Synthesis, Characterization and Thermal Degradation of Some New 3,5-dimethyl Pyrazole Derivatives

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The purpose of this research is to synthesize, characterize and thermal degradation of new heterolytic derivates with potential biological properties. The derivates synthesis was done by obtaining new molecules with pyrazole structure which combine two pharmacophore entities: the amidosulfonyl-R1,R2-phenoxyacetil with the 3,5-dimethyl pyrazole which can have potential biological properties. 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 and thermostability study which makes evident the temperature range proper for their use and storage. The obtained results were indicative of a good correlation of the structure with the thermal stability as estimated by means of the initial degradation temperatures as well as with the degradation mechanism by means of the TG-FTIR analysis.

Keywords: hydrazides, 3,5-dimethyl pyrazole, spectral measurements, thermal analysis, degradation mechanism

The pyrazoles and its derivates belong to heterocyclic family which is mainly important due to antioxidant, antiviral, antitumor, antibacterial, hypoglycemic properties. Numerous researchers are using it in structural simulation in order to boost biological properties [1-13]. As most heterocyclic families they are a fascinating group of compounds with practical application: medicines with diverse pharmacological actions, dyes or substances used for analytical control, macromolecular substances.

In the last few years research have focused on obtaining biological active products with use in the agriculture as herbicides, growth biosimulators, acaricides, fungicides, etc. Among the diverse studied classes lately, ariloxialchil herbicides, growth biosimulators, acaricides, fungicides, etc. The purpose of this research is to develop new heterocyclic derivates with biological properties. The most important arguments of this study is: their use as herbicides, as growth biosimulators, acaricides, fungicides part of an important of nonsteroidal anti-inflammatory agents prescribed in case of fever, arthritis, and muscular pains, this class of compounds undergoing a continuous development.

Experimental part

Materials

Hydrazine monohydrate 98%, acetylacetone, dimethylformamide, then is added 1.1 g (0.011 mmol) of formamide, then is added 0.011 moles of acetylacetone.

Preparation of 1-(2-methyl, 4-buthyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole derivatives (1)

3.30 g (0.01 mmol) hydrazide of 2-methyl-4-buthyl-amidosulfonyl-phenoxyacetil-3,5-dimethyl pyrazole wih puridies by solvind it in acetone, at warm temperature, active coal treatment, cooling and crystallization [28, 29].

General procedure of the synthesis

0.01 moles of hydrazide of amidosulfonyl-R1,R2-phenoxyacetil is dissolved in 20 mL dimethylformamide, then is added 0.011 moles of acetylacetone. The mix is heated for 30 minutes, by cooling and adding 20 mL of water precipitating N-hydrazide. The product is purified by dissolving it in 20 mL of methanol, active coal treatment and its dilution with 25 mL of water. By cyclization of the intermediary in final product, it gets dissolved in 20 mL of ethilic alchool, adding 0.1 mL of aqueous solution of HCl 10%, the mix maininting for an hour to refluxing. A part of solvent gets distilled, in vacumm, and by reaction mass cooling gets precipitate 1-phenoxyacetil-3,5-dimethyl pyrazole wich puridies by solvind it in acetone, at warm temperature, active coal treatment, cooling and crystalization [28, 29].

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In the last few years research have focused on obtaining biological active products with use in the agriculture as herbicides, growth biosimulators, acaricides, fungicides, etc. Among the diverse studied classes lately, ariloxialchil herbicides, growth biosimulators, acaricides, fungicides, etc.

Moreover, besides important analgesic and anti-inflammatory effects recent data shows that these compounds family presents antioxidant, antibacterial, antitumor, anticnvolusion, hypoglycemic, properties, etc. [17-23]. Discovery of new derivates in the nestoride anti-inflammatory class with both a pharmaceutical profile and therapeutic safety present a great interest among researches [24-27].

The purpose of this research is to develop new heterocyclic derivates with biologic properties. The most important arguments of this study is: their use as herbicides, as growth biosimulators, acaricides, fungicides part of an important of nonsteroidal anti-inflammatory agents prescribed in case of fever, arthritis, and muscular pains, this class of compounds undergoing a continuous development.

Experimental part

Materials

Hydrazine monohydrate 98%, acetylacetone, dimethylformamide were purchased from Sigma-Aldrich. All reagents and solvents had purity grade and were obtained from commercial suppliers.

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dissolved in 20 mL of ethylalcohol, adding 0.1 mL of aqueous solution of HCl 10 %, the mix maiminting for an hour to refluxing. A part of solvent gets distilled, in vacum, and by reaction mass cooling gets precipitate 1-(2-methyl,4-diethyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole wích puridies by solving it in acetone, at warm temperature, active coal treatment, cooling and crystallization.

Yield: 78.25 %; m.p. 172-129°C; white powder; Anal. Calcd. for C₂₁H₃₀N₃O₄SCl: C, 55.99, H, 6.59, N, 11.08; Found: C, 56.94, H, 6.64, N, 11.12; FT-IR (KBr, cm⁻¹): 1639 (-C=N-(-SO₂-N-), 1748 (-C=O), 3248 (-NH-), 1232 (-C-N), 1009), 1604 (C=C), 1579 (-C-C-), 3051 (C-H), 1232 (C-S), 1141 (Ar-Cl), 3586 (Ar-O-) cm⁻¹; H-NMR d/ppm (400 MHz, DMSO): 0.92 (d, 6H, -CH₃), 1.36 (s, 2H, -CH₂-), 1.58 (s, 2H, -CH₂-), 2.1 (s, 1H, -NH-), 2.39 (s, 3H, Ar-CH₃), 2.75 (d, 6H, -CH₂- of pyrazole ring), 3.20 (s, 2H, -CH₂-), 4.81 (s, 2H, -CH₂-), 5.12 (s, 2H, -CH₂-), 6.05 (s, H, -CH of pyrazole ring), 7.03 (s, H, Ar-H), 7.67 (d, 2H, Ar-H).

Preparation of 1-(4-chloro, 2-diethyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole derivatives (2)

3.38 g (0.01 mmol) hydrazide of 4-chlor-2-diethyl-amidosulfonyl-phenoxyacetic acid is dissolved in 20 mL dimethylformamide, then is added 1.1 g (0.011 mmol) of acetylacetone. The mix is heated for 30 min, by cooling and adding 20 mL of water precipitating N-hydrazide. The product is purified by dissolving it in 20 mL of methanol, active coal treatment and its dillution with 25 mL of water. By cyclization of the intermediary in final product, it gets dissolved in 20 mL of ethilic alchool, adding 0.1 mL of aqueous solution of HCl 10 %, the mix maininting for an hour to refluxing. A part of solvent gets distilled, in vacum, and by reaction mass cooling gets precipitate 1-(4-chlor-2-diethyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole wích puridies by solving it in acetone, at warm temperature, active coal treatment, cooling and crystallization.

Yield: 79.35 %; m.p. 182-184°C; white powder; Anal. Calcd. for C₁₇H₂₂N₃O₄SCl: C, 55.32, H, 6.58, N, 9.22; Found: C, 55.28, H, 6.64, N, 9.26; FT-IR (KBr, cm⁻¹): 1640 (-C=N-), 1738 (-C=O), 3253 (-NH-), 1242 (-C-N), 1110 (Ar-Cl), 3754 (Ar-O-) cm⁻¹; H-NMR d/ppm (400 MHz, DMSO): 0.92 (d, 6H, -CH₃), 1.39 (d, 4H, -CH₂-), 1.52 (d, 4H, -CH₂-), 2.59 (d, 6H, -CH of pyrazole ring), 3.18 (d, 4H, -CH₂-), 5.15 (s, 2H, -CH₂- of pyrazole ring), 6.90 (s, H, -CH of pyrazole ring), 7.88 (s, H, Ar-H). The product is purified by dissolving it in 20 mL of ethilic alchool, adding 0.1 mL of aqueous solution of HCl 10 %, the mix maininting for an hour to refluxing. A part of solvent gets distilled, in vacum, and by reaction mass cooling gets precipitate 1-(2-chlor-4-ethyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole wích puridies by solving it in acetone, at warm temperature, active coal treatment, cooling and crystallization.

Yield: 79.32 %; m.p. 173-175°C; white powder; Anal. Calcd. for C₂₂H₃₅N₃O₄S: C, 60.41, H, 8.00, N, 9.61; Found: C, 60.35; H, 8.12; N, 9.68; FT-IR (KBr, cm⁻¹): 1640 (-C=N-), 1605 (C=C), 1580 (-C=C-), 3052 (C-H), 1238 (C-S), 1150 (-SO₂-N-), 1734 (-C=O), 3196 (-NH-), 1242 (-C-N), 1110 (Ar-Cl), 3754 (Ar-O-) cm⁻¹; H-NMR d/ppm (400 MHz, DMSO): 0.92 (d, 6H, -CH₃), 1.39 (d, 4H, -CH₂-), 1.52 (d, 4H, -CH₂-), 2.59 (d, 6H, -CH of pyrazole ring), 3.18 (d, 4H, -CH₂-), 5.15 (s, 2H, -CH₂- of pyrazole ring), 6.90 (s, H, -CH of pyrazole ring), 7.88 (s, H, Ar-H). The product is purified by dissolving it in 20 mL of ethilic alchool, adding 0.1 mL of aqueous solution of HCl 10 %, the mix maininting for an hour to refluxing. A part of solvent gets distilled, in vacum, and by reaction mass cooling gets precipitate 1-(2-chlor-4-ethyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole wích puridies by solving it in acetone, at warm temperature, active coal treatment, cooling and crystallization.

Thermal analysis

The thermogravimetric (TG) and differential scanning calorimeter (DSC) were performed by using a Perkin-Elmer Pyris Diamond TG/DSC thermodalance which records simultaneously the TG and DSC curves. The DTG
curves were obtained by numerical differentiation of the TG curves. The working conditions were the following: sample mass 10 mg, heating rate 10°C min⁻¹, temperature range 30 - 600°C in nitrogen stream (800 mL min⁻¹).

**Results and discussions**

**Synthesis**

Synthesis of derivatives was performed in order to obtain new molecules with amidosulfonyl R₁,R₂-phenoxyacetil-3,5-dimethyl-pyrazoles structures by attaching to nucleus the synthetized compounds which combine two pharmacore entities have the following structure (fig. 2).

The structures of the newly obtained derivatives were also confirmed by IR, ¹H-NMR spectral measurements and elemental analysis. The spectral analyses were in accordance with the assigned structures.

**Structure elucidation by spectral measurement**

**Spectrum IR**

Spectrum analysis of pyrazoles derivatives, infrared, reveal vibration frequencies of main functional groups. It can be noticed a band movement due to valence vibrations of carbonyl groups C=O from 1650 - 1690 cm⁻¹ to higher frequencies due to growth of rings of carbonyl groups. This shows that carbonyl group, from azoyle, (heterocycle of 5 terms containing two or more nitrogen atoms, of one of being connected to a acyl group) appear at relatively high frequencies of 1734 - 1748 cm⁻¹. In the case of C=N string from pyrazolyc cycle the frequency is of 1639 - 1648 cm⁻¹.

In case of derivates, where sulfonamidic group is entirely substituted it can be observed the band dissapearance due to valency vibration of N-H. The absorption band in the case of -NH group is between 3198 - 3253 cm⁻¹. The IR spectrum of compounds were identified the vibration frequencies according to the benzenic rings of 1576 - 1588 cm⁻¹, corresponding to vibrations νC-C and absorptions at 3045 - 3070 cm⁻¹ generated by aromatic νC-H, plus intense bands of substitutes from aromatic nucleus at 1009-1115 cm⁻¹ and those of 1506 - 1512 cm⁻¹ of distorted vibration δCH₃.

**Ar-O band is between 3586 - 3754 cm⁻¹ and in the case of S-N rings is between 1672 - 1790 cm⁻¹. The band of valency vibration for C-N is at 1200 - 1242 cm⁻¹ being a very intense one [30-33].**

**Spectrum RMN**

The structure of these compounds was strongly confirmed by ¹H-NMR spectral data. In the pyrazole derivatives spectrum the heterocyclic -N- group of adequate δ values is to be found. In ¹H-NMR spectra the occurrence of pyrazole cycle is sustained by protons signales of CH group (6.74-6.50 ppm) and at the same time there were identified the corresponding protons of substitutes of pyrazole nucleus (radicals CH₃, δ = 2.55 - 2.98 ppm).

Within the domain of the aromatic protons the presence of the ethylene =C- proton can be noticed. The proton of the -N-C- group is the most unscreened one and it occurs after the aromatic protons. 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 pyrazole derivatives.

**Thermal analysis**

The thermal methods (TG, DTG, DSC) were previously used by us in the study of thermal behavior of various materials [34–37]. This method allows the specification of the temperature range where the material is thermally stable and can be used. More recent the thermal methods (TG, DTG, DSC) were coupled with the FTIR analysis (TG-FTIR method) [38, 39], this method giving supplementary information crucial in the prediction of the thermal degradation mechanism. By analysing the gaseous species resulted on thermal degradation, this method gives useful information regarding the possible impact over the environment pollution, if in the material processing the initial degradation temperature is exceeded. The gaseous species were identified in the TG-FTIR analysis by means of their specific absorbances [38-40].

The TG, DTG, DSC and Gram-Schmidt curves of the new compounds resulting by working under N₂ (nitrogen)
Fig. 3. Thermograms of the new sample: the TG, DTG, DSC, and Gram-Schmidt curves, respectively; a. of the 1 sample, b. of the 2 sample; c. of the 3 samples; d. of the 4 samples; e. of the 5 samples

Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>Degradation stage</th>
<th>T_{\text{onset}} °C</th>
<th>T_{\text{peak}} °C</th>
<th>T_{\text{end}} °C</th>
<th>W</th>
<th>%</th>
<th>T_{\text{10}} °C</th>
<th>T_{\text{50}} °C</th>
<th>T_{\text{max(GS)}} °C</th>
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<tr>
<td>1</td>
<td>I residue</td>
<td>163</td>
<td>323</td>
<td>384</td>
<td>86.09</td>
<td>14.00</td>
<td>267</td>
<td>328</td>
<td>242</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>186</td>
<td>207</td>
<td>221</td>
<td>1.98</td>
<td>20.08</td>
<td>219</td>
<td>289</td>
<td>258</td>
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<td></td>
<td>II</td>
<td>243</td>
<td>282</td>
<td>289</td>
<td>37.43</td>
<td>40.46</td>
<td>219</td>
<td>289</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>288</td>
<td>315</td>
<td>362</td>
<td>322</td>
<td>308</td>
<td>219</td>
<td>289</td>
<td>258</td>
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<tr>
<td>3</td>
<td>I</td>
<td>178</td>
<td>210</td>
<td>235</td>
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<td>14.20</td>
<td>231</td>
<td>307</td>
<td>206</td>
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<tr>
<td></td>
<td>II</td>
<td>252</td>
<td>276</td>
<td>284</td>
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<td></td>
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<td>256</td>
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<tr>
<td>5</td>
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<td>77.55</td>
<td>22.45</td>
<td>263</td>
<td>312</td>
<td>229</td>
</tr>
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</table>

The TG-DTG curve analysis shows that the degradation process is a complex and specific one. The samples are thermal degraded in major steps (step II, III) in temperature range of 150 - 386°C showing a similarity between sample 1 and 5 with present a thermal degradation process which occurs in a single stage while atmosphere within the 10-600°C temperature range are depicted in figures 3a-e.
the other samples present a more complex degradation process, containing at least three degradation stages.

The parameters that characterize the thermal decomposition of the samples: \( T_{\text{onset}} \) - the temperature at which the thermal decomposition begins; \( T_{\text{peak}} \) - the temperature at which the degradation rate is maximum; \( T_{\text{endset}} \) - the temperature at end of the process; \( T_{10}, T_{50} \) - the temperature corresponding to 10 and 50 wt. % weight losses; \( T_{\text{max}} \) - temperature at which the maximum amount of gas released (from Gram-Schmidt curve); \( W \) - weight loss, are presented in table 1.

The total weight losses varies between 35.34 - 86%. Also, the thermal stability of the three compounds is differently. The 3 sample presents a better thermal stability as comparative with the other samples. The temperatures \( T_{10} \) (10% weight losses) vary between 183 - 267 °C, while \( T_{50} \) (50% weight losses) varies between 289 - 328 °C and depend on the structure of samples.

The initial degradation temperatures resulting from DTG are indicative of the following order of the thermal stabilities:

\[
2 > 3 > 5 \geq 1 > 4
\]

With every sample under study the DSC curves show a strongly endothermic peak within the 10 - 220°C range where the sample mass is clearly constant corresponding to the melting interval and the temperature at the peak maximum represents the melting point. The melting points of the samples are the same within the limits of the experimental errors.

The DSC curves for the thermal degradation of the samples are similar. The same behavior as that resulting from the TG-DTG analysis was noticed with the difference only that the DSC curves of all samples showed a slightly endothermic peak within the 300 - 510°C range while the sample weights (from TG) did not change although a slight shift of DTG from the basic line was noticed. The other characteristic temperatures from DSC are in agreement with those from TG-DTG.

In figure 4 the absorbance versus temperature is plotted for the gaseous species resulted by thermal degradation of the 1 sample under nitrogen atmosphere making evident both their nature and the elimination order as well as their content in the gaseous mixture.

As results from figure 4 the gas species eliminated by thermal degradation of new derivatives in nitrogen atmosphere over the endothermic domain (10 - 600 °C) are: CO, CO\(_2\), H\(_2\)O, NH\(_3\), HCl, SO\(_2\), intermediates (HNCO, C\(_2\)H\(_4\), CH\(_2\)-NH).

Based on the TG-FTIR analysis the most probable overall mechanism of the thermal degradation in nitrogen was presented in figure 5.

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. 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.

The above conclusions are confirmed by the 3D spectra presented in figures 6a-e.

**Conclusions**

By combining the dimethyl-pyrazole ring with amidosulfonyl-R1,R2-phenoxyacetil moiety we designed new compounds with potential biological properties.

We have described a simple and accessible method to obtain these derivatives and confirmed their structures by IR and \(^{1}H\)-NMR spectroscopic analysis and elemental analytical data.

The TG-DTG-DSC curves obtained with the pyrazol derivatives under study are indicative of complex and
specific degradation mechanisms and consequently of the structure influence.

The TG-FTIR analysis affords the conclusion that the gaseous species evolved by degradation are in accordance to those resulting from TG, DTG, DSC analysis. The thermal stability depends on the chemical structure of new pyrazole derivatives making possible to ascertain the temperature range proper for using and storing these.

References

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