Preparation of Some Functionalized Quinoxaline 1,4-Dioxides

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The preparation of some functionalized quinoxaline 1,4-dioxides is described from the reaction of benzofurazan oxide with 2-acetylbutyrolactone, ethyl acetopyruvate, and acetylacetaldehyde dimethylacetal.

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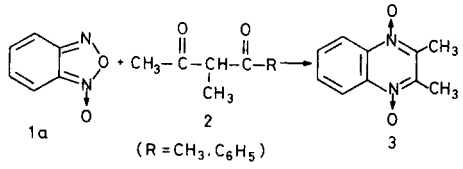
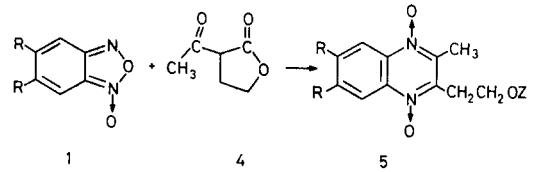
Previous work in our laboratory has shown that, in the presence of base, benzofurazan oxide (BFO, **1a**) reacts with 2-substituted 1,3-dicarbonyl substrates, such as **2**, to give 2,3-dialkylquinoxaline 1,4-dioxides (**3**, Scheme 1) (1).

Scheme 1



We now report that this reaction may be extended to the cyclic substrate **4** to give functionalized quinoxaline 1,4-dioxides of the hitherto inaccessible type **5** (Scheme 2).

Scheme 2



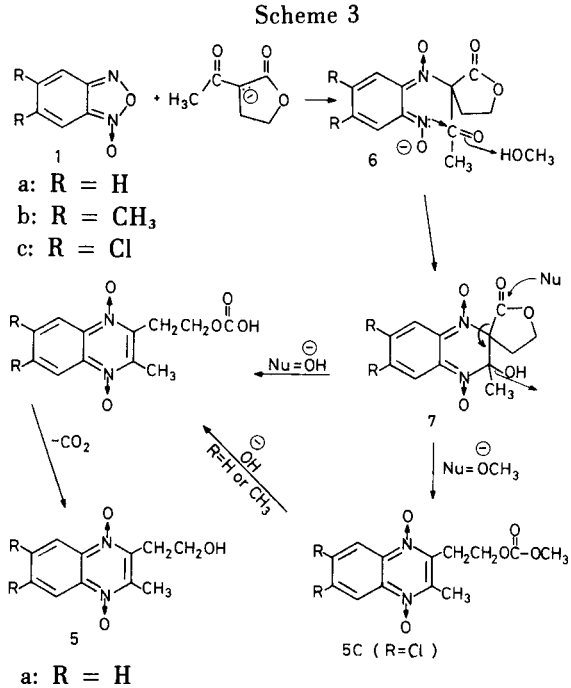
a: R = H
b: R = CH_3
c: R = Cl

a: R = H, Z = H
b: R = CH_3, Z = H
c: R = Cl, Z = $\overset{\overset{O}{\|}}{C}$-$OCH_3$

In the presence of methanolic potassium hydroxide BFO (**1a**) reacts readily with 2-acetylbutyrolactone (**4**) to give in 50% yield 2-(2′-hydroxyethyl)-3-methylquinoxaline 1,4-dioxide (**5a**), a homolog of the biologically highly active metabolite 2-hydroxymethyl-3-methylquinoxaline 1,4-dioxide (2). When 5,6-dimethylbenzofurazan oxide (**1b**) is substituted for BFO in Scheme 2, the reaction takes a similar course giving **5b**. Surprisingly, with 5,6-dichlorobenzofurazan oxide (**1c**), the product is not the expected hydroxyethyl derivative (**5**, R = Cl, Z = H) but the corresponding carbonate ester (**5c**). The yield of this ester (40%) is substantially increased (81%) when methanolic sodium methoxide is substituted for methanolic potassium hydroxide as the base. The proposed structures are corroborated by chemical and spectroscopic evidence. Treatment of **5a** with acetic anhydride-pyridine gives an acetate from which **5a** can be regenerated by hydrolysis. Products **5a, 5b,** and **5c** show characteristic infrared absorption in the 1350 cm^{-1} region (N → O stretching) (3). In addition, **5a** and **5b** show a broad band in the hydroxyl stretching region; this band is absent in **5c**, which shows intense absorption at 1750 cm^{-1} (carbonate ester) (4). The nmr spectra are consistent with the proposed structures (Experimental).

A plausible mechanism for the reaction of BFO with the

Scheme 3



a: R = H
b: R = CH_3

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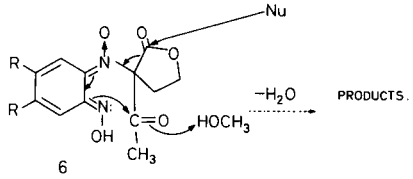
enolate anion of 2-acetylbutyrolactone is outlined in Scheme 3, in which heterocyclic ring closure of **6** to **7** is depicted as preceding nucleophilic attack on the lactone ring of **7**. However, an alternative mechanism may be envisaged (Scheme 4) whereby nucleophilic attack on the lactone ring of **6** precedes or is concerted with heterocyclic ring closure (5). Our data to date do not permit a clear preference between the two possibilities.

Scheme 4



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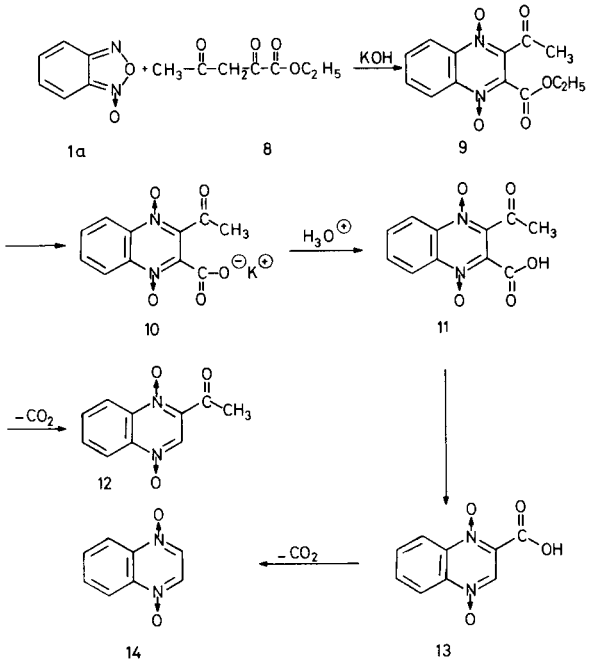
It is somewhat paradoxical that 2-acetylquinoxaline 1,4-dioxide (**12**), one of the simplest functionalized derivatives of the series, is not easily available. In principle, **12** would be expected to result from the Beirut Reaction (3) of BFO and acetylacetaldehyde (**15a**) but, in practice, the reaction of BFO with the sodium salt of acylacetaldehydes is apparently attended with deacylation giving quinoxaline 1,4-dioxide (6). A recent patent describing the preparation of **12** by peracid oxidation of 2-acetylquinoxaline, reports neither yield nor physical constants for the product (7). In this paper we report a preparation of **12** by a method which obviates the (usually) troublesome step of peracid oxidation. The key step of our method (Scheme 5) consists in treating BFO (**1a**) with ethyl acetopyruvate (**8**) in the presence of ethanolic potassium hydroxide, and allowing the mixture to stand for several hours, whereupon the potassium salt of 2-acetylquinoxaline 1,4-dioxide-3-carboxylic acid (**10**) precipitates (presumably by hydrolysis of **9**). Acidification of an aqueous solution of **10** gives the free acid (**11**) which, upon heating, readily decarboxylates to the desired product (**12**). Interestingly, dissolution of **11** in excess aqueous base is attended with a remarkably facile deacylation giving, after acidification, quinoxaline 1,4-dioxide-2-carboxylic acid (**13**). This acid, in refluxing 1-propanol or in warm acetic acid undergoes decarboxylation to quinoxaline 1,4-dioxide (**14**).

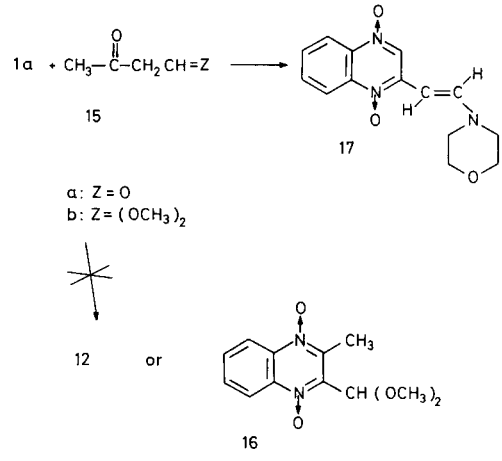
Scheme 5



1a 8 9 10 11 12 13 14

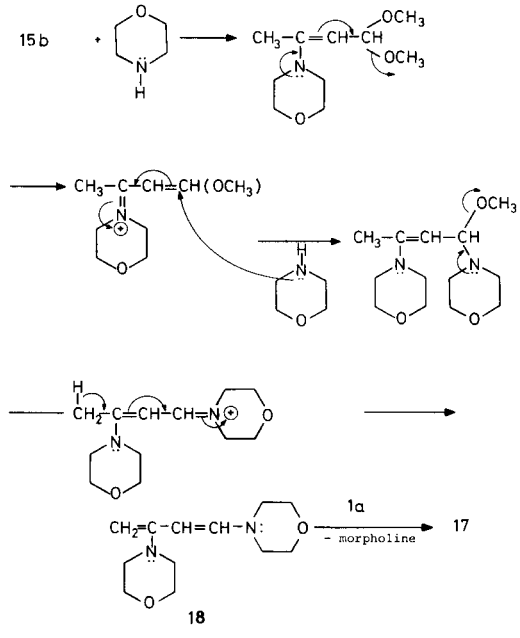
In an attempt to find an alternative route to **12**, we treated a morpholine solution of BFO with acetylacetaldehyde dimethylacetal (**15b**, Scheme 6) hoping to obtain **12** or **16**. Unexpectedly, the product of this reaction is

Scheme 6



15 17 12 16

Scheme 7



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neither **12** nor **16**, but the enamino compound **17**, probably resulting from the reaction of BFO with the less hindered enamino moiety of the dienamino intermediate **18**. Scheme 7 outlines a possible way by which this intermediate may arise. Compound **17** belongs to a novel class of quinoxaline 1,4-dioxides for which an efficient synthesis has been reported recently from BFO and buta-1,3-dienylamines (8).

EXPERIMENTAL

Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer models 621 and 257 spectrophotometers, and nmr spectra were obtained with a Varian T60 spectrometer using TMS as an internal standard. Elemental analyses were performed by F. Pascher, Mikroanalytisches Laboratorium, Bonn, Germany. Reported yields are for recrystallized products.

2(2′-Hydroxyethyl)-3-methylquinoxaline 1,4-Dioxide (**5a**).

A solution of BFO (9) (3.40 g.) in 25 ml. of 5% methanolic potassium hydroxide and 5 ml. of water was added in small portions, with continuous stirring, to a solution of 2-acetylbutyrolactone (3.20 g.) in 10 ml. methanol. An exothermic reaction took place and a dark-red color developed. The reaction mixture was cooled to room temperature and allowed to stand for slow evaporation of the solvent. Within 24 hours a voluminous precipitate was formed. Recrystallization from methanol gave yellow-brown needles of **5a** melting at 188-189°, yield 2.80 g. (50%); ir (potassium bromide): 3330-3390 (broad), 1500, 1420, 1390, 1340, 1320, 1200, 1160, 1090, 1060, 830, 800 cm^{-1}; nmr (trifluoroacetic acid): δ 2.71 (s, 3H), 3.35 (t, 2H), 3.95 (t, 2H). (DMSO-d_6): δ 7.75 (m, 2H) and 8.25 (m, 2H).

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: C, 59.93; H, 5.44; N, 12.71. Found: C, 59.72; H, 5.52; N, 12.79.

Acetylation of **5a** (acetic anhydride-pyridine) gave bright yellow crystals of 2(2′-acetoxyethyl)-3-methylquinoxaline 1,4-dioxide melting at 158-160° (ethanol); ir (potassium bromide): 1725, 1500, 1480, 1415, 1380, 1320, 1240, 1220, 1090, 1025, 935, 770 cm^{-1}; nmr deuteriochloroform): δ 2.01 (s, 3H), 2.77 (s, 3H), 3.53 (t, 2H), 4.55 (t, 2H), 7.80 (m, 2H), 8.60 (m, 2H).

Anal. Calcd. for $C_{13}H_{14}O_4N_2$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.42; H, 5.44; N, 10.64.

2-(2′-Hydroxyethyl)-3-methyl-6,7-dimethylquinoxaline 1,4-Dioxide (**5b**).

A warm solution of **1b** (10) (0.65 g.) in 20 ml. of methanol, 5 ml. of water, and 5 ml. of 5% methanolic potassium hydroxide was added to a solution of 2-acetylbutyrolactone (0.51 g.) in 5 ml. of methanol. The yellow product, which started to precipitate within 6 hours, was collected after 20 hours, washed with methanol, and recrystallized from methanol, yield 0.38 g. (38%), m.p. 208-209°; ir (bromoform): 3320 (broad), 1510, 1380, 1325, 1265, 1090, 1040, 945 cm^{-1}; nmr (trifluoroacetic acid): δ 2.20 (s, 6H), 2.55 (s, 3H), 3.22 (t, 2H), 4.1 (t, 2H), 7.03 (broad signal, 2H).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.73; H, 6.52; N, 11.34.

Carbonate ester **5c**.

A warm solution of **1c** (10) (0.41 g.) in 5 ml. of methanol and 8 ml. of 2.5% methanolic sodium methoxide was added, with shaking and cooling, to a warm solution of 2-acetylbutyrolactone (0.26 g.) in 5 ml. of methanol. The product, which precipitated within 15 minutes, was collected and recrystallized from propanol to give bright yellow crystals of **5c** melting at 175-177°, yield 0.47 g. (81%); ir (potassium bromide): 1750, 1600, 1500, 1450, 1425, 1400, 1315, 1275, 1170, 1120, 1110, 1020, 940, 920, 850, 800 cm^{-1}; nmr (deuteriochloroform): δ 2.67 (s, 3H), 3.46 (t, 2H), 3.70 (s, 3H), 4.53 (t, 2H), 8.57 (s, 2H).

Anal. Calcd. $C_{13}H_{12}O_5N_2Cl_2$: C, 44.9; H, 3.45; N, 8.06; Cl, 20.46. Found: C, 45.3; H, 3.68; N, 8.16; Cl, 20.94.

2-Acetylquinoxaline 1,4-Dioxide (**12**).

A warm solution of benzofurazan oxide (0.68 g.) in 7 ml. of 5% ethanolic potassium hydroxide and 2 ml. of water was added to a solution of ethyl acetopyruvate (11) (0.79 g.) in 5 ml. of ethanol. A dark -red color developed immediately and gradually faded to bright red. The product (**10**) was collected after seven hours (if necessary after cooling), washed with ethanol, dried, dissolved in water, and acidified with concentrated hydrochloric acid. The precipitated product (**11**, 0.60 g.) dissolved readily in dilute sodium bicarbonate; ir (potassium bromide): 1725, 1480, 1350, 1270, 1075, 930, 770 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2O_5$: C, 53.23; H, 3.25; N, 11.29. Neutralization equivalent 248. Found: C, 53.25; H, 3.29; N, 11.42. Neutralization equivalent 247.

Recrystallization of **11** from propanol was attended with decarboxylation to 2-acetylquinoxaline 1,4-dioxide (**12**), yield 0.48 g. (47%), m.p. 185-188° dec.; ir (potassium bromide): 1675, 1600, 1490, 1430, 1360, 1210, 1085, 870, 825, 780 cm^{-1}; nmr (deuteriotrifluoroacetic acid): δ 3.0 (s, 3H), 8.15 (m, 2H), 8.70 (m, 2H), 9.35 (s, 1H).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.80; H, 3.92; N, 13.70; O, 23.5. Found: C, 58.93; H, 3.98; N, 13.74; O, 23.4.

Quinoxaline 1,4-Dioxide (**14**).

2-Acetylquinoxaline 1,4-dioxide-3-carboxylic acid (**11**, 1.20 g.) was dissolved in 10 ml. of 10% aqueous sodium hydroxide. A dark-red color developed immediately. Acidification of the solution caused precipitation of a product (**13**), which was readily soluble in dilute sodium bicarbonate; ir (potassium bromide): 1735, 1620, 1380, 1175, 1100, 910, 840, 770 cm^{-1}.

Anal. Calcd. for $C_9H_6N_2O_4$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.40; H, 3.07; N, 13.70.

When the acid **13** was refluxed for 7 hours in propanol it underwent decarboxylation to give a product identical (mixture m.p., tlc, ir) with an authentic sample of quinoxaline 1,4-dioxide (12), yield 0.38 g. (47%).

Reaction of BFO with Acetylacetaldehyde Dimethylacetal.

BFO (2.0 g.), acetylacetaldehyde dimethylacetal (3 ml.) (Aldrich Chemical Company, Inc., U.S.A.), morpholine (6 ml.), and benzene (75 ml.) were placed in a roundbottomed flask equipped with a reflux condenser and a Dean-Stark water separator. The solution was refluxed for 9 hours and cooled. The preipitated product was collected, washed with cold benzene, and recrystallized from ethanol to give orange-red crystals of **17** melting at 235-238° dec. [lit. (8) m.p. 245°], yield 2.0 g. (47%); ir (potassium bromide): 1625, 1595, 1530, 1410, 1380, 1355, 1280, 1260, 1230, 1210, 1150, 1110, 1080, 1020, 955, 860, 760 cm^{-1}; nmr (deuteriochloroform): δ 3.56 (morpholine pattern, 8H), 5.48 (d, 1H, J 13 cps), 7.70 (m, 2H), 8.26 (s, 1H), 8.51 (m, 3H).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.66; H, 5.74; N, 15.29.

Acknowledgement.

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