New Mannich Bases with Pharmacological Properties

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Six new Mannich bases were synthesized by a reaction between substrates: barbituric acid, N,N‘-dimethylbarbituric acid, 2-hydroxy-4,6-dimethylpyrimidine and formaldehyde, respectively cyclic aliphatic amines (piperidine, morpholine and 2,5-dimethylpiperazine). The obtained compounds have potential pharmacological properties and have been characterized by UV-VIZ, FT-IR, NMR spectroscopy.

Keywords: barbituric acid, N,N‘-dimethylbarbituric acid, 2-hydroxy-4,6-dimethylpyrimidine, piperidine, morpholine and 2,5-dimethylpiperazine, Mannich bases

The Mannich reaction of numerous heterocyclic compounds are very well known [1] as well some Mannich bases obtained from pyrimidines compounds with a pronounced anti-inflammatory [2-4], spasmolytic [5], antidiabetic and antioesity activity [7-11]. Compounds C- and N- aminomethylated with anti-inflammatory [2, 11] and cytostatic [15-17] activity, obtained from barbituric acid have been reported.

According to the interest for Mannich reaction, in this work we report the synthesis and characterization of some new Mannich compounds with pharmacological properties. The reactions were carried out starting with the substrates: barbituric acid, N,N‘-dimethylbarbituric acid, 2-hydroxy-4,6-dimethylpyrimidine with formaldehyde and cyclic aliphatic amines (piperidine, morpholine and 2,5-dimethylpiperazine).

Experimental part

The Mannich bases were obtained by the usual procedure according to the reaction indicated in scheme 1.

0,01mol pyrimidine compound was dissolved in 16 mL anhydrous ethanol and to it was added 0,6 g (0,02 mol) formaldehyde (30% aqueous solution) by stirring. The obtained solution was then treated with 0,011 mol cyclic amine. In the case of compound 3, the molar ratio of reacting substances was 2:2:1. The mixture was stirred for 8 h at room temperature. The solid raw product, overnight crystallized, at low temperature was filtered in vacuum. The obtained Mannich bases were recrystallized from the solvents indicated in table 1. The reaction yields are between 50-85% for the solid raw products.

The reagents used in these reactions were the commercial ones, delivered by Merck and Fluka, excepting N,N‘-dimethylbarbituric acid that was synthesized by us via the condensation reaction between N,N‘-dimethylurea and malonic acid in acetic anhydride [18].

The melting points are uncorrected and were recorded on a KRÜSS-OPTRONIC-KSPI apparatus.

The purity was checked by thin layer chromatography. TLC was carried out on silica gel Merck plates with a mixture acetonitril : water (1:1, vol) as eluent and developed with a UV lamp (λ=265 nm). UV-VIS spectra were recorded on a HITACHI L 200 apparatus, using absolute methanol as solvent, at the concentration of the substances 10-4 M, in a 1 cm quartz tube.

FT-IR spectra (in KBr pelets) were recorded in the 4000-400 cm⁻¹ range using a FT-IR apparatus JASCO 430 using for the obtained pellet 5g KBr and 10 mg substance for analysis.

NMR spectra were recorded on a Varian Gemini 300 Spectrometer operating at 300 MHz (1H-NMR) and 75 MHz (13C-NMR) respectively, in DMSO-d6, with tetramethylsilane (TMS) as the internal standard.

MS were recorded on a VARIAM MAT apparatus.

Results and discussion

The aminomethylation via Mannich reaction is a condensation reaction between a substrate which contains active hydrogen atoms with an aliphatic aldehyde and a secondary amine [12]. Generally, the solution of

Scheme 1. Condensation Mannich reaction

Scheme 2. Condensation Mannich reaction. The obtaining of bis-Mannich base

In the case of compound 3, listed in table 1, the reaction carries out to the bis-Mannich base (scheme 2).

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formaldehyde 30% is the most used [13, 14]. The condensation reaction was carried out in a single step (scheme 1).

The 2,4,6-triceto-hexahidropyrimidine barbituric acid has active hydrogen atoms in position 5 as well as in position 1 or 3. In fact the Mannich reaction can be carried out both at the azote atoms, in positions 1 or 3 and at the carbon atom in position 5 [11]. By blocking the hydrogen atoms from the azote atoms, the Mannich reaction will be carried out only at the hydrogen atoms in position 5.

In the case of the Mannich reaction between N,N′-dimethylbarbituric acid, formaldehyde and 2,5-dimethylpiperazine, the condensation reaction is carried out at both terminal azote atoms in order to obtain a bis-Mannich base (scheme 2).

The representative properties for the obtained products are presented in table 1. The solid raw products were recrystallized from the solvents indicated in table 1. The purity of the new compounds was checked by thin layer chromatography using silica gel Merck plates with fluorescence.

The UV-VIZ spectrum registered bands at the values indicated in table 2, values which are assignable to the π→π* transitions. The molecular peaks from the mass spectrum are a proof for the proposed molecular structures.

The FT-IR spectra reflect the molecular structure of the new compounds (table 2). The IR spectrum presents a band in the 3377-3474 cm\(^{-1}\) due to the \(\nu_{\text{OH}}\) assigned to the group OH from the position 4 of the pyrimidine ring of the Mannich compounds and a band in the 1631-1743 cm\(^{-1}\) due to the \(\nu_{\text{CO}}\) assigned to the group CO.

Therefore these bands are a proof for the presence of the two functional groups on the pyrimidine ring. And the other bands listed in table 2 are a proof of the molecular structure for the obtained compounds. The split band in the 1374-1383 due to the \(\delta_{\text{CH}_3}\) assigned to the methyl group and the other bands due to the \(\nu_{\text{NCH}}\) and to enolic hydroxyl confirm the proposed molecular structure.
The assignments made in the $^1$H-NMR spectra and in the $^{13}$C-NMR, in the DMSO-d$_6$, are in accordance with the proposed structures in schemes 1, 2 respectively in table 1. The chemical shifts for the new compounds are listed in table 3 and 4.

The chemical shifts, $\delta$ ppm from the both NMR spectra are in a reciprocal correlation and confirm the established molecular structures.

**Conclusions**

Six new Mannich bases were obtained in a single step condensation of some pyrimidine compounds with formaldehyde and cyclic aliphatic amines. The compounds were obtained with good yields, were purified by recrystallization, checked by thin layer chromatography and characterized by several spectra: UV-VIZ, FT-IR, $^1$H-NMR, $^{13}$C-NMR and mass spectrum. Some preliminary biological tests show some pharmacological properties and the results will be reported later.

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