Pyrrolothieno[1,4]diazepines: Synthesis of Alkoxy Derivatives

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Reactivity of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile and of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarboxamide was evaluated against various alkoxides. The synthetic pathways involved in these reactions which led to new 4- and 6-alkoxypyrrolothieno[1,4]diazepines are described.

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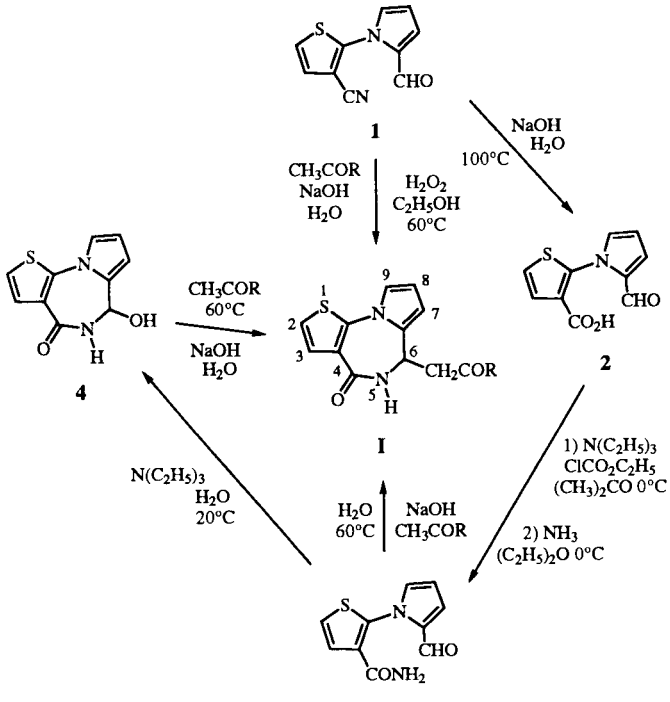
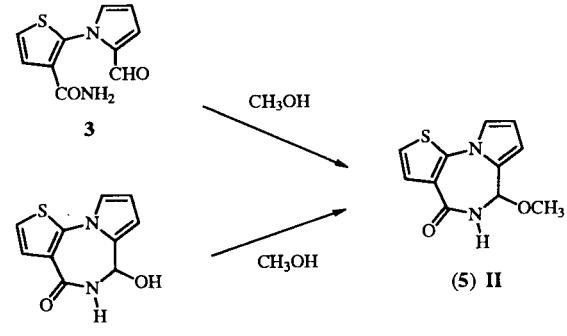
We recently described the reaction pathway involved in the synthesis of 6-aryl and 6-alkyloxomethylpyrrolothieno[1,4]diazepines **I** obtained by treatment either of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile **1**, or 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarboxamide **3** or 5,6-dihydro-6-hydroxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepin-4-one **4** with various methyl ketones in alkaline medium (Scheme 1) [1].

Scheme 1



In order to extend this cyclization reaction to the synthesis of new 6-alkoxypyrrolothienodiazepines **II** by replacing methyl ketones with alkoxides, we reconsidered the preliminary results described by Rault [2] who had postulated that treatment of cyano compound **1** with primary alcohols in alkaline medium gave **II** supposing that the mechanism of cyclization should be the same as with

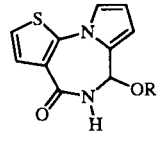
Scheme 2



methyl ketones. Surprisingly, during the course of our study, we found that the reaction products obtained starting from **1** or **3** in the presence of methanol were not the same contrary to that observed with methyl ketones. So, it was true to say that treatment of **3** with refluxing methanol gave the 6-methoxy-4-oxopyrrolothienodiazepine **5** of type **II** analogous to **I** (Scheme 2).

This structure was supported by the following analysis of ir and nmr spectra. The ir spectrum of **5** exhibited effectively a strong carbonyl absorption at 1640 cm^{-1} and NH lactam absorptions between 2900 and 3300 cm^{-1}. The ^1H-nmr spectrum was similar to those of compounds **I** with particularly an H6 signal at 5.3 ppm affected by a

Scheme 3



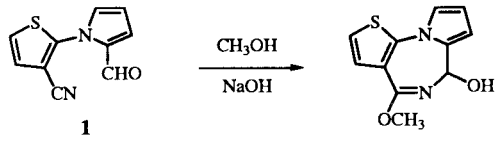
II

R =	$-CH_3$	**5**	R =	$-CH_2CH(CH_3)_2$	**11**
	$-CH_2CH_3$	**6**		$-CH_2$-cyclopropyl	**12**
	$-CH_2CH_2CH_3$	**7**		cyclopentyl	**13**
	$-CH(CH_3)_2$	**8**		$-CH_2-CH=CH_2$	**14**
	$-CH_2CH_2CH_2CH_3$	**9**		$-CH_2CH_2OCH_3$	**15**
	$-CH(CH_3)CH_2CH_3$	**10**		$-CH_2$-phenyl	**16**

deuterable coupling constant $J_{H6\,NH}$ of 6.3 Hz. This structure was also confirmed by the reaction of 6-hydroxy-4-oxopyrrolothienodiazepine **4** with refluxing methanol which led, so well as **3**, to **5** under the same conditions. Then application of this pathway to various alcohols gave the 6-alkoxy derivatives **5-16** (Scheme 3).

On the other hand, the structural elucidation of product **17** obtained by treatment of cyano compound **1** with boiling methanol in alkaline medium was carried out by studying its analytical data and chemical properties. Thanks to this, we established a new type **III** of pyrrolothienodiazepines (Scheme 4).

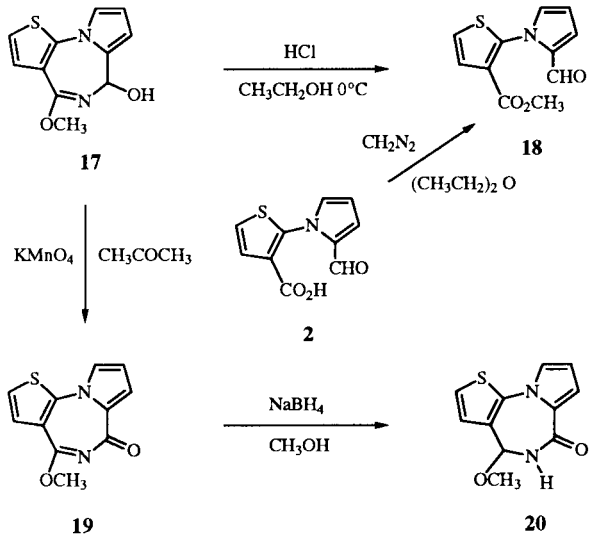
Scheme 4



1 (17) **III**

The ir spectrum of **17** exhibited a weak absorption at 1640 cm^{-1} corresponding not to a carbonyl absorption but to an imine absorption and a broad band centered at 3380 cm^{-1} due to an OH absorption. The ^{13}C-nmr spectrum of **17** showed a signal at 154 ppm corresponding to C4 attached to the imino group as a part of the ring while the spectrum of **5** showed a carbonyl signal at 163 ppm. However, the ^1H-nmr spectra of **5** and **17** were very similar, chemical shifts of the thiophene and the pyrrole protons were respectively the same and further the H6 proton of **17** gave a doublet at 5.6 ppm showing a deuterable coupling constant with OH of 6.1 Hz while the H6 signal of **5** was also a doublet centered at 5.3 ppm with a deuterable coupling constant of 6.3 Hz with the NH group. Finally the structure of **17** was clearly established by two discriminatory chemical reactions (Scheme 5).

Scheme 5

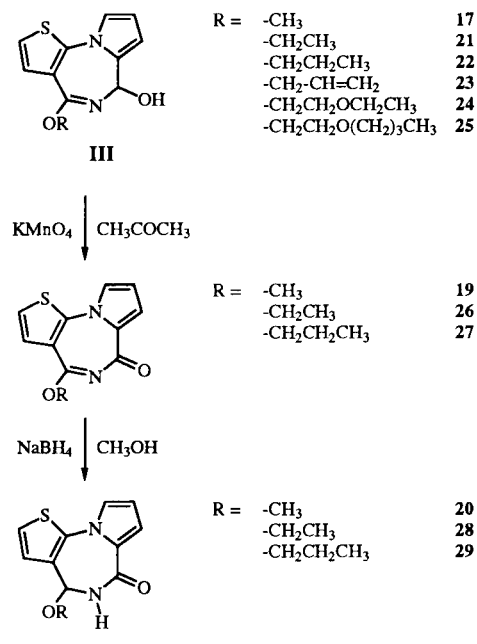


17 **18** **2** **19** **20**

Treatment of **17** with aqueous hydrochloric acid under mild conditions gave the formyl ester **18** while **5** was unaffected by this reaction. The unequivocal synthesis of **18** was achieved by treating the carboxylic acid **2** with diazomethane in ether. Moreover oxidation of **17** with potassium permanganate in acetone at room temperature gave the new 4-methoxy-6-oxopyrrolothienodiazepine **19** while **5** produced no reaction.

A carbonyl absorption at 1630 cm^{-1} in the ir spectrum of **19** and the large deshielding of pyrrolic protons in its ^1H-nmr spectrum was in favor of an oxidation of the hydroxy group at the 6 position. Furthermore, reduction of the imine double bond of **19** with sodium borohydride gave the methoxydiazepine **20** whose ^1H-nmr spectrum had presented a signal at 5.25 ppm corresponding to H4 with a deuterable coupling constant of 5.8 Hz with the NH. These pathways were applied to various primary alcohols to give compounds **17**, **19-29** (Scheme 6).

Scheme 6



Starting from **1**, it is therefore possible by treatment with alcohols in alkaline medium to obtain two series of pyrrolothienodiazepines: lactams **II** and iminoethers **III**. Concerning **III**, due to the experimental conditions (aqueous alcoholic sodium hydroxide solution, temperature above 40°) the attack of the alkoxide formed in the reaction mixture precedes the hydrolysis of the nitrile group. Starting from the carboxamide **3**, the reaction pathway is similar to that for the methyl ketones and leads to the lactams **II**.

However, contrary to the synthesis of **I**, the presence of sodium hydroxide is not necessary to the formation of **II**.

EXPERIMENTAL

General Methods.

Melting points were determined on a Köfler block and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. The 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.

6-Alkoxy-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-4-ones **5-16**. General Procedures.

Method A.

A solution of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarboxamide **3** (1 g, 0.0045 mole) in the appropriate alcohol (50 ml) was refluxed for 1 hour. The solvent was then removed under reduced pressure and the solid residue was recrystallized to give **5-8**.

Method B.

The appropriate alcohol (0.0050 mole) was added to a solution of 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarboxamide **3** (1 g, 0.0045 mole) in acetonitrile (50 ml). The reaction mixture was refluxed for 90 minutes and then evaporated to dryness under reduced pressure. The oily residue was taken up in water (100 ml) and the solid which appeared was filtered off, dried and recrystallized to give **9-16**.

5,6-Dihydro-6-methoxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-4-one **5**.

This compound was obtained by method A (alcohol: methanol) as colorless crystals (85%), mp 186° (ether); ir (potassium bromide): 3260, 3180 (NH), 1635 (CO); ^{1}H-nmr (DMSO-d_6): 9.12 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.37 (dd, $J_{H7\ H6}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 6.30 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 5.28 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.14 (s, CH_3); ^{13}C nmr (DMSO-d_6): 163.2 (C4), 142.8 (C9b), 130.9 (C3a), 128.6 (C3), 123.0 (C6a), 121.8 (C2), 117.5 (C9), 110.9 (C8), 110.1 (C7), 77.5 (C6), 54.3 (CH_3); ms: (m/z, %) 234 (M^+, 5), 203 (42), 175 (21).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.95; S, 13.68. Found: C, 56.65; H, 4.37; N, 11.96; S, 13.87.

5,6-Dihydro-6-ethoxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-4-one **6**.

This compound was obtained by method A (alcohol: ethanol) as colorless crystals (80%), mp 140° (acetone); ir (potassium bromide): 3260, 3180 (NH), 1640 (CO); ^{1}H-nmr (deuteriochloroform): 7.8 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.39 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.01 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.86 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 6.30 (m, H8 and H7), 5.44 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.46 (q, J = 6.3 Hz, CH_2) 1.08 (t, J = 6.3 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 57.98; H, 4.66; N, 11.55; S, 12.61.

5,6-Dihydro-6-propoxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-4-one **7**.

This compound was obtained by method A (alcohol: 1-propanol) as yellow crystals (85%), mp 160° (2-propanol); ir (potassium bromide): 3260, 3160 (NH), 1640 (CO); ^{1}H-nmr (deuteriochloroform): 7.38 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.07 (br s, NH), 7.02 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.86 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 6.27 (m, H7 and H8), 5.41 (d, J = 6.3 Hz, H6), 3.48 (t, J = 6.3 Hz, CH_2), 1.48 (m, CH_2), 0.72 (t, J = 6.3 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.37; H, 5.23; N, 10.39; S, 12.43.

5,6-Dihydro-6-methylethoxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepin-4-one **8**.

This compound was obtained by method A (alcohol: 2-propanol) as colorless crystals (93%), mp 165° (2-propanol); ir (potassium bromide): 3270, 3180 (NH) 1645 (CO); ^{1}H-nmr (deuteriochloroform): 7.38 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.10 (m, H9 and NH), 6.86 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 6.29 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 6.25 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.52 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.79 (m, CH), 1.71 (d, J = 6.3 Hz, 2 CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.37; N, 10.67; S, 12.22. Found: C, 59.71; H, 5.36; N, 10.84; S, 12.18.

6-Butoxy-5,6-dihydro-6-ethoxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepin-4-one **9**.

This compound was obtained by method B (alcohol: 1-butanol) as colorless crystals (78%), mp 117° (2-propanol); ir (potassium bromide): 3290, 3190 (NH), 1650 (CO); ^{1}H-nmr (DMSO-d_6): 9.10 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.34 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 6.29 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.37 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.30 (m, CH_2), 1.32 (m, CH_2), 1.05 (m, CH_2), 0.72 (t, J = 6.3 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; S, 11.60. Found: C, 60.69; H, 5.79; N, 10.25; S, 11.58.

5,6-Dihydro-6-(1-methylpropoxy-4*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepin-4-one **10**.

This compound was obtained by method B (alcohol: 2-butanol) as colorless crystals (82%), mp 150° (2-propanol); ir (potassium bromide): 3290, 3200 (NH), 1645 (CO); ^{1}H-nmr (DMSO-d_6): 9.03 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.30 (m, H7 and H8), 5.45 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.54 (m, CH), 1.23 (m, CH_2), 0.97 (d, J = 6.3 Hz, CH_3), 0.54 (t, J = 6.3 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; S, 11.60. Found: C, 60.90; H, 5.78; N, 10.26; S, 11.78.

5,6-Dihydro-6-(2-methylpropoxy-4*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepin-4-one **11**.

This compound was obtained by method B (alcohol: 2-methyl-1-propanol) as colorless crystals (74%), mp 124° (2-methyl-1-propanol); ir (potassium bromide): 3250 (NH), 1645 (CO); ^{1}H-nmr (DMSO-d_6): 9.12 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.34 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 6.29 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.36 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.11 (m, CH_2), 1.60 (m, CH), 0.63 (d, J = 6.3 Hz, 2 CH_3).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; S, 11.60. Found: C, 60.99; H, 5.77; N, 10.19; S, 11.63.

6-Cyclopropanemethoxy-5,6-Dihydro-4*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepin-4-one **12**.

This compound was obtained by method B (alcohol: cyclopropanemethanol) as colorless crystals (72%), mp 143° (2-propanol); ir (potassium bromide): 3270, 3190, (NH), 1650 (CO); ^{1}H-nmr (DMSO-d_6): 9.07 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.34 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 6.28 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.41 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.17 (d, J = 7.3 Hz, CH_2), 0.83 (m, CH), 0.33 (d, J = 8.3 Hz, 2 CH_2).

Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.38; H, 5.02; N, 10.25; S, 11.70.

6-Cyclopentyloxy-5,6-Dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepin-4-one **13**.

This compound was obtained by method B (alcohol: cyclopentanol) as orange crystals (75%), mp 158° (ether); ir (potassium bromide): 3270, 3190 (NH), 1645 (CO); ^{1}H-nmr (DMSO-d_6): 9.03 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.34 (dd, $J_{H8\ H7}$ = 3.5 Hz, $J_{H8\ H9}$ = 3.5 Hz, H8), 6.28 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.41 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 4.00 (m, CH), 1.5 (m, 4 CH_2).

Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71; S, 11.12. Found: 62.39; H, 5.42; N, 9.83; S, 11.07.

6-(1-Allyloxy)-5,6-Dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-4-one **14**.

This compound was obtained by method B (alcohol: 2-propen-1-ol) as colorless crystals (74%), mp 170° (2-propanol); ir (potassium bromide): 3270, 3190 (NH), 1650 (CO); ^{1}H-nmr (DMSO-d_6): 9.17 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.35 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 6.30 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.71 (m, CH), 5.42 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 5.08 (m, CH_2), 3.94 (m, CH_2).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 60.02; H, 4.71; N, 10.69; S, 12.29.

5,6-Dihydro-6-(2-methoxyethoxy)-4*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepin-4-one **15**.

This compound was obtained by method B (alcohol: 2-methoxyethanol) as colorless crystals (85%), mp 130° (2-methoxyethanol); ir (potassium bromide): 3270, 3190 (NH), 1645 (CO); ^{1}H-nmr (DMSO-d_6): 9.10 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.20 (m, H2, H3 and H9), 6.36 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 6.30 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.42 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 3.40 (m, 2 CH_2), 2.08 (s, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.07; S, 11.52. Found: C, 56.11; H, 5.02; N, 10.19; S, 11.55.

6-Benzyloxy-5,6-Dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepin-4-one **16**.

This compound was obtained by method B (alcohol: benzylalcohol) as colorless crystals (86%), mp 150° (ether); ir (potassium bromide): 3260, 3190 (NH), 1635 (CO); ^{1}H-nmr (deuteriochloroform): 7.53 (d, $J_{NH\ H6}$ = 6.3 Hz, NH), 7.41 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.20 (m, C_6H_5), 7.03 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.88 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 6.29 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 6.23 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 5.44 (d, $J_{H6\ NH}$ = 6.3 Hz, H6), 4.53 (dd, J = 5.3 Hz, CH_2).

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.02; S, 10.33. Found: C, 65.51; H, 4.37; N, 9.22; S, 10.45.

2-(2-Formyl-1*H*-pyrrol-1-yl)-3-carbomethoxythiophene **18**.

2-(2-Formyl-1*H*-pyrrol-1-yl)thiophene-3-carboxylic acid **2** (3 g, 0.014 mole) was added portionwise to an ice-cooled saturated solution of diazomethane in ether (60 ml). The reaction mixture was stirred so that the temperature reached 10° and then the solvent was removed under reduced pressure to give **18**. Colorless crystals were obtained (94%), mp 55° (ether/acetone); ir (potassium bromide): 1710 and 1660 (CO); ^{1}H-nmr (DMSO-d_6): 9.57 (s, CHO), 7.70 (d, $J_{H5\ H4}$ = 5.9 Hz, H5), 7.50 (d, $J_{H4\ H5}$ = 5.9 Hz, H4), 7.43 (dd, $J_{H5'\ H4'}$ = 2.9 Hz, $J_{H5'\ H3'}$ = 1.5 Hz, H5'), 7.30 (dd, $J_{H3'\ H4'}$ = 3.4 Hz, $J_{H3'\ H5'}$ = 1.5 Hz, H3'), 6.53 (dd, $J_{H4'\ H3'}$ = 3.4 Hz, $J_{H4'\ H5'}$ = 2.9 Hz, H4'), 3.65 (s, CH_3).

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.17; H, 3.86; N, 5.96; S, 13.61. Found: C, 56.32; H, 3.96; N, 6.00; S, 13.45.

4-Alkoxy-6-hydroxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepines **17, 21**. General Procedure.

A mixture of aqueous sodium hydroxide solution (20%, 50 ml), the appropriate alcohol (100 ml) and 2-(2-formyl-1*H*-pyrrol-1-yl)-3-thiophenecarbonitrile **1** (10 g, 0.049 mole) was heated gradually so that the temperature reached 50° in 2 hours. Water (500 ml) was added to the reaction mixture from which the compound was precipitated. The solid was filtered, washed with water (100 ml), dried and recrystallized to give **17, 21-25**.

6-Hydroxy-4-methoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepine **17**.

This compound was obtained as colorless crystals (alcohol: methanol) in 77% yield, mp 200° (acetone); ir (potassium bromide): 3380 (OH), 1640 (CN); ^{1}H-nmr (DMSO-d_6): 7.30 (d, $J_{H2\ H3}$ = 5.6 Hz, H2), 7.14 (d, $J_{H3\ H2}$ = 5.6 Hz, H3), 7.10 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.34 (m, H8 and H7), 6.18 (br s, OH), 5.60 (d, $J_{H6\ OH}$ = 6.10 Hz, H6), 3.70 (s, CH_3); ^{13}C-nmr (DMSO-d_6): 154.5 (C4), 144.4 (C9b), 136.7 (C3a), 125.7 (C2), 120.0 (C6a), 119.8 (C3 and C9), 111.5 (C8), 105.7 (C7), 77.0 (C6), 53.0 (CH_3); ms: (m/z, %) 234 (M^+, 53), 217 (31).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.95; S, 13.68. Found: C, 56.39; H, 4.39; N, 12.00; S, 13.83.

4-Ethoxy-6-hydroxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepine **21**.

This compound was obtained (alcohol: ethanol) as colorless crystals (67%), mp 140° (ether); ir (potassium bromide): 3400 (OH), 1620 (CN); ^{1}H-nmr (DMSO-d_6): 7.31 (d, $J_{H2\ H3}$ = 5.6 Hz, H2), 7.14 (d, $J_{H3\ H2}$ = 5.6 Hz, H3), 7.11 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.20 (m, H7, H8 and OH), 5.60 (d, $J_{H6\ OH}$ = 6.1 Hz, H6), 4.16 (q, J = 7 Hz, CH_2), 1.10 (t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28; S, 12.91. Found: C, 58.32; H, 5.16; N, 11.02; S, 12.63.

6-Hydroxy-4-propoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepine **22**.

This compound was obtained (alcohol: 1-propanol) as colorless crystals (62%), mp 120° (ether); ir (potassium bromide): 3400-3300 (OH) 1630 (CN); ^{1}H-nmr (DMSO-d_6): 7.31 (d, $J_{H2\ H3}$ = 5.6 Hz, H2), 7.15 (d, $J_{H3\ H2}$ = 5.6 Hz, H3), 7.10 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.30 (m, H7, H8 and OH), 5.66 (d, $J_{H6\ NH}$ = 6.1 Hz, H6), 4.08 (t, J = 7 Hz, CH_2), 1.63 (m, CH_2), 0.95 (t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.50; H, 5.30; N, 10.72; S, 12.21.

4-(1-Allyloxy)-6-hydroxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepine **23**.

This compound was obtained (alcohol: 2-propen-1-ol) as colorless crystals (64%), mp 122° (ether); ir (potassium bromide): 3360 (OH), 1630 (CN), 1635 (CO); ^{1}H-nmr (DMSO-d_6): 7.33 (d, $J_{H2\ H3}$ = 5.6 Hz, H2), 7.16 (d, $J_{H3\ H2}$ = 5.6 Hz, H3), 7.10 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.20 (m, H7, H8 and OH), 5.93 (m, CH), 5.63 (d, $J_{H6\ OH}$ = 6.1 Hz, H6), 4.63 (m, CH_2), 5.21 (m, CH_2).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.75; S, 12.32. Found: C, 60.15; H, 4.68; N, 10.73; S, 12.20.

4-(2-Ethoxyethoxy)-6-hydroxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepine **24**.

This compound was obtained (alcohol: 2-ethoxyethanol) as colorless crystals (71%), mp 138° (ether); ir (potassium bromide): 3350 (OH), 1630 (CN); ^{1}H-nmr (DMSO-d_6): 7.33 (d, $J_{H2\ H3}$ = 5.6 Hz, H2), 7.13 (d, $J_{H3\ H2}$ = 5.6 Hz, H3), 7.08 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.30 (m, H7, H8 and OH), 5.63 (d, $J_{H6\ OH}$ = 6.1 Hz, H6), 4.13 and 3.50 (m, 3 CH_2), 1.11 (t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.53; H, 5.52; N, 9.59; S, 10.95. Found: C, 57.44; H, 5.50; N, 9.69; S, 10.88.

4-(2-Butoxyethoxy)-6-hydroxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepine **25**.

This compound was obtained (alcohol: 2-butoxy ethanol) as colorless crystals (75%), mp 81° (ether); ir (potassium bromide): 3350, 3190 (OH), 1620 (CN); ^{1}H-nmr (DMSO-d_6): 7.35 (d, $J_{H2\ H3}$ = 5.6 Hz, H2), 7.11 (d, $J_{H3\ H2}$ = 5.6 Hz, H3), 7.08 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.30 (m, H7, H8 and OH), 5.63 (d, $J_{H6\ OH}$ = 6.1 Hz, H6), 4.20 and 3.50 (5 CH_2), 1.0 (t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{16}H_{20}N_2O_3S$: C, 59.99; H, 6.29; N, 8.75; S, 10.06. Found: C, 59.95; H, 6.23; N, 8.66; S, 9.93.

4-Alkoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-6-ones **19, 26, 27**. General Procedure.

A solution of 4-alkoxy-6-hydroxy-6*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepine **17**, **21** or **22** (0.04 mole) and potassium permanganate (20 g, 0.120 mole) in acetone (500 ml) was stirred at room temperature for 4 hours. The insoluble material was filtered and the filtrate was evaporated to dryness under reduced pressure to give a solid which was recrystallized to give **19**, **26** or **27**.

4-Methoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-6-one **19**.

The starting material was 6-hydroxy-4-methoxy-6*H*-pyrrolo-[1,2-*a*]thieno[3,2-*f*][1,4]diazepine **17**; colorless crystals (50%) had mp 154° (ether); ir (potassium bromide): 1630 (CO), 1600 (CN); ^{1}H-nmr (DMSO-d_6): 7.70 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 7.43 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.30 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 7.08 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 6.63 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 3.93 (s, CH_3).

Anal. Calcd. for $C_{11}H_8N_2O_2S$: C, 56.89; H, 3.47; N, 12.06; S, 13.80. Found: C, 57.01; H, 3.31; N, 12.02; S, 13.61.

4-Ethoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-6-one **26**.

The starting material was 4-ethoxy-6-hydroxy-6*H*-pyrrolo-[1,2-*a*]thieno[3,2-*f*][1,4]diazepine **21**; colorless crystals (55%) had mp 188° (ether); ir (potassium bromide): 1635 (CO), 1590 (CN); ^{1}H-nmr (DMSO-d_6): 7.65 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 7.40 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.30 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 7.01 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 6.60 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 4.35 (q, J = 7 Hz, CH_2), 1.34 (t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.48; H, 4.04; N, 11.29; S, 13.23.

4-Propoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-6-one **27**.

The starting material was 6-hydroxy-4-propoxy-6*H*-pyrrolo-[1,2-*a*]thieno[3,2-*f*][1,4]diazepine **22**; colorless crystals (55%) had mp 130° (ether); ir (potassium bromide): 1640 (CO), 1600 (CN); ^{1}H-nmr (DMSO-d_6): 7.68 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 7.45 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.31 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 7.08 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 6.65 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 4.31 (t, J = 6.8 Hz, CH_2), 1.78 (m, CH_2), 1.00 (t, J = 6.8 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 59.84; H, 4.55; N, 10.75; S, 12.45.

4-Alkoxy-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-6-ones **20, 28, 29**. General Procedure.

Sodium borohydride (1.25 g, 0.0320 mole) was added portion-wise to a solution of 4-alkoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-6-one **19**, **26** or **27** (0.008 mole) in methanol (200 ml). The reaction mixture was stirred at room temperature for 3 hours and the solvent was then removed under reduced pressure. The solid residue was triturated in water (50 ml), filtered, dried and recrystallized to give **20, 28** or **29**.

4-Methoxy-5,6-dihydro-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-6-one **20**.

The starting material was 4-methoxy-6*H*-pyrrolo[1,2-*a*]-thieno[3,2-*f*][1,4]diazepin-6-one **19**; colorless crystals (74%) had mp 205° (ether); ir (potassium bromide): 3260 (NH), 1650 (CO); ^{1}H-nmr (deuteriochloroform): 7.30 (br s, NH), 7.26 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.17 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 6.93 (m, H3 and H7), 6.40 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 5.25 (d, $J_{H4\ NH}$ = 5.8 Hz, H4), 3.35 (s, CH_3).

Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.30; N, 11.96; S, 13.68. Found: C, 56.39; H, 4.21; N, 11.99; S, 13.52.

5,6-Dihydro-4-ethoxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-6-one **28**.

The starting material was 4-ethoxy-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepin-6-one **26**; colorless crystals (70%) had mp 170° (ether); ir (potassium bromide): 3260 (NH), 1640 (CO); ^{1}H-nmr (DMSO-d_6): 9.05 (d, $J_{NH\ H4}$ = 6.3 Hz, NH), 7.37 (dd, $J_{H9\ H8}$ = 3.5 Hz, $J_{H9\ H7}$ = 1.5 Hz, H9), 7.25 (d, $J_{H2\ H3}$ = 5.8 Hz, H2), 7.11 (d, $J_{H3\ H2}$ = 5.8 Hz, H3), 6.97 (dd, $J_{H7\ H8}$ = 3.5 Hz, $J_{H7\ H9}$ = 1.5 Hz, H7), 6.37 (dd, $J_{H8\ H9}$ = 3.5 Hz, $J_{H8\ H7}$ = 3.5 Hz, H8), 5.32 (d, $J_{H4\ NH}$ = 6.3 Hz, H4), 3.48 (q, J = 7 Hz, CH_2), 0.98 (t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 57.88; H, 4.74; N, 11.35; S, 12.77.

5,6-Dihydro-4-propoxy-4*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepin-6-one **29**.

The starting material was 4-propoxy-6*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepin-6-one **27**; colorless crystals (54%) had mp 160° (ether); ir (potassium bromide): 3295 (NH), 1650 (CO); ^{1}H-nmr (DMSO-d_6): 9.03 (d, $J_{NH\ H4}$ = 6.3 Hz, NH), 7.36 (dd,

$J_{H9\,H8}$ = 3.5 Hz, $J_{H9\,H7}$ = 1.5 Hz, H9), 7.25 (d, $J_{H2\,H3}$ = 5.8 Hz, H2), 7.11 (d, $J_{H3\,H2}$ = 5.8 Hz, H3), 6.97 (dd, $J_{H7\,H8}$ = 3.5 Hz, $J_{H7\,H9}$ = 1.5 Hz, H7), 6.35 (dd, $J_{H8\,H9}$ = 3.5 Hz, $J_{H8\,H7}$ = 3.5 Hz, H8), 5.32 (d, $J_{H4\,NH}$ = 6.3 Hz, H4), 3.39 (t, J = 7 Hz, CH_2), 1.36 (m, CH_2), 0.65 (t, J = 7 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.27; H, 5.25; N, 10.67; S, 12.06.

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