633. isoQuinolines. Part III.* The Nitration of 3 : 4-Dihydro- and 1 : 2 : 3 : 4-Tetrahydro-isoquinolines.

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Nitration of 3 : 4-dihydro- and 1 : 2 : 3 : 4-tetrahydro-*iso*quinoline is shown to lead to substitution in position 7. The hitherto unknown 7-nitro-*iso*quinoline has been prepared.

It has been shown (McCoubrey and Mathieson, *J.*, 1949, 696; McCoubrey, *J.*, 1950, 1833) that nitration of 3 : 4-dihydro-1-phenyl*iso*quinoline derivatives leads to introduction of a nitro-group at position 7. It appeared possible therefore that nitration and subsequent dehydrogenation of 3 : 4-dihydro- or 1 : 2 : 3 : 4-tetrahydro-*iso*quinoline might afford a route to the hitherto unknown 7-nitro*iso*quinoline.

* Part II, *J.*, 1950, 1833.

Treatment of 3 : 4-dihydro*iso*quinoline with sulphuric acid–potassium nitrate gave a nitro-compound, presumably 3 : 4-dihydro-7-nitro*iso*quinoline, which was dehydrogenated, without further purification, over palladium black in decalin. The product was shown to be 7-nitro-*iso*quinoline by catalytic reduction of the nitro-group, to give 7-amino*iso*quinoline, identical with a sample synthesised by Robinson's method (*J. Amer. Chem. Soc.*, 1947, **69**, 1939) and kindly supplied by Dr. M. Kulka. The acetyl derivative had the melting point reported by Manske and Kulka (*Canad. J. Res.*, 1949, **27**, *B*, 161) for 7-acetamido*iso*quinoline. Finally, the ultra-violet absorption characteristics of the two samples of 7-amino*iso*quinolines were identical.

Under similar conditions, tetrahydro*iso*quinoline gave a mononitro-derivative from which catalytic reduction readily afforded the corresponding aminotetrahydro*iso*quinoline. Dehydrogenation of the nitro-compound under a variety of conditions failed to give a pure product and the structure was demonstrated indirectly. 2-Benzoyltetrahydro-nitro*iso*quinoline, obtained by benzoylation of the above nitration product, was reduced in two stages, first catalytically in the presence of Raney nickel to give amino-2-benzoyltetrahydro*iso*quinoline and, secondly, with lithium aluminium hydride to amino-2-benzyltetrahydro*iso*quinoline. The last product was identical with 7-amino-2-benzyltetrahydro*iso*quinoline synthesised by Mann and Beeby's method (*J.*, 1949, 1799). Thus 2-2′-chloroethyl-5-nitrobenzyl chloride and benzylamine afforded 2-benzyl-1 : 2 : 3 : 4-tetrahydro-7-nitro*iso*quinoline which was reduced catalytically to the corresponding amino-derivative. Furthermore, nitration of 2-benzyltetrahydro*iso*quinoline yielded 2-benzyl-7-nitrotetrahydro*iso*quinoline, indicating that *N*-alkylation had no influence on the point of entry of the nitro-group, a conclusion which is supported by the observation below. Nitration of 2-*n*-butyltetrahydro*iso*quinoline gave a nitro-derivative, the hydrochloride of which had a similar melting point to that of the 2-*n*-butyl-7-nitrotetrahydro*iso*quinoline hydrochloride described by Mann and Beeby (*loc. cit.*), but a mixed melting point with a sample kindly supplied by Dr. Mann did not afford unequivocal evidence of identity owing to the range of melting point over which both materials melted.

Experimental.

All hydrogenations were effected at atmospheric pressure and room temperature.

7-*Nitro*iso*quinoline*.—3 : 4-Dihydro*iso*quinoline (Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, **395**, 308) (600 mg.) in sulphuric acid (*d* 1·84; 2·5 c.c.) was added to potassium nitrate (500 mg.) in sulphuric acid (*d* 1·84; 2·5 c.c.), the temperature being kept at 0°. The mixture was allowed to attain room temperature during 2 hours and then warmed to 60° for 4 hours. The product was poured on ice; neutralisation with ammonia solution gave a light brown material (700 mg.), m. p. 88—90° (softens at 40° and resolidifies at ~45°). Dehydrogenation was effected by refluxing this compound in decalin (10 c.c.) for 2 hours with palladium black (200 mg.). The solution was filtered, diluted with its own volume of chloroform, and extracted with 2N-hydrochloric acid. Solid potassium hydroxide was cautiously added, with ice-cooling, a light brown crystalline mass (170 mg.) being obtained, m. p. 155—160°. This was sublimed at 180°/20 mm. and crystallised from light petroleum (b. p. 100—120°), giving 7-*nitro*iso*quinoline* in colourless needles, m. p. 177—178° (Found: C, 62·5; H, 3·5; N, 15·9. $C_9H_6O_2N_2$ requires C, 62·1; H, 3·4; N, 16·1%).

7-*Amino*iso*quinoline*.—7-Nitro*iso*quinoline (50 mg.) in ethanol (10 c.c.) was shaken with hydrogen in the presence of palladised charcoal (30%; 100 mg.). 26 c.c. of hydrogen were absorbed during 20 minutes. The solution was filtered and evaporated. The residue (45 mg.) crystallised from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 201—202° alone or in admixture with a specimen kindly supplied by Dr. M. Kulka. The acetyl derivative, made in the usual manner, had m. p. 148—149°. Manske and Kulka (*loc. cit.*) cite m. p. 147—148°.

1 : 2 : 3 : 4-*Tetrahydro*-7-*nitro*iso*quinoline*.—Tetrahydro*iso*quinoline (10·5 g.) (Wegler and Frank, *Ber.*, 1937, **70**, 1279) was converted into the sulphate by dissolution in the theoretical amount of 5N-sulphuric acid and evaporation to dryness. The powdered residue was added to a solution of potassium nitrate (10 g.) in sulphuric acid (*d* 1·84; 50 c.c.) with ice cooling and, after being kept overnight at room temperature, the whole was poured on ice and cautiously neutralised with aqueous ammonia. The base was extracted with chloroform and dried (K_2CO_3), and the chloroform removed at room temperature under reduced pressure. The residue was extracted with hot light petroleum (b. p. 60—80°), and the extract evaporated under reduced pressure at room temperature. The free base was unstable, especially in the presence of alkali, and was converted into the *hydrochloride* (12·5 g.) which crystallised from aqueous acetone in prisms, m. p. 261° (Found: N, 13·4; Cl, 16·6. $C_9H_{10}O_2N_2$,HCl requires N, 13·1; Cl, 16·6%). The *picrate* crystallised from acetone in large brown prisms, m. p. 190—192° (Found: N, 17·0. $C_9H_{10}O_2N_2$,$C_6H_3O_7N_3$ requires N, 17·2%). The p-*nitrobenzoyl* derivative crystallised from ethanol in yellow prisms, m. p. 209—210° (Found: N, 12·7. $C_{16}H_{13}O_5N_3$ requires N, 12·8%). The *benzoyl* derivative crystallised from alcohol in yellow plates, m. p. 125° (Found: N, 10·2. $C_{16}H_{14}O_3N_2$ requires N, 9·9%).

7-*Amino*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline*.—Tetrahydro-7-nitro*iso*quinoline hydrochloride (5 g.) in ethanol (150 c.c.) was shaken with hydrogen in the presence of platinum oxide (300 mg.). 1580 c.c.

of hydrogen were absorbed during 65 minutes. The solution was filtered, evaporated, and made alkaline with sodium hydroxide solution, and the base extracted with ether. *7-Amino-1 : 2 : 3 : 4-tetrahydroisoquinoline* (2·35 g.) crystallised from benzene in prisms, m. p. 120—121° (Found : C, 73·1; H, 8·5; N, 18·9. $C_9H_{12}N_2$ requires C, 72·9; H, 8·1; N, 18·9%).

7-Amino-2-benzoyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—2-Benzoyltetrahydro-7-nitroisoquinoline (4·3 g.) in ethanol (100 c.c.) was shaken with hydrogen in the presence of Raney nickel (2 g.). 1070 c.c. of hydrogen were absorbed during 3 hours. The *base* (3·8 g.) crystallised from light petroleum (b. p. 60—80°) in cream-coloured plates, m. p. 129° (Found : N, 11·4. $C_{16}H_{16}ON_2$ requires N, 11·1%).

7-Amino-2-benzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—(*a*) 7-Amino-2-benzoyltetrahydroisoquinoline (1 g.) was added to a solution of lithium aluminium hydride (500 mg.) in dry ether (100 c.c.) and refluxed overnight. The mixture was decomposed by addition of 2N-sodium hydroxide, and the ethereal solution separated and dried (K_2CO_3). The residue (900 mg.) remaining after evaporation of the ether crystallised from light petroleum (b. p. 80—100°) in long yellow needles, m. p. 86—87° alone or on admixture with the material synthesised as in (*b*) below.

(*b*) *2-Benzyl-1 : 2 : 3 : 4-tetrahydro-7-nitroisoquinoline.* 2-2′-Chloroethyl-5-nitrobenzyl chloride (Mann and Beeby, *loc. cit.*) (2·5 g.) was refluxed in ethanol (25 c.c.) with benzylamine (3·5 g.) for 1 hour. The mixture was poured into water and extracted with ether. The extract was dried (K_2CO_3) and the *hydrochloride* (3 g.) precipitated by dry hydrogen chloride. It crystallised from ethanol in prisms, m. p. ~248° (softens at 234°) (Found : N, 9·6. $C_{16}H_{16}O_2N_2$,HCl requires N, 9·2%).

7-Amino-2-benzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—2-Benzyltetrahydro-7-nitroisoquinoline (1 g.) in ethanol (10 c.c.) was shaken with hydrogen in the presence of Raney nickel (1 g.). 225 c.c. of hydrogen were absorbed during 10 hours. The *product* (500 mg.) crystallised from light petroleum (b. p. 60—80°) in cream-coloured plates, m. p. 88° (Found : C, 80·6; H, 7·6; N, 11·8. $C_{16}H_{18}N_2$ requires C, 80·7; H, 7·6; N, 11·8%).

2-Benzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—*iso*Quinoline (5 g.) and benzyl chloride (5 g.) were refluxed in ethanol (10 c.c.) for 6 hours. The product was precipitated by addition of dry ether, dried, and dissolved in a minimum of water, and excess of potassium iodide added. *2-Benzylisoquinolinium iodide* (14 g.) was filtered off and crystallised from methanol; it formed yellow prisms, m. p. 178° (Found : N, 4·0. $C_{16}H_{14}NI$ requires N, 4·0%). This product (10 g.) was suspended in methanol (100 c.c.) and shaken with hydrogen in the presence of platinum oxide (300 mg.), and the whole filtered. 1400 c.c. of hydrogen were absorbed during 6 hours. The base (6·2 g.) was isolated and distilled, having b. p. 200—205° (bath-temp.)/20 mm. The *hydrochloride* crystallised from ethanol in plates, m. p. 204° (Found : N, 5·5. $C_{16}H_{17}N$, HCl requires N, 5·4%). Nitration of the base, as described for tetrahydroisoquinoline, gave the 2-benzyl-1 : 2 : 3 : 4-tetrahydro-7-nitroisoquinoline hydrochloride, m. p. 248° (softens at 234°) described in (*b*) above (Found : N, 9·6%).

2-n-Butyl-1 : 2 : 3 : 4-tetrahydro-7-nitroisoquinoline.—*n*-Butyltetrahydroisoquinoline (12 g.) in sulphuric acid (*d* 1·84; 60 c.c.) was added to potassium nitrate (12 g.) in sulphuric acid (*d* 1·84; 60 c.c.) with ice cooling. The product was isolated as described for tetrahydro-7-nitroisoquinoline. The hydrochloride crystallised from ethanol in prisms, m. p. 234—235° (rapid heating; with slow heating, m. p. ~225°) (Found : C, 57·7; H, 7·2; N, 10·6. Calc. for $C_{13}H_{18}O_2N$,HCl : C, 57·8; H, 7·3; N, 10·5%). There was no depression in m. p. observed with a sample kindly supplied by Dr. Mann (cf. Mann and Beeby, *loc. cit.*, who cite m. p. 224—226°).

Ultra-violet absorption spectra.—These were measured in ethanol using a Hilger " Uvispek " photoelectric spectrophotometer; cell path 1 cm.

Since ethanolic solutions of both 7- and 5-aminoisoquinolines exhibit an intense blue fluorescence—a property associated with deviation from Beer's law (cf. *inter al.*, Braude, Fawcett, and Timmons, *J.*, 1950, 1019)—comparisons of the ultra-violet absorption spectra of the two samples of 7-aminoisoquinolines were made at the same molar concentrations. For this reason also no comparison has been attempted with the data presented by Ewing and Steck (*J. Amer. Chem. Soc.*, 1948, **70**, 3397) for 1-, 4-, and 5-aminoisoquinoline. Results were : Our sample ($10·25 \times 10^{-3}$ moles/l.), λ_{max} 238, 284, and 361 mμ. (log. $\epsilon_{max.}$ 4·55, 3·98, and 3·41, respectively). Dr. Manske's sample ($10·1 \times 10^{-3}$ moles/l.), $\lambda_{max.}$ 238, 284, and 361 mμ. (log. $\epsilon_{max.}$ 4·56, 3·98, and 3·42, respectively).

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