New Access to 4-Phenyl-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*]-[1,4]diazepines

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Pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepines were obtained in an original one step synthesis by treatment of imines **1** with paraformaldehyde in refluxing ethanol. The intermediate Mannich bases were also converted into the thienooxadiazocines **12** and the diazepine *N*-oxide **13**.

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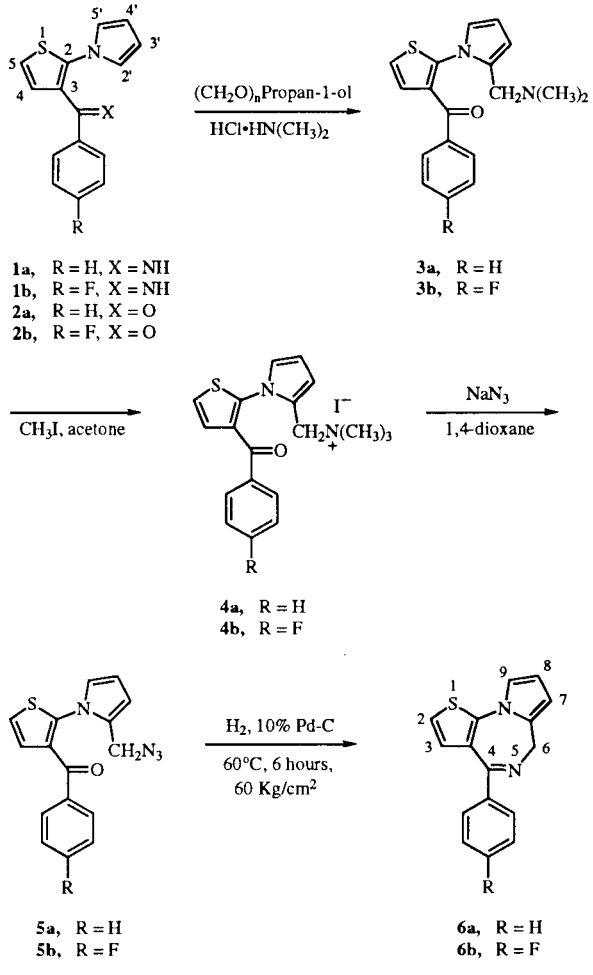
We recently described [1] the original and quick access to pyrrolobenzodiazepines concerning the synthesis of new compounds in this series [2-5].

These compounds have been synthesized in 5 steps starting from 3-phenyl-[2-(pyrrol-1-yl)thienyl]methylenimines **1a** and **1b** [3] (Scheme 1). These imines were converted easily into ketones **2a** and **2b** under acidic conditions [3]. Treatment with paraformaldehyde and dimethylamine hydrochloride in refluxing propan-1-ol, *via* the Mannich reaction gave the bases **3a** and **3b** in 80% yield. The quaternary salts **4a** and **4b** were respectively obtained in good yield by stirring the Mannich bases **3a** and **3b** with an excess (3 equivalents) of methyl iodide in acetone at room temperature. The introduction of the azido group was accomplished by displacement of trimethylamine from the quaternary salts **4a** and **4b** using sodium azide and a catalytic amount of dibenzo-18-crown-6 in refluxing 1,4-dioxane to give **5a** and **5b** in 70% yield. Reduction of these azido compounds with hydrogen in presence of 10% palladium-charcoal did not lead to the expected aminomethyl derivatives but led directly to diazepines **6a** and **6b** in 55-60% yield *via* reduction and subsequent cyclization.

To shorten this sequence and to increase the overall yield we wanted to introduce directly the missing carbon of **1** to afford the diazepine ring. We studied Mannich reactions with imines **1a** and **1b** (Scheme 2). Treatment

Scheme 1



1a, R = H, X = NH
1b, R = F, X = NH
2a, R = H, X = O
2b, R = F, X = O

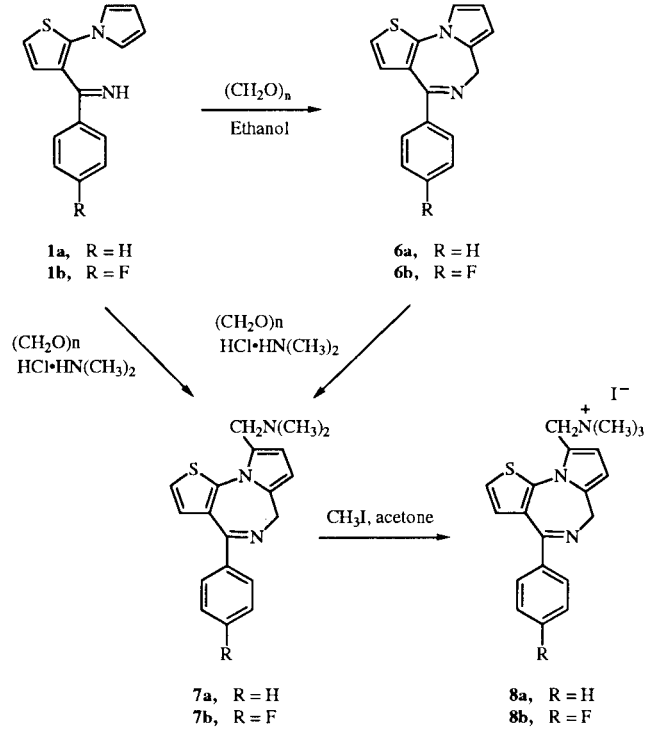
3a, R = H
3b, R = F

4a, R = H
4b, R = F

5a, R = H
5b, R = F

6a, R = H
6b, R = F

Scheme 2



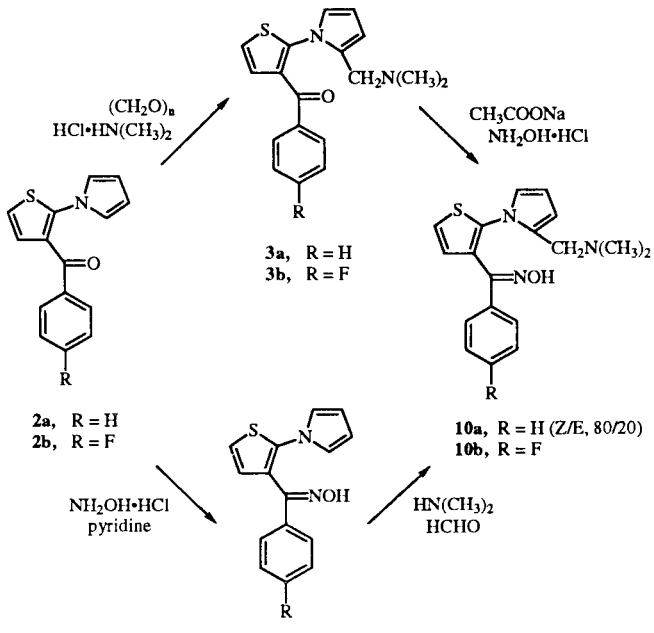
1a, R = H
1b, R = F

6a, R = H
6b, R = F

7a, R = H
7b, R = F

8a, R = H
8b, R = F

Scheme 3

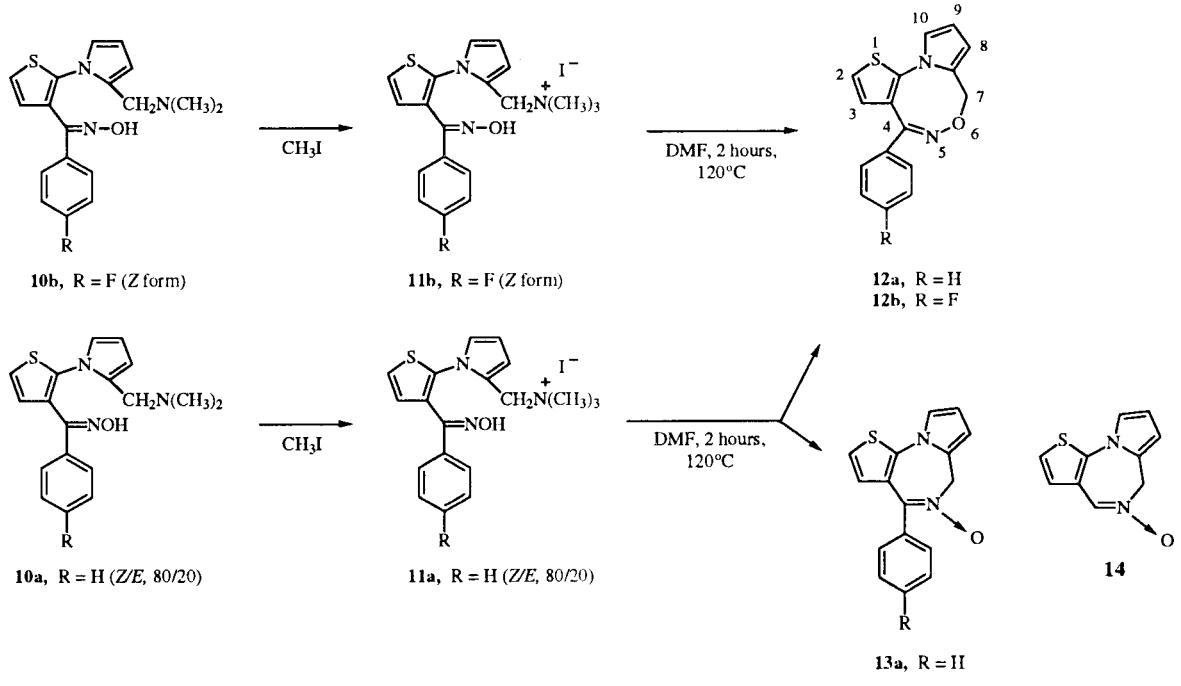


with paraformaldehyde and dimethylamine hydrochloride gave surprisingly the diazepines **7a** and **7b** dimethylaminomethylated at the α position of the pyrrole ring, probably as the result of two different reactions: a normal Mannich reaction and an abnormal cyclization. In order to accomplish this cyclization and to avoid the aminomethylation, we treated the imino compounds **1a** and **1b** with paraformaldehyde alone in refluxing ethanol. In accordance with our hypothesis, diazepines **6a** and **6b** were then isolated in 50% yield. We synthesized starting from the dimethylamimethylated diazepines **7a** and **7b**, the corresponding quaternary salt **8a** and **8b**.

On the other hand, ketones **2a** and **2b** were unreactive towards paraformaldehyde under the same conditions. This difference in reactivity could be explained by the nucleophilic character of ketones **2** which possess an amide vinylog structure compared to the nucleophilic character of imines **1** with an amidine vinylog structure. So, in the case of **1** cyclization followed hydroxymethylation and in the case of **2** retroaldolization led to the starting material.

With these Mannich bases, we explored another route which also led to thienodiazepines and thienooxadiazocines. This route has already been studied in the benzodiazepine series by Garcia [6].Starting from Mannich bases **3a** and **3b** we synthesized oximes **10a** and **10b** using an excess of sodium acetate and hydroxylamine hydrochloride in refluxing ethanol (Scheme 3). Starting from the fluoro derivative **3b** we isolated only one isomer and starting from the unsubstituted Mannich base **3a** we observed a mixture of *Z* and *E* isomers in the proportion of 80/20. No nmr parameters were able to assign *E* and *Z* forms. In order to study these assignments, we accomplished the synthesis of oximes **9a** and **9b** starting from the corresponding ketones **2a** and **2b** and the results were the same. Ketone **2b** gave only one oxime and ketone **2a** gave

Scheme 4



a mixture of isomers in the same proportion as above (80/20). The Mannich reaction conducted with these oximes gave Mannich bases **10a** (80/20) and **10b**. Finally we applied Garcia' s cyclization which demonstrated that starting with a *syn*-oxime (*Z* form), cyclization afforded benzoxadiazocine (*O*-alkylation of a *syn*-oxime), and starting with an *anti*-oxime (*E* form) cyclization afforded a benzodiazepine *N*-oxide (*N*-alkylation of an *anti*-oxime).

Therefore Mannich bases **10a** and **10b** were then alkylated with methyl iodide to give respectively **11a** (80/20) and **11b** (Scheme 4). Treatment of **11b** in DMF at 120° for 2 hours gave a unique product **12b** which exhibited a nmr methylene signal at 5.40 ppm in the nmr spectrum. Treatment of **11a** in a similar manner gave a mixture of two compounds (80/20) separated by chromatography. The major compound **12a** exhibited a 7 methylene nmr signal at 5.49 ppm and the minor compound **13a** a methylene signal at 5.08 ppm. Comparison of these results with Garcia's nmr spectra allowed us to attribute to the major compound **12a** the oxadiazocine structure and to the minor compound **13a** the *N*-oxide structure. Furthermore the mass spectrum of the *N*-oxide **13a** showed a mass loss of 16 characteristic of *N*-oxides. The structure was also confirmed by the synthesis of **14** (will be published elsewhere) in which the methylene proton appeared at 4.97 ppm. Thus the major form of oxime was the *Z* form in the unsubstituted series.

EXPERIMENTAL

Melting points were determined on a Köfler bank apparatus and were uncorrected. Infrared spectra (potassium bromide disks) were recorded on a Philips PU 9716 spectrophotometer (ν max in cm^{-1}). The ^1H-nmr spectra are recorded on a JEOL JNM-FX 200 with tetramethylsilane as the internal standard. Chemical shift data are reported in parts per million (δ in ppm) where br s, s, d, m designate broad singlet, singlet, doublet and multiplet respectively. Electron impact mass spectra were recorded on a JEOL JMS D300 spectrometer. Thin layer chromatography were performed on Merck silica gel 60 plates with fluorescent indicator. Column chromatography was conducted on Merck 60 silica gel (230-240 mesh).

3-Phenyl[(2'-Dimethylaminomethylpyrrol-1'-yl)thien-2-yl] Ketone (**3a**).

A stirred mixture of ketone **2a** (30 g, 0.11 mole), paraformaldehyde (18 g) and dimethylamine hydrochloride (48.28 g, 0.59 mole) in propan-1-ol (500 ml) was heated under reflux for 8 hours. The solvent was evaporated *in vacuo* and to the remaining oil, water (200 ml) was added. The resulting solution was basified with 1*N* aqueous sodium hydroxide (*p*H = 8-9) and extracted with dichloromethane (3 x 150 ml). The combined organic layers were dried (calcium chloride) and evaporated *in vacuo*. The residual oil was purified by flash chromatography using chloroform:methanol (9:1, v/v) as eluents to yield 29.75 g (81%) of **3a** as a yellow oil; ir (potassium bromide): ν 1645 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.91 (s, 6H, 2 CH_3), 3.15 (s, 2H, CH_2), 5.90 (m, 2H, 3'-H and 4'-H), 6.75 (m, 1H, 5'-H), 7.22 (d, 1H, 4-H, J = 5.86 Hz), 7.34-7.65 (m, 6H, phenyl protons and 5-H).

Anal. Calcd. for $C_{18}H_{18}N_2OS$ (310.41): C, 69.65; H, 5.84; N, 9.02. Found: C, 69.35; H, 5.92; N, 8.91.

3-(4-Fluorophenyl)[(2'-Dimethylaminomethylpyrrol-1'-yl)thien-2-yl] Ketone (**3b**).

This compound has been prepared from ketone **2b** by the same procedure as **3a**. The resulting solid was recrystallized from ether-petroleum ether to yield **3b** (85%), mp 74°; ir (potassium bromide): ν 1655 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.91 (s, 6H, 2 CH_3), 3.15 (s, 2H, CH_2), 5.92 (s, 2H, 3'-H and 4'-H), 6.77 (t, 1H, 5'-H), 7 15-7.74 (m, 6H, phenyl protons, 4-, and 5-H).

Anal. Calcd. for $C_{18}FH_{17}N_2OS$ (328.40): C, 65.83; H, 5.22; N, 8.53. Found: C, 65.71; H, 5.42; N, 8.72.

3-Phenyl [(2'-Dimethylaminomethylpyrrol-1'-yl)thien-2-yl] Ketone Methiodide (**4a**).

To a solution of the dimethylaminopyrrole (**3a**) (10 g, 32.2 mmoles) in acetone (200 ml), methyl iodide (6.02 ml, 96.6 mmoles) was added and the mixture stirred at room temperature for 17 hours. The suspension was filtered off and washed with acetone. The white solid was recrystallized from ethanol to give 10.95 g (75%) of **4a**, mp 189°; ir (potassium bromide): ν 1650 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.92 (s, 9H, 3 CH_3), 4.49 (s, 2H, CH_2), 6.28 (t, 1H, 4'-H), 6.57 (t, 1H, 3'-H), 7.10 (d, 1H, 5'-H), 7.29 (d, 1H, 4-H, J = 5.86 Hz), 7.47-7.81 (m, 6H, phenyl protons and 5-H).

Anal. Calcd. for $C_{19}H_{21}IN_2OS$ (452.35): C, 50.45; H, 4.68; N, 6.19. Found: C, 50.17; H, 4.65; N, 6.17.

3-(4-Fluorophenyl)[(2'-Dimethylaminomethylpyrrol-1'-yl)thien-2-yl] Ketone Methiodide (**4b**).

This compound has been prepared from dimethylaminomethylpyrrole (**3b**) by the same procedure as **4a**. The resulting white solid was recrystallized from propan-1-ol (72%), mp 227°; ir (potassium bromide): ν 1655 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.91 (s, 9H, 3 CH_3), 4.46 (s, 2H, CH_2), 6.29 (s, 1H, 4'-H), 6.57 (s, 1H, 3'-H), 7.14 (d, 1H, 5'-H), 7.30-7.83 (m, 6H, phenyl protons, 4-H and 5-H).

Anal. Calcd. for $C_{19}FH_{20}IN_2OS$ (470.43): C, 48.52; H, 4.29; N, 5.96. Found: C, 48.75; H, 4.12; N, 6.17.

3-Phenyl [(2'-Azidomethylpyrrol-1'-yl)thien-2-yl] Ketone (**5a**).

A mixture of quaternary salt **4a** (7.25 g, 16 mmoles), sodium azide (3.29 g, 49 mmoles) and few crystals of dibenzo-18-crown-6 in 1,4-dioxane (200 ml) was refluxed for 17 hours. After cooling the sodium iodide was filtered off and the filtrate was evaporated *in vacuo*. The residue was partitioned between ether (200 ml) and dilute hydrochloric acid solution (150 ml). The organic layer was separated and washed successively with a saturated aqueous solution of sodium hydrogen carbonate (150 ml) and brine (150 ml), dried (magnesium sulfate) and concentrated *in vacuo*. The residual oil was purified by flash chromatography using cyclohexane:ethyl acetate (9:1, v/v) as eluents to yield 3.45 g (70%) of **5a** as a solid, mp 61°; ir (potassium bromide): ν 2080 (N_3), 1640 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.28 (s, 2H, CH_2), 6.01 (t, 1H, 4'-H), 6.18 (dd, 1H, 3'-H), 6.91 (dd, 1H, 5'-H), 7.28 (d, 1H, 4-H, J = 5.86 Hz), 7.37-7.71 (m, 6H, phenyl protons and 5-H).

Anal. Calcd. for $C_{16}H_{12}N_4OS$ (308.35): C, 62.32; H, 3.92; N, 18.70. Found: C, 62.56; H, 3.92; N, 18.45.

3-(4-Fluorophenyl)[(2'-Azidomethylpyrrol-1'-yl)thien-2-yl] Ketone (**5b**).

This compound has been prepared from the quaternary salt **4b** by the same procedure as **4a**. The residual oil was purified by flash chromatography using cyclohexane:ethylacetate (9:1, v/v) as eluents to afford the azide as a brown oil (71%); ir (potassium bromide): ν 2090 (N_3), 1645 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.29 (s, 2H, CH_2), 6 02 (t, 1H, 4'-H), 6.19 (dd, 1H, 3'-H), 6.92 (dd, 1H, 5'-H), 7.17-7.76 (m, 6H, phenyl protons, 4-H and 5-H).

Anal. Calcd. for $C_{16}FH_{11}N_4OS$ (326.34): C, 58.89; H, 3.40; N, 17.17. Found: C, 58.59; H, 3.29; N, 17.26.

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

Procedure A.

To a solution of azide **5a** (10 g, 32.4 mmoles) in methanol (250 ml) was added a catalytic amount of palladium on activated carbon 10%, and the mixture was hydrogenated at 60° under 60 Kg/cm^2 of hydrogen for 6 hours. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. The residual material was purified by flash chromatography using cyclohexane:ethyl acetate (9:1, v/v) as eluents to afford the diazepine **6a** as a white solid which was recrystallized from ether-petroleum ether (5.05 g, 60%), mp 110°; ir (potassium bromide): ν 1590 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.58 (br s, 2H, 6-H), 6.17 (dd, 1H, 8-H), 6.35 (t, 1H, 7-H), 6.87 (d, 1H, 3-H, J = 5.86 Hz), 7.19 (dd, 1H, 9-H), 7.35-7.55 (m, 6H, phenyl protons and 2-H).

Anal. Calcd. for $C_{16}H_{12}N_2S$ (264.34): C, 72.70; H, 4.58; N, 10.60. Found: C, 72.47; H, 4.53; N, 10.78.

Procedure B.

A stirred mixture of imine **1a** (0.5 g, 1.9 mmoles), paraformaldehyde (1 g) in ethanol (10 ml) was heated under reflux for 24 hours. The solvent was evaporated *in vacuo*, and to the residue was added ether (60 ml). The organic layer was washed with water (2 x 25 ml) and finally with 0.5 *N* aqueous solution of hydrochloric acid (20 ml). This acid aqueous layer was washed with ether (2 x 20 ml) and basified with 6*N* sodium hydroxide (*p*H = 9) and finally extracted with ether (3 x 50 ml). The combined organic layers were dried (magnesium sulfate) and evaporated *in vacuo* to afford an oil which crystallized as a white solid (0.28 g, 54%), identical in all respects to that isolated above.

4-(4-Fluorophenyl)-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]-diazepine (**6b**).

Procedure A.

This compound has been prepared from the azide **5b** by the same procedure as **6a**. The residual material was purified by flash chromatography using cyclohexane:ethyl acetate (97:3 to 80:20, v/v) as eluents to afford the diazepine **6b** as a white solid (82%), mp 102°; ir (potassium bromide): ν 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.57 (br s, 2H, 6-H), 6.17 (d, 1H, 8-H), 6.35 (t, 1H, 7-H), 6.89 (d, 1H, 3-H, J = 5.86 Hz), 7.18-7.26 (m, 3H, aromatic protons), 7.38 (d, 1H, 2-H, J = 5.86 Hz), 7.53-7.60 (m, 2H, phenyl protons).

Anal. Calcd. for $C_{16}FH_{11}N_2S$ (282.33): C, 68.07; H, 3.93; N, 9.92. Found: C, 68.27; H, 4.09; N, 10.06.

Procedure B.

This compound has been prepared from imine **1b** following the same procedure as **6a** to give a white solid (44%), identical in all respects to that prepared above.

9-Dimethylaminomethyl-4-phenyl-6*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepine (**7a**).

Procedure A.

A stirred mixture of imine **1a** (3 g, 11.8 mmoles), paraformaldehyde (3 g) and dimethylamine hydrochloride (2.44 g, 30 mmoles) in ethanol (30 ml) was heated under reflux for 24 hours. The solvent was evaporated *in vacuo* and to the remaining oil, aqueous solution of 1*N* sodium hydroxide (50 ml) was added and extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried (calcium chloride) and evaporated *in vacuo*. The residual oil was purified by flash chromatography using dichloromethane:methanol (98:2, v/v) as eluents, to afford a yellow oil which crystallized in a mixture of ether-petroleum ether as a pale yellow solid (1.52 g, 40%), mp 144°; ir (potassium bromide): ν 1595 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.16 (s, 6H, 2 CH_3), 3.26 and 3.55 (d, 2H, CH_2, J = 11.75 Hz), 3.96 and 5.03 (d, 2H, 6-H, J = 12.45 Hz), 6.07 (d, 1H, 8-H), 6.19 (d, 1H, 7-H), 6.85 (d, 1H, 3-H, J = 5.86 Hz), 7.42-7.55 (m, 6H, phenyl protons and 2-H).

Anal. Calcd. for $C_{19}H_{19}N_3S$ (321.44): C, 70.99; H, 5.95; N, 13.07. Found: C, 70.82; H, 6.04; N, 12.81.

Procedure B.

A stirred mixture of diazepine **6a** (1 g, 3.78 mmoles), paraformaldehyde (2 g) and dimethylamine hydrochloride (0.61 g, 7.57 mmoles) in ethanol (20 ml) was heated under reflux for 14 hours. The solvent was evaporated *in vacuo* and to the remaining oil dichloromethane (100 ml) was added. The organic layer was washed successively with water (2 x 50 ml) and saturated aqueous solution of sodium hydrogen carbonate (50 ml), dried (calcium chloride) and concentrated *in vacuo* to give an oil which crystallized from ether-petroleum ether as a pale yellow solid (0.6 g, 48%), identical in all respects to that prepared above.

9-Dimethylaminomethyl-4-(4-fluorophenyl)-6*H*-pyrrolo[1,2-*a*]-thieno[3,2-*f*][1,4]diazepine (**7b**).

Procedure A.

A stirred mixture of imine **1b** (1 g, 3.69 mmoles), paraformaldehyde (1 g) and dimethylamine hydrochloride (0.60 g, 7.39 mmoles) in ethanol (20 ml) was heated under reflux for 22 hours. The solvent was evaporated *in vacuo* and to the remaining oil 1*N* aqueous solution of sodium hydroxide (50 ml) was added and extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried (calcium chloride) and evaporated *in vacuo*. The residual oil crystallized in petroleum ether. The solid was separated and recrystallized from ether-petroleum ether to afford **7b** (0.36 g, 29%), mp 149°; ir (potassium bromide): ν 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.16 (s, 6H, 2 CH_3), 3.25 and 3.56 (d, 2H, CH_2, J = 13.64 Hz), 3.96 and 5.02 (d, 2H, 6-H, J = 12.49 Hz), 6.08 (d, 1H, 8-H), 6.21 (d, 1H, 7-H), 6.88 (d, 1H, 3-H, J = 5.59 Hz), 7.24 (t, 2H, phenyl protons), 7.46 (d, 1H, 2-H, J = 5.59 Hz), 7.58 (t, 2H, phenyl protons).

Anal. Calcd. for $C_{19}H_{18}FN_3S$ (339.42): C, 67.23; H, 5.34; N, 12.38. Found: C, 67.32; H, 5.15; N, 12.24.

Procedure B.

A stirred mixture of diazepine **6b** (4.80 g, 17 mmoles),

paraformaldehyde (3 g) and dimethylamine hydrochloride (6.39 g, 8.5 mmoles) in propan-1-ol (300 ml) was heated under reflux for 2 hours. The solvent was evaporated *in vacuo* and to the remaining oil, water (150 ml) was added. The resulting solution was basified with 1*N* aqueous sodium hydroxide (*p*H = 8-9) and extracted with dichloromethane (3 x 100 ml). The combined organic layers were dried (calcium chloride) and evaporated *in vacuo* to afford an oil which crystallized from petroleum ether (3.62 g, 62%), identical in all respects to that prepared above.

9-Dimethylaminomethyl-4-phenyl-6*H*-pyrrolo[1,2-*a*]thieno-[3,2-*f*][1,4]diazepine Methiodide (**8a**).

To a solution of dimethylaminomethyl (**7a**) (1 g, 3. 1 mmoles) in acetone (30 ml) was added methyl iodide (0.38 ml, 6.2 mmoles). The reaction mixture was stirred at room temperature for 17 hours. The suspension was filtered off and washed with ether to yield a white solid (1.26 g, 88%), mp >260°; ir (potassium bromide): ν 1590 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.81 (s, 9H, 3 CH_3), 4.81 and 4.98 (d, 2H, CH_2, J = 14.64 Hz), 3.97 and 5.12 (d, 2H, 6-H, J = 13.18 Hz), 6.39 (d, 1H, 8-H), 6.79 (d, 1H, 7-H), 7.03 (d, 1H, 3-H, J = 5.37 Hz), 7.38-7.54 (m, 5H, phenyl protons), 7.69 (d, 1H, 2-H, J = 5.37 Hz).

Anal. Calcd. for $C_{20}H_{22}IN_3S$ (463.37): C, 51.84; H, 4.79; N, 9.07. Found: C, 51.54; H, 4.82; N, 9.14.

9-Dimethylaminomethyl-4-(4-fluorophenyl)-6*H*-pyrrolo-[1,2-*a*]thieno[3,2-*f*][1,4]diazepine Methiodide (**8b**).

To a solution of dimethylaminomethyl (**7b**) (2 g, 5.89 mmoles) in acetone (50 ml) was added methyl iodide (1.10 ml, 1.76 mmoles). The reaction mixture was stirred at room temperature for 17 hours. The suspension was filtered off and washed with acetone to yield a pale yellow solid which was recrystallized from methanol to give yellow crystals. (2.15 g, 75%), mp 240°; ir (potassium bromide): ν 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2 86 (s, 9H, 3 CH_3), 3.96 and 5.12 (d, 2H, 6-H, J = 12.77 Hz), 4.91 and 5.00 (d, 2H, CH_2, J = 14.65 Hz), 6.39 (d, 1H, 8-H), 6.83 (d, 1H, 7-H), 7.05 (d, 1H, 3-H, J = 5.49 Hz), 7.27 (m, 2H, phenyl protons), 7.59 (m, 2H, phenyl protons), 7.72 (d, 1H, 2-H, J = 5.49 Hz).

Anal. Calcd. for $C_{20}H_{21}FIN_3S$ (481.37): C, 49.90; H, 4.40; N, 8.73. Found: C, 49.79; H, 4.29; N, 8.79.

3-Phenyl [(Pyrrol-1'-yl)thien-2-yl] Ketoxime (**9a**).

To a stirred solution of ketone **2a** (5 g, 19 mmoles) in pyridine (30 ml) was added hydroxylamine hydrochloride (13.71 g, 0.197 mole). The reaction mixture was heated under reflux for 2 hours and the solvent was evaporated *in vacuo*. The residue was partitioned between water (100 ml) and ether (100 ml) and the organic layer was separated. The aqueous layer was extracted twice more with ether (2 x 100 ml). The combined organic layers were washed with 0.5 *N* hydrochloric acid, dried (magnesium sulfate) and concentrated *in vacuo* to afford an oil which crystallized after cooling. The resulting yellow solid was recrystallized from ether-petroleum ether to give a mixture of oxime **9a** (*Z*/*E*, 80/20) (5 g, 94%), mp 166°; ir (potassium bromide): ν 3310-3000 (OH), 1590 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.99 (s, 2H, 3'-H and 4'-H, 20%, *E* form), 6.09 (s, 2H, 3'-H and 4'-H, 80%, *Z* form), 6.76 (s, 2H, 2'-H and 5'-H, 20%, *E* form), 6.82 (s, 2H, 2'-H and 5'-H, 80%, *Z* form), 6.88 (d, 1H, 4-H, J = 5.86 Hz, 80%, *Z* form), 6.96 (d, 1H, 4-H, J = 5.86 Hz, 20%, *E* form), 7.29-7.40 (m, 6H, phenyl protons and 5-H, 20%, *E* form), 7.44 (d, 1H, 5-H, J = 5.37 Hz, 80%, *Z* form), 11.65 (s, 1H, OH, 20%, *E* form), 11.70 (s, 1H, OH, 80%, *Z* form).

Anal. Calcd. for $C_{15}H_{12}N_2OS$ (268.33): C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.20; H, 4.46; N, 10.40; S, 11.74.

3-(4-Fluorophenyl)[(Pyrrol-1'-yl)thien-2-yl] Ketoxime (**9b**).

This compound has been prepared from ketone **2b** by the same procedure as **9a**. Yellow crystals (89%) were obtained from ether-petroleum ether, mp 154°; ir (potassium bromide): ν 3320 (OH), 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.08 (t, 2H, 3'-H and 4'-H), 6.83 (d, 2H, 2'-H and 5'-H), 6.94 (d, 1H, 4-H, J = 5.37 Hz), 7.12-7.39 (m, 4H, phenyl protons), 7.48 (d, 1H, 5-H, J = 5.37 Hz), 11.71 (s, 1H, OH).

Anal. Calcd. for $C_{15}H_{11}FN_2OS$ (286.33): C, 62.92; H, 3.87; F, 6.64; N, 9.78; S, 11.20. Found: C, 63.02; H, 3.79; F, 6.77; N, 9.59; S, 11.04.

N-[3-Benzohydroxyimino)thien-2-yl]pyrrol-2-yl-*N*,*N*-dimethylamine (**10a**).

Procedure A.

To a stirred solution of Mannich base **3a** (14 g, 0.045 mole) in ethanol (250 ml) was added a solution of sodium acetate (18.50 g, 0.225 mole), hydroxylamine hydrochloride (15.67 g, 0.225 mole) in a minimum amount of water. The reaction mixture was refluxed for 7 hours, ethanol was evaporated *in vacuo* and water was added (100 ml). The aqueous layer was made alkaline with 1*N* aqueous solution of sodium hydroxide and extracted with ether (3 x 100 ml). The organic layers were combined, dried (magnesium sulfate) and evaporated *in vacuo* to give (10 g, 68%) of a yellow pale solid which was recrystallized from ether-petroleum ether to give **10a** as a mixture of oximes (*Z*/*E*, 80/20), mp 124°; ir (potassium bromide): ν 3400 (OH), 1625 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.00 (s, 6H, 2 CH_3), 3.19 (s, 2H, CH_2), 5.81 (s, 2H, 3,-H and 4'-H, 20%, *E* form), 5.90 (s, 2H, 3'-H and 4'-H, 80%, *Z* form), 6.58 (s, OH, 5'-H, 20%, *E* form), 6.64 (s, 1H, 5'-H, 80%, *Z* form), 6.98 (d, 1H, 4-H, J = 5.59 Hz, 80%, *Z* form), 7.01 (d, 1H, 4-H, J = 5.59 Hz, 20%, *E* form), 7.23-7.35 (m, 5H, phenyl protons), 7.50 (d, 1H, 5-H, J = 5.59 Hz, 20%, *E* form), 7.57 (d, 1H, 5-H, J = 5.59 Hz, 80%, *Z* form), 11.55 (s, 1H, OH, 20%, *E* form), 11.64 (s, 1H, OH, 80%, *Z* form).

Anal. Calcd. for $C_{18}H_{19}N_3OS$ (325.42): C, 66.44; H, 5.88; N, 12.91; S, 9.85. Found: C, 66.47; H, 5.91; N, 12.72; S, 9.61.

Procedure B.

To a solution of acetic acid (5 ml) was slowly added at 0° dimethylamine (40% solution in water, 1.1 equivalent, 0.012 mole) and formaldehyde (37% solution in water, 1.1 equivalent, 0.012 mole). The ice-bath was removed and to the reaction mixture was added oxime **9a** (2.68 g, 0.01 mole), this mixture was heated at 70° for 1.5 hours. After cooling the reaction mixture, it was poured into 8*N* aqueous sodium hydroxide (25 ml). The aqueous layer was extracted with ether (3 x 70 ml). The combined organic layers were washed with water (100 ml), dried (magnesium sulfate) and concentrated *in vacuo* to yield a yellow oil which crystallized from petroleum ether. The solid was separated by filtration and recrystallized from ether-petoleum ether to give **10a** as a mixture of oximes (*Z*/*E*, 80/20) (2.11 g, 65%), identical in all respects to that prepared above.

N-[3-(4-Fluoro)benzohydroxyimino)thien-2-yl]pyrrol-2-yl-*N*,*N*-dimethylamine (**10b**).

Procedure A.

This compound has been prepared from Mannich base **3b** following the same procedure as for **10a**. Yellow crystals (50%, *Z* isomer) were obtained from ether-petroleum ether, mp 160°; ir (potassium bromide): ν 3200 (OH), 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.96 (s, 6H, 2 CH_3), 3.15 (m, 2H, CH_2), 5.86 (s, 2H, 3'-H and 4'-H), 6.59 (s, 1H, 5'-H), 6.96 (d, 1H, 4-H, J = 5.37 Hz), 7.02 (m, 2H, phenyl protons), 7.32 (m, 2H, phenyl protons), 7.53 (d, 1H, 5-H, J = 5.37 Hz), 11.61 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{18}FN_3OS$ (343.41): C, 62.95; H, 5.28; N, 12.23. Found: C, 63.10; H, 5.38; N, 11.96.

Procedure B.

This compound has been prepared from oxime **9b** by the same procedure as **9a**. Yellow crystals (45%) were isolated as **10b** identical in all respects to that prepared above.

N-[3-Benzohydroxyimino)thien-2-yl]pyrrol-2-yl-*N,N*-dimethylamine Methiodide (**11a**).

To a solution of oxime **10a** (5 g, 0.015 mole) in acetone (70 ml) was added methyl iodide (2.86 ml, 0.046 mole). The reaction mixture was stirred at room temperature for 17 hours. The resulting solid was separated and recrystallized from propan-2-ol to give **11a** as a mixture of oximes (*Z/E*, 80/20) as a yellow-green solid (4.80 g, 66%), mp 195°; ir (potassium bromide): ν 3180 (OH), 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.83 (s, 9H, 3 CH_3, 80%, *Z* form), 2.96 (s, 9H, 3 CH_3, 20%, *E* form), 4.40 (s, 2H, CH_2, 80%, *Z* form), 4.44 (s, 2H, CH_2, 20%, *E* form), 6.20 (s, 1H, 4'-H, 80%, *Z* form), 6.23 (s, 1H, 4'-H, 20%, *E* form), 6.50 (s, 1H, 3'-H), 7.02 (s, 1H, 5'-H, 20%, *E* form), 7.07 (s, 1H, 5'-H, 80%, *Z* form), 7.20 (d, 1H, 4-H, J = 5.59 Hz, 80%, *Z* form), 7.30-7.36 (m, 6H, phenyl protons and 1H, 4-H, J = 5.59 Hz, 20%, *E* form), 7.71 (d, 1H, 5-H, J = 5.59 Hz, 20%, *E* form), 7.83 (d, 1H, 5-H, J = 5.59 Hz, 80%, *Z* form), 11.44 (s, 1H, OH, 20%, *E* form), 12.02 (s, 1H, OH, 80%, *Z* form).

Anal. Calcd. for $C_{19}H_{22}IN_3OS$ (467.36): C, 48.83; H, 4.74; N, 8.99. Found: C, 48.72; H, 4.61; N, 9.08.

N-[3-(4-Fluoro)benzohydroxyimino)thien-2-yl]pyrrol-2-yl-*N,N*-dimethylamine Methiodide (**11b**).

To a solution of oxime **10b** (2 g, 5.8 mmoles) in ethanol (6 ml) was slowly added methyl iodide (0.47 ml, 7.57 mmoles). The solution was heated under reflux for 30 minutes, the solvent was evaporated *in vacuo*, the resulting precipitate was separated and washed with ether and recrystallized from propan-2-ol to afford a white solid (2.14 g, 76%), mp 175°; ir (potassium bromide): ν 3200 (OH), 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.82 (s, 9H, 3 CH_3), 4.32 (s, 2H, CH_2), 6.15 (t, 1H, 4'-H), 6.45 (d, 1H, 3'-H), 7.01-7.36 (m, 6H, phenyl protons, 4-H and 5'-H), 7.84 (d, 1H. 5-H, J = 5.37 Hz), 11.98 (s, 1H, OH).

Anal. Calcd. for $C_{19}H_{21}FIN_3OS$ (385.35): C, 47.02; H, 4.36; N, 8.66. Found: C, 46.87; H, 4.60; N, 8.42.

4-Phenyl-7*H*-pyrrolo[1,2-*f*]thieno[3,2-*d*][1,2,6]oxadiazocine (**12a**) and 4-Phenyl-6*H*-pyrrolo[1,2-*a*]thieno[3,2-*f*][1,4]diazepine 5-Oxide (**13a**).

A solution of the quaternary salt **11a** (2 g, 4.27 mmoles) in dimethylformamide (20 ml) was heated at 120° for 2 hours and after cooling water (100 ml) was added in the reaction mixture. The brown solid formed was separated, dried and purified by flash chromatography using ethyl acetate:cyclohexane (9:1, v/v) as eluents to yield a yellow oil **12a** (0.49 g, 41%), ir (potassium bromide): ν 1580 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.49 (s, 2H, 7-H), 6.07 (m, 1H, 9-H), 6.18 (t, 1H, 8-H). 6.73 (d, 1H, 3-H, J = 5.68 Hz), 6.84 (d, 1H, 10-H), 7.11 (d, 1H, 2-H, J = 5.68 Hz), 7.30-7.55 (m, 5H, phenyl protons), ms: (70eV, electron impact, relative intensity) m/z 280 (molecular ion, 13), 279 (17), 250 (43), 41, (100).

Anal. Calcd. for $C_{16}H_{12}N_2OS$ (280.34): C, 68.55; H, 4.31; N, 9.99. Found: C, 68.41; H, 4.42; N, 9.83.

The flash column was continued with a gradient of ethyl acetate and cyclohexane until 3:7, v/v. The pure fractions were collected to give **13a** as a pale yellow solid (0.30 g, 25%), mp 188°; ir (potassium bromide): ν 1570 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.09 (s, 2H, 6-H), 6.38 (dd, 1H, 8-H), 6.45 (t, 1H, 7-H), 6.61 (d, 1H, 3-H, J = 5.77 Hz), 6.94 (d, 1H, 2-H, J = 5.77 Hz), 7.07 (dd, 1H, 9-H), 6.34-7.67 (m, 5H, phenyl protons), ms: m/z (70eV, electron impact, relative intensity) 280 (molecular ion, 11), 279 (80), 264 (4), 263 (5), 149 (100).

4-(4-Fluorophenyl)-7*H*-pyrrolo[1,2-*f*]thieno[3,2-*d*][1,2,6]oxadiazocine (**12b**).

A solution of the quaternary salt **11b** (1 g, 2 mmoles) in dimethylformamide (30 ml) was heated at 120-130° for 2 hours and after cooling, water (100 ml) was added in the reaction mixture. The aqueous layer was extracted with ether (3 x 75 ml), the combined organic layers were washed with water (3 x 100 ml), dried (magnesium sulfate) and concentrated *in vacuo* to afford an orange oil (0.33 g, 54%); ir (potassium bromide): ν 1600 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.40 (s, 2H, 7-H), 6.11 (d, 1H, 9-H), 6.17 (t, 1H, 8-H), 6.89 (d, 1H, 3-H, J = 5.86 Hz), 6.96 (d, 1H, 10-H), 7.21-7.56 (m, 5H, phenyl protons and 2-H).

Anal. Calcd. for $C_{16}H_{11}FN_2OS$ (298.33): C, 64.41; H, 3.71; F, 6.36; N, 9.38. Found: C, 64.12; H, 4.08; F, 6.49; N, 9.26.

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