HETEROTRICYCLIC SYSTEMS : SYNTHESIS AND REACTIVITY OF THIENO[2,3(3,2)-*b*]INDOLIZIDIN-9-ONES

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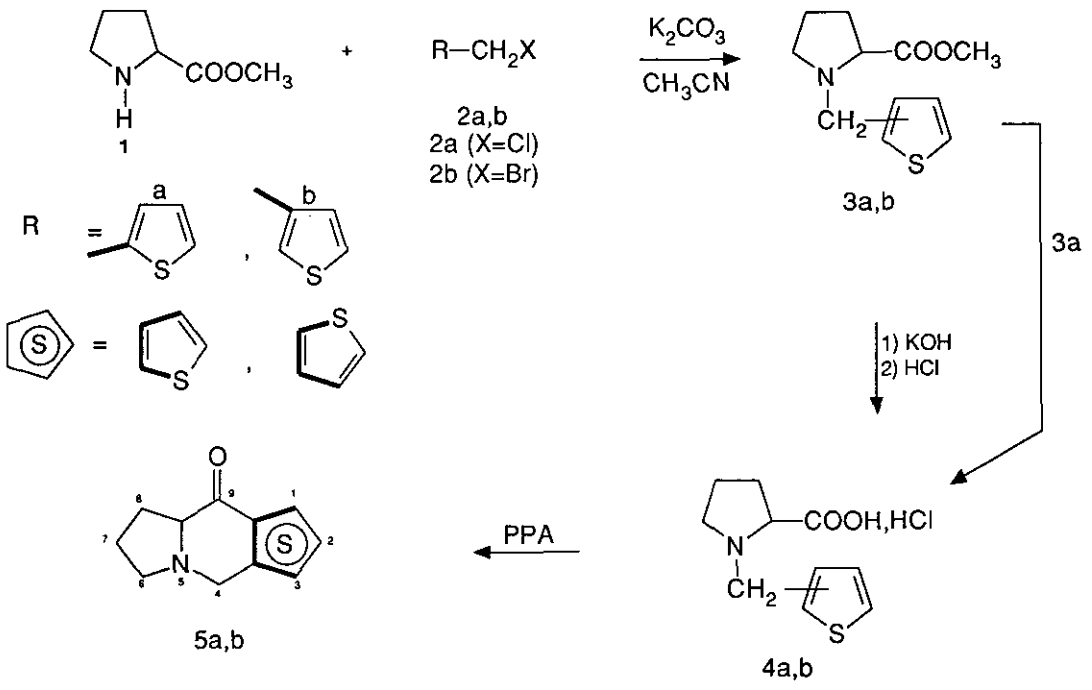
Abstract------ A simple and efficient synthesis of thieno [2,3(3,2)-*b*] indolizidin-9-ones is described starting from 2(3)-halogenomethylthiophene. The reactivity (Beckmann and Schmidt rearrangements) of these ketones is studied and compared with the reactivity of thienoquinolizidinones and thienoindolizidinediones

In carrying on our exploration of the pharmacological potential of heteropolycyclic structures, we previously synthesized several thienoindolizidinediones[1] leading to thienopyrrolidino[1,3]diazepinediones or thieno[1,5]naphthyridones[2] and several thienoquinolizidinones leading to thienopiperidino[1,3] or [1,4]diazepinones.[3] Now, we wish to report the synthesis and the reactivity of thienoindolizidinones to study the influence of the size of the starting cyclic amino acid and the presence of a carbonyl group in that cycle.

Thieno[3,2-*b*]indolizidin-9-one (**5a**) and thieno[2,3-*b*]indolizidin-4-one (**5b**) are synthesized according to the Scheme 1. Condensation of the halogenomethylthiophenes (**2a,b**) with L-methyl prolinate (**1**)[4] gave the condensed products (**3a,b**). It was necessary to use potassium carbonate as the base and acetonitrile as solvent to get the expected compounds (**3a,b**) in 75 % yield. Other conditions (sodium hydride in benzene,[1] potassium carbonate in dimethylformamide,[3] or

potassium in tetrahydrofuran[5]) did not give the substitution products or insignificant yields.

Scheme I



Saponification of the esters (**3a,b**) led to the corresponding amino acids (**4a,b**) isolated as hydrochloride salts respectively in 95 and 91% yields. Acidic hydrolysis of the amino ester (**3a**) gave directly the hydrochloride salt (**4a**) in 99% yield, unfortunately in the same condition (**3b**) was decomposed. We previously reported that *N*-thienylmethyl-5-oxoprolines were cyclised to ketones through a Friedel-Crafts intramolecular cyclisation [1] and *N*-thienylmethylpipecolinic acids were cyclised to ketones with polyphosphoric acid.[3] With *N*-thienylmethylprolines, the best results were observed when the hydrochloride salts of the amino acids (**4a,b**) were treated with polyphosphoric acid at 100 °C during 6 hours under a nitrogen atmosphere. In these conditions, the ketones (**5a,b**) were obtained respectively in 50 and 53% yields.

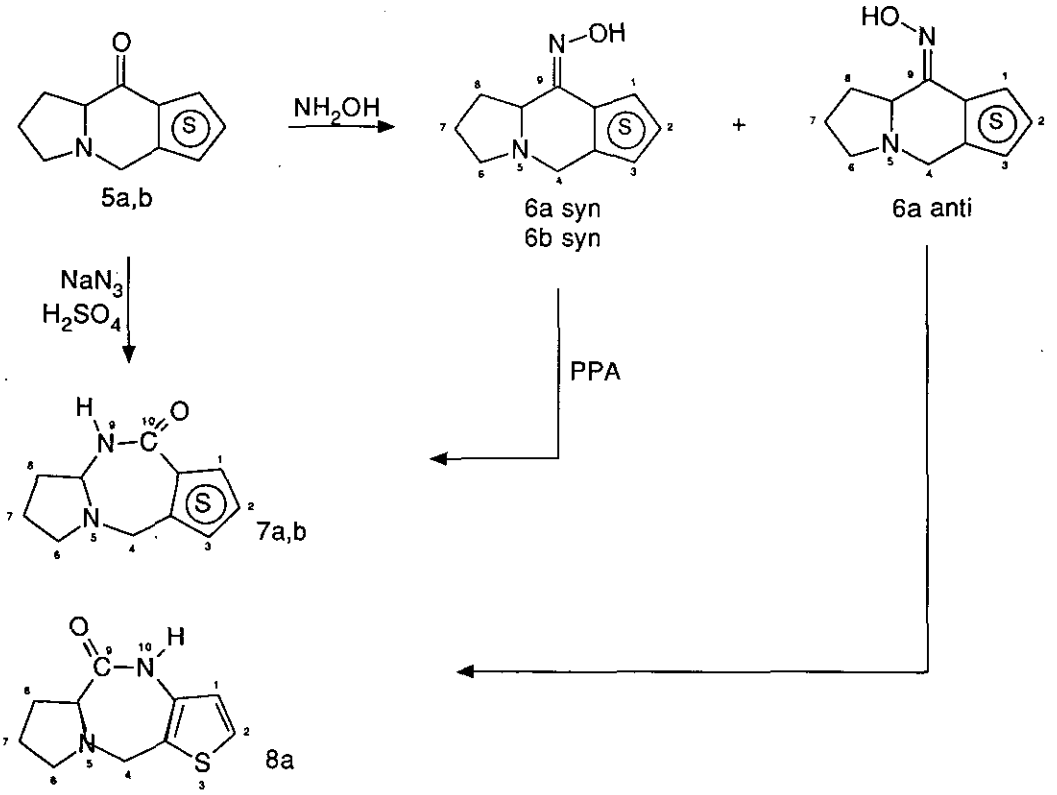
All of these compounds were characterized by ir and nmr spectroscopy and microanalysis. Details are reported in the experimental section, but there are a number of interesting features. The -CH_2-N protons in amino esters (**3a,b**) and amino acids (**4a,b**) appear as an AB system in accordance with the observations made with *N*-thienyloxoproline or *N*-thienylpipecoline derivatives.[1,3] The C-4 protons in ketones (**5a,b**) appear as a doublet with chemical shifts of 4.35 and 4.25 ppm for the equatorial (eq) proton and a doublet of doublet with chemical shifts of 3.90 and 3.64 ppm for the axial (ax) proton and coupling constants of J = 17 Hz (H_4-ax, H_4-eq) and J = 2 Hz (H_4-ax, H_{8a}-ax). This allows to assign to compounds (**5a,b**) a *trans* configuration and to be in accordance with the observations made by Sollhuber [6] in the quinolizidine series.

The above ketones (**5a,b**) treated with hydroxylamine hydrochloride in the presence of sodium acetate afforded the corresponding oximes (**6a**) (*syn* + *anti*) and (**6b**) (*syn*). These results are similar to those obtained previously with thienoindolizidinones oximes[1] and show that the pyrrolidine ring is not hindered enough to produce the single syn isomer of **6a** as with a piperidine ring.[3] For these oximes the two protons attached to C-4 are not equivalent in the nmr spectrum. The position of the axial proton H-4 ax is at higher magnetic field (3.65 - 3.77 ppm) than the equatorial proton H-4 eq (3.98 - 4.60 ppm) as in the corresponding ketones. Furthermore the deshielding of + 0.35 ppm of the H-8a proton of the oxime (**6a**) *anti* compared to the H-8a proton of the ketone (**5a**) is in accordance with our observation[1] on thienoindolizidinones oximes (+ 0.30 ppm) and much less than that observed in the thienoquinolizidinones oximes (+ 1.42 ppm) previously reported.[3]

When oximes (**6a,b**) are heated with polyphosphoric acid at 90 °C under nitrogen, we formed with the mixture *syn* + *anti* isomers of **6a** only the [1,3]diazepine (**7a**) (50% yield) corresponding to the Beckmann rearrangement of the *syn* isomer. We observed a completely degradation of the oxime *anti*, the migration of the thiophene ring did not occur, and no isomerization of the oxime could be detected. The oxime (**6b**) (*syn*) gave the expected rearrangement product (**7b**) in 60% yield. Because the rearrangement product of the *anti* isomer of **6a** could not be detected, we tested the Schmidt rearrangement of the initial ketones. Then, the ketone (**5a**) treated with sodium azide in

concentrated sulfuric acid at room temperature gave a mixture of the [1,4]diazepine (**8 a**) (35%) and the [1,3]diazepine (**7 a**) (65%). This mixture is in accordance with the percentage observed during the formation of the oximes. This result is particularly interesting because the Beckmann rearrangement had not given the [1,4]diazepine (**8 a**) probably due to the too high necessary temperature of the reaction compared to the room temperature used in the Schmidt rearrangement.

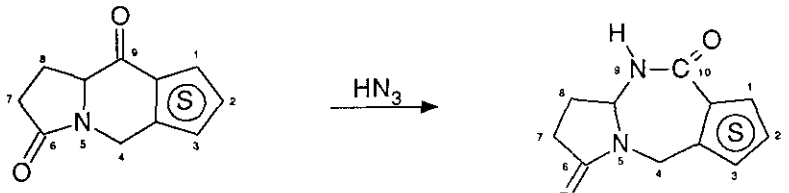
Scheme 2



Furthermore, to complete the understanding of this reaction, we can compare this result with those observed with thienoquinolizidinones[3] and indolizidinones[1] previously described. We reported that the former gave only [1,3]diazepines and now we report the reactivity of the latter. Actually, when the thieno[3,2-*b*]indolizidine-6,9-dione (**9 a**)[1] was treated with sodium azide in concentrated sulfuric acid we obtained the 4,7,8,8a-tetrahydropyrrolo[1,2-*a*]thieno[3,2-*e*][1,3]diazepine-6,10(9*H*)-dione (**10 a**) in 75% yield. We did not observe the possible [1,4]diazepine consecutive to the migration of the thiophene ring, no more the [1,5]naphthyridine that we formed during the Beckmann

rearrangement of the corresponding oxime of the ketone (**9 a**). It seems that the temperature is not enough high to break the amide link in the pyrrolidinone system. In a similar manner, the indolizidinedione (**9 b**) led to the single 4,7,8,8a-tetrahydropyrrolo[1,2-*a*]thieno[2,3-*e*][1,3]diazepin-6,10(9*H*)-dione (**10 b**) in 70% yield. On the other hand, according to the above results, the Schmidt reaction of the ketone (**5 b**) gave the single 4*H*-pyrrolidino[1,2-*a*]thieno[2,3-*e*][1,3]diazepin-10(9*H*)-one (**7 b**) in 85% yield.

Scheme 3

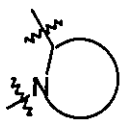
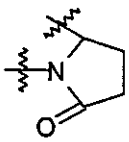
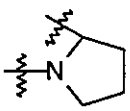
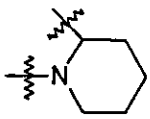
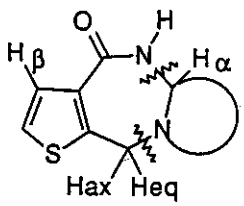
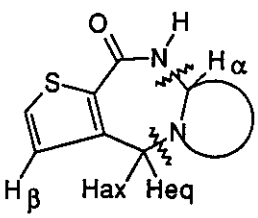
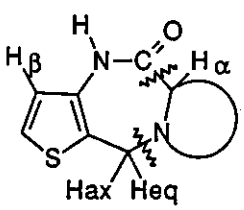
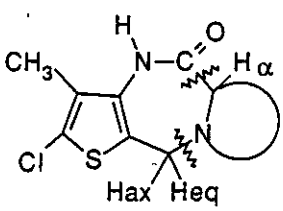


9a,b 10a,b

The structures of the [1,3]diazepines (**7 a,b**) and the [1,4]diazepine (**8 a**) are supported by their ir and nmr spectra as well as by their microanalyses. Details are reported in the experimental section and in Table 1. The stronger difference between the [1,3] or [1,4]diazepine is the chemical shift of the proton attached to the carbon located between the two nitrogen atoms (case of the [1,3]-diazepine) or between one nitrogen atom and the carbonyl group (case of the [1,4]diazepine). The former is shifted downfield 4.30 - 4.45 or 4.55 - 4.75 ppm compared to the latter 3.35 - 3.50 ppm. In addition the signal is a doublet of doublet in the [1,4]diazepine with coupling constants of J = 3 Hz and J =10 Hz with the two near close protons of the pyrrolidine ring. The multiplet for the signal of the equivalent proton of the [1,3]diazepine is due to the proximity of the N-H proton. Moreover the Hβ of the thiophene ring is also influenced by its proximity. Actually the chemical shift of Hβ is 6.63 ppm for the [1,4]diazepine and 7.14 and 6.86 ppm respectively for the [1,3]diazepines (**7 a** and **b**). Finally, the C_4-Hax and C_4-Heq (equatorial) appear as an AB system with chemical shift of 4.16 or 4.18 ppm for the equatorial proton and 4.03 or 3.97 ppm for the axial proton. The non-equivalence of the C_4-Hax and C_4-Heq protons and their chemical shifts are similar to these observed with a

piperidine ring but shifted higherfield compared to these observed with an oxopyrrolidine ring (see Table 1).

Table 1

					
		δ (ppm) J (Hz)	δ (ppm) J (Hz)	δ (ppm) J (Hz)	
	Hα	5.10 - 5.21 m	4.55 - 4.75 m	3.84 - 3.95 m	
	Hax	4.63 d 16.4	4.03 d 14.0	4.01 d 15.6	
	Heq	4.75 d 16.4	4.16 d 14.0	4.09 d 15.6	
	Hβ	7.23 d 5.4	7.14 d 5.2	7.28 d 5.2	
	Hα	5.11 - 5.20 m	4.30 - 4.45 m	4.58 - 4.72 m	
	Hax	4.42 d 17.6	3.97 d 16.2	3.94 d 16.9	
	Heq	4.83 d 17.6	4.18 d 16.2	4.28 d 16.9	
	Hβ	7.05 d 5.0	6.86 d 5.0	6.92 d 5.0	
	Hα		3.35 - 3.50 m 3.0, 6.5		
	Hax		3.92 d 14.8		
	Heq		4.27 d 14.8		
	Hβ		6.63 d 5.4		
	Hα			2.57 dd 2.5, 6.2	
	Hax			3.58 d 15.5	
	Heq			3.99 d 15.5	

In conclusion, the smoothness of the Schmidt reaction allows to get a mixture of thieno[1,4]-diazepine and thieno[1,3] with suitable substrate while the Beckmann rearrangement always give the thieno[1,3]diazepine since we have not yet observed the migration of the thiophene ring in the intermediate nitrene. Further investigations about these reactions are in progress.

EXPERIMENTAL

Melting points were taken on a hot-stage apparatus, elemental analyses were obtained in the microanalysis laboratory of the Institut National des Sciences Appliquées, Rouen. ^{1}H-Nmr spectra were recorded on a Brucker AC200 instrument for $CDCl_3$ solution and chemicals shifts (δ) are expressed in ppm relative to internal hexamethyldisiloxane. Infrared spectra were measured with a Beckmann IR 20 spectrophotometer.

L-Methyl *N*-Thien-2-ylmethylprolinate (**3 a**)

A mixture of **1** (29.7 g, 0.23 mol), potassium carbonate (23.8 g, 0.17 mol) and 150 ml of acetonitrile was stirred under reflux for 1 h. Then, a solution of 2-chloromethylthiophene (**2 a**) (33 g, 0.25 mol) in 50 ml of acetonitrile was added slowly and the mixture was refluxed for 15 min. The cooled resulting suspension was filtered off. The resultant solution was concentrated and a distillation under reduced pressure gave the alkylated product (**3 a**) as an oil in 75% (38.8 g) yield, $bp_{0.05}$ 100-102 °C;ir: 1730 (-COOMe) cm^{-1};^{1}H-nmr (deuteriochloroform): δ 1.65-2.20 (m, 4H, proline), 2.95-3.10 (m, 2H, proline), 3.15-3.35 (m, 1H, proline), 3.60 (s, 3H, $COOCH_3$), 3.85 (d, J = 14.0 Hz, 1H, CH_2N), 4.05 (d, J = 14.0 Hz, 1H, CH_2N), 6.75-6.90 (m, 2H, H_3 and H_4 thiophene), 7.20 (dd, J = 1.2, 5.0 Hz, 1H, H_5 thiophene). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.53; H, 6.49; N, 6.11.

L-Methyl *N*-Thien-3-ylmethylprolinate (**3 b**)

In a same manner as above 3-bromomethylthiophene (**2 b**) (44.2 g, 0.25 mol), potassium carbonate (23.8 g, 0.17 mol) and L-methylprolinate (29.7 g, 0.23 mol) afforded the alkylated product (**3 b**) as an oil in 75% (38.8 g) yield $bp_{0.05}$ 100-103 °C; ir: 1730 ($COOCH_3$) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.70-2.20 (m, 4H, proline), 2.20-2.60 (m, 1H, proline), 2.90-3.35 (m, 2H, proline), 3.65 (s, 3H, $COOCH_3$), 3.75 (d, J = 14.0 Hz, 1H, CH_2N), 3.90 (d, J = 14.0 Hz, 1H, CH_2N), 7.00-7.35 (m, 3H,

H_3, H_4, H5-thiophene. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.71; H, 6.50; N, 6.41.

L-*N*-Thien-2-ylmethylproline hydrochloride (**4 a**)

A mixture of the ester **3a** (4.95 g, 0.022 mol), potassium hydroxide in pellets (1.5 g, 0.27 mol) and 30 ml of ethanol was refluxed for 3 h. 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 acetone-ethanol gave the hydrochloride (**4 a**) as white crystals in 95% (5.16 g) yield, mp 197-199 °C; ^{1}H-nmr (DMSO-d_6): δ 1.75-2.15 (m, 3H, proline), 2.30-2.60 (m, 1H, proline), 3.20-3.40 (m, 1H, proline), 3.40-3.60 (m, 1H, proline), 4.30-4.50 (m, 1H, proline), 4.60 (d, J = 14.3 Hz, 1H, CH_2N), 4.75 (d, J = 14.3 Hz, 1H, CH_2N), 7.10 (dd, J = 1.2, 3.4 Hz, 1H, H_3 thiophene), 7.40 (dd, J = 3.4, 5.0 Hz, 1H, H_4 thiophene), 7.70 (dd, J = 1.2, 5.0 Hz, 1H, H_5 thiophene). Anal. Calcd for $C_{10}H_{14}NO_2ClS$: C,48.48; H, 5.70;N 5.65. Found: C, 48.20; H, 5.40; N, 5.30.

L-*N*-Thien-3-ylmethylproline hydrochloride (**4 b**)

In a same manner as above, the ester (**3 b**), gave the hydrochloride (**4 b**) as white crystals in 91% (4.94 g) yield, mp 199-201 °C; ^{1}H-nmr (DMSO-d_6): δ 1.70-2.15 (m, 3H, proline), 2.25-2.55 (m, 1H, proline), 3.25-3.45 (m, 1H, proline), 3.40-3.65 (m, 1H, proline), 4.30-4.50 (m, 1H, proline), 4.35 (d, J = 13.7 Hz, 1H, CH_2N), 4.50 (d, J = 13.7 Hz, 1H, CH_2N), 7.30 (dd, J = 1.2, 4.8 Hz, 1H, H_4 thiophene), 7.65 (dd, J = 1.2, 3.1 Hz, 1H, H_2 thiophene), 7.75 (dd, J = 3.1, 4.8 Hz, 1H, H_5 thiophene). Anal. Calcd for $C_{10}H_{14}NO_2ClS$: C, 48.48;H, 5.70; N, 5.65. Found : C, 48.40; H, 5.81; N, 5.48.

L-*N*-Thien-2-ylmethylproline hydrochloride (**4 a**)

A mixture of ester **3 a** (5 g, 0.022 mol) in 20 ml of a 10 N hydrochloric acid solution was refluxed for 2 h. The resulting solution was evaporated to dryness to give a solid. Crystallization from a mixture acetone-ethanol gave the hydrochloride (**4 a**) in 99% (5.39 g) yield. Physical constants are indentical to those described above.

Thieno[3,2-*b*]indolizidin-9-one (**5 a**)

A suspension of the acid **4 a** (5 g, 0.024 mol) in polyphosphoric acid (100 g) was stirred under nitrogen at 100 °C during 6 h. The dark solution was poured slowly on to crushed ice and treated at 20 °C with 40% sodium hydroxide to pH=7. The crystallized ketone was filtered and the filtrate was extracted with dichloromethane (3 X 150 ml). The organic layer was washed with saturated brine, dried, filtered and concentrated to give an additional amount of the ketone as an orange solid. Both crystals were solubilized in the minimum of dichloromethane, then passed through a silica gel column eluting with dichloromethane-acetone (95/5). The yellowish eluted solid was then recrystallized from ligroine to afford the ketone (**5 a**) in 50% (2.32 g) yield, mp 75-77 °C ; ir : 1690 (CO) cm^{1} ;^{1}H-nmr (deuteriochloroform): δ 1.75-2.00 (m, 2H, proline), 2.00-2.25 (m, 2H, proline), 2.65 (dd, *J* = 8.4, 16.8 Hz, 1H, proline), 3.05-3.20 (m, 2H, proline), 3.90 (dd, *J* = 2.4, 15.8 Hz, 1H, CH_2N), 4.35 (d, *J* = 15.8 Hz, 1H, CH_2N), 7.13 (d, *J* = 5.2 Hz, 1H, H_4 thiophene), 7.40 (d, *J* = 5.2 Hz, 1H, H_5 thiophene). Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.05; H, 5.62; N, 7.01.

Thieno [2,3-*b*]indolizidin-9-one (**5 b**)

The acid (**4 b**) (5 g, 0.024 mol) in polyphosphoric acid (100 g) was treated in the same manner as above to give the ketone (**5 b**) as yellowish crystals in 53% (2.45 g) yield, mp 95-97 °C, ir: 1690 (CO) cm^{-1} ^{1}H-nmr (deuteriochloroform): δ 1.80-1.95 (m, 2H, proline), 2.08-2.20 (m, 2H, proline), 2.58 (dd, *J* = 8.4, 16.8 Hz, 1H, proline), 3.06-3.22 (m, 2H, proline), 3.64 (dd, *J* = 2.8, 15.8 Hz, 1H, CH_2N), 4.25 (d, *J* = 15.8 Hz, 1H, CH_2N), 6.98 (d, *J* = 4.8 Hz, 1H, H_4 thiophene), 7.66 (d, *J* = 4.8 Hz, 1H, H_5 thiophene). Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.44; H, 5.80; N, 7.22.

4*H*-Pyrrolidino[1,2-*a*]thieno[3,2-*e*][1,3]diazepin-10(9*H*)-one (**7 a**) and

4*H*-pyrrolidino[1,2-*a*]thieno[3,2-*e*][1,4]diazepin-9(10*H*)-one (**8 a**)

A well stirred solution of ketone (**5 a**)(0.96 g, 0.005 mol) in 20 ml of dichloromethane was treated dropwise with 98% sulfuric acid (2.4 ml) under cooling in an ice bath for 10 min. After, sodium azide (0.95 g, 0.015 mol) was added for 30 min and the reaction mixture was stirred at room temperature for one night. The mixture was poured onto crushed ice (50 ml) and basified with portions of potassium carbonate to pH=10. The aqueous solution was extracted with saturated brine, dried

(sodium sulfate) filtered and concentrated to give a yellowish solid. The mixture of [1,3]diazepine (65%) and [1,4]diazepine (35%) was separated by column chromatography on silica gel eluting with dichloromethane-acetone (50-50).

The [1,4]diazepine (**8 a**) was obtained with 31.5% (0.33 g) yield as white crystals recrystallized from ethanol, mp 205-207 °C; ir: 3300-2850 (NHCO), 1670 (CO) cm^{-1};^{1}H-nmr (deuteriochloroform : δ 1.75-2.05 (m, 3H, pyrrolidine), 2.45-2.80 (m, 2H, pyrrolidine), 3.17-3.35 (m, 1H, pyrrolidine), 3.35-3.50 (dd, *J* = 3.0, 6.5 Hz, 1H, pyrrolidine), 3.92 (d, *J* = 14.8 Hz, 1H, CH_2N), 4.27 (d, *J* = 14.8 Hz, 1H, CH_2N), 6.63 (d, *J* = 5.4 Hz, 1H, H_4 thiophene), 7.10 (d, *J* = 5.4 Hz, 1H, H_5 thiophene), 8.50 (s, 1H, N-H). Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.76; N, 13.45. Found: C, 57.35; H, 5.46; N, 13.25.

The [1,3]diazepine (**7 a**) was obtained with 58.5% (0.61 g) yield as white crystals recrystallized from ethanol, mp 204-206 °C; ir: 3300-2850 (NHCO), 1690 (CO) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.65-2.45 (m, 4H, pyrrolidine), 2.75-3.05 (m, 2H, pyrrolidine), 4.03 (d, *J* = 14.0 Hz, 1H, CH_2N), 4.16 (d, *J* = 14.0 Hz, 1H, CH_2N), 4.55-4.75 (m, 1H, pyrrolidine), 7.01 (s, 1H, NH), 7.14 (d, *J* = 5.2 Hz, 1H, H_4 thiophene), 7.40 (d, *J* = 5.2 Hz, 1H, H_5 thiophene). Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.76; N, 13.45. Found: C, 57.90; H, 5.74; N, 13.28.

4*H*-Pyrrolidino[1,2-*a*]thieno[2,3-*e*][1,3]diazepin-10 (9*H*)-one (**7 b**)

In the same manner as above, ketone (**5 b**) gave the [1,3]diazepine (**7 b**) in 85% (0.88 g) yield as white crystals recrystallized from ethanol, mp 187-189 °C; ir: 3300-2850 (-NHCO), 1670 (CO) cm^1 ;^{1}H-nmr (deuteriochloroform): δ 1.80-2.40 (m, 4H, pyrrolidine), 2.50-2.75 (m, 1H, pyrrolidine), 3.10-3.30 (m, 1H, pyrrolidine), 3.97 (d, *J* = 16.2 Hz, 1H, CH_2N), 4.18 (d, *J* = 16.2 Hz, 1H, CH_2N), 4.30-4.45 (m, 1H, pyrrolidine), 6.86 (d, *J* = 5.0 Hz, 1H, H_4 thiophene), 7.44 (d, *J* = 5.0 Hz, 1H, H_5 thiophene), 7.59 (s, 1H; -NH). Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.76; N, 13.45. Found: C, 57.89; H, 6.08; N, 13.78.

4,7,8,8a-Tetrahydropyrrolo[1,2-*a*]thieno[3,2-*e*][1,3]diazepin-6,10(9*H*)-dione (**10 a**)

In a same manner as above, ketone (**9 a**) (1 g, 0.0048 mol) treated with sodium azide (0.95 g, 0.015 mol) and 98% sulfuric acid (2.4 ml) at room temperature during 48 h gave after recrystallization 0.80 g (75%) of the [1,3]diazepine(**10**), mp 209-211 °C (lit.[2]: 210-211°C); ir: 3300-2850 (-NHCO),

1690 (CO) cm^{-1};^{1}H-nmr (DMSO-d_6): δ 2.13-2.30 (m, 1H, oxopyrrolidine), 2.35-2.93 (m, 3H, oxopyrrolidine), 4.63 (d, *J* = 16.4 Hz, 1H, CH_2N), 4.75, (d, *J* = 16.4 Hz, 1H, CH_2N), 5.10-5.21 (m, 1H, oxopyrrolidine), 7.23 (d, *J* = 5.4 Hz, 1H, H_4 thiophene), 7.40 (d, *J* = 5.4 Hz, 1H, H_5 thiophene), 8.62 (s, 1H, N-H).

4,7,8,8a-Tetrahydropyrrolo[1,2-*a*]thieno[2,3-*e*][1,3]diazepin-6,10 (9*H*)-dione (**10b**)

In a same manner as above, ketone(**9b**)(1 g, 0.0048 mol) treated with sodium azide (0.95 g, 0.015 mol) and 98% sulfuric acid (2.4 ml) at room temperature during 48 h gave after chromatography on silica gel (eluting with dichloromethane-acetone 80-20) and recrystallization 0.76 g (70%) of the [1,3]diazepine (**10b**), mp 270-272 °C (lit.[2] : 273-275 °C); ir: 3300-2850 (-NHCO), 1690 (CO) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.04-2.61 (m, 4H, oxopyrrolidine), 4.42 (d, *J* = 17.6 Hz, 1H, CH_2N), 4.83 (d, *J* = 17.6 Hz, 1H, CH_2N), 5.11-5.20 (m, 1H, oxopyrrolidine), 7.05 (d, *J* = 5.0 Hz, 1H, H_4 thiophene), 7.75 (d, *J* = 5.0 Hz, 1H, H_5 thiophene), 8.68 (s, 1H, NH).

Oximes **6a** *syn* and **6a** *anti* of the thieno[3,2-*b*]indolizidin-9-one

A mixture of ketone (**5a**) (0.96 g, 0.005 mol), hydroxylamine hydrochloride (0.69 g, 0.01 mol) and sodium acetate (0.82 g, 0.01 mol) in ethanol (10 ml) and water (10 ml) was refluxed for 5 h. On cooling, the oxime precipitated and was filtered and washed with a mixture ethanol-water (50-50). Recrystallization of the solid from ethanol gave 0.52 g (50%) of a mixture of *syn* (60%) and *anti* (40%) oximes isomers. It was not possible to separate this mixture by column chromatography. This mixture melted at 180-181 °C.

Oxime **6a** *anti*: ^{1}H-Nmr (DMSO-d_6): δ 1.60-2.20 (m, 4H, pyrrolidine), 2.35-2.40 (m, 1H, pyrrolidine), 2.75-2.85 (m, 1H, pyrrolidine), 3.42-3.55 (m, 1H, pyrrolidine), 3.69 (d, *J* = 14.2 Hz, 1H, CH_2N), 3.98 (d, *J* = 14.2 Hz, 1H, CH_2N), 7.21 (d, *J* = 5.2 Hz, 1H, H_4 thiophene), 7.36 (d, *J* = 5.2 Hz, 1H, H_5 thiophene), 10.86 (s, 1H, OH).

Oxime **6a** *syn*: ^{1}H-Nmr (DMSO-d_6): δ 1.65-2.25 (m, 4H, pyrrolidine), 2.25-2.35 (m, 1H, pyrrolidine), 2.88-3.02 (m, 1H, pyrrolidine), 3.02-3.20 (m, 1H, pyrrolidine), 3.63 (d, *J* = 15.6 Hz, 1H, CH_2N), 4.25 (d, *J* = 15.6 Hz, 1H, CH_2N), 7.40 (d, *J* = 5.2 Hz, 1H, H_4 thiophene), 7.91 (d, *J* = 5.2 Hz, 1H, H_5 thiophene), 11.06 (s, 1H, OH). Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.76; N, 13.45. Found: C, 58.00; H, 5.86; N, 13.26.

Oxime **6 b** *syn* of the thieno[2,3-*b*]indolizidin-9-one

In a same manner as above, ketone (**5 b**) gave 0.62 g (60%) of the oxime (**6 b**) as white crystals, recrystallized from ethanol mp 213-215 °C; ^{1}H-nmr (DMSO-d_6): δ 2.14-2.62 (m, 4H, pyrrolidine), 2.68-2.82 (m, 1H, pyrrolidine), 3.37-3.50 (m, 1H, pyrrolidine), 3.50-3.65 (m, 1H, pyrrolidine), 3.77 (d, J = 16.0 Hz, 1H, CH_2N), 4.60 (d, J = 16.0 Hz, 1H, CH_2N), 7.40 (d, J = 5.4 Hz, 1H, H_4 thiophene), 8.10 (d, J = 5.4 Hz, 1H, H_5 thiophene), 11.64 (s, 1H, OH). Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.76; N, 13.45. Found: C, 57.46; H, 5.63; N, 13.12.

Beckmann rearrangement of **6 a** (*syn*+*anti*). 4*H*-Pyrrolidino[1,2-*a*]thieno[3,2-*e*][1,3]diazepin-10(9*H*)-one (**7 a**)

Finely powdered oxime (**6 a**) (*syn*+*anti*) (0.5 g, 0.0024 mol) was quickly added to warm (90 °C) stirred polyphosphoric acid (10 g). The mixture was vigorously stirred for 2 h and then poured onto crushed ice (100 ml) and basified at 20 °C with 40% sodium hydroxide to pH=9. The aqueous solution was extracted with chloroform (3X50 ml). The organic phases were washed with saturated brine, dried (sodium sulfate), filtered and concentrated to give a brown solid. Crystallization from ethanol afforded 0.25 g (50%) of pure [1,3]diazepine (**7 a**) identical to these obtained before.

Beckmann rearrangement of oxime **6b**. 4*H*-Pyrrolidino[1,2-*a*]thieno[2,3-*e*][1,3]diazepin-10(9*H*)-one (**7 b**)

In a same manner as above, oxime (**6 b**) (0.5 g, 0.0024 mol) treated with polyphosphoric acid (10 g) furnished 0.3 g (60%) of pure [1,3]diazepine (**7 b**) identical to these obtained before.

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