SYNTHESIS OF MONOSUBSTITUTED AMIDES OF 2,6-DIMETHYL-1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLIC ACID

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Monosubstituted amides of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid were obtained when acetoacetic acid anilide and 2-pyridylamide were used in place of acetoacetic ester in the Hantzsch synthesis.

1,4-Dihydropyridine derivatives [1] have long been studied as model compounds of the redoxy coenzyme NADH. These compounds were recently investigated as antioxidants [2, 3] and coronary dilators [4].

Little study has been devoted to the amide analogs of "Hantzsch dihydropyridines." In addition to information regarding the synthesis of the oxide form of several compounds, 2,6-dimethyl-4-phenyl-3,5-dicarbamoyl-1,4-dihydropyridine [5] and several substituted anilides of 2,4,6-trimethyl-1,4-dihydropyridine, 3,5-dicarboxylic acid [6, 7] have been mentioned in the literature without a detailed description of their synthesis and properties.

We have synthesized 1,4-dihydropyridines by the Hantzsch method using acetoacetic acid anilide and 2-pyridylamide. As one should have expected [1], these compounds are less stable with respect to oxidation than their 3,5-diethoxycarbonyl analogs, inasmuch as the stabilizing effect of the carbonyl groups is weakened. For this reason, the synthesis and crystallization should be carried out in the absence of air oxygen. This is especially important for the preparation of 4-unsubstituted derivatives I and II, although the synthetic method [3] does not require additional refluxing, particularly in the presence of increased amounts of urotropin. The known 2,6-dimethyl-3,5-di(phenylcarbamoyl)pyridine was obtained not only by oxidation of dihydropyridine I with chloranil but also by prolonged heating of a solution of I. The remaining compounds (III-XI, Table 1) were obtained by refluxing a solution of the anilide or 2-pyridylamide of acetoacetic acid, the aromatic or heterocyclic aldehyde, and ammonia in methanol [8]. The physical constants, yields, and results of microanalysis are also given in Table 1. The UV spectra of the compounds obtained in this study are, in general, in agreement with the UV spectra of the known 3,5-diethoxycarbonyl analogs. Because of the presence of aromatic or heteroaromatic components, it was pointless to study the spectra at 200-220 nm. At 220-400 nm there are two or three absorption bands. The long-wave maximum characteristic for 1,4-dihydropyridine vanishes on oxidation. Just as in the case of 3,5-diethoxycarbonyl derivatives, the introduction of a substituent into the 4 position causes a hypsochromic shift of the long-wave maximum.

EXPERIMENTAL

2,6-Dimethyl-3,5-di(phenylcarbamoyl)-1,4-dihydropyridine (I). A solution of 3.0 g (0.02 mole) of hexamethylenetetramine and 2.0 g (0.02 mole) of ammonium acetate in 10 ml of water was added to a solution of 10.62 g (0.06 mole) of acetoacetanilide in 30 ml of ethanol, and the mixture was refluxed on a water bath for 2 min while carbon dioxide was bubbled through the solution. The resulting crystalline precipitate was removed by filtration and washed with cold ethanol to give 9.15 g (84%) of I as a light-yellow substance with bluish fluorescence in UV light.

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I-XI

TABLE 1. Monosubstituted Amides of 2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylic Acid

Compound	R_1	R_2	mp, °C	Empirical formula	Found, %				Calculated, %				UV spectrum, λ_{max}, nm (log ε)	Yield, %
					C	H	N	Cl	C	H	N	Cl		
I	C_6H_5	H	220—225[a]	$C_{21}H_{21}N_3O_2 \cdot H_2O$	68,9	6,6	11,7	—	69,0	6,3	11,5	—	268(4,37), 370(3,94)	84
II	2-Pyridyl	H	131—136[b]	$C_{19}H_{19}N_5O_2 \cdot 2H_2O$	59,5	5,8	18,0	—	59,2	6,0	18,2	—	285(4,36), 385(3,91)	71
III	C_6H_5	C_6H_5	230[c]	$C_{27}H_{25}N_3O_2$	76,5	6,3	9,5	—	76,6	6,0	9,9	—	259(4,46), 346(4,09)	63
IV	C_6H_5	3-Pyridyl	242—243[a]	$C_{26}H_{24}N_4O_2$	73,9	5,7	13,3	—	73,6	5,7	13,2		262(4,46), 346(4,00)	59
V	C_6H_5	$C_6H_3Cl_2$	229—232[b]	$C_{27}H_{23}N_3O_2Cl_2$	66,3	5,0	8,7	14,7	65,9	4,7	8,5	14,4	237(4,37), 267(4,30), 337(3,91)	39
VI	C_6H_5	$C_6H_4NO_2$	234—236[d]	$C_{27}H_{24}N_4O_4$	69,3	5,1	11,7	—	69,2	5,2	12,0	—	264(4,49), 337(4,00)	80
VII	2-Pyridyl	C_6H_5	229—231[b]	$C_{25}H_{23}N_5O_2$	70,5	5,9	15,8	—	70,6	5,5	16,5	—	247(4,31), 287(4,33), 359(4,01)	80
VIII	2-Pyridyl	$C_6H_3(OCH_3)_2$	207—210[b]	$C_{27}H_{27}N_5O_4$	66,9	5,8	14,5	—	66,8	5,6	14,4	—	232(3,98), 266(4,00), 289(4,08), 373(3,68)	68
IX	2-Pyridyl	3-Pyridyl	223—225[b]	$C_{24}H_{22}N_6O_2$	67,4	5,1	19,5	—	67,6	5,2	19,7	—	257(4,30), 286(4,33), 356(3,97)	75
X	2-Pyridyl	$C_6H_3Cl_2$	229—231[d]	$C_{25}H_{21}N_5O_2Cl_2$	60,9	4,3	14,1	14,2	60,7	4,3	14,2	14,3	237(4,41), 284(4,39), 352(3,99)	95
XI	2-Pyridyl	$C_6H_4NO_2$	237—239[d]	$C_{25}H_{22}N_6O_4$	64,0	4,6	17,9	—	63,8	4,7	17,9	—	283(4,43), 327(3,97)	43

[a] From dimethylformamide—water.

[b] From ethanol.

[c] From dioxane.

[d] From butanol.

Oxidation of I. A solution of 0.25 g (0.001 mole) of chloranil in 5 ml of benzene was added to a suspension of 0.38 g (0.001 mole) of I in 50 ml of benzene, and the mixture was heated for 15 min. The hot solution was filtered to give 0.32 g (90%) of crystalline 2,6-dimethyl-3,5-di(phenylcarbamoyl)pyridine with mp 292-294° (from ethanol). UV spectrum in ethanol, λ_{max}, nm (log ε): shoulder at 235 (4.16), 254 (4.22), and shoulder at 272 (4.18). Found: C 72.7; H 5.4; N 12.0%. $C_{21}H_{19}N_3O_2$. Calculated: C 73.0; H 5.5; N 12.1%.

2,6-Dimethyl-3,5-(2-pyridylcarbamoyl)-1,4-dihydropyridine (II). This compound (a light-yellow substance) was obtained from acetoacetic acid 2-pyridylamide by the method used to obtain I.

2,6-Dimethyl-3,5-di(phenylcarbamoyl)-4-phenyl-1,4-dihydropyridine (III). An 11-ml (0.1 mole) sample of benzaldehyde and 10 ml (0.2 mole) of 25% ammonium hydroxide were added to a solution of 35.4 g (0.2 mole) of acetoacetanilide in 60 ml of methanol, and the mixture was refluxed on a water bath for 3 h. The resulting yellow precipitate was removed by filtration to give 26.6 g (63%) of a product that fluoresces in UV light.

Compounds IV-XI were similarly synthesized.

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