SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3,3-DIPHENYL-4- AND 5-CARBOXY-2-OXOINDOLINE-1-ACETIC ACIDS AND SOME DERIVATIVES

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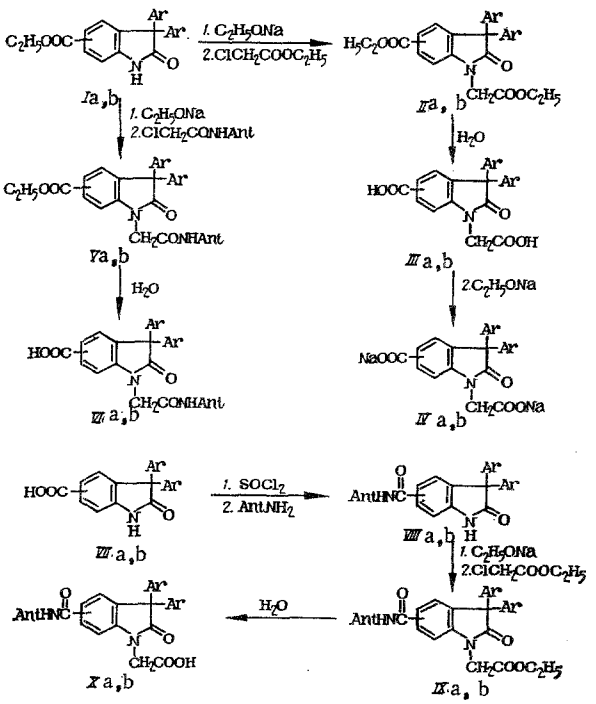
Compounds have previously been identified [1-3] in series of 3,3-diaryl-2-oxoindoline-1-acetic acids, 3,3-diaryl-2-oxoindoline-4- and 5-carboxylic acids, and their derivatives, which possess antiinflammatory and hypotensive activity.

Continuing a search for compounds whith biological activity in 2-oxoindolines, we have synthesized 3,3-diphenyl-4- and 5-carboxy-2-oxoindoline-1-acetic acids (IIIa, b). The starting materials used in the syntheses were esters of 3,3-diphenyl-2-oxoindoline-4- and 5-carboxylic acids (Ia, b) [2]. Reaction of the latter with ethyl chloroacetate in the presence of sodium ethoxide afforded the ethyl esters of 3,3-diphenyl-4- and 5-ethoxycarbonyl-2-oxoindoline-1-acetic acids (IIa, b).

The acids (IIIa, b) were obtained by hydrolyzing the esters (IIa, b) with sodium hydroxide solution. They were obtained as colorless crystalline solids, insoluble in water but soluble in organic solvents (acetic acid, dioxane, and ethanol). Treatment with a solution of sodium ethoxide in ethanol gave the disodium salts (IVa, b), which were readily soluble in water.

In view of the promising nature of a search for compounds with antiinflammatory and analgetic activity amongst acylated 4-aminoantipyrins [5], we synthesized the 4-antipyrylamides of 3,3-diphenyl-4- and 5-carboxy-2-oxoindoline-1-acetic acids (IVa, b), together with 3,3-diphenyl-4- and 5-(antipyrylcarbamoyl)-2-oxoindoline-1-acetic acids (Xa, b).

The antipyrylamides (IVa, b) were obtained by reaction of the esters (Ia, b) with chloroacet-4-antipyrylamide in the presence of sodium ethoxide, followed by hydrolysis of the resulting esters (Va, b).



4- and 5-(4-antipyrylaminocarbonyl)-2-oxoindoline-1-acetic acids (Xa, b) were obtained

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TABLE 1. 3,3-Diphenyl-4- and 5-Carboxy-2-oxoindoline-1-acetic Acids and Their Derivatives

Compound	Yield, %	Mp. °C	Found, N, %	Empirical formula	Calculated, N, %	R_f
IIa	83	146—7	3,22	$C_{27}H_{25}NO_5$	3,15	...
IIIa	55	276—8	3,97	$C_{25}H_{17}NO_5$	3,61	0,41
IIIb	50	268—70	3,59	$C_{25}H_{17}NO_5$	3,61	0,41
Va	88	243—6	9,70	$C_{35}H_{31}N_4O_5$	9,48	...
Vb	85	256—8	9,53	$C_{35}H_{31}N_4O_5$	9,48	...
VIa	38	280—82 (decomp.)	10,57	$C_{33}H_{27}N_4O_5$	10,22	0,58
VIb	60	292—4	10,45	$C_{33}H_{27}N_4O_5$	10,22	0,56
IXa	75	222—3	9,28	$C_{36}H_{33}N_4O_5$	9,32	...
IXb	98	229—30	9,60	$C_{36}H_{33}N_4O_5$	9,32	...
Xa	65	246—8	9,92	$C_{34}H_{29}N_4O_5$	9,78	0,35
Xb	95	260—63	9,90	$C_{34}H_{29}N_4O_5$	9,78	0,37

Note: Compounds (IIa), (Vb), (IXa), (IXb), (Xa), and (Xb) were recrystallized from aqueous ethanol, and (IIIa), (IIIb), (Va), (VIa), and (VIb) from aqueous acetic acid. pKa_1 of (IIIa) 5.58, pKa_2 7.15; pKa_1 of (IIIb) 5.55, pKa_2 7.11

by hydrolysis of the esters (IXa, b). The latter were obtained from the antipyrylamides (VIIIa, b), which in the presence of sodium ethoxide underwent condensation with ethyl chloroacetate.

Compounds (IIa, b), (VIa, b), (IXa, b), and (Xa, b) were colorless, crystalline solids, insoluble in water, but soluble in organic solvents (alcohol, dioxane, and dimethylformamide).

The structures of the compounds obtained were confirmed by their IR spectra. The IR spectra of the esters (IIa, b) showed absorption characteristic of ester $\nu_{C=O}$ at 1732 cm^{-1} and of the lactam ring $\nu_{C=O}$ at 1710 cm^{-1}. The IR spectra pf the acids (IIIa, b) showed, in addition to these bands, absorption at 3000 cm^{-1} (associated OH). The absorptions at 3180, 1735, 1720, 1672, and 1647 cm^{-1} in (IXa, b) were assiged to ν_{NH}, ester $\nu_{C=O}$, $\nu_{C=O}$ of the 2-oxoindoline ring $\nu_{C=O}$ of the exocyclic amide group, and $\nu_{C=O}$ of the antipyrine ring respectively. Similar spectra, differing in showing a broad band at 3300-3000 cm^{-1} (associated OH and NH groups), were exhibited by (Xa, b).

The constants of the compounds obtained are given in Table 1.

EXPERIMENTAL (CHEMICAL)

The IR spectra of the compounds were obtained on a UR-20 spectrophotometer (East Germany) in KBr disks (concentration of compound 1%). R_f values were measured on Silufol UV-254 plates in the system propan-2-ol—ammonia—water (10:1:1), and the pK_a values of the acids were determined using a pH-340 pH meter by potentiometric titration in solution in 60% dioxane in water.

Ethyl 3,3-Diphenyl-5-ethoxycarbonyl-2-oxoindoline-1-acetate (IIa). To a solution of 0.23 g (0.01 mole) of sodium in 10 ml of absolute ethanol was added 3.57 g (0.01 mole) of ethyl 3,3-diphenyl-2-oxoindoline-4-carboxylate (Ia) and 30 ml of toluene. Excess alcohol was distilled off until the temperature of the reaction mixture reached 110°C. To the cooled solution was added 1.2 ml (0.011 mole) of ethyl chloroacetate and a few crystals of phenolphthalein. The solution was boiled until the color of the phenolphthalein disappeared (approximately 1.5 h), the toluene evaporated, and the residue washed with water and crystallized from ethanol.

Similary, from (Ib) was obtained the easter (IIb), which was used in subsequent reactions without prior recrystallization (yield 95%).

3,3-Diphenyl-4-carboxy-2-oxoindoline-1-acetic Acid (IIIa). The ester (IIa) (1g) was boiled with 10 ml of 20% sodium hydroxide prepared with a mixture of ethanol and water (1:1). The solution was cooled, and poured into 50 ml of water. The solution was acidified with hydrochloric acid, and the solid which separated was filtered off, washed with water, and crystallized from acetic acid.

Compound (IIIb) was obtained similarly.

The disodium salts (IVa, b) were obtained by mixing solutions of 0.0025 mole of the acid (IIIa or b) in 10 ml of ethanol with 0.005 mole of sodium ethoxide in 5 ml of ethanol, followed by addition of ether until a turbidity appeared.

3,3-Diphenyl-4-ethoxycarbonyl-2-oxindoline-1-acet-4-antipyrylamide (Va). To 0.01 mole of the disodium derivative of (Ia), obtained as described above for the preparation of (IIa), was added 2.79 g (0.01 mole) of chloroacet-4-antipyrylamide. The mixture was boiled for 1.5 h, the toluene evaporated, and the residue washed with water and recrystallized from ethanol.

3,3-Diphenyl-4-ethoxy-oxoindoline-1-acet-4-antipyrylamide (VIa). This was obtained by hydrolysis of the ester carbonyl 2 (Va) for 30 min as described for the preparation of (IIIa).

In the same way, acids (VIb) and (Xa, b) were obtained from the esters (Vb) and (IXa, b) respectively.

3,3-Diphenyl-2-oxoindoline-4-carbon-4-antipyrylamide (VIIIa). To 3.3 g (0.01 mole) of 3.3-diphenyl-2-oxoindoline-4-carboxylic acid (VIIa) was added 10 ml of thionyl chloride, and the mixture boiled for 1 h. The excess reagent was distilled off under reduced pressure, and the residue treated with 10 ml of dry chlorofom, 1.4 ml (0.01 mole) of triethylamine, and 2.03 g (0.01 mole) of 4-aminoantipyrine. The mixture was kept for 30 min, boiled for 40 min, evaporated, and the residue washed with water and recrystallized from alcohol to give 2.7 g (50%) of product, mp 207-208°C. Found, %: N 10.83. $C_{32}H_{27}N_4O_3$. Calculated %, N 10.88.

Ethyl 4-(4-Antipyrylaminocarbonyl)-3,3-diphenyl-2-oxoindoline-1-acetate (IXa). This was obtained from (VIIIa) and ethyl chloroacetate in the presence of sodium ethoxide, as described for the ester (IIa).

EXPERIMENTAL (PHARMACOLOGICAL)

The acids (IIIa, b) and the 4-antipyrylamides (VIa, b) and (Xa, b) were tested for anti-inflammatory and analgetic activity.

The antiinflammatory activity of the compounds was assessed by their anti-exudative effects in mice weighing 18-20 g, by a method which has been described previously [3]. The phlogogenic agent used was 2.5% formalin solution. The test compounds were adminstered internally in a dose of 50 mg/kg. Parallel tests were carried out with phenylbutazone in the same dose.

Analgetic activity was determined in mice by the change in pain sensitivity in animals following chemical irritation induced by the intraperitoneal adminsitration of 3% acetic acid solution at the rate of 300 mg/kg [6]. The test compounds were administered internally in a dose of 50 mg/kg one hour before the test. The reaction of the animals to the administration of acetic acid was followed for the first 20 min following administration of the irritant. For the comparative evaluation of analgetic activity, experiments were carried out with Analgin in the same dose.

Salts (IVa, b) were tested for hypotensive activity. The tests were carried out in white rats of both sexes weighing 200-300 g. The test compounds were administrered intravenously as the 1% aqueous solutions in doses of 5, 10, and 20 mg/kg. The hypotensive activity of the compounds was assessed by their effects on the arterial pressure in intact rats in acute experiments [3].

The results showed that of the compounds tested the greatest antiinflammatory activity was shown by the antipyrylamides (VIb) and (Xb), which are derivatives of 3,3-diphenyl-5-carboxy-2-oxoindoline-1-acetic acid (IIIb). They were 1.5 times as active as phenylbutazone. The antiinflammatory activity of the acids (IIIa, b) and the antipyrylamides (VIa) and (Xa) was less than that of (VIb) and (Xb).

The greatest analgetic activity was shown by (VIa, b) and (Xa). Their analgetic activity was 1.6 times greater than that of Analgin. The activity of the remaining compounds was lower by a factor 2-2.5 than that of Analgin.

No hypotensive activity was found in the salts (IVa, b).

The acute toxicities of (VIa, b) and (Xa, b) were determined in mice, by the internal route. Observations were continued for 24 h. The LD_{50} values of these compounds, calculated by the method described in [4], were 5000 mg/kg or more.

Hence, these derivatives of 3,3-diphenyl-4- and 5-carboxy-2-oxoindoline-1-acetic acids are of low toxicity, and they constitute a promising class of compounds in the search for compounds with high antiinflammatory and analgetic activity.

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