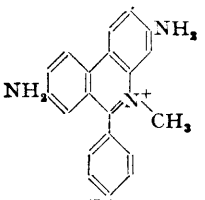
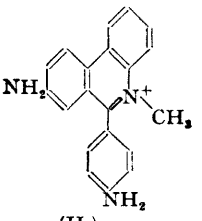
148. *Contributions to the Chemistry of* isoQuinolines. *Part I. The Synthesis of Diamino-*1-*phenyl*isoquinoline *Methiodides in a Search for New Trypanocides, with Some Observations on the Nitration of* 1-*Phenyl*isoquinoline.

By A. McCoubrey and D. W. Mathieson.

Whereas *iso*quinoline undergoes nitration in the 5 and 8 positions (Andersag, *Med. u. Chem. Abh. med. chem. Forsch. I.G. Farbenind.*, 1934, **2**, 377; *Chem. Zentr.*, 1934, I, 3595), 3 : 4-dihydro-derivatives have been found to substitute in position 7. Quaternary derivatives of basically substituted 1-phenyl*iso*quinolines have been prepared and examined for trypanocidal activity.

Consideration of the trypanocidally active 9-phenylphenanthridinium compounds (I) and (II) (Morgan and Walls, *J.*, 1938, 389; Walls, *J.*, 1945, 294) prompted the query whether this molecule could be simplified without loss of activity.


(I.)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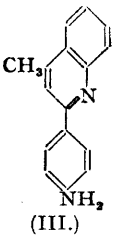
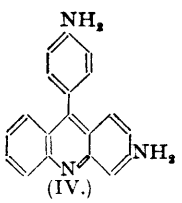

(III.)

Ehrlich (*Berlin klin. Woch.*, 1907, **44**, 282) had earlier prepared (III), (IV), and (V), which can be regarded as modifications of the phenanthridine structure in the light of later publications, and noted these to be devoid of trypanocidal activity. The hetero-nitrogen is, however, non-quaternary, a fact which might be expected to reduce considerably any activity in these types of compound (Morgan and Walls, *loc. cit.*; see Oesterlin " Chemotherapie ", pp. 140—148) as would the presence of but one primary amino-group (cf. Morgan and Walls, *J.*, 1931, 2447).

Lack of information on the possible therapeutic effect of the *iso*quinoline moiety prompted the examination of diamino-1-phenyl*iso*quinolinium salts derived as shown from the 9-phenyl-phenanthridinium structure (VI). The corresponding 3 : 4-dimethyl analogue was prepared in order to ascertain (*a*) whether the nucleus " A " (VI) could be replaced, as in the carcinogenic field, by two methyl groups, and (*b*) if the 3 : 4-dimethyl grouping led to a reduction of toxicity (cf. Sugasawa and Sugionoto, *J. Pharm. Soc. Japan*, 1941, **61**, 26).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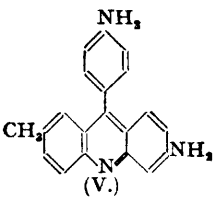
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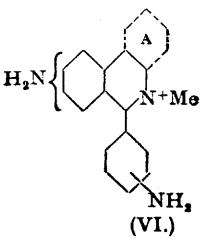
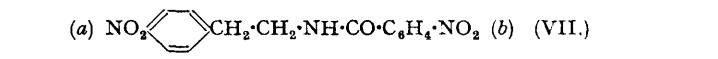

(VI.)

The ready availability of 2-phenylethylamine seemed to offer the simplest route to such *iso*quinoline derivatives, and from the appropriately substituted benzoyl derivatives the following 3 : 4-dihydro*iso*quinolines were synthesised by Bischler–Napieralski cyclisation using phosphoric oxide or phosphorus oxychloride: 1-phenyl- (Späth, Berger, and Kuntara, *Ber.*, 1930, **63**, 138; Pictet and Kay, *Ber.*, 1909, **42**, 1973), 1-*p*-nitrophenyl- (Rodionov and Yavorskaya, *J. Gen. Chem. Russia*, 1941, **11**, 446), and 1-*m*-nitrophenyl- (*idem*, *ibid.*, 1943, **13**, 491), from which were obtained, by dehydrogenation with palladium black, 1-phenyl- (Späth *et al.*, *loc. cit.*), 1-p-*nitrophenyl-*, and 1-m-*nitrophenyl-*iso*quinoline*.

Ethyl β-hydroxy-β-phenyl-α-methylbutyrate (Rupe, Steiger, and Fiedler, *Ber.*, 1914, **47**, 68; Burton and Shoppee, *J.*, 1935, 1160; Kloetzel, *J. Amer. Chem. Soc.*, 1940, **62**, 1708) when heated with iodine (Hibbert, *J. Amer. Chem. Soc.*, 1915, **37**, 1748) gave ethyl αβ-dimethylcinnamate and thence by catalytic reduction ethyl β-phenyl-α-methylbutyrate (Ruzicka *et al.*, *Helv. Chim. Acta*,

1932, **15**, 140). Hydrolysis to β-phenyl-α-methylbutryic acid followed by Curtius degradation of the carboxyl group afforded 2-amino-3-phenylbutane (cf. U.S.P. 2,394,092). The p-*nitrobenzoyl* derivative was cyclised to 1-*p*-nitrophenyl-3 : 4-dimethyl-3 : 4-dihydro*iso*quinoline in poor yield by being refluxed with either phosphorus oxychloride or phosphoric oxide in toluene, the product being characterised as the *picrate*. In either case a considerable proportion of *p*-nitrophenyl cyanide was also produced (see below).

Nitration of 2-phenylethylamine gave 2-*p*-nitrophenylethylamine (Ehrlich and Pistschimuka, *Ber.*, 1912, **45**, 2431) characterised as the *picrate* and *tosyl* derivative. Cyclisation of the p-*nitrobenzoyl* derivative by either phosphoric oxide or phosphorus oxychloride gave 7-*nitro*-1-p-*nitrophenyl*-3 : 4-*dihydro*iso*quinoline* in extremely poor yield, the main product being *p*-nitrophenyl cyanide. Indeed, this low yield might have been expected from the deactivating influence of the nitro-group (*a*) (VII) on the 2-phenylethylamine moiety :



and that this deactivation was operative was supported by our inability to cyclise *N*-benzoyl-2-*p*-nitrophenylethylamine in more than 1·9% yield, while, as noted above, *N*-*p*-nitrobenzoyl-2-phenylethylamine gave the required *iso*quinoline in good yield. Similar treatment of N-m-*nitrobenzoyl*-2-p-*nitrophenylethylamine* gave mainly *m*-nitrophenyl cyanide and a small proportion of 7-*nitro*-1-m-*nitrophenyl*-3 : 4-*dihydro*iso*quinoline*. Formation of these cyanides recalls the reactions of the so-called imino-chlorides of von Braun (*Ber.*, 1904, **37**, 2818; cf. Hantzsch, *Ber.*, 1931, **64**, 667). Dehydrogenation of the above 3 : 4-dihydro-derivatives of *iso*quinoline gave 7-*nitro*-1-p-*nitrophenyl*iso*quinoline* and 7-*nitro*-1-m-*nitrophenyl*iso*quinoline*.

In view of the very small yields obtained in the above cyclisations an approach *via* the 2-(*p*-acylamidophenyl)ethylamines was attempted. Fries and Bestian (*Annalen*, 1937, **533**, 72) have described the preparation of 6-benzamido-1-methyl-3 : 4-dihydro*iso*quinoline by cyclisation of *N*-acetyl-2-(*m*-benzamidophenyl)ethylamine. Accordingly N-p-*nitrobenzoyl*-2-(m-*benzamidophenyl*)*ethylamine* was synthesised and subjected to attempted cyclisation under identical conditions to those of the acetyl derivative described above. Much charring resulted, and only small amounts of unchanged starting material were isolated. Attempts to synthesise 2-(*p*-acetamidophenyl)ethylamine met with small success, as the catalytic reduction of *p*-nitrocinnamic acid to β-*p*-aminophenylpropionic acid proved difficult, and subsequent acetylation of the crude reaction product gave the required β-*p*-acetamidophenylpropionic acid in only very poor yield.*

In the course of determination of the orientation of a nitro-group following nitration the following synthesis was also carried out. *o*-Chlorobenzaldehyde (from *o*-chlorobenzoic acid by the method of McFadyen and Stevens, *J.*, 1936, 584) was condensed with malonic acid to yield *o*-chlorocinnamic acid and thence, by reduction, β-*o*-chlorophenylpropionic acid, Curtius degradation of which afforded 2-o-*chlorophenylethylamine* in good yield (Buck, *J. Amer. Chem. Soc.*, 1933, **55**, 2594, records hydrochloride, m. p. 204°). Cyclisation of the p-*chlorobenzoyl* derivative gave 5-*chloro*-1-p-*chlorophenyl*-3 : 4-*dihydro*iso*quinoline* and thence 5-*chloro*-1-p-*chlorophenyl*iso*quinoline*.

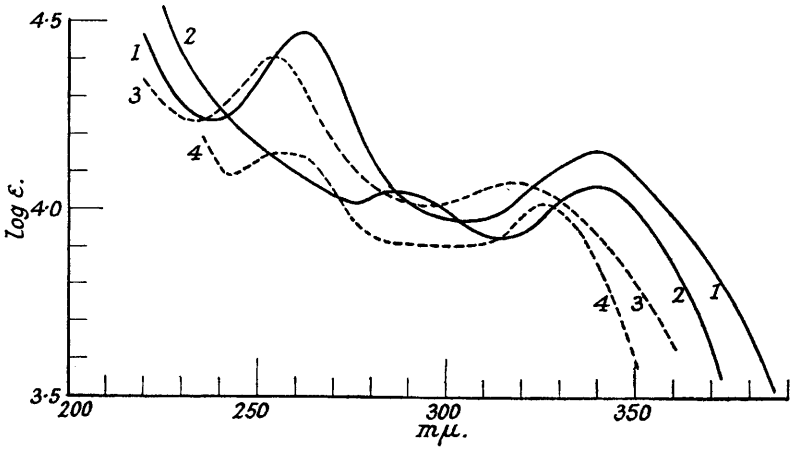
Nitration Studies.—Treatment of 1-*p*-nitrophenyl*iso*quinoline with potassium nitrate and sulphuric acid (*d*, 1·84) gave a dinitrophenyl*iso*quinoline which by analogy with *iso*quinoline itself (Le Fèvre and Le Fèvre, *J.*, 1935, 1470; Tyson, *J. Amer. Chem. Soc.*, 1939, **61**, 183) appeared to contain the second nitro-group in position 5 of the *iso*quinoline ring. Oxidation with potassium permanganate in acid solution gave, however, *p*-nitrobenzoic acid and not the expected nitrophthalic acid, while *x*-nitro-1-*p*-nitrophenyl*iso*quinolinium methiodide on treatment with alkaline potassium permanganate gave no useful product. Accordingly *x*-nitro-1-*p*-nitrophenyl*iso*quinoline was reduced to the diamino-derivative and thence by a Sandmeyer reaction to 5-*chloro*-1-p-*chlorophenyl*iso*quinoline*, shown to be identical by m. p. and mixed m. p. with the synthetic sample above.

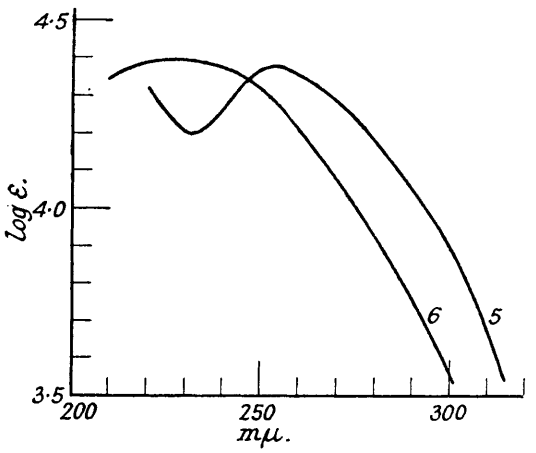
Nitration of 1-phenyl*iso*quinoline yielded a dinitro-derivative which on the basis of the present work is assigned the structure 5-*nitro*-1-m-*nitrophenyl*iso*quinoline*. This substance proved to be photosenstive, the initial pale yellow crystalline form becoming pink on exposure to light, moderately quickly in the solid state and much more so in solution. In view of adverse biological results no further work was carried out on this compound.

During dehydrogenation experiments an attempt was made to utilise nitric acid to oxidise

* 2-(*p*-Acetamidophenyl)ethylamine had m. p. 91° in agreement with Swiss P. 125,375. Gabriel and Steudemann (*Ber.*, 1882, **15**, 844) record m. p. 143°.

1-phenyl-3 : 4-dihydro*iso*quinoline (Rodionov and Yavorskaya, *loc. cit.*). Instead of the 1-phenyl*iso*quinoline claimed by these authors, however, there was obtained a dinitro-compound (cf. Gilman and Gainer, *J. Amer. Chem. Soc.*, 1947, **69**, 1946) the ultra-violet absorption spectrum of which suggested that it still contained the 3 : 4-dihydro-grouping. This was confirmed following its identification as 7-nitro-1-*m*-nitrophenyl-3 : 4-dihydro*iso*quinoline by comparison with an authentic sample. Nitration of 1-*m*-nitrophenyl-3 : 4-dihydro*iso*quinoline yielded the





		$\lambda_{max.}$, A.	log $\epsilon_{max.}$
1.	7-Nitro-1-*p*-nitrophenyl-3 : 4-dimethyl*iso*quinoline	2600, 3400	4·47, 4·16
2.	5-Nitro-1-*p*-nitrophenyl*iso*quinoline	2850, 3400	4·05, 4·06
3.	7-Nitro-1-*p*-nitrophenyl*iso*quinoline	2550, 3175	4·40, 4·07
4.	1-*p*-Nitrophenyl*iso*quinoline	2550, 3260	4·15, 4·02
5.	7-Nitro-1-*p*-nitrophenyl-3 : 4-dihydro*iso*quinoline	2550	4·38
6.	7-Nitro-1-*m*-nitrophenyl-3 : 4-dihydro*iso*quinoline	2275	4·40

same product, and subsequent dehydrogenation of either sample gave 7-*nitro*-1-m-*nitrophenyl*-iso*quinoline*. 1-*p*-Nitrophenyl-3 : 4-dihydro*iso*quinoline yielded on nitration 7-nitro-1-*p*-nitrophenyl-3 : 4-dihydro*iso*quinoline identical with a synthetic sample above. Nitration of 1-*p*-nitrophenyl-3 : 4-dimethyl-3 : 4-dihydro*iso*quinoline introduced a second nitro-group assigned on the basis of the present work to the 7-position, and dehydrogenation of this by palladium black gave 7-*nitro*-1-p-*nitrophenyl*-3 : 4-*dimethyl*iso*quinoline*. Although this has not been proved by unambiguous synthesis the structure is supported by the ultraviolet absorption spectrum.

Spectra.—Light extinction curves were measured over the entire range with a band width of 1 mμ or less using a Beckmann Spectrophotometer (model DU), cell thickness 1 cm. Ethyl alcohol was used as a solvent for all compounds (see Figure).

Quaternary Salts.—7-*Nitro*-1-m-*nitrophenyl*-, 7-*nitro*-1-p-*nitrophenyl*-, 5-*nitro*-1-p-*nitrophenyl*- and 7-*nitro*-1-p-*nitrophenyl*-3 : 4-*dimethyl*-iso*quinoline methiodide* were prepared by interaction of the above dinitro-1-phenyl*iso*quinolines with methyl sulphate in nitrobenzene and subsequent conversion into the iodides. Reduction with iron dust in boiling aqueous solution gave the corresponding 7-*amino*-1-m-*aminophenyl*-, 7-*amino*-1-p-*aminophenyl*-, 5-*amino*-1-p-*aminophenyl*- and 7-*amino*-1-p-*aminophenyl*-3 : 4-*dimethyl*-iso*quinoline methiodide*. These last were tested *in vivo* in the form of their methoacetates against *T. equiperdum* and *T. congolense*. None of these compounds showed noteworthy activity.

Experimental.

p-Nitrophenylethylamine (Ehrlich and Pistschimuka, *loc. cit.*) was characterised as the *picrate*, which crystallised from ethanol in yellow prisms, m. p. 152—158° (Found : N, 17·7. $C_{14}H_{13}O_9N_5$ requires N, 17·7%), and as the *tosyl* derivative which crystallised from ethanol in cream coloured plates, m. p. 153° (Found : N, 8·8. $C_{15}H_{16}O_4N_2S$ requires N, 8·8%).

Ethyl αβ-Dimethylcinnamate.—Ethyl β-hydroxy-β-phenyl-α-methylbutyrate (25 g.) and iodine (0·5 g.) were heated at 120—130° for 0·5 hour; water and iodine distilled. The residue was washed first with sodium thiosulphate solution and then with water, dried ($CaCl_2$), and distilled. The product, a pale yellow liquid (21 g.; 92%), had b. p. 132—135°/13 mm.

β-Phenyl-α-methylbutyric Acid.—Ethyl αβ-dimethylcinnamate (50 g.) in alcohol (200 c.c.) was shaken with hydrogen and Raney nickel (2 g.) at atmosphere temperature and pressure. 0·85 Mol. of hydrogen was absorbed in 8 hours. The resulting ester (40·2 g.; 80%) had b. p. 135—140°/19 mm.; it (11·4 g.) was refluxed for 2 hours with a solution of potassium hydroxide (6 g.) in 25% aqueous ethanol (40 c.c.). The solution was washed with ether and acidified, and the resulting oil taken up in ether and dried. The acid (8·6 g.), b. p. 102—110°/0·01 mm., crystallised from benzene–light petroleum in prisms (6·4 g.; 65%), m. p. 132°.

2-*Amino*-3-*phenylbutane.*—β-Phenyl-α-methylbutyric acid (20 g.) was left overnight with thionyl chloride (20 c.c.). Excess of thionyl chloride was removed under reduced pressure, and the product added dropwise to a stirred solution of sodium azide (14·8 g.) in 50% acetone (350 c.c.) at *ca.* 5°. The solution was extracted with benzene, and the extract thoroughly dried ($CaCl_2$), then decanted and refluxed until evolution of nitrogen was complete (1 hour). Hydrochloric acid (*d* 1·16; 40 c.c.) was added, and refluxing continued until evolution of carbon dioxide ceased. The acid layer was separated, basified, and extracted with ether, and the extract was dried and distilled. The product, a colourless oil (16·1 g.; 96%), had b. p. 109—111°/14 mm.; it readily absorbed carbon dioxide.

N-*Acyl*-2-*phenylethylamines.*—The requisite 2-phenylethylamine or its hydrochloride (1 mol.) was dissolved in dry pyridine (10 mols.), and the appropriate acyl chloride (1·1 mols.) was added portionwise with cooling if necessary. Reaction was completed by 1 hour's heating on the steam-bath, and the solution was then cooled and poured into ice–water. The acylamide was collected and recrystallised from ethanol. The following were thus prepared (yields in parentheses) : N-p-*nitrobenzoyl*-2-p-*nitrophenylethylamine* (71%), m. p. 195° (Found : C, 57·0; H, 4·1; N, 13·3. $C_{15}H_{13}O_5N_3$ requires C, 57·2; H, 4·1; N, 13·3%); *N*-benzoyl-2-*p*-nitrophenylethylamine (91%) (Barger and Walpole, *J.*, 1909, **95**, 174), m. p. 162°; *N*-benzoyl-2-phenylethylamine (83%) (Bischler and Napieralski, *Ber.*, 1893, **26**, 1907), m. p. 113°; *N-p*-nitrobenzoyl-2-phenylethylamine (82·5%) (Braun, Dengel, and Jacon, *Ber.*, 1937, **70**, 994), m. p. 151°; N-m-*nitrobenzoyl*-2-p-*nitrophenylethylamine* (74·5%), m. p. 145° (Found : N, 13·3%); *N-m*-nitrobenzoyl-2-phenylethylamine (62%), m. p. 125° (Rodionov and Yavorskaya, *J. Gen. Chem. Russia*, 1943, **13**, 491, give m. p. 119—120°) (Found : N, 10·4. Calc. for $C_{15}H_{14}O_3N_2$: N, 10·4%); N-p-*nitrobenzoyl*-2-m-*benzamidophenylethylamine* (88%), m. p. 174° (Found : N, 11·0. $C_{22}H_{19}O_4N_3$ requires N, 10·8%); N-p-*chlorobenzoyl*-2-o-*chlorophenylethylamine* (87%), m. p. 86° (Found : N, 4·8; Cl, 24·1. $C_{15}H_{13}ONCl_2$ requires N, 4·8; Cl, 24·1%).

2-p-*Nitrobenzamido*-3-*phenylbutane.*—2-Amino-3-phenylbutane (5·4 g.) was shaken with a solution of sodium hydroxide (2·0 g.) in 50% acetone (60 c.c.) while *p*-nitrobenzoyl chloride (8 g.) was added portionwise, the temperature of the mixture being kept at *ca.* 20°. Water (100 c.c.) was added, and the mixture cooled to 0° and filtered. The residual *compound* was air dried, and crystallised from benzene to yield yellowish needles (8·8 g.; 80%) of indefinite m. p. (138—143°) (Found : C, 69·2; H, 5·8; N, 9·6. $C_{17}H_{18}O_3N_2$ requires C, 68·5; H, 6·0; N, 9·4%).

7-*Nitro*-1-p-*nitrophenyl*-3 : 4-*dihydro*iso*quinoline.*—(*a*) *N-p*-Nitrobenzoyl-2-*p*-nitrophenylethylamine (5 g.) was heated with phosphoric oxide (30 g.) in boiling nitrobenzene (125 c.c.) for 1 hour. The mixture was cooled, treated cautiously with water, and left overnight. Nitrobenzene was removed in steam, and the residue filtered hot. A white solid, which separated in the condenser towards the termination of steam distillation, crystallised from hot water in plates (*A*), m. p. 148—149°. The filtered solution was basified and cooled in ice; a small amount of solid crystalline material was precipitated; it crystallised from a large bulk of ethanol in small glistening pale yellow prisms (*B*) (0·6 g.; 12·7%), m. p. 205° (Found : C, 60·2; H, 3·8; N, 14·2. $C_{15}H_{11}O_4N_3$ requires C, 60·6; H, 3·7; N, 14·2%). This proved to be 7-*nitro*-1-p-*nitrophenyl*-3 : 4-*dihydro*iso*quinoline* (cf. below).

(*b*) *N-p*-Nitrobenzoyl-2-*p*-nitrophenylethylamine (5 g.) was heated with phosphorus oxychloride (2 c.c.) in boiling nitrobenzene (50 c.c.). After 15 minutes, aluminium chloride (0·2 g.) or stannic chloride (0·2 c.c.) was added, and the mixture heated for a further 45 minutes. Nitrobenzene was removed under reduced pressure, and the residue extracted with ether to give *p*-nitrophenyl cyanide as a white solid (1·5 g.) which crystallised from ethanol in colourless plates (m. p. 148° undepressed in admixture with an authentic specimen), identical with product (*A*) above (Found : C, 56·8; H, 3·3; N, 18·3. Calc. for $C_7H_4O_2N_2$: C, 56·8; H, 2·7; N, 18·9%); Borsche (*Ber.*, 1909, **42**, 3597) gives m. p. 149°. The ether-insoluble material was extracted with hot water; the solution on basification gave a

yellow crystalline material which crystallised from a large volume of ethanol in pale yellow prisms (0·3 g.), m. p. 205°, identical by mixed m. p. with the product (*B*) above.

7-*Nitro*-1-*phenyl*-3 : 4-*dihydro*isoquinoline.—*N*-Benzoyl-2-*p*-nitrophenylethylamine (5·7 g.) was heated in nitrobenzene (50 c.c.) with phosphoric oxide (13 g.) for 1 hour. The *product* crystallised from alcohol–ether in small colourless prisms (0·1 g.; 1·9%), m. p. 203° (Found: N, 11·8. $C_{15}H_{12}O_2N_2$ requires N, 11·1%).

1-p-*Nitrophenyl*-3 : 4-*dihydro*isoquinoline (Rodionov and Javorskaya, 1941, *loc. cit.*).—*N*-*p*-Nitrobenzoyl-2-phenylethylamine (5 g.) was refluxed in diphenyl ether or tetralin (100 c.c.) with phosphoric oxide (13 g.) for 0·5 hour. The product (3·45 g.; 74%) had m. p. 120°.

7-*Nitro*-1-m-*nitrophenyl*-3 : 4-*dihydro*isoquinoline.—*N*-*m*-Nitrobenzoyl-2-*p*-nitrophenylethylamine (5 g.) was refluxed in nitrobenzene (75 c.c.) with phosphoric oxide (14 g.) for 1 hour. The product crystallised from ethanol in yellow prisms (0·1 g.), m. p. 167°, giving no depression with the nitration product of 1-phenyl-3 : 4-dihydro*iso*quinoline. By working up the product as in (*b*) above, *m*-nitrophenyl cyanide (1 g.), m. p. 114—115°, was isolated, giving no depression with an authentic specimen.

1-m-*Nitrophenyl*-3 : 4-*dihydro*isoquinoline.—*N*-*m*-Nitrobenzoyl-2-phenylethylamine (5 g.) was refluxed in tetralin (100 c.c.) with phosphoric oxide (13 g.) for 15 minutes, and the base isolated as hydrochloride. The *picrate* crystallised from acetone in small yellow prisms, m. p. 197—198° (sinters at 195°) (Found: C, 52·1; H, 3·3; N, 14·5. $C_{21}H_{15}O_9N_5$ requires C, 52·4; H, 3·1; N, 14·5%). The free base distilled at 160°/0·03 mm. (bath temp.) as a thick yellow oil which crystallised (1·95 g.; 42%) (m. p. 58—60°) after 3 days but could not be recrystallised from any solvent (Rodionov and Yavorskaya, *J. Gen. Chem. Russia*, 1943, **13**, 491, give m. p. 51—52°, yield 64·3%).

1-p-*Nitrophenyl*-3 : 4-*dimethyl*-3 : 4-*dihydro*isoquinoline.—2-*p*-Nitrobenzamido-3-phenylbutane (5 g.) was refluxed with phosphoric oxide (20 g.) in toluene (100 c.c.) for 3 hours. The product was treated with water, the toluene separated, and the aqueous layer neutralised with ammonia, extracted with ether, dried, and distilled. The product (1·5 g.; 32%), b. p. 155°/0·02 mm. (bath temp.), formed a hard yellow glass and was characterised as the *picrate*, yellow plates from ethanol, m. p. 175—186° (Found: C, 54·0; H, 3·8; N, 13·7. $C_{23}H_{19}O_9N_5$ requires C, 54·2; H, 3·7; N, 13·8%). Evaporation of the toluene under reduced pressure gave a crystalline residue from which cold ethanol extracted unchanged material (0·5 g.). The residue (1 g.) proved to be *p*-nitrophenyl cyanide, m. p. 148°, giving no depression with an authentic sample.

5-*Chloro*-1-p-*chlorophenyl*-3 : 4-*dihydro*isoquinoline.—*N*-*p*-Chlorobenzoyl-2-*o*-chlorophenylethylamine (7 g.) was refluxed in tetralin (100 c.c.) with phosphoric oxide (20 g.) for 40 minutes. The *product* crystallised from light petroleum (b. p. 80—100°) in colourless prisms (2 g.; 30%), m. p. 101° (Found: N, 5·0; Cl, 25·5. $C_{15}H_{11}NCl_2$ requires N, 5·1; Cl, 25·7%).

7-*Nitro*-1-m-*nitrophenyl*-3 : 4-*dihydro*isoquinoline.—(*a*) 1-Phenyl-3 : 4-dihydro*iso*quinoline (5 g.) was dissolved in nitric acid (*d* 1·5; 50 c.c.), and the solution left at 0° for 24 hours, poured into water (500 c.c.) and left overnight; the precipitated *nitrate* (4·6 g.) crystallised from acetone in pale yellow plates, m. p. 181° (decomp.) (Found: C, 50·6; H, 3·4; N, 15·7. $C_{15}H_{11}O_4N_3,HNO_3$ requires C, 50·0; H, 3·3; N, 15·6%). The above nitrate and the aqueous mother liquors were bulked and treated with 2N-sodium hydroxide to yield the free *base* as a yellow solid which crystallised from ethanol in greenish prisms (6·3 g.; 88%), m. p. 167° (Found: C, 60·9; H, 4·0; N, 14·2. $C_{15}H_{11}O_4N_3$ requires C, 60·6; H, 3·7; N, 14·1%).

(*b*) 1-*m*-Nitrophenyl-3 : 4-dihydro*iso*quinoline (1·4 g.) in sulphuric acid (*d* 1·84; 4 c.c.) was heated on the steam-bath with a solution of potassium nitrate (2·8 g.) in sulphuric acid (*d* 1·84; 8 c.c.) for 2 hours. The product was poured into water and basified. The precipitated oil, which soon solidified, crystallised from acetone in pale yellow plates (1·3 g.; 78%), m. p. 167°.

The products from (*a*) and (*b*) gave no depression of melting point on admixture, and no depression with the product of cyclisation of *m*-nitrobenzoyl-2-*p*-nitrophenylethylamine.

7-*Nitro*-1-p-*nitrophenyl*-3 : 4-*dihydro*isoquinoline.—1-*p*-Nitrophenyl-3 : 4-dihydro*iso*quinoline (1·7 g.) was nitrated as in (*b*) above. The *product* crystallised from acetone in minute yellow prisms (1·6 g.; 80%), m. p. 205° (Found: N, 14·3. $C_{15}H_{11}O_4N_3$ requires N, 14·1%). No depression of m. p. was observed with the product of cyclisation of *p*-nitrobenzoyl-2-*p*-nitrophenylethylamine.

7-*Nitro*-1-p-*nitrophenyl*-3 : 4-*dimethyl*-3 : 4-*dihydro*isoquinoline.—1-*p*-Nitrophenyl-3 : 4-dimethyl-3 : 4-dihydro*iso*quinoline (6·4 g.) was nitrated as described above; the *product* crystallised from benzene–light petroleum in small yellow prisms (5·4 g.; 73%), m. p. 156—161°. By evaporation a further 1·2 g. was obtained (Found: N, 12·5. $C_{17}H_{15}O_4N_3$ requires N, 12·9%).

5-*Nitro*-1-p-*nitrophenyl*iso*quinoline*.—1-*p*-Nitrophenyl*iso*quinoline (1·45 g.) in sulphuric acid (*d* 1·84; 4 c.c.) was added to a cold solution of potassium nitrate (2·5 g.) in sulphuric acid (*d* 1·84; 8 c.c.), and left at room temperature for 12 hours. The solution was poured into water and basified; the *product* crystallised from acetone or nitrobenzene in yellow plates (1·45 g.; 85%), m. p. 217° (Found: C, 61·1; H, 3·2; N, 14·0. $C_{15}H_9O_4N_3$ requires C, 61·0; H, 3·1; N, 14·2%).

5-*Nitro*-1-m-*nitrophenyl*iso*quinoline*.—Nitration as above of 1-phenyl*iso*quinoline gave the m-*nitro*-compound as buff crystals (80%) from acetone, m. p. 242°, which assumed a pink colour when exposed to light (Found: N, 14·4%).

Dehydrogenation.—This was effected by heating an intimate mixture of the 3 : 4-dihydro-base (1—2 g.) with 10% of palladium black; sublimation under reduced pressure of the product from the melt, or extraction with hydrochloric acid, was followed by crystallisation from acetone. The following were thus obtained, temperature and time of heating being given for each case: 1-p-*nitrophenyl*iso*quinoline* (260°/10 minutes), pale yellow needles (47%), m. p. 155° (Found: C, 72·5; H, 4·2; N, 11·0. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0; N, 11·2%); 7-*nitro*-1-p-*nitrophenyl*iso*quinoline* (220°/30 minutes), yellow needles (60%), m. p. 283° (Found: C, 60·8; H, 2·9; N, 14·3. $C_{15}H_9O_3N_3$ requires C, 60·6; H, 3·05; N, 14·2%); 7-*nitro*-1-m-*nitrophenyl*iso*quinoline* (230—240°/5 minutes), buff needles (50%), m. p. 211—212° (Found: C, 61·5; H, 3·3; N, 14·1%); 7-*nitro*-1-p-*nitrophenyl*-3 : 4-*dimethyl*iso*quinoline* (230—240°/2 minutes), buff needles (43%), m. p. 239—240° (Found: C, 63·1; H, 4·2; N, 12·9. $C_{17}H_{13}O_4N_3$ requires C, 63·2; H, 4·0; N, 13·0%).

Benzenesulphonyl-o-chlorobenzhydrazide.—*o*-Chlorobenzhydrazide (Sah, *Rec. Trav. chim.*, 1940, **59**,

1036) (10 g.) in pyridine was treated with benzenesulphonyl chloride (7·6 c.c.) during 45 minutes, the whole being immersed in a freezing mixture. After 2 hours the mixture was poured on ice; the *product* crystallised from ethanol in colourless plates (15 g.; 82%), m. p. 158° (Found: N, 8·9. $C_{13}H_{11}O_3N_2ClS$ requires N, 9·0%).

o-*Chlorobenzaldehyde*.—Benzenesulphonyl-*o*-chlorobenzhydrazide (40 g.) was dissolved in ethylene glycol (250 c.c.) at 160°. Anhydrous sodium carbonate (32 g.) was added immediately, and the mixture heated for 75 seconds then diluted with water. The whole was extracted with ether and the extract dried ($CaCl_2$). The product (11 g.; 61%) had b. p. 94—98°/20 mm.

o-*Chlorocinnamic Acid*.—*o*-Chlorobenzaldehyde (39·6 g.) was dissolved in dry pyridine (100 c.c.) containing piperidine (2 c.c.) and malonic acid (53·5 g.), and heated in a steam-bath for 3 hours. The solution was poured into water; the precipitate crystallised from ethanol in colourless needles (35·8 g.; 70%), m. p. 195—208°.

2-p-*Chlorophenylethylamine*.—β-*o*-Chlorophenylpropionic acid (Stoermer, *Ber.*, 1911, **44**, 459) (29·3 g.) was treated with thionyl chloride (30 c.c.) at room temperature overnight, and excess of thionyl chloride removed under reduced pressure, then finally in a vacuum desiccator over sodium hydroxide. The acid chloride was added dropwise to a stirred solution of sodium azide (21 g.) in 50% aqueous acetone (360 c.c.) immersed in an ice-bath. The solution was extracted with cold benzene and the extract thoroughly dried at 0° ($CaCl_2$). The filtered solution was refluxed until no more nitrogen was evolved, then cooled; hydrochloric acid (*d* 1·16; 60 c.c.) was added and refluxing continued until evolution of carbon dioxide ceased. The acid layer was separated, basified, and extracted with ether, and the extract dried (K_2CO_3), filtered, and distilled. The product (18·25 g.; 84%) had b. p. 120°/15 mm. The *tosyl* derivative crystallised from benzene–light petroleum (b. p. 40—60°) in large white prisms, m. p. 73° (Found: N, 4·6; Cl, 11·3. $C_{15}H_{16}O_2NClS$ requires N, 4·6; Cl, 11·5%).

5-*Amino*-1-p-*aminophenyl*iso*quinoline*.—5-Nitro-1-*p*-nitrophenyl*iso*quinoline (3·1 g.) was dissolved in hot hydrochloric acid (15%; 80 c.c.) and refluxed while reduced iron (9 g.) was added as rapidly as possible with stirring. Refluxing was continued for 1 hour and the solution then filtered. The filtrate was basified with aqueous ammonia and filtered, and the residue washed free from inorganic matter. The residue was repeatedly extracted with hot ethanol (charcoal). The filtrate was acidified and evaporated to small bulk, diluted with water, and basified. The precipitated *amino*-compound crystallised from ethanol in brown needles (1·9 g.), m. p. 189—190° (Found: C, 76·8; H, 5·8; N, 17·6. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·6; N, 17·9%).

5-*Chloro*-1-p-*chlorophenyl*iso*quinoline*.—(*a*) 5-Chloro-1-*p*-chlorophenyl-3 : 4-dihydroiso*quinoline* (1·9 g.) was mixed with palladium black (0·2 g.) and heated at 220—240° for 5 minutes. The melt was extracted thoroughly with hot hydrochloric acid and filtered. Basification gave the *base* as an oil which soon solidified, and crystallised from ethanol in colourless prisms (0·6 g.; 31·6%), m. p. 149° (Found: N, 5·1; Cl, 25·7. $C_{15}H_9NCl_2$ requires N, 5·1; Cl, 25·9%).

(*b*) 5-Amino-1-*p*-aminophenyl*iso*quinoline (1·5 g.) in hydrochloric acid (*d* 1·16; 10 c.c.) and water (10 c.c.) was tetrazotised at 0° by dropwise addition of sodium nitrite (0·9 g.) in water (5 c.c.). The solution was left at 0° for 30 minutes and then slowly added to a stirred mixture of cuprous chloride (2·5 g.) and hydrochloric acid (*d* 1·16; 10 c.c.) kept at *ca.* −5°. The mixture was allowed to warm to room temperature during 2 hours, and then heated to 60°. Excess of aqueous ammonia was added, and the precipitate crystallised from ethanol. The product (0·25 g.; 14·3%) sublimed in a vacuum in long white needles, m. p. 148—149°, and showed no depression in m. p. with the product obtained in (*a*) (Found: N, 5·4; Cl, 25·5%).

Quaternary Salts.—These were prepared by dissolving the bases in nitrobenzene at 160°, adding methyl sulphate (2 mols.), and allowing to cool. The methosulphates were extracted with water, the aqueous solution washed with ether, and the methiodide precipitated by addition of potassium iodide. Thus were obtained: 7-*nitro*-1-p-*nitrophenyl*iso*quinoline methiodide*, red needles (69%) from water, m. p. 279° (losing its colour at 245°) (Found: N, 9·7; I, 28·7. $C_{16}H_{12}O_4N_3I$ requires N, 9·6; I, 29·0%); 5-*nitro*-1-p-*nitrophenyl*iso*quinoline methiodide*, red prisms (83%) from water, m. p. 218—219° (decomp.) (Found: N, 9·8; I, 29·3%); 7-*nitro*-1-m-*nitrophenyl*iso*quinoline methiodide*, red prisms (80%) from water, m. p. 221° (decomp.) (Found: N, 9·5; I, 28·6%); 7-*nitro*-1-p-*nitrophenyl*-3 : 4-*dimethyl*iso*quinoline methiodide*, red needles (90% calculated on material which reacted) from water, m. p. 239° (Found: N, 9·2; I, 27·4. $C_{18}H_{16}O_4N_3I$ requires N, 9·0; I, 27·3%).

Reduction to the diamino-quaternary derivative was effected by dissolving the dinitro-derivative (1 part) in boiling water (60 parts) containing 2N-hydrochloric acid (2 parts), and adding the solution rapidly to a stirred suspension of reduced iron (1 part) in boiling water (60 parts). The mixture was refluxed for 1·5 hours and filtered, and the iron removed from the filtrate by addition of a slight excess of aqueous ammonia: traces of iron were removed if necessary from the filtrate by addition of a little aqueous hydrogen sulphide. The filtrate was then evaporated to small bulk, and the product precipitated as the methiodide by addition of solid potassium iodide (10 parts); it crystallised from water or methanol. The following were thus obtained: 7-*amino*-1-p-*aminophenyl*iso*quinoline methiodide*, orange needles (81%) from methanol, m. p. 247° (Found: C, 50·4; H, 4·6; N, 10·9; I, 33·2. $C_{16}H_{16}N_3I$ requires C, 51·0; H, 4·3; N, 10·8; I, 33·7%); 5-*amino*-1-p-*aminophenyl*iso*quinoline methiodide*, yellow needles (65%), m. p. 234° (Found: N, 11·2; I, 33·6%); 7-*amino*-1-m-*aminophenyl*iso*quinoline methiodide*, yellow needles (48·5%), m. p. 267° (Found: N, 11·2; I, 33·6%); 7-*amino*-1-p-*aminophenyl*-3 : 4-*dimethyl*iso*quinoline methiodide*, yellow needles (86%), m. p. 294° (Found: C, 53·4; H, 5·1; N, 10·3; I, 30·8. $C_{18}H_{20}N_3I$ requires C, 53·3; H, 4·9; N, 10·4; I, 31·3%).

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