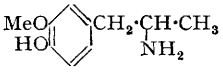
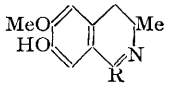
136. *The Synthesis of* 3-*Methyl*isoquinolines. *Part I.*

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

The ready synthesis of 3-methyldihydro*iso*quinolines of type (II) from eugenol is described.

As one aspect of some work proceeding in these laboratories, we have synthesised the hitherto little described 3-methyldihydro*iso*quinolines of type (II). In view of the recent appearance of an abstract of the paper (*Ber.*, 1943, **76**, 1216), in which Fodor describes the synthesis of 1 : 3-dimethyl*iso*quinolines from *iso*eugenol ψ-nitrosite, it appears desirable to place our results to date on record.

(I.) 



(II.)

The literature contains few references to the synthesis of any phenolic *iso*quinolines. These have been prepared, by a modified Decker method, from acyl-β-phenylethylamines or *iso*propylamines in which the

hydroxyl groups have been suitably protected (Tomita and Watanabe, *J. Pharm. Soc. Japan*, 1938, **58**, 783; Späth, Orechoff, and Kuffner, *Ber.*, 1934, **67**, 1214; Späth, *Monatsh.*, 1922, **43**, 477). The lack of data on such type (II) phenolic *iso*quinolines is doubtless due to the previous inaccessibility of phenolic β-phenyl-*iso*propylamines, on account of the several stages involved in their preparation from the appropriate aldehydes by Claisen and Reformatsky condensations (cf. Buck and Ide, *J. Amer. Chem. Soc.*, 1939, **62**, 425). 3-Methyl-*iso*quinolines (type II) are likely to be of pharmacological interest, since the introduction of *C*-methyl groups usually tends to lower the toxicity (cf. Sugasawa and Sugimito, *J. Pharm. Soc. Japan*, 1941, **61**, 62).

The starting material for the work now described is 4-*hydroxy*-3-*methoxy*-β-*phenyl*iso*propylamine* (I), which is now easily obtainable from eugenol. The preparation of this compound from vanillin benzyl ether has also been described (Robinson and Lowe and I.C.I. Ltd., B.P. 519,894).

Treatment of eugenol with hydrogen bromide yields β-bromodihydroeugenol (cf. addition of hydrogen bromide to safrole and methyleugenol, Robinson and Zaki, J., 1927, 2489; Orcutt and Bogert, *J. Amer. Chem. Soc.*, 1936, **58**, 2057; Lin and Robinson, J., 1938, 2008). The addition of hydrogen chloride is readily effected in a similar manner, giving β-chlorodihydroeugenol. This closely resembles the β-bromo-compound in properties, but the greater reactivity of the bromine atom in the latter renders it more useful in the preparation of bases.

Eugenol does not readily react in the cold with gaseous hydrogen bromide, but with the saturated aqueous acid, addition occurs slowly.

Although β-bromodihydroeugenol is readily polymerised by dilute sodium hydroxide solution, it reacts under pressure with alcoholic ammonia to give 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine (I). Alcoholic methylamine reacts similarly, yielding 4-*hydroxy*-3-*methoxy*-β-*phenyl*-N-*methyl*iso*propylamine*. The yield of the former amine is not appreciably increased by protecting the phenolic group by benzoyl, the latter being readily split off as benzamide. None of the methods used by Backeberg and Marais (J., 1942, 381) improved the yield of amine. Attempts to prepare it by the Gabriel method were unsuccessful, because of the low reactivity of the bromine atom and the tendency of the bromo-compound to lose hydrogen bromide at higher temperatures.

The method used by Fränkel and Zeimer (*Biochem. Z.*, 1920, **110**, 244) for the cyclisation of tyramine failed when applied to 4-hydroxy-3-methoxy-β-phenyl*iso*propylamine, but the diacetyl derivative of the latter amine was smoothly cyclised to the corresponding 3 : 4-dihydro*iso*quinoline by phosphorus oxychloride in toluene. This work is being extended.

Experimental.

β-Bromodihydroeugenol.—Eugenol (7 g., freshly distilled; b. p. 95—97°/2 mm.) was saturated with dry hydrogen bromide at 0°. Aqueous hydrogen bromide (28 g., saturated at 0°) was added gradually with shaking and ice-cooling, and the mixture kept for 3 or 4 days with occasional shaking at room temperature. The precipitated oil was taken up in chloroform, washed with water and sodium bicarbonate solution till neutral, dried (sodium sulphate), and distilled in a vacuum (slight decomp.) as a faintly pink viscous oil (7·7 g., b. p. 130—134°/2 mm.).

Benzoyl-β-bromodihydroeugenol.—β-Bromodihydroeugenol (0·5 g.) was dissolved in pure dry pyridine (0·5 c.c.), and benzoyl chloride added dropwise with mixing. The product became warm, and the white pasty mass was kept for 10 minutes at room temperature, and then diluted with water. The precipitated oil soon crystallised to a white solid, and was recrystallised twice from dilute alcohol, forming glistening leaflets (0·6 g.), m. p. 80—81° (Found: C, 57·7; H, 5·0. $C_{17}H_{17}O_3Br$ requires C, 58·3; H, 4·9%).

β-Chlorodihydroeugenol.—Eugenol (6 g., freshly distilled) was saturated with dry hydrogen chloride at 0°. Aqueous hydrogen chloride (23 c.c. saturated at 0°) was added, this addition and the subsequent treatment being as for the bromo-compound, except that occasional saturation with hydrogen chloride was necessary. The product was a colourless, viscous oil (5 g., b. p. 112—115°/2 mm.).

Benzoyl-β-chlorodihydroeugenol.—β-Chlorodihydroeugenol (0·5 g.) was benzoylated and the product worked up exactly as in the case of the bromo-compound, to give glistening leaflets from dilute alcohol (0·5 g., m. p. 79—80·5°. Found: C, 66·5; H, 5·8. $C_{17}H_{17}O_3Cl$ requires C, 66·9; H, 5·6%).

4-*Hydroxy*-3-*methoxy*-β-*phenyl*iso*propylamine.*—β-Bromodihydroeugenol (5·5 g.) was dissolved in alcohol (55 c.c.) in a thick-walled tube, the solution cooled in ice, and saturated with dry ammonia. A white crystalline ammonium salt separated. The tube was sealed, and heated in the boiling water-bath for 15 hrs. Excess of alcohol was removed by distillation, and the brown residue taken up in 2N-hydrochloric acid (12 c.c.). The solution was extracted thrice with warm chloroform to remove non-basic material, then saturated with sodium carbonate and repeatedly extracted with hot chloroform. The chloroform was removed from the dried extracts, and the residual gum rubbed with ether until crystalline. The crude brown solid (2·5 g.) was purified by sublimation at 2 mm., and the white crystalline sublimate (1·8 g.) crystallised twice from alcohol, forming small, creamy-white prisms (1·5 g., m. p. 156—157·5°. Found: C, 66·2; H, 8·4; N, 7·4. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·4; N, 7·7%). The *hydrochloride*, from the base and dry hydrogen chloride in alcohol, forms colourless plates, m. p. 251° (decomp.) (Found: Cl, 16·4. $C_{10}H_{15}O_2N$,HCl requires Cl, 16·3%). The *picrate* crystallised from dilute methanol in bright red prisms, m. p. 162—163° (sinters 159°) (Found: C, 47·0; H, 4·85. $C_{10}H_{15}O_2N$,$C_6H_3O_7N_3$ requires C, 46·8; H, 4·45%).

4-*Hydroxy*-3-*methoxy*-β-*phenyl*-N-*methyl*iso*propylamine.*—Methylamine hydrochloride (10·5 g.) was mixed with methanol (10 c.c.) in a thick-walled tube, and the mixture cooled in ice. A cool solution of potassium hydroxide (8 g.) in methanol (13 c.c.) and water (2 c.c.) was added, the mixture kept in ice for one hour, with occasional shaking, and β-bromodihydroeugenol (5 g.) in methanol (3 c.c.) added. The subsequent procedure was exactly as for the lower homologue, and the crude base distilled as a colourless gum (b. p. 138—140°/2 mm.). On rubbing with light petroleum, it crystallised to a soft white solid, which, crystallised thrice from ethyl acetate and once from light petroleum (charcoal), formed small rosettes of colourless plates (1 g.), m. p. 114—115° (Found: C, 67·2; H, 8·4; N, 7·2. $C_{11}H_{17}O_2N$ requires C, 67·6; H, 8·7; N, 7·9%). Better yields are obtained, but not so conveniently, by using 10—20% methyl-alcoholic methylamine in place of the hydrochloride. The *hydrochloride* crystallised from acetone–methanol in clusters of colourless plates, m. p. 206—208° (Found: C, 57·6; H, 8·0; Cl, 15·3. $C_{11}H_{17}O_2N$,HCl requires C, 57·1; H, 7·9; Cl, 15·3%). The *picrate* crystallised from methanol in small golden-yellow needles, m. p. 145—147·5° (Found: C, 48·8; H, 5·2. $C_{11}H_{17}O_2N$,$C_6H_3O_7N_3$ requires C, 48·2; H, 4·8%).

4-*Acetoxy*-3-*methoxy*-β-*phenylacetoisopropylamide*.—4-Hydroxy-3-methoxy-β-phenyl*iso*propylamine (1·55 g.) was dissolved in dry pyridine (1·7 c.c.) and acetic anhydride (2·5 c.c.). To the solution at 0°, acetyl chloride (1·7 c.c.) was added dropwise with stirring, and the mixture kept for 2 hrs. at room temperature, then diluted with water. The clear solution was concentrated in a vacuum on the water-bath, and the residual gum taken up in chloroform, and shaken with saturated sodium carbonate solution, water, and finally with 2N-hydrochloric acid. The chloroform solution was dried (sodium sulphate), the chloroform removed, and the clear gummy residue treated with light petroleum until crystalline; it recrystallised from benzene–light petroleum in small, white, water-soluble rosettes (1·8 g., m. p. 112—113·5°. Found: C, 63·6; H, 7·7. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·3%).

7-*Acetoxy*-6-*methoxy*-1 : 3-*dimethyl*-3 : 4-*dihydroisoquinoline Hydrochloride*.—The foregoing compound (1 g.) was dissolved in toluene (5 c.c.), phosphorus oxychloride (4 g.) added, and the mixture heated under reflux for one hour, moisture being excluded. The cooled solution was diluted with light petroleum, the precipitated gum washed with light petroleum, taken up in dilute hydrochloric acid, and the solution extracted with benzene to remove non-basic impurities. The aqueous solution was saturated with potassium carbonate, and the precipitated yellow oil taken up in chloroform, dried (sodium sulphate), the chloroform removed, and the residue dissolved in benzene (4 c.c.). The benzene solution was saturated with dry hydrogen chloride at 0°, the sticky gum rubbed with acetone until crystalline, and the creamy-white *hydrochloride* recrystallised from acetone–methanol, forming clusters of colourless, glistening prisms (0·6 g.), m. p. 198—199° (decomp.) (Found: Cl, 12·4. $C_{14}H_{17}O_3N,HCl$ requires Cl, 12·5%).

The free base, obtained by decomposition of the hydrochloride with potassium carbonate, distilled at 155—160°/2 mm. to give a pale yellow glass. The *picrate*, from the base in methanolic solution, crystallised from methanol in stout, pale yellow prisms, m. p. 181—182·5° (Found: C, 50·7; H, 4·0. $C_{14}H_{17}O_3N,C_6H_3O_7N_3$ requires C, 50·4; H, 4·2%). The *methiodide*, formed by refluxing the base with methyl iodide for one hour in acetone solution, separated as a pale yellow, crystalline solid, and crystallised from alcohol in small, pale yellow, glittering plates, m. p. 201—202° (decomp.) (Found: C, 45·8; H, 5·5; I, 32·0. $C_{14}H_{17}O_3N,CH_3I$ requires C, 46·2; H, 5·2; I, 32·6%).

7-*Hydroxy*-6-*methoxy*-1 : 3-*dimethyl*-3 : 4-*dihydroisoquinoline Hydrochloride*.—The foregoing acetylated base (0·5 g.) was dissolved in concentrated hydrochloric acid (2 c.c.) and water (2 c.c.). The solution was heated for 2 hours on the water-bath, and evaporated in a vacuum on the water-bath, leaving a clear yellow gum, which crystallised on treatment with acetone, and was recrystallised from acetone–methanol, forming faintly greenish-white clusters of prisms [0·5 g., m. p. 223—224° (decomp.). Found: Cl, 14·0. $C_{12}H_{15}O_2N,HCl$ requires Cl, 14·7%].

The free *base* was obtained by adding potassium carbonate to a warm aqueous solution of the hydrochloride (0·5 g.). The precipitated orange-coloured oil was taken up in warm chloroform, the solution dried (potassium carbonate), and the chloroform removed. The residual gum crystallised on rubbing with light petroleum, and recrystallised from acetone in creamy-white leaflets or prisms (0·4 g., m. p. 141—142°. Found: C, 70·5; H, 7·3. $C_{12}H_{15}O_2N$ requires C, 70·3; H, 7·4%), readily soluble in water to give a bright-yellow solution.

The *picrate*, from the base in methanolic solution, crystallised from methanol in long, golden-yellow needles, m. p. 208—209° (Found: C, 49·8; H, 3·8. $C_{12}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 49·8; H, 4·1%).

We thank the Colonial Products Research Council for permission to publish these results and for a grant to one of us (J. H. T.).

KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE UPON TYNE, 2.

[*Received, April 26th*, 1945.]