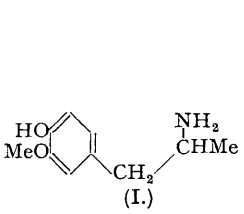
145. *The Synthesis of* 3-*Methyl*isoquinolines. *Part II.*

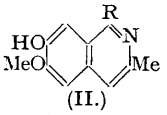
By G. R. Clemo and J. H. Turnbull.

The preparation of a series of 3-methyldihydro*iso*quinolines from 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine (I, cf. Part I, *J.*, 1945, 533) is described. These dihydro*iso*quinolines have been converted into *iso*quinolines of type (II), and their 1 : 2 : 3 : 4-tetrahydro-derivatives. One of the type (II) bases is isomeric with papaverine.

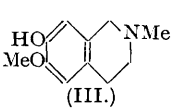
THE value of papaverine as a spasmolytic agent was early recognised by Macht (*J. Pharm. Exp. Ther.*, 1918, **11**, 389) and several papaverine analogues have since been made (Kulz and Hornung, U.S.P. 2,223,373; B.P. 512,560; v. Fodor, *Ber.*, 1943, **76**, 1216; v. Fodor, *Wien. Chem. Ztg.*, 1942, **45**, 241; Scheuing and Walach, D.-R.P. 576,532; Mannich and Falber, *Arch. Pharm.*, 1929, **267**, 601). Recently several dihydro- and tetrahydro-*iso*quinolines have been synthesised and have shown promising pressor, depressor, and convulsant properties (cf. Hjört, *J. Pharm. Exp. Ther.*, 1942, **76**, 64, 71, 252).

The *iso*quinoline derivatives now described all possess the 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine unit, which may be expected to confer low toxicity on the compounds (cf. Gunn, Gurd, and Sachs, *J. Physiol.*, 1939, **95**, 485). The 7-hydroxy-6-methoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline structure is present in a few of the simpler naturally occurring bases, *e.g.*, corypalline (III), codamine (IV), and coclaurine (V), and some of the tetrahydro-bases here described are of interest in their resemblance to these alkaloids.


(I.)


(II.)

[R = H; Me; Ph; CH_2Ph; $CH_2{\cdot}C_6H_3(OMe)_2$ (3 : 4)]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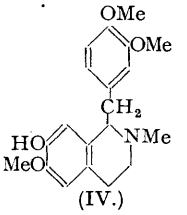
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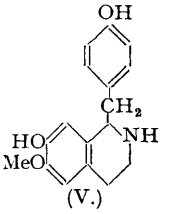

(V.)

The parent dihydro*iso*quinoline (corresponding to type II, R = H) has been made from the *N*-formyl derivative of the *iso*propylamine (I), after suitably protecting the free hydroxyl group. The most direct route to the required dihydro*iso*quinoline is from the *ON*-diformyl derivative of the amine (I). There are, however, few references in the literature to the preparation of *O*-formyl derivatives, and no satisfactory method of making the *ON*-diformyl*iso*propylamine has, so far, been found. The method of Einhorn and Hollandt (*Annalen*, 1898, **301**, 113) could not be applied to the *iso*propylamine, while refluxing the amine with formic acid gave only the amine monoformate.

Attempts to prepare the dihydro*iso*quinoline from the *N*-formyl-*O*-acetyl*iso*propylamine failed. The *N*-formyl*iso*propylamine was obtained by heating the amine formate (cf. Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, **395**, 282), but on acetylation gummy products of doubtful purity were obtained. These gums could not be cyclised satisfactorily. The formyl group is probably involved in side-reactions during acetylation of the phenolic hydroxyl (cf. Nef, *Annalen*, 1892, **270**, 278; Pictet and Crépieux, *Jahresber.*, 1888, 1693; Pictet, *Ber.*, 1890, **23**, 3013; Friedmann and Backeberg, *J.*, 1938, 469).

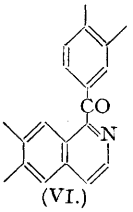
Attention was finally turned to the *O*-benzoyl-*N*-formyl*iso*propylamine. This might be made by formylation of the amino-group in the *O*-benzoyl derivative of the *iso*propylamine (I). The basic monobenzoate of (I), however, could not be obtained, as treatment of 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine hydrochloride with benzoyl chloride (cf. Mannich and Merz, *Arch. Pharm.*, 1927, **265**, 26) always resulted in *N*-benzoylation to give only non-basic products.

The required *O*-benzoyl-*N*-formyl*iso*propylamine was eventually made by benzoylation of the *N*-formyl derivative under Schotten–Baumann conditions. Cyclisation of the amide, however, gave only a small yield of the dihydro*iso*quinoline. Other workers have reported poor yields in similar ring closures (cf. Decker and Becker, *Annalen*, 1911, **382**, 369; Späth, Berger, and Kuntara, *Ber.*, 1930, **63**, 134).

The 1-phenyldihydro*iso*quinolines were obtained from the *ON*-dibenzoyl derivative of the base (I) using the usual modified Bischler–Napieralski method.

The 1-benzyldihydro*iso*quinolines were prepared similarly by cyclising the *ON*-bisphenylacetyl*iso*propylamine. They formed stable salts, but the free bases melted indefinitely and rapidly underwent oxidation in air to yield well-defined crystalline bases of sharp m. p. These bases formed yellow salts, and gave a Prussian blue coloration on boiling with acetic anhydride. They are evidently 1-benzoyldihydro*iso*quinolines resembling those investigated by Buck, Haworth, and Perkin (*J.*, 1924, 2176).

The 1-benzyl bases were stable to warm 10% alcoholic potassium hydroxide, and underwent no appreciable oxidation. This result contrasts with the findings of Buck and co-workers (*loc. cit.*) who were able simultaneously to oxidise the dihydro*iso*quinoline ring and the 1-benzyl group to give a papaveraldine type (VI).


(VI.)

The 1-(3 : 4-dimethoxybenzyl)dihydro*iso*quinolines are more susceptible to atmospheric oxidation than the 1-benzyl compounds. Homoveratric acid (Bide and Wilkinson, *J. Soc. Chem. Ind.*, 1945, **64**, 84) was converted into the acid chloride, which was used to make the *ON*-dihomoveratroyl derivative of the amine (I). The amide was cyclised in a hydrogen atmosphere. The unstable 1-(3 : 4-dimethoxybenzyl) base was isolated as a very sparingly soluble perchlorate. The stable hydrochloride of the base was obtained by decomposition of the perchlorate with ammonia followed by conversion of the free base into the hydrochloride.

The *iso*quinolines (II, R = H; Me; Ph; CH_2Ph) were prepared from the dihydro-bases by dehydrogenation with palladium black (cf. Späth and Polgar, *Sitzungsber.*, 1928, **137**, 1142). One of the *iso*quinolines

made by this method (II, R = Me) has been prepared by v. Fodor from eugenol ψ-nitrosite (*Ber.*, 1943, **76**, 1216).

Attempts to dehydrogenate the 1-(3 : 4-dimethoxybenzyl)dihydro*iso*quinoline were not promising, because of the unstable nature of the dihydro-base. Reduction of the dihydro-base, however, gave a stable tetrahydro-compound, and this was successfully dehydrogenated to give the base [II; R = $CH_2{\cdot}C_6H_3(OMe)_2$ (3 : 4)]. This base is of interest in its resemblance to papaverine, with which it is isomeric. Both bases give a violet coloration on warming with sulphuric acid; with Marquis' reagent (Warren, *J. Amer. Chem. Soc.*, 1915, **37**, 2402) papaverine gives a rose pink, whereas the isomer gives a slowly developed light red.

Reduction of the dihydro*iso*quinolines to the tetrahydro-bases was readily effected in aqueous solutions of the hydrochlorides using hydrogen in the presence of palladised charcoal, or Adams's catalyst.

Experimental.

4-Hydroxy-3-methoxy-β-phenylisopropylamine Formate.—4-Hydroxy-3-methoxy-β-phenyl*iso*propylamine (0·48 g.) was dissolved in formic acid (50%, 2 c.c.), and the solution evaporated to dryness under reduced pressure on the water-bath. The residue crystallised from acetone–methanol in pinkish white nodules (0·4 g., m. p. 152—154°). It is readily soluble in water, and on basifying with potassium carbonate its solution deposits a solid, m. p. 156—157·5° not depressed by admixture with an authentic specimen of 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine. The formate was dried in a vacuum at 80° for analysis (Found: N, 6·2. $C_{10}H_{15}O_2N,CH_2O_2$ requires N, 6·2%).

Formo-4-hydroxy-3-methoxy-β-phenylisopropylamide.—The crude syrupy formate obtained above was heated at 145° for 4 hours, and the product extracted with boiling benzene (20 c.c.). On keeping, small white rosettes (0·44 g., m. p. 92—94°) were deposited which recrystallised from benzene in silky needles, m. p. 96—98°. The *amide* was somewhat soluble in water, the solution giving a blue coloration with ferric chloride (Found: N, 6·5. $C_{11}H_{15}O_3N$ requires N, 6·7%).

Benzoylation of 4-Hydroxy-3-methoxy-β-phenylisopropylamine Hydrochloride.—The foregoing compound (0·45 g.) was suspended in xylene (6 c.c.) and benzoyl chloride (0·37 g.) added. The mixture was refluxed for 2 hours with stirring and then cooled. The xylene layer was decanted from the oily residue which was repeatedly extracted with hot water, leaving a pasty solid (*A*). The aqueous extracts were extracted with ether and basified with dilute sodium hydroxide solution, but no 4-benzoxy-3-methoxy-β-phenyl*iso*propylamine could be isolated. The solution was then acidified (Congo-red) with hydrochloric acid and saturated with sodium carbonate; 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine (80 mg.) was then deposited. The solid (*A*) was crystallised from dilute methanol and extracted with cold dilute sodium hydroxide solution, and the extracts were acidified with hydrochloric acid yielding a white solid (0·2 g., m. p. 133—136°) which recrystallised from dilute alcohol to give *benzo-4-hydroxy-3-methoxy-β-phenylisopropylamide* as clusters of delicate white needles, m. p. 136—137° (Found: N, 4·9. $C_{17}H_{19}O_3N$ requires N, 4·9%).

On the addition of benzoyl chloride to the amide dissolved in cold dilute sodium hydroxide solution a white solid separated, which recrystallised from dilute alcohol to give benzo-4-benzoxy-3-methoxy-β-phenyl*iso*propylamide as clusters of small white needles, m. p. 165—166·5°, undepressed by admixture with an authentic specimen.

Formo-4-benzoxy-3-methoxy-β-phenylisopropylamide.—Formo-4-hydroxy-3-methoxy-β-phenyl*iso*propylamide (0·7 g.) was dissolved in ice-cold 0·5N-sodium hydroxide solution (35 c.c.), and a solution of benzoyl chloride (0·6 g.) in ether (6 c.c.) was added dropwise with stirring during 40 minutes. The pasty material which separated was taken up in chloroform, shaken with dilute hydrochloric acid, and then with water. The chloroform solution was dried (Na_2SO_4) the chloroform removed, and the gummy residue treated with light petroleum until crystalline. The solid obtained (0·5 g., m. p. 73—83°) was recrystallised first from benzene–light petroleum and finally from dilute alcohol, giving rosettes of minute white needles (0·3 g.), m. p. 98—99° (Found: N, 4·7. $C_{18}H_{19}O_4N$ requires N, 4·5%).

7-Benzoxy-6-methoxy-3-methyl-3 : 4-dihydroisoquinoline.—The foregoing compound (0·4 g.) was dissolved in chloroform (4 c.c.), phosphoryl chloride (0·8 c.c.) added, and the solution gently refluxed for one hour. The chloroform and excess of phosphoryl chloride were removed under reduced pressure, and the residue was extracted with hot dilute acetic acid. Much reddish material remained undissolved. The acid extracts were shaken with benzene, cooled, and basified with potassium carbonate. The base was isolated by extraction with chloroform, and converted into the hydrochloride which crystallised from acetone in white needles (94 mg.). The free *base*, liberated from an aqueous solution of the hydrochloride by potassium carbonate, slowly crystallised to a white solid (80 mg., m. p. 123—126°), and was recrystallised twice from light petroleum (b. p. 100—120°) to form clusters of colourless needles, m. p. 125—126°. The *picrate*, obtained by mixing aqueous solutions of the above hydrochloride and potassium picrate, recrystallised from methanol in long pale-yellow silky needles, m. p. 202—203° (Found: C, 55·6; H, 4·0. $C_{18}H_{17}O_3N,C_6H_3O_7N_3$ requires C, 55·1; H, 3·9%).

7-Hydroxy-6-methoxy-3-methyl-3 : 4-dihydroisoquinoline.—The foregoing hydrochloride (90 mg.) was dissolved in alcohol (1 c.c.) and 10% sodium hydroxide solution (2 c.c.) was added. The mixture was heated in the water-bath for one hour, and acidified with hydrochloric acid; benzoic acid (15 mg., m. p. 119—121°) then separated. The solution was basified with potassium carbonate, and the liberated base was isolated by extraction with chloroform and treated with light petroleum until crystalline. The white solid (40 mg., m. p. 141—143°) was somewhat soluble in water, giving a yellow solution. It crystallised from benzene (charcoal) in large colourless plates, falling to a white powder at 100° (Found: C, 68·8; H, 6·8. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·9%).

Benzo-4-benzoxy-3-methoxy-β-phenylisopropylamide.—4-Hydroxy-3-methoxy-β-phenyl*iso*propylamine (0·5 g.) was dissolved in 0·5N-sodium hydroxide solution (40 c.c.), a solution of benzoyl chloride (0·94 g.) in benzene (3 c.c.) was added dropwise with stirring, and the white solid which separated was collected and recrystallised twice from dilute alcohol, giving the *amide* as clusters of small white needles (0·5 g.), m. p. 165—167° (Found: C, 74·2; H, 5·8. $C_{24}H_{23}O_4N$ requires C, 74·1; H, 6·0%).

7-Benzoxy-6-methoxy-1-phenyl-3-methyl-3 : 4-dihydroisoquinoline.—The foregoing amide (0·5 g.) was dissolved in toluene (2·7 c.c.) and phosphoryl chloride (0·8 c.c.) was added. The mixture was refluxed for one hour, cooled, light petroleum added, the precipitated gum washed with light petroleum, and volatile material removed. The residue was dissolved in hot water, and the cooled solution was extracted once with ether, and basified with ammonium hydroxide. The white solid which separated (0·45 g., m. p. 156—157·5°) crystallised from dilute alcohol in glistening white leaflets, m. p. 157—158·5° (Found: C, 77·9; H, 5·7. $C_{24}H_{21}O_3N$ requires C, 77·6; H, 5·7%). The *picrate* crystallised from alcohol in clusters of yellow needles, m. p. 181—182·5° (Found: N, 9·8. $C_{24}H_{21}O_3N,C_6H_3O_7N_3$ requires N, 9·4%). The *methiodide*, formed by refluxing the base for 2 hours with methyl iodide in acetone solution, crystallised from acetone in bright yellow prisms, m. p. 215° (decomp.) (Found: C, 58·3; H, 4·3. $C_{24}H_{21}O_3N,CH_3I$ requires C, 58·5; H, 4·7%). The hydrochloride of the base crystallised from acetone–methanol in clusters of white glistening prisms, m. p. 174—175° (decomp.).

7-*Hydroxy*-6-*methoxy*-1-*phenyl*-3-*methyl*-3 : 4-*dihydro*isoquinoline *Hydrochloride*.—The foregoing base (0·8 g.) was dissolved in concentrated hydrochloric acid (7·5 c.c.) and water (7·5 c.c.); the solution was heated for 4 hours on the water-bath, cooled, filtered from benzoic acid (0·2 g.), and evaporated. The gummy residue crystallised from acetone–methanol, gave the *hydrochloride* in stout golden yellow prisms (0·6 g.), m. p. 206—207° (decomp.) (Found: N, 4·4. $C_{17}H_{17}O_2N$,HCl requires N, 4·6%).

The free *base*, liberated from an aqueous solution of the hydrochloride, crystallised from ethyl acetate (charcoal) in rosettes of creamy-white small needles, m. p. 103—105° (Found: C, 75·7; H, 6·6. $C_{17}H_{17}O_2N$ requires C, 76·3; H, 6·4%). The picrate crystallised from alcohol in bright-yellow prisms, m. p. 223—225° (decomp.).

Phenylaceto-4-*phenylacetoxy*-3-*methoxy*-β-*phenyliso*propylamide.—4-Hydroxy-3-methoxy-β-phenyl*iso*propylamine (0·3 g.) was dissolved in 0·5N-sodium hydroxide solution, and a solution of phenylacetyl chloride (1·1 g.) in benzene (3·3 c.c.) was dropped in during one hour with stirring. The crude amide obtained was recrystallised from dilute alcohol (0·45 g., m. p. 113—115·5°). A portion after further recrystallisation formed a fluffy mass of small white needles, m. p. 116—117° (Found: N, 3·4. $C_{26}H_{27}O_4N$ requires N, 3·4%).

7-*Phenylacetoxy*-6-*methoxy*-1-*benzyl*-3-*methyl*-3 : 4-*dihydro*isoquinoline *Hydrochloride*.—The foregoing amide (1·2 g.) was dissolved in chloroform (12 c.c.); phosphoryl chloride (1·8 c.c.) was added, and the solution refluxed for one hour. The chloroform was removed under reduced pressure, the residue dissolved in ice-cold methanol, and water added to incipient cloudiness. The cool mixture was basified with potassium carbonate; the base then separated as a pale yellow oil. It was rapidly taken up in warm chloroform, the extract dried (Na_2SO_4), and the chloroform removed. The residual gum was rubbed with a slight excess of ice-cold dilute hydrochloric acid; a solid separated (0·7 g., m. p. 185—190°) and was recrystallised twice from acetone–methanol to give a mass of small white needles (0·42 g.), m. p. 207—208° (decomp.) (Found: C, 71·2; H, 5·7. $C_{26}H_{25}O_3N$,HCl requires C, 71·6; H, 6·0%). The *picrate* of the base, prepared directly from a methanolic solution of the hydrochloride, crystallised from alcohol in long glistening yellow needles, m. p. 165·5—166·5° (Found: C, 61·1; H, 4·5. $C_{26}H_{25}O_3N,C_6H_3O_7N_3$ requires C, 60·9; H, 4·3%).

The free *base*, liberated from a dilute methanolic solution of the hydrochloride by the addition of potassium carbonate, crystallised from dilute alcohol in long colourless prisms and was dried in a vacuum. On standing in the air it became sticky and melted indefinitely between 60° and 70° (Found: C, 75·0; H, 6·6. $C_{26}H_{25}O_3N,H_2O$ requires C, 74·8; H, 6·5%).

7-*Phenylacetoxy*-6-*methoxy*-1-*benzoyl*-3-*methyl*-3 : 4-*dihydro*isoquinoline.—The hydrochloride of the foregoing base (220 mg.) was decomposed as usual, the unstable base dissolved in methanol (3 c.c.), allowed to stand in an open vessel at room temperature for 14 days with frequent additions of solvent and evaporated to dryness under reduced pressure; the gummy residue crystallised from dilute methanol to give a creamy-white solid (40 mg., m. p. 136—141°) which recrystallised from dilute methanol in colourless glistening leaflets, m. p. 144—145° (Found: C, 75·4; H, 5·5. $C_{26}H_{23}O_4N$ requires C, 75·5; H, 5·6%). It dissolved in sulphuric acid to give a yellow solution which turned pale orange on warming. Its solution in warm acetic anhydride slowly developed a Prussian-blue colour on boiling.

7-*Hydroxy*-6-*methoxy*-1-*benzyl*-3-*methyl*-3 : 4-*dihydro*isoquinoline *Hydrochloride*.—7-Phenylacetoxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydro*iso*quinoline hydrochloride (0·7 g.) was mixed with water (12 c.c.) and concentrated hydrochloric acid (12 c.c.), heated for two hours in the water-bath, and evaporated to dryness. The residual gum crystallised from acetone as a white solid [0·5 g., m. p. 215° (decomp.)] which recrystallised from acetone–methanol in glistening faintly greenish prisms, m. p. 219—221° (decomp.) (Found: C, 67·4; H, 6·1. $C_{18}H_{19}O_2N$,HCl requires C, 68·0; H, 6·3%). The *picrolonate* of the base, prepared by mixing aqueous solutions of potassium picrolonate and the hydrochloride, crystallised from alcohol in buff-yellow needles, m. p. 233—234° (Found: C, 61·9; H, 4·7. $C_{18}H_{19}O_2N,C_{10}H_8O_5N_4$ requires C, 61·6; H, 5·0%).

The free base crystallised from dilute methanol in clusters of long, pale yellow, silky needles (m. p. 98—107°), which rapidly underwent oxidation in the air.

7-*Hydroxy*-6-*methoxy*-1-*benzoyl*-3-*methyl*-3 : 4-*dihydro*isoquinoline.—The foregoing free base from the hydrochloride (0·25 g.) was dissolved in methanol (3 c.c.) and the solution allowed to oxidise as above. The crystalline material which was slowly deposited was rubbed with dilute methanol giving a solid (124 mg., m. p. 160—163°) which was recrystallised once from benzene–light petroleum (b. p. 100—120°) and finally from dilute methanol when it formed clusters of pale yellow prismatic needles, m. p. 164—165° (Found: C, 73·6; H, 6·0. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8%). A trace of the substance gave a colourless solution in warm acetic anhydride and slowly developed a Prussian-blue coloration on boiling.

The *hydrochloride* crystallised from acetone–methanol in rosettes of small pale yellow needles, m. p. 200—201° (decomp.), which were readily soluble in cold water giving a bright yellow solution (Found: C, 65·9; H, 5·1. $C_{18}H_{17}O_3N$,HCl requires C, 65·3; H, 5·4%).

Homoveratro-4-*homoveratroyloxy*-3-*methoxy*-β-*phenyliso*propylamide.—4-Hydroxy-3-methoxy-β-phenyl*iso*propylamine (0·3 g.) was dissolved in 0·5N-sodium hydroxide solution (30 c.c.) and homoveratroyl chloride (0·85 g.) in benzene (3·5 c.c.) was dropped in with stirring. The amide (0·65 g.), a gum, was obtained by extraction with chloroform.

7-*Homoveratroyloxy*-6-*methoxy*-1-*veratryl*-3-*methyl*-3 : 4-*dihydro*isoquinoline *Perchlorate*.—The foregoing crude amide (0·6 g.) was dissolved in chloroform (8 c.c.), phosphoryl chloride (1 c.c.) added, and air swept out of the apparatus by a current of hydrogen. The solution was gently refluxed in a stream of hydrogen for one hour, cooled, and shaken with potassium bicarbonate solution until alkaline. The chloroform layer was then run off and evaporated under reduced pressure at 30° in a stream of hydrogen. The gummy residue was immediately extracted with hot dilute acetic acid (40 c.c.), and the extract shaken with warm benzene and finally with ether. The acid solution was cooled, and a slight excess of dilute perchloric acid added drop by drop. The bulky precipitate was collected and recrystallised from acetic acid giving a pale yellow solid (0·34 g., m. p. 207—209°) which recrystallised from acetic acid (charcoal) in a mass of creamy-white minute needles, m. p. 209—210° (Found: C, 57·8; H, 5·8. $C_{30}H_{33}O_7N,HClO_4$ requires C, 58·1; H, 5·5%). The *picrolonate*, prepared directly from a solution of the perchlorate in hot dioxan, crystallised from alcohol as a ginger-brown microcrystalline powder, m. p. 190—191·5° (Found: C, 61·1; H, 5·8. $C_{30}H_{33}O_7N,C_{10}H_8O_5N_4$ requires C, 61·2; H, 5·3%).

The *hydrochloride* was prepared by suspending the foregoing perchlorate (300 mg.) in benzene, and passing in ammonia till the solid had dissolved. The mixture was filtered at once, concentrated as above, cooled, and hydrogen chloride passed in. The gummy hydrochloride was crystallised from acetone–methanol; 190 mg., m. p. 201° (decomp.). It was freed from traces of ammonium perchlorate by washing with cold water, and was finally recrystallised from acetone–methanol, giving a fluffy mass of small white needles, m. p. 201° (decomp.) (Found: C, 64·0; H, 5·9. $C_{30}H_{33}O_7N$,HCl requires C, 64·7; H, 6·1%).

7-*Hydroxy*-6-*methoxy*-1-*veratryl*-3-*methyl*-3 : 4-*dihydro*isoquinoline *Hydrochloride*.—The foregoing hydrochloride (80 mg.) was mixed with water (1·5 c.c.) and concentrated hydrochloric acid (1·5 c.c.), and heated for two hours on the water-bath. The *hydrochloride*, isolated in the usual way, crystallised on treatment with acetone to give a creamy-white solid [52 mg., m. p. 210—211°, decomp.)] which recrystallised from acetone–methanol in small, very faintly yellow needles (46 mg.), m. p. 210—211° (decomp.) (Found: C, 63·5; H, 6·1. $C_{20}H_{23}O_4N$,HCl requires C, 63·5; H, 6·1%).

The *picrolonate*, prepared as above from the hydrochloride, crystallised from alcohol as clusters of orange-yellow prisms, m. p. 178—179° (Found : C, 59·4; H, 5·3. $C_{20}H_{23}O_4N,C_{10}H_8O_5N_4$ requires C, 59·5; H, 5·2%).

7-*Hydroxy*-6-*methoxy*-1 : 3-*dimethylisoquinoline*.—7-Acetoxy-6-methoxy-1 : 3-dimethyl-3 : 4-dihydro*iso*quinoline (0·3 g.) and palladium black (0·14 g., prepared according to Willstätter, *Ber.*, 1921, **54**, 123) were heated to 175° in a sublimation tube during 10 minutes, and maintained at 173—175° for a further 30 minutes. The temperature was then lowered to 120—130° and the pressure reduced to 2 mm.; a colourless gum then condensed on the upper part of the tube. It crystallised on rubbing with ether to give a white solid (0·13 g.) which was hydrolysed by warming for one hour on the water-bath with water (0·5 c.c.) and concentrated hydrochloric acid (0·5 c.c.). A crystalline hydrochloride slowly separated from which the free base was obtained and crystallised from acetone; 0·1 g., m. p. 181—182° (Fodor records m. p. 175°) (Found : C, 71·0; H, 6·1; N, 6·9. Calc. for $C_{12}H_{13}O_2N$: C, 70·8; H, 6·4; N, 6·9%). The base was somewhat soluble in water, the solution showing a deep green fluorescence at high dilutions. The *picrate* crystallised from alcohol in deep yellow platelets, m. p. 243° (decomp.) (Found : C, 50·3; H, 3·8. $C_{12}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 50·0; H, 3·7%).

7-*Benzoxy*-6-*methoxy*-1-*phenyl*-3-*methylisoquinoline*.—7-Benzoxy-6-methoxy-1-phenyl-3-methyl-3 : 4-dihydro*iso*quinoline (0·2 g.) was mixed with palladium black (90 mg.) and heated for 1·5 hours to 170—175°/2 mm. The chloroform extract was converted into the hydrochloride, recrystallised from water and the free *base* obtained as colourless needles from dilute alcohol, 85 mg., m. p. 140—141° (Found : N, 4·1. $C_{24}H_{19}O_3N$ requires N, 3·8%). The picrate crystallised from alcohol in felted masses of small yellow needles, m. p. 210—211°.

7-*Hydroxy*-6-*methoxy*-1-*phenyl*-3-*methylisoquinoline*.—The foregoing hydrochloride (70 mg., m. p. 187—190°), dissolved in alcohol (1 c.c.), was heated for 3 hours on the water-bath with 10% sodium hydroxide (1·5 c.c.). Excess of alcohol was removed, the product acidified (hydrochloric acid), and the warm solution basified (potassium carbonate). The *base* crystallised on cooling (45 mg., m. p. 181—184°), and recrystallised from toluene (charcoal) in fan-shaped clusters of colourless prisms (35 mg.), m. p. 206—207° (Found : C, 76·7; H, 5·6. $C_{17}H_{15}O_2N$ requires C, 76·9; H, 5·7%). The *picrate* crystallised from alcohol in lemon-yellow prisms, m. p. 227° (Found : C, 56·6; H, 3·6. $C_{17}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 56·0; H, 3·7%).

7-*Hydroxy*-6-*methoxy*-1-*benzyl*-3-*methylisoquinoline*.—7-Phenylacetoxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydro*iso*quinoline hydrochloride (160 mg.) was decomposed with potassium carbonate in the usual way, and the unstable free base mixed with palladium black (80 mg.). The pressure was reduced to 2 mm., and the temperature raised to 163° during 15 minutes and kept at 163—165° for a further 30 minutes. The dehydrogenated base was converted into the hydrochloride, which was crystallised from acetone, and warmed with 10% sodium hydroxide solution (1 c.c.) for two hours on the water-bath. The crystalline sodium salt which separated was decomposed with hydrochloric acid to give a white solid hydrochloride (23 mg.). The free *base*, liberated from the hydrochloride, crystallised from dilute methanol in colourless plates (15 mg.), m. p. 157—158°, which fell to a white powder on drying at 100°/2 mm. (Found : C, 77·5; H, 6·2. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1%). A dilute aqueous solution of the base showed a deep green fluorescence. The *picrate* recrystallised from dilute methanol in long slender yellow prisms, m. p. 199—200° (Found : C, 57·0; H, 4·0. $C_{18}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 56·7; H, 4·0%).

7-*Hydroxy*-6-*methoxy*-1 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline*.—7-Hydroxy-6-methoxy-1 : 3-dimethyl-3 : 4-dihydro*iso*quinoline (0·1 g.) was dissolved in dilute hydrochloric acid (5 c.c.), a solution of palladium chloride (40 mg.) in dilute hydrochloric (5 c.c.) added, and the mixture shaken with charcoal (0·1 g.) at 40° for 12 hours in hydrogen. The colourless solution was filtered and evaporated; the liberated *base* (170 mg.) crystallised from acetone in colourless leaflets, m. p. 169—170° (Found : C, 69·9; H, 8·2. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·3%). The *picrate* crystallised from ethyl acetate–methanol in yellow-orange prisms, m. p. 200—201° (decomp.) (Found : C, 49·8; H, 4·6. $C_{12}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 49·6; H, 4·6%).

7-*Hydroxy*-6-*methoxy*-1-*phenyl*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline Hydrochloride*.—7-Hydroxy-6-methoxy-1-phenyl-3-methyl-3 : 4-dihydro*iso*quinoline (50 mg.) was hydrogenated in dilute hydrochloric acid solution using palladium chloride (20 mg.) and charcoal as above. The *hydrochloride* of the tetrahydro-base separated as a sparingly soluble white solid [40 mg., m. p. 310° (decomp.)]. It crystallised from methanol–acetone in masses of minute silky needles, m. p. 320° (decomp.) (Found : C, 66·4; H, 6·6. $C_{17}H_{19}O_2N,HCl$ requires C, 66·7; H, 6·6%).

The free *base* crystallised from dilute methanol in clusters of colourless needles, m. p. 142—143·5° (Found : C, 75·5; H, 7·1. $C_{17}H_{19}O_2N$ requires C, 75·7; H, 7·1%).

7-*Hydroxy*-6-*methoxy*-1-*benzyl*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline Hydrochloride*.—7-Hydroxy-6-methoxy-1-benzyl-3-methyl-3 : 4-dihydro*iso*quinoline hydrochloride (0·1 g.) was dissolved in water (6 c.c.) and shaken with platinum oxide (10 mg.) in hydrogen for 12 hours. The pale yellow solution became colourless. The *hydrochloride* of the tetrahydro-base crystallised from acetone–methanol in small white needles [85 mg., m. p. 243° (decomp.)]. The free *base* recrystallised from light petroleum (b. p. 100—120°) in rosettes of colourless needles, m. p. 118—119° (Found : C, 75·7; H, 7·3. $C_{18}H_{21}O_2N$ requires C, 76·2; H, 7·5%). The picrate crystallised from methanol in bright yellow prisms, m. p. 230—231° (decomp.).

7-*Hydroxy*-6-*methoxy*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline*.—7-Hydroxy-6-methoxy-3-methyl-3 : 4-dihydro*iso*quinoline (43 mg.) was dissolved in 0·5N-hydrochloric acid (10 c.c.) and the mixture shaken for 3 hours in hydrogen with platinum oxide (5 mg.). The colourless solution was evaporated giving a white solid hydrochloride (50 mg., m. p. 285°). The free *base* crystallised from benzene in small white rosettes (38 mg.), m. p. 151—152° (Found : C, 68·5; H, 7·7. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·9%).

7-*Hydroxy*-6-*methoxy*-1-*veratryl*-3-*methyl*-1 : 2 : 3 : 4-*tetrahydroisoquinoline*.—7-Hydroxy-6-methoxy-1-veratryl-3-methyl-3 : 4-dihydro*iso*quinoline hydrochloride (68 mg.) was dissolved in water (10 c.c.) and shaken in hydrogen with platinum oxide (8 mg.) for 4 hours. The colourless solution yielded a white solid hydrochloride (54 mg.) which crystallised from dilute hydrochloric acid (1·5 c.c.) in colourless, glistening plates (43 mg.). The free *base* crystallised from dilute methanol in colourless prisms (30 mg.), m. p. 120—121° (Found : C, 69·9; H, 7·5. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3%).

7-*Hydroxy*-6-*methoxy*-1-*veratryl*-3-*methylisoquinoline*.—The tetrahydro-base (50 mg.) was mixed with palladium black (30 mg.) and the mixture dehydrogenated as in the case of the 1-benzyl compound. The *product*, isolated by extraction with chloroform, recrystallised from benzene (charcoal) as glistening leaflets (30 mg.), m. p. 173—174° (Found : C, 71·3; H, 6·3. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·3%).

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