Synthesis and Reactivity of Oxopyrrolidinothieno[2]azepinones: [3]Benzazepine Antidepressant Analogs

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A synthesis of oxopyrrolidino[2]azepinones annelated to a thiophene ring **3a,b,c** is described starting from succinimide and halogenomethylthiophenes **6a,b,c**. Stereoselective reduction, Schmidt reaction and the Beckmann rearrangement of the oximes of the ketones **3a,b,c** are studied.

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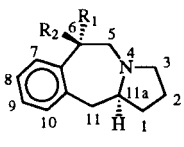
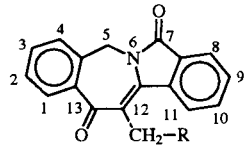
In previous studies concerning non-benzodiazepine drugs which exhibit more significant CNS activity (Central Nervous System), it was found that *trans*-2,3,5,6,11,11a-hexahydro-6-phenyl-1*H*-pyrrolo[2,1-*b*][3]benzazepine (**1**) [1] and 12-methyl (or 12-diethylaminomethyl)-5*H*-isoindolo[2,1-*b*]-[2]benzazepine-7,13-dione (**2a**, R = H; **2b**, R = N $(Et)_2$) [2] (Chart I) are respectively clinical anti-depressant effects and most patent protective effect against nitrogen-induced hypoxia.

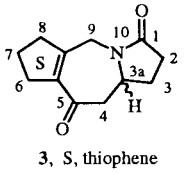
Chart I



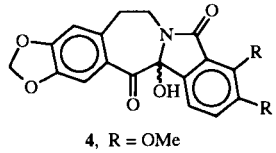
1, R_1, R_2 = H, Ph



2, **a**, R = H; **b**, R = N(Et)$_2$



3, S, thiophene



4, R = OMe

In connection with our work on new thieno-fused *N*-heterocycles with potential pharmacologic activity, we have recently described some thienoazepinones fused to a piperidine ring [3] or an isoindolone ring [4]. Now, we wish to report herein the studies on a new series of thieno-azepinones annelated to an oxopyrrolidinone ring as in **3** containing the pyrrolidinoazepine skeleton incorporated in the structure of compounds **1** and **2** cited above, and in chilenine (**4**) a natural berberine alkaloid [5,6]. Our attention was first directed toward the strategy which could be used to synthesis the acetic acid derivatives **11a,b,c** as key products in this synthesis sequence. So, two major synthetic routes, illustrated in Chart II were possibilities in obtaining the acetic acid side chain, the pyroglutamic acid (**5a**) and/or the succinimide (**5**) routes.

The first pathway, using the *N*-alkylation process with halogenomethylthiophenes **6a,b,c** of the known [7,8] methyl 5-oxo-2(*S*)-homoprolinate (**5f**) followed by an alkaline hydrolysis furnished the desired acids **11a,b,c**. As for the requisite product **5f**, it was prepared in five steps in two satisfactory manners from the commercially available L-pyroglutamic acid (**5a**) [7] and 2(*S*)-amino-3-methyl-1-butanol [8a,b] respectively. We have opted for the succinimide route which is short, and offered major potential reactivity of the ω–carbinol lactam intermediates **8a,b,c** as a new class of precursors for the highly reactive α-acyliminium ion demonstrated earlier by Speckamp [9a-i]. Thus, according to the synthetic succinimide route shown in Chart II, succinimide (**5**) was *N*-alkylated by halogeno-methylthiophenes **6a,b,c** under solid-liquid phase transport catalysis using anhydrous potassium carbonate as a base and a mixture of 0.1 molar equivalent of potassium iodide

Table 1

Sodium Borohydride/Methanol Reduction of *N*-Thienylmethylsuccinimides **7a,b,c**

Substrate	T°	Time (min)	Co-solvent	Acid	(%) of product and yield (%)					
7a	0-5	60	THF	-	(0%)	**8a**	-	(100%)	**9a**	(91)
	20-25	240	THF	TFA	(0%)	**8a**	-	(0%)	**9a**	-
	0-5	55	THF	HCl	(10%)	**8a**	(9) [a]	(90%)	**9a**	(78) [a]
	-5-0	60	-	HCl	(100%)	**8a**	(97)	(0%)	**9a**	-
7b	0-5	60	THF	-	(0%)	**8b**	-	(100%)	**9b**	(95)
	20-25	240	THF	TFA	-	**8b**	(25)	(0%)	**9b**	-
	0-5	55	THF	HCl	(0%)	**8b**	-	(100%)	**9b**	(92)
	-5-0	45	-	HCl	(100%)	**8b**	(90)	(0%)	**9b**	-
7c	-5-0	90	-	HCl	(100%)	**8c**	(89)	(0%)	**9c**	-

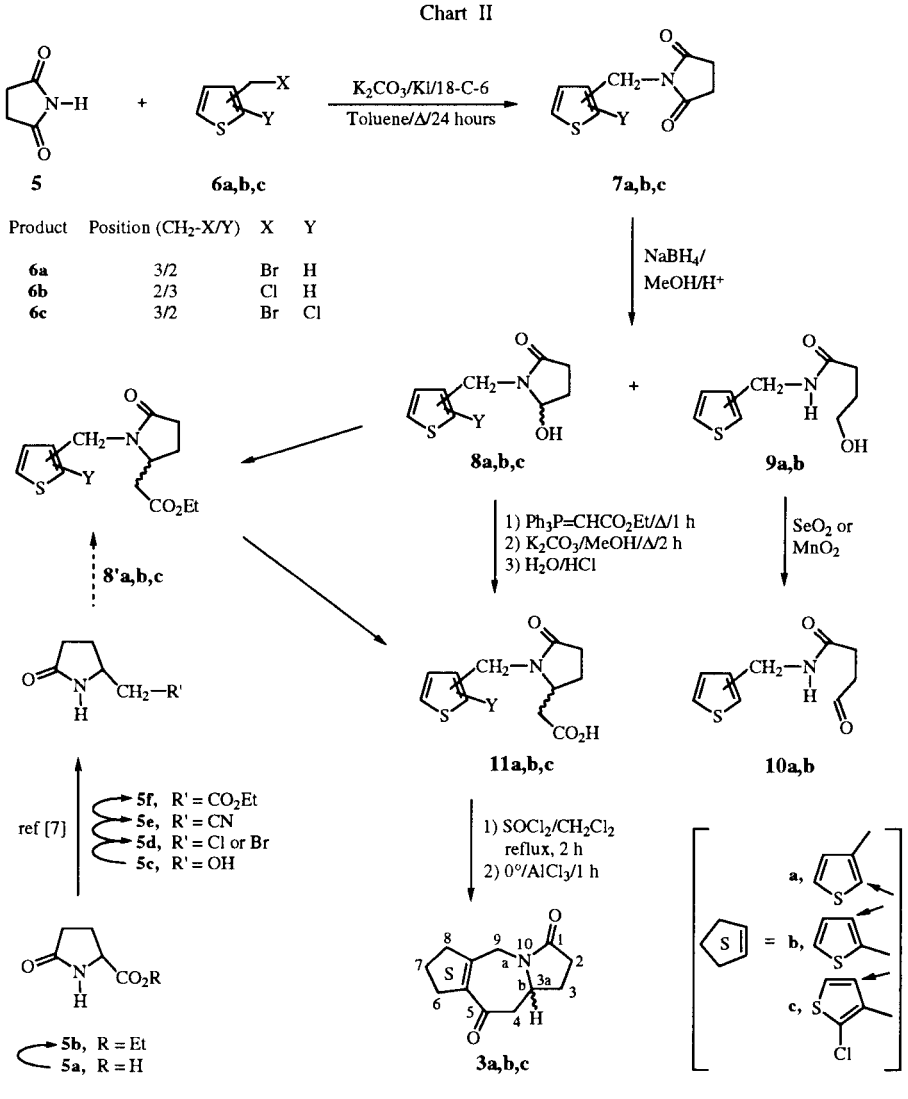
[a] Determined in the crude product by ^{1}H nmr spectroscopy.

and 1% of 18-C-6 as catalysts [10]. The resulting *N*-alkylated succinimides **7a,b,c** were isolated after refluxing in toluene for 24 hours in good yields of 70 to 75%. Reduction of these adducts with a large excess of sodium borohydride in anhydrous methanol gave hydroxylactams **8a,b,c**, hydroxymethylamides **9a,b** or a mixture of these alcohols in accordance with the procedures described in the literature [9h,11]. The reduction reaction monitored by tlc (silica gel, dichloromethane/hexane 4/1) was carried out in a satisfactory manner selectively to the ω-carbinol lactams or to the cleaved alcohols (Table I).

In fact, in the presence of hydrochloric acid, the reaction led exclusively to ω-carbinol lactams **8a,b,c** in excellent yields of about 97, 90 and 89% respectively, but with an additional tetrahydrofuran as co-solvent in acidic medium or not, in general only the cleavage reaction occurred to furnish primary alcohols **9a** and **9b** with small amounts of the hydroxylactam **8a** (9%). These results were in contrast to these observed for similar structures [9i,12]. Finally, when hydrochloric acid was exchanged with trifluoroacetic acid in tetrahydrofuran, interestingly only imide **7b** was reduced to hydroxylactam **8b** in moderate yield (25%) whereas imides **7a,c** showed more resistance toward these reduction conditions. In all these latter cases, the starting materials were recovered. Several attempts were used to convert the hydroxymethylamides **9a,b** into the corresponding ω-carbinol lactams **8a,b**, unfortunately the oxidization reaction using activated manganese dioxide or selenium dioxide in anhydrous toluene or dioxane followed by an alkaline treatment with sodium hydride in dry *N,N*-dimethylformamide led invariably to the formylamides **10a,b** in good yields and no trace of **8a,b** were observed.

Conversion of alcohols **8a,b,c** to a racemate of acetic acid derivatives **11a,b,c** *via* the corresponding ethyl acetates was accomplished by applying the elegant Wittig type condensation of ω-carbinol lactams **8a,b,c** with ethoxycarbonylmethylidenetriphenylphosphorane. Because of the difficulty

Chart II

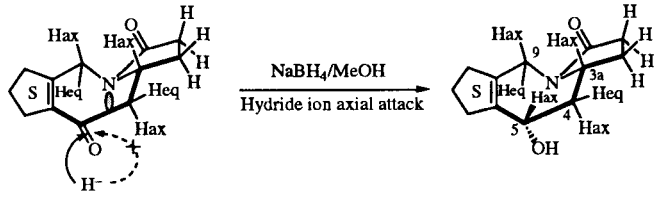


encountered in the separation of ethyl esters and triphenylphosphine oxide formed during the reaction, we have submitted this mixture to an alkaline hydrolysis by potassium carbonate solution followed with an acidic treatment [2,9f]. The expected substituted acetic acids **11a,b,c** were isolated as crystalline white materials in good yields of 62 to 75% calculated from the corresponding ω-carbinol lactams. It is also interesting to note that when our hydroxylactams **8a,b,c** were allowed to react with triethyl phosphonoacetate according to the procedures reported earlier for similar ω-carbinol lactams [9f,13], the reaction did not occur whatever the alterations made in experimental reaction conditions (solvent, temperature, time). The starting alcohols were recovered in all these cases.

The above acetic acids **11a,b,c** were treated with thionyl chloride in dichloromethane and the resulting acid chloride under Friedel and Crafts cyclization conditions using aluminium trichloride of high quality (99.99%) as catalyst gave the expected ketone **3a,b,c** in 90, 80 and 86% yields, respectively. The structure of these new triheterocyclic ketones and all of the unknown intermediates reported herein, were supported by the ir, ^{1}H nmr and ^{13}C nmr spectra as well as by the microanalysis. Details are reported in the Experimental but there are a number of interesting features. The methylene protons (CH_2-N) in imides **7a,b,c** appear as a singlet with a chemical shift of about δ 4.60 ppm and they appear as an AB system due to the diastereotopic effect in compounds **3**, **8** and **11a,b,c** shifted at about δ 4.10 ppm and δ 4.80 ppm with a coupling constant of about 15 Hz characteristic of *gem* protons. Likewise, the protons attached to C_4 in the ketones **3a,b,c** are non equivalents and appear as a doublet of doublet with chemical shifts of about δ 2.80 ppm for H_{4ax} (pseudoaxial:ax) and δ 3.10 ppm for H_{4eq} (pseudoequatorial:eq) and coupling constants of about J = 15 Hz (H_{4ax}-H_{4eq}), J = 6.4 Hz (H_{4ax}-H_{3a}) and J = 4.3 Hz (H_{4eq}-H_{3a}).

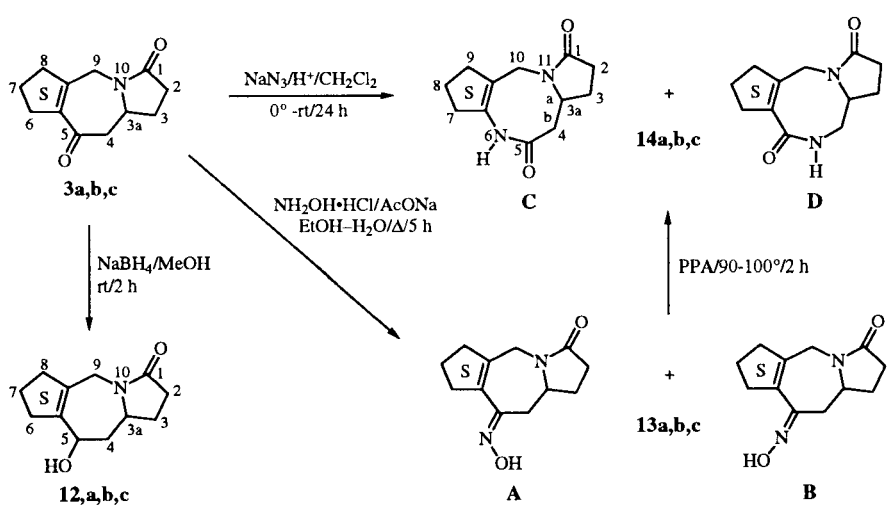
Reactivity of the carbonyl group was investigated in compounds **3a,b,c**. So, as shown in Charts III and IV, the reduction was carried out with an excess of sodium borohydride in dry methanol at room temperature and gave the expected alcohols **12a,b,c** in very good yields of 89 to 92%.

Chart III



The ^{1}H nmr spectrum of alcohol **12a** revealed the presence of only one isomer and the stereochemical assignment was based on the coupling constant values of protons H_5 and H_4. In fact, the signal of H_5 appears as a doublet of doublet with a chemical shift of δ 5.14 ppm with coupling constants of J = 10.2 Hz (H_{5ax}-H_{4ax}) corresponding to the *trans* coupling and J = 3.1 Hz (H_{5ax}-H_{4eq}) corresponding to the *cis* coupling. These values strongly suggest a *cis* structure for alcohol **12a** in which the OH group has a pseudo equatorial position consecutively to the stereospecificity hydride ion axial attack of the carbonyl group (Chart III). Actually, the hydride attack on the equatorial position was hindered by the lone pair on the nitrogen atom. Furthermore for the alcohols **12b** and **12c**, the ^{1}H nmr spectra showed the same fact. These results are in contrast to those reported during the reduction of piperidinothienoazepinones [3] since under those conditions only stereoselectivity was observed. Finally, the C_9 protons appear as an AB system with usual coupling constant (J = 15 Hz) corresponding to the *gem* protons as described above, but the C_4 protons appear as a multiplet not resolved with the other protons of the oxopyrrolidine ring.

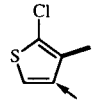
Chart IV



According to Chart IV, treatment of ketones **3a** and **3b** with hydroxylamine hydrochloride in the presence of sodium acetate in a mixture of ethanol-water (4/1) at reflux for five hours, led to the corresponding oximes **13a** and **13b** in good yields of 85 and 75% respectively. The ^{1}H nmr spectra indicated that the oxime **13a** exists in two forms which could not be separated, configuration **A** as a major product (77%) in which the OH group of the oxime is *anti* to the thiophene ring and configuration **B** as a minor product (23%) in which the OH group is *syn* while the oxime **13b** exists as a single configuration **A** (*anti*). This oxime **13b(A)** was isomerized upon standing at room temperature into a mixture of configuration **A** (85%) and configuration **B** (15%). The major products of these oximes can be explained by the chemical shifts of C_4 protons (δ H_{4eq} = 3.36 ppm, δ H_{4ax} = 2.76 ppm for **13a(A)** and δ H_{4eq} = 3.32 ppm, δ H_{4ax} = 2.73 ppm for **13b(A)**) similar to those observed for the oximes of hexahydrodibenzazepines [14]. These results were in contrast with the observations made earlier for thienoindolizidinone oximes [15a,b] and thienoquinolizidinone oximes [16] in which the *syn* configuration was the major product. When oximes **13a** and **13b** were heated under Beckmann conditions using polyphosphoric acid at 90-100° under nitrogen for two hours, we formed with the oxime **13b(A)** the oxopyrrolidinothieno[1,5]diazocinone **14b(C)** in a yield of 52% corresponding to the *anti* thiophene group migration. But with the mixture of *anti* and *syn* oximes **13a**, we have always isolated only the oxopyrrolidinothieno[1,5]diazocinone **14a(C)** in a moderate yield of 45% corresponding to the *anti* thiophene ring migration. Our results were in contrast to those previously reported for Beckmann transposition of thienoindolizidinone oximes [15a,b] and thienoquinolizidinone oximes [16] in which the *anti* alkyl or thiophene group migration was observed. Since no trace of oxopyrrolidinothieno-[1,4]diazocinones **14a,b(D)** corresponding to the *anti* oxopyrrolidine ring migration was detected coupled with the moderate yields observed for these Beckmann rearrangements, we propose that the *syn* oxime was unstable under acidic conditions.

To confirm these results, the Schmidt rearrangement of ketones **3a,b,c** provided a successful route to the expected triheterocyclic diazocinones **14a,b,c** (Chart IV).

Table II
Isomeric Percentage of Oximes **13a,b,c** and Lactams **14a,b,c**

Product →	a, 		b, 		c, 	
Oximes	**13a(A)**	**13a(B)**	**13b(A)**	**13b(B)**	**13c(A)**	**13c(B)**
%	77	23	100	0	-	-
Lactams	**14a(C)**	**14a(D)**	**14b(C)**	**14b(D)**	**14c(C)**	**14c(D)**
%	100	0	100	0	100	0

So, treatment of ketone **3a** with sodium azide in concentrated sulfuric acid at room temperature in dry dichloromethane for 24 hours, gave selectively the oxopyrrolidinothieno[1,5]diazocinone **14a(C)** in 65% yield. In a similar manner, ketones **3b** and **3c** furnished only the [1,5]diazocinones **14b(C)** and **14c(C)** in 70 and 45% yields respectively. These [1,5]diazocinones **14** are identical to products obtained from Beckmann transposition of the major *anti* oximes **13a** and **13b** (Table II). The structures of these lactams were supported by their ir, ^{1}H nmr and ^{13}C nmr spectra as well as by their microanalyses. In fact, for products **14a,b,c**, the C_4 protons adjacent to the carbonyl group appear as a multiplet obscured by other oxopyrrolidine protons and have chemical shifts of 2.22 to 2.51 ppm, 2.20 to 2.55 ppm and 2.18 to 2.61 ppm, respectively. These values were close to those observed for 2,2-dimethylbenzoxazepinones [17]. Furthermore for these lactams, the H_β proton of the thiophene ring of **14b** and the H_α of the thiophene ring of **14c** is also influenced and has a chemical shift of 6.78 ppm and 6.86 ppm while the same protons were shifted downfield to 7.07 ppm and 7.81 ppm in the corresponding ketones **3b** and **3c**. These values were comparable with the chemical shift of the same proton of the reported 4*H*-pyrrolidino[1,2-*a*]thieno[3,2-*e*][1,4]diazepin-9(10*H*)-one [15a] (δ 6.63 ppm) and the corresponding ketone namely thieno[3,2-*b*]indolizin-9-one (δ 7.13 ppm). This fact is not observed for lactam **14a** in which H_β is shifted to 7.07 ppm compared to that of the corresponding ketone **3a** which is shifted to 7.01 ppm.

In summary, some oxopyrrolidinothieno[2]azepinones were synthesized in four steps starting from succinimide and suitable halogenomethylthiophenes. These ketones **3a,b,c** showed some reactivities, in particular their stereospecific reduction furnished *cis* alcohols while their treatment under Beckmann and Schmidt rearrangement conditions led specifically to [1,5]diazocinones annelated to thiophene and oxopyrrolidine rings corresponding to an *anti* aryl migration. Further investigations about these ketones are in progress and the results will be published soon.

EXPERIMENTAL

All melting points were determined using a Leitz hot plate apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The nuclear magnetic resonance spectra (^{1}H and ^{13}C) were taken on a Bruker AC-200 (200 MHz) instrument in the solvent indicated. Chemical shift 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.

1-Thienylmethylsuccinimides (**7a,b,c**).

General Procedure.

To a mixture of succinimide (**5**) (0.99 g, 10 mmoles) and 18-C-6 (1% w/w) in 15 ml of dry toluene was added solid potassium carbonate (1.34 g, 11 mmoles) and 0.1 equivalent per mmole of potassium iodide. After stirring for 10 minutes, 12 mmoles of thienylmethyl halide either substituted or unsubstituted **6a**, **6b** or **6c** in 10 ml of dry toluene was added slowly dropwise over a period of 15 minutes. The mixture was then refluxed for 24 hours under a nitrogen atmosphere and cooled. The heterogeneous solution was filtered over a short column of celite which was washed twice with 10 ml of toluene. The organic phase was evaporated *in vacuo* and the resulting crude colorless solid was recrystallized from anhydrous ethanol to give the desired *N*-alkylated imide **7**.

1-(Thien-3'-ylmethyl)succinimide (**7a**).

This compound was obtained as yellow needles in 75% yield, mp 85°; ir: 1695 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.67 (s, 4H, 4H-succinimide), 4.63 (s, 2H, CH_2-N), 7.04-7.11 (m, 1H, 1H-thiophene), 7.16-7.22 (m, 1H, 1H-thiophene), 7.25-7.29 (m, 1H, 1H-thiophene).

Anal. Calcd. for $C_9H_9NO_2S$ (195.23): C, 55.37; H, 4.65; N, 7.17. Found: C, 55.12; H, 4.58; N, 7.05.

1-(Thien-2'-ylmethyl)succinimide (**7b**).

This product was obtained as a white solid in 70% yield, mp 96°; ir: 1696 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.71 (s, 4H, 4H-succinimide), 4.80 (s, 2H, CH_2-N), 6.91-6.98 (m, 1H, 1H-thiophene), 7.03-7.12 (m, 1H, 1H-thiophene), 7.14-7.21 (m, 1H, 1H-thiophene).

Anal. Calcd. for $C_9H_9NO_2S$ (195.23): C, 55.37; H, 4.65; N, 7.17. Found: C, 55.29; H, 4.49; N, 6.99.

1-(2'-Chlorothien-3'-ylmethyl)succinimide (**7c**).

This compound was obtained as white needles in 72% yield, mp 78°; ir: 1694 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.69 (s, 4H, 4H-succinimide), 4.61 (s, 2H, CH_2-N), 6.91 (d, 1H, J = 5.7 Hz, $H_{4'}$-thiophene), 6.99 (d, 1H, J = 5.7 Hz, $H_{5'}$-thiophene).

Anal. Calcd. for $C_9H_8ClNO_2S$ (229.68): C, 47.06; H, 3.52; N, 6.10. Found: C, 46.97; H, 3.33; N, 6.06.

1-(Thienylmethyl)succinamidals **8a,b,c**.

General Procedure.

To a stirred solution of 12.6 mmoles of *N*-alkylated succinimide **7a**, **7b** or **7c** in 15 ml of dry methanol was added slowly in portions of sodium borohydride (2.83 g, 75 mmoles) at -5-0° over a period of 10 minutes. While the temperature was kept at -5-0°, 2*N* hydrochloric acid in ethanol (3 drops) was added to the reaction mixture at regular intervals of 10 minutes during the reaction time summarized in Table I (60, 45 or 90 minutes for imide **7a**, **7b** or **7c** respectively). The excess of sodium borohydride was destroyed adding 5 ml of cold water then a solution of 10% hydrochloric acid in ethanol at 0-5° to *p*H 3. After removal of the solvent, the residue was diluted with 40 ml of water and extracted with dichloromethane. The organic layers were washed with saturated brine, dried over sodium sulfate and evaporated *in vacuo*. The oily residue after trituration with diethyl ether was recrystallized from ethanol to give ω-carbinol lactams **8a**, **8b** or **8c** as colorless crystals.

5-Hydroxy-1-(thien-3'-ylmethyl)-2-pyrrolidinone (**8a**).

This product was obtained as a yellow solid in a yield of 97%, mp 100°; ir: 3163 (O-H), 1641 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.8-1.95 (m, 1H, 1H-pyrrolidinone), 2.13-2.46 (m, 2H, 2H-pyrrolidinone), 2.53-2.69 (m, 1H, 1H-pyrrolidinone), 4.21 (d, 1H, J = 14.6 Hz, CH_2-N), 4.3-4.45 (m, 1H, OH), 4.75 (d, 1H, J = 14.6 Hz, CH_2-N), 5-5.13 (m, 1H, CH), 6.87-6.99 (m, 1H, 1H-thiophene), 7.12-7.18 (m, 1H, 1H-thiophene), 7.20-7.28 (m, 1H, 1H-thiophene).

Anal. Calcd. for $C_9H_{11}NO_2S$ (195.23): C, 54.80; H, 5.62; N, 7.10. Found: C, 54.54; H, 5.48; N, 7.00.

5-Hydroxy-1-(thien-2'-ylmethyl)-2-pyrrolidinone (**8b**).

This product was isolated as a yellow solid in a yield of 90%, mp 107°; ir: 3189 (O-H), 1652 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.78-2 (m, 1H, 1H-pyrrolidinone), 2.16-2.4 (m, 2H, 2H-pyrrolidinone), 2.48-2.65 (m, 1H, 1H-pyrrolidinone), 4.0-4.55 (br, 1H, OH), 4.38 (d, 1H, J = 15.3 Hz, CH_2-N), 4.92 (d, 1H, J = 15.3 Hz, CH_2-N), 5.11-5.19 (m, 1H, CH(OH)), 6.81-6.92 (m, 2H, 2H-thiophene), 7.17-7.25 (m, 1H, 1H-thiophene).

Anal. Calcd. for $C_9H_{11}NO_2S$ (195.23): C, 54.80; H, 5.62; N, 7.10. Found: C, 54.78; H, 5.50; N, 7.03.

1-(2'-Chlorothien-3'-ylmethyl)-5-hydroxy-2-pyrrolidinone (**8c**).

This product was isolated as orange needles in a yield of 89%, mp 89°; ir: 3201 (O-H), 1678 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.8-2.14 (m, 2H, 2H-pyrrolidinone), 2.19-2.62 (m, 2H, 2H-pyrrolidinone), 4.12 (d, 1H, J = 14.8 Hz, CH_2-N), 4.2-4.36 (br, 1H, OH), 4.64-4.73 (m, 1H, CH(OH)), 4.65 (d, 1H, J = 14.8 Hz, CH_2-N), 6.85 (d, 1H, J = 5.6 Hz, $H_{4'}$-thiophene), 7.04 (d, 1H, J = 5.6 Hz, $H_{5'}$-thiophene).

Anal. Calcd. for $C_9H_{10}ClNO_2S$ (239.61): C, 46.66; H, 4.35; N, 6.05. Found: C, 46.51; H, 4.12; N, 5.98.

3-(*N*-Thienylmethylamido)propan-1-ol **9a,b**.

General Procedure.

To a stirred solution of *N*-thienylmethylsuccinimide **7a** or **7b** (0.5 g, 2.55 mmoles) dissolved in 10 ml of dry methanol and 15 ml of anhydrous tetrahydrofuran cooled at 0-5°, was added slowly sodium borohydride (0.38 g, 10.24 mmoles) in portionwise over a period of 15 minutes. After 1 hour of reaction at the same temperature, the reaction was quenched by the addition of 10% aqueous hydrochloric acid (20 ml). After removal of the solvents *in vacuo*, the resulting residue was diluted with 30 ml of water, extracted with dichloromethane and worked up in the usual manner. The oily residue was purified by flash chromatography on a short column of silica gel (40 g) eluting with dichloromethane-diethyl ether (4-1) and gave the pure primary alcohols **9a** or **9b** as yellow solids in good yields.

3-(*N*-(Thien-3'-ylmethyl)amidopropan-1-ol (**9a**).

This product was obtained by recrystallization from diethyl ether in a yield of 91%, mp 50°; ir: 3290 (O-H and N-H), 1692 (C=O), 1675 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.6-1.75 (m, 2H, CH_2(-CH_2-OH)), 2.16 (t, 2H, CH_2(-CO-NH-)), 3.25-3.5 (t, 2H, CH_2-OH), 4.25 (d, 2H, J = 5.9 Hz, CH_2-NH), 4.45-4.5 (m, 1H, OH

exchanged with deuterium oxide), 7.02 (dd, 1H, 1H-thiophene), 7.22 (dd, 1H, 1H-thiophene), 7.46 (dd, 1H, 1H-thiophene), 8.26 (t, 1H, J = 5.9 Hz, HN-CH_2 exchanged with deuterium oxide).

Anal. Calcd. for $C_9H_{13}NO_2S$ (199.26): C, 54.25; H, 6.58; N, 7.03. Found: C, 54.13; H, 6.51; N, 7.01.

3-(*N*-(Thien-2'-ylmethyl)amidopropan-1-ol (**9b**).

This product was obtained by recrystallization from diethyl ether-hexane in a yield of 95%, mp 64°; ir: 3310 (O-H and N-H), 1687 (C=O), 1659 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.56-1.74 (m, 2H, CH_2(-CH_2-OH)), 2.15 (t, 2H, CH_2(-CO-NH-)), 3.30-3.51 (t, 2H, CH_2-OH), 4.37 (d, 2H, J = 4.8 Hz, CH_2-NH), 4.42-4.57 (m, 1H, OH exchanged with deuterium oxide), 6.91-6.98 (m, 2H, 2H-thiophene), 7.30-7.39 (m, 1H, 1H-thiophene), 8.42 (t, 1H, J = 4.8 Hz, HN-CH_2 exchanged with deuterium oxide).

Anal. Calcd. for $C_9H_{13}NO_2S$ (199.26): C, 54.25; H, 6.58; N, 7.03. Found: C, 54.09; H, 6.54; N, 6.93.

1-(Thienylmethyl)-2-pyrrolidinone-5-acetic acids **11a,b,c**.

General Procedure.

A mixture of **8a**, **8b** or **8c** (1.12 mmoles) and ethoxycarbonylmethylidenetriphenylphosphorane (0.5 g, 1.43 mmoles) in 10 ml of dry toluene was refluxed with stirring for 2 hours and then evaporated *in vacuo*. To the residue was added a solution of potassium carbonate (0.3 g, 2.17 mmoles) in 3 ml of methanol and 1 ml of water. The resulting mixture was refluxed with stirring for 2 hours then concentrated under reduced pressure. Water and dichloromethane were added and the organic layer was separated. The aqueous layer was washed with dichloromethane and made acidic by hydrochloric acid (10%) to *p*H 2.5. The precipitate formed was filtered off and recrystallized from acetone.

1-(Thien-3'-ylmethyl)-2-pyrrolidinone-5-acetic Acid (**11a**).

This compound was isolated in a yield of 65%, mp 104°; ir: 3082 (O-H), 1717 (C=O), 1622 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.73-1.91 (m, 1H, 1H-pyrrolidinone), 2.11-2.55 (m, 4H, 3H-pyrrolidinone and $CH_2(CO_2H)$), 2.65 (dd, 1H, J = 4.0, 15.2 Hz, $CH_2(CO_2H)$), 3.8-4 (m, 1H, 1H pyrrolidinone), 4.08 (d, 1H, J = 15.0 Hz, CH_2-N), 4.83 (d, 1H, J = 15.0 Hz, CH_2-N), 6.90-6.98 (m, 1H, 1H-thiophene), 7.09-7.14 (m, 1H, 1H-thiophene), 7.21-7.25 (m, 1H, 1H-thiophene), 8.30-8.40 (br, 1H, OH acid).

Anal. Calcd. for $C_{11}H_{13}NO_3S$ (239.28): C, 55.21; H, 5.48; N, 5.85. Found: C, 55.16; H, 5.23; N, 5.69.

1-(Thien-2'-ylmethyl)-2-pyrrolidinone-5-acetic Acid (**11b**).

This compound was obtained in 62% yield, mp 108°; ir: 3095 (O-H), 1718 (C=O), 1618 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.72-1.95 (m, 1H, 1H-pyrrolidinone), 2.12-2.6 (m, 4H, 3H-pyrrolidinone and $CH_2(CO_2H)$), 2.72 (dd, 1H, J = 4.0, 15.6 Hz, $CH_2(CO_2H)$), 3.87-4.05 (m, 1H, 1H pyrrolidinone), 4.23 (d, 1H, J = 15.3 Hz, CH_2-N), 5.0 (d, 1H, J = 15.3 Hz, CH_2-N), 6.85-6.91 (m, 2H, 2H-thiophene), 7.18-7.24 (m, 1H, 1H-thiophene), 9.01-9.17 (s, 1H, OH acid).

Anal. Calcd. for $C_{11}H_{13}NO_3S$ (239.28): C, 55.21; H, 5.48; N, 5.85. Found: C, 55.11; H, 5.35; N, 5.65.

1-(2'-Chlorothien-3'-ylmethyl)-2-pyrrolidinone-5-acetic Acid (**11c**).

This compound was obtained in a yield of 75%, mp 99°; ir: 3108 (O-H), 1709 (C=O), 1629 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.7-1.95 (m, 1H, 1H-pyrrolidinone), 2.1-2.62 (m, 4H, 3H-pyrrolidinone and $CH_2(CO_2H)$), 2.74 (dd, 1H, J = 3.5, 15.8 Hz, $CH_2(CO_2H)$), 3.73-3.92 (m, 1H, 1H pyrrolidinone), 4.11 (d, 1H, J = 15.0 Hz, CH_2-N), 4.75 (d, 1H, J = 15.0 Hz, CH_2-N), 6.81 (d, 1H, J = 5.7 Hz, $H_{4'}$-thiophene), 7.03 (d, 1H, J = 5.7 Hz, $H_{5'}$-thiophene), 8.26-8.41 (br, 1 H, OH acid).

Anal. Calcd. for $C_{11}H_{12}ClNO_3S$ (273.73): C, 48.27; H, 4.52; N, 5.12. Found: C, 48.09; H, 4.35; N, 5.06.

Oxopyrrolidinothieno[2]azepinones **3a,b,c**.

General Procedure.

A stirred suspension of 2.21 mmoles of acetic acid **11a**, **11b** or **11c** 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 by portionwise addition of aluminium trichloride (99.99%) (0.7 g, 5.13 mmoles) at 0-5°. 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 and water, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The resulting solid was recrystallized from ethanol to give ketone **3**.

3,3a,4,9-Tetrahydro-2*H*-pyrrolo[1,2-*b*]thieno[2,3-*f*][2]azepine-1,5-dione (**3a**).

This compound was obtained in a yield of 90%, mp 135°; ir: 1676 (C=O), 1636 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.65-1.85 (m, 1H, 1H-pyrrolidinone), 2.18-2.49 (m, 3H, 3H-pyrrolidinone), 2.96 (dd, 1H, J = 6.5, 15.6 Hz, H_{4ax}), 3.15 (dd, 1H, J = 4.3, 15.6 Hz, H_{4eq}), 4.03-4.17 (m, 1H, H_{3a}), 4.41 (d, 1H, J = 16.9 Hz, H_{9ax}), 5.05 (d, 1H, J = 16.9 Hz, H_{9eq}), 7.01 (d, 1H, J = 5.1 Hz, $H_{4'}$-thiophene), 7.55 (d, 1H, J = 5.1 Hz, $H_{5'}$-thiophene); ^{13}C nmr (deuteriochloroform): δ 26.0 (CH_2), 30.7 (CH_2), 40.9 (C_4), 47.5 (C_9), 54.5 (CH), 129.4 (CH), 133.5 (CH), 141.1 (C), 144.5 (C), 173.7 (CO), 190.8 (CO).

Anal. Calcd. for $C_{11}H_{11}NO_2S$ (221.27): C, 59.71; H, 5.01; N, 6.33. Found: C, 59.65; H, 4.97; N, 6.22.

3,3a,4,9-Tetrahydro-2*H*-pyrrolo[1,2-*b*]thieno[3,2-*f*][2]azepine-1,5-dione (**3b**).

This product was isolated in a yield of 80%, mp 120°; ir: 1692 (C=O), 1654 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.71-1.9 (m, 1H, 1H-pyrrolidinone), 2.17-2.63 (m, 3H, 3H-pyrrolidinone), 2.88 (dd, 1H, J = 5.9, 15.0 Hz, H_{4ax}), 3.15 (dd, 1H, J = 4.3, 15.0 Hz, H_{4eq}), 4.06-4.2 (m, 1H, H_{3a}), 4.59 (d, 1H, J = 16.7 Hz, H_{9ax}), 5.04 (d, 1H, J = 16.7 Hz, H_{9eq}), 7.07 (d, 1H, J = 5.4 Hz, $H_{4'}$-thiophene), 7.36 (d, 1H, J = 5.4 Hz, $H_{5'}$-thiophene); ^{13}C nmr (deuteriochloroform): δ 25.8 (CH_2), 31.0 (CH_2), 39.2 (C_4), 47.5 (C_9), 54.7 (CH), 123.6 (CH), 128.3 (CH), 140.4 (C), 147.1 (C), 173.7 (CO), 192.4 (CO).

Anal. Calcd. for $C_{11}H_{11}NO_2S$ (221.27): C, 59.71; H, 5.01; N, 6.33. Found: C, 59.48; H, 4.89; N, 6.09.

8-Chloro-3,3a,4,9-tetrahydro-2*H*-pyrrolo[1,2-*b*]thieno[4,3-*f*][2]-azepine-1,5-dione (**3c**).

This product was isolated in a yield of 86%, mp 192°; ir: 1685 (C=O), 1671 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.6-1.87 (m, 1H, 1H-pyrrolidinone), 2.15-2.59 (m, 3H, 3H-pyrrolidinone), 2.8 (dd, 1H, J = 6.5, 14.7 Hz, H_{4ax}), 3.2 (dd, 1H, J = 4.5, 14.7 Hz, H_{4eq}), 4.0-4.17 (m, 1H, H_{3a}), 4.25 (d, 1H, J = 16.1 Hz, H_{9ax}), 5.0 (d, 1H, J = 16.1 Hz, H_{9eq}), 7.81 (s, 1H, $H_{5'}$-thiophene);

^{13}C nmr (deuteriochloroform): δ 25.2 (CH_2), 30.8 (CH_2), 37.9 (C_4), 46.5 (C_9), 54.9 (CH), 127.7 (C), 129.4 (CH), 133.8 (C), 140.8 (C), 173.5 (CO), 191.8 (CO).

Anal. Calcd. for $C_{11}H_{10}ClNO_2S$ (255.71): C, 51.67; H, 3.94; N, 5.48. Found: C, 51.55; H, 3.89; N, 5.33.

General Procedure for Alcohols **12a,b,c**.

To a stirred solution of **3a**, **3b** or **3c** (4 mmoles) in 15 ml of dry methanol at 0° was added portionwise during 10 minutes, sodium borohydride (0.5 g, 13.2 mmoles). After reaction at room temperature for 2 hours, the solution was poured into 15 ml of water and acidified to *p*H 4 with hydrochloric acid solution (15%). After concentration *in vacuo*, the residue obtained was extracted again with dichloromethane and evaporated. The resulting solid was recrystallized from a mixture of diethyl ether-ethyl acetate to furnish the alcohol **12** in good yield.

2,3,3a,4,5,9-Hexahydro-5-hydroxypyrrolo[1,2-*b*]thieno[2,3-*f*]-[2]azepin-1-one (**12a**).

This product was isolated in a yield of 89%, mp 184°; ir: 3321 (OH), 1662 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45-2.0 (m, 3H, 2H-pyrrolidinone and H_{4ax}), 2.16-2.49 (m, 3H, 2H-pyrrolidinone and H_{4eq}), 3.77 (d, 1H, J = 15.3 Hz, H_{9ax}), 3.87-4.03 (m, 1H, H3a), 4.91-4.98 (br, 1H, OH), 5.14 (dd, 1H, J = 3.1, 10.2 Hz, H_{5ax}), 5.15 (d, 1H, J = 15.3 Hz, H_{9eq}), 6.94 (d, 1H J = 5.1 Hz, $H_{4'}$-thiophene), 7.06 (d, 1H, J = 5.1 Hz, $H_{5'}$-thiophene).

Anal. Calcd. for $C_{11}H_{13}NO_2S$ (223.28): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.08; H, 5.80; N, 6.19.

2,3,3a,4,5,9-Hexahydro-5-hydroxy-pyrrolo[1,2-*b*]thieno[3,2-*f*]-[2]azepin-1-one (**12b**).

This product was isolated in a yield of 92%, mp 171°; ir: 3439 (OH), 1667 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.6-1.92 (m, 2H, 1H-pyrrolidinone and H_{4ax}), 2.08-2.37 (m, 4H, 3H-pyrrolidinone and H_{4eq}), 3.09-3.17 (br, 1H, OH), 3.8-4.0 (m, 1H, H_{3a}), 3.94 (d, 1H, J = 15.6 Hz, H_{9ax}), 4.95 (dd, 1H, J = 2.4, 10.5 Hz, H_{5ax}), 5.08 (d, 1H, J = 15.6 Hz, H_{9eq}), 7.01 (d, 1H, J = 4.6 Hz, $H_{4'}$-thiophene), 7.07 (d, 1H, J = 4.6 Hz, $H_{5'}$-thiophene).

Anal. Calcd. for $C_{11}H_{13}NO_2S$ (223.28): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.01; H, 5.68; N, 6.21.

8-Chloro-2,3,3a,4,5,9-hexahydro-5-hydroxypyrrolo[1,2-*b*]-thieno[4,3-*f*][2]azepin-1-one (**12c**).

This product was isolated in a yield of 91%, mp 171°; ir: 3315 (OH), 1662 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.5-1.85 (m, 3H, 2H-pyrrolidinone and H_{4ax}), 2.12-2.4 (m, 3H, 2H-pyrrolidinone and H_{4eq}), 3.52 (d, 1H, J = 15.3 Hz, H_{9ax}), 3.71-3.78 (br, 1H, OH), 3.8-3.96 (m, 1H, H_{3a}), 4.87 (dd, 1H, J = 2.4, 9.7 Hz, H_{5ax}), 5.34 (d, 1H, J = 15.3 Hz, H_{9eq}), 6.99 (s, 1H, $H_{5'}$-thiophene).

Anal. Calcd. for $C_{11}H_{12}ClNO_2S$ (257.73): C, 51.26; H, 4.68; N, 5.43. Found: C, 51.07; H, 4.61; N, 5.23.

General Procedure for Oximes **13a,b**.

A mixture of ketone **3a** or **3b** (1 g, 4.51 mmoles), hydroxylamine hydrochloride (0.69 g, 10 mmoles) and sodium acetate (0.82 g, 10 mmoles) in 15 ml of aqueous ethanol (80%) was refluxed for 5 hours. Ice water cooling afforded a white solid precipitate, which was collected, washed with cold ethanol, water and air dried. An analytical sample of oxime **13** was obtained by recrystallization from aqueous ethanol.

5-Oximino-3,3a,4,9-tetrahydro-2*H*-pyrrolo[1,2-*b*]thieno[2,3-*f*]-[2]azepin-1-one (**13a**).

This product was isolated as a mixture of *anti* form (**A**) (77%) and *syn* form (**B**) (23%) in a yield of 85%, mp 198°; ir: 3172 (OH), 1636 (C=O and C=N) cm^{-1}.

Compound **13a**(**A**) had ^1H nmr (DMSO-d_6): δ 1.65-1.9 (m, 1H, 1H-pyrrolidinone), 1.98-2.64 (m, 3H, 3H-pyrrolidinone), 2.76 (dd, 1H, J = 5.4, 14.8 Hz, H_{4ax}), 3.36 (dd, 1H, J = 3.3, 14.8 Hz, H_{4eq}), 4.05-4.12 (m, 1H, H_{3a}), 4.16 (d, 1H, J = 16.4 Hz, H_{9ax}), 4.79 (d, 1H, J = 16.4 Hz, H_{9eq}), 6.98 (d, 1H, J = 5.1 Hz, $H_{4'}$-thiophene), 7.32 (d, 1H, J = 5.1 Hz, $H_{5'}$-thiophene), 8.6-8.69 (br, 1H, OH exchanged with deuterium oxide).

Compound **13a**(**B**) had ^1H nmr (DMSO-d_6): δ 1.65-1.9 (m, 1H, 1H-pyrrolidinone), 1.98-2.64 (m, 4H, 3H-pyrrolidinone and H_{4ax}), 3.13 (dd, 1H, J = 3.5, 14.8 Hz, H_{4eq}), 4.05-4.12 (m, 1H, H_{3a}), 4.19 (d, 1H, J = 15.5 Hz, H_{9ax}), 4.88 (d, 1H, J = 15.5 Hz, H_{9eq}), 7.01 (d, 1H, J = 4.9 Hz, $H_{4'}$-thiophene), 7.57 (d, 1H, J = 4.9 Hz, $H_{5'}$-thiophene), 8.28-8.35 (br, 1H, OH exchanged with deuterium oxide).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$ (236.28): C, 55.92; H, 5.12; N, 11.86. Found: C, 55.45; H, 5.13; N, 11.68.

5-Oximino-3,3a,4,9-tetrahydro-2*H*-pyrrolo[1,2-*b*]thieno[3,2-*f*]-[2]azepin-1-one (**13b**).

This product was isolated as a *anti* form (**A**) (77%) in a yield of 75%, mp 196°; ir: 3148 (OH), 1625 (C=O and C=N) cm^{-1}.

Compound **13b**(**A**) had ^1H nmr (DMSO-d_6): δ 1.64-1.85 (m, 1H, 1H-pyrrolidinone), 2.0-2.68 (m, 3H, 3H-pyrrolidinone), 2.73 (dd, 1H, J = 5.5, 14.5 Hz, H_{4ax}), 3.32 (dd, 1H, J = 3.5, 14.7 Hz, H_{4eq}), 3.94-4.06 (m, 1H, H_{3a}), 4.38 (d, 1H, J = 16.4 Hz, H_{9ax}), 4.84 (d, 1 H, J = 16.4 Hz, H_{9eq}), 7.14 (d, 1H, J = 5.1 Hz, $H_{4'}$-thiophene), 7.32 (d, 1H, J = 5.1 Hz, $H_{5'}$-thiophene), 8.65-8.92 (br, 1H, OH exchanged with deuterium oxide).

Compound **13b**(**B**) had ^1H nmr (DMSO-d_6): δ 1.64-1.85 (m, 1H, 1H-pyrrolidinone), 2-2.68 (m, 4H, 3H-pyrrolidinone and H_{4ax}), 2.93 (dd, 1H, J = 5.4, 13.5 Hz, H_{4eq}), 3.94-4.06 (m, 1H, H_{3a}), 4.23 (d, 1H, J = 16.4 Hz, H_{9ax}), 4.98 (d, 1H, J = 16.4 Hz, H_{9eq}), 7.14 (d, 1H, J = 5.1 Hz, $H_{4'}$-thiophene), 7.51 (d, 1H, J = 5.1 Hz, $H_{5'}$-thiophene), 8.94-8.99 (br, 1H, OH exchanged with deuterium oxide).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$ (236.28): C, 55.92; H, 5.12; N, 11.86. Found: C, 55.59; H, 5.09; N, 11.56.

Oxopyrrolidinothieno[1,5]diazocinones **14a,b,c**.

Procedure A. Beckmann Rearrangement of Oximes **13a,b**.

Finely powdered oxime **13a,b** (7.5 mmoles) was added with stirring into 20 g of polyphosphoric acid at 90-100°. The mixture was allowed to react under a nitrogen atmosphere for 2 hours. The hot solution was hydrolyzed with crushed ice (200 g) and the resulting mixture was basified to *p*H 8-9 with 50% sodium hydroxide solution at 10-20°. The organic phase was washed with saturated brine, dried, and concentrated to give a solid which was recrystallized from dry ethanol.

2,3,3a,4,6,10-Hexahydropyrrolo[1,2-*a*]thieno[2,3-*f*][1,5]diazocine-1,5-dione (**14a**(**C**)).

This product was obtained in a yield of 45%, mp 251°; ir: 3289 (OH and NH), 1689 (C=O), 1678 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.52-1.7 (m, 1H, 1H-pyrrolidinone), 1.85-2.51 (m, 5H, 3H-pyrrolidinone and 2-H_4), 4.11 (d, 1H, J = 17.2 Hz, H_{10ax}), 4.61-4.67 (m, 2H, H_{3a} and NH exchanged with deuterium oxide), 5.34 (d, 1H, J = 17.2 Hz, H_{10eq}), 7.08 (d, 1H,

J = 5.1 Hz, $H_{4'}$-thiophene), 7.58 (d, 1H, J = 5.1 Hz, $H_{5'}$-thiophene); ^{13}C nmr (deuteriochloroform): δ 20.7 (CH_2), 29.1 (CH_2), 42.0 (C_4), 49.9 (C_{10}), 58.7 (CH), 128.9 (CH), 131.2 (CH), 139.4 (C), 150.4 (C), 173.5 (CO), 174.5 (CO).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$ (236.28): C, 55.92; H, 5.12; N, 11.86. Found: C, 55.78; H, 5.11; N, 11.84.

2,3,3a,4,6,10-Hexahydropyrrolo[1,2-*a*]thieno[3,2-*f*][1,5]diazocine-1,5-dione(**14b(C)**).

This product was obtained in a yield of 52%, mp 218°; ir: 3256 (OH and NH), 1681 (C=O), 1656 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43-1.76 (m, 1H, 1H-pyrrolidinone), 2.2-2.55 (m, 5H, 3H-pyrrolidinone and 2-H_4), 3.66 (d, 1H, J = 15.3 Hz, H_{10ax}), 3.9-3.98 (m, 1H, H_{3a}), 5.17 (d, 1H, J = 15.3 Hz, H_{10eq}), 6.78 (d, 1H, J = 5.4 Hz, $H_{4'}$-thiophene), 7.18 (d, 1H, J = 5.4 Hz, $H_{5'}$-thiophene), 8.39 (s, 1H, NH exchanged with deuterium oxide); ^{13}C nmr (deuteriochloroform): δ 25.8 (CH_2), 30.4 (CH_2), 36.5 (C_4), 42.4 (C_{10}), 56.5 (CH), 123.9 (CH), 124.8 (CH), 130.4 (C), 134.4 (C), 172.8 (CO), 173.5 (CO).

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$ (236.28): C, 55.92; H, 5.12; N, 11.86. Found: C, 55.66; H, 4.99; N, 11.75.

Procedure B. Schmidt Rearrangement of Ketones **3a,b,c**.

A well stirred solution of ketone **3a,b,c** (2.71 mmoles) in 20 ml of dry dichloromethane was added dropwise with cooling over 15 minutes to 2 ml of concentrated sulfuric acid. After reacting for 10 minutes, sodium azide (0.7 g, 10.7 mmoles) was added over a period of 30 minutes and the reaction mixture was allowed to react at room temperature for 24 hours. The reaction solution was basified with potassium carbonate solution to *p*H 8-9 and decanted. The aqueous solution was extracted with dichloromethane (2 x 20 ml). The organic phase was washed with saturated brine, dried, filtered and concentrated to give a solid. Crystallization from ethanol afforded diazocinones **14a,b,c**. Compounds **14a** (65%) and **14b** (70%) were identical to those prepared above.

9-Chloro-2,3,3a,4,6,10-Hexahydropyrrolo[1,2-*a*]thieno[4,3-*f*]-[1,5]diazocine-1,5-dione (**14c(C)**).

This product was obtained in a yield of 45%, mp 264°; ir: 3214 (OH and NH), 1682 (C=O), 1654 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.62-1.82 (m, 1H, 1H-pyrrolidinone), 2.18-2.61 (m, 5H, 3H-pyrrolidinone and 2-H_4), 3.34 (d, 1H, J = 15.6 Hz, H_{10ax}), 3.82-3.88 (m, 1H, H_{3a}), 5.37 (d, 1H, J = 15.6 Hz, H_{10eq}), 6.86 (s, 1H, $H_{5'}$-thiophene), 7.95 (s, 1H, NH exchanged with deuterium oxide); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_2), 30.3 (CH_2), 36.0 (C_4), 41.3 (C_{10}), 57.5 (CH), 115.2 (CH), 130.3 (C), 132.2 (C), 134.2 (C), 173.2 (CO), 173.6 (CO).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2S$ (270.73): C, 48.88; H, 4.11; N, 10.37. Found: C, 48.72; H, 4.02; N 10.15.

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