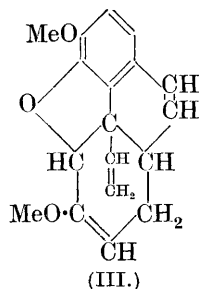
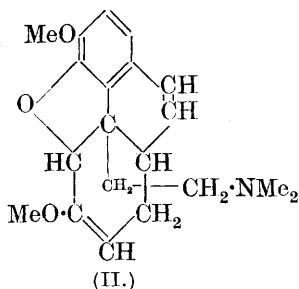
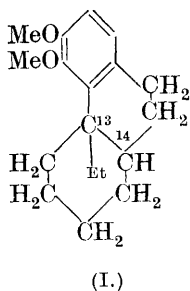


XCII.—*Further Degradative Experiments in the Morphine Group.*

By ROBERT SIDNEY CAHN.

THE following experiments are a continuation of earlier work (J., 1926, 2562) which had as its object the preparation, with a view to later synthesis, of 3:4-dimethoxy-13-ethyloctahydrophenanthrene (I) from the natural alkaloids of the morphine group. They have had to be discontinued * short of ultimate success and are here placed on record for reference.

The route chosen must give no opportunity for wandering of the ethanamine side chain from C13 to C14 or other positions (compare Schöpf and Bardowsky, *Annalen*, 1927, **458**, 148), and it is therefore worth noting that both dihydrothebainone, the initial material of the previous experiments, and dihydrothebaine, that of this series, undoubtedly contain the ethanamine chain attached to C13 and that no wandering was possible under the conditions of the later reactions.



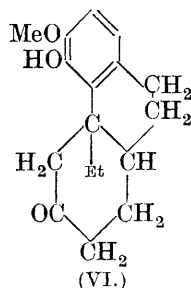
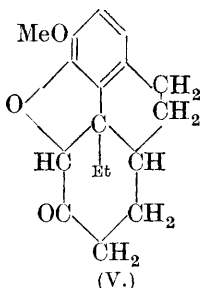
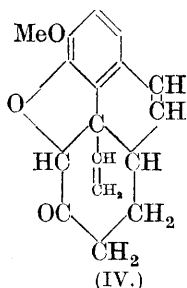
By heating the methiodide of dihydrothebainemethine † (II) with amyl-alcoholic potassium hydroxide, Freund and Speyer (*Ber.*, 1920, **53**, 2250) obtained the vinyl compound (III) mixed with a red impurity. They gave the melting point of (III) as 150—151°, but their analyses showed the product to be impure. The formation of the red impurity has been confirmed, but the vinyl compound has been obtained pure by transforming the methiodide by means of silver oxide into the methohydroxide and refluxing this in *iso*amyl-alcoholic solution; the pure substance melts at 120—121°.

Hydrochloric acid readily hydrolyses 6-methoxy-13-vinyltetrahydromorphenol methyl ether (III) to 6-keto-13-vinylhexahydromorphenol methyl ether (IV), which absorbs two molecules of

* The author's skin became sensitive to the catalytic reduction products of thebaine. (Cure: frequent bathing with very hot boracic solution.)

† For nomenclature, see J., 1926, 2564, footnote.

hydrogen in the presence of platinised charcoal to give 6-keto-13-ethyloctahydromorphenol methyl ether (V). The ether bridge in (V)



is reduced by aluminium amalgam and moist ether, yielding 6-keto-13-ethyloctahydromorphol 3-methyl ether (VI), which has been prepared by a different route by Wieland and Kotake (*Annalen*, 1925, **444**, 87). Neither method gives a good yield, probably because of partial reduction of the keto-group. Attempts to proceed further with the small quantity of (VI) available were unsuccessful.

The methohydroxide of dihydrothebainemethine (II) on decomposing gives only 30% of the vinyl compound (III), and 50% of the methine formed by loss of methyl alcohol can be recovered. The latter reaction was found to occur almost exclusively with three bases in the previous investigation (Cahn, *loc. cit.*), but reaches only negligible proportions in other cases, *e.g.*, thebenol and thebenone. Notwithstanding certain apparent regularities, it seems impossible to foretell the course of the degradation of these complicated bases; for instance, hydroxydihydrocodeinonemethine, which is structurally intermediate between the examples mentioned above, may be compared with the base (II), giving 48% of trimethylamine, whereas the closely related dihydromethylhydroxydihydrothebainonemethine gives less than 10% (Freund and Speyer, *J. pr. Chem.*, 1916, **94**, 135; Schöpf, *Annalen*, 1927, **452**, 256). The contradictions do not appear capable of explanation along the lines of the theoretical views of Ingold and his collaborators (J., 1927, 997; 1928, 3125). In particular are they noteworthy when the deduction is drawn that the elimination of methyl alcohol from substances of the type $R-CH_2-CH_2-NMe_3OH$ reaches a limit of 25% when R is *n*-butyl, and the statement is made (J., 1929, 2338) that there is no known instance of "a complete disappearance of the reaction leading to an olefin, a tertiary amine and water." The consideration that the many-branched nature of the morphine radicals should increase the elimination of methyl alcohol applies equally to all these bases.

EXPERIMENTAL.

All the analyses recorded in this paper are microanalyses made by Dr. Ing. A. Schoeller of Berlin.

6-Methoxy-13-vinyltetrahydromorphenol Methyl Ether (III).—A hot solution of dihydrothebainemethine methiodide (14 g.) in methyl alcohol (350 c.c.) was poured on silver oxide (precipitated from 7 g. of silver nitrate and washed free from alkali with water and then three times with methyl alcohol), cooled at once, shaken mechanically for 30 minutes, and filtered. The solvent was removed by distillation, and a solution of the residual oily quaternary hydroxide in *isoamyl* alcohol (140 c.c.) refluxed for $5\frac{1}{2}$ hours. After removal of the *amyl* alcohol in steam, an insoluble oil was obtained which readily solidified. It was collected and dissolved in hot glacial acetic acid, the solution poured into ether, and the whole shaken with water. On basification of the acid layer pure dihydrothebainemethine (4.8 g.; 50% of the theoretical quantity) was precipitated. From the ethereal layer, dried over calcium chloride and evaporated, the vinyl compound (III) was obtained as a solid residue (2.5 g.; yield, 30%): on crystallisation from alcohol or slightly diluted acetic acid it formed colourless plates, m. p. 120—121° (Found: C, 76.2; H, 6.5; MeO, 21.9. Calc. for $C_{18}H_{18}O_3$: C, 76.55; H, 6.4; 2MeO, 22.0%). The same substance was on one occasion obtained, mixed with small red prisms, by heating the quaternary hydroxide for 2 hours on the steam-bath and working up the product as above, but several attempts to repeat the experiment failed.

6-Keto-13-vinylhexahydromorphenol Methyl Ether (IV).—Concentrated hydrochloric acid (1.5 c.c.) and a solution of the dimethoxy-compound (III) (1.4 g.) in alcohol (14 c.c.) were heated together for 30 minutes on the water-bath and hot water was then added until a turbidity was produced. The ketone (IV) (1.36 g.), which was deposited on cooling, crystallised from alcohol in colourless elongated prisms, m. p. 149°.

6-Keto-13-ethyloctahydromorphenol Methyl Ether (V).—A solution of the substance (IV) (1.2 g.) in alcohol (120 c.c.), containing 1 g. of charcoal on which the palladium from 0.2 g. of palladous chloride had been precipitated, was stirred in the presence of hydrogen. Absorption ceased after 275 c.c. of hydrogen (all volumes are corrected to N.T.P.) had been absorbed in 3 minutes. In a blank experiment the same amount of catalyst in alcohol (120 c.c.) adsorbed 81 c.c. The effective absorption was therefore 194 c.c. (2 mols. = 191 c.c.). After the reduction the solution was filtered and concentrated to small bulk; on cooling, *substance* (V) (1.1 g.) was deposited in clusters of rods, m. p. 113° (Found: C, 74.9; H, 7.3.

$C_{17}H_{20}O_3$ requires C, 74.9; H, 7.4%). The *semicarbazone*, crystallised from a little alcohol, melted at 191° after previous sintering (Found: N, 12.75. $C_{18}H_{23}O_3N_3$ requires N, 12.8%).

6-*Keto-13-ethyloctahydromorphol 3-Methyl Ether* (VI).—Freshly amalgamated aluminium (8 g.) was added to a solution of the substance (V) (0.5 g.) in wet ether (50 c.c.) and drops of water were added occasionally with shaking during 16 hours. After filtration and evaporation of the solvent the substance (VI) was obtained as an oil which soon solidified; after two crystallisations from alcohol it formed long prisms, m. p. $148-150^\circ$ (Wieland and Kotake, *loc. cit.*, give $148-150^\circ$). The low yield (0.25 g. after one crystallisation) was doubtless due to partial reduction of the keto-group, for in a later experiment with a larger proportion of amalgam the oily product would not solidify. In attempts to eliminate the oxygen from ring III the crystalline material and the oily product were subjected to reduction by Clemmensen's method, but an uncrystallisable oil was obtained in both cases. These last oils did not yield well-defined products when refluxed in benzene solution with methyl sulphate or methyl iodide in the presence of potassium carbonate. An attempt to methylate the crystalline substance (VI) by methyl sulphate and sodium hydroxide solution also failed.

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