632. *Quinoxalines and Related Compounds. Part III.* Some 2-Substituted Quinoxalines.*

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Various replacement reactions with 2-substituted quinoxalines have been investigated and quinoxaline derivatives prepared.

In the present work certain replacement reactions with 2-chloro-, 2-methylthio-, and 2-methylsulphonyl-quinoxaline were studied and various methyl derivatives of 2-amino-, 2-hydroxy-, and 2-mercapto-quinoxaline prepared. These compounds were required for spectroscopic examination.

The common starting material was 2-hydroxyquinoxaline which was conveniently prepared from *o*-phenylenediamine and *n*-butyl glyoxylate in aqueous solution. 2-Hydroxyquinoxaline was converted into 2-chloroquinoxaline by the method of Gowenlock, Newbold, and Spring.[1] These authors had prepared 2-aminoquinoxaline from 2-chloroquinoxaline by heating the chloro-compound with dry ethanolic ammonia at 150° for 7 hours.[1] Similar reactions give 2-methylamino-, 2-dimethylamino-, 2-benzylamino-, and 2-morpholino-quinoxaline. 2-Benzylaminoquinoxaline had been obtained previously, but less conveniently, by condensing 2-aminoquinoxaline and benzyl chloride in the presence of sodium hydride.[2]

2-Mercaptoquinoxaline was prepared from 2-chloroquinoxaline by the method of Wolfe, Wilson, and Tishler.[3] With methyl iodide in alkali it gave 2-methylthioquinoxaline in good yield, with a small amount of an unidentified product. This methylation procedure was apparently superior to that used recently for the preparation of several methylthioquinoxalines.[4] Preliminary attempts to cause 2-methylthioquinoxaline to react with ethanolic methylamine and dimethylamine indicated that the 2-methylthio- was less readily replaceable than a 2-chloro-substituent. Oxidation of 2-methylthioquinoxaline with chlorine water [5, 6] gave chlorine-containing products, but treatment with hydrogen peroxide in glacial acetic acid at room temperature furnished mainly 2-methylsulphonylquinoxaline, together with 2-methylsulphonylquinoxaline 4-oxide and 2 : 3-dihydroxyquinoxaline. These were the only products isolated on oxidation of 2-methylthioquinoxaline or 2-methylsulphonylquinoxaline with hydrogen peroxide in glacial acetic acid at 55°. Landquist [7a] had previously observed several examples of concurrent formation of quinoxaline *N*-oxide and 2 : 3-dihydroxyquinoxaline, and Wolfe, Wilson, and Tishler [3] obtained sulphones on oxidation of three quinoxinalinyl sulphides with hydrogen peroxide. The methylsulphonyl substituent of 2-methylsulphonylquinoxaline and its 4-oxide was readily replaced by hydroxyl on treatment with aqueous alkali. The formation of the known 2-hydroxyquinoxaline 4-oxide [7b] from 2-methylsulphonylquinoxaline 4-oxide confirmed the identity of this compound.

2-Chloroquinoxaline was converted in high yield into 2-methoxyquinoxaline, and the *N*-methyl derivative of 2-hydroxyquinoxaline, 1 : 2-dihydro-1-methyl-2-oxoquinoxaline, prepared also in 30% yield by interaction of *N*-methyl-*o*-phenylenediamine and *n*-butyl glyoxylate in dilute acetic acid. It is of interest that Usherwood and Whiteley [8] isolated only 1-methylbenziminazole-2-carboxylic acid from the parallel reaction between the *N*-methyldiamine and glyoxylic acid. The most convenient method for the preparation

* Part II, *J.*, 1955, 3308.

[1] Gowenlock, Newbold, and Spring, *J.*, 1945, 622.
[2] Gardner and Stevens, *J. Amer. Chem. Soc.*, 1949, **71**, 1868.
[3] Wolf, Wilson, and Tishler, *J. Amer. Chem. Soc.*, 1954, **76**, 2266.
[4] Morrison and Furst, *J. Org. Chem.*, 1956, **21**, 470.
[5] Sprague and Johnson, *J. Amer. Chem. Soc.*, 1935, **57**, 2252.
[6] Andrews, Anand, Todd, and Topham, *J.*, 1949, 2490.
[7] Landquist, *J.*, 1953, (*a*) 2816, (*b*) 2830.
[8] Usherwood and Whiteley, *J.*, 1923, 1069.

of 1 : 2-dihydro-1-methyl-2-oxoquinoxaline was by methylation of 2-hydroxyquinoxaline with methyl sulphate and alkali.[9a] (We regret incorrect citation from the literature in an earlier paper [9a] with respect to another synthesis of this compound.[10])

Experimental

2-Hydroxyquinoxaline.—*o*-Phenylenediamine (86 g., 0·8 mole) in hot water (400 c.c.) was added to a solution of *n*-butyl glyoxylate, prepared [11] from *n*-butyl tartrate (105 g., 0·4 mole), sodium metaperiodate (85 g., 0·4 mole), and water (1·2 l.). The mixture was stirred overnight at room temperature, and the product then filtered off, washed with water, and heated under reflux with 96% ethanol (1 l.). After cooling, 2-hydroxyquinoxaline (100 g., 86%), m. p. (mainly) 267—269°, was collected. Atkinson *et al.* give m. p. 268—270°.

2-Chloroquinoxaline.—A mixture of 2-hydroxyquinoxaline (101 g.) and freshly distilled phosphoryl chloride (500 c.c.) was heated under reflux for 1 hr. The product was isolated in the usual manner and 2-chloroquinoxaline (110 g., 95%; m. p. 48—49°) obtained. Distillation gave needles, m. p. 49—49·5°, b. p. 100°/1·4 mm. (Found: C, 58·4; H, 3·2; N, 16·9. Calc. for $C_8H_5N_2Cl$: C, 58·4; H, 3·1; N, 17·0%). Gowenlock *et al.*[1] give b. p. 80°/0·5 mm., m. p. 46—47°.

2-Methylaminoquinoxaline.—2-Chloroquinoxaline (16·5 g., 0·1 mole) was heated with ethanolic methylamine (33% w/w; 60 g.) at 150° for 7 hr. Solvent and excess of methylamine were then removed in a vacuum. The residue was ground with water and the insoluble *2-methylaminoquinoxaline* (15·1 g., 95%) filtered off. Crystallisation from benzene (5 parts) (charcoal) gave a product, m. p. 129—131° (Found: C, 68·05; H, 5·85; N, 26·6. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%).

2-Dimethylaminoquinoxaline.—Dimethylamine (27 g.) was added to an ice-cooled solution of 2-chloroquinoxaline (16·5 g., 0·1 mole) in ethanol (20 c.c.). The mixture was heated at 150° for 7 hr., and *2-dimethylaminoquinoxaline* (17·2 g., 99%) isolated as above. The m. p. was 94—95° after crystallisation from light petroleum (b. p. 60—80°; 15 parts) (charcoal) (Found: C, 69·2; H, 6·5; N, 24·8. $C_{10}H_{11}N_3$ requires C, 69·4; H, 6·4; N, 24·3%).

2-Benzylaminoquinoxaline.—A mixture of 2-chloroquinoxaline (3·3 g., 0·02 mole) and benzylamine (10 c.c.) was heated at 150° for 7 hr. After cooling, benzene and water were added, and the benzene layer separated, washed with water, and evaporated in a vacuum. Distillation of the residue gave *2-benzylaminoquinoxaline* (3·3 g., 70%), b. p. (mainly) 228°/1 mm., m. p. 70—72°. The m. p. was raised to 73—75° by crystallisation from light petroleum (b. p. 60—80°; 25 parts) (Found: C, 76·8; H, 5·7; N, 18·0. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·6; N, 17·85%). Gardner and Stevens [2] give m. p. 62—64° but no analytical data.

2-Morpholinoquinoxaline.—A mixture of 2-chloroquinoxaline (3·3 g., 0·02 mole) and morpholine (6 c.c.) was heated until reaction occurred, and then kept at 100° for 30 min. Water was added. The precipitate of *2-morpholinoquinoxaline* (4·3 g., 100%), crystallised from light petroleum (b. p. 60—80°; 15 parts) (charcoal), had m. p. 87—89° (Found: C, 67·3; H, 6·3; N, 20·0. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·0; N, 19·6%).

2-Piperidinoquinoxaline, similarly prepared in 100% yield and crystallised from light petroleum (b. p. 40—60°; 4 parts) (charcoal), had m. p. 62—63° (Found: C, 73·3; H, 7·2; N, 19·9. Calc. for $C_{13}H_{15}N_3$: C, 73·2; H, 7·1; N, 19·7%). Wear and Hamilton [12] give m. p. 59—60·5°.

2-Methylthioquinoxaline.—2-Mercaptoquinoxaline was prepared from 2-chloroquinoxaline (91 g.) by the method of Wolf, Wilson, and Tishler [3] but without isolation of the intermediate thiuronium salt. The crude product was extracted with N-sodium hydroxide (700 c.c.), insoluble matter removed, and the filtrate shaken with methyl iodide (90 g.) for 1½ hr. The product was isolated in ether and benzene, and the solvents were removed in a vacuum. Distillation of the residue gave *2-methylthioquinoxaline* (73 g., 75%), b. p. 134°/1 mm. The m. p. was 46—47° after crystallisation from light petroleum (b. p. 40—60°) (Found: C, 61·3; H, 4·7; S, 18·1. $C_9H_8N_2S$ requires C, 61·35; H, 4·6; S, 18·2%). The *picrate*, prepared in ethanol, had m. p.

[9] Cheeseman, *J.*, 1955, (*a*) 1804, (*b*) 3308.
[10] Kühling and Kaselitz, *Ber.*, 1906, **39**, 1314; King and Clark-Lewis, *J.*, 1951, 3379.
[11] Atkinson, Brown, and Simpson, *J.*, 1956, 26.
[12] Wear and Hamilton, *J. Amer. Chem. Soc.*, 1950, **72**, 2893.

127—128° (Found : C, 44·3; H, 2·9; S, 7·7. $C_{15}H_{11}O_7N_5S$ requires C, 44·45; H, 2·7; S, 7·9%). Benzene (25 c.c.) was added to the residue from the distillation; the precipitate (4·2 g.) crystallised from benzene (10 parts) as brownish-yellow needles, m. p. 176—178° (Found : C, 67·1; H, 4·1; N, 17·6; S, 10·3%).

Oxidation of 2-Methylthioquinoxaline.—(*a*) Hydrogen peroxide (30% w/v; 25 c.c.) was added to a water-cooled solution of 2-methylmercaptoquinoxaline (8·8 g., 0·05 mole) in acetic acid (50 c.c.). The mixture was set aside at room temperature for 2 days, then poured into water (500 c.c.). After cooling, the crystalline product was filtered off, washed with water, dried, and then heated under reflux with benzene (100 c.c.). The benzene-insoluble material (1·8 g.) had m. p. above 300°, and on crystallisation from acetic acid gave 2 : 3-dihydroxyquinoxaline (Found : C, 58·9; H, 3·7; N, 17·6. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7; N, 17·3%). This was further identified by conversion into 1 : 2 : 3 : 4-tetrahydro-1 : 4-dimethyl-2 : 3-dioxoquinoxaline, m. p. and mixed m. p. 252—253°,[9a] and 2 : 3-dichloroquinoxaline, m. p. and mixed m. p. 151—153°.[9a] The benzene extract was evaporated in a vacuum and the crystalline residue (m. p. *ca.* 134—145°) heated under reflux with *cyclo*hexane (1 l.). On cooling, the extract deposited crystals of *2-methylsulphonylquinoxaline* (3·4 g., m. p. 124—126°); these were filtered off, and the filtrate used to re-extract the *cyclo*hexane-insoluble material. This extract after concentration to *ca.* 200 c.c. yielded a further 2·15 g., m. p. (mainly) 124—126°, of the methylsulphonyl derivative (total yield, 53%). The m. p. was raised to 126—127° by crystallisation from *cyclo*hexane (150 parts) (Found : C, 52·2; H, 4·0; N, 14·0; S, 15·7. $C_9H_8O_2N_2S$ requires C, 51·9; H, 3·9; N, 13·5; S, 15·4%). The residue (1 g.), m. p. (mainly) 173—183°, from the *cyclo*hexane extractions, on crystallisation from benzene (50 c.c.), gave crystals (0·65 g.), m. p. 191—194°, not depressed on admixture with 2-methylsulphonylquinoxaline 4-oxide, prepared as described below.

(*b*) A mixture of 2-methylthioquinoxaline (8·8 g., 0·05 mole), acetic acid (100 c.c.), and hydrogen peroxide (30% w/v; 50 c.c.) was heated at 55° for 25 hr. then cooled and poured into water (1 l.). After cooling, the crystalline product was filtered off, washed with water, dried, and heated under reflux with benzene (300 c.c.). The benzene-insoluble material (2·0 g.) had m. p. above 300°; the benzene extract on concentration to *ca.* 100 c.c. yielded *2-methylsulphonylquinoxaline 4-oxide* (4·0 g., 36%), m. p. 197—199° after successive crystallisations from benzene (75 parts) and ethanol (130 parts) (charcoal) (Found : C, 48·5; H, 3·7; N, 12·7; S, 14·0. $C_9H_8O_3N_2S$ requires C, 48·2; H, 3·6; N, 12·5; S, 14·3%).

Oxidation of 2-Methylsulphonylquinoxaline.—2-Methylsulphonylquinoxaline (16·6 g., 0·08 mole), acetic acid (160 c.c.), and hydrogen peroxide (30% w/v; 80 c.c.) were heated at 55° for 19 hr., then cooled, and poured into water (1·6 l.). After cooling, the crystalline product was filtered off, washed with water, dried, and heated under reflux with benzene (500 c.c.). The benzene-insoluble material (0·85 g.) had m. p. above 300°; the benzene extract yielded 2-methylsulphonylquinoxaline 4-oxide (8·7 g., 49%), m. p. (mainly) 196—198°, after concentration to *ca.* 100 c.c.

Reaction of 2-Methylsulphonylquinoxaline with Alkali.—The methylsulphonyl derivative (0·65 g.) was heated with 2N-sodium hydroxide (10 c.c.) at 95° for 15 min. The resulting solution was cooled and brought to pH 4 with acetic acid, 2-hydroxyquinoxaline (0·44 g., 97%), m. p. 261—264°, being precipitated. This was identified by mixed m. p. and conversion into 1 : 2-dihydro-1-methyl-2-oxoquinoxaline, m. p. and mixed m. p. 120—121°.[9a]

Reaction of 2-Methylsulphonylquinoxaline 4-Oxide with Alkali.—A mixture of the *N*-oxide (6·7 g., 0·03 mole) and 2N-sodium hydroxide (60 c.c.) was kept at 95° for 15 min., then cooled and brought to pH 4 with acetic acid; 2-hydroxyquinoxaline 4-oxide (4·7 g., 97%), m. p. 273—274° (decomp.), was precipitated. Sublimation at 210°/0·5 mm. and crystallisation from ethanol gave pale yellow crystals, m. p. 274—275° (decomp.) (Found : C, 59·7; H, 3·8; N, 17·1. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7; N, 17·3%). Landquist [7b] gives m. p. 274—275°. The hydroxy-compound was treated with methyl iodide and alkali as described by Landquist.[7b] Pale yellow needles of 1 : 2-dihydro-1-methyl-2-oxoquinoxaline 4-oxide were obtained, having m. p. 210—211° after sublimation at 200°/0·5 mm. and crystallisation from methanol (75 parts) (Found : C, 61·4; H, 4·4; N, 15·7. Calc. for $C_9H_8O_2N_2$: C, 61·35; H, 4·6; N, 15·9%). Landquist gives m. p. 208—209°.

2-Methoxyquinoxaline.—2-Chloroquinoxaline (9·9 g., 0·06 mole) was caused to react with a slight excess of methanolic sodium methoxide as described previously.[9a] Distillation of the crude product gave colourless needles of *2-methoxyquinoxaline* (8·65 g., 90%), b. p. 101—102°/1·5

mm., m. p. 26—27°. The m. p. was raised to 31·5—33° by two crystallisations from light petroleum (b. p. 40—60°; 1 part) (Found: C, 67·3; H, 5·1; N, 17·5. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

Reaction of N-*Methyl*-o-*phenylenediamine with* n-*Butyl Glyoxylate*.—Some heat was evolved when *n*-butyl glyoxylate (2·6 g., 0·02 mole) was added to a solution of the diamine [9b] (2·44 g., 0·02 mole) in 3N-acetic acid (10 c.c.). The mixture was set aside at room temperature, overnight, then heated at 95° for 1 hr. After cooling, 2N-sodium hydroxide was added and the pH brought to 4. The product (3·3 g.) was isolated in chloroform; it was partly soluble in benzene (20 c.c.). The benzene solution was filtered through a column of alumina (100 g.; Spence, type H; mesh 100—200). Elution with benzene (100 c.c.) gave an unidentified yellow compound (0·07 g.; m. p. 234—236°); further elution with benzene (1 l.) and benzene–ether (1 : 1; 300 c.c.) yielded 1 : 2-dihydro-1-methyl-2-oxoquinoxaline (0·95 g., 30%), m. p. (mainly) 122—123°, not depressed on admixture with an authentic specimen.[9a]

This research was carried out during the tenure of an Imperial Chemical Industries Fellowship awarded by the University of London. Analyses were carried out in the Organic Microanalytical Laboratory of Imperial College.

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[*Received, March 28th,* 1957.]