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A Study of the Structures of Intermediates in the Reaction of 1,3-Diketones and Hydrazines

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Intermediates formed in the reactions of nicotinoylhydrazine and benzoylhydrazine with acetylacetone have been isolated and their structures determined by IR and NMR spectroscopy. These intermediates are cyclic monohydrazones, *i.e.* 1-acyl-5-hydroxy-2-pyrazolines, which are easily dehydrated to give the corresponding pyrazoles. In contrast the intermediate isolated from the reaction of acetylacetone and hydrazine was shown to have an open structure.

In the synthesis of pyrazoles from 1,3-diketones and hydrazines, monohydrazones have occasionally been isolated as intermediates.[1] They are easily converted to the corresponding stable pyrazoles. These intermediates seem to be most stable and thus most easily isolated when they are substituted with aryl groups.[1] However, a monohydrazone has been isolated under very mild conditions in the reaction between acetylacetone and unsubstituted hydrazine.[2] In these cases it had not been established whether the isolated monohydrazones have an open or cyclic structure. Recently intermediates in the cyclization of benzoylacetone semicarbazones and in the reaction of benzoylacetone with phenylhydrazine were characterized and shown to have a 5-hydroxy-2-pyrazoline structure.[3]

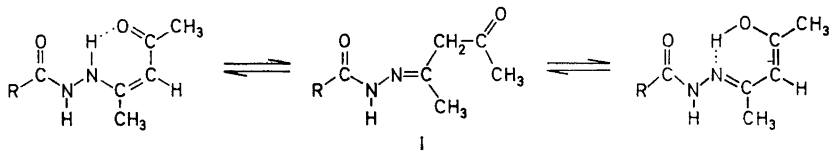
In connection with an investigation of antilipolytic compounds related to nicotinic acid,[4] it was necessary to prepare 1-nicotinoyl-3,5-dimethylpyrazole. During this preparation an intermediate was isolated and it seemed interesting to investigate the structure of this and analogous intermediates in some detail.

INTERMEDIATES IN THE REACTION OF NICOTINOYLHYDRAZINE AND BENZOYLHYDRAZINE WITH ACETYLACETONE

The intermediate in the reaction of nicotinoylhydrazine with acetylacetone was first isolated after a short (3 min) reaction time in a mixture of 2 M aqueous hydrochloric acid and 2-propanol (1:125) at 80°C. It was later prepared in a higher yield by reaction in aqueous solution at room temperature. The inter-

mediate in the reaction of benzoylhydrazine and acetylacetone was prepared in the same way. The elemental analyses showed that the isolated compounds were monohydrazones. These are easily dehydrated by refluxing in 2-propanol, the reaction being catalysed by acids, to form the corresponding stable pyrazoles.

The possible open and cyclic structures of the isolated monohydrazones together with the corresponding pyrazoles are given below. R stands for a phenyl or a 3-pyridyl group.



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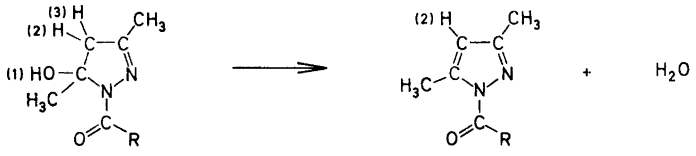

II III

It will be shown in the following that the isolated intermediates correspond to the cyclic structure II.

The IR data of the intermediates given in Table 1 show the presence of a hydroxyl group with no strong intramolecular hydrogen bond. The low frequency of the carbonyl group indicates that its π-electrons are interacting with the lone electron pair of the neighbouring nitrogen atom. This leads to a geometry of II, which apparently prevents the formation of an intramolecular hydrogen bond between the carbonyl group and the nearby hydroxyl group. In the corresponding pyrazole (III) this interaction is weaker, because the lone electron pair on the adjacent nitrogen atom now is also involved in the π-electron system of the aromatic pyrazole nucleus, and thus a lower carbonyl frequency is observed. In order to substantiate this qualitative explanation of the difference in the carbonyl frequencies of structures II and III, a HMO calculation on the π-electron systems of II and III (R = phenyl) was performed. Good correlations between carbonyl frequencies and carbonyl bond orders from HMO calculations have been found.[5] Using the heteroatom parameters given by Pullman and Pullman,[6] the carbonyl bond order of structure II is 0.832 and that of structure III 0.857. The ratio of these bond orders is in fair agreement with the corresponding ratio of the measured IR frequencies.

Table 1. IR data of intermediates (II) and pyrazole products (III).

Reaction	Sample	II		III	
		Band cm^{-1}	Assignment	Band cm^{-1}	Assignment
Nicotinoyl-hydrazine	KBr pellet	3200 1630	OH C=O	— 1690	no OH or NH C=O
+acetyl-acetone	Dilute solution in CCl_4	3550 1630	OH C=O	— 1690	no OH or NH C=O
Benzoyl-hydrazine	KBr pellet	3400 1610	OH C=O	— [a] 1680	no OH or NH C=O
+acetyl-acetone	Dilute solution in CCl_4	3500 1620	OH C=O	— 1690	no OH or NH C=O

[a] Liquid film on KBr plate.

The pertinent NMR data are given in Table 2. The AB quartet in the spectra of the intermediates establish the two non-equivalent protons (2) and (3) in structure II. Furthermore the broad peak in the same spectra, which disappears upon treatment with D_2O, can be assigned to the hydroxyl proton of structure II. The peak in the spectra of the pyrazoles (III) corresponding to the proton of the pyrazole nucleus is easily assigned and different from any peak in the spectra of the intermediates. This peak is a singlet only slightly broadened due to long range coupling with the methyl groups.

The open structures I apparently do not fit the spectroscopic data given in Tables 1 and 2.

Table 2. NMR data of intermediates (II) and pyrazole products (III).

Reaction	Shift δ ppm		
	II		III
	H(1)	H(2) and H(3)	H(2)
Nicotinoylhydrazine +acetylacetone	5.27 broad, disappears upon treatment with D_2O	2.73 and 3.14 AB quartet $J_{AB}=19\pm1$ cps	6.10
Benzoylhydrazine +acetylacetone	5.18 broad, disappears upon treatment with D_2O	2.73 and 3.14 AB quartet $J_{AB}=21\pm1$ cps	6.07

THE STRUCTURE OF THE INTERMEDIATE ISOLATED IN THE REACTION OF HYDRAZINE WITH ACETYLACETONE

The IR spectrum of this intermediate does not change upon changing the sample from a KBr pellet to a dilute solution in carbon tetrachloride. The spectrum contains a broad band around 3250 cm^{-1} and a very broad, weak band in the region 1560 – 1700 cm^{-1}. This spectrum is very different from that of 3,5-dimethylpyrazole, the stable product, which is easily formed from the unstable intermediate. These IR data indicate the presence of a strong intramolecular hydrogen bond and the intermediate should therefore correspond to one or a mixture of both of the hydrogen bonded tautomers of the open monohydrazone (I) in the previous figure.

EXPERIMENTAL

Spectroscopy. The IR spectra were recorded on a Unicam SP 200 instrument using samples in either potassium bromide pellets (KBr in Table 1) or dilute solutions in carbon tetrachloride (CCl_4 in Table 1). The NMR spectral data were obtained with a Varian A60A instrument using 20 % solutions of the samples in deuteriochloroform. Tetramethylsilane (TMS) was used as an internal reference.

Isolation of the intermediate 1-nicotinoyl-3,5-dimethyl-5-hydroxy-2-pyrazoline. A mixture of nicotinoylhydrazine (3.4 g, 25 mmole), acetylacetone (2.5 g, 28 mmole) and 2 M hydrochloric acid (0.20 ml) was shaken with 25 ml of 2-propanol for 3 min at 80°C. A light yellow homogeneous solution was obtained. The residue, after evaporation of the solvent at 60°C bath temperature, was treated with 25 ml of water. The mixture was neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted five times with 20 ml ether. The ether solution was washed twice with 10 ml of sodium hydrogen carbonate solution and twice with 10 ml of a saturated aqueous solution of sodium sulphate and dried over anhydrous sodium sulphate. Evaporation of the solvent gave 1.0 g partly crystalline product. Recrystallization from hexane gave 0.45 g colourless crystals, m.p. 115–118°C.* (Found: C 60.2; H 6.32; N 19.1; O 14.5. Calc. for $C_{11}H_{13}N_3O_2$: C 60.3; H 5.96; N 19.2; O 14.6). The spectroscopic data are given in Tables 1 and 2.

It was later found that the 2-pyrazoline could be obtained in a much better yield by the following procedure: Acetylacetone (0.50 g, 5.6 mmole) was added to a mixture of nicotinoylhydrazine (0.68 g, 5.0 mmole) in 5 ml of water. The yellow solution was allowed to stand at room temperature for 2 h and was then kept in the refrigerator overnight. Colourless crystals weighing 0.65 g (60 %) separated from the solution, m.p. 115–118°C, identical (IR and NMR) with the material described above.

Preparation of 1-nicotinoyl-3,5-dimethylpyrazole. A mixture of nicotinoylhydrazine (3.43 g, 25.0 mmole), acetylacetone (2.50 g, 28.0 mmole) and 2 M hydrochloric acid (0.19 ml) was refluxed with 25 ml of 2-propanol for 1 h and the homogeneous solution obtained was allowed to stand at room temperature overnight. Evaporation of the solvent at reduced pressure gave 4.9 g yellow oil. This product was treated with 25 ml of water and the colourless solid filtered off and dried. Yield 4.2 g (84 %), m.p. 43.0–44.0°C. Recrystallization from petroleum ether gave 3.4 g colourless crystals, m.p. 43.5–44.5°C (Found: C 65.0; H 5.58; N 21.4; O 8.34. Calc. for $C_{11}H_{11}N_3O$: C 65.7; H 5.51; N 20.9; O 7.95. Equiv. wt. (titration as base): Found: 201. Calc. 201). The spectroscopic data are given in Tables 1 and 2. The structure of this compound has recently been published.[7] The procedure employed here has been used previously [8] to prepare 1-isonicotinoyl-3,5-dimethylpyrazole.

Transformation of 1-nicotinoyl-3,5-dimethyl-5-hydroxy-2-pyrazoline to 1-nicotinoyl-3,5-dimethylpyrazole. A mixture of the 2-pyrazoline (0.55 g, 2.5 mmole) and 2 M hydrochloric acid (0.02 ml) was refluxed with 2.5 ml of 2-propanol for 1 h and the reaction mixture

* All melting points given are uncorrected and measured with a Leitz Heiztisch microscope.

worked up as described in the preceding preparation. Yield 0.40 g, m.p. 43.0–44.0°C. NMR and IR data showed that the product is 1-nicotinoyl-3,5-dimethylpyrazole.

Thin layer chromatography of the reaction solution. A reaction mixture, warmed for 3 min at 80°C as in the isolation experiment described above, was chromatographed on precoated sheets (Eastman) with silica layers using 1-propanol as eluent. Authentic samples of the reactants nicotinoylhydrazine and acetylacetone, the isolated intermediate, and the product 1-nicotinoyl-3,5-dimethylpyrazole were used as references. The reaction solution gave three spots on the chromatogram, the position of which corresponded to the positions of the spots for nicotinoylhydrazine, the intermediate, and 1-nicotinoyl-3,5-dimethylpyrazole, the spot corresponding to the intermediate being the largest one. No spot corresponding to acetylacetone could be detected (UV light on sheets prepared with fluorescent indicator or treatment with iodine vapour) on the chromatogram of the reaction solution or the authentic sample. The intermediate kept at room temperature in a mixture of 2 M hydrochloric acid (0.2 ml) and 2-propanol (2.5 ml) was slowly converted to the product according to chromatograms taken at different intervals of time.

Isolation of the intermediate 1-benzoyl-3,5-dimethyl-5-hydroxy-2-pyrazoline. Acetylacetone (3.0 g, 33 mmole) was added to a solution of benzoylhydrazine (4.1 g, 30 mmole) in a mixture of 90 ml of water and 5 ml of ethanol at room temperature. The reaction mixture was kept for a few hours at room temperature, overnight in the refrigerator and was then extracted four times with ether. The extract was dried over sodium sulphate and the ether evaporated to give 4.5 g yellow oil. Trituration with petroleum ether gave a colourless crystalline product. Yield 3.2 g (47 %), m.p. 78.5–81.5°C. (Found: C 66.1; H 6.45; N 13.3; O 14.5. Calc. for $C_{12}H_{14}N_2O_2$: C 66.0; H 6.46; N 12.8; O 14.7). The spectroscopic data are given in Tables 1 and 2.

Preparation of 1-benzoyl-3,5-dimethylpyrazole. This substance was prepared from benzoylhydrazine and acetylacetone as described previously.[9] The spectroscopic data are given in Tables 1 and 2.

Transformation of 1-benzoyl-3,5-dimethyl-5-hydroxy-2-pyrazoline to 1-benzoyl-3,5-dimethylpyrazole. The 2-pyrazoline (0.50 g, 2.5 mmole) was refluxed with a mixture of 2 M hydrochloric acid (0.02 ml) and 2-propanol (2.5 ml) for 2 h as described above for the transformation of the other intermediate. The reaction mixture was then filtered, water added and the solution extracted with ether. The extract was dried over sodium sulphate and the solvent evaporated to give 0.25 g yellow oil. NMR and IR data showed that this product is 1-benzoyl-3,5-dimethylpyrazole.

The intermediate in the reaction of hydrazine with acetylacetone was prepared as described previously.[2]

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