1,3-Dipolar Cycloadditions of Heterocycles XXVII.* Stereoselective Preparation of 3-Aryl-4-oxo-6-alkoxy-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazoles and 2-Phenyl-6-aryl-3-hydroxy-1,2,3,3a,6a,7-hexahydroisoxazolo[4,5-*d*]pyridazin-7-ones

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The synthesis of 3-aryl-4-oxo-6-alkoxy-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazoles *III*—*XV* was carried out straightforwardly and highlighted by a regio- and stereoselective 1,3-dipolar cycloaddition of substituted benzonitrile oxides with 5-methoxy- or 5-ethoxy-5*H*-furan-2-one. In each case a cycloadduct results from an anti approach to the 5-alkoxy substituent, the oxygen of the 1,3-dipole being attached to C-4 of furan. Reaction of *III*—*XV* with phenylhydrazine led exclusively to *exo*-hexahydroisoxazolo[4,5-*d*]pyridazin-7-ones with *trans* relationship of the H-3 to the H-3a and H-6a bridge hydrogen atoms.

The interest in stereoselective syntheses has provided new impulse to the study of stereocontrolled versions of classical organic reactions. Along this line, an impressive effort has been devoted to the synthetic application of the 1,3-dipolar cycloaddition of nitrile oxides to alkenes [1—3]. In continuation of our efforts [4—7] to utilize heterocyclic compounds as a dipolarophile in 1,3-dipolar cycloaddition aiming at the synthesis of biologically effective compounds, we have found regio- and stereoselective 1,3-dipolar cycloadditions of arylnitrile oxides to 5-ethoxy- and 5-acetoxy-5*H*-furan-2-ones [8, 9]. In this communication we report on the possible extension of this method to the stereoselective synthesis and stereoselective reaction with phenylhydrazine of 3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazoles possessing an *exo* configuration of the methoxy and ethoxy group.

From the reaction of substituted benzonitrile oxides *II* with 5-methoxy-5*H*-furan-2-one (*Ia*, where the substituent is 2-Cl, 4-Cl, 2,4-diCl, 2-F, 2-Br, 4-Br, 3-NO_2, 4-NO_2, 2,4,6-triCH_3), or with 5-ethoxy-5*H*-furan-2-one (*Ib*, where the substituent is 2-Cl, 2,4-diCl, 3,4-diCl, 4-Br) only one cycloadduct, a condensed isoxazoline with an *exo* configuration of the substituent in position 6 was isolated. The structure of the isolated adduct as 3-(X-phenyl)-4-oxo-6-alkoxy-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazole *III*—*XV* (Table 1) was identified from its NMR spectra (Tables 2 and 3) and by comparison with the adducts previously reported by us [8—10]. Also in this case the cycloadducts *III*—*XV* result only from addition to the less hindered face of the furanone with an antiperiplanar relationship between the new C—C bond and the alkoxy substituent, a situation that leads to products with *exo* configuration (Scheme 1). The cycloaddition proceeded regiospecifically, the oxygen atom of the nitrile oxide is attached to the β-carbon of the enone unit of furanone. Neither of the other three possible adducts [9] could be detected despite a careful search, only dimers of nitrile oxides [1, 2] were isolated. The obtained results corroborate the explanation of the exclusive regio- and stereoselective 1,3-dipolar cycloaddition to 5-alkoxy-5*H*-furan-2-ones and other heterocyclic enones, which has been published previously by us [8—11] and others [12] and which is based on AM1 calculations of the reactants and on the consideration of the steric effects [11].

The 5-alkoxy-5*H*-furan-2-one grouping represents a valuable precursor in the synthesis of 2-pyrrolines [13] and 2*H*-pyridazin-3-ones [14],

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Table 1. Characterization of the Prepared Compounds

Compound	R	X	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/% M.p./°C	λ_{max}/nm log (ε/(m^2 mol^{-1}))
III	CH_3	2-Cl	$C_{12}H_{10}ClNO_4$	53.84	3.76	5.23	42	245
			267.66	53.44	3.81	5.60	89—90	2.75
IV	CH_3	4-Cl	$C_{12}H_{10}ClNO_4$	53.84	3.76	5.23	36	267
			267.66	53.90	3.68	5.22	143—145	3.21
V	CH_3	2,4-diCl	$C_{12}H_9Cl_2NO_4$	47.70	3.00	4.63	31	248
			302.11	47.56	3.04	5.07	124—126	2.93
VI	CH_3	2-F	$C_{12}H_{10}FNO_4$	57.37	4.01	5.57	24	257
			251.20	57.08	3.92	5.35	69—70	2.99
VII	CH_3	2-Br	$C_{12}H_{10}BrNO_4$	46.17	3.23	4.49	30	
			312.11	45.90	3.16	4.39	74—75	
VIII	CH_3	4-Br	$C_{12}H_{10}BrNO_4$	46.17	3.23	4.49	38	267
			312.11	46.18	3.14	4.36	149—151	3.29
IX	CH_3	3-NO_2	$C_{12}H_{10}N_2O_6$	51.80	3.62	10.07	41	255
			278.22	51.84	3.36	10.21	109—111	3.32
X	CH_3	4-NO_2	$C_{12}H_{10}N_2O_6$	51.80	3.62	10.07	46	290
			278.22	51.66	3.37	10.28	209—211	3.22
XI	CH_3	2,4,6-triCH_3	$C_{15}H_{17}NO_4$	65.43	6.22	5.09	29	
			275.30	65.24	6.41	4.84	124—126	
XII	C_2H_5	2-Cl	$C_{13}H_{12}ClNO_4$	55.43	4.29	4.97	48	244
			281.70	55.64	4.41	5.30	82—84	2.78
XIII	C_2H_5	2,4-diCl	$C_{13}H_{11}Cl_2NO_4$	49.38	3.50	4.43	33	254
			316.13	49.12	3.48	4.63	78—79	3.09
XIV	C_2H_5	3,4-diCl	$C_{13}H_{11}Cl_2NO_4$	49.38	3.50	4.43	46	269
			316.13	49.19	3.38	4.58	98—100	3.15
XV	C_2H_5	4-Br	$C_{13}H_{12}BrNO_4$	47.87	3.71	4.29	46	270
			326.14	47.74	3.68	4.56	135—136	3.32

pharmacologically interesting compounds with long-lasting antihypertensive activity. Although the reaction of condensed analogues of the alkoxy 5*H*-furan-2-ones with amines and hydrazines proceeded under formation of both possible diastereoisomers, we have observed, in one case,

Table 2. ^{1}H NMR Spectral Data of the Prepared Compounds

Compound	δ						$J_{3a,6a}$/Hz
	H-6 s	H-6a d	H-3a d	H_{arom} m	CH_2	CH_3	
III	5.53	5.29	5.03	7.21—7.55	–	3.56	9.0
IV	5.56	5.26	4.61	7.36—7.81	–	3.56	9.0
V	5.56	5.33	5.10	7.27—7.54	–	3.56	9.0
VI	5.56	5.28	4.92	7.15—7.50	–	3.60	9.0
VII	5.56	5.31	5.06	7.29—7.67	–	3.58	9.0
VIII	5.56	5.28	4.67	7.57—7.79	–	3.60	9.0
IX	5.61	5.37	4.79	7.63—8.77	–	3.62	9.1
X	5.93	5.52	5.45	8.12—8.35	–	3.54	9.0
XI	5.58	5.28	4.46	5.58—6.91	–	3.60[a]	9.3
XII	5.61	5.27	5.04	7.24—7.57	3.80	1.21	9.0
XIII	5.61	5.27	5.00	7.26—7.49	3.80	1.22	9.0
XIV	5.68	5.32	4.68	7.52—8.06	3.87	1.28	9.0
XV	5.70	5.32	4.70	7.61—7.85	3.88	1.30	9.0

a) 2.29 (s, 3H, CH_3), 2.19 (s, 6H, CH_3).

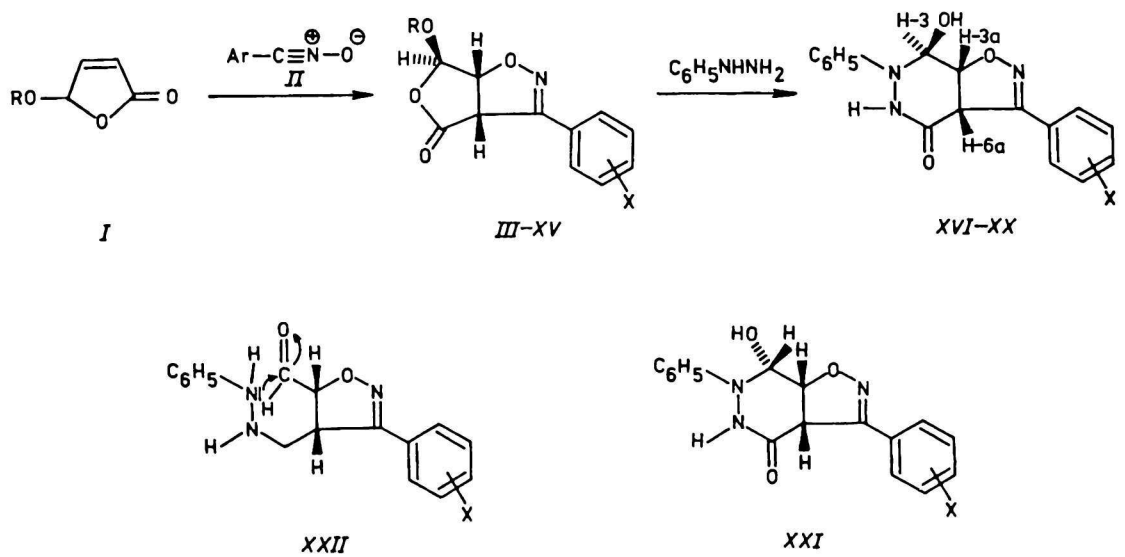
Table 3. ^{13}C NMR Chemical Shifts of the Prepared Compounds

Compound	δ							
	C-4	C-3	C-6	C-6a	C-3a	C_{arom}	CH_2	CH_3
III	169.31	152.32	108.09	86.74	55.16	133.10, 131.70, 130.60, 127.23, 125.62		57.52
IV	169.64	151.72	107.95	87.15	53.90	137.16, 129.58, 129.46, 128.83, 125.26, 122.57		57.57
V	169.23	151.50	108.04	86.86	54.90	137.43, 133.89, 132.47, 130.63, 127.70, 124.20		57.54
VI	169.40	158.78	107.76	86.87	54.52	149.57, 132.75, 130.11, 124.65, 116.55, 114.60		57.46
VII	169.29	153.26	108.13	86.69	55.38	133.64, 131.90, 127.73, 127.63, 122.16		57.52
VIII	169.64	151.85	107.95	87.18	53.85	132.14, 128.37, 125.63, 125.59		57.57
IX	169.33	151.92	107.84	87.03	53.87	133.32, 131.19, 129.82, 129.51, 124.12, 121.63		57.44
X	170.14	152.63	106.11	88.32	53.65	148.22, 129.93, 129.35, 127.90		58.88
XI	169.16	152.63	108.87	85.69	57.32	139.81, 136.92, 128.87, 122.35		57.74[a]
XII	169.37	152.35	106.95	86.94	55.23	133.04, 131.69, 130.52, 127.19, 125.67	66.23	14.80
XIII	169.36	152.34	106.94	86.93	55.83	133.03, 131.69, 130.52, 127.18, 125.66	66.22	14.80
XIV	169.49	150.94	106.83	87.64	53.76	135.26, 133.27, 129.53, 127.01, 126.72	66.34	14.80
XV	169.78	151.82	106.83	87.40	53.94	132.10, 129.35, 125.67	66.28	14.80

a) 21.17 (q, CH_3), 19.72 (q, CH_3).

in the reaction with phenylhydrazine the unusual formation of only one stereoisomer *XVI* (unsubstituted). Therefore, a more detailed study of the reaction of phenylhydrazine with the cycloadducts *III*—*XV* has been performed.

Indeed, in contrast with the published data [13, 14] the reaction of the substituted cycloadducts *III*—*XV* with phenylhydrazine proceeded, like in the case of the unsubstituted derivative *XVI* (Ref. [8]), anomalously. Once again, out of the two



Scheme 1

Table 4. Characterization of the Prepared Compounds

Compound	X	Formula	w_i(calc.)/% w_i(found)/%			Yield/%	M.p./°C
		M_r	C	H	N		
XVII	2-Cl	$C_{17}H_{14}ClN_3O_3$	59.39	4.10	12.21	55	200—202
		343.77	59.67	4.25	12.07		
XVIII	4-Cl	$C_{17}H_{14}ClN_3O_3$	59.39	4.10	12.21	60	188—190
		343.77	59.31	4.37	12.32		
XIX	2-F	$C_{17}H_{14}FN_3O_3$	62.38	4.31	12.83	45	208—210
		327.32	62.48	4.14	12.66		
XX	4-F	$C_{17}H_{14}FN_3O_3$	62.38	4.31	12.83	44	196—198
		327.32	62.15	4.43	12.71		

possible diastereoisomers the reaction gave only the new *exo* isomer *XVII—XX* (Table 4) in which the H-3 hydrogen atom stands *trans* to the H-3a and H-6a bridge hydrogen atoms. ^{13}C NMR spectroscopy (Table 5) showed that it was a single compound rather than a mixture of diastereoisomers *XVI—XX* and *XXI*. The stereochemistry of isolated adducts *XVII—XX* can be deduced from couplings H-3—H-3a and H-3a—H-6a. The value $J \approx 9$ Hz for the latter is characteristic of the *cis*-4,5-dihydroisoxazole unit. The *trans* relationship of the H-3 and H-3a atoms was established by the presence of a doublet ($J_{H,OH} \approx 2$ Hz, $J_{3,3a} = 0$ Hz) which is observed in the ^1H NMR spectrum (Table 6) for the H-3 atom in all cases as expected from the molecular modelling studies of the angles between the vicinal hydrogens in a *trans* relationship in the bicyclic products [15] in which the torsion angle H-3—C-3—C-3a—H-3a is much greater than that expected for the alternative structure *XXI*. The stereospecific formation of the *exo* derivatives *XVI—XX*, rather than *endo* derivative *XXI*, can be explained by smaller repulsive interactions in the transition state on the way from primarily formed intermediate *XXII* to the product *XVI—XX* than in the transition state leading to the *endo* epimer *XXI*. The reaction of condensed furanones with phenylhydrazine seems to be controlled by the steric effects.

EXPERIMENTAL

Melting points were determined on a Kofler hotplate apparatus. ^1H NMR spectra were recorded on Tesla BS 487 C (80 MHz) and Varian VXR 300 instruments, respectively, and ^{13}C NMR spectra on Jeol JX-100 and Varian VXR 300 spectrometers in deuterochloroform (compounds *III—XV*) and deuterodimethyl sulfoxide (compounds *XVII—XX*), tetramethylsilane as internal standard. Ultraviolet spectra were obtained on a spectrometer M-40 (Zeiss, Jena) in methanol.

Table 5. ^{13}C NMR Chemical Shifts of the Prepared Compounds

Compound	δ					
	C-7	C-6	C-3a	C-3	C-6a	C_{arom}
XVI	167.39	150.24	83.81	77.45	53.49	154.76, 154.78, 146.73, 130.32, 129.18, 128.80, 128.54, 127.92, 119.42, 118.44, 113.00, 111.77
XVII	168.66	150.23	82.92	78.13	55.73	153.35, 146.57, 132.01, 131.64, 131.41, 130.32, 129.15, 128.84, 127.25, 126.82, 119.48, 118.18
XVIII	167.33	150.22	83.89	77.48	53.40	154.06, 148.67, 135.04, 129.86, 129.19, 128.91, 128.80, 126.64, 119.44, 118.46, 113.00, 111.76
XIX	168.99	150.21	82.96	77.62	54.57	161.40, 158.04, 151.36, 146.67, 132.38, 130.87, 129.17, 128.83, 119.45, 118.41, 112.96, 111.77
XX	167.39	150.23	83.71	77.46	53.58	164.88, 161.57, 153.93, 148.70, 130.37, 129.19, 124.38, 119.44, 118.46, 115.61, 113.01, 111.78

Table 6. ^{1}H NMR Spectral Data of the Prepared Compounds

Compound	δ					J/Hz	
	O—H	H-3a	H-6a	H-3	H_{arom}	$J_{3a,6a}$	$J_{3,OH}$
XVII	5.77	5.17	4.85	4.74	6.60—7.87	11.7	2.0
XVIII	5.77	5.13	4.84	4.76	6.54—7.93	9.3	2.7
XIX	5.76	5.14	4.80	4.75	6.57—7.90	9.3	2.7
XX	5.77	5.13	4.84	4.76	6.56—7.99	9.3	2.2

Chlorides of benzohydroximic acids were prepared by chlorination of the corresponding benzaldehyde oximes in chloroform according to [16], 2,4,6-trimethylbenzonitrile oxide was synthesized according to [17]. 5-Ethoxy- and 5-methoxy-5*H*-furan-2-one were prepared by irradiation of 2-furancarbaldehyde with a 600 W medium-pressure lamp in ethanol and methanol, respectively, in the presence of eosin and with introduction of a strong current of air, according to [18].

3-Aryl-4-oxo-6-alkoxy-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazoles *III—XV*

Dry triethylamine (11 mmol) in dry ether (20 cm^3) was added dropwise at −5—0 °C to a stirred cooled solution of the corresponding benzohydroximoyl chloride (10 mmol) and 5-alkoxy-5*H*-furan-2-one (10 mmol) in dry ether (50 cm^3) during 1 h. After stirring for 1 h at 0 °C and standing overnight at room temperature, the precipitated triethylammonium chloride was removed by filtration and the filtrate was concentrated *in vacuo*. The products were triturated with ethanol (5 cm^3) and purified by crystallization from ethanol–water. The cycloaddition of 2,4,6-trimethylbenzonitrile oxide was performed in the following way: The nitrile oxide (10 mmol) and dipolarophile (10 mmol) in dry benzene (30 cm^3) were heated to 80 °C for 4 h. After cooling, the worked-up mixture was concentrated and processed further as described above.

2-Phenyl-6-aryl-3-hydroxy-1,2,3,3a,6a,7-hexahydroisoxazolo[4,5-*d*]pyridazin-7-ones *XVI—XX*

A mixture of phenylhydrazine (4 mmol), acetic acid (8 cm^3), and water (6 cm^3) was added in one portion to a hot solution of the corresponding isoxazole in this work and in [8] (2 mmol) in ethanol (6 cm^3). After heating to reflux for 2 h, the reaction mixture was concentrated *in vacuo*. The products were obtained by chromatography of the residue on a column of silica gel in cyclohexane–ethyl acetate (φ_r = 1 : 3) and crystallized from ethanol.

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