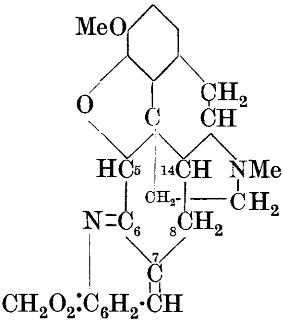
XCV.—*The Condensation of Certain Aldehydes with Ketones of the Morphine Group.*

By JOHN MASSON GULLAND.

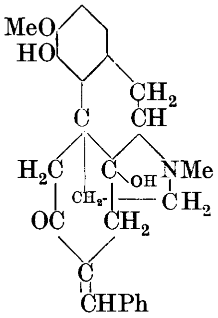
THE position of the hydroxyl group in hydroxycodeinone and its derivatives (Freund and Speyer, *J. pr. Chem.*, 1916, **94**, 135; Speyer, Selig, and Heil, *Annalen*, 1922, **430**, 1) is an important factor in determining the constitution of thebaine. Gulland and Robinson (*Mem. Manchester Phil. Soc.*, 1925, **69**, No. 10), in showing that the properties of hydroxycodeinone are satisfied only by placing the hydroxyl in position 14, proved that hydroxydihydrocodeinone contains the group $CO{\cdot}CH_2$. One of the steps of this proof consisted in the preparation of dianhydro-6-aminopiperonalhydroxydihydrocodeinone by the condensation of the ketone with 6-aminopiperonal. This quinoline derivative exhibited no fluorescence when dissolved in concentrated sulphuric acid, and thus differed from the simple methylenedioxyquinolines and also from dianhydro-6-aminopiperonalthebainone (Gulland and Robinson, J., 1923, **123**, 998). The absence of this apparently characteristic fluorescence might be considered to weaken the evidence in favour of the presence of a $CO{\cdot}CH_2$ group, but it is now shown that dihydrocodeinone condenses with 6-aminopiperonal, yielding *dianhydro*-6-*aminopiperonaldihydrocodeinone* (I), which dissolves in concentrated sulphuric acid and in other solvents without exhibiting fluorescence. Dihydrocodeinone undoubtedly contains a $CO{\cdot}CH_2$ group, and it would thus appear that the quinoline bases of this type, in which the attached groups form the larger part of the molecule, do not necessarily yield fluorescent solutions.

The present communication contains also a brief account of a number of experiments which were carried out in the hope of demonstrating, by the preparation of crystalline benzylidene derivatives, that the phenolic ketones of the morphine series contain a $CH_2{\cdot}CO{\cdot}CH_2$ group (compare Gulland and Robinson, *ibid.*, pp. 980, 998). It may readily be shown that these bases contain one reactive methylene group; for example, *benzylidenehydroxydihydrothebainone* (II) is formed in quantitative yield when hydroxydihydrothebainone (Freund and Speyer, *loc. cit.*) is condensed with benzaldehyde in alkaline solution. Attempts to show the presence of the second methylene group by the interaction of this benzylidene derivative with 6-aminopiperonal were fruitless, and, as Schöpf has already indicated (*Annalen*, 1927, **452**, 211), this inactivity is comparable with that observed in the case of dehydrocholic acid (Borsche and Frank, *Ber.*, 1924, **57**, 1373) and 3-methyl*cyclo*hexanone (Ruzicka, *Helv. Chim. Acta*, 1926, **9**, 101).

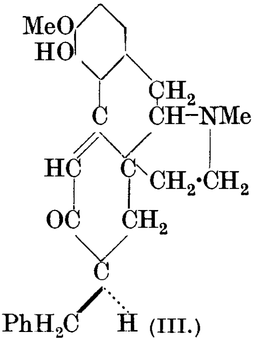
Piperonylidene- and *benzylidene-thebainone* have now been obtained in crystalline condition, and the catalytic reduction of the latter substance yields a mixture of two *benzylthebainones* (III), (A) m. p. 229° and (B) m. p. 179°, which are presumably stereoisomeric about carbon atom 7. These substances are isomeric with, but different from, *benzylidenethebainol*, which is prepared by the condensation of benzaldehyde and thebainol.



(I.)



(II.)



(III.)

EXPERIMENTAL.

Dianhydro-6-aminopiperonaldihydrocodeinone.—A solution of sodium (1 g.) in hot ethyl alcohol (25 c.c.) is mixed with a solution of dihydrocodeinone (2 g.) and 6-aminopiperonal (1·1 g.) in ethyl alcohol (5 c.c.) and boiled gently for several minutes. The product, which separates from the hot solution in yellow leaflets, after being washed, and dried at 100° (2·2 g.), crystallises from benzene in colourless, rectangular leaflets, m. p. 270—271·5° (Found : C, 73·3; H, 5·8. $C_{26}H_{24}O_4N_2$ requires C, 72·9; H, 5·6%). It is very sparingly soluble in hot methyl or ethyl alcohol or in ethyl acetate. The solution in concentrated sulphuric acid is colourless and shows no fluorescence. The substance is a non-phenolic base, which contains a methylenedioxy-group, since it responds to Gadamer's test (*Arch. Pharm.*, 1920, **258**, 148).

The *methiodide*, prepared by boiling the base and an excess of methyl iodide in methyl alcohol under reflux for 20 minutes, evaporating the solvent, rubbing the residual yellow gum with hot ethyl acetate, and grinding the hardened mass with boiling chloroform (the chloroform contains a small quantity of material which was not examined), is obtained, after crystallising twice from methyl alcohol, in pale yellow tablets which become orange at 200°, gradually soften, and decompose finally at about 260° (Found: C, 56·7; H, 4·9. $C_{26}H_{24}O_4N_2$,MeI requires C, 56·8; H, 4·7%).

Benzylidenehydroxydihydrothebainone.—A solution of benzaldehyde (4 g.) and hydroxydihydrothebainone (2·5 g.) in alcoholic potassium hydroxide (25 c.c. of 4%), after being kept at room temperature for 48 hours, is mixed with water, acidified with hydrochloric acid, and extracted with ether. The residual ether having been removed in a current of air, potassium bicarbonate precipitates a small fraction only of the product, which may be crystallised from benzene–ligroin and then from ethyl alcohol. The remainder of the *benzylidene* derivative separates as an oil when the aqueous filtrate is heated on the water-bath for 30 minutes, and solidifies on cooling. It separates from ethyl alcohol in yellow, coarse, pyramidal crystals, m. p. 188° (Found: C, 74·0; H, 6·7. $C_{25}H_{27}O_5N$ requires C, 74·1; H, 6·7%). The colorations developed with concentrated sulphuric acid, concentrated hydrochloric acid, and alcoholic sodium hydroxide are orange-red, very faint yellow, and orange-yellow, respectively. Attempts to prepare a quinoline derivative by condensing the substance with 6-aminopiperonal were fruitless.

Benzylidenethebainone.—A solution of thebainone (Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160) (12 g.) and freshly distilled benzaldehyde (16 g.) in ethyl-alcoholic potassium hydroxide (120 c.c. of 5%) is kept in a closed flask at room temperature for 48 hours. The red colour due to the presence of the sodium salt of thebainone changes to a very intense crimson. The solution is poured into water (600 c.c.), just acidified with dilute hydrochloric acid, extracted twice with benzene to remove the excess of benzaldehyde, and neutralised with potassium bicarbonate solution. The flocculent precipitate slowly becomes crystalline, but readily when seeded. After being washed thoroughly with water to remove all traces of bicarbonate, dried on porous tile and then in a vacuum desiccator, it is crystallised from ethyl alcohol, *benzylidenethebainone* being obtained in canary-yellow needles, m. p. 233° (Found: C, 77·7; H, 6·7. $C_{25}H_{25}O_3N$ requires C, 77·5; H, 6·5%). This substance dissolves readily in benzene and chloroform, is insoluble in light petroleum, forms an intense crimson solution in dilute alkali, is easily soluble in organic acids or in dilute mineral acids, yielding yellow solutions, and develops a brilliant green colour with alcoholic ferric chloride. In concentrated hydrochloric or sulphuric acid a deep red colour is produced which is discharged on dilution with water.

The *methiodide* (compare Gulland and Robinson, *loc. cit.*), prepared by warming a suspension of the base (1 g.) in ethyl alcohol (5 c.c.) and methyl iodide (1 c.c.) until it dissolves, separates, on cooling, in fine yellow needles, and recrystallises from ethyl alcohol in the same form, m. p. 195—197° (decomp.) (Found: C, 59·0; H, 5·3. $C_{25}H_{25}O_3N,MeI$ requires C, 59·0; H, 5·3%).

Piperonylidenethebainone is prepared from thebainone (2 g.), piperonal (4 g.), and ethyl-alcoholic potassium hydroxide (20 c.c. of 5%) in the manner described in the case of benzylidenethebainone (yield of yellow, semi-crystalline product, 2·7 g.). It is extremely soluble in the usual organic solvents, except ligroin, but it crystallises from a little ethyl alcohol in yellow, wart-like aggregates of crystals, m. p. 176° after drying at 100° (Found: C, 72·1; H, 5·7. $C_{26}H_{25}O_5N$ requires C, 72·4; H, 5·8%). The solution in concentrated hydrochloric or sulphuric acid is intensely reddish-purple and becomes pale yellow on dilution with water.

Reduction of Benzylidenethebainone. The Isomeric Benzylthebainones (A) *and* (B).—A solution of benzylidenethebainone (6·5 g.) in water (80 c.c.) and acetic acid (5 c.c.), when shaken with palladous chloride solution (15 c.c. of 1%) in an atmosphere of hydrogen, absorbs 1 mol. of the gas in about 20 minutes. Absorption then ceases. The palladium is precipitated and removed, and potassium bicarbonate solution added to the filtrate. The colourless, amorphous precipitate produced is dried on porous tile and dissolved in the minimum of boiling alcohol; on cooling, small colourless needles form on the sides of the vessel, and these are collected (A, 0·3 g.) before the appearance of a mass of felted needles, which fill the body of the liquid. The filtrate, after being concentrated, slowly deposits colourless needles or plates (B, 5 g.).

Benzylthebainone (A) is sparingly soluble in alcohol, and separates from this solvent in colourless needles, m. p. 229° (Found: C, 77·0; H, 6·9. $C_{25}H_{27}O_3N$ requires C, 77·1; H, 6·9%). The sodium salt is orange in colour, and the base exhibits an orange halochromic colour in concentrated hydrochloric acid and a bright red in concentrated sulphuric acid. It was recovered unchanged after an attempt to condense it with 6-aminopiperonal in presence of hot ethyl-alcoholic sodium ethoxide.

The *semicarbazone* is formed when a mixture of the base and an excess of semicarbazide hydrochloride and potassium acetate in dilute acetic acid is kept at room temperature over-night. The product is precipitated by ammonia, and after drying, is obtained as a microcrystalline powder, m. p. 155—160°, by repeated precipitation from benzene by means of ligroin (Found: N, 12·2. $C_{26}H_{30}O_3N_4$ requires N, 12·5%).

Benzylthebainone (B) separates from ethyl alcohol in plates, m. p. 179° (Found : C, 76·8; H, 7·0. $C_{25}H_{27}O_3N$ requires C, 77·1; H, 6·9%), or in needles which lose solvent and become pasty at about 110° (Found: loss at 100°, 5·3. Required for $\frac{1}{2}$EtOH, 5·6%. Found in dried material : C, 77·3; H, 7·1%). Each of these forms may be obtained free from the other by utilising the following facts : (i) The plates separate first and pass into the needle form after remaining for some time in contact with the solvent, and (ii) the needles dissolve more rapidly than the plates when a suspension of the two forms is warmed with ethyl alcohol. Both forms of this substance are more soluble than the isomeride (A), and show the same halochromic colours; the sparingly soluble, orange sodium salt separates in needles when a hot slightly alkaline solution is cooled. The base was recovered unchanged after an attempt to condense it with 6-aminopiperonal.

The *semicarbazone*, prepared as described in the case of the isomeride (A), crystallises from dilute ethyl alcohol in needles, m. p. 140—145° (unaltered by further crystallisation) (Found in material dried at 100°; C, 69·0; H, 6·8. $C_{26}H_{30}O_3N_4$ requires C, 69·9; H, 6·8%).

The *oxime*, prepared in a similar manner, is precipitated by sodium carbonate, collected, and dried on porous tile. It becomes crystalline on boiling with ethyl alcohol, and is then collected and recrystallised from the same solvent, from which it separates in colourless columns, m. p. 152° (Found : N, 6·7. $C_{25}H_{28}O_3N_2$ requires N, 6·9%). This oxime is not reduced when a solution in dilute acetic acid is shaken with palladium and hydrogen (compare Speyer, Selig, and Heil, *loc. cit.*).

Benzylidenethebainol.—The condensation of benzaldehyde (3 g.) with thebainol (2 g.) is carried out in the manner described in the case of benzylidenethebainone. *Benzylidenethebainol* crystallises from ethyl alcohol in faintly yellow needles, m. p. 100—102° (Found in material dried at 100°; C, 77·1; H, 7·2. $C_{25}H_{27}O_3N$ requires C, 77·1; H, 6·9%). The solution in concentrated sulphuric acid is orange-red, in concentrated hydrochloric acid yellow, and these colours are discharged on dilution with water. The solution in alcoholic or hot aqueous sodium hydroxide is orange-yellow.

The author wishes to thank Professor Robinson for the interest which he has taken in this work, and acknowledges his indebtedness to the Chemical Society for a grant which has defrayed a part of the cost of the investigation.

THE DYSON PERRINS LABORATORY,
OXFORD.

[*Received, February 3rd,* 1928.]