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FIVE-MEMBERED 2,3-DIOXOHETEROCYCLES

3.* THE REACTION OF 5-ARYL-2,3-DIHYDROFURAN-2,3-DIONES WITH ALIPHATIC AND AROMATIC NITRILES

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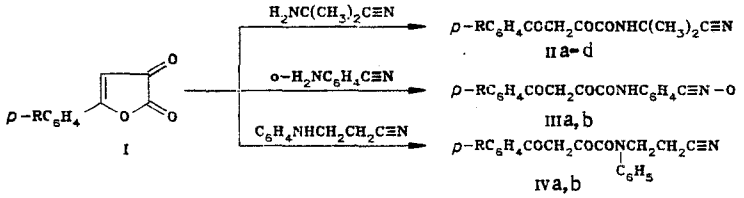
UDC 547.298'484.7'724.07:543.422

On reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with α-aminoisobutyronitrile, o-aminobenzonitrile, and β-anilinopropiononitrile, we obtained aroylpyruvic acid N-(1-methyl-1-cyanoethyl)-, N-(o-cyanophenyl)-, and N-phenyl-N-(cyanoethyl)-amides, respectively. On reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with cyanoacetamide we obtained aroylacetic acid N-(cyanoacetyl)amides, while in the case of methyleneaminoacetonitrile and p-dimethylaminobenzonitrile we obtained (6-aryl-4-oxo-2,3-dihydro-1,3-oxazin-3-yl)acetonitriles and 2-(p-dimethylaminophenyl)-6-aryl-1,3-oxazine-4-ones, respectively.

Earlier it was noted that aroylketenes generated by thermolysis of 5-aryl-2,3-dihydrofuran-2,3-diones (I) do not react in a $(4\pi + 2\pi)$-cycloaddition with aliphatic and aromatic nitriles but react with N,N-disubstituted-N-cyanoamines, forming 2-amino-6-aryl-1,3-oxazin-4-ones [2,3]. If the C≡N group in the reagent is directly linked with a primary or secondary amino group, then ring opening of compound I proceeds with the formation of aroylpyruvic acid N-cyanoamides, accompanied by the addition of α-enolic hydroxyl to C≡N, and 2-imino-5-phenacylidene-4-oxazolidones appear as reaction products [4, 5]. In connection with this, it was of interest to react aminonitriles which contained unlinked amino and cyano groups with compounds I. Among such reagents we used α-aminoisobutyronitrile, o-aminobenzonitrile, β-anilinopropionitrile, cyanoacetic acid amides, and p-dimethylaminobenzonitrile.

On investigation of the interaction of compound I with α-aminobutyronitrile, 0-aminobenzonitrile, and β-anilinopropiononitrile, it was established that, due to nucleophilic attack of the amino group on the lactone carbonyl of compound I, furan ring opening ensues and the products of reaction are, respectively, N-(1-methyl-1-cyanoethyl)-(IIa,d), N-(o-cyanophenyl)-(IIIa,b), and N-phenyl-N-(cyanoethyl)-(IVa,b) arolypyruvic acid amides.



I—IV a R=H, b R=CH_3; II c R=C_2H_5O, d R=Br

*For Communication 2, see [1].

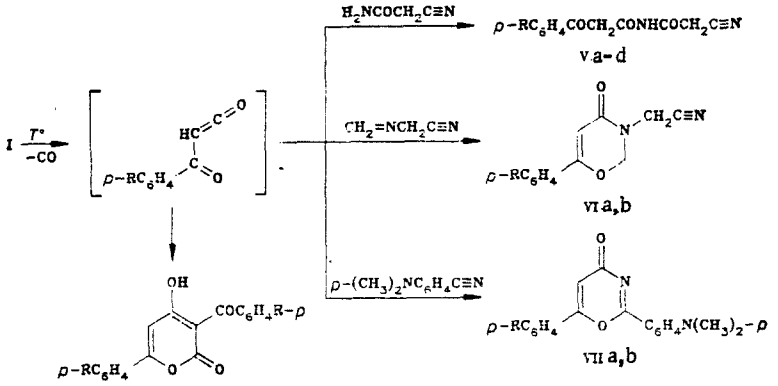
Perm State Pharmaceutical Institute, Perm 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 740-743, June, 1987. Original article submitted November 10, 1985.

 0009-3122/87/2306-0610$12.50 ©1987 Plenum Publishing Corporation

The reaction takes place at 5-40°C, i.e., under milder conditions than was necessary for the generation of aroylketenes, and is not accompanied by cyclization. The cyclization of compounds II-IV was not successful on prolonged heating in toluene, and similarly on passing hydrogen chloride. On the other hand, nucleophilic opening of the furan ring with o-chlorophenylcyanamide and α-cyanophenylhydrazine is accompanied by the cyclization of the compound at 20°C without participation of a catalyst [5, 6]. The results obtained are evidence that for cyclization to occur, both the activating influence on C≡N of a strongly electron-donating group and a favorable mutual spatial disposition of C≡N to the α-enolic hydroxyl group in the aroylpyruvic acid residue are necessary.

A characteristic absorption band for C≡N at 2255-2260, and also bands at 3370-3410 and 1672-1700 cm^{-1} caused by NH vibration and amide carbonyl, respectively, are present in the IR spectra of the synthesized compounds. A broad band for enolic hydroxyl at 13-14 ppm is present in the PMR spectra of the amides II-IV ($CDCl_3$), as well as a multiplet for aromatic protons centered at 7.41-7.49 and a singlet for methine at 6.98-7.19. The absence of a signal for a methylene proton is evidence of the complete enolization of these compounds. Apart from the indicated signals, a singlet for two methyl groups at 1.78-1.82 is present in the spectra of compounds IIa-d, and for compounds IVa,b there are singlets for two methylene groups at 4.05-4.10 and 2.78-2.83 ppm. The spectral characteristics obtained correspond to the earlier published data on spectra of aroylpyruvic acid alkyl and aryl amides [7].

Cyanoacetamide reacts with compounds I at 80-110°C with formation of aroylacetic acid N-cyanoacetylamides (Va-d) caused by the lessening of the nucleophilic properties of the amino group in the reagent due to acylation. Consequently the amino group loses the capacity to open the furan ring and allows the generation of aroylketenes. The addition of aroylketenes to NH_2 of the cyanoacetamide leads to the formation of products Va-d.



The IR spectra of these compounds contain the following absorption bands: 3240-3254 and 3140-3160 (NH), 2255-2260 (C≡N), 1680-1695, and 1600-1610 cm^{-1} (C=O). In the PMR spectra, obtained in DMSO-D6, are observed two signals for two methylene groups at 3.86-4.00 and 4.18-4.27, a singlet for NH at 10.47-10.93, and also a multiplet for aromatic protons centered at 7.61-7.65 ppm. Besides the indicated peaks, a signal is present for a methine proton at 6.30-6.35 ppm. The relationship of its intensity to that of the methylene group in the aroylacetyl fragment is evidence of 5-10% enolization for compounds Va-d.

A molecular ion peak is present in the mass-spectrum of compound Vd with m/e 264/266, and also peaks for fragment ions $[M - NHCOCH_2CN]^+$ 181/183, $[ClC_6H_4CO]^+$ 139/141, $[ClC_6H_4]^+$ 111/113, $[C_6H_4]^+$ 76, $[COCHCO]^+$ 69, $[COCH_2CN]^+$ 68.

Methyleneaminoacetonitrile is not able to react with compounds I as an internal nucleophile, and takes on the role of a dienophile in a cycloaddition reaction. As was established, the C=N bond takes part in the cycloaddition and the products of reaction are (6-aryl-4-oxo-2,3-dihydro-1,3-oxazin-3-yl)acetonitriles (VIa,b), in agreement with the great reactivity of C=N compared with C≡N in cycloaddition reactions with acylheterocumulenes.

p-Dimethylaminobenzonitrile reacts with compounds I with participation of C≡N due to activation of this bond by conjugation with the dimethylamino group. However, in this instance, together with the products of the reaction – 2-(dimethylaminophenyl)-6-aryl-1,3-oxazin-4-ones (VIIa,b) – dimers of arolyketenes – 6-aryl-4-oxo-3-aroyl-2-pyranones – separate from the reaction mixture [8]. These are a consequence of incomplete relaying of conjugation of the dimethylamino group to C≡N by the benzene nucleus.

TABLE 1. Properties of Synthesized Compounds

Compound	mp, °C	Found, %			Molecular formula	Calculated, %			Yield, %
		C	H	N (Hal)		C	H	N (Hal)	
IIa	123—125	64,9	5,1	10,5	$C_{14}H_{14}N_2O_3$	65,1	5,4	10,9	93
IIb	136—138	66,0	5,5	10,1	$C_{15}H_{16}N_2O_3$	66,1	5,9	10,3	80
IIc	106—108	63,4	5,7	9,0	$C_{16}H_{18}N_2O_4$	63,6	6,0	9,3	85
IId	153—155	49,5	3,7	8,2 (23,7)	$C_{14}H_{13}BrN_2O_3$	49,9	3,9	8,7 (23,7)	89
IIIa	126—128	69,7	4,0	9,4	$C_{17}H_{12}N_2O_3$	69,9	4,1	9,6	78
IIIb	168—169	70,4	4,5	9,1	$C_{18}H_{14}N_2O_3$	70,6	4,6	9,1	75
IVa	69—70	71,1	4,9	8,7	$C_{19}H_{16}N_2O_3$	71,2	5,0	8,8	97
IVb	103—104	71,7	5,3	8,3	$C_{20}H_{18}N_2O_3$	71,9	5,4	8,4	99
Va	152—153	62,6	4,3	12,1	$C_{12}H_{10}N_2O_3$	62,6	4,4	12,2	69
Vb	191—192	63,7	4,8	11,4	$C_{13}H_{12}N_2O_3$	63,9	4,9	11,5	78
Vc	165—166	61,0	4,8	10,3	$C_{14}H_{14}N_2O_4$	61,3	5,1	10,2	99
Vd	183—185	46,5	3,0	8,7 (25,7)	$C_{12}H_9BrN_2O_3$	46,6	2,9	9,1 (25,9)	77
Vd	162—163	54,4	3,0	9,5 (13,4)	$C_{12}H_9ClN_2O_3$	54,4	3,4	9,5 (13,4)	84
VIa	140—142	67,1	4,6	12,9	$C_{12}H_{10}N_2O_2$	67,3	4,7	13,1	70
VIb	143—144	68,2	5,1	12,1	$C_{13}H_{12}N_2O_2$	68,4	5,3	12,3	74
VIIa	213—214	73,8	5,4	9,5	$C_{18}H_{16}N_2O_2$	74,0	5,5	9,6	45
VIIb	241—243	74,4	5,6	9,1	$C_{19}H_{18}N_2O_2$	74,5	5,9	9,2	32
VIIIa	224—226	56,2	3,6	5,2	$C_{12}H_{10}NO_4Na$	56,5	3,9	5,5	75
IXa	159—160	55,6	3,6	3,1 (18,3)	$C_{20}H_{16}BrNO_5$	65,8	3,7	3,2 (18,6)	93

The PMR spectra of compounds VIa,b have a signal at 5.90-5.93 ppm characteristic of 2,3-dihydro-1,3-oxazin-4-ones [9]. Two singlets for methylene protons at 4.35-4.39 and 5.31-5.34 and a multiplet for aromatic protons centered at 7.46-7.50 ppm are also observed in the spectrum.

Absorption bands in the region 1668-1672 cm^{-1} are observed in the IR spectra of compounds VIa,b, explained by the stretching vibrations of amide carbonyl. Since the intensity of the band for C=N in the spectrum is very small, compound VIa was hydrolyzed by alkali to the sodium salt VIIIa, from which (6-phenyl-4-oxo-2,3-dihydro-1,3-oxazin-3-yl)acetic acid p-bromophenacyl ester IXa was then obtained using p-bromophenacyl bromide.

The IR spectra of compounds VIIa,b contain absorption bands in the region 1655-1658 (C=O amide) and 3068-3071 cm^{-1} (=C–H). A singlet is observed in the PMR spectra of these compounds for the methine proton at 6.45-6.55, a singlet for two methylene protons at 2.98-3.00, and also a multiplet for aromatic protons centered at 7.68-7.78 ppm. The data obtained from IR and PMR spectra of compounds VIIa,b agree well with the corresponding data for 2-aryl-1,3-oxazin-4-ones [10].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in vaseline oil, the PMR spectra on a PC-60 instrument (60 MHz), internal standard HMDS; the mass-spectra were obtained on an AEJM-50 instrument with direct introduction of samples into the ionic current, at an ionization energy of 50 eV, electron inversion current 1.5 mA, and temperatures near the mp of specimens.

The properties of the synthesized compounds are cited in Table 1.

Aroylpyruvic Acid N-(1-Methyl-1-cyanoethyl)- (IIa-d), N-(o-Cyanophenyl)- (IIIa,b), and N-Phenyl-N-(cyanoethyl)- (IVa,b)amides. To a mixture of compound I (0.01 mole) in 20 ml dioxane is added α-aminoisobutyronitrile(o-aminobenzonitrile, β-anilinopropiononitrile) (0.01 mole) at 5-40°C. The reaction mixture is stirred for 10 min. The solvent is evaporated, and the residue recrystallized from acetonitrile or isopropanol.

Aroylacetic Acid N-(Cyanoacetyl)amides (Va-d). A solution of compound I (0.01 mole) and cyanoacetamide (0.01 mole) in 25 ml of dioxane is boiled. The residue after removal of solvent is recrystallized from ethanol.

(6-Aryl-4-oxo-2,3-dihydro-1,3-oxazin-3-yl)acetonitriles (VIa,b). A mixture of compound I (0.01 mole) and methyleneaminoacetonitrile (0.01 mole) is boiled in 30 ml toluene for 1.5 h. The reaction mixture is cooled, and the precipitate removed by filtration and recrystallized from toluene.

2-(p-Dimethylaminophenyl)-6-aryl-1,3-oxazin-4-ones (VIIa,b). A mixture of compound I (0.01 mole) and p-dimethylaminobenzonitrile (0.01 mole) is heated in toluene (20 ml) for 1.5 h After cooling the reaction mixture, the precipitate is removed by filtration and recrystallize from ethanol. 6-Aryl-4-oxo-3-aroyl-2-pyranones separate from the filtrate after removal of solvent.

Sodium Salt of (6-Phenyl-4-oxo-2,3-dihydro-1,3-oxazin-3-yl)acetic Acid (VIIIa). To the solution of compound VIa (0.01 mole) in ethanol (20 ml) is added water (2 ml) and sodium hydrox ide (0.01 mole); the resulting mixture is boiled for 2 h. The precipitate is removed by filtration and recrystallized from 45% ethanol. IR spectrum: 1665 (C=O amide), 1620, 1390 cm^{-1} (COO^-). PMR spectrum (D_2O): 3.98 (2H, s, CH_2); 5.26 (2H, s, CH_2); 5.91 (1H, s, CH), 7.35-7.88 ppm (5H, m, C_6H_5).

p-Bromophenacyl Ester of (6-Phenyl-4-oxo-23,3-dihydro-1,3-oxazin-3-yl)acetic Acid (IXa). Compound VIIIa (0.01 mole) is dissolved in ethanol (30 ml), p-bromophenacyl bromide (0.01 mole) is added, and the mixture boiled for 3 h. The reaction mixture is cooled, and the precipitate removed by filtration and recrystallized from ethanol. IR spectrum: 1745 (C=O ester), 1708 (C=O ketone), 1668 cm^{-1} (C=O amide). PMR spectrum: (DMSO-D6): 4.45 (2H, s, CH_2); 5.55 (4H, d, $2CH_2$); 6.15 (1H, s, CH); 7.38-7.93 ppm (9H, m, H aromatic).

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