Internal Oxidation-Reduction of Quinoxaline-2-carboxaldehyde 1,4-Dioxide (1)

Arthur F. Kluge and Michael L. Maddox*

Institute of Organic Chemistry, Syntex Research Palo Alto, California 94022

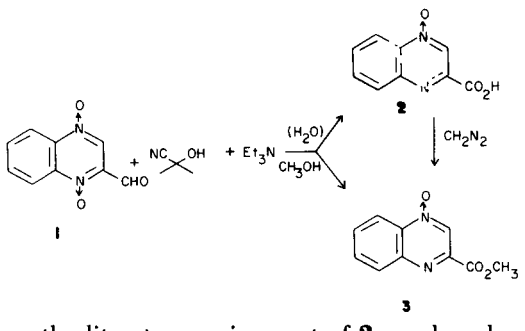
Received July 16, 1979

Reaction of carboxaldehyde **1** with acetone cyanohydrin gives carboxylic acid **2**. Reaction of **1** with acetone cyanohydrin in methanol affords the methyl ester **3**. The structural assignment for **2** is supported by ^{13}C nmr data and by the decarboxylation of deuterated **2** to give **4b**. The internal oxidation-reduction upon going from **1** to **2** is explained in terms of a mechanism whereby **1** is converted into its cyanohydrin **5** and then to acyl cyanide **6**. Acyl cyanide **6** then reacts with either water or methanol to give **2** or **3**.

J. Heterocyclic Chem., **17**, 1107 (1980).

Reaction of quinoxaline-2-carboxaldehyde 1,4-dioxide (**1**) with acetone cyanohydrin and trace triethylamine gave a carboxylic acid instead of the expected cyanohydrin. The molecular formula ($C_9H_6N_2O_3$) of this acid showed that it was isomeric to the starting aldehyde **1**. Reaction of **1** with acetone cyanohydrin and triethylamine in methanol gave a methyl ester which was identical to the product obtained by reacting the carboxylic acid product with diazomethane. Our carboxylic acid product was identical to a sample prepared by hydrogen peroxide-acetic acid oxidation of quinoxaline-2-carboxylic acid, a compound which had been assigned the structure **2** (2). The assignment of **3** was given to the methyl ester.

Scheme I

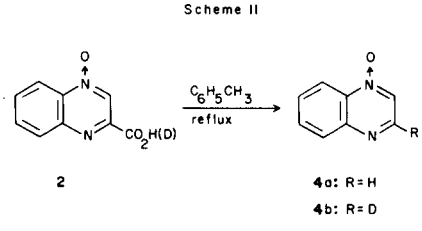


Since the literature assignment of **2** was based on the presumption of a regiospecific oxidation of quinoxaline-2-carboxylic acid (3), we felt that further evidence was required to support the structural assignment. The ^{13}C nmr (DMSO-d_6) spectra of **2** and **3** contained upfield absorptions for a proton-bearing carbon, assignable to C-2, at 129.7 and 129.8 ppm, respectively, while the absorptions assignable to C-3 (no attached proton) appeared downfield at 146.4 and 145.2 ppm. The chemical shifts of these upfield carbons were in accord with their being adjacent to an *N*-oxide nitrogen (4).

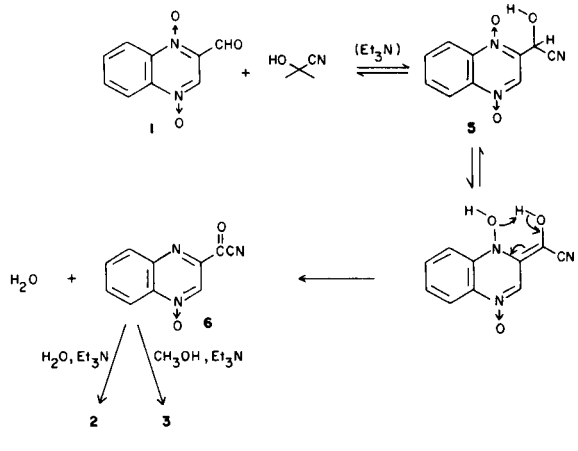
Further evidence for the correctness of structure **2** was provided by chemical degradation (Scheme II). Quinoxaline-3-carboxylic acid 1 oxides are known to decarboxylate under mild conditions (5). Thus, **2** in refluxing toluene was transformed cleanly into the known quinoxaline 1-oxide (**4a**) (6). Exchange of the carboxylate proton in **2** with deuterium followed by decarboxylation gave the specifically deuterated **4b**. Comparison of the ^1H nmr spectra (DMSO-d_6) of **4a** and **4b** showed a change of the 3.5 Hz doublets at δ 8.66 (H-2) and δ 8.81 (H-3) in **4a** to a singlet at δ 8.66 (H-2) in **4b** (7).

Comparison of the ^{13}C nmr spectra of **4a** and **4b** showed that the doublet (J = 164.4 Hz) at 147.2 ppm for C-3 in **4a** was transformed to a triplet (J = 31.6 Hz) at 146.9 ppm in **4b**. Both the change in splitting and the slight upfield shift are in accord with expectations for deuterium substitution at C-3 in **4b** (8). Since the deuterium is fixed at C-3 in **4b**, the carboxylate must have been at C-3 in **2**.

Scheme II



Scheme III



0022-152X/80/051107-02$02.25

A mechanism that explains the internal oxidation-reduction of **1** is shown in Scheme III. Formation of an intermediate cyanohydrin **5** followed by prototropic shift and loss of water would give an intermediate acylcyanide **6**. The acylcyanide **6** would react under the basic conditions with either water or methanol to give **2** or **3**.

EXPERIMENTAL (9)

Quinoxaline-3-carboxylic Acid 1 Oxide (**2**).

A mixture of 4.98 g. (0.0239 mole) of quinoxaline-2-carboxaldehyde 1,4-dioxide hydrate (**1**) (10), 15 g. of acetone cyanohydrin, and five drops of triethylamine was heated on a steam bath for 8 hours. The product was collected by filtration and was washed with water. Recrystallization from ethanol-water gave 3.02 g. (66%) of **2** having m.p. 195-196° dec (lit. (2) m.p. 180-182°) and m.m.p. 195-196° dec; ^{1}H nmr: δ 7.85-8.6 (m, 4H), 8.91 (s, 1H, H-2); ^{13}C nmr: 118.4 (C-2), 130.9 (C-5), 132.2 (C-7), 132.7 (C-6), 137.2 (C-9), 144.1 (C-10), 146.4 (C-3), 164.1 (CO).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.7; H, 3.18; N, 14.82.

Methyl Quinoxaline-3-carboxylate 1-Oxide (**3**).

A mixture of 2.08 g. (0.01 mole) of **2** hydrate, 9 g. of acetone cyanohydrin, 20 ml. of methanol, and 10 drops of triethylamine was stirred at room temperature for 30 minutes. Evaporation afforded a residue which was chromatographed from 60 g. silica gel (60-230 mesh) with 150 ml. diethyl ether and then with 240 ml. ethyl acetate. Evaporation of the ethyl acetate eluate gave a solid which was triturated with 50 ml. of diethyl ether and was collected by filtration to afford 1.52 g. (74%) of **3** having m.p. 154-155°; ir: 1714 cm^{-1}; ^{1}H nmr: δ 3.97 (s, 3H), 7.9-8.53 (m, 4H), 8.9 (s, 1H, H-2); ^{13}C nmr: δ 53.2 (OCH_3), 118.4 (C-8), 129.8 (C-2), 130.9 (C-5), 132.4 (C-7), 132.8 (C-6), 137.4 (C-9), 144.1 (C-10), 145.2 (C-3), 163.2 (CO).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.86; H, 3.88; N, 13.83.

Compound **3** was identical by ir, tlc, and mixture melting point to the compound obtained by treating **2** in tetrahydrofuran with excess etheral diazomethane.

Quinoxaline 1-Oxide (**4a**).

A mixture of 1 g. (0.0053 mole) of **2** and 15 ml. of toluene was heated at reflux for 16 hours. The solvent was removed by evaporation and the residue was chromatographed from 100 g. of silica gel (60-230 mesh) with 2% methanolic dichloromethane to obtain 0.7 g. of **4a** (90%) as a tan powder having m.p. 123-124° (lit (6) m.p. 122-123°) and m.m.p. 123-124°; ^{1}H nmr: δ 7.7-8.2 (m, 3H), 8.4-8.54 (m, 1H), 8.66 (d, 1H, J = 3.5 Hz, H-2), 8.81 (d, 1H, J = 3.5 Hz, H-3); ^{13}C nmr: δ 118.4 (C-8), 129.7 (C-2), 129.9 (C-5), 130.4 (C-7), 132 (C-6), 136.8 (C-9), 145.4 (C-10), 147.2 (C-3).

3-Deuterioquinoxaline-1-Oxide (**4b**).

A mixture of 0.71 g. (0.0037 mole) of **2**, 20 ml. of deuterium oxide (99.8% deuterium), and 0.05 g. of sodium carbonate was stirred at room temperature for 30 minutes. To this mixture was added 200 ml. toluene and the mixture was heated at reflux while removing water with a Dean-Stark trap. The reflux was continued for 16 hours. Solvent was removed by evaporation and the residue was filtered through 15 g. of silica gel (60-230 mesh) with 2% methanolic dichloromethane to obtain 0.49 g. (90%) of **4b** as tan crystals having m.p. 124-126°; ^{1}H nmr: δ 7.8-8.7 (m, 4H), 8.66 (s, 1H); ^{13}C nmr: δ 118.4 (C-8), 129.7 (C-2), 129.9 (C-5), 130.5 (C-7), 131.9 (C-6), 136.9 (C-9), 145.4 (C-10), 146.9 (C-3); ms: (70 eV) 147 (M^+, 100%), 146 (M-1, 6%).

REFERENCES AND NOTES

(1) Contribution No. 534 from the Institute of Organic Chemistry and No. 2 from Analytical Research.

(2) A. S. Elina and O. Yu. Magidson, *J. Gen. Chem. U.S.S.R*, **25**, 145 (1955); *Chem. Abstr.*, **50**, 1839 g (1956).

(3) E. Hayashi and C. Iijima, *Yakagaku Zasshi* **84**, 163 (1964); *Chem. Abstr.*, **61**, 3108 g (1964).

(4) A. F. Kluge, M. L. Maddox and G. S. Lewis, *J. Org. Chem.*, accepted for publication.

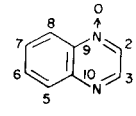
(5) J. P. Dirlam and J. W. McFarland, *J. Org. Chem.*, **42**, 1360 (1977).

(6) J. K. Landquist, *J. Chem. Soc.*, 2816 (1953).

(7) The proton assignments are supported by the spectra of the monomethylquinoxaline monoxides in which H-2 appears as a singlet at δ 8.61 in 3-methyoquinoxaline 1-oxide, and H-3 appears as a singlet at δ 8.88 in 2-methylquinoxaline 1-oxide. See also reference 4.

(8) F. W. Wehrli and T. Wirthin, "Interpretation of Carbon-13 NMR Spectra", Heyden, New York, N.Y., 1976, pp. 107-108.

(9) Melting points (uncorrected) were determined on a Fisher-Johns apparatus. For both proton and carbon nmr dimethyl sulfoxide-d_6 was the solvent with tetramethylsilane as internal standard. Proton spectra were determined on a Varian HA-100 spectrometer. Carbon spectra were determined at 22.62 MHz in rotating 10 mm tubes on a Bruker WH-90 operating in the pulse Fourier transform mode. The pulse width was 5 microseconds (15 microseconds = 90°). The sample temperature was maintained at 305°K. The repetition rate for noise decoupled spectra was 0.7 seconds and the free induction decays (6000-9000 accumulations) were stored in 8192 points. A 0.8 Hz line broadening function was applied before zero filling to 16,384 points and Fourier transformation yielding a digital resolution of 0.783 Hz. The convention used in numbering the positions in the quinoxaline 1-oxide skeleton is as shown below:



(10) C. H. Issidorides and M. J. Haddidin, *British Patent* 1,215,815 (1970); *Chem. Abstr.*, **74**, 141,873b (1971).