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SYNTHESIS OF PYRIDAZINONE DERIVATIVES

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The reaction of methyl esters of 3-methyl-2-oxo- and 2-oxo-3-phenyl-3-pentenoic acids with hydrazine hydrate and phenylhydrazine was used to synthesize new pyridazinone derivatives. These products are formed through intermediate hydrazides with subsequent cyclization. 4-Hydroxy-3-oxotetrahydropyridazines are mainly formed using equimolar amounts of the starting reagents, while the corresponding hydrazones of 3,4-dioxohexahydropyridazines are formed in the case of a two-fold excess of hydrazine hydrate or phenylhydrazine. Evidence was obtained indicating the existence of a keto–enol tautomerism for 4-hydroxy-3-oxopyridazines.

Keywords: hydrazine, methyl esters of 3-methyl-2-oxo- and 2-oxo-3-phenyl-3-pentenoic acids, pyridazinone, phenylhydrazine, keto–enol tautomerism.

Pyridazinones hold considerable interest relative to the preparation of organic intermediates and physiologically active compounds [1-4]. Some of the reported methods for the synthesis of these compounds involve the condensation of 3-aroylpropionic or β-acetylacrylic acids with alkyl- and arylhydrazines [5, 6]. Various pyridazine derivatives can also be obtained by the reaction of aryldiazonium salts with the ethyl ester of methylenemalonic acid [1].

3-Pyrrolinone derivatives are obtained in good yield from methyl esters of 3-methyl-2-oxo- (**1a**) and 2-oxo-3-phenyl-3-pentenoic acids (**1b**) and primary amines [7]. This finding suggested that pyridazinone derivatives could be obtained by replacing primary amines with hydrazine or hydrazine derivatives.

In the present work, we studied the reaction of keto esters **1a**,**b** with hydrazine hydrate (**2a**) and phenylhydrazine (**2b**). Pathways I, II, and III are theoretically possible for this reaction.

Pathways I and II feature initial hydrazinolysis of the ester group in **1** followed by cyclization to give a six-membered (pathway I) or five-membered heterocycle (pathway II). Competing pathway III entails initial addition of hydrazine **2** at the unsaturated bond in ester **1** with subsequent cyclization. We have found that **1** and **2** react according to pathway I. In the case of equimolar amounts of these reagents, keto enols, namely, substituted 4-hydroxy-3-oxotetrahydropyridazines **3a-d** are mainly formed. On the other hand, monohydrazones **4a-d** of the ketonic tautomers of **3a-d** are mainly formed using a two-fold excess of hydrazine **2** (Scheme 1).

We should note that replacing hydrazine hydrate with 64% hydrazine in the synthesis of **4a** hardly affects the product yield, which is 62.7% in the former case and 57.5% in the latter.

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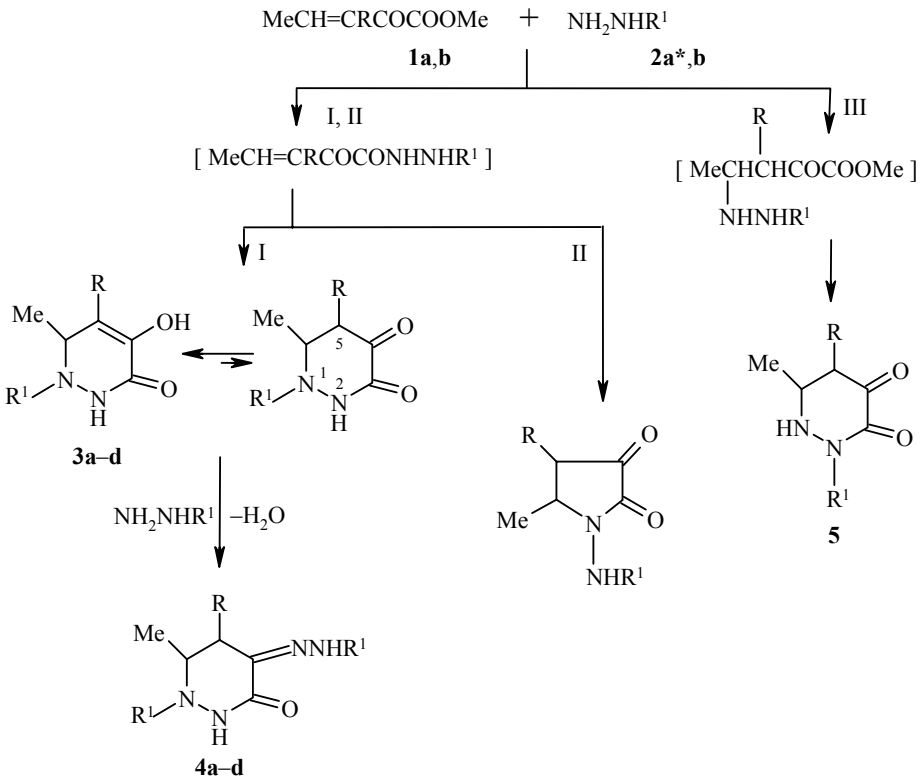
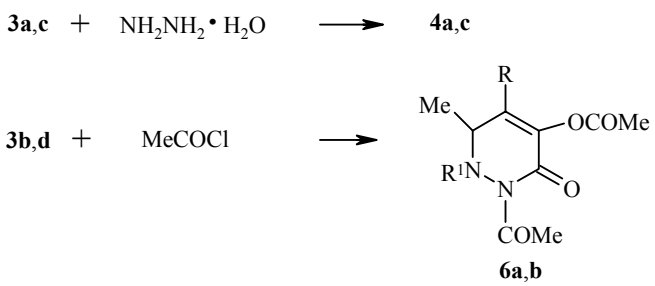
Scheme 1



1 a R = Me, **b** R = Ph; **2 a** R^1 = H (* hydrate), **b** R^1 = Ph;
3, **4 a** R = Me, R^1 = H; **b** R = Me, R^1 = Ph; **c** R = Ph, R^1 = H; **d** R = R^1 = Ph

The composition and structure of the products were supported by elemental analysis (Table 1) and IR and NMR spectroscopy (Table 2). Thus, the IR spectra of **3** and **4** have a band for the amide carbonyl group at 1665-1668 cm^{-1} characteristic for six-membered cyclic amides. The lack of coupling between the NH and CH protons in the ^1H NMR spectrum of **3d** is evidence for the structure given. When these groups are adjacent as in structure **5** (obtained through pathway III), the usual values of the coupling constant J = 5-6 Hz.

The spectral and experimental results indicate that products **3** and **4** are mainly formed in the enol form. In a detailed study of the keto–enol equilibrium of these compounds, we carried out the reaction of **3a**,**c** with hydrazine hydrate to give the corresponding hydrazones **4a**,**c** and the reaction of **3b**,**d** with acetyl chloride to give acetyl derivatives **6a**,**b** (Tables 1 and 2).



6 a R = Me, R^1 = Ph; **b** R = R^1 = Ph

TABLE 1. Characteristics of Products

Compound	Empirical formula	Found, % / Calculated, %			$[M]^+$, *m*/*z*	mp, °C*	Yield, % (method)
		C	H	N			
3a	$C_6H_{10}N_2O_2$	50.80 / 50.70	7.34 / 7.04	20.29 / 19.72	142	134-135	40.3
3b	$C_{12}H_{14}N_2O_2$	66.48 / 66.06	6.87 / 6.42	12.70 / 12.84	218	146-168	57.5
3c	$C_{11}H_{12}N_2O_2$	64.86 / 64.71	6.23 / 5.88	13.66 / 13.73	204	152-154	56.3
3d	$C_{17}H_{16}N_2O_2$	72.20 / 72.86	6.19 / 5.71	9.97 / 10.00	280	205-206	53.5
4a	$C_6H_{12}N_4O$	46.37 / 46.15	7.86 / 7.70	36.09 / 35.90	156		62.7(A), 57.5 (B), 92.8 (C)
4b	$C_{18}H_{20}N_4O$	69.77 / 70.13	6.84 / 6.49	18.64 / 18.18	308	165-166	41.8 (A)
4c	$C_{11}H_{14}N_4O$	61.13 / 60.55	6.92 / 6.42	26.00 / 25.69	218	165-167	92.5 (A), 67 (C)
4d	$C_{17}H_{16}N_2O_2$	72.33 / 72.86	6.05 / 5.71	9.78 / 10.00	280	210-211	68.4 (A)
6a	$C_{16}H_{18}N_2O_4$	63.97 / 63.57	5.67 / 6.00	9.53 / 9.27	302	121-122	85.7
6b	$C_{21}H_{20}N_2O_4$	69.53 / 69.23	6.16 / 5.49	8.02 / 7.69	364	dec.	93.6

* Compound **4a** - bp 133-136°C (5 mm Hg).

TABLE 2. Spectral Data of Products

Compound	IR spectrum, ν, cm^{-1}	^1H spectrum NMR, δ, ppm (*J*, Hz)
1	2	3
3a	1625 (C=C); 1667 (C=O); 3150-3400 (NH, OH)	1.28 (3H, d, *J* = 6.6, 6-CH_3); 1.98 (3H, s, 5-CH_3); 3.97 (1H, q, *J* = 6.6, 6-H); 4.56 (1H, br. s, 1-H); 7.55 (1H, br. s, OH); 9.78 (1H, br. s, 2-H)
3b	690, 760, 1590, 3040 (arom.); 1620 (C=C); 1665 (C=O); 3200-3375 (NH, OH)	1.27 (3H, d, *J* = 6.6, 6-CH_3); 1.96 (3H, s, 5-CH_3); 3.9 (1H, q, *J* = 6.6, 6-H); 6.80-7.20 (5H, m, C_6H_5); 7.85 (1H, s, OH); 9.80 (1H, br. s, 2H)
3c	690, 755, 1595, 3035 (arom.); 1620 (C=C); 1665 (C=O); 3200-3350 (NH, OH)	1.28 (3H, d, *J* = 6.6, 6-CH_3); 3.90 (1H, q, *J* = 6.6, 6-H); 4.60 (1H, br. s, 1-H); 6.90-7.20 (5H, m, C_6H_5); 8.02 (1H, s, OH); 9.80 (1H, br. s, 2-H)
3d*	690, 755, 1590, 3030 (arom.); 1665 (C=O); 3200-3375 (NH, OH)	1.38 (3H, d, *J* = 6.6, 6-CH_3); 4.62 (1H, q, *J* = 6.6, 6-H); 6.68 (2H, d, *J* = 7.8, *o*-H in 1-C_6H_5); 6.71 (1H, m, *J* = 7.2, *p*-H in 1-C_6H_5); 7.21 (1H, *J* = 7.2, *o*-H in 5-C_6H_5); 7.12 (2H, m, *J* = 7.5, *m*-H in 5-C_6H_5); 7.35 (2H, m, J = 7.8, *m*-H in 1-C_6H_5); 7.65 (2H, d, *J* = 7.8, *o*-H in 5-C_6H_5); 8.06 (1H, s, OH); 9.99 (1H, s, NH)
4a	1620 (C=N); 1665 (C=O); 2200-3375 (NH)	0.96-1.28 (6H, m, 5- and 6-CH_3); 3.00-4.10 (2H, m, 5- and 6-H); 4.58 (1H, br. s, 1-H); 7.00 (2H, br. s, NH_2); 9.88 (1H, br. s, 2-H)
4b	690, 755, 1590, 3035 (arom.); 1620 (C=N); 1665 (C=O); 200-3350 (NH)	0.98-1.26 (6H, m, 5- and 6-CH_3); 3.10-4.10 (2H, m, 5- and 6-H); 7.00-7.20 (10H, m, $2C_6H_5$); 8.21 (1H, br. s, NHPh); 9.85 (1H, br. s, 2-H)
4c	690, 750, 1590, 3035 (arom.); 1625 (C=N); 1665 (C=O); 3200-3370 (NH)	1.28 (3H, d, *J* = 6.6, 6-CH_3); 3.90 (1H, m, 6-H); 4.62 (1H, br., 1-H); 5.06 (1H, br., 5-H); 7.00-7.40 (7H, m, NH_2 and C_6H_5); 9.85 (1H, br. s, 2-H)

TABLE 2 (continued)

1	2	3
4d	690, 750, 1595, 3035 (arom.); 1620 (C=N), 1668 (C=O); 3200-3350 (NH)	1.29 (3H, d, *J* = 6.6, 6-CH_3); 3.90 (1H, m, 6-H); 5.08 (1H, d, *J* = 6.0, 5-H); 8.19 (1H, br. s, NHPh); 7.00-7.20 (15H, m, $3C_6H_5$); 9.82 (1H, br. s, 2-H)
6a	690, 1750, 1590, 3035 (arom.);1665 (C=O); 1170, 1240, 1725 (COO); 1680-1685 (C=O)	1.29 (3H, d, *J* = 6.6, 6-CH_3); 1.93; 1.96 and 2.00 (9H, three s, 5-CH_3 and $2CH_3CO$); 3.80 (1H, q, *J* = 6.6, 6-H); 7.20 (5H, m, C_6H_5
6b	690, 1755, 1590, 3030 (arom.); 1625 (C=C); 1170, 1220, 1725 (COO); 1660-1665 (C=O)	1.27 (3H, d, *J* = 6.5, 6-CH_3); 1.98 and 2.10 (6H, two s, CH_3CO); 3.80 (1H, q, *J* = 6.5, 6-H); 7.00-7.20 (10H, m, $2C_6H_5$)

* ^{13}C NMR spectrum, δ, ppm: 17.75 (6-CH_3), 54.25 (6-C), 111.87 (*o*-C in 1-C_6H_5), 118.40 (*p*-C in 1-C_6H_5), 126.21 (*p*-C in 5-C_6H_5), 126.73 (*o*-C in 5-C_6H_5), 127.66 (*m*-C in 5-C_6H_5), 128.24 (*m*-C in 1-C_6H_5), 162.54 (CO), 121.53, 131.89, 142.04, and 147.53 (double signals for nuclei 4-C and 5-C). The signals were assigned using a two-dimensional heteronuclear correlation spectrum and the HMQC method.

The relatively low yield of hydrazone **4c** may be attributed to the presence of a phenyl group at $C_{(5)}$ of the hexahydropyridazinone ring, which favors formation of the enol form giving a more conjugated system and hindering the reaction of this form with hydrazine hydrate. This hypothesis finds support in the results of the reaction of keto esters **1a**,**b** with primary amines, leading to pyrrolinones [7].

Thus, we have developed a convenient one-step synthesis for pyridazinone derivatives, which have not been readily available until now, from keto esters **1a**,**b**.

EXPERIMENTAL

The IR spectra were taken for samples in vaseline oil on a UR-20 spectrometer and the ^{1}H NMR spectra were taken on a Perkin–Elmer R-12B spectrometer at 60 MHz and a Varian Mercury 300 spectrometer at 300 MHz for solutions in 1:3 DMSO-d_6–CCl_4. The ^{13}C NMR spectra were taken on a Varian Mercury spectrometer at 75 MHz with complete suppression of ^{13}C and ^{1}H nuclei in CCl_4 using TMS as the internal standard. The mass spectra were taken on an MKh-1320 mass spectrometer with direct sample inlet into the ionization chamber. The ionization voltage was 70 eV.

The gas-liquid chromatographic analysis of the starting reagents was carried out on an LKhM-80 chromatograph using a 2-m × 3-mm column packed with 10% Apiezon L on Inerton-AW (0.20-0.25 mm). The column temperature was raised from 100 to 220°C at 16°C/min. The helium gas carrier flow rate was 60 ml/min.

1-R^1-5-R-4-Hydroxy-6-methyl-1,6-dihydropyridazin-3(2H)-ones (3a-d). (General Method). A 20% solution of hydrazine hydrate (0.02 mol) in ethanol was added dropwise over 30 min with stirring to a solution of keto ester **1** (0.02 mol) in ethanol (6 ml) maintained at from -12 to -10°C. The reaction mixture was stirred at this temperature for 30 min, then for 2 h 30 min at room temperature, maintained under these conditions for about 16 h, and finally heated at reflux for 2 h. The solvent was removed and the residue (product **3**) was washed with ether and then hexane and finally recrystallized from ethanol.

1-R^1-5-R-4-(R^1-Hydrazino)-6-methyl-1,4,5,6-tetrahydro-3(2H)-ones (4a-d). A. Products **4a-d** were obtained analogously to **3**, using hydrazine hydrate (0.04 mol).

B. Product **4a** was obtained according to Method A using 64% hydrazine (0.04 mol).

C. Products **4a**,**c** were synthesized analogously to **3** using **3a**,**c** instead of keto esters **1a**,**c**.

1-R[1]-5-R-4-Acetoxy-2-acetyl-6-methyl-1,6-dihydropyridazin-3(2H)-ones (6a,b). Acetyl chloride (0.015 mol) was added very slowly dropwise to a solution of **3b** or **3d** (0.006 mol) in pyridine (4 ml) with cooling in an ice bath. A precipitate formed immediately. Cooling was terminated. The reaction mixture was maintained at room temperature for about 16 h and then 2% hydrochloric acid (160 ml) was carefully added with good stirring. The crystalline precipitates of **6a**,**b** were filtered off and recrystallized from ethanol.

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