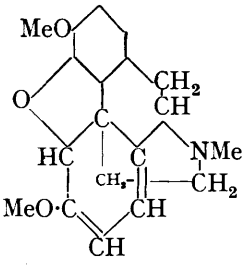
245. *Metathebainone.*

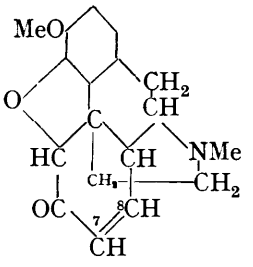
By Robert S. Cahn.

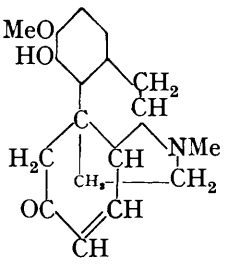
Addition of thebaine (I) to cold, concentrated hydrochloric acid gives a red, halochromic solution which contains 7% of codeinone (II) (formed by hydrolysis), but no unchanged thebaine; the remainder of the alkaloid is transformed into unstable, phenolic substances. Reduction of thebaine by stannous chloride and concentrated hydrochloric acid leads to 12—55% of thebainone (III) and 50—19% of metathebainone * (IV), the relative proportions in which the two substances are formed varying greatly according to the experimental conditions (Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160; Knorr, *ibid.*, p. 3171; Gulland and Robinson, J., 1923, **123**, 998; Schöpf and collaborators, *Annalen*, 1927, **458**, 158; 1930, **483**, 170; 1931, **489**, 224). It will be noted that formation of metathebainone involves a change of ring structure. Schöpf gives excellent reasons to show that

* Prior to 1927 the substance now termed metathebainone was called thebainone.

metathebainone is not formed to any large extent by way of codeinone; in order to explain the results, he postulates that the " red solution " (*i.e.*, the solution of thebaine in cold,

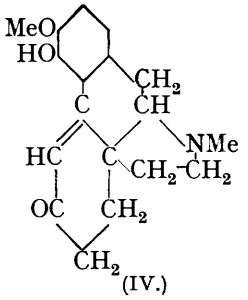

(I.)

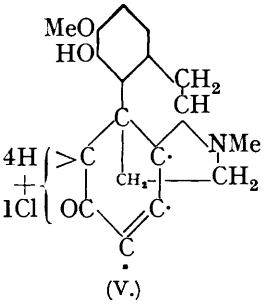

(II.)

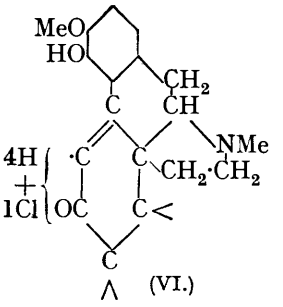

(III.)

concentrated hydrochloric acid) contains, besides 7% of codeinone, approximately equal amounts of two intermediates which are the precursors of thebainone and metathebainone. In 1927 he assigned complete formulæ to these intermediates, but later reverted to the more indefinite representations, (V) and (VI), respectively.

It has now been found that hydrogenation of the " red solution " in the presence of palladised charcoal gives nearly 85% of metathebainone and a small amount of


(IV.)


(V.)


(VI.)

dihydrocodeinone [as (II), with the ethylenic linking reduced] and other non-phenolic substances. This result is in strong contrast to the results obtained with stannous chloride. Considered together, these reductions necessitate the assumption of an equilibrium between (V) and (VI). Schöpf, however, considered that (V) and (VI) were formed directly and mainly independently from thebaine, and that it was improbable that the very stable grouping Ar·Ċ:Ċ·CO·ĊH·ĊH· would be in equilibrium with an approximately *equal quantity* (as his theory demands) of Ar·Ċ·ĊH·CO·Ċ:Ċ·. There is, moreover, no apparent reason why the presence of the catalyst should shift the equilibrium greatly in favour of (VI), so that this factor cannot be invoked. Even if the existence in terpene chemistry of equilibria demanding complicated ring changes be held to weaken Schöpf's objection, a further difficulty arises. The formation of dihydrocodeinone from the very small amount of codeinone present in the " red solution " shows that reduction of the 7 : 8-ethylenic linking is not hindered by the concentrated acid used as solvent (cf. Mannich and Löwenheim, *Arch. Pharm.*, 1920, **258**, 307). This linking is also present in (V) and should be as liable to reduction in (V) as in codeinone; consequently, dihydrothebainone should be formed in large amount. This, however, was not the case.

If these objections are valid, the mechanism of the change proposed by Schöpf and its extension to the formation of morphothebaine and apomorphine must be rejected (cf. Gulland and Virden, J., 1928, 922). It should, however, also be remembered that formula (IV) for metathebainone is not conclusively proved. It was hoped to make these experiments the beginning of an attack on these, as yet, unsolved sections of morphine chemistry. Circumstances, however, make this impossible. The method described is by far the best means of preparing metathebainone.

Experimental.

Thebaine (20 g.) was added in small portions to concentrated hydrochloric acid (200 c.c.) at 0°. When solution was complete, palladium–norite (2 g., 10% Pd) was added, and the mixture was shaken at room temperature in hydrogen. Absorption (1556 c.c. at N.T.P.; 1 mol. = 1500 c.c.) was complete in 2 hours. The filtered, orange-red solution was diluted to about 750 c.c., made slightly alkaline by 40% sodium hydroxide solution (cooling), acidified, made alkaline again by sodium hydrogen carbonate, and extracted 4 times with chloroform. A fifth extraction removed only a trace of resin. The extracts were shaken repeatedly with 2—3% sodium hydroxide solution until the alkali was no longer coloured (use of a more concentrated solution precipitated the sodium salt of the phenol). The chloroform, when dried and evaporated, gave 1·9 g. of non-phenolic, gummy bases; rubbing with ethyl acetate induced crystallisation; two crystallisations from ethyl acetate and one from alcohol gave a little dihydrocodeinone, m. p. 190—192°; mixed with an authentic specimen (m. p. 198°) it had m. p. 192—195°, and identity was confirmed by preparation of the oxime, decomp. 264° (sparingly soluble in alcohol and ethyl acetate; crystallised from chloroform–alcohol). The alkaline extracts were acidified, made alkaline with sodium bicarbonate, and extracted five times with chloroform. When dried and evaporated, the extract gave metathebainone as a resin which crystallised when rubbed with methyl alcohol; yield of crystals washed with a little methyl alcohol, 18·2 g. (85%). Recrystallisation from methyl alcohol gave 17·2 g. (81%) of pure base, m. p. 120—120·5° (decomp.) (lit. 115—118°) [Found: C, 68·5; H, 7·7; OMe, 18·7. Calc. for $C_{17}H_{18}O_2N(OMe)$,MeOH: C, 68·8; H, 7·6; OMe, 18·7%]. Identity was confirmed by preparation of the anhydrous form (m. p. 90°; thick, six-sided plates, often greatly elongated, from water; mixed m. p. of both forms with specimens prepared by stannous chloride) and of the picrate (decomp. *ca.* 245°, uncorr.).

When a solution of thebaine (10 g.) in cold concentrated hydrochloric acid (25 c.c.) was diluted at 0° with water (225 c.c.) and shaken with palladium–charcoal (1 g.) in hydrogen, no reduction took place. In a second experiment, however, when the thebaine (4 g.) in acid (20 c.c.) was added to cold water (200 c.c.) and shaken with the catalyst (1 g.), about 200 c.c. (= 0·66 mol.) of hydrogen were absorbed in 20 mins., and absorption then ceased. There were obtained 1·1 g. of recrystallised metathebainone, m. p. 118—119° (alone or mixed m. p.), and oily non-phenolic bases which partly crystallised from ethyl acetate but were not further investigated.

An attempt to reduce metathebainone by Clemmensen's method failed.

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University College of N. Wales, Bangor. [*Received, June 21st*, 1933.]