

Carlos Corral\*, Ana Lasso, Jaime Lissavetzky and Ana M. Valdeolmillos

Instituto de Química Médica (C.S.I.C.), Juan de la Cierva 3,  
28006 Madrid, Spain

Received February 20, 1985

A series of the title compounds has been synthesized by two alternative methods in order to study their potential neuroleptical activity and to compare it with the pharmacological data already obtained for compounds of other isomeric or related series.

*J. Heterocyclic Chem.*, **22**, 1345 (1985).

As it is well known a number of 10-piperazinyl derivatives of dibenzo[*b,f*][1,4]thiazepines **1**, (Y = S), oxazepines **1**, (Y = O) and diazepines **1**, (Y = NH) have significant CNS activity. The most relevant members of this series are clothiapine **1**, (Y = S, X = 2 Cl), methiapine **1**, (Y = S, X = 2 CH<sub>3</sub>), loxapine **1**, (Y = O, X = 2 Cl) and its *N*-de-

methyl derivative amoxepine and clozapine **1**, (Y = NH, X = 8 Cl). Clothiapine, methiapine and loxapine behave as classical neuroleptics, *i.e.* they show the same pattern of pharmacological activity as the neuroleptic phenothiazines whereas amoxapine has additional antidepressant activity. On the other hand, clozapine is an effective anti-

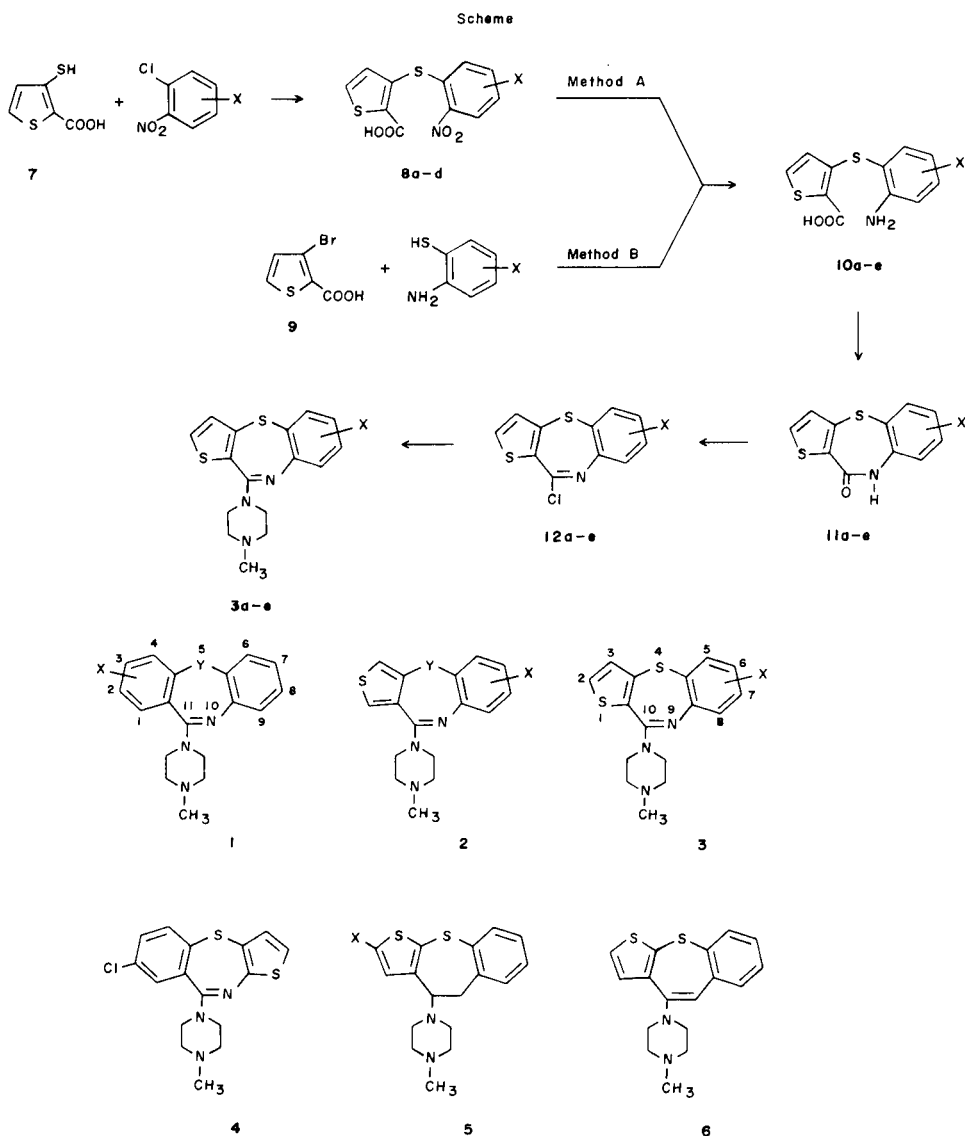
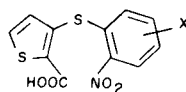


Table 1

## 3-(2-Nitrothiophenoxy)thiophene-2-carboxylic Acid

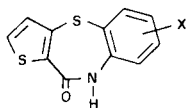


Compound	X	Reaction time (hours)	Yield (%) (Method)	Mp (°C) [a]	Molecular formula	Analysis %		
						Calcd./Found	C	H
<b>8a</b>	H	24	33	193-195	C <sub>11</sub> H <sub>7</sub> NO <sub>4</sub> S <sub>2</sub>	46.97	2.49	4.98
						46.84	2.45	4.76
<b>8b</b>	4Cl	16	73	205-206	C <sub>11</sub> H <sub>6</sub> ClNO <sub>4</sub> S <sub>2</sub>	41.84	1.90	4.44
						41.99	1.84	4.52
<b>8c</b>	6Cl	16	75	220-222	C <sub>11</sub> H <sub>6</sub> ClNO <sub>4</sub> S <sub>2</sub>	41.84	1.90	4.44
						41.87	1.79	4.55
<b>8d</b>	4CF <sub>3</sub>	4	83	197-199	C <sub>12</sub> H <sub>6</sub> F <sub>3</sub> NO <sub>4</sub> S <sub>2</sub>	41.26	1.72	4.01
						41.35	1.83	4.15

[a] Recrystallized from ethanol. All these compounds showed the following common ir and <sup>1</sup>H-nmr spectroscopic data: ir (nujol): ν 3200-2500 (OH), 1690-1670 (C=O), 1540-1520, 1360-1340 (NO<sub>2</sub>); <sup>1</sup>H-nmr (dimethylsulfoxide-d<sub>6</sub>): δ 6.8-7.3 (d, J = 5 Hz, 1H, H-4 thiophene), 7.3-8.0 (m, 2 or 3H, benzene protons), 8.0-8.1 (d, J = 5 Hz, 1H, H-5 thiophene), 8.3-8.6 (m, 1H, H-3 benzene protons).

Table 2

## 3-(2-Aminothiophenoxy)thiophene-2-carboxylic Acid



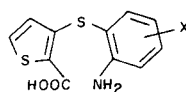
Compound	X	Yield (%) (Method)	Mp (°C) [a]	Molecular formula	Analysis %		
					Calcd./Found	C	H
<b>10a</b>	H	86 (A) 60 (B)	175-176	C <sub>11</sub> H <sub>9</sub> NO <sub>2</sub> S <sub>2</sub>	52.59	3.58	5.58
					52.47	3.56	5.54
<b>10b</b>	4Cl	99 (A) 38 (B)	194-195	C <sub>11</sub> H <sub>8</sub> ClNO <sub>2</sub> S <sub>2</sub>	46.27	2.80	4.90
					46.32	2.93	4.71
<b>10c</b>	6Cl	98 (A)	204-206	C <sub>11</sub> H <sub>8</sub> ClNO <sub>2</sub> S <sub>2</sub>	46.27	2.80	4.90
					46.22	2.89	4.75
<b>10d</b>	4CF <sub>3</sub>	96 (A)	164-165	C <sub>12</sub> H <sub>8</sub> F <sub>3</sub> NO <sub>2</sub> S <sub>2</sub>	45.14	2.50	4.39
					45.29	2.65	4.15
<b>10e</b>	5Cl	42 (B)	182-183	C <sub>11</sub> H <sub>8</sub> ClNO <sub>2</sub> S <sub>2</sub>	46.27	2.80	4.90
					46.11	2.83	4.76

[a] Recrystallized from ethanol-water. All these compounds showed the following common ir and <sup>1</sup>H-nmr spectroscopic data: ir (nujol): ν 3480, 3330 (NH<sub>2</sub>), 3200-2500 (OH), 1690-1670 (C=O); <sup>1</sup>H-nmr (dimethylsulfoxide-d<sub>6</sub>): δ 2.7-3.9 (s, 2H, exchangeable with deuterium oxide, NH<sub>2</sub>), 6.1-6.3 (d, J = 5 Hz, 1H, H-4 thiophene), 6.6-7.8 (m, 3 or 4H, benzene protons), 7.6-7.8 (d, J = 5 Hz, 1H, H-5 thiophene).

psychotic agent with a very low tendency for causing extrapyramidal side effects and an exceptional pharmacological and biochemical profile. The advantageous properties of clozapine are tempered by the observation that it may cause hematologic disturbances (agranulocytosis and leukopenia). Looking for new agents with clozapine-like activity, a benzenic nucleus in **1** (Y = NH) has already been substituted by thiophene [1-4]. Also the synthesis of a

number of compounds of structure **2** (Y = O, S) has been recently reported and their neuroleptical activities investigated [4]. With the same aim the synthesis of a series of the title compounds **3** has been now accomplished and it is described in this paper. Although compound **4**, an isomer of **3b**, has been reported to be practically devoid of neuroleptical activity [5], the fact that the piperaziny group is attached to a carbon atom linked to the thiophenic ring in

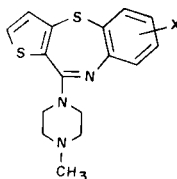
Table 3

9*H*-10-Oxothieno[3,2-*b*][1,5]benzothiazepines

Compound	X	Yield (%)	Mp (°C) [a]	Molecular formula	Analysis %		
					Calcd./Found	C	H
<b>11a</b>	H	60	260-261	C <sub>11</sub> H <sub>7</sub> NOS <sub>2</sub>	56.65	3.00	6.00
					56.36	2.93	6.06
<b>11b</b>	7Cl	68	289-290	C <sub>11</sub> H <sub>6</sub> ClNOS <sub>2</sub>	49.35	2.24	5.23
					49.62	2.42	5.29
<b>11c</b>	5Cl	65	287-289	C <sub>11</sub> H <sub>6</sub> ClNOS <sub>2</sub>	49.35	2.24	5.23
					49.26	2.28	4.96
<b>11d</b>	7CF <sub>3</sub>	72	248-249	C <sub>12</sub> H <sub>6</sub> F <sub>3</sub> NOS <sub>2</sub>	47.84	1.99	4.65
					47.52	1.71	4.35
<b>11e</b>	6Cl	54	261-262	C <sub>11</sub> H <sub>6</sub> ClNOS <sub>2</sub>	49.35	2.24	5.23
					49.21	2.06	5.45

[a] Recrystallized from ethyl acetate. All these compounds showed the following common ir and <sup>1</sup>H-nmr spectroscopic data: ir (nujol):  $\nu$  3200-3050 (NH), 1670-1645 (C=O); <sup>1</sup>H-nmr (dimethylsulfoxide-d<sub>6</sub>):  $\delta$  7.15-7.25 (d, J = 5 Hz, 1H, H-4 thiophene), 7.0-7.8 (m, 3 or 4H, benzene protons), 7.9-8.1 (d, J = 5 Hz, 1H, H-5 thiophene), 10.4-10.9 (s, 1H, exchangeable with deuterium oxide, NH).

Table 4

10-(4-Methyl-1-piperaziny)thieno[3,2-*b*][1,5]benzothiazepines

Compound	X	Yield (%)	Mp (°C) [a]	Molecular formula	Analysis %		
					Calcd./Found	C	H
<b>3a</b>	H	63	144-145	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> S <sub>2</sub>	60.92	5.43	13.32
					60.66	5.63	13.33
<b>3b</b>	7Cl	55	140-141	C <sub>16</sub> H <sub>16</sub> ClN <sub>3</sub> S <sub>2</sub>	54.93	4.58	12.02
					54.79	4.35	11.90
<b>3c</b>	5Cl	54	145-147	C <sub>16</sub> H <sub>16</sub> ClN <sub>3</sub> S <sub>2</sub>	54.93	4.58	12.02
					55.02	4.36	11.89
<b>3d</b>	7CF <sub>3</sub>	58	155-157	C <sub>17</sub> H <sub>16</sub> F <sub>3</sub> N <sub>3</sub> S <sub>2</sub>	53.26	4.18	10.96
					53.34	4.22	10.73
<b>3e</b>	6Cl	57	102-103	C <sub>16</sub> H <sub>16</sub> ClN <sub>3</sub> S <sub>2</sub>	54.93	4.58	12.02
					54.68	4.72	11.93

[a] Recrystallized from isopropanol. All these compounds showed the following common <sup>1</sup>H-nmr spectroscopic data: <sup>1</sup>H-nmr (carbon tetrachloride):  $\delta$  2.2-2.3 (s, 3H, CH<sub>3</sub>), 2.4-2.5 (t, 4H, H-3 and H-5, piperazine), 3.5-3.6 (t, 4H, H-2 and H-6, piperazine), 6.7-7.4 (m, 3 or 4H, benzene protons), 6.8-6.9 (d, J = 5 Hz, 1H, H-4 thiophene), 7.2-7.4 (d, J = 5 Hz, 1H, H-5 thiophene).

compounds **3** may be advantageous since other related compounds such as **5** [6-8] and **6** [9] are potent CNS depressants with relatively weak cataleptogenic activity.

The synthetic route to compounds **3** is outlined in the Scheme.

Two methods were used to obtain sulfides **10**. In method A, an ethanolic solution of the sodium salt of 3-mercapto-

thiophene-2-carboxylic acid (**7**) was made to react with the appropriate *o*-chloronitrobenzene and the resulting nitro-sulfide **8** was reduced in almost quantitative yield in ethanol to the corresponding compound **10** by palladium on charcoal catalytic hydrogenation at room temperature. In method B, an Ullmann copper catalyzed reaction at *ca.* 220° of potassium 3-halo-(bromo or chloro)-thiophene-2-

carboxylate (**9**) with the dry sodium salt of the corresponding *o*-aminothiophenol was employed. Method A appears to be a convenient method since *o*-chloronitrobenzenes are more easily available than *o*-aminothiophenols. Cyclic compounds **11** were obtained by heating compounds **10** for a short time at 200-220° in an oil-bath. Compounds **11** were transformed into the title compounds **3**. This was accomplished by allowing compounds to react with phosphorus pentachloride/phosphorus oxychloride to produce the corresponding iminochlorides **12** which were made to react with *N*-methylpiperazine.

## EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Varian EM-390 (90 MHz) spectrometer with TMS as internal reference.

3-Mercaptothiophene-2-carboxylic acid [10,11], 3-halo-(bromo or chloro)-2-carboxylic acids [12], 2-amino-4-chlorothiophenol hydrochloride [13] and 2-amino-5-chlorothiophenol hydrochloride [14] were obtained according to the literature. All the other starting products were obtained from Fluka A.G.

### 3-(2-Aminothiophenoxy)thiophene-2-carboxylic Acids **10a-e**.

Method A.

#### 3-(2-Nitrothiophenoxy)thiophene-2-carboxylic Acids **8a-d**.

Anhydrous potassium carbonate (6.9 g, 0.005 mole) was added at 65° to a stirred solution of the corresponding *o*-chloronitrobenzene (0.05 mole) and 3-mercaptothiophene-2-carboxylic acid (**7**) (8 g, 0.05 mole) in dimethylsulfoxide (40 ml). The reaction mixture was heated at 90° for the time indicated in Table 1 and once cooled poured into ice-water and the resulting mixture was extracted with ether to recover little amounts of unreacted *o*-chloronitrobenzenes. The aqueous layer was acidified with hydrochloric acid and extracted repeatedly with ether. The ethereal extracts were washed with water, dried over magnesium sulfate, evaporated to dryness and the residue was crystallized from ethanol to yield yellow solids. Properties and yields of compounds **8a-d** are shown in Table 1.

#### 3-(2-Aminothiophenoxy)thiophene-2-carboxylic Acids **10a-d**.

To a suspension of compounds **8a-d** (2 g) in ethanol (200 ml) was added palladium on charcoal (10%) (200 mg) as catalyst and the mixture was hydrogenated at 60 psi. The catalyst was filtered off, the solvent was evaporated to dryness and the residue was crystallized from ethanol-water to yield colorless solids. Properties and yields of compounds **10a-d** are shown in Table 2.

Method B.

#### 3-(2-Aminothiophenoxy)thiophene-2-carboxylic Acids **10a,b,e**.

The potassium salt of 3-halo (bromo or chloro)thiophene-2-carboxylic acid and traces of copper were added to the sodium salt of the corresponding 2-aminophenol (0.04 mole). These salts were prepared by treating 2-aminothiophenol, 2-amino-4-chlorothiophenol hydrochloride or 2-amino-5-chlorothiophenol hydrochloride with 2*M* sodium methoxide solution (20 ml) (or 40 ml for the hydrochlorides) and evaporation to dryness of the reaction mixture. This reaction mixture was then heated at ca. 220° in an oil bath and once cooled was treated with water and ether. The aqueous layer was acidified with a 10% hydrochloric acid solution

and extracted repeatedly with ether. The ethereal extracts were washed with water, dried over magnesium sulfate, evaporated to dryness and the residue was crystallized from ethanol-water to yield colorless solids. Properties and yields of compounds **10a,b,e** are shown in Table 2.

#### 9*H*-10-Oxothieno[3,2-*b*][1,5]benzothiazepines **11a-e**.

Compounds **10a-e** were heated at 200-220° in an oil-bath for 15-30 minutes without solvent and, once cooled, the corresponding thiazepinones crystallized as colorless solids which were recrystallized from ethyl acetate. Properties and yields of compounds **11a-e** are shown in Table 3.

#### 10-(4-Methyl-1-piperazinyl)thieno[3,2-*b*][1,5]benzothiazepines **3a-e**.

A mixture of the corresponding compound **11a-e** (0.01 mole), phosphorus pentachloride (5.2 g, 0.025 mole) and phosphorus oxychloride (15 ml) was heated at 120° for 4 hours and, once cooled, the resulting reaction mixture was poured into *n*-hexane-ice. The hexane layer was immediately separated to avoid the hydrolysis of the iminochloride, dried over magnesium sulfate and evaporated to dryness to yield the corresponding iminochlorides as yellow solids. These compounds showed good chromatographic purity and were not crystallized to avoid hydrolysis to the thiazepinones **11a-e**.

*N*-Methylpiperazine (5 ml) was added to a solution of the corresponding iminochlorides in anhydrous toluene. On leaving the reaction mixture overnight at room temperature, the *N*-methylpiperazine hydrochloride precipitated. The solvent was removed and the residue was treated with ether and water. The ethereal extracts were dried over magnesium sulfate and evaporated to dryness to yield compounds **3a-e** as yellow solids, which were crystallized from isopropyl alcohol. Properties and yields of compounds **3a-e** are shown in Table 4.

## Acknowledgements.

We are indebted to our Department of Analyses and Instrumental Techniques for all the analytical and spectroscopic data.

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