SYNTHESIS AND CHARACTERIZATION FOR SOME PHENOXYACETIC ACID'S SULPHONAMIDE DERIVATIVES

SINTEZA ŞI CARACTERIZAREA UNOR DERIVAŢI SULFONAMIDAŢI AI ACIDULUI FENOXIACETIC

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Abstract*. In the phenoxyacetic acid derivatives class, the introduction of sulphonamide group into the nucleus determined pronouncedly decreased products toxicity and in conjunction with the existing substitutes offered a wide range of biological actions. Many derivatives containing sulphonamide group have revealed other interesting effects due to the number, position and nature of substitutes into the aromatic or heterocyclic nucleus. We aimed to obtain new derivatives with sulphonamide group with broad spectrum, including stimulating and auxinic, growth regulator effects, non-cumulative and biodegradable, with no toxicity towards humans, bees and fish. A new class of compounds was obtained, with auxinic, growth stimulators activity, represented by sulphonamides of the chloro – phenoxy - alkyl carboxylic acids, with very low toxicity. The derivatives were synthesized and characterized further by physical - chemical analyses. Different soluble forms were tested on cultures of sugar beet, tomato, carrot, wheat, with significant results.*
Key words: phenoxyacetic, sulfonamides, growth stimulators

Rezumat. *In clasa derivaţilor acidului fenoxiacetic, prin introducerea grupei sulfonamidice în nucleu se obţine o scădere pronunţată a toxicităţii produselor si în corelaţie cu ceilalţi substituenţi existenţi apare o gama larga de acţiuni biologice. Foarte mulţi derivati continând grupare sulfonamidică s-au evidenţiat prin alte efecte interesante determinate de numărul, poziţia şi natura substituenţilor din nucleul de baza aromatic sau heterociclic. S-a dorit astfel obtinerea de noi derivaţi cu grupare sulfonamidică, cu spectru larg de acţiune, incluzând efecte stimulatoare, regulatoare de creştere şi auxinice, lipsite de toxicitate pentru om, albine, peşti, necumulative si biodegradabile. S-a obţinut o nouă clasa de compuşi cu activitate auxinică şi stimulatoare de creştere reprezentată prin sulfonamidele acizilor clor - fenoxi-alchilcarboxilici cu toxicitate foarte redusă. Derivaţii de bază au fost sintetizaţi şi caracterizaţi ulterior prin analize fizico-chimice de laborator. Diferite forme de condiţionare au fost testate pe culturi de sfeclă de zahar, tomate, morcov, grâu, cu rezultate semnificative.*
Cuvinte cheie: fenoxiacetic, sulfonamide, stimulator de crestere

INTRODUCTION

Sulphonamides are synthetic chemicals obtained through economically viable technologies, which are characterized by extremely valuable biological

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effects, low toxicity, and biodegradability. Put into practice, first as derivatives of 4 amino-benzene sulphonamide with antibacterial effects used in therapy to treat bacterial infections (Oniscu, 1969), sulphonamides have enjoyed great attention, many derivatives containing sulphonamide group per molecule proved other interesting effects due to the number, position and nature of the substitutes in the aromatic or heterocyclic nucleus, leading to their use as anti-seizures (Oniscu, 1988), anti-inflammatory, psychic energizers (Oniscu and Dumitrascu, 2005), diuretics, anti-diabetes (sulfonic ureides), immune modulatory, and more recently, anti-cancer drugs (Fulga et al., 2004)

In an effort to capitalize the phenoxy family auxinic activity, new structures have been designed, that maintain a chlorine atom in the aromatic nucleus and introduce a sulphonamide group, which is expected to increase the auxinic and growth regulating activity and simultaneously to reduce toxicity (Oniscu, 1969; Trofin, 2003).

MATERIAL AND METHOD

The general scheme for obtaining sulphonamide phenoxy alkyl carboxylic derivatives includes the following steps:

- the synthesis of the R-phenoxyacetic acids from phenols through monochloroacetic acid condensation in alkaline medium (NaOH);
- the synthesis of the methyl or ethyl-esters from the acids;
- the synthesis of the chloro-sulfonic esters;
- the condensation of the chloro-sulfonic esters with ammonia, substituted amines or other compounds with aminic groups in their structure.

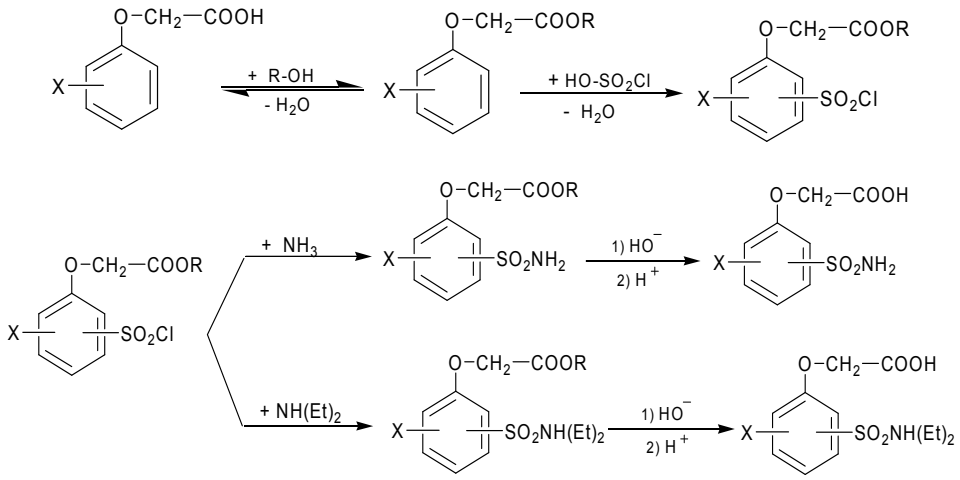


Fig. 1 - Synthesis steps in obtaining sulphonamide phenoxy-alkyl carboxylic derivatives

For the phenoxy acetic acid's esters preparation step, we used o-chloro-phenol and p-chloro-phenol, monochloroacetic acid and sodium hydroxide for the synthesis of the proper chloro-phenoxy-acetic acids, purified in the laboratory, and for the esterification step, 95% purity (volume) methanol. As catalysts, we chose H_2SO_4 98 % in ratio of 0,8 % related to the organic acid, in the homogenous process and Dowex-

50 and Amberlite-IR 120 with sulphonic groups (-SO_3H) in quantities of 3, 5 and 10 g each for the heterogeneous process.

The reaction with the chloro-sulfonic acid takes place with maximum efficiency (80-95%) in molar excess of chloro sulfonic acid of 7: 1, for an hour, at variable temperature depending on the nature of the substrate. Alkaline hydrolysis of the obtained esters, followed by acidification, leads to the corresponding acids.

The general obtaining procedure is:

- over 0.7 chloro sulfonic acid cooled at 0 – 5^0C in ice, 0.1 molls methyl ester is poured, under continuous stirring, in small portions, so the temperature will not exceed 5^0C;
- the reaction mass is maintained as the same temperature for 30 – 40 minutes, then the temperature is raised to values specific to the ester type, 30^0C, respectively 35^0C, maintaining the temperature for 90 – 100 minute, when the sulpho-chlorine is formed;
- in the last step of the process, the reaction mass is cooled at 5 – 6^0C and is poured over a water – ice mixture under energetic stirring, in order to destroy the unconsumed chloro-sulphonic acid and to precipitate the sulpho-chlorines;
- the derivative is filtered, washed with water until pH = 6.5 of the waste waters, crystalized again from a water : acetone mixture (2 : 1), then it is dried at temperatures under sub 40^0C.

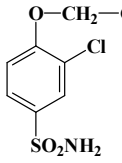
In the next step, the sulpho-chlorines solutions are treated with ammonia, in a ratio of 1 molls: 2 molls, under continuous stirring for 30 minutes, and after the precipitation of the corresponding sulfonamide esters, they are filtered and crystalized again from an alcohol : water mixture (2 : 1). The esters are hydrolysed with NaOH in hot water solution, in a ratio of 1 : 1, 30 minute at reflux; after that, the mass is treated with activated charcoal, which is filtered afterwards. The cooled, clear filtrate is treated with HCl 10% until pH = 2.

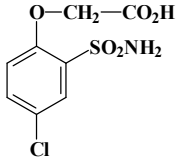
The obtained sulphonamide acids are filtered, dried and crystalized again from an alcohol: water mixture (2 : 1).

RESULTS AND DISCUSSIONS

The 2-chloro-4-sulphonamide-phenoxyacetic and 4-chloro-2-sulphonamide-phenoxyacetic acids are obtained through chemical synthesis, using accessible and easily controllable methods, which do not generate issues concerning human health and do not release pollutants into the environment. These compounds can be used as products defined by herbicide or growth regulating and auxinic effect or as intermediary derivatives in other syntheses.

There are presented as follows the results for the elemental and spectral analysis for the two obtained acids:

2 - chloro – 4 -sulphonamide – phenoxyacetic acid		
 **$C_8H_8ClNSO_5$: M=265.6662g/moll**	Theoretical values: C: 36.17 % H: 3.03 % N: 5.29 % S: 12.06 % Found values :	**Spectral data:** FT-IR (ATR in solid, ν cm^{-1}): ν NH_2 sulphonamide- 3348 and 3255 cm^{-1}, ν CH phenyl ring – 3090 cm^{-1}, ν COOH - 1737 cm^{-1}, ν C=C phenyl ring – 1586, 1494 cm^{-1}, ν CH_2 – 1429 cm^{-1}, $\nu_{as}SO_2$- 1319 cm^{-1}, ν_sSO_2-1154 cm^{-1}, ν CH

	C: 37.43 % H: 4.03 % N: 6.57 % S: 13.98 %	aromatic – 1076 cm^{-1}, ν S-N – 997 cm^{-1}, ν C-Cl -820 cm^{-1}.
4 – chloro – 2 - sulphonamide - phenoxyacetic acid		
 **$C_8H_8ClNSO_5$** **M=265.6662g/moll**	Theoretical values: C: 36.17 % H: 3.03% N: 5.29 % S: 12.06 % Found values : C: 36.05 % H: 3.04% N: 5.63 % S: 12.05 %	**Spectral data :** FT-IR (ATR in solid, ν cm^{-1}): ν NH_2 sulphonamide- 3383 si 3300 cm^{-1}, ν CH phenyl ring – 3040 cm^{-1}, ν COOH -1725 cm^{-1}, ν C=C phenyl ring – 1590, 1581, 1472 cm^{-1}, ν CH_2 – 1423 cm^{-1}, $\nu_{as}SO_2$-1329 cm^{-1}, ν_sSO_2-1160 cm^{-1}, ν CH aromatic – 1079 cm^{-1}, ν S-N – 951 cm^{-1}, ν C-Cl -821 cm^{-1}.

The compound were tested in a soluble form as sodium, potassium and dimethyl amine salts as growth stimulators for sugar beet, wheat and tomato plants in different development stages and proved to be affordable, with an auxinic biological activity in small concentrations, of 20 respectively 25 ppm for tomato plants and between 12.5 ppm and 50 ppm for wheat. The compounds are stable, easy to apply along with other foliar treatments (fertilization, herbicides application).

CONCLUSIONS

1. The synthesis of the studied phenoxyacetic sulphonamide derivatives can be performed under easy to control laboratory conditions, without risks;

2. The studied chloro-phenoxyacetic acids' sulphonamides present low toxicity, the DL-50 value being over 6000 mg/kg;

3. Applied as growth stimulators on crops, they lead to significant results: for sugar beet, production increased to 5.2 – 7.14 t sugar/ha compared to 3,21 t sugar/ha for the control; for tomato culture, we registered production increases between 40.6% and 125% and for the wheat, between 14% and 63.9%.

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