2,3-Dimethylquinoxaline-6-carboxaldehyde 1,4-Dioxide

M. L. Edwards and R. E. Bambury*

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215

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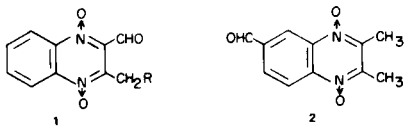
A series of derivatives of 2,3-dimethylquinoxaline-6-carboxaldehyde 1,4-dioxide was prepared. Derivatives prepared included nitrones, semicarbazide, and aminooxazolidinone.

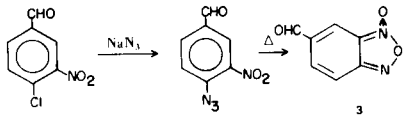
We have shown that nitrones of 3-methylquinoxaline-2-carboxaldehyde 1,4-dioxide (**1**, R = H) and 3-hydroxymethylquinoxaline-2-carboxaldehyde 1,4-dioxide (**1**, R = OH) exhibit interesting antibacterial activity (1,2). As an extension of this work, we wish to report a series of derivatives of **2** which contain the nitrone function on the benzo



rather than the pyrazine ring. The reported (3) antibacterial activity of 2,3-dimethylquinoxaline 1,4-dioxide further suggested that derivatives of **2** might exhibit antibacterial activity.

The starting material for the preparation of **2** was 6-formylbenzofuroxan (**3**) prepared by the procedure of Ghosh and Whitehouse (4) (Scheme I). They made the azide by heating a mixture of 4-chloro-3-nitrobenzaldehyde and sodium azide in dimethylsulfoxide at 75°. In order to

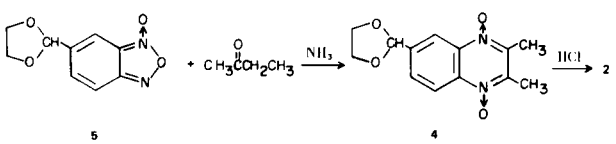
Scheme I



keep this exothermic reaction under control in large-scale (100 g.) reactions, sodium azide should be added in small portions to a solution of the aldehyde in dimethylsulfoxide at a rate which keeps the reaction mixture at 75-80°.

The protected quinoxaline aldehyde (**4**) was isolated in 80% yield from the Beirut reaction (5) of the dioxolane of 6-formylbenzofuroxan and 2-butanone (Scheme II). Attempts to use the unprotected aldehyde (**3**) in the

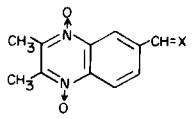
Scheme II

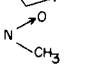
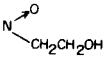


Beirut Reaction lead to tar formation. Dilute acid hydrolysis of the dioxolane (**4**) gave **2**. The preparation of derivatives of **2** (Table I) was straightforward and no problems were encountered.

Although **8** demonstrated some antibacterial activity in an *in vivo* test against *Proteus mirabilis*, this activity was considerably less than that of nitrones prepared from the aldehydes of structure **1** (1,2). The other compounds in Table I were inactive at the dose level (250 mg./kg.) used.

Table I



Compound Number	X	M.p. °C	Yield, %
2	O	217-218	60
4		209-210	80
6		281-283	81
7		263-264	66
8		239	69
9		209	49
10		211	35

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were determined in pressed potassium bromide disks. All compounds gave nmr, ir and uv spectra consistent with the proposed structure.

2,3-Dimethylquinoxaline-6-carboxaldehyde 1,4-Dioxide (**2**).

Compound **4** (15 g.) was suspended in a mixture of water (150 ml.) and concentrated hydrochloric acid (7 ml.). The mixture was stirred at room temperature for 24 hours and filtered to give 11.3 g. of yellow solid. Recrystallization from DMF gave 9.0 g. of yellow solid (60%), m.p. 217-218°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.62; H, 4.64; N, 12.71.

6-Formylbenzofuroxan (**3**).

A solution of 4-chloro-3-nitrobenzaldehyde (100 g., 0.54 mole) in 300 ml. of DMSO was heated to 75° on a steam bath. The bath was removed and sodium azide (35.2 g., 0.54 mole) was added in small portions, keeping the temperature of the reaction mixture below 80°. The mixture was heated at 75° for 15 minutes after the addition was complete, poured onto ice (1 kg.) and the aqueous mixture was extracted with ether (5 x 400 ml.). The combined extracts were dried (magnesium sulfate), filtered free of drying agents and evaporated to give 4-azido-3-nitrobenzaldehyde. An ir spectrum showed a strong azide bond at 2130 cm^{-1}. The azide was dissolved in 500 ml. of toluene and the solution was heated at reflux for 45 minutes. The solution was evaporated and the residue was taken up in 200 ml. of ethyl acetate. The solution was decolorized, filtered, diluted with 200 ml. of petroleum ether (b.p. 40-60°), then chilled and filtered to give 69 g. (78%) of 6-formylbenzofuroxan, m.p. 66-68°. Lit. (4) m.p. 68.5-69°.

2-(2,3-Dimethyl-1,4-dioxidoquinoxaline-6-yl)-1,3-dioxolane (**4**).

A mixture of **5** (95.0 g., 0.58 mole) and methanol (800 ml.) was stirred while ammonia gas was bubbled through the mixture. The benzofuroxan gradually dissolved as the mixture heated to 50-55°. The gas addition was halted and the mixture was stirred another 16 hours, chilled and filtered to give 126 g. (80%) of pale yellow solid, m.p. 209-210°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.43; H, 5.29; N, 10.64.

6-(1,3-Dioxolan-2-yl)benzofuroxan (**5**).

A mixture of **3** (137 g., 0.84 mole), benzene (1.5 l.), ethylene glycol (74.4 g., 1.2 mole) and *p*-toluenesulfonic acid (0.2 g.) was heated at reflux under a water separator until the theoretical amount of water (15 g.) had collected. A small amount of sodium bicarbonate was added and the mixture was filtered. The filtrate was evaporated and the residue was recrystallized from isopropyl alcohol to give 150 g. (86%) of pale yellow solid, m.p. 67.5-69°.

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.39; H, 3.87; N, 13.46. Found: C, 51.54; H, 3.78; N, 13.58.

2,3-Dimethylquinoxaline-6-carboxaldehyde 1,4-Dioxide Semicarbazone (**6**).

A mixture of **2** (10.9 g., 0.05 mole), semicarbazide hydrochloride (5.6 g., 0.05 mole), sodium acetate (5 g.) and water (150 ml.) was heated at reflux for 10 minutes, chilled, filtered. The solid which remained was triturated with boiling water (200 ml.) and DMF (200 ml.) to give 11 g. (81%) of yellow solid, m.p. 281-283°.

Anal. Calcd. for $C_{12}H_{13}N_5O_3$: C, 52.26; H, 4.76; N, 25.44. Found: C, 52.03; H, 4.85; N, 25.47.

2,3-Dimethyl-6-[(2-oxooxazolidin-3-yl)iminomethyl]quinoxaline 1,4-Dioxide (**7**).

Compound **2** (10.9 g., 0.05 mole) and 3-amino-2-oxazolidinone (5.1 g., 0.05 mole) were suspended in 200 ml. of 95% ethanol and the mixture was stirred for 56 hours. The mixture was filtered and the solid was triturated with 200 ml. of hot DMF to give 10.1 g. (66%) of yellow solid, m.p. 263-264°.

Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.25; H, 4.62; N, 18.57.

α-(2,3-Dimethylquinoxaline-6-yl)-*N*-methylnitrone 1,4-Dioxide (**8**).

Compound **2** (12 g., 0.054 mole) and sodium bicarbonate (14.5 g., 0.052 mole) were suspended in 300 ml. of denatured ethanol. *N*-Methylhydroxylamine hydrochloride (4.5 g., 0.054 mole) was added in small portions over 30 minutes. The mixture was stirred for 18 hours and filtered. The solid was washed with water and hot DMF to give 9.5 g. (69%) of yellow solid, m.p. 239° dec.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 57.87; H, 5.24; N, 17.01.

α-(2,3-Dimethylquinoxaline-6-yl)-*N*-(2-hydroxyethyl)nitrone 1,4-Dioxide (**9**).

Compound **2** (10.9 g., 0.05 mole) and hydroxylaminoethanol oxalate (6.1 g., 0.025 mole) were suspended in ethanol (300 ml.) and sodium bicarbonate (4.2 g., 0.05 mole) was added in small portions over 30 minutes. The mixture was stirred for 48 hours and filtered. The bright yellow solid was recrystallized from DMF to give 6.8 g. (49%) of product, m.p. 209° dec.

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 55.90; H, 5.34; N, 15.45.

α-(2,3-Dimethylquinoxalin-6-yl)-*N*-phenylnitrone 1,4-Dioxide (**10**).

Compound **2** (16.5 g., 0.074 mole) and phenylhydroxylamine (7.4 g., 0.074 mole) were suspended in benzene (700 ml.) and the mixture was heated at reflux under a water separator until the theoretical amount of water was collected (30 minutes). The mixture was cooled, filtered to give 10.4 g. of yellow solid, m.p. 204-206°. The filtrate was concentrated to 150 ml., chilled and filtered to give 4.8 g. of unreacted aldehyde. The product was triturated with hot DMF (300 ml.) and air dried to give 8.1 g. (35%) of gold-yellow solid, m.p. 211° dec.

Anal. Calcd. for $C_{17}H_{25}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.92; H, 4.95; N, 13.71.

REFERENCES

(1) H. K. Kim (to Richardson-Merrell), U.S. Patent 3,644,363 (1972).

(2) M. L. Edwards, R. E. Bambury and H. W. Ritter, *J. Med. Chem.*, 18, 637 (1975).

(3) J. Francis, J. K. Landquist, A. A. Lwi, J. A. Seth and J. M. Thorp, *Biochem. J.*, 63, 455 (1956).

(4) P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.*, 11, 305 (1968).

(5) K. Ley, F. Seng, U. Eholzen, R. Nast and R. Schubart, *Angew. Chem. Intern. Edit. Engl.*, 8, 596 (1969).