Alkylation and an Unusual Reductive Ring Opening of Some Thieno[3,4-*b*][1,5]benzoxazepin-10-ones

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As part of a program towards the syntheses of novel tricyclic compounds, some derivatives of thieno[3,4-*b*]-[1,5]benzoxazepin-10-one system **1** were prepared and were subsequently subjected to reduction reactions using lithium aluminum hydride. Although thienobenzoxazines **4** were obtained as the sole product of the reduction in most cases, unusual ring-opened products, namely 3-hydroxymethylthiophenes **5**, were also formed during several reductions.

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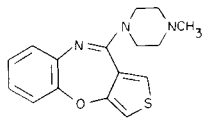
The thieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-one system **1** (2) was developed as a precursor to the biologically active piperazine derivative **2**. The preliminary assessment of the



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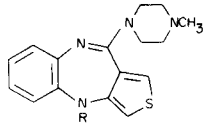

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CNS properties of **2** as well as novel thieno[3,4-*b*][1,5]-benzodiazepines **3** have previously been reported (3). In this report we describe the alkylation of **1** to give lactams **1a-g** as well as subsequent reduction of several of these derivatives with excess lithium aluminum hydride.

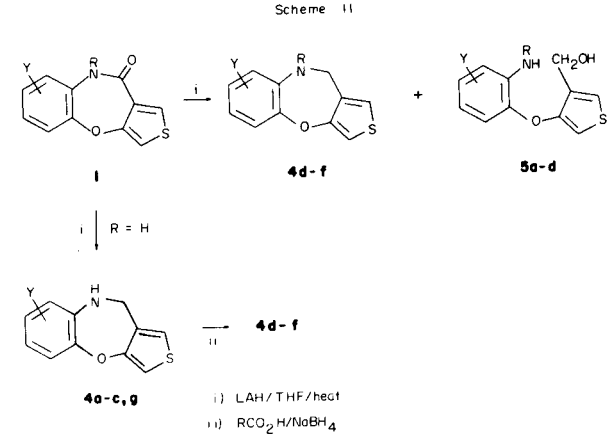
The method of Press, *et al.* (2,3a) was employed in the synthesis of the unsubstituted lactams **1**. This was achieved by condensation of the appropriate *o*-aminophenol with 4-ethoxy-3-thiophenecarbonyl chloride and subsequent cyclization of the intermediate amide. *N*-Alkylation of the resultant lactams was accomplished by deprotonation of **1** with sodium hydride in *N,N*-dimethylformamide followed by addition of the desired alkyl halide at room temperature to give **1a-g** (Table I) in moderate yield (Scheme I).

Scheme I

i) NaH / DMF / room temperature
ii) RX / DMF / room temperature

When compounds **1** were treated with excess lithium aluminum hydride in tetrahydrofuran at elevated temperatures, the corresponding thieno[3,4-*b*][1,5]benzoxazepines **4** and/or the ring cleaved 4-aminophenoxy-3-hydroxymethylthiophenes **5** formed in good combined yield (Scheme II). In the case of the unsubstituted lactams (R = H), only ring closed benzoxazepines **4a-c, g** were isolated from this reaction (Table II). When *N*-methyl lactams **1a, 1d-e** were treated similarly, a mixture of ring closed and ring opened products arose, namely, **4e** and **5d**, **4d** and **5b** and **4f** and **5e**, respectively (Table II, III). *N*-Methyl lactam **1f** gave only the ring opened product **5d** under the same conditions (Table III). Attempts to vary these reaction results by altering solvents (THF, diethyl ether or benzene), reaction times or the molar ratio of reducing agent failed.

Scheme II



i) LAH / THF / heat
ii) $RCO_2H/NaBH_4$

Scheme III

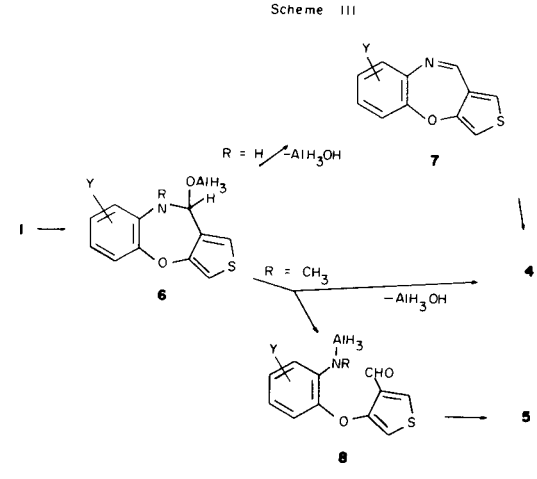
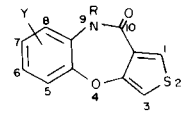


Table I

9-Alkylthieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-ones **1a-g**

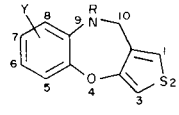


Compound No.	R	Y	Mp. °C	M⁺ (m/e)	Yield, %	Formula
1a	Methyl	H	132-133	231	58	$C_{12}H_9NO_2S$ (a)
1b	Dimethylamino-ethyl	H	85-86	288	38	$C_{15}H_{16}N_2O_2S$
1c	Morpholinoethyl	H	88-89	330	24	$C_{17}H_{18}N_2O_3S$ (b)
1d	Methyl	7-CH_3	86-87	245	27	$C_{13}H_{11}NO_2S$
1e	Methyl	7-Cl	88-90	265	46	$C_{12}H_8ClNO_2S$
1f	Methyl	6-CH_3	92-93	245	72	$C_{13}H_{11}NO_2S$
1g	Methyl	8-CH_3	98-99	245	44	$C_{13}H_{11}NO_2S$

(a) The pmr are: 7.94 (d, 1H, thiophene), 7.18 (m, 4H, aromatic), 6.08 (d, 1H, thiophene), 3.50 (s, 3H, N-CH_3); ir: 1640 cm^{-1}; uv: 253, 205 nm. (b) Calcd.: C, 61.79. Found: C, 61.28.

Table II

9,10-Dihydro-4*H*-thieno[3,4-*b*][1,5]benzoxazepines **4a-g**

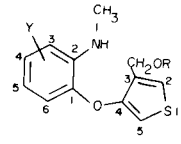


Compound No.	R	Y	Mp, °C	M⁺ (m/e)	Yield, %	Formula
4a	H	H	87-88	203	59	$C_{11}H_9NOS$
4b	H	7-CH_3	98-99	217	69	$C_{12}H_{11}NOS$
4c	H	7-Cl	89-90	237	74	$C_{11}H_8ClNOS$
4d	CH_3	7-CH_3	51-52	231	17	$C_{13}H_{13}NOS$ (a)
4e	CH_3	H	146-148	217	52	$C_{12}H_{11}NOS$·HCl (b)
4f	CH_3	7-Cl	139-141	251	52	$C_{12}H_{10}ClNOS$·HCl (c)
4g	H	6-CH_3	108-109	217	27	$C_{12}H_{11}NOS$

(a) Calcd.: S, 13.06. Found: S, 13.24. (b) The pmr are: 7.56 (d, 1H, thiophene), 7.42 (d, 1H, thiophene), 7.22 (m, 2H, aromatic), 7.13 (m, 2H, aromatic), 4.46 (s, 2H, methylene), 2.98 (s, 3H, N-CH_3). (c) Calcd.: Cl, 24.60. Found: Cl, 23.94.

Table III

4-(2-Methylaminophenoxy)-3-hydroxymethylthiophenes **5a-e**



Compound No.	R	Y	Mp, °C	M⁺ (m/e)	Yield, %	Formula
5a	H	H	70-71	235	20	$C_{12}H_{13}NO_2S$ (a)
5b	H	4-CH_3	57-58	249	17	$C_{13}H_{15}NO_2S$
5c	H	4-Cl	92-93	269	42	$C_{12}H_{12}ClNO_2S$
5d	H	5-CH_3	150-151	249	16	$C_{13}H_{15}NO_2S$·HCl
5e	CH_3	H	125-127	249	30	$C_{13}H_{15}NO_2S$·HCl (b)

(a) The pmr are: 7.12 (d, 1H, thiophene), 6.32 (d, 1H, thiophene), 6.86 (m, 2H, aromatic), 6.70 (m, 1H, aromatic), 6.60 (m, 1H, aromatic), 4.55 (s, 2H, methylene), 3.25 (s, 1H, OH), 2.85 (s, 3H, N-CH_3); uv: 295, 245, 200 nm. (b) Calcd.: Cl, 12.41. Found: Cl, 11.88. pmr: 7.88 (d, 1H, thiophene), 7.30 (m, 2H, aromatic), 7.04 (m, 2H, aromatic), 6.82 (d, 1H, thiophene), 4.46 (s, 2H, CH_2O), 3.36 (s, 3H, NCH_3), 3.16 (s, 3H, OCH_3). uv: 293, 263, 245 nm.

Table IV

Elemental Analyses of New Compounds

Compound No.	Formula	Calcd. C	Found C	Calcd. H	Found H	Calcd. N	Found N	Calcd. S	Found S	Calcd. Cl	Found Cl
1a	$C_{12}H_9NSO_2$	62.31	62.39	3.92	4.15	6.06	6.02	13.87	13.71		
1b	$C_{15}H_{16}N_2SO_2$	62.48	62.45	5.59	5.69	9.72	9.57	11.12	11.08		
1c	$C_{11}H_{18}N_2SO_3$	61.79	61.28	5.49	5.28	8.48	8.66	9.70	9.67		
1d	$C_{13}H_{11}NSO_2$	63.65	63.36	4.52	4.60	5.71	5.77	13.07	13.17		
1e	$C_{12}H_8ClNSO_2$	54.24	54.08	3.03	3.20	5.27	5.37	12.07	11.99	13.34	13.20
1f	$C_{13}H_{11}NSO_2$	63.65	63.71	4.52	4.61	5.71	5.75	13.07	13.42		
1g	$C_{13}H_{11}NSO_2$	63.65	63.88	4.52	4.83	5.71	5.74	13.07	13.16		
4a	$C_{11}H_9NSO$	64.99	64.80	4.46	4.85	6.89	6.78	15.78	15.68		
4b	$C_{12}H_{11}NSO$	66.33	66.20	5.10	5.22	6.45	6.39	14.76	14.44		
4c	$C_{11}H_8ClNSO$	55.58	55.76	3.39	3.66	5.89	5.94	13.44	13.37	14.92	15.05
4d	$C_{13}H_{13}NSO$	67.44	67.21	5.67	5.91	6.06	5.82	13.86	13.24		
4e	$C_{12}H_{11}NSO\cdot HCl$	56.80	56.40	4.77	4.87	5.52	5.44	12.64	12.56	13.97	13.80
4f	$C_{12}H_{10}ClNSO\cdot HCl$	50.01	50.44	3.85	4.13	4.86	4.94	11.13	11.30	24.60	23.94
4g	$C_{12}H_{11}NSO$	66.33	66.31	5.10	5.05	6.45	6.50	14.76	14.80		
5a	$C_{12}H_{13}NSO_2$	61.55	61.60	5.60	5.60	5.90	5.89	13.62	13.55		
5b	$C_{13}H_{15}NSO_2$	62.62	62.77	6.07	6.13	5.62	5.46	12.86	12.91		
5c	$C_{12}H_{12}ClNSO_2$	53.43	53.67	4.48	4.53	5.19	4.84	11.88	11.50	13.14	13.00
5d	$C_{13}H_{15}NSO_2\cdot HCl$	54.63	54.51	5.64	5.75	4.90	4.94	11.22	11.80	12.41	12.40
5e	$C_{13}H_{15}NSO_2\cdot HCl$	54.63	54.61	5.64	5.50	4.90	5.10	11.22	11.06	12.41	12.08

In order to prepare *N*-methylbenzoxazepines, **4d-f** without product separation problems, an alternative reaction sequence was employed. Reductive alkylation of **4a-c** by means of sodium borohydride and formic acid (4) gave **4d-f** cleanly and in high-yield (Scheme II).

The exclusive formation of **4a-c, g** in the case of unsubstituted lactams **1** is probably the result of initial carbonyl reduction to give intermediate **6** (Scheme III). When R = H, elimination of trihydridoaluminum hydroxide gives imine **7** which is reduced by hydride in the reaction medium to **4**. When R = CH_3, simple elimination as above can not occur and the fate of **9** has two possibilities. If additional hydride attacks **6**, **4** may form directly. The *N*-methyl of **9** sterically crowds additional hydride approach and ring opening of **6** to aldehyde **8** can also occur. Subsequent reduction and work up gives the methanol derivative **5**.

EXPERIMENTAL

Melting points were determined in a Mel-Temp apparatus and are uncorrected. We wish to thank Mr. L. Brancone and staff for microanalytical elemental analyses; Dr. W. Gore and G. Jordan and staff for ir, uv and pmr determinations; and Dr. R. Hargreaves and staff for mass spectral measurements. The pmr measurements were obtained on a Varian Associates HA-100A spectrometer, and shift values are reported in δ units downfield from TMS and are measured in either deuteriochloroform or DMSO-d_6. Typical pmr absorptions are given as footnotes in Tables I, II and III.

Thieno[3,4-*b*][1,5]benzoxazepin-10-ones (**1**).

The lactams were prepared according to the procedure of Press (2) and were identical in all respects to the materials reported (3a).

9-Alkylthieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-ones (**1a-g**, Table I).

To a stirred solution of 0.009 mole of the lactam (2) in 30 ml of dry dimethylformamide was added 0.029 mole of sodium hydride that had been prewashed with petroleum ether. The reaction mixture was stirred for 2 hours at room temperature and 0.011 mole of the appropriate alkyl halide was added. After stirring overnight, the mixture was poured into ice water and the product which separated after stirring for 2 hours was collected by filtration, washed with water and dried. Recrystallizations were carried out with methanol, or methanol and water. In some cases, when crystallization could not be achieved, the crude products were extracted with methylene chloride, dried over sodium sulfate, evaporated *in vacuo* and the oily residue then crystallized from hexane.

Reduction of 9-Alkylthieno[3,4-*b*][1,5]benzoxazepin-10(9*H*)-ones (**1**) with Lithium Aluminum Hydride. Formation of 9-Alkyl-9,10-dihydro-4*H*-thieno[3,4-*b*][1,5]benzoxazepines (**4**, Table II) and 4-(2-Methylaminophenoxy)-3-hydroxymethylthiophenes (**5**, Table III).

In the general procedure, a solution of 0.009 mole of lactam **1** in 50 ml of dry tetrahydrofuran was added with stirring and cooling under nitrogen to a solution of 0.05 mole of lithium aluminum hydride in 50 ml of dry tetrahydrofuran. The reaction mixture was heated under reflux for 24-30 hours, cooled and treated dropwise with stirring and in succession with 7.6 ml of water, 7.6 ml of 15% sodium hydroxide and 24 ml of water. The resulting complex was filtered, washed with methylene chloride and the filtrate was extracted 4 times with methylene chloride. The combined methylene chloride extracts were washed with water, dried over sodium sulfate, filtered and concentrated to dryness. Addition of cold hexanes to the oily product caused the residue to form white crystals of the 9,10-dihydro-4*H*-thieno[3,4-*b*][1,5]benzoxazepine base as the only product isolated in the cases of **4a-c, g**. These were purified by recrystallization from hexanes. When tlc indicated the presence of a second major component, as in the reduction of **1d**, the mixture was chromatographed on alumina (Act II). Elution with 5% ethyl acetate in hexanes gave **4d** as the less polar component. Elution with 30% ethyl acetate in hexanes then gave the ring-cleaved product **5b**. In the reductions of **1a, e**, the crude oily products obbtained from work-up were crystallized from hexanes at -78° to give thiophenemethanols **5a, c**.

9-Alkyl-9,10-dihydro-4*H*-thieno[3,4-*b*][1,5]benzoxazepines by Reductive Alkylation (**4d-f**, Table II).

The 9,10-dihydro-4*H*-thieno[3,4-*b*][,5]benzoxazepines (**4a-c**, 0.003 mole) were dissolved in 6 ml of formic acid. The mixture was cooled in ice water and stirred while 0.03 mole of sodium borohydride pellets was added during ½ hour. After stirring overnight, the reaction mixture was cooled, made alkaline with ammonium hydroxde and extracted four times with methylene chloride. The organic layer was dried over sodium sulfate, filtrered and evaporated to give the 9-alkyl-9,10-dihydro-4*H*-thieno[3,4-*b*][1,5]benzoxazepine bases. In the cases where the products were yellow oils, they were converted to hydrochloride salts (**4e-f**).

REFERENCES AND NOTES

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