FIVE-MEMBERED 2,3-DIOXOHETEROCYCLES.

8.* RECYCLIZATION OF 5-ARYL-2,3-DIHYDROFURAN-2,3-DIONES BY ACTION OF AMIDE OXIMES AND HYDROXYUREA

I. V. Krylova, D. D. Nekrasov,
and Yu. S. Andreichikov

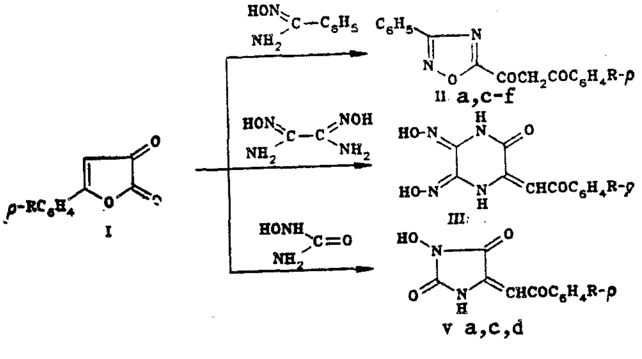
UDC 547.861.3'793.2'783.07'723'
298.73.04:543.422

The reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with benzamide oxime, diaminoglyoxime, and hydroxyurea gave 3-phenyl-5-aroylacetyl-1,2,4-oxadiazoles, 5,6-dihydroxyimino-3-phenacylidenepiperazin-2-ones, and 3-hydroxy-5-phenacylideneimidazolidine-2,4-diones, respectively. 6-Phenacylidene-5-oxo-4,5,6,7-tetrahydrofurazano[3,4-b]pyrazines are formed in the reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with diaminofurazan.

We have shown that hydroxylamine opens the ring of 5-aryl-2,3-dihydro-2,3-diones (I) almost instantaneously with the formation of 4-aryl-2,4-dioxobutyrohydroxamic acids [2]. With compounds (I) under more drastic conditions hydroxylamine hydrochloride forms the recyclization products 3-aryl-5-hydroxy-1,2-oxazin-6-ones [3].

1,2-Hydroxyamino compounds are even less susceptible to entry into recyclization and o-aminophenol open the ring of furandiones (I), and the reaction products are N-(2-hydroxyethyl)- and N-(2-hydroxyphenyl)aroylpyruvamides. In the case of o-aminophenol the products from the recyclization of compounds (I), i.e., 3-phenacylidene-1,4-benzoxazin-4-ones, can be obtained by heating the reagents at 160-170°C [2].

In this connection it seemed of interest to bring amide oximes and hydroxyureas, which are the analogs of the previously investigated 1,2-hydroxyamino compounds and contain nucleophilic groups at the C=N and C—N bonds, into reaction with the furandiones (I). As found, the furandiones (I) undergo recyclization in reaction with benzamide oxime under significantly milder conditions (dioxane, 100-110°C, 15-30 min) than the other previously investigated hydroxyamino compounds. However, recyclization only takes place through one functional group in compounds (Ia-f), i.e., the lactone carbonyl, and the reaction products are 3-phenyl-5-aroylacetyl-1,2,4-oxadiazoles (IIa, c-f).



I—III, V a R=H, b R=CH_3, c R=Br, d R=Cl, e R=CH_3O, f R=F

In the PMR spectrum of (IIa) in addition to the multiplet for the ten aromatic protons centered at 7.43 ppm there is a singlet for the methine proton at 7.17 ppm and a broadened signal for the proton of the enolic hydroxyl at 15.4 ppm. The PMR spectra of the other compounds (IIc-f) are similar. In the IR spectra of compounds (IIa, c-f) there is a strong

---

*For Communication 7, see [1].

Perm Pharmaceutical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1457-1460, November, 1988. Original article submitted April 1, 1987.

0009-3122/88/2411-1204$12.50 © 1989 Plenum Publishing Corporation

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Molecular formula	Calculated, %			Yield, %
		C	H	N (Hal)		C	H	N (Hal)	
IIa	134...135	69,8	3,9	9,0	$C_{17}H_{12}N_2O_3$	69,9	4,1	9,6	48
IIc	144...146	54,9	2,8	7,9 (21,1)	$C_{17}H_{11}BrN_2O_3$	55,0	2,9	7,6 (21,6)	98
IId	139...140	62,3	3,4	8,9 (11,4)	$C_{17}H_{11}ClN_2O_3$	62,5	3,4	8,6 (10,9)	89
IIe	132...133	67,0	4,2	8,4	$C_{18}H_{14}N_2O_4$	67,1	4,3	8,7	53
IIf	135...136	65,6	3,3	8,8	$C_{17}H_{11}FN_2O_3$	65,8	3,5	9,0	82
IIIa	251...252	52,4	3.5	20,2	$C_{12}H_{10}N_4O_4$	52,6	3,6	20,4	41
IIIb	237...238	54,0	3,9	19,3	$C_{13}H_{12}N_4O_4$	54,1	4,1	19,4	50
IIIc	267...268	40,5	2,4	15,6 (22,5)	$C_{12}H_9BrN_4O_4$	40,8	2,5	15,8 (22,6)	45
IIId	273...274	46,5	2,8	18,1 (11,4)	$C_{12}H_9ClN_4O_4$	46,6	2,9	18,1 (11,5)	54
IVb	276...278	57.6	3.7	20,6	$C_{13}H_{10}N_4O_3$	57,7	3,7	20,7	70
IVc	293...295	42,8	2,0	16,6 (23,7)	$C_{12}H_7BrN_4O_3$	42,9	2,0	16,7 (23,8)	65
IVd	278...280	49.5	2.3	19,1 (12,1)	$C_{12}H_7ClN_4O_3$	49,5	2,4	19,3 (12,2)	60
IVe	280...282	54,4	3,4	19.4	$C_{13}H_{10}N_4O_4$	54,5	3,5	19,6	74
Va	238...239	56,7	3,4	11,9	$C_{11}H_8N_2O_4$	56,9	3,4	12,0	10
Vc	249...251	42,3	2.1	8.7 (25,7)	$C_{11}H_7BrN_2O_4$	42,4	2,2	9,0 (25,7)	7
Vd	252...253	49,4	2,5	10.5 (13,2)	$C_{11}H_7ClN_2O_4$	49,5	2,6	10,5 (13,3)	6

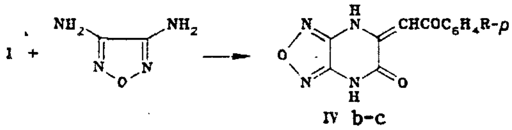
IIb

IIIb

broad band at 1600-1610 cm^{-1}, due to the carbonyl group included in a strong intramolecular hydrogen bond [4]. Thus, the spectral data indicate that one of the carbonyl groups in the β-dicarbonyl fragment of compounds (IIa, c-f) is fully enolized.

The recyclization of the furandiones (I) by the action of diaminoglyoxime does not take place through the amide oxime groups. The reagent in this reaction exhibits the characteristics of a 1,2-diamine, and the reaction products are the 5,6-dihydroxyimino-3-phenacylidenepiperazin-2-ones (IIIa-d) [5]. The PMR spectrum of (IIIa) contains a singlet for the methine proton at 6.28 ppm, a multiplet for the five protons of the phenyl ring centered at 7.71 ppm, signals for the protons of the two groups at 10.85 and 12.55 ppm, and a signal for the two protons of the two OH groups at 11.55 ppm. The PMR spectra of compounds (IIIb-d) are similar in nature. The IR spectra of compounds (IIIa)d) contain absorption bands at 1620-1640 (ketone carbonyl) and 1700-1710 cm^{-1} (amide carbonyl) and also a broad band at 3100-3300 cm^{-1}, due to the stretching vibrations of the hydroxyl and amino groups. In the UV spectra of these compounds λ_{max} is at 341-343 nm (log ε 4.23-4.27).

The mass spectrum of (IIIb) contains peaks with the following m/z values: 288 $[M]^{+\cdot}$, 270 $[M - H_2O]^{+\cdot}$, 255 $[M - NHOH]^+$, 119 $[CH_3C_6H_4CO]^+$, 91 $[CH_3C_6H_4]^+$. The obtained spectral data agree well with the structure proposed for compounds (IIIa-d), but they also correspond to some degree to the structure of 3-(2-hydroxyamidino)-5-aroylacetyl-1,2,4-oxadiazoles, the formation of which is possible during recyclization of the furandiones (I) through one of the amide oxime groups of the diaminoglyoxime. In order to compare the spectral data of compounds (IIIa-d) with the corresponding data for the structurally similar compounds, which are known to have the structure of 5,6-dihydroxyiminopiperazin-2-one, we brought 3,4-diaminofurazan into reaction with the furandiones (I). As found, the recyclization of the furandiones (I) by the action of this reagent takes place in boiling dioxane in 1 h, and its products are 6-phenacylidene-5-oxo-4,5,6,7-tetrahydrofurazano[3,4-b]pyrazines (IVb-e).



IV b-c

The IR spectra of compounds (IVb-e) contain bands at 1600-1615 (ketone carbonyl), 1700-1710 (amide carbonyl), and 3100-3300 cm^{-1} (NH stretching vibrations). This agrees closely with the IR spectra of compounds (IIIa-d) and with the data in [6].

In the UV spectra of compounds (IVb-e) λ_{max} is at ~358-362 nm (log ε 4.24-4.32), and the form of the spectra curves and the position of the absorption maxima for compounds (IIIa-d) and (IVb-e) are very similar. This makes it possible to reject finally the structure of 1,2,4-oxadiazoles for compounds (IIIa-d).

The products in the reactions of furandiones (I) with hydroxyurea in acetamide at 110-120°C are 3-hydroxy-5-phenacylideneimidazolidine-2,4-diones (Va, c, d). Thus, hydroxyurea enters this reaction not as a 1,2-hydroxyamino compound but as a 1,1-diamino compound.

In the IR spectra the stretching vibrations of the ketone carbonyl in the phenacylidene substituent appear at ~1670-1675 cm^{-1}, and the stretching vibrations of the carbonyl at positions 4 and 2 of the heterocycle corresponds to absorption at 1735-1740 and 1800-1805 cm^{-1}. In addition, the spectra contain absorption at 3300-3310 cm^{-1}, due to the NH groups, and at 3550-3555 cm^{-1} due to the hydroxy group. The PMR spectrum of (Va) contains a singlet for the methine proton at 6.88 ppm, a multiplet for the aromatic protons centered at 7.81 ppm, and a broad signal for the two protons of the hydroxyl and amino groups at 11.15 ppm. The PMR spectra of compounds (Vc, d) have the same character. In the UV spectra of these compounds λ_{max} lies at ~330 nm [7]. The spectral characteristics of compounds (Va, c, d) agree well with the corresponding characteristics of 5-phenacylidene-2,4-imidazolidine-2,4-diones not having a hydroxyl group at position 3 [8].

The mass spectrum of (Va) contains peaks with the following m/z values: 232 $[M]^+$, 215 $[M - OH]^+$, 201 $[M - NOH]^+$, 173 $[M - CONOH]^+$, 145 $[C_6H_5COCH{=}C{=}NH]^+$, 105 $[C_6H_5CO]^+$, 77 $[C_6H_5]^+$.

Thus, the amide oximes and hydroxyurea react with the furandiones (I) like 1,2-hydroxyamino compounds only in the case where there are no structural possibilities for the formation of more favorable heterocyclic systems by these binucleophiles, where they act as 1,1- and 1,2-diamino compounds.

EXPERIMENTAL

The IR spectra of the compounds were recorded on a UR-20 spectrophotometer in Vaseline oil. The UV spectra were obtained on a Specord UV-vis spectrophotometer in ethanol at concentrations of 10^{-3}-10^{-5} M. The PMR spectra were recorded on an RS-60 spectrometer at 60 MHz in DMSO-d_6 with HMDS as internal standard. The mass spectra were recorded on a Varian-301 instrument at 50 eV with an electron inversion current of 1.5 mA at temperatures close to the melting points of the substances. The characteristics of the synthesized compounds are given in Table 1.

3-Phenyl-5-aroylacetyl-1,2,4-oxadiazoles (IIa, c-f). To a solution of 0.01 mole of (I) in 150 ml of dioxane we added 0.01 mole of the benzamide oxime. The mixture was boiled for 30 min, and after evaporation of the solvent the product was recrystallized from acetonitrile. trile.

5,6-Dihydroxyimino-3-phenacylidenepiperazin-2-ones (IIIa-d). To a solution of 0.0042 mole of the dioxime in 30 ml of dioxane we added 0.0042 mole of compound (I). The mixture was boiled for 2 h, and the precipitate was filtered off and recrystallized from alcohol or dioxane.

6-Phenacylidene-5-oxo-4,5,6,7-tetrahydrofurazano[3,4-b]pyrazines (IVb-e). To a solution of 0.005 mole of diaminofurazan in 30 ml of dioxane we added 0.005 mole of compound (I). The mixture was boiled for 1 h, and the product was recrystallized from a 1:1 mixture of dioxane and water.

3-Hydroxy-5-phenacylideneimidazolidine-2,4-diones (Va, c, d). A mixture of 0.01 mole of (I) and 0.01 mole of hydroxyurea in 10 g of acetamide was melted on a paraffin bath at 110-120°C for 1.5 h. The melt was poured into water, and the precipitate was filtered off and recrystallized from acetonitrile.

LITERATURE CITED

1. Yu. S. Andreichkiov and I. V. Krylova, Zh. Org. Khim., 24, 2212 (1988).
2. Yu. S. Andreichikov, L. A. Voronova, and A. V. Milyutin, Zh. Org. Khim., 4, 847 (1979).
3. Yu. S. Andreichikov, I. Yu. Voronova, and I. Yu. Astaf'eva, Inventor's Certificate No. 819102; Byul. Izobr., No. 13, 97 (1981).
4. R. M. Silverstein, G. C. Bassler, and T. Morril, Spectrophotometric Identification of Organic Compounds [Russian translation], Mir, Moscow (1977), p. 177.
5. Yu. S. Andreichikov and D. D. Nekrasov, USSR Inventor's Certificate No. 914556; Byul. Izobr., No. 11, 107 (1982).
6. A. V. Eremeev, V. G. Andrianov, and I. P. Piskunova, Khim. Geterotsikl. Soedin., No. 5, 613 (1978).
7. Yu. S. Andreichikov and D. D. Nekrasov, Khim. Geterotsikl. Soedin., No. 2, 166 (1985).
8. V. S. Zalesov, Yu. S. Andreichikov, Yu. A. Nalimova, S. P. Tendryakova, S. M. Starkova, and N. A. Podushkina, Khim.-Farm. Zh., No. 7, 93 (1978).