Intramolecular Cyclization of Amido Acids into Pyrrolidinothieno(or [1]benzothieno)[3]azepinediones

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The synthesis of pyrrolidino[2,1-*b*]thieno[3,2(2,3)-*f*][3]azepinediones **7a,b** and pyrrolidino[2,1-*b*]-[1]benzothieno[3,2(2,3)-*f*][3]azepinediones **7c,d** are described starting from thiophenes or [1]benzothiophenes acetic acids. Their selective reduction using triethylsilane led to the corresponding azepinones **17a-d**.

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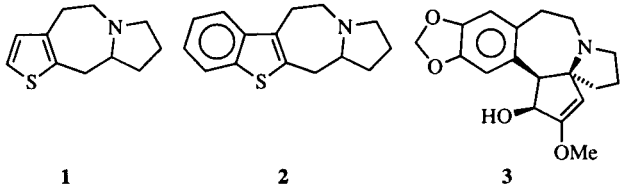
In carrying on our exploration of the pharmacological potential of heteropolycyclic structures we previously synthesized several piperidinothieno[2]azepinones [1] and pyrrolidinothieno[2]azepinones [2] analogues to piperidino[2]benzazepines [3,4] which have cardiovascular or tranquillizer potentialities. Now, we wish to report the synthesis and the reactivity of pyrrolidinothieno[3]azepines as **1** or pyrrolidino[1]benzothieno[3]azepinediones as **2** which have the pyrrolidinoazepine moiety subunit of the cephalotaxine alkaloid **3**.



1 **2** **3**

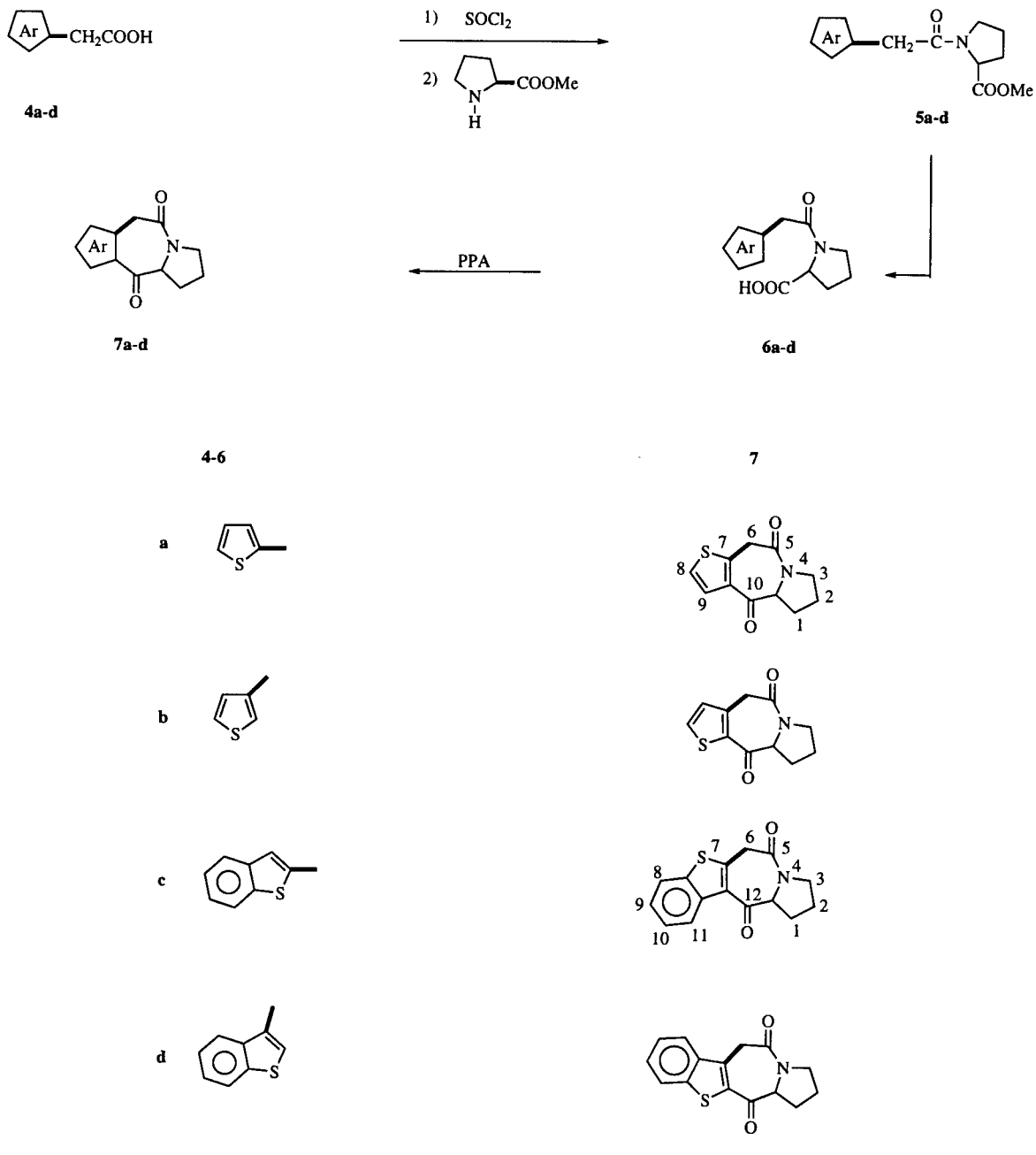
Our approach started from thiophenes or [1]benzothiophenes substituted with an acetic acid group on position 2 or 3 as shown in Scheme I. Treatment of the aromatic acetic acid **4a-c** with thionyl chloride produced the corresponding acid chlorides and without isolation or purification, they were treated with L-methyl prolinate [5] in refluxed acetonitrile in the presence of anhydrous potassium carbonate to give amido esters **5a-d** in satisfactory yield (80% to 90%). Saponification of the latter esters led to the corresponding amido acids **6a-d** in good yield (70% to 84%). We previously reported that *N*-thienylmethyl-5-oxoprolines were cyclized to ketones through a Friedel-Crafts intramolecular cyclization [6] and *N*-thienylmethylprolines were cyclized to ketones with polyphosphoric acid [7]. With the amido acids **6a-d**, the best results were observed when they were treated with polyphosphoric acid at 80° during 6 hours under a nitrogen atmosphere. In these conditions, the ketones **7a-d** were obtained in a bad yield (25% to 35%) for the thiophene serie and in a moderate yield for the [1]benzothiophene serie (55% to 60%). In contrast to the result cited above [6], the Friedel-Crafts cyclization did not give the expected ketones **7** whatever the modifications of the conditions of the reaction.

Several attempts to synthesize a pyrrolidino[2,1-*b*]thieno[3,4-*f*][3]azepinedione were unsuccessful. As shown in Scheme II starting from the 3-bromomethyl-2-chlorothiophene (**8**) [8] the amido acid **11** was obtained in a three step sequence. Since the α position of thiophene is blocked with a chlorine atom the cyclization using polyphosphoric acid as the cyclodehydrating agent should occur on the 4 position of the thiophene to furnish the thieno[3,4-*f*] fused derivative **12**. Unfortunately no reaction was observed, and an intractable tar was obtained.

It is interesting to note that using ethyl pipecolinate instead of L-methyl prolinate (Scheme III), the amido acid **13** was synthesized in good yield. Nevertheless, attempts to cyclize **13** into the piperidino[2,1-*b*]thieno[3,2-*f*][3]-azepine-6,11-dione **14** were unsuccessful probably due to the geometry of the amide. A similar disappointment had been recently published with *N*-alkynoyltetrahydroquinoline-3-carboxylic acids [9]. An increasing of the temperature could allow the change of the geometry [10] but the amido acid **13** was unstable in that condition under the action of polyphosphoric acid.

The thieno or [1]benzothieno[3]azepines **7a-d** are white crystalline solids, which exhibit the expected spectroscopic properties. For example, the carbonyl frequencies in the ir spectra occur in the range 1650-1654 cm^{-1} (both C=O and -N-C=O) for **7c,d** and 1678 cm^{-1} (C=O) and 1646 cm^{-1} (N-C=O) for **7a,b**. In the ^1H nmr spectrum of **7a** the signals of the protons attached to C_6 are not equivalent. The pseudoequatorial proton ($H_{6\text{-eq}}$) is at lower magnetic field δ = 4.21 ppm than the pseudoaxial proton ($H_{6\text{-ax}}$) δ = 3.86 ppm and appear as an AB system with a coupling constant of J = 16 Hz characteristic of *gem* protons. On the other hand, the signal of the proton H_{10a} between the carbonyl group and the nitrogen atom appears as a doublet of doublet due to the *cis* (J = 1.8 Hz) and *trans* (J = 7.8 Hz) coupling with the two protons H_1 and a chemical shift of δ = 4.59 ppm. The mass spectrum of **7a** reveal the mo-

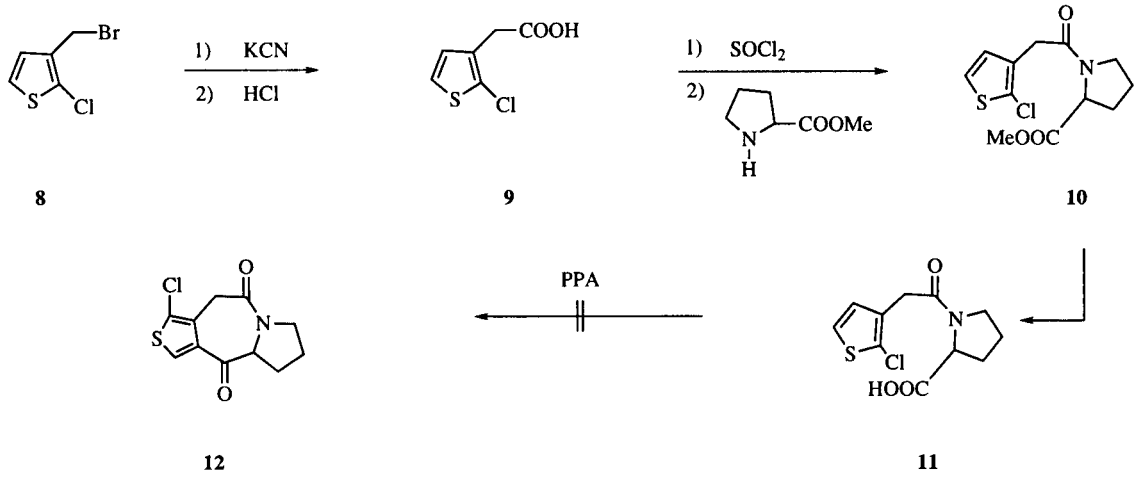
Scheme I



lecular ion M^+ = 221. Furthermore in the spectrum of **7c**, the benzenic proton H_{11} is strongly shifted downfield (δ = 8.72 ppm) compared to the corresponding proton of **7d** (δ = 7.82-7.91 ppm) and appears as a doublet with a coupling constant of J = 8 Hz.

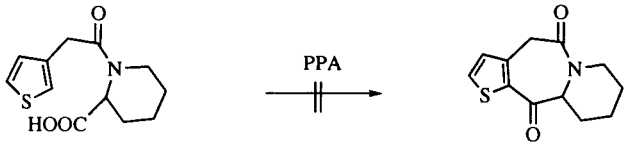
To explore reactivities of these new amido ketones, some chemical transformations were next examined. Compound **7a** (Scheme IV) was treated with hydroxylamine hydrochloride in the presence of sodium acetate to afford a single oxime. The hydroxyl group is *syn* to the thiophene ring. The proximity between the H_9 proton of the thiophene ring and the hydroxyl group lead to a deshielding effect on the H_9 proton (δ = 8.13 ppm). We have observed a similar effect in the *syn* configuration of thienoindolizinones oximes [7] or pyrrolopyridazinoisoindolone oximes [11]. In a similar manner **7b** furnished a single *syn* isomer as the corresponding thieno[2,3-*b*]indolizin-9-one [7]. Under these conditions ketones **7c,d** did

Scheme II



8 9 10 11 12

Scheme III



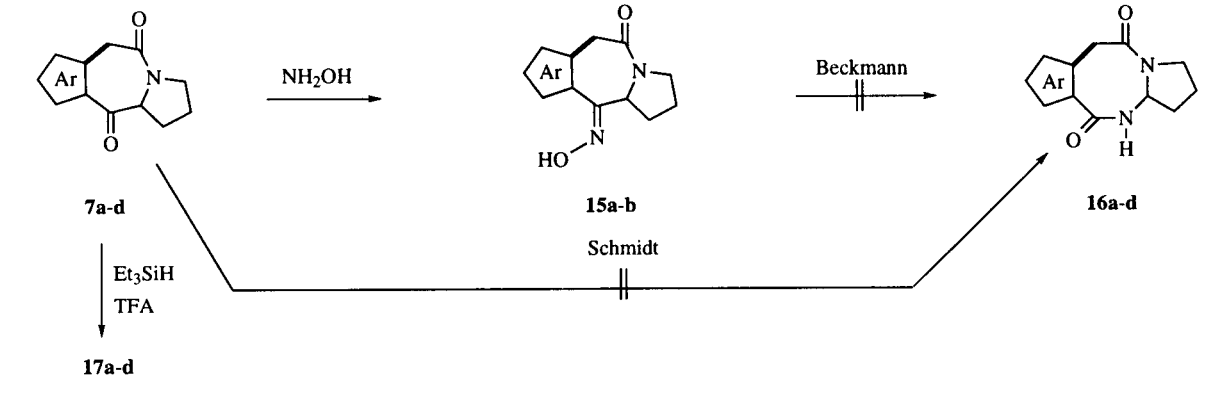
13 14

not react, even using pyridine as the solvent and base as previously described [12]. The Beckmann rearrangement using polyphosphoric acid, whatever the conditions of the reaction led to a decomposition of the starting material.

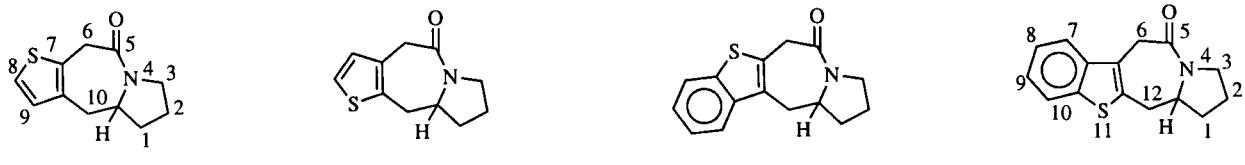
The Schmidt rearrangement (sodium azide, sulfuric acid or chlorhydric acid in dichloromethane) of the ketones **7a-d** did not give the expected pyrrolothienodiazocinones **16a-d.** The structures **7a-d** or **15a,b** seem to be very sensitive to an acidic medium.

On the other hand, the selective reduction of the ketones **7a-d** was effective using two equivalents of triethylsilane in trifluoroacetic acid at room temperature. The tricyclic amides **17a-d** were obtained in a very good yield (70% to 95%) as crystalline products. These structures have been characterized by ir, nmr spectra and microanalysis. Details are reported in the Experimental but there are a number of interesting features. For exam-

Scheme IV



7a-d 15a-b 16a-d 17a-d



17a 17b 17c 17d

ple the ^{1}H nmr spectrum of amide **17d** reveal a doublet of quadruplet for the proton H_{12a} (δ = 4.45 ppm, $J_{H_{12a}\text{-}H_{1(cis)}}$ = 2.8 Hz, $J_{H_{12}\text{-}H_{12a}} = J_{H_{12a}\text{-}H_{1(trans)}}$ = 7.6 Hz). The two protons H_{12} are equivalent and the signal is a doublet (δ = 3.07 ppm, $J_{H_{12}\text{-}H_{12a}}$ = 7.6 Hz) while the two protons H_6 appear as a singlet with a chemical shift of δ = 3.91 ppm and the two H_3 protons appear as a triplet ($J_{H_3\text{-}H_2}$ = 7.3 Hz) with a chemical shift of δ = 3.62 ppm. Similar remarks are observable in the spectra of ketones **17a,b,c**.

Some other aspects of the reactivity of the amido ketones **7a-d** are in progress, in particular the reduction in alcohol of the carbonyl group. The results will be published soon.

EXPERIMENTAL

All melting points were determined by using a Leitz hot plate apparatus and are uncorrected. Infrared spectra were recorded on a Hewlett-Packard FT-IR spectrometer. The nuclear magnetic resonance spectra (^{1}H nmr and ^{13}C nmr) were taken on a Bruker AC-200 (200 MHz) instrument in the solvent indicated (deuteriochloroform or DMSO-d_6). Chemical shifts values are reported in ppm from tetramethylsilane (TMS) as an internal reference and are given in δ units (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet). Elemental analyses were obtained in the microanalysis laboratory of the Institut National des Sciences Appliquées, place Emile Blondel, 76131 Mont Saint-Aignan cedex, France.

L-Methyl *N*-acylprolinates **5a-d, 10**. General Procedure.

A mixture of 2(3)thiophene([1]benzothiophene) acetic acid (0.25 mole) and 100 ml of thionyl chloride was refluxed for 3 hours and the resulting dark solution was evaporated *in vacuo*. A mixture of *L*-methyl prolinate (29.7 g, 0.23 mole), potassium carbonate (21 g, 0.15 mole) and 150 ml of acetonitrile was stirred under reflux for 20 minutes. To this mixture was added dropwise the crude acid chloride in 40 ml of acetonitrile and the mixture was refluxed for 4 hours. The cooled resulting suspension was filtered off. The filtrate was concentrated and the oily residue was purified by column chromatography (silica gel-dichloromethane) to give the esters **5a-d, 10**.

L-Methyl *N*-(Thien-2-ylacetyl)prolinate (**5a**).

This compound was obtained in 87% yield; ir: 1741 (C=O), 1640 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.50-2.10 (m, 3H, proline), 3.52-3.67 (m, 3H, proline), 3.7 (s, 3H, COOCH_3), 3.8 (s, 2H, -CH_2- CO-N), 4.4-4.5 (m, 1H, proline), 6.92-6.94 (m, 1H, H_4 thiophene), 7.1-7.2 (m, 2H, H_3 and H_5 thiophene).

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.96; N, 5.53. Found: C, 57.04; H, 6.01; N, 5.50.

L-Methyl *N*-(Thien-3-ylacetyl)prolinate (**5b**).

This compound was obtained in 80% yield; ir: 1740 (C=O), 1650 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.90-2.10 (m, 3H, proline), 3.60-3.70 (m, 3H, proline), 3.70 (s, 3H, COOCH_3), 3.90 (s, 2H, -CH_2-CO-N), 4.50-4.61 (m, 1H, proline), 6.81-6.90 (m, 1H, H_4 thiophene), 7.51-7.62 (m, 2H, H_2 and H_5 thiophene).

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.96; N, 5.53. Found: C, 57.10; H, 5.99; N, 5.59.

L-Methyl *N*-([l]Benzothien-2-ylacetyl)prolinate (**5c**).

This compound was obtained in 85% yield, mp 120-122° (from dichloromethane/hexane); ir: 1746 (C=O), 1645 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.82-2.26 (m, 3H, proline), 3.58-3.70 (m, 3H, proline), 3.72 (s, 3H, COOCH_3), 3.93 (s, 2H, -CH_2-CO-N), 4.49-4.55 (m, 1H, proline), 7.18-7.28 (m, 3H, H arom), 7.65-7.76 (m, 2H, H arom).

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.30; H, 5.71; N, 4.65.

L-Methyl *N*-([l]Benzothien-3-ylacetyl)prolinate (**5d**).

This compound was obtained in 90% yield; ir: 1742 (C=O), 1649 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.94-2.13 (m, 3H, proline), 3.50-3.67 (m, 3H, proline), 3.70 (s, 3H, COOCH_3), 3.84 (s, 2H, -CH_2CO-N), 4.49-4.55 (m, 1H, proline), 7.28-7.40 (m, 3H, H arom), 7.71-7.76 (m, 2H, H arom).

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62. Found: C, 63.40; H, 5.62; N, 4.65.

L-Methyl *N*-(2-Chlorothien-3-ylacetyl)prolinate (**10**).

This compound was obtained in 74% yield; ir: 1740 (C=O), 1640 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.77-2.27 (m, 3H, proline), 3.42-3.57 (m, 3H, proline), 3.60 (s, 2H, CH_2-CO-N), 3.68 (s, 3H, COOCH_3), 4.40-4.50 (m, 1H, proline), 6.96 (d, J = 6 Hz, 1H, H_4 thiophene), 7.03 (d, J = 6 Hz, 1H, H_5 thiophene).

Anal. Calcd. for $C_{12}H_{14}ClNO_3S$: C, 50.09; H, 4.90; N, 4.87. Found: C, 50.33; H, 5.13; N, 4.64.

DL-Ethyl *N*-(Thien-3-ylacetyl)pipecolinate.

In the same manner as above, pipecolinate gave the ester in 84% yield; ir: 1742 (C=O), 1640 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15-1.23 (m, 6H, 3H COOCH$_2$-CH_3 and 3H pipecoline), 1.32-1.71 (m, 3H, pipecoline), 2.04-2.32 (m, 1H, pipecoline), 3.29-2.90 (m, 1H, pipecoline), 3.72 (s, 2H, CH_2-CO-N), 4.11 (q, J = 6 Hz, 2H, COOCH_2-CH$_3$), 5.38-5.31 (m, 1H, pipecoline), 6.90-7.01 (m, 1H, H_4 thiophene), 7.05-7.11 (m, 1H, H_2 thiophene), 7.18-7.26 (m, 1H, H_5 thiophene).

Anal. Calcd. for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 60.02; H, 7.11; N, 5.08.

L-*N*-Acylprolines **6a-d, 11**. General Procedure.

To the ester **5a-d** or **10** (0.008 mole) in 20 ml of ethanol was added (0.64 g, 0.016 mole), sodium hydroxide in 20 ml of water. The reaction mixture was stirred at room temperature for 12 hours, concentrated *in vacuo* diluted with water and washed with dichloromethane. The aqueous layer was acidified with (10%) hydrochloric acid solution to *p*H = 2 and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization from toluene afforded **6a-d** or **11**.

L-*N*-(Thien-2-ylacetyl)proline (**6a**).

This compound was obtained in 74%, mp 122-123°; ir: 2836 (OH), 1716 (C=O), 1599 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.02-2.33 (m, 4H, proline), 3.50-3.76 (m, 2H, proline), 3.89 (s, 2H, -CH_2-CO-N), 4.55-4.58 (m, 1H, proline), 6.92-6.94 (m, 1H, H_4 thiophene), 7.10-7.24 (m, 2H, H_3 and H_5 thiophene).

Anal. Calcd. for: $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85. Found: C, 55.63; H, 5.60; N, 5.83.

L-*N*-(Thien-3-ylacetyl)proline (**6b**).

This compound was obtained in 70% yield, mp 121-123°; ir:

2885 (OH), 1712 (C=O), 1596 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.90-2.11 (m, 4H, proline), 3.61-3.72 (m, 2H, proline), 3.90 (s, 2H, -CH_2-CO-N), 4.54-4.62 (m, 1H, proline), 6.80-6.91 (m, 1H, H_4 thiophene), 7.51-7.62 (m, 2H, H_2 and H_5 thiophene).

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85. Found: C, 55.42; H, 4.71; N, 5.90.

L-*N*-([l]Benzothien-2-ylacetyl)proline (**6c**).

This compound was obtained in 80% yield, mp 155-157°; ir: 2877 (OH), 1713 (C=O), 1606 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.00-2.17 (m, 4H, proline), 3.44-3.80 (m, 2H, proline), 3.97 (s, 2H, -CH_2-CO-N), 4.59-4.63 (m, 1H, proline), 7.16 (s, 1H, H arom), 7.25-7.34 (m, 2H, H arom).

Anal. Calcd. for $C_{15}H_{15}NO_3S$: C, 62.27; H, 5.23; N, 4.84. Found: C, 62.20; H, 5.25; N, 4.92.

L-*N*-([l]Benzothien-3-ylacetyl)proline (**6d**).

This compound was obtained in 84% yield, mp 145-147°; ir: 2971 (OH), 1731 (C=O), 1661 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.87-2.00 (m, 4H, proline), 3.48-3.51 (m, 2H, proline), 3.89 (s, 2H, -CH_2-CO-N), 4.57-4.63 (m, 1H, proline), 7.33-7.39 (m, 4H, 3H arom and OH), 7.70-7.75 (m, 1H, H arom) 7.82-7.86 (m, 1H, H arom).

Anal. Calcd. for $C_{15}H_{15}NO_3S$: C, 62.27; H, 5.23; N, 4.84. Found: C, 62.39; H, 5.20; N, 4.82.

L-*N*-(2-Chlorothien-3-ylacetyl)proline (**11**).

This compound was obtained in 80% yield, mp 159-161°; ir: 2882 (OH), 1738 (C=O), 1613 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.88-2.24 (m, 4H, proline), 3.51-3.55 (m, 2H, proline), 3.62 (s, 2H, CH_2-CO-N), 4.51-4.55 (m, 1H, proline), 6.94 (d, 1H, H_4 thiophene, J = 6 Hz), 7.06 (d, 1H, H_5 thiophene, J = 6 Hz).

Anal. Calcd. for $C_{11}H_{12}ClNO_3S$: C, 48.27; H, 4.42; N, 5.12. Found: C, 48.42; H, 4.56; N, 5.01.

DL-*N*-(Thien-3-ylacetyl)pipecoline (**13**).

This compound was obtained in 70% yield, mp 115-117°; ir: 2948 (OH), 1726 (C=O), 1593 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.23-1.47 (m, 3H, pipecoline), 1.53-1.75 (m, 3H, pipecoline), 2.15-2.32 (m, 2H pipecoline), 3.11-3.26 (m, 1H, pipecoline), 3.79 (s, 2H, CH_2-CO-N), 5.41-5.43 (m, 1H, pipecoline), 6.97 (dd, 1H, H_4 thiophene, J = 1.4, 6.0 Hz), 7.10-7.12 (m, 1H, H_5 thiophene), 7.25-7.28 (m, 1H, H_2 thiophene).

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.96; N, 5.53. Found: C, 57.14; H, 6.22; N, 5.35.

Azepinediones **7a-d**. General Procedure.

A suspension of the acid **6a-d** (4 g, 0.016 mole) in polyphosphoric acid (80 g) was stirred under nitrogen at 84° during 6 hours. The mixture was poured on to crushed ice and treated at 0° with 40% sodium hydroxide to *p*H = 5. The crystallized ketone was extracted with ethyl acetate (3 x 150 ml). The organic layer was washed with saturated brine, dried and concentrated. The ketones were purified by column chromatography (silica gel-dichloromethane) then recrystallized from (dichloromethane-hexane) to afford pure ketones **7a-d**.

2,3,5,6,10,l0a-Hexahydro-1*H*-pyrrolo[2,1-*b*]thieno[2,3-*f*][3]-azepine-5,10-dione (**7a**).

This compound was obtained in 25% yield, mp 146-148°; ir: 1678 (C=O),1646 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.74-2.08 (m, 3H, proline), 2.80-2.89 (m, 1H, proline), 3.44-3.51 (m, 2H, proline), 3.86 (d, 1H, -CH_2-CO-N, J = 16 Hz), 4.21 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.55 (dd, 1H, proline, J = 1.8, 7.8 Hz), 7.06 (d, 1H, H_4 thiophene, J = 6 Hz), 7.47 (d, 1H, H_5 thiophene, J = 6 Hz); ^{13}C nmr: δ 23.7 (CH_2), 25.7 (CH_2), 38.8 (CH_2), 46.7 (CH_2), 64.6 (CH), 123.1 (CH thiophene), 128.4 (CH thiophene), 136.6 (C thiophene), 145.7 (C thiophene), 167.8 (C=O), 187.4 (C=O).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.60; H, 5.11; N, 6.35.

2,3,5,6,10,10a-Hexahydro-l*H*-pyrrolo[2,1-*b*]thieno[3,2-*f*][3]-azepine-5,10-dione (**7b**).

This compound was obtained in 35% yield, mp 134-135°; ir: 1676 (C=O), 1642 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.79-2.01 (m, 3H, proline), 2.77-2.82 (m, 1H, proline), 3.41-3.48 (m, 2H, proline), 3.80 (d, 1H, -CH_2-CO-N, J = 16 Hz), 4.00 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.58 (dd, J = 1.8, 7.8 Hz), 6.99 (d, 1H, H_4 thiophene, J = 4 Hz), 7.57 (d, 1H, H_5 thiophene, J = 4 Hz); ^{13}C nmr: δ 23.3 (CH_2), 25.7 (CH_2), 40.1 (CH_2), 46.7 (CH_2), 64.2 (CH), 130.8 (CH thiophene), 134.0 (CH thiophene), 137.7 (C thiophene), 142.5 (C thiophene), 168.8 (C=O), 188.6 (C=O).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.83; H, 4.82; N, 6.26.

2,3,5,6,12,12a-Hexahydro-1*H*-pyrrolo[2,1-*b*][l]benzothieno[2,3-*f*]-[3]azepine-5,12-dione (**7c**).

This compound was obtained in 60% yield, mp 183-185°; ir: 1654 (2 C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.73-2.16 (m, 3H, proline), 2.85-2.98 (m, 1H, proline), 3.48-3.53 (m, 1H, proline), 3.93 (d, 1H, -CH_2-CO-N, J = 16 Hz,), 4.36 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.65 (dd, 1H, proline, J = 1.8, 7.8 Hz), 7.37-7.49 (m, 2H, H arom), 7.75 (d, 1H, H arom, J = 8 Hz,), 8.72 (d, 1H, H arom, J = 8 Hz,); ^{13}C nmr: δ 23.3 (CH_2), 26.0 (CH_2), 40.1 (CH_2), 46.7 (CH_2), 65.4 (CH), 121.4 (CH arom), 125.3 (CH arom), 125.5 (CH arom), 126.1 (CH arom), 129.2 (C arom), 136.6 (C arom), 138.4 (C arom), 150.5 (C arom), 167.1 (C=O), 188.3 (C=O).

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.00; H, 4.51; N, 5.20.

2,3,5,6,12,12a-Hexahydro-1*H*-pyrrolo[2,1-*b*][l]benzothieno-[3,2-*f*][3]azepine-5,12-dione (**7d**).

This compound was obtained in 55% yield, mp 219-221°; ir: 1650 (2 C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.74-2.20 (m, 3H, proline), 2.81-2.96 (m, 1H, proline), 3.40-3.56 (m, 2H, proline), 4.07 (d, 1H,-CH_2-CO-N, J = 16 Hz), 4.25 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.74 (dd, 1H, proline, J = 1.8, 7.8 Hz), 7.39-7.52 (m, 2H, H arom), 7.82-7.91 (m, 2H, H arom); ^{13}C nmr: δ 23.3 (CH_2), 25.8 (CH_2), 37.4 (CH_2), 46.8 (CH_2), 64.4 (CH), 123.0 (CH arom), 123.9 (CH arom), 125.0 (CH arom), 128.2 (CH arom), 137.7 (2C arom), 138.6 (C arom), 141.6 (C arom), 168.3 (C=O), 188.1 (C=O).

Anal. Calcd. for $C_{15}H_{13}NO_2S$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.05; H, 4.85; N, 5.18.

Azepinones **17a-d**. General Procedure.

Trifluoroacetic acid (3 ml) was added to a stirred solution of **7a-d**, (0.001 mole) in triethylsilane (0.64 ml, 0.004 mole), and the resulting solution was stirred at room temperature for 12

hours. The reaction mixture was concentrated *in vacuo,* diluted with water, washed with 10% potassium carbonate solution and extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with water, dried and concentrated. The residue was subjected to chromatography (silica gel-dichloromethane) to give **17a-d**.

2,3,5,6,10,10a-Hexahydro-1*H*-pyrrolo[2,1-*b*]thieno[2,3-*f*][3]azepin-5-one (**17a**).

This compound was obtained in 75% yield, mp 105-106°; ir: 1640 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.63-2.01 (m, 3H, proline), 2.10-2.30 (m, 1H, proline), 2.61-2.80 (m, 2H, proline), 3.39-3.58 (m, 2H, $-CH_2-$), 3.5 (d, 1H, $-CH_2$-CO-N, J = 16 Hz), 4.06 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.19-4.38 (m, 1H, proline), 6.60 (d, 1H, H_4 thiophene, J = 6 Hz), 7.00 (d, 1H, H_5 thiophene, J = 6 Hz); ^{13}C nmr: δ 22.9 (CH_2), 32.6 (CH_2), 35.5 (CH_2), 36.7 (CH_2), 46.2 (CH_2), 55.4 (CH), 122.2 (CH thiophene), 127.8 (CH thiophene), 128.4 (C thiophene), 133.8 (C thiophene), 169.2 (C=O).

Anal. Calcd. for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.78. Found: C, 63.87; H, 6.27; N, 6.86.

2,3,5,6,10,10a-Hexahydro-1*H*-pyrrolo[2,1-*b*]thieno[3,2-*f*][3]azepin-5-one (**17b**).

This compound was obtained in 70% yield, mp 103-105°; ir: 1650 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.62-2.01 (m, 3H, proline), 2.10-2.31 (m, 1H, proline), 2.60-2.80 (m, 2H, proline), 3.41-3.61 (m, 2H, CH_2), 3.51 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.01 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.20-4.38 (m, 1H, proline), 6.80 (d, 1H, H_4 thiophene, J = 6 Hz), 7.00 (d, 1H, H_5 thiophene, J = 6 Hz); ^{13}C nmr: δ 23.0 (CH_2), 32.5 (CH_2), 35.5 (CH_2), 36.6 (CH_2), 46.2 (CH_2), 57.0 (CH), 123.0 (CH thiophene), 129.1 (CH thiophene), 130.2 (C thiophene), 135.0 (C thiophene), 172.0 (C=O).

Anal. Calcd. for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.78. Found: C, 63.71; H, 6.29; N, 6.84.

2,3,5,6,12,12a-Hexahydro-1*H*-pyrrolo[2,1-*b*][1]benzothieno[2,3-*f*]-[3]azepin-5-one (**17c**).

This compound was obtained in 95% yield, mp 159-161°; ir: 1654 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.88-2.09 (m, 3H, proline), 2.28-2.42 (m, 1H, proline), 2.88-3.04 (m, 2H, CH_2-CHN-CH_2), 3.56-3.64 (m, 3H, 1H, CH_2-C-N and 2H, CH_2-N), 4.23 (dt, 1H, CH_2-CO-N, J = 2, 16 Hz), 4.28-4.40 (m, 1H, CH_2-CHN-CH_2), 7.28-7.33 (m, 2H, H arom), 7.48-7.52 (m, 1H, H arom), 7.72-7.75 (m, 1H, H arom); ^{13}C nmr: δ 23.0 (CH_2), 32.9 (CH_2), 34.2 (CH_2), 37.5 (CH_2), 46.4 (CH_2), 55.1 (CH), 120.5 (CH arom), 122.0 (CH arom), 124.1 (CH arom), 124.2 (CH arom), 127.7 (C arom), 129.3 (C arom), 137.5 (C arom), 140.5 (C arom), 168.8 (C=O).

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44. Found: C, 69.81; H, 5.96; N, 5.45.

2,3,5,6,12,12a-Hexahydro-1*H*-pyrrolo[2,1-*b*][1]benzothieno-[3,2-*f*][3]azepin-5-one (**17d**).

This compound was obtained in 80% yield, mp 195-197°; ir: 1638 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.87-2.07 (m, 3H, proline), 2.25-2.43 (m, 1H, proline), 3.07 (d, 2H, CH_2-CHN, J = 7.6 Hz), 3.62 (t, 2H CH_2-N, J = 7.3 Hz), 3.91 (s, 2H, CH_2-C-N), 4.45 (qd, 1H, CH_2-CHN-CH_2 J = 2.8, 7.6 Hz), 7.25-7.38 (m, 2H, H arom), 7.61-7.72 (m, 2H, H arom); ^{13}C nmr: δ 23.0 (CH_2), 32.7 (CH_2), 35.4 (CH_2), 35.7 (CH_2), 46.4 (CH_2), 55.4 (CH), 121.1 (CH arom), 121.9 (CH arom), 122.8 (C arom), 124.1 (2 CH arom), 135.6 (C arom), 138.1 (C arom), 140.0 (C arom), 169.7 (C=O).

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44. Found: C, 70.19; H, 6.09; N, 5.48.

Oximes **15a,b**.

A mixture of ketone **7a,b** (0.442 g, 0.002 mole), hydroxylamine hydrochloride (0.28 g, 0.004 mole) and sodium acetate (0.33 g, 0.004 mole) in ethanol (10 ml) and water (10 ml) was refluxed for 6 hours. On cooling the oxime precipitated and was filtered then washed with a mixture of ethanol water (50-50). Recrystallization of the solid from ethanol gave **15a,b**.

2,3,5,6,10,10a-Hexahydro-10-oximino-1*H*-pyrrolo[2,1-*b*]-thieno[2,3-*f*][3]azepin-5-one (**15a**).

This compound was obtained in 84% yield, mp 223-225°; ir: 2850 (OH), 1640 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.82-1.98 (proline), 2.64-2.67 (m, 1H, proline), 3.27-3.42 (m, 2H, proline), 3.53 (d, 1H, CH_2-CO-N, J = 16 Hz), 4.47 (d, 1H, CH_2-CO-N, J = 16 Hz), 5.02-5.06 (m, 1H, proline), 7.33 (d, 1H, H_4 thiophene, J = 5.5 Hz), 8.13 (d, 1H, H_5 thiophene, J = 5.5 Hz), 11.46 (s, 1H, OH); ^{13}C nmr: δ 23.4 (CH_2), 27.6 (CH_2), 38.2 (CH_2), 45.9 (CH_2), 59.1 (CH), 121.9 (CH thiophene), 128.7 (C thiophene), 131.7 (CH thiophene), 137.5 (C thiophene), 144.4 (C=N-OH), 167.8 (C=O).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.85. Found: C, 55.65; H, 5.02; N, 11.47.

2,3,5,6,10,10a-Hexahydro-10-oximino-1*H*-pyrrolo[2,1-*b*]thieno-[3,2-*f*][3]azepin-5-one (**15b**).

This compound was obtained in 80% yield, mp 258-260°; ir: 2816 (OH), 1635 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.85-2.00 (m, 3H, proline), 2.73-2.75 (m, 1H, proline), 3.23-3.49 (m, 2H, proline), 3.56 (d, 1H, CH_2CO-N, J = 16 Hz), 4.32 (d, 1H, CH_2-CO-N, J = 16 Hz), 5.16-5.19 (m, 1H, proline), 7.03 (d, 1H, H_4 thiophene, J = 5.1 Hz), 7.67 (d, 1H, H_5 thiophene, J = 5.1 Hz), 12.05 (s, 1H, OH); ^{13}C nmr: δ 23.2 (CH_2), 26.7 (CH_2), 39.9 (CH_2), 45.8 (CH_2), 58.5 (CH), 125.5 (C thiophene), 129.1 (CH thiophene), 129.6 (CH thiophene), 135.3 (C thiophene), 144.6 (-C=N-OH), 168.9 (C=O).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.85. Found: C, 56.01; H, 5.15; N, 12.09.

(2-Chlorothien-3-yl)acetic Acid (**9**).

To a solution of 2-chloro-3-bromomethylthiophene (**8**) (2.1 g, 0.01 mole) in 50 ml of benzene was added potassium cyanure (3.90 g, 0.06 mole). The mixture was stirred for 4 days, filtered and concentrated *in vacuo.* The residue obtained was dissolved in 50 ml of concentrated chlorhydric acid and refluxed for 14 hours. The mixture was poured on to crushed ice, extracted with diethyl ether. The organic layer was washed with 10% potassium carbonate solution, dried and concentrated to give the acid in 82% yield, mp 90-94°; ir: 2940 (OH), 1716 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.66 (s, 2H, CH_2-), 6.95 (d, 1H, H4 thiophene, J = 6 Hz), 7.07 (d, 1H, H_5 thiophene, J = 6 Hz).

Anal. Calcd. for $C_6H_5ClO_2S$: C, 40.80; H, 2.85. Found: C, 41.03; H, 3.06.

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