

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

Alan R. Katritzky\*, Olga Rubio, and Radi Awartani

Department of Chemistry, University of Florida, Gainesville,  
Florida 32611 USA

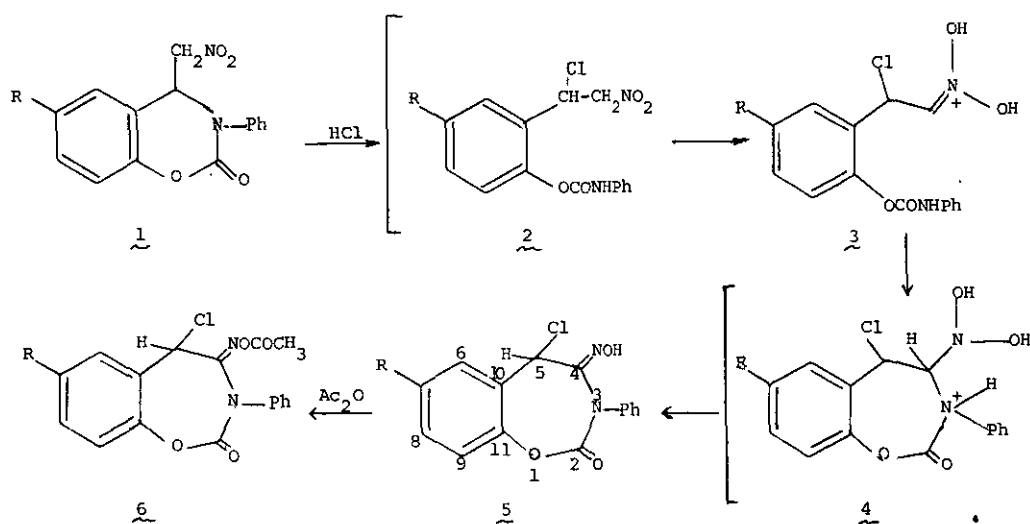
Nazih Latif\*, Nawal Mishriky, and Fahmy M. Assad

National Research Centre Dokki, Cairo, Egypt

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

One of our groups has described<sup>1</sup> 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, 6b). Structures were assigned on the basis of spectroscopic data.



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

The conversion process (1)  $\rightarrow$  (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  $C_6H_5N=C=O$ .<sup>†</sup> 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 %) |                |                | Molecular Formula        | MW Found <sup>a</sup> (Required) |
|-------------------|-----------|---------|---------------------------------|----------------------|----------------|----------------|--------------------------|----------------------------------|
|                   |           |         |                                 | C                    | H              | N              |                          |                                  |
| (5a) <sup>b</sup> | 35        | 225-226 | Dioxan <sup>c</sup>             | 59.23<br>(59.64)     | 3.68<br>(3.67) | 8.92<br>(9.28) | $C_{15}H_{11}ClN_2O_3$   | 302.0454<br>(302.0458)           |
| (5b)              | 32        | 230-232 | Dioxan <sup>c</sup>             | 53.68<br>(53.61)     | 3.18<br>(3.00) | 8.63<br>(8.34) | $C_{15}H_{10}Cl_2N_2O_3$ | 336.0087<br>(336.0068)           |
| (6a)              | 80        | 185-186 | Benzene/<br>hexane <sup>d</sup> | 59.39<br>(59.22)     | 3.78<br>(3.80) | 8.05<br>(8.13) | $C_{17}H_{13}ClN_2O_4$   | 344.0563<br>(344.0594)           |
| (6b)              | 78        | 198-200 | Benzene <sup>c</sup>            | 54.40<br>(54.01)     | 3.30<br>(3.20) | 7.32<br>(7.41) | $C_{17}H_{12}Cl_2N_2O_4$ | 378.0175<br>(378.0174)           |

<sup>a</sup> By high resolution MS. <sup>b</sup> Cl: Found 11.77. Required 11.74%. <sup>c</sup> Crystal form: needles. <sup>d</sup> Crystal form: rods.

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

Table 2. - Ir and <sup>1</sup>H Nmr <sup>a</sup> of 1,3-Benzoxazepines (5) and (6).

| Comp. No. | $\nu_{OH}$ | Ir. $\nu_{C=O}$ | <sup>1</sup> H Nmr           |              |                          |                         |
|-----------|------------|-----------------|------------------------------|--------------|--------------------------|-------------------------|
|           |            |                 | Aromatic Region ( $\delta$ ) | Region (m) H | Methine $\delta$ (1H, s) | Methyl $\delta$ (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                    |

<sup>a</sup> Solvent DMSO- $d_6$ ; chemical shifts ( $\delta$ ) in ppm.; H = number of protons;

M = multiplicity; s = singlet, m = multiplet.

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

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

The  $^{13}\text{C}$  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 derivatives. 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.<sup>2</sup> Although it is difficult to assign unambiguously all the carbons (Table 3), the  $^{13}\text{C}$  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. -  $^{13}\text{C}$  Nmr <sup>a</sup> of 1,3-Benzoxazepines (5) and (6).

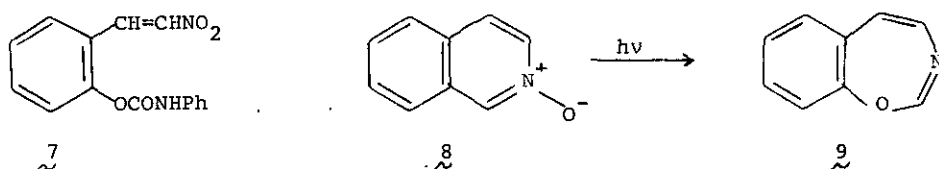
| Comp. No.         | COCH <sub>3</sub> (s) | C-2 <sup>b</sup> (s) | C-4 <sup>b</sup> (s) | C-5 (d) | Other Aromatic-C (s)                     | Other Aromatic-C (d)                            |
|-------------------|-----------------------|----------------------|----------------------|---------|------------------------------------------|-------------------------------------------------|
| (5a)              | -                     | 149.3                | 148.5                | 64.4    | 116.8, 136.1 <sup>b</sup> , 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 <sup>b</sup> , 139.5 | 118.3, 126.4, 127.2, 128.4, 129.5, 131.1        |
| (6a) <sup>c</sup> | 166.0                 | 149.4                | 148.1                | 64.3    | 115.5, 139.3, 146.7 <sup>b</sup>         | 116.2, 124.8, 126.7, 127.1, 128.1, 129.3, 130.9 |
| (6b) <sup>d</sup> | 166.3                 | 148.4                | 147.8                | 63.8    | 117.6, 128.6, 139.2, 146.2 <sup>b</sup>  | 118.5, 126.4, 127.2, 128.4, 129.5, 131.1        |

<sup>a</sup> Solutions in DMSO- $d_6$  with 39.5 ppm as reference. <sup>b</sup> Assignments could be interchanged. <sup>c</sup> CH<sub>3</sub>: 18.7 (q). <sup>d</sup> CH<sub>3</sub>: 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  $\alpha,\beta$ -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.<sup>1</sup> Intermediate (3) is a protonated nitronic acid, species which are prone to nucleophile addition.<sup>3</sup>

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



#### EXPERIMENTAL

Mp's were determined using a hot-stage microscope and are uncorrected. Spectra were recorded with a Varian EM-360L (<sup>1</sup>H at 60 MHz), Jeol JNM-FX 100 [<sup>1</sup>H(100 MHz), and <sup>13</sup>C(25.0 MHz)] and Nicolet NT 300 (<sup>13</sup>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.<sup>1</sup> 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.

#### ACKNOWLEDGEMENT

We thank the Office of Naval Research, U.S.A., Ban C. Chen, Nabil Grant and Waheed Basyouni for experimental assistance, and the National Sciences Foundation for a grant for Nicolet NT-300 spectrometer (at University of Florida).

#### REFERENCES

1. N. Latif, N. Mishriky and F.M. Assad. Aust. J. Chem., 1982, 35, 1037.
2. G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists" 2nd ed., Wiley, New York, 1980.
3. A.T. Nielsen, "The Chemistry of the Nitro and Nitroso Groups", Part I, H. Feuer Ed., Wiley, New York, 1969, p. 349.
4. a) O. Buchardt, C. Lohse, A.M. Duffield, and C. Djerassi, Tetrahedron Letters, 1967, 2741. b) A. Albin, E. Fasani, and L.M. Dacrema, J. Chem. Soc. Perkin Trans. 1, 1980, 2738.
5. H. Iida, S. Aoyaki, K. Kawano and C. Kibayashi, Chem. and Pharm. Bull. Japan, 1978, 26, 3229.

Received, 23rd December, 1983