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REACTION OF BENZOFURAZAN OXIDE WITH UNSYMMETRICAL 1,3-DIKETONES; STERIC AND POLAR EFFECTS

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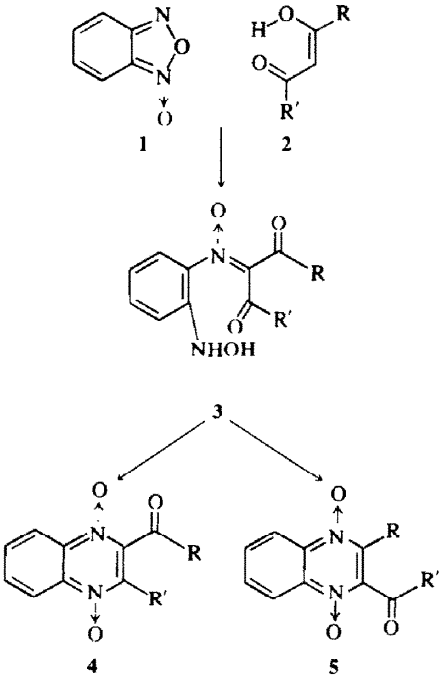
Abstract—The reaction of benzofurazan oxide **1** with unsymmetrical 1,3-diketones **6a–6w** gives isomeric quinoxaline-1,4-dioxides **7** and/or **8**. The regiospecificity of ring closure to **7** or **8** is influenced by steric and polar factors in the 1,3-diketone. Mechanistic implications of these findings are presented.

Recent interest in quinoxaline-1,4-dioxides stems from their antibacterial and growth promoting activity. Although human use has not been reported yet, some compounds in this class are remarkably effective and currently used as animal feed additives.[1]

Earlier work from this laboratory[2] showed that benzofurazan oxide **1** reacts with symmetrical 1,3-diketones (**2**, R = R') to give 2,3-disubstituted quinoxaline-1,4-dioxides (**4**, identical with **5** when R = R'). Subsequent work from another laboratory[3] provided more examples of this reaction, and recently Mason and Tennant[4] presented evidence for an intermediate hydroxylamine-nitrone **3** which gives products via cyclization and elimination.



With unsymmetrical 1,3-diketones the reaction could possibly give two isomeric di-*N*-oxides (**4** and **5**) by attack of the hydroxylamino nitrogen on one or the other of the carbonyl groups of the Mason-Tennant intermediate. The purpose of this study was to assess the effect of polar and steric factors on the regiospecificity of ring closure with unsymmetrical 1,3-diketones of type **6**. Twenty three such diketones were prepared (**6a–6w**, Table 1) and characterized; these diketones were found by NMR to exist predominantly (>90%) in the enol form (keto form δ 3·8–4·0 for the methylene protons; enol form δ 5·6–6·2 for the vinylic proton).[cf 5]

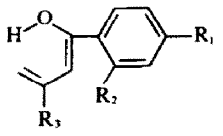
Addition of **1** to **6** in triethylamine at room temperature produced a dark coloration followed by slow precipitation of a yellow solid. In each case, the mother-liquor was concentrated under reduced pressure, and the residue was subjected to repeated preparative thin-layer chromatography in search of more di-*N*-oxides. The products showed a strong IR band at 1330–1340 cm^{-1} (*N*-oxide). The assignment to a product of structure either **7** or **8** was based on the position of its carbonyl absorption band: 1660–1680 cm^{-1} for **7** (aroyl substituent) and 1700–1710 cm^{-1} for **8** (acyl substituent). The NMR spectra typically showed a multiplet at δ 8·40–8·50 for the protons at C_5 and C_8, and a multiplet at δ 7·70–7·80 for the protons at C_6 and C_7. The NMR data were used to confirm the structural assignments and to determine the isomeric ratio of **7**:**8** in a mixture. For example, for R_3 = ethyl, the different chemical shifts of the methyl triplets for **7** (δ 1·23–1·27) and **8** (δ 1·02–1·06) permitted estimation of the ratio of these isomers in a mixture. Similarly for R_3 = isopropyl, the position of the doublet for the methyl protons permitted estimation of the ratio of **7** (δ 1·37–1·41) to **8** (δ 0·94–0·99). In this manner, reliable estimates were made for the isomeric pairs **7b–8b**, **7c–8c**, **7n–8n**, **7p–8p**, **7q–8q**, **7r–8r** (Table 2). These estimates were in agreement with those obtained by measurement of the carbonyl band intensities at 1660–1680 cm^{-1} for **7** and at 1700–1710 cm^{-1} for **8**.

The experimental data in Table 2 have been grouped in discrete sets of reactions in order to delineate more clearly the effect of substituents on the regiospecificity of cyclization.

In the first set of reactions, benzofurazan oxide was treated with 1,3-diketones **6a–d**, in which competition for attack by the hydroxylamino nitrogen is between a benzoyl group and an acyl group of increasing bulkiness (R_3 = methyl, ethyl, isopropyl, tert. butyl). The data show borderline cases with R_3 = ethyl (**6b**) giving **7b** and **8b** in a ratio of 9:1, and with R_3 = isopropyl (**6c**) giving **7c** and **8c** in a ratio of 1:2. With the least bulky methyl group (**6a**) attack is exclusively on the acyl carbonyl giving **7a**, whereas with the bulkiest tert-butyl group (**6d**) attack is exclusively on the benzoyl carbonyl giving **8d**. It should be noted that no isomerization was observed when **7b** alone or **8b** alone was dissolved in triethylamine and allowed to stand under the usual reaction conditions.

In the second and third sets of reactions, an acetyl

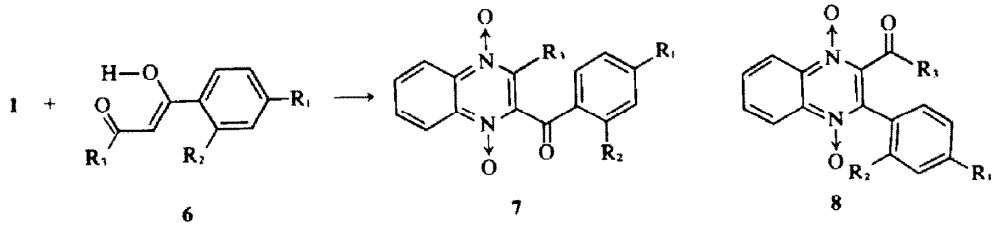
Table 1.



6	R_1	R_2	R_3	% Yield	B.p./mmHg or m.p.	% Enol	Analyses, Found C	H	N	Br
a[1]	H	H	Me	—	—	94·5[2]	—	—	—	—
b[3]	H	H	Et	54	140/1·0	90	—	—	—	—
c	H	H	i-Pr	60	128/0·3	94	75·58	7·55	—	—
d	H	H	t-Bu	16	119/0·35	96	76·27	7·87	—	—
e[4]	MeO	H	Me	29	55–56	94·7[2]	—	—	—	—
f[5]	Me	H	Me	46	126–8/6	95·7[2]	—	—	—	—
g[5]	Br	H	Me	40	90–91	100[2]	—	—	—	—
h[6]	NO_2	H	Me	50	112–113 (EtOH)	100[2]	—	—	—	—
i	H	MeO	Me	37	146/0·5	82	68·50	6·28	—	—
j	H	Me	Me	25	116/4	95	74·71	7·02	—	—
k[6]	H	NO_2	Me	57	53–54	91	—	—	—	—
l	MeO	H	Et	47	180/1·5	85	69·61	6·94	—	—
m	Me	H	Et	58	158/1·4	89	75·99	7·48	—	—
n	Br	H	Et	47	188/6	90	51·10	4·15	—	32·62
o[7]	NO_2	H	Et	24	94–95 (EtOH)	100	59·66	4·95	6·28	—
p	MeO	H	i-Pr	54	170/0·75	88	71·02	7·35	—	—
q	Me	H	i-Pr	26	136/0·4	90	76·24	7·79	—	—
r	Br	H	i-Pr	44	158/0·75	97	53·25	4·77	—	29·91
s[7]	NO_2	H	i-Pr	13	65–66 (EtOH)	100	61·27	5·56	5·95	—
t	MeO	H	t-Bu	17	186/0·4	92	71·73	7·78	—	—
u	Me	H	t-Bu	9	144/0·5	95	77·18	8·25	—	—
v	Br	H	t-Bu	12	158/0·5	98	55·13	5·31	—	28·05
w	H	MeO	t-Bu	5	160/0·75	95	71·54	7·72	—	—

All the above 1,3-diketones gave positive $FeCl_3$ test and showed strong IR bands (neat) at 1595–1610 cm^{-1} for chelated carbonyl groups and broad bands at 2500–2700 cm^{-1} for chelated OH. [1]Commercially available. [2]J. U. Lowe Jr. and L. N. Ferguson, *J. Org. Chem.* **30**, 3000 (1965), data in CCl_4. [3]R. Levine, J. A. Conroy, J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.* **67**, 1510 (1945). [4]E. Chapman, A. G. Perkin and R. Robinson, *J. Chem. Soc.* 3033 (1927). [5]K. V. Auwer and P. Heimke, *Ann.* **458**, 219 (1927). [6]H. G. Walker, Jr. and C. R. Hauser, *J. Am. Chem. Soc.* **68**, 2742 (1946). [7]BF_3 used as acylating agent.

Table 2.



6 **7** **8**

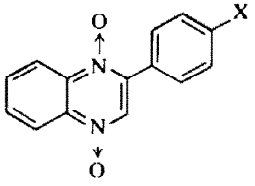
		R_1	R_2	R_3	7:8		R_1	R_2	R_3	7:8
1	a	H	H	Me	Only 7	4	l	CH_3O	H	Et	Only 7
	b	H	H	Et	9:1		m	CH_3	H	Et	Only 7
	c	H	H	i-Pr	1:2		n	Br	H	Et	3:1
	d	H	H	t-Bu	Only 8		o	NO_2	H	Et	Only 8
2	e	CH_3O	H	Me	Only 7	5	p	CH_3O	H	i-Pr	12:1
	f	CH_3	H	Me	Only 7		q	CH_3	H	i-Pr	7:1
	g	Br	H	Me	Only 7		r	Br	H	i-Pr	1:3
	h	NO_2	H	Me	Only 7		s	NO_2	H	i-Pr	Only 8
3	i	H	CH_3O	Me	Only 7	6	t	CH_3O	H	t-Bu	Only 8
	j	H	CH_3	Me	Only 7		u	CH_3	H	t-Bu	Only 8
	k	H	NO_2	Me	Only 7		v	Br	H	t-Bu	Only 8
							w	H	CH_3O	t-Bu	Only 8

group competes with a benzoyl group carrying an ortho or para substituent. In all cases (**6e–h** and **6i–k**), regardless of the polar effect or the position of the substituent, attack occurs on the acetyl group giving **7e–k**.

In view of the ethyl group's borderline position in Set 1 (Table 2), it is not surprising that the polar effect of substituents becomes discernible in Set 4, where a propionyl group (**6**, R_3 = ethyl) competes with a para substituted benzoyl group. With a bromine substituent (**6n**) attack occurs on either carbonyl to give a mixture of **7n** and **8n** in the ratio of 3:1. With the more electron releasing (carbonyl deactivating) methoxyl and methyl substituents (**6l** and **6m**) attack occurs exclusively on the acyl carbonyl giving respectively **7l** and **7m**. Complete reversal is observed with the strongly electron attracting para nitro substituent **6o**, which gives only **8o**.

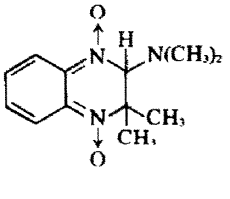
The results of Set 5 are comparable to those of Set 4 and consistent with the greater bulk of an isopropyl as compared with an ethyl group for R_3. Finally, with the bulkiest tertiary butyl group (**6t–w**, Set 6) attack is, exclusively and in sharp contrast with Sets 2 and 3, on the substituted benzoyl group regardless of position or polar effect of the substituent.

Regiospecificity trends similar to those reported in Table 2 were observed when diethylamine was substituted for triethylamine in the reaction of **1** and **6**. Diethylamine gave faster reactions but caused deacylation of certain quinoxaline-di-*N*-oxides (**8n, o, r, s→14**), the extent of which depended on the reaction time.

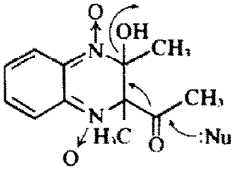


14a X = Br, NO_2

In an attempt to obtain products analogous to the bis-nitrone diene **9** reported by McFarland[6] for the quinoxaline-di-*N*-oxides (**8n, o, r, s→14a**), the extent of which depended on the reaction time.

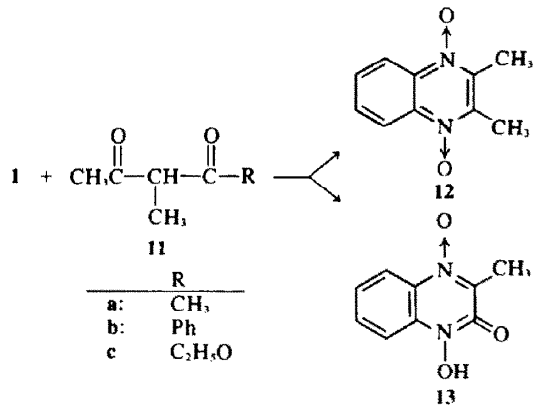


9



10

diethylamine with 1,3-diketones carrying one substituent on the methylene carbon (**11**). In no case could we isolate cyclic bis-nitrones such as the expected **10** from **11a**. Both **11a** and **11b** gave the same product (**12**), whereas **11c** gave the cyclic hydroxamic acid-nitrone **13**. Although these products could arise by diethylamine induced fragmentation of **10** (from **11a**), we believe that a more plausible mechanism in all cases, but especially so in the case of **11c**, entails fragmentation at an earlier stage: nucleophilic attack on the α, α-disubstituted, and therefore highly vulnerable,[7] carbonyl group of **14b** to give the hydroxylamino-nitrone **15**, which then cyclizes normally to give **13**. It is surprising that only **12** (along with the expected *N,N*-diethylbenzamide) was obtained from **11b**.



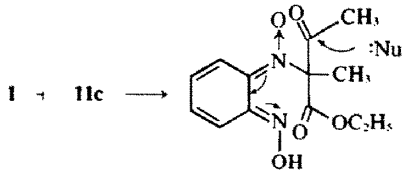
11

	R
a:	CH_3
b:	Ph
c	C_2H_5O

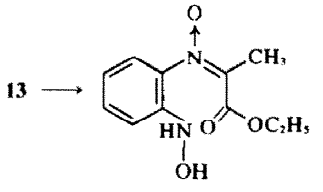
12

13

Work-up of the reaction mixture gave no indication of the presence of any 2 - phenyl - 3 - methyl - quinoxaline - di - *N* - oxide. We are investigating these reactions further.



14b



15

EXPERIMENTAL

M.ps were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra (KBr) were taken on a Perkin-Elmer 257 Spectrophotometer. NMR were run in $CDCl_3$ on a Varian A60-D Spectrometer. Elemental analyses were performed by F. Pascher, Bonn, Germany. Silica gel GF_{254} (Merck) was used in TLC.

The 1,3-diketones listed in Table 1 were prepared by Adams–Hauser[8] procedure with occasional minor modification. Unless indicated otherwise, reasonably fresh $NaNH_2$ (BDH) was used as the acylating agent.

General procedure for the reaction of 1,3-diketones with benzofurazan oxide. A warm solution of the specific 1,3-diketone (25 mmole, unless mentioned otherwise) in triethylamine (10 ml) was mixed with a warm solution of benzofurazan oxide (25 mmole) in triethylamine (10 ml). The solution, which was allowed to stand at room temperature, developed a deep red color with a rise in temperature, and the yellow quinoxaline-1,4-dioxide precipitated in the period of a few minutes to few hours. The yellow solid, often thinned with triethylamine, was collected and washed with triethylamine. The washings were added to the mother liquor which upon further standing at room temperature gave additional crop(s). The formation of a mixture of isomers was monitored by TLC, IR and NMR. After the reaction was complete, the solvent was evaporated in a stream of air under the hood. The deep thick red residue was subjected to repeated thick layer chromatography (2–3 times) with benzene-trace of methanol as eluent, and authentic samples as references. It was observed that the quinoxaline-1,4-dioxides **7** move slightly faster than **8** on TLC.

Substitution of diethylamine for triethylamine resulted in faster reactions. Since most of the products were collected over different intervals, the weight of the crop, the name of the compound(s), and the reaction time are mentioned in this order.

2 - *methyl* - 3 - *benzoylquinoxaline* - 1,4 - *dioxide* (**7a**). The reaction was performed on a 50 mmole scale. 4·7 g, **7a**, 16 h; 5·6 g, **7a**, 7 days. Yield 10·3 g (74%; 70% in diethylamine). **7a**, m.p. 223–4° (MeOH). IR ν_{max} 1672, 1600, 1455, 1328, 1250, 1075, 960, 815, 770, 720, 660 cm^{-1}. NMR 2·5 (s, 3H), 7·5–8 (m, 7H), 8·55 (m, 2H). (Found: C, 68·55; H, 4·30; N, 10·09. Calc. for $C_{16}H_{12}O_3N_2$: C, 68·56; H, 4·32; N, 10·00%).

2 - *Ethyl* - 3 - *benzoylquinoxaline* - 1,4 - *dioxide* (**7b**) *and* 2-*phenyl* - 3 - *propionylquinoxaline* - 1,4 - *dioxide* (**8b**). 1·83 g, **7b**, 24 h; 0·34 g, **7b** and **8b** (5:9), 24 h; 0·39 g, **7b** and **8b** (15:2), one week; longer standing yielded an additional **7b** (0·08 g), the ratio of the total **7b**:**8b** was 9:1. Pure **7b** and **8b** were isolated by fractional crystallization from MeOH. The same reaction, in diethylamine, yielded 1·44 g of **7b** and 0·48 g of **8b** (3:1). **7b**, m.p. 199–200 (d). IR ν_{max} 1675, 1595, 1510, 1450, 1342, 1312, 1238, 1095, 915, 820, 765, 715, 640 cm^{-1}. NMR 1·27 (t, 3H, J = 7 Hz), 2·93 (q, 2H, J = 7 Hz), 7·7 (m, 7H), 8·53 (m, 2H). (Found: C, 69·18; H, 4·73; N, 9·48. Calc. for $C_{17}H_{14}O_3N_2$: C, 69·37; H, 4·80; N, 9·52%). **8b**, m.p. 157–8°. IR ν_{max} 1702, 1600, 1340, 1275, 1090, 900, 770, 505 cm^{-1}. NMR 1·02 (t, 3H, J = 7 Hz), 2·63 (q, 2H, J = 7 Hz), 7·60 (m, 7H), 8·48 (m, 2H). (Found: C, 69·30; H, 4·69; N, 9·55. Calc. for $C_{17}H_{14}O_3N_2$: C, 69·37; H, 4·80; N, 9·52%).

2 - *Phenyl* - 3 - *isobutyrylquinoxaline* - 1,4 - *dioxide* (**8c**) *and* 2-*isopropyl* - 3 - *benzoylquinoxaline* - 1,4 - *dioxide* (**7c**). The reaction was run on a 30 mmole scale. 0·64 g, **8c**, 2 days; 0·06 g, **8c**, 24 h; 0·36 g, **8c** and **7c**, 4 days; 0·34 g, **8c** and **7c**, three weeks. Yield 1·4 g. **7c** and **8c** (1:2) were isolated pure on repeated recrystallization from methanol. Repeated TLC on the residue yielded 37 mg of **7c**. The same reaction was run in diethylamine and **8c** was the only isolable product (15%). **7c**, m.p. 151–2° (MeOH). IR ν_{max} 1670, 1590, 1495, 1362, 1310, 1242, 1105, 1018, 942, 810, 770, 729, 657 cm^{-1}. (Found: C, 69·38; H, 5·04; N, 8·91. Calc. for $C_{18}H_{16}O_3N_2$: C, 70·11; H, 5·23; N, 9·09%). **8c**, m.p. 175°. IR ν_{max} 1710, 1598, 1450, 1340, 1265, 1095, 1030, 913, 860, 767, 700, 680 cm^{-1}. NMR 0·94 (d, 6H, J = 7 Hz), 2·75 (sep, 1H, J = 7 Hz), 7·37 (s, 5H), 7·63 (m, 2H), 8·43 (m, 2H). (Found: C, 69·98; H, 5·35; N, 8·96. Calc. for $C_{18}H_{16}O_3N_2$: C, 70·11; H, 5·23; N, 9·09%).

2 - *Phenyl* - 3 - *pivalylquinoxaline* - 1,4 - *dioxide* (**8d**). The reaction was run on a 15 mmole scale. 0·30 g, **8d**, 24 h; 0·95 g, **8d**, 1 week, 1·33 g, **8d**, 6 weeks. Yield 2·58 g (53%). Repeated TLC yielded 24 mg of **8d**. The same reaction in diethylamine gave **8d** (44%) exclusively. **8d**, m.p. 224–5° (MeOH). IR ν_{max} 1700, 1600, 1480, 1340, 1285, 1095, 905, 885, 765, 700 cm^{-1}. NMR 0·94 (s, 9H), 7·4 (s, 5H), 7·75 (m, 2H), 8·44 (m, 2H). (Found: C, 70·59; H, 5·55; N, 8·61. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·79; H, 5·63; N, 8·69%).

2 - *Methyl* - *p* - *methoxybenzoylquinoxaline* - 1,4 - *dioxide* (**7e**). The reaction was run on a 50 mmole scale. 9·6 g, **7e**, 4 days; 2 g on long standing. Yield 11·6 g (75%; 77% in diethylamine). **7e**, m.p. 217° (d) (MeOH). IR ν_{max} 1665, 1590, 1330, 1250, 1075, 945, 820, 780 cm^{-1}. NMR 2·48 (s, 3H), 3·82 (s, 3H), 6·95 (d, 2H, J = 9 Hz), 7·85 (m, 4H), 8·55 (m, 2H). (Found: C, 65·93; H, 4·53; N, 9·22. Calc. for $C_{17}H_{14}O_4N_2$: C, 65·80; H, 4·55; N, 9·03%).

2 - *Methyl* - *p* - *methylbenzoylquinoxaline* - 1,4 - *dioxide* (**7f**). The reaction was run on a 5 mmole scale. 0·42 g, 7f, 24 h; long standing gave 0·78 g. Yield 1·20 g (82%, 70% in diethylamine). **7f**, m.p. 223 (d) ($CHCl_3$–MeOH). IR ν_{max} 1665, 1600, 1330, 1250, 1185, 1075, 950, 820, 770 cm^{-1}. NMR 2·41 (s, 3H), 2·48 (s, 3H). 7·25 (d, 2H, J = 7 Hz), 7·75 (m, 4H), 8·55 (m, 2H). (Found: C, 69·42; H, 4·76; N, 9·46. Calc. for $C_{17}H_{14}O_3N_2$: C, 69·37; H, 4·80; N, 9·52%).

2 - *Methyl* - *p* - *bromobenzoylquinoxaline* - 1,4 - *dioxide* (**7g**). The reaction was performed on a 10 mmole scale. 2·55 g, **7g**, 2 days; long standing gave 0·05 g. Yield 2·6 g (72%, 70% in diethylamine). **7g**, m.p. 224–5° (MeOH). IR ν_{max} 1670, 1585, 1335, 1270, 1250, 1070, 950, 810, 775 cm^{-1}. NMR 2·48 (s, 3H), 7·82 (m, 6H), 8·20 (m, 2H), 8·55 (m, 2H). (Found: C, 53·59; H, 3·12; N, 7·81; Br, 22·10. Calc. for $C_{16}H_{11}O_3N_2Br$: C, 53·50; H, 3·09; N, 7·80; Br, 22·25%).

2 - *Methyl* - *p* - *nitrobenzoylquinoxaline* - 1,4 - *dioxide* (**7h**). The reaction was run on a 5 mmole scale. 0·46 g, **7h**, 24h; 0·19 g, **7h**, 48 h; 0·20 g, 4 days. Yield 0·85 g (52%, 54% in diethylamine). **7h**, m.p. 217–8° (MeOH). IR ν_{max} 1682, 1600, 1525, 1320, 1240, 1072, 950, 810, 775, 720 cm^{-1}. NMR 2·5 (s, 3H), 8·8–7·8 (m, 8H). (Found: C, 58·90; H, 3·47; N, 13·02. Calc. for $C_{16}H_{11}O_5N_3$: C, 58·08; H, 3·41; N, 12·92%).

2 - *Methyl* - *o* - *methoxybenzoylquinoxaline* - 1,4 - *dioxide* (**7i**). 1·10 g, **7i**, 8h; 1·17 g, 7l, 24 h; 2·27 g, **7i**, 4 days; an additional 1·60 g was collected within 6 weeks. Yield 6·14 g (79%). The same reaction was performed in diethylamine and **7i** (76%) was the only isolable product. TLC on both residues yielded traces of **7l** and no **8i**. **7i**, m.p. 212–3° (MeOH). IR ν_{max} 1655, 1595, 1470, 1335, 1250, 1080, 1015, 950, 825, 790, 755, 660 cm^{-1}. NMR 2·47 (s, 3H), 3·46 (s, 3H), 8·65–6·67 (m, 6H), 8·47 (m, 2H). (Found: C, 65·92; H, 4·59; N, 8·86. Calc. for $C_{17}H_{14}O_4N_2$: C, 65·80; H, 4·55; N, 8·86%).

2 - *Methyl* - 3 - *o* - *methylbenzoylquinoxaline* - 1,4 - *dioxide* (**7j**). 0·42 g, **7j**, 7 h; 1·89 g, **7j**, 6 days; 1·89 g, **7j**, 2 weeks; the fifth crop (0·72 g, **7j**) was collected after 1 month. Yield 4·92 g (67%). Repeated TLC gave 30 mg of **7j** and no **8j**. Similar results were obtained with diethylamine as a solvent (70%). **7j**, m.p. 217° (d) (MeOH). IR ν_{max} 1670, 1600, 1330, 1240, 1100, 1070, 945, 825, 773, 750, 655 cm^{-1}. NMR 2·48 (s, 3H), 2·72 (s, 3H), 7·25 (m, 4H), 7·72 (m, 2H), 8·42 (m, 2H). (Found: C, 69·65; H, 5·10; N, 9·63. Calc. for $C_{17}H_{14}O_3N_2$: C, 69·37; H, 4·80; N, 9·52%).

2 - *Methyl* - 3 - *o* - *nitrobenzoylquinoxaline* - 1,4 - *dioxide* (**7k**). The reaction was performed on a 10 mmole scale. 0·85 g, **7k**, 24 h; 0·68 g, **7k**, 6 days. Yield 1·53 g (47%). The reaction gave the same product (**7k**, 65%) in diethylamine as a solvent. TLC of the residue did not reveal the presence of **8k**. **7k**, m.p. 201–2° (d) (MeOH-$CHCl_3$). IR ν_{max} 1680, 1600, 1525, 1330, 1090, 1070, 935, 860, 810, 795, 770, 765, 750, 740, 705, 650 cm^{-1}. NMR 2·63 (s, 3H), 8·52–7·42 (m, 6H), 8·55 (m, 2H). (Found: C, 59·16; H, 3·32; N, 12·73. Calc. for $C_{16}H_{11}O_5N_3$: C, 59·08; H, 3·41; N, 12·92%).

2 - *Ethyl* - *p* - *methoxybenzoylquinoxaline* - 1,4 - *dioxide* (**7l**). The reaction was performed on a 10 mmole scale. 0·73 g, **7l**, 24 h; 0·40 g, **7l**, 30 h; 0·32 g, **7l**, 30 h; 0·32 g, **7l**, 10 days. Yield 1·45 g (46%). The same reaction was run in diethylamine as a solvent and **7l** (28%) was the only insolable product. TLC showed no traces of **8l**.

7l, m.p. 183° (MeOH-$CHCl_3$). IR ν_{max} 1660, 1595, 1340, 1260, 1170, 1090, 1030, 915, 820, 770, 645 cm^{-1}. NMR 1·24 (t, 3H, J = 7 Hz), 2·83 (q, 2H, J = 7 Hz), 3·78 (s, 3H), 6·83 (d, 2H, J = 8 Hz), 7·74 (m, 4H), 8·41 (2H). (Found: C, 66·52; H, 5·02; N, 8·79. Calc. for $C_{16}H_{16}O_4N_2$: C, 66·66; H, 4·97; N, 8·64%).

2 - *Ethyl* - 3 - *p* - *methylbenzoylquinoxaline* - 1,4 - *dioxide* (**7m**). 1·56 g, **7m**, 24 h; 1·45 g, **7m**, 2 days; 0·96, **7m**, 4 days; 0·66 g, **7m**, 13 days. Yield 4·63 g (60%). The same reaction yielded **7m** (27%) only, with diethylamine as solvent. TLC gave traces of additional **7m** and no **8m**. **7m**, m.p. 197–8° (MeOH). IR ν_{max} 1665, 1600, 1510, 1340, 1240, 1180, 1090, 1030, 920, 830, 770, 673 cm^{-1}. NMR 1·23 (t, 3H, J = 7 Hz), 2·38 (s, 3H), 2·83 (q, 2H, J = 7 Hz), 7·17 (d, 2H, J = 8 Hz), 7·72 (m, 4H), 8·42 (m, 2H). (Found: C, 70·04; H, 5·16; N, 9·13. Calc. for $C_{18}H_{16}O_3N_2$: C, 70·11; H, 5·23; N, 9·09%).

2 - *Ethyl* - 3 - *p* - *bromobenzoylquinoxaline* - 1,4 - *dioxide* (**7n**), 2-p - bromophenyl - 3 - propionylquinoxaline - 1,4 - dioxide (**8n**), and 2 - *p* - *bromophenylquinoxaline* - 1,4 - *dioxide*. 1·14 g, **7n**, 4·5 h; 0·74 g, **7n** and **8n**, 9 h; 1·9 g, **7n** and **8n**, 24 h; 0·45 g, **7n** and **8n**, 33 h; 0·63 g, **7n** and **8n**, 3 days. Yield 5·01 g, **7n** and **8n** (54%). 3·77 g, **7n** and 1·09 g, **8n** and 0·13 g of 2 - p - bromophenylquinoxaline - 1,4 - dioxide which resulted from the cleavage of **8n**. The ratio of **7n**:**8n** was 3:1. The cleavage of **8n** into 2 - p - bromophenylquinoxaline - 1,4 - dioxide was more pronounced (60%) when the reaction was run in diethylamine. The ratio of **7n**:**8n** was 5:2. TLC on the residues from both reactions gave traces (20 mg) of **7n**. **7n**, m.p. 210–2° (MeOH). IR ν_{max} 1675, 1585, 1445, 1335, 1240, 1095, 1070, 915, 820, 770 cm^{-1}. NMR 1·23 (t, 3H, J = 7 Hz), 2·84 (q, 2H, J = 7 Hz), 7·75 (m, 6H), 8·47 (m, 2H). (Found: C, 54·67; H, 3·49; N, 7·53; Br, 21·62. Calc. for $C_{17}H_{13}O_3N_2Br$: C, 54·71; H, 3·51; N, 7·51; Br, 21·41%). **8n**, m.p. 168° (MeOH). IR ν_{max} 1720, 1590, 1340, 1280, 1090, 1015, 897, 780 cm^{-1}. (Found: C, 54·54; H, 3·42; N, 7·50; Br, 21·23. Calc. for $C_{17}H_{13}O_3N_2Br$. C, 54·71; H, 3·51; N, 7·51; Br, 21·41%). 2 - p - Bromophenylquinoxaline - 1,4 - dioxide, m.p. 236–7° ($CHCl_3$). IR ν_{max} 1585, 1578, 1490, 1360, 1340, 1243, 1015, 870, 820, 770, 745 cm^{-1}. NMR ($CDCl_3$-CF_3COOH) 7·87 (s, 4H), 8·17 (m, 2H), 9·10 (s, 1H). (Found: C, 53·13; H, 2·83; N, 8·78; Br, 25·34. Calc. for $C_{14}H_9O_2N_2Br$: C, 53·02; H, 2·86; N, 8·83; Br, 25·18%).

2 - *p* - *Nitrophenyl* - 3 - *propionylquinoxaline* - 1,4 - *dioxide* (**8o**) *and* 2 - *p* - *nitrophenylquinoxaline* - 1,4 - *dioxide*. The reaction was performed on a 15 mmole scale. 0·52 g, **8o**, 27 h; 0·1 g, **8o**, 4 days. 0·14 g of 2 - p - nitrophenylquinoxaline - 1,4 - dioxide which resulted from the cleavage of **8o**. The reaction, in diethylamine, yielded 1·04 g, **8o**, and 0·25 g of 2 - p - nitrophenylquinoxaline - 1,4 - dioxide. TLC on both reaction residues yielded traces of **8o** (20 mg). None of **7o** was detected. Authentic **8o** was found to cleave to 2 - p - nitrophenylquinoxaline - 1,4 - dioxide in diethylamine. **8o**, m.p. 200-1° (MeOH-$CHCl_3$). IR ν_{max} 1710, 1600, 1515, 1345, 1280, 1095, 895, 855, 775, 710 cm^{-1}. NMR 1·06 (t, 3H, J = 7 Hz), 2·74 (q, 2H, J = 7 Hz), 7·76 (m, 4H), 8·48 (m, 4H). (Found: C, 60·19; H, 3·85; N, 12·25. Calc. for $C_{17}H_{13}O_5N_3$: C, 60·17; H, 3·86; N, 12·39%). 2 - p - Nitrophenylquinoxaline - 1,4 - dioxide, m.p. 272–3° (MeCOOH-MeOH-$CHCl_3$). IR ν_{max} 1600, 1515, 1350, 1250, 1100, 880, 850, 840, 775, 760, 745, 700 cm^{-1}. NMR ($CDCl_3$-CF_3COOH) 7·85–9·30 (m). (Found: C, 59·17; H, 3·20; N, 14·77. Calc. for $C_{14}H_9O_4N_3$: C, 59·36; H, 3·20; N, 14·84%).

2 - *Isopropyl* - 3 - *p* - *methoxybenzoylquinoxaline* - 1,4 - *dioxide* (**7p**) *and* 2 - *p* - *methoxyphenyl* - 3 - *isobutyrylquinoxaline* - 1,4 - *dioxide* (**8p**). Precipitation of **7p** (2·02 g, 5 days) was affected by the addition of a few drops of methanol and rubbing the reaction mixture against the sides of the reaction flask, 1·11 g, **7p**, 11 days; 0·51 g, 24 h, **7p** and **8p**; 0·66 g, **7p** and **8p**, one week; 0·20 g, **7p**, 2 weeks. Yield 3·99 g (47%) **7p** to **8p** was 12:1 (NMR). The same reaction, in diethylamine, gave **7p** (23%) only. Repeated TLC on residues from both reactions yielded traces of **7p** (25 mg).

7p, m.p. 195–6° (MeOH-$CHCl_3$). IR ν_{max} 1660, 1588, 1510, 1445, 1365, 1315, 1260, 1163, 1020, 950, 865, 775, 665 cm^{-1}. NMR 1·40 (d, 6H, J = 7 Hz), 3·2 (sep, 1H, J = 7 Hz), 3·9 (s, 3H), 6·93 (m, 2H), 7·83 (m, 4H), 8·50 (m, 2H). (Found: C, 67·24; H, 5·34; N, 8·16. Calc. for $C_{19}H_{18}O_4N_2$: C, 67·44; H, 5·36; N, 8·28%).

2 - *Isopropyl* - 3 - *p* - *methylbenzoylquinoxaline* - 1,4 - *dioxide* (**7q**) *and* 2 - *p* - *methylphenyl* - 3 - *isobutyrylquinoxaline* - 1,4 - *dioxide* (**8q**). 0·91 g, **7q**, one week; 0·59 g, 3 weeks; 0·26 g, **7q** and **8q**, 17 days. Yield 1·76 g (22%) **7q** to **8q** was 7:1 (NMR). TLC on the reaction residue gave 55 mg of **7q** and **8q**. The same reaction, in diethylamine, afforded **7q** in low yield (4%). **7q**, m.p. 172–3 (MeOH-$CHCl_3$). IR ν_{max} 1670, 1605, 1340, 1280, 1185, 1100, 1020, 900, 865, 775 cm^{-1}. NMR 1·41 (d, 6H, J = 7 Hz), 2·40 (s, 3H), 3·18 (sep, 1H, J = 7 Hz), 7·43 (m, 2H), 7·78 (m, 4H), 8·48 (m, 2H). (Found: C, 70·83; H, 5·64; N, 8·67. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·79; H, 5·63; N, 8·69%).

2 - *Isopropyl* - 3 - *p* - *bromobenzoylquinoxaline* - 1,4 - *dioxide* (**7r**), 2 - *p* - *bromophenyl* - 3 - *isobutyrylquinoxaline* - 1,4 - *dioxide* (**8r**), *and* 2 - *p* - *bromophenylquinoxaline* - 1,4 - *dioxide*. 0·71 g, **8r**, 3 h; after 18 days, triethylamine was decanted and the oily residue was rubbed with methanol to yield 2·45 g of a mixture of **7r** and **8r** in a 1:2 ratio (NMR): on long standing (27 days), 0·05 g of 2 - p - bromophenylquinoxaline - 1,4 - dioxide was isolated. Total yield 3·16 g of **7r** and **8r** (1:3). Repeated TLC on the residue of the reaction gave 18 mg of a mixture of **7r** and **8r**. The same reaction was run in diethylamine and **8r** (0·8 g, 7 h) along with 2 - p - bromophenylquinoxaline - 1,4 - dioxide (0·16 g, 7 h) were obtained. **8r** was found to be cleaved to 2 - p - bromophenylquinoxaline - 1,4 - dioxide on treatment with diethylamine.

8r, m.p. 157–8 (MeOH). IR ν_{max} 1710, 1590, 1485, 1340, 1270, 1100, 1040, 1020, 920, 865, 775 cm^{-1}. NMR 0·98 (d, 6H, J = 7 Hz), 2·84 (sep, 1H, J = 7 Hz), 8·00–7·2 (m, 6H), 1·5 (m, 2H). (Found: C, 55·82; H, 4·20; N, 7·38; Br, 20·90. Calc. for $C_{18}H_{15}O_3N_2Br$: C, 55·83; H, 3·90; N, 7·23; Br, 20·64%).

2 - *p* - *Nitrophenyl* - 3 - *isobutyrylquinoxaline* - 1,4 - *dioxide* (**8s**) *and* 2 - *p* - *nitrophenylquinoxaline* - 1,4 - *dioxide*. The reaction was performed on 10 mmole scale. 0·54 g, **8s**, 24 h; 0·32 g, **8s**, 2 days. Yield 0·86 g (24%), and 0·1 g of 2 - p - nitrophenylquinoxaline - 1,4 - dioxide after 3 weeks. TLC of the reaction residue gave 20 mg of **8s**. The latter was found to cleave into 2 - p - nitrophenylquinoxaline - 1,4 - dioxide on treatment with diethylamine. **8s**, m.p. 189° ($CHCl_3$–MeOH). IR ν_{max} 1710, 1600, 1510, 1345, 1270, 1220, 1100, 1045, 920, 850, 770 cm^{-1}. NMR 0·97 (d, 6H, J = 7 Hz), 3·0 (sep, 1H, J = 7 Hz), 7·75 (m, 4H), 8·35 (m, 4H). (Found: C, 61·15; H, 4·19; N, 11·87. Calc. for $C_{18}H_{15}O_5N_3$: C, 61·19; H, 4·28; N, 11·89%).

2 - *p* - *Methoxyphenyl* - 3 - *pivalylquinoxaline* - 1,4 - *dioxide* (**8t**). 0·33 g, **8t**, 3 days; 0·91 g, **8t**, 6 days; 0·53 g, **8t**, 10 days, and 1·44 g, **8t**, 6 weeks. Yield 3·21 g (37%). The same reaction, in diethylamine, gave 2·91 g (33%) of **8t**. TLC of the reaction residue gave traces (16 mg) of **8t** and none of **7t**. **8t**, m.p. 182–3° (MeOH). IR γ_{max} 1710, 1610, 1500, 1335, 1280, 1265, 1185, 1090, 1025, 910, 890, 830, 800, 775, 620 cm^{-1}. NMR 0·99 (s, 9H), 3·79 (s, 3H), 6·91 (m, 2H), 7·42 (d, 2H, J = 8·5 Hz), 7·78 (m, 2H), 8·48 (m, 2H). (Found: C, 67·94; H, 5·82; N, 7·98. Calc. for $C_{20}H_{20}O_4N_2$: C, 68·17; H, 5·72; N, 7·95%).

2 - *p* - *Methylphenyl* - 3 - *pivalylquinoxaline* - 1,4 - *dioxide* (**8u**). The reaction was performed on a 10 mmole scale. 0·25 g, **8u**, 4 days; 0·5 g, **8u**, 5 days; 0·63 g, **8u**, 3 weeks. Yield 1·38 g (41%). The same reaction was run in diethylamine and **8u** (36%) was the only di-*N*-oxide. TLC of the residues of both reactions gave traces of **8u** only. **8u**, m.p. 192–3° (MeOH). IR ν_{max} 1700, 1600, 1500, 1335, 1275, 1095, 1055, 1025, 905, 890, 820, 800, 780, 670 cm^{-1}. NMR 0·98 (s, 9H), 2·39 (s, 3H), 7·28 (m, 4H), 7·63 (m, 2H), 8·46 (m, 2H). (Found: C, 71·34; H, 6·04; N, 8·06. Calc. for $C_{20}H_{20}O_3N_2$: C, 71·41; H, 5·99; N, 8·33%).

2 - *p* - *Bromophenyl* - 3 - *pivalylquinoxaline* - 1,4 - *dioxide* (**8v**). The reaction was performed on a 15 mmole scale. 0·69 g, **8v**, 24 h; 0·60 g, **8v**, 24 h; 1·32 g, **8v**, one week; 1·0 g, **8v**, 3 weeks. Yield 3·70 g (62%). The same reaction, in diethylamine, gave **8v** (39%). TLC on the reaction residue gave no traces of any di-*N*-oxide. **8v**, m.p. 214 (MeOH-$CHCl_3$). IR ν_{max} 1700, 1595, 1480, 1335, 1285, 1090, 1070, 1015, 910, 890, 820, 780 cm^{-1}. NMR 0·99 (s, 9H), 7·62 (m, 6H), 8·47 (m, 2H). (Found: C, 56·63; H, 4·28; N, 6·92; Br, 19·99. Calc. for $C_{19}H_{17}O_3N_2Br$: C, 56·87; H, 4·27; N, 6·98; Br, 19·92%).

2 - *o* - *Methoxyphenyl* - 3 - *pivalylquinoxaline* - 1,4 - *dioxide* (**8w**). The reaction was performed on a 5 mmole scale. 0·83 g, **8w**, 2 weeks; 0·25 g, **8w**, 3 weeks. Yield 1·08 g (61%). The same reaction was run in diethylamine and yielded 0·83 g (47%) of **8w**. TLC of the residue gave 30 mg of **8w** and no **7w**. **8w**, m.p. 207–208° (MeOH). IR ν_{max} 1700, 1600, 1500, 1475, 1340, 1255, 1090, 1053, 1025, 910, 890, 770, 670 cm^{-1}. NMR 1·00 (s, 9H), 3·76 (s, 3H), 7·15 (m, 4H), 7·73 (m, 2H), 8·44 (m, 2H). (Found: C, 68·15; H, 5·93; N, 8·22. Calc. for $C_{20}H_{20}O_4N_2$: C, 68·17; H, 5·72; N, 7·95%).

2,3 - *Dimethylquinoxaline* - 1,4 - *dioxide* (**12**). A solution of benzofurazan oxide (25 mmole) and diketone **11b**[9] in diethylamine (20 ml) was allowed to stand at room temperature for 20 h. The title compound was collected as a yellow solid (26% yield). Evaporation of the mother-liquor and steam distillation on the residue gave *N,N*-diethylbenzamide, m.p. 48° (MeOH). The same reaction was performed with **11a** as the diketone and **12** was isolated in 52% yield. The identity of **12** was established by comparison with an authentic sample prepared from benzofuran oxide and 2-butanone in diethylamine (73% yield). **12**, m.p. 192–3° ($CHCl_3$-hexane) (lit.[10] 181–3°). IR ν_{max} 1600, 1515, 1370, 1315, 1100, 820, 785, 640 cm^{-1}. (Found: C, 63·20; H, 5·26; N, 14·73. Calc. for $C_{10}H_{10}O_2N_2$: C, 63·15; H, 5·20; N, 14·73%).

1 - *Hydroxy* - 3 - *methyl* - 2 - *quinoxalinone* - 4 - *oxide* (**13**). Benzofurazan oxide and an equimolar amount of **11c**[11] were dissolved in diethylamine. The mixture was allowed to stand at room temperature for 5 h and the precipitated brown solid (**13**, as diethylammonium salt) was collected and washed with diethylamine. Yield 15%, m.p. 145–150°. IR γ_{max} 3400, 1600, 1330, 1230, 1065, 950, 850, 760 cm^{-1}. NMR 1·3 (t, 6H), 2·6 (s, 3H), 2·9 (q, 4H), 7–8·4 (m, 4H), 9·35 (s, 2H). When a sample of this salt was heated at 90° for 24 h, it lost diethylamine to give **13**,[10] m.p. 230° (EtOH). IR γ_{max} 2650, 1640, 1590, 1330, 1255, 1220, 1110, 1050, 770, 740, 710 cm^{-1}. NMR (DMSO-d_6) 2·2 (s, 3H), 7–8 (m, 4H). (Found: C, 56·46; H, 4·29; N, 14·58. Calc. for $C_9H_8O_3N_2$: C, 56·25; H, 4·20; N, 14·58%). Compound **13** (which could also be obtained from its diethylammonium salt by acidification) gave a deep red color with iron(III) chloride in methanol, was converted by warm acetic anhydride into an N-acetoxy derivative with a characteristic IR band at 1800 cm^{-1}, and could be deoxygenated by sodium dithionite to give 3-methyl-2-quinoxalinone of known structure.[12]

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