Synthesis of New Sulphonamide Phenoxyacetic Derivatives

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This paper presents experimental data regarding the synthesis of several new sulphonamide phenoxyacetic derivatives. These new compounds have been analysed by physico-chemical technics (elemental analyses, ^{1}H-NMR, ^{13}C-NMR, FT IR, thin layer chromatography).

Keywords: phenoxyacetic acid derivatives, sulphonamide, growth-stimulators

Sulphonamides are today an important class of chemical products characterized by herbicide or growth regulating auxinic effects, by the lack of toxicity towards human beings, animals, bees, and fish and by the fact that they are biodegradable. The main characteristic of the sulphonamides is represented by the fact that introducing the sulphonamide group into an aromatic nucleus or heterocyclic nucleus we induce a pronounced decrease of the toxicity and in correlation with the pre-existing substituents in these nuclei, the substance acquires a wide range of biological features. We propose to introduce the sulphonamide group into the aromatic nucleus of phenoxyacetic derivatives in order to obtain new, innovative, unlisted in literature sulphonamide compounds. We choose as a support for the sulphonamide group the phenoxyacetic derivatives because they have reduced toxicity, are biodegradable, have not cumulative action in the organisms, do not generate undesired effects, fact proved by Penicillin V (phenoxymetil-penicilin) and by Percluson, an anti-rheumatic drug, with para-clorophenoxy-diethylamino-ethylacetamide in its structure, product far less toxic than Phenylbutazone and with less secondary effects and reduced toxicity; chlorinated phenoxyacetic derivatives are used today in agricultural practice. These examples prove the advantages brought by the phenoxyacetic derivatives [1-6].

In this paper, we furnish the experimental details of the synthesis of new sulphonamide phenoxyacetic derivatives (fig. 1)

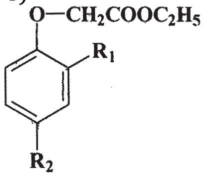

Fig. 1. Structure of the sulphonamide phenoxyacetic derivatives
R_1 = Cl R_2 = Cl

Experimental part

Melting points were determined in opened capillary on Melting point apparatus OptiMelt and are uncorrected.

Progress of the reaction was followed by TLG on Merck silica gel 60F_{254} plates eluted with the solvent system : chloroform: methanol: ammoniac (43:43:14) (v:v:v), benzene:methanol:acid acetic (30:2.5:2.5) (v:v:v). The plates were detected by UV light irradiation (λ= 254 nm).

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$, , on two instruments Varian, Varian Gemini 300 BB (operating at 300 MHz for proton and 75 MHz for carbon) and UNITY 400 Plus(operating at 400 MHz for proton and 100 MHz for carbon).Tetramerthylsilane as internal standard was the reference for the chemical shifts. All chemical shifts are given in the delta scale (ppm *vs* internal TMS). FT IR were recorded on a instrument Bruker Vertex 70 with diamond optic. Elemental analyses of carbon, hydrogen, nitrogen and sulphur have been performed using Perkin Elmer precisely series II CHNS/O Analyzer 2400.

Synthesis of 4-chlorophenoxiacetic acid

0.5 Mol (64.28 g) *para*-chloro-phenol is dissolved in 120 ml 20% NaOH, then add 0.7 mol (66.15 g) monocloracetic acid dissolved in 145 mL water. The reaction mixture is stired (the *p*H of the solution should remain between 8.5-9.0). at reflux for 3 h and then is cooled to 20^{0}C, acidify with sulfuric acid 50%. The precipitate formed is filtered, washed with water, dried and 4- clorophenoxiacetic acid was afforded with m.p.: 157.5-159^{0}C, yeld. 90%

$C_8H_7ClO_3$: M= 186.5933 g/mol
calcd.: C: 51.50% H: 3,78% Cl: 19.00%
found : C: 51.23% H: 3,65% Cl: 18.86%

FT-IR(ATR in solid, ν cm^{-1}): 3040 CH aromatic, 1619,1595,1487 C=C phenyl nucleus, 1115,1086,1022 CH phenyl, 796 phenyl *para*-substituted 1269 C-O(phenolic), 1274, 1576, 1731,1702, 1427, 1230, 930 COOH, 1450 CH_2 adjacent group COOH, 631 C-Cl

2-chlorophenoxiacetic acid

m.p. : 147.1-148.3^{0}C; yeld 83%
$C_8H_7ClO_3$: M= 186.5933 g/mol
calcd.: C: 51.50% H: 3.78% Cl: 19.00%
found : C: 51.24% H: 3,63% Cl: 18.90%

FT-IR(ATR in solid, ν cm^{-1}): 3040 CH aromatic (phenyl nucleus), 1587,1522,1483 C=C phenyl nucleus, 1136,1086,1051 CH phenyl, 1288 C-O(phenolic), 742 phenyl *orto*-substituted, 1241, 1578, 1707, 1739, 1421, 1241, 937 COOH, 1444 CH_2 adjacent group COOH, 666 C-Cl

Synthesis of 4-chlorophenoxiacetic acid ethyl ester

The esterification of 4-chlorophenoxyacetic with ethylic alcohol is done in homogeneous acid catalysis using a molar ratio alcohol: organic acid of 1:10 to reflux for 3 h.A mixture of 4chloro-phenoxy acetic acid (0.5 moles, 93.3 g), ethylic alcohol (143 mL) of sulfuric acid conc. (0.5% compared to the amount of alcohol) is heated while stirring and heating under reflux for 3 h.The reaction mixture is distilled in vacuum to remove excess alcohol. Over the residue from the distillation add a 1N NaOH solution (until basic *p*H), then filter and wash with water. Ethyl ester of 4-chlorophenoxyacetic was afforded with m.p.: 49-50.1^{0}C, yeld. 97%

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$C_{10}H_{11}ClO_3$. M= 214.6469 g/mol
calcd.: C: 55.96% H: 5,16% Cl: 16.52%
found: C: 56.03% H: 4.95% Cl: 16.42%

FT-IR(ATR in solid, ν cm^{-1}): 3062 CH phenyl nucleus 1683,1595,1483 C=C phenyl nucleus, 1110,1096,1022 CH phenyl nucleus 786 phenyl *para*-substituted, 1281 C-O(phenolic), 1742, 1389, 1213 COOR, 1447 CH_2 adjacent group COOR, 631 C-Cl

2-chlorophenoxiacetic acid ethyl ester

m.p.: 29.7-30.7° C; yeld. 88%
$C_{10}H_{11}ClO_3$. M= 214.6469 g/mol
Calcd.: C: 55.96% H: 5.16% Cl: 16.52%
found: C: 56.193% H: 5.01% Cl: 16.36%

FT-IR(ATR in solid, ν cm^{-1}): 3064 CH phenyl nucleus, 1703,1590, 1479 C=C phenyl nucleus, 1136,1081,1041 CH phenyl nucleus, 747 phenyl *orto*-substituted, 1281 C-O (phenolic), 1740, 1377, 1242 COOR, 1447 CH_2 adjacent group COOR, 682 C-Cl

Synthesis of 2-chlorosulphonyl-4-chloro-phenoxyacetic acid ethyl ester

Over a solution of ethyl ester of 4-chloro-phenoxyacetic acid (0.09 mol, 19.32 g) in 200 mL chloroform, cooled to 0°C are introduced 0.63 mol (42.2 mL) clorsulphonic acid so that the temperature does not exceed 5-6°C. After adding clorsulphonic acid continue stirring cold for 30 min, then gradually raise the temperature of reaction to 35° C and maintained at that temperature for 2 h. Finally the mixture is poured over 200g (ice + water). Separate the chloroform layer. May be extracted from the aqueous layer 2 times with chloroform. Combined organic solutions are washed with water, dry on anhydrous sodium sulfate and concentrate in vacuum. Crude product obtained is recristalizations of alcohol. 2-chlorosulphonyl-4-chloro-phenoxyacetic acid ethyl ester was afforded with m.p.: 74.1-74.7°C, yeld. 50%

$C_{10}H_{10}Cl_2SO_5$: M= 313.15 g/mol
calcd.: C: 38.35% H: 3.22% Cl: 22.64% S: 10.24%
found : C: 38.88% H: 3.09% Cl: 22.18% S: 10.16%

Synthesis of 2-chloro-4-chlorosulphonylphenoxy acetic acid ethyl ester

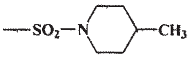
More than 0.405 mol (27 mL) clorsulphonic acid cooled on ice bath to 0°C are added, while stirring, 0.09 mol (19.39 g) ethyl ester of 2-chlorophenoxy acetic acid with such speed that the temperature should not exceed 5-6 ° C. After adding cold ester continue stirring for 30 min, then gradually raise the temperature to 32-35°C and maintain at that temperature for 2 h. Finally the mixture is cooled to 15-20° C, then is poured over a water-ice mixture. 2-chloro-4-chlorosulphonyl-phenoxyacetic acid ethyl ester is extracted with chloroform (200 mL). May be extracted from the aqueous layer 2 times with chloroform. Combined organic solutions are washed with water, dried on anhydrous sodium sulfate and concentrated in vacuum. Crude product obtained is purified from alcohol. 2-chloro-4-chlorosulphonyl-phenoxy acetic acid ethyl ester was afforded with m.p.: 67.1-68.7°C, yeld. 60%

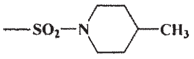
$C_{10}H_{10}Cl_2SO_5$: M= 313.15 g/mol
calcd.: C: 38.35% H: 3,22% Cl: 22.64% S: 10.24%
found : C: 88.63% H: 2.96% Cl: 22.43% S: 10.15%

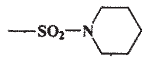
Synthesis of 2-[(4'-methyl-piperidino)-sulphonyl]-4-chloro-phenoxyacetic acid ethyl ester (S 1A)

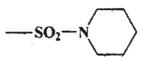
To a solution of 2-chlorosulphonyl-4-chloro-phenoxy-acetic acid ethyl ester (3.13 g, 0.01 mol) in CH_2Cl_2, under stirring and cooling with ice (0°C) was added 4-methyl-piperidine (0.04 mol, 3.97 g, 4.82 mL).Mixture is agitated at 0°C for 2 h, after which the temperature raised to 30°C and more agitated further at the same temperature for 2 h. The reaction mass is poured over 100 mL water.The separate aqueous extract will be kept with dichloromethane 2 times longer. Combined organic solutions are washed with water to dry on anhydrous sodium sulphate and evaporated. Crude product is purified from ethyl alcohol. Pure 2 – [(4'-methyl-piperidino)-sulphonyl]-4-chloro-phenoxy ethyl acetate - S-1A: was afforded with m.p.: 86-86.9°C, yeld. 60%

$C_{16}H_{22}ClNSO_5$ M=375.8648g/mol
calcd.: C: 51.13% H: 5.90% Cl: 9.43% N: 3.73% S: 8.53%









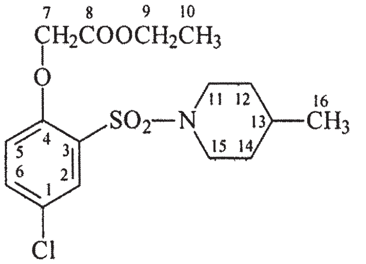


Fig. 2. 2-[(4'-methyl-piperidino)-sulphonyl]-4-chloro-phenoxy acetic acid ethyl ester (S 1A)

found : C: 51,39% H: 5.60% Cl: 9.48% N: 4.00% S: 8.71%

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.91(d, 1H, H-2, 2.6); 7.42(dd, 1H, H-6, 2.6, 8.9); 6.82(d, 1H, H-5, 8.9); 4.72(s, 2H, H-7); 4.29(q, 2H, H-9, 7.3); 3.84(m, 2H, $H\text{-}11_{eq}$, $H\text{-}15_{eq}$, $^{gem}J(H^{11eq}\text{-}H^{11axial})= {}^{gem}J(H^{15eq}\text{-}H^{15axial})=12.2$ Hz); 2.71(td, 2H, $H\text{-}11_{ax}$, $H\text{-}15_{ax}$, $^{gem}J(H^{11eq}\text{-}H^{11axial})= {}^{gem}J(H^{15eq}\text{-}H^{15axial})= 12.2$ Hz, $^3J(H^{11ax}\text{-}H^{12ax})=12.2$ Hz, $^3J(H^{11ax}\text{-}H^{12eq})=2.5$ Hz); 1.66(dd, 2H, $H\text{-}12_{eq}$, $H\text{-}14_{eq}$, $^3J(H^{11ax}\text{-}H^{12eq})=2.5$ Hz, $^3J(H^{15ax}\text{-}H^{14eq})=2.5$ Hz, $^{gem}J(H^{12ax}\text{-}H^{12eq})=12.6$ Hz, $^{gem}J(H^{14ax}\text{-}H^{14eq})=12.6$ Hz,); 1.43(m, 1H, H-13); 1.26(m, 2H, $H\text{-}12_{ax}$, $H\text{-}14_{ax}$); 1.30(t, 3H, H-10, 7.3); 0.93(d, 3H, H-16, 6.5).

^{13}C-NMR($CDCl_3$, δ ppm): 168.78(C-8); 154.89(C-4); 134.67(C-6); 132.61(C-2); 130.58(C-1); 127.91(C-3); 116.18(C-5); 67.51(C-7); 62.73(C-9); 47.29(C-11, C-15); 34.99(C-12, C-14); 31.46(C-13); 22.61(C-16); 15.21(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 3082w; 2954m; 2924m; 2871m; 1767s; 1734s; 1582w; 1476s; 1434m; 1388m; 1333s; 1278s; 1246s; 1199s; 1160vs; 1110m; 1080s; 1054s; 953w; 927s; 815m; 760s; 589s; 547w; 501m.

2-[(-piperidino)-sulphonyl]-4-chlorophenoxyacetic acid ethyl ester (S 1B)

m.p.: 112.5-113.4°C; yeld. 53%
$C_{15}H_{20}ClNSO_5$ M= 361.838 g/mol
Calcd.: C: 49.79% H: 5.57% Cl: 9.80% N: 3.87% S: 8.86%
found : C: 49.97% H: 5.35% Cl: 9.92% N: 4.14% S: 9.07%

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.91(d, 1H, H-2, 2.6); 7.41(dd, 1H, H-6, 2.6, 8.9); 6.83(d, 1H, H-5, 8.9); 4.72(s, 2H, H-7); 4.29(q, 2H, H-9, 7.3); 3.26(m, 4H, H-11, H-15); 1.63(m, H, H-12, H-14); 1.52(m, 2H, H-13); 1.30(t, 3H, H-10, 7.3).

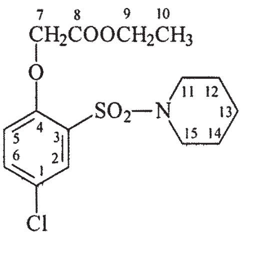


Fig. 3. 2-[(piperidino)-sulphonyl]-4-chloro-phenoxy acetic acid ethyl ester (S 1B)

^{13}C-NMR($CDCl_3$, δ ppm): 167.74(C-8); 153.86(C-4); 133.65(C-6); 133.59(C-2); 129.47(C-1); 126.86(C-3); 115.16(C-5); 66.50(C-7); 61.70(C-9); 46.83(C-11, C-15); 25.77(C-12, C-14); 23.84(C-13); 14.17(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 3107w; 2990w; 2940m; 2858w; 1748s; 1586w; 1470s; 1447m; 1390m; 1334m; 1300m; 1196vs; 1161vs; 1082s; 1057m; 1024m; 937m; 904w; 840w; 811m; 730m; 693w; 648w; 572m; 537w.

2-chloro-4-[(4'-methyl-piperidino)-sulphonyl]-phenoxyacetic acid ethyl ester (S 1C) m.p.:118,1-119^{0}C; yeld. 78%

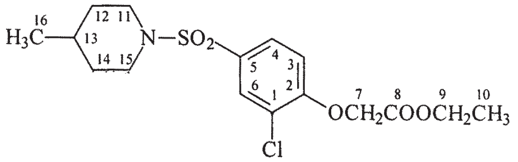


Fig. 4. 2-chloro-4-[(4'-methyl-piperidino)-sulphonyl]-phenoxy acetic acid ethyl ester (S 1C)

^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.79(d, 1H, H-6, 2.4); 7.60(dd, 1H, H-4, 2.4, 8.7); 6.90(d, 1H, H-3, 8.7); 4.78(s, 2H, H-7); 4.29(q, 2H, H-9, 7.2); 3.72(m, 2H, H-11$_{eq}$, H-15$_{eq}$, $^{gem}J(H^{11eq}$-$H^{11axial}) = {}^{gem}J(H^{15eq}$-$H^{15axial}) = 11.9$ Hz); 2.28(td, 2H, H-11$_{ax}$, H-15$_{ax}$, $^{gem}J(H^{11eq}$-$H^{11axial}) = {}^{gem}J(H^{15eq}$-$H^{15axial}) = 11.9$ Hz, $^{3}J(H^{11ax}$-$H^{12ax}) = 11.9$ Hz, $^{3}J(H^{11ax}$-$H^{12eq}) = 2.2$ Hz); 1.68(m, 2H, H-12$_{eq}$, H-14$_{eq}$); 1.30(t, 3H, H-10, 7.2); 1.29(m, 3H, H-12$_{ax}$, H-14$_{ax}$, H-13$_{ax}$); 0.92(d, 3H, H-16, 6.5).

^{13}C-NMR($CDCl_3$, δ ppm): 167.54(C-8); 156.74(C-2); 130.37(C-5); 129.99(C-6); 127.66(C-4); 124.03(C-1); 112.91(C-3); 66.09(C-7); 61.83(C-9); 46.42(C-11, C-15); 33.34(C-12, C-14); 30.11(C-13); 21.44(C-16); 14.14(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 3073w; 2961w; 2918m; 2872w; 2843w; 1754s; 1585m; 1508m; 1480m; 1444w; 1386m; 1335m; 1309m; 1245w; 1197s; 1161vs; 1087vs; 1049m; 1021w; 925m; 844w; 810w; 729m; 710m; 653w; 597m; 555w.

2-chloro-4-[(piperidino)-sulphonyl]-phenoxyacetic acid ethyl ester (S 1D)

m.p.:104,6-106,1^{0}C; yeld. 93%.

$C_{15}H_{20}ClNSO_5$ M= 361.838 g/mol

calcd.: C: 49.79% H: 5.57% Cl: 9.80% N: 3.87% S: 8.86%

found : C: 49.85% H: 5.35% Cl: 9.90% N: 4.21% S: 8.98%

^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.79(d, 1H, H-6, 2.2); 7.60(dd, 1H, H-4, 2.2, 8.7); 6.90(d, 1H, H-3, 8.7); 4.78(s, 2H, H-7); 4.29(q, 2H, H-9, 7.3); 2.99(m, 4H, H-11, H-15); 1.65(qv, 4H, H-12, H-14, 5.7); 1.44(m, 2H, H-13); 1.31(t, 3H, H-10, 7.3).

^{13}C-NMR($CDCl_3$, δ ppm): 167.56(C-8); 156.75(C-2); 130.35(C-5); 129.98(C-6); 127.67(C-4); 124.04(C-1); 112.91(C-3); 66.09(C-7); 61.84(C-9); 46.95(C-11, C-15); 25.17(C-12, C-14); 23.48(C-13); 14.15(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 2988w; 2942m; 2853w; 2837w; 1754s; 1586m; 1481m; 1442m; 1379m; 1361w; 1338s; 1309m; 1281m; 1204vs; 1167vs; 1159vs; 1085vs; 1050m; 1018m; 923s; 900w; 846m; 816m; 720m; 706m; 654w; 608m; 596m; 554w.

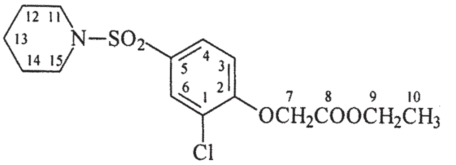
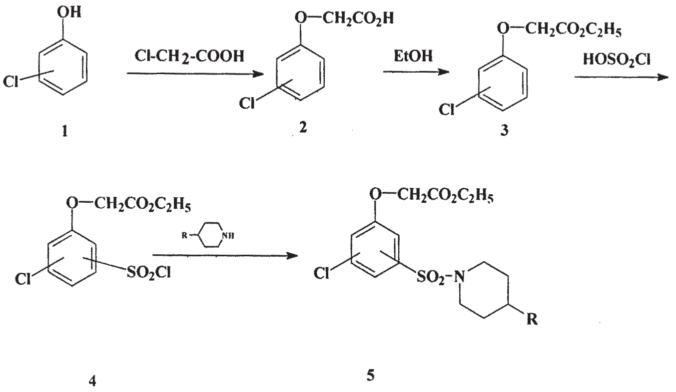


Fig. 5. 2-chloro-4-[(piperidino)-sulphonyl]-phenoxy acetic acid ethyl ester (S 1D)



Scheme 1

Results and disscusions

In this paper it is presented the synthesis (scheme 1) of four chloro-[(piperidino)-sulphonyl]-phenoxyacetic acid ethyl esters by the condensation of chlorosulphonyl-chloro-phenoxyacetic acid ethyl esters (4) with piperidine or 4-methyl piperidine[9].

The obtaining of the esters (4) mentioned above involves the condensation of sodium salts of *orto* and *para* chloro-phenols (1) with monochloroacetic acid in alkaline medium [7], esterification of chloro-phenoxy-acetic acids (2) in acid catalysis[7] followed by the chlorosulphonation ethyl chloro-phenoxyacetate (3) at specific parameters [2-6,8], determined by the ester structure. The synthesized products are purified through recrystallization. The structure of the new compounds was confirmated by physico-chemical technics: elemental analysis, IR spectroscopy, H-RMN and C-RMN spectrometry and thin layer chromatography.

Conclusions

In conclusion, we have synthesized new intermediates to be used for obtaining new sulphonamide phenoxyacetic derivatives. The structure of the new compounds was confirmated by physico-chemical technics:

- elemental analysis;
- IR spectroscopy;
- H-RMN and C-RMN spectrometry;
- thin layer chromatography.

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