Reactivity of 1,2-Benzisoxazole 2-Oxides

A. J. Boulton * and Petros G. Tsoungas
School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ
Chris Tsiamis
Faculty of Chemistry, University of Thessaloniki, GR-54006 Thessaloniki, Greece

Nitration, bromination, and reaction with acetic anhydride, with halogen acids, and with sodium alkoxide, have been explored in the 1,2-benzisoxazole 2-oxide series. The nitration proceeded by simple substitution; the other reactions took place with rupture of the heterocyclic ring. Deoxygenation to the 1,2-benzisoxazoles could be accomplished, under forcing conditions.

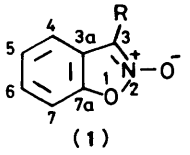
In earlier reports we presented aspects of the synthesis[1] and mass spectra[2] of the 1,2-benzisoxazole 2-oxides, a new class of heterocyclic *N*-oxide. Here we report on some of the chemical reactions of these compounds.

Fundamental to the chemistry of *N*-oxides is their electronic push-pull character. It is evident from a study of the valence-bond formalism of the compounds (**1**) discussed here, that the $=\overset{+}{N}-\overset{-}{O}$ group may exert electron-acceptor properties from the ring positions 3, 4, 6, and 7a, while the same positions may also receive electrons, and at the same time the ring oxygen atom may act as electron-donor to these positions as well as to the complementary positions (2, 3a, 5, 7).

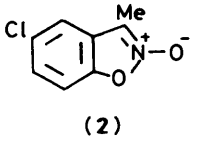
Chiari and Viterbo[3] have determined the molecular dimensions of the 5-chloro-3-methyl derivative (**2**) by *X*-ray crystallography. A very short exocyclic (1.247 Å) and an unusually long endocyclic (1.468 Å) N–O bond was found. These two characteristics are reflected to some extent in the chemical properties which we describe here.

Results and Discussion

3-Methyl- (**3**) and 3-ethyl-1,2-benzisoxazole 2-oxides were readily mononitrated, using mixed acid at 0 °C. From the simple ABX pattern in the ^{1}H n.m.r. spectrum, with one *ortho* coupling constant (8 Hz) only, the substituent had evidently entered at the 5- or the 6-position. Since the products of nitration of the 3-alkyl compounds were different from the 3-alkyl-5-nitro compounds, which had been prepared by oxidation of the corresponding hydroxy-nitroketoximes,[1] their structures were established to be the 6-nitro derivatives, as (**4**).



(1)



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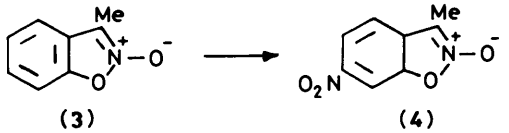
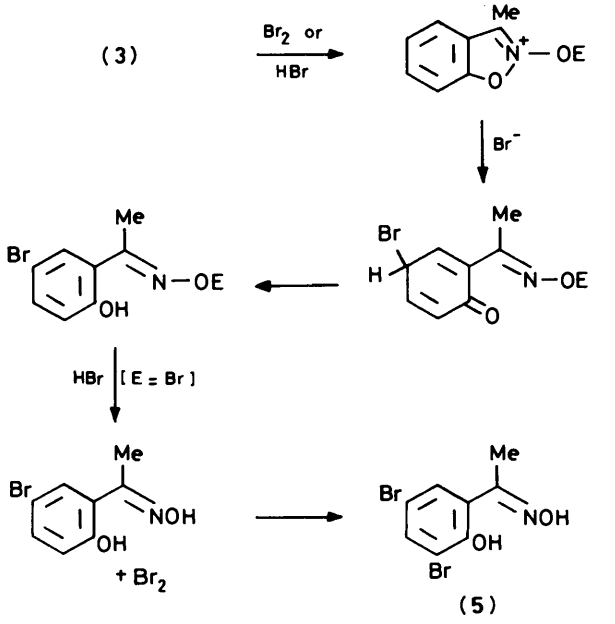


(3) (4)

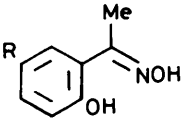
Nitration of 3-methyl-5-nitro-1,2-benzisoxazole 2-oxide (fuming nitric acid, 15 h, 20 °C) gave the 5,7-dinitro compound, which proved identical with the hypochlorite oxidation product of 2-hydroxy-3,5-dinitroacetophenone oxime.[1]

By contrast, bromination (Br_2/CH_2Cl_2 or $Br_2/I_2/CCl_4$) of (**3**) took an unexpected course, providing the dibromo oxime (**5**). A possible explanation is outlined in Scheme 1: the entry of the first halogen, and the cleavage of the heterocyclic ring, are

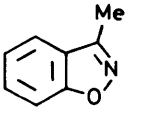


Scheme 1.

brought about by halide ion attack at the benzene ring, activated by complexation at the *N*-oxide group. Bromine is regenerated, and this electrophilically substitutes in the now activated phenol. A similar nucleophilic attack appears to take place on reflux of (**3**) in concentrated hydrochloric acid, to give 2-hydroxy-5-chloroacetophenone [the expected oxime (**6**) is presumably hydrolysed under the reaction conditions]. Hydriodic acid, on the other hand, cleaved the heterocyclic ring reductively, but without substitution. The corresponding product (**7**) was also formed using zinc and HCl.



(6) R = Cl
(7) R = H



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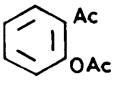


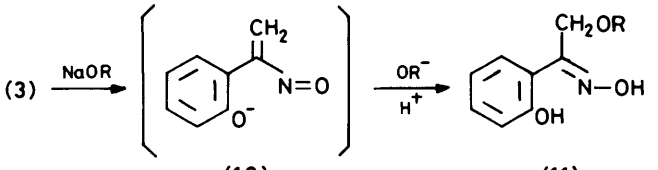
(9)

Treatment with triethyl phosphite effected deoxygenation of (3), to form the benzisoxazole (8), but the conditions required were vigorous (45 h reflux in toluene with a six-fold excess of the reagent). Milder conditions (phosphite in refluxing ethanol), which are usually sufficient to deoxygenate benzofuroxans, were ineffective.

The methylbenzisoxazole oxide (3) was heated to reflux in acetic anhydride for 4 days, during which period slow evolution of brown nitrous fumes was observed. Chromatography of the product yielded 2-acetoxyacetophenone (9) and 3-methyl-1,2-benzisoxazole (8), along with considerable quantities of polymeric material.

Extensive decomposition of the starting material was observed when (3) was treated with phenylmagnesium bromide, but no product was identified. Neither 3-methyl-5- nor 3-methyl-6-nitro-1,2-benzisoxazole 2-oxide underwent the halogeno-alkoxy substitution reaction,[4] using potassium methoxide and sodium hypochlorite.

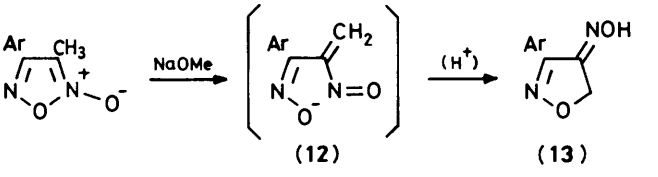
With sodium methoxide or ethoxide, 3-methyl-1,2-benzisoxazole 2-oxide was substituted in the methyl group, with concomitant ring-opening, forming the alkoxymethyl oxime (11) (Scheme 2). This reaction is reminiscent of the Angeli



(10) (11)

Scheme 2.

rearrangement of 3-methylfuroxanes,[5,6] although in the latter case a recyclisation takes place, the products being isoxazole derivatives (Scheme 3). The postulated mechanism of Scheme 3 includes a 5-*endo-trig* cyclisation step, which is not a favoured process, according to Baldwin's rules (or guidelines);[7] nevertheless the product structure (13) is securely based, and an alternative mechanism seems difficult to conceive. Apparently, if the nitroso olefin (10) is an intermediate in the formation of (11), it is more rule-abiding than (12).



(12) (13)

Scheme 3.

Experimental

The preparation of 3-methyl and 3-ethyl-1,2-benzisoxazole 2-oxides, and their corresponding 5-nitro derivatives, were as described earlier.[1] Spectral and analytical procedures were also as earlier stated.[6] Unless otherwise specified, n.m.r. data are for solutions in $CDCl_3$.

3-*Methyl*-6-*nitro*-1,2-*benzisoxazole* 2-*Oxide* (4).—The *N*-oxide (3) (0.6 g, 3 mmol) in conc. sulphuric acid (10 ml) was cooled to 0 °C and stirred vigorously, while conc. nitric acid (*d.* 1.42) and conc. sulphuric acid (molar ratio 1:3; 5 ml) was added dropwise. After addition was complete the reaction was allowed to reach room temperature and stirring was continued for a further 15 min. The mixture was allowed to stand for 30 min and then poured into ice–water. The light brown precipitate of the *nitro-product* (4) was filtered off, washed with water, dried, and recrystallised from ethanol as yellow needles (0.5 g, 65%), m.p. 189 °C. $\nu_{max.}$($CHBr_3$) 1 620w, 1 590s (ring), 1 520s, 1 340s (NO_2), and 1 215s cm^{-1}. ^1H N.m.r.: δ[$(CD_3)_2SO$] 7.78—8.16 (3 H, ABXm, J_o 8.0, J_m 2.0, J_P 1.0 Hz) and 2.38 (3 H, s); (*m*/*z*) 194 (M^+), 178 ($M^+ - 16$) and 164 ($M^+ - 30$) (Found: C, 49.2; H, 2.9; N, 14.2. $C_8H_6N_2O_4$ requires C, 49.5; H, 3.1; N, 14.4%).

3-*Ethyl*-6-*nitro*-1,2-*benzisoxazole* 2-*Oxide*.—This was prepared in the same way as above, from 3-ethyl-1,2-benzisoxazole 2-oxide; it formed needles (0.64 g, 82%) (from ethanol), m.p. 125 °C; $\nu_{max.}$ (Nujol) 1 615s, 1 590s (ring), 1 530s, 1 340s (NO_2), and 1 200s cm^{-1}. δ 7.47—8.20 (3 H, ABX m, J_o 9.0, J_m 2.7, J_P 0.8 Hz), 2.88 (2 H, q), and 1.38 (3 H, t) (J 7 Hz; Et); (*m*/*z*) 208 (M^+), 192, and 178 (Found: C, 52.1; H, 3.8; N, 13.3. $C_9H_8N_2O_4$ requires C, 51.9; H, 3.8; N, 13.4%).

3-*Methyl*-5,7-*dinitro*-1,2-*benzisoxazole* 2-*Oxide*.—3-Methyl-5-nitro-1,2-benzisoxazole 2-oxide[1] (0.15 g) was dissolved in nitric acid (*d.* 1.51; 5 ml), and then allowed to stand at 20 °C for 15 h. The mixture was then poured into ice–water, and the precipitated solids were collected, washed with water, and dried. Recrystallisation from ethanol gave the dinitro compound as yellow needles (0.05 g, 25%), m.p. 198—201 °C, identical with the product of oxidation of 2-hydroxy-3,5-dinitroacetophenone oxime;[1] $\nu_{max.}$(Nujol) 1 610m (ring), 1 550s, 1 350s (NO_2), and 1 215s cm^{-1}; (*m*/*z*) 239 (M^+), 223, and 209.

Reactions of 3-*Methyl*-1,2-*benzisoxazole* 2-*Oxide* (3).—(a) *With bromine*. Bromine (1.1 g, 6.8 mmol) was added dropwise over 5 min to 3-methyl-1,2-benzisoxazole 2-oxide (1.0 g, 6.7 mmol) in dichloromethane (15 ml). The mixture was stirred for 30 min at 20 °C to give a yellow solid. When precipitation was complete the solid was filtered off, recrystallised from ethanol, and identified as 3,5-dibromo-2-hydroxyacetophenone oxime (5), (1.62 g, 80%), m.p. 211—212 °C (lit.[8] m.p. 201 °C), by comparison with a sample prepared from the dibromohydroxyacetophenone and hydroxylamine.

(b) *With hydrochloric acid*. 3-Methyl-1,2-benzisoxazole 2-oxide (0.2 g) was refluxed for 12 h in aqueous ethanol (95%) containing concentrated hydrochloric acid (0.09 ml). Evaporation of the solvent and sublimation of the residue gave 5-chloro-2-hydroxyacetophenone (0.2 g, 90%), m.p. 56 °C (lit.,[9] m.p. 55 °C).

(c) *With hydriodic acid*. The benzisoxazole oxide (0.5 g) was treated with hydriodic acid (47%, 2 ml) at room temperature. Iodine was liberated and a dark red solid was formed. The mixture was extracted with ether, the extract evaporated, and the residue recrystallised from light petroleum, to give needles (0.28 g, 55%) of the oxime (7), m.p. 116—117 °C, identical with an authentic sample.

(d) *With zinc and hydrochloric acid*. Zinc powder (0.86 g, 13.2 mmol) was slowly added to a refluxing solution of the benzisoxazole oxide (1.0 g) in 95% ethanol (15 ml) containing hydrochloric acid (10M, 5 ml). The mixture was refluxed for a further 40 h, after which it was cooled and filtered. The filtrate was evaporated to leave an oily residue, which solidified on cooling and was recrystallised from benzene–light petroleum (1:1) to give needles of the oxime (7) (0.76 g, 75%), m.p. 117 °C, identical with the product from (c) above.

(e) *With triethyl phosphite*. The benzisoxazole 2-oxide (3) (0.5 g) in toluene (10 ml) was refluxed with triethyl phosphite (1.1 g, 2 mol equiv.) for 45 h under nitrogen . The mixture was cooled and the solvent evaporated to leave an oily residue which was hydrolysed by dilute aqueous hydrochloric acid. 3-Methyl-1,2-benzisoxazole (8) (0.38 g, 87%) was recovered by ether extraction, drying, solvent evaporation, and distillation (95 °C/12 mmHg).

(f) *With acetic anhydride.* The benzisoxazole oxide (**3**) (0.5 g) in dry dioxane (15 ml) was refluxed for 4 days with acetic anhydride (0.68 g, 2 mol equiv.). Some evolution of yellow–brown oxides of nitrogen fumes was observed. After completion of the reaction (monitored by t.l.c.) the solvent was removed under reduced pressure and the dark red oily residue was separated by chromatography (SiO_2; CH_2Cl_2). 2-Acetoxyacetophenone (R_F (0.31) (0.2 g, 35%), (**9**), m.p. 88—89 °C (lit.,[10] 89 °C), and 3-methyl-1,2-benzisoxazole (**8**) (0.045 g, 10%), identified by comparison with an authentic sample, were isolated.

(g) *With phenylmagnesium bromide.* Phenylmagnesium bromide (from 0.5 g bromobenzene) in ether was slowly dropped into a stirred solution of the benzisoxazole oxide (**3**) (0.3 g) in ether at 20 °C. Stirring was continued for 12 h, with warming to 30—35 °C. The solution was cooled and treated with dilute hydrochloric acid, and the ethereal layer was dried, and the solvent evaporated, to leave a dark red oily residue. Chromatography (SiO_2; light petroleum) provided biphenyl (0.18 g, 43%), m.p. 64—66 °C (lit.,[11] 69 °C), *m/z* 154 (100%). The remainder on the column proved to be a multi-component mixture, which was not resolved.

(h) *With sodium alkoxides.* Sodium (0.15 g) was dissolved in dry ethanol (10 ml), the benzisoxazole oxide (**3**) (1.0 g) was added, and the mixture was refluxed for 1 h and then stirred at room temperature for a further 12 h. The solvent was evaporated and the residue was treated with water and dilute hydrochloric acid, leaving a crystalline solid which crystallised from ethanol to give white flakes of the *oxime* (**11**; R = OEt) (1.0 g, 77%) m.p. 192 °C (Found: C, 61.3; H, 6.5; N, 7.0. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.0; N, 7.1%); *m/z* 195 (M^+).

The same procedure repeated with methanol instead of ethanol afforded the *methoxymethyl analogue* (**11**; R = OMe) (1.03 g, 85%), m.p. 99—101 °C; δ 7.0—7.55 (4 H, m), 4.4 (2 H, s), and 3.4 (3 H, s); *m/z* 181 (M^+) (Found: C, 59.7; H, 6.0; N, 7.6. $C_9H_{11}NO_3$ requires C, 59.6; H, 6.0; N, 7.7%).

Treatment of Nitrobenzisoxazole Oxides with Sodium Hypochlorite and Potassium Hydroxide.—3-Methyl-5- or 3-methyl-6-nitro-1,2-benzisoxazole 2-oxide (1.0 g) in methanol (100 ml) and aqueous sodium hypochlorite (0.8 M; 125 ml) were added simultaneously to a vigorously stirred solution of potassium hydroxide (0.86 g) in methanol (25 ml). Potassium chloride was precipitated, but upon solvent removal only the starting nitrobenzisoxazole oxide was recovered.

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