

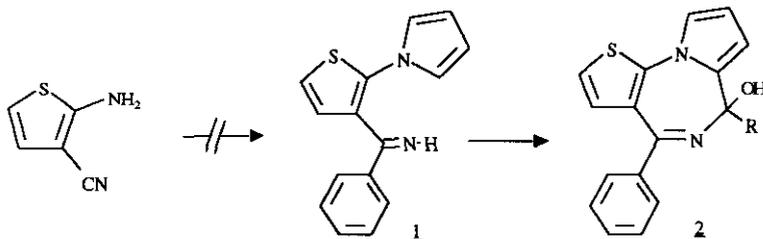
**PYRROLO[1,2-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES:
NEW 4*H* AND 4*H*-5,6-DIHYDRO DERIVATIVES**

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Abstract-Synthesis of 4*H* and 4*H*-5,6-dihydro pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines from 3-[2-(1-pyrrolyl)thienyl]benzylamine is described.

In the course of our work on the synthesis of pyrrolothienodiazepines (PTD),¹ we have recently published a three step synthesis of 4-phenyl-6-hydroxy-6*H*-PTD derivatives (**2**)² from 2-aminothienyl-3-carbonitrile *via* 2-(1-pyrrolyl) thien-3-ylphenylmethylenimine (**1**).



We describe herein the synthesis of some 4*H*-PTD and 4*H*-5,6-dihydro PTD (**5**, **7-8**), from 3-[2-(1-pyrrolyl)thienyl]benzylamine (**3**). The latter was obtained in quantitative yield by hydrogenation of the imine (**1**) with sodium borohydride in refluxing methanol. Then, the treatment of **3** with acetic anhydride in acetic acid or with chloroacetyl chloride or ethyl oxalyl chloride in THF gave the corresponding amides (**4a-c**). Cyclization of the diazepine ring was then achieved by refluxing phosphoryl chloride to lead 4*H*-PTD (**5a-c**). The unsubstituted 4*H*-PTD (**5d**) on the 6 position was obtained by treatment of a solution of ethyl diazepinecarboxylate (**5c**) with aqueous 2*N* sodium hydroxide. The reaction did not allow the isolation of the carboxylic acid which was decarboxylated in the conditions of this reaction.

On the other hand, treatment of the benzylamine (**3**) with benzaldehyde substituted or not gave the Schiff bases (**6a-e**). The ring closure of these latter into 4*H*-5,6-dihydro PTD.HCl (**7a-e**) was realized in mild conditions. The best results were obtained when an isopropanolic solution of **6a-e** was treated with 10 equivalents of 12*N* hydrochloric acid at room temperature to permit the precipitation of the diazepinium chlorides (**7a-e**) in about 60% yield. Further, when an ethanolic solution of **3** was treated with 20 equivalents of acetone in presence of aqueous hydrochloric acid (20 equivalents) at reflux, it gave the dimethyl-4*H*-5,6-dihydro PTD (**8**).

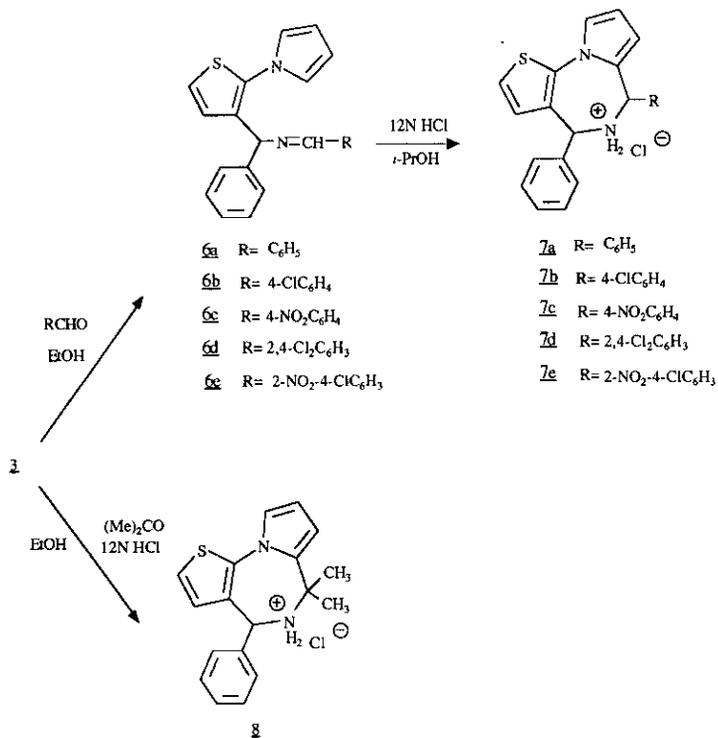
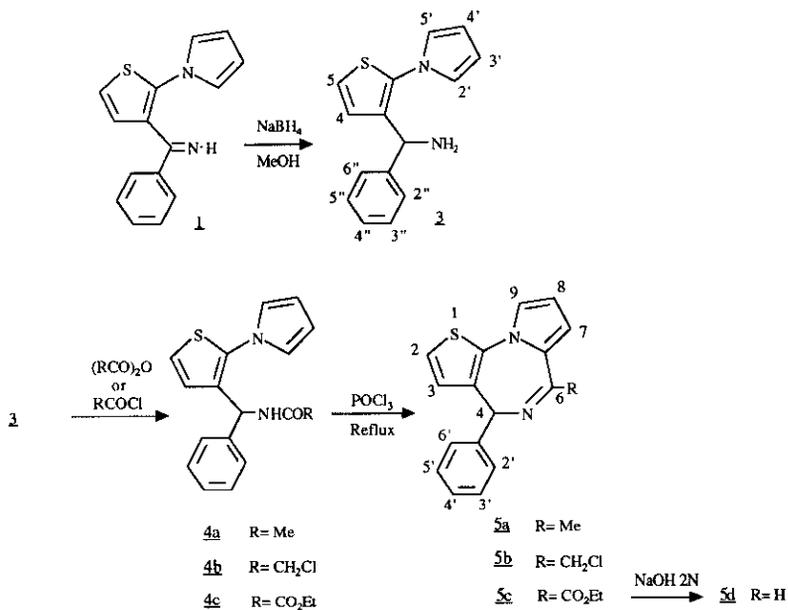


Table 1 Spectroscopic and microanalytical data of compounds (3-8)

Compd	Yield (%)	mp or bp(°C) (Solvnt of cryst)	Ir(KBr) $\nu_{\max}(\text{cm}^{-1})$	^1H Nmr (DMSO- d_6) δ ppm/TMS J (Hz)	Molecular Formula	Elemental analysis		
						Calcd (%)		
						(Found)		
C	H	N						
3	90	200/5 mmHg	3350/3280 (NH ₂)	7.28 (m, H"-Phenyl) 7.06 (d, $J=5.86$, H-5) 7.00 (d, $J=5.86$, H-4) 6.79 (s, H-2'5') 6.29 (s, H-3'4') 5.09 (s, CH) 1.80 (s, NH ₂)	C ₁₅ H ₁₄ N ₂ S	70.83 (70.68)	5.55 (5.63)	11.01 (10.95)
4a	95	138 (ether)	3220 (NH) 1640 (CO)	8.81 (d, $J=8.30$, NH) 7.41 (d, $J=5.86$, H-5) 7.27 (m, H-3"4"5") 7.09 (d, $J=7.33$, H-2"6") 7.00 (d, $J=5.86$, H-4) 6.93 (s, H-2'5') 6.25 (s, H-3'4') 6.05 (d, $J=8.30$, CH) 1.90 (s, CH ₃)	C ₁₇ H ₁₆ N ₂ OS	68.89 (68.77)	5.44 (5.41)	9.45 (9.45)
4b	77	50 (ether)	3210 (NH) 1640 (CO)	9.19 (d, $J=8.30$, NH) 7.44 (d, $J=5.86$, H-5) 7.32 (m, H-3"4"5") 7.12 (d, $J=7.33$, H-2"6") 7.00 (d, $J=5.86$, H-4) 6.92 (s, H-2'5') 6.26 (s, H-3'4') 5.99 (d, $J=8.30$, CH) 4.13 (s, CH ₂)	C ₁₇ H ₁₅ N ₂ OCIS	61.72 (61.51)	4.57 (4.64)	8.47 (8.39)
4c	74	130 (ether)	3260 (NH) 1730 (CO) 1670 (CO)	9.82 (d, $J=8.30$, NH) 7.44 (d, $J=5.86$, H-5) 7.30 (m, H-3"4"5") 7.17 (m, H-2"6") 7.17 (m, H-4) 6.91 (s, H-2'5') 6.25 (s, H-3'4') 6.07 (d, $J=8.30$, CH) 4.24 (q, $J=6.84$, CH ₂) 1.27 (t, $J=6.84$, CH ₃)	C ₁₉ H ₁₈ N ₂ O ₃ S	64.39 (64.28)	5.12 (5.09)	7.90 (7.88)
5a	53	200/1 mmHg	1620 (C=N)	7.58 (d, $J=7.81$, H-2'6') 7.46 (s, H-9) 7.37 (m, H-3'4'5') 7.13 (d, $J=5.37$, H-2) 6.89 (d, $J=3.91$, H-7) 6.46 (t, $J=3.91$, H-8) 6.13 (d, $J=5.37$, H-3) 5.23 (s, CH) 2.33 (s, CH ₃)	C ₁₇ H ₁₄ N ₂ S	73.35 (73.20)	5.07 (5.15)	10.05 (10.10)
5b	40	200/1 mmHg	1600 (C=N)	7.60 (d, $J=6.83$, H-2'6') 7.41 (m, H-3'4'5') 7.39 (s, H-9) 7.20 (d, $J=5.37$, H-2) 6.95 (d, $J=3.91$, H-7)	C ₁₇ H ₁₃ N ₂ CIS	65.28 (65.20)	4.16 (4.05)	8.96 (8.90)

				6 51 (t, $J=3$ 91, H-8) 6 15 (d, $J=5$ 37, H-3) 5 35 (s, CH) 4 84 (d, $J=12$ 21, CH ₂) 4 51 (d, $J=12$ 21, CH ₂)				
5c	40	205/1 mmHg	1720 (C=O) 1600 (C=N)	7 57 (d, $J=6$ 83, H-2'6') 7 43 (m, H-3'4'5') 7 41 (s, H-9) 7 34 (d, $J=5$ 37, H-2) 6 95 (d, $J=3$ 91, H-7) 6 52 (t, $J=3$ 91, H-8) 6 19 (d, $J=5$ 37, H-3) 5.49 (s, CH) 4 84 (q, $J=6$ 84, CH ₂) 1 28 (t, $J=6$ 84, CH ₃)	C ₁₉ H ₁₆ N ₂ O ₂ S	67.85 4.76 8.33 (67.75 4.70 8.25)		
5d	50	202/1 mmHg	1600 (C=N)	7 43 (m, H'-Phenyl-H-2, H-6) 7 18 (m, H-9) 6.87 (d, $J=5$ 86, H-3) 6 35 (d, $J=3$ 91, H-8) 6 17 (t, $J=3$ 91, H-7) 4 58 (s, H-4)	C ₁₆ H ₁₂ N ₂ S	72.72 4.54 10.60 (72.75 4.50 10.55)		
6a	74	138 (isopropanol)	1665 (C=N)	8 31 (s, CH) 7 79 (d, $J=5$ 37, H-2''6''') 7 43 (m, H-3'''4'''5''') 7 42 (d, $J=5$ 86, H-5) 7.29 (s, H''-Phenyl) 7 10 (d, $J=5$ 86, H-4) 6 93 (s, H-2'5') 6 27 (s, H-3'4') 5 49 (s, CH)	C ₂₂ H ₁₈ N ₂ S	77.16 5.30 8.18 (77.01 5.27 8.21)		
6b	57	140 (isopropanol)	1630 (C=N)	8 32 (s, CH) 7 82 (d, $J=5$ 37, H-3'''5''') 7.52 (d, $J=5$ 37, H-2''6''') 7 43 (d, $J=5$ 86, H-5) 7 27 (s, H''-Phenyl) 7 10 (d, $J=5$ 86, H-4) 6 94 (s, H-2'5') 6 28 (s, H-3'4') 5 50 (s, CH)	C ₂₂ H ₁₇ N ₂ ClS	70.11 4.55 8.17 (70.37 4.25 8.20)		
6c	72	180 (isopropanol)	1620 (C=N)	8 47 (s, CH) 8 30 (d, $J=5$ 37, H-2''6''') 8.05 (d, $J=5$ 37, H-3'''5''') 7 45 (d, $J=5$ 86, H-5) 7 29 (s, H''-Phenyl) 7 11 (d, $J=5$ 86, H-4) 6.95 (s, H-2'5') 6.28 (s, H-3'4') 5.58 (s, CH)	C ₂₂ H ₁₇ N ₃ O ₂ S	68.2 4.42 10.85 (67.87 4.35 10.62)		
6d	75	94 (isopropanol)	1710 (C=N)	8 57 (s, CH) 8 07 (d, $J=8$ 79, H-5''') 7 68 (s, H-3''') 7 50 (d, $J=8$ 79, H-6''') 7.42 (d, $J=5$ 86, H-5) 7 30 (s, H''-Phenyl) 7 04 (d, $J=5$ 86, H-4)	C ₂₂ H ₁₆ N ₂ Cl ₂ S	64.24 3.92 6.81 (64.36 3.94 6.78)		

				6.93 (s, H-2'5')				
				6.27 (s, H-3'4')				
				5.60 (s, CH)				
6e	84	95 (isopropanol)	1680 (C=N)	8.56 (s, CH)	$C_{22}H_{16}N_3O_2ClS$	62.63	3.79	9.96
				8.17 (s, H-3''')		(62.55)	3.70	10.10)
				8.05 (d, $J=8.79$, H-5''')				
				7.88 (d, $J=8.79$, H-6''')				
				7.43 (d, $J=5.86$, H-5)				
				7.28 (s, H''-Phenyl)				
				7.04 (d, $J=5.86$, H-4)				
				6.99 (s, H-2'5')				
				6.28 (s, H-3'4')				
				5.56 (s, CH)				
7a	54	228 (isopropanol)	2900/2480 (NH_2^+)	10.78 (m, NH_2)	$C_{22}H_{19}N_2ClS$	69.74	5.05	7.39
				10.51 (m, NH_2)		(69.55)	5.14	7.42)
				7.46 (m, H-Phenyl'', H-Phenyl')				
				7.38 (s, H-9)				
				7.29 (d, $J=5.86$, H-2)				
				6.41 (d, $J=5.86$, H-3)				
				6.34 (t, $J=3.42$, H-8)				
				5.91 (s, H-7)				
				5.54 (m, H-4)				
				5.37 (m, H-6)				
7b	51	229 (methanol)	2900/2500 (NH_2^+)	10.83 (m, NH_2)	$C_{22}H_{18}N_2Cl_2S$	61.20	4.63	6.79
				10.63 (m, NH_2)		(61.51)	4.43	6.69)
				7.69 (m, H-3''5'' and H-2'6')				
				7.52 (m, H-2''6'' and H-3'4'5')				
				7.36 (s, H-9)				
				7.34 (d, $J=5.86$, H-2)				
				6.42 (d, $J=5.86$, H-3)				
				6.35 (s, H-8)				
				5.96 (s, H-7)				
				5.41 (m, H-4)				
				5.66 (m, H-6)				
7c	62	244 (methanol)	3000/2400 (NH_2^+)	11.04 (m, NH_2)	$C_{22}H_{18}N_3O_2ClS$	62.33	4.28	9.91
				8.31 (d, $J=8.3$, H-3''5'')		(62.11)	4.16	9.10)
				7.98 (d, $J=8.3$, H-2''6'')				
				7.70 (d, $J=8.79$, H-2'6')				
				7.44 (m, H-3'4'5')				
				7.44 (s, H-9)				
				7.33 (d, $J=5.86$, H-2)				
				6.42 (d, $J=5.86$, H-3)				
				6.35 (s, H-8)				
				5.91 (s, H-7)				
				5.42 (m, H-4)				
				5.81 (m, H-6)				
7d	72	195 (ethanol)	3040/2580 (NH_2^+)	10.95 (m, NH_2)	$C_{22}H_{17}N_2Cl_3S$	59.01	3.83	6.26
				8.13 (d, $J=8.30$, H-5''')		(58.80)	3.86	5.93)
				7.72 (m, H-3''6'' and H-2'6')				
				7.48 (m, H-3'4'5', H-2, H-9)				
				6.53 (d, $J=5.86$, H-3)				
				6.30 (s, H-8)				
				5.66 (s, H-7, H-6)				
				5.56 (s, H-4)				

7e	74	166 (ethanol)	3000/2500 (NH ₂ ⁺)	10.48 (m, NH ₂) 8.21 (m, H-3") 8.02 (d, J= 8.30, H-5") 7.95 (d, J= 8.30, H-6") 7.32 (m, H-Phenyl', H-2, H-9) 6.51 (d, J=5.86, H-3) 6.24 (s, H-8) 6.12 (s, H-7, H-6) 5.54 (s, H-4)	C ₂₂ H ₁₇ N ₃ O ₂ Cl ₂ S	57.65 3.74 9.17 (57.83 3.45 9.17)
8	46	222 (isopropanol)	3000/2600 (NH ₂ ⁺)	10.88 (m, NH ₂) 9.80 (m, NH ₂) 7.51 (d, J= 8.79, H-2'6') 7.41 (m, H-3'4'5') 7.31 (s, H-9) 7.27 (d, J= 5.86, H-2) 6.47 (d, J=5.86, H-3) 6.38 (s, H-7) 6.32 (s, H-8) 5.82 (m, H-4) 1.81 (s, CH ₃) 1.67 (s, CH ₃)	C ₁₈ H ₁₉ N ₂ ClS	65.34 5.79 8.47 (65.01 5.81 8.29)

EXPERIMENTAL

All melting points were measured using a Kofler bank apparatus and were uncorrected. Infrared spectra were recorded on a Philips PU 9716 spectrophotometer. ¹H Nmr spectra were taken on a JEOL JNM-FX 200 in DMSO-d₆ solution using TMS as an internal standard.

3-[2-(1-pyrrolyl)thienyl]benzylamine (3)

To a solution of phenyl-3-[2-(1-pyrrolyl)thienyl]methylenimine (**1**) (2 g, 7.93 mmol) in methanol (100 ml), was added NaBH₄ (1.2 g, 31 mmol, 4 equivalents) by small portions. The mixture was heated under reflux for 3 h and the methanol was evaporated in vacuo. The residue was cooled, triturated with water and extracted with ether. The organic layer was dried (MgSO₄) and the ether was evaporated in vacuo to give **3** (1.81 g, 90%).

N-benzyl-3-[2-(1-pyrrolyl)thienyl]acetamide (4a)

The benzylamine (**3**) (2 g, 7.87 mmol) in a mixture of acetic acid (5 ml, 0.087 mol) and acetic anhydride (5 ml, 0.053 mol) was stirred at room temperature for 6 h. The reaction mixture was then poured on ice and the precipitate was filtered, washed with petroleum ether, dried and recrystallized from ether to give **4a** (2.21 g, 95%).

General procedure for the synthesis of amides (4b-c)

The benzylamine (**3**) (2 g, 7.87 mmol) in THF (30 ml) solution was treated with an excess of triethylamine (14.17 mmol, 1.43 g, 1.8 equivalents) and the corresponding acid chlorides (11.08 mmol, 1.5 equivalents). The reaction mixture was stirred at room temperature for 3 h. Then, it was poured on water, stirred for 2 h and extracted with ether. The organic layer was washed with saturated NaHCO₃, dried (MgSO₄) and the ether was evaporated in vacuo to give **4b** (2 g, 77%), **4c** (2.06 g, 74%).

General procedure for the synthesis of 4H-PTD (5a-c)

To the amides (**4a**) (1 g, 3.37 mmol) or (**4b**) (1 g, 3.02 mmol) or (**4c**) (1 g, 2.82 mmol) was added phosphoryl chloride (20 ml, 0.2 mol) and the mixture was heated at reflux for 30 min (**4a**), 10 min (**4b**) or 60 min (**4c**). Then the excess of POCl_3 was evaporated in vacuo. After cooling, the residue was triturated with 6N NaOH and extracted with ethyl acetate. The organic layer was washed with water, and with saturated NaHCO_3 , dried (MgSO_4) and the ethyl acetate was evaporated in vacuo to give **5a** (0.5 g, 53%), **5b** (0.32 g, 40%), **5c** (0.38 g, 40%).

4-Phenyl-4H-pyrrolo[1,2-a]thieno[3,2-f][1,4]diazepine(5d)

5c (1 g, 2.97 mmol) in 10 ml of 6N sodium hydroxide (60 mmol) was heated at reflux for 1 h. Then, water was added and the mixture was extracted with ether. The organic layer was dried (MgSO_4) and the ether was evaporated in vacuo to give **5d** (0.39 g, 50%).

General procedure for the synthesis of Schiff bases (6a-e)

To benzylamine (**3**) (1 g, 3.93 mmol) in ethanol (25 ml) was added the corresponding aromatic aldehyde (3.93 mmol, 1 equivalent). The mixture was heated at reflux for 30 min. After cooling, the precipitate was filtered, washed with ether and recrystallized to give **6a** (1 g, 74%), **6b** (0.84 g, 57%), **6c** (1.09 g, 72%), **6d** (1.21 g, 75%), **6e** (1.40 g, 84%).

General procedure for the synthesis of 4H-5,6-dihydro-PTD (7a-e)

To *N*-arylidene-3-[2-(1-pyrrolyl)thienyl]benzylamine (2.25 mmol) in 2-propanol (15 ml), was added dropwise aqueous 12N hydrochloric acid (1 ml, 0.012 mol). The mixture was stirred at room temperature for 2 h. The precipitate was filtered, washed with anhydrous ether and recrystallized to give **7a** (0.46 g, 54%), **7b** (0.49 g, 51%), **7c** (0.59 g, 62%), **7d** (0.72 g, 72%), **7e** (0.76 g, 74%).

6-Dimethyl-4-phenyl-5,6-dihydro-4H-pyrrolo[1,2-a]thieno[3,2-f][1,4]diazepinium hydrochloride(8)

To benzylamine (**3**) (1 g, 3.93 mmol) in ethanol (25 ml) was added acetone (5.9 ml, 0.078 mol) and 12N hydrochloric acid (2.5 ml, 0.078 mol). The mixture was heated at reflux for 10 min and the mixture was concentrated to half volume. After cooling, the precipitate was filtered, washed with anhydrous ether and recrystallized to give **8** (0.6 g, 46%).

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