2-OXOPYRIDINE DERIVATIVES

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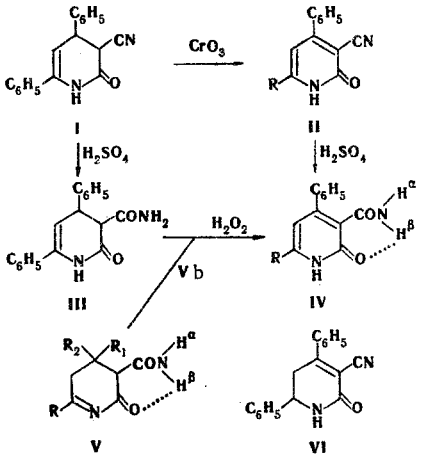
UDC 547.824.07:543.422.25.4.6

On the basis of IR, UV, and PMR spectra it was established that, depending on the starting compounds and the reaction conditions, 1,2-dihydro-2-oxopyridine and 1,2,3,4-tetrahydro- and 2, 3, 4, 5-tetrahydro-2-oxopyridine derivatives are obtained by condensation of malondiamide or cyanacetamide with α, β-unsaturated mono-ketones (benzylideneacetophenone, benzylideneacetone, and mesityl oxide).

In a continuation of our research on the synthesis of nitrogen-containing heterocycles [1, 2] we have accomplished the synthesis of 2-oxopyridine derivatives that are of interest as potential physiologically active compounds [3, 4].

2-Oxo-3-cyano-4,6-diphenyl-1,2,3,4-tetrahydropyridine (I) was isolated from the condensation of cyanacetamide under the conditions of the Michael reaction with benzylidineacetophenone. Oxidation of I with chromium trioxide gave 2-oxo-3-cyano-4,6-diphenyl-1,2-dihydropyridine (IIa), previously synthesized in [5]. The structures of I and II were confirmed by spectroscopy.



II, IV a $R=C_6H_5$; b $R=CH_3$; V a $R=CH_3$, $R_1=C_6H_5$, $R_2=H$; b $R=R_1=C_6H_5$, $R_2=H$; c $R=R_1=R_2=CH_3$

The absorption band of a cyclic amide carbonyl group appears at 1695 cm^{-1} in the IR spectrum of I, and nitrile group absorption appears at 2263 cm^{-1}. Because of conjugation, a shift in the absorption bands of the amide carbonyl group to 1650 cm^{-1} and of the nitrile group to 2228 cm^{-1} is observed in the IR spectrum of IIa. The 1,2,3,4-tetrahydropyridine structure in the case of I was proved by means of the PMR spectra, which, in addition to signals from phenyl groups and an amide proton, contain signals from the protons attached to C_3, C_4, and C_5 of the pyridine ring at, respectively, δ 4.10, 4.50, and 5.30 ppm. In addition to signals from phenyl groups and an amide proton. The signal of a vinyl proton in the form of a lone singlet at δ 6.72 ppm is observed in the PMR spectrum of IIa. Oxopyridine IIa has maxima at 206, 258, 290 (inflection), and 368 nm in the UV region, whereas the long-wave absorption maximum in the case of I

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1108-1111, August, 1975. Original article submitted September 16, 1974.

TABLE 1. Characteristics of the Synthesized 2-Oxopyridines (I-V)

Compound	mp, °C	Crystallization solvent	Empirical formula	Found, %			Calc., %			IR spectra, cm^{-1} (% absorption)			UV spectra, λ, nm ($\varepsilon \cdot 10^{-3}$)	Yield, %
				C	H	N	C	H	N	$\nu_{C=O}$	ν_{CN}	ν_{NH}		
I	222—224	Ethanol+ acetic acid	$C_{18}H_{14}N_2O$	78,82	4,95	10,31	78,81	5,14	10,21	1695 (82)	2260 (38)	3223 (85) 3120 (80)	203 (24,5) 225 (16,9) 277 (5,9)	62
IIa	313—315[5]	Acetic acid	$C_{18}H_{12}N_2O$	79,21	4,32	10,31	79,39	4,44	10,29	1650 (70)	2228 (74)	3150 (52) 3035 (58)	206 (17,5) 258 (13,5) 290sh(5,3) 368 (10,2)	50
IIb	274—275[5]	Acetic acid	$C_{13}H_{10}N_2O$	74,24	4,78	13,25	74,27	4,79	13,32	1665 (68)	2230 (73)	3150 (46) 3065 (59)	207 (18,8) 245 (19,3) 280 (9,3) 350 (9,8)	39
III	168—170	Acetone+ hexane	$C_{18}H_{16}N_2O_2$	73,69	5,70	9,31	73,95	5,51	9,58	1690 sh*(70) 1670 (80)	—	3425 (48) 3215 (52)	203 (25,3) 225sh(15,0) 280 (5,1)	67
IVa	254—256	Ethanol	$C_{18}H_{14}N_2O_2$	74,32	4,78	9,40	74,47	4,86	9,64	1665 (68) 1632 (70)	—	3418 (58) 3368 (58)	203 (24,3) 252 (14,4) 347 (9,1)	75
IVb	253—255	Ethanol	$C_{13}H_{12}N_2O_2$	68,58	5,25	11,95	68,41	5,29	12,27	1678 (78) 1650 (54)	—	3415 (40) 3312 (40)	203 (22,2) 235 (18,6) 265sh(6,0) 330 (7,3)	80
Va	261—262	Acetic acid	$C_{13}H_{14}N_2O_2$	67,91	6,10	12,29	67,81	6,13	12,16	1718 (78) 1670 (82)	—	3180 (72) 3100 (72)	209 (10,2)	65
Vb	250—251	Ethanol	$C_{18}H_{16}N_2O_2$	74,15	5,57	9,74	73,95	5,51	9,58	1710 (79) 1675 (82)	—	3185 (60) 3060 (55)	205 (8,6)	62
Vc	271—272	Ethanol	$C_9H_{14}N_2O_2$	59,42	7,62	15,66	59,32	7,74	15,37	1715 (58) 1683 (61)	—	3145 (52) 3065 (52)	203 (3,6)	40

is found at 277 nm (Table 1). Thus the IR, PMR, and UV spectra confirm structure I rather than the previously assigned [5-7] isomeric oxopyridine structures V and VI.

The cyano groups of I and IIa are saponified relatively readily to amide groups to give III and IVa, which were also obtained by alternative synthesis. The UV spectra of amido derivatives III and IVa are similar to the spectra of cyano derivatives I and II (Table 1).

Depending on the catalyst, two products are obtained by condensation of cyanacetamide with benzylideneacetone. With piperidine as the catalyst, the known 2-oxo-3-cyano-4-phenyl-6-methyl-1,2-dihydropyridine (IIb) [5], which undergoes hydrolysis to give IVb, was isolated. The signal of the protons of an exocyclic amide appears in the PMR spectrum of IVb as two broad singlets centered at δ 6.93 (H^{α}) and 7.70 ppm (H^{β}). The signal of the protons of a cyclic amide is observed at 11.95 ppm. We were unable to isolate the hydrogenated derivative of pyridine with the I structure in this case. Oxidation apparently occurs during the reaction. Using a more basic catalyst – sodium methoxide – we obtained 2-oxo-3-carbamolyl-4-phenyl-6-methyl-2,3,4,5-tetrahydropyridine (Va). Compound Vb was obtained by condensation of benzylideneacetophenone with malondiamide, and Vc was obtained by condensation of mesityl oxide with cyanacetamide. In the latter case the nitrile group is saponified to an amide group. As in the case of III, the absorption of two amide carbonyl groups at 1710-1718 and 1670-1683 cm^{-3} is observed in the IR spectra of V, but, in contrast to III, only one maximum at 203-209 nm appears in the UV spectrum of V. The 2,3,4,5-tetrahydropyridine structure of V was proved by means of PMR spectra. Thus, for example, the PMR spectrum of Va contains signals of methyl protons at δ 1.51 ppm, of phenyl protons at δ 7.20 ppm, of methylidyne protons attached to C_3 and C_4 centered at 3.52 and 2.98 ppm, and of methylene protons attached to C_3 at 2.00 ppm. The signal from the amide protons appears as two broad peaks at 8.76 (H^{α}) and 8.87 ppm (H^{β}). Compounds V are 1.6 isomers of hydrogenated pyridine III (Δ5, 6); this isomerism is the reason for the markedly different spectroscopic properties.

In [8, 9] the structure of 2,3,4,5-tetrahydropyridine derivatives was proved by means of chemical transformations. We proved the structures for Va-c by means of their IR, UV, and PMR spectra.

All of the oxopyridine derivatives except Va-c have fluorescence in UV light.

EXPERIMENTAL METHOD

The IR spectra of suspensions of the compounds in paraffin oil and hexachlorobutadiene were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of d_6-dimethyl sulfoxide solutions were recorded with a Perkin-Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard.

2-Oxo-3-cyano-4,6-diphenyl-1,2,3,4-tetrahydropyridine (I). An 8-g (38.4 mmole) sample of benzylideneacetophenone and 3.22 g (38.4 mmole) of cyanacetamide were refluxed in 40 ml of 3% sodium methoxide, after which the mixture was cooled and poured into acidified water. The resulting precipitate was removed by filtration and crystallized.

2-Oxo-3-cyano-4,6-diphenyl-1,2-dihydropyridine (IIa). A 2-g (7.3 mmole) sample of I was suspended in acetic acid, and a solution of 1.46 g (14.6 mmole) of chromium trioxide in 5 ml of water was added. The resulting solution was refluxed for 30 min and allowed to stand overnight. It was then diluted with water and filtered.

2-Oxo-3-cyano-4-phenyl-6-methyl-1,2-dihydropyridine (IIb). A mixture of 2 g (13.7 mmole) of benzylideneacetone, 1.15 g (13.7 mmole) of cyanacetamide, and 1 ml of piperidene in 10 ml of absolute ethanol was refluxed for 7 h, after which a portion of the solvent was evaporated, and the precipitate was separated.

2-Oxo-3-carbamoyl-4,6-diphenyl-1,2,3,4-tetrahydropyridine (III). A) A mixture of 2 g (9.6 mmole) of benzylideneacetophenone, 0.98 g (9.6 mmole) of malondiamide, and 5 ml of 3% sodium methoxide was refluxed in 30 ml of absolute ethanol for 15 min, after which a portion of the solvent was evaporated, and the residue was poured into acidified water. The resulting precipitate was removed by filtration and crystallized to give 1.88 g (67%) of III with mp 168-170°.

B) A mixture of 3.0 g (10.9 mmole) of I and 15 ml of concentrated sulfuric acid was heated on a water bath for 5 h, after which the solution was cooled and poured into water, and the aqueous mixture was neutralized with ammonia to give 2.0 g (63%) of III with mp 170-171°. No melting-point depression was observed for a mixture of this product with the product obtained by method A. Compound IVb was similarly obtained from IIb.

2-Oxo-3-carbamoyl-4,6-diphenyl-1,2-dihydropyridine (IVa). A) This compound, with mp 254-256°, was obtained in 75% yield from IIa by the method used to prepare III. Compound IVb was similarly obtained from IIb.

B) A mixture of 0.5 g (1.7 mmole) of Vb, 0.15 g of potassium hydroxide, and I ml of hydrogen peroxide was refluxed in 10 ml of methanol for 5 h, after which another I ml of hydrogen peroxide was added, and the mixture was refluxed for another 2 h. It was then cooled and poured into acidified water to give 0.25 g (50%) of a product with mp 252-255°. No melting-point depression was observed for a mixture of this product with a sample obtained by method A.

C) The same product was similarly obtained from III in 40% yield.

2-Oxo-3-carbamoyl-4-phenyl-6-methyl-2,3,4,5-tetrahydropyridine (Va). A mixture of 5.0 g (34.0 mmole) of benzylideneacetone, 3.47 g (34.0 mmole) of malondiamide, and 5 ml of 3% sodium methoxide was refluxed in 20 ml of absolute ethanol for 1 h, after which it was cooled, and the precipitated Va was removed by filtration.

2-Oxo-3-carbamoyl-4,6-diphenyl-2,3,4,5-tetrahydropyridine (Vb). As in the preceding experiment, this compound was obtained from benzylideneacetophenone and malondiamide by refluxing for 3.5 h, after which the mixture was poured into acidified water.

2-Oxo-3-carbamoyl-4,4,6-trimethyl-2,3,4,5-tetrahydropyridine (Vc). This compound was similarly prepared from mesityl oxide and cyanacetamide. PMR spectrum: δ_{2CH_3} 1.10, δ_{CH_3} 1.42, δ_{CH_2} 1.70, and δ_{NH_2} 8.82 ppm.

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