Thiophene Systems. 6. An Unexpected Bromine Migration during the Synthesis of Thieno[3,4-*b*][1,5]benzoxazepin-10-ones (1)

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7-Bromothieno[3,4-*b*][1,5]benzoxazepin-10-one (**1a**) was unexpectedly formed upon acid catalyzed ring closure of 5-bromo-4-ethoxy-2'-hydroxy-3-thiophenecarboxanilide (**2a**). Ring closure of the chlorine analogue **2c** proceeded normally to give 3-chlorothieno[3,4-*b*][1,5]benzoxazepin-10-one (**1b**).

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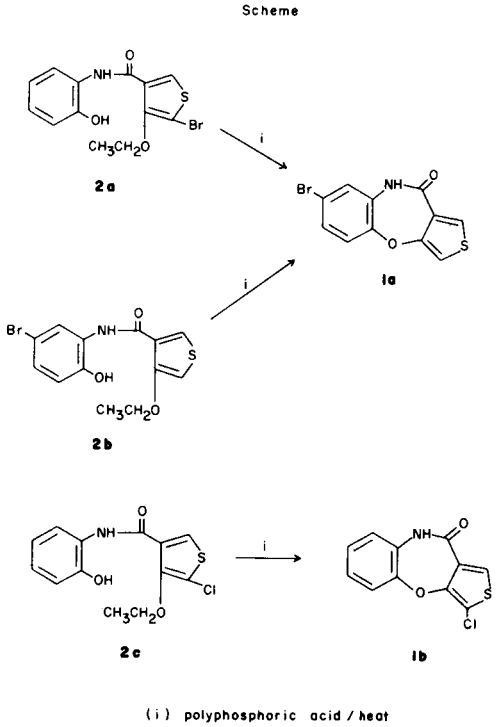
Discussion.

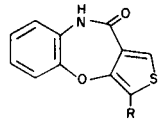
Previous reports from these laboratories (1-4) describe syntheses of novel thieno[3,4-*b*]-fused tricyclic ring systems and their development as potential CNS agents. While preparing several derivatives of one such tricyclic system, namely thieno[3,4-*b*][1,5]benzoxazepin-10-one (**1**) (1,3), an interesting bromine migration occurred which we report herein.

The general synthesis of system **1** involves acid catalyzed ring closure of hydroxy ether **2** with concomitant elimination of ethanol. Such closure presumably results from the acid lability of the enol ether-like moiety of **2** and the intermediacy of an unisolated ketal (3). When bromohydroxy ether **2a** was treated with polyphosphoric acid at 120°, the 7-bromolactam **1a** was the only isolated product in yields typical of this procedure.

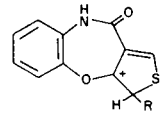
Scheme



Such bromine rearrangement may result from the initial formation of the lactam **1c** with subsequent protonation to form an oxygen-stabilized carbonium ion **3a**. Subsequent collapse of **3a** to form the all protio lactam **1d** and one equivalent of bromonium ion with ultimate recombination



1c R = Br
1d R = H



3a R = Br
3b R = Cl

at the 7 position of the ring leads to the formation of the more stable product **1a**. The 7-bromolactam **1a** was predictably prepared by ring closure of **2b** and was identical in all respects to the material derived from **2a**.

In contrast, 3-chlorolactam **1b** has been prepared from amide **2c** using standard procedures. Under these conditions, the chloronium ion does not appear to be a stable leaving group and no chlorine migration occurs. 3-Chlorolactam **1b** prepared by the chlorination of **1d** *via* the intermediacy of **3b** (3) is identical in all respects to the lactam derived from **2c**.

EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All compounds are homogeneous by thin layer chromatographic analysis using Whatman K5F (5 × 10 cm) silica gel analytical plates. ^{1}H-nmr measurements were obtained on a Varian Associates HA-100A spectrometer with tetramethylsilane as the internal standard.

5-Bromo-4-ethoxy-2'-hydroxy-3-thiophenecarboxanilide (**2a**).

5-Bromo-4-ethoxy-3-thiophenecarboxylic acid (**4**) (24.00 g, 0.096 mole) was treated with purified thionyl chloride (29 ml) dropwise over 0.5 hour. The reaction mixture was warmed to 110° for 2 hours, excess thionyl chloride was removed and the product distilled as a yellow liquid (23.85 g, 92%), bp 100-102° (0.1 mm Hg). The acid chloride was dissolved in methylene chloride (100 ml) and added dropwise to a solution of *o*-aminophenol (9.66 g, 0.0855 mole) and triethylamine (12.5 ml, 0.085 mole) in methylene chloride (100 ml) and mixture was stirred overnight. Methylene chloride was removed *in vacuo*, the residue was triturated with water (500 ml) and the precipitate was collected by filtration and air dried

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(28.40 g, 94%). The analytical sample was crystallized from methylene chloride/hexanes, mp 148-150°; ir (potassium bromide): 1642 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 9.90 (broad s, 1H, NH), 9.59 (broad s, 1H, OH), 8.32 (m, 1H, aromatic-H), 8.11 (s, 1H, thiophene-H), 6.90 (m, 3H, aromatic-H), 4.36 (q, 2H, CH_2), 1.50 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{12}BrNO_3S$ (342.2): C, 45.62; H, 3.53; N, 4.09; S, 9.37; Br, 23.35. Found: C, 45.55; H, 3.73; N, 4.09; S, 9.60; Br, 23.63.

5-Chloro-4-ethoxy-2'-hydroxy-3-thiophenecarboxanilide (**2c**).

5-Chloro-4-ethoxy-2'-hydroxy-3-thiophenecarboxylic acid (**4**) (14.66 g, 0.071 mole) was treated with thionyl chloride (17.52 ml) as above and worked up to give the product as a yellow liquid (15.62 g, 98%), bp 95-97° (0.15 mm Hg). The acid chloride was dissolved in methylene chloride (80 ml) and added dropwise to a solution of *o*-aminophenol (7.57 g, 0.069 mole) and triethylamine (9.77 ml, 0.069 mole) in methylene chloride (80 ml). Reaction and work-up as above gave the product as a tan solid (19.94 g, 97%). Recrystallization from ethanol afforded the analytical sample as white crystals, mp 151-153°; ir (potassium bromide) 1645 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 9.89 (broad s, 1H, NH), 9.60 (broad s, 1H, OH), 8.32 (m, 1H, aromatic-H), 7.90 (s, 1H, thiophene-H), 6.90 (m, 3H, aromatic-H), 4.40 (q, 2H, CH_2), 1.50 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{12}ClNO_3S$ (297.8): C, 52.44; H, 4.06; Cl, 11.91; N, 4.70; S, 10.77. Found: C, 52.31; H, 4.04; Cl, 11.83; N, 4.67; S, 10.86.

7-Bromothieno[3,4-*b*][1,5]benzoxazepin-10-(9*H*)one (**1a**).

A mixture of 5-bromo-4-ethoxy-2'-hydroxy-3-thiophenecarboxanilide (**2a**) (5.00 g, 0.015 mole) and polyphosphoric acid (50 g) was stirred and heated to 110° for 1 hour. The mixture was cooled, poured into ice water (400 ml) and stirred for 1 hour. The precipitate was collected by filtration and air dried (2.60 g, 60%) and extracted with ethyl acetate in a soxhlet apparatus to give the pure product (1.70 g, 40%), mp 234-237°, lit (1) mp 245-249°, mixed mp 236-239°; ir (potassium bromide): 1675 cm^{-1}; ^{1}H-nmr (DMSO): δ 10.25 (broad s, 1H, NH), 8.17 (d, 1H, thiophene-H), 7.25 (m, 4H, thiophene and aromatic −H). This compound was identical in all respects to the previously reported material (1).

Anal. Calcd. for $C_{11}H_6BrNO_2S$ (296.7): C, 44.61; H, 2.04; Br, 26.98; N, 4.73; S, 10.83. Found: C, 44.54; H, 2.16; Br, 27.19; N, 4.47; S, 11.17.

3-Chlorothieno[3,4-*b*][1,5]benzoxazepin-10-(9*H*)one (**1b**).

A mixture of 5-chloro-4-ethoxy-2'-hydroxy-3-thiophenecarboxanilide (**2c**) (17.0 g, 0.057 mole) was treated with polyphosphoric acid (170 g) at 110° for 3 hours and worked up as above to give the product (7.6 g, 53%), mp 235-244°. A small sample of this material was sublimed to give the analytical sample, mp 254-258°, lit (3) mp 258-260°. Lactam **1b** was identical in all respects to the previously reported material obtained by chlorination of thieno[3,4-*b*][1,5]-benzoxazepin-10-(9*H*)one (**1d**) (3).

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REFERENCES AND NOTES

(1) For the previous paper in this series see J. B. Press, C. M. Hofmann, N. H. Eudy, I. P. Day, E. N. Greenblatt and S. R. Safir, *J. Med. Chem.* **24**, 154 (1981).

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