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Novel Synthesis Method of Pyrimidine and Pyrazole Derivatives

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The purpose of this work is the development of a synthetic method that allows access to some heterocyclic compounds containing pyrimidine and pyrazole nuclei. The dehydroacetic acid has been extensively studied as a starting material for the synthesis of natural products that exhibit valuable pharmacological properties. In the first part, we have shown that the pyrimidines can be obtained by reacting dehydroacetic acid with nitrogen binucleophiles reagents. In the second part, we presented the reactivity of the previously synthesized derivatives towards hydrazine to yield derivatives involving pyrimidine and pyrazole motifs. All the synthesized products were subjected to IR, ^{1}H NMR and mass spectra studies.

Keywords: Dehydroacetic acid, Pyrimidine, Pyrazole.

INTRODUCTION

The chemistry of 2-pyrones has undergone considerable development owing to their presence in natural compounds and their application in biological and food industry. Dehydroacetic acid plays a pioneering role in the synthesis of different heterocyclic compounds such as pyrimidine, pyrazole, 1,5-benzodiazepine. The choice of such compounds is mainly based on their pharmacological properties[1-3].

Modified pyrimidines have keenly interested the chemist and pharmacologist because of their impact in the therapeutic field. Indeed, these compounds after some modifications showed antibiotic, anticancer, antiviral[4] and agrochemical properties[5-7]. Pyrazoles, in their turn, constitute an important development in the field of fine chemistry because of their importance in medicinal chemistry or during the preparation of pesticides and insecticides[8]. The pyrazole pattern is found in a large number of compounds known for their therapeutic value mainly as anti-inflammatory[9], antitumor[10-15] hypnotic and sedative properties[16-18]. Some of these structures have shown, in addition to their analgesic properties[19] and antimicrobial activity[20].

In the context of the investigation dealing with the use of dehydroacetic acid **1** and its derivatives in heterocyclic synthesis, we report in this work the synthesis of new molecules (pyridopyrimidine, pyrazole) susceptible to present interesting pharmacological properties.

The adopted synthesis pathways involve, on one hand, the opening of pyranic ring by binucleophiles reagents such as 2-amino-3-benzyloxypyridine and on the other hand, the actions of hydrazine hydrate on the pyridopyrimidine.

EXPERIMENTAL

The ^{1}H NMR spectra were performed on Bruker AC spectrometer 200 and 300 MHz. Chemical shifts are given in ppm relative to TMS (internal reference). The ^{13}C NMR spectra were performed on a J-modulated Bruker AC spectrometer 200 and 300 MHz. Infrared spectra are recorded on a Perkin Elmer 225 network spectrophotometer, compounds are in solid suspension in Nujol. The results are given in cm^{-1}. Mass spectra were performed on a Nermag R10-10C spectrometer with the ionization mode by electronic impact at 70 ev and/or by chemical ionization by NH_3. Melting points are taken on using a Köfler bench.

Synthesis of pyridopyrimidine 2 and 3: In refluxing in butanol, 0.01 mol of 3-(benzyloxy) pyridin-2-amine and 0.01 mol of dehydroacetic acid were stayed to react for 24 h. After evaporation of the solvent under reduced pressure, compound **2** was obtained after purification using column chromatography on silica gel (eluent: $CHCl_3$/EtOAc, 9:1).

Synthesis of pyrazole 4: To 3.65 g (0.01 mol) of **2** is added 0.32 g (0.01 mol) of hydrazine hydrate in 20 mL of ethanol. The solution is heated under reflux for 3 h. After

decrease in the volume of ethanol, a yellow solid precipitates. It is filtered and recrystallized in ethyl acetate.

4a is obtained after purification *via* chromatography on column of silica gel (eluent: $CHCl_3$/EtOAc 9/1).

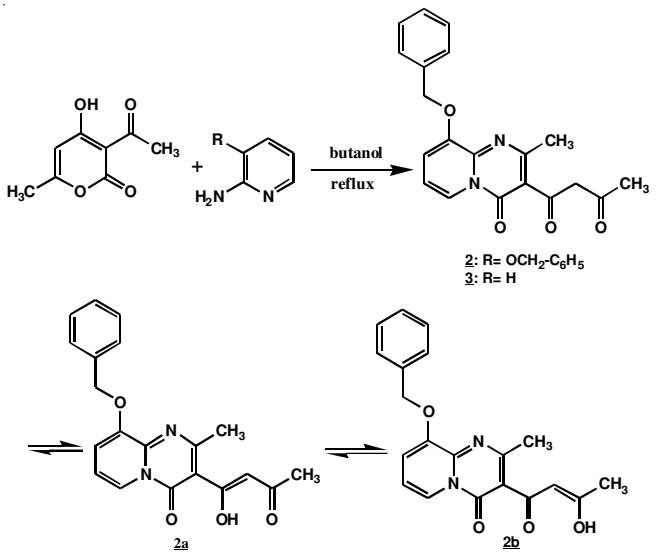
RESULTS AND DISCUSSION

As a first step, we are interested in the synthesis of novel condensed pyrimidinic derivatives, forming a heterocyclic class with interesting pharmacological properties.

As a matter of fact we have reacted 2-amino-3-benzyloxy-pyridine on dehydroacetic acid under reflux in butanol. The reaction leads to the pyridopyrimidine **2**, which is present in solution as two tautomeric forms **2a** and **2b** (**Scheme-I**).

The formation of compound **2** can be explained by the following mechanism (**Scheme-II**): the exocyclic amino group NH_2 of 2-amino-3-benzyloxypyridine attacks the carbonyl of acetyl group of dehydroacetic acid. The resulting intermediate [A] rearranges by loss of a water molecule, leading to a second non-isolable intermediate [B], which rearranges in turn by attack of endocyclic grouping NH of pyridine ring on carbonyl in position **2** pyranic, giving thus produce to compound **2**.

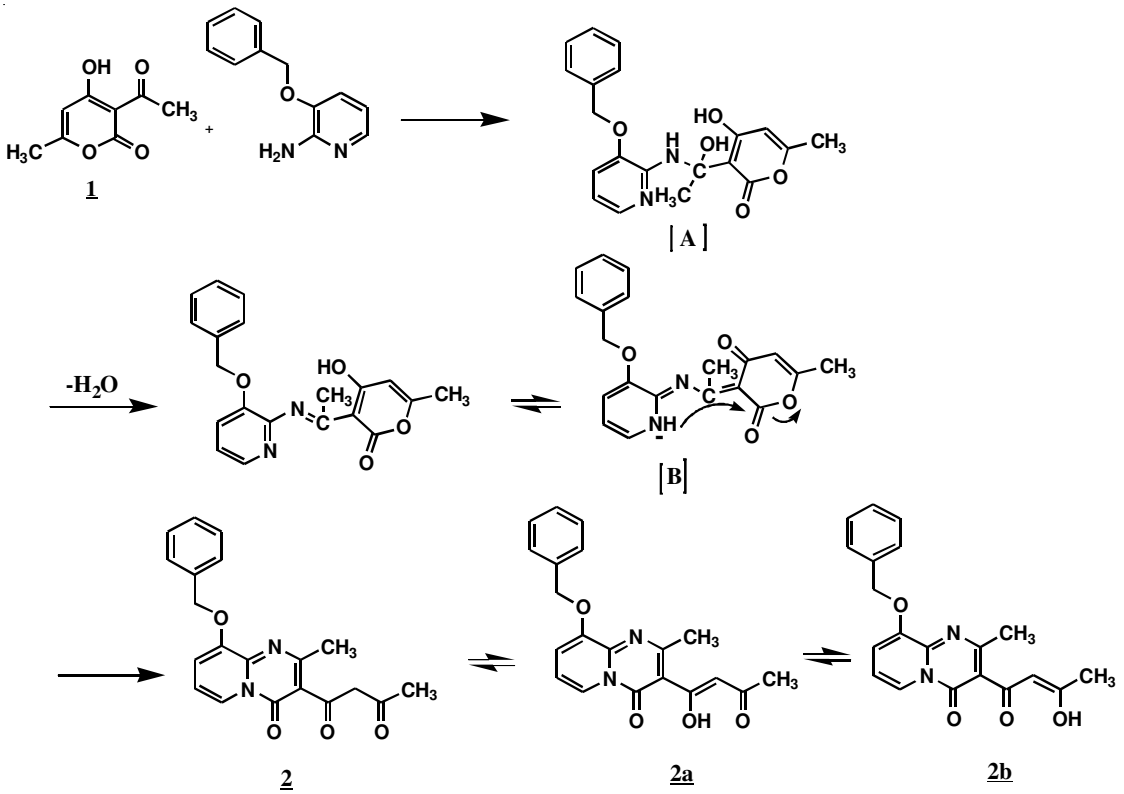
The study of the ^{1}H NMR spectrum at 300 MHz of derivatives **2** and **3** shows every time the expected signals for the considered structure. The ^{1}H NMR spectrum of compound **2** discloses two tautomeric forms **2a** and **2b** evidenced particularly by the presence of two singlets at 4.10 and 6.95 ppm, due, respectively to the methylenic and vinylic protons of both forms. In both derivatives **2** and **3** the absence of two signals at about 6.14 ppm and the presence of a broad peak at 15 ppm correspond to the ethylenic protons at the position 5 and to the group OH at the position 4.



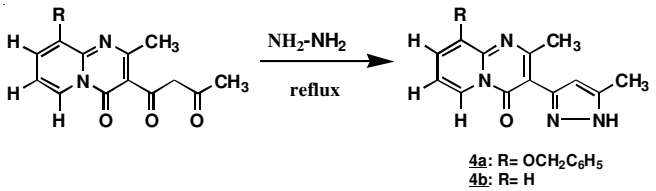
Scheme-I: Reaction of 2-amino-3-benzyloxypyridine on dehydroacetic acid under reflux in butanol, leading to the pyridopyrimidine (**2**), which exists in solution in two tautomeric forms **2a** and **2b**

The structures of compounds **2** and **3** were confirmed by ^{13}C NMR spectra, which show particularly, the signals assigned to the methylenic and vinylic carbons of the two forms, respectively at 59 and 103 ppm. The side chain a dicarbonylic of the prepared compounds **2** and **3** is suitable syntone for the synthesis of novel heterocyclic compounds.

The action of hydrazine hydrate on the compound **2**, heated under reflux in ethanol for 3 h, leads to the formation of the 9-(benzyloxy)-2-methyl-3-(5-methyl-1*H*-pyrazol-3-yl)-4*H*-pyrido[1,2-a]pyrimidin-4-one (**Scheme-III**).



Scheme-II: Formation of product **2** by attack of the carbonyl of the acetyl group of the dehydroacetic acid by the exocyclic amino group NH_2 of pyridine



Scheme-III: Obtaining pyrazole **4** by the action of hydrazine hydrate on **2** and **3**

In the ^{1}H NMR spectra of the two compounds **4a** and **4b**, it is worthy to note the appearance of a peak at 6.33-6.35 ppm, corresponding to the pyrazole proton.

In the ^{13}C NMR spectrum, we note particularly the disappearance of the two peaks (C = O) of the side chain α, β-dicarbonyl of compound **3**. In addition, we note in the two compounds **4a** and **4b**: The presence of a peak at around 106 ppm due to the carbon in position 4. The appearance of the signals at 135, 142 ppm corresponds to quaternary carbons in positions 3 and 5.

Characteristics of compound 2: Yield = 65 %. m.p. = 130 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.34 (s, 3H, CH_3), 2.23^{a,b} (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.58^{a,b} (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 5.17 (s, 2H, CH_2), 5.17^{a,b} (s, 2H, CH_2), 6.16-7.23 (m, 6H, H_{arom}), 6.16-7.23^{a,b} (m, 6H, H_{arom}). ^{13}C NMR ($CDCl_3$, 300 MHz): 25(C_{26}), 31(C_{14}), 59(C_{23}), 72(C_{16}), 196(C_{24}), 203(C_{12}), 156(C_2), 135(C_3), 157(C_4), 145(C_6), 151(C_7), 115-116-117121-127-128-129 (C_{arom}). 25^{a,b} (C_{26}), 26^{a,b} (C_{14}), 103^{a,b} (C_{23}), 72^{a,b} (C_{16}), 191^{a,b} (C_{24}), 185^{a,b} (C_{12}), 156^{a,b} (C_2), 135^{a,b} (C_3), 168^{a,b} (C_4); 145^{a,b} (C_6), 168^{a,b} (C_4); 115-116-117121-127-128-129^{a,b} (C_{arom}). S.M (IE, 70 ev): [M^+] = 350.

Characteristics of compound 3: Under the same experimental conditions we carry out the synthesis of derivative **3** with a yield of 68 % and m.p. = 140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.38 (s, 3H, CH_3), 2.32^{a,b} (s, 3 H, CH_3), 2.70 (s, 3H, CH_3), 2.67^{a,b} (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.92^{a,b} (s, 1H, CH), 6,96-7,6 (m, 4H, H_{arom}), 6.96-7, 6^{a,b} (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$, 300 MHz): 24(C_{26}), 32(C_{14}), 57(C_{23}), 70(C_{16}), 198(C_{24}), 201(C_{12}), 174(C_2), 133(C_3), 154(C_4), 143(C_6), 150(C_7), 116-125-136-141 (C_{arom}). 25^{a,b} (C_{26}), 30^{a,b} (C_{14}), 10^{2a,b} (C_{23}), 73^{a,b} (C_{16}), 195^{a,b} (C_{24}), 198^{a,b} (C_{12}), 152 ^{a,b} (C_2), 131^{a,b} (C_3), 169^{a,b} (C_4), 144^{a,b} (C_6), 151^{a,b} (C_4), 116-125-136-141^{a,b} (C_{arom}). S.M (IE, 70 ev): [M^+] = 244.

Characteristics of compound 4a: Yield = 75 %. m.p. = 196 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.32 (s, 3H, CH_3), 2.76 (S, 3H, CH_3), 5.33 (s, 2H, CH_2), 6.35 (s, 2H, CH_2), 6.90-8.70 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$, 300 MHz): 13(C_{16}), 27(C_{18}), 71(C_{20}), 106(C_{12}), 142(C_5), 135(C_3), 151(C_6), 151(C_{11}), 147(C_9), 157(C_{15}), 161(C_7), 114-115-119-127-128-129 (C_{arom}). S.M (IE, 70 ev): [M^+] = 346.

Characteristics of compound 4b: Under the same experimental conditions we carry out the synthesis of derivative **4b** with a yield of 60 % and m.p. = 205 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.38 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 6.16 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$, 300 MHz): 15(C_{16}), 27(C_{18}), 106(C_4), 135(C_5), 140(C_3), 134(C_6), 152(C_{11}), 148(C_9), 161(C_7), 116-121-125-136 (C_{arom}). S.M (IE, 70 ev): [M^+] = 240.

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