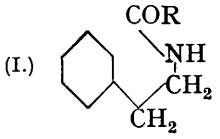
76. *Attempts to prepare Derivatives of* 1 : 2-*Dihydro*isoquinoline. *New Interpretation of J. S. Buck's Experiments on the Synthesis of So-called* 1 : 2-*Dihydropapaverine.*

By P. C. Young and Robert Robinson.

The contrast between the relative ease of ring-closure by dehydration in the system (I) and the difficulty experienced in bringing about analogous reactions in (II) is all the more striking in that the carbonyl in the former case is deactivated by union with a nitrogen atom.

We have made numerous further trials with the object of realising the synthesis of 1 : 2-dihydro*iso*quinolines and it will be conceded that the cases selected were the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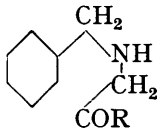
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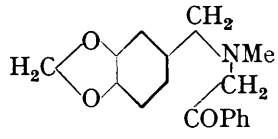
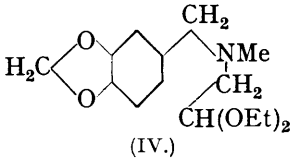

(III.)

most favourable possible; the nitrogen was tertiary, the nucleus was activated in the *o*-position, and the carbonyl was that of an aldehyde group in one case and of a phenyl ketone in another.

The ring-closure of (III) and (IV) under a variety of conditions did not proceed smoothly and desired products such as (V) and (VI) could only be isolated in small yield. Further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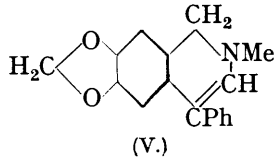
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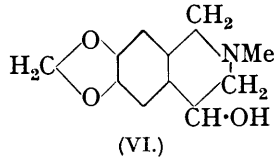
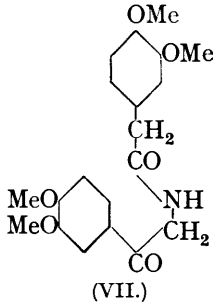

(VI.)

comment on these experiments, which are recorded in the experimental section, is unnecessary. 1 : 2-Dihydro*iso*quinolines in the berberine and cryptopine series have been extensively studied by Perkin (J., 1916, **109**, 815) and found to exhibit interesting transformations. Apart from these researches, little is known of their properties and, as shown below, the supposed 1 : 2-dihydropapaverine is probably 3 : 4-dihydropapaverine; the use of the former name should be discontinued.

J. S. Buck (*J. Amer. Chem. Soc.*, 1930, **52**, 3610) treated homoveratroyl-ω-aminoacetoveratrone (VII) with phosphoryl chloride and regarded the product as (VIII). The compound considered to be (VIII) was hydrogenated in the presence of a very active platinum–palladium catalyst to a substance formulated as (IX). It is significant that in regard to (VIII) and (IX) the following comment was made (*loc. cit.*): " No derivatives of the carbonyl or hydroxyl groups were isolated and the basic properties are so suppressed that the bases form no well-defined salts. Indeed (IX) may be recrystallised unchanged from fairly strong hydrochloric acid."

It is very improbable that the basic properties of a substance of the constitution (IX) would be so feebly developed. A further improbability is the assumed direction of the initial *facile* condensation, because the nucleus is rendered less vulnerable by its union with a carbonyl group. The substance formulated as (IX) gave the alleged 1 : 2-dihydropapaverine (X) on treatment with phosphorus pentachloride in a cold chloroformic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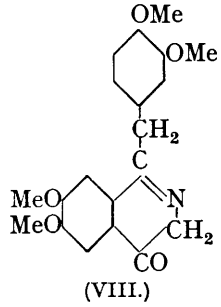
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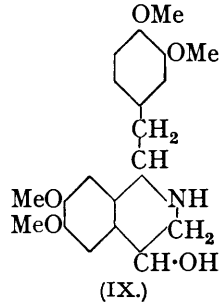
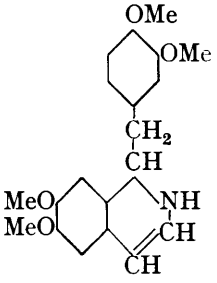

(IX.)

medium. The base (X) was undoubtedly a dihydropapaverine, because it furnished papaverine on catalytic dehydrogenation.

In 1907—8, one of us in collaboration with the late Professor W. H. Perkin, jun.,

attempted the synthesis of papaverine * by the above method, but it was soon found that the dehydration of (VII) with a variety of reagents afforded a very feeble base, crystallising from benzene–light petroleum in slender colourless needles, m. p. 116°, giving violet fluorescent solutions in neutral organic solvents. This substance, evidently identical with the compound (VIII) of Buck, was not further examined, but analogous work was instituted with more accessible material and a general synthesis of oxazole derivatives from keto-amides, R·CO·CH_2·NH·COR, was developed (J., 1909, **95**, 2167; 1912, **101**, 1297; 1913, **103**, 1768). From its method of formation and properties there can be no doubt that the substance hitherto considered to be (VIII) is in reality 5-*veratryl*-2-*homoveratryloxazole* (XI). In order to explain the ultimate synthesis of papaverine in Buck's experiments it is necessary to recognise that (XI) is catalytically reducible to homoveratro-β-veratrylethylamide (XII) (Pictet and Finkelstein, *Ber.*, 1909, **42**, 1979), and the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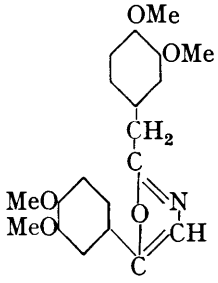
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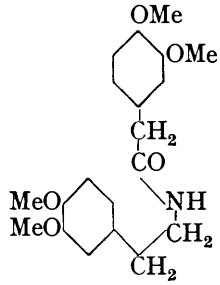
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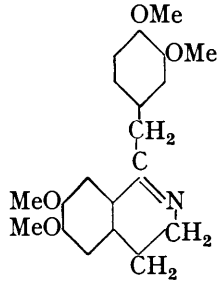
(XIII.)

m. p. and other properties of the substance (IX) as recorded by Buck (*loc. cit.*) are in complete agreement with this deduction. This is an indication of the existence of a general method which may have many useful applications.

Finally the ring-closure to an *iso*quinoline derivative occurs in the last stage (XII ⟶ XIII) and not in the first as suggested by Buck. The conditions are remarkably mild and this is a second interesting point emerging from these experiments and their new interpretation. We have confirmed this stage of the processes using homoveratroveratrylethylamide made by Pictet and Finkelstein's method. The 1 : 2-dihydropapaverine of Buck is therefore the known 3 : 4-dihydropapaverine (Pictet and Finkelstein, *loc. cit.*; Buck, Haworth, and Perkin, J., 1924, **125**, 2183); but it should be noted that Buck has obtained this base in a pure crystalline form, whereas previously it was only known as a yellow oil. Some minor discrepancies in regard to the derivatives of the base may originate in the varying degrees of purity of the specimens. Buck (*loc. cit.*) stated that his supposed 1 : 2-dihydropapaverine gave a different oxidation product from that previously obtained from 3 : 4-dihydropapaverine; significant divergence does not appear, however, in the published descriptions, for example, m. p. 187° against 190—191°.

Experimental.

Preparation of Some Secondary Bases.—The following expts. have been carried out by Mr. J. C. Resuggan and most of the analyses are the work of Mr. F. Hall. It has been found that the electrolytic reduction of many Schiff bases proceeds smoothly and that the method is preferable in most cases to the alternatives (cf. Knudsen, *Ber.*, 1909, **42**, 3994).

Benzylethylamine was prepared in the following manner. Anhydr. $EtNH_2$ (2 mols., 4·2 g.) was added slowly with shaking to benzaldehyde (5 g.), dissolved in MeOH (25 c.c.) and cooled in ice, and the whole kept for 3 hr. Dil. H_2SO_4 (160 c.c., 10% by wt.) was added, and the solution reduced at a Pb cathode for 5 hr. at a current density of 0·02 amp./sq. cm. at 12—15°. 4·5 G. of benzylethylamine (70% of theo.), b. p. 198°/750 mm., were isolated by means of Et_2O.

* This was ultimately effected by the use of a method identical in principle (but different in some experimental detail) with that of Pictet and Gams (*Ber.*, 1909, **42**, 2943). The synthesis was not published on account of the anticipation by Pictet and Gams and also because our work was incomplete to the extent that the penultimate product of the synthesis was not obtained in a crystalline condition. —R. R.

The following secondary amines were prepared similarly : Anisylmethylamine, b. p. 228°/755 mm.; hydrochloride, m. p. 168° (cf. Tiffeneau, *Bull. Soc. chim.*, 1911, **9**, 825) (Found : N, 7·4. Calc. for $C_9H_{13}ON$,HCl : N, 7·5%). Yield, 85%. p-*Toluenesulphonamide*, plates from EtOH, m. p. 85° (Found : N, 4·6. $C_{16}H_{19}O_3NS$ requires N, 4·5%).

Piperonylethylamine, b. p. 128°/1 mm.; yield, 72% (Andree, *Ber.*, 1902, **35**, 420); hydrochloride, m. p. 200° (Found : C, 56·1; H, 6·5; N, 6·2. Calc. for $C_9H_{11}O_2N$,HCl : C, 55·8; H, 6·5; N, 6·5%). p-*Toluenesulphonamide*, plates from EtOH, m. p. 108° (Found : N, 4·1. $C_{17}H_{19}O_4NS$ requires N, 4·2%).

Vanillylethylamine, prisms from C_6H_6, m. p. 101° (Found : C, 66·3; H, 8·3; N, 7·6. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%). Yield, 70%. *Di*-p-*toluenesulphonamide*, prisms from EtOH, m. p. 108° (Found : N, 2·8. $C_{24}H_{27}O_6NS_2$ requires N, 2·8%).

o-*Vanillylmethylamine*, prisms from C_6H_6, m. p. 89° (Found : C, 64·5; H, 7·7; N, 8·3. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8; N, 8·3%). Yield, 70%. p-*Toluenesulphonamide*, flat prisms from EtOH, m. p. 115° (Found : N, 4·6. $C_{16}H_{19}O_4NS$ requires N, 4·3%).

o-*Vanillylethylamine*, prisms from C_6H_6, m. p. 76° (Found : C, 66·0; H, 8·3; N, 7·5. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%). Yield, 80%.

The physiological properties of some of these bases, especially the *o*-vanillylalkylamines, have features of interest which will be reported in another place.

Benzylmethylamine was prepared from benzaldehyde and methylamine as above and in a similar manner from benzylamine (5 g.) and CH_2O aq. Yield, 4 g.; b. p. 184°/759 mm.

Homopiperonylmethylamine, $CH_2O_2{:}C_6H_3{\cdot}CH_2{\cdot}NHMe$.—In the prepn. of this base no advantage was conferred by the isolation of pure piperonylidenemethylamine as an intermediate stage. NH_2Me (5 g.) in EtOH was added to piperonal (20 g.) in EtOH (50 c.c.) and, after being kept at 0° for 48 hr., the solution was mixed with 10% H_2SO_4 aq. (600 c.c.) and reduction effected as in Mr. Resuggan's expts. Yield, 16 g.; b. p. 95—126°/0·1 mm. The base was purified through its hydrobromide, colourless prisms, m. p. 186—186·5°. Other salts are : hydrochloride, colourless plates from EtOH, m. p. 188·5°; hydrogen oxalate, plates from EtOH, m. p. 176°, or needles from EtOH–Et_2O, m. p. 177°; neutral oxalate, prisms from EtOH, m. p. 202·5° (decomp.), also needles from EtOH–Et_2O; picrate, yellow needles or prisms from EtOH, m. p. 153·5°; quaternary methiodide, plates from EtOH, darkens at 223°, m. p. 226° (decomp.) (cf. Andree, *loc. cit.*).

Phenacylhomopiperonylmethylamine (III).—When homopiperonylmethylamine (4·7 g., 2 mols.) in Et_2O (20 c.c.) was added to phenacyl bromide (2·9 g., 1 mol.) in Et_2O (20 c.c.), a ppt. of $CH_2O_2{:}C_6H_3{\cdot}CH_2{\cdot}NH_2MeBr$ was quickly deposited; after 48 hr., the solid weighed 3·2 g. (m. p. 186°), and picric acid (5 g.) in the minimum of acetone was added to the filtrate. The *picrate* was pptd. by Et_2O and crystallised from EtOH in yellow cubes (4·09 g.), m. p. 146—147° (approx.) (Found : C, 54·0; H, 4·0; N, 11·0. $C_{23}H_{20}O_{10}N_4$ requires C, 53·9; H, 3·9; N, 10·9%). The base was rendered to Et_2O from the picrate and NaOH aq. and could be distilled (0·1 mm.) but not crystallised; it afforded the original picrate and also a hydrobromide, small rods and leaflets from EtOH–Et_2O, m. p. 194°, an oxalate, m. p. 138·5—141°, and a methiodide, rectangular plates from EtOH, m. p. 166°.

6 : 7-*Methylenedioxy*-4-*phenyl*-2-*methyl*-1 : 2-*dihydro*isoquinoline (V).—The dehydration of the phenacyl derivative by P_2O_5 gave uncrystallisable bases and salts thereof, and unmanageable mixtures were produced by $POCl_3$.

80% H_2SO_4 aq. saturated with HCl, at various temps. and during various times led to the production of an amorphous solid, pptd. as the chief product by H_2O. The acid filtrate, however, basified and extracted with Et_2O, afforded a base, of which the dimorphous *picrate* crystallised from EtOH in feathery needles or felted, long, flexible, yellow needles, m. p. 186—187° (Found : C, 56·2; H, 3·3; N, 11·3. $C_{23}H_{18}O_9N_4$ requires C, 55·9; H, 3·6; N, 11·3%). The needles appear to consist of a labile form, changing to more compact needles or plates, m. p. 186—187°. In some expts. using 80% H_2SO_4 (+ HCl), a colourless base, m. p. 146° (Found : C, 71·8; H, 6·0; N, 5·1%), was isolated. The analysis is difficult to interpret ($C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6; N, 5·2%; hence phenacylhomopiperonylamine ?); the picrate had m. p. 182° (decomp.), and, mixed with that already described (m. p. 186—187°), 174°. When the phenacylhomopiperonylmethylamine was heated with conc. HCl on the steam-bath, a small quantity of the base yielding the picrate of m. p. 186—187° was isolated. The main product was an unidentified white solid, sparingly sol. in dil. HCl but readily in conc. HCl.

Homopiperonylmethylaminodiethylacetal (IV).—A mixture of homopiperonylmethylamine

(20·0 g.) and bromoacetal (13·4 g.) was gradually heated to 100° and kept at this temp. for 1 hr. EtOAc (10 c.c.) was then added, and the mixture refluxed for several hrs., cooled, and filtered. The homopiperonylmethylamine hydrobromide was weighed (the amount was usually about 90% of that corresponding to 10 g. base) and from this the HBr necessary to ppt. unreacted secondary base was calculated and added to the filtrate. The solution filtered from the hydrobromide was concentrated and distilled; final b. p. 141° (approx.) /0·1 mm. The colourless oil was the required tertiary base and formed almost quantitatively a characteristic *methiodide*, colourless plates from Ac_2O, m. p. 153° (Found : C, 45·6; H, 6·2; N, 3·1. $C_{16}H_{26}O_4NI$ requires C, 45·4; H, 6·2; N, 3·3%), readily sol. in hot EtOH and moderately readily in the cold solvent.

The methochloride, obtained from AgCl and the iodide in H_2O, crystallised from EtOH–Et_2O in colourless plates, m. p. 171—172°.

The *dimethylacetal*, b. p. 138°/0·1 mm., was prepared in similar fashion (Found : C, 61·5; H, 7·5; N, 5·7. $C_{13}H_{19}O_4N$ requires C, 61·7; H, 7·5; N, 5·5%).

Cyclisation of Homopiperonylmethylacetalylamines.—The action of AcOH–conc. HCl on the diethylacetal in a solution heated to 40° and then kept for 14 hr. furnished a base, the *methiodide* of which had m. p. 216—218° (Found : C, 41·2; H, 4·7; N, 3·8. $C_{12}H_{16}O_3NI$ requires C, 41·3; H, 4·6; N, 4·0%). The base is therefore an aldehyde, $CH_2O_2{:}C_6H_3{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CHO$, or the related 4-hydroxytetrahydro*iso*quinoline (VI); the *crude* substance affords a red *p*-nitrophenylhydrazone, m. p. 191—196° (decomp.).

Conc. HCl alone gave similar results; anhydr. $H_2C_2O_4$ was also tried but without success.

Homopiperonylmethylaminodiethylacetal (6·9 g.) was treated with $POCl_3$ (10 c.c.) in CS_2 and when the initial reaction subsided the mixture was refluxed for 3·5 hr. After appropriate treatment the bases were isolated by Et_2O extraction from a strongly alkaline solution. The first extract gave 2·3 g. of a colourless oil, b. p. 136—138°/3—4 mm. (black residue, 3·7 g.) (the combined later extracts gave 0·45 g. of basic oil; picrate, m. p. 185° with decomp.). The oil afforded a sticky methiodide and oxalate, m. p. 163—170°, and was obviously a mixture of bases. The picrates were fractionally crystallised, the oil (1·6 g.) and picric acid (2 g.) furnishing 2·5 g. of crude salts by pptn. with Et_2O from acetone soln. From EtOH (50 c.c.) a crop (A, 1·6 g.) of lemon-yellow pointed prisms, m. p. 145—149°, was followed by one of 0·68 g., m. p. *ca.* 120°, later divided into (B) (0·1 g.), diamond-shaped prisms, m. p. 185—186° (decomp.), and (C) needles, m. p. 147—148° with softening at 144°. Fractional crystn. of (A) gave 5 crops of m. p.'s 155—156°, 149—151°, 150—152°, 150—152·5°, 149—151°, mixtures of which had undepressed m. p.'s; but mixed with homopiperonylmethylamine picrate (m. p. 151°), the m. p. was below 120°.

Mixtures of (B) and (C) had m. p. 148—149°; (A) and (B) softened at 148°, m. p. 170° (decomp.); (A) and (C), m. p. below 134°.

Analysis and other investigations indicated that (A) and (B) were almost pure substances but (C) was probably a mixture.

(A) crystallised from acetone in well-defined pointed prisms, m. p. 153—155° (Found : C, 49·2; H, 4·4; N, 12·0. $C_{19}H_{20}O_{19}N_4$ requires C, 49·1; H, 4·3; N, 12·1%). This *picrate* is therefore derived from a base, $C_{13}H_{17}O_3N$, which is the original acetal less C_2H_6O and probably 6 : 7-*methylenedioxy*-4-*ethoxy*-2-*methyltetrahydro*isoquinoline.

(B) is much more sparingly sol. in EtOH and acetone than (A) (Found : C, 46·8; H, 3·7; N, 13·1. $C_{17}H_{16}O_{10}N_4$ requires C, 46·8; H, 3·7; N, 12·8%). The composition is thus C_2H_4 less than that of (A) and most probably the salt is 4-*hydroxy*-6 : 7-*methylenedioxy*-2-*methyltetrahydro*isoquinoline *picrate* (picrate of VI).

The composition of (C) approximates to that of (B) (Found : C, 45·7; H, 3·6%).

Homopiperonylmethylaminodimethylacetal (3·9 g.) was heated on the steam-bath with 10% HCl aq. for 1 hr. Colourless crystals separated (1·5 g.) and the salt crystallised from hot H_2O in clusters of long, pale yellow prisms, m. p. 256° (decomp.) after softening and darkening from 235° (Found : Cl, 14·8; N, 6·1. $C_{11}H_{13}O_3N$,HCl requires Cl, 14·6; N, 5·8%). This salt is very sparingly sol. in acetone and EtOAc and moderately readily sol. in hot EtOH; it does not give a satisfactory picrate and is clearly not the hydrochloride of the base of which (B) ($POCl_3$ expts. above) is the picrate. The salt is not quaternary and the base obtained from it does not react with *p*-nitrophenylhydrazine. It is proposed to make a further study of the reaction.

The action of Ac_2O–H_2SO_4 and of conc. HCl on the methiodide and the methochloride of

the basic acetals has been investigated and cryst. products isolated, but in such small yield that the work was abandoned.

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