SYNTHESIS AND STRUCTURE OF SUBSTITUTED 3,4-DIHYDROPYRIDIN-2-ONES

A. A. Krauze, É. É. Liepin'sh,
Z. A. Kalme, Yu. É. Pelcher,
and G. Ya. Dubur

UDC 547.823: 542.953.2:
543.422.25

The condensation of benzylideneacetonacetic ester with cyanoacetamide in the presence of triethylamine yielded 3-carbamoyl-3,4-dihydropyridin-2-one, while the condensation of arylidenecyanoacetamides with β-aminocrotonic ester in acetic acid yielded 3-cyano-3,4-dihydropyridin-2-ones. It was established by NMR spectroscopy that 3-cyano-4-R-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridin-2-ones exist in solutions in the form of a mixture of cis- and trans-stereoisomers in a 10:1 ratio.

Continuing a study of 3,4-dihydropyridin-2-ones [1, 2], in this work we discussed hydrogenated pyridin-2-ones containing electron acceptor substituents at the $C_{(3)}$ and $C_{(5)}$ atoms of the pyridine ring.

The condensation of benzylideneacetoacetic ester (I) with cyanoacetamide (II) yields 3-carbamoyl-4-phenyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridin-2-one (III) (Table 1). The essence of the method consists of intramolecular cyclization of the intermediate δ-ketonitrile.

3,4-Dihydropyridin-2-one III is also formed in the condensation of the ethyl ester of β-aminocrotonic acid (V) with benzylidenemalonodiamide (VI). Moreover, in this case 2,6-dimethyl-3,5-diethoxycarbonyl-4-phenyl-1,4-dihydropyridine (VII) and malonodiamide (VIII) are also formed, which is an indication of partial cleavage of VI under the conditions of the reaction. In contrast to benzylidenemalonodiamide VI, arylidenecyanoacetamides IX are more stable in acid medium, and in the reaction with the ethyl ester of β-aminocrotonic acid, 3-cyano-4-phenyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridin-2-ones (X) were isolated with good yields. Arylidenemalononitriles (XII) form 2-amino-3-cyano-4-aryl-5-ethoxycarbonyl-6-methylpyridines (XIII) as the main products in the reaction with the ethyl ester of β-aminocrotonic acid V. In the latter case hydrogenated pyridin-2-ones could not be isolated.

The oxidation of 3,4-dihydropyridin-2-ones III and X by chromium trioxide or dilute nitric acid yielded the corresponding 3-carbamoyl- (IV) and 3-cyano-4-phenyl-5-ethoxycarbonyl-6-methylpyridin-2-ones (XI).

In the IR spectra of the compounds synthesized, the characteristic absorption bands of the C=O, C≡N and NH groups are observed (Table 1). In the case of 3-cyanopyridin-2-ones XI and 2-amino-3-cyanopyridines XIII, in comparison with 3-cyano-3,4-dihydropyridin-2-ones X, the band of C≡N is shifted by 30-40 cm^{-1} in the direction of lower frequencies, which is evidence of the presence of a more conjugated system.

In the UV spectra of compounds IV, XI, and XIII long-wave absorption is observed at 320-340 nm, which is absent in 3,4-dihydroderivatives of pyridin-2-ones- III and X.

In the PMR spectra of 3-cyanoderivatives X, in contrast to 3-carbamoyl analogs III (Tables 2 and 3), signals corresponding to cis- and trans-isomers in a ratio of ~10:1 are observed. The signals with a large value of the SSCC ($J_{3,4} \approx 6$-7 Hz, Table 3) were assigned to the cis-isomer, by analogy with the data of [3]. The substantial difference of the observed $J_{3,4}$ in the trans-isomer of X from that of the analog ($J \approx 3$ Hz in X and $J \approx 13.2$ Hz in [3]) indicates a predominant trans-diaxial orientation of the substituents (CN, R) in compounds X, which is evidently due to the unprofitable steric interaction between the 5-COOEt group and the 4-R ring in the case of an equatorial arrangement of the latter.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1504-1508, November, 1984. Original article submitted February 6, 1984.

0009-3122/84/2011-1241$08.50

TABLE 1. Characteristics of the Compounds III, IV, X, XI, and XIII

Compound	R	Mp, °C	R_f	IR spectrum, cm^{-1}			UV spectrum, λ, nm (log ε)	Found, %			Gross formula	Calculated, %			Yield, %
				C=C, C=O	C≡N	NH or NH_2		C	H	N		C	H	N	
IIIa	C_6H_5	217—218	0,26	1623, 1674, 1685	—	3136, 3206, 3350, 3456	287 (4,20)	63,2	5,8	9,2	$C_{16}H_{18}N_2O_4$	63,6	6,0	9,7	37, 13*
IV	C_6H_5	266—268	0,10	1671, 1684, 1720	—	3172, 3326, 3368	252 (4,26), 320 (3,95)	64,4	5,1	9,3	$C_{16}H_{16}N_2O_4$	64,0	5,4	9,3	37
Xa	C_6H_5	104—106	0,70	1635, 1700, 1720	2262	3158, 3258	283 (4,08)	66,8	5,8	9,7	$C_{16}H_{16}N_2O_3$	67,6	5,7	9,9	66
Xb	4-$NO_2C_6H_4$	103—105	0,64	1630, 1700, 1720	2258	3164, 3250, 3360	219 sh(4,02), 273 (4,28)	57,8	5,0	12,6	$C_{16}H_{15}N_3O_5$	58,3	4,6	12,8	69
Xc	3-$NO_2C_6H_4$	182—184	0,64	1640, 1695, 1705 sh	2260	3095, 3215	217 sh (4,20), 273 (4,27)	58,0	4,8	12,6	$C_{16}H_{15}N_3O_5$	58,3	4,6	12,8	66
Xd	4-ClC_6H_4	157—159	0,70	1633, 1702, 1724	2260	3176, 3262	219 sh (4,15), 282 (4,11)	60,0	5,0	8,5	$C_{16}H_{15}ClN_2O_3$	60,3	4,7	8,8	46
Xe	4-$CH_3OC_6H_4$	183—185	0,67	1637, 1706, 1721	2261	3134, 3234	226 (4,00), 280 (4,02)	64,6	5,8	8,9	$C_{17}H_{18}N_2O_4$	65,0	5,8	8,9	51
Xf	Furyl-2	152—154	0,65	1635, 1708, 1736	2272	3190, 3288	216 (4,23) 283 (4,27)	61,7	5,4	10,3	$C_{14}H_{14}N_2O_4$	61,3	5,1	10,2	63
XI	C_6H_5	220—222	0,40	1640, 1728	2232	3150, 3305	254 (4,30), 340 (4,06)	67,4	5,3	9,9	$C_{16}H_{14}N_2O_3$	68,1	5,0	9,9	35
XIIIa	C_6H_5	231—233	0,75	1654 sh., 1715	2223	3155, 3322, 3384	256 (4,34), 333 (3,92)	68,6	5,3	15,0	$C_{16}H_{15}N_3O_2$	68,3	5,4	14,9	30
XIIIb	4-$NO_2C_6H_4$	245—246	0,75	1665, 1720	2225	3165, 3325, 3370	269 (4,20), 338 (3,75)	58,1	4,2	17,1	$C_{16}H_{14}N_4O_4$	58,0	4,3	17,2	40

*In the condensation of V + VI

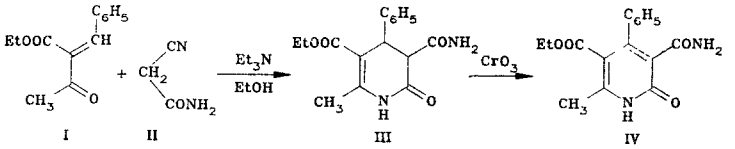
TABLE 2. PMR Spectra of Compounds III, IV, X, XI, and XIII in DMSO-D_6

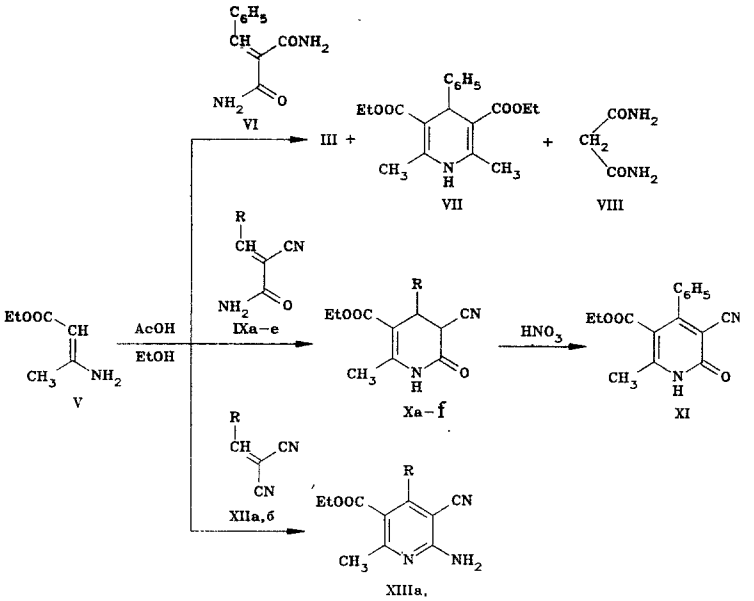
Compound	R	Chemical shifts, (multiplicity)												SSCC $J_{3,4}$, Hz	
		NH (n.s.)		$CONH_2$, 2-NH_2 (n.s.)	R (m)	H_3 (d)		H_4 (b)		CH_2CH_3 (m and t)		6-CH_3 (c)			
		cis	trans			cis	trans	cis	trans	cis	trans	cis	trans	cis	trans
III	C_6H_5	—	10,1	7,71; 7,20	7,30	—	3,29	—	4,40	—	4,02; 1,05	—	2,32	—	1,9
IV	C_6H_5	12,28		7,57; 7,15	7,44—7,18	—	—	—	—	3,75 and 0,69		2,30		—	—
Xa	C_6H_5	10,48	10,58	—	7,36—7,12	4,93	4,16	4,35	4,48	4,00; 1,09	3,98; 1,05	2,37	2,35	6,7	4,0
Xb[a]	4-$NO_2C_6H_4$	8,5	8,5	—	7,40; 8,18	4,22	3,70	4,60	4,67	4,11; 1,17	4,11; 1,17	2,44	2,49	7,2	2,6
Xc	3-$NO_2C_6H_4$	10,68	10,70	—	8,25—7,64	5,06	4,38	4,61	4,63	4,01; 1,11	3,97; 0,96	2,36	2,36	7,0	5,0
Xd	4-ClC_6H_4	10,49	10,56	—	7,40; 7,18	4,93	4,17	4,36	4,47	3,99; 1,11	3,99; 1,02	2,33	2,32	6,9	4,2
Xe[f]	4-$CH_3OC_6H_4$	10,51	10,60	—	7,11; 6,87	5,04	4,07	4,33	4,42	4,03; 1,11	4,03; 1,11	2,33	2,30	6,4	3,0
Xn[g]	Furyl-2	10,40	10,60	—	7,51 (H_5'), 6,31 (H_4'), 6,76 (H_3')	4,79	4,20	4,56	4,56	4,02; 1,11	4,03; 1,11	2,18	2,22	6,4	3,0
XI	C_6H_5	12,53		—	7,53—7,23	—	—	—	—	3,80 and 0,70		2,40		—	—
XIIIa	C_6H_5	—	—	7,30	7,51—7,22	—	—	—	—	3,84 and 0,75		2,39		—	—
XIIIb	4-$NO_2C_6H_4$	—	—	7,50	8,31; 7,61	—	—	—	—	3,87 and 0,78		2,44		—	—

[a]In $CDCl_3$. [b]Signal of the OCH_3 protons 3.74 (sec). [c]Internal standard HMDS.

TABLE 3. SSCC in 3-Cyano-4,6-diphenyl-5-R^1-3,4-dihydropyridin-2-ones XIV and XV

Compound	R^1	Isomer	$J_{^{13}C-^1H}$, Hz				$J_{3,4}$, Hz
			4-H, $C_{(2)}$	3-H, $C_{(2)}$	4-H, CN	3-H, CN	
XIV	H	cis	7,7	7,7	1,0	10,8	6,7
		trans	2,7	8,0	3,4	10,8	13,2
XV	COOEt	cis	8,3	8,3	0,2	10,7	6,7
		trans	7,5	7,5	5,0	10,9	3,2





a $R=C_6H_5$; b $R=4\text{-}NO_2C_6H_4$; c $R=3\text{-}NO_2C_6H_4$; d $R=4\text{-}ClC_6H_4$; e $R=4\text{-}CH_3OC_6H_4$; f R= furyl-2

The assignment of the signals in the PMR spectrum to cis, and trans-isomers of X was confirmed by a study of the long-range spin-spin interaction of ^{13}C-^1H in the ^{13}C NMR spectra. For this purpose the ^{13}C NMR spectra of model compounds — 3-cyano-4,6-diphenyl-3,4-dihydropyridin-2-one (XIV) [4] and 3-cyano-4,6-diphenyl-5-ethoxycarbonyl-3,4-dihydropyridin-2-one (XV) [5] — were recorded. The measured SSCC (Table 3) also are evidence of a different orientation of the 4-H protons relative to the cyano group or the C=O carbon of the ring in 3,4-dihydropyridin-2-ones X and XIV.

Using the Karplus function for the SSCC $^3J_{^{13}C-C-C-H}$ [6, 7], it can be shown that the 4-phenyl ring in cis- and in trans-X has a predominantly axial orientation. In contrast to trans-X, in the trans-XIV molecule there is an equatorial 4-R group. In the cis-isomer of XIV, the 4-R substituent is also axially oriented.

The absence of any appreciable strong-field shift of the CH_3 protons of the 5-ethoxycarbonyl group agrees with the predominant axial arrangement of the aryl group in 3,4-dihydropyridin-2-ones X (Table 2), observed, for example, in oxidized derivatives of pyridin-2-ones IV and XI.

Judging by the low value of the SSCC $J_{3,4}$ for 3-carbamoyl derivatives of III (~2, Table 2), these compounds exist exclusively in the transform with pseudoaxial 4-phenyl and 3-carbamoyl groups.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in liquid petrolatum, the UV spectra on a Specord UV-vis instrument in ethanol, the PMR spectra on a WH 90/DC instrument (90 MHz), internal standard TMS. Experiments on the selective resonance of $^{13}C\{^1H\}$ were conducted on a WM-360 spectrometer (360 MHz). The course of the reaction and the individuality of the substances were monitored by thin-layer chromatography on Silufol UV-254 plates in the system chloroform–acetone–hexane, 2:1:1. The main characteristics of the synthesized substances are given in Tables 1 and 2.

3-Carbamoyl-4-phenyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropropyliden-2-one (III). A mixture of 2.18 g (10 mmoles) of the benzylideneacetoacetic ester I, 0.84 g (10 mmoles) of cyanoacetamide II, and 1.0 ml of triethylamine in 10 ml abs. ethanol was boiled for 2 h on a water bath. The hot reaction mixture was filtered off. After cooling III crystallized (1.15 g, 37%, mp 217-218°C (from ethanol).

Condensation of benzylidenemalonodiamide VI with the ethyl ester of β-aminocrotonic acid V. A mixture of 1.9 g (10 mmoles) of benzylidenemalonodiamide VI, 1.42 g (11 mmoles) of the ethyl ester of β-aminocrotonic acid V, 5 ml of glacial acetic acid, and 10 ml of abs. ethanol was boiled for 1 h. After cooling a mixture of products crystallizes. The residue is filtered off and the product is recrystallized from ethanol. The less soluble malonodiamide VIII crystallizes out. Yield 0.35 g (34%) of compound VIII, mp 169-170°C. The filtrates were combined, evaporated, and the residue chromatographed through a column filled with Al_2O_3, using a mixture of chloroform–acetone–hexane, 2:1:1, as the eluent. Fractions with R_f 0.8 and 0.26 were collected. Yield 0.9 g (27%) of compound VII, mp 156-157°C, which gave no depression of the melting point with a known sample [8], and 0.38 g (13%) of compound III.

3-Carbamoyl-4-phenyl-5-ethoxycarbonyl-6-methylpyridin-2-one (IV). A mixture of 1.51 g (5 mmoles) of 3,4-dihydropyridin-2-one III, 1 g chromium trioxide in 4 ml of water, and 3 ml of glacial acetic acid was boiled for 1 h, cooled, and 10 ml of water added. The precipitate was filtered off, washed with water, and dried. Yield 0.55 g (37%) IV, mp 266-268°C (from ethanol).

3-Cyano-4-phenyl-5-ethoxycarbonyl-6-methyl-3,4-dihydropyridin-2-one (Xa). A mixture of 1.72 g (10 mmoles) 3-cyano-4-phenylacrylamide IXa, 1.42 g (11 mmoles) of the ethyl ester of β-aminocrotonic acid V, 5 ml glacial acetic acid, and 10 ml abs. ethanol was boiled for 4 h on a water bath. The hot mixture was filtered. After cooling 1.88 g (66%) Xa, mp 104-106°C (from ethanol) crystallized out.

Compounds Xb-f were produced analogously.

3-Cyano-4-phenyl-5-ethoxycarbonyl-6-methylpyridin-2-one (XI). A mixture of 1.42 g (5 mmoles) 3,4-dihydropyridin-2-one Xa and 10 ml dilute HNO_3 (1:7) was heated for 10 min on a water bath, cooled, diluted with water, and neutralized with ammonia. The precipitate was filtered off, washed with water, and dried. Yield 0.5 g (35%) XI, mp 220-222°C (from ethanol).

2-Amino-3-cyano-4-phenyl-5-ethoxycarbonyl-6-methylpyridine (XIIIa). Analogously to III, from 1.42 g (11 mmoles) of the ethyl ester of β-aminocrotonic acid V, 1.54 g (10 mmoles) benzylidenemalonodinitrile XII in 5 ml glacial acetic acid, and 10 ml abs. ethanol, we obtained 0.85 g (30%) XIIIa, mp 231-233°C (from ethanol). Compound XIIIb was produced analogously.

3-Cyano-4,6-diphenyl-3,4-dihydropyridin-2-one (XIV) was synthesized by the method of [4]. ^{13}C NMR spectrum (DMSO-D_6): cis-isomer 164.18 (2-C); 139.00 (6-C); 117.33 (CN); 105.71 (5-C); 43.10 (4-C); 40.97 (3-C); trans-isomer: 164.64 (2C); 141.32 (6-C); 117.89 (CN); 107.13 (5-C); 42.75 (4-C); 41.81 (3-C).

3-Cyano-4,6-diphenyl-5-ethoxycarbonyl-3,4-diphydropyridin-2-one (XV) was synthesized by the method of [5]. ^{13}C NMR spectrum (DMSO-D_6): cis-isomer: 165.85 (COO); 162.51 (2-C); 149.09 (6-C); 114.52 (CN); 109.13 (5-C); 42.65 (4-C); 41.73 (3-C); 61.20 (CH_2); 13.96 (CH_3); trans-isomer: 166.07 (COO); 161.54 (2-C); 146.41 (6-C); 115.76 (CN); 108.11 (5-C); 44.00 (4-C); 40.60 (3-C); 61.20 (CH_2); 13.96 (CH_3).

LITERATURE CITED

1. Z. A. Bomika, Yu. É. Pelcher, G. Ya. Dubur, A. A. Krauze, and É. É. Liepin'sh, Khim. Geterotsikl. Soedin., No. 10, 1377 (1979).

2. Z. A. Bomika, Yu. É. Pelcher, A. A. Krauze, G. Sh. Gol'dberg, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 6, 783 (1981).
3. J. Kuthan, P. Neswadba, Z. Donnerova, and P. Trška, Collect. Czech. Chem. Commun., 42, 2152 (1977).
4. Z. A. Bomika, M. B. Andaburskaya, Yu. E. Pelcher, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 8, 1108 (1975).
5. C. Seonane, J. L. Soto, P. Zamorano, and M. Quinteiro, J. Heterocycl. Chem., 18, 309 (1981).
6. R. B. Martin, J. Phys. Chem., 83, 2404 (1979).
7. V. F. Bystrov, Prog. NMR Spectrosc., 10, 41 (1976).
8. R. Schiff and J. Politi, Chem. Ber., 16, 1607 (1983).

PHOTOCYCLIZATION OF 1,2-DIARYL- AND PHOTOBICYCLIZATION OF 1,2,6-TRIARYLPYRIDINIUM CATIONS*

A. R. Katritzky, B. Agha,
G. Z. de Ville, E. Lunt,
M. I. Knyazhanskii, Ya. R. Tymyanskii,
and A. I. Pyshchev

UDC 547.821.3'828: 541.144'124

New 1,2-diaryl- and 1,2,6-triarylpyridinium salts, containing various five- and six-membered heteroaromatic substituents in the 1, 2, and 6-positions of the pyridinium ring, were synthesized. New tetra- and hexacyclic compounds were prepared by photocyclization of the cations of these salts. Photocyclization proceeds through a singlet excited state with nonadiabatic formation of a dihydro intermediate, followed by its oxidative dehydrogenation. The structure and quantum yield of the formation of photoproducts are determined by steric and electronic effects of the substituents, and in bichromophore compounds by the presence of S—S intramolecular interfragment energy transfer.

The present article represents a generalization of results on the reaction of photocyclization of polyaryl-substituted pyridinium cations and consists of two parts. The first includes the results of preparative photosynthesis of new heterosubstituted systems, conducted at the laboratory of the University of East Anglia and Florida under the supervision of Prof. A. R. Katritzky. The second part discusses the structural and energy metabolism of the photoreaction, as well as the photophysical processes that compete with it. The results of this part of the work were obtained at the laboratory of photochemistry of the Scientific-Research Institute of Physical and Organic Chemistry of Rostov State University.

1. PHOTOCYCLIZATION AS A METHOD OF PRODUCING NEW HETEROCYCLIC COMPOUNDS

The work on the photocyclization of 1,2-diaryl-cations (I → II) and the photobicyclization of 1,2,6-triarylpyridinium cations (I → III) was conducted by A. R. Katritzky's group [1] and followed the work of G. N. Dorofeenko et al. [2], in which these photoconversions were detected for the first time. This section presents the results of a broader investigation of photocyclization for pyridinium cations with various heteroaryl substituents.

Most of the pyridinium derivatives were produced from the corresponding pyrylium salts and amines by conventional methods (Table 1). The yields were good except for the case of Ic, where adverse steric and electronic effects are associated with the presence of an ortho-carboxy group.

*The article is dedicated to the memory of Professor G. N. Dorofeenko.

School of Chemical Sciences, University of East Anglia, Norwich, NR4 7TJ, UK. Department of Chemistry, University of Florida, Gainesville, Florida 32611. Scientific-Research Institute of Physical and Organic Chemistry at M. A. Suslov Rostov State University, Rostov-on-Don 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1509-1518, November, 1984. Original article submitted June 23, 1983; revision submitted April 24, 1984.

