6. *Cinnolines and Other Heterocyclic Types in Relation to the Chemotherapy of Trypanosomiasis. Part XI.* Some Reactions of Simple Quinoxaline Derivatives.*

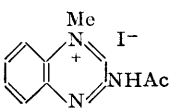
By C. M. Atkinson, C. W. Brown, and (the late) J. C. E. Simpson.

Quaternisation of 2-acetamidoquinoxaline has been shown to occur at position 4.

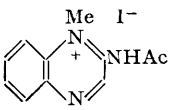
The orientation of the products from the reaction between 1 : 2-diamino-4-nitrobenzene with *n*-butyl glyoxylate has been established by comparison with derivatives of 7-amino-2-hydroxyquinoxaline.

In Part IX (*J.*, 1954, 2023) we described the synthesis of azoquinoxaline derivatives for conversion into potential trypanocides. The difficulties encountered in that work emphasised the importance of investigating the reactions of simple members of this series before proceeding with the bis-heterocyclic types. This paper describes some of these reactions.

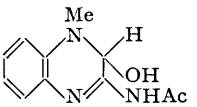
2-Aminoquinoxaline was prepared both by acid-hydrolysis of alloxazine (cf. Wolf, Beutel, and Stevens, *J. Amer. Chem. Soc.*, 1948, **70**, 2572) and from the 2-hydroxy-derivative *via* the chloro- and the phenoxy-compound. The increased stability of these quinoxaline derivatives compared with corresponding members of the cinnoline and phthalazine series was evident from the much longer time required for phenoxylation and from the negligible yield of amine obtainable from 2-phenoxyquinoxaline and molten ammonium acetate; the chloro-compound was unchanged by refluxing with 0·1N-hydrochloric acid during two hours.



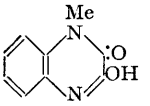
(*a*) (I)



(*b*)



(II)



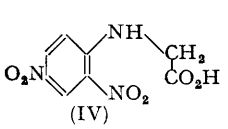
(III)

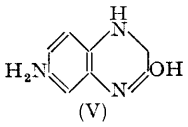
Attempts to quaternise 2-aminoquinoxaline gave discouraging results, the products being either intractable gums or solids which were obtained pure in only very low yield. However, 2-acetamidoquinoxaline reacted smoothly with methyl toluene-*p*-sulphonate; the product was isolated as the methiodide. Degradation of this by boiling alkali yielded one equivalent of ammonia and the sodium salt of (III) (cf. Usherwood and Whiteley, *J.*, 1923, 1039) which was converted into 2 : 3-dichloroquinoxaline by phosphorus pentachloride. Thus it appears that 2-acetamidoquinoxaline is quaternised at position 4 (cf. I*a*) and that atmospheric oxidation of the intermediate (II) takes place during the treatment with alkali. The alternative structure (I*b*) would yield 1-methyl-2-quinoxalone on treatment with alkali, and hydroxylation of this compound, necessary to provide (III), was shown not to occur under the conditions of the decomposition.

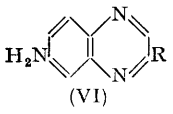
* Part X, *J.*, 1955, 4236.

The diminished reactivity of substituents in the hetero-ring of quinoxaline prompted a study of *Bz*-nitro-compounds which might also be used as models for reactions in the azoquinoxaline series. There appeared to be no known unambiguous synthesis of a *Bz*-nitroquinoxaline derivative. Wolf and his co-workers (*J. Amer. Chem. Soc.*, 1949, **71**, 6) prepared mixed 2-hydroxy-6- and -7-nitroquinoxaline and separated the 2-chloro-derivatives which they designated " 6a " and " 6b." A simple method to determine the orientation of these isomers was suggested by the conversion of 2-(2 : 4-dinitroanilino)-ethanol into 2-(2-amino-4-nitroanilino)ethanol by Ramage and Trappe (*J.*, 1952, 4406). 7-Amino-3 : 4-dihydro-2-hydroxyquinoxaline was prepared by Waldmann (*J. prakt. Chem.*, 1915, **91**, 190) from 2 : 4-dinitrophenylglycine (IV) and it was expected that mono-reduction of this by Ramage's method would lead to 2-hydroxy-7-nitroquinoxaline; however, no definite product could be isolated. Wolf's " 6a " series was shown to be identical with 7-nitroquinoxaline derivatives as follows.

Repetition of Waldmann's work showed that the quantities of tin and hydrochloric acid specified for the conversion of the acid (IV) into the dihydroquinoxaline were insufficient. In our hands the anhydrous base had m. p. *ca.* 280° (decomp.), compared with m. p. 181° reported by Waldmann, but was undoubtedly the required compound since oxidation yielded 7-amino-2-hydroxyquinoxaline (VI; R = OH). The ease with which this oxidation was effected with alkaline hydrogen peroxide or simply by boiling the dihydro-compound with water is in contrast to Waldmann's failure to oxidise his product with a variety of reagents. Treatment of the hydroxy-amine (VI; R = OH) with phosphorus oxychloride gave, at best, a poor yield of the chloro-compound (VI; R = Cl) which was only partially converted by prolonged treatment with potassium hydroxide in phenol into 7-amino-2-phenoxyquinoxaline (VI; R = OPh). This was identical with the compound formed from 2-chloro-" 6a "-nitroquinoxaline by phenoxylation and subsequent catalytic reduction.


(IV)


(V)


(VI)

Confirmation of this identity was obtained by hydrolysis of 2-chloro-" 6a "-nitroquinoxaline and subsequent reduction to yield a high-melting amino-hydroxy-derivative which was shown to be identical with (VI; R = OH) by paper chromatography and by comparison of the acetyl derivatives. This decision on the orientation of Wolf's " 6a "-nitro-series is the only one to be taken, apart from the identification of the " 6a "-methyl compounds as genuine 6-methylquinoxalines by Platt (*J.*, 1948, 1310).

Experimental

2-Hydroxyquinoxaline.—A solution of sodium toluene-*p*-sulphonate (1·7 g.) in N-sulphuric acid (8·4 c.c.) was dried (Dean and Stark trap) by refluxing with benzene (600 c.c.) for 5—6 hr. Tartaric acid (150 g.) and butan-1-ol (276 c.c.) were added and the mixture refluxed for 24 hr., the theoretical volume of water being collected. The mixture was washed with water and dilute alkali, benzene and excess of butanol were removed, and the residue was distilled, to yield di-*n*-butyl tartrate (239 g., 91%), b. p. 178—180°/14 mm., n_D^{15} 1·4474. This material (50 g.) was stirred vigorously with 0·402M-sodium periodate solution (475 c.c.) and ether-extracted, to provide by distillation pure *n*-butyl glyoxylate (43 g., 86%), b. p. 55°/14 mm., n_D^{18} 1·4443.

A mixture of *n*-butyl glyoxylate (2·5 g.), ethanol (20 c.c.), and *o*-phenylenediamine (2 g.) was refluxed for 2 hr., then cooled and 2-hydroxyquinoxaline (2·52 g., 94%), m. p. 267—269°, was collected; this was purified by dissolution in alkali, treatment with carbon, and precipitation with acid (2·35 g.; m. p. 268—270°).

2-Phenoxyquinoxaline.—Prepared as usual from the chloro-compound (1·75 g.; Gowenlock, Newbold, and Spring, *J.*, 1945, 622; isolation modified by pouring reaction mixture into iced sodium hydroxide solution and extraction with ether) and potassium hydroxide (0·72 g.) in phenol (7 g.) at 95° for 14 hr., *2-phenoxyquinoxaline* (2·23 g.), m. p. 100—101°, crystallised from

light petroleum (b. p. 60—80°) (Found: C, 75·85; H, 4·5; N, 12·65. $C_{14}H_{10}ON_2$ requires C, 75·65; H, 4·5; N, 12·6%).

2-Aminoquinoxaline.—A mixture of alloxazine (12 g.) and 80% (v/v) sulphuric acid (60 c.c.) was heated at 195—200° for 30 min., then cooled and poured on crushed ice (600 c.c.). After removal of insoluble green material the combined filtrates from this and two similar experiments (with 15 g. and 13 g. of alloxazine) were clarified with charcoal and basified with ammonia (*d* 0·880), and the yellow needles of 2-aminoquinoxaline (12 g., 45%), m. p. 151—153°, were collected.

Quaternisation of 2-Aminoquinoxaline.—(*a*) The base (0·46 g.) and methyl toluene-*p*-sulphonate (0·65 g.) were heated at 105° until the red melt became much more viscous (7 min.), then cooled, water (5 c.c.) was added, and the filtrate (from a trace of solid) was extracted with ether to remove excess of ester. Addition of saturated potassium iodide (equal volume) slowly gave a black solid (0·5 g.), m. p. 190—205°. Digestion of this with hot water left an insoluble fraction (0·02 g.), m. p. 248—251°, and there separated from the filtrate the dark red *methiodide* (0·09 g.), m. p. 185—187° raised to 188° by two recrystallisations from water (Found: C, 36·1; H, 3·9; N, 12·2; I, 40·9. $C_9H_{10}N_3I$ requires C, 36·5; H, 3·7; N, 14·2; I, 42·9%).

2-Acetamidoquinoxaline Methiodide.—The base (5 g.) and methyl toluene-*p*-sulphonate (5 g.) were heated at 100—110° for 30 min. (the melt solidified). The mixture was dissolved in water (75 c.c.), and the *iodide* (7·4 g.), m. p. 328—340° (decomp.), isolated as above and recrystallised from water to provide red needles (5·8 g.), m. p. 343—344° (decomp.) (Found: C, 40·35; H, 3·7; N, 13·7; I, 34·8. $C_{11}H_{12}ON_3I$ requires C, 40·1; H, 3·7; N, 12·75; I, 38·5%).

Alkaline decomposition. A solution of the salt (2 g.) in water (180 c.c.) was refluxed with 40% aqueous sodium hydroxide (29·5 c.c.) in a Kjeldahl apparatus through which nitrogen passed. After 1½ hr., one equiv. of ammonia had been evolved and the solution was concentrated in a desiccator. A sodium salt (0·7 g.), m. p. 360°, separated from 90 c.c. and further concentration to 40 c.c. gave more solid (0·6 g.), m. p. *ca.* 300°. Acidification of the former material (0·2 g.) with concentrated hydrochloric acid gave a solid (0·154 g.), m. p. 261—267°, which separated as colourless needles, m. p. 287·5—288°, from nitromethane or 2-ethoxyethanol (Found: C, 61·5; H, 4·35; N, 15·95. Calc. for $C_9H_8O_2N_2$: C, 61·4; H, 4·6; N, 15·9%). This was identical with 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (prepared from *N*-methyl-*o*-phenylenediamine according to Usherwood and Whiteley, *loc. cit.*). Both materials gave 2 : 3-dichloroquinoxaline, m. p. 145—148°, on reaction for 15 min. with phosphorus pentachloride at 160°, decomposition with water, and recrystallisation from aqueous ethanol.

7-Amino-3 : 4-dihydro-2-hydroxyquinoxaline (cf. Waldmann, *loc. cit.*).—2 : 4-Dinitrophenylglycine (10 g.; m. p. 205—206°) and granulated tin (30 g.) were treated with portions of concentrated hydrochloric acid (total, 100 c.c.), with cooling towards the end of the addition. After 2 hours' heating on a steam-bath the solution was diluted with water (750 c.c.) and filtered and tin salts were removed by hydrogen sulphide. The precipitated sulphides were digested three times with boiling water (total, 750 c.c.), and the combined digests and filtrate were evaporated to a small volume. Colourless needles of the dihydrochloride (8 g., 82%) which separated overnight were washed with ethanol and ether and dissolved in the minimum volume of hot water, and crystalline sodium acetate (8 g.) was added. The dihydrate of the base was collected and recrystallised from water, from which it formed yellow cubes (5·7 g.), m. p. 288° (decomp.). Heating the dihydrate (1·0 g.) for 3—4 hr. at 130—140° yielded the anhydrous base, m. p. 288° (decomp.). This (0·4 g.) was refluxed for 30 min. with acetic anhydride (2 c.c.), and the cold mixture diluted with ether. The yellow solid (0·42 g.), m. p. 290—295° (decomp.), was recrystallised twice from formamide; the pure brownish-yellow *diacetyl derivative* had m. p. 294—295° (decomp.) (Found: C, 58·7; H, 5·55; N, 17·6. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3; N, 17·0%).

7-Amino-2-hydroxyquinoxaline.—A solution of the foregoing dihydrate (10 g.) in 2N-sodium hydroxide (105 c.c.) was heated on a steam-bath for 30 min. with 3% aqueous hydrogen peroxide (95 c.c.). The hot, dark red solution was filtered and acidified with acetic acid, and the crude solid (7·2 g.), m. p. 360°, collected. Pure *7-amino-2-hydroxyquinoxaline*, m. p. 360°, was obtained by recrystallisation from nitrobenzene (Found: C, 59·45; H, 4·4; N, 26·4. $C_8H_7ON_3$ requires C, 59·61; H, 4·4; N, 26·1%).

7-Amino-2-chloroquinoxaline.—The hydroxy-compound (2 g.) was heated on the steam-bath for 15 min. with phosphoryl chloride (10 c.c.), and the mixture poured on ice (300 c.c.) and 2N-sodium hydroxide (300 c.c.). The washed, dried, and clarified (carbon) ethereal extract was evaporated to dryness under reduced pressure and the residue of yellow needles (0·37 g.; m. p. 200—201°) was recrystallised from chloroform to provide the *chloro-compound*, m. p. 200—201°

(Found : C, 53·65; H, 3·35; N, 23·65; Cl, 19·95. $C_8H_6N_3Cl$ requires C, 53·48; H, 3·37; N, 23·4; Cl, 19·73%).

7-*Amino*-2-*phenoxyquinoxaline*.—The foregoing chloro-compound (0·2 g.) was heated on a steam-bath for 16 hr. with potassium hydroxide (0·08 g.) in phenol (1 g.), and the mixture poured into 2N-sodium hydroxide. The suspension was extracted with ether, and the extract washed with 2N-sodium hydroxide and water, dried ($MgSO_4$), and evaporated to give a crude product (0·22 g.), m. p. 115—150°. Recrystallisation from chloroform gave unchanged material (20 mg.) but addition of light petroleum (b. p. 60—80°) to the chloroform mother-liquor produced crystalline material (0·11 g.), m. p. 125—127°, on storage overnight. The *phenoxy-compound*, m. p. 126—128°, separated from chloroform–light petroleum (b. p. 60—80°) in golden needles (Found : C, 70·9; H, 4·9; N, 17·8. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·7; N, 17·7%).

7-*Acetamido*-2-*hydroxyquinoxaline*.—A suspension of 7-amino-2-hydroxyquinoxaline (0·5 g.) in acetic anhydride (5 c.c.) was refluxed for 1 hr., then diluted with ether, and the solid (0·565 g.), m. p. 344—346° (decomp.), was collected. Recrystallisation from boiling nitrobenzene (500 parts) provided the *acetamido-compound*, m. p. 348—350°, as pale yellow needles (Found : C, 59·15; H, 4·2; N, 20·5. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·5; N, 20·7%). This material was identical (mixed m. p.) with that prepared by acetylation of the " 6a "-amino-hydroxyquinoxaline.

2-*Chloro*-6- *and* -7-*nitroquinoxaline*.—1 : 2-Diamino-4-nitrobenzene (9·2 g.; 197—198°) in 95% ethanol (72 c.c.) and *n*-butyl glyoxylate (8·7 g.) were refluxed with stirring for 2 hr., then cooled and filtered, and the mixed hydroxy-compounds (10·9 g.), m. p. 245—255°, washed and dried. This material (4 g.) was heated with phosphoryl chloride (40 c.c.) and phosphorus pentachloride (8 g.) on a steam-bath for 1 hr. and the clear brown solution was poured on crushed ice (800 c.c.). The solid (3·8 g.; m. p. 160—165°) was washed with sodium hydrogen carbonate solution (200 c.c.) and water, and dried in a desiccator over sodium hydroxide (the solid must be acid-free to prevent resinification during recrystallisation). Two recrystallisations from benzene gave pale yellow needles of 2-chloro-" 6a "-nitroquinoxaline (1·65 g.), m. p. 185—186° (Wolf *et al.*, *loc. cit.*, give m. p. 184—186°); the mother-liquors gave colourless needles (0·2 g.), m. p. 158—160°, after concentration and repeated recrystallisation from benzene–light petroleum (b. p. 60—80°) (Wolf *et al.* give m. p. 160—161° for their " 6b " isomer).

2-*Hydroxy*-" 6a "-*nitroquinoxaline*.—The chloro-compound (1 g.; m. p. 185—186°) was refluxed for 2½ hr. with N-hydrochloric acid (20 c.c.) and ethanol (5 c.c.), and the suspension cooled. The 2-*hydroxy-compound* (0·82 g.) had m. p. 275—276°, unchanged by recrystallisation from nitromethane from which it separated in orange needles (Found : C, 50·05; H, 2·85; N, 22·45. $C_8H_5O_3N_3$ requires C, 50·3; H, 2·6; N, 22·0%).

" 6a "-*Amino*-2-*hydroxyquinoxaline*.—A suspension of finely powdered 2-hydroxy-" 6a "-nitroquinoxaline (0·4 g.) in glacial acetic acid (3 c.c.) was treated with the " stannous chloride–acetic anhydride reagent " of Albert and Linnell (*J.*, 1936, 1617) (8 c.c.). The red mixture, which was formed with much evolution of heat, was set aside for 50 min., poured into water (20 c.c.), and filtered. The hot filtrate was freed from tin, and the filtrate evaporated to dryness. " 6a "-Amino-2-hydroxyquinoxaline (0·14 g.), m. p. 360°, was isolated as a yellow granular solid by dissolution of the dry residue in 2N-sodium hydroxide, treatment with carbon, and acidification with acetic acid. The amino-compound, more of which (0·08 g.) was obtained by digestion of the tin sulphides with hot water (30 c.c.), had the same solubility characteristics as 7-amino-2-hydroxyquinoxaline (above).

" 6a "-*Nitro*-2-*phenoxyquinoxaline*.—2-Chloro-" 6a "-nitroquinoxaline (1 g.) was heated on a steam-bath with a solution of potassium hydroxide (0·3 g.) in phenol (5 g.) for 2¾ hr., then poured into 2N-sodium hydroxide (*ca.* 100 c.c.), and the solid product was collected in ether. Washing, drying ($MgSO_4$), treatment with charcoal, and evaporation gave a product (0·82 g.), m. p. 80—85°. Recrystallisation from light petroleum (b. p. 60—80°) yielded the *phenoxy-compound* (0·42 g.), m. p. 105—106° unchanged by further recrystallisation, as colourless needles (Found : C, 62·85; H, 3·3; N, 15·9. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4; N, 15·7%).

Attempted phenoxylation of the chloro-compound (0·1 g.) with phenol (0·3 g.) and ammonium carbonate (0·1 g.) on a steam-bath for 0·5—15 hr. gave only unchanged material (0·07 g.), 184—185°.

" 6a "-*Amino*-2-*phenoxyquinoxaline*.—A solution of the foregoing nitro-compound (0·38 g.) in ethanol (75 c.c.) was shaken with platinum oxide (0·02 g.) and hydrogen at 1 atm. until absorption ceased (2½ hr.). Filtration and concentration under reduced pressure yielded a product (0·315 g.), m. p. 110—115°. Removal of some ether-insoluble impurity and two crystallisations from chloroform–light petroleum (b. p. 60—80°) provided the amine (0·095 g.)

as golden-yellow needles, **m. p. 128—129°** not depressed on admixture with 7-amino-2-phenoxyquinoxaline (above).

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