Synthesis of 1*H*- and 2*H*-Pyrazolo[3,4-*c*][2,1]benzothiazepines

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Starting from ethyl chlorosulfonylpyrazole-4-carboxylates we have carried out the synthesis of ketones **3** and **4** which are the first two structures of the novel 1*H*- and 2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine ring systems

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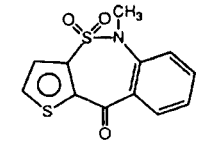
In connection with a program directed towards the search of derivatives of thieno[3,2-*c*] and thieno[3,4-*c*]-[2,1]benzothiazepine, we have described in a preceding paper [1] the synthesis of compounds **1** and **2** which were used as intermediate synthons for the preparation of more complex molecules with potential psychotropic activity. The known pharmacological properties of certain derivatives of pyrazole [2,3] and our interest in the development of more active compounds in this field, led us to extend our previous work to the synthesis of the pyrazole-containing tricyclic ketones **3** and **4.** Since only some derivatives of pyrazolo[3,4-*b*][1,4]-, pyrazolo[3,4-*b*][1,5]-, pyrazolo[3,4-*c*][1,5]-, pyrazolo[4,3-*b*][1,5]- and pyrazolo[4,3-*i*][1,5]benzothiazepine are described in the bibliographie [4-11], **3** and **4** are new compounds and the first representatives of the hitherto unknown 1H- and 2H-pyrazolo[3,4-*c*][2,1]benzothiazepine ring systems.

The synthesis of these compounds is illustrated in Schemes 1 and 2. Thus, the starting ethyl aminopyrazole-carboxylates **5** and **6** (Scheme 1) were prepared from the condensation of ethyl 2-cyano-3-ethoxyacrylate with hydrazine and *N*-benzylidene-*N'*-methylhydrazine respectively according to procedures previously described [12,13].

The transformation of these compounds into the chlorosulfonyl derivatives **9** and **10** was carried out through a modification of the method employed by Bellemin and Festal [14] which involves a Meerwein type reaction [15] of the diazonium salt **8** with sulfur dioxide and cupric chloride in acetic acid. In this method, the diazotization reaction takes place in a mixture of acetic and formic acids because of the low solubility of the aminopyrazole-carboxylate **6** in aqueous media but, as we have observed, the presence of this solvent mixture makes difficult the



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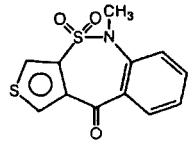

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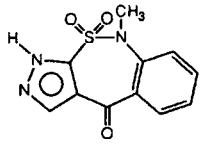

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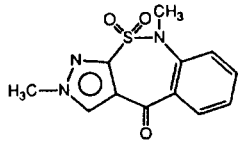

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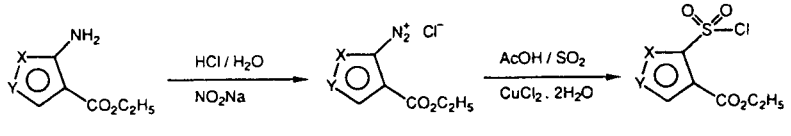


5 X=NH ; Y=N

6 X=N ; Y=NCH3

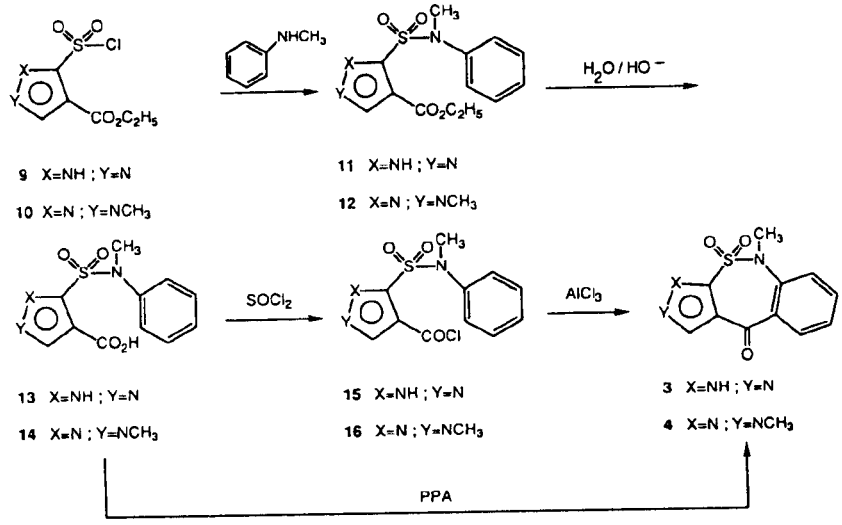
7 X=NH ; Y=N

8 X=N ; Y=NCH3

9 X=NH ; Y=N

10 X=N ; Y=NCH3

Scheme 1



Scheme 2

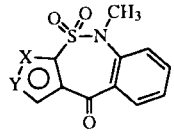
subsequent isolation and purification of the chlorosulfonyl derivatives **9** and **10**. We have found that a portionwise addition of the aminopyrazoles to aqueous concentrated hydrochloric acid permits their solution and consequently the easy formation of the diazonium salts and their transformation into compounds **9** and **10** in good yields and purity.

The 1*H*- and 2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepinones **3** and **4** were obtained by following the synthetic route indicated in Scheme 2. Thus, heating at reflux temperature a solution of chlorosulfonyl derivatives **9** and **10** and an excess of *N*-methylaniline in tetrahydrofuran gave the corresponding ethyl sulfamoylpyrazole-4-carboxylates **11** and **12** in 97 and 92% yield respectively. These sulfamoyl-carboxylates were readily converted to the carboxylic acids **13** and **14** by hydrolysis in aqueous 1*N* potassium hydroxide and subsequent acidification of the alkaline solution with concentrated hydrochloric acid. The precipitated compounds **13** and **14** were white crystalline solids which were collected by filtration in nearly quantitative yields. For their analysis and identification, both compounds were recrystallized from water or acetonitrile. In the routine work, however, they were used for the next reaction step directly without purification.

The final step of this synthesis consisted in the cyclization of these carboxy derivatives to the target ketones **3** and **4**. This was accomplished by a Friedel-Crafts reaction of the intermediate acyl chlorides **15** and **16** or by a direct intramolecular cyclodehydration of **13** and **14**. In the first process, the acyl chlorides **15** and **16**, previously obtained from their respective carboxylic acids by reaction with an excess of thionyl chloride and catalytic amounts of *N*,*N*-dimethylformamide [16], were dissolved in carbon disulfide and heated in the presence of aluminum(III) chloride as the catalyst. In the second process, the carboxy derivatives **13** and **14** were ring closed in a mixture of polyphosphoric acid and xylene at reflux temperature. Although both methods were successful in giving **3** and **4** in good yields (Table 1), the second one was more generally employed due to its better scale up in the laboratory .

The structure of the ketones **3** and **4** was supported and characterized by elemental and spectroscopic analyses. Their ir spectra showed bands at 1620-1640 cm^{-1} (CO), 1340-1350 and 1160-1180 cm^{-1} (SO_2). The ^{1}H-nmr spectra exhibited the signals corresponding to the sulfonamide methyl protons as singlets at δ 3.10-3.25 and the mass spectra showed the expected molecular peaks at m/z 263 and 277 respectively.

Table 1



NO.	X	Y	IR (cm^{-1}) (SO_2)	IR (cm^{-1}) (C=O)	Method	Yield (%)
3	NH	N	1180, 1340	1640	A	93
					B	68
4	N	NCH_3	1160, 1350	1620	A	73
					B	72

In summary, the synthesis of the tricyclic ketones **3** and **4** has been accomplished by cyclization of the sulfamoylpyrazole-4-carboxylic acids **13** and **14** following a methodology which had already been utilized in the formation of the 5,10-dihydro-5-methyl-4,4,10-trioxoth-

ieno[3,2-*c*][2,1]benzothiazepines **1** and **2** [1]. The accessibility of the starting chloro sulfonylpyrazole-4-carboxylates, which has been revised, and the simplicity of their conversion to the corresponding carboxylic acids are other facts which make more attractive this novel synthesis of 1*H*- and 2*H*-pyrazolo[3,4-*c*][2,1]benzothiazepines.

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 the 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.

Ethyl Chlorosulfonylpyrazole-4-carboxylates **9** and **10**.

General Method.

The ethyl chlorosulfonylpyrazole-4-carboxylate **5** or **6** [12,13] (0.16 mole) was added portionwise to a cooled (ice bath) and stirred 35% hydrochloric acid solution (50 ml). After addition of each portion a solution of sodium nitrite (12 g, 0.17 mole) in water (20 ml) was added dropwise until the thick mass which formed has disappeared. This operation was repeated until all the aminopyrazole was added. The temperature of the reaction was maintained at 10-12°. The resulting diazonium salt was stirred for one more hour at this temperature and then added to a freshly prepared solution of cupric chloride (6.4 g) in glacial acetic acid (128 ml) saturated with sulfur dioxide. The reaction mixture was poured into ice water (600 ml) and the solid so formed was collected, washed with water, dried and crystallized.

Ethyl 3(5)-Chlorosulfonylpyrazole-4-carboxylate **9**.

This compound was prepared by the method described above from ethyl 3(5)-aminopyrazole-4-carboxylate (**5**) as white crystals (63%) of mp 188-190° (ethanol); ir (nujol): 3300 cm^{-1} (NH), 1710 cm^{-1} (CO), 1390, 1195 cm^{-1} (SO_2); ^{1}H nmr (DMSO-d_6): δ 1.25 (t, 3H, J = 7.0 Hz, CH_3), 4.20 (q, 2H, J = 7.0 Hz, CH_2), 7.90 (s, 1H, pyrazole), 13.80 (s, 1H, NH, exchangeable with D_2O).

Anal. Calcd. for $C_6H_7ClN_2O_4S$: C, 30.19; H, 2.96; N, 11.74; S, 13.44. Found: C, 30.21; H, 3.07; N, 11.61; S, 13.78.

Ethyl 3-Chlorosulfonyl-1-methylpyrazole-4-carboxylate **10**.

This compound was formed in the same manner from ethyl-3-amino-1-methylpyrazole-4-carboxylate (**6**) (76%) as a white solid of mp 80-81° (ethyl ether- petroleum ether). Lit. [14] mp 79-81°.

Ethyl Sulfamoylpyrazolo-4-carboxylates **11** and **12**.

General Method

A solution of the corresponding ethyl chlorosulfonylpyrazolecarboxylate (0.1 mole) and *N*-methylaniline (0.2 mole) in tetrahydrofuran (70 ml) was heated at reflux temperature for one hour. Then the mixture was concentrated under reduced pressure and the residue was washed with cold water. The solid formed was filtered, dried and recrystallized to give the required methyl sulfamoylpyrazolecarboxylate.

Ethyl 3(5)-(*N*-Phenyl-*N*-methyl)sulfamoylpyrazole-4-carboxylate **11**.

This compound was obtained in 97% yield from ethyl 3(5)-chlorosulfonylpyrazole-4-carboxylate (**9**) following the above method. It was a white crystalline solid of mp 133-135° (ethanol/water); ir (potassium bromide): 3300 cm^{-1} (NH), 1710 cm^{-1} (CO), 1345, 1180 cm^{-1} (SO_2); ^{1}H nmr (DMSO-d_6): δ 1.25 (t, 3H, J = 7.5 Hz, CH_3), 3.40 (s, 3H, CH_3), 4.20 (q, 2H, J = 7.5 Hz, CH_2), 7.35 (m, 5H, benzene), 8.50 (s, 1H, pyrazole).

Anal. Calcd. for $C_{13}H_{15}N_3O_4S$: C, 50.46; H, 4.90; N, 13.58; S, 10.36. Found: C,50.53; H, 5.01; N, 13.45; S, 10.11.

Ethyl 1-Methyl-3-(*N*-phenyl-*N*-methyl)sulfamoylpyrazole-4-carboxylate **12**.

This compound was formed in 92% yield from 3-chlorosulfonyl-1-methylpyrazole-4-carboxylate (**10**) as a white crystalline solid of mp 80-81° (ethanol); ir (potassium bromide): 1710 cm^{-1} (CO), 1385, 1150 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 1.30 (t, 3H, J = 8.2 Hz, CH_3), 3.50 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 4.25 (q, 2H, J = 8.2 Hz, CH_2), 7.20-7.55 (m, 5H, benzene), 7.90 (s, 1H, pyrazole).

Anal. Calcd. for $C_{14}H_{17}N_3O_4S$: C, 52.01; H, 5.26; N, 13.00; S, 9.90. Found: C, 52.15; H, 5.34; N, 13.22; S, 10.09.

Sulfamoylpyrazole-4-carboxylic Acids **13** and **14**.

General Method.

A suspension of the ethyl sulfamoylpyrazole-4-carboxylate **11** or **12** (0.1 mole) in 1*N* potassium hydroxide solution (1000 ml) was heated under reflux temperature for 30 minutes. After cooling with an ice bath, the resulting solution was acidified with concentrated hydrochloric acid at p*H* 4. The precipitated solid was filtered, washed with water and dried to give the desired sulfamoylpyrazolecarboxylic acid.

3(5)-(*N*-Phenyl-*N*-methyl)sulfamoylpyrazole-4-carboxylicAcid **13**.

This compound was obtained in 99% yield from ethyl 3(5)-(*N*-phenyl-*N*-methyl)sulfamoylpyrazole-4-carboxylate (**11**) as a white crystalline solid of mp 181-183° (water); ir (potassium bromide): 3300 cm^{-1} (NH), 1710 cm^{-1} (CO), 1320, 1180 cm^{-1} (SO_2); ^{1}H nmr (DMSO-d_6): δ 3.40 (s, 3H, CH_3), 7.35 (m, 5H, benzene), 8.40 (s, 1H, pyrazole).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S$: C, 46.96; H, 3.94; N, 14.94; S, 11.40. Found: C, 46.79; H, 3.85; N, 14.78; S, 11.77.

1-Methyl-3-(*N*-phenyl-*N*-methyl)sulfamoylpyrazole-4-carboxylic Acid **14**.

This compound was prepared in 98% yield from ethyl 1-methyl-3-(*N*-phenyl-*N*-methyl)sulfamoylpyrazole-4-carboxylate (**12**) as a white solid of mp 224-225° (acetonitrile); ir (potassium bromide): 1690 cm^{-1} (CO), 1340, 1155 cm^{-1} (SO_2); ^{1}H nmr (DMSO-d_6): δ 3.40 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 7.35 (m, 5H, benzene), 8.40 (s, 1H, pyrazole).

Anal. Calcd. for $C_{12}H_{13}N_3O_4S$: C, 48.80; H, 4.44; N, 14.23; S, 10.86. Found: C, 49.13; H, 4.42; N, 14.14; S, 10.98.

Pyrazolo[2,1]benzothiazepinones **3** and **4**.

Method A.

A mixture of the corresponding sulfamoylpyrazole-4-carboxylic acid **13** or **14** (0.032 mole), thionyl chloride (20 ml) and *N,N*-dimethylformamide (0.3 ml) was heated under reflux for 2 hours. The mixture was concentrated *in vacuo* and the residue, containing the crude carboxylic acid chloride, was dissolved in dry carbon disulfide (100 ml). To this solution, anhydrous aluminum(III) chloride (21.2 g, 0.16 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 (100 ml) and ice (100 g). The resulting solid was filtered, washed with water, dried and recrytallized from the appropriate solvent.

Method B.

A stirred mixture of powdered sulfamoylpyrazolecarboxylic acid **13** or **14** (0.1 mole), polyphosphoric acid (300 g) and xylene (300 ml) was heated under reflux for 2 hours. After cooling, the xylene was decanted and the viscous residue was poured onto a mixture of ice and water (300 g). The precipitated solid was filtered, washed with water, dried and recrystallized to give the target ketones identical with those obtained by method A.

4,9-Dihydro-9-methyl-4,10,10-trioxo-1*H*-pyrazolo[3,4-*c*][2,1]-benzothiazepine **3** .

This compound was obtained from **13** in 92% (method A) and 68% (method B) yields as a white crystalline solid of mp 205-207° (water); ir (potassium bromide): 3300 cm^{-1} (NH), 1640 cm^{-1} (CO), 1340, 1180 (SO_2); ^1H nmr (DMSO-d_6): δ 3.10 (s, 3H, CH_3), 7.40-7.90 (m, 3H, benzene), 8.00 (dd, 1H, J_m = 1.5 Hz, J_o = 9.0 Hz, benzene), 8.70 (s, 1H, pyrazole).

Anal. Calcd. for $C_{11}H_9N_3O_3S$: C, 50.19; H, 3.42; N, 15.97; S, 12.17. Found: C, 50.22; H, 3.44; N, 16.06; S, 11.94.

4,9-Dihydro-2,9-dimethyl-4,10,10-trioxo-2*H*-pyrazolo[3,4-*c*]-[2,1]benzothiazepine **4**.

This compound was prepared from **14** by methods A (73%) and B (72%) as a white solid of mp 203-205° (methanol); ir (potassium bromide): 1620 cm^{-1} (CO), 1350, 1160 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 3.25 (s, 3H, CH_3), 4.05 (s, 3H, CH_3), 7.30-7.60 (m, 3H, benzene), 8.10 (dd, 1H, J_m = 2.2 Hz, J_o = 8.2 Hz, benzene), 8.20 (s, 1H, pyrazole).

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 3.97; N, 15.16; S, 11.55. Found: C, 52.30; H, 4.19; N, 15.01; S, 11.23.

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