SYNTHESIS OF SOME 4,5-DIHYDROXYPYRAZOLES

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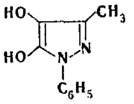
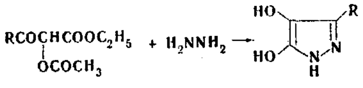
Several 3-alkyl- and 3-phenyl-4,5-dihydroxypyrazoles were obtained by the reaction of α-acetoxyacylacetic esters with hydrazine hydrate and phenylhydrazine.

Dimroth and Schweizer synthesized 1-phenyl-3-methyl-4,5-dihydroxypyrazole (I) by mixing α-acetoxyacetoacetic ester with excess phenylhydrazine and subsequent heating of the reaction mixture [1], but we have been unable to reproduce their experiments. As it turned out, I is readily formed when the reaction is carried out in alcohol in the presence of ammonia.

The reaction of some α-acetoxyacylacetic esters (II) with hydrazine hydrate gives dihydroxypyrazoles III in 35-75% yields.



I



II III

The synthesized 4,5-dihydroxypyrazoles (Table 1) are colorless crystals that gradually become red in air and particularly rapidly in solutions. They reduce silver nitrite in alkaline sulfite solutions. Their molecular absorption is shifted to the long-wave region as compared with the absorption of 5-pyrazolones [2-4]. Moreover, the spectra of 3-alkyl-4,5-dihydroxypyrazoles consist of one absorption band with λ_{max} 258 (log ε 3.8, in alcohol), while those of the corresponding 5-pyrazolones consist of two bands with λ_{max} 220 and 242 nm, which, according to [2], correspond to the absorption of the enol and keto forms, respectively. A shift of the tautomeric equilibrium to favor 4-hydroxy-5-pyrazolones or 5-hydroxy-4-pyrazolones apparently occurs in the case of the dihydroxypyrazoles because of stabilization of the carbonyl group by intramolecular hydrogen bonding. This is also indicated by the presence of a broad band at 2200-3400 cm^{-1} in the IR spectra of the substances. The photo properties of 4,5-dihydroxypyrazoles are discussed in [5,6].

EXPERIMENTAL*

α-Acetoxyacylacetic Acid Ethyl Esters (II). A 0.1-mole sample of lead tetraacetate was added gradually to a solution of 0.1 mole of ethyl acylacetate in 40 ml of glacial acetic acid in such a way that the temperature did not exceed 45° as a result of spontaneous heating. The solution was stirred for 1 h and diluted with 100 ml of water. The product was extracted with ether, and the extract was dried with anhydrous sodium sulfate. The ether was removed by distillation, and the residue was vacuum-distilled (Table 2).

3-Alkyl-4,5-dihydroxypyrazoles (III). A 0.01-mole sample of ethyl α-acetoxyacylacetate and 0.01 mole of 25% hydrazine hydrate solution were mixed, during which warming to 40-50° was observed. The mixture was heated for 5 min on a boiling-water bath, and the resulting precipitate was removed by filtration and washed with alcohol and alcohol–dry ether or triturated with dry ether (Table 1).

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TABLE 1. 3-Alkyl-4,5-dihydroxypyrazoles (III)

R	mp, °C	Empirical formula	N, %		Yield, %
			found	calc.	
CH_3	183—185	$C_4H_6N_2O_2$	24,6	24,6	46
C_2H_5	174—175	$C_5H_8N_2O_2$	22,0	21,9	35
n-C_3H_7	157—158	$C_6H_{10}N_2O_2$	19,8	19,7	35
n-C_4H_9	141—142	$C_7H_{12}N_2O_2$	18,2	17,9	32
n-C_5H_{11}	153	$C_8H_{14}N_2O_2$	16,3	16,5	43
n-C_6H_{13}	164—165	$C_9H_{16}N_2O_2$	15,3	15,2	39
n-C_7H_{15}	156—158	$C_{10}H_{18}N_2O_2$	13,7	14,1	42
n-C_8H_{17}	151—153	$C_{11}H_{20}N_2O_2$	13.1	13,2	75
n-C_9H_{19}	156—158	$C_{12}H_{22}N_2O_2$	12,0	12,3	64

TABLE 2. α-Acetoxy-β-keto Esters (II)

R	bp, °C (mm)	n_D^{20}	d_4^{20}	MR_D		Empirical formula	Found, %		Calc., %		Yield, %
				found	calc		C	H	C	H	
CH_3	111—113 (6)[a, b]	1,4290	1,1352	42,81	42.46	$C_8H_{12}O_5$	—	—	—	—	47
C_2H_5	116—117,5 (9)	1,4318	1,1090	47,26	47,08	$C_9H_{14}O_5$	52,9	7,1	53,4	7,0	47
n-C_3H_7	115—116 (8)[a]	1,4335	1,0869	51,74	51,69	$C_{10}H_{16}O_5$	55,6	7,1	55,4	7,5	48
n-C_4H_9	127—128 (7)[a]	1,4375	1,0852	55,92	56,31	$C_{11}H_{18}O_5$	56.9	7,6	57,4	7,9	62
n-C_5H_{11}	141—142 (9)[a]	1,4352	1,0347	61,32	60,94	$C_{12}H_{20}O_5$	59,0	8,5	59,0	8,3	55
n-C_6H_{13}	150—151 (9)[d]	1,4417	1,0378	65,81	65,55	$C_{13}H_{22}O_5$	59,3	8,3	60,4	8,6	51
n-C_7H_{15}	158—159 (9)[d]	1,4427	1,0262	70,30	70,17	$C_{14}H_{24}O_5$	61,0	8,8	61,7	8,9	47
n-C_8H_{17}	159—160 (10)[d]	1,4437	1,0204	74,48	74,78	$C_{15}H_{26}O_5$	63,0	9,0	62,9	9,1	63
n-C_9H_{19}	176—177 (8)[d]	1,4457	1,0026	79,84	79,40	$C_{16}H_{28}O_5$	63,5	9,3	64,0	9,4	52
C_6H_5	174—178 (10)[d,e]	1,5110	1,1766	62,52	61,95	$C_{13}H_{14}O_5$	—	—	—	—	46

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[a] The freshly distilled compound was a pale-yellow liquid that became colorless on standing [1].

[b] Bp 120-122° (15 mm) [1].

[c] These are the n_D^{25} and d_4^{25} values.

[d] Colorless liquid.

[e] Bp 140-143° (1 mm) [1].

3-Phenyl-4,5-dihydroxypyrazole Hydrochloride. A mixture of 2.5 g (0.01 mole) of ethyl α-acetoxybenzoylacetate and 3.3 g (0.015 mole) of 25% hydrazine hydrate solution was stirred for 2 h and heated on a boiling-water bath for 30 min. The precipitate was removed by filtration, crystallized from 10 ml of hydrochloric acid (sp. gr. 1.18), dried, and washed with benzene to give 1.2 g (52%) of colorless crystals with mp 165-167°; λ_{max}, nm (log ε): <220 (>3.9), 297 (3.99). Found: C 46.9; 46.9; H 4.9, 5.0; N 12.4, 12.7%. $C_9H_8N_2O_2 \cdot HCl \cdot H_2O$. Calculated: C 46.9; H 4.8; N 12.1%.

1-Phenyl-3-methyl-4,5-dihydroxypyrazole (I). A 5.4-g (0.05 mole) sample of phenylhydrazine was added to a solution of 9.4 g (0.05 mole) of α-acetoxyacetoacetic ester in 25 ml of alcohol under nitrogen, followed by the gradual addition of 6 ml of 28% ammonium hydroxide. The mixture was heated at 60° on a water bath, and the alcohol was then removed by vacuum distillation. The residue was treated with 10.7 ml of hydrochloric acid (sp. gr. 1.18), and the yellow precipitate was dried and washed with petroleum ether to give 3.5 g (37%) of a product with mp 205-206°. Crystallization from 45 ml of glacial acetic acid and washing with 50 ml of dry benzene gave 2.15 g of pale-yellow crystals of I with mp 231-233° (mp 225° [1]); λ_{max}, nm (log ε): 230 (3.93), 274 (3.69). Found: N 15.0, 14.6%. $C_{10}H_{10}N_2O_2$. Calculated: N 14.7%.

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