 194—195° ; mixed with the perchlorate of methyldeoxytetrahydro-α-methylmorphimethine (m. p. 206—208°), it melted unsharply over the range 195—206°, even when the substances had been melted together on a watch-glass and allowed to resolidify. The depression obtained with the hydriodides, however, leaves no doubt that these two substances are different.

Methyldihydrothebainonemethine (VII). — Dihydrothebainone * (18 g.) was shaken with 10% sodium hydroxide solution (180 c.c.), the base going into solution and separating later as a paste of

* Freed from dihydrothebaine, which always accompanied the phenolic base in the reduction product of thebaine, by solution in alkali and precipitation by carbon dioxide. The crystalline base thus obtained melted at 140—150°, being contaminated with dihydrothebainol (Skita, *Ber.*, 1921, **54**, 1560), but was pure enough for further work.

crystalline sodium salt.   Methyl sulphate (15 c.c.) was added in portions with shaking until a clear red solution was formed.   Addition of a concentrated solution of potassium iodide (20 g.) precipitated the methiodide of methyldihydrothebainone as a rapidly solidifying oil which, after standing for 1 hour, was collected in a glass Gooch crucible and drained.   A portion, recrystallised from methyl alcohol, melted at 258—260° (decomp.) after darkening at *ca*. 255°.   Gulland and Robinson (J., 1923, **123**, 1009) prepared this compound by a different method and state that it darkens slightly at 257—258°.   The crude methiodide was dissolved in boiling water (180 c.c.), 10% sodium hydroxide solution added, and boiling continued for 10 minutes.   The deposited oil was cooled, taken up in ether, and dried over potassium carbonate.   On removal of the solvent, *methyldihydrothebainonemethine* was obtained as a pink oil which solidified on cooling.   It is very soluble in ethyl and methyl alcohols and in benzene, slightly less soluble in ethyl acetate, insoluble in dilute sodium hydroxide solution, although appreciably soluble in water, from which it is precipitated by strong alkali. It is best purified by distillation in a high vacuum (b. p. 184—186°/2 mm.), being obtained as a colourless, very viscous oil, which slowly solidifies and is pure enough for further work.   On recrystallisation from ligroin, it melts at 89·5° (Found : C, 72·65 ; H, 8·2. $C_{20}H_{27}O_3N$ requires C, 72·9 ; H, 8·2%) (yield of distilled product, 12 g. ; 61%).   The *hydriodide* separates from water in columns, m. p. 211—212° (Found : I, 27·7. $C_{20}H_{28}O_3NI$ requires I, 27·8%). The *semicarbazone* was prepared by warming the base (0·5 g.) with sodium acetate (2 g.) and semicarbazide hydrochloride (1 g.) in dilute acetic acid (10 c.c.) for 5 minutes at 80°, cooling the mixture, keeping it for 5 minutes, rendering it alkaline with sodium carbonate, and extracting it with chloroform.   The oil left on removal of the solvent crystallised on being rubbed with alcohol and separated from this solvent in needles, m. p. 184° (Found: N, 13·8. $C_{20}H_{30}O_3N_4,H_2O$ requires N, 13·9%).   On allowing the base (0·5 g.) to stand for 70 hours with a solution of potassium hydroxide (0·2 g.) and piperonal (0·5 g.) in alcohol (10 c.c.), a yellow colour was developed, and the *monopiperonylidene* derivative was obtained in the usual way, as a yellow oil, which gave with concentrated sulphuric acid a deep yellowish-red solution becoming colourless on slight dilution. No attempt was made to prepare a dipiperonylidene derivative. The *methiodide* was readily formed as a red oil on gently warming the base with 1 part each of methyl alcohol and methyl iodide and evaporating the mixture.   A portion slowly crystallised after several days ; recrystallised from a minimum of methyl alcohol and dried in a vacuum at 100°, it melted at *ca*. 189°, but was not quite pure.

Attempts to degrade this methiodide (a) by heating with aqueous sodium hydroxide solution, (b) by transformation into the quaternary hydroxide by means of silver oxide and heating this for several hours on the steam-bath or for 30 minutes at 200°, and (c) by transformation into the methochloride and reduction of this by 5% sodium amalgam, were all unsuccessful. By the last method, a very small quantity of a neutral substance, m. p. 138—141°, was obtained but it was not further investigated.

Dihydromethyldihydrothebainonemethine.—A solution of methyldihydrothebainonemethine (12 g., distilled) in 4% acetic acid solution (120 c.c.), on being stirred with hydrogen in the presence of colloidal palladium (from 20 c.c. of standard catalyst solution), absorbed 790 c.c. (corrected to $N.T.P.$) in 17 minutes (1 mol. = 820 c.c.). After flocculation of the colloid and filtration, the base was rendered to ether after addition of ammonia and dried over potassium carbonate. On removal of the solvent, *dihydromethyldihydrothebainonemethine* (11·5 g.) was obtained as a colourless oil which rapidly solidified. It is very soluble in ether and ethyl and methyl alcohols. Recrystallised from light petroleum, it melts at 70·5—72° (Found : C, 72·8; H, 9·1. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·85%). Mixed with the unreduced base, it melted at 57—59°, but equal quantities melted together on a watch-glass could not be induced to crystallise on cooling. The *hydriodide* separates from water in needles, m. p. 224—225° (Found : I, 27·7. $C_{20}H_{30}O_3NI$ requires I, 27·6%) ; the *perchlorate* melts at 216°. The *semicarbazone* was obtained as a gum which slowly crystallised. Recrystallised from alcohol, it melted at 176—178° (Found : N, 13·5, 13·6. $C_{21}H_{32}O_3N_4,H_2O$ requires N, 13·8%). On boiling a methyl-alcoholic solution of the base for a few minutes with excess of methyl iodide and subsequently removing the solvents, the methiodide was obtained as an uncrystallisable oil, which set to a glass on cooling. It is very soluble in water and alcohol ; addition of sodium acetate and perchloric acid to its solution in water precipitates the *methoperchlorate*, which crystallises from water in needles, m. p. 185—186°. The same salt can also be prepared from *dihydro-dihydrothebainonemethine.** This base was prepared in several ways by Wieland and Kotake (*Annalen*, 1925, **444**, 89), who gave m. p. 154—156°. The present author prepared it according to their directions by catalytic reduction of dihydrothebainemethine, but in two separate experiments the highest m. p. which could be obtained was 138—139°. The substance was identified by its picrate, m. p. 185—187° (Wieland and Kotake, 185—188°), and by conversion into thebenone, m. p.

* Wieland and Kotake (*loc. cit.*), adopting the German notation (see footnote, p. 2564), call this " dihydrode-N-methyldihydrothebainone."

134—137°. Wieland and Kotake report that this phenolic base is very difficult to methylate, but this observation has not been confirmed. Dihydro-dihydrothebainonemethine (5 g.) was shaken with 2N-sodium hydroxide solution, and methyl sulphate (14 c.c.) added in small portions with cooling, shaking being continued until a homogeneous liquid was obtained. Addition of perchloric acid precipitated the *methoperchlorate* of *dihydromethyldihydrothebainonemethine*, which separated from alcohol in needles, m. p. 185° (yield 5 g.; 71%). No depression of m. p. was observed with a mixture with the same salt obtained by the alternative method given above. For comparison, the *perchlorate* of *dihydro-dihydrothebainonemethine* was prepared; it separated from water in long, thin needles, m. p. 233°.

Methyldihydrodeoxytetrahydro - α - methylmorphimethine (V).—
Method B. Dihydromethyldihydrothebainonemethine (4 g.) in 17% hydrochloric acid (100 c.c.) was heated on the steam-bath with amalgamated zinc turnings (40 g.); after 1 hour more of the acid was added from time to time to maintain a brisk evolution of hydrogen; after 3½ hours, during which time an oil gradually separated and later solidified (probably the hydrochloride or zinc double salt), the solution was cooled and treated with an excess of ammonia. Two extractions with ether removed the *methyldihydro-deoxytetrahydro-α-methylmorphimethine*, which was obtained, after drying over potassium carbonate and evaporation of the solvent, as a colourless, uncrystallisable oil (3·5 g.). The *hydriodide*, recrystallised twice from water, formed needles, m. p. 177·5—178·5° (Found in material dried at 100° in a vacuum : C, 54·1, 54·3; H, 7·4, 7·4; I, 28·5; MeO, 14·0. $C_{20}H_{32}O_2NI$ requires C, 53·9; H, 7·25; I, 28·5; 2MeO, 13·9%). Mixed with the hydriodide of methyldeoxytetrahydro-α-methylmorphimethine, it melted at 153—156°; mixed with the hydriodide (m. p. 174—176°) of the base obtained by method A, it melted at 175—177°. The perchlorate, after one recrystallisation from water, melted at 184—185°, and after a second, at 190—191°. Mixed with the perchlorate (m. p. 194—195°) of the base prepared by method A, it melted at 191—193°. On gently warming the base (1 g.) with methyl alcohol (2 c.c.) and methyl iodide (2 c.c.) for 5 minutes and then removing the solvents, the methiodide was obtained as an uncrystallisable oil (see method A). This was refluxed for 2 hours in amyl alcohol with the addition of potassium hydroxide (2 g.), and on treatment as in method A there were obtained a very small neutral fraction and a base (0·5 g.), which was identified as the original substance by the m. p.'s of its hydriodide (m. p. 176·5—178°) and perchlorate (m. p. 182—184°, not recrystallised). The decomposition of the methiodide proceeds, therefore,

as in method A, with loss of the methyl group. This unusual reaction and the m. p.'s recorded above appear to establish the identity of the bases prepared by the two methods; nevertheless, because of the failure (see p. 2568) of the perchlorate of the base prepared by method A to depress the m. p. of the perchlorate of (X), no great stress can be laid on identification of bases of this series by means of the perchlorates.

The Isomerism of the α- *and* β-*Tetrahydrodeoxycodeines.*—From a study of the literature it appeared that the important isomerism of the α- and β-tetrahydrodeoxycodeines (Knorr and Waentig, *Ber.*, 1907, **40**, 3683; Freund, Melber, and Schlesinger, *J. pr. Chem.*, 1920, **101**, 1) might be fallacious and due to the α-isomeride being a mixture of unreduced deoxycodeine and the β-tetrahydro-derivative. Nearly all the recorded properties of α-tetrahydrodeoxycodeine and its derivatives approximate very closely either to those of deoxycodeine or to those of its β-isomeride. For example, α-tetrahydrodeoxycodeine (prepared for this investigation by reduction of chlorocodide with sodium and alcohol) was purified by recrystallisation from methyl alcohol, conversion into the hydriodide, which was twice recrystallised, and crystallisation of the liberated base from methyl alcohol; it was still an ill-defined substance, sintering at 115° and melting at *ca.* 125—130°. Mixed with deoxycodeine (m. p. *ca.* 126°), it melted at *ca.* 130°. On the other hand, the *hydriodide* of the α-isomeride (not hitherto described) crystallised from water in elongated prisms, m. p. 242—243°, and that of the β-isomeride in prismatic needles, m. p. 240—241°, whilst a mixture of the two melted at 241°. On obtaining these results it was decided to test the above hypothesis, the hydrochlorides being chosen for this purpose. Deoxycodeine hydrochloride is sparingly soluble in alcohol, sinters at 165° (decomp.) and melts at *ca.* 270° (decomp.), and has $[\alpha]_D + 86°$. The hydrochloride of α-tetrahydrodeoxycodeine is also sparingly soluble in alcohol, melts at *ca.* 155° (decomp.), and has $[\alpha]_D - 17°$. The hydrochloride of the β-isomeride, however, is readily soluble in alcohol and melts at *ca.* 262°. If the above hypothesis were correct, it should be possible by fractional crystallisation of the α-salt to obtain a *dextrorotatory*, least soluble fraction and to concentrate the β-salt into the mother-liquors. Accordingly, the hydrochloride (7·5 g.) of the crude α-isomeride was fractionally crystallised from alcohol; after six crystallisations the least soluble fraction (0·8 g.) melted at 158° (decomp.) and had $[\alpha]_D^{17°} - 40°$; the base prepared from it, recrystallised from methyl alcohol, melted at 134—135° after sintering at 125°, and was lævorotatory. The liquor containing the most soluble fraction gave on evaporation a brown oil from which the base was extracted by ether after

addition of ammonia; after removal of the solvent, a red oil was obtained which could not be crystallised from methyl alcohol, although the β-base crystallises well from this solvent. As no separation had occurred and the only result of the fractionation was the preparation of α-tetrahydrodeoxycodeine in a state of slightly greater purity than hitherto, this experiment may be taken as a much-needed confirmation of the homogeneity of this base and of the reality of the isomerism. The absence of depressions noted above is remarkable, but two similar cases among closely related compounds were recorded earlier in this paper.