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The Synthesis of 1-Phenyl-3-methyl-4-acyl-pyrazolones-5

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A new synthesis of 4-acyl-1-phenyl-3-methyl-pyrazolones-5 is presented. Condensations of acid chlorides or anhydrides with 1-phenyl-3-methyl-pyrazolone-5 in dioxane, catalyzed by suspended calcium hydroxide, have been found to produce the 4-acylated derivatives directly and in good yields.

The following new compounds have been prepared: 4-propionyl-, 4-butyryl-, 4-trifluoroacetyl-, 4-chloroacetyl,- 4-ethoxycarbonyl-, 4-*p*-bromobenzoyl-, 4-*p*-nitrobenzoyl-1-phenyl-3- methyl-pyrazolone-5 and 4-benzoyl-1-*p*-nitrophenyl-3-methyl-pyrazolone-5.

The compounds thus prepared are promising chelating agents for the extraction of metal ions.

During a search for new chelating agents for the extraction of metal ions it was found [1] that 1-phenyl-3-methyl-4-acetyl-pyrazolone-5 possessed valuable properties as such. Hence the syntheses of other 4-acyl substituted pyrazolones were planned for an investigation of their properties.

Previously the 4-acetyl-, 4-benzoyl- and 4-oxalyl-1-phenyl-3-methyl-pyrazolones [2–4] have been synthetisized by conventional Claisen condensations of esters with the pyrazolone, the reaction being catalysed by the sodium salt of the acid or sodium ethoxide. The yield was not reported for the acetyl derivative, it was low for the benzoyl derivative and was exellent for the oxalyl derivative.

A new method of synthesis of these compounds has been evaluated. Recognizing the phenolic character of the rather acid 1-phenyl-3-methyl-pyrazolone-5 a Fries rearrangement of the 5—O acylated derivative to the 4—C acylated derivative by anhydrous zink chloride was tried. The 5—O acylated pyrazolones were easily prepared by a Schotten-Baumann acylation reaction. In fact the expected product was obtained by the reaction, however, accompanied by large amounts of coloured by-products. Further experiments showed that a suspension of calcium hydroxide in dioxane, with a small amount of water added, served equally well or better as a catalyst for the acyl migration from position 5 to position 4. Finally it was found that a direct one step synthesis was effected by treating a solution of 1-phenyl-3-methyl-pyrazolone-5 in dioxane containing suspended calcium hydroxide as a catalyst

with an acid chloride or anhydride. A rapid reaction led directly to the calcium complex of the 4-acylpyrazolone which is stable under the alkaline conditions, and which is expected to protect the wanted derivative from further reactions.

This method was successfully used to prepare the acetyl-, propionyl-, butyryl-, valeryl-, chloroacetyl-, benzoyl-, *p*-bromobenzoyl-, *p*-nitrobenzoyl- and ethoxycarbonyl derivatives of 1-phenyl-3-methyl-pyrazolone-5 and to prepare the benzoyl derivative of 1-*p*-nitrophenyl-3-methyl-pyrazolone-5. It failed to give a product capable of metal extraction with pivalyl chloride. An oily product was isolated which was not further characterized.

When an attempt was made to prepare the 5-trifluoroacetate of the pyrazolone by reacting trifluoroacetic anhydride with the pyrazolone in dry pyridine, a vigorous reaction led directly to the 4-trifluoroacetyl-pyrazolone. It was not tried to prepare this compound by the present method.

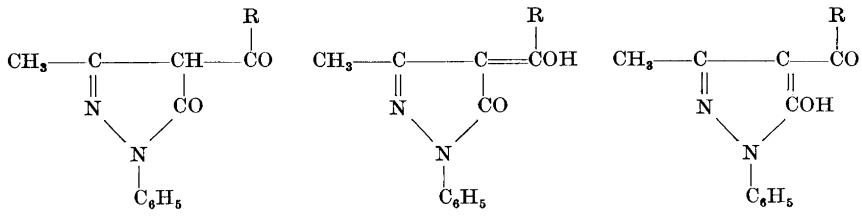

Fig. 1.

The 4-acyl-pyrazolones are good crystallizing compounds often obtainable both in the keto form (Fig. 1 a) by recrystallization from polar solvents as alcohol-water or dioxane-water mixtures, and in the enol form (Fig. 1 b, c) by recrystallization from nonpolar solvents as ligroin, chloroform *etc.* The enol forms are yellowish coloured solids, whereas the keto forms are colourless. Michaelis and Engelhardt also reported the isolation of both the keto and enol forms of 1-phenyl-3-methyl-4-benzoyl-pyrazolone-5.

The Schotten-Baumann 5—O acylation was found to be endothermic indicating a large heat absorption in the enolization of the 5-keto group. This indicates that in the unsubstituted pyrazolone, the keto form is much more stable than the enol form and that the resonance energy of the pyrazole nucleus is small. The enolization of the 4-acylated pyrazolones is believed to occur in the side chain. In this way energy is gained due to the extended conjugation which arises (Fig. 1 b). If the 5-keto group enolizes, the gain in energy will be smaller as the system becomes cross-conjugated (Fig. 1 c). This is because the pyrazole nucleus as indicated above is best represented as a cyclic unsaturated hydrazone.

The acid strength of the 4-acyl-pyrazolones is of the same magnitude as that of carboxylic acids, *i.e.* their pK values vary from 3—5. Their molecular-weights were obtained by titration in water-alcohol mixtures with phenolphtalein as indicator [5].

EXPERIMENTAL

The procedure for the preparation of the different compounds is the same. One typical synthesis is described in detail. For the other compounds prepared, only the solvent for recrystallization is noted together with the constants of the compounds.

1-Phenyl-3-methyl-4-benzoyl-pyrazolone-5. 15 g of 1-phenyl-3-methyl-pyrazolone were placed in a flask equipped with a stirrer, separatory funnel and a reflux condenser and dissolved in 60–80 ml dioxane (Merck reagent grade) by application of heat. Twelve g of calcium hydroxide were added, and 9.9 ml of benzoylchloride were added dropwise within 1 min. The reaction mixture became a thick paste and the temperature increased during the first few minutes. The mixture was heated to reflux for 30 min. The calcium complex in the flask was decomposed by pouring the mixture into dilute hydrochloric acid (200 ml, 2 N) which caused cream coloured crystals to separate. The crystals were collected on a Büchner funnel. They were recrystallized from methanol-water slightly acidified to destroy any undecomposed calcium-complex. Yield of pure product 70 %. m. p. keto 122°C, enol 92°C. Literature [3] m. p. 120°C.

1-Phenyl-3-methyl-4-acetyl-pyrazolone-5. Recryst. MeOH–H_2O. Yield 56 %, m. p. keto 58°C, Lit. 58°C. $C_{12}H_{12}N_2O_2$ (216.2), found 218.

1-Phenyl-3-methyl-4-propionyl-pyrazolone-5. Recryst. MeOH–H_2O. Yield 50 %, m. p. keto 62°C. $C_{13}H_{14}N_2O_2$ (230.3), found 236. (Found: C 67.80; H 6.14. Calc.: C 67.7; H 6.14.)

1-Phenyl-3-methyl-4-butyryl-pyrazolone-5. Recryst. MeOH–H_2O. Yield 57 %, m. p. keto 80°C. (Found: C 68.75; H 6.58. Calc.: C 68.8; H 6.60.) $C_{14}H_{16}N_2O_2$ (244.3), found 245.

1-Phenyl-3-methyl-4-chloroacetyl-pyrazolone-5. Recryst. MeOH–H_2O. Yield 73 %, m. p. keto 88°C, enol 140°C. $C_{12}H_{11}N_2O_2Cl$, H_2O (268.7), found 267. (Found: C 53.75; H 5.01. Calc.: C 53.8; H 4.87.)

1-Phenyl-3-methyl-4-ethoxycarbonyl-pyrazolone-5. Recryst. MeOH–H_2O. Yield 46 %, m. p. keto 122°C, enol 72°C. $C_{13}H_{14}N_2O_3$, H_2O (245.3), found 248. (Found: C 63.08; H 5.92. Calc.: C 62.9; H 6.48.)

1-Phenyl-3-methyl-4-p-bromobenzoyl-pyrazolone-5. Recryst. Dioxane-water. Yield 82 %, m. p. keto 167 C, enol 122°C. $C_{17}H_{13}N_2O_2Br$ (357.3), found 357. (Found: C 57.03; H 3.57. Calc.: C 57.1; H 3.67.)

1-Phenyl-3-methyl-4-p-nitrobenzoyl-pyrazolone-5. Recryst. Dioxane-water. Yield 79 %, m. p. keto 200°C, enol 192°C. $C_{17}H_{13}N_3O_4$ (323.3), found 324. (Found: C 63.37; H 4.49. Calc.: C 63.1; H 4.05.)

1-p-Nitrophenyl-3-methyl-4-benzoyl-pyrazolone-5. Recryst. Dioxane-water. Yield 50 %, m. p. keto 174°C, enol 224°C. $C_{17}H_{13}N_3O_4$ (323.3), found 323. (Found: C 63.17; H 4.13. Calc.: C 63.1; H 4.05.)

1-Phenyl-3-methyl-4-trifluoroacetyl-pyrazolone-5. To a solution of 8.5 g 1-phenyl-3-methyl-pyrazolone in 50 ml anhydrous pyridine 10 g trifluoroacetic anhydride were added dropwise. Heat was evolved and the flask was cooled under tap water. The reaction mixture became red brown. After one hour at room temperature the contents of the flask were poured into 200 ml of water whereby no precipitate was formed. After acidification the compound crystallized. Recrystallization from ethanol-water mixture gave 78 % yield of pure product, m. p. keto 144°C, enol 132°C. $C_{12}H_9N_2O_2F_3$ (273.3), found 273. (Found: C 53.27; H 3.47. Calc.: C 53.3; H 3.36.)

All melting points were measured on a Kofler hot bench. Microanalyses have been performed by Mr. P. Hansen at the Chemical Laboratory of the University of Copenhagen, and the syntheses by Mr. O. Jørgensen at the Chemical Laboratory of the Danish Atomic Energy Research Establishment, Risø.

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