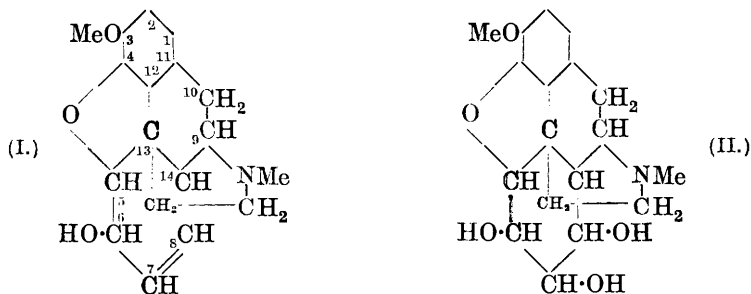CXXVI.—*The Morphine Group. Part IV. A New Oxidation Product of Codeine.*

By ROBERT SIDNEY CAHN and ROBERT ROBINSON.

THE secondary alcohol codeine can be oxidised to the corresponding ketone by means of chromic acid or of potassium permanganate in acetone solution, and apart from the hydroxycodeine which accompanies codeinone in the former case (Ach and Knorr, *Ber.*, 1903, **36**, 3067) no other products of direct oxidation of the base have been described. This has perhaps led to the impression that the attack of oxidising agents is invariably on the alcoholic group, although attention has occasionally been directed to the fact that the sensitiveness of codeine to permanganate is greater than that of any known saturated alcohol and strongly suggests the existence of an ethenoid group in the molecule (compare Wieland and Kotake, *Annalen*, 1925, **444**, 69 ; Gulland and Robinson, *Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10). The remarkable ease with which codeine may be converted into a dihydro-derivative by catalytic hydrogenation is in harmony with this hypothesis, and we now bring forward further evidence tending in the same direction. The action of potassium permanganate on codeine (I) in very dilute aqueous solution leads to the addition of two hydroxyl groups to the molecule and the product is dihydroxydihydrocodeine (II). This substance yields a basic triacetyl derivative and its form-

ation demonstrates the existence of an ethylenic linking in codeine. The position chosen for the double bond in (I) is that independently

$$
\begin{array}{ll}
\text{(I.)} & \text{(II.)}
\end{array}
$$

MeO$_3$ — ... — ¹¹ / ¹² / ¹⁰CH$_2$ / O — C ₉CH — NMe / CH ¹⁴CH — CH$_2$ / CH$_2$· — ĊH$_2$ / HO·CH ₈CH / ⁷CH

MeO — CH$_2$ / O — C CH — NMe / CH CH CH$_2$ / CH$_2$· — ĊH$_2$ / HO·CH CH·OH / CH·OH

selected by Wieland and Kotake and by Gulland and Robinson for different reasons. It is especially required to explain the codeine–ψ-codeine change (analogy to geraniol–linalool) and the reactivity of the chlorine atom of chlorocodide (analogy to allyl chloride and benzyl chloride). A possible objection (compare Gulland and Robinson, *loc. cit.*) is that ψ-codeinone reacts with benzaldehyde as if it contained the group ·CH$_2$·CO·, whereas it should contain ·O·CH·CH:CH·CO· on the suggested basis. The difficulty is removed by recognising the following system of tautomerides :

$$
\text{·CH·CH:CH·CO·} \rightleftharpoons \text{·C:CH·CH:C(OH)·} \rightleftharpoons \text{·C:CH·CH}_2\text{·CO·}
$$

which might be equilibrated in presence of alcoholic potassium ethoxide or similar reagents. Although it seems probable that general agreement will soon be reached in regard to the occurrence of the group ·CH(OH)·CH:CH· in codeine and its isomerides, and the morphine problem will to that extent be simplified, there is still room for differences of opinion in regard to the point of attachment of the ethanamine chain. Wieland and Kotake (*loc. cit.*) have noted that some substances which on the basis of (I) should contain the group ·CH$_2$·CO·CH$_2$· nevertheless have only one reactive position * and prefer the formula (III) for codeine.

On the other hand, a consideration of the behaviour of the unsaturated centres in the methylmorphimethines appears to us to provide further evidence favouring the formula (I). If (III) represented codeine, we imagine that β-methylmorphimethine would be

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* The attachment of the ethanamine chain in position 13, as in (I), was not based on the production of dipiperonylidene derivatives of thebainol and dihydrothebainone but on the arguments put forward in Part I of this series, to which, with the modification made in our note in the *Manchester Memoirs*, we adhere.—J. M. G., R. R.

(IV), a naphthalene derivative. That the bond migrating from the position 7—8 should halt in the position 8—14 and not proceed to

(III.)   (IV.)
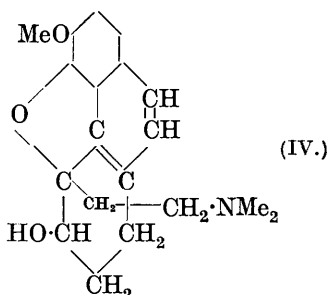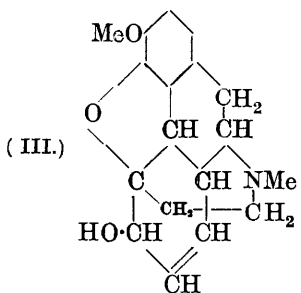
13—14, where it assists in the formation of a new aromatic nucleus, seems highly improbable. Now β-methylmorphimethine appears to contain non-aromatic unsaturated centres, since it very readily reduces permanganate, more readily than neopine * does, and on catalytic hydrogenation gives a 9 : 10-dihydro-derivative (von Braun, *Festschr. phys. Ver.*, Frankfort a. M., 1924, Sept.; Cahn, *Dissert.*, Frankfort, 1925). The formula (I), on the other hand, affords a satisfactory explanation of the relations of codeine, neopine, and α- and β-methylmorphimethines.

EXPERIMENTAL.

Dihydroxydihydrocodeine (II).—An aqueous solution of potassium permanganate (332 c.c. of 1%) was added during 1·5—2 hours to a mechanically stirred solution of codeine † (10 g.) in water (1500 c.c.) mixed with ice (500 g.) and cooled in an ice-bath. The manganese dioxide was precipitated from the colloidal solution by passing carbon dioxide for ½ hour and stirring for a further equal period, and the almost colourless filtered liquid was then concentrated to about 400 c.c. by distillation under diminished pressure. Much frothing and decomposition occurred. By means of ether codeine (1·4—1·6 g.) was extracted from the dark brown solution, which was then concentrated to about 40 c.c. and treated with saturated aqueous potassium carbonate (150 c.c.), a semi-solid, almost black material being precipitated. The mixture was twice extracted with 200 c.c. of chloroform, and the solutions were dried with sodium sulphate and evaporated, leaving 5 g. of an amorphous, hygro-

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* β-Methylmorphimethine is also neopinemethine (Van Duin, Robinson, and Smith, this vol., p. 903).

† A similar experiment was carried out with ψ-codeine, but necessarily in much more dilute solution owing to the sparing solubility of the base in cold water. A large fraction of the ψ-codeine was recovered and no other crystalline product was isolated.

scopic, dark brown residue (A), which was taken up in dry ethyl alcohol (15 c.c.). Crystallisation was induced by rubbing and after some hours the crude base (1·2 g. or 11·5%) was collected and twice recrystallised from absolute alcohol (yield 0·6 g.) in colourless, glistening, diamond-shaped plates, m. p. 208—209° (Found in material dried in a vacuum at 100° : C, 64·8; H, 7·0; N, 4·5; MeO, 9·4. $C_{18}H_{23}O_5N$ requires C, 64·8; H, 7·0; N, 4·2; MeO, 9·3%). This substance is easily soluble in water to strongly alkaline solutions but, when pure, it is not very hygroscopic; it is sparingly soluble in ether and benzene and in cold anhydrous methyl or ethyl alcohol. The base does not exhibit many of the colour reactions characteristic of codeine; with Froehde's reagent, it yields a yellow solution which becomes brown on warming, and with Mandelin's reagent it gives a brown solution which on gently warming becomes light green. Unlike codeine, it is only slowly attacked by potassium permanganate in dilute aqueous solution. The salts of this base, including the methiodide, were not obtained in a crystalline condition. As the substance has the same state of oxidation as codeinone and thebaine, a specimen was submitted to the action of hydrochloric acid under the conditions which are employed for the preparation of thebenine from thebaine, but no change occurred. The low yield of the trihydroxy-base is probably due to side reactions, further oxidation and possibly the production of stereoisomerides.

The *triacetyl* derivative is characteristic and may be most conveniently obtained from the material (A) mentioned above. 3 G. of this, heated with acetic anhydride (30 c.c.) for 75 minutes on the steam-bath, gave a brown solution which was decomposed with water, rendered alkaline by ammonia and extracted with chloroform. After removal of the solvent the residue was dissolved in methyl alcohol (10 c.c.) and the crystals which separated on cooling were collected (0·3 g.) and recrystallised from methyl alcohol in colourless plates, m. p. 200° (Found in material dried at 100° over phosphoric anhydride in a vacuum : C, 62·9; H, 6·6; N, 3·3. $C_{24}H_{29}O_8N$ requires C, 62·7; H, 6·4; N, 3·1% and $C_{22}H_{27}O_7N$ requires C, 63·3; H, 6·5; N, 3·4%). As the analytical results were in approximate agreement with the theoretical requirements of the formulæ of both the diacetyl and the triacetyl derivative of the parent base, it was vitally important to estimate the acetyl groups directly. We are greatly indebted to Professor K. Freudenberg and Dr. E. Weber, who have kindly carried out the estimations by a new micro-analytical method (Freudenberg, *Annalen*, 1923, **433**, 230; Freudenberg and Weber, *Z. angew. Chem.*, 1925, **38**, 280) [Found : $CH_3 \cdot CO$, 27·93, 27·78, 27·87. $C_{18}H_{20}O_5N(CO \cdot CH_3)_3$

requires $CH_3 \cdot CO$, 28·09%]. The acetyl groups were somewhat resistant to hydrolysis, and two distillations were necessary; the standard process gave $CH_3 \cdot CO$, 24·6%. This might suggest that one of the acetyl groups is attached to nitrogen, were it not for the fact that the substance is a strong base readily soluble even in dilute acetic acid. A compound identical with the above-described derivative was obtained by acetylation of pure dihydroxydihydrocodeine.

Triacetyldihydroxydihydrocodeine is sparingly soluble in water and in cold methyl alcohol; its *perchlorate* crystallises from water in slender, colourless needles, m. p. 281° with slight previous decomposition.