Reaction of 2,1,3-Benzoxadiazole 1-Oxide with Ethyl 2,4-Dioxo-4-phenylbutyrate. A Route to 2-Benzoylquinoxaline, its 1,4-Dioxide, and Related Compounds

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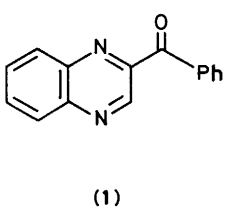
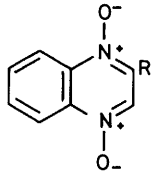
The Beirut reaction of 2,1,3-benzoxadiazole 1-oxide and ethyl 2,4-dioxo-4-phenylbutryate in ethanol, or acetonitrile, catalysed by triethylamine gave first ethyl 3-benzoylquinoxaline-2-carboxylate 1,4-dioxide and then, in a slower reaction, 2-benzoylquinoxaline 1,4-dioxide. The latter was isolated in two distinct stable crystalline forms. The effects of changing the proportions of the reactants, the tertiary alkylamine used, and the temperature have been studied. Both above-mentioned 1,4-dioxides were reduced to the corresponding quinoxalines. Ethyl 3-benzoylquinoxaline-2-carboxylate 1,4-dioxide decomposed slowly to several products in ethanol in the presence of triethylamine or diethylamine and was converted by ethanolic potassium hydroxide into the potassium salt of quinoxaline-2-carboxylic acid 1,4-dioxide.

2-Acylquinoxaline 1,4-dioxides and their derivatives possess useful biological activity, particularly antibacterial properties,[1] and are precursors of 2-acylquinoxalines. 2-Benzoylquinoxaline (**1**) was required for studies into the photochemistry of 2-acylquinoxalines. As its preparation using published procedures[2,3] involved several stages and/or low yield, we investigated a route *via* the 1,4-dioxide (**11**), the expected product of the Beirut reaction[4] between 2,1,3-benzoxadiazole 1-oxide (**5**) and benzoylacetaldehyde (**3**).† However, attempts at this reaction using



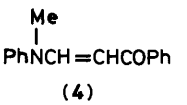
(**1**)



(**2**)

a: R = H
b: R = CO_2H

$PhCOCH_2CHO$ (**3**)



(**4**)

the aldehyde (**3**)[5] or the derived morpholine enamine[6] both failed, a low yield of quinoxaline 1,4-dioxide being the sole product. The reaction of 2,1,3-benzoxadiazole 1-oxide with the less reactive enamine (**4**) was attempted but little reaction occurred after 24 h in ethyl acetate, acetonitrile, or dimethylformamide. We then investigated an indirect route to the dioxide (**11**) *via* the ester (**8**). To prepare the ester, 2,1,3-benzoxadiazole 1-oxide was allowed to react with ethyl 2,4-dioxo-4-phenylbutyrate (**6**) using typical Beirut reaction conditions: neat diethylamine as catalyst and solvent and at room temperature. A complex mixture containing a little quinoxaline 1,4-dioxide (**2a**) resulted. This led us to explore alternative conditions. During this work we became aware of conditions[7] for the preparation of 2-benzoylquinoxaline 1,4-dioxide (**11**) (reported yield 63%) directly from 2,1,3-benzoxadiazole 1-oxide (**5**) and ester (**6**) in triethylamine. Using this procedure, on a 1 mmol scale, we obtained only a low yield of a solid [$\nu_{max.}$(Nujol) 1 680 and 1 645 cm^{-1}] which yielded 2-benzoylquinoxaline 1,4-dioxide (15%) on crystallisation from ethanol.

† The reaction of 2,1,3-benzoxadiazole 1-oxide with 1,3-diketones provides a general route to 2-acyl-3-alkyl(or aryl)-quinoxaline dioxides.[4]

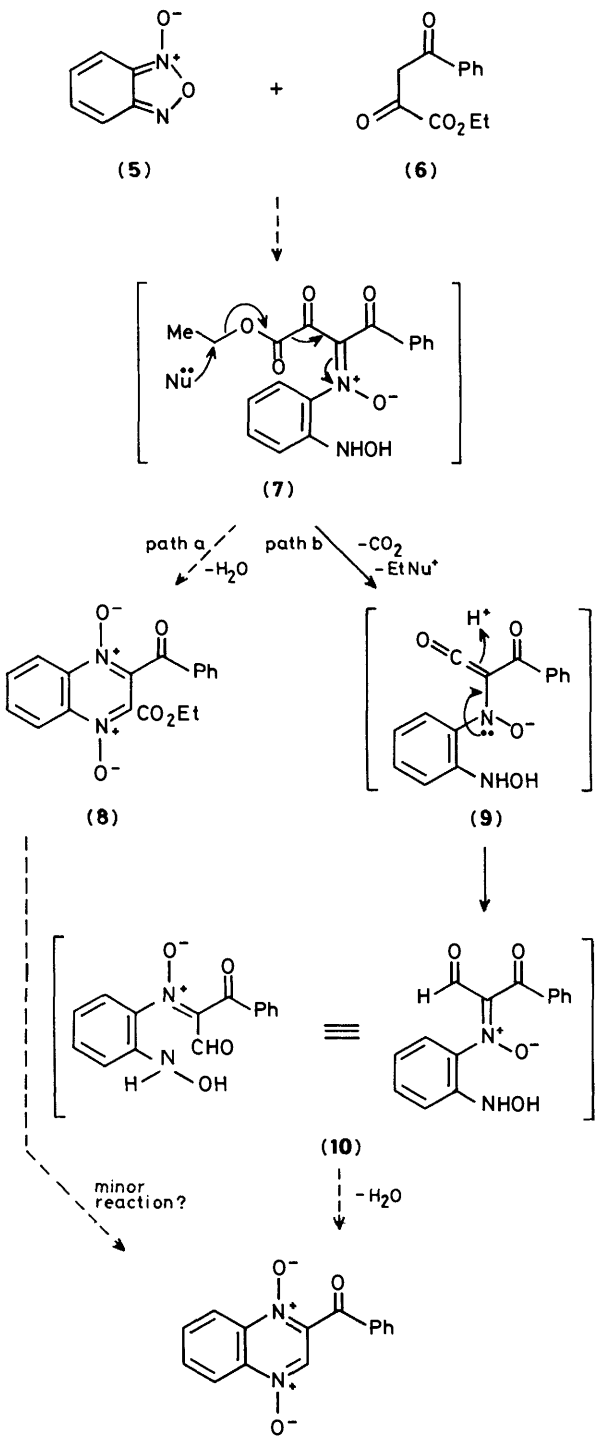
Table. Base-catalysed reaction of 2,1,3-benzoxadiazole 1-oxide (**5**) with the α-keto ester (**6**)

Entry	Equivalents[a] (**5**)	Equivalents[a] NEt_3	Solvent[b]	Time (days)	Product yield (%)[c]
i	1.25	2	EtOH	50	66 (**11**)
ii	1.1	0.1	EtOH	8	14 (**8**)
iii	1	2	MeCN	7	35 (**11**)
iv	1	4	EtOH[d]	1.25	12 (**13**)
v	1	2 (Et_2NH)	EtOH	14	19 (**11**)
vi	1	2 [$EtNPr^i_2$]	EtOH	36	45 (**11**)
vii	1.1	2	EtOH	2	15 (**8**)
				9	38 (**11**)[e]

[a] 1 Equiv. of the ester (**6**) used in all cases. [b] Reaction at room temperature unless otherwise stated. [c] Product shown in parentheses. [d] Reaction mixture heated under reflux for 12 h and left for 18 h at room temperature. [e] Yield of (**11**) 47% after 33 days.

In general, solutions containing 2,1,3-benzoxadiazole 1-oxide (**5**) and the α-keto ester (**6**) together with triethylamine (1—4 equiv.) were left for several days in the dark at room temperature, when crystals of a product, usually the 1,4-dioxide (**11**), were formed (see Table). The highest yield of dioxide (**11**), 66%, was obtained using a small excess of 2,1,3-benzoxadiazole 1-oxide and 2 equiv. of triethylamine, with ethanol as the solvent (entry i). The maximum yield of (**11**) under particular reaction conditions is approached after *ca.* 30 days. With only a catalytic amount of triethylamine (entry ii) no dioxide (**11**) was formed and instead, the quinoxaline dioxide ester (**8**) was isolated in low yield (14%). Diethylamine was inferior to triethylamine as a base catalyst (entry v). In an attempt to prevent the probable base-catalysed loss of the ethoxycarbonyl group, and hence to produce the ester (**8**), the hindered base *N,N*-di-isopropylethylamine was used (entry vi), but the quinoxaline dioxide (**11**) was the only product isolated (45%). At reflux temperature, no dioxide (**11**) was isolated, instead the mono-oxide (**13**) was formed in low yield (entry iv).

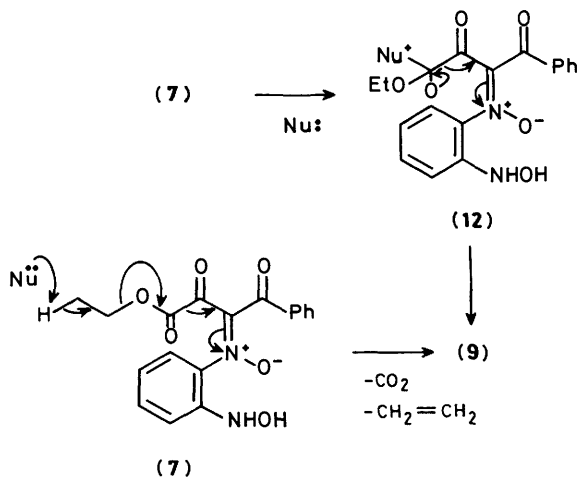
By monitoring the course of the reaction (t.l.c.) it was shown that the ester dioxide (**8**) was formed initially, reaching a maximum concentration in *ca.* 2 days. Build-up of the concentration of dioxide (**11**) became significant after 3—4 days, little



Scheme 1.

being present after 2 days. After 7 days little if any of the ester dioxide (**8**) remained in the mixture. Compound (**8**) was isolated by cooling the mixture after 2 days to induce crystallisation (Table, entry vii). After filtering off the dioxide (**8**), the filtrate was left for a period of several days and then the dioxide (**11**) was collected. The ester dioxide (**8**) both formed and decomposed more rapidly in higher concentrations of triethylamine (see Table, entries ii and vii). In ethanol, the ester (**8**) decomposed slowly at room temperature in the presence of triethylamine or diethylamine but little dioxide (**11**) was present in the resulting complex mixture. Hence, the dioxide (**8**) is not a significant intermediate in formation of the dioxide (**11**). Hydroxide ion (ethanolic potassium hydroxide) reacted rapidly with the ester dioxide (**8**) to give quinoxaline-2-carboxylic acid 1,4-dioxide (**2b**) in 58% yield after acidification of the initially formed potassium salt. A similar deacylation and hydrolysis of ethyl 3-formylquinoxaline-2-carboxylate 1,4-dioxide to give the acid (**2b**) has been described.[8] When 2,1,3-benzoxadiazole 1-oxide reacted in ethanolic potassium hydroxide with ethyl 2,4-dioxopentanoate (the only other reported reaction with an α,γ-dioxo ester) the product was 3-acetylquinoxaline-2-carboxylic acid 1,4-dioxide.[9] Deacetylation to quinoxaline-2-carboxylic acid 1,4-dioxide only occurred in aqueous alkali.

Pathways for the formation of the dioxides (**8**) and (**11**) are suggested in Scheme 1. The intermediate (**7**) is of the type proposed previously for the Beirut reaction of 2,1,3-benzoxadiazole 1-oxide with carbonyl compounds.[4] Cyclisation and dehydration, path a, leads to the ester dioxide (**8**). Nucleophilic attack on compound (**7**) (*e.g.*, Nu = NEt_3) with concomitant loss of carbon dioxide, path b, yields, after protonation of intermediate (**9**), the aldehyde (**10**). Subsequent cyclodehydration produces the dioxide (**11**). Alternative mechanisms for the conversion of (**7**) into (**9**) involve nucleophilic attack at the ester carbonyl group or base-catalysed elimination of ethylene and carbon dioxide (Scheme 2). The former, however,

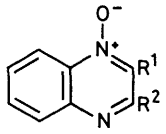


Scheme 2.

requires nucleophilic attack at the least reactive of the three carbonyl groups and further reaction of species (**12**) would require fission of the C–CO bond (as indicated) rather than the more likely fission of the C–$\overset{+}{N}$uu bond. The latter mechanism is more consistent with formation of the dioxide (**11**) when a hindered base was used (entry vi). The relative rates of formation and yields of the dioxides (**8**) and (**11**) described above may be explained if the rate of reaction (**7**)→(**10**) is approximately twice that of reaction (**7**)→(**8**), and if both rates are significantly higher than that of reaction (**10**)→(**11**).

Both dioxides (**8**) and (**11**) were readily reduced in methanol by sodium dithionite to the quinoxalines (**14**) (85%) and (**1**) (74%) respectively.

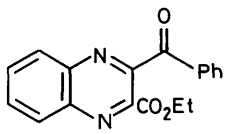
2-Benzoylquinoxaline 1,4-dioxide (**11**), as obtained from most preparations, shows i.r. absorption for the carbonyl group at 1 660 cm^{-1} (Nujol). In two out of four preparations when acetonitrile was the solvent (conditions as in the Table, entry iii), and once when ethanol was the solvent (conditions as in Table, entry i), the crystalline product had an i.r. spectrum somewhat similar to that of the more usually obtained '1 660' product (see



(13)

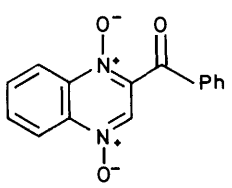
R^1, COPh, R^2, CO_2Et

or R^1, CO_2Et, R^2, COPh

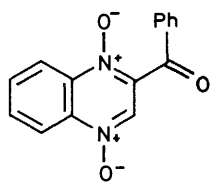


(14)

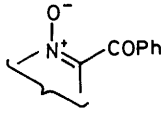
Experimental section), the major difference being that the carbonyl absorption occurred at 1 690 cm^{-1}. Crystallisation of the '1 690' product from ethanol or chloroform gave the '1 660' material, whereas crystallisation of the '1 660' product from acetonitrile gave a mixture of both materials. A pure sample of the '1 690' material was obtained by seeding a cold filtered solution of the '1 660' product in acetonitrile with a crystal of the '1 690' product. The n.m.r. (in $CDCl_3$) and u.v. spectra (in acetonitrile or methanol) of the '1 660' material were identical with those of the '1 690' material even when measured within 2—3 min of dissolving the material in the solvent. Both solids gave essentially the same m.s. It is clear from these observations that the dioxide (**11**) exists in two isomeric forms which are stable in the crystalline state but are readily interconverted in solution. Differences in the i.r. spectra appear too great to be consistent with different crystal structures but not great enough to result from different molecular structures. Only one carbonyl absorption is present, at 1 680 cm^{-1}, in the spectrum of either isomer in chloroform or acetonitrile. Either the carbonyl absorptions of each isomer in solution overlap to give the broad band at 1 680 cm^{-1} or a single isomer predominates.



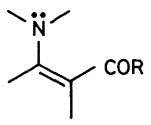
(11a) 's-*cis*'



(11b) 's-*trans*'



(15)



(16)

One explanation for the above observations is that the isomers are s-*cis* and s-*trans* rotamers [with respect to the N(1)–C(2) bond], (**11a**) and (**11b**) respectively, which are stabilised in the crystal lattice but are rapidly interconverted in solution. The partial structure (**15**) in dioxide (**11**) has some similarity to that of an enone or a *cis*-β-amino enone (**16**) in which the carbonyl absorption has been shown to be at a higher frequency in the s-*cis* rotamer than in the s-*trans* rotamer.[10,11] Hence, the benzoyl group frequencies of 1 690 and 1 660 cm^{-1} in the two isomers of (**11**) may be assigned to s-*cis* (**11a**) and s-*trans* (**11b**) rotamers respectively.

The methods described above for the synthesis of dioxides (**8**) and (**11**) should be adaptable to the synthesis of other 2-aroyl- and 2,3-diacylquinoxalines and their 1,4-dioxides. The results also provide a little further information on the nature of the Beirut reaction.

Experimental

I.r. spectra were recorded as Nujol mulls and n.m.r. spectra were recorded in $CDCl_3$ with $SiMe_4$ as internal standard, unless otherwise stated. For u.v. spectra, $\log_{10} \varepsilon_{max.}$ is quoted in parentheses.

Preparation of the Quinoxaline 1,4-*Dioxides* (**8**) *and* (**11**) *and the Mono-oxide* (**13**).—A solution of 2,1,3-benzoxadiazole 1-oxide (**5**), ethyl 2,4-dioxo-4-phenylbutyrate (**6**), and an alkylamine (usually triethylamine) was left at room temperature (unless otherwise indicated in the Table) for several days in the dark. Reactions were carried out on a 1—30 mmol scale with respect to the ester (**6**). The mixture was cooled and the product was collected by filtration and washed with the cold solvent. Details of the solvent and alkylamine used, the reaction time, and the relative amounts of the reactants [1 equiv. of ester (**6**) in all cases] are given in the Table. Where both dioxides (**8**) and (**11**) were obtained from the same reaction (entry vii), the mixture was first cooled to obtain the dioxide (**8**) and the filtrate, after removing (**8**), was left for a further period before collecting dioxide (**11**).

Quinoxaline oxides prepared in this way were *ethyl* 3-*benzoylquinoxaline*-2-*carboxylate* 1,4-*dioxide* (**8**), m.p. 172 °C (from ethanol) (Found: C, 63.95; H, 4.2; N, 8.2. $C_{18}H_{14}N_2O_5$ requires C, 63.9; H, 4.2; N, 8.3%); $\nu_{max.}$ 3 090, 1 730, 1 675, and 1 360 cm^{-1}; δ1.13 (3 H, t, *J* 8 Hz, Me), 4.32 (2 H, q, *J* 8 Hz, CH_2), 7.4—7.8 (3 H, m, phenyl 3-, 4-, and 5-H), 7.8—8.1 (4 H, m, ArH), and 8.45—8.8 (2 H, m, quinoxaline 5- and 8-H); *m/z* 338 (M^+, 1.5%), 201 (10), 149 (23), 129 (30), 111 (21), 110 (54), 105 (100), 103 (17), 97 (15), 91 (13), 81 (15), and 77 (88); 2-benzoylquinoxaline 1,4-dioxide (**11**), m.p. 220—222 °C (from methanol) (Found: C, 67.9; H, 3.7; N, 10.4. Calc. for $C_{15}H_{10}N_2O_3$: C, 67.7; H, 3.8; N, 10.5%); $\lambda_{max.}$(EtOH) 237 (4.44), 268 (4.37), and 387 nm (4.05); $\lambda_{max.}$(MeCN) 235 (4.46), 268 (4.47), and 397 nm (4.07); $\nu_{max.}$ for the two isomers of (**11**), with major differences italicised; i, *3 110w*, *3 080w*, *1 660vs*, 1 600s, *1 585m*, 1 535m, 1 505m, 1 455s, 1 370vs, *1 335s*, 1 315m, *1 270vs*, 1 230s, 1 215s, 1 185m, 1 170s, 1 150w, 1 095s, 990m, 945w, 840s, 780s, 745w, *735w*, 715vs, 685s, and 680s; ii, *3 070m*, *3 030m*, 1 690vs, 1 600s, *1 580w*, 1 540m, 1 505m, 1 450s, 1 380vs, *1 305m*, *1 260s*, 1 225s, 1 220vs, 1 180m, 1 165m, 1 150m, 1 090s, *1 020w*, 985m, 930w, *885m*, 830s, 770s, 745w, *735m*, 715s, 685s, and 675s cm^{-1}; $\nu_{max.}$($CHCl_3$ or MeCN) 1 680 cm^{-1}; δ($CDCl_3$ + [$^2H_6$]Me_2SO) 7.35—7.8 (3 H, m, phenyl 3-, 4-, and 5-H), 7.8—8.1 (4 H, m, ArH), 8.38 (1 H, s, quinoxaline 3-H), and 8.5—8.75 (2 H, m, quinoxaline 5- and 8-H); *m/z* 266 (M^+, 9%), 206 (23), 204 (21), 157 (20), 145 (20), 129 (73), 105 (90), 102 (32), 90 (19), and 77 (100) [lit.,[7] m.p. 240—243 °C; $\lambda_{max.}$($CHCl_3$) 249 (2.92) and 270 nm (2.92); $\nu_{max.}$(KBr) 1 695, 1 660, and 1 540 cm^{-1}]; *ethyl* 3-*benzoyl-quinoxaline*-2-*carboxylate mono-oxide* (**13**), m.p. 191 °C (from ethanol) (Found: C, 67.0; H, 4.1; N, 9.1. $C_{18}H_{14}N_2O_4$ requires C, 67.1; H, 4.4; N, 8.7%); $\nu_{max.}$ 1 725, 1 690, and 1 375 cm^{-1}; δ 1.2 (3 H, t, *J* 8 Hz, Me), 4.37 (2 H, q, *J* 8 Hz, CH_2), 7.4—7.75 (3 H, m, phenyl 3-, 4-, and 5-H), 7.75—8.1, (4 H, m, ArH), and 8.25—8.7 (2 H, m, quinoxaline 5- and 8-H); *m/z* 323 [(M + 1)$^+$, 6%], 229 (34), 201 (51), 129 (100), 105 (70), 102 (30), and 77 (88).

Ethyl 3-*Benzoylquinoxaline*-2-*carboxylate* (**14**).—A solution of sodium dithionite (*ca.* 85% purity) (1.0 g) in water (4 ml) was added dropwise to a warm solution of the 1,4-dioxide (**8**) (0.5 g) and conc. hydrochloric acid (1 ml) in methanol (30 ml). At the end of the reaction the solution remained dark blue for 5—10 min. Water (25 ml) was added and the resulting emulsion was kept for 18 h at *ca.* 4 °C to give *ethyl* 3-*benzoylquinoxaline*-2-*carboxylate* (0.386 g, 85%), m.p. 115—116 °C and m.p. 119 °C (after crystallisation from methanol) (Found: C, 70.25; H, 4.45; N, 8.9. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.1%); $\nu_{max.}$

3 060, 1 720, and 1 685 cm^{-1}; δ 1.26 (3 H, t, *J* 7 Hz, Me), 4.37 (2 H, q, *J* 7 Hz, CH_2), 7.3—7.7 (3 H, m, phenyl 3-, 4-, and 5-H), and 7.7—8.5 (6 H, m, ArH); *m/z* 306 (M^+, 4%), 233 (16), 105 (100), and 77 (57).

2-*Benzoylquinoxaline* (**1**).—A solution of 2-benzoylquinoxaline 1,4-dioxide (0.55 g) and conc. hydrochloric acid (1 ml) in hot methanol (*150* ml) was treated, as in the above experiment, with sodium dithionite (1.1 g) in water (5 ml). The mixture was worked up and diluted with water (150 ml) to yield a crystalline product (0.36 g, 74%), m.p. 77—78 °C, which on crystallisation from water–methanol (1:4) gave 2-benzoylquinoxaline, m.p. 79 °C (lit.,[2b] m.p. 80—81 °C; $\nu_{max.}$ 1 665 cm^{-1}).

Treatment of Ethyl 3-*Benzoylquinoxaline*-2-*carboxylate* 1,4-*Dioxide* (**8**) *with Base.*—*i*, A solution of potassium hydroxide (0.185 g) in ethanol (5 ml) was added to a solution of the dioxide (**8**) (0.338 g) in ethanol (20 ml). The insoluble potassium salt which formed rapidly was collected and dissolved in water (5 ml). Acidification with glacial acetic acid yielded quinoxaline-2-carboxylic acid 1,4-dioxide (**2b**) (0.12 g, 58%), m.p. 227—229 °C (decomp.) [lit.,[12] m.p. 221 °C (decomp.)].

ii, Solutions of the dioxide (**8**) in ethanol containing triethylamine or diethylamine (4 equiv.) were left for several days at room temperature. Slow decomposition to several products (t.l.c.) occurred with little, if any, of the dioxide (**11**) being formed.

3-*N*-Methylanilino-1-phenylprop-2-enone (**4**)[13] and ethyl 2,4-dioxo-4-phenylbutyrate (**6**)[14] were prepared according to literature procedures.

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