845. *Tetrahydroquinoxalines. A New Route from o-Amino-N-2′-hydroxyethylanilines.*

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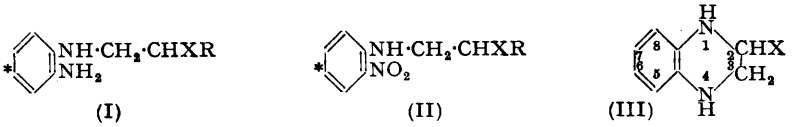
Cyclisation of some derivatives of *o*-amino-*N*-2′-hydroxyethylanilines (I) is described and provides a convenient route to 1 : 2 : 3 : 4-tetrahydroquinoxaline (III; X = H) and its 6-nitro-derivative.

In connection with similar work on pyrimidine derivatives described in the following paper, an investigation was undertaken of the preparation of 1 : 2 : 3 : 4-tetrahydroquinoxalines by the cyclisation of *o*-amino-*N*-2′-hydroxy- and -chloro-ethylanilines (I; R = OH or Cl, X = H). This was necessitated by the striking difference in behaviour of 5-amino-2-chloro-4-2′-hydroxyethylaminopyrimidine and its 6-methyl derivative towards hydriodic acid, and also in order to investigate conditions which would allow cyclisation of the former.

The ready ring closure of 2-*o*-aminophenylethyl alcohol to dihydroindole under mild conditions has been reported by Bennett and Hafez (*J.*, 1941, 287), who later (*ibid.*, p. 652) indicated that the reaction proceeds through the intermediate *o*-aminophenylethyl chloride which was not, however, detected.

1 : 2 : 3 : 4-Tetrahydroquinoxaline was first prepared by reaction of catechol and ethylenediamine (Merz and Ris, *Ber.*, 1887, **20**, 1190) but the yield is variable and the product impure (Cavagnol and Wiselogle, *J. Amer. Chem. Soc.*, 1947, **69**, 795). Tetrahydro-2-methylquinoxaline was similarly prepared from propylenediamine and catechol (Ris, *Ber.*, 1888, **21**, 378). The only other tetrahydroquinoxalines reported are those obtained by reduction of such quinoxalines as can be prepared from *o*-phenylenediamines and glyoxal or 1 : 2-diketones (see, *e.g.*, Gibson, *J.*, 1927, 342).



(I) (II) (III)

* NO_2 in route to tetrahydro-6-nitroquinoxaline.

Condensation of *o*-chloronitrobenzene with 2-aminoethanol to yield (II; R = OH, X = H) has been described by Kremer (*J. Amer. Chem. Soc.*, 1939, **61**, 1321) who used sodium carbonate without solvent but much *o*-chloroaniline was also formed. Hippchen used pyridine as solvent (*Chem. Ber.*, 1947, **80**, 263) but we found *n*-butanol to be most effective. Reduction of the nitro-group in (II; R = OH, X = H) has been described by Kremer (*loc. cit.*), who used stannous chloride and hydrochloric acid, but we found sodium disulphide to be preferable. Cyclisation failed under mild conditions, *e.g.*, with benzenesulphonyl chloride as used by Bennett and Hafez (*loc. cit.*), with boron trifluoride, or on prolonged refluxing with hydrochloric acid, alone or in the presence of zinc chloride or toluene-*p*-sulphonic acid. 1 : 2 : 3 : 4-Tetrahydroquinoxaline (III; X = H) was

readily available in good yield by the action of either hydrochloric acid at 150—160° or constant-boiling hydrobromic acid under reflux. The use of hydriodic acid was unsatisfactory since it results in hydrolytic fission to give *o*-phenylenediamine. Cyclisation can also be achieved by the conversion of (I; R = OH, X = H), by phosphorus oxychloride, into *o*-amino-*N*-2′-chloroethylaniline (I; R = Cl, X = H) which, without purification, was refluxed in ethanol to form the hydrochloride of (III; X = H). A more satisfactory alternative procedure involved the conversion of *N*-2′-hydroxyethyl-*o*-nitroaniline (II; R = OH, X = H) into the corresponding chloro-compound (II; R = Cl, X = H) with phosphorus oxychloride, followed by reduction with stannous chloride and hydrochloric acid to (I; R = Cl, X = H) which was cyclised in refluxing ethanol. Dehydrogenation of tetrahydroquinoxaline in the vapour phase occurred readily in the presence of palladium on charcoal and gave quinoxaline.

The method appeared to be capable of modification so as to make available tetrahydroquinoxalines with substituents in the heterocyclic ring. When, however, it was applied to the preparation of 1 : 2 : 3 : 4-tetrahydro-2-methylquinoxaline (III; X = Me), the cyclisation stage was much more difficult, so the overall yield was poor. Kremer (*loc. cit.*) described the preparation of (II; R = OH, X = Me) and its reduction to (I; R = OH, X = Me), but we prepared them essentially as above except that *o*-chloronitrobenzene was condensed with 2-hydroxypropylamine in *n*-butanol in the presence of sodium carbonate. Attempts to cyclise (I; R = OH, X = Me) were unsatisfactory, mild treatment giving much unchanged material and more drastic conditions causing hydrolytic fission to *o*-phenylenediamine. The remarkable ease of fission of (I; R = OH, X = Me) may be illustrated by the fact that it occurred to an appreciable extent on 2 hours' refluxing with constant-boiling hydrobromic acid, whereas with (I; R = OH, X = H) 9 hours' refluxing caused no apparent fission. The use of hydrobromic acid has given 1 : 2 : 3 : 4-tetrahydro-2-methylquinoxaline in low yield. The alternative procedure of first preparing the chloro-derivative (II; R = Cl, X = Me) by the action of phosphorus oxychloride, followed by reduction to *o*-amino-*N*-2′-chloro-*n*-propylaniline (I; R = Cl, X = Me) and cyclisation, was no more successful.

1 : 2 : 3 : 4-Tetrahydro-6-nitroquinoxaline was readily prepared by cyclisation of 2-amino-*N*-2′-chloroethyl-4-nitroaniline (I; R = Cl, X = H) in refluxing ethanol. The method used for the preparation of (I; R = Cl, X = H) was substantially that of Hippchen (*loc. cit.*): 2-aminoethanol was condensed with 1-chloro-2 : 4-dinitrobenzene in ethanol to give (II; R = OH, X = H); this was reduced with sodium disulphide to 2-amino-*N*-2′-hydroxyethyl-4-nitroaniline which on treatment with thionyl chloride gave the necessary intermediate.

Although the method described provides an alternative route to 1 : 2 : 3 : 4-tetrahydroquinoxaline and the only route to the 6-nitro-derivative, it is not yet satisfactory for the preparation of 2-alkyl derivatives. The methyl group in the side chain inhibits cyclisation to tetrahydroquinoxalines, and this can be compared with the corresponding effect of the 4(6)-methyl group in the pyrimidine ring, described in the following paper.

Experimental

Analyses marked * are by Drs. Weiler and Strauss, Oxford.

N-2′-*Hydroxyethyl*-o-*nitroaniline* (II; R = OH, X = H).—A mixture of *o*-chloronitrobenzene (31·5 g., 0·2 mol.) and ethanolamine (25·0 g., 0·41 mol.) in *n*-butanol (70 c.c.) was refluxed for 12 hours. The butanol was removed on the water-bath under reduced pressure, and the residue diluted with water (150 c.c.) and extracted with ether. The ethereal extracts were washed twice with dilute hydrochloric acid, once with dilute sodium carbonate solution, then with water, and dried (Na_2SO_4). The ether was removed and the residue crystallised from benzene to give *N*-2′-hydroxyethyl-*o*-nitroaniline (21·2 g.; 58% based on *o*-chloronitrobenzene), in massive, bright red prisms, m. p. 74—75°.

o-*Amino*-N-2′-*hydroxyethylaniline* (I; R = OH, X = H).—A solution of sulphur (6·4 g., 0·2 g.-atom) and sodium sulphide (48 g., 0·2 mole) in water (150 c.c.) was refluxed for 2 hours with *N*-2′-hydroxyethyl-*o*-nitroaniline (18·2 g., 0·1 mole). On cooling, *o*-amino-*N*-2′-hydroxyethylaniline (11·9 g., 78%) crystallised in colourless plates, m. p. 105—106°. It was unchanged

after being refluxed with hydriodic acid (*d* 1·7) for a short period but after 6 hours the isolated product on sublimation gave *o*-phenylenediamine, m. p. 99·5—101°.

N-2′-*Chloroethyl*-o-*nitroaniline* (II; R = Cl, X = H).—*N*-2′-Hydroxyethyl-*o*-nitroaniline (15 g.) was added to phosphorus oxychloride (75 c.c.) during 15 minutes, and the mixture heated for 1 hour on the water-bath. Excess of oxychloride was removed under reduced pressure, and the residue warmed with water (100 c.c.) to decompose any remaining. After cooling, the product was extracted with benzene, and the extracts were washed with sodium carbonate and dried (Na_2SO_4). Removal of the benzene and distillation of the residue *in vacuo* gave a fraction (11·8 g.), b. p. 145—150°/0·5 mm., which readily solidified to an orange-coloured solid, m. p. 55—57°, and on crystallisation from alcohol gave *N*-2′-chloroethyl-*o*-nitroaniline as needles, m. p. 59°. Karrer and Naef (*Helv. Chim. Acta*, 1936, **19**, 1029) record m. p. 59°.

1 : 2 : 3 : 4-*Tetrahydroquinoxaline* (III; X = H).—(*a*) *o*-Amino-*N*-2′-hydroxyethylaniline (2 g.) and concentrated hydrochloric acid (10 c.c.) were heated at 150—160° in a sealed tube for 15 hours. The resulting solution was taken to dryness, and the residue dissolved in water (15 c.c.). When the clarified (charcoal) solution was made strongly alkaline with solid potassium carbonate, 1 : 2 : 3 : 4-tetrahydroquinoxaline separated; it crystallised from *cyclo*hexane in colourless plates (0·93 g.), m. p. 98°, not depressed on admixture with material made by the method of Merz and Ris (*loc. cit.*) (Found: N, 20·8. Calc. for $C_8H_{10}N_2$: N, 20·9%). Extraction of the aqueous mother-liquors with ether gave a further quantity (0·15 g.).

(*b*) A solution of *o*-amino-*N*-2′-hydroxyethylaniline (5 g.) in hydrobromic acid (25 c.c.; *d* 1·6) was refluxed for 9 hours. On cooling, a hydrobromide separated which was filtered off and dissolved in water (20 c.c.), and the aqueous solution was made alkaline and gave 1 : 2 : 3 : 4-tetrahydroquinoxaline (2·78 g.), m. p. 98°.

(*c*) *o*-Amino-*N*-2′-hydroxyethylaniline (2 g.) and phosphorus oxychloride (10 c.c.) were heated on the water-bath for 30 minutes. Excess of oxychloride was removed under reduced pressure, and the residue dissolved in water (20 c.c.), made alkaline with potassium carbonate, and extracted with ether. The ethereal extracts were washed with water and dried (Na_2SO_4), and the ether was removed, finally at room temperature under reduced pressure. The residue was refluxed in ethanol (100 c.c.) for 5 hours, the solvent removed, and an aqueous solution made alkaline as above, giving 1 : 2 : 3 : 4-tetrahydroquinoxaline (0·35 g.).

(*d*) *N*-2′-Chloroethyl-*o*-nitroaniline (10 g.) was heated on the water-bath (gently at first) with a solution of stannous chloride (50 g.) in concentrated hydrochloric acid (50 c.c.) for 5—10 minutes. With cooling in an ice-bath, the almost colourless solution was made strongly alkaline with sodium hydroxide solution (30%) and extracted with ether. The procedure under (*c*) then gave crude *o*-amino-*N*-2′-chloroethylaniline (8·15 g.) which was heated under reflux in alcohol. The resulting tetrahydroquinoxaline (5·35 g.) was distilled at 1 mm., and the solid distillate on crystallisation gave 1 : 2 : 3 : 4-tetrahydroquinoxaline (3·38 g.), m. p. 98°.

Quinoxaline.—1 : 2 : 3 : 4-Tetrahydroquinoxaline (1·0 g.) was sublimed, by heating at 100°/10^{-4} mm., through a 30-cm. column of palladium–charcoal (0·7 g.; 30%) on glass-wool (1·5 g.) kept at 150°. The solid product (0·9 g.) collecting on a cold finger during 6 hours was crystallised from light petroleum (b. p. <40°) and had m. p. 28° as recorded for quinoxaline [monohydrate, m. p. 37° (Platt, *Nature*, 1946, **157**, 439); oxalate (from alcohol), m. p. 179°].

N-2′-*Hydroxy*-n-*propyl*-o-*nitroaniline* (II; R = OH, X = Me).—A mixture of *o*-chloronitrobenzene (15·75 g., 0·1 mole), 2-hydroxypropylamine (7·5 g., 0·1 mole), anhydrous sodium carbonate (11·5 g., 0·11 mole), and *n*-butanol (35 c.c.) was refluxed with stirring for 12 hours. The butanol was removed on the water-bath under reduced pressure, and the residue diluted with water (100 c.c.) and steam-distilled. The product remained as an oil which readily solidified on cooling and was filtered off, washed with water, and dried in a desiccator. Crystallisation from carbon tetrachloride gave yellow needles (13·0 g., 66% based on 2-hydroxypropylamine), m. p. 67—68°.

o-*Amino*-N-2′-*hydroxy*-n-*propylaniline* (I; R = OH, X = Me).—A suspension of *N*-2′-hydroxy-*n*-propyl-*o*-nitroaniline (19·6 g., 0·1 mole) in a solution of sodium sulphide (48 g., 0·2 mole) and sulphur (6·4 g., 0·2 g.-atom) in water (140 c.c.) was refluxed for 4 hours. On cooling, the suspended oil solidified to almost colourless plates, which were filtered off, washed with a little water, and dried in a desiccator. Crystallisation from benzene gave *o*-amino-*N*-2′-hydroxy-*n*-propylaniline as colourless plates (14·2 g., 86%), m. p. 88—89°.

N-2′-*Chloro*-n-*propyl*-o-*nitroaniline* (II; R = Cl, X = Me).—*N*-2′-Hydroxy-*n*-propyl-*o*-nitroaniline (10 g.) was added during 15 minutes to phosphorus oxychloride (50 c.c.), and the mixture heated for 1 hour on the water-bath before the excess of oxychloride was removed under reduced pressure. The residue was warmed gently with water (50 c.c.), cooled, and

extracted with ether. The combined extracts were washed with aqueous sodium carbonate and dried (Na_2SO_4), the solvent was removed, and the residue (9·3 g.) distilled. The fraction, b. p. 137—140°/0·2 mm., solidified, on cooling, to a yellow solid (6·95 g.), m. p. 29—32°. N-2′-*Chloro*-n-*propyl*-o-*nitroaniline* was obtained as yellow-orange plates, m. p. 40°, by crystallisation from an equal volume of ether (*Found: C, 50·0; H, 4·8; Cl, 16·5. $C_9H_{11}O_2N_2Cl$ requires C, 50·4; H, 5·2; Cl, 16·5%).

1 : 2 : 3 : 4-*Tetrahydro*-2-*methylquinoxaline* (III; X = Me).—(*a*) A solution of *o*-amino-*N*-2′-hydroxy-*n*-propylaniline (1 g.) in hydrobromic acid (4 c.c.; *d* 1·6) was refluxed for 9 hours, then diluted with acetone (10 c.c.), and the hydrobromide (0·55 g.) filtered off, dissolved in water (3 c.c.), and made alkaline with saturated potassium carbonate solution. A white solid (0·2 g.) separated, which was filtered off and dried, and on crystallisation from *cyclo*hexane gave 1 : 2 : 3 : 4-tetrahydro-2-methylquinoxaline, m. p. 67—69°, raised to m. p. 71° on recrystallisation from light petroleum (b. p. 40—60°). Ris (*loc. cit.*) records m. p. 72°.

(*b*) *N*-2′-Chloro-*n*-propyl-*o*-nitroaniline (10 g.) was reduced with stannous chloride, the recovered oil heated under reflux in alcohol, and the product (6·51 g.) isolated by ether as previously described. After distillation through a 3″ Vigreux column the fraction (2·6 g.), b. p. 150—170°/5 mm., partly solidified on cooling. On sublimation at 130—140°/4 mm., a slightly sticky solid (1·15 g.) was obtained, which on crystallisation from light petroleum (b. p. 40—60°) gave 1 :2 : 3 : 4-tetrahydro-2-methylquinoxaline (0·43 g.) as white plates which darkened slowly in air and had m. p. 67—68°, raised to 71° on further recrystallisation.

N-2′-*Hydroxyethyl*-2 : 4-*dinitroaniline* (II; R = OH, X = H) (cf. Hippchen, *loc. cit.*).—A solution of 2-aminoethanol (12·5 g., 0·2 mole) in ethanol (20 c.c.) was added slowly (1 hour) with stirring to a solution of 1-chloro-2 : 4-dinitrobenzene (20·25 g., 0·1 mole) in ethanol (30 c.c.) at 60°; the solution was then kept at room temperature and finally refluxed for a further hour and, while hot, diluted with water (50 c.c.) to incipient turbidity. On cooling, *N*-2′-hydroxyethyl-2 : 4-dinitroaniline (20·8 g., 92%) separated as large yellow needles, which were filtered off, washed with a little aqueous alcohol (60%), and dried; m. p. 89—91°.

2-*Amino*-N-2′-*hydroxyethyl*-4-*nitroaniline* (I; R = OH, X = H).—A solution of sodium sulphide (25·2 g., 0·105 mole) and sulphur (3·4 g., 0·104 g.-atom) in water (65 c.c.) was added to *N*-2′-hydroxyethyl-2 : 4-dinitroaniline (22·7 g., 0·1 mole) in aqueous alcohol (80%; 150 c.c.) under reflux during 30 minutes, and refluxing continued for a further 5 hours. Alcohol (110 c.c.) was distilled off on the water-bath and, on cooling, 2-amino-*N*-2′-hydroxyethyl-4-nitroaniline separated as brown needles, which were filtered off, washed with aqueous alcohol (50%), and dried (15·2 g., 78%; m. p. 134—135°). Further crystallisation from water gave orange-brown needles, m. p. 135°.

2-*Amino*-N-2′-*chloroethyl*-4-*nitroaniline* (I; R = Cl, X = H) (cf. Hippchen, *loc. cit.*).—The foregoing amine (5 g.) was added to thionyl chloride (15 c.c.) at room temperature. After the initial vigorous evolution of gas had ceased, the mixture was heated on a water-bath for 5—10 minutes until all the solid had dissolved. Excess of thionyl chloride was removed on the water-bath under reduced pressure, and the residue treated with ice-water (100 c.c.) and made alkaline with aqueous ammonia. The product was extracted with ether, and the ethereal extracts were washed with water, dried, and evaporated to 25 c.c. After cooling, filtration gave 2-amino-*N*-2′-chloroethyl-4-nitroaniline (5·05 g., 92·5%), m. p. 113—115°, which on crystallisation from methanol gave bright prisms with a blue reflex, m. p. 115—116°.

1 : 2 : 3 : 4-*Tetrahydro*-6-*nitroquinoxaline* (III; X = H).—2-Amino-*N*-2′-chloroethyl-4-nitroaniline (10 g.) was refluxed in ethanol (500 c.c.) for 30 hours. Evaporation to *ca.* 60 c.c. gave the hydrochloride, which separated and was filtered off and dissolved in water (100 c.c.); the free base (6·8 g.) was precipitated with aqueous ammonia as an oil which solidified on cooling. Crystallisation from benzene gave 1 : 2 : 3 : 4-*tetrahydro*-6-*nitroquinoxaline* as broad red needles with a green reflex, m. p. 116° (*Found: C, 54·0; H, 5·1. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·1%). The *picrate* crystallised from ethanol in ochre-coloured prisms, m. p. 180° (decomp.) (*Found: N, 20·6. $C_{14}H_{12}O_9N_6$ requires N, 20·6%).

THE TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, August 6th*, 1952.]