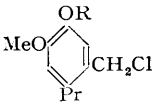
137. *The Chloromethylation of Eugenol and the Preparation of Some New* iso*Quinoline Bases.*

By G. R. Clemo and R. W. Temple.

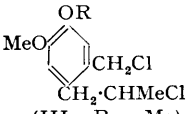
Various derivatives of eugenol have been chloromethylated. 4 : 5-Dimethoxy-2-propylbenzyl chloride has been used in the synthesis of a series of 1-substituted 3 : 4-dihydro-7 : 8-dimethoxy-5-propyl*iso*quinolines and related 1 : 2 : 3 : 4-tetrahydro*iso*quinolines. The chloromethylation products from β-chlorodihydroeugenol derivatives furnish 2-aryl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-3-methyl*iso*quinolines on condensation with aromatic amines.

In continuation of work on eugenol (*J.*, 1945, 533; 1946, 701; 1947, 124, 613, 1692), the methyl ether and the benzoate of dihydroeugenol and of β-chlorodihydroeugenol have been chloromethylated smoothly at 60° by use of hydrochloric acid and formaldehyde, yielding (I—IV). All are stable solids except (III) which is an extremely viscous liquid.

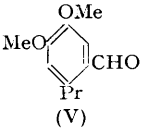
Attempts to orientate the chloromethyl compounds by oxidation were unsuccessful, except in the case of (I), which yielded an aldehyde different from 2 : 3-dimethoxy-5-propylbenzaldehyde on oxidation with potassium permanganate in acetone and must therefore be 4 : 5-dimethoxy-2-propylbenzaldehyde (V), showing that the chloromethyl group enters position 5 as expected. No trace of a second isomer was found in any of the reactions. The benzoyl group in (II) and (IV) remained intact in spite of the reaction's being carried out at 60° in saturated hydrochloric acid.



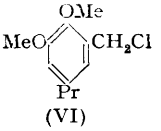
(I; R = Me)
(II; R = Bz)



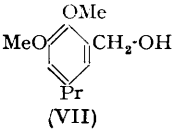
(III; R = Me)
(IV; R = Bz)



(V)



(VI)

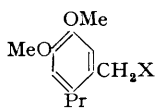


(VII)

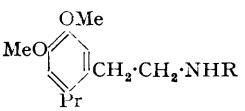
2 : 3-Dimethoxy-5-propylbenzyl chloride (VI) was made for comparison from methyl dihydroeugenol alcohol (VII) which was prepared from dihydroeugenol by the action of sodium hydroxide and formaldehyde, followed by methylation.

4 : 5-Dimethoxy-2-propylbenzyl chloride behaved similarly to 3 : 4-dimethoxybenzyl chloride on treatment with alcoholic potassium cyanide (Bide and Wilkinson, *Chem. and Ind.*, 1945, **64**, 84). Methanolic potassium cyanide gave only 4 : 5-dimethoxy-2-propylbenzyl methyl ether (VIII); aqueous-ethanolic potassium cyanide gave a small amount of the required cyanide (IX), which was eventually obtained in good yield by the method

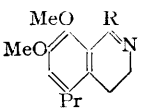
of Kindler and Gehlhaar (*Arch. Pharm.*, 1936, **274**, 377). Reduction of the benzyl cyanide (IX) over a platinum catalyst in acetic anhydride (Carothers and Jones, *J. Amer. Chem. Soc.*, 1925, **47**, 3051) was very slow and required a large amount of catalyst which had to be added in two parts or the resulting *N*-acetyl-2-phenylethylamine (X) was contaminated with unchanged cyanide. Reduction at higher pressures in alcohol saturated with ammonia and Raney nickel (Schwoegler and Adkins, *J. Amer. Chem. Soc.*, 1929, **61**, 3499) gave a good yield of the 2-phenylethylamine (XI). The acetyl (X), benzoyl (XII), phenylacetyl (XIII), and β-3 : 4-dimethoxybenzoyl (XIV) derivatives of the 2-phenylethylamine underwent the modified Bischler–Napieralski ring closure to give the corresponding dihydro*iso*quinolines (XV), (XVI), (XVII), (XVIII). The hydrochlorides of these were all extracted from a hydrochloric acid solution by chloroform and this method gave a much improved yield. Keeping 3 : 4-dihydro-7 : 8-dimethoxy-1-[2-(3 : 4-dimethoxyphenyl)ethyl]-5-propyl*iso*quinoline (XVIII) as its hydrochloride throughout the working up obviated the necessity of working under nitrogen, as the free base is unstable and undergoes rapid oxidation at room temperature to the ketone (XIX) which gave the characteristic Prussian-blue colour in boiling acetic anhydride. Reduction of (XV) and (XVIII) gave the corresponding tetrahydro*iso*quinolines (XXI) and (XXII). Dehydrogenation of the tetrahydro*iso*quinoline (XXII) in *p*-cymene with palladium black yielded the papaverine-type base (XXIV), as did dehydrogenation of the unstable base (XVIII) under nitrogen.



(VIII; X = OMe)
(IX; X = CN)

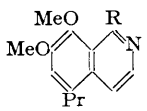


(X; R = Ac)
(XI; R = H)
(XII; R = Bz)
(XIII; R = CO·CH_2Ph)
[XIV; R = CO·CH_2·C_6H_3(OMe)$_2$]



(XV; R = Me)
(XVI; R = Ph)
(XVII; R = CH_2Ph)
[XVIII; R = CH_2·C_6H_3(OMe)$_2$]
[XIX; R = CO·C_6H_3(OMe)$_2$]
(XX; R = H)

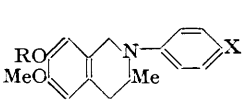
(XXI; R = Me)
[XXII; R = CH_2·C_6H_3(OMe)$_2$]
(XXIII; R = H)



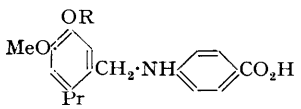
[XXIV; R = CH_2·C_6H_3(OMe)$_2$]

Attempts to prepare the parent dihydro*iso*quinoline (XX) by ring closure of the *N*-formyl derivative of (XI) were unsuccessful, as were attempts to prepare the tetrahydro*iso*quinoline (XXIII) by ring closure of the 2-phenylethylamine (XI) with formaldehyde or methylal and hydrochloric acid.

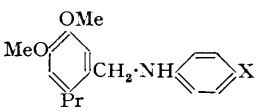
The only known practical method of preparing 2-aryl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines is the condensation of 2-2′-bromoethylbenzyl bromide with aromatic amines (von Braun and Zobel, *Ber.*, 1923, **56**, 2142 : Holliman and Mann, *J.*, 1942, 737) and since this bromo-compound is obtained from *o*-toluidine in a maximum overall yield of 8·5% (Holliman and Mann, *loc. cit.*) the two chloromethyl compounds (III) and (IV) are of special interest.



(XXV; R = Me, X = CO_2H)
(XXVI; R = Me, X = CO_2Et)
(XXVII; R = Me, X = NO_2)
(XXVIII; R = Bz, X = CO_2H)



(XXIX; R = Me)
(XXX; R = Bz)
(XXXI; R = H)



(XXXII; X = CO_2Et)
(XXXIII; X = NO_2)

2-2′-Chloropropyl-4 : 5-dimethoxybenzyl chloride (III) can be prepared from eugenol in an overall yield of about 50% and, although the chlorine attached to the propyl group is rather unreactive, condensation occurs with primary aromatic amines in boiling pyridine, giving 2-aryl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-3-methyl-

*iso*quinolines. With *p*-aminobenzoic acid, ethyl *p*-aminobenzoate, or *p*-nitroaniline the corresponding 2-aryltetrahydro*iso*quinolines (XXV, XXVI, and XXVII) were produced. With one or two mols. of *p*-aminobenzoic acid the same compound was obtained. 5-Benzoyloxy-2-2′-chloropropyl-4-methoxybenzyl chloride (IV) also condensed with *p*-aminobenzoic acid, to yield the tetrahydro*iso*quinoline (XXVIII) in rather poor yield. The corresponding open-chain compounds (XXIX—XXXIII) were made from the chloromethyl compounds (I) and (II).

Some of the above compounds have been submitted for physiological tests.

Experimental

Anhydrous sodium sulphate was used as drying agent.

4 : 5-*Dimethoxy-2-propylbenzyl Chloride*.—Dihydroeugenyl methyl ether (30 g.) was added to a mixture of aqueous formaldehyde (90 ml.; 40%) and concentrated hydrochloric acid (90 ml.), saturated with hydrogen chloride at 60°. The whole was stirred vigorously for 3·5 hours at 60° while hydrogen chloride was passed in. After cooling, the mixture was poured on ice, the liquor poured off, and the gummy organic layer taken up in ether, washed with water, dried and distilled, giving the *chloromethyl* compound (30·4 g.), b. p. 128—134°/2 mm., colourless prisms, m. p. 53—54° (from light petroleum) (Found: C, 62·5; H, 7·3; Cl, 15·8. $C_{12}H_{17}O_2Cl$ requires C, 63·0; H, 7·4; Cl, 15·5%).

Oxidation of 4 : 5-*Dimethoxy-2-propylbenzyl Chloride*.—Potassium permanganate (12 g.) was added during 2 hours to the chloromethyl compound (2 g.) and sodium carbonate (0·5 g.) in boiling acetone (100 ml.). The acetone was distilled off after 6 hours' boiling and the residue shaken with hot 2% potassium hydroxide solution. The undissolved yellow oil was extracted with ether, dried, and distilled, giving 4 : 5-*dimethoxy-2-propylbenzaldehyde* as a bright yellow oil, b. p. 117—120°/1 mm. (0·85 g.) (Found: C, 69·25; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone* formed dark red needles, m. p. 199—201°, from ethanol–ethyl acetate (Found: C, 55·7; H, 5·4. $C_{18}H_{20}O_6N_4$ requires C, 55·7; H, 5·15%), depressed to 174° on admixture with 2 : 3-dimethoxy-5-propylbenzaldehyde dinitrophenylhydrazone (m. p. 200—201°).

5-*Benzoyloxy-4-methoxy-2-propylbenzyl Chloride*.—Dihydroeugenyl benzoate (20 g.) was chloromethylated in a similar fashion to dihydroeugenyl methyl ether. The *chloromethyl* compound (19·6 g.) forms colourless prisms, m. p. 97·5—99° from light petroleum (b. p. 80—100°) (Found: C, 68·0; H, 6·4; Cl, 10·8. $C_{18}H_{19}O_3Cl$ requires C, 67·8; H, 6·0; Cl, 11·1%).

β-*Chlorodihydroeugenyl Methyl Ether*.—Concentrated hydrochloric acid (110 ml.) was added to *O*-methyleugenol (28 g.) and then saturated with hydrogen chloride at 0°. After 6 days (occasional shaking and saturation with hydrogen chloride), the oil was extracted with chloroform, washed with sodium hydrogen carbonate solution and water, dried, and distilled, giving the *product*, b. p. 109—111°/1 mm. (26 g.) (Found: C, 61·5; H, 6·7. $C_{11}H_{15}O_2Cl$ requires C, 61·5; H, 7·0%).

2-2′-*Chloropropyl*-4 : 5-*dimethoxybenzyl Chloride*.—β-Chlorodihydroeugenyl methyl ether (17·7 g.) was chloromethylated for 4 hours at 60°. The *chloromethyl* compound is a very viscous oil, b. p. 144—146°/1 mm. (16·7 g.) (Found: C, 54·8; H, 6·1. $C_{12}H_{16}O_2Cl_2$ requires C, 54·7; H, 6·1%).

5-*Benzoyloxy-2-2′-chloropropyl-4-methoxybenzyl Chloride*.—β-Chlorodihydroeugenyl benzoate (15 g.) was chloromethylated at 60° for 4 hours. The *chloromethyl* compound (9·6 g.) forms prisms, m. p. 107—109°, from light petroleum (Found: C, 60·7; H, 5·25; Cl, 20·2. $C_{18}H_{18}O_3Cl_2$ requires C, 61·2; H, 5·1; Cl, 20·1%).

Action of Methanolic Potassium Cyanide on 4 : 5-*Dimethoxy-2-propylbenzyl Chloride*.—The benzyl chloride (5 g.) in dry methanol (50 ml.) was refluxed with potassium cyanide (1·6 g.) for 7 hours. The colourless precipitate was washed with methanol, the methanol removed, and the residue taken up in ether, washed with water, dried, and distilled, giving 4 : 5-*dimethoxy-2-propylbenzyl methyl ether*, b. p. 121—123°/0·2 mm. (4 g.) (Found: C, 70·0; H, 9·1. $C_{13}H_{20}O_3$ requires C, 69·6; H, 8·9%).

4 : 5-*Dimethoxy-2-propylbenzyl Cyanide*.—4 : 5-Dimethoxy-2-propylbenzyl chloride (23 g.) in benzene (50 ml.) was refluxed with potassium cyanide (15 g.) in water (70 ml.) for 3·5 hours with vigorous stirring. The benzene layer was separated, washed with water, and dried. Removal of the solvent and distillation gave the *cyanide* (19 g.), b. p. 153—155°/1 mm., colourless needles, m. p. 66—68° (from benzene–light petroleum) (Found: C, 71·3; H, 8·1. $C_{13}H_{17}O_2N$ requires C, 71·2; H, 7·8%)

Reduction of the Cyanide.—(a) *In acetic anhydride.* The above cyanide (7·3 g.) and platinum oxide (0·1 g.) in acetic anhydride (20 ml.) were shaken with hydrogen at 100 lb. per sq. in. After 20 hours, further catalyst (0·1 g.) was added and shaking with hydrogen continued for 20 hours. After filtration, the excess of acetic anhydride was decomposed by warm water, the resulting acetic acid removed, and the residual oil dissolved in benzene. Addition of light petroleum precipitated N-*acetyl*-2-(4 : 5-*dimethoxy*-2-*propylphenyl*)*ethylamine* as needles (7·0 g.), m. p. 91—93°. Twice recrystallised from benzene–light petroleum it had m. p. 96—98° (Found : C, 67·95; H, 8·7. $C_{15}H_{23}O_3N$ requires C, 67·9; H, 8·7%). The amide was hydrolysed by boiling 40% hydrochloric acid (6 hours), and the resulting 2-(4 : 5-*dimethoxy*-2-*propylphenyl*)*ethylamine hydrochloride* crystallised from acetone–ethanol as plates, m. p. 241—243° (Found : C, 59·6; H, 8·4. $C_{13}H_{21}O_2N$,HCl requires C, 60·1; H, 8·5%).

2-(4 : 5-Dimethoxy-2-propylphenyl)ethylamine had b. p. 115—120°/0·1 mm., m. p. 43—46°. The *picrate* crystallised from aqueous alcohol in yellow prisms, m. p. 192—194° (Found : C, 50·8; H, 5·3. $C_{19}H_{24}O_9N_4$ requires C, 50·4; H, 5·3%).

(b) *By Raney nickel.* A solution of the benzyl cyanide (12 g.) in ethanol (100 ml.) was saturated with ammonia at 0° and reduced at 100°/100 atm. for 1·75 hours over Raney nickel (0·6 g.). Distillation gave 2-(4 : 5-dimethoxy-2-propylphenyl)ethylamine (10 g.), identical with that obtained above.

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-1-*methyl*-5-*propyl*iso*quinoline.*—*N*-Acetyl-2-(4 : 5-dimethoxy-2-propylphenyl)ethylamine (1 g.) was refluxed in toluene (5 ml.) with phosphorus oxychloride (4 g.) for 2·5 hours with exclusion of moisture. The solution was diluted with light petroleum, and the precipitated gum washed with light petroleum and extracted with dilute hydrochloric acid. The acid solution was washed with benzene and basified (solid sodium carbonate). The precipitated oil was extracted with chloroform, dried, and distilled, giving the *dihydro*iso*quinoline*, b. p. 142—144°/2 mm. (0·6 g.) (Found : C, 72·65; H, 9·0. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5%). The *picrate* (from acetone–methanol) had m. p. 192—193° (Found : C, 52·4; H, 5·4. $C_{15}H_{21}O_2N,C_6H_3O_7N_3$ requires C, 52·9; H, 5·0%).

1 : 2 : 3 : 4-*Tetrahydro*-7 : 8-*dimethoxy*-1-*methyl*-5-*propyl*iso*quinoline.*—The dihydro*iso*quinoline hydrochloride (1·4 g.) was reduced over platinum at atmospheric pressure in 25% hydrochloric acid (35 ml.). The resulting *tetrahydro*iso*quinoline hydrochloride* crystallised from acetone–ether in prisms, m. p. 167—169° (1·25 g.) (Found : C, 63·0; H, 8·6. $C_{15}H_{24}O_2NCl$ requires C, 63·05; H, 8·4%). The *picrate* (from ether–methanol) had m. p. 158—160° (Found : C, 53·1; H, 5·8. $C_{15}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 52·7; H, 5·4%).

N-*Benzoyl*-2-(4 : 5-*dimethoxy*-2-*propylphenyl*)*ethylamine.*—Benzoyl chloride (1 ml.) was added slowly to the amine (1·1 g.) suspended in sodium hydroxide solution (15 ml.; 10%), with stirring, and the white solid which separated recrystallised from benzene–light petroleum (b. p. 60—80°), giving the *amide* (1 g.) as needles, m. p. 117—118·5° (Found : C, 73·3; H, 8·1. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·65%).

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-1-*phenyl*-5-*propyl*iso*quinoline Hydrochloride.*—The foregoing amide (1 g.) was refluxed in toluene (4 ml.) with phosphorus oxychloride (3·2 g.) for 3·5 hours, then cooled, the solution was diluted with light petroleum, and the precipitated gum washed with light petroleum and extracted with hot 30% hydrochloric acid. The acid solution was extracted three times with chloroform. The extracts were dried and evaporated, leaving the *hydrochloride* (0·9 g.), which formed yellow prisms, m. p. 192·5—194° (decomp.), from acetone (Found : C, 69·8; H, 7·4. $C_{20}H_{24}O_2NCl$ requires C, 69·5; H, 6·95%). The base was obtained as a glass. The *picrate*, from methanol–ether, forms prisms, m. p. 144—146° (Found : C, 57·95; H, 5·0. $C_{20}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 58·0; H, 4·8%). The *methiodide* crystallised from acetone as small yellow needles, m. p. 184—185° (Found : C, 55·6; H, 6·0. $C_{21}H_{26}O_2NI$ requires C, 55·9; H, 5·8%).

2-(4 : 5-*Dimethoxyphenyl*-2-*propyl*)-N-*phenylacetylethylamine.*—Phenylacetyl chloride (1·25 ml.) was added to the ethylamine (1·5 g.) suspended in 10% sodium hydroxide solution (15 ml.). The *amide* which separated crystallised from benzene–light petroleum as needles, m. p. 94—96° (1·4 g.) (Found : C, 73·8; H, 8·2. $C_{21}H_{27}O_3N$ requires C, 73·9; H, 7·9%).

1-*Benzyl*-3 : 4-*dihydro*-7 : 8-*dimethoxy*-5-*propyl*iso*quinoline Hydrochloride.*—The foregoing amide (1 g.) in chloroform (8 ml.) was refluxed with phosphorus oxychloride (2 ml.) for 3·5 hours, the solvent and excess of oxychloride were removed, the residue was washed with light petroleum and dissolved in methanol, and water added to incipient cloudiness. Basification with sodium carbonate precipitated a yellow oil which was extracted with chloroform, dried, and evaporated. Hydrogen chloride was passed through an ethereal solution of the base and the precipitated yellow *hydrochloride* crystallised from acetone–ether as pale yellow prisms,

m. p. 155—156° (decomp.) (0·4 g.) (Found: C, 69·9; H, 7·3. $C_{21}H_{26}O_2NCl$ requires C, 70·1; H, 7·2%). The base crystallised from aqueous methanol in prisms, m. p. 97—99°. The *picrate*, prisms (from methanol), had m. p. 127—128·5° (Found: C, 58·7; H, 5·3. $C_{21}H_{25}O_2N,C_6H_3O_7N_3$ requires C, 58·7; H, 5·1%). The *methiodide* crystallised from acetone in bright yellow prisms, m. p. 131—132·5° (Found: C, 56·6; H, 6·2. $C_{22}H_{28}O_2NI$ requires C, 56·8; H, 6·0%).

N-(3 : 4-*Dimethoxyphenyl*)*acetyl*-2-(4 : 5-*dimethoxy*-2-*propylphenyl*)*ethylamine*.—The acid chloride (from 9 g. of homoveratric acid) in benzene (20 ml.) was added with stirring to the ethylamine (8·5 g.) suspended in 15% potassium hydroxide (80 ml.). The buff-coloured precipitate crystallised from benzene–light petroleum (b. p. 60—80°) (charcoal) as colourless needles, m. p. 119—120° (11 g.) (Found: C, 68·9; H, 8·1. $C_{23}H_{31}O_5N$ requires C, 68·8; H, 7·7%).

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-1-(3 : 4-*dimethoxybenzyl*)-5-*propyl*isoquinoline *Hydrochloride*.—The foregoing amide (5 g.) in chloroform (40 ml.) was refluxed with phosphorus oxychloride (15 ml.) for 1·5 hours. The solvent was removed, the residual gum washed with light petroleum and extracted four times with hot 30% hydrochloric acid, and the acid extract washed with ether, extracted with chloroform, and dried. Removal of the chloroform left a yellow gum, which dissolved in acetone and was precipitated by ether, giving the *hydrochloride* (4 g.) as yellow prisms, m. p. 154—158° (decomp.), raised by recrystallisation from acetone–ether to m. p. 161—163° (3·75 g.) (Found: C, 66·0; H, 7·4. $C_{23}H_{30}O_4NCl$ requires C, 65·8; H, 7·15%). The *picrate* crystallised from methanol as prisms, m. p. 131—134° (Found: C, 57·2; H, 5·7. $C_{23}H_{29}O_4N,C_6H_3O_7N_3$ requires C, 56·9; H, 5·2%).

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-1-(3 : 4-*dimethoxybenzoyl*)-5-*propyl*isoquinoline.—The foregoing hydrochloride (0·3 g.) in water was basified with potassium carbonate, the free base extracted with ether and dried, and the ether removed. The residual slightly yellow oil was dissolved in methanol and set aside in an open vessel at room temperature. Soon small colourless prisms appeared. After 20 hours more methanol was added and the yellow solution treated with charcoal; most of the methanol was removed and water added to incipient cloudiness. Cooling gave the oxidised *base* as cubes, m. p. 138—140° (108 mg.), raised to 139—141° by crystallisation from aqueous methanol (Found: C, 69·9; H, 7·0. $C_{23}H_{27}O_5N$ requires C, 69·5; H, 6·8%). A trace of the base in acetic anhydride developed a Prussian-blue colour on boiling. The *picrate* (from methanol) formed prisms, m. p. 167—169° (Found: C, 55·25; H, 5·1. $C_{23}H_{27}O_5N,C_6H_3O_7N_3$ requires C, 55·6; H, 4·8%). The *methiodide* crystallised from acetone–ether as orange prisms, m. p. 170—173° (Found: C, 53·4; H, 6·1. $C_{24}H_{30}O_5NI$ requires C, 53·4; H, 5·6%).

1 : 2 : 3 : 4-*Tetrahydro*-7 : 8-*dimethoxy*-1-(3 : 4-*dimethoxybenzyl*)-5-*propyl*isoquinoline.—The corresponding dihydro*iso*quinoline hydrochloride (1·3 g.) in water (50 ml.) was shaken with hydrogen at one atm. over platinum. After 2·5 hours the hydrogen uptake was 98%. Filtration, concentration, and basification precipitated a gum which was isolated by means of ether. It crystallised from light petroleum (b. p. 60—80°), giving the *tetrahydro*isoquinoline as colourless needles, m. p. 84—86° (0·9 g.) (Found: C, 71·5; H, 8·5. $C_{23}H_{31}O_4N$ requires C, 71·7; H, 8·05%). The *hydrochloride* crystallised from acetone as needles, m. p. 178—180° (Found: C, 65·4; H, 7·9. $C_{23}H_{32}O_4NCl$ requires C, 65·5; H, 7·6%). The *picrate* formed needles, m. p. 181—183°, from ethanol (Found: C, 56·6; H, 5·6. $C_{23}H_{31}O_4N,C_6H_3O_7N_3$ requires C, 56·7; H, 5·5%).

7 : 8-*Dimethoxy*-1-(3 : 4-*dimethoxybenzyl*)-5-*propyl*isoquinoline *Hydrochloride*.—(a) *From the tetrahydro*isoquinoline. The tetrahydro*iso*quinoline (0·2 g.) and palladium black (0·15 g.) in *p*-cymene (3 ml.) were refluxed for 24 hours. The *p*-cymene was removed in a vacuum and the residual yellow oil extracted with hot 25% hydrochloric acid. The acid extract was washed with ether and extracted with chloroform, dried, and evaporated, leaving a yellow glass which was dissolved in acetone. Addition of ether precipitated the iso*quinoline hydrochloride* as light yellow prisms (80 mg.), m. p. 176—178° (decomp.), raised to 179—180° (decomp.) by crystallisation from acetone–ether (Found: C, 65·7; H, 7·05. $C_{23}H_{27}O_4NHCl$ requires C, 66·1; H, 6·7%). The *picrate* formed prisms, m. p. 157—158·5°, from methanol (Found: C, 57·3; H, 4·7. $C_{23}H_{27}O_4N,C_6H_3O_7N_3$ requires C, 57·1; H, 4·9%). When this hydrochloride was shaken in water with hydrogen and platinum two mols. were absorbed, and the tetrahydro*iso*quinoline hydrochloride obtained had m. p. and mixed m. p. 172—175°.

(b) *From the dihydro*isoquinoline. A solution of 3 : 4-dihydro-7 : 8-dimethoxy-1-(3 : 4-dimethoxybenzyl)-5-propyl*iso*quinoline hydrochloride (0·3 g.) in water was basified with potassium carbonate, and the precipitated oil quickly extracted with ether and dried. The ether was removed in nitrogen and the residual oil refluxed in *p*-cymene (4 ml.) with palladium black

(0·1 g.) under nitrogen for 10 hours. The product was worked up as in (*a*), giving, after two crystallisations from acetone–ether, the *iso*quinoline hydrochloride, m. p. 177—178° (120 mg.), identical with the product obtained as in (a).

p-(4 : 5-*Dimethoxy*-2-*propylbenzylamino*)*benzoic Acid*.—4 : 5-Dimethoxy-2-propylbenzyl chloride (1 g.) and *p*-aminobenzoic acid (0·7 g.) in pyridine (2 ml.) were boiled for 3 minutes, cooled, and diluted with water, and the precipitated gum was rubbed until solid. Recrystallisation from aqueous ethanol gave the *amino-acid* as prisms, m. p. 199—201° (Found : C, 69·2; H, 7·5. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·0%).

2-p-*Carboxyphenyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-3-*methyl*iso*quinoline*.—2-2′-Chloropropyl-4 : 5-dimethoxybenzyl chloride (2 g.) and *p*-aminobenzoic acid (1 g., 1 equiv.) in pyridine (4 ml.) were refluxed for 1·5 hours. The cooled solution was poured on ice, and the precipitated gum washed with water and rubbed with methanol till solid (0·8 g.). Two crystallisations from methanol (charcoal) gave the *product* as cream-coloured prisms, m. p. 220—223° (Found : C, 69·8; H, 6·5%; equiv., 329. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·4%; equiv., 327).

The same experiment with 2 equivs. of *p*-aminobenzoic acid gave the same product, m. p. and mixed m. p. 219—222°.

p-(4 : 5-*Dimethoxy*-2-*propylbenzylamino*)*ethyl Benzoate*.—The chloride (2 g.) and ethyl *p*-aminobenzoate (1·5 g.) in boiling pyridine (4 ml.) (3 hours) gave the substitued *ester* as prisms, m. p. 100—102° (from methanol) (Found : C, 70·9; H, 7·9. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6%).

2-p-*Carbethoxyphenyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-3-*methyl*iso*quinoline*.—2-2′-Chloropropyl-4 : 5-dimethoxybenzyl chloride (2·6 g.) and ethyl *p*-aminobenzoate (1·7 g.) in pyridine (5 ml.) were refluxed for 1·75 hours. The *tetrahydro*iso*quinoline* crystallised from methanol as plates, m. p. 139—141° (1 g.) (Found : C, 71·1; H, 7·2. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%).

N-(4 : 5-*Dimethoxy*-2-*propylbenzyl*)-p-*nitroaniline*.—Prepared from the chloride (2 g.) and *p*-nitroaniline (1·4 g.) in boiling pyridine (1 hour), this *base* crystallised from methanol in yellow prisms (1·1 g.), m. p. 147·5—149·5° (Found : C, 65·3; H, 6·9. $C_{18}H_{22}O_4N_2$ requires C, 65·45; H, 6·7%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-3-*methyl*-2-p-*nitrophenyl*iso*quinoline*.—*p*-Nitroaniline (1·8 g.) and 2-2′-chloropropyl-4 : 5-dimethoxybenzyl chloride (3 g.) in pyridine (7 ml.) were refluxed for 1·5 hours. The tetrahydro*iso*quinoline, worked up as above, formed yellow prisms, m. p. 157—159° (0·5 g.), from methanol (Found : C, 65·8; H, 6·5. $C_{18}H_{20}O_4N_2$ requires C, 65·85; H, 6·1%).

p-(5-*Benzoyloxy*-4-*methoxy*-2-*propylbenzylamino*)*benzoic Acid*.—*p*-Aminobenzoic acid (1 g.) and 5-benzoyloxy-4-methoxy-2-propylbenzyl chloride (2 g.) in pyridine were refluxed for 1·5 hours. The *product* crystallised from methanol in prisms, m. p. 220—222° (Found : C, 71·8; H, 5·95. $C_{25}H_{25}O_5N$ requires C, 71·6; H, 6·0%).

p-(5-*Hydroxy*-4-*methoxy*-2-*propylbenzylamino*)*benzoic Acid*.—The foregoing benzoate (8 g.) in alcohol (75 ml.) was refluxed with sodium hydroxide (10 g.) in water (35 ml.) for 2·5 hours. Evaporation, dilution with water, washing with chloroform, acidification to pH 6 with concentrated hydrochloric acid, and crystallisation of the precipitate (5·3 g.) twice from benzene (charcoal) and once from aqueous alcohol gave the acid as plates, m. p. 162—164° (Found : C, 68·7; H, 7·0. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7%).

7-*Benzoyloxy*-2-p-*carboxyphenyl*-1 : 2 : 3 : 4-*tetrahydro*-6-*methoxy*-3-*methyl*iso*quinoline*.—A solution of 5-benzoyloxy-2-2′-chloropropyl-4-methoxybenzyl chloride (7·5 g.) and *p*-aminobenzoic acid (3·3 g.) in pyridine (13 ml.) was refluxed for 4 hours, cooled, and poured on crushed ice. The precipitated yellow solid was washed with water and treated with charcoal in acetone. Removal of most of the acetone and cooling gave the *tetrahydro*iso*quinoline* as prisms (0·95 g.), m. p. 212—215° (after recrystallisation) (Found : C, 72·1; H, 5·9. $C_{25}H_{23}O_5N$ requires C, 71·9; H, 5·5%).

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KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE-ON-TYNE, 1.

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