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Starting from [4,3-*c*] and [3,2-*c*] methyl chlorosulfonylthiophenecarboxylates the synthesis of ketones **7** and **8** is described. These compounds are the first two representatives of the new thieno[3,4-*c*] and thieno-[3,2-*c*][2,1]benzothiazepine ring systems. The formation of methyl 3-chlorosulfonylthiophene-2-carboxylate is also revised.

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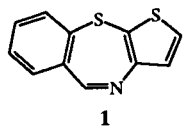
During recent years, fused tricyclic structures bearing a thiazepine central ring system have been the object of intense study due to the interesting pharmacological activities found in several of their derivatives [1]. Thus, many dibenzo[1,2]thiazepines were synthesized but only the thiophene systems of thieno[2,3-*b*][1,4] **1**, thieno-[2,3-*b*][1,5] **2**, thieno[3,2-*b*][1,4] **3**, thieno[3,2-*b*][1,5] **4**, thieno[3,4-*b*][1,5] **5** and thieno[3,4-*c*][1,5]benzothiazepine **6** were so far described in these heterocyclic series [2-6].



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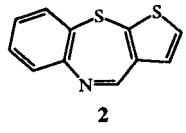

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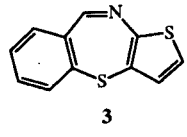

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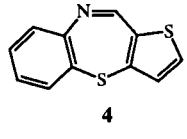

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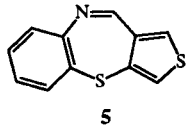

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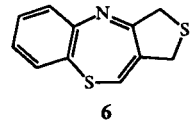
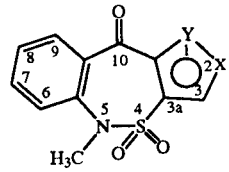


6

These observations and our interest in the field of heterocyclic sulfonamides [7,8] led us to explore the possible routes of access to the novel tricyclic systems of thieno[3,4-*c*][2,1]benzothiazepine and thieno[3,2-*c*]-[2,1]benzothiazepine. In this context, we have first synthesized the new ketones 5,10-dihydro-5-methyl-4,4,10-trioxothieno[3,4-*c*][2,1]benzothiazepine **7** and 5,10-dihydro-5-methyl-4,4,10-trioxothieno[3,2-*c*][2,1]benzothiazepine **8** which are useful compounds *per se* and for their potential as building blocks for the preparation of thiophene isosteres of known antipsychotic and antidepressive agents.



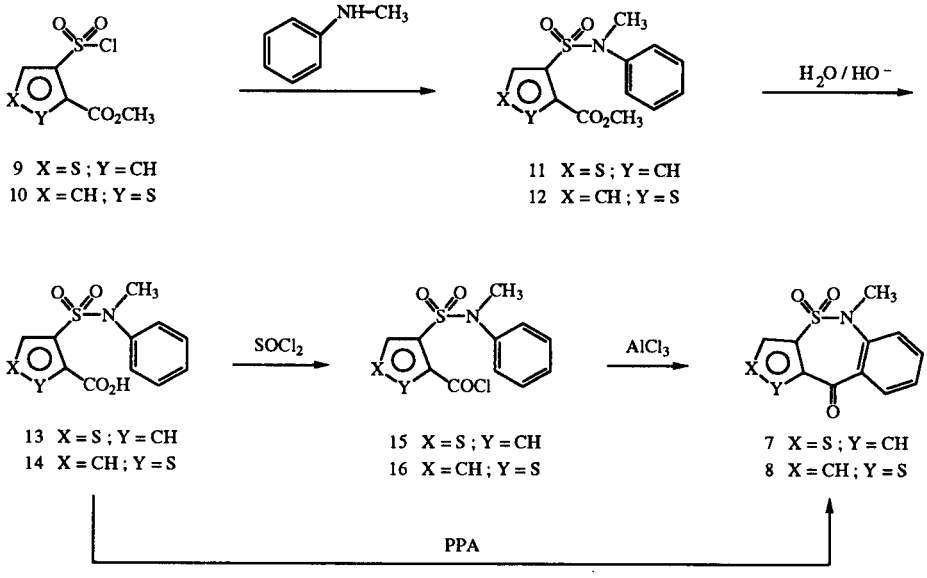
7 X = S; Y = CH
8 X = CH; Y = S

The synthesis of compounds **7** and **8** was carried out following the route depicted in Scheme 1. Thus, starting with chlorosulfonyl derivatives **9** and **10**, they were converted to the corresponding sulfonamides **11** and **12** by reaction with *N*-methylaniline in tetrahydrofuran. These sulfonamides were white crystalline solids which were isolated in excellent yields (99 and 94% respectively) by elimination of the solvent at reduced pressure followed by repeated washings with water. Hydrolysis of the ester functionality of compounds **11** and **12** in aqueous 1*N* potassium hydroxide and subsequent acidification of the resulting alkaline solution led to the respective sulfonamidocarboxylic acids **13** and **14** which, in turn, were cyclized to the target compounds **7** and **8** by two different methods.

Method A involves the previous transformation of **13** and **14** into their respective acid chlorides **15** and **16**, and cyclization of these latter compounds through a Friedel-Crafts reaction. The process was carried out in a two-step synthetic sequence, without isolation of the acyl chlorides **15** and **16** which were obtained by refluxing **13** and **14** in thionyl chloride. After elimination of the thionyl chloride, the residue was dissolved in carbon disulfide and heated in the presence of aluminum(III) chloride as the catalyst. Method B consists of a direct intramolecular cyclodehydration of carboxylic acids **13** and **14** by polyphosphoric acid. The reaction was realized by heating to the reflux temperature a mixture of polyphosphoric acid and the acids **13** or **14** in toluene as the solvent. In both methods the tricyclic ketones **7** and **8** were obtained in good yields (Table 1) and their structures were confirmed by elemental and spectroscopic analyses.

As regards the starting chlorosulfonyl derivatives, methyl 4-chlorosulfonylthiophene-3-carboxylate **9** was readily synthesized according to a published procedure [9] which involves the mild dehydrogenation, by the

Scheme 1



9 X = S ; Y = CH
10 X = CH ; Y = S

11 X = S ; Y = CH
12 X = CH ; Y = S

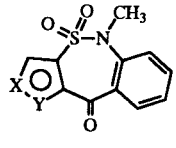
13 X = S ; Y = CH
14 X = CH ; Y = S

15 X = S ; Y = CH
16 X = CH ; Y = S

7 X = S ; Y = CH
8 X = CH ; Y = S

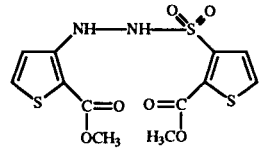
action of sulfuryl chloride, of dimethyl 4,4'-dithiobis(2,5-dihydrothiophene-3-carboxylate), easily obtained in four steps from methyl thioglycolate and methyl acrylate. Methyl 3-chlorosulfonylthiophene-2-carboxylate **10**, was prepared by a Meerwein type reaction of the diazonium salt of the corresponding methyl-3-aminothiophene-2-carboxylate with sulfur dioxide and cupric chloride in acetic acid [10].

Table 1



No.	X	Y	IR (cm^{-1}) (SO_2)	(C=O)	Method	Yield(%)
7	S	CH	1150, 1340	1640	A	78
					B	79
8	CH	S	1150, 1350	1630	A	82
					B	87

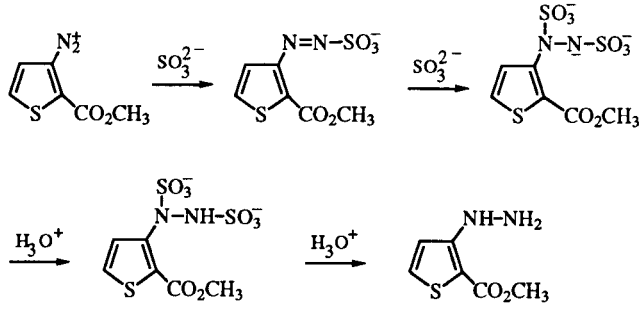
In this latter reaction, together with **10**, which was obtained in 61% yield, another compound in variable amounts was also formed. The compound was a white crystalline solid easily recrystallizable from acetone which was transformed into a new product on heating in a higher boiling point solvent like, for example, acetonitrile. To explain the formation of this compound, the hypothesis of a possible nucleophilic substitution on position 3 of the thiophene ring by the chloride ion, well documented in the bibliography [11], was first considered. However, such an hypothesis was immediately ruled out by an infrared spectrum of the compound which indicated the presence of bands characteristic of the NH and SO_2 groups. On the other hand, its ^1H nmr spectrum exhibited signals corresponding to the protons of two methyl groups (δ 3.75 and δ 4.00 ppm), two exchangeable protons (δ 7.90 and δ 8.30 ppm) which demonstrated the presence of two NH groups, and four aromatic protons.



17

These spectroscopic data and the above mentioned thermal instability, typical of sulfonhydrazides, were consistent with a structure like **17** for the byproduct. Such a

Scheme 2



structure was confirmed by elemental analysis and by mass spectrometry which showed peaks at m/z 312 and 171 indicating loss of sulfur dioxide and thienosulfonyl fragments respectively.

We suggest that this side process can be explained through the well known reduction reaction of diazonium salts to hydrazines by sulfite ions [12]. As outlined in Scheme 2, the process probably involves a hydrazinosulfonic acid derivative [13] which, under the acidic conditions of the reaction, is converted to the hydrazine. Then the hydrazine would react with chlorosulfonyl derivative **10** to give compound **17**.

In conclusion, starting from [4,3-*c*] and [3,2-*c*] methyl chlorosulfonylthiophenecarboxylates, we have carried out the synthesis of the first two representatives of the new tricyclic ring systems thieno[3,4-*c*] and thieno[3,2-*c*]-[2,1]benzothiazepine. These compounds have been demonstrated as useful intermediates for the preparation of more complex molecules with potential pharmacological activities [14]. Moreover, the structure and possible formation mechanism of a byproduct obtained in the synthesis of methyl 3-chlorosulfonylthiophene-2-carboxylate have also been determined.

EXPERIMENTAL

All melting points (uncorrected) were determined using a Gallenkamp capillary apparatus. The ir spectra were recorded on a Shimadzu IR-435 instrument. The ^{1}H nmr spectra were measured with a Bruker AM-200 and a Varian XL-300 spectrometers using TMS as internal standard. The purity of compounds was verified by thin-layer chromatography (tlc) which was run on silica gel GF_{254} (Merck) with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v respectively) as eluents.

Sulfamoylthiophenecarboxylates **11** and **12**.

General Method.

To a solution of the corresponding methyl chlorosulfonylthiophenecarboxylate (0.1 mole) in tetrahydrofuran (50 ml) was slowly added a solution of *N*-methylaniline (0.2 mole) in tetrahydrofuran (20 ml). The mixture was stirred for 2 hours and then concentrated *in vacuo*. The residue was treated with water (150 ml) and the white crystalline solid obtained was filtered, washed with water and dried to give the required methyl sulfamoylthiophenecarboxylate.

Methyl 4-(*N*-Phenyl-*N*-methyl)sulfamoylthiophene-3-carboxylate **11**.

This compound was prepared by the method described above from methyl 4-chlorosulfonylthiophene-3-carboxylate **9** and N-methylaniline as white crystals (99%) of mp 66-68° (cyclohexane); ir (potassium bromide): 1715 cm^{-1} (CO), 1340, 1160 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 3.45 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 7.30 (s, 5H, benzene), 7.85 (d, 1H, J = 3.7 Hz, thiophene), 8.05 (d, 1H, J = 3.7 Hz, thiophene).

Anal. Calcd. for $C_{13}H_{13}NO_4S_2$: C, 50.14; H, 4.21; N, 4.50; S, 20.59. Found: C, 50.21; H, 4.19; N, 4.65; S, 21.06.

Methyl 3-(*N*-Phenyl-*N*-methyl)sulfamoylthiophene-2-carboxylate **12**.

This compound was formed in 94% yield from methyl 3-chlorosulfonylthiophene-2-carboxylate **10** and *N*-methylaniline as white crystals of mp 79-81° (ethanol); ir (potassium bromide): 1750 cm^{-1} (CO), 1365, 1180 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 3.40 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 7.15 (m, 5H, benzene), 7.30 (d, 1H, J = 5.1 Hz, thiophene), 7.75 (d, 1H, J = 5.1 Hz, thiophene).

Anal. Calcd. for $C_{13}H_{13}NO_4S_2$: C, 50.14; H, 4.21; N, 4.50; S, 20.59. Found: C, 50.15; H, 4.30; N, 4.61; S, 20.61.

Sulfamoylthiophenecarboxylic Acids **13** and **14**.

General Method.

A suspension of the above sulfamoylthiophenecarboxylates (0.1 mole) in 1*N* sodium hydroxide solution (1000 ml) was heated under reflux temperature for 30 minutes. After cooling, the resulting solution was acidified with concentrated hydrochloric acid to *p*H 4. The precipitated solid was filtered, washed with water and dried to give the desired carboxylic acid. In this way were prepared:

4-(*N*-Phenyl-*N*-methyl)sulfamoylthiophene-3-carboxylic Acid **13**.

This compound was obtained from **11** in 90% yield as a white crystalline solid of mp 151-153° (benzene); ir (potassium bromide): 1710 cm^{-1} (CO), 1350, 1170 cm^{-1} (SO_2); ^{1}H nmr (DMSO-d_6): δ 3.35 (s, 3H, CH_3), 7.30 (m, 5H, benzene), 8.10 (d, 1H, J = 3.7 Hz, thiophene), 8.30 (d, 1H, J = 3.7 Hz, thiophene).

Anal. Calcd. for $C_{12}H_{11}NO_4S_2$: C, 48.47; H, 3.73; N, 4.71; S, 21.57. Found: C, 48.51; H, 3.93; N, 5.07; S, 21.27.

3-(*N*-Phenyl-*N*-methyl)sulfamoylthiophene-2-carboxylic Acid **14**.

This compound was obtained from **12** in 96% yield as a white crystalline solid of mp 134-135° (water); ir (potassium bromide): 1700 cm^{-1} (CO), 1350, 1140 cm^{-1} (SO_2); ^{1}H nmr (DMSO-d_6): δ 3.40 (s, 3H, CH_3), 7.15 (d, 1H, J = 5.3 Hz, thiophene), 7.30 (s, 5H, benzene), 7.75 (d, 1H, J = 5.3 Hz, thiophene).

Anal. Calcd. for $C_{12}H_{11}NO_4S_2$: C, 48.47; H, 3.73; N, 4.71; S, 21.57. Found: C, 48.45; H, 3.68; N, 4.92; S, 21.66.

Thieno[2,1]benzothiazepinones **7** and **8**..

Method A.

A mixture of the corresponding sulfamoylthiophenecarboxylic acid **13** or **14** (0.016 mole), thionyl chloride (10 ml) and *N,N*-dimethylformamide (3 drops) was heated under reflux for 2 hours. Then it was concentrated under reduced pressure and the residue, containing the crude acid chloride **15** or **16**, was dissolved in dry carbon disulfide (50 ml). To this solution anhydrous aluminum(III) chloride (10.6 g, 0.08 mole) was added and the mixture was stirred at room temperature overnight. Then the reaction mixture was refluxed for 1 hour and, after cooling, it

was cautiously poured onto 10% aqueous hydrochloric acid (50 ml) and ice (50 g). The resulting solid was fitered, washed with water and recrystallized.

Method B.

A stirred mixture of the sulfamoylthiophenecarboxylic acid **13** or **14** (0.035 mole), polyphosphoric acid (104 g) and toluene (500 ml) was heated under reflux for 3 hours. The hot toluene was decanted and the inorganic residue was refluxed again with toluene (100 ml). The organic extracts were combined and concentrated in vacuo to give the target ketones identical with those obtained by Method A.

5,10-Dihydro-5-methyl-4,4,10-trioxothieno[3,4-*c*][2,1]benzothiazepine **7**.

This compound was obtained in 78% by Method A and 79% by Method B as a white crystalline solid of mp 137-139° (ethanol); ir (potassium bromide): 1640 cm^{-1} (CO), 1340, 1150 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 3.20 (s, 3H, CH_3), 7.30-7.70 (m, 3H, benzene), 8.05 (d, 1H, J = 3.7 Hz, thiophene), 8.20 (dd, 1H, J_m = 2.2 Hz, J_o = 9.0 Hz, benzene), 8.50 (d, 1H, J = 3.7 Hz, thiophene).

Anal. Calcd. for $C_{12}H_9NO_3S_2$: C, 51.59; H, 3.25; N, 5.01; S, 22.96. Found: C, 52.01; H, 3.35; N, 5.16; S, 23.34.

5,10-Dihydro-5-methyl-4,4,10-trioxothieno[3,2-*c*][2,1]benzothiazepine **8**.

This compound was obtained in 82% by Method A and 87% by Method B as a yellow crystalline solid of mp 176-178° (toluene); ir (potassium bromide): 1630 cm^{-1} (CO), 1350, 1150 cm^{-1} (SO_2); ^1H nmr (DMSO-d_6): δ 3.20 (s, 3H, CH_3), 7.50-7.90 (m, 4H, 3 benzene and 1 thiophene), 8.10 (dd, 1H, J_m = 1.5 Hz, J_O = 9.0 Hz, benzene), 8.35 (d, 1H, J = 5.2 Hz, thiophene).

Anal. Calcd. for $C_{12}H_9NO_3S_2$: C, 51.59; H, 3.25; N, 5.01; S, 22.96. Found: C, 51.60; H, 3.32; N, 5.04; S, 22.51.

Methyl 3-[*N'*-(2-Carbomethoxythien-3-yl)-*N*-hydrazinosulfonyl]thiophene-2-carboxylate **17**.

This compound was formed as a byproduct in the synthesis of methyl 3-chlorosulfonylthiophene-2-carboxylate from methyl-3-aminothiophene-2-carboxylate [10]. It was obtained by treating the crude reaction product with dichloromethane which dissolves the chlorosulfonyl derivative **10**. The insoluble residue was **17** (20-30%), a white solid of mp 170-172° (dec, gas evolution) (acetone); ir (potassium bromide): 3350, 3250 cm^{-1} (NH), 1750, 1670 cm^{-1} (CO), 1260, 1090 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 3.75 (s, 3H, CH_3), 4.00 (s, 3H, CH_3), 7.15 (d, 1H, J = 5.2 Hz, thiophene), 7.40 (d, 1H, J = 5.2 Hz, thiophene), 7.60 (s, 2H, thiophene), 7.90 (s, 1H, NH, exchangeable with deuterium oxide), 8.30 (s, 1H, NH, exchangeable with deuterium oxide); ms: m/z 376 (M^+, 13%), 312 ($M^+ - SO_2$, 2%), 171 ($M^+ - C_6H_5O_4S_2$, 100%).

Anal. Calcd. for $C_{12}H_{12}N_2O_6S_3$: C, 38.28; H, 3.21; N, 7.44; S, 25.55. Found: C, 38.31; H, 3.40; N, 7.23; S, 25.27.

Acknowledgements.

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