SYNTHESIS OF ANTIVIRAL β-HYDRAZONES OF ANGULAR BENZISATINS

L. I. Mazhilis, A. P. Stankyavichyus,
P. B. Terent'ev, L. V. Korobchenko,
and E. I. Boreko

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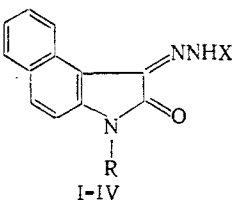
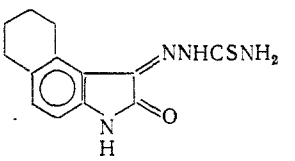
In extensive research carried out on the antiviral activity of compounds structurally similar to methisazone (1-methylisatin-3-thiosemicarbazone, see review [2]), the corresponding benzo derivatives have been insufficiently investigated [5]. It was our aim to synthesize and study the properties of β-hydrazones of angular benzisatins (I-XVI), while taking into account the differences in the spatial distribution and nature of the annelated rings, as well as the nature of the hydrazone component.



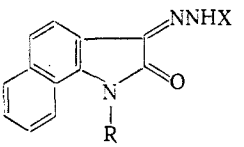
I-IV

syn-Benzo[e]-isatin-β-hydrazones: R = H (I-III); X = $CONH_2$ (I); $CSNH_2$ (II); $C(=NH)NH_2 \cdot HCl$ (III); R = Me (IV), X = $CSNH_2$ (IV)



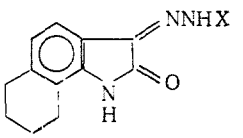
V

syn-6,7,8,9-Tetrahydrobenz[e]-isatin-β-thiosemicarbazone (V)



VI-X

Benz[d]-isatin-β-hydrazones R = H (VI-IX); X = $CONH_2$-syn(VI), anti (VII); $CSNH_2$-syn (VIII); $C(=NH)NH_2 \cdot HCl$-syn (IX); R = Me (X); X = $CSNH_2$-syn (X)



XI-XVI

6,7,8,9-Tetrahydrobenz[d]-isatin-β-hydrazones: X = $CONH_2$-syn (XI), anti (XIII); $CSNH_2$-syn (XIII); $C(=NH)NH_2 \cdot HCl$-syn (XIV); $C(=NH)NH_2$-syn (XV); COPh-syn (XVI)

The β-hydrazones formed in the reaction of benz[e]isatins with hydrazine derivatives exist in the syn form exclusively as a result of the characteristic features of the spatial distribution of the rings in these structures. In β-hydrazones of benzisatins of the [g]-series, a syn–anti isomerism is possible. Thus, in the reaction of 6,7,8,9-tetrahydrobenz[g]isatin with semicarbazide hydrochloride, a mixture of syn- and anti-semicarbazones XI and XII was obtained. The anti-isomer was isolated in the pure state by crystallization of the mixture from ethanol; action of hydrochloric acid on the mixture led to the formation of the syn-isomer. The mass-spectrometric behavior of the two forms is similar. The main process in the dissociation of the molecular ions during the electron impact is the loss of the HNCO fragment (an intense peak with m/z 215). At the same time, comparison of the PMR and UV spectra of products XI and XII makes it possible to establish their steric structure unequivocally. Thus, in the anti-semicarbazone XII, the proton at C_4 undergoes a stronger descreening action of the hydrazone group; moreover, because of the formation of a hydrogen bond with the α-carbonyl group of the pyrrole ring, the signal of the —N—NH— proton of syn-semicarbazone XI is shifted downfield compared with the anti-isomer. The shift of the longwave absorption bands in the UV spectrum of the syn-isomer XI, compared

Z. Yanushkyavichyus Scientific-Research Institute of the Physiology and Pathology of the Cardiovascular System. M. V. Lomonosov Moscow State University. Belorussian Scientific-Research Institute of Epidemiology and Microbiology, Minsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 5, pp. 580-583, May, 1987. Original article submitted March 4, 1986.

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TABLE 1. Synthesis and Physical Properties of Benzisatin β-Hydrazones

Compound	Content of solvents in reaction, ml		Duration of boiling, min	Yield, %	Solvent for crystallization*	mp, °C	R_f
	water	ethanol					
I	10	15	120	100	A	305—7	0,28
II	10	15	30	85,7	A	312—4	0,53
III	20	—	180	85,6	—	285→323**	—
IV	35	20	35	100	A	305—6	0,56
V	10	15	30	79,2	B	280—1	0,71
VI+VII	35	8	25	100	—	—	—
VI	—	—	—	—	B	339—40	0,51
VII	—	—	—	—	C	348—9	0,05
VIII	10	15	10	85,7	B	292—3	0,71
XI	20	20	15	84,4	—	285→335**	—
X	20	10	30	100	A	270—1	0,78
XI+XII	20	15	3	76,9	—	—	—
XI	—	—	—	—	B	285—6	0,22
XII	—	—	—	—	C	288—9	0,05
XIII	20	15	30	100	B	266—8	0,71
XIV	20	—	15	62,3	—	270—1	—
XV	—	—	—	—	—	287—8	—
XVI	20	25	15	84,4	A	282—3	0,78

*A, dimethylformamide—water; B, ethanol—water—hydrochloric acid; C, ethanol.

**Splitting of HCl takes place, followed by melting.

with the anti-XII, indicates a greater coplanarity of the former, which agrees well with the steric models of the compounds.

Similar phenomena were also noticed for syn- and anti-semicarbazones of the aromatic series VI and VII.

On transition from semicarbazones to thiosemicarbazones and further to guanyl and benzoylhydrazones of the [g]-series, in analogy with the previously studied complex isatin structures [2], the corresponding anti-forms were found to be less stable, and only the corresponding syn-forms VIII-X, XIII-XVI were isolated in the pure state.

Study of the antiviral activity of the benzisatin derivatives synthesized led to the discovery of several regularities, differing from the two noted activity tendencies of the hydrazones of the isatin series [2]. Thus, benz[e]isatin syn-β-thiosemicarbazone II was found to be most active. The compound is not toxic for fibroblasts of embryo cultures (FEC) in a concentration of 800 μg/ml (maximal for the concentrations studied). At this concentration and less, up to 50 μg/ml, a complete absence of platelets, formed by the smallpox vaccine, is observed, which, taking into account the amount of the introduced virus, corresponded to lowering of the virus titer, compared with the control cultures, by more than 1.62 log BOU/ml. Thus, the ratio of the maximal tolerable concentration (MTC)/minimal active concentration for a given compound was less than 16. The remaining compounds did not exhibit activity.

Thus, in this series, the antiviral properties were most pronounced in a compound containing an [e]-annelated benzene ring and a β-thiosemicarbazone function, and with no substituent at the nitrogen atom. Examining the literature data on hydrazones of isatins not containing additionally annelated rings [2], we should note the fact that besides the thiosemicarbazones, β-guanylhydrazones also exhibited a pronounced activity, which was not observed in the benzisatin series. Moreover, in the case of isatins, the 7-substitution has a favorable effect, which in a sense is analogous to [g]-annelation; in fact, in the benzisatin series, even the compound with an opposite disposition, an [e]-disposition of the annelated ring, is more active. And finally, methisazone, the β-thiosemicarbazone of N-methylisation, is appreciably more active than its unsubstituted analog, while in the series of the benzisatin structures studied, N-substitution did not lead to a decrease in the activity.

We believe that the above tendencies of the antiviral activity of β-hydrazones of angular benzisatins may be of value in further search for highly effective antiviral compounds among members of this series.

EXPERIMENTAL CHEMICAL

The PMR spectra were recorded in a Hitachi–Perkin–Elmer spectrometer (Japan) with a working frequency of 90 MHz, using HMDS as internal standard and deuterated DMSO as solvent; the chemical shifts (in ppm) are given on the δ scale. The mass spectra were taken on a MAT-112 mass spectrometer (GFR) with a direct introduction of the substance into the ionic source, at an ionization energy of 70 eV. The UV spectra were recorded on a Specord UV-VIS spectrophotometer (GDR), using 95% ethanol as solvent. The TLC was carried out on Silufol UV-254 plates (Czechoslovakia), using a CCl_4–ethyl acetate (1:1) mixture as eluent; the spots were detected in visible and UV light.

The starting benzisatins were synthesized by known methods [2-6].

General Procedure for the Reaction of Benzisatins with Hydrazine Derivatives. A 0.00265-0.0027 mole portion of a substituted hydrazine hydrochloride (in the preparation of XVI – benzoyl-hydrazine and 1 ml of 10% HCl) and ethanol are added to a suspension of 0.0025 mole of benzisatin in water. The mixture is boiled, cooled, and the precipitate that separates is filtered with suction, washed with water, and dried. The amounts of water and ethanol in the reaction mixture, times of boiling, and also the yield of the hydrazones formed, melting points, and solvents for crystallization are listed in Table 1.

syn-Benz[g]isatin-3-semicarbazone (VI). A 0.2-g portion of a mixture of VI and VII is dissolved in 40 ml of ethanol, 4 ml of concentrated HCl is added, and the mixture is left to stand at room temperature to complete evaporation. Yield quantitative. The melting point and R_f are given in Table 1. Found, %: N 22.27. $C_{13}H_{10}N_4O_2$. Calculated, %: N 22.04. PMR spectrum: 6.82 br.s (NH_2), 7.3-7.7 (m, 4H), 7.84 (d.d, 1H), 8.04 (d.d, 1H) – aromatic H; 11.61 s (pyrrole H), 11.68 s (=N–NH–).

anti-Benz[g]isatin-3-semicarbazone (VII). A 0.2-g portion of a mixture of VI and VII is crystallized from 16 ml of ethanol to yield 0.11 g of a yellow product. The melting point and R_f are given in Table 1. Found, %: N 22.18. $C_{13}H_{10}N_4O_2$. Calculated, %: N 22.04. PMR spectrum: 6.78 br. s (NH_2); 7.3-7.7 (m, 3H), 7.84 (d.d, 1H), 8.12 (m, 2H) – aromatic H; 11.37 s (pyrrole H); 10.26 s (=N–NH–).

syn-6,7,8,9-Tetrahydrobenz[g]isatin-3-semicarbazone (XI) was obtained from a mixture of XI and XII in a similar way as syn-semicarbazone VI. Found, %: N 22.05. $C_{13}H_{14}N_4O_2$. Calculated, %: N 22.04. PMR spectrum: 1.5-1.8 (m, 4H), 2.3-2.7 (m, 4H) – aliphatic H; 6.68 (d, H_5); 6.96 br. s (NH_2); 7.23 (d, H_4); 10.86 s (pyrrole H), 11.61 s (=N–NH–).

Mass spectrum, m/z (relative intensity, %): 258 (16), 215 (100), 187 (21), 186 (18), 171 (13), 170 (11), 159 (16), 158 (21), 156 (11), 143 (9), 131 (9). UV spectrum, λ_{max}, nm (log ε):208 (4.41), 229 (3.95), 273 (4.14), 343 (4.07).

anti-6,7,8,9-Tetrahydrobenz[g]isatin-3-semicarbazone (XIII) was isolated from a mixture of XI and XII in a similar way as anti-semicarbazone VII. Found, %: N 21.97. $C_{13}H_{14}N_4O_2$. Calculated, %: N 21.70. PMR spectrum: 1.4-1.8 (m, 4H), 2.3-2.7 (m, 4H) – aliphatic H; 6.65 (d, H_5), 6.76 (br. s (NH_2), 9.87 s (=N–NH–), 10.44 s (pyrrole H). Mass spectrum: 258 (16), 215 (100), 187 (44), 186 (40), 170 (27), 159 (27), 158 (37), 156 (20), 144 (32), 143(20), 130 (20). UV spectrum, λ_{max}, nm (log ε): 207 (4.33), 228 (3.39), 258 (4.12), 325 (4.04).

syn-6,7,8,9-Tetrahydrobenz[g]isatin-3-guanylhydrazone (XV). A 0.3-g portion of hydrochloride (XIV) is dissolved in 200 ml of water and a mixture of 25% ammonia and water (1:10) is added dropwise to pH 10.0 according to universal indicator paper. A yellow precipitate separates, which is suction-filtered, washed with water, and dried. The melting point and R_f are given in Table 1. Found, %: N 27.13. $C_{13}H_{15}N_5O$. Calculated, %: N 27.22. PMR spectrum: 1.5-1.8 (m, 4H), 2.3-2.7 (m, 4H) – aliphatic H; 6.68 (d, H_5). 6.90 br. s (NH_2), 7.24 (d, H_4), 7.55 br. s (guanyl NH), 10.78 s (pyrrole H), 11.60 s (=N–NH–).

EXPERIMENTAL BIOLOGICAL

The antiviral properties were studied in experiments on tissue cultures infected by smallpox, simple herpes of the first type, classical plague, Newcastle disease, vesicular stomatitis, Venezuela equine encephalomyelitis, and ECHO 6 viruses by the primary screening method [7], followed by determination of the quantitative parameters of the revealed antiviral action by reduction of platelets, as described in [1].

The studies with the ECHO virus were carried out on single layer culture passivated by skin-muscular cells of human embryo, and with the remaining viruses, on single layer cultures of primarily-trysinylated FEC.

The determination of the quantitative characteristics of the antiviral effect was preceded by finding the MTC of the compounds studied for noninfected tissue cultures after 96 h incubation in their presence.

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STRUCTURE–ACTIVITY RELATIONSHIPS IN FLAVONOIDS.

3. PREDICTION OF NOVEL CHALCONES

É. T. Oganesyan, V. I. Yakovenko, and V. S. Cherevatyi

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In designing the synthesis of the chalcones previously described by us [9], we employed a logico-structural approach, taking into account features characterizing antibacterial activity. In the dialogical extension of the description, we adopted the resorcinol, salicylic acid, and saligenin fragments as nonresolvable features [7, 8, 11]. The use of these in the synthesis of the chalcones enabled them to be converted into resolvable features.

In making further predictions in the chalcone series using the logicostructural approach, we set ourselves the task of synthesizing compounds with given antimicrobial, capillary strengthening, and antiinflammatory activity, differing from those described in communication 1 [9] in being of lower toxicity.

Biological test results for the chalcones prepared by us enabled an initial choice of features to be made. For this purpose, substituents in positions 2'-5' of fragment A, which dictate the type of biological activity, were chosen as the reference set of parameters. The process of generation of the structures is shown in Fig. 1.

Also used as parameters were the hydrophobicity constants (π-constants), and the sums of the contributions of the electronic constants ($\Sigma\bar{\sigma}$) of the substituents.

A study of the correlations between physicochemical parameters, structure, and activity in chalcones [10] has shown that for the occurrence of antimicrobial, capillary strengthening, and antiinflammatory activity a necessary condition is the presence of hydroxyl groups in positions 2' and 4' of fragment A. This structural fragment of the molecule corresponds to a $\Sigma\bar{\sigma}$ value of -0.740 and $\pi = -0.324$. It appears that this combination of hydroxyl groups in fragment A is responsible for the degree of universality of the 2',4'-dihydroxychalcone molecule. On the other hand, the introduction of the latter substituents

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