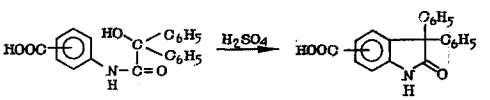
SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF SOME 3,3-DIPHENYL-2-OXOINDOLINE CARBOXYLIC ACIDS AND THEIR AMIDES

V. V. Bolotov, P. A. Petyunin,
V. V. Drugovina, and A. I. Bereznyakova

UDC 615.276:547.756

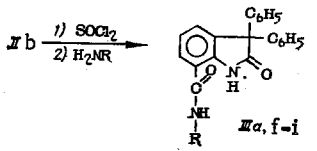
In an earlier paper [1], we described some 3,3-diaryl-2-oxoindoline-1-acetic acids and their derivatives. Some of these compounds were found to be more effective anti-inflammatory agents than butadione, and we have now synthesized and studied the anti-inflammatory activity of some related compounds — the 3,3-diaryl-2-oxoindolinecarboxylic acids (IIa-c), which have a carboxyl group attached to the fused benzene ring, and some derivatives of these compounds.



Ia-c (in Ia, the COOH group is at position 4, Ib at position 2 of benzene ring).

IIa-c (in IIa, the COOH group is at position 5, IIb at position 4, and IIc at position 7).

IIc $\xrightarrow[2.\ H_2NR]{1.\ SOCl_2}$



IIIa, f-i

The acids IIa-c were prepared by the intramolecular cyclization of the arylamides of the diarylglycolic acids Ia-c using concentrated sulfuric acid [2, 3]; 3,3-diphenyl-2-oxoindoline-4-carboxylic acid (IIb) had not been prepared before. Cyclization of the arylamide Ib can proceed in two ways, to give either the acid IIb or 3,3-diphenyl-2-oxoindoline-6-carboxylic acid (cf. [4]). However, we isolated only one acid, the structure of which was determined from the NMR spectrum of its ethyl ester; in this spectrum, the protons of the two phenyl substituents on the heterocyclic ring give rise to a signal (7.08 ppm) which overlaps a multiplet (7.30 ppm) from the three protons of the fused benzene ring. There is no deshielding effect on the protons at positions 6 and 7; the proton at position 5 is weakly deshielded because steric hindrance prevents free rotation of the ester group at position 4.

The acid IIb is a colorless, crystalline substance, insoluble in water and soluble in dioxane, alcohol, and acetic acid.

The IR spectrum of the acid IIb contains absorptions at 3260 cm^{-1} (NH), 3070-2570 cm^{-1} (OH), and 1704 cm^{-1} (ring C=O), and 1724 cm^{-1} (carboxyl) C=O).

Because some amides of 2-oxoindoline-3-carboxylic acid are known to have high antiinflammatory activity [5], we synthesized a number of amides of general formula IIIa-i and examined their activity.

The amides IIIa-i (Table 1) were prepared by the reaction of the hydrochloride of IIc with the appropriate amine, or by aminolysis of the ester. The amides III are colorless crystalline substances, soluble in alcohol, dioxane, and acetic acid. The IR spectra of the amides IIIa-i contain absorptions at 1720-1695 cm^{-1} (C=O of the lactam ring) and at 1650-1635 cm^{-1} (C=O of the amide group).

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 14, No. 12, pp. 39-42, December, 1980. Original article submitted February 18, 1980.

 0091-150X/80/1412-0858$07.50

TABLE 1. Amides of 3,3-Diphenyl-2-oxoindoline-7-carboxylic Acid

Compound	R	Yield, %	Melting point, °C	Found, % N	Empirical formula	Calc., % N
IIIa	H	72	263—4	9,03	$C_{21}H_{16}N_2O_2$	8,53
IIIb	OH	75	206 (with decomposition	7,84	$C_{21}H_{16}N_2O_3$	8,13
IIIc	CH_2CH_2OH	79	186—187	7,53	$C_{23}H_{20}N_2O_3$	7,52
IIId	CH_2CH_2Cl	62	183—185	7,09	$C_{23}H_{19}ClN_2O_2$	7,17
IIIe	$CH_2CH_2N(CH_2)_4O$	51	210—212	9,43	$C_{27}H_{27}N_3O_3$	9,51
IIIf	C_6H_5	73	251—252	6,95	$C_{27}H_{20}N_2O_2$	6,93
IIIg	n-$C_6H_4OCH_3$	80	223—224	6,55	$C_{28}H_{22}N_2O_3$	6,45
IIIh	n-C_6H_4OH	61	275 (with decomposition	7,02	$C_{27}H_{20}N_2O_3$	6,66
IIIi	$=C_6H_4COOH$	78	263—244	6,58	$C_{28}H_{20}N_2O_4$	6,25

Note. Compounds IIIg-i were recrystallized from acetic acid, IIIa and f from a mixture of alcohol and dioxane.

EXPERIMENTAL (PHARMACOLOGICAL)

The pharmacological screening of the acids IIa-c and the amides IIIa, b, and e-i for antiinflammatory activity was conducted on models of acute inflammation in mice weighing 19-20 g using the method described in [6]; the activity was compared with that of butadione. Antiinflammatory activity was judged by the ability of the compounds to lower formalin-induced edema of the paw. Compounds were introduced in doses of 0.15 g/kg, 2 h before the formalin injection and 5 and 18 h after it. The decrease in the edema was determined 24 h after the introduction of the formalin.

It was found that the antiinflammatory activity of the acids IIa-c depends on the position of the carboxyl group. Compound IIc was 1.7 times as active as butadione, IIb was somewhat less active than butadione, and IIa showed no antiinflammatory activity.

The greatest activity was shown by compounds with an anthranilic acid residue in the molecule.

The antiinflammatory activity of the amides IIIa and g was slightly higher than that of butadione and that of IIIb, d, and i somewhat lower. Compounds IIIe and h showed no anti-inflammatory activity.

The acute toxicity of the more active compounds was determined by intraperitoneal injection [7]. The LD_{50}'s for compounds IIc, IIg, and IIIa were 734, 600, and 1410 mg/kg respectively. The results of the biological tests were treated statistically (P = 0.05-0.001).

EXPERIMENTAL (CHEMICAL)

A UR-20 spectrophotometer was used for IR spectra which were run as KBr pellets (1% of compound in KBr). NMR spectra were taken in CF_3COOH at 40 MHz using cyclohexane as an internal standard.

3-Carboxyanilide of Benzilic Acid (Ib). To a solution of 6.86 g (0.05 mole) of m-aminobenzoic acid in 30 ml of acetic acid was added 7.03 ml (0.05 mole) of triethylamine and 13.26 g (0.05 mole) of diphenylchloroacetyl chloride. The mixture was left at room temperature for 30 min, heated to boiling, and then allowed to cool and 1 ml of 5% sodium hydroxide solution added. The mixture was again heated to boiling, and after the addition of 10 ml of water, left to crystallize. A yield of 7.73 g (42%) of Ib with mp 213-215°C (with decomp. from acetic acid) was obtained. Found, %: N 3.92. $C_{21}H_{17}NO_4$. Calculated, %: N 4.03.

3,3-Diphenyl-2-oxoindoline-4-carboxylic Acid (IIb). Concentrated sulfuric acid was slowly added to a solution of 7.73 g of Ib in 170 ml of acetic acid until no more color was produced (about 380 ml). The solution was poured into 2.5 ml of water, and the precipitate filtered off, and recrystallized from dioxane. A yield of 4.7 g (69%), mp 268-270°C (with decomp.) was obtained. Found, %: N 4.26. $C_{21}H_{13}NO_3$. Calculated, %: N 4.25.

Ethyl 3,3-Diphenyl-2-oxoindoline-4-carboxylate. To 1 g (0.003 mole) of IIb dissolved in a mixture of 15 ml of absolute ethanol and 5 ml of dioxane was added 3 ml of concentrated

sulfuric acid. The solution was refluxed for 10 h and the precipitate which formed on cooling filtered off (1 g) and recrystallized from ethanol. A 92% yield of product with mp 237°C was obtained. Found, %: N 3.94. $C_{23}H_{19}NO_3$. Calculated, %: N 3.92.

Amide of 3,3-Diphenyl-2-oxoindoline-7-carboxylic Acid (IIIa, f-i). A mixture of 3.3 g (0.10 mole) of IIc and 10 ml of thionyl chloride was refluxed for 3 h. The excess thionyl chloride was removed *in vacuo*, and to the residue was added 25 ml of dry benzene and 0.02 mole of the amine (for IIa, the benzene solution of the hydrochloride was poured into excess concentrated ammonia solution). After standing for 30 min, the solution was refluxed for 15 min, concentrated, and the precipitate obtained filtered off, washed with water, acidified with hydrochloric acid and recrystallized.

3,3-Diphenyl-2-oxoindoline-7-carbohydroxamic Acid (IIIb). To a solution of hydroxylamine, obtained from 0.63 g (0.009 mole) of hydroxylamine and 1.68 g (0.03 mole) of potassium hydroxide, in 20 ml of ethanol was added 1.0 g (0.003 mole) of methyl 3,3-diphenyl-2-oxoindoline-7-carboxylate [3] in 5 ml of dioxane. The solution was heated on the water bath for 8 min, and after standing at room temperature for 10 h, treated with water, and acidified with hydrochloric acid. The precipitated material was filtered off and recrystallized from dioxane.

β-Hydroxyethylamide of 3,3-Diphenyl-2-oxoindoline-7-carboxylic Acid (IIIc). A mixture of 5.25 g (0.015 mole) of the methyl ester of IIc [3] and 30 ml of monoethanolamine was refluxed for 2 h and then poured into water. The precipitated material was filtered off and recrystallized from alcohol.

β-Chloroethylamide of 3,3-Diphenyl-2-oxoindoline-7-carboxylic Acid (IIId). A mixture of 4.24 g of IIIc and 15 ml of thionyl chloride was refluxed for 2 h. The excess thionyl chloride was removed *in vacuo* and the residue recrystallized from ethanol.

β-Morpholinoethylamide of 3,3-Diphenyl-2-oxoindoline-7-carboxylic Acid (IIIe). A solution of 2.7 g (0.007 mole) of IIId in 10 ml of dioxane was refluxed for 3 h with 2 ml of morpholine, left for 12 h, diluted with water, and made alkaline with 5% sodium carbonate solution. The precipitated material was filtered off and recrystallized from dioxane.

LITERATURE CITED

1. V. V. Bolotov, V. V. Drugovina, P. A. Petyunin, et al., Khim.-Farm. Zh., No. 11, 45-49 (1979).
2. P. A. Petyunin, A. F. Soldatova, and A. K. Sukhomlinov, Khim. Geterosikl. Soedin., No. 4, 702-704 (1969).
3. P. A. Petyunin and N. G. Panferova, ibid., No. 2, 182-183 (1972).
4. P. A. Petyunin, Zh. Obshch. Khim., 22, 296-302 (1952).
5. U. S. Patent, No. 3634453 (1972); R. Zh. Khim., No. 21, No. 21N262P (1972).
6. E. Yu. Strel'nikov, Farmacol. Toksicol., No. 6, 526-530 (1960).
7. M. L. Belen'kii, Elements of Quantitative Evaluation of Pharmacological Effects [in Russian], Riga (1959).