

Synthesis and Schmidt Rearrangement into  
[1,3]Diazepines Derivatives

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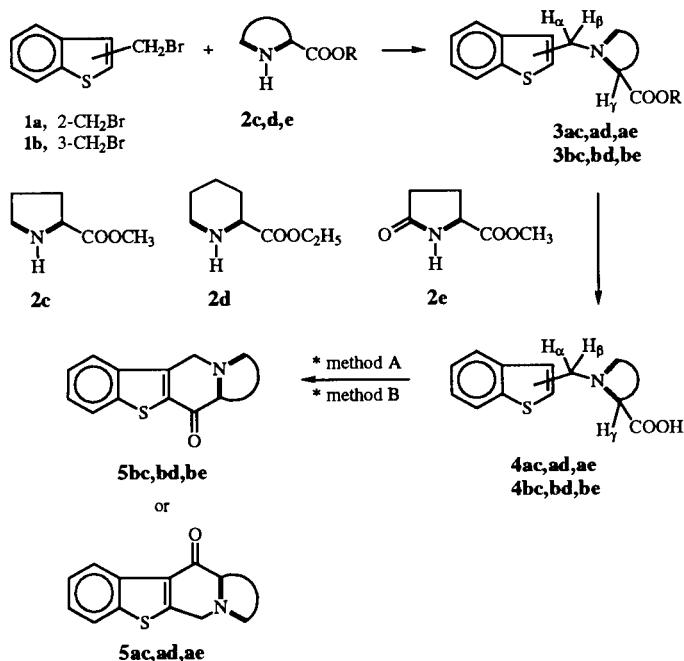
Dedicated to the memory of Professor Nicholas Alexandrou

[1]Benzothienoindolizidinones **5ac,ae,bc** and [1]Benzothienoquinolizidinone **5ad** were synthesized from 2(3)-bromomethyl[1]benzothiophene and methyl prolinates, methyl oxoprolinate and ethyl pipercolinate. The Schmidt rearrangement of ketones **5** led exclusively to the [1,3]diazepines derivatives **6**.

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Within the scope of a research program on cyclized derivatives of both [1]benzothiophene and pyrrolidine or piperidine we have studied the cyclization of the *N*-(2-[1]benzothienylmethyl)-5-oxoproline, *N*-(2-[1]benzothienylmethyl)pipecoline, *N*-(2(3)-[1]benzothienylmethyl)proline into indolizidinones, or quinolizidinones fused to a [1]benzothiophene system. Investigations have been performed by us in the [1]benzothiophene series [1,2] or the thiophene series [1-4].

Scheme 1



\* method A: Polyphosphoric acid, 90°  
\* method B: 1) SOCl<sub>2</sub> 2) AlCl<sub>3</sub>

Indolizidines **4ac,ae,bc** or quinolizidine **4ad** are synthesized according to Scheme 1. Condensation of the 2(3)-bromomethyl[1]benzothiophenes **1a,b** [5,6] with amino esters **2c,d** [2,7], amino ester **2e** [8] gave the condensed products **3ac,ad,ae,bc**. The reaction was carried out in the

presence of acetonitrile and an equivalent of potassium carbonate when amino esters **2c,d** were used and in the presence of dimethylformamide with the sodium salt of **2e** (prepared by the action of sodium hydride with 5-oxoproline methyl ester). Saponification of the esters **3ac,bc** led to the corresponding amino acids **4ac,bc** isolated as hydrochloride salts in 77 and 90% yields, respectively. Saponification of the amido ester **3ae** gave the amido acid **4ae** in 71% yield. Saponification of the amino ester **3ad** gave a bad result, so an acidic hydrolysis was used and the acid **4ad** was obtained directly as the hydrochloride salt in 64% yield.

We previously reported [2] that *N*-(3-[1]benzothienylmethyl)pipecolinic acid (**4bd**) was cyclized to ketone **5bd** with polyphosphoric acid and *N*-(3-[1]benzothienylmethyl)-5-oxoproline (**4be**) was cyclized to ketone **5be** through a Friedel-Crafts intramolecular cyclization [1]. With *N*-(2(3)[1]benzothienylmethyl)prolines **4ac,bc** and *N*-(2-[1]benzothienylmethyl)pipecoline **4ad** the best results were observed when the hydrochloride salts of the amino acids were treated with polyphosphoric acid (method A) at 90° during 6 hours under a nitrogen atmosphere. In these conditions, the ketones **5ac,bc,ad** were obtained in an acceptable yield (see Table 1). In a similar manner the *N*-(2-[1]benzothienylmethyl)-5-oxoproline **4ae** gave the ketone **5ae** in a 51% yield. For this latter case the best result was obtained when the amido acid **4ae** was treated according to method B. Actually, it was first treated with thionyl chloride in dichloromethane and the resulting acid chloride, under Friedel-Crafts cyclization conditions using aluminium trichloride of high quality as a catalyst, gave the ketone **5ae** in better yield (81%).

All of these compounds were characterized by ir and nmr spectroscopy and microanalysis. Details are reported in Table 1 and in the Experimental. In the <sup>1</sup>H nmr spectra of all the ketones **5** we observe the non equivalence of the methylene protons H<sub>α</sub> and H<sub>β</sub> located between the thiophene nucleus and the nitrogen atom. The H<sub>α</sub> (axial) and H<sub>β</sub> (equatorial) protons have a marked difference in chemical shifts according to the observation made by Sollhuber

Table 1

No.	Compound	Cyclization method A or B and yield (%)	<sup>1</sup> H NMR (deuteriochloroform), δ (ppm)		
			δ H <sub>α</sub> δ H <sub>β</sub>	J (Hz) α,β-α,γ	δ H <sub>γ</sub>
5ac		A 52	3.90 dd 4.39 d	16-2.3 16	3.08-3.15 m
5ad		A 48	3.82 dd 4.13 d	16-2.3 16	3.03-3.09 m
5ae		A 51 B 81	4.39 dd 5.45 d	18-1.8	4.29-4.33 m
5bc		A 50	3.79 dd 4.50 d	15-2.3 15	3.19-3.28 m
5bd		A 62	3.66 dd 4.37 d	18-2.4 18	2.94-3.14 m
5be		B 70	4.48 dd 5.42 d	18-1.7 18	4.63-4.73 m

[9] and by us in our previously reported papers [1,3,4]. Furthermore the axial proton appears as a doublet of a doublet with coupling constants of  $J = 15-18$  Hz ( $H_{\alpha}$ ,  $H_{\beta}$ ) and  $J = 1.7-2.4$  Hz ( $H_{\alpha}$ ,  $H_{\gamma}$ ) while the equatorial proton appears as a doublet with a coupling constant of  $J = 15-18$  Hz ( $H_{\alpha}$ ,  $H_{\beta}$ ). This allows us to assign compound **5** a *trans* indolizidine or quinolizidine configuration.

We reported that thienoindolizidinones [3], thienoquinolizidinones [4] and thienoindolizidinediones [3] under Schmidt rearrangement conditions (ketone in solu-

tion of dichloromethane, sodium azide, concentrated sulfuric acid, room temperature) gave [1,3] or/and [1,4]diazepines. The mixture [1,3]- and [1,4]diazepines was observed when the carbonyl group occupies the  $\beta$  position of the thiophene ring. In all other cases only the [1,3]diazepine was obtained. Therefore, it was interesting to study the influence of a [1]benzothiophene ring annelated to an indolizidinone or quinolizidinone system (Scheme 2).

Whatever the starting ketone **5** treated with sodium azide in concentrated sulfuric acid we isolated only the [1,3]diazepines **6** in 45 to 80% yields (see Table 2). In contrast to the results observed in the thiophene series we did not observe the possible [1,4]diazepine concurrent with the migration of the [1]benzothiophene system.

The structures of the [1,3]diazepines **6** are supported by their ir and nmr spectra as well as their microanalyses. Details are reported in the Experimental and in Table 2. In the <sup>1</sup>H nmr spectra of **6** we observe that the chemical shifts of the  $H_{\gamma}$  proton 4.5-4.7 ppm (**6ac,ad,bc,bd**) and 5.3-5.5 ppm (**6ae,be**) are in accordance with those observed for the thiophene analog respectively, 4.3-4.7

Scheme 2

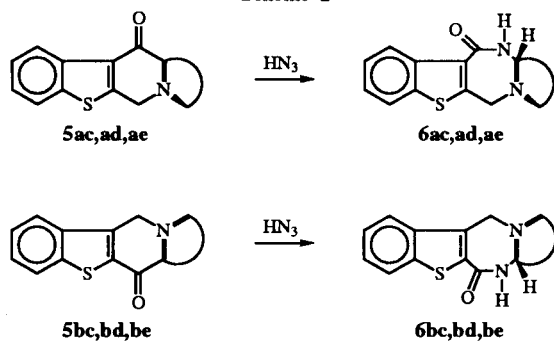


Table 2

No.	Compound	Cyclization method A or B and yield (%)	<sup>1</sup> H NMR (deuteriochloroform), δ (ppm)			δNH
			δ H <sub>α</sub> δ H <sub>β</sub>	J (Hz) α,β-α,γ	δ H <sub>γ</sub>	
6ac		65	4.23 d 4.49 d	15.6 15.6	4.46-4.57 m	7.15 s
6ad		51	4.27 d 4.52 d	14.1 14.1	4.71-4.80 m	6.88 s
6ae		51	4.45 d 4.79 d	17.3 17.3	5.43-5.53 m	7.21 s
6bc		80	4.19 d 4.45 d	15.2 15.2	4.44-4.54 m	7.12 s
6bd		53	4.29 d 4.51 d	17.9 17.9	4.64-4.78 m	8.12 s
6be		45	4.72 d 5.23 d	18.4 18.4	5.32-5.45 m	9.05 s

ppm and 5.1-5.2 ppm because H<sub>γ</sub> is located between the two nitrogen atoms in [1,3]diazepine **6**. The signal is shifted downfield compared to the corresponding ketone **5** ( $\Delta\delta = 1.1$  to  $1.5$  ppm). On the other hand, the H<sub>α</sub> and H<sub>β</sub> protons appear as doublets with a coupling constant of 14.1 to 18.4 Hz.

In summary, we report an efficient synthesis of [1]benzothienindolizidinones and [1]benzothienoquinolizidinones. The Schmidt rearrangement of these ketones gave exclusively [1,3]diazepine derivatives concurrent with the migration of the alkyl group and no migration of the [1]benzothiophene group was observed.

## EXPERIMENTAL

Melting points were taken on a hot-stage apparatus and elemental analyses were obtained in the microanalysis laboratory of the Institut National des Sciences Appliquées, Rouen. The <sup>1</sup>H and <sup>13</sup>C nmr spectra were recorded on a Bruker AC200 instrument in deuteriochloroform and chemical shifts ( $\delta$ ) are expressed in ppm relative to internal TMS. The infrared spectra

of solids (potassium bromide) and liquids (neat) were recorded on a Perkin Elmer, Paragon 1000 spectrometer. The required 2(3)-bromomethyl[1]benzothiophenes were synthesized as previously described [5,6].

### Esters **3ac,ad,bc**. General Procedure.

A mixture of **2** (0.035 mole), potassium carbonate (5.4 g, 0.026 mole) and 50 ml of acetonitrile was stirred under reflux for 1 hour. Then, a solution of 2(3)-bromomethyl[1]benzothiophene **1a(1b)** (7.95 g, 0.035 mole) in 20 ml of acetonitrile was added slowly and the mixture was refluxed for 15 minutes. The cooled resulting suspension was filtered off. The resultant solution was concentrated and a distillation under reduced pressure or a recrystallization gave the alkylated products **3**.

### 2-[(2-Methoxycarbonyl)pyrrolidin-1-ylmethyl][1]benzothiophene (**3ac**).

This compound was obtained in a yield of 68%, bp<sub>0.3</sub> 125-130°; ir: 1730 (CO) cm<sup>-1</sup>; <sup>1</sup>H nmr:  $\delta$  1.66-2.00 (m, 3H, 3H proline), 2.00-2.41 (m, 3H, 3H proline), 3.41-3.48 (m, 4H, O-CH<sub>3</sub> and H<sub>γ</sub> proline), 4.01 (d, 1H, J = 12 Hz, H<sub>α</sub>), 4.88 (d, 1H, J = 12 Hz, H<sub>β</sub>), 7.00-7.33 (m, 3H, 3H benzothiophene), 7.53-7.83 (m, 2H, 2H benzothiophene).

Anal. Calcd. for C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub>S: C, 65.42; H, 6.22; N, 5.08. Found: C, 65.16; H, 6.01; N, 4.81.

3-[(2-Methoxycarbonyl)pyrrolidin-1-ylmethyl][1]benzothiophene (**3bc**).

This compound was obtained in a yield of 70%, mp 60-61° (petroleum ether); ir: 1730 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  1.68-2.00 (m, 3H, 3H proline), 3.41-3.49 (m, 3H, 3H proline), 3.69-3.75 (m, 4H, OCH<sub>3</sub> and H <sub>$\gamma$</sub> ), 4.1 (d, 1H, J = 12 Hz, H <sub>$\alpha$</sub> ), 4.22 (d, 1H, J = 12 Hz, H <sub>$\beta$</sub> ), 7.30-7.70 (m, 3H, 3H benzothiophene), 7.81-8.12 (m, 2H, 2H benzothiophene).

*Anal.* Calcd. for C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub>S: C, 65.42; H, 6.22; N, 5.08. Found: C, 65.30; H, 5.98; N, 4.92.

2-[(2-Ethoxycarbonyl)piperidin-1-ylmethyl][1]benzothiophene (**3ad**).

This compound was obtained in a yield of 61%, mp 124-125° (petroleum ether); ir: 1735 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  1.26 (t, 3H, CH<sub>3</sub> ethyl), 1.38-1.68 (m, 4H, 4H piperidine), 1.73-1.94 (m, 2H, 2H piperidine), 2.29-2.42 (m, 1H, 1H piperidine), 2.89-3.05 (m, 1H, 1H piperidine), 3.27 (t, 1H, H <sub>$\gamma$</sub>  piperidine), 3.85 (d, 1H, J = 14.5 Hz, H <sub>$\alpha$</sub> ), 4.01 (d, 1H, J = 14.5 Hz, H <sub>$\beta$</sub> ), 4.17 (q, 2H, CH<sub>2</sub> ethyl), 7.16-7.35 (m, 3H, 3H benzothiophene), 7.58-7.82 (m, 2H, 2H benzothiophene).

*Anal.* Calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>2</sub>S: C, 67.29; H, 6.97; N, 4.61. Found: C, 67.18; H, 6.91; N, 4.55.

2-[(2-Methoxycarbonyl-5-oxopyrrolidin-1-ylmethyl)[1]benzothiophene (**3ae**).

Sodium hydride (1.25 g of a 60% mineral emulsion, 0.028 mole of sodium hydride) was washed with hexane and suspended in 50 ml of anhydrous dimethylformamide. The stirred suspension was treated under nitrogen with a solution of 5-oxoproline methyl ester **2e** (4.0 g, 0.028 mole) in 40 ml of dimethylformamide. The solution was stirred at 65° for 4 hours, then the 2-bromomethyl[1]benzothiophene (**1a**) (6.4 g, 0.028 mole) dissolved in 20 ml of dimethylformamide was added. After 12 hours under reflux, the precipitate was filtered off through Celite and recrystallized in a mixture of dichloromethane-hexane (30/70) to afford the ester **3ae** in a 68% yield, mp 78-79°; ir: 1745 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  2.00-2.79 (m, 4H, 4H oxoproline), 3.80 (s, 3H, O-CH<sub>3</sub>), 4.31-4.39 (m, 1H, H <sub>$\gamma$</sub>  oxoproline), 4.42 (d, 1H, J = 15.4 Hz, H <sub>$\beta$</sub> ), 5.38 (d, 1H, J = 15.4 Hz, H <sub>$\alpha$</sub> ), 7.32-7.58 (m, 3H, 3H benzothiophene), 7.77-8.03 (m, 2H, 2H benzothiophene).

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub>S: C, 62.26; H, 5.22; N, 4.84. Found: C, 61.82; H, 5.01; N, 4.74.

**Acids 4ac,ae,bc.** General Procedure.

A mixture of the ester **3ac,ae,bc** (0.024 mole), potassium hydroxide in pellets (1.45 g, 0.026 mole) and 30 ml of ethanol was refluxed for 3 hours. The resulting solution was evaporated to dryness. The residue was treated with 25% hydrochloric acid solution to pH = 1. The solution was evaporated to dryness and the residue treated with 50 ml of warm ethanol and filtered. The organic layer was evaporated to give a solid. Crystallization from a mixture of acetone-ethanol gave the corresponding hydrochloride **4ac,ae,bc**.

*N*-(2-[1]Benzothienylmethyl)-2-pyrrolidinecarboxylic Acid Hydrochloride (**4ac**).

This compound was obtained in a yield of 77%, mp 176-177°; ir: 3215 (OH), 1720 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  1.98-2.43 (m, 6H, 6H proline), 4.00 (t, 1H, H <sub>$\gamma$</sub> ), 4.25 (d, 1H, J = 16 Hz, H <sub>$\alpha$</sub> ), 5.12 (d, 1H, J = 16 Hz, H <sub>$\beta$</sub> ), 7.10 (s, 1H, H<sub>3</sub> benzothiophene), 7.17-7.28 (m, 2H, 2H benzothiophene), 7.59-7.70

(m, 2H, 2H benzothiophene), 10.2 (br, 1H, OH).

*Anal.* Calcd. for C<sub>14</sub>H<sub>16</sub>ClNO<sub>2</sub>S: C, 56.46; H, 5.41; N, 4.70. Found: C, 56.35; H, 5.21; N, 4.59.

*N*-(3-[1]Benzothienylmethyl)-2-pyrrolidinecarboxylic Acid Hydrochloride (**4bc**).

This compound was obtained in a yield of 90%, mp 181-182°; ir: 3225 (OH), 1730 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  2.10-2.41 (m, 6H, 6H proline), 4.09 (m, 1H, H <sub>$\gamma$</sub> ), 4.28 (d, 1H, J = 16 Hz, H <sub>$\alpha$</sub> ), 5.15 (d, 1H, J = 16 Hz, H <sub>$\beta$</sub> ), 7.21-7.31 (m, 3H, H<sub>2</sub> and 2H benzothiophene), 7.60-7.72 (m, 2H, 2H benzothiophene) 9.8 (br, 1H, OH).

*Anal.* Calcd. for C<sub>14</sub>H<sub>16</sub>ClNO<sub>2</sub>S: C, 56.46; H, 5.41; N, 4.70. Found: C, 56.19; H, 5.29; N, 4.51.

*N*-(2-[1]Benzothienylmethyl)-5-oxo-2-pyrrolidinecarboxylic Acid (**4ae**).

This compound was obtained in a yield of 71%, mp 155-156°; ir: 3250 (OH), 1750 (CO acid), 1694 (CO amide)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  1.92-2.65 (m, 4H, oxoproline), 4.08 (m, 1H, H <sub>$\gamma$</sub>  oxoproline), 4.33 (d, 1H, J = 16 Hz, H <sub>$\alpha$</sub> ), 5.08 (d, 1H, J = 16 Hz, H <sub>$\beta$</sub> ), 7.35-7.37 (m, 3H, H<sub>3</sub> and 2H benzothiophene), 7.77-8.89 (m, 2H, 2H benzothiophene), 9.59 (s, 1H, OH).

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>NO<sub>3</sub>S: C, 61.07; H, 4.76; N, 5.09. Found: C, 60.82; H, 4.65; N, 4.98.

*N*-(2-[1]Benzothienylmethyl)-2-piperidinecarboxylic Acid Hydrochloride (**4ad**).

A mixture of ester **3ad** (3.0 g, 0.010 mole) in 10 *N* hydrochloric acid (50 ml) was refluxed for 4 hours. The resulting solution was evaporated to dryness to give a solid. Crystallization from a mixture acetone-ethanol gave 2.0 g (64%) of acid **4ad** mp 207-208°; ir: 3320 (OH), 1750 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO-*d*<sub>6</sub>):  $\delta$  1.46-1.72 (m, 4H, piperidine), 1.74-1.95 (m, 2H, piperidine), 2.30-2.43 (m, 1H, piperidine), 2.87-3.02 (m, 1H, piperidine), 3.32 (t, 1H, H <sub>$\gamma$</sub>  piperidine), 4.32 (d, 1H, J = 15 Hz, H <sub>$\alpha$</sub> ), 4.47 (d, 1H, J = 15 Hz, H <sub>$\beta$</sub> ), 7.51 (m, 3H, H<sub>3</sub> and 2H benzothiophene), 7.84 (m, 2H, 2H benzothiophene), 9.1 (br, 1H, OH).

*Anal.* Calcd. for C<sub>15</sub>H<sub>18</sub>ClNO<sub>2</sub>S: C, 57.77; H, 5.83; N, 4.49. Found: C, 57.58; H, 5.60; N, 4.81.

**Ketones 5ac,ad,ae,bc.** General Procedure.

A suspension of the acid **4ac,ad,ae,bc** (8.2 mmoles) in polyphosphoric acid (10 g) was stirred under nitrogen at 90° during 6 hours. The dark solution was poured slowly onto crushed ice and treated at 20° with 40% sodium hydroxide to pH = 7. The crystallized ketone was filtered and the filtrate was extracted with dichloromethane (3 x 50 ml). The organic layer was washed with saturated brine, dried, filtered and concentrated to give an additional amount of the ketone. Both crystals were solubilized in the minimum amount of dichloromethane, then passed through a silica gel column eluting with dichloromethane-hexane. The eluted solid was then recrystallized in the appropriate solvent to afford **5ac,ad,ae,bc**.

1,2,3,11a-Tetrahydro[1]benzothieno[2,3-*f*]indolizin-11(5*H*)-one (**5ac**).

This compound was obtained in a yield of 52%, mp 83-84° (petroleum ether), ir: 1690 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  1.84-1.94 (m, 2H, 2H proline), 2.12-2.23 (m, 2H, 2H proline), 2.59-2.72 (m, 1H, 1H proline), 3.08-3.15 (m, 1H, H <sub>$\gamma$</sub> ), 3.18-3.28 (m, 1H, 1H proline), 3.90 (dd, 1H, J = 16 Hz, J = 2.3 Hz, H <sub>$\alpha$</sub> ), 4.39 (d, 1H, J = 16 Hz, H <sub>$\beta$</sub> ), 7.31-7.48 (m, 2H, 2H benzothiophene),

7.74-7.78 (m, 1H, 1H benzothiophene), 8.58-8.62 (m, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{14}H_{13}NOS$ : C, 69.11; H, 5.38; N, 5.76. Found: C, 68.87; H, 5.16; N, 5.53.

1,2,3,11a-Tetrahydro[1]benzothieno[3,2-*f*]indolizin-11(5*H*)-one (5*bc*).

This compound was obtained in a yield of 50%, mp 86-87° (petroleum ether); ir: 1690 (CO)  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  1.83-1.93 (m, 2H, 2H proline), 2.16-2.23 (m, 2H, 2H proline), 2.67 (m, 1H proline), 3.19-3.28 (m, 2H,  $H_\gamma$  and 1H proline), 3.79 (dd, 1H,  $J = 15$  Hz,  $J = 2.3$  Hz,  $H_\alpha$ ), 4.50 (d, 1H,  $J = 15$  Hz,  $H_\beta$ ), 7.43-7.55 (m, 2H, 2H benzothiophene), 7.76-7.80 (m, 1H, 1H benzothiophene), 7.90-7.95 (m, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{14}H_{13}NOS$ : C, 69.11; H, 5.38; N, 5.76. Found: C, 69.01; H, 5.22; N, 5.49.

1,11a-Dihydro[1]benzothieno[2,3-*f*]indolizine-3,11(2*H*,5*H*)-dione (5*ae*).

This compound was obtained in a yield of 51%, mp 182-183° (ethanol); ir: 1695 (CO), 1670 (CO, amide)  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  2.40-2.53 (m, 4H, 4H oxoproline), 4.29-4.33 (m, 1H,  $H_\gamma$ ), 4.39 (dd, 1H,  $J = 18$  Hz,  $J = 1.8$  Hz,  $H_\alpha$ ), 5.45 (d, 1H,  $J = 18$  Hz,  $H_\beta$ ), 7.33-7.45 (m, 2H, 2H benzothiophene), 7.73-7.77 (m, 1H, 1H benzothiophene), 8.55-8.59 (m, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{14}H_{11}NO_2S$ : C, 65.35; H, 4.32; N, 5.44. Found: C, 64.98; H, 4.42; N, 5.50.

9,10,11,11a-Tetrahydro-6*H*-[1]benzothieno[3,2-*b*]quinolizin-12(8*H*)-one (5*ad*).

This compound was obtained in a yield of 48%, mp 102-103° (petroleum ether); ir: 1675 (CO)  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  1.65-1.68 (m, 3H, 3H piperidine), 1.82-1.90 (m, 1H, 1H piperidine), 2.35-2.46 (m, 2H, 2H piperidine), 2.83-2.86 (m, 1H, 1H piperidine), 3.03-3.09 (m, 1H,  $H_\gamma$ ), 3.43-3.46 (m, 1H, 1H piperidine), 3.82 (dd, 1H,  $J = 16$  Hz,  $J = 2.3$  Hz,  $H_\alpha$ ), 4.13 (d, 1H,  $J = 16$  Hz,  $H_\beta$ ), 7.30-7.47 (m, 2H, 2H benzothiophene), 7.37-7.77 (m, 1H, 1H benzothiophene), 8.56-8.60 (m, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{15}H_{15}NOS$ : C, 70.01; H, 5.87; N, 5.44. Found: C, 69.70; H, 5.79; N, 5.29.

Compound 5*ae* from the Acid 4*ae* under Friedel-Crafts Conditions.

A stirred solution of acid 4*ae* (0.01 mole) and dichloromethane (30 ml) was treated rapidly with thionyl chloride (1.3 g, 0.011 mole). After being refluxed overnight the chilled solution was treated in portions over 2 hours with high-purity aluminium trichloride (4 g, 0.031 mole) with stirring and external cooling (-5 to 0°). The mixture was stirred with cooling for 1 hour and at room temperature for 1.5 hours. The mixture was chilled with ice-water and the reaction was quenched by cautious addition of ice chips and then diluted with water. Dichloromethane was added and the mixture was agitated thoroughly until all the solid dissolved. The phases were separated and the aqueous phase was extracted with dichloromethane (50 ml). The combined organic phase was washed with water and saturated brine, dried, filtered and concentrated to an oil, which crystallized to give the crude ketone 5*ae*. Recrystallization from ethanol gave pure ketone 5*ae* in a 81% yield, identical to those reported just before.

[1,3]Diazepines 6*ac,ad,ae,bc*. General Procedure.

A well stirred solution of ketone 5*ac,ad,ae,bc* (4 mmoles) in

20 ml of dichloromethane was treated dropwise with 98% sulfuric acid (2.5 ml) under cooling in an ice bath for 10 minutes. After sodium azide (0.76 g, 12 mmoles) was added for 20 minutes and the reaction mixture was stirred at room temperature for 72 hours. The mixture was poured on to crushed ice (50 ml) and basified with portions of potassium carbonate to pH = 10. The aqueous solution was extracted with 100 ml of dichloromethane. The organic layer dried (sodium sulfate) filtered and concentrated gave a solid. Recrystallization from ethanol of this solid gave pure diazepines 6; for compounds 6*bd*, 6*be* (see references [2] and [4]).

1,2,3,3a-Tetrahydro-11*H*-[1]benzothieno[3,2-*e*]pyrrolo[1,2-*a*]-[1,3]diazepin-5(4*H*)-one (6*ac*).

This compound was obtained in a yield of 65%, mp 151-152°; ir: 3320 (NH), 1670 (CO)  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  1.91-2.41 (m, 4H, 4H proline), 2.74-2.86 (m, 1H, 1H proline), 3.39-3.48 (m, 1H, 1H proline), 4.23 (dd, 1H,  $J = 15.6$  Hz,  $J = 2$  Hz,  $H_\alpha$ ), 4.49 (d, 1H,  $J = 15.6$  Hz,  $H_\beta$ ), 4.46-4.57 (m, 1H,  $H_\gamma$ ), 7.15 (s, 1H, NH), 7.44 (m, 2H, 2H benzothiophene), 7.71 (d, 1H, 1H benzothiophene), 7.87 (d, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{14}H_{14}N_2OS$ : C, 65.09; H, 5.46; N, 10.84. Found: C, 65.00; H, 5.32; N, 11.08.

8,9,10,11,11a,12-Hexahydro[1]benzothieno[3,2-*e*]pyrido[1,2-*a*]-[1,3]diazepin-13(6*H*)-one (6*ad*).

This compound was obtained in a yield of 51%, mp 211-212°; ir: 3250 (NH), 1690 (CO)  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  1.39-1.98 (m, 6H, 6H piperidine), 2.42 (d, 1H,  $H_\delta$  piperidine), 2.94-2.96 (m, 1H,  $H_\delta$  piperidine), 4.27 (d, 1H,  $J = 14.1$  Hz,  $H_\alpha$ ), 4.52 (d, 1H,  $J = 14.1$  Hz,  $H_\beta$ ), 4.71-4.80 (m, 1H,  $H_\gamma$ ), 6.88 (s, 1H, NH), 7.33-7.47 (m, 2H, 2H benzothiophene), 7.67 (d, 1H, 1H benzothiophene), 7.84 (d, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{15}H_{16}N_2OS$ : C, 66.14; H, 5.93; N, 10.29. Found: C, 66.31; H, 5.83; N, 10.19.

2,3,3a,4-Tetrahydro-1*H*-[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]-[1,3]diazepine-1,5(11*H*)-dione (6*ae*).

This compound was obtained in a yield of 51%, mp 196-197°; ir: 3350 (NH), 1665 (CO), 1690 (CO)  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  2.33-2.83 (m, 4H, 4H oxoproline), 4.45 (d, 1H,  $J = 17.3$  Hz,  $H_\alpha$ ), 4.79 (d, 1H,  $J = 17.3$  Hz,  $H_\beta$ ), 5.43-5.53 (m, 1H,  $H_\gamma$ ), 7.21 (s, 1H, NH), 7.55 (m, 2H, 2H benzothiophene), 7.98 (d, 1H, 1H benzothiophene), 8.10 (d, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{14}H_{12}N_2O_2S$ : C, 61.74; H, 4.45; N, 10.29. Found: C, 61.51; H, 4.19; N, 10.01.

1,2,3,3a-Tetrahydro-11*H*-[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]-[1,3]diazepin-5(4*H*)-one (6*bc*).

This compound was obtained in a yield of 80%, mp 174-175°; ir: 3325 (NH), 1670 (CO),  $cm^{-1}$ ;  $^1H$  nmr:  $\delta$  1.83-2.54 (m, 4H, 4H proline), 2.68-2.92 (m, 1H, 1H proline), 3.32-3.52 (m, 1H, 1H proline), 4.19 (d, 1H,  $J = 15.2$  Hz,  $H_\alpha$ ), 4.45 (d, 1H,  $J = 15.2$  Hz,  $H_\beta$ ), 4.44-4.54 (m, 1H,  $H_\gamma$ ), 7.12 (s, 1H, NH), 7.42 (m, 2H, 2H benzothiophene), 7.68 (d, 1H, 1H benzothiophene), 7.85 (d, 1H, 1H benzothiophene).

*Anal.* Calcd. for  $C_{14}H_{14}N_2OS$ : C, 65.09; H, 5.46; N, 10.84. Found: C, 65.05; H, 5.29; N, 10.38.

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