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THE PREPARATION OF 3,4-DIHYDRO-2*H*-1,5,6-BENZODIOXAZONINE DERIVATIVES

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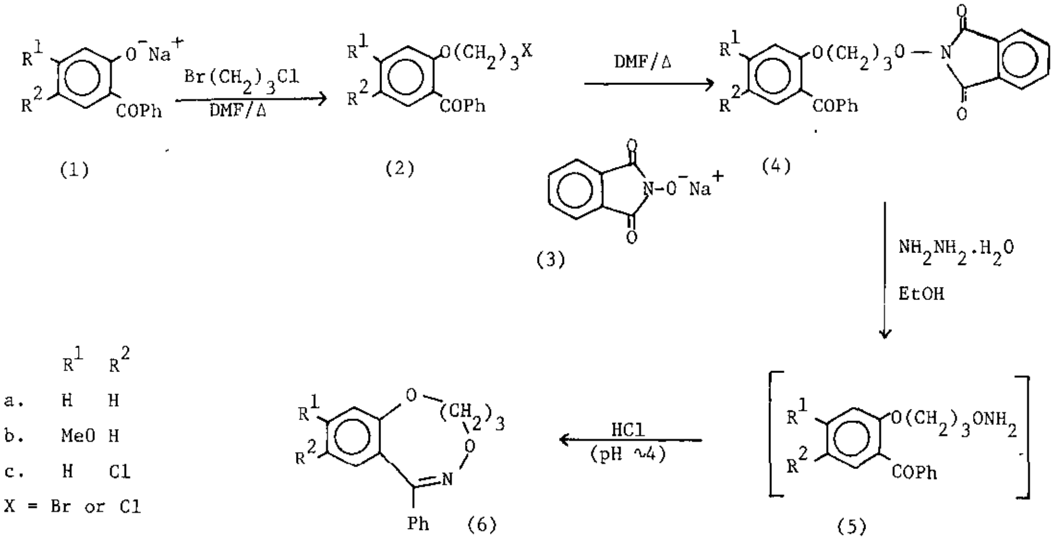
Abstract — Derivatives (6a–c) of the new 2*H*-1,5,6-benzodioxazonine ring system have been prepared in low to moderate yields by hydrazinolysis of {2-[3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)oxypropyloxy]aryl}phenylmethanones (4a–c), and cyclisation of the assumed intermediate *O*-substituted hydroxylamines (5a–c) under mildly acidic conditions.

There is current interest in this Department in the preparation of benz-fused medium ring oxaza heterocycles.[cf 1,2] Few of the related benzodioxaza medium ring systems are known. Derivatives of two benzodioxazocine rings, the 1,4,5[3] and 2,5,3[4] isomers, have been reported, but otherwise only the 1,7,4-benzodioxazonine[5] and 2,8,5-benzodioxaazacycloundecine[6] ring systems have been described.

The preparation of three derivatives of the new 2*H*-1,5,6-benzodioxazonine ring (6) (Scheme 1) is now reported.

The (2-hydroxyaryl)phenylmethanone sodium salts (1) were condensed with 1-bromo-3-chloropropane in *N*,*N*-dimethylmethanamide (DMF) to give the mixed halides (2)[7], which were reacted, without isolation, with the sodium salt of 2-hydroxy-1*H*-isoindole-1,3(2*H*)-dione (3). The resulting condensation products (4) were cleaved by refluxing with hydrazine hydrate in dilute ethanolic solution to the assumed intermediate *O*-substituted hydroxylamines (5). These were cyclised directly by the addition of dilute hydrochloric acid to pH ~4, and further refluxing. The benzodioxazonines (6) were readily separated from intermolecular condensation products by chromatography on alumina and elution with toluene. Little cyclisation was observed in the absence of acid. Presumably protonation of the deactivated and sterically hindered carbonyl group in (5) aids the intramolecular nucleophilic addition of the ONH_2 group. Infrared spectra of (6) showed no carbonyl absorption; bands near 1590 (m) cm^{-1} are ascribed to C=N stretching vibrations.



	R^1	R^2
a.	H	H
b.	MeO	H
c.	H	Cl

X = Br or Cl

Scheme 1

Experimental —— 7-Phenyl-3,4-dihydro-2H-1,5,6-benzodioxazonine (6a): A solution of the sodium salt of (2-hydroxyphenyl)phenylmethanone (11 g) and 1-bromo-3-chloropropane (13 g) in dry DMF (70 ml) was heated up to 120° over 1 h, kept near 140° for 2 h, and solvent and excess alkyl halide removed in vacuum. The crude residual (2a) was redissolved in DMF (50 ml) and added to a suspension in DMF (50 ml) of (3) (freshly precipitated from a solution of 8.2 g of the N-hydroxy precursor and 2.7 g sodium methoxide in methanol at 0-5°). The mixture was stirred and heated at 80° for 22 h, then raised to 135° over 5 h, as the red colour discharged. The reaction mixture was poured into water, and the precipitate recrystallised from ethanol to give (4a) (8.4 g, 39%) m.p. 127-128°.[8]

To a stirred and refluxing solution of (4a) (2.8 g) in ethanol (200 ml) was added dropwise over 2h a solution of hydrazine hydrate (0.33 g) in ethanol (150 ml), and the solution was refluxed 18 h. Hydrochloric acid (0.5 M, 6 ml) was added dropwise with stirring over 20 min, refluxing continued for 18 h, and the solvent removed. The residue was basified with 5% aqueous sodium carbonate, extracted with dichloromethane, and filtered. Evaporation of the solvent left a semi-solid residue which was chromatographed on alumina in toluene. The cyclised material, which eluted in the first fractions, was recrystallised from toluene and light petroleum as prisms of (6a) (0.77 g, 46%) m.p. 168-169° (Found: C, 75.8; H, 6.0; N, 5.3. $C_{16}H_{15}NO_2$ requires C, 75.9; H, 6.0; N, 5.5%) (Found: $M^{+\cdot}$ 253.1096. $C_{16}H_{15}NO_2$ requires $M^{+\cdot}$ 253.1103). N.m.r. δ ($CDCl_3$) 1.55-1.9, m, CH of CH_2; 2.1-2.6, m, CH of CH_2; 3.8-4.2, m, CH_2; 4.5-4.8, m, CH_2; 7.0-7.3, m, 3 x ArH; 7.3-7.5, m, 4 x ArH; 7.5-7.7, m, 2 x ArH.

10-Methoxy-3,4-dihydro-2H-1,5,6-benzodioxazonine (6b) was similarly prepared. Reaction of (2b) with (3) at 75° for 18 h gave (4b) (46%) m.p. 113-114°.[8] Hydrazinolysis of (4b) (4.3 g) as described, followed by addition of hydrochloric acid (0.5 M, 30 ml), refluxing for 5 h, and work up as above gave (6b) (1.20 g, 42%) m.p. 150-151° as prisms from diethyl ether (Found: C, 72.1; H, 6.2; O, 17.3. $C_{17}H_{17}NO_3$ requires C, 72.1; H, 6.0; O, 17.0%) (Found: $M^{+\cdot}$ 283.1189. $C_{17}H_{17}NO_3$ requires 283.1208). N.m.r. δ ($CDCl_3$) 1.6-2.0, m, CH of CH_2; 2.2-2.7, m, CH of CH_2; 3.88, s, OCH_3; 3.9-4.2, m, CH_2; 4.55-4.8, m, CH_2; 6.65-6.8, m, 2 x ArH; 6.9-7.0, m, 1 x ArH; 7.3-7.5, m, 3 x ArH; 7.5-7.7, m, 2 x ArH.

9-Chloro-3,4-dihydro-2H-1,5,6-benzodioxazonine (6c) was prepared by reaction of (2c) with (3) at 105° for 18 h to give (4c) (31%) m.p. 118-119°.[8] Hydrazinolysis of (4c) (3.6 g), followed by 6 h refluxing with hydrochloric acid (0.5 M, 15 ml), and the described method of isolation, gave (6c) (0.46 g, 19%) m.p. 144-145° as prisms from diethyl ether and light petroleum (Found: C, 67.0; H, 5.0; Cl, 12.4. $C_{16}H_{14}ClNO_2$ requires C, 66.8; H, 4.9; Cl, 12.3%) (Found: $M^{+\cdot}$ 287.0704. $C_{16}H_{14}ClNO_2$ requires 287.0703). N.m.r. δ ($CDCl_3$) 1.55-1.9, m, CH of CH_2; 2.2-2.6 m, CH of CH_2; 3.8-4.2, m, CH_2; 4.55-4.8, m, CH_2; 4.55-4.8, m, CH_2; 7.0-7.15 m, 2 x ArH; 7.25-7.7, m, 6 x ArH.

No cyclised products were isolated from attempted direct condensation of (2b) with hydroxylamine by the method of Luts.[3]

It is hoped to compare the properties of derivatives of this new ring with those of other benzodioxaza derivatives being approached by alternative routes.

The mass spectra were determined by Mr. J.C. Bignall and Mr. M. Power (Central Science Laboratory, University of Tasmania).

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7. Spectroscopic evidence indicated that in each of the mixed halides (2a-c) the ratio of Br:Cl was approx.3:2, suggesting that some halogen exchange may occur in solution.
8. The intermediates (4) gave satisfactory elemental analyses and spectroscopic measurements.

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