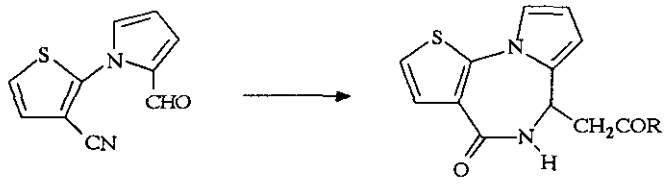
PYRROLOTHIENO[1,4]DIAZEPINES PART I : SYNTHESIS AND STUDY OF THE REACTION PATHWAY

Michel Boulouard, Sylvain Rault, Patrick Dallemagne, and Max Robba*

Centre d'Etudes et de Recherche sur le Médicament de Normandie
U.F.R. des Sciences Pharmaceutiques - 1 rue Vaubénard - 14032 CAEN cedex, France

Abstract - Synthesis of 5,6-dihydro-4-oxo-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepines is achieved starting from 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile. Reaction pathway is demonstrated *via* isolation of intermediates involved in the synthetic reaction.

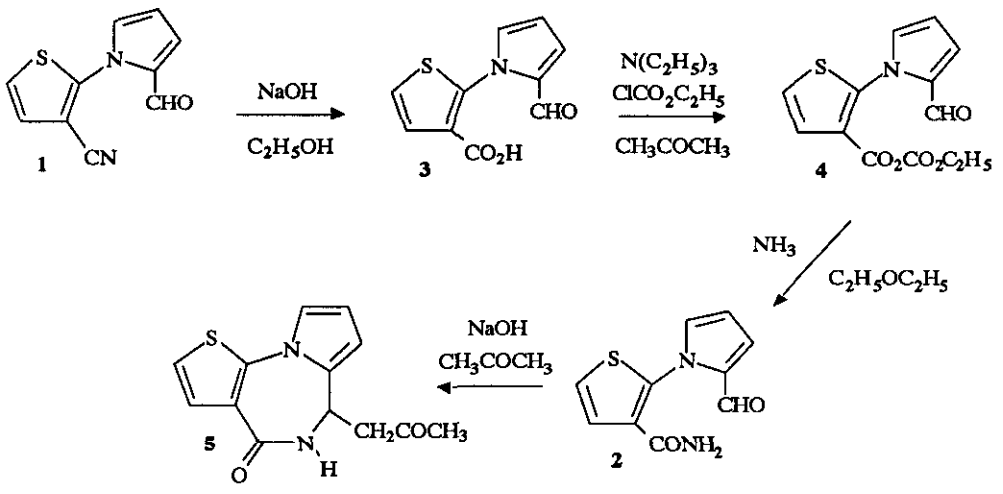
During the course of our work concerning the synthesis of new [1,4]diazepines with potential therapeutic interest, we have described in a preliminary paper [1] the one pot access to pyrrolothienodiazepinones (**I**) (Scheme 1). This original method involved reaction between cyano and formyl groups of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile (**1**) [2] with a methyl ketone in alkaline medium. However, due to the conditions of the reaction (aqueous alcoholic (100 / 2) solution of starting material), this method remained limited to few examples using very water-soluble methyl ketones. So, in order to extend this reaction to various ketones and to other nucleophiles, we reinvestigated the mechanism involved in this original cyclization of the diazepine ring.



1 **I**

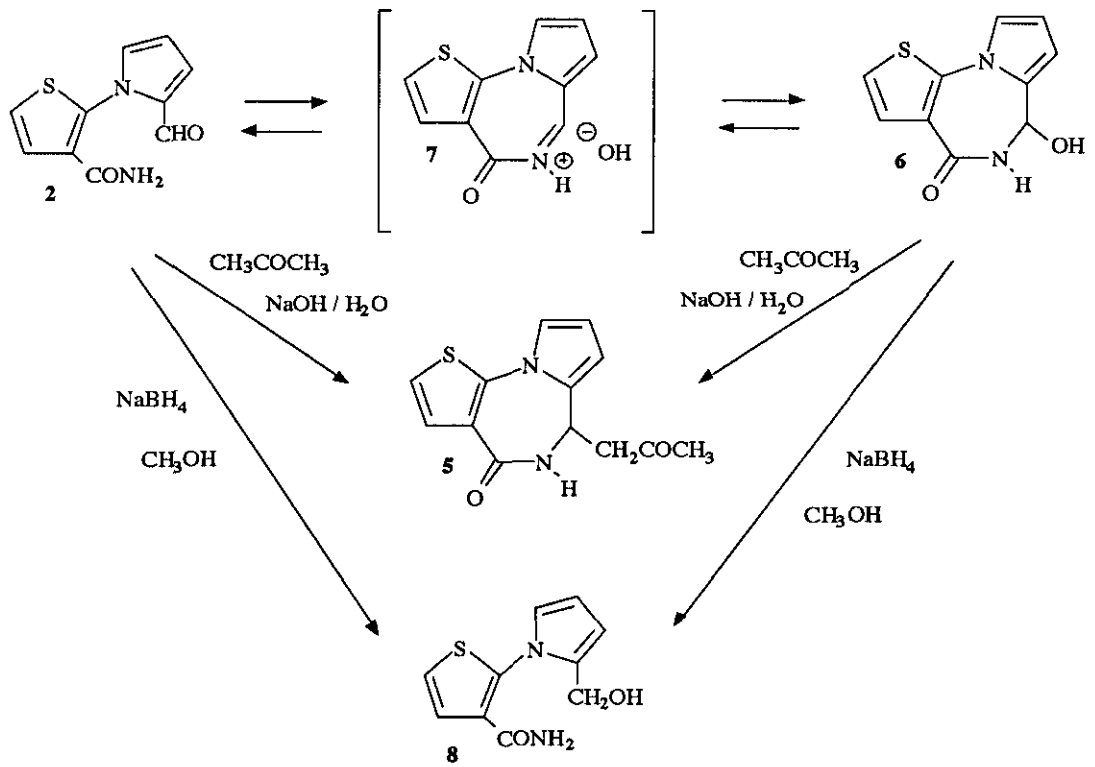
Scheme 1

We advanced that the reaction proceeded from the intermediate carboxamide (**2**) (Scheme 2). Nevertheless, all attempts to isolate **2** during the course of the reaction failed. This failure prompted us to prepare **2** in non-aqueous medium *via* the carboxylic acid (**3**). The latter was obtained by alkaline hydrolysis of nitrile compound (**1**) realized with refluxing aqueous alcoholic sodium hydroxide solution. The yield of this reaction was increased to 95% and its time was decreased to 15 minutes by using micro-waves energy. The carboxamide (**2**) was obtained by treatment of **3** in acetone solution by triethylamine then by ethyl chloroformate leading to anhydride (**4**). The latter derivative was immediately treated by gaseous ammonia at 0°C in ether leading to **2** which precipitated in the reaction mixture. Compound (**2**) was stirred at room temperature in acetone in aqueous alkaline medium giving the 5-acetonyldiazepine (**5**) with 60% yield.



Scheme 2

In order to explain the last step of the reaction sequence (**2** to **5**), we postulate the involving of a new intermediate formed in alkaline medium. With the aim to determinate this intermediate we have treated compound (**2**) by aqueous triethylamine solution without acetone. The reaction led to a new cyclic compound whose ir and nmr spectral analysis was in favor of a 5-hydroxydiazepine (**6**) (Scheme 3).



Scheme 3

Compound (**6**) was reacted in a similar manner as for **2** with acetone in alkaline medium to give also derivative (**5**). The identical chemical reactivity of **2** and **6** led us to advance that they were two entities on equilibrium as it was reported with natural alkaloids called pseudobases. [3] Concerning **2** and **6**, although we could not isolate neither ammonium hydroxide intermediate (**7**) nor demonstrate the conversion **6** to **2** we think that a such equilibrium exists in this case. In fact, treatment of **2** and **6** by sodium borohydride in methanol led in the two cases to hydroxyamine (**8**) (Scheme 3). In conclusion, it is now clear that mild alkaline hydrolysis of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile (**1**) gave a water soluble intermediate which reacted with keto carbanions formed in the alkaline reaction mixture.

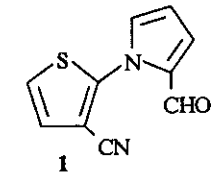
According to this pathway, treatment of aqueous alcoholic (100 / 100) solution of **1** with various methyl ketones in presence of hydrogen peroxide led to compounds (**5**, **9-21**) (Scheme 4).

EXPERIMENTAL

Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. Nmr spectra were recorded on a Jeol FX 200 using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS.

2-(2-Formyl-1*H*-pyrrol-1-yl)-3-thiophenecarboxamide (**2**). Triethylamine (3.4 ml, 0.025 mol) was added at 0°C to a stirred mixture of 2-(2-formyl-1*H*-pyrrol-1-yl)thiophene-3-carboxylic acid (**3**) (5 g, 0.023 mol) in ether (200 ml). After 10 min, ethyl chloroformate (2.2 ml, 0.025 mol) was added dropwise to the reaction mixture at 0°C. After 20 min, the insoluble was filtered and ammonia was bubbled at 0°C into the filtrate for 30 sec. The precipitate was filtered, washed with ether and recrystallized from ether to give **2** as colorless crystals (4 g, 78%) : mp 148°C; ir (KBr) 3480, 3430, 3290, 3160, 3110 cm^{-1} (NH_2), 1675, 1650 (CO); ^{1}H-nmr ($CDCl_3$) 9.59 (s, CHO), 7.39 (d, $J_{H5\,H4}$ = 5.9 Hz, H5), 7.27 (d, $J_{H4\,H5}$ = 5.9 Hz, H4), 7.18 (dd, $J_{H3',H4'}$ = 3.4 Hz, $J_{H3',H5'}$ = 1.5 Hz, H3'), 7.11 (dd, $J_{H5',H4'}$ = 2.9 Hz, $J_{H5',H3'}$ = 1.5 Hz, H5'), 6.50 (dd, $J_{H4',H3'}$ = 3.4 Hz, $J_{H4',H5'}$ = 2.9 Hz, H4'), 5.50 (br s, NH_2). Anal. Calcd for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72; S, 15.56. Found : C, 54.58; H, 3.76; N, 12.71; S, 15.39.

2-(2-Formyl-1*H*-pyrrol-1-yl)thiophene-3-carboxylic acid (**3**). A 6N aqueous sodium hydroxide solution (50 ml) was added to a suspension of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile (**1**) (20 g, 0.10 mol) in ethanol (200 ml). The reaction mixture was refluxed for 15 min under microwaves. Ethanol was removed under reduced pressure. The aqueous solution was cooled, diluted with water (300 ml) and brought to pH=1 with 35% hydrochloric acid. The precipitate appeared was collected by filtration, washed with water (100 ml), dried and recrystallized from ethanol to give **3** as colorless crystals (21 g, 95%) : mp 208°C; ir (KBr) 1710, 1665, 1625 cm^{-1} (CO); ^{1}H-nmr 13.00 (br s, OH), 9.51 (s, CHO), 7.50 (m, H4, H5 and H5'), 7.23 (dd, $J_{H3',H4'}$ = 3.4 Hz, $J_{H3',H5'}$ = 1.5 Hz, H3'), 6.46 (dd, $J_{H4',H3'}$ = 3.4 Hz, $J_{H4',H5'}$ = 2.9 Hz, H4'). Anal. Calcd for $C_{10}H_7NO_3S$: C, 54.30; H, 3.19; N, 6.37; S, 14.47. Found : C, 54.49; H, 3.05; N, 6.57; S, 14.36.



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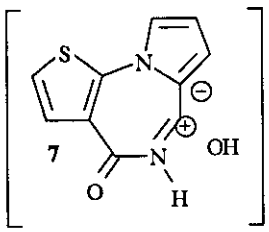

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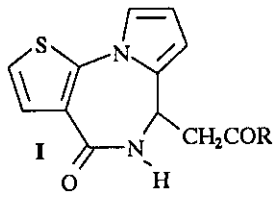

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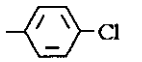
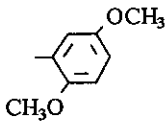
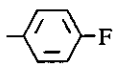
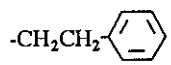
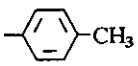
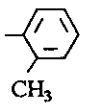
R =	$-CH_3$	**5**	R =		**17**
	$-CH(CH_3)_2$	**9**			**18**
		**10**			
	$-CH_2CH_2CH_3$	**11**			**19**
		**12**			**20**
	$-C(CH_3)_3$	**13**			**21**
		**14**			
		**15**			
		**16**			

Scheme 4

5,6-Dihydro-6-hydroxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**6**). Triethylamine (1.25 ml, 0.09 mol) was added to a solution of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarboxamide (**2**) (2 g, 0.009 mole) in water (60 ml). The reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered, dried and recrystallized from water to give **6** as colorless crystals (1.35 g, 68%) : mp 172°C; ir (KBr) 3330 (OH), 3220 (NH), 1610 (CO); ^{1}H-nmr (DMSO) 8.94 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 7.20 (m, H2, H3 and H9), 6.33 (d, $J_{OH\ H6}$ = 3.6 Hz, OH), 6.25 (m, H7 and H8), 5.62 (dd, $J_{H6\ NH}$ = 4.4 Hz, $J_{H6\ OH}$ = 3.6 Hz, H6). Anal. Calcd for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.71; S, 14.56. Found : C, 54.36 ; H, 3.69; N, 12.58; S, 14.39.

2-(2-Hydroxymethyl-1*H*-pyrrol-1yl)-3-thiophenecarboxamide (**8**).

Method A : Sodium borohydride (0.34 g, 0.009 mol) was added to a solution of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarboxamide (**2**) (1 g, 0.0045 mol) in methanol (150 ml). The reaction mixture was stirred for 15 min at room temperature and then refluxed for 30 min under microwaves. The solvent was removed under reduced pressure and the solid residue was taken up in ether (200 ml). The solution was filtered and the filtrate was washed with water (100 ml). The organic layer was separated, dried over magnesium sulfate and the solvent was evaporated to give a solid which was recrystallized from ether to give **8** as colorless crystals (0.65 g, 63%) : mp 147°C; ir (KBr) 3300 (OH), 3250 (NH), 1675 (CO); ^{1}H-nmr ($CDCl_3$) 7.43 (d, $J_{H5\ H4}$= 5.9 Hz, H5), 7.25 (d, $J_{H4\ H5}$ = 5.9 Hz, H4), 6.80 (m, H5'), 6.30 (m, H3' and H4') 5.90 and 5.30 (br s, NH_2), 4.53 (s, CH_2), 2.00 (br s, OH). Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60; S, 14.42. Found : C, 54.30; H, 4.44; N, 12.56; S, 14.26.

Method B : The same procedure as for method A was applied to 5,6-dihydro-6-hydroxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**6**) (1 g) to give **8** (0.6 g, 60%).

5,6-Dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-ones (**5, 9-21**)

General procedure : A stirred mixture of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile (**1**) (2 g, 0.01 mol) and the appropriate ketone (0.10 mol) in ethanol (50 ml) was refluxed with alkaline hydrogen peroxide (1 ml of a 33% aqueous solution in 50 ml of a 6N aqueous sodium hydroxide solution) for 1 h. The solvent was removed under reduced pressure and the residual solution was poured into cold water (200 ml). The mixture was extracted with ether (250 ml) and the organic layer was washed twice with water (2 x 100 ml), separated and evaporated to dryness under reduced pressure. The solid residue was washed with a mixture of ether/petroleum ether, filtered and recrystallized to give **5, 9-21**.

6-(2-Oxopropyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**5**). (ketone : acetone) yellow crystals (60%) : mp 240°C (acetone); ir (KBr) 3270, 3180 (NH); ^{1}H-nmr ($CDCl_3$) 7.36 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 6.94 (m, H3 and H9), 6.38 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 6.28 (dd, $J_{H8\ H7}$ = 3.4 Hz , $J_{H8\ H9}$ = 2.9 Hz, H8), 6.02 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 4.94 (dt, $J_{H6\ CH2}$ = 6.8 Hz, $J_{H6\ NH}$ = 4.4 Hz, H6), 3.06 (d, $J_{CH2\ H6}$ = 6.8 Hz, CH_2), 2.16 (s, CH_3). Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.99; H, 4.65; N, 10.77; S, 12.30. Found : C, 59.92; H, 4.58; N, 10.96; S, 12.04.

5,6-Dihydro-6-(3-methyl-2-oxobutyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**9**). (ketone : 3-methylbutan-2-one) yellow crystals (58%) : mp 160°C (ethanol); ir (KBr) 3280, 3175 (NH), 1710, 1650 (CO); ^{1}H-nmr (DMSO) 8.20 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 7.31 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 7.23 (d, J_{H3H2} = 5.9 Hz, H3), 7.16 (dd, $J_{H9\ H8}$ = 2.9 Hz , $J_{H9\ H7}$ = 1.5 Hz, H9), 6.27 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.12 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 4.64 (dt, $J_{H6\ CH2}$ = 6.8 Hz, $J_{H6\ NH}$ = 4.4 Hz, H6), 3.23 (d, $J_{CH2\ H6}$ = 6.8 Hz, CH_2), 2.70 (d, $J_{CH\ CH3}$ = 6.8 Hz, CH), 1.06 (d, $J_{CH3\ CH}$ = 6.8 Hz, CH_3). Anal. Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.49; H, 5.59; N, 9.72; S, 11.10. Found : C, 62.50; H, 5.80; N, 9.69; S, 11.07.

5,6-Dihydro-6-phenacyl-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**10**). (ketone : acetophenone) colorless crystals (55%) : mp 205°C (ethanol); ir (KBr) 3320 (NH) ,1675, 1640 (CO); ^{1}H-nmr ($CDCl_3$) 7.94 (d, $J_{H2'\ H3'}$ = 7.8 Hz, H2'and H6'), 7.58 (dd, $J_{H4'\ H3'}$ = $J_{H4'\ H5'}$ = 7.8 Hz, H4), 7.31 (m, H2, H3'and H5'), 6.95 (m, , H3 and H9), 6.90 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 6.29 (dd, $J_{H8\ H7}$ = 3.4 Hz , $J_{H8\ H9}$ = 2.9 Hz, H8), 6.06 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$=1.5 Hz, H7), 5.13 (dt, $J_{H6\ NH}$ = 4.4 Hz, $J_{H6\ CH2}$ = 6.8 Hz, H6), 3.62 (d, $J_{CH2\ H6}$ = 6.8 Hz). Anal. Calcd for $C_{18}N_2O_2S$: C, 67.07; H, 4.38; N, 8.69; S, 9.93. Found : C, 67.35; H, 4.63; N, 8.80; S, 9.68.

5,6-Dihydro-6-(2-oxopentyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**11**). (ketone : pentan-2-one) yellow crystals (68 %) : mp 186°C (ether/acetone); ir (KBr) 3275, 3170 (NH), 1705, 1640 (CO); ^{1}H-nmr ($CDCl_3$) 7.36 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 7.06 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 6.96 (m, H3 and H9); 6.28 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.00 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 4.96 (m, H6), 3.07 (m, CH_2), 2.46 (t, $J_{CH2\ CH3}$ = 7.3 Hz, CH_2), 1.60 (m, CH_2), 0.90 (t, $J_{CH3\ CH2}$ = 7.3 Hz, CH_3). Anal. Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.49; H, 5.59; N, 9.72; S, 11.10. Found : C, 62.48; H, 5.50; N, 9.72; S, 11.23.

6-(2-Cyclopropyl-2-oxoethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**12**). (ketone : cyclopropyl methyl ketone) colorless crystals (57%) : mp 200°C (ether/acetone); ir (KBr) : 3270, 3180 (NH), 1685, 1640 (CO); ^{1}H-nmr ($CDCl_3$) 7.38 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 6.96 (m, H_3 and H_9), 6.50 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 6.29 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.05 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 4.96 (dt, $J_{H6\ CH2}$ = 6.8 Hz, $J_{H6\ NH}$ = 4.4 Hz, H6), 3.22 (d, $J_{CH2\ H6}$ = 6.8 Hz, CH_2), 1.96 (m, CH), 1.10 (m, CH_2), 0.98 (m, CH_2). Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.92; N, 9.78; S, 11.19. Found : C, 62.87; H, 4.93; N, 9.81; S, 11.05.

5,6-Dihydro-6-(3,3-dimethyl-2-oxobutyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**13**). (ketone : pinacolone) colorless crystals (26%) : mp 170°C (ether); ir (KBr) : 3260, 3170 (NH), 1735, 1700 (CO) ; ^{1}H-nmr ($CDCl_3$) 7.38 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 6.96 (dd, $J_{H9\ H8}$ = 2.9 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.93 (d, J_{H3H2} = 5.9 Hz, H3), 6.28 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.13 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 6.03 (dd, J_{H7H8} = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 4.98 (m, H6), 3.11 (m, CH_2), 1.54 (s, $3CH_3$). Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 5.99; N, 9.26; S, 10.60. Found : C, 63.20; H, 5.72; N, 8.99; S, 10.41.

5,6-Dihydro-6-(4-phenyl-2-oxobutyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**14**). (ketone : benzyl--acetone) colorless crystals (19%) : mp 172°C (ether); ir (KBr) : 3270, 3170 (NH), 1710, 1645 (CO); ^{1}H-nmr ($CDCl_3$) 7.34 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 7.25 (s, H arom), 6.92 (m, H3 and H9), 6.73 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 6.26 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 5.98 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 4.95 (m, H6), 3.03 (m, CH_2), 2.86 (m, CH_2), 2.82 (m, CH_2). Anal. Calcd for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99; S, 9.15. Found : C, 68.22; H, 5.36; N, 7.90; S, 8.85.

5,6-Dihydro-6-(4'-methylphenacyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**15**). (ketone : 4'-methyl--acetophenone) colorless crystals (44%) : mp 130°C (ether); ir (KBr) : 3320 (NH), 1670 (CO); ^{1}H-nmr ($CDCl_3$) 7.84 (d, $J_{H2',\ H3'}$ = 8.6 Hz, H2' and H6'), 7.32 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 7.26 (d, $J_{H3',\ H2'}$= 8.6 Hz, H3' and H5'), 6.92 (m, H3 and H9), 6.70 (br s, NH), 6.27 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.05 (dd, $J_{H7\ H8}$ = 2.9 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.11 (dt, $J_{H6\ CH2}$ = 6.8 Hz, $J_{H6\ NH}$ = 4.4 Hz, H6), 3.58 (d, $J_{CH2\ H6}$ = 6.8 Hz, CH_2), 2.42 (s, CH_3). Anal. Calcd for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33; S, 9.53. Found : C, 68.09; H, 5.01; N, 8.13; S, 9.23.

5,6-Dihydro-6-(2'-methylphenacyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**16**). (ketone : 2'-methyl--acetophenone) grey crystals (44%) : mp 180°C (ether); ir (KBr) 3270, 3160 (NH), 1680, 1650 (CO); ^{1}H-nmr ($CDCl_3$) 7.68 (d, $J_{H6',\ H5''}$ = 8.6 Hz, H6'), 7.30 (m, H2, H3', H4' and H5'), 7.02 (br s, NH), 6.95 (m, H3 and H9), 6.27 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.04 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.10 (dt, $J_{H6\ CH2}$ = 6.8 Hz, $J_{H6\ NH}$ = 4.4 Hz, H6), 3.58 (d, $J_{CH2\ CH3}$ = H6 = 6.8 Hz, CH_2), 2.48 (s, CH_3). Anal. Calcd for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33; S, 9.53. Found : C, 67.72; H, 4.82; N, 8.44; S, 9.43.

6-(4'-Chlorophenacyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**17**). (ketone : 4'-chloro--acetophenone) colorless crystals (24%) : mp 224°C (ethanol); ir (KBr) : 3320 (NH), 1740, 1635 (NH); ^{1}H-nmr ($CDCl_3$) 7.87 (d, $J_{H2',\ H3'}$ = 8.6 Hz, H2' and H6'), 7.45 (d, $J_{H3',\ H2'}$ = 8.6 Hz, H3' and H5'), 7.31 (d, $J_{H2\ H3}$ = 5.9 Hz, H2), 6.98 (dd, $J_{H9\ H8}$ = 2.9 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.94 (d, $J_{H3\ H2}$ = 5.9 Hz, H3), 6.60 (d, $J_{NH\ H6}$= 4.4 Hz, NH), 6.29 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.05 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.12 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.05 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.12 (dt, $J_{H6\ CH2}$ = 6.8 Hz, $J_{H6\ NH}$ = 4.4 Hz, H6), 3.57 (d, $J_{CH2\ H6}$= 6.8 Hz, CH_2). Anal. Calcd for $C_{18}H_{13}N_2O_2ClS$: C, 60.58; H, 3.67; N, 7.85; Cl, 9.93. Found : C, 60,87; H, 3.66; N, 7.60; Cl, 10.22.

5,6-Dihydro-6-(2',5'-dimethoxyphenacyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**18**). (ketone : 2',5'-dimethoxyacetophenone) colorless crystals (19%) : mp 180°C (acetonitrile); ir (KBr) : 3260, 3190 (NH), 1675 (CO); ^{1}H-nmr 7.37 (d, $J_{H2\ H3}$= 5.9 Hz, H2), 7.29 (s, H6'), 7.00 (m, H3, H9, H3' and H4'), 6.52 (d, $J_{NH\ H6}$ = 4.4 Hz, NH), 6.27 (dd, $J_{H8\ H7}$ = 3.4 Hz, $J_{H8\ H9}$ = 2.9 Hz, H8), 6.04 (dd, $J_{H7\ H8}$ = 3.4 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.10 (m, H6), 3.88 (s, CH_3), 3.78 (s, CH_3), 3.66 (m, CH_2). Anal. Calcd for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74; N, 7.32. Found : C, 62.75; H, 4.76; N, 7.34.

5,6-Dihydro-6-(4'-fluorophenacyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**19**). (ketone : 4'-fluoro -acetophenone) colorless crystals (21%) : mp 170°C (ether); ir (KBr) : 3320 (NH), 1670, 1640 (CO); ^{1}H-nmr ($CDCl_3$) 7.91 (d, $J_{H2' H3'}$ = 8.6 Hz, H2' and H6'), 7.35 (d, $J_{H2 H3}$ = 5.9 Hz, H2), 7.00 (m, H3, H9, H3' and H6'), 6.45 (d, $J_{NH H6}$ = 4.4 Hz, NH), 6.29 (dd, $J_{H8 H7}$ = 3.4 Hz, $J_{H8 H9}$ = 2.9 Hz, H8), 6.07 (dd, $J_{H7 H8}$ = 3.4 Hz, $J_{H7 H9}$ = 1.5 Hz, H7), 5.19 (m, H6), 3.55 (m, CH_2). Anal. Calcd for $C_{18}H_{13}N_2O_2FS$: C, 63.51; H, 3.84; F, 5.58; S, 9.41. Found : C, 63.61; H, 3.66; F, 5.40; S, 9.12.

5,6-Dihydro-6-(2-oxo-2-(2-thienyl)ethyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**20**). (ketone : 2-acetylthiophene) colorless crystals (20%) : mp 186°C (ethanol); ir (KBr) : 3320 (NH),1655, 1640 (CO); ^{1}H-nmr ($CDCl_3$) 7.73 (m, H3' and H5'), 7.37 (d, $J_{H2 H3}$ = 5.9 Hz, H2), 7.16 (m, H4'), 6.97 (m, H3 and H9), 6.59 (br s, NH), 6.29 (dd, $J_{H8 H7}$ = 3.4 Hz, $J_{H8 H9}$ = 2.9 Hz, H8), 6.10 (dd, $J_{H7 H8}$ = 3.4 Hz, $J_{H7 H9}$ = 1.5 Hz, H7), 5.13 (dt, $J_{H6 CH2}$ = 6.8 Hz, $J_{H6 NH}$ = 4.4 Hz, H6), 3.55 (d, $J_{CH2 H6}$ = 6.8 Hz, CH_2). Anal. Calcd for $C_{16}H_{12}N_2O_2S_2$: C, 58.52; H, 3.68; S, 19.52. Found : C, 58.33; H, 3.91; S, 19.34.

5,6-Dihydro-6-(2-(2-furyl)-2-oxoethyl)-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-4-one (**21**). (ketone : 2-acetylfuran) yellow crystals (20%) : mp 174°C (ether); ir (KBr) : 3180 (NH), 1670, 1640 (CO); ^{1}H-nmr 7.62 (m, H3' and H5'), 7.38 (d, $J_{H2 H3}$ = 5.9 Hz, H2), 6.98 (m, H3 and H9), 6.51 (m, H4'), 6.47 (br s, NH), 6.29 (dd, $J_{H8 H7}$ = 3.4 Hz, $J_{H8 H9}$ = 2.9 Hz, H8), 6.09 (dd, $J_{H7 H8}$ = 3.4 Hz, $J_{H7 H9}$ = 1.5 Hz, H7), 5.11 (dt, $J_{H6 CH2}$ = 6.8 Hz, $J_{H6 NH}$ = 4.4 Hz, H6), 3.48 (d, $J_{CH2 H6}$ = 6.8 Hz, CH_2). Anal. Calcd for $C_{16}H_{12}N_2O_3S$: C, 61.53; H, 3.87; S, 10.26. Found : C, 61.29; H, 3.69; S, 10.41.

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