SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-SUBSTITUTED 5-ARYL-2,3-DIHYDRO-3-FURANONES

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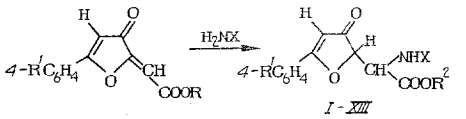
UDC 615.31:547.724].012.1.07

A previous work has shown that the 3-furanones, and specifically the 5-aryl-2,3-dihydro-3-furanones, display some potential in the search for compounds that exhibit a wide range of biological activity [7]. With this in mind we obtained the 5-aryl-2-(arylamino) alkoxycarbonylmethyl-2,3-dihydro-3-furanones (I-V) by reacting 2-alkoxycarbonylmethylene-5-aryl-2,3-dihydro-3-furanones with arylamines (method A) [1, 2]. Addition of 2,4-dinitrophenylhydrazine (method B) or the hydrazones of benzaldehyde and p-nitrobenzaldehyde (method C) at the 2-exoethylene bond of the 5-aryl-2-methoxycarbonylmethylene-2,3-dihydro-3-furanones yielded the structurally-similar 5-aryl-2-(hydrazino)methoxycarbonylmethyl-2,3-dihydro-3-furanones (VI-XIII) [5].

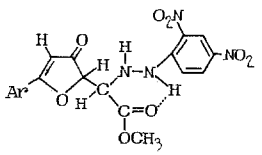


I-XIII

R^1=H(I—III, VI, XI, XII), CH_3(VII, XIII), CH_3O(IV, VIII), Br(IX), Cl(V, X); R^2=CH_3(I, II, IV—XIII), C_2H_5(III); X=C_6H_5(I); 4-$CH_3C_6H_4$(II, V), 4-$CH_3OC_6H_4$(III, IV), 2,4-$(NO_2)_2C_6H_3NH$(VI—X), C_6H_5CH=N(XI, XIII), 4-$NO_2C_6H_4CH$=N(XII).

The physicochemical and spectral characteristics of 3-furanones I-IV are cited in works [1, 2] and those of compounds V-XIII are given in Table 1. The structure of the synthesized substances was corroborated by IR, PMR, MS, and elemental analysis.

The IR spectra of 5-aryl-2-(2^1,4^1-dinitrophenylhydrazino)methoxycarbonylmethyl-2,3-dihydro-3-furanones VI-X (see Table 1) showed that the valence vibration band for the ester group carbonyl (1711-1717 cm^{-1}) is displaced 30 cm^{-1} into the lower frequency region as compared to that of the 5-aryl-2-(arylamino)alkoxycarbonylmethyl-2,3-dihydro-3-furanones [2]. This is due to the formation of an intramolecular hydrogen bond between the ester fragment carbonyl oxygen atom and the secondary amino group hydrogen atom of the 2,4-dinitrophenylhydrazine fragment.



The mass spectrum of 3-furanone VI has molecular and fragment ion peaks with the following mass numbers (relative intensity, %): 428 (2) M^+; 369 (1) $M—CH_3O—CO^+$; 231 (15) $M—2,4\text{-}(NO_2)_2C_6H_3NHNH^+$; 230 (17); 200 (10) $M—2,4\text{-}(NO_2)_2C_6H_3NHNH+CH_3O^+$; 199(20); 198(4) $2,4\text{-}(NO_2)_2C_6H_3NHNH_2^+$ 172(5) $M—CH_3O—CO—2,4\text{-}(NO_2)_2C_6H_3NHNH^+$; 160(100); 147(19) $C_6H_5COCH_2CO^+$; 129(5) $C_6H_5C{\equiv}C—C{\equiv}O^+$; 105(31) $C_6H_5CO^+$; 102(28) $C_6H_5C{\equiv}CH^+$; 69(24) $O{\equiv}C—CH{=}C{=}O^+$. Ta-

Perm Pharmaceutical Institute, Perm. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 26, No. 2, pp. 35-38, February, 1992. Original article submitted March 14, 1991.

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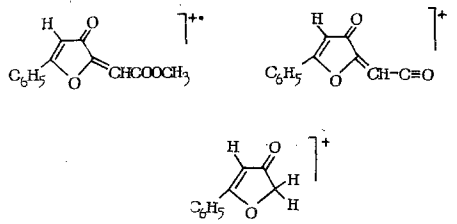
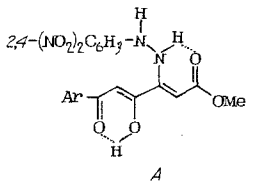
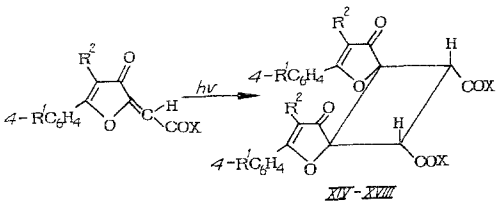


This type of fragmentation is entirely consistent with the structure of compounds VI-X. These compounds cannot have the structure of acyclic isomers, namely the methyl esters of 6-aryl-4-hydroxy-3-(2^1,4^1-dinitrophenyl)hydrazino-6-oxo-2,4-hexadiene acids (A), as the mass spectrum shows a maximum intensity m/z 160 peak, which could not be the result of an alternative structure. This is borne out by the absence of m/z 323 ($M-C_6H_5CO^+$), 281 ($M-C_6H_5COCH_2C\equiv O^+$) peaks.



A

Exposure of thin layers of 5-aryl-2-acylmethylene-2,3-dihydro-3-furanone crystals to visible light yields quantitative amounts of solid-phase dimerization products – the 11,12-disubstituted cis-, cis-, cis-2,8-diaryl-1,7-dioxadispiro[4.0.4.2]dodeca-2,8-diene-4,10-diones (XIV-XVIII) [4, 6].



XIV-XVIII

R^1=H(XIV), CH_3(XV, XVI), CH_3O(XVII), Br(XVIII); R^2= =H(XIV, XV, XVIII), CH_3(XVII), Br(XVI); X=CH_3O(XIV–XVI), C_2H_5O(XVII), 4-BrC_6H_4(XVIII).

Constants and spectral characteristics for the compounds obtained, including x-ray diffraction analysis data for photodimer XIV, are cited in [6].

EXPERIMENTAL (CHEMICAL)

IR spectra of the synthesized compounds were taken on a UR-20 spectrometer (paste in Vaseline). PMR spectra were recorded on an RYa-2310 instrument (60 MHz) in DMSO-d_6 and $CDCl_3$, internal standard HMDS. Mass spectra were obtained on a Varian MAT-311 with direct sample insertion, emission current 1000 mA, ionizing electron energy 70 eV, vaporizer temperature 120-150°C. The homogeneity of the compounds was confirmed using Silufol UV-254 plates in 3:2 benzene–ether and 10:9:1 benzene–ether–acetone systems; the plates were developed with iodine or examined in UV light.

The properties of the newly-synthesized compounds are given in Table 1. Elemental analysis data was in line with calculated values.

2-(p-Tolylamino)Methoxycarbonylmethyl-5-p-chlorophenyl-2,3-dihydrofuranone (V). To a solution of 2.65 g (10 mmoles) of 2-methoxycarbonylmethylene-5-p-chlorophenyl-2,3-dihydro-3-furanone [1] in 150 ml of toluene was added 1.07 g (10 mmoles) of p-toluidine; the mixture was boiled for 30 min (method A). The solvent was evaporated off and the residue recrystallized from acetone.

Substituted 5-Aryl-2-(hydrazino)methoxycarbonylmethyl-2,3-dihydro-3-furanones (VI-XIII). To a solution of 5 mmoles of 5-aryl-2-methoxycarbonylmethylene-2,3-dihydro-3-furanones [1] in 100 ml of ethanol was added 1.0 g (5 mmoles) of 2,4-dinitrophenylhydrazine, then the mixture was boiled for 2-3 h (method B); or to the solution was

TABLE 1. Physicochemical and Spectral Characteristics of 2-Substituted 5-Aryl-2,3-Dihydro-3-Furanones V-XIII

Compound	Synthesis method	Yield, %	mp, °C, (decomp.)	Empirical formula	IR spectrum, ν, cm^{-1}, crystals	PMR spectrum, δ, ppm, DMSO-d_6
V	A	44	167—168	$C_{20}H_{18}ClNO_4$	3325 (NH), 1748 ($COOCH_3$), 1695 [C(3)=O] 1590—1610 (C=C)	3,72 (3H, s, CH_3O); 4,71, 5,62, (2H, two d, CH—CH); 5,25 (1H, s NH); 6,48 [1H, s, C(4)H]; 6,90—7,55 (8H, m, $2C_6H_4$)
VI	B	72	191—192	$C_{19}H_{16}N_4O_8$	3355 (NH), 3233 (NH chel), 1711 ($COOCH_3$), 1662 [C(3)=O], 1580—1608 (C=C)	3,86 (3H, s, CH_3O); 4,37, 5,30 (2H, two d, CH—CH); 6,42 (1H, s, C^4H); 7,33—8,18 (9H, m, C_6H_5, C_6H_3); 8,55 (1H,sext,NH); 9,93 (1H, sext., NH chel.)
VII	B	65	197—198	$C_{20}H_{18}N_4O_8$	3360 (NH), 3242 (NH chel), 1712 ($COOCH_3$), 1667 [C(3)=O], 1585—1610 (C=C)	2,42 (3H, s, CH_3); 3,95 (3H, s, CH_3O); 4,43, 5,18 (2H, two d, CH—CH); 6,15 [1H, s, C(4)H]; 7,22 7,60 (7H, m, C_6H_4, C_6H_3); 8,94 (1Hsext, NH); 9,82 (1H,sext.,NH chel.)*
VIII	B	52	181—182	$C_{20}H_{18}N_4O_6$	3345(NH), 3237 (NH chel), 1713 ($COOCH_3$), 1650 [C(3)=O], 1580—1605 (C=C)	3,84 (3H, s CH_3O); 3,89 (3H, s, CH_3O); 4,45, 5,28 (2H, two d,(CH—CH); 6,32 [1H, s, C(4); 6,95 7,82 (7H, m, C_6H_4, C_6H_3); 8,63 (1H, sext., NH); 10,02 (1H,sext NH chel.)
IX	B	55	187—188	$C_{19}H_{15}BrN_4O_6$	3347 (NH), 3238 (NH chel), 1717 ($COOCH_3$), 1652 [C(3)=O], 1582, 1615 (C=C)	3,85 (3H, s, CH_3O), 4,45, 5,30 (2H, two d, CH—CH); 6,50 [1H, s,C(4)]; 6,95 7,70 (7H, m, C_6H_4, C_6H_3); 8,60 (1H, m., NH); 9,90 (1H, sext., NH chel.)
X	B	68	206—207	$C_{19}H_{15}ClN_4O_8$	3347 (NH), 3238 (NH chel), 1712 ($COOCH_3$), 1647 [C(3)=O], 1575—1610 (C=C)	3,89 (3H, s, CH_3O); 4,48, 5,36 (2H, two d, CH—CH); 6,53 [1H, s, C(4)]; 7,37 8,13 (7H, m C_6H_4, C_6H_3); 8,68 (1H, sext.,NH); 9,98 (1H, sext., NH chel.)
XI	C	34	184—185	$C_{20}X_{18}N_2O_4$	3222 (NH), 1728 ($COOCH_3$), 1674 [C(3)=O], 1562, 1585 1598 (C=N), (C=C)	3,68 (3H, s, CH_3O); 4,61 (2H,sext,CH—CH); 5,16 (1H, d, NH); 6,43 [1H, s, C(4)H]; 7,25 (1H, s, CH); 7,40—7,85 (10H, m, $2C_6H_5$)
XII	C	48	186—187	$C_{20}H_{17}N_3O_6$	3233(NH), 1717 ($COOCH_3$), 1668 [C(3)=O], 1560, 1585 1595 (C=N), (C=C)	3,77 (3H, s, CH_3O); 4,73 (2H,sext.,CH—CH); 5,22 (1H, d,, NH); 6,35 [1H, s, C(4)H]; 7,62 (1H, s, CH); 7,52 8,18 (9H, m, C_6H_5, C_6H_4)
XIII	C	50	169—170	$C_{21}H_{20}N_2O_4$	3232 (NH), 1726 ($COOCH_3$), 1677 [C(3)=O], 1567, 1592—1610 (C=N), (C=C)	2,25 (3H, s, CH_3); 3,70 (3H, s, CH_3O); 4,50 (2H,sext CH—CH); 5,13 (1H, d, NH), 6,35 [1H, s, C(4)H]; 7,10 7,85 (10H, m, CH, C_6H_5, C_6H_3)

*Spectrum taken in $CDCl_3$

added with stirring 0.6 g (5 mmoles) of benzaldehyde hydrazone or 0.83 g (5 mmoles) of p-nitrobenzaldehyde hydrazone, then the mixture was boiled for 10-20 min (method C). The solvent was evaporated off and the residue recrystallized from ethanol or acetonitrile. Method B yielded compounds VI-X and method C gave compounds XI-XIII.

2-(Benzylidenehydrazino)Methoxycarbonylmethyl-5-phenyl-2,3-dihydro-3-furanone (XI).

Mass spectra m/z (I, %): 350(16) M^{7+}; 291(25); $M-CH_3OCO^{7+}$, 249(11) $M-C_6H_5C\equiv C^{7+}$, 232(23) $M-C_6H_6CHN_2^{7+}$, 231(100); 230(31) — cf. formula or $M-C_6H_5CH=NNH_2^{7+}$; 199(41), 191(81) $C_6H_5CH=NN=CHCOOCH_3^{7+}$; 173(23) M—$-C_6H_5CHN_2-CH_3OCO^{7+}$, 160(74), 131(31) $C_6H_5CH=NHC\equiv N^{7+}$; 120(74) $C_6H_5CH=NNH_2^{7+}$; 119(23) $C_6H_5CH=NNH^{7+}$, 105 $C_6H_5CH=NH^{7+}$; 104(48) $C_6H_5C\equiv NH^{7+}$, 103(31). $C_6H_5C\equiv N^{7+}$; 102(67) $C_6H_5C\equiv CH^{7+}$.

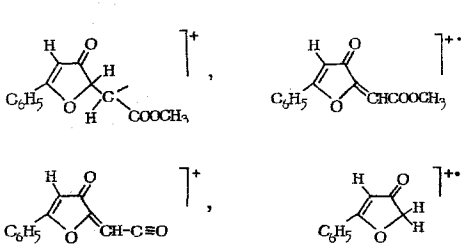


TABLE 2. Antimicrobial Activity of Compounds I-XVIII

Compound	MIC, μg/ml	
	E. coli M_{17}	St. aureus P-209
I	500	500
II	500	250
III	1000	500
IV	1000	1000
V	500	250
VI	1000	1000
VII	Inactive	Inactive
VIII	1000	1000
IX	1000	1000
X	1000	1000
XI	1000	500
XII	1000	500
XIII	1000	500
XIV	1000	1000
XV	1000	500
XVI	500	500
XVII	1000	1000
XVIII	Inactive	1000
Mercuric chloride	1000	1000
Lactate ethacrydine	2000	500

EXPERIMENTAL (BIOLOGICAL)

A study was made of the antimicrobial, anti-inflammatory, and analgesic activity of the synthesized compounds.

The median lethal dose, LD_{50}, of the compounds was determined using the method developed by G. N. Pershin [9] by intraperitoneal injection into white mice of 20-24 g weight, introducing the compounds as suspensions in 2% starch mucilage.

The antimicrobial activity of the compounds with respect to the reference strains of Escherichia coli M_{17} and Staphylococcus aureus P-209 was measured using the standard method of doubling dilution in beef-extract broth [9] with a bacterial load of 250,000 microbic units per ml of solution. The minimum inhibitory concentration (MIC) of the compound, i.e., the maximum dilution that completely suppresses the growth of test microbes, was taken as the effective dose. The antimicrobial activity of the new compounds (Table 2) was compared with that of mercuric chloride [8, 10] and lactate ethacrydine, the antimicrobial preparation used in medicine.

Anti-inflammatory properties were studied using a simulation of acute inflammatory edema, which involved injecting into the sole of the rear paw of white rats (body weight 180-200 g) 0.1 ml of a 1% karragenin solution (in line with the "Methodological Recommendations on the Experimental Study of Non-Steroid Anti-Inflammatory Substances," approved by the Pharmacological Committee of the USSR Health Ministry on November 11, 1982, Record No. 22). The anti-inflammatory effects were gaged from the degree of exudation inhibition (as a percentage of the control) for intraperitoneal injection of the compounds in the form of a suspension in 2% starch mucilage in doses of 50 and 150 mg/kg, comparing the results with amidopyrine [3] (Table 3).

Analgesic activity was investigated using the "hot plate" method [11] on white mice of 16-24 g body weight for intraperitoneal infusions of the compounds in dosages of 50 and 150 mg/kg. Reflex times were compared to those for amidopyrine (see Table 3).

The median lethal dose of the tested compounds was in excess of 500 mg/kg; they are considerably less toxic than the antimicrobial activity reference compounds – mercuric chloride (LD_{50} 3.9 mg/kg [11]) and lactate ethacrydine (LD_{50} 70.0 mg/kg), and less toxic than amidopyrine, which has both anti-inflammatory and analgesic properties (LD_{50} 249 mg/kg [3]).

From the antimicrobial study (see Table 2) it was found that 5-aryl-2,3-dihydro-3-furanones display slightly bacteriostatic properties for MIC between 250 and 1000 μg/ml; two compounds (VII and XVIII) are inactive. The greatest anti-inflammatory activity was exhibited by compound XIV, which in dosage of 150 mg/kg, or 0.28 LD_{50}, has a similar effect

TABLE 3. Anti-Inflammatory and Analgesic Activity of Compounds II, V, XIV, and XVI

Compound	LD_{50}, mg/kg	Dose, mg/kg	Anti-inflammatory activity		Analgesic activity			
			mean vol. increase of rat's paw, % of initial size	exudation inhibition, % of control	reflex time after injection of compound, h			
					0,5	1,0	2,0	3,0
II	>1000	50	—	—	15,7	15,4	17,4	14,5
		150	65,3	37,9	23,7	24,1	25,0	18,8
V	>1000	50	91,3	13,0	11,3	14,1	12,8	10,4
		150	59,0	43,8	—	—	—	—
XIV	540	50	94,6	10,0	10,9	13,7	12,9	11,6
	(394,9—745,2)	150	47,6	54,7	20,7	19,1	21,8	17,2
XVI	708,0	50	—	—	16,2	15,9	14,2	14,8
	(429,5—1019,5)	150	90,9	13,5	19,7	22,0	22,1	18,1
2% starch mucilage (control)	—	—	150,0	—	10,2	12,0	11,6	11,6
Amidopyrine	249	50	94,0	10,5	13,6	11,5	16,8	14,2
	(208,3—297,5)	100	42,0	60,0	27,6	18,6	17,7	14,1

to that shown by amidopyrine at almost $1^1/_2$ times the equitoxic dose (0.40 LD_{50}). Compounds II, XIV, and XVI showed slight analgesic activity, somewhat less than that of amidopyrine.

LITERATURE CITED

1. Yu. S. Andreichikov, V. O. Koz'minykh, and E. N. Manelova, Zh. Org. Khim., 21, No. 2, 402-406 (1985).
2. Yu. S. Andreichikov and V. O. Koz'minykh, Zh. Org. Khim., 25, No. 3, 618-622 (1989).
3. I. S. Berdinskii, O. G. Min'kina, and A. F. Goleneva, Biological Activity of the Products of Organic Synthesis and Natural Compounds [in Russian], Perm (1982), pp. 56-62.
4. V. O. Koz'minykh and E. N. Koz'minykh, Man: Horizons of Research [in Russian], Perm (1990), p. 77.
5. V. O. Koz'minykh, E. N. Koz'minykh, N. M. Igidov, and Yu. S. Andreichikov, Oxygen-Containing Heterocyclic Compounds [in Russian], Krasnodar (1990), p. 115.
6. V. O. Koz'minykh, E. N. Koz'minykh, and Z. G. Aliev, Zh. Org. Khim., 27, No. 7, 1509-1511 (1991).
7. V. O. Koz'minykh, N. M. Igidov, and E. N. Koz'minykh, Khim.-farm. Zh., No. 12, 43 (1991).
8. M. D. Mashkovskii, Medicinal Preparations [in Russian], Vol. 2, Moscow (1985), pp. 398, 409.
9. G. N. Pershin, Methods of Experimental Chemotherapy [in Russian], Moscow (1971), pp. 100, 109-117, 318.
10. Z. Franke, The Chemistry of Toxins [in Russian], Vol. 1, Moscow (1973), pp. 412-413.
11. L. Woolfe and A. D. McDonald, J. Pharmacol. Exp. Ther., 80, 300-307 (1944).