Preparation of 1,2-Benzisoxazole 2-Oxides

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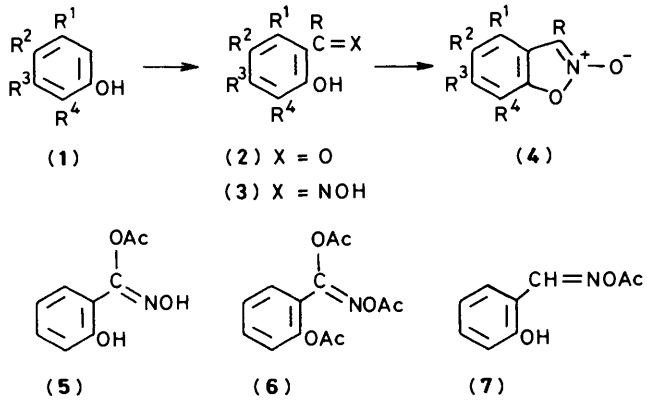
1,2-Benzisoxazole 2-oxides are prepared by the oxidative cyclisation of *o*-acylphenol oximes, using either lead(IV) acetate or sodium hypochlorite. The scope and limitations of the reaction are discussed.

In a recent communication [1] we reported preliminary results on the synthesis of the 1,2-benzisoxazole (indoxazene) 2-oxide system (**4**). This was effected by oxidative cyclisation of *o*-acylphenol oximes (**3**) using lead (IV) acetate (Scheme 1). In this paper we present a fuller account of these preparations, and give details of modifications, which in some cases are more convenient than the methods originally applied.

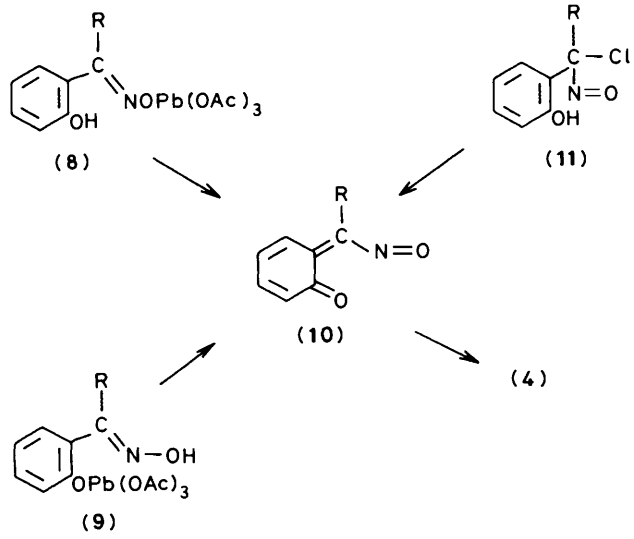


Scheme 1. For specification of R–R^4, see the Table

The *o*-acylphenols (**2**) were either commercial products or were prepared from the phenols (**1**) by standard methods. Oxime formation [2] could have produced either or both of the possible stereoisomers. As a rule, we have no evidence as to the form adopted by our products (**3**), except in those cases where the oximes were re-formed by reduction of the oxide (**4**),[3] and which were presumably *E* and were identical with those formed from the ketones; also the oxime (**3a**) was examined by high resolution ^{13}C n.m.r. spectroscopy; the ^{13}C–$^{13}C(H_3)$ one-bond coupling was consistent with the *E*-rather than the *Z*-configuration (N lone-pair opposite rather than on the same side as the methyl group).[4] In any case, from a consideration of the mechanism of the oxidation (see later), it seems likely that the configuration of the oximes is unimportant.

The first experiments on the oxidation of the oximes (**3**) were conducted using lead (IV) acetate in diethyl ether. Fair (50—70%) yields of the oxides (**4**) (after recrystallisation) were obtained from the oximes (R—R^4 = Me, Et, Ph). Attempts to isolate the unsubstituted compound (**4**; R—R^4 = H) by this method were all unsuccessful; instead, the three acetylated compounds (**5**)—(**7**) were identified, the last two being found only in small amounts. Their formation is not unexpected in view of the known [5] capacity of the reagent to act as an acetoxylating and/or acetylating agent as well as an oxidant. We later found that sodium hypochlorite was just as effective (and considerably cheaper), in the oxidation of the oximes, and, using this reagent, a very small amount (1%) of the parent *N*-oxide (**4**; R = H) was isolated and partially characterised, from salicylaldehyde oxime. However, despite numerous attempts we have been unable to repeat this preparation.

The oxidation of a variety of phenolic compounds by lead (IV) acetate has been discussed by Criegee,[6] who proposed a mechanism involving an organolead intermediate formed in either a cyclic or an acyclic transition state. Two possibilities (**8**) and (**9**) may exist for the analogous intermediate in the case of the reaction of the oximes (**3**); either may break down to acetic acid, lead(II) acetate, and the nitroso quinonemethide (**10**), which would cyclise to the benzisoxazole oxide (**4**). If this pathway is followed, the oxime configuration would seem to be unimportant.



In the hypochlorite oxidation, the oxime may be *C*-chlorinated, to form compound (**11**), or a phenolic hypochlorite may be produced. In either case, loss of HCl would generate compound (**10**) and thus the *N*-oxide. A variety of other oxidising agents have been tried, but to date the only successes have been achieved using phenyl iodosodiacetate,[7] and by electrochemical oxidation in acetic acid, at a lead anode.[8] In the electrochemical experiments quantitative conversions were never achieved, and the separation of the products from the starting oximes was troublesome.

The Table lists the ketones and the oximes used in this study, and yields and melting points of the benzisoxazole oxides prepared by the oxime oxidations.

The mass spectra of the oxides show prominent parent ions, usually weak ($P^+ - 16$), and strong ($P^+ - 30$) fragments. Details of these spectra are presented elsewhere.[9] The ^1H n.m.r. spectra show the expected patterns. Oxidation of oximes (**3**; R = Me) to the 3-methylbenzisoxazole oxides (**4**; R = Me)

Table. Ketones (**2**), oximes (**3**), and 1,2-Benzisoxazole oxides (**4**)

No.	R	R^1	R^2	R^3	R^4	Ref. to (**2**)	M.p. of (**3**) (°C)	Lit. m.p. (°C) (ref.)	M.p. of (**4**) (°C)	Yield of (**4**) (%)	Method[a]
a	Me	H	H	H	H	*b*	116	117 (14)	96	60 (55)	A (B)
b	Me	H	Br	H	H	15	172		117	70	B
c	Me	H	Br	H	Br	16	211	201 (17)	89	70 (68)	A (B)
d	Me	H	Cl	H	H	18	216	218 (18)	133	65	A
e	Me	H	Me	H	H	19	143—4	144 (17)	74	60	A
f	Me	H	NO_2	H	H	20	230—231	131 (21)	176	50 (53)	A (B)
g	Me	H	NO_2	H	NO_2	20	239		198—201	40	B
h	Me	H	H	OMe	H	*b*	159—161	123 (22)	132—135	20[c]	B
i	Et	H	H	H	H	*b*	93—94	94 (23)	37	50	A
j	Et	H	NO_2	H	H	24	88—90	90 (20)	125	80	A
k	Ph	H	H	H	H	*b*	142—143	143 (25)	90	80 (76)	A (B)
l	Ph	H	Cl	H	H	26	145	145 (2)	150	60	A
m	Ph	H	Me	H	H	27	140—141	141 (28)	90	70 (69)	A (B)
n	Ph	H	H	OMe	H	*b*	167—169		120	65	B
p	Ph	H	Br	H	Br	29	198—200	175 (29)	178	70	B
q	Me	Me	H	Me	H	*b*	190—191	191 (14,28)	118·5—120	0[d]	A, B

[a] See the Experimental section. [b] Commercially available. [c] Repeated recrystallisation was necessary to obtain acceptable purity. [d] Isolated by oxidation with phenyl iodosodiacetate of the oxime (**3q**).[10]

results in a *ca.* 0.1 p.p.m. downfield shift of the methyl group signal. The ^{1}H n.m.r. spectrum of 3-methyl-1,2-benzisoxazole (in $CDCl_3$) showed the methyl signal at δ 2.50, a further 0.1 p.p.m. downfield of that of the *N*-oxide.[10] In the ^{13}C n.m.r. spectrum, C-3 in the methyl derivative (**4a**) appeared at δ 118 p.p.m.; in 1,2-benzisoxazole C-3 is reported at 147 p.p.m.,[11] and in the 3-methyl compound it is found at 155 p.p.m. (in $CDCl_3$).[10] The ^{1}H and ^{13}C n.m.r. spectra of these compounds will be reported in detail elsewhere.

In the i.r. spectra, two absorptions of very high intensity were observed. The first appeared as a relatively broad envelope or as a group of discrete bands in the range 1570—1615 cm^{-1}; the second was in the range 1200—1240 cm^{-1}. Although the latter band is in the region (1200—1300) commonly assigned to *N*-oxide stretching vibrations,[12] it is at its lower end, and since it has been found that the indoxazene oxides have an unusually short N–O(exocyclic) bond,[13] its assignment to this mode of vibration is not secure.

Experimental

All n.m.r. spectra were taken in $CDCl_3$. The ^{1}H spectra were obtained with a JEOL PMX60 instrument. The high-resolution ^{13}C measurements on the oxime (**3a**) were conducted at 67.8 MHz.

o-*Acylphenols* (**2**).—These were prepared either by Friedel-Crafts reaction or Fries rearrangement from the corresponding phenols or their esters, respectively (Table), or were commercially available.

o-*Acylphenol Oximes* (**3**).—These were in all cases obtained following the method of Walker and Smith,[2] and were characterised by i.r. spectroscopy, elemental analysis, and melting point. *Oxime* (**3a**) ^{13}C n.m.r.: 8.29 (*J* 42.1 Hz to C=NOH), 114.25, 116.43, 116.74, 125.30, 127.67, 155.03, and 155.15.

1,2-*Benzisoxazole 2-Oxides* (**4**).—*Method A: Using lead* (IV) *acetate.* The oxime (1 mol) in dry ether was cooled to 0 °C, and powdered lead (IV) acetate (1.2 mol) was then added over 10 min with vigorous stirring. Stirring was continued for a further 24 h at room temperature, when the precipitated lead(II) acetate was removed by filtration and extracted with ether. The combined ether portions were filtered through anhydrous sodium sulphate, the solvent was removed under reduced pressure, and the residue was recrystallised from ethanol. Addition of a little water, before the filtration stage, to precipitate lead(IV) oxide, was sometimes found to be advantageous.

Method B: Using sodium hypochlorite. To the oxime (1 mol) in ether, cooled in ice–water, was slowly added a solution of sodium hypochlorite (commercial grade: 5% Cl_2; 1.2 mol) with vigorous stirring. After the addition was complete stirring was continued for 24 h, during which time the reaction was allowed to warm to room temperature. The ether layer was separated and dried, and worked up as in method A. Alternatively, the phenolic oxime was dissolved in water containing the minimum of sodium hydroxide to effect solution, and sodium hypochlorite (1.2 mol) was added slowly, with cooling to 0 °C and stirring. The benzisoxazole oxide separated and was recovered by filtration.

The Table lists the benzisoxazole oxides prepared by the methods described above. All gave satisfactory analytical data; these are listed and the list deposited as a supplementary publication [Sup. No. 56612 (2 pp)].* Spectral data for the products are listed in brief below.

3-*Methyl*-1,2-*benzisoxazole* 2-*oxide* (**4a**): $\nu_{max.}$($CHBr_3$) 1 615sh, 1 590s, and 1 215s cm^{-1}; δ_H 7.10—7.50 (m, 4 H) and 2.37 (3 H, s); *m/z* 149 (M^+), 133 ($M^+ - 16$), and 119 ($M^+ - 30$).

5-*Bromo*-3-*methyl*-1,2-*benzisoxazole* 2-*oxide* (**4b**): $\nu_{max.}$(Nujol) 1 605—1 590s, and 1 220s cm^{-1}; H: δ_H 6.84—7.52 (m, 3 H, J_{ortho} 9, J_{meta} 3, J_{para} 0.5 Hz) and 2.35 (3 H, s); *m/z* 229/227 (M^+), 213/211 ($M^+ - 16$), and 199/197 ($M^+ - 30$).

5,7-*Dibromo*-3-*methyl*-1,2-*benzisoxazole* 2-*oxide* (**4c**): $\nu_{max.}$($CHBr_3$) 1 600s and 1 240s cm^{-1}; δ_H 7.5—7.75 (2 H, AB system, J_{meta} 1.8 Hz), and 2.85 (3 H, s); *m/z* 307 (M^+), 291 ($M^+ - 16$), and 277 ($M^+ - 30$).

5-*Chloro*-3-*methyl*-1,2-*benzisoxazole* 2-*oxide* (**4d**): $\nu_{max.}$($CHBr_3$) 1 605s, 1 585s, and 1 210s cm^{-1}; δ_H 7.0—7.4 (m, 3 H, J_{ortho} 10, J_{meta} 2, J_{para} 0.7 Hz) and 2.36 (3 H, s); *m/z* 183 (M^+), 167 ($M^+ - 16$), and 153 ($M^+ - 30$).

3,5-*Dimethyl*-1,2-*benzisoxazole* 2-*oxide* (**4e**): $\nu_{max.}$($CHBr_3$) 1 615sh, 1 590s, and 1 215s cm^{-1}; δ_H 6.9—7.3 (3 H, m, J_{ortho} 10,

* For details of supplementary publications scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans 1*, 1986, Issue 1.

J_{meta} 2, J_{para} 0.8 Hz), 2.40 and 2.37 (2 × 3 H); *m/z* 163 (M^+), 147 ($M^+ - 16$), and 133 ($M^+ - 30$).

3-*Methyl*-5-*nitro*-1,2-*benzisoxazole* 2-*oxide* (**4f**): $\nu_{max.}$($CHBr_3$) 1605s, 1585s, 1525s and 1330s (NO_2), and 1200s cm^{-1}; δ_H 7.2—8.44 (ABX pattern, J_{ortho} 9, J_{meta} 3, J_{para} 0.7 Hz), 2.46 (3 H, s); *m/z* 194 (M^+), 178 ($M^+ - 16$), 164 ($M^+ - 30$).

3-*Methyl*-5,7-*dinitro*-1,2-*benzisoxazole* 2-*oxide* (**4g**): yellow needles; $\nu_{max.}$(Nujol) 1610m, 1550s and 1350s (NO_2), and 1215s cm^{-1}; *m/z* 239 (M^+), 223 ($M^+ - 16$), and 209 ($M^+ - 30$).

6-*Methoxy*-3-*methyl*-1,2-*benzisoxazole* 2-*oxide* (**4h**): $\nu_{max.}$(Nujol) 1605—1595s, 1210s cm^{-1}; δ_H 6.65—7.32 (ABX pattern, J_{ortho} 9, J_{meta} 2, J_{para} 1 Hz, 3.8 (3 H, s), 2.34 (3 H, s); *m/z* 179 (M^+), 163 ($M^+ - 16$), and 149 ($M^+ - 30$).

3-*Ethyl*-1,2-*benzisoxazole* 2-*oxide* (**4i**): $\nu_{max.}$(Nujol) 1600sh and 1585s, and 1200s cm^{-1}; δ_H 7.0—7.5 (4 H, m), 2.85 (q, 2 H, *J* 7 Hz), and 1.33 (t, 3 H, *J* 7 Hz) *m/z* 163 (M^+), 147 ($M^+ - 16$), and 133 ($M^+ - 30$).

3-*Ethyl*-5-*nitro*-1,2-*benzisoxazole* 2-*oxide* (**4j**): $\nu_{max.}$(Nujol) 1615s, 1590s, 1530 and 1345s (NO_2), and 1200s cm^{-1}; δ_H 7.15—8.4 (3 H, m, J_{ortho} 9, J_{meta} 2.8, J_{para} 0.8 Hz), 2.95 (2 H, q, *J* 7 Hz), and 1.40 (3 H, t, *J* 7 Hz); *m/z* 208 (M^+), 192 ($M^+ - 16$), and 178 ($M^+ - 30$).

3-*Phenyl*-1,2-*benzisoxazole* 2-*oxide* (**4k**): $\nu_{max.}$(Nujol) 1600—1560s and 1200s cm^{-1}; δ_H 7.30—7.65 (5 H, m) and 7.82—8.05 (4 H, m); *m/z* 211 (M^+), 195 ($M^+ - 16$), and 181 ($M^+ - 30$).

5-*Chloro*-3-*phenyl*-1,2-*benzisoxazole* 2-*oxide* (**4l**): $\nu_{max.}$($CHBr_3$) 1600s, 1580s, 1570s, and 1205s cm^{-1}; δ_H 7.1—7.7 (3 H, m, J_{ortho} 9, J_{meta} 2, J_{para} 1 Hz) and 7.90—8.1 (5 H, m); *m/z* 245 (M^+), 229 ($M^+ - 16$), and 215 ($M^+ - 30$).

5-*Methyl*-3-*phenyl*-1,2-*benzisoxazole* 2-*oxide* (**4m**): $\nu_{max.}$ 1600sh, 1570s, and 1215 cm^{-1}; δ_H 7.0—7.6 (3 H, m, J_{ortho} 9, J_{meta} 2, J_{para} 1 Hz), 7.95—8.15 (5 H, m), and 2.31 (3 H); *m/z* 225 (M^+), 209 ($M^+ - 16$), and 185 ($M^+ - 30$).

6-*Methoxy*-3-*phenyl*-1,2-*benzisoxazole* 2-*oxide* (**4n**): $\nu_{max.}$ 1600—1580s and 1210s cm^{-1}; δ_H 7.30—7.54 (5 H, m), 6.60—8.0 (3 H, m, J_{ortho} 9, J_{meta} 2.4, J_{para} 0.8 Hz), and 3.8 (3 H, s); *m/z* 241 (M^+), 225 ($M^+ - 16$), and 211 ($M^+ - 30$).

5,7-*Dibromo*-3-*phenyl*-1,2-*benzisoxazole* 2-*oxide* (**4p**): $\nu_{max.}$ 1600—1570s and 1240s cm^{-1}; *m/z* 369 (M^+), 353 ($M^+ - 16$), and 339 ($M^+ - 30$). The product was recrystallised from acetic acid; its insolubility in common solvents prevented its ^1H n.m.r. spectrum being taken.

Oxidation of Salicylaldehyde Oxime (**3**; R = H).—(*a*) Salicylaldehyde oxime was oxidised with lead(IV) acetate according to method A. Upon work-up a greenish viscous oil was obtained, which was separated by t.l.c. on silica [CH_2Cl_2–light petroleum (3:2)]. The most polar product (**5**), R_F 0.1, formed needles, m.p. 124—126 °C (50%); $\nu_{max.}$($CHBr_3$) 3425sh, 3200, and 1760 cm^{-1}; δ_H 7.0—7.18 (4 H, m), 8.85 and 9.75 (2 × 1 H), and 2.30 (3 H, s); *m/z* 195 (M^+). Compound (**6**), R_F 0.2, formed needles, m.p. 148—150 °C (10%); $\nu_{max.}$ 1775 and 1765 cm^{-1}; *m/z* 279 (M^+). Compound (**7**), R_F 0.6, powder (2%), $\nu_{max.}$ 3400 and 1770; *m/z* 179 (M^+), had m.p. 71—73 °C (lit.,[31] m.p. 75 °C).

(*b*) Many attempts were made to oxidise the oxime with hypochlorite, using both variants of method B. On one occasion work-up of the ether layer left, after solvent evaporation, a viscous liquid which deposited colourless plates on standing (1%), m.p. 39—40 °C, *m/z* 135, 119, and 105. From other attempts, using the ether solution method, much starting oxime, and some salicylaldehyde was recovered. Using the alternative technique, large amounts of sticky brown tar were invariably formed; no identifiable products could be isolated from this.

Oxidation of 2-*Hydroxy*-4,6-*dimethylacetophenone Oxime* (**3q**).—This was performed with lead(IV) acetate, according to method A, and a red viscous oil was obtained, showing ill-defined i.r. and ^1H n.m.r. spectra with no characteristic absorptions of the expected *N*-oxide. [Recently, it has been found[10] that the oxide (**4q**) can be obtained by oxidation using phenyl iodosodiacetate].

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