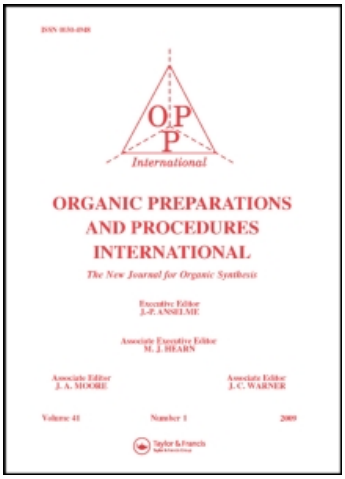

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SYNTHESIS OF SOME 2-PYRAZOLIN-5-ONE DERIVATIVES STRUCTURALLY RELATED TO CERTAIN ANALGESIS AND ANTIPYRETIC DRUGS

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SYNTHESIS OF SOME 2-PYRAZOLIN-5-ONE DERIVATIVES STRUCTURALLY RELATED TO CERTAIN ANALGESIS AND ANTIPYRETIC DRUGS

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(05/01/84)

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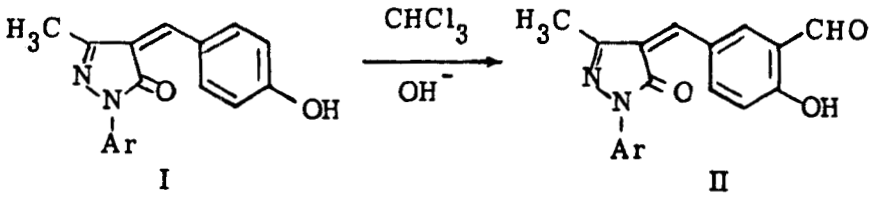
The present manuscript describes the synthesis of some 2-pyrazolin-5-one derivatives structurally related to certain analgesic and antipyretic drugs.[1,2] The Riemer-Tiemann reaction of 4-(p-hydroxybenzylidene)-3-

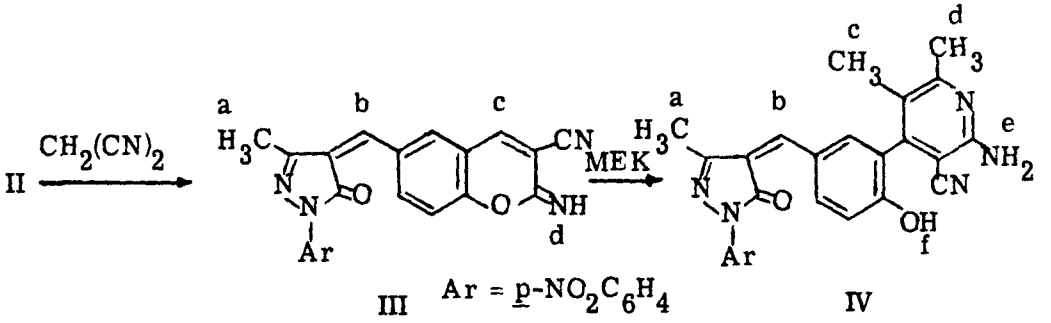


I II

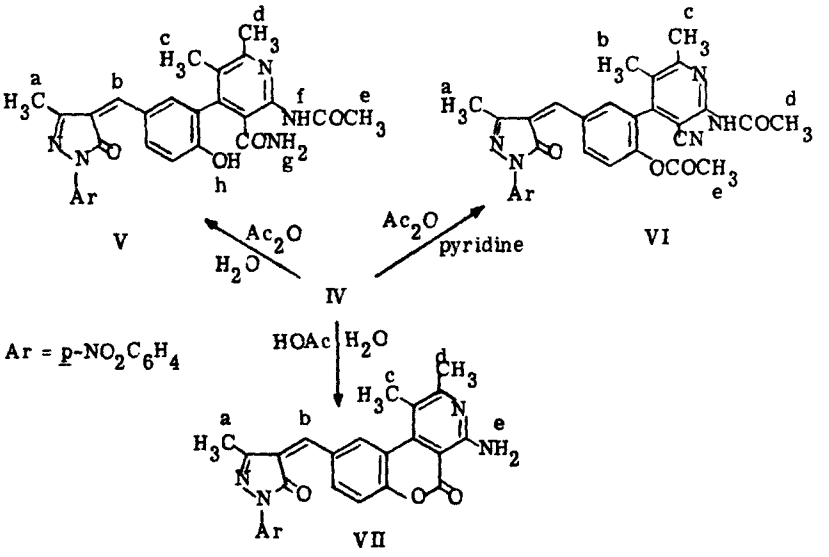
Ar = p-$NO_2C_6H_4$

methyl-1-(p-nitrophenyl)-2-pyrazolin-5-one (I) resulted in the formation of α-[3-methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidine]-2,5-cresotaldehyde in good yield.

The condensation of II with malononitrile (molar ratio 1:1) in the presence of ammonium acetate (2 equiv.) gave 2-imino-6-[[3-methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidene]methyl]-2H-1-benzopyran-3-carbonitrile (III). Compound IV which was obtained by the condensation of III with methyl ethyl ketone, could also be prepared directly by the condensation II with malononitrile and methyl ethyl ketone (molar ratio of 1:1:1) in the presence of ammonium acetate (1 mole or a slight excess).



Treatment of IV with acetic anhydride in water gave 2-acetamido-5-methyl-4-[6-hydroxy-α-[3-methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidene]-m-tolyl]-6-methylnicotinamide (V) while the same reaction carried out in



pyridine led to VI. On the other hand, when heated with acetic acid containing a few drops of water in the presence of ammonium acetate, IV underwent cyclization to 4-amino-1-methyl-1,10b-dihydro-2-methyl-9-[[3-methyl-1-(p-nitrophenyl)]-5-oxo-3-pyrazolin-4-ylidene]methyl]-5H-[1]-benzopyrano[3,4-c]-pyridin-5-one (VII). Its NMR spectrum showed signals at δ 1.8 (s, 6H, protons a and d), 1.7 (s, 3H, proton c) and 5.5 (s, 2H, proton d); and no signal for the methyl singlet observed in VI (proton e), its IR spectrum showed no absorption attributable to a C≡N group.

EXPERIMENTAL SECTION

All the melting points are uncorrected. The IR spectra were determined as KBr pellets on a Pye Unicom SP 2000 spectrophotometer. The NMR spectra were determined in DMSO-d_6 at 60 MHz, using TMS as the internal standard on a Varian 360 EM.

α-[3-Methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidene]-2,5-cresotaldehyde (II).- A solution of sodium hydroxide (40 g in 80 ml of water) was added to a solution of I (0.14 mole) in 60 ml of 95% ethanol with stirring. Then chloroform (0.2 mole) was added dropwise to the reaction mixture at 70-80° and stirring was continued for 1 hr after all the chloroform had been added. The water and ethanol were removed under reduced pressure. The oily residue was acidified with 0.1 N hydrochloric acid and the solid product was crystallized from ethanol to give 0.8 g (90%) as brown-red crystals, mp. 207°.

Anal. Calcd for $C_{18}H_{13}N_3O_5$: C, 61.53; H, 3.72; N, 11.96

Found: C, 61.71; H, 4.00; N, 12.22

IR: 3500-3360 cm^{-1} (H-bonded OH); 2720 and 2820 cm^{-1} (CHO); 1710 cm^{-1} (C=O aldehyde); 1600, 1670, 1635 cm^{-1} (C=C, C=N, C=O). nmr: δ 1.7 (s, 3H, CH_3), 6.5 (s, 1H, =CH-), 8.5 (s, 1H, CHO), 10.2 (s, 1H, OH), 6.55-8.20 (m, 7H, ArH).

2-Imino-6-[[-3-methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidene]-meth-

yl]-2H-1-benzopyran-3-carbonitrile (III).- A mixture of malononitrile (0.06 mole), compound II (0.06 mole) and ammonium acetate (0.06-0.07 mole) in ethanol (30 ml) was refluxed for 1 hr. The brown solid product obtained on dilution with water, was recrystallized from ethanol to yield 0.7 g (60%) of pale brown powder of III, mp. > 360°.

Anal. Calcd for $C_{21}H_{13}N_5O_4$: C, 63.15; H, 3.28; N, 17.53

Found: C, 62.93; H, 3.55; N, 17.81

IR: 1640 cm^{-1} (C=NH), 2210 cm^{-1} (CN). nmr: δ 1.8 (s, 3H, protons a), 6.4 (s, 1H, proton b), 6.7 (s, 1H, proton c), 5.5 (s, 1H, proton d), 6.9-8 (m, 7H, ArH).

2-Amino-5-methyl-4-[6-hydroxy-α-[3-methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidene]-m-tolyl]-6-methylnicotinonitrile (IV).- A mixture of malononitrile (0.07 mole), methyl ethyl ketone (0.06 mole), and ammonium acetate (0.06-0.07 mole) in ethanol (30 ml) was refluxed for 3 hrs. The crystals which precipitated during the reaction were collected and recrystallized from dimethylformamide to yield 0.6 g (60%) of brown crystals of IV, mp. > 360°.

Anal. Calcd for $C_{25}H_{20}N_6O_4$: C, 64.08; H, 4.30; N, 17.93

Found: C, 63.61; H, 4.70; N, 17.95

IR: 3450 and 3350 cm^{-1} (NH_2), 3600 cm^{-1} (free OH). nmr: δ 1.8 (s, 3H, protons a), 6.4 (s, 1H, proton b), 1.4 (s, 3H, proton c), 1.2 (s, 3H, protons d), 2.6 (s, 1H, proton e), 8.7 (s, 1H, proton f), 6-8 (m, 7H, ArH).

2-Acetamido-5-methyl-4-[6-hydroxy-α-[3-methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidene]-m-tolyl]-6-methylnicotinamide (V).- Acetic anhydride (5-8 ml) was added to IV (4 mmole), and the mixture was heated for a few minutes. After cooling, a few drops of water were added to the reaction mixture; a crystalline precipitate was thus formed. Recrystallization from a mixture of acetone-ethanol afforded 0.6 g (50%) of brown crystals of V,

mp. > 360°.

Anal. Calcd for $C_{27}H_{24}N_6O_6$: C, 61.35; H, 4.57; N, 15.90

Found: C, 61.34; H, 4.81; N, 16.11

IR: broad at 3400-3500 cm^{-1} (NH), 3600 cm^{-1} (free OH) and broad at 1650-1700 cm^{-1} ($NHCOCH_3$). nmr: δ 1.5 (s, 3H, protons a), 6.3 (s, 1H, proton b), 1.2 (s, 3H, protons c), 2.8 (s, 3H, protons d), 2.1 (s, 3H, protons e), 9.6-9.9 (broad, 1H, proton f), 6.8 (broad, 2H, protons g), 8.2 (s, 1H, protons h), 7-8 (m, 7H, ArH).

Reaction of IV with Ac_2O-Pyridine.- Formation of VI.- To a solution of IV (0.8 g) dissolved in pyridine, acetic anhydride (20 ml) was added. The mixture was heated for 5 hrs. After the mixture had been allowed to stand at room temperature, the resulting precipitate was recrystallized from ethanol to yield 0.4 g (45%) of brown crystals of VI, mp. > 360°.

Anal. Calcd for $C_{29}H_{24}N_6O_6$: C, 63.03; H, 4.37; N, 15.20

Found: C, 62.56; H, 4.61; N, 15.11

IR: broad at 3400-3500 cm^{-1} (NH), 2220 cm^{-1} (CN), broad at 1650-1700 cm^{-1} ($O-COCH_3$, $NHCOCH_3$). nmr: δ 1.8 (s, 3H, protons a), 0.9 (s, 1H, proton b), 0.8 (s, 3H, protons c), 1.9 (s, 3H, protons d), 2.28 (s, 3H, protons e), 6.5-8 (m, 7H, ArH).

4-Amino-1-methyl-1,10b-dihydro-2-methyl-9-[[-3-methyl-1-(p-nitrophenyl)-5-oxo-2-pyrazolin-4-ylidene]methyl]-5H-[1]-benzopyrano[3,4-c]pyridin-5-one (VII). A mixture of IV (0.4 g), acetic acid (5 ml), water (1 ml), and ammonium acetate (1 g) was refluxed for 1 hr. The crystals which were thus precipitated were collected and recrystallized from dimethylformamide to yield 0.5 g (50%) of brown crystals of VII, mp. > 360°.

Anal. Calcd for $C_{25}H_{21}N_5O_5$: C, 63.96; H, 4.07; N, 14.91

Found: C, 63.93; H, 4.35; N, 15.11

IR: 3445-3330 cm^{-1} (NH_2), 1725 (CO, α-pyrone), nmr: δ 1.8 (s, 3H, pro-

tons a), 6.4 (s, 1H, proton b), 1.7 (s, 1H, proton c), 1.8 (s, 3H, protons d), 5.5 (s, 2H, protons d), 6.9-8 (m, 7H, ArH).

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OXIDATION OF FURFURALDEHYDES WITH SODIUM CHLORITE

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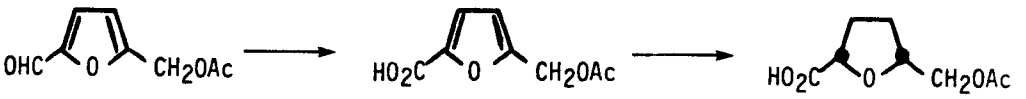
In connection with another project,[1] we required an effective route to 5-acetoxymethyl-cis-2-tetrahydrofuroic acid (3). This material should be readily prepared by the hydrogenation of 5-acetoxymethyl-2-furoic acid (2), which in turn could be obtained by the oxidation of 5-acetoxymethyl-2-furfuraldehyde (1). However, oxidation of aldehyde 1, readily prepared in



1 2 3

a 90% yield from 5-hydroxymethyl-2-furfuraldehyde by the method of Karashima,[2] with oxidizing agents such as potassium permanganate did not give the desired carboxylic acid 2 but rather furan 2,5-dicarboxylic acid. Milder oxidizing agents such as aqueous alkaline silver oxide[3] resulted in oxidation of the aldehyde, accompanied by hydrolysis of the acetoxy group