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SYNTHESIS OF N-METHYL-3-CARBOXY-2-CHLORO-DIBENZO[*c,f*][1,4,5]OXA-THIAZEPINE S,S-DIOXIDE AND ITS DERIVATIVES

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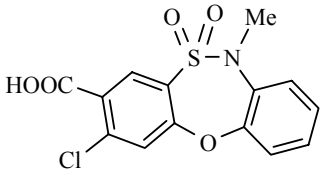
A new dibenzo-condensed oxathiazepinecarboxylic acid was obtained starting from the methyl ester of 2,4-dichloro-5-chlorosulfonylbenzoic acid. Derivatives were obtained from N-phenylamide and N-methylamide of 2,4-dichloro-5-chlorosulfonylbenzoic acid. Methods for the preparation of the starting aromatic sulfonyl chlorides were proposed.

Keywords: dibenzoxathiazepinecarboxylic acid, diacid chloride of 2,4-dichloro-5-sulfobenzoic acid, methyl ester, N-phenylamide and N-methylamide of 2,4-dichloro-5-chlorosulfonylbenzoic acid.

In a continuous of previous work [1-3] on the synthesis of sulfonylamides of dibenzo-condensed seven-membered heterocyclic compounds, we have developed a method for the preparation of aromatic carboxylic acid **1**, which contains a sulfonyl group in a seven-membered ring. This compound is an interesting candidate for pharmaceutical purposes since a compound with a similar structure, namely, the tricyclic antidepressant *tianeptine* **2,** is commonly used in medical practice [2].



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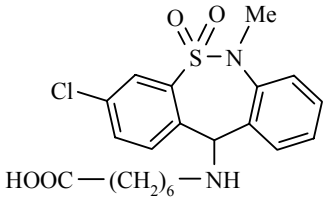

2

Aromatic carboxylic acid **1** may be synthesized from sulfonylamide **3**, but the latter could not be obtained by the reaction of sulfonyl chloride **4** with N-methyl-2-aminophenol **5** due to tar formation.

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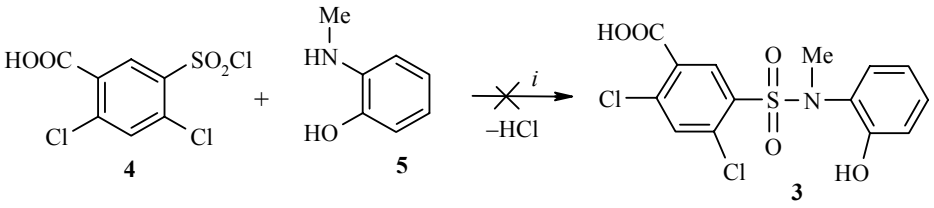
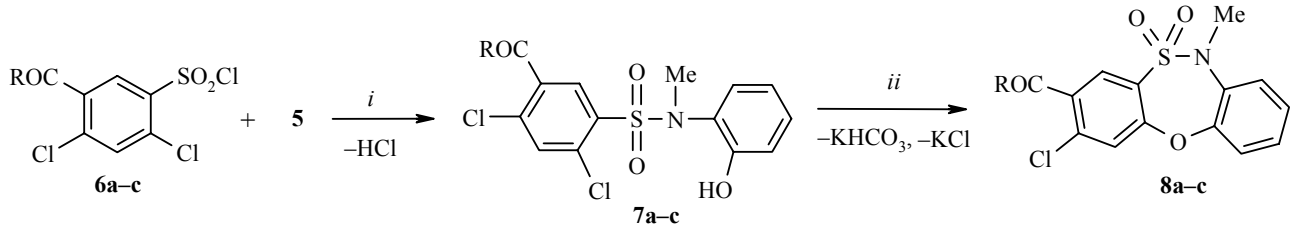


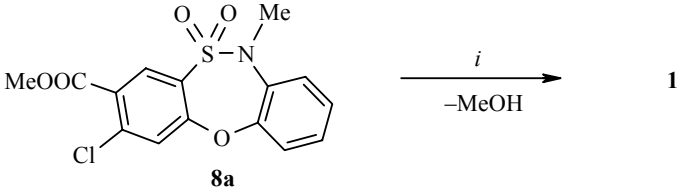
i: MeCN, 40°C, 40 min

The use of carboxyl group derivative **6** instead of sulfonyl chloride **4** considerably facilitates the preparation of the corresponding sulfonylamides. Thus, the reaction of aminophenol **5** with the methyl ester **6a**, N-phenylamide **6b**, and N-methylamide of 2,4-dichloro-5-chlorosulfonylbenzoic acid **6c** at 40°C over 40 min in acetonitrile as solvent gave in yields over 85% the corresponding sulfonylamides **7**, which convert to dibenzoxathiazepines **8** upon heating at 70°C in DMF in the presence of K_2CO_3 over 10 min practically in quantative yields.



i: MeCN, 40°C, 40 min; *ii:* DMF, K_2CO_3, 70°C, 10 min;
6–8 a R = OMe, **b** R = NHPh, **c** R = NHMe

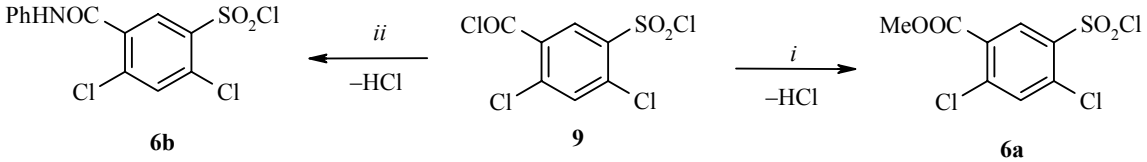
The alkaline hydrolysis of the ester group in **8a** leads to the preparation of the desired aromatic carboxylic acid **1**.



i: 1. KOH, H_2O, reflux; 2. H^+

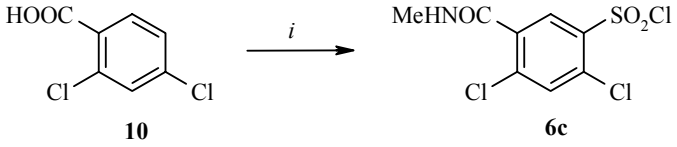
The presence of a carboxyl group and chlorine atom opens pathways for further functionalization of the product obtained.

The synthesis of the starting sulfonyl chlorides **6a**,**b** is based on the significant difference in the reactivity of the chloroformyl and sulfonyl chloride groups of the dichloride of the 3-sulfobenzoic acid in its reactions with methanol [5] and aniline [6, 7].



i: MeCN, MeOH, NEt_3, 20°C, 1 h; *ii:* MeCN, $PhNH_2$, 20°C, 1 h

We were unable to carry out a regioselective reaction of dichloride **9** with an aliphatic amine. Analysis of the reaction mixture showed replacement at both functional groups in addition to a side-product [7]. Thus, we developed a synthesis for sulfonyl chloride **6c** based on the prior sulfochlorination of 2,4-dichlorobenzoic acid **10** with subsequent amidation of the carboxyl group of the N-methylsulfaminic acid without isolation of the intermediate 2,4-dichloro-5-chlorosulfonylbenzoic acid [8].



10 **6c**

i: 1) $HClSO_3$, 140°C, 2 h; 2) 110°C, $MeHNSO_3H$, 2 h

Under these conditions, the desired chlorosulfonylbenzamide **6c** was obtained in 89% yield. The substitution of the N-methylsulfaminic acid with the corresponding urea derivative $CO(NHMe)_2$ permitted us to increase the yield of the final product **6c** to 95% with lowering of the amidation reaction temperature to 90°C.

It proved impossible to obtain products **6a-c** used in the synthesis of both dibenzoxathiazepinecarboxylic acid **1** and derivatives of this acid **8a-c** by the direct sulfochlorination of the corresponding derivatives of 2,4-dichlorobenzoic acid due to the polyvariant opening of the sulfo group to give benzanilides or the chemical instability of the ester and amide groups under the conditions of this reaction.

EXPERIMENTAL

The ^1H NMR spectra were taken on a Bruker DRX 500 spectrometer at 500 MHz in DMSO-d_6 with TMS as the internal standard. The nitrogen, carbon, and hydrogen contents were determined on a FLASH 1112 elemental analyzer, while the sulfur content was determined titrimetrically by combustion in a Shöniger flask.

Commercial samples of 2,4-dichlorobenzoic acid **10** and N-methyl-2-aminophenol were used [9].

Sulfonyl chloride **4** and dichloride **9** were synthesized analogously to the sulfonyl chlorides of benzoic acid and the dichloride derivatives of 3-sulfobenzoic acid. The general methods for these procedures were given by Pisarev [8] and Timoshenko [6], respectively.

The methyl ester **6a** [5], N-phenylamide **6b** [6], and N-methylamide of 2,4-dichloro-5-chlorosulfonylbenzoic acid **6c** [8] were obtained by procedures given in our previous work.

Methyl ester of 2,4-dichloro-5-chlorosulfonylbenzoic Acid (6a) was obtained in 72% yield; mp 59-61°C. Found, %: C 32.25; H 1.64; Cl 33.88; S 10.78. $C_8H_5Cl_3O_4S$. Calculated, %: C 31.65; H 1.66; Cl 35.04; S 10.56.

N-Phenylamide of 2,4-dichloro-5-chlorosulfonylbenzoic Acid (6b) was obtained in 80% yield; mp 143-145°C. Found, %: C 42.80; H 2.10; Cl 29.11; N 3.75; S 8.77. $C_{13}H_8Cl_3NO_3S$. Calculated, %: C 42.82; H 2.21; Cl 29.17; N 3.84; S 8.79.

N-Methylamide of 2,4-dichloro-5-chlorosulfonylbenzoic Acid (6c) was obtained in 95% yield; mp 167-168°C. Found, %: C 31.68; H 1.91; Cl 35.14; N 4.65; S 10.54. $C_8H_6Cl_3O_3S$. Calculated, %: C 31.76; H 2.00; Cl 35.15; N 4.63; S 10.60.

Synthesis of sulfonylamides 7a-c (General Method). A sample of the corresponding sulfonyl chloride **6a-c** (4 mmol) was added with stirring to a solution of N-methyl-2-aminophenol **5** (8 mmol) in acetonitrile (2 ml) in a three-necked flask equipped with a stirrer and thermometer. The reaction mixture was heated at 40°C for 40 min, cooled to room temperature, and poured into water (30 ml). The precipitate formed was filtered off, recrystallized from 2-propanol–DMF 1:2, and dried in a desiccator to constant weight.

Methyl ester of 2,4-dichloro-5-[(2-hydroxyphenyl)methylsulfamoyl]benzoic acid (7a) was obtained in 88% yield; mp 146-147°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.25 (3H, s, SO_2NCH_3); 3.57 (3H, s, CO_2CH_3); 6.75-6.81 (2H, m, H-4', H-6'); 7.09 (1H, dd, *J* = 7.9, *J* = 1.3, H-3'); 7.15 (1H, t.d, *J* = 8.9, *J* = 1.4, H-5'); 8.05 (1H, s, H-3); 8.15 (1H, s, H-6); 9.73 (1H, s, OH). Found, %: C 46.36; H 3.30; N 3.73; S 8.00. $C_{15}H_{13}Cl_2NO_5S$. Calculated, %: C 46.17; H 3.36; N 3.59; S 8.22.

N-Phenyl-2,4-dichloro-5-[(2-hydroxyphenyl)methylsulfamoyl]benzamide (7b) was obtained in 91% yield; mp 197-200°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.26 (3H, s, SO_2NCH_3); 6.76 (1H, td, *J* = 7.7, *J* = 1.3, H-5'); 6.84 (1H, dd, *J* = 8.2, *J* = 1.3, H-3'); 7.08-7.17 (3H, m, H-2", H-3", H-4"); 7.36 (2H, t, *J* = 8.1, H-1", H-5"); 7.66 (2H, d, *J* = 7.7, H-6'); 7.90 (1H, s, H-3); 8.01 (1H, s, H-6); 9.57 (1H, s, OH); 10.52 (1H, s, CONH). Found, %: C 52.83; H 3.53; N 6.53; S 7.00. $C_{20}H_{16}Cl_2N_2O_4S$. Calculated, %: C 53.23; H 3.57; N 6.21; 7.10.

N-Methyl-2,4-dichloro-5-[(2-hydroxyphenyl)methylsulfamoyl]benzamide (7c) was obtained in 89% yield; mp 207-208.5°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.74 (3H, d, *J* = 4.6, $COHNCH_3$); 3.25 (3H, s, SO_2NCH_3); 6.75 (1H, td, *J* = 7.7, *J* = 1.4, H-5'); 6.82 (1H, d, *J* = 8.2, *J* = 1.3, H-6'); 7.06 (1H, dd, *J* = 7.9, *J* = 1.6, H-3'); 7.14 (1H, td, *J* = 8.1, *J* = 1.7, H-4'); 7.59 (1H, s, H-3); 7.91 (1H, s, H-6); 8.5 (1H, br. s, CONH); 9.56 (1H, s, OH). Found, %: C 46.58; H 3.66; N 7.38; S 8.11. $C_{15}H_{14}Cl_2N_2O_4S$. Calculated, %: C 46.28; H 3.63; N 7.20; S 8.24.

An attempt to synthesize sulfonylamide **3** was carried out analogously to the procedure for preparation of sulfonylamides **7a-c**.

Synthesis of dibenzoxathiazepines 8a-c (General Method). A solution of corresponding sulfonylamide **7a-c** (3 mmol) in DMF (10 ml) and potassium carbonate (6 ml) was heated with stirring at 70°C for 10 min, then cooled to room temperature, and poured into (10 ml) water. The precipitate formed was recrystallized from 2-propanol–DMF, 1:1, and dried in a desiccator to constant weight.

N-Methyl-2-chloro-3-methoxycarbonyldibenzo[*c*,*f*][1,4,5]oxathiazepine S,S-Dioxide (8a) was obtained in 92% yield; mp 165-166°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.3 (3H, s, SO_2NCH_3); 3.89 (3H, s, CO_2CH_3); 7.38 (1H, td, *J* = 7.6, *J* = 1.7, H-8); 7.44-7.51 (2H, m, H-7, H-9); 7.55 (1H, dd, *J* = 7.8, *J* = 1.6, H-10); 7.85 (1H, s, H-1); 8.5 (1H, s, H-4). Found, %: C 51.03; H 3.43; N 4.11; S 8.63. $C_{15}H_{12}ClNO_5S$. Calculated, %: C 50.93; H 3.42; N 3.96; S 9.06.

N-Methyl-2-chloro-3-phenylcarbamoyldibenzo[*c*,*f*][1,4,5]oxathiazepine S,S-Dioxide (8b) was obtained in 94% yield; mp 176-178°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.26 (3H, s, SO_2NCH_3); 7.13 (1H, t, *J* = 7.4, H-8); 7.34-7.40, 7.45-7.52, 7.56 (6H, m, H-11, H-12, m, H-13, H-14, H-15, dd, *J* = 1.5, *J* = 7.9, H-10); 7.68 (2H, d, *J* = 7.9, H-7, H-9); 7.85 (1H, s, H-1), 8.0 (1H, s, H-4); 10.52 (1H, s, CONH). Found, %: C 58.10; H 3.69; N 6.77; S 7.48. $C_{20}H_{15}ClN_2O_4S$. Calculated, %: C 57.90; H 3.64; N 6.75; S 7.73.

N-Methyl-2-chloro-3-methylcarbamoyldibenzo[*c*,*f*][1,4,5]oxathiazepine S,S-Dioxide (8c) was obtained in 91% yield; mp 201-203°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.77 (1H, d, *J* = 4.6, $CONHCH_3$); 3.30 (3H, s, SO_2NCH_3); 7.35 (1H, td, *J* = 7.5, *J* = 1.7, H-8); 7.43-7.50 (2H, m, H-7, H-9); 7.54 (1H, dd, *J* = 7.9, *J* = 1.6, H-10); 7.76 (1H, s, H-1); 7.80 (1H, s, H-4); 8.51 (1H, s, CONH). Found, %: C 51.45; H 3.75; N 8.14; S 8.94. $C_{15}H_{13}ClN_2O_4S$. Calculated, %: C 51.07; H 3.71; N 7.94; S 9.09.

N-Methyl-3-carboxy-2-chlorodibenzo[*c*,*f*][1,4,5]oxathiazepine S,S-dioxide (1). A mixture of aromatic carboxylic acid methyl ester **8a** (2 mmol), KOH (4 mmol), and water (10 ml) was heated at reflux until the solid residue dissolved, cooled to room temperature, and filtered to remove the mechanical impurities. The filtrate was made acidic by adding 10% hydrochloric acid. The precipitate formed was filtered off and dried in a desiccator to constant weight. The yield of acid **1** was 95%; mp 213-215°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.22 (3H, s, SO_2NCH_3); 7.38 (1H, td, *J* = 8.4, *J* = 1.4, H-8); 7.44-7.51 (2H, m, H-7, H-9); 7.55 (1H, dd, *J* = 8.1, *J* = 0.8, H-10); 7.8 (1H, s, H-1); 8.21 (1H, s, H-4); 13.8 (1H, br. s, CO_2H). Found, %: C 49.01; H 2.86; N 4.03; S 9.21. $C_{14}H_{10}ClNO_5S$. Calculated, %: C 49.49; H 2.97; N 4.12; S 9.44.

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