A NOVEL PREPARATION OF THE 1,3-BENZOXAZEPINE RING SYSTEM

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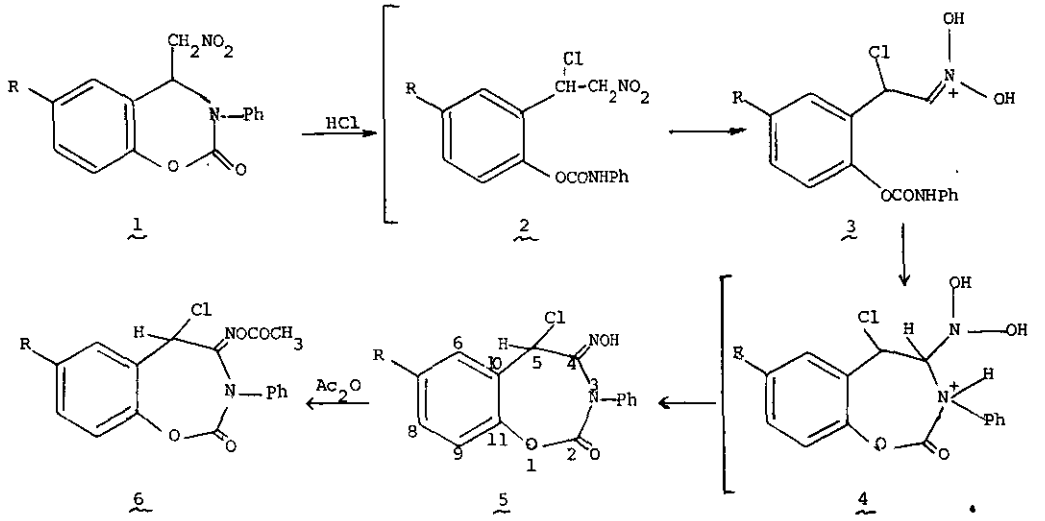
Abstract - Novel 1,3-benzoxazepines (5) are obtained by a new ring expansion rearrangement of benzoxazinones (1).

One of our groups has described[1] the preparation of a series of 3,4-dihydro-2H-1,3-benzoxazin-2-ones [cf. (1)]: we now demonstrate that these compounds are precursors for novel 1,3-benzoxazepine derivatives.

Treatment of the oxazinones (1a) and (1b) with HCl gave colorless crystalline products (5a) and (5b) which were readily acetylated to corresponding acetates (6a, b). Structures were assigned on the basis of spectroscopic data.



1 2 3 4 5 6

Scheme a: R=H; b: R=Cl

The conversion process (1) ⟶ (5) involves the loss of OH and the incorporation of a chlorine atom. The elemental analyses are in agreement with these molecular formulae (Table 1), and in particular confirm the presence of chlorine in (5a). Conclusive evidence for the molecular formulae was obtained from the high resolution molecular ions (Table 1). Base peaks in these compounds appeared at m/z 119 (C_7H_5NO) due to $C_6H_5N{=}C{=}O$.† Loss of OH was also observed in the mass spectra.

Table 1. - Preparation of 1,3-Benzoxazepines (5) and (6).

Comp. No.	Yield (%)	Mp (°C)	Recryst. Solvent	Found % (Required %) C	H	N	Molecular Formula	MW Found[a] (Required)
(5a)[b]	35	225-226	Dioxan[c]	59.23 (59.64)	3.68 (3.67)	8.92 (9.28)	$C_{15}H_{11}ClN_2O_3$	302.0454 (302.0458)
(5b)	32	230-232	Dioxan[c]	53.68 (53.61)	3.18 (3.00)	8.63 (8.34)	$C_{15}H_{10}Cl_2N_2O_3$	336.0087 (336.0068)
(6a)	80	185-186	Benzene/ hexane[d]	59.39 (59.22)	3.78 (3.80)	8.05 (8.13)	$C_{17}H_{13}ClN_2O_4$	344.0563 (344.0594)
(6b)	78	198-200	Benzene[c]	54.40 (54.01)	3.30 (3.20)	7.32 (7.41)	$C_{17}H_{12}Cl_2N_2O_4$	378.0175 (378.0174)

[a] By high resolution MS. [b] Cl: Found 11.77. Required 11.74%. [c] Crystal form: needles. [d] Crystal form: rods.

The ir spectra of the oxazepines (5) showed νC=0 1700-1690 cm^{-1}, a decrease from the νC=0 at 1760 cm^{-1} for the parent compounds (1). The acetates (6) showed νC=0 at 1710 cm^{-1} and 1800 cm^{-1}. The latter frequency is consistent with a $CH_3COON{=}C$ group. In compounds (5), νOH absorbed in the region 3300-3200 cm^{-1} (Table 2).

Table 2. - Ir and ^1H Nmr [a] of 1,3-Benzoxazepines (5) and (6).

Comp. No.	Ir. νOH	Ir. νCO	^1H Nmr Aromatic Region (m) δ	H	Methine δ (1H,s)	Methyl δ (3H,s)
(5a)	3225	1690	7.2-7.6	9	6.12	--
(5b)	3250	1700	7.2-7.6	8	6.13	--
(6a)	3400(w)	1790;1705	7.3-7.8	9	6.55	2.18
(6b)	3430(w)	1800;1700	7.3-7.6	8	6.38	2.15

[a] Solvent DMSO-d_6; chemical shifts (δ) in ppm.; H = number of protons; M = multiplicity: s = singlet, m = multiplet.

† Also referred to as the benzo[f]-1,3-oxazepine.[5]

The ^{1}H nmr (DMSO-d_6) (Table 2) of compounds (5) and (6) showed a methine proton at δ 6.1 - 6.5 and aromatic resonances in the region δ 7.2 - 7.8. The acetate derivatives (6) disclosed the methyl resonance at δ 2.1.

The ^{13}C nmr (DMSO-d_6) of compounds (5) showed doublets at ca. 64 ppm due to aliphatic methine carbons, the aromatic carbons appeared at 118-148 ppm, and the carbonyl carbons at ca. 148 ppm for the acid hydrolysis products, and at 148.3 and 166.0 ppm for the acetate derivates. The signals at 148.5 (5a), 148.1 (5b) and (6a), and 147.8 (6b) were tentatively assigned to C=N in oximes and oxime acetate respectively.[2] Although it is difficult to assign unambigously all the carbons (Table 3), the ^{13}C nmr was particularly important for structure corroboration since it disclosed the correct number of signals of each type: 13 signals due to (5a) and (5b) [5 singlets and 8 doublets for (5a), and 6 singlets and 7 doublets for (5b)], and 15 signals due to (6a) and (6b) [6 singlets, 8 doublets and 1 quartet for (6a) and 7 singlets, 7 doublets and 1 quartet for (6b)].

Table 3. - ^{13}C Nmr [a] of 1,3-Benzoxazepines (5) and (6).

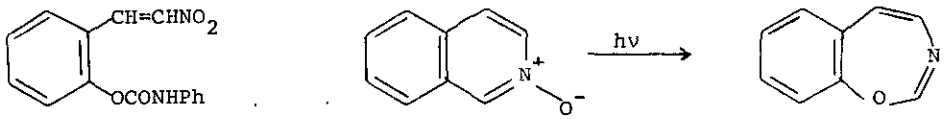
Comp. No.	$COCH_3$ (s)	C-2[b] (s)	C-4[b] (s)	C-5 (d)	Other Aromatic-C (s)	Other Aromatic-C (d)
(5a)	-	149.3	148.5	64.4	116.8, 136.1[b], 139.7	116.1, 124,8, 126.7, 127.2, 128.1, 129.3, 130.6
(5b)	-	148.3	148.1	63.9	118.9, 128.4, 135.5[b], 139.5	118.3, 126.4, 127.2, 128.4 129.5, 131.1
(6a)[c]	166.0	149.4	148.1	64.3	115.5, 139.3, 146.7[b]	116.2, 124.8, 126.7, 127.1, 128.1, 129.3, 130.9
(6b)[d]	166.3	148.4	147.8	63.8	117.6, 128.6, 139.2, 146.2[b]	118.5, 126.4, 127.2, 128.4, 129.5, 131.1

[a] Solutions in DMSO-d_6 with 39.5 ppm as reference. [b] Assignments could be interchanged. [c] CH_3: 18.7 (q). [d] CH_3: 18.8 (q).

The formation of 1,3-benzoxazepines (5) from the benzoxazinones (1) can be rationalized by ring opening to (2), followed by protonation to give (3), cyclisation to (4) and dehydration to give (5), (Scheme). The α,β-unsaturated nitro compound (7) is not an intermediate, as it was obtained unchanged after heating with HCl under similar conditions.

Carbamates of type (7) have already been described.[1] Intermediate (3) is a protonated *nitronic acid, species* which are prone to nucleophile addition.[3]

Most previously described 1,3-benzoxazepines have been prepared from isoquinoline-2-oxides (8)→(9):[4] 4,5,6,7-tetrahydroderivatives have been obtained by ring-closure.[5]



7 8 9

EXPERIMENTAL

Mp's were determined using a hot-stage microscope and are uncorrected. Spectra were recorded with a Varian EM-360L (^{1}H at 60 MHz), Jeol JNM-FX 100 [^{1}H(100 MHz), and ^{13}C(25.0 MHz)] and Nicolet NT 300 (^{13}C at 75.5 MHz) nmr spectrometers, and AEI MS 30 mass spectrometer.

The 3,4-dihydro-2H-1,3-oxazin-2-ones (1a) and (1b) were prepared as described previously.[1] Hydrochloric acid was "B.D.H. AR grade", and dioxan was "Fluka, spec. grade".

Preparation of 1,3-Benzoxazepines (5). A suspension of the benzoxazinone (1) (0.01 mol) in a mixture of HCl/dioxan (8 ml conc. HCl and 12 ml dioxan) was refluxed for 10 h, left to cool and few drops of water added. The separated solid was filtered off, dried, and recrystallised from the appropriate solvent to give (5) as colourless crystals.

Acetylation of 1,3-Benzoxazepines (5). A suspension of (5) (1 mmol) in acetic anhydride was refluxed for 2 h, left to cool, poured into ice-cold water, and left standing overnight. The separated solid was filtered off, washed with water, dried, and recrystallised from the appropriate solvent to give (6) as

colourless crystals.

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