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New 1-amidosulphonyl- phenoxyacetyl- 3-methyl-pyrazolin-5-one derivatives

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Abstract

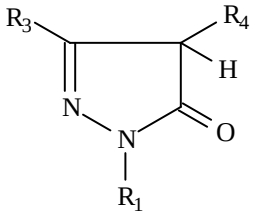
In view of the reported biological properties of pyrazolin-5-one derivatives we attempted the synthesis of some 1-amidosulphonyl-phenoxyacetyl-3-methyl-pyrazolin-5-ones for their evaluation as medication for central nervous system. IR and ^{1}H-NMR spectral along with some tautomerism investigations are included.

Keywords: pyrazolin-5-one, sulphonamidated phenoxyacetyl derivatives

Introduction

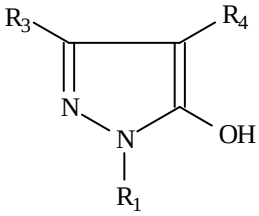
Since the discovery by Knorr of 3-methyl-1-phenyl-2-pyrazolin-5-one and of ***Antipyrine***, numerous studies have been published on analgesic, anti-inflammatory, antipyretic, anti-diabetic, cardiovascular and antifungal activities of pyrazoline-5-one derivatives [1-3]. This kind of derivatives are though, by far, especially well known for their analgesic, antipyretic and anti-inflammatory actions on central nervous system, ***Aminophenazone***, ***Nifenazone***, ***Morazone***, ***Ampyrone*** being some examples in this view. Pirazolin-5-one derivatives have also found application in colour photographical technique and in mass spectroscopy, as adjuvants [3,4].

A lot of attention has been devoted to the tautomerism of pyrazolin-5-ones, which can exist in three tautomeric forms (1-3). Some authors have denoted these forms the *CH*, *OH* and *NH* forms and some other authors defined them as Δ_2, *hydroxy* and Δ_3 forms, respectively [3, 5-10].



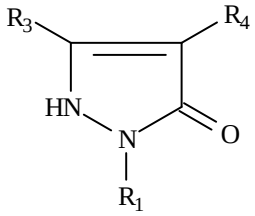
2-pyrazolin-5-one
CH (Δ_2) form

(1)



5-hydroxy pyrazole
OH (*hydroxy*) form

(2)



3-pyrazolin-5-one
NH (Δ_3) form

(3)

In the current paper we aimed at bringing together in the same molecule 3-methyl-pyrazoline-5-one pharmacophore and a sulphonamidated phenoxyacetyl residue in order to obtain products having possible effects on the central nervous system (CNS). Both 5-pyrazolone ring and sulphonamidated aryloxyacyl group are to be found in numerous drugs for CNS. In addition, the latest one exhibited an extremely low toxicity, even at high doses like in the case of ***Romener***® which is clinically used as antidepressant, anticonvulsant, and cerebral stimulant medication [11].

Materials and methods

The synthesis and characterization of starting hydrazides have been reported in this journal [12]. Melting points (M.p.) were determined on a Boetzius micromelting point microscope and were uncorrected. Infrared (IR) spectra were recorded on a UNICAM SP-100 device using KBr pellets. Nuclear Magnetic Resonance (^{1}H-NMR) spectra were registered at 300.1 MHz on a BRUKER-AM 300 spectrometer, using deuterated dimethylsulphoxide (DMSO-d_6) as solvent, at ambient temperature. Chemical shifts were referred to hexamethyldisiloxane (HMDS) as internal reference. The nitrogen content was determined by Dumas method. All evaporations were performed under vacuum.

Typical examples for 1-(amidosulphonyl- R_1, R_2- phenoxyacetyl)- 3-methyl-pyrazoline-5-ones synthesis are given bellow:

1-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl)-3-methyl-pyrazolin-5-one

Method A.

1.56 g (0.012 mole) ethyl acetoacetate were added to a solution of 3.29 g (0.01 mole) 2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl hydrazide in 10 mL acetone. After stirring the mixture at room temperature for 20 min. a solid phase occurred in the system, which dissolved by refluxing the mixture for 1 hour. After cooling the *N*-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl) hydrazone of ethyl acetoacetate separated as a white powder. M.p. = 133°C. η=94% (4.12 g). The hydrazone intermediate was then dispersed in 20 mL *n*-decane and refluxed under a good stirring for 18 hours. The separated product after cooling was recrystallized from dimethylformamide to give 1.65 g 1-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl)-3-methyl-pyrazolin-5-one as a white powder. M.p. = 205°C. $\%N_{calc.}$ = 10.63; $\%N_{found}$ = 10.38. η=42%.

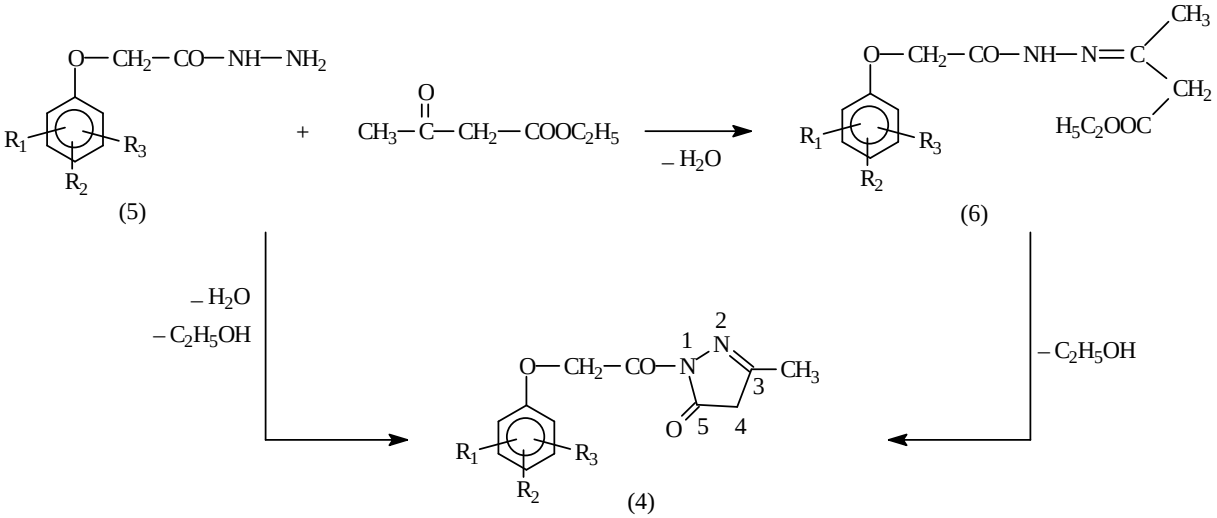
Method B.

The heterogeneous mixture consisting of 3.29 g (0.01 mole) 2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl hydrazide, 1.56 g (0.012 mole) ethyl acetoacetate and 20 mL water was refluxed for 30 min. to give a clear solution. After refluxing for other 30 min. a solid phase occurred and filtered off. After recrystallization of the crude product from dimethylformamide 3.43 g of 1-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl)-3-methyl-pyrazolin-5-one were obtained as a white powder. M.p. = 205°C. η=87%.

Results and discussion

1-Amidosulphonyl-phenoxyacetyl-3-methyl-5-pyrazolones derivatives (4) were prepared either directly by the action of the acetyl acetoacetate on the hydrazides (5) in acetone media or via the hydrazone intermediate (6) in water, according to the reaction scheme given in figure 1.

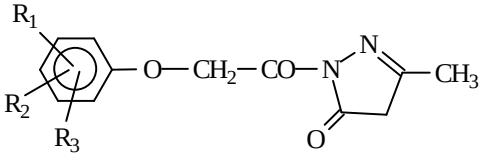
The six thus obtained 1-amidosulphonyl-phenoxyacetyl-3-methyl- pyrazolin-5-one derivatives (Table 1) were purified by recrystallization from the appropriate solvents, depending on their solubility. The products are white powders with characteristic melting points, soluble in dimethylformamide and dimethylsulfoxide, insoluble in water, acetone, acetyl acetoacetate or chloroform and slightly soluble in alcohol. The hydrazone intermediates are white crystals soluble in warm alcohol and acetone.



where: $R_1 = CH_3$; $R_2 = H, CH_3$; $R_3 = SO_2NH_2, SO_2N(C_2H_5)_2, SO_2N(C_3H_7)_2, SO_2N(C_4H_9)_2, SO_2NH\text{-}i\text{-}C_3H_7, SO_2NH\text{-}t\text{-}C_4H_9$

Figure 1. Synthetic route for 1-amidosulphonyl-phenoxyacetyl-3-methyl-pyrazolin-5-one derivatives obtaining

Table 1. Some characteristics of 1-amidosulphonyl-phenoxyacetyl-3-methyl- pyrazolin-5-one derivatives

General structure							
No.	***R_1***	***R_2***	***R_3***	***% N***		***M.p. [°C]***	
				calc.	***found***	***pyrazolone***	***hydrazone***
1.	2-CH_3	3-CH_3	4-SO_2NH_2	12.39	12.09	301	184-185
2.	2-CH_3	3-CH_3	4-$SO_2N(C_2H_5)_2$	10.63	10.38	205	133
3.	2-CH_3	3-CH_3	4-SO_2NH-*i*-C_3H_7	11.02	10.98	225	154
4.	2-CH_3	3-CH_3	4-SO_2NH-*t*-C_4H_9	10.63	10.42	248	102
5.	H	2-CH_3	4-SO_2N(*n*-$C_3H_7)_2$	10.27	10.05	189	170-175
6.	H	2-CH_3	4-SO_2N(*n*-$C_4H_9)_2$	9.61	9.39	212-213	174

The new compounds were analyzed by means of elemental analysis, IR- and ^{1}H-NMR spectral measurements.

For our further discussion the product 1-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl)-3-methyl-pyrazolin-5-one and its intermediate, *N*-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl) hydrazone of ethyl acetoacetate were taken as examples. In the infrared absorption spectra of the above mentioned hydrazone the band occurring at 1735 cm^{-1} was assigned to the carbonyl from methyl ester group, this band lacking from the starting hydrazides. The strong peak appeared at 1640 cm^{-1} and the shoulder

at 1560 cm^{-1} was found for the ν_{CO-NH} amidic valence vibrations (the bands denoted by amide I and amide II, respectively). The intense band in the range of 1580-1590 cm^{-1} was attributed to $\nu_{C=N}$ valence vibration while the band centered at 3340 cm^{-1} was ascribed to the valence bond NH associated by hydrogen bonds with the oxygen atom from the ester group [13, 14]. For the 2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl residue, the characteristic bands are to be found more or less at the same frequencies as in the starting hydrazides.

In the ^{1}H-NMR spectra of the hydrazone we observed the characteristic signals of the diethyl radicals attached to the sulphonamide group as a triplet at δ = 1.15 ppm (6H) for the methyl group and as a quartet at δ = 3.2 ppm (4H) for the methylene moiety. The methyl and methylene groups from the esteric part of the molecule were found at 1.9 ppm (3H, triplet) and 4.75 ppm (2H, quartet), respectively. The remaining protons belonging to the acetyl acetoacetate residue appeared at 1.98 ppm (3H, singlet) and 3.25 ppm (2H singlet). The chemical shifts for the protons in the two methyl groups attached to the aromatic moiety were: 2.2 ppm (3H, singlet) for the methyl group adjacent to the oxymethylene (–O–CH_2–) residue and 2.42 ppm for the methyl group next to the diethyl-sulphonamide residue. The two protons from the oxymethylene moiety were found as a singlet at 5.2 ppm whereas for the two aromatic protons two doublets centered at 6.75 and 7.65 ppm were assigned. For the hydrogen attached to the nitrogen atom from the hydrazone, a singlet at 10.42 ppm was detected.

As a result of the *N*-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl) hydrazone of ethyl acetoacetate cyclization to 1-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl)-3-methyl-pyrazolin-5-one, the disappearance of the absorption band characteristic for the carbonyl bond from the esteric group (1735 cm^{-1}) in the IR spectrum was noticed. Additionally, the appearance of other three bands was observed: an intense band at approximately 1600 cm^{-1} for C=N vibration in pyrazolone ring, a band at 1650 cm^{-1} for CO–NH amidic valence vibrations and a large band in the range of 3150-3300 cm^{-1} attributed to the intermolecular hydrogen bonds from the tautomeric forms *OH* and *NH*. Normally, this band should have not existed if the product was in the *CH* form exclusively. This result is consonant with the published data, which confirm the prevalence of *OH* and *NH* forms of the pirazolones in solid state (KBr) against *CH* form. Besides, some authors signalled the fact that in the IR spectra of such compounds the carbonyl group from pirazolinone ring appeared at 1700 cm^{-1}, due to the changing of the C_4 hybridization state: from sp^3 in *CH* form to sp^2 in *OH* and *NH* forms [6-8]. The lack of this band in the case of our product led to the elimination of the *CH* form in solid state. Moreover, the fact that the band at 3150-3300 cm^{-1} is slightly cleaved pleads for the coexistence of the *OH* and *NH* forms in solid state. The differentiation between the *OH* and *NH* forms is less simple because strong hydrogen bonding blurs the distinction between the two tautomeric forms. Proton transfer may well occur in the crystal rendering these two designation equivalent.

In the ^{1}H-NMR spectra (300.1 MHz, DMSO-d_6 / TMS) of 1-(2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl)-3-methyl-pyrazolin-5-one, besides the chemical shifts of the protons from 2,3-dimethyl-4-diethylamidosulphonyl-phenoxyacetyl residue (1.05 ppm, 6H, t, CH_3 from diethyl-sulphonamide group; 2.2 ppm, 3H, s, CH_3 and 2.42 ppm, 3H, s, CH_3 for the two methyl groups attached to the aromatic ring; 3.2 ppm, 4H, q, CH_2 from diethyl-sulphonamide group; 4.66 ppm, 2H, s, OCH_2; 6.9 ppm, d, 1H and 7.7 ppm, d, 1H for the aromatic protons) three signals assigned to the protons from the pyrazoline ring were also seen. Beside the singlet at 2.55 ppm, which was attributed to the methyl group from pyrazoline ring, other two singlets corresponding to one proton each were noticed at 7.225 and 10.2 ppm, respectively. These last two signals could be attributed as follows: the first one to the proton from C_4 and the second, either to the NH proton in *NH* (Δ_3) form or to the OH proton in the *hydroxy* form, respectively. In the case we would have assumed the possibility of the coexistence of the two tautomeric forms, duplication of the pyrazoline protons as well

as of O–CH_2–CO protons should have been noticed. Being given the absence of supplementary signals and due to the fact that some authors stipulated that DMSO solvent favoured the *OH* form of pyrazolin-5-ones (in fact, the *pyrazole* form) we concluded that in DMSO the product is to be found in *OH* form. An additional argument for this conclusion consists in the shifting of the proton attached to C_4 in pirazoline ring towards the aromatic region (7.225 ppm), which is concordant with the proposed *pyrazole* structure.

In order to establish a quantitative relationship between the tautomeric forms of the synthesized product we attempted to complete the analysis by IR, NMR and UV spectroscopy in solvents having different polarities. The results were though not successful due to the extremely low solubility of the compounds in solvents such as chloroform, carbon tetrachloride, hexane, water, etc., which are typical solvents, used in the tautomerism study of the pyrazoline derivatives.

In the absence of some quantitative data regarding the three possible tautomeric forms of 1-amidosulphonyl- phenoxyacetyl- 3-methyl-pyrazolin-5-one derivatives we expressed the structure of these compounds as an equilibrium between the *CH*, *NH* and *OH* forms (Figure 2).

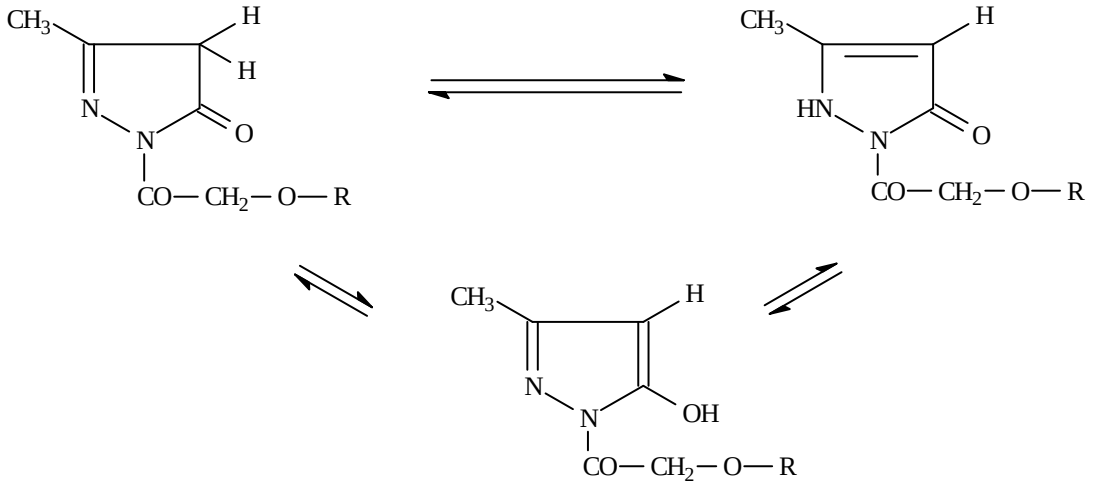


Figure 2. The equilibrium of the *CH*, *NH* and *OH* tautomeric forms of 1-amidosulphonyl- phenoxyacetyl- 3-methyl-pyrazolin-5-one derivatives (R=aryl sulphonamidated moiety)

Conclusions

New compounds with potential analgesic, antipyretic and anti-inflammatory activities were designed by bringing together into the same molecule a sulphonamidated phenoxyacetyl residue and a pyrazolin-5-one ring. The synthesis of 6 original compounds was carried out by the reaction between the corresponding sulphonamidated phenoxyacetyl hydrazides and ethyl acetoacetate either by a direct cyclization or through a hydrazone intermediate. The pyrazolin-5-one derivatives can exist in three tautomeric forms denoted the *CH* or Δ_2, *OH* or *hydroxy*, and *NH* or Δ_3 forms, respectively. From the IR spectra (KBr pellets) of the compounds we concluded that in solid state the compounds coexist in the *OH* (structure of 5-hydroxy-pyrazole type) and *NH* (structure of 3-pyrazolin-5-one type) forms. The ^{1}H-NMR data taken in DMSO-d_6 revealed that the products exist in the *OH* tautomeric form. The attempts to establish a quantitative relationship between the three possible tautomeric forms of the compounds by a more extended UV, IR and NMR analysis failed because of the extremely low solubility of the compounds in solvents such as chloroform, carbon tetrachloride, hexane, water, etc., which are typical solvents, used in the tautomerism study of the pyrazoline derivatives.

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