Synthesis of Some New Compounds with Potential Biological Action obtained from the Hydrazides of the Sulfonamidated Aryloxyalkylcarboxylic Acids

ANCA MIHAELA MOCANU*, CONSTANTIN LUCA

“Gheorghe Asachi” Technical University of Iasi, Faculty of Chemical Engineering and Environmental Protection, Department of Organic, Biochemical and Food Engineering, 71 A D.Mangeron Ave, 700050, Iasi, Romania

The derivatives of the sulfonamidated aryloxyalkylcarboxylic acids represent a class of a particular importance in virtue of their significant biological action. In recent years much attention has been paid to the corresponding hydrazides of these acids as well as to their condensation products showing also potential biological action. By taking these considerations into account the present paper is aimed to obtain new sulfonamidated derivatives of the aryloxyalkylcarboxylic acids (azomethines, metallic complexes, diazoaminoderivatives) and to synthesize their active forms able to interact with various specific substrates. The approached investigations are new and original since the newly obtained products with potential pharmaceutical activities and herbicidal and growing regulators properties are not mentioned in literature. The synthesis stages of the new products are presented as well as the elemental analysis data and IR, ¹H-NMR spectral measurements made for elucidating the chemical structures. In addition to that, the thermal degradation studies revealed the structure-thermal stability-degradation mechanism correlation making also evident the temperature range where these products could be used and stocked which is particularly important for their potential practical uses.

Keywords: hydrazide, azomethine, metallic complexes, diazoaminoderivatives, elemental analysis, IR, ¹H-NMR spectral measurements, thermal analysis.

The researches on the obtaining new biologically active compounds to be applied in the medical [1-4] and agriculture fields have been much extended [5-8].

The sulphonamides belong to an important class of chemical products showing a wide range of pharmaceutical and herbicidal properties being at the same time non-toxic and biodegradable. The fact that the sulfonamide group attached to aromatic and heterocycle rings causes a significant toxicity lowering and a wide range of biological action correlated with the presence of the other substitutes is the main characteristic of the sulfonamides.

A great number of new sulfonamidated derivatives show remarkable antitumor and antiviral activities [9,10]. The researchers are also concerned with the diuretic sulfonamides [11] of thiazine structure and high activity the cardiovascular diuretic sulfonamides of a lower diuretic effect and hypotensive action applied in treating the arterial high blood pressure, anti-diabetic sulfonamides [12,13] and those with nootrop action [14].

We have chosen to obtain the new sulfonamidated aryloxyalkylcarboxylic derivatives (azomethines, metallic complexes, diazoaminoderivatives) since the sulfonamidated aryloxyalkyl-carboxylic derivatives show a low toxicity, are biodegradable, do not show cumulative properties within the organism and do not cause harmful effects.

The azomethines have many technical and commercial applications and that is why they have been largely synthesised [15-18]. The azomethines and diazoaminoderivatives have been proved to show antibacterial, anticonvulsant and antituberculous activities. Apart from this, they are also used as herbicides, acaricides, fungicides and plant growing stimulators.

By condensing the hydrazides with some anorganic salt a series of metallic complexes were obtained proved to be efficient in treating various diseases [19,20]. The structures of the newly obtained derivatives have been confirmed by elemental analysis data and spectral measurements.

Experimental part

The azomethine with o-nitrobenzaldehyde

The syntheses were carried out at a reagent equimolecular ratio by refluxing in an ethanol medium with low amounts of acetic acid as a catalyst. 0.5g (1.9 mmol) hydrazide, dissolved in 15 mL acetone, was treated with 0.336g (1.9 mmol) of o-nitrobenzaldehyde in 10 mL ethanol and 3 drops of acetic acid and heated for 45 min. under stirring. The reaction mixture was finally cooled and the solid product filtered off and washed with ethanol on the filter. The obtained reaction yields of 90% were much dependent on the product solubility in ethanol. An yellow powder was obtained after purification from toluene or from ethanol as well as from the DMF-ethyl ether two-solvent mixture.

Metallic complex with manganese

0.783 g (0.002 mols) hydrazide was solved in 15 mL acetone and 0.0013 mols manganese chloride solved in 5 mL water added. The reaction mixture was heated on water bath under stirring for about 15 min. The solution was left at room temperature overnight. The precipitate was filtered and washed on the filter with water and with diethyl ether. The obtained product was purified by recrystallisation from ethanol or from acetone.

* email: ancamocanu2004@yahoo.com
The diazoaminoderivative synthesized with Schaffer acid.

The diazotization was carried out by treating the hydrazide with aqueous hydrogen chloride, in a 1:5 HCl/amine ratio. The hydrazide (0.650g; 2.5mmol) was treated with conc. HCl (0.365g; 10 mmol; 0.31mL) and 2mL water and then again with 10 mL water. After cooling with ice at 0-5°C a solution of sodium nitrite (0.172g; 2.5 mmol) in 2 mL water was added dropwise to the amine hydrochloride. The acidity was finally checked (pH=2-3).

Coupling:
The Schaffer acid (0.55g; 2.5mmol) was treated with NaOH (0.2g; 5 mmol) and 4 mL water. The resulting sodium salt diluted with another 5mL water was cooled at 10°C. The diazoderivative was added and also solid Na2CO3 to maintain the alkaline pH (8-8.5). The pH had turned into acid before filtration. \(\eta = 78\%\).

The diazoaminoderivative synthesized with resorcine

The hydrazide (0.650g; 2.5mmol) was treated with conc. HCl (0.365g; 0.31mL; 10 mmol) and then diluted with water (10 mL). After cooling the reaction mixture to 0-5°C with ice a sodium nitrite (0.172g; 2.5 mmol) solution in 2 mL water was added dropwise on the resulting amine hydrochloride. The acidity was finally checked (pH=2-3). Coupling: The resorcine (0.275g; 2.5mmol) dissolved in water (5mL) was added to the diazonium salt previously obtained and the mixture heated for one hour. The suspension of the diazoaminoderivative was filtered off and the solid product thoroughly washed with water \(\eta = 80\%\).

The diazoaminoderivatives were purified from organic solvents such as ethanol, toluene, o-xylene or two combined solvent DMF-ethyl ether.

Results and discussions

Synthesis of new compounds (azomethine, metallic complexes, diazoaminoderivatives)

By taking the potential biological activity of the hydrazides of the sulfonamidated aryloxyalkylcarboxylic acids into account new compounds (azomethines, metallic complexes, diazoaminoderivatives) were synthesized by the condensation of these hydrazide with o-nitrobenzaldehyde, manganese chloride and some coupling compounds such as resorcine and Schaffer acid [21,22] (fig.1).

The performing of the diazotization-coupling reactions made possible the preparation of diazoaminoderivatives of structures similar to azomethines with the only difference of replacing of the imino group (-N=CH-) by the azo group. This structural change results in significant physico-chemical characteristics to every compound. For instance, while the azomethines are easily split by hydrolysis with diluted strong acids the diazoaminoderivatives are stable under these conditions.

The newly synthesized compounds, their denominations, some physico-chemical characteristics and

![Fig. 1. New compounds synthesized from the sulfonamidated phenoxyacetic acid hydrazides](http://www.revistadechimie.ro)
elemental analysis data are given below (fig.2 and table 1).

**Spectral measurements**

The structures of the newly obtained derivatives were elucidated by IR and 1H-NMR spectral measurements.

**IR measurements**

The azomethines are known to show an absorption within the 1630-1680 cm\(^{-1}\) range. In the spectra under study a quite strong absorption band attributable to the νC=N vibrations is to be found between 1638-1674 cm\(^{-1}\). Vibration bands for νNO\(_2\) were noticed within the 1330.88 - 1357.88 cm\(^{-1}\) range, as very strong bands. The benzene rings are responsible for the band between 1581.63-1581.63 cm\(^{-1}\) corresponding to the νC-C vibrations as well as for one or two absorptions between 3035-3086 cm\(^{-1}\) generated by the aromatic νC-H vibrations.

For the manganese-containing metallic complexe the C=C vibration bands are placed within the 1585.48-1631.56 cm\(^{-1}\) range, as strong or very strong bands. Vibrations bands for νC=O bond are to be found in the 1551.25-1651.05 cm\(^{-1}\) range, as very strong bands. The C=S band appears between 1103.28 and 1114.85 cm\(^{-1}\).

The peaks corresponding to Ar-O are to be found at 1195.86-1253.73 cm\(^{-1}\). The S=O and S-N bonds are present between 1045.42 and 1103.28 cm\(^{-1}\).

The deformation ring vibration bands are placed within the 482.20-613.36 cm\(^{-1}\) and 910.40-991.41 cm\(^{-1}\) ranges. The valency vibration bands of the C-N bond appear at 1105.21-1138.00 cm\(^{-1}\).

Since the diazoaminoderivatives are of an aromatic structure, their vibrations are to be found especially within the νC-H (2956.87-3043.66 cm\(^{-1}\)) and νC-H (1454.25-1651.05) cm\(^{-1}\) valence vibration or C-H (658.65-894.04 cm\(^{-1}\)) deformation vibration ranges.

The azo group gives weak infrared absorptions, for even unsymmetrical molecules. With the aromatic azo-derivatives absorption bands at 1566± 8 cm\(^{-1}\) and 1053± 14 cm\(^{-1}\) are to be found but their position in spectra is rather difficult to be exactly identified [23-25].

**NMR measurements**

The 1H-NMR spectra show the signals given in table 3. The 1H-NMR spectra attest the presence of the structural components characteristic of the compounds under study. In the azometine spectrum the heterocyclic -N- group of adequate δ values is to be found. In the domain of the aromatic protons the presence of the ethylene =C- proton can be noticed. The proton of the N=CH group is the most unscreened one and occurs after the aromatic protons. The values of the chemical shifts and the peak intensities in the H-NMR spectra are in good agreement with proton types and number in azomethine.

The metallic complexe and diazoaminoderivatives aromatic protons in the phenyl residue could be differentiated according to their vicinities and couplings. For the compounds containing nonsymmetrically substituted benzene ring two singlets of very close values correspond to them [26]. The values of the chemical shifts and the peak intensities in the 1H-NMR spectra are in good
agreement with the proton types and number in every compounds.

**Thermal analysis**

The thermogravimetric (TG) and differential thermal analysis (DTA) were performed by using a Perkin-Elmer Pyris Diamond TG/DTA thermobalance which records simultaneously the TG and DTA curves. The DTG curves were obtained by numerical differentiation of the TG curves. The working conditions were the following: sample mass 12 mg, heating rate 10°C min⁻¹, temperature range 30-900°C in nitrogen stream (800 mL min⁻¹).

The study on the thermal behaviour of these compounds gives useful information on the temperature domain suitable for their stability, storage and practical applications. At the same time the degradation mechanism gives indications regarding the environmental impact of the degradation products when the initial degradation temperature is exceeded.

The analysis of the TG-DTG-DTA curves reveals the thermal degradation to show two domains as a function of temperature (time): an endothermic one and an exothermal one, these domains including also the release of the gaseous species resulting by degradation [27-29].

A good correlation was also noticed between the structure, thermal stability appreciated from the initial degradation temperatures from TG and DTG and the degradation mechanism advanced [29-31].

The thermal degradation mechanisms of the samples are complex and specific developing by successive-simultaneous reactions depending on the structure and nature of the substitutes in the molecule. In the present paper the degradation mechanism of every compound is advanced which was possible to be done by applying the TG, DTG, DTA analysis in order to follow the structure-thermal stability-degradation mechanism correlation.

The TG, DTG and DTA curves of the compounds 2 and 3 are depicted in figures 4 and 5:

![Fig. 3. TG and DTG curves of the compound (2)](image-url)
In table 4 the characteristic temperatures from DTA are given.

**Conclusions**

Due to the biological activity found for previously known sulfonamidated aryloxyalkyl-carboxylic acids we considered opportune to synthesize and characterize new compounds of the same class.

By performing coupling reactions of the hydrazides sulfonamidated aryloxyalkylcarboxylic acids with o-nitrobenzaldehyde, manganese chloride, resorcine and Schaffer acid, new compounds were obtained.

The derivatives have been separated from reaction mixture and purified by recrystallization from ethanol or two combined solvent, DMF- diethyl ether.

The newly obtained final products were characterized by means of elemental analysis data and spectral measurements (IR, 1H-NMR) which undoubtedly confirmed the advanced structures of the new compounds.

Due to the importance of these compounds as possible reaction initiators and also as potentially bioactive substances (herbicides, acaricides, fungicides) the study on their thermal degradation could give useful information on the environmental impact of the degradation products resulting by the thermal processing of the plants after possible retention of these compounds when the initial degradation temperature is exceeded.

**References**

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