NEW PHENOXYALKYL CARBOXYLIC ACIDS DERIVATIVES SYNTHESIS AND CHARACTERIZATION

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Abstract: In the present paper the studies on the sulphon-amidated aryloxy-alkylcarboxylic acids are extended by their attaching on certain substrata able to confer some especial biological properties to the final products, such as anti-tumor and antioxidant actions useful in treating inflammatory processes, ulcer, convulsions and diabetes, as well as herbicidal action.
The stepwise syntheses of the sulphonamidated aryloxyalkylcarboxylic acid derivatives and their characterization by elemental analysis data and IR and ^{1}H-NMR spectral measurements are described.
The newly obtained compounds could show potential pharmaceutical and herbicide properties.

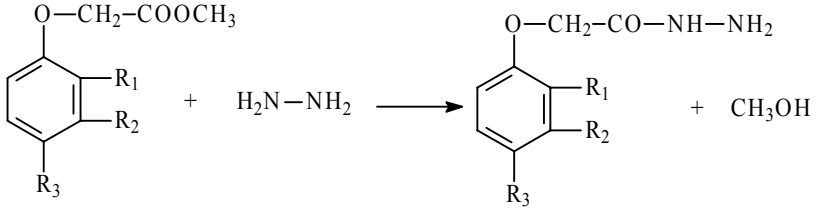
Keywords: *hydrazide, coupling components, diazoaminoderivatives, elemental analysis, IR, ^{1}H-NMR spectral measurements*

INTRODUCTION

The sulphonamides belong to an important class of therapeutically agents applied in the modern medical science. The sulphonamidic moiety is much used for designing new biologically active compounds [1 – 3].
Modifications of the sulphonamide structure afforded new compounds showing improved biological properties, such as hypoglycemic, diuretic, antihypertensive activities acting also as carbonic anhydrase inhibitors.
The "*in vivo*" and "*in vitro*" antitumoural activities found recently with these new compounds is particularly interesting. Although their structures have in common an aromatic/heterocyclic residue and a sulphonamidic group their action mechanisms and pharmacological effects are different [4 – 6].
A particular attention is paid to the derivatives acting in microbial/viral infections, to those favoring the immunity system and also to the sulphonamides with immunomodulating effect [7 – 9], blocking effects in viral infections [10], inhibiting effects on the nonpeptidic proteases and HIV proteases being applied as anti-HIV drugs [11 – 18]. Many sulphonamidic derivatives can be used as drugs with anticancer-anti-inflammatory double action.
The derivatives of the aryloxyalkylcarboxylic acids have a particularly high biological potential. In recent years, their hydrazides and the corresponding alkyl-hydrazones as condensation products, draw the attention in the field of synthetic chemistry and inorganic chemistry due to their various biological actions.
By taking this fact into account we obtained some diazoaminoderivatives, starting from hydrazides and several coupling components.

EXPERIMENTAL - SYNTHESIS OF DIAZOAMINODERIVATIVES

The syntheses of dizoaminoderivatives were carried out into two stages, beginning with the synthesis of the sulphonamidated phenoxyacetic acid hydrazides according to the following reaction:



R1= H, Cl, CH3,
R2= H, CH3;
R3= aminosulfonil;

Figure 1. *Syntheses of hydrazides*

In the second stage, the above mentioned hydrazides were submitted to the diazotization reaction followed by couplings with the following components: dimethylformamide (DMFA), resorcine, β-naphthol.

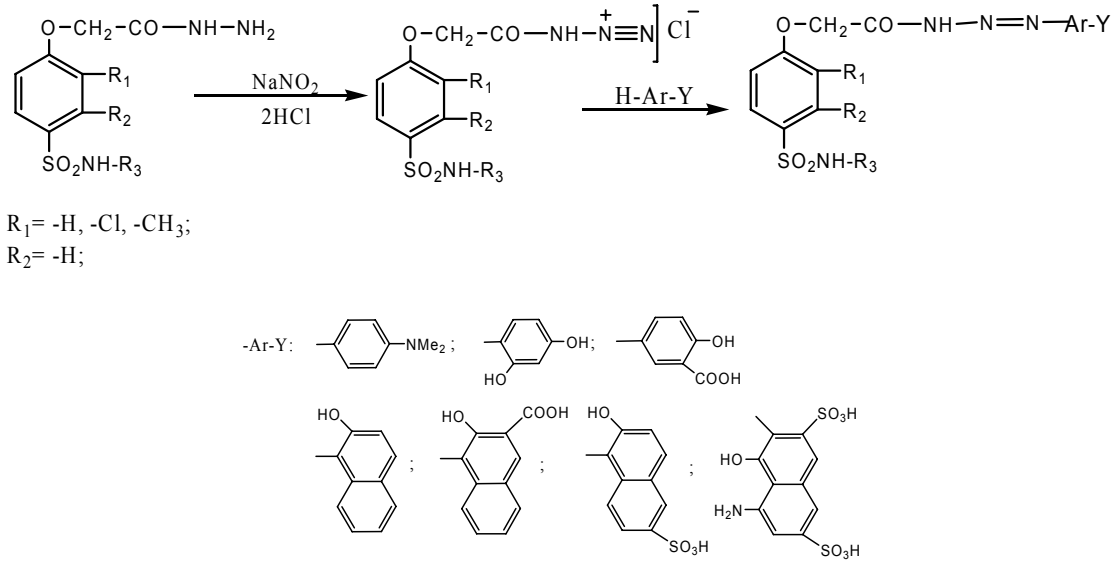


Figure 2. *Syntheses of diazoaminoderivatives*

The diazotization was carried out by treating the hydrazide with aqueous hydrogen chloride, in a 1:4.5 or 1:5 HCl/amine ratio. The suspension was cooled at 0 – 5 °C, and the required amount of 10% $NaNO_2$ solution then added stepwise, under stirring. The mixture was stirred for another 15 minutes at the same temperature.

The diazotizations are usually carried out at low temperatures (0 – 5 °C), sometimes below 0 °C, in order to avoid the degradation of the diazonium salts although the reaction rate much increases with increasing temperature.

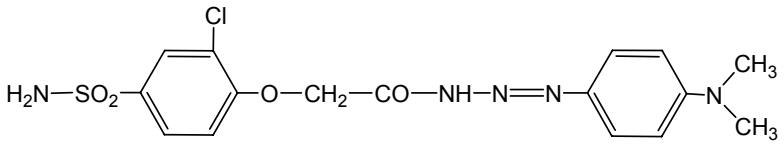
The coupling was made in the following variants:

- The addition of the diazonium salt solution on the coupling component solved in ethanol followed by the diazoderivative precipitation with sodium acetate.
- The buffering of the diazonium salt solution with sodium acetate followed by treating with the coupling component as an aqueous solution or NaOH solution.
- The addition of the diazonium salt solution on the alkalinized coupling component followed by pH adjustment by Na_2CO_3.

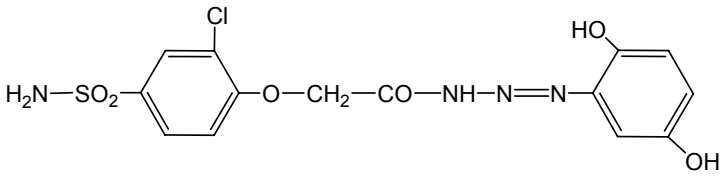
The diazoaminoderivatives were purified from organic solvents such as ethanol, toluene, o-xylene or two combined solvents (DMF – ethylic ether, ethylacetate – ethylic ether, toluene – petroleum ether). The purification by column chromatography with aluminum oxide was simultaneously applied. CH_2Cl_2-isopropanol [9:1(v/v)] or ethyl acetate-hexane mixtures were used.

RESULTS AND DISCUSSION

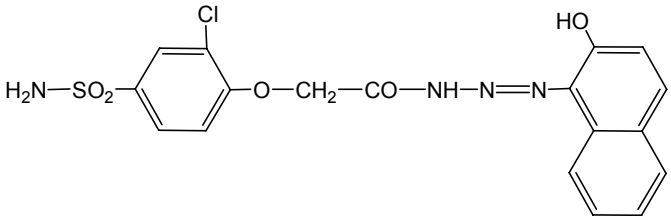
The newly synthesized diazoaminoderivatives, their denominations, obtaining reaction mechanism as well as some of the physical-chemical characteristics and elemental analysis data are given in figure 3, tables 1 and 2.



4-(3-{2-[4-(aminomethyl)2-chlorphenoxy]ethyl}triaz-1-enyl)-dimethylformamide (1)



1-(3-{2-[4-(aminomethyl)2-methylphenoxy]ethyl}triaz-1-enyl)-resorcine (2)



1-(3-{2-[4-(aminomethyl)2-methylphenoxy]ethyl}triaz-1-enyl)-2-naphthol (3)

Figure 3. *Structures of diazoaminoderivatives*

Table 1. *Physical-chemical characteristics and elemental analysis data of the new diazoaminoderivatives of the sulphonamidated phenoxyalchyl carboxylic acids*

No.	Ar-Y	R_1	R_2	R_3	Empirical formula	M [g.mol^{-1}]	Melting point [^{o}C]	Color
1	DMFA	Cl	H	amino sulphonyl	$C_{16}H_{18}N_5O_4SCl$	411.5	246-248	gray-green
2	resorcine	Cl	H	amino sulphonyl	$C_{14}H_{13}N_4O_6SCl$	400.5	220-222	beige
3	β-naphtol	Cl	H	amino sulphonyl	$C_{18}H_{15}N_4O_5SCl$	434.5	236-237	reddish brown

Table 2. *Elemental analysis data*

Compound	C%		H%		N%	
	calc.	found	calc.	found	calc.	found
1	46.65	46.54	4.37	4.49	17.01	17.12
2	41.94	41.82	3.24	3.32	10.48	10.59
3	49.17	49.06	3.45	3.56	12.88	12.30

The structures of the newly obtained derivatives were elucidated by IR and ^{1}H-NRM spectral measurements and are shown in tables 3 and 4.

The IR spectra show the band characteristic of the νC=N vibration at 1639.49 cm^{-1} (β-naphtol dye) or the lower frequency (1602.84 cm^{-1}) superimposed on the νC-C absorption in aromatic rings. The azo group gives weak infrared absorptions, for even unsymmetrical molecules. With the aromatic azoderivatives absorption bands at 1587 ± 8 cm^{-1} and 1107 ± 14 cm^{-1} are to be found but their position in spectra is rather difficult

to be exactly identified. Since the diazoaminoderivatives are of an aromatic structure, their vibrations are to be found especially within the νC-H (2995.59 – 3099.6 cm^{-1}) and νC-H (1454.32 – 1654.92 cm^{-1}) valence vibration or C-H (646.15 – 883.40 cm^{-1}) deformation vibration ranges [19 – 22].

Table 3. *IR spectra of the obtained diazoaminoderivatives*

Compound	Characteristic bands and (cm^{-1}) their intensity
1	433.98 M, 449.41 W, 466.77 W,489.92 M, 507.28 S, 549.71 M, 580.57 S, 592.15 S, 725.23 S, 748.38 S, 758.02 S, 906.54 M, 927.76 W, 941.26 W, 964.41 M, 989.48 W, 1109.07 S, 1166.79 S,1228.65 S, 1265.30 M, 1382.96 M, 1587.41 S, 1679.99 VS, 1693.50 VS, 2995.44 M, 3066.81 S.
2	433.98 M, 491.85 S, 507.28 S, 551.64 M, 582.50 VS, 592.15 VS, 725.23 VS, 813.96 VS, 904.61 VS, 964.41 S, 1107.14 M, 1172.72 S, 1230.58 S,1265.30 M,1276.87 S, 1489.04 S, 1575.84 S,1589.34 S, 1681.92 VS, 2995.44 S, 3068.74 VS, 3192.18 VS, 3689.82 M.
3	439.77 M, 472.56 S, 486.06 S, 505.35 S, 532.35 S, 584.43 S, 594.07 S, 711.73 S, 756.09 VS, 819.74 VS, 829.39 VS, 111.00 M, 1213.22 W, 1263.37 M,1276.87 M,1384.89 M,1487.11 M, 1496.76 M, 1639.49 S, 3099.60 S, 3647.38 W.

(VS = very intense, S = intense, M = medium intensity, W = weak, VW = very weak)

Table 4. *H^1-NMR spectra of the diazoaminoderivatives*

Compound	Characteristic bands DMSO, δ (ppm)
1	2,05(s, 2H, -NH_2); 2,09(s, 3H, -CH_3); 4,92(s, 2H,-CH2-); 5,00(s, 1H, -OH); 7,08(s, 1H, H-5); 7,29(s, 1H, H-9); 7,49 (s, 1H, H-4); 7,73(s, 1H, H-10); 7,91(s, 1H, H-12); 8,16 (s, 1H, -NH-); 11,8(s, 1H, -COOH);
2	2,00(s, 2H, -NH_2); 2,13(s, 3H, -CH_3); 4,62 (s, 2H,-CH2-); 4,88(s, 1H, -OH); 6,97(s, 1H, H-13); 7,0(s, 1H, H-5); 7,25 (s, 1H, H-2); 7,33(s, 1H, H-1); 7,47(s, 1H, H-7); 7,59(s, 1H, H-4); 7,65(s, 1H, H-3); 7,89(d, 2H, H-12); 8,09 (s, 1H, -NH-);
3	2,08(s, 2H, -NH_2); 4,80 (s, 2H,-CH2-); 5,19(s, 1H, -OH); 6,98(s, 1H, H-10); 7,12(s, 1H, H-5); 7,17 (d, 2H, H-2, H-11); 7,27(s, 1H, H-1); 7,40(s, 1H, H-7); 7,47(d, 2H, H-3, H-4); 7,81(s, 1H, H-13); 8,09 (s, 1H, -NH-);

The fact can be noticed that by carrying out the diazotization-coupling pair operations the possibility of preparing diazoaminoderivatives of a structure similar to the azomethines has risen. Their only structural difference is the imino group (-N=CH-) replacement by the azo group. This structure modification causes significant physical-chemical features for every compound. For instance, while the azomethines are easily splitted hydrolytically in diluted strong acid media the diazoaminoderibvatives are rather stable under such conditions.

The ^{1}H-NRM spectra confirm the presence of the characteristic structural elements in every compound. The spectrum aliphatic region shows all types of the methyl groups (NH_2, N-CH_3, N$(CH_3)_2$, O-CH_3, CH_3, Ar-CH_3) at the corresponding δ values. The aromatic protons in the phenyl residue could be differentiated according to their vicinities and couplings. With the compounds containing unsymmetrically substituted benzene ring, two singlets of very close values correspond to them. The values of the

chemical shifts and the peak intensities in the H-NRM spectra are in total agreement with the proton types and number in every diazoaminoderivative. The ^{1}H-NRM spectra confirm undoubtedly the structures of the newly obtained diazoaminoderivatives.

CONCLUSIONS

The place, role and importance of the phenoxyacetic acid derivatives among the biologically active compounds were made evident.
Due to the particular biological potential of the sulphonamidated substituted phenoxyacetic acids, our researches have been extended to the obtaining of new derivatives able to show such properties in view of their possible applications as pharmaceuticals as well as selective herbicides.
The newly obtained final products were characterized by means of elemental analysis data and spectral measurements (IR, ^{1}H-NRM) which have undoubtedly confirmed the advanced structures of the diazoaminoderivatives.

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