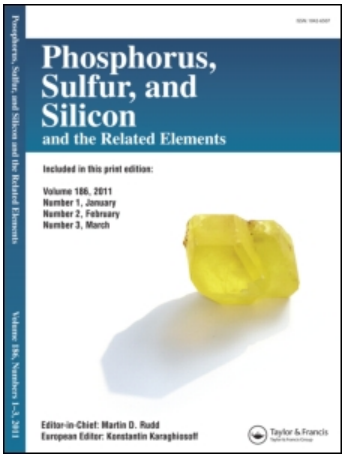

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REGIOSELECTIVE CONVERSION OF LACTAM TO CORRESPONDING THIOLACTAM IN TETRAHYDROPYRROLO[1,2-A]THIENO[3,2-E] [1,3]DIAZEPINE

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REGIOSELECTIVE CONVERSION OF LACTAM TO CORRESPONDING THIOLACTAM IN TETRAHYDROPYRROLO[1,2-A]THIENO[3,2-E][1,3]DIAZEPINE

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Starting from the tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepine (**2a**) we obtained thio-and dithiolactam **3a** and **4a** by action of one or two equivalents of Lawesson's reagent. Dithiolactam **4a** treated with mercuric chloride in boiling water led to the monolactam **5a**. This latter was also synthesized with good yields using another pathway in which the thionation reaction was performed on N-(thien-2'-ylmethyl)-5-oxoproline methyl ester precursor (**1a**) before the cyclization step.

Keywords: Lawesson's reagent; thionation; pyrrolothienodiazepine; mercuric chloride;schmidt reaction

INTRODUCTION

The synthesis of pyrrolo[1,4]benzodiazepines has been of interest since these compounds exhibit interesting pharmacological activities.[1] Recently we have reported the synthesis of pyrrolothienol[1,3]diazepines[2,3] analogous to benzo[1,3]diazepines which are less described in the literature. In order to synthesize derivatives of tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepines (**2a**), we decided to investigate the conversion of lactam to thio- and dithiolactam in order to improve the low reactivity of the two lactam functions.[4,5]

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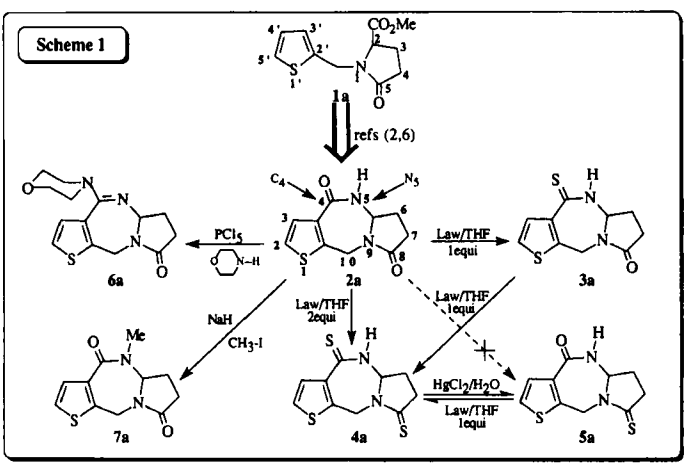
RESULTS AND DISCUSSION

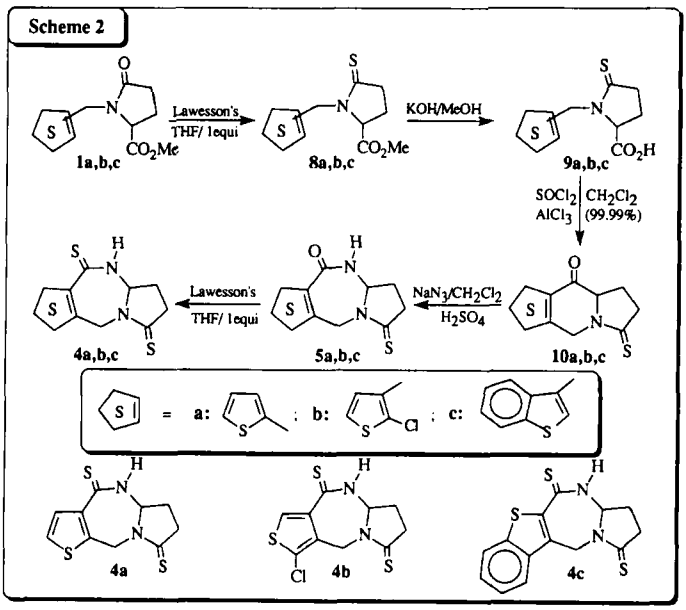
Starting compound **2a** was obtained from N-(thien-2′-ylmethyl)-5-oxoproline methyl ester (**1a**) *via* a Schmidt reaction on a thienoindolizinedione which gave better results than the Beckmann rearrangement of the corresponding oxime.[6] The thiolactams **3a** and **5a** were selectively obtained as indicated in Scheme 1.

In fact, dilactam **2a** was treated with one or two equivalents of Lawesson's reagent in boiling tetrahydrofuran which led to the thiolactam **3a** and the dithiolactam **4a**, respectively. Whatever the amount of Lawesson's reagent used, thiolactam **5a** was not directly obtained from the corresponding dilactam **2a**. This latter was synthesized by boiling in water the mercuric chloride salt of dithiolactam **4a** as previously reported for the [1,4]benzodiazepine systems.[7] As expected, only the C_4-N_5 lactam moiety of **2a** was sensitive to nucleophilic or electrophilic reagents. Nucleophilic substitution on C_4 atom was performed *via* a non isolated imidoylchloride derivative by action of phosphorus pentachloride in dry toluene which then reacted with anhydrous morpholine to form the aminodiazepine **6a** in a yield of 77%.[8,9] On the other hand, the N_5-alkylation of dilactam **2a** was accomplished as follow. The intermediate sodium salt, resulting from the reaction between **2a** and sodium hydride (60% in mineral oil) in dry N,N-dimethylformamide, was converted to the expected N-methylderivative **7a** in 89% yield by reaction with methyl iodide.[8,9]

In order to improve the yield of the synthesis of **5a** (29% from starting N-(thien-2′-ylmethyl)-5-oxoproline methyl ester (**1a**); Scheme 1) we have investigated another way in which the cyclization step takes place after thionation (Scheme 2). Actually N-(thien-2′-ylmethyl)-5-oxoproline methyl ester (**1a**) was



SCHEME 1



SCHEME 2

thionated with one equivalent of Lawesson's reagent in THF at reflux. This led to the corresponding thione **8a**. Classical saponification of the ester function of **8a** gave the carboxylic acid **9a** which was cyclized under Friedel-Crafts conditions[10] using aluminium trichloride of high quality (99.99%) as a catalyst. The expected ketone **10a** was obtained in a good yield (75%). Finally, the Schmidt reaction of the ketone function of **10a** gave the thione **5a**. As reported elsewhere,[6] it must be pointed out that this reaction led only to a [1,3]diazepine and that we did not observe the possible [1,4]diazepine. The overall yield for the five steps transformation starting from **1a** was 46%. We have extended this scope to the synthesis of thieno[4,3-e][1,3]diazepine **5b** and [1]benzothieno[2,3-e][1,3]diazepine **5c**. As described above, N-(2′-chlorothien-3′-ylmethyl)-5-oxoproline methyl ester (**1b**) and N-([1]benzothien-3′-ylmethyl)-5-oxoproline methyl ester (**1c**) led to **5b** in an overall yield of 55% and **5c** in an overall yield of 32%, respectively. The low yield of **5c** can be explained by the low reactivity of the [1]benzothiophene ring compared to the thiophene nucleus.

All the intermediates and final compounds have been characterized by their IR and NMR spectra as well as by their microanalysis; details of the data are reported in the experimental section (see Tables I to V), but there are some features of interest. Thus the ^{1}H NMR spectrum of compound **5a** showed great similarities with the one of the non thionated analogue **2a**.[10] In particular, the

TABLE I Analytical and spectral data of esters **8a,b,c** and carboxylic acids **9a,b,c**

N°	mp°C	Yield%	Recrystallization chromatography*	Formula	Analyses: Calcd./Found		
					C%	H%	N%
8a	liquid	87	SiO_2-A-B	$C_{11}H_{13}NO_2S_2$	51.74/51.49	5.13/5.09	5.49/5.38
8b	liquid	83	SiO_2-B-C	$C_{11}H_{12}ClNO_2S_2$	45.59/45.35	4.17/4.11	4.83/4.79
8c	89	82	A-B	$C_{15}H_{15}NO_2S_2$	58.99/58.90	4.95/4.89	4.59/4.38
9a	116	82	B-C	$C_{10}H_{11}NO_2S_2$	49.77/49.58	4.59/4.38	5.80/5.67
9b	126	87	C	$C_{10}H_{10}ClNO_2S_2$	43.55/43.45	3.66/3.49	5.08/4.99
9c	166	85	A-C	$C_{14}H_{13}NO_2S_2$	57.71/57.60	4.50/4.31	4.81/4.72

N°	IR (KBr) ν in cm^{-1} C=O	O-H(br)	^1H NMR data ($CDCl_3$/TMS internal), δ in ppm. Pyr: pyrrolidine; Th: thiophene and Bt: [1]benzothiophene.
8a	1705	—	2.14–2.46 (m, 2H, 2H-Pyr), 3.10–3.16 (m, 2H, 2H-Pyr), 3.8 (s, 3H, CH_3), 4.5 (dd, 1H, J = 3.3 and 9.3 Hz, 1H-Pyr), 4.72 (d, 1H, J = 14.8HzH, CH_2-N), 5.86 (d,1H, J = 14.8 Hz, CH_2-N), 6.95–7.13 (m, 2H, 2H-Th),7.32–7.40 (m, 1H, 1H-Th).
8b	1712	—	1.82–2.33 (m, 2H, 2H-Pyr), 2.91–3.1 (m, 2H, 2H-Pyr), 3.63 (s, 3H, CH_3), 4.25(dd,1H, J = 3.3 and 9.4 Hz, 1H-Pyr), 4.5 (d, 1H, J = 14.8 Hz, CH_2-N), 5.38(d, 1H, J = 14.8 Hz, CH_2-N), 6.92 (d, 1H, J = 5.7 Hz, 1H-Th), 7.01(d,1H,J = 5.7Hz, 1H-Th).
8c	1723	—	2.0–2.16 (m, 2H, 2H-Pyr), 3.06–3.12 (m, 2H, 2H-Pyr), 3.57 (s, 3H, CH_3), 4.15(dd, 1H, J =3.3 and 9.4 Hz, 1H-Pyr), 4.71 (d, 1H, J = 14.8 Hz, CH_2-N), 5.85(d, 1H, J =14.8 Hz, CH_2-N), 7.3 (s, 1H, 1H-Bt), 7.34–7.37 (d, 2H, 2H-Bt),7.82–7.84 (m, 2H, 2H-Bt).
9a	1688	3423	2.02–2.42 (m, 2H, 2H-Pyr), 2.44–2.78 (m, 2H, 2H-Pyr), 4.23 (dd, 1H, J = 3.4 and 9.5Hz, 1H-Pyr), 4.28 (d, 1H, J = 14.5 Hz, CH_2-N), 5.26 (d, 1H, J = 14.5Hz, CH_2-N),6.81–6.96 (m, 2H, 2H-Th), 7.09–7.23 (m, 1H, 1H-Th), 10.05 (br, 1H,OH).
9b	1638	3359	2.07–2.39 (m, 2H, 2H-Pyr), 2.39–2.68 (m, 2H, 2H-Pyr), 4.04 (dd, 1H, J = 3.2 and 9.4 Hz,1H-Pyr), 4.15 (d, 1H, J = 15 Hz, CH_2-N), 4.91 (d, 1H, J = 15 Hz, CH_2-N),6.85(d,1H, J = 5.6 Hz, 1H-Th), 7.05(d, 1H, J = 5.6 Hz, 1H-Th), 9.68 (br,1H, OH).
9c	1724	3450	1.64–1.92 (m, 2H, 2H-Pyr), 2.55–2.82 (m, 2H, 2H-Pyr), 3.61–3.82 (m,1H, 1H-Pyr),4.17(d, 1H, J =15 Hz, CH_2-N), 5.55 (d,1H, J = 15 Hz, CH_2-N),6.92–6.94 (m, 2H, 2H-Bt),7.03 (s, 1H, 1H-Bt),7.41–7.44 (m, 2H,2H-Bt), 10.1(br, 1H, OH).

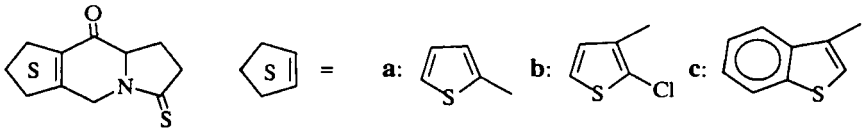
*:Solvents used for recrystallization or chromatography, A: Dichloromethane, B: Hexane, C: Diethyl ether, D: Ethanol, E: Ethyl acetate. (br): broad.

protons of the methylene group (CH_2-N) appear as an AB system with a marked difference of chemical shift of 1,1 ppm in **5a** compared to those of the dilactam **2a** (0.39 ppm).

EXPERIMENTAL SECTION

All melting points were determined using a Leitz heat plate apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR paragon

TABLE II Yields and physical data of cyclic Thioamide-Ketones **10a,b,c**



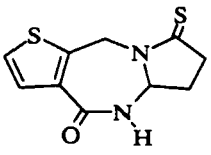
10a,b,c **10a** **10b** **10c**

N°	mp°C	Yield%	Recrystallization	Formula	Analyses: Calcd./Found		
					C%	H%	N%
10a	168	75	diethyl ether	$C_{10}H_9NOS_2$	53.79	4.06	6.27
					53.65	3.99	6.18
10b	154	85	diethyl ether	$C_{10}H_8ClNOS_2$	46.60	3.13	5.43
					46.49	3.05	5.32
10c	129	70	hexane/ligroïn	$C_{14}H_{11}NOS_2$	61.51	4.06	5.12
					61.48	4.00	5.06

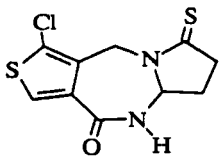
N°	IR (KBr) υ in cm^{-1}		^1H and ^{13}C NMR ($CDCl_3$/TMS internal), δ in ppm. Pyr: pyrrolidine; Th: thiophene and Bt: [1]benzothiophene.
	C=O	C=S	
10a	1711	1200	2.30–2.54 (m, 4H, 4H-Pyr), 4.21 (m, 1H, 1H-Pyr), 4.31 (d, 1H, J = 17.6 Hz, CH_2-N), 5.39 (d, 1H, J = 17.6 Hz, CH_2-N), 7.16 (d, 1H, J = 5.3 Hz, 1H-Th), 7.36 (d, 1H, J = 5.3 Hz, 1H-Th). 20.1 (CH_2), 29.8 (CH_2), 39.3 (CH_2), 61.4 (CH), 124.5 (CH), 125 (CH), 135.5(C), 150.8 (C), 173.8 (C=S), 189.1 (C=O).
10b	1682	1252	2.34–2.39 (m, 2H, 2H-Pyr), 2.40–2.45 (m, 2H, 2H-Pyr), 3.95 (d, 1H, J = 15.4 Hz, CH_2-N), 4.11–4.42 (m, 1H, 1H-Pyr), 4.3 (d, 1H, J = 15.4 Hz, CH_2-N), 8.13 (s, 1H, 1H-Th). 19.6 (CH_2), 29.9 (CH_2), 38.1 (CH_2), 62.1 (CH), 124.9 (C), 129.5 (CH), 130.9 (C),134.1 (C), 173.8 (C=S), 189.1 (C=O).
10c	1676	1267	1.15–1.21 (m, 2H, 2H-Pyr), 2.44–2.60 (m, 2H, 2H-Pyr), 4.37 (d, 1H, J = 18 Hz, CH_2-N), 4.43–4.46 (m, 1H, 1H-Pyr), 5.54 (d, 1H, J = 18 Hz, CH_2-N), 7.37–7.57 (m, 2H, 2H-Bt),7.76–7.92 (m, 2H, 2H-Bt). 22.6 (CH_2), 29.6 (CH_2), 39.2 (CH_2), 62.3 (CH), 123.6 (CH), 124 (CH), 125.4 (CH), 128.8 (CH), 133.8 (C), 135.9 (C), 143.1 (C), 143.5 (C), 174.4 (C=S), 189.4 (C=O).

1000 spectrometer. The nuclear magnetic resonance spectra (^1H and ^{13}C) were taken on a Bruker AC-200 (200 MHz) instrument in the solvent indicated. Chemical shifts values are reported in ppm from tetramethylsilane as an internal reference and are given in δ units and the following abbreviations are used: s for singlet, d for doublet, dd for doublet of doublet, t for triplet, br for broad and finally m for multiplet. Elemental analyses were obtained in the microanalysis laboratory of the I.N.S.A at Rouen, F 76130 Mt-St-Aignan. Ascending thin layer chromatography was performed on precoated plates of silica gel 60f 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60F (70–300 mesh) was used for column chromatography. Esters **1a,b,c** were prepared according to the procedure described in the literature.[10]

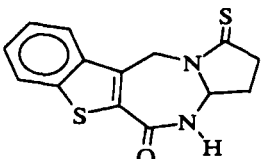
TABLE III Yields and physical data of monothiolactams **5a,b,c**



5a



5b



5c

N°	mp°C	Yield%	recrystallization chromatography*	Formula	Analyses: Calcd./Found		
					C%	H%	N%
5a	189	87	A–B	$C_{10}H_{10}N_2OS_2$	50.40	4.23	11.75
					50.29	4.11	11.56
5b	154	90	B	$C_{10}H_9ClN_2OS_2$	44.03	3.33	10.27
					43.89	3.21	10.19
5c	120	65	SiO_2-A-C	$C_{14}H_{12}N_2OS_2$	58.31	4.19	09.71
					58.12	4.09	09.66

N°	IR (KBr) υ in cm^{-1}		^1H and ^{13}C NMR (DMSO), δ in ppm. Pyr: pyrrolidine; Th: thiophene et Bt: [1]benzothiophene.
	C=O	C=S	
5a	1696	1254	2.01–2.30 (m, 2H, 2H-Pyr), 2.31–2.41 (m, 2H, 2H-Pyr), 4.35 (d, 1 H, J = 16 Hz, CH_2-N), 4.72 (d, 1H, J = 16 Hz, CH_2-N), 5.13–5.17 (m, 1H, 1H-Pyr), 7.26 (d, 1H, J = 5.4 Hz, 1H-Th), 7.47 (d, 1H, J = 5.4 Hz, 1H-Th), 8.72 (d, 1H, NH-amide). 23.7 (CH_2), 29.5 (CH_2), 40.7 (CH_2), 65.8 (CH), 124.6 (C), 129.3 (C), 135.1 (CH), 139.4 (CH), 165.6 (C=S), 172.4 (C=O).
5b	1645	1215	1.90–2.07 (m, 2H, 2H-Pyr), 2.23–2.47 (m, 2H, 2H-Pyr), 4.08 (d, 1H, J = 15.3 Hz, CH_2-N), 4.69 (d, 1H, J = 15.3 Hz, CH_2-N), 4.96–5.01 (m, 1H, 1H-Pyr), 8.14 (s, 1H, 1H-Th), 8.77 (d, 1H, NH-amide). 18.6 (CH_2), 29.4 (CH_2), 42.1 (CH_2), 69.1 (CH), 124.7 (C), 132.8 (CH), 136.9 (C), 138.2 (C), 175.8 (C=S), 181.7 (C=O).
5c	1682	1247	1.99–2.69 (m, 4H, 4H-Pyr), 4.63 (d, 1H, J = 15.4 Hz, CH_2-N), 4.90–4.96 (m, 1H, 1H-Pyr), 5.18 (d, J = 15.4 Hz, CH_2N), 7.41–7.56 (m, 2H, 2H-Bt), 7.82 (d, 1H, J = 7.7 Hz, 1H-Bt), 7.99 (d, 1H, J = 7.7 Hz, 1H-Bt), 8.25 (d, 1H, NH-amide). 25.4 (CH_2), 28.1 (CH_2), 37.1 (CH_2), 75.2 (CH), 108.6 (C), 113.4 (C), 122.5 (CH), 123.8 (CH), 126.1 (CH), 128.3 (CH), 136.1 (C), 140.8 (C), 142.2 (C=S), 174.1 (C=O).

*:Solvents for crystallization or chromatography, A: Dichloromethane, B: Hexane, C: Diethyl ether.

5a,6,7,10-Tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepin-8-one-4(5H)-thione (3a)

A solution of dilactam **2a** (0.5 g, 2.25 mmoles) and Lawesson's reagent (0.46 g, 1.13 mmoles) in dry THF (30 ml) was stirred at gentle reflux for 24 hours. After concentration of the solution, the resultant oily solid residue was passed through a short chromatography column on silica gel eluting with dichloromethane-ligroïn (9:1). The monothiolactam **3a** was obtained in 75% yield; mp = 240°C; IR (KBr) ν cm^{-1}: 3159 (N-H), 1667 (C=O), 1240 (C=S); ^1H NMR (DMSO):

δ ppm 1.97–2.13 (m, 1H, 1H-pyrrolidine), 2.28–2.38 (m, 1H, 1H-pyrrolidine), 2.91–3.03 (m, 2H, 2H-pyrrolidine), 4.82 (d, 1H, J = 17.4 Hz, CH_2-N), 5.14 (d, 1H, J = 17.4 Hz, CH_2-N), 5.42–5.48 (m, 1H, 1H-pyrrolidine), 7.28 (d, 1H, J = 5.4 Hz, 1H-thiophene), 7.55 (d, 1H, J = 5.4 Hz, 1H-thiophene), 8.95 (d, 1H, NH-lactam); ^{13}C NMR (DMSO): δ ppm 25 (CH_2), 42.9 (CH_2), 44.9 (CH_2), 72.8 (CH), 125.5 (CH), 128.9 (CH), 135.3 (C), 138.2 (C), 165.5 (C=S), 199.3 (C=O). *Anal.* Calcd. for $C_{10}H_{10}N_2OS_2$ (238.32): C, 50.40; H, 4.23; N, 11.75. Found: C, 50.18; H, 4.13; N, 11.61.

5a,6,7,10-Tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepine-4(5H),8-dithione (**4a**)

Method A: This compound was obtained in 91% yield according to the procedure described above starting from dilactam **2a** (0.5 g, 2.25 mmoles) and Lawesson's reagent (0.92 g, 2.27 mmoles). The physical and spectral data of this product are summarized in Table IV.

Method B: Monothiolactam **3a** or **5a** (0.5 g, 2.1 mmoles) with Lawesson's reagent (0.46 g, 1.13 mmoles) was transformed in the same manner as for **3a** into the expected dithiolactam **4a** in a yield of 89 and 90%, respectively. Characteristics of this product are identical to those cited in Table IV.

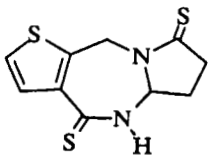
1-Chloro-5a,6,7,10-tetrahydropyrrolo[1,2-a]thieno[4,3-e][1,3]diazepine-4(5H),8-dithione (**4b**) *and 2,3,3a,11-Tetrahydropyrrolo[1,2-a][1]benzothieno[2,3-e][1,3]diazepine-1(4H),5-dithione* (**4c**)

These products were obtained in the same manner as described for dithione **4a** by reaction between thioamide **5b** or **5c** and 1 equivalent of Lawesson's reagent. Physical data of these products are collected in Table IV.

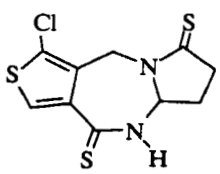
5a,6,7,10-Tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepin-4(5H)-one-8-thione (**5a**)

To a stirred solution of the dithiolactam **4a** (0.5 g, 1.97 mmoles) in 30 ml of water was added 5.35 g (19.7 mmoles) of mercuric chloride. After 12 hours of reflux, the cold solution was diluted with dichloromethane and filtered. The biphasic filtrate was evaporated to dryness under reduced pressure. The yellow residue was recrystallized from diethyl ether-hexane to give **5a** in 92% yield. Physical data of this product are identical to those reported in Table III.

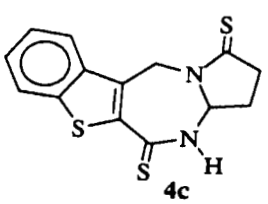
TABLE IV Yields and physical data of pyrrolothieno([1]benzothieno])diazepinedithiones **4a,b,c**



4a



4b



4c

N°	*mp°C*	*Yield%*	*chromatography*	*Formula*	*Analyses: Calcd./Found*		
					C%	*H%*	*N%*
4a	213	91	SiO_2-A-B	$C_{10}H_{10}N_2S_3$	47.22	3.96	11.01
					47.09	3.85	10.88
4b	141	85	SiO_2-B-C*	$C_{10}H_9ClN_2S_3$	41.59	3.14	9.70
					41.48	3.05	9.50
4c	263	77	SiO_2-A-D	$C_{14}H_{12}N_2S_3$	55.23	3.97	9.20
					55.17	3.70	9.09

N°	IR (KBr)υ In cm^{-1}		^1H and ^{13}C NMR (DMSO), δ in ppm.
	C=S	N-H(br)	Pyr: pyrrolidine; Th: thiophene et Bt: [1]benzothiophene.
4a	1266	3163	2.04–2.35 (m, 2H, 2H-Pyr), 2.83–3.06 (m, 2H, 2H-Pyr), 4.63 (d, 1H, J = 17.5 Hz, CH_2-N), 5.08 (d, 1H, J = 17.5 Hz, CH_2-N), 5.55 (d, 1H, J = 5.4 Hz, 1H-Pyr), 7.44 (d, 1H, J = 5.3 Hz, 1H-Th), 7.48 (d, 1H, J = 5.4 Hz, 1H-Th), 10.04 (s, 1H, NH-amide).
	1203		24.2 (CH_2), 43 (CH_2), 45.1 (CH_2), 75.5 (CH), 124.9 (CH), 131.8 (CH), 134.4 (C), 140.8 (C), 194.2 (C=S), 199.6 (C=S).
4b	1254	3187	2.11–2.30 (m, 2H, 2H-Pyr), 2.85–3.11 (m, 2H, 2H-Pyr), 4.23 (d, 1H J = 16 Hz, CH_2-N), 5.21 (d, 1H, J = 16 Hz, CH_2-N), 5.40–5.43 (m, 1H, 1H-Pyr), 8.16 (s, 1H, 1H-Th), 8.84 (s, 1H, NH-amide).
	1200		20.6 (CH2), 39.4 (CH2), 48.1 (CH2), 72.1 (CH), 124.5 (C), 129.5 (CH), 138.9 (C), 142.1 (C), 193.8 (C=S), 198.1 (C=S).
4c	1250	3163	2.31–2.37 (m, 2H, 2H-Pyr), 2.91–3.06 (m, 2H, 2H-Pyr), 5.20 (s, 2H, CH_2-N), 5.71–5.74 (m, 1H, 1H-Pyr), 7.48–7.53 (m, 2H, 2H-Bt), 7.92–8.09 (m, 2H, 2H-Bt), 8.6 (s, 1H, NH-amide).
	1198		25.3 (CH_2), 42.6 (CH_2), 45.7 (CH_2), 75.1 (CH), 122.9 (CH), 123.5 (CH), 125.2 (CH), 127.3 (CH), 129.3 (C), 137.9 (C), 141.1 (C), 142.2 (C), 191.7 (C=S), 200.8 (C=S).

*: Solvents of chromatography, A: Diethyl ether, B: Ethyl acetate, C: Ligroïn, D: Hexane. Product **4b** was purified again by recrystallization from diethyl ether-ligroïn. br: broad.

4-(4'-Morpholinyl)-5a,6,7,10-tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepin-8-one (**6a**)

A mixture of 1 g (4.49 mmoles) of 5a,6,7,10-tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepine-4(5H),8-dione (**2a**), 1.1 g (5.3 mmoles) of phosphorus pentachloride and 25 ml of dry toluene was stirred at room temperature for 30

minutes and then at reflux for 15 minutes. The reaction mixture was concentrated in *vacuo*. To this iminochloride was added 10 ml of dry morpholine and the mixture was refluxed with stirring for 2 hours. The reaction mixture was cooled and concentrated in *vacuo* and the residue was triturated with 100 ml of dry diethyl ether and filtered. Removal of the solvent in *vacuo* afforded an oily product which was purified by passing through a silica gel column using diethyl ether as eluent. Evaporation of the solvent afforded a solid in 77% yield. An analytical sample of **6a** (mp = 118°C) was obtained as yellow prisms by recrystallization from diethyl ether-ligroïn; IR (KBr) ν cm^{-1}: 2965-2859 (C-H), 1657 (C=O), 1654 (C=N); ^1H NMR ($CDCl_3$): δ ppm 1.80–2.02 (m, 2H, 2H-pyrrolidine), 2.29–2.37 (m, 6H, 2H-pyrrolidine + 4H-morpholine), 3.49–3.53 (m, 2H, 2H-morpholine), 4.35 (dd, 1H, J = 2.5 and 7.8 Hz, 1H-pyrrolidine), 4.69 (d, 1H, J = 15.4 Hz, CH_2-N), 4.81 (d, 1H, J = 15.4 Hz, CH_2-N), 7.09 (d, 1H, J = 5.4 Hz, 1H-thiophene), 7.26 (d, 1H, J = 5.4 Hz, 1H-thiophene); ^{13}C NMR ($CDCl_3$): δ ppm 16.8 (CH_2), 29.4 (CH_2), 37.3 (CH_2), 46.2 ($2CH_2$), 66.5 ($2CH_2$), 76.3 (CH), 110.1 (C), 114.4 (C), 126.7 (CH), 127.9 (C=N), 174.2 (C=O). *Anal.* Calcd. for $C_{14}H_{17}N_3O_2S$ (291.36): C, 57.71; H, 5.88; N, 14.42. Found: C, 57.38; H, 5.63; N, 14.21.

5-Methyl-5a,6,7,10-tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepine-4,8-dione (**7a**)

To a well stirred suspension of 0.24 g (10 mmoles) of sodium hydride (60% in mineral oil) and 15 ml of anhydrous N,N-dimethylformamide in a nitrogen atmosphere was added slowly 1 g (4.49 mmoles) of 5a,6,7,10-tetrahydropyrrolo[1,2-a]thieno[3,2-e][1,3]diazepine-4(*5H*),8-dione (**2a**). When the addition was complete, the mixture was stirred at room temperature for 2 hours, then a solution of 1 g (7 mmoles) of methyl iodide in 5 ml of DMF was added dropwise. After reaction under stirring for 2 hours, the reaction mixture was poured onto crushed ice and the cristalline material formed was filtered off, dried and recrystallized from diethyl ether to give pure dilactam **7a** in 89% yield. mp = 162°C; IR (KBr) ν cm^{-1}: 2946-2865 (C-H), 1685 (C=O), 1709 (C=O); ^1H NMR ($CDCl_3$): δ ppm 2.13–3.22 (m, 4H, 4H-pyrrolidine), 3.61 (s, 3H, CH_3-N), 4.31 (d, 1H, J = 15.8 Hz, CH_2-N), 4.81 (d, 1H, J = 15.8 Hz, CH_2-N), 5.39 (t, 1H, 1H-pyrrolidine), 7.13 (d, 1H, J = 5.4 Hz, 1H-thiophene), 7.31 (d, 1H, J = 5.4 Hz, 1H-thiophene); ^{13}C NMR ($CDCl_3$): δ ppm 21.2 (CH_2), 28.5 (CH_2), 30.6 (CH_2), 39.6 (CH_3), 70.6 (CH), 124.1 (CH), 129.2 (CH), 136.1 (C), 166.6 (C=O), 172.2 (C=O). *Anal.* Calcd. for $C_{11}H_{12}N_2O_2S$ (236.29): C, 55.92; H, 5.12; N, 11.86. Found: C, 55.68; H, 5.03; N, 11.71.

N-thienylmethyl (or N-[1]benzothienylmethyl)-5-thioproline methyl ester **8a,b,c**: *General Procedure*

To a stirred solution of N-thienylmethyl (or N-[1]benzothienylmethyl)-5-oxoproline methyl ester **1a,b,c** (2 mmoles) in 20 ml of dry THF was added 0.6 g (1.5 mmoles) of Lawesson's reagent. The mixture was refluxed for 12 hours, cooled, then concentrated in *vacuo* under reduced pressure. The crude oily residue was purified by chromatography on silica gel column to give suitable products in good yields. In the case of thioamide-ester **8c**, an analytical sample was obtained by recrystallization from dichloromethane-hexane. All physical data of these products are summarized in Table I.

N-thienylmethyl (or N-[1]benzothienylmethyl)-5-thioprolines **9a,b,c**: *General Procedure*

A stirred mixture of N-thienylmethyl (or N-[1]benzothienylmethyl)-5-thioproline methyl ester **1a,b,c** (0.1 mole) and 150 ml of 1.5 M potassium hydroxide solution was refluxed for 90 min. The cold solution was washed with dichloromethane and the aqueous solution was acidified with concentrated HCl. The cristalline precipitate was filtered off, washed with cold water and recrystallized from a suitable solvent as indicated in Table I. Sometimes, the carboxylic acid was extracted from the aqueous solution by dichloromethane.

Thieno or [1]benzothienoindolizinonethiones **10a,b,c**: *General Procedure*

A stirred suspension of 2.21 mmoles of carboxylic acids **9a**, **9b** or **9c** in 15 ml of dry dichloromethane was treated slowly with thionyl chloride (0.29 g, 2.43 mmoles) and refluxed for 1.5 hours. After cooling, the solution was concentrated in *vacuo* and the liquid residue was dissolved in 20 ml of anhydrous dichloromethane then treated portionwise with aluminium trichloride (99.99%) (0.7 g, 5.13 mmoles) at 0–5°C. After reaction for 1 hour at room temperature, the solution was poured into cold water and decanted. The aqueous layer was extracted with dichloromethane (10 ml) and the organic layers were washed with brine, water, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The resulting solid was recrystallized from a suitable solvent to give ketone **10**. Physical data of the ketones are summarized in Table II.

Schmidt Rearrangement of Thioamides-ketones 10a,b,c into [1,3]diazepinonethiones 5a,b,c

To a well stirred solution of ketone **10a,b,c** (2.71 mmoles) in 20 ml of dry dichloromethane was added dropwise under cooling over 15 minutes 2 ml of concentrated sulfuric acid. After 10 minutes of reaction, sodium azide (0.7 g, 10.7 mmoles) was added over a period of 30 minutes and the reaction mixture was allowed to stand at room temperature for 24 hours. The solution was basified with potassium carbonate solution to pH 8–9 and decanted. The aqueous solution was extracted with dichloromethane (2 × 20 ml). The organic phase was washed with saturated brine, dried, filtered and concentrated to give a solid. Recrystallization or chromatography as indicated in Table III afforded diazepinonethiones **5a,b,c**. Compound **5a** (87%) was identical to the sample prepared above from dilactam **2a** and Lawesson's reagent.

References and Notes

[1] D. E. Thurston, V. S. Murty, D. R. Langley and G. B. Jones, *Synthesis*, **81**, (1980).
[2] S. Marchalin and B. Decroix, *J. Heterocyclic Chem.*, **30**, 667, (1993).
[3] A. Daïch,P. Ohier and B. Decroix, *J. Heterocyclic Chem.*, **32**, 1731, (1995).
[4] D. E. Thurston and D. R. Langley, *J. Org. Chem.*, **51**, 705, (1986).
[5] T. Kaneko, H. Wong and T. W. Doyle, *Tetrahedron Lett.*, **24**, 5165, (1983).
[6] D. Lebosquain and B. Decroix, *Heterocycles*, **36**, 2303, (1993).
[7] M. P. Foloppe, S. Rault and M. Robba, *Tetrahedron Lett.*, **33**, 2803, (1992).
[8] A. Daïch and B. Decroix, *Bull. Soc. Chim. France*, **129**, 360, (1992).
[9] F. Povazanec, B. Decroix and J. Morel, *J. Heterocyclic Chem.*, **29**, 1507, (1992).
[10] S. Marchalin, B. Decroix and J. Morel, *Acta Chemica Scand.*, **47**, 287, (1993).