Monatshefte für Chemie 138, 469–476 (2007)
DOI 10.1007/s00706-007-0591-8
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

On the Synthesis of Pyrrolobenzo[*b*]thieno[1,4]diazepines

Hussein El-Kashef[1,*], **Pascal Rathelot**[2], **Patrice Vanelle**[2], and **Sylvain Rault**[3]

[1] Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt
[2] Laboratoire de Chimie Organique Pharmaceutique (LCOP) UMR CNRS 6517, Faculté de Pharmacie, Université de la Méditerranée, Marseille, France
[3] UPRES-EA 2126: Centre d'Etudes et de Recherche sur le Médicament de Normandie, U.F.R. des Sciences pharmaceutiques, Université de Caen Basse-Normandie, Caen, France

Received September 22, 2006; accepted (revised) September 29, 2006; published online February 26, 2007

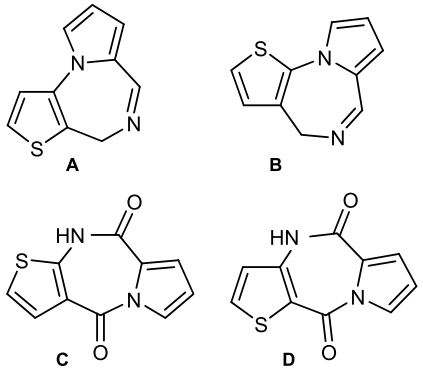
Summary. 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile was converted into the corresponding 2-(pyrrol-1-yl) derivative, followed by reduction of the latter compound into the corresponding amine. This amine and its acyl, aroyl, and arylidene derivatives were used as synthons in the synthesis of several title compounds.

Keywords. [1,4]Diazepines; Thieno[1,4]diazepines; Tetrahydrobenzothieno[1,4]diazepines; Pyrrolobenzothienodiazepines.

Introduction

Pyrrolo[2,1-*a*][1,4]benzodiazepines (*PBD*s) are a family of antitumor antibiotics derived from various Streptomyces species. Family members include Anthramycin, Tomamycin, Sibiromycin, Neothramycins, Chicamycin, Porothramycin, Prothracarcin, Abbeymycin, and *DC-81*. Their antitumor activity is based on their ability to form covalent adducts in the minor groove of *DNA* [1].

The *PBD* analogs in which the benzene ring is replaced by a thiophene nucleus, namely pyrrolothienodiazepines, such as pyrrolo[1,2-*a*]thieno-[2,3-*f*], [3,2-*f*], [2,3-*e*], and [3,2-*e*][1,4]diazepines **A**–**D**, were the subject of several publications in the last two decades [2–23]. These diazepines showed a variety of interesting therapeutic activity such as antitumorals [3], antiischemics, hypolipemics, antihypertensives [18], cholecystokinins antagonists [19], and central nervous system active agents [20]. To the best of our knowledge, no work on this topic appeared in the literature after the paper reported in 2002 by *Rault et al.* [3].

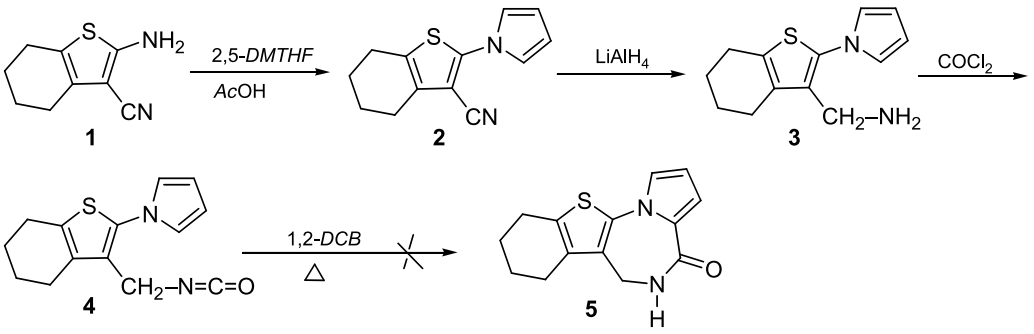


Results and Discussion

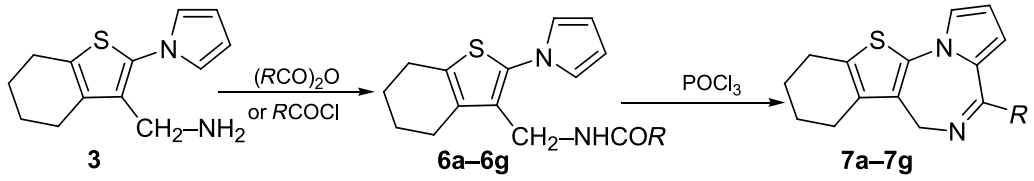
In continuation of our interest in the synthesis of 1,4-diazepines with biological activity, we describe herein the synthesis of several unknown pyrrolo[1,2-*a*]benzo[*b*]thieno[3,2-*f*]diazepine derivatives.

The amino group of the 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**1**), prepared easily by the method of *Gewald* [6], was converted

* Corresponding author. E-mail: elkashef15@hotmail.com



Scheme 1



a: *R* = methyl, **b**: *R* = ethyl, **c**: *R* = butyl, **d**: *R* = cyclobutyl, **e**: *R* = phenyl, **f**: *R* = 4-nitrophenyl, **g**: *R* = 3,4-dichlorophenyl

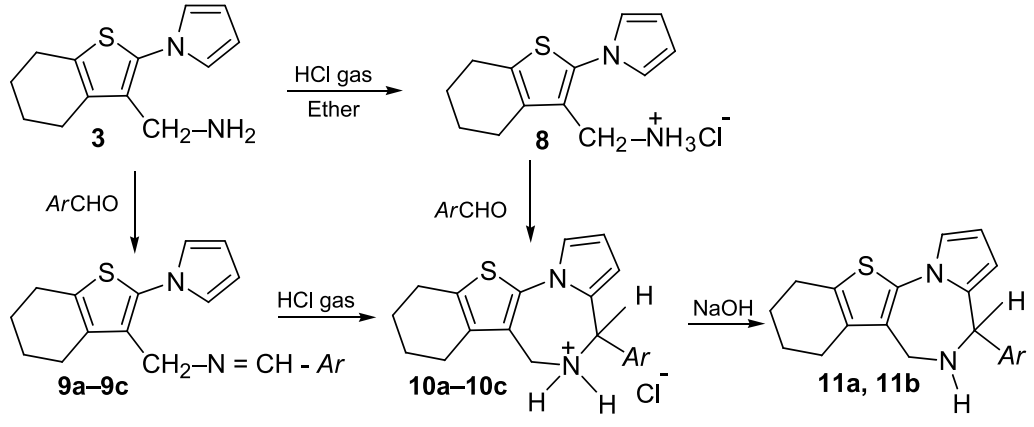
Scheme 2

into the corresponding pyrrol-1-yl group by the reaction with dimethoxytetrahydrofurane (*DMTHF*) giving **2** [7]. $LiAlH_4$ reduction of the latter compound gave the methylamine derivative **3** [7].

When the methylamine **3** was interacted with phosgene in boiling toluene, the product was identified as the methylisocyanate **4**. Several attempts to ring-close **4** into the diazepine **5** upon heating under reflux in a high boiling inert solvent, such as 1,2-dichlorobenzene, were unsuccessful (Scheme 1).

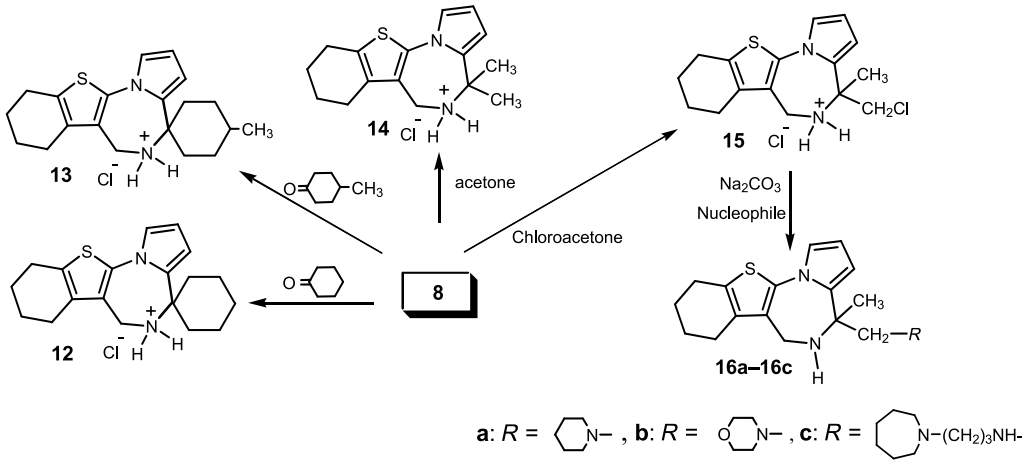
However, when the methylamine **3** was acylated and/or aroylated using acid chlorides or anhydrides, the corresponding amides **6a**–**6g** were obtained. Cyclodehydration of the latter amides under *Bischler-Napieralsky* reaction conditions gave a series of 4-substituted-7,8,9,10-tetrahydro-6*H*-pyrrolo[1,2-*a*]benzo[*b*]thieno[3,2-*f*]diazepines (Scheme 2).

The methylamine **3** could be also used as starting point for the synthesis of other diazepine derivatives. Thus, the reaction of **3** with aromatic aldehydes gave



a: *Ar* = $C_6H_4CH_3$ (*p*), **b**: *Ar* = $C_6H_4OCH_3$ (*p*), *Ar* = C_6H_4OH (*m*)

Scheme 3



Scheme 4

the corresponding anils **9a**–**9c** which were then subjected to *Pictet-Spengler* cycloaddition reaction by passing a current of dry HCl gas in their ethereal solutions (method A) to give the diazepine hydrochlorides **10a**–**10c**. Alternatively, another easier route of synthesis was followed *via* the conversion of the amine **3** into its hydrochloride salt **8** followed by reacting the latter with the respective adehydes in boiling ethanol (method B) to give directly the diazepine hydrochlorides **10a**–**10c**. The free bases **11a**, **11b** could be obtained upon heating **10a**, **10b** in boiling NaOH (Scheme 3).

In the same way when **8** was allowed to react with cycloketones (cyclohexanone and 4-methylcyclohexanone), the corresponding spirodiazepine hydrochlorides **12** and **13** were obtained (Scheme 4). On the other hand, when aliphatic ketones (acetone and chloroacetone) were used in the latter reaction, the products were identified as the hydrochlorides of 4,4-dimethyl- and 4-chloromethyl-4-methyl derivatives **14** and **15**. Nucleophilic substitution of the labile chlorine atom of **15** using nitrogen nucleophiles gave the corresponding diazepines **16a**–**16c** (Scheme 4).

The diazepines prepared were tested for their adenosine receptor affinity, however they showed no affinity at human A_1 and A_3 adenosine receptors. Also they were tested for their antiviral activity against cytomegalovirus in human embryonic lung (HEL) cells. No specific activity was shown (that is activity at a concentration more than five-folds lower than the *MCC* or CC_{50}) except with **10b**, which showed some selectivity against CMV (AD-169 strain) (IC_{50} is about 6-7-fold lower than *MCC*).

Experimental

All melting points were determined on a *Kofler* melting point apparatus. IR spectra were recorded on a Pye Unicam SP3-100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer (*TMS* as internal reference, δ values in ppm). Elemental analyses were carried out using a Perkin-Elmer 240 C Micro analyser at Assiut University. Their results were found in good agreement with the calculated values. Compound **1** was prepared according to the method of *Gewald* [6]. Compounds **2** and **3** were prepared according to Ref. [7].

(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-yl) methylisocyanate (**4**, $C_{14}H_{14}N_2OS$)

To a solution of 4.6 g **3** (0.02 mol) in 50 cm^3 toluene, a solution of phosgene (5 equivalents, 20% in toluene) was added. The reaction mixture was stirred at r.t. for 1.5 h, and then was heated under reflux for 30 min. The excess of phosgene was eliminated by passing a current of N_2 gas in the cold reaction mixture for 0.5 h. followed by filtration. The filtrate was decolourized with charcoal and evaporated under reduced pressure to give a colourless oil. Yield 4 g (75%), $bp_{0.05\,mmHg}$ 140°C; IR(KBr): $\bar{\nu} = 3020$, 2920, 2850 (CH), 2250 (−N=C=O), 1730 (C=O), other principal bands: 1580, 1490, 1390, 1095, 730 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.78$ (m, $H_{5,6}$), 2.56 (m, $H_{4,7}$), 4.53 (s, CH_2), 6.18 (m, $H_{3',4'}$-pyrrole), 6.81 (m, $H_{2',5'}$-pyrrole) ppm.

N-(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-ylmethyl)acetamide (**6a**, $C_{15}H_{18}N_2OS$)

A solution of 4.6 g **3** (0.02 mol) in a mixture of 15 cm^3 acetic anhydride and 10 cm^3 acetic acid was stirred at room temperature for 2 h. Then it was poured on 100 cm^3 crushed ice-H_2O mixture. The precipitate formed was filtered off, washed with H_2O, dried and recrystallized from methanol into colourless crystals. Yield 5.2 g (96%), mp 200°C. IR(KBr): $\bar{\nu} = 3250$ (NH), 3050, 2950, 2860, 2840 (CH), 1630 (C=O), other principal bands: 1580, 1520, 1455, 1345, 1295, 1200, 1020, 725 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.81$ (m,

$H_{5,6}$), 2.30 (s, CH_3), 2.61 (m, $H_{4,7}$), 3.91 (s, $C\underline{H_2}NHCO$), 6.16 (m, $H_{3',4'}$-pyrrole), 6.88 (m, $H_{2',5'}$-pyrrole), 7.83 (s, NH) ppm.

N-(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-ylmethyl)propionamide (**6b**, $C_{16}H_{20}N_2OS$)
A solution of 4.6 g **3** (0.02 mol) in 15 cm^3 propionic anhydride was stirred at room temperature for 2 h. The reaction mixture was then poured into 50 cm^3 ice-H_2O mixture and stirred for 1 h. The solid precipitate was filtered, washed with H_2O, dried, and recrystallized from methanol-H_2O mixture into colourless crystals. Yield 5.4 g (95%), mp 172°C. IR(KBr): $\bar{\nu} = 3270$ (NH), 3050, 2960, 2880, 2840 (CH), 1630 (C=O), other principal bands: 1575, 1520, 1450, 1340, 1290, 1210, 1030, 725 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 0.96$ (t, $J = 7.1$ Hz, $CH_2C\underline{H_3}$), 1.73 (m, $H_{5,6}$), 2.03 (q, $J = 7.1$ Hz, $C\underline{H_2}CH_3$), 2.60 (m, $H_{4,7}$), 3.91 (s, $C\underline{H_2}NHCO$) 6.11 (m, $H_{3',4'}$-pyrrole), 6.86 (m, $H_{2',5'}$-pyrrole), 7.78 (s, NH) ppm.

N-(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-ylmethyl)butyramide (**6c**, $C_{17}H_{22}N_2OS$)
This compound was obtained using butanoic anhydride following the same procedure as that of **6b**. Recrystallization from methanol gave colourless needles, yield 5.6 g (93%), mp 150°C. IR(KBr): $\bar{\nu} = 3240$ (NH), 3060, 2950, 2870, 2820 (CH), 1630 (C=O), other principal bands: 1580, 1540, 1445, 1300, 1215, 1200, 1020, 730 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 0.83$ (t, $J = 7.1$ Hz, CH_3), 1.48 (m, $CH_2C\underline{H_2}CH_3$), 1.73 (m, $H_{5,6}$), 1.98 (t, $J = 7.0$ Hz, $C\underline{H_2}CH_2CH_3$), 2.63 (m, $H_{4,7}$), 3.91 (d, $C\underline{H_2}NHCO$), 6.15 (m, $H_{3',4'}$-pyrrole), 6.86 (m, $H_{2',5'}$-pyrrole), 7.83 (s, NH) ppm.

N-(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-ylmethyl)cyclobutanecarboxamide (**6d**, $C_{18}H_{22}N_2OS$)
To a solution of 4.6 g **3** (0.02 mol) in 20 cm^3 pyridine was added dropwise with stirring at ambient temperature 2.3 g cyclobutanoyl chloride (0.02 mol). Stirring was continued for additional 1 h. Then the reaction mixture was poured on 60 cm^3 cold H_2O. The precipitate thus formed was filtered, washed with diluted HCl, and then with H_2O. Recrystallization from methanol gave colourless needles, yield 5.9 g (94%), mp 194°C. IR(KBr): $\bar{\nu} = 3240$ (NH), 3090, 3050, 2990, 2850 (CH), 1625 (C=O), other principal bands: 1580, 1540, 1460, 1345, 1205, 1255, 1100, 895, 740, 730 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.73$ (m, $H_{5,6}$), 2.00 (m, cyclobutyl), 2.53 (m, $H_{4,7}$), 3.00 (m, cyclobutyl), 3.93 (s, $C\underline{H_2}NHCO$), 6.13 (m, $H_{3',4'}$-pyrrole), 6.86 (m, $H_{2',5'}$-pyrrole), 7.71 (s, NH) ppm.

N-(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-ylmethyl)benzamide (**6e**, $C_{20}H_{20}N_2OS$)
This compound was obtained using 2.8 g benzoyl chloride (0.02 mol) following the same procedure as that of **6d**. Recrystallization from methanol gave colourless needles, yield 6.3 g (94%), mp 170°C. IR(KBr): $\bar{\nu} = 3310$ (NH), 3090, 2920, 2850 (CH), 1620 (C=O), other principal bands: 1570, 1520, 1480, 1345, 1310, 1200, 1010, 895, 735 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.70$ (m, $H_{5,6}$), 2.63 (m, $H_{4,7}$), 4.16 (s, $C\underline{H_2}NHCO$), 6.15 (m, $H_{3',4'}$-pyrrole), 6.96 (m, $H_{2',5'}$-pyrrole), 7.41 (m, phenyl), 7.78 (m, phenyl), 8.30 (s, NH) ppm.

N-(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-ylmethyl)-4-nitrobenzamide (**6f**, $C_{20}H_{19}N_3O_3S$)
This compound was obtained using 3.7 g 4-nitrobenzoyl chloride (0.02 mol) following the same procedure as that of **6d**. Recrystallization from methanol gave yellow needles, yield 7.0 g (92%), mp 178°C. IR(KBr): $\bar{\nu} = 3260$ (NH), 2930, 2860 (CH), 1630 (C=O), 1540, 1350 (NO_2), other principal bands: 1590, 1310, 1480, 1280, 1010, 870, 725 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.73$ (m, $H_{5,6}$), 2.63 (m, $H_{4,7}$), 4.16 (s, $C\underline{H_2}NHCO$), 6.15 (m, $H_{3',4'}$-pyrrole), 6.96 (m, $H_{2',5'}$-pyrrole), 7.93 (d, $J = 9.0$ Hz, phenyl), 8.18 (d, $J = 9.0$ Hz, phenyl), 8.85 (s, NH) ppm.

N-(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-ylmethyl)-3,4-dichlorobenzamide (**6g**, $C_{20}H_{18}Cl_2N_2OS$)
This compound was obtained using 4.2 g 3,4-dichlorobenzoyl chloride (0.02 mol) following the same procedure as that of **6d**. Recrystallization from methanol gave yellow crystals, yield 7.3 g (91%), mp 164°C. IR(KBr): $\bar{\nu} = 3270$ (NH), 2920, 2850, 2820 (CH), 1620 (C=O), other principal bands: 1580, 1510, 1460, 1310, 1245, 903, 725 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.75$ (m, $H_{5,6}$), 2.60 (m, $H_{4,7}$), 4.16 (s, $C\underline{H_2}NHCO$), 6.15 (m, $H_{3',4'}$-pyrrole), 6.93 (m, $H_{2',5'}$-pyrrole), 7.88 (m, phenyl), 8.3 (m, phenyl), 8.70 (s, NH) ppm.

*General Procedure for Preparation of **7a–7g***
A solution of **6a–6g** (0.01 mol) in 15 cm^3 $POCl_3$ was heated under gentle reflux for 20 min. The excess of $POCl_3$ was eliminated under reduced pressure and the residue was treated with 30 cm^3 cold solution of 6 *N* NaOH followed by extraction with ether. The ethereal layer was washed with H_2O, dried over anhydrous magnesium sulphate and the solvent was eliminated under reduced pressure. The residue was distilled if it is an oil or recrystallized if it is a solid compound.

4-Methyl-7,8,9,10-tetrahydro-6H-pyrrolo[1,2-a]benzo[b]thieno[3,2-f][1,4]diazepine (**7a**, $C_{15}H_{16}N_2S$)
This compound was obtained from 2.7 g **6a**, as a pale yellow oil, yield 2.3 g (90%), $bp_{0.05\ mmHg}$ 150°C. IR(KBr): $\bar{\nu} = 2930$, 2840 (CH), 1615 (C=N), 1580 (C=C), other principal bands: 1435, 1350, 1310, 1265, 1010, 920, 730 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.75$ (m, $H_{8,9}$), 2.25 (s, CH_3), 2.60 (m, $H_{7,10}$), 4.15 (s, H_6), 6.30 (dd, $J = 2.7$, 3.6 Hz, H_2-pyrrole), 6.76 (dd, $J = 3.6$, 1.5 Hz, H_3-pyrrole), 7.25 (dd, $J = 2.7$, 1.5 Hz, H_1-pyrrole) ppm.

4-Ethyl-7,8,9,10-tetrahydro-6H-pyrrolo[1,2-a]benzo[b]thieno[3,2-f][1,4]diazepine (**7b**, $C_{16}H_{18}N_2S$)
This compound was obtained from 2.9 g **6b**, as a yellow oil, yield 2.4 g (89%), $bp_{0.05\ mmHg}$ 160°C. IR(KBr): $\bar{\nu} = 2930$, 2850, 2830 (CH), 1610 (C=N), 1515 (C=C), other principal bands: 1435, 1350, 1240, 920, 720 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 0.98$ (t, $J = 7.10$ Hz, $CH_2C\underline{H_3}$), 1.75 (m, $H_{8,9}$), 2.58 (m, $C\underline{H_2}CH_3$), $H_{7,10}$), 4.17 (s, H_6), 6.23 (dd, $J = 2.7$, 3.6 Hz, H_2-pyrrole), 6.66 (dd, $J = 3.6$, 1.5 Hz, H_3-pyrrole), 7.16 (dd, $J = 2.7$, 1.5 Hz, 1H, H_1-pyrrole) ppm.

4-Propyl-7,8,9,10-tetrahydro-6H-pyrrolo[1,2-a]benzo[b]thieno[3,2-f][1,4]diazepine (**7c**, $C_{17}H_{20}N_2S$)
This compound was obtained from 3 g **6c**, as a pale yellow oil, yield 2.4 g (87%), $bp_{0.05\,mmHg}$ 165°C. IR(KBr): $\bar{\nu} = 2950$, 2930, 2860, 2840 (CH), 1610 (C=N), 1580 and 1515 (C=C), other principal bands: 1440, 1350, 1110, 930, 722 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 0.83$ (t, $J = 7.07$ Hz, 3H, CH_3), 1.50 (m, $CH_2C\underline{H}_2CH_3$), 1.73 (m, $H_{8,9}$), 2.63 (m, $C\underline{H}_2CH_2CH_3 + H_{7,10}$), 4.22 (s, H_6), 6.36 (dd, $J = 2.7$, 1.5 Hz, H_2-pyrrole), 6.90 (dd, $J = 3.6$, 2.7 Hz, H_3-pyrrole), 7.33 (dd, $J = 3.6$, 1.5 Hz, H_1-pyrrole) ppm.

4-Cyclobutyl-7,8,9,10-tetrahydro-6H-pyrrolo[1,2-a]benzo[b]thieno[3,2-f][1,4]diazepine (**7d**, $C_{18}H_{20}N_2S$)
This compound was obtained from 3.1 g **6d**, as yellow semi solid, yield 2.5 g (89%), mp 50°C. IR(KBr): $\bar{\nu} = 2930$, 2850, 2830 (CH), 1605 (C=N), 1580 and 1515 (C=C), other principal bands: 1432, 1250, 930, 725 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.76$ (m, $H_{8,9}$), 2.60 (m, $H_{7,10}$), 2.06 (m, CH_2), 2.60 (m, $H_{7,10}$ + cyclobutyl), 3.56 (m, cyclobutyl), 4.25 (s, H_6), 6.33 (dd, $J = 2.7$, 3.6 Hz, H_2-pyrrole), 6.71 (dd, $J = 3.6$, 1.5 Hz, H_3-pyrrole), 7.28 (dd, $J = 2.7$, 1.5 Hz, H_1-pyrrole) ppm.

4-Phenyl-7,8,9,10-tetrahydro-6H-pyrrolo[1,2-a]benzo[b]thieno[3,2-f][1,4]diazepine (**7e**, $C_{20}H_{18}N_2S$)
This compound was obtained from 3.4 g **6e**, as pale yellow crystals, yield 4.4 g (74%), mp 104°C. IR(KBr): $\bar{\nu} = 2930$, 2850, 2830 (CH), 1580 (C=N), 1560, 1510 (C=C), other principal bands: 1435, 1400, 1350, 910, 775, 710 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.73$ (m, $H_{8,9}$), 2.60 (m, $H_{7,10}$), 4.36 (s, H_6), 6.36 (m, $H_{2,3}$-pyrrole), 7.36 (m, H_1-pyrrole + phenyl) ppm.

4-(4-Nitrophenyl)-7,8,9,10-tetrahydro-6H-benzo[b]thieno[3,2-f]pyrrolo[1,2-a][1,4]diazepine
(**7f**, $C_{20}H_{17}N_3O_2S$)
This compound was obtained from 3.8 g **6f**, as yellow crystals, yield 2.6 g (72%), mp 172°C. IR(KBr): $\bar{\nu} = 3080$, 2980, 2960, 2830 (CH), 1575 (C=C),1570, 1435 (NO_2), other principal bands: 1435, 1100, 910, 850, 730, 715 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.73$ (m, $H_{8,9}$), 2.56 (m, $H_{7,10}$), 4.40 (s, H_6), 6.30 (m, $H_{2,3}$-pyrrole), 7.35 (m, H_1-pyrrole), 7.70 (d, $J = 8.5$ Hz, phenyl), 8.13 (d, $J = 8.5$ Hz, phenyl) ppm.

4-(3,4-Dichlorophenyl)-7,8,9,10-tetrahydro-6H-benzo[b]thieno[3,2-f]pyrrolo[1,2-a][1,4]diazepine
(**7g**, $C_{20}H_{16}Cl_2N_2S$)
This compound was obtained from 4 g **6g**, as yellow crystals (ether), yield 2.9 g (75%), mp 165°C. IR(KBr): $\bar{\nu} = 2930$, 2910, 2830 (CH), 1575, 1540, 1510 (C=C), other principal bands: 1250, 1030, 920, 835, 780, 730 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.93$ (m, $H_{5,6}$), 2.60 (m, $H_{4,7}$), 4.36 (s, H_6), 6.38 (m, $H_{2,3}$-pyrrole), 7.38 (m, H_1-pyrrole), 7.42 (m, phenyl), 7.70 (d, $J = 1.7$ Hz, phenyl) ppm.

(2-(Pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-yl)methylamine hydrochloride (**8**, $C_{13}H_{17}N_2SCl$)
A rapid current of HCl gas was passed during 5 min. into a solution of 10 g **3** in 100 cm^3 dry ether. The solid precipitate thus formed was filtered off, washed with ether, and recrystallized in ethanol as buff crystals. Yield 10.9 g (94%), mp >260°C. IR(KBr): $\bar{\nu} = 2920$, 2840, 2700, 2600 ($^+NH_3$), other principal bands: 1570, 1500, 1070, 720 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.76$ (m, $H_{5,6}$), 2.66 (m, $H_{4,7}$), 3.65 (s, $C\underline{H}_2$), 6.21 (t, $H_{3',4'}$-pyrrole), 7.00 (t, $H_{2',5'}$-pyrrole), 8.50 ($^+NH_3$) ppm.

N-Arylidene(2-(pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-yl)methylamine ***9a–9c***
An equimolar (0.01 mol) mixture of **3** and aromatic aldehydes in 30 cm^3 ethanol was heated under reflux for 1 h. After cooling, the solid product formed was filtered off, dried, and recrystallized. If otherwise no solid was precipitated, then the resulting solution was evaporated under reduced pressure and the residue was dissolved in ether, decolorized with animal charcoal, filtered, evaporated and the oily product was then distilled under reduced pressure.

N-(4-Methylbenzylidene)(2-(pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-yl)methylamine (**9a**, $C_{21}H_{22}N_2S$)
This compound was obtained from 1.2 g 4-methylbenzaldehyde as yellow oil, yield 3.2 g (96%), $bp_{0.05\,mmHg}$ 120°C. IR(KBr): $\bar{\nu} = 3110$, 3080, 2910, 2820 (CH), 1630 (C=N), other principal bands: 1620, 1575, 1505, 1460, 1430, 1335, 1170, 810, 725 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.73$ (m, $H_{5,6}$), 2.28 (s, $C\underline{H}_3$), 2.58 (m, $H_{4,7}$), 4.38 (s, $C\underline{H}_2$), 6.13 (m, $H_{3',4'}$-pyrrole), 6.90 (m, $H_{2',5'}$-pyrrole), 7.13 (d, $J = 8.32$ Hz, phenyl), 7.52 (d, $J = 8.32$ Hz, phenyl), 8.15 (s, N=C$\underline{H}$) ppm.

N-(4-Methoxybenzylidene)(2-(pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-yl)methylamine
(**9b**, $C_{21}H_{22}N_2OS$)
This compound was obtained from 1.4 g 4-methoxybenzaldehyde as yellow oil, yield 3.2 g (91%), $bp_{0.05\,mmHg}$ 195°C. IR(KBr): $\bar{\nu} = 2920$, 2820 (CH), 1630 (C=N), other principal bands: 1595, 1570, 1500, 1460, 1300, 1250, 1030, 830, 735 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.73$ (m, $H_{5,6}$), 2.62 (m, $H_{4,7}$), 3.75 (s, $OC\underline{H}_3$), 4.37 (s, $C\underline{H}_2$), 6.18 (m, $H_{3',4'}$-pyrrole), 6.90 (m, $H_{2',5'}$-pyrrole + phenyl), 7.62 (d, $J = 8.4$ Hz, phenyl), 8.15 (s, N=C$\underline{H}$) ppm.

N-(3-Hydroxybenzylidene)(2-(pyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[b]thien-3-yl)methylamine
(**9c**, $C_{20}H_{20}N_2OS$)
This compound was obtained from 1.2 g 3-hydroxybenzaldehyde as colourless crystals, yield 3.0 g (90%), mp 150°C (ether/pet. ether 60–80°C). IR(KBr): $\bar{\nu} = 2940$, 2920, 2840 (CH), 2710–2360 (OH), other principal bands: 1585, 1570, 1500, 1450, 1270, 1170, 725, 690 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta =$ (m, $H_{5,6}$), 2.63 (m, $H_{4,7}$), 4.40 (s, CH_2), 6.17 (t, $H_{3',4'}$-pyrrole), 6.90 (m, $H_{2',5'}$-pyrrole + phenyl), 7.13 (m, phenyl), 8.12 (s, N=CH), 9.47 (s, OH) ppm.

*General Procedure for Preparation of **10a–10c***

Method A:

A rapid current of dry HCl gas was bubbled at ambient temperature in a solution of **9a–9c** (0.01 mol) in 50 cm^3 dry ether until the formation of a gummy precipitate. Ether was decanted and the precipitate was washed abundantly with ether and then crystallized from methanol.

4-(4-Methylphenyl)-4,5,7,8,9,10-hexahydro-6H-benzo[b] thieno[3,2-f]pyrrolo[1,2-e][1,4]diazepin-5-ium chloride (**10a**, $C_{21}H_{23}ClN_2S$)

This compound was obtained from 3.3 g **9a** as colourless crystals, yield 2.9 g (74%), mp 253°C. IR(KBr): $\bar{\nu} = 3090$, 2910, 2840 (CH), 2710, 2530 ($^+NH_2$), other principal bands: 1575, 1510, 1460, 1445, 1400, 1350, 1180, 815, 740, 725 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.77$ (m, $H_{8,9}$), 2.33 (s, CH_3), 2.70 (m, $H_{7,10}$), 3.97 (2d, $J = 14.5$ Hz, H_6), 5.27 (d, $J = 0.9$ Hz, H_4), 5.65 (ddd, $J = 3.6$, 1.8, 0.9 Hz, H_3-pyrrole), 6.16 (dd, $J = 3.6$, 3.0 Hz, H_2-pyrrole), 7.17 (dd, $J = 3.0$, 1.8 Hz, H_1-pyrrole), 7.25 (d, $J = 8.3$ Hz, phenyl), 7.52 (d, $J = 8.3$ Hz, phenyl), 10.33 (s, $^+NH_2$) ppm.

4-(4-Methoxyphenyl)-4,5,7,8,9,10-hexahydro-6H-benzo[b] thieno[3,2-f]pyrrolo[1,2-e][1,4]diazepin-5-ium chloride (**10b**, $C_{21}H_{23}ClN_2OS$)

This compound was obtained from 3.5 g **9b** as buff crystals, yield 2.9 g (75%), mp 250°C. IR(KBr): $\bar{\nu} = 2910$, 2810 (CH), 2720, 2640, 2550 ($^+NH_2$), other principal bands: 1600, 1565, 1505, 1450, 1430, 1300, 1250, 825, 720 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.75$ (m, $H_{8,9}$), 2.67 (m, $H_{7,10}$), 3.70 (s, OCH_3), 3.91 (2d, $J = 14.5$ Hz, H_6), 5.20 (d, $J = 0.9$ Hz, H_4), 5.67 (ddd, $J = 3.6$, 1.8, 0.9 Hz, H_3-pyrrole), 6.13 (dd, $J = 3.6$, 3.0 Hz, H_2-pyrrole), 6.83 (d, $J = 8.5$ Hz, phenyl), 7.10 (dd, $J = 3.0$, 1.8 Hz, H_1-pyrrole), 7.90 (d, $J = 8.5$ Hz, phenyl), 10.50 (s, $^+NH_2$) ppm.

4-(3-Hydroxyphenyl)-4,5,7,8,9,10-hexahydro-6H-benzo[b] thieno[3,2-f]pyrrolo[1,2-e][1,4]diazepin-5-ium chloride (**10c**, $C_{20}H_{21}ClN_2OS$)

This compound was obtained from 3.4 g **9c** as buff crystals. Yield 2.9 g (78%), mp 260°C. IR(KBr): $\bar{\nu} = 3230$ (OH), 2930, 2840 (CH), 2740, 2580, 1620 ($^+NH_2$), other principal bands: 1550, 1460, 1320, 1140, 815, 790, 700 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.77$ (m, $H_{8,9}$), 2.67 (m, $H_{7,10}$), 4.17 (dd, $J = 14.5$ Hz, H_6), 5.17 (d, $J = 0.9$ Hz, H_4), 5.70 (ddd, $J = 3.6$, 1.8, 0.90 Hz, H_3-pyrrole), 6.15 (dd, $J = 3.6$, 3.0 Hz, H_2-pyrrole), 7.13 (m, H_1-pyrrole + phenyl), 9.70 (s, OH), 10.50 (s, $^+NH_2$) ppm.

Method B:

An equimolar (0.02 mol) mixture of the amine hydrochloride **9** and the appropriate aromatic aldehyde in 50 cm^3 ethanol was heated under reflux for 1 h. The reaction mixture was then concentrated and left to cool. The solid precipitate was filtered off and recrystallized from methanol. All mps and IR spectra of the products obtained by the two methods **A** and **B** were identical. Compound **10a** was obtained in 79% yield, compound **10b** in 83%, and compound **10c** in 82%.

*4-Aryl-4,5,7,8,9,10-hexahydro-6H-benzo[b]thieno[3,2-f] pyrrolo[1,2-e][1,4]diazepines **11a, b***

A suspension of the diazepinium chloride (0.01 mol) **10a**, **10b** in 40 cm^3 6 *N* NaOH solution was heated at reflux for 20 min. After cooling the solid precipitate was filtered off, washed with H_2O, and recrystallized from ethanol.

4-(4-Methylphenyl)-4,5,7,8,9,10-hexahydro-6H-benzo[b] thieno[3,2-f]pyrrolo[1,2-e][1,4]diazepine (**11a**, $C_{21}H_{22}N_2S$)

This compound was obtained from 3.7 g **10a** as yellow crystals, yield 3.2 g (91%), mp 119°C. IR(KBr): $\bar{\nu} = 3320$ (NH), 2920, 2850, 2830 (CH), other principal bands: 1585, 1520, 1460, 1360, 1140, 800, 710 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.85$ (m, $H_{8,9}$), 2.25 (s, CH_3), 2.40 (m, $H_{7,10}$), 3.78 (d, $J = 16.8$ Hz, H_6), 3.10 (s, NH), 4.80 (d, $J = 0.9$ Hz, H_4), 5.15 (ddd, $J = 3.6$, 1.8, 0.9 Hz, H_3-pyrrole), 5.90 (dd, $J = 3.6$, 2.7 Hz, H_2-pyrrole); 6.80 (dd, $J = 2.7$, 1.8 Hz, H_1-pyrrole), 7.03 (d, $J = 8.32$ Hz, phenyl), 7.20 (d, $J = 8.32$ Hz, phenyl) ppm.

4-(4-Methoxyphenyl)-4,5,7,8,9,10-hexahydro-6H-benzo[b] thieno[3,2-f]pyrrolo[1,2-e][1,4]diazepine (**11b**, $C_{21}H_{22}N_2OS$)

This compound was obtained from 3.9 g **10a** as yellow crystals, yield 3.3 g (91%), mp 136°C. IR(KBr): $\bar{\nu} = 3320$, 1620 (NH), 2940, 2840, 2820 (CH), other principal bands: 1600, 1520, 1405, 1325, 1250, 1025, 810, 750 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.88$ (m, $H_{8,9}$), 2.58 (m, $H_{7,10}$), 3.08 (sb, NH), 3.70 (s, OCH_3), 3.78 (2d, $J = 16.8$ Hz, H_6), 4.78 (d, $J = 0.9$ Hz, H_4), 5.16 (ddd, $J = 3.6$, 1.8, 0.9 Hz, H_3-pyrrole), 5.92 (dd, $J = 3.6$, 2.7, H_2-pyrrole), 6.82 (dd, $J = 2.7$, 1.8 Hz, H_1-pyrrole), 6.87 (d, $J = 8.4$ Hz, phenyl), 7.53 (d, $J = 8.4$ Hz, phenyl) ppm.

4,5,7,8,9,10-Hexahydro-6H-benzo[b]thieno[3,2-f] pyrrolo[1,2-a][1,4]diazepin-5-ium-4-spirocyclohexane chloride (**12**, $C_{19}H_{25}N_2SCl$)

A mixture 3.4 g amine hydrochloride **8** (0.02 mole) and 1.96 g cyclohexanone in 50 cm^3 ethanol was heated under reflux for 1 h. The reaction mixture was concentrated and the precipitate formed after cooling was filtered off and recrystallized from ethanol to give colourless crystals, yield 2.9 g (85%), mp 240°C (dec.). IR(KBr): $\bar{\nu} = 2920$, 2850 (CH), 2700, 2650, 2600, 2500 ($^+NH_2$), other principal bands: 1580, 1460, 1330, 1170, 1030, 805, 720 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.30$ (m, $C\underline{H}_2$-cyclohexane), 1.90 (m, $H_{8,9}$ and $2C\underline{H}_2$-cyclohexane), 2.63 (m, $H_{7,10}$ and $2C\underline{H}_2$-cyclohexane), 3.80 (s, H_6), 6.23 (dd, 1H, $J = 3.6$, 3.0 Hz, H_2-pyrrole), 6.41 (dd, $J = 3.6$, 1.8 Hz, H_3-pyrrole), 7.06 (dd, $J = 3.0$, 1.8 Hz, H_1-pyrrole), 9.93 (bs, 2H, $^+NH_2$) ppm.

4,5,7,8,9,10-Hexahydro-6H-benzo[b]thieno[3,2-f] pyrrolo[1,2-a][1,4]diazepin-5-ium-4-spiro-4-methylcyclohexane chloride (**13**, $C_{20}H_{27}N_2SCl$)
This compound was prepared following the same method reported for **12** using 2.24 g 4-methylcyclohexanone. Colourless crystals from ethanol, yield 6.3 g (88%), mp 245°C (dec.). IR(KBr): $\bar{\nu} = 2930$, 2900, 2850 (CH), 2780, 2730, 2680, 2650, 2500 ($^+NH_2$), other principal bands: 1580, 1560, 1460, 1340, 1225,1030, 805, 725 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 0.87$ (d, $J = 7.20$ Hz, CH_3), 1.48 (m, C<u>H</u>-cyclohexane), 1.71 (m, $H_{8,9}$ and 2C<u>H$_2$</u>-cyclohexane), 2.00 (m, 2C<u>H$_2$</u>-cyclohexane), 2.30 (m, $H_{7,10}$), 3.81 (s, H_6), 6.17 (dd, $J = 3.0$, 3.6 Hz, H_2-pyrrole), 6.27 (dd, $J = 3.6$, 1.8, H_3-pyrrole), 7.00 (dd, $J = 3.0$, 1.8 Hz, H_1-pyrrole), 9.66 (sb, $^+NH_2$) ppm.

4,4-Dimethyl-4,5,7,8,9,10-hexahydro-6H-benzo[b] thieno[3,2-f]pyrrolo[1,2-a][1,4]diazepin-5-ium chloride (**14**, $C_{16}H_{21}N_2SCl$)
A suspension of 2.7 g amine hydrochloride **8** (0.01 mol) in 50 cm^3 acetone was heated under reflux for 1 h, during which the suspension got into solution followed by the formation of a colourless precipitate. After cooling, the solid precipitate was filtered off and recrystallized from ethanol to give colourless crystals, yield 2.7 g (90%), mp >260°C. IR(KBr): $\bar{\nu} = 2920$, 2900, 2840 (CH), 2740, 2710, 2680, 2620, 2500 ($^+NH_2$), other principal bands: 1570, 1560, 1380, 1230, 1145, 980, 795, 715 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.55$ (s, $2CH_3$), 1.75 (m, $H_{8,9}$), 2.63 (m, $H_{7,10}$), 3.96 (s, H_6), 6.16 (dd, $J = 3.6$, 3.0 Hz, H_2-pyrrole), 6.23 (dd, $J = 3.6$, 1.8 Hz, H_3-pyrrole), 7.30 (dd, $J = 3.0$, 1.8 Hz, H_1-pyrrole), 10.10 (sb, $^+NH_2$) ppm.

4-Chloromethyl-4-methyl-4,5,7,8,9,10-hexahydro-6H-benzo[b]thieno[3,2-f]pyrrolo[1,2-a][1,4]diazepin-5-ium chloride (**15**, $C_{16}H_{20}N_2SCl_2$)
This compound was obtained following the same procedure described for **12** using 0.94 g monochloroacetone. Recrystallization from ethanol gave colourless crystals, yield 3.2 g (94%), mp >260°C. IR(KBr): $\bar{\nu} = 2920$, 2840 (CH), 2700, 2600, 2550, 2480 ($^+NH_2$), other principal bands: 1575, 1560, 1460, 1345, 1200, 1160, 730 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.66$ (s, CH_3), 1.75 (m, $H_{8,9}$), 2.63 (m, $H_{7,10}$), 3.95 (s, C<u>H$_2$</u>Cl), 4.00 (2d, $J = 16.6$ Hz, H_6), 6.20 (dd, $J = 3.6$, 2.7 Hz, H_2-pyrrole), 6.36 (dd, $J = 3.6$, 1.8 Hz, H_3-pyrrole), 7.10 (dd, $J = 2.7$, 1.8 Hz, H_1-pyrrole), 10.53 (sb, $^+NH_2$) ppm.

4-Methyl-4-piperidinomethyl-4,5,7,8,9,10-hexahydro-6H-benzo[b]thieno[3,2-f]pyrrolo[1,2-a][1,4]diazepine (**16a**, $C_{21}H_{29}N_3S$)
A mixture of 1.7 g chloromethyl derivative **15** (0.005 mole), 0.51 g piperidine (0.006 mol), and 1.1 g Na_2CO_3 (0.01 mol) in 25 cm^3 *DMF* was heated under reflux for 1.5 h. After cooling, the reaction mixture was poured into cold H_2O and extracted with ether. The ethereal layer was washed with H_2O dried ($MgSO_4$), treated with charcoal, and filtered. The solvent was eliminated under reduced pressure and the residual oil was distilled under vacuum giving a yellow oil. Yield 1.4 g (79%), $bp_{0.05\,mmHg}$ 85°C. IR(KBr): $\bar{\nu} = 3315$ (NH), 2960, 2920, 2860 (CH), other principal bands: 1590, 1510, 1440, 1330, 1200, 950, 720 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.36$ (s, C<u>H$_3$</u>), 1.41 (m, C<u>H$_2$</u>-piperidine), 1.76 (m, $H_{8,9}$), 2.63 (m, $H_{7,10}$), 2.90 (m, 2C<u>H$_2$</u>-piperidine), 3.08 (m, C<u>H$_2$</u>-N + 2 C<u>H$_2$</u>-piperidine), 3.56 (d, $J = 16.6$ Hz, H_6), 3.90 (bs, NH), 6.03 (m, $H_{2,3}$-pyrrole), 6.76 (m, H_1-pyrrole) ppm.

4-Methyl-4-morpholinomethyl-4,5,7,8,9,10-hexahydro-6H-benzo[b]thieno[3,2-f]pyrrolo[1,2-a][1,4]diazepine (**16b**, $C_{20}H_{27}N_3OS$)
A mixture of 1.7 g **15** (0.005 mol), 0.52 g morpholine (0.006 mol), and 1.1 g Na_2CO_3 (0.01 mol) in 25 cm^3 *DMF* was heated under reflux for 1.5 h. After cooling, the reaction mixture was poured into cold H_2O. The solid precipitate was filtered off and recrystallized from ether-petroleum ether mixture to give yellow crystals. Yield 1.3 g (73%), mp 104°C. IR(KBr): $\bar{\nu} = 3240$ (NH), 3080, 2930, 2840, 2800 (CH), other principal bands: 1590, 1510, 1450, 1300, 950, 720 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.13$ (s, CH_3), 1.76 (m, $H_{8,9}$), 2.63 (m, $H_{7,10}$), 2.68 (m, 2C<u>H$_2$</u>-morpholine), 3.13 (m, C<u>H$_2$</u>-N + 2C<u>H$_2$</u>-morpholine), 3.56 (d, $J = 16.6$ Hz, H_6), 3.95 (bs, NH), 5.96 (dd, $J = 3.6$, 3.0 Hz, H_2-pyrrole), 6.03 (dd, $J = 3.6$, 1.8 Hz, H_3-pyrrole), 6.66 (dd, $J = 3.0$, 1.8 Hz, H_1-pyrrole) ppm.

4-Methyl-4-(3-(azepin-1-yl)propylaminomethyl)-4,5,7,8,9,10-hexahydro-6H-benzo[b]thieno[3,2-f] pyrrolo[1,2-a][1,4]diazepine (**16c**, $C_{25}H_{38}N_4S$)
This compound was prepared using 1.7 g **15** (0.005 mol) and 0.52 g 1-(3-aminopropyl)azepane (0.006 mol) following the same procedure as that of **16a**. Pale yellow oil, yield 1.8 g (86%), $bp_{0.05\,mmHg}$ 100°C. IR(KBr): $\bar{\nu} = 3320$, 3250 (NH), 2980, 2840, 2910, 2810 (CH), other principal bands: 1575, 1510, 1440, 1320, 1150, 710 cm^{-1}; ^1H NMR (*DMSO*-d_6, 200 MHz): $\delta = 1.26$ (s, CH_3), 1.44 (m, $3CH_2$), 1.71 (m, $H_{8,9} + 2CH_2$), 2.40 (m, $H_{7,10} + 3CH_2$), 2.80 (m, $3CH_2$), 3.70 (d, $J = 16.6$ Hz, H_6), 3.02 (bs, NH), 4.05 (bs, NH), 5.85 (dd, $J = 3.6$, 3.0 Hz, H_2-pyrrole), 5.96 (dd, $J = 3.6$, 1.8 Hz, H_3-pyrrole), 6.56 (dd, $J = 3.0$, 1.8 Hz, H_1-pyrrole) ppm.

Acknowledgements

The authors would like to thank Professor *E. De Clercq*, Rega Institute for Medical Research, Leuven, Belgium and Professor *P. A. Borea*, Faculty of Pharmacy, Ferrara, Italy for the biological evaluation.

References

[1] a) Thurston DE (1993) Mol Aspects Anticancer Drug-DNA Interact p 54; b) Thurston DE, Bose S (1994) Chem Rev **2**: 433
[2] Rault S, Enguehard C, Lancelot J-Ch, Robba M, Atassi G, Pierre A, Caignard D-H, Renard P (2000) Jpn Kokai Tokkyo Koho JP 2000044572, p 12

[3] Lisowski V, Fabis F, Pierre A, Caignard D-H, Renard P, Rault S (2002) J Enzyme Inhib Med Chem **17**: 403
[4] Jolivet-Fouchet S, Fabis F, Rault S (1998) Tetrahedron Lett **39**: 819
[5] Boulouard M, Dallemagne P, Rault S (1997) J Heterocycl Chem **34**: 1219
[6] Mamouni A, Netchitailo P, Daich A, Decroix B (1996) Phosph Sulf Silic Rel Elem **119**: 169
[7] Boulouard M, Dallemagne P, Alsaidi A, Rault S (1996) J Heterocycl Chem **33**: 1743
[8] Boulouard M, Rault S, Dallemagne P, Alsaidi A, Robba M (1996) J Heterocycl Chem **33**: 87
[9] Foloppe M-P, Sonnet P, Bureau I, Rault S, Robba M (1996) J Heterocycl Chem **33**: 75
[10] Daich A, Ohier P, Decroix B (1995) J Heterocycl Chem **32**: 1731
[11] Foloppe M-P, Sonnet P, Rault S, Robba M (1995) Tetrahedron Lett **36**: 3127
[12] Boulouard M, Rault S, Dallemagne P, Robba M (1995) Heterocycles **41**: 515
[13] Vega S, Gil MS, Darias V, Sanchez Mateo CC, Exposito MA, Tello ML, Albertos LM (1994) Arch Pharm **327**: 721
[14] Rault I, Rault S, Robba M (1994) Heterocycles **38**: 811
[15] Daich A, Morel J, Decroix B (1994) J Heterocycl Chem **31**: 341
[16] Rault I, Foloppe M-P, Rault S, Robba M (1993) Heterocycles **36**: 2059
[17] Daich A, Morel J, Decroix B (1993) J Heterocycl Chem **30**: 675
[18] Rault S, Boulouard M, Robba M, Guardiola B, Devissaguet M (1991) Eur Pat Appl EP 449728, p 66
[19] Rault S, Boulouard M, Dallemagne P, Robba M, Guardiola B, Devissaguet M (1991) Eur Pat Appl EP 446133, p 102
[20] Fujimori K, Hara K, Ito K, Shikayama Y, Mori T, Kadominami T (1977) Jpn Kokai Tokkyo Koho JP 52100496, p 11
[21] Rault S, Cugnon de Sevricourt M, Robba M (1979) Heterocycles **12**: 1009
[22] Rault S, Cugnon de Sevricourt M, Robba M, Nguyen HD (1979) Tetrahedron Lett 643
[23] Rault S, Cugnon de Sevricourt M, Robba M (1978) C R Acad Sci C Sci Chim **287**: 117
[24] Gewald K, Schimke E, Bottcher H (1966) Chem Ber **99**: 94
[25] Gonzalez SG (1989) An Real Acad Farm **55**: 339