20. A. B. Swanson, D. D. Chambliss, J. C. Blomquist, et al., Mutat. Res., 60, 143-153 (1979); Ref. Zh. Biokhim., No. 16 - No. 16x 98 (1979).
21. S. Tanura, H. Okubo, and H. Kaneta, Nippon Nogei-Kagaku Kaishi, 28, 4-8 (1954); Chem. Abstr., 51 (1957).
22. C. A. Winter, E. A. Richley, and G. W. Nuss, Proc. Soc. Exp. Biol. (N.Y.), 111, 544-547 (1962).

SYNTHESIS, PROPERTIES AND BIOLOGICAL ACTIVITY OF 2-[N-(1^1-ADAMANTYL)-IMINO]-4-R^1-5-p-R-PHENYL-2,3-DIHYDRO-3-FURANONES AND THEIR HYDROLYSIS PRODUCTS

T. N. Yanborisov, S. N. Shurov, Yu. S. Andreichikov, I. P. Rudakova, É. N. Semenova, and G. N. Novoselova

UDC 615.276:[547.724+547.484.3].012.1.07

As is known, adamantane derivatives have a wide biological activity spectrum. Introduction of the adamantyl radical into a molecule frequently leads to modification of the biological activity, usually with its increase [5].

It has shown earlier that N-substituted 2-imino-5-aryl-2,3-dihydro-3-furanones are hydrolyzed under mild conditions to give N-substituted amides of aroylpyruvic acids [3]. Compounds were discovered among the amides of aroylpyruvic acids having anti-inflammatory activity [1].

In order to find biologically active compounds in the series of N-substituted 2-iminofuranones and their transformation products, we synthesized 2-[N-(1^1-adamantyl)imino]-4-R^1-5-p-R-phenyl-2,3,-dihydro-3-furanones (IIIa-f) and hydrolyzed them to N-(1^1-adamantyl)-amides of 4-p-R-benzoylpyruvic acids (IVa-d).

Furanones IIIa-f were obtained by the reaction of equimolar amounts of 5-p-R-phenyl-4-R^1-2,3-dihydro-2,3-furandiones (Ia-f) with adamantyl isocyanide (II) in a benzene-octane (1:1) mixture at 85-90°C (R^1 = H) or in boiling xylene at 140°C (R^1 = Br). The synthesized furanones IIIa-f are yellow crystalline compounds, which are readily soluble in $CHCl_3$, DMFA, and DMSO.

There appears an intense absorption in the 1705-1690 cm^{-1} region in the IR spectra of the synthesized compounds, which is due to the superposition of the stretching vibrations of the C=O and C=N bonds. The absorption in the 1595-1580 cm^{-1} region belongs to the stretching vibrations of the carbon-carbon double bonds of the heterocyclic ring and the substituent at the 5 position. In the PMR spectra there are signals of 15 adamantyl protons in the 1.85-1.91 ppm region, a singlet of the methine proton at the 4-position of the heterocyclic ring in the 5.98-6.15 ppm (for compounds IIIa-d), a quadruplet (for compounds IIIb-d,f) or a multiplet (for compounds IIIa,e) of aromatic protons in the 7.18-7.63 ppm region.

The furanones IIIa-f obtained undergo hydrolysis in an aqueous dioxane medium in the presence of equimolecular amounts of HCl. Hydrolysis of the 4-bromo-substituted furanones IIIe,f resulted in ω-chloro-p-R-acetophenones (Va,b) and 1-adamantylamine hydrobromide (VI), which are described in the literature. Hydrolysis of furanones IIIa-d unsubstituted at the 4-position resulted in N-(1^1-adamantyl)amides or 4-p-R-benzoylpyruvic acids (IVa-d), which occur in the enol form with an intramolecular hydrogen bond like the N-aryl analogs [2].

Perm Pharmaceutical Institute, Perm University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 12, pp. 1470-1473, December, 1989. Original article submitted April 5, 1989.

0091-150X/89/2312-0995$12.50

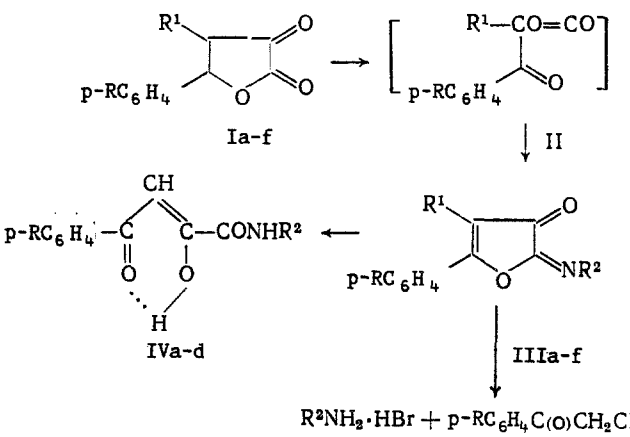
TABLE 1. Physicochemical Properties of Synthesized Compounds

Compound	Yield, %	mp., °C	Empirical formula
IIIa	95,1	174—176	$C_{20}H_{21}NO_2$
IIIb	98,2	178—179	$C_{21}H_{23}NO_3$
IIIc	68,1	180—182	$C_{20}H_{20}BrNO_2$
IIId	52,0	161—162	$C_{20}H_{20}ClNO_2$
IIIe	50,0	188—190	$C_{20}H_{20}BrNO_2$
IIIf	39,6	180—182	$C_{20}H_{19}BrClNO_2$
IVa	69,3	79—80	$C_{20}H_{23}NO_3$
IVb	82,4	146—148	$C_{21}H_{25}NO_4$
IVc	78,8	161—162	$C_{20}H_{22}BrNO_3$
IVd	63,9	159—161	$C_{20}H_{22}ClNO_3$

Note. The elemental analysis results and the calculated data coincide satisfactorily.

TABLE 2. Antimicrobal Activity and Toxicity of Synthesized Compounds

Compound	MIC, μg/ml		LD_{50}, mg/kg
	St. aureus	E. coli	
IIIa	250	250	27
IIIb	500	500	25
IIIc	1000	31	85
IIId	1000	7,8	89
IIIe	62	15,6	...
IIIf	1000	1000	...
IVa	1000	7,8	378
IVb	125	1000	3110
IVc	125	15,6	461
IVd	1000	31	490



R = H (Ia, e, IIIa, e, IVa, Va), Me (Ib, IIIb IVb), Br (Ic, IIIc, IVc), Cl (Id, f, IIId, f, IVd, Vb); R^1 = Br (Ie, f, IIIe, f), H (Ia-d, IIIa-d, IVa-d); R^2 – 1-adamantyl

The synthesized amides IVa-d are weakly colored crystalline compounds, which are soluble in $CHCl_3$, benzene, DMFA, and DMSO. The IR spectra of the synthesized compounds show stretching vibration bands of the NH bond in the 3390-3320 cm^{-1} region, of the amide carbonyl at 1675-1665 cm^{-1} region, and of the ketonic carbonyl group in the 1600-1595 cm^{-1} region. In the PMR spectra of the amides, signals of 15 adamantyl protons were observed with a center at about 1.85 ppm, a singlet of a methine proton in the 6.85-7.11 ppm, a broadened signal of the NH group proton in the 6.71-6.88 ppm region, and a broadened signal in the 14.15-14.65 ppm region due to an enol hydroxide proton.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on a UR-20 spectrophotometer in mineral oil. The PMR spectra were run on a RYA-2310 spectrometer in $CDCl_3$, using HMDS as an internal standard. The individual state of the compounds was confirmed by the TLC method on Silufol plates.

2-[N-(1^1-Adamantyl)imino]-5-p-R-phenyl-2,3-dihydro-3-furanones (IIIa-d). A mixture of 0.01 mole of 5-p-R-phenyl-2,3-dihydrofurandione (Ia,d) and 0.01 mole of 1-adamantyl isocyanide (II) was boiled for 1 h in 80 ml of a benzene—octane (1:1) mixture. After cooling the reaction mixture to 0°C, the precipitate was filtered off, and recrystallized from dry dioxane.

2-N-(1^1-Adamantyl)imino]-4-bromo-5-p-R-phenyl-2,3-dihydro-3-furanones (IIIe,f). A mixture of 0.01 mole of 4-bromo-5-p-R-phenyl-2,3-dihydrofurandione (Ie,f) and 0.01 mole of 1-adamantyl isocyanide (II) was boiled for 1 h in 50 ml of xylene. After cooling the reaction mixture to room temperature, 50 ml of hexane was added, and the mixture was allowed to stand at 5-0°C for 12 h. The product was filtered off and recrystallized from octane.

N-(1^1-Adamantyl)amides of 4-p-R-Benzoylpyruvic Acids (IVa-d). A 0.01 mole portion of 2-[N-(1^1-adamantyl)imino]-5-p-R-phenyl-2,3-dihydro-3-furanone (IIIa-d) was dissolved in 50 ml of dioxane and 0.01 mole of 5% HCl was added. After 3 h, the solvent was evaporated, and the residue was recrystallized from pentane (compound IVa) and from octane (IVb-d).

Hydrolysis of 2-[N-(1^1-Adamantyl)imino]-4-bromo-5-phenyl-2,3-dihydro-3-furanone (IIIe). A 0.01 mole portion of compound IIIe was dissolved in 50 ml dioxane, and 0.01 mole of 5% HCl was added. After 3 h the solvent was evaporated, the residue was suspended in benzene, and 1-adamantylamine hydrobromide salt (VI) was filtered off. Yield 40%. The IR and PMR spectra, and the analysis results matched an authentic sample. The filtrate was chromatographed on a column with Al_2O_3, using a benzene—hexane (1:1) mixture as eluent. After evaporation of the solvent, the ω-chloroacetophenone (Va) obtained was recrystallized from hexane. Yield 56%, mp 57-59°C (literature data [9]: mp 58-59°C). The IR and PMR spectra, and also a mixed melting point probe matched an authentic sample.

Hydrolysis of 2-[N-(1^1-Adamantyl)imino]-4-bromo-5-p-chloro-phenyl-2,3-dihydro-3-furanone (IIIf) was carried out in a similar way as the hydrolysis of compound (IIIe) Compound VI, yield 45%, and ω-chloro-p-chloroacetophenone (Vb), yield 51%, mp 101-102°C were isolated (literature data [9]: mp 101-102°C). The IR and PMR spectra matched an authentic sample.

EXPERIMENTAL (BIOLOGICAL)

Compounds IIIa-f and IVa-d were subjected to testing for antimicrobial activity with respect to two types of test-microbes: *St. aureus* and *E. coli*, using the method of double serial dilutions. After inoculation with the corresponding cultures, the test tubes were incubated at 37-38°C. The results were recorded after 18-20 h. The antimicrobial activity [the minimal inhibiting concentration (MIC) in μg/ml] was determined from the maximal dilution at which the growth of the microorganisms was no longer visually observed [6].

The acute toxicity of compounds IIIa-d, IVa-d was determined according to Pershin [7]. The investigations were carried out on white mice of both sexes, with an average weight of 18-20 g. The examination of the compounds was carried out intraperitoneally in 2% starch mucilage, each dose being tested on 5-7 mice.

The anti-inflammatory activity of compounds IVa-d was established by means of an inflammation model, produced by a subplanar administration of 0.1 ml of 1% solution of Carragheen [8].

The analgetic activity was evaluated by using the "hot plate" method [10]. The analgetic activity of the compounds was determined from the change in the latent period of a reflex.

The LD_{50} of compounds IVa-d is in the range within 378-490 mg/kg. Hence they are slightly toxic, while compound IVb having LD_{50} 3110 mg/kg is practically nontoxic [4]. The LD_{50} of furanones IIIa-d is 27-89 mg/kg, which is much higher than in the corresponding amides IVa-d.

Furanones IIIc,d,e exhibited pronounced anti-Staphylococcus activity at an MIC of 31; 7.8; 15.6 μg/ml, respectively. Adamantyl amides of benzoylpyruvic acids IVa-d displayed an anti-staphylococcus activity in the same MIC range (7.8-31 μg/ml), but at the same time were slightly toxic compounds.

Our investigations have shown that N-(1[1]-adamantyl)amides of 4-p-R-benzoylpyruvic acids do not have analgetic and anti-inflammatory activity, unlike their structural analog, 4-p-bromo-phenyl amide of benzoylpyruvic acid [1].

LITERATURE CITED

1. Inventor's Certificate No. 686408 (USSR); Otkrytiya, No. 16 (1981).
2. Yu. S. Andreichikov, Yu. A. Nalimova, S. P. Tendryakova, and Ya. M. Vilenchik, Zh. Org. Khim., **14**, No. 1, 110-163 (1978).
3. Yu. S. Andreichikov, S. N. Shurov, V. V. Zalesov, and N. N. Shapet'ko, Zh. Org. Khim., **22**, No. 4, 857-862 (1986).
4. N. F. Izmerov, I. V. Sanotskii, and K. K. Sidorov, Toxicometry Parameters of Industrial Poisons during a One Time Action [in Russian], Moscow (1977), p. 197.
5. M. E. Kovalev, Khim.-farm. Zh., **11**, No. 3, 19-27 (1977).
6. G. N. Pershin, Methods of Experimental Chemotherapy [in Russian], Moscow (1959), pp. 109-117, 456-460.
7. G. N. Pershin and M. L. Belen'kii, Elements of Quantitative Evaluation of Pharmacological Effect [in Russian], Leningrad (1983), p. 51.
8. L. S. Salyamon, Therapeutic Control of Inflammatory Process [in Russian], Leningrad (1958), pp. 11-43.
9. Beilsteins Handbuch der Organischen Chemie, Vol. 7, Berlin (1925), p. 285.
10. J. Woolfe and A. Macdonald, J. Pharmacol. Exp. Ther., **80**, 300 (1964).

SULFUR-CONTAINING 5-HYDROXYBENZOFURAN DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY

S. A. Zotova, V. I. Shvedov, N. T. Pryanishnikova, and L. M. Demina

UDC 615.216.2:547.722.1].012.1

As a result of the interest shown in benzofuran derivatives as compounds having anesthetic [5], cardiovascular [1] and other types of activities, we undertook in the present work the synthesis of sulfur containing derivatives of 2-methyl-5-hydroxybenzo-furan and studied their anesthetic properties.

We used as starting compounds the previously described 2-bromomethyl-3-ethoxycarbonyl-5-acetoxy-(I) [2], 2-bromomethyl-3-ethoxy carbonyl-5-methoxy-(II) [7] and 2-bromomethyl-3-ethoxy-carbonyl-5-methoxy-6-bromobenzofurans (III) [3]. 2-Bromomethyl-3-acetyl-5-acetoxybenzofuran (IV) was obtained by us for the first time by bromination of 2-methyl-3-acetyl-5-acetoxybenzofuran [8] with N-bromosuccinimide. The ethyl ester of 2-methyl-5-hydroxybenzofuranyl-3-acetic acid (V) was obtained from the known 2-methyl-5-methoxybenzofuranyl-3-acetic acid [9] by demethylation with HBr and subsequent esterification with ethanol in the presence of a KU-2-8 resin. Ester V was acetylated by Ac_2O to the corresponding 5-acetoxy derivative (VI). Still another starting compound in the synthesis of the desired compounds was obtained — the ethyl ester of 2-bromomethyl-5-acetoxybenzofuranyl-3-acetic acid (VII) by the action of N-bromosuccinimide on compound VI. In the NMR spectrum of compound VII, the presence of two singlets with δ 3.6 and 4.6 ppm was observed, which indicated that the bromination occurred at the methyl group in the 2-position.

S. Ordzhonikidze All-Union Scientific-Research Chemical Pharmaceutical Institute, Moscow. Order of Lenin Central Advanced Training Institute for Physicians, Ministry of Public Health, Moscow.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 12, pp. 1473-1477, December, 1989. Original article submitted March 30, 1989.

0091-150X/89/2312-0998$12.50