SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-OXOINDOLINYLIDENE-3-HYDRAZIDES OF OXANILIC ACIDS

V. V. Bolotov, A. Nambelbai,
S. M. Drogovoz, and V. P. Vereitinova

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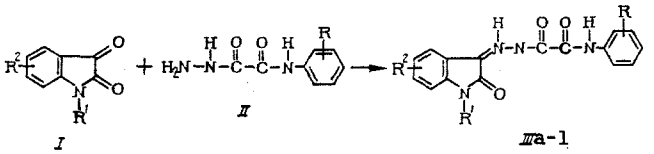
In the series of 2-oxoindolinylidene-3-hydrazides of aliphatic acids there are substances that exhibit a high degree of antiinflammatory activity [2]. However, there have been no biological or chemical studies of the 2-oxoindolinylidene-3-hydrazides of oxanilic acids. These compounds would seem to be of doubtless interest in the search for substances with anti-inflammatory and analgesic activity since they constitute structural analogs of the aforementioned compounds and contain residues of isatin and oxanilic acid hydrazides among which there are known active analgesics [3, 5].

2-oxoindolinyliden-3-hydrazides of oxanilic acid (IIIa-l) were synthesized by the condensation of isatins (I) with oxanilic acid hydrazides (II) which were obtained by method [4] in DMFA.



I II IIIa-l

R = 2-COOH (IIIa-d,l), H (IIIe), 2-Cl (IIIf), 4-COOH (IIIg), 4-NO_2 (IIIh), 4-OH (IIIi), 4-Br (IIIj), 3-COOH (IIIk), R′ = H (IIIa,b,d-l), CH_3 (IIIc);
R′ = H (IIIa), 5-Br (IIIb,c), 5-NO_2 (IIId), 7-COOH (IIIe-l).

The hydrazides IIIa-l are yellow-brown crystalline substances that are insoluble in water. They dissolve in DMFA and dioxane.

The structures of the resultant compounds were confirmed by their IR-spectra. The IR-spectra of substances IIIa-l exhibited broad bands in the 3400-2800 cm^{-1} region (ν-associated NH and OH), two or three intensive bands with inflections on the high-frequency side in the region 1720-1680 cm^{-1} (ν C = O), 1540-1507 cm^{-1} (δNH). Bands in the region 1520-1500 cm^{-1} ($\nu_{as}NO_2$) and 1350-1340 cm^{-1} ($\nu^{s}NO_2$) are also characteristic of the spectra for compounds IIId, h. Constants for the substances IIIa-l are given in the Table.

EXPERIMENTAL—CHEMICAL

The IR-spectra were recorded on a UR-20 spectrophotometer (GDR) in KBr pellets (substance concentration 1%).

2-Carboxyoxanilic 2-Oxoindolinyliden-3-hydrazide (IIIa). A 2.23-g portion (0.01 mole) of 2-carboxyoxanilic hydrazide was added to 1.47 g (0.01 mole) of isatin in 15 ml of DMFA. The reaction mixture was boiled for 1 h and decanted into water. The solution was acidified by HCl up to an acid reaction and the resultant precipitate was filtered off and redissolved in DMFA. The solution was then cooled, acidified by HCl to a weak reaction point, and left for 12 h. The precipitate which formed on standing was filtered off and washed with alcohol. Compounds IIIb-l were obtained in a similar fashion from corresponding isatins and oxanilic hydrazides.

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TABLE 1. Oxanilic 2-oxoindolinyliden-3-hydrazides (IIIa-l)

Compound	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated, %
IIIa	65	330	15,98	$C_{17}H_{12}N_4O_5$	15,90
IIIb	80	320—322	12,86	$C_{17}H_{11}BrN_4O_5$	12,99
IIIc	78	308—310	12,69	$C_{18}H_{13}BrN_4O_5$	12,58
IIId	82	332—333	17,57	$C_{17}H_{11}N_5O_7$	17,62
IIIe	65	340—342	15,92	$C_{17}H_{12}N_4O_5$	15,90
IIIf	67	346—348	14,56	$C_{17}H_{11}ClN_4O_5$	14,48
IIIg	76	316—318	14,28	$C_{18}H_{12}N_4O_7$	14,13
IIIh	61	360—362	17,75	$C_{17}H_{11}N_5O_7$	17,62
IIIi	73	310—312	15,47	$C_{17}H_{12}N_4O_6$	15,21
IIIj	63	400	12,83	$C_{17}H_{11}BrN_4O_5$	12,99
IIIk	54	270—272	14,25	$C_{18}H_{12}N_4O_7$	14,13
IIIl	69	336—338	14,36	$C_{18}H_{12}N_4O_7$	14,13

Note. All compounds decomposed on melting.

EXPERIMENTAL—BIOLOGICAL

Acute inflammation induced by the subplantar injection of 0.1 ml of 2.5% formalin solution into the femur mass of a mouse's rear paw was used to test the antiinflammatory activity of the IIIa-l hydrazides on mice weighing 18-20 g [6]. The compounds were administered orally as a 1% aqueous suspension, stabilized by Tween-80 (1 drop per 2 ml of suspension) 2 h before and 5 and 18 h after the formalin was injected in doses that were equimolecular to the ED_{50} for indomethacin, i.e., 15 mg/kg, which was administered in parallel tests. The control animals were given a corresponding volume of water with Tween-80. The antiinflammatory activity of the substances under study was evaluated by the degree of anti-exudative action 24 h after the injection of formalin.

The analgesic activity of compounds IIIa-l was determined in the mice by the spasms induced by the intraperitoneal injection of a 3% acetic acid solution at a dosage of 300 mg/kg. The test substances were administered orally as a 1% aqueous suspension, obtained as described above, 1 h before the tests at doses equimolecular to the ED_{50} for analgin, i.e., 55 mg/kg [7] which was also administered in a parallel test. Analgesic activity was evaluated by the compound's ability to reduce (in percent) the number of spasms (counted within a 20 min period) in comparison to the control animals [8].

DISCUSSION AND RESULTS

Our experiments showed that compounds IIIa, h, j, and l exhibit antiinflammatory activity. Their activity is two times weaker than that of indomethacin. The rest of the compounds had no effect on the inflammatory process.

The compounds under study exhibited analgesic activity to a greater extent. That activity for compounds IIIb, d, j, and l was equivalent to the analgesic action of analgin. The analgesic effect of hydrazides IIIc, f, h, and i was one-half of analgin's activity, and the rest of the compounds exhibited no analgesic action.

We determined the acute toxicity in mice for the most active compounds IIIb, d, j, and l by the oral administration of the substances in accordance with the method [1]. The LD_{50} of the aforementioned compounds (in mg/kg) were 3500, 5000, 5000, 3500 respectively (the LD_{50} for indomethacin was 47 and it was 570 for analgin).

A comparison of the compound's structure to their biological activity demonstrated that the antiinflammatory and analgesic properties of substances IIIa-l simultaneously depend on the nature and position of the substituent in the isatin residue and on the oxanilic acid residue in the benzene ring. Simultaneous antiinflammatory and analgesic activity was exhibited by hydrazides IIIh, j, and l which constitute derivatives of isatin-7-carboxylic acid and contain residues of 2-carboxy-, 4-brom-, and 4-nitrooxanilic acids.

The IIIb and d derivatives of 5-brom and 7-nitroisatin exhibited only analgesic action which disappeared when the hydrogen atom in position 1 of the isatin compound was replaced by a methyl group (compound IIIc).

Compound IIIa, which is a derivative of isatin and 2-carboxyoxanilic acid, exhibited antiinflammatory activity only.

Thus, the oxanilic 2-oxoindolinyliden-3-hydrazides are compounds with low toxicity and constitute a promising group of substances in the search for compounds with antiinflammatory and analgesic activity.

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N-ARYLACETYLFORMAMIDOXIME THIOSEMICARBAZONES AND THEIR TUBERCULOSTATIC PROPERTIES

S. F. Khalilova, I. A. Poplavskaya, L. I. Blonskaya, and Ya. A. Blagodarnyi

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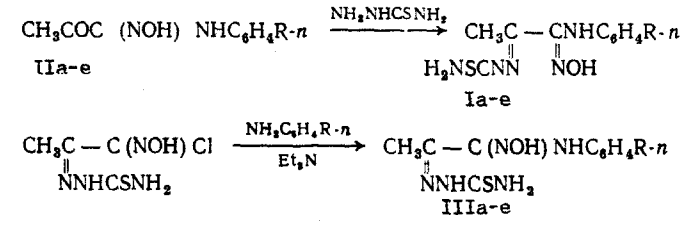
Thiosemicarbazones of certain carbonyl compounds have long been recognized as antitubercular agents [5]. We synthesized a number of N-arylacetylformamidoxime thiosemicarbazones in order to study their biological properties.

Carbonyl group derivatives of acetylformamidoximes can be obtained by two methods: 1) from acetylformamidoximes and hydrazines (or hydroxylamine), or 2) by the interaction of appropriate derivatives, i.e., α-chloro-α-isonitroacetone and amines. As a rule, this results in identical products [2] that have been antistructure. This is due to the antistructure of the starting hydroxamolchlorides and the steric orientation involved in the addition of amines to their dehydrochlorination products, i.e., nitrile oxides, with the resultant formation of Z-amidoximes [6, 7].

In the case of acetylformamidoxime thiosemicarbazones, the compounds (Ia-e) obtained from N-arylacetylformamidoximes (IIIa-e) and thiosemicarbazide are different from substances synthesized by the counter-flow method. Whereas the classification of amphi-isomers [4] can be given to thiosemicarbazones (IIIa-e) synthesized from arylamines and from α-isonitrosoacetone thiosemicarbazone (IV) which has an amphi-structure, compounds Ia-e, as is the case with other derivatives of acetylformamidoximes (e.g., semicarbazones [3]), can be considered to be anti-isomers.



Ia, IIa, IIIa: R = CH_3; Ib, IIb, IIIb: R = CH_3O; Ic, IIc, IIIc: R = C_2H_5O; Id, IId, IIId, R = Cl; Ie, IIe, IIIe: R = $N(CH_3)_2$

The acetylformamidoximes IIa-e were reacted with thiosemicarbazide in an acid medium (pH 3.0-4.0) at room temperature. The resultant thiosemicarbazides Ia-e constituted stable easily crystallized substances that formed hydrochlorides which retained, however, an excess of HCl so that satisfactory element analysis data could only be obtained for the hydrochlorides of Ia and Ib.

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