The Reactions of Benzofurazan 1-Oxides with Enamines

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Novel quinoxaline 1,4-dioxides are readily obtained from the reactions of benzofurazan 1-oxide and its derivatives with enamines. A general discussion of the reaction is presented.

We have previously published a brief report [1] of the reaction of benzofurazan 1-oxide (Ia) (BFO) with enamines to give quinoxaline 1,4-dioxides. The versatility of this reaction has since been demonstrated by the finding that a variety of systems related to enamines react readily with BFO giving, in one step, products that are difficult to obtain by other methods: substituted quinoxaline 1,4-dioxides (from BFO and 1,3-dicarbonyl compounds);[2] phenazine di-*N*-oxides (from BFO and phenols);[3] and benzimidazole oxides (from BFO and aliphatic nitro-compounds).[3] We now present a general discussion and experimental details of the reaction of enamines with substituted benzofurazan 1-oxides; a few data have been included on the reaction of the latter with 1,3-diketones.

The benzofurazan 1-oxides were prepared by oxidation of the appropriate *o*-nitroanilines, with hypochlorite or by pyrolysis of the corresponding nitrophenyl azides (Table).† A variety of enamines react satisfactorily, but the less reactive morpholine enamines give higher yields and more easily isolable products.

In general, the BFO was dissolved in a suitable solvent (usually warm methanol) and the enamine was added in small portions to the stirred solution. A deep red colouration was produced and the solution became warm. The quinoxaline 1,4-dioxides, some of which precipitated within a few minutes, were obtained after cooling the mixture overnight. The yellow products (yields 50–90%) displayed strong i.r. absorption in the 1320 cm^{-1} region, attributable to the *N*-oxide function.

Of the enamines used, 1-morpholinocyclopent-1-ene (II; $n = 5$) reacted most readily, and 1-morpholino-1-phenylethylene (III) least readily. This order of reactivity is probably related to steric and electronic factors affecting the overlap between the nitrogen lone electron pair and the double bond of the enamine. In the enamine derived from cyclopentanone this overlap is enhanced because it establishes a double bond exocyclic to a five-membered ring.[4] Benzofurazan oxides reacted with this enamine so readily that cooling was necessary to control the reaction; in fact, with the highly

† The possibility of tautomerism leads to ambiguities in the nomenclature of compounds of this series. Thus, 5-chloro- and 6-chloro-benzofurazan 1-oxide are interconvertible and cannot be isolated separately at normal temperatures. To avoid ambiguity, such compounds are referred to in this paper with both numbers, the larger number in parentheses, *e.g.*, 5(6)-chlorobenzofurazan 1-oxide (see A. J. Boulton and P. B. Ghosh, *Adv. Heterocyclic Chem.*, 1969, **10**, 5).

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[2] (*a*) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, 1966, **31**, 4067; (*b*) K. Ley, F. Sang, U. Eholzer, R. Nast, and R. Schubert, *Angew. Chem. Internat. Edn.*, 1969, **8**, 596.

[3] J. D. Johnston, M. Abu-el-Haj, E. Abushanab, B. W. Dominy, J. W. McFarland, C. H. Issidorides, and M. J. Haddadin, (*a*) IUPAC Meeting, London, July 1968, Abstracts, H 4, 437; (*b*) A.C.S. 156th National Meeting, Atlantic City, September 1968, Abstracts, MEDI 015.

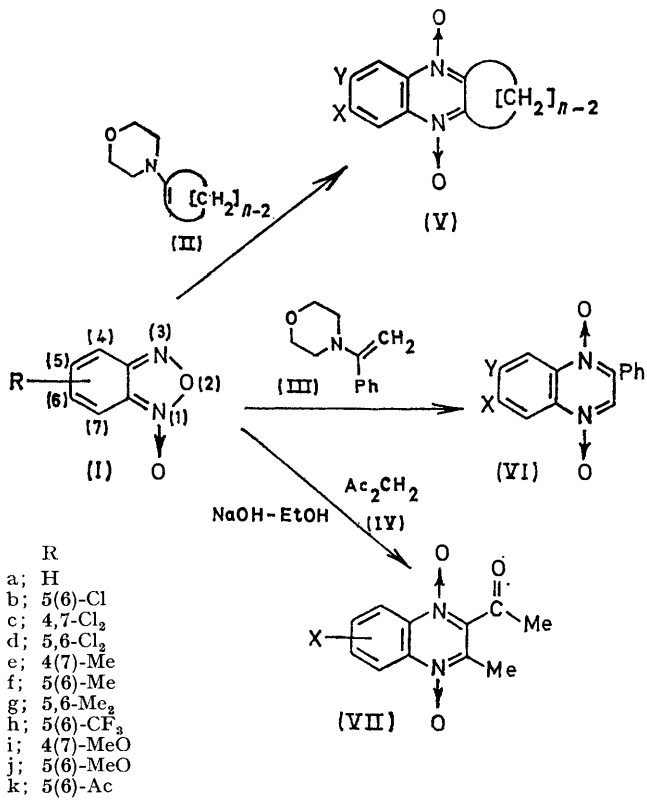
[4] H. C. Brown, J. H. Brewster, and H. Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467; H. C. Brown, *J. Org. Chem.*, 1957, **22**, 439.

Reactions of BFO and derivatives with enamines and with pentane-2,4-dione

Starting materials	Reaction solvent	Product	X	Y	n	M.p. (°C)	Cryst. from	Yield (%)	Formula	Found (%) C	H	N	Cl(F)	Required (%) C	H	N	Cl(F)
(If),a,b (II)	MeOH	(Va)	Me	H	5	168—171	MeOH–PhH	52	$C_{12}H_{12}N_2O_2$	66·7	5·7	12·8		66·7	5·6	13·0	
(Ig),c (II)	Me_2SO–MeOH	(Vb)	Me	Me	5	198—202	PhH	78	$C_{13}H_{14}N_2O_2$	67·7	6·2	12·2		67·8	6·1	12·2	
(Ij),a,b (II)	MeOH	(Vc)	MeO	H	5	183—185	MeOH–PhH	65	$C_{12}H_{12}N_2O_3$	62·1	5·3	12·0		62·1	5·2	12·1	
(Ib),a,b (II)	MeOH	(Vd)	Cl	H	6	188—192 d	MeOH–PhH	52	$C_{12}H_{11}ClN_2O_3$	57·5	4·4	11·0	14·0	57·5	4·4	11·2	14·1
(Id),c (II)	MeOH	(Ve)	Cl	Cl	6	203—205	MeOH–PhH	48	$C_{12}H_{10}Cl_2N_2O_2$	50·6	3·6	9·7	24·8	50·6	3·5	9·8	24·9
(If),a,b (II)	MeOH	(Vf)	Me	H	6	212—214 e	MeOH–PhH	79	$C_{13}H_{14}N_2O_2$	67·7	6·1	12·3		67·8	6·1	12·2	
(Ig),c (II)	MeOH	(Vg)	Me	Me	6	215—216	MeOH–PhH	70	$C_{14}H_{16}N_2O_2$	69·0	6·6	11·2		68·8	6·6	11·5	
(Ih),f (II)	MeOH	(Vh)	CF_3	H	6	183—185	MeOH		$C_{13}H_{11}F_3N_2O_2$	55·1	3·9	10·0	20·2	54·9	3·9	9·9	20·1
(Ij),a,b (II)	MeOH	(Vi)	MeO	H	6	205—208 g	MeOH–PhH	49	$C_{13}H_{14}N_2O_3$	63·4	5·7	11·3		63·4	5·7	11·4	
(Ik),h (II)	MeCN	(Vj)	Ac	H	6	189—191	MeCN	27	$C_{14}H_{14}N_2O_3$	65·3	5·4	10·9		65·1	5·5	10·9	
(Ia),i (II)	MeOH	(Vk)	H	H	7	172—174 j	MeOH–PhH	65	$C_{13}H_{14}N_2O_2$	67·7	6·0	12·3		67·8	6·1	12·2	
(Ib),a,b (II)	MeOH	(Vl)	Cl	H	7	175—176	MeOH–PhH	84	$C_{13}H_{13}ClN_2O_3$	59·1	4·9	10·6	13·4	59·0	5·0	10·6	13·4
(Id),c (II)	MeOH	(Vm)	Cl	Cl	7	197—198	$CHCl_3$	87	$C_{13}H_{12}Cl_2N_2O_2$	52·2	4·1	9·4	23·9	52·2	4·0	9·4	23·7
(If),a,b (II)	MeOH	(Vn)	Me	H	7	163—164	MeOH	82	$C_{14}H_{16}N_2O_2$	68·9	6·6	11·5		68·8	6·6	11·5	
(Ig),c (II)	MeOH	(Vo)	Me	Me	7	215—217	MeOH–PhH	75	$C_{15}H_{18}N_2O_2$	69·7	7·0	10·5		69·7	7·0	10·9	
(Ij),a,b (II)	MeOH	(Vp)	MeO	H	7	174—176	MeOH–PhH	77	$C_{14}H_{16}N_2O_3$	64·7	6·2	10·8		64·6	6·2	10·8	
(Ia),i (II)	MeOH	(Vq)	H	H	8	169—171	CF_3CO_2H–PhH–MeOH	80	$C_{14}H_{16}N_2O_2$	68·9	6·7	11·3		68·8	6·6	11·5	
(Ib),a,b (II)	MeOH	(Vr)	Cl	H	8	142—146	MeOH–PhH	71	$C_{14}H_{13}ClN_2O_3$	60·5	5·5	10·1	12·8	60·3	5·5	10·1	12·7
(Id),c (II)	MeOH	(Vs)	Cl	Cl	8	201—203	CF_3CO_2H–MeOH	71	$C_{14}H_{14}Cl_2N_2O_2$	53·8	4·7	8·8	22·5	53·7	4·5	9·0	22·6
(Ig),c (II)	MeOH	(Vt)	Me	Me	8	197—199	MeOH–PhH	90	$C_{16}H_{20}N_2O_2$	70·5	7·5	10·3		70·6	7·4	10·3	
(Ij),a,b (II)	MeOH	(Vu)	MeO	H	8	206—207	CF_3CO_2H–MeOH–PhH	90	$C_{15}H_{18}N_2O_3$	65·7	6·7	10·2		65·7	6·6	10·2	
(Ib),a,b (III)	MeOH	(VIa)	Cl (or H)	H (or Cl)		216—220	CF_3CO_2H–MeOH	39	$C_{14}H_9ClN_2O_2$	61·8	3·5	10·3	13·2	61·7	3·3	10·3	13·0
(Id),c (III)	MeOH	(VIb)	Cl	Cl		249—251	CF_3CO_2H–MeOH	50	$C_{14}H_8Cl_2N_2O_2$	54·6	2·8	9·0	23·2	54·7	2·6	9·1	23·1
(Ie),k (IV)	EtOH l	(VIIa)	5- (or 8-) Me			169—170	$CHCl_3$–C_6H_{14}	2·4	$C_{12}H_{12}N_2O_3$	62·0	5·3	12·1		62·1	5·2	12·1	
(Ig),c (IV)	EtOH m	(VIIb)	6,7-Me_2			200—202	$CHCl_3$–C_6H_{14}	64	$C_{13}H_{14}N_2O_3$	63·7	6·0	12·1		63·4	5·7	11·4	
(Ih),f (IV)	EtOH m	(VIIc)	6- (or 7-) CF_3			152—153	PrⁱOH	6·5	$C_{12}H_9F_3N_2O_3$	50·6	3·3	9·8		50·4	3·2	9·8	
(Ih),f (IV)	EtOH m	(VIId)	7- (or 6-) CF_3			167—168	$CHCl_3$–C_6H_{14}	2·4	$C_{12}H_9F_3N_2O_3$	50·5	3·2	9·7		50·4	3·2	9·8	

a K. H. Pausacker and J. E. Scroggie, *J. Chem. Soc.*, 1954, 4499. b R. J. Gaughram, J. P. Picard, and J. V. R. Kaufman, *J. Amer. Chem. Soc.*, 1954, **76**, 2233. c F. B. Mallory, S. L. Manath, and C. S. Wood, *J. Amer. Chem. Soc.*, 1965, **87**, 5433. d J. K. Landquist, *J. Chem. Soc.*, 1956, 2551 [m.p. 186—188° (EtOH)]. e Ref. *d* [m.p. 208—210° (EtOH)]. f Liquid product was not analysed but used directly in the preparation of compounds (Vb), (VIIc), and (VIId). G.l.c. indicated product was approximately 90% pure. g Ref. *d* [m.p. 204—206° (EtOH)]. h Calc.: C, 53·9; H, 3·4; N, 15·7. Found: C, 54·1; H, 3·5; N, 16·1%. This compound, as well as compound (Ib), was prepared by the general method described by P. A. S. Smith and J. H. Boyer, *Org. Synth.*, 1963, Coll. Vol. IV, p. 75. i F. B. Mallory, *Org. Synth.*, 1963, Coll. Vol. IV, p. 74. j Ref. *d* [m.p. 172—173° (PhH)]. k T. Zincke and P. Schwarz, *Annalen*, 1899, **307**, 28. l Reaction time 216 h; temp. 40°. m Reaction time 24 h; temp. 25°.

reactive 5(6)-chlorobenzofurazan-1-oxide (Ib) and 5,6-dichlorobenzofurazan 1-oxide (Id), reaction with this enamine at −5 °C led to tars from which no definite product could be isolated. On the other hand, the degree of overlap between the nitrogen lone pair and the double bond is decreased in the enamine derived from acetophenone because of the bulk of the phenyl group and the competing cross conjugation with the aromatic ring. This enamine reacted sluggishly with BFO,[1] but responded readily to the more reactive derivatives (Ib and d).



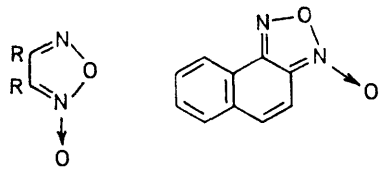
The reaction of BFO with enamines formally involves a 1,4-cycloaddition, followed by steps leading to a fully heteroaromatic system. The possibility that the initial step is a four-centre addition reaction of the Diels–Alder type is ruled out by the observation that BFO does not react with tetracyanoethylene and other dienophiles. The reaction with enamines is closely related to that with enolate anions,[2] in that the former entails attack by the β-carbon atom of the enamine and deamination, whereas the latter entails attack by a carbanion (enolate) and dehydration. Recently, Mason and Tennant demonstrated that carbanions attack BFO at N-3,[5] and one of us proposed 2,3-dihydroquinoxaline 1,4-dioxides as likely intermediates in the reaction between BFO and enamines.[6] A major factor contributing to the reactivity of BFO is apparently the gain in resonance energy associated with the developing benzenoid ring during the first stage of the reaction.* In support of this premise is the observation that the BFO analogues (VIII) and (IX) (for which this factor is not operating) or (X) (for which it is of lesser significance) do not react with enamines. Interestingly, but not unexpectedly, 6-chloro-2-phenylbenzotriazole oxide (XI), a nitrogen analogue of 5(6)-chlorobenzofurazan 1-oxide, also failed to react with both 1-morpho-

* See mechanisms proposed in refs. 2*a* and 6.

[5] J. C. Mason and G. Tennant, *Chem. Comm.*, 197[illegible] 9€

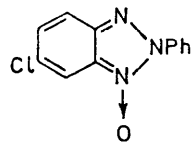
[6] J. W. McFarland, *J. Org. Chem.*, 1971, **36**, 1842.

linocyclopent-1-ene and 1-morpholinocyclohex-1-ene. In this case, reaction would not lead to stable heteroaromatic *NN*-dioxide products.



(VIII) R = Me
(IX) R = Ph

(X)



(XI)

In principle the reaction of a monosubstituted BFO with 1-morpholino-1-phenylethylene or with pentane-2,4-dione should give two isomeric products. This situation has been realized in the reaction of 5(6)-trifluoromethylbenzofurazan 1-oxide (Ih) with the dione: the isomeric quinoxaline 1,4-dioxides (VIIc and d) were isolated in low yield after fractional crystallization. On the other hand, the reaction of 5(6)-chlorobenzofurazan oxide (Ib) with 1-morpholino-1-phenylethylene appears to give a single product (VIa), as shown by t.l.c.

Whereas BFO and its 5(6)-monosubstituted and 5,6-disubstituted congeners react rapidly at room temperature with many enamines, the 4(7)-monosubstituted and 4,7-disubstituted derivatives react much more sluggishly. In fact compounds (Ic, e, and i) did not react with enamines at room temperature even during several hours. Nevertheless, certain normal reaction products can be obtained provided a sufficiently long reaction period is used or the reaction mixture is heated. Compound (VIIa), for instance, is produced under more severe conditions than those employed for BFO or its 5(6)-substituted and 5,6-disubstituted congeners. The greatly reduced reactivity of the 4-substituted or 4,7-disubstituted derivatives is probably due to repulsive interactions between the 1- (or 4-) oxide and the 8- (or 5-) substituents on the developing quinoxaline system. There is, however, a notable exception to the retarding effect of 4(7)-substituents: nitro-substituted derivatives, regardless of the position of the nitro-group [4(7)-, 5(6)-, or 4,6-], react vigorously with enamines giving unstable products. Although none of these products have been characterized, spectral and analytical data suggest that they are probably not quinoxalines or related materials. Mallory has reported [7] that nitrobenzofurazan oxides undergo some remarkable ring substitution reactions. It is probable, therefore, that the reaction of enamines with nitrobenzofurazan oxides follows a course other than that leading to quinoxaline 1,4-dioxides.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer model 257 spectrophotometer. Analyses were performed by F. Pascher Mikroanalytisches Laboratorium, Bonn, Germany. The preparation of enamines from morpholine and the appropriate ketone was based on the method described for 1-morpholinocyclohex-1-ene.[8] M.p.s were determined on a Fisher–Johns apparatus. Many of the products melted with decomposition over a wide range, even when analytically pure. The following two examples illustrate the general procedure.

6,7,8,9,10,11-*Hexahydrocyclo-octa*[b]*quinoxaline* 5,12-*Dioxide* (Vq).—To a warm solution of BFO (Ia) (2·7 g, 0·02 mol) in methanol (25 ml), 1-morpholinocyclo-oct-1-ene (4·5 g, 0·023 mol) was added in small portions with shaking. The mixture was cooled overnight and the precipitate (4·0 g, 80%) collected by suction filtration; m.p. 170—172° Three recrystallizations from trifluoroacetic acid–methanol–benzene gave *material* of m.p. 169—171°; $\nu_{max.}$ (Nujol) 1350, 1323, 1309, 1205, 1098, 1050, 1035, 982, 854, and 771 cm^{-1}.

2-*Acetyl*-3,6,7-*trimethylquinoxaline* 1,4-*Dioxide* (VIIb).—A solution containing 5,6-dimethylbenzofurazan 1-oxide (Ig) (16·4 g, 0·1 mol), pentane-2,4-dione (12·0 g, 0·12 mol), 10N-sodium hydroxide (1·0 ml), and ethanol (100 ml) was stirred overnight at room temperature. A thick precipitate was collected (24·5 g), m.p. 183—185° (decomp.). One recrystallization from chloroform–hexane gave *material* (15·8 g, 64%) of m.p. 200—202°.

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[7] F. B. Mallory and S. P. Varimbi, *J. Org. Chem.*, 1963, **28**, 1656.

[8] S. Hunig, E. Lucke, and W. Brenninger, *Org. Synth.*, 1961, **41**, 65.