VILSMEIER-HAACK FORMYLATION OF SOME 1-(2-PYRIMIDINYL)-3-METHYLPYRAZOLIN-5-ONES.

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Abstract:
1-(2-Pyrimidinyl)-3-methyl-4-formylpyrazolin-5-ones **2a,b**, **3a,b** were synthesized by Vilsmeier-Haack method. Structural assignments were made on the basis of chemical, analytical and spectral data.

INTRODUCTIONS

Since the first pyrazolinone was developed by Knorr, many papers have been published on 1-phenylpyrazolin-5-one analgesics. Some 1-phenylpyrazolin-5-one derivatives with formyl group in the position 4 exhibit a significant analgesic and antiinflammatory activity (1-4). Because of enolization, the aldehydes form an intern chelate structure, comparable to that of salicylic acid, which may be account for the antiinflammatory and anticoagulating properties of these compounds.

The pyrazolone system which contains the pyrimidine ring in the position 1 exhibits less toxicity than 1-phenylpyrazolin-5-one and presents a very high interest by its potent biological activity. There have been several reports (5-9) on the synthesis and pharmacological studies on 1-pyrimidinylpyrazolin-5-ones.

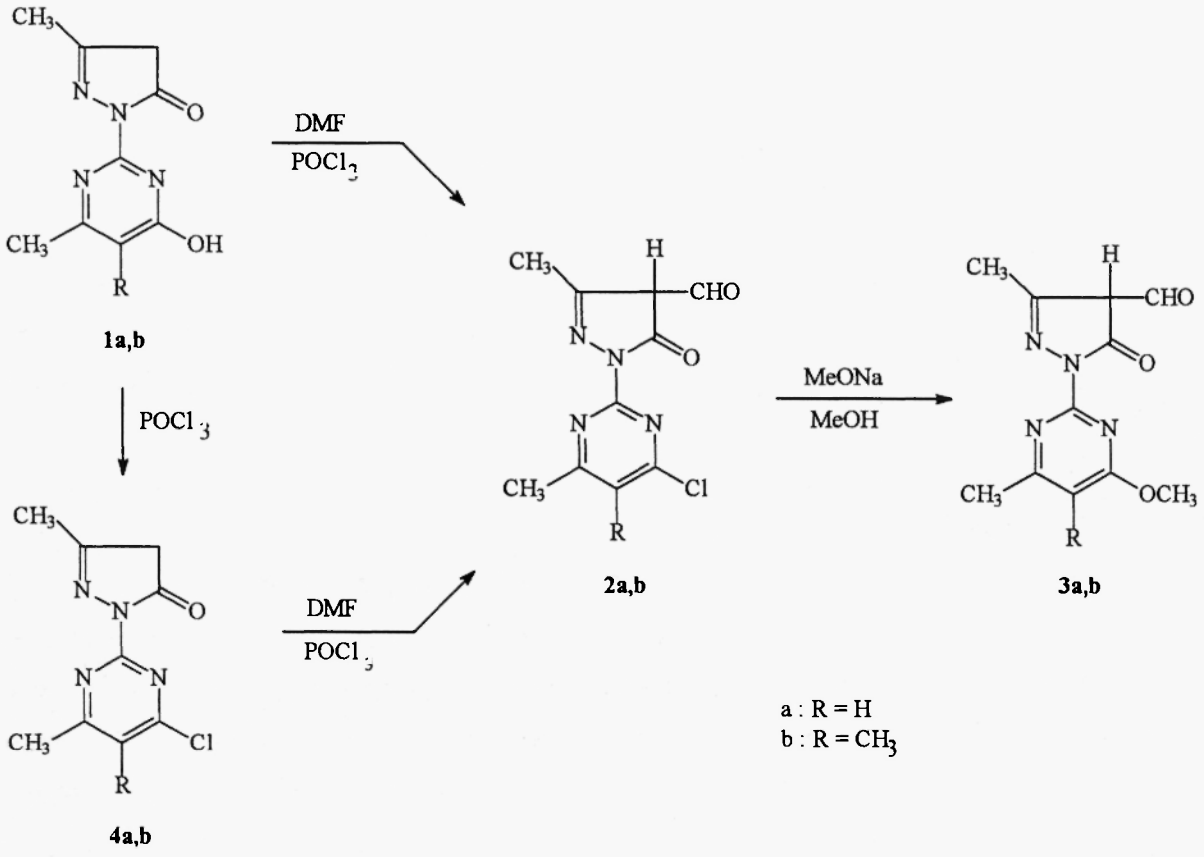
In order to find new analgesics and antiinflammatories, we extended the Vilsmeier-Haack formylation to this heterocyclic system.

RESULTS AND DISCUSSION

In present paper, 1-(2-pyrimidinyl)-3-methyl-4-formylpyrazolin-5-ones **2a,b** ,**3a,b** were synthesized, and structural assignments concerning tautomeric forms of the aldehydes were studied.

1-(2-Pyrimidinyl)-3-methylpyrazolin-5-ones **1a,b**, obtained by an one pot synthesis from aminoguanidine salts and appropriate β-keto esters (9), were allowed to react with

$POCl_3$-DMF under the conditions of the Vilsmeier-Haack reaction, to give the formylated products **2a,b** , in about 60-64% yields (Scheme 1).



Scheme 1

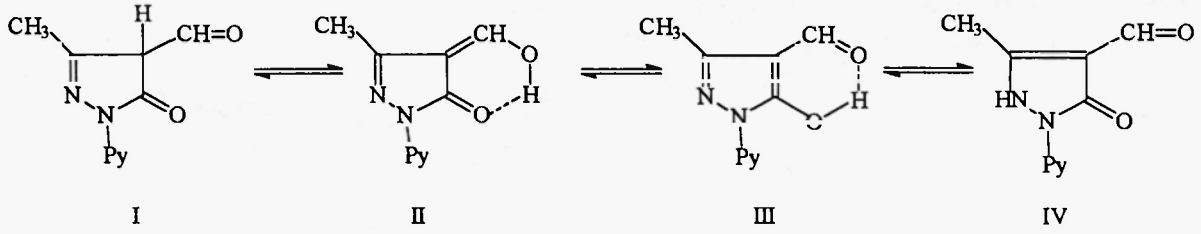
The same aldehydes **2a,b** were also obtained by another route, starting from **1a,b** which were converted in refluxing $POCl_3$ to the compounds **4a,b** (5) and then with $POCl_3$-DMF (Vilsmeier-Haack conditions) to the compounds **2a,b**. Treatment of **2a,b** with an equivalent amount of MeONa in refluxing MeOH afforded the expected methoxy-derivatives **3a,b,** in about 70% yield.

It is well known (5-8) that the methoxy group in the pyrimidine ring enhance analgesic and antiinflammatory activity of these compounds.

The structure of the compounds **2a,b** and **3a,b** was established by chemical and UV-vis, IR, ^{1}H-NMR spectroscopic methods. The elemental analyses of these substances, their oximes, 2,4-NO_2-phenylhydrazones and semicarbazones show that the compounds **2** and **3** are monoformyl derivatives. The IR spectra recorded in solid state (KBr), exhibit an intense band at 3430-3450 cm^{-1}, due to the associated hydroxyl group, sharp bands at 1630-1695 cm^{-1} and 1420-1450 cm^{-1} due to C=O and C=N stretching vibrations.

The ^{1}H-NMR spectra of all the compounds **2** and **3** show a singlet in the region δ= 9.70-9.98 due to the formyl group (CHO).

The aldehydes obtained can exist in an equilibrium mixture of four tautomeric forms (I ⇌ II ⇌ III ⇌ IV , Scheme 2).



Scheme 2

The enolic structures II and III which can form an intern chelate structure by intramolecular hydrogen bonding, predominate in the equiljbrium mixture.

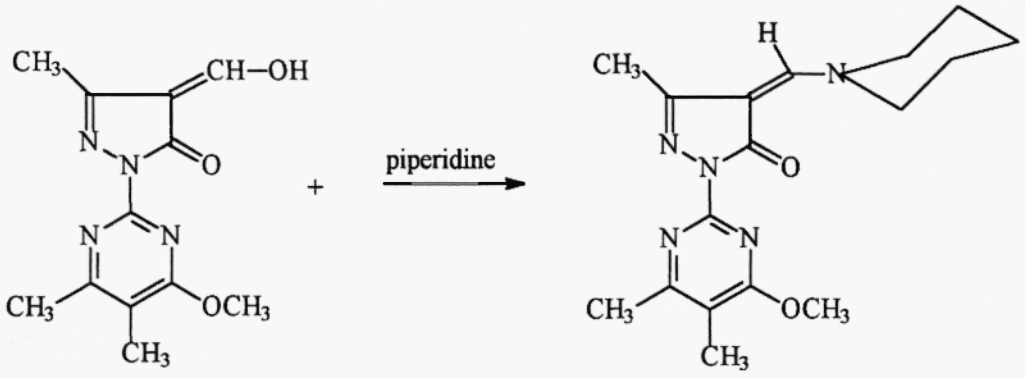
Indeed, FT-IR spectra recorded in diluted solution (10^{-3} M in benzene) exhibit a sharp peack in the region 3430-3450 cm^{-1} attributed to the hydroxyl group associated by intramolecular hydrogen bonding. In nonpolar solvents as CCl_4, benzene, the vibrations characteristic to NH stretching are missing (tautomeric form IV), and there appear intense vibrations at 1640-1670 cm^{-1}, characteristic to a conjugated carbonyl group. Also, the acidity constants (pKa= 6.50-6.75) of the aldehydes, measured by potentiometric titration, show that these compounds are weak acids comparable to the starting pyrazolones (pKa= 5.25-5.90) (10). This behaviour, demonstrates that the acidic hydrogen is blocked by intramolecular hydrogen bonding in the formylated compounds.

The aldehydes **2** and **3** react readily with secondary amines (piperidine, pyrrolidine and morpholine) to give enamines, in very high yields (85-90%). For exemple, the aldehyde **3b** reacts with piperidine in refluxing benzene for 1 hour to give the enamine **5b** (m.p. 186^{0}C, recryst. EtOH, 85 % yield, Scheme 3). The enamine **5b** was obtained only from enolic structure II. Electronic spectra recorded for enamines have been identically with those of the aldehydes (λ_{max}=275 nm), showing the same electronic structures.

The stereochemistry of the exocyclic double bond was confirmed by a NOE correlation experiment with the enamine **5b**. Thus irradiation of the proton from the exocyclic double bond caused enhancement for the methyl group from the position 3 of the pyrazolone

ring. This observation is consistent with a *trans* orientation of the hydrogen atom to the carbonyl group and provides additional confirmation of the Z-configuration of the exocyclic double bond in enamines.

Details concerning the synthesis and the biological tests of about twenty five new derivatives of these aldehydes will be the topic of a next paper.



3b **5b**

Z-isomer

Scheme 3

In conclusion, these aldehydes obtained by Vilsmeier-Haack formylation, prevail in the enolic tautomeric form (II or III), probably responsible for the antiinflammatory activities.

EXPERIMENTAL

Melting points were determined in capillaries and are uncorrected. IR spectra were recorded with a FT-IR 5300 JACSO apparatus in solid state (KBr). 1H-NMR spectra were recorded with 300 Mhz Varian spectrometer using TMS as an internal standard in $CDCl_3$. Electronic spectra were recorded in MeOH on a "SPECORD" spetrophotometer.

General procedure for formylation

To a mixture of 50 ml ice-cooled DMF and 25 ml $POCl_3$, 10 g of 1 was then added portionwise with vigorous stirring. The mixture was heated at 70°C for 3 hours and then poured on 200 g ice. The pH was adjusted at 7 with 1M Na_2CO_3 and allowed to stand at room temperature for two hours. The precipitate was extracted with $CHCl_3$, dried with Na_2SO_4 anh. The compounds were recrystallized from methanol : water 2:1.

2a : M.p. 102°C, 62%; IR (KBr), 3450, 1650, 1430; ^{1}H-NMR ($CDCl_3$, δ ppm), 9.98 (1H, s, CHO), 7.25 (1H, s, C_5 pyrim.), 5.4-5.6 (OH, broad), 2.62 (3H, s, CH_3 pyrim.), 2.40 (3H, s, CH_3 pyrazol.).

2b : M.p. 89°C, 64%; IR (KBr),3455, 1665, 1440; ^{1}H-NMR ($CDCl_3$, δ ppm), 9.95 (1H, s, CHO), 5.4-5.6 (OH, broad), 2.61 (3H, s, CH_3 pyrim.), 2.50 (3H, s, CH_3 pyrim.), 2.38 (3H, s, CH_3 pyrazol.).

Treatment of **2a,b** (0.01 mol) with an equivalent amount of MeONa in 10 ml MeOH at 60°C for 1 hour afforded the expected methoxy-derivatives **3a,b** (recrystallized from benzene).

3a : M.p. 112°C, 71%; IR (KBr), 3440, 1670, 1445; ^{1}H-NMR ($CDCl_3$, δ ppm), 9.70 (1H, s, CHO), 7.20 (1H, s, C_5 pyrim.), 5.4-5.6 (OH, broad), 3.85 (3H, s, OCH_3), 2.63 (3H, s, CH_3 pyrim.), 2.38 (3H, s, CH_3 pyrazol.).

3b : M.p. 106°C, 70%; IR (KBr), 3435, 1675, 1435; ^{1}H-NMR ($CDCl_3$, δ ppm), 9.72 (1H, s, CHO), 5.4-5.6 (OH, broad), 3.90 (3H, s, OCH_3), 2.65 (3H, s, CH_3 pyrim.), 2.52 (3H, s, CH_3 pyrim.), 2.35 (3H, s, CH_3 pyrazol.).

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