PYRROLO[1,2-*a*]THIENO[3,2-*f*][1,4]DIAZEPINES : AN EFFICIENT SYNTHESIS

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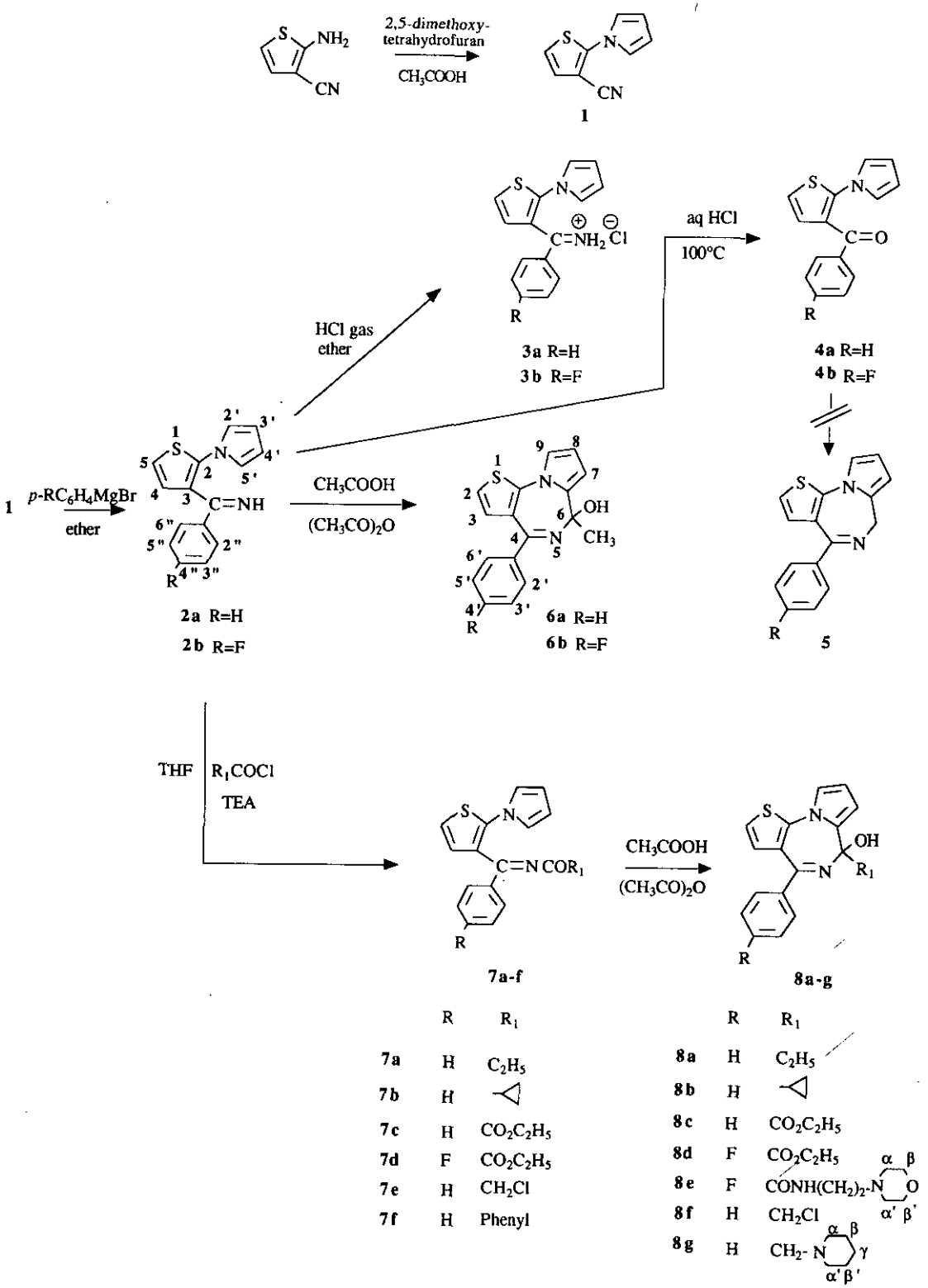
Abstract-Synthesis of pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines from 2-(1-pyrrolyl)thien-3-ylphenylmethylenimine is described.

In continuation of our work concerned with the preparation and the biological evaluation of new heterocyclic compounds from the synthesis of phenyl- or thienylpyrroles,[1] we wish to describe the synthesis of 4-phenyl-6-hydroxypyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepine (PTD). We have recently published an original three-step synthesis of pyrrolobenzodiazepines from anthranilonitrile,[2] which can be adapted to the formation of the title compounds.

Starting with 2-(1-pyrrolyl)thienyl-3-carbonitrile (**1**) prepared from 2-aminothienyl-3-carbonitrile according to the method of Clauson-Kaas,[3] the first key step is the treatment with phenyl-(or *p*-fluorophenyl)magnesium bromide. Under mild conditions, this reaction allowed us to isolate the methylenimines (**2a-b**) as stable solids. These imines were converted to their stable hydrochlorides (**3a-b**) and subsequently to the ketones (**4a-b**) in acidic conditions.These ketones are utilised in the synthesis of PTD (**5**) following the well known pathway in the synthesis of [1,4]benzodiazepines from aminobenzophenones.[4] However, methylenimines (**2a-b**) which possess the imine double bond can be employed to form the diazepine ring in one or two steps.Thus, treatment of **2** in a mixture of acetic acid and acetic anhydride at room temperature gave the 6-hydroxy-6-methyl PTD (**6a-b**) in high yield. Reaction of acid chlorides (R_1COCl) with **2a-b** in THF in the presence of an excess of triethylamine at room temperature permitted the isolation of the acylimines (**7a-f**). This reaction did not undergo the subsequent cyclization contrary to that was observed with homologous benzoderivatives.[2] However, treatment of these acylimines in acidic medium allowed the cyclization reaction to take place to give the desired PTD's (**8a-g**). The best results were obtained with the same mixture as above acetic acid and acetic anhydride at room temperature. Unfortunately, we have not yet found conditions to successfully cyclize the benzoylimine (**7f**). The employment of ethyl oxalyl chloride or chloroacetyl chloride with **2a-b** permitted to develop the preparation of numerous substituted PTD derivatives such as amide (**8e**) from **8d** or amine (**8g**) from **8f**. The reactivity of the hydroxy group in 6 position is very poor and all attempts of functionalization have failed so far. The failure of this reaction may be due to the great instability of this tricyclic ring system in acidic medium.

SCHEME 1



	R	R_1
7a	H	C_2H_5
7b	H	cyclopropyl
7c	H	$CO_2C_2H_5$
7d	F	$CO_2C_2H_5$
7e	H	CH_2Cl
7f	H	Phenyl

	R	R_1
8a	H	C_2H_5
8b	H	cyclopropyl
8c	H	$CO_2C_2H_5$
8d	F	$CO_2C_2H_5$
8e	F	$CONH(CH_2)_2$-N(α β / α' β')O
8f	H	CH_2Cl
8g	H	CH_2-N(α β γ / α' β')

Table 1 Spectroscopic and microanalytical data of compounds (2a-8g).

Compd No	Yield (%)	mp (°C) (Solvt of cryst.)	Ir (KBr) υ_{max}(cm^{-1})	^1H Nmr (DMSO-d_6) δ ppm / TMS J (Hz)	Molecular Formula	Elemental analysis Required (%) (Found)		
						C	H	N
2a	84	78 (ether/ petroleum ether)	3220 (NH) 1600 (C=N)	10.20 (s, NH) 7.52 (d, J=7.32, H-2"6") 7.43 (d, J=5.37, H-5) 7.31 (m, H-3"4"5") 7.03 (d, J=5.37, H-4) 6.77 (s, H-2'5') 6.00 (s, H-3'4')	$C_{15}H_{12}N_2S$	71.44 (71.70)	4.79 (4.94)	11.10 (10.94)
2b	71	68 (ether/ petroleum ether)	3200 (NH) 1600 (C=N)	10.51 (s, NH) 7.58 (dd, J=8.79 and 5.37, H-2"6") 7.42 (d, J=5.86, H-5) 7.07 (dd, J=9.28 and 8.79, H-3"5") 7.06 (d, J=5.86, H-4) 6.77 (s, H-2'5') 6.03 (s, H-3'4')	$C_{15}H_{11}N_2FS$	C 66.65 (66.36)	H 4.10 (4.29)	F 7.03 (6.97)
3a	96	250 (decomp.) (isopropanol)	3100/2600(NH_2^+) 1600 (C=N^+)	12.76 (s, NH_2^+) 7.72 (d, J=5.86, H-5) 7.64 (d, J=7.82, H-2"6") 7.56 (d, J=5.86, H-4) 7.40 (m, H-3"4"5") 6.84 (s, H-2'5') 5.94 (s, H-3'4')	$C_{15}H_{13}N_2ClS$	C 62.39 (62.32)	H 4.54 (4.66)	N 9.70 (9.99)
3b	95	250 (decomp.) (isopropanol)	3100/2700(NH_2^+) 1630 (C=N^+)	12.85 (s, NH_2^+) 7.68 (m, H-2"6", H-5) 7.21 (m, H-3"5", H-4) 6.84 (s, H-2'5') 6.04 (s, H-3'4')	$C_{15}H_{12}N_2ClFS$	C 58.72 (58.52)	H 3.91 (3.86)	N 9.13 (9.05)
4a	90	62 (isopropanol)	1640 (C=O)	7.64 (d, J=8.3, H-2"6") 7.50 (m, H-5, H-4") 7.38 (m, H-3"5") 7.20 (d, J=5.86, H-4) 6.84 (s, H-2'5') 6.03 (s, H-3'4')	$C_{15}H_{11}NOS$	C 71.12 (71.18)	H 4.38 (4.34)	N 5.53 (5.59)
4b	80	68 (ether/ petroleum ether)	1640 (C=O)	7.79 (dd, J=8.79 and 5.37, H-2"6") 7.53 (d, J=5.37, H-5) 7.25 (d, J=5.86, H-4") 7.19 (t, J=8.79, H-3"5") 6.85 (s, H-2'5') 6.05 (s, H-3'4')	$C_{15}H_{10}NOFS$	C 66.41 (66.70)	H 3.71 (3.79)	F 7.00 (6.99)
6a	70	218 (ethyl acetate)	3200 (OH) 1640 (C=N)	8.88 (s, OH) 7.23 (m, H-9, H-Phenyl) 7.05 (d, J=5.37, H-2) 7.00 (d, J=5.37, H-3) 6.17 (s, H-7, H-8) 1.84 (s, CH_3)	$C_{17}H_{14}N_2OS$	C 69.36 (69.60)	H 4.79 (4.76)	N 9.52 (9.62)

6b	51	222 (ethyl acetate)	3210 (OH) 1645 (C=N)	8.90 (s, OH) 7.26 (m, H-2'6') 7.16 (s, H-9) 7.04 (m, H-2, H-3, H-3'5') 6.17 (s, H-7, H-8) 1.84 (s, CH_3)	$C_{17}H_{13}N_2OFS$	C 65.37 (65.22)	H 4.19 (4.24)	F 6.08 (6.30)
7a	80	96 (ether/ petroleum ether)	1690 (C=O) 1630 (C=N)	7.53 (m, H-3"4"5") 7.47 (d, J=5.86, H-5) 7.39 (m, H-2"6") 7.05 (d, J=5.86, H-4) 6.87 (s, H-2'5') 6.07 (s, H-3'4') 2.28 (q, J=7.32, CH_2) 0.91 (t, J=7.32, CH_3)	$C_{18}H_{16}N_2OS$	C 70.10 (70.05)	H 5.23 (5.21)	N 9.08 (9.06)
7b	82	90 (ether/ petroleum ether)	1665 (C=O) 1630 (C=N)	7.55 (m, H-3"4"5") 7.46 (d, J=5.86, H-5) 7.40 (m, H-2"6") 7.08 (d, J=5.86, H-4) 6.88 (d, J=2.45, H-2'5') 6.03 (d, J=2.45, H-3'4') 1.78 (m, CH) 0.89 (m, CH_2)	$C_{19}H_{16}N_2OS$	C 71.22 (71.03)	H 5.03 (5.00)	N 8.74 (8.63)
7c	80	94 (ether)	1730 (C=O) 1695 (C=O) 1640 (C=N)	7.55 (m, H-3"4"5") 7.48 (d, J=5.86, H-5) 7.38 (m, H-2"6") 7.02 (d, J=5.86, H-4) 6.86 (s, H-2'5') 6.01 (s, H-3'4') 4.20 (q, J=6.84, CH_2) 1.19 (t, J=6.84, CH_3)	$C_{19}H_{16}N_2O_3S$	C 64.76 (64.94)	H 4.58 (4.56)	N 7.95 (7.89)
7d	74	76 (ether/ petroleum ether)	1740 (C=O) 1700 (C=O) 1630 (C=N)	7.63 (dd, J=8.79 and 5.37, H-2"6") 7.58 (d, J=5.86, H-5) 7.19 (t, J=8.79, H-3"5") 7.04 (d, J=5.86, H-4) 6.87 (s, H-2'5') 6.04 (s, H-3'4') 4.22 (q, J=6.84, CH_2) 1.18 (t, J=6.84, CH_3)	$C_{19}H_{15}N_2O_3FS$	C 61.61 (61.55)	H 4.08 (4.01)	F 5.12 (5.30)
7e	70	95 (ether/ petroleum ether)	1700 (C=O) 1625 (C=N)	7.55 (m, H-3"4"5") 7.45 (d, J=5.86, H-5) 7.35 (m, H-2"6") 7.12 (d, J=5.86, H-4) 6.83 (s, H-2'5') 6.03 (s, H-3'4') 4.39 (s, CH_2)	$C_{17}H_{13}N_2OClS$	C 62.10 (62.11)	H 3.98 (4.04)	Cl 10.78 (11.02)

7f	80	136 (ether)	1660 (C=O) 1620 (C=N)	7.84 (m, H-2"'6"') 7.64 (m, H-3"'4"'5"') 7.50 (m, H-3"4"5") 7.50 (d, J=5.37, H-5) 7.42 (m, H-2"6") 6.86 (s, H-2'5') 6.78 (d, J=5.37, H-4) 6.01 (s, H-3'4')	$C_{22}H_{16}N_2OS$	C 61.61' (61.55)	H 4.08 (4.01)	N 5.12 (5.30)
8a	70	210 (ethyl acetate)	3250 (OH) 1640 (C=N)	8.80 (s, OH) 7.21 (m, H-9, H-Phenyl) 7.05 (d, J=5.37, H-2) 7.00 (d, J=5.37, H-3) 6.18 (s, H-7, H-8) 2.15 (q, J=7.32, CH_2) 0.93 (t, J=7.32, CH_3)	$C_{18}H_{16}N_2OS$	C 70.10 (70.33)	H 5.23 (5.35)	N 9.08 (9.04)
8b	83	240 (ethyl acetate)	3250 (OH) 1640 (C=N)	9.11 (s, OH) 7.22 (m, H-9, H-Phenyl) 7.06 (d, J=5.37, H-2) 7.00 (d, J=5.37, H-3) 6.17 (s, H-7, H-8) 1.76 (m, CH) 0.60 (m, CH_2)	$C_{19}H_{16}N_2OS$	C 71.22 (71.49)	H 5.03 (5.15)	N 8.74 (8.57)
8c	85	150 (ether/ petroleum ether)	3200 (OH) 1745 (C=O) 1675 (C=N)	9.67 (s, OH) 7.27 (m, H-9, H-Phenyl) 7.07 (d, J=5.37, H-2) 7.02 (d, J=5.37, H-3) 6.24 (s, H-7) 6.18 (s, H-8) 4.17 (q, J=6.84, CH_2) 1.22 (t, J=6.84, CH_3)	$C_{19}H_{16}N_2O_3S$	C 64.76 (64.70)	H 4.58 (4.76)	N 7.95 (8.19)
8d	36	142 (ether/ petroleum ether)	3200 (OH) 1740 (C=O) 1670 (C=N)	8.83 (s, OH) 7.37 (dd, J=8.79 and 5.37, H-2'6') 7.23 (s, H-9) 7.12 (m, H-2, H-3, H-3'5') 6.30 (d, J=2.93, H-7) 6.20 (t, J=2.93, H-8) 3.39 (q, J=6.84, CH_2) 2.50 (t, J=6.84, CH_3)	$C_{19}H_{15}N_2O_3FS$	C 61.61 (61.50)	H 4.05 (4.09)	N 7.56 (7.50)
8e	49	118 (ether/ petroleum ether)	3200 (OH, NH) 1665 (C=O) 1630 (C=N)	9.05 (s, OH) 8.61 (t, J= 6.35, NH) 7.42 (dd, J=8.79 and 5.37, H-2'6') 7.24 (s, H-9) 7.13 (m, H-2, H-3, H-3'5') 6.35 (d, J=2.93, H-7) 6.21 (t, J=2.93, H-8) 3.52 (m, H-ββ') 3.23 (m, CH_2-NH) 2.36 (m, H-αα', CH_2)	$C_{23}H_{23}N_4O_2FS$	C 60.78 (60.58)	H 5.10 (5.07)	F 4.18 (4.32)

8f	70	212 (ether/ petroleum ether)	3200 (OH) 1660 (C=N)	9.36 (s, OH) 7.30 (m, H-9, H-Phenyl) 7.09 (d, J=5.37, H-2) 7.03 (d, J=5.37, H-3) 6.20 (s, H-7, H-8) 4.18 (s, CH_2)	$C_{17}H_{13}N_2OClS$	C 62.10 (62.32)	H 3.98 (4.20)	Cl 10.78 (10.82)
8g	95	120 (ether/ petroleum ether)	3200 (OH) 1650 (C=N)	8.45 (s, OH) 7.28 (m, H-3'4'5') 7.24 (s, H-9) 7.21 (m, H-2'6') 7.08 (s, H-2, H-3) 6.19 (s, H-7, H-8) 2.88 (s, CH_2-N) 2.38 (m, H-αα') 1.47 (m, H-ββ'γ)	$C_{22}H_{23}N_3OS$	C 70.00 (70.25)	H 6.14 (6.18)	N 11.13 (11.11)

EXPERIMENTAL

All melting points were measured using a Köfler 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-d_6 solution using TMS as an internal standard.

General procedure for the synthesis of the imines (**2a-b**)

A freshly prepared solution of phenylmagnesium bromide (0.2 mol) for **2a** or (*p*-fluoro)phenylmagnesium bromide (0.2 mol) in the case of **2b** in anhydrous ether (200 ml) was added dropwise under argon to a well stirred solution of **1** (0.1 mol) in anhydrous ether (400 ml), (prepared as in ref. 3 by refluxing a solution of 2-aminothienyl-3-carbonitrile and an equivalent amount of 2,5-dimethoxytetrahydrofuran in acetic acid for 1.5 h). The resulting mixture was refluxed for 16 h, cooled and poured slowly into a cold aqueous solution of hydrochloric acid (800 ml, 0.5 N). The aqueous layer was separated, washed with ether (2x100 ml), made slightly alkaline by addition of a cold aqueous solution of sodium hydroxide (100 ml, 4 N) and was extracted with ether (3x300 ml). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated in vacuo to give a yellow solid which was recrystallized from ether/petroleum ether to give **2a** (20.74 g, 84%) and **2b** (24.5 g, 71%)

General procedure for the synthesis of the iminium hydrochlorides (**3a-b**)

To a stirred solution of **2a** (1 g, 3.96 mmol) or **2b** (1 g, 3.7 mmol) in anhydrous ether (15 ml), was added dropwise a solution of ether saturated with HCl gas. The precipitate was filtered, washed with ether, dried and recrystallized from isopropanol to give **3a** (1.10 g, 96%) and **3b** (1.08 g, 95%).

General procedure for the synthesis of ketones (**4a-b**)

The imines (**2a**) (10 g, 39.6 mmol) or **2b** (10 g, 37 mmol) in an aqueous solution of hydrochloric acid (400 ml, 0.5 N) (1<pH<2) was heated under reflux for 1 h. After cooling, the aqueous layer was decanted and the residue was extracted with ether. The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and the ether was evaporated in vacuo to give **4a** (9 g, 90%) and **4b** (8 g, 80%).

General procedure for the synthesis of [1,4]diazepines (**6a-b**)

The imines (**2a**) (1 g, 3.96 mmol) or **2b** (1 g, 3.7 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 18 h. The reaction mixture was then poured on ice and the precipitate was filtered, washed with ether, dried and recrystallized from ethyl acetate to give **6a** (0.8 g, 70 %) and **6b** (0.6 g, 51 %).

General procedure for the synthesis of acylimines (**7a-f**)

The imines (**2a**) (1 g, 3.96 mmol) or (**2b**) (1.07 g, 3.96 mmol) in THF solution was treated with an excess of triethylamine (7.13 mmol, 1.8 equivalents) and the corresponding acid chlorides (4.36 mmol, 1.1 equivalents). The reaction mixture was stirred at room temperature for 2 h. After filtration of the precipitate of triethylamine hydrochloride, the filtrate was evaporated in vacuo. The residue was triturated with water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo to give **7a** (1 g, 70%), **7b** (1.04 g, 82%), **7c** (1.14 g, 80%), **7d** (0.92 g, 74%), **7e** (1.2 g, 70%), **7f** (1.15 g, 80%).

General procedure for the synthesis of [1,4]diazepines (**8a-b-c-d-f**)

The acylimines (**7a**) (1 g, 3.24 mmol), **7b** (1 g, 3.12 mmol), **7c** (1 g, 2.83 mmol), **7d** (1 g, 2.69 mmol) or **7e** (1 g, 3.04 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 18 h. The reaction mixture was then poured on ice. The precipitate was filtered, washed with ether, dried and recrystallized to give **8a** (0.70 g, 70%), **8b** (0.83 g, 83%), **8c** (0.85 g, 85%), **8d** (0.36 g, 36%) or **8f** (0.7 g, 70%).

N-Morpholinoethyl-(6-hydroxy-4-(*p*-fluoro)phenyl-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-6-yl)-carboxamide (**8e**)

To the [1,4]diazepine (**8d**) (1 g, 2.69 mmol) was added *N*-(2-aminoethyl)morpholine (2 ml, 15.4 mmol, 5.7 equivalents). The mixture was heated at 150°C for 1.5 h, cooled and extracted with ether. The organic layer was washed several times with an aqueous solution of hydrochloric acid (0.5 N), dried ($MgSO_4$) and the ether was evaporated in vacuo. The yellow solid obtained was recrystallized from ether to give **8e** (0.6 g, 49%).

6-(Piperidinomethyl)-6-hydroxy-4-phenyl-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepine (**8g**)

8f (1 g, 3.04 mmol) in piperidine (20 ml, 0.2 mol) was heated under reflux for 2 h. After cooling, the mixture was poured on an ice/water solution. The precipitate was filtered, washed with water, dried and recrystallized from ether/petroleum ether to give **8g** (1.05 g, 95%).

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