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SYNTHESIS, PROPERTIES, AND BIOLOGICAL ACTIVITY OF 3,3,3',3'-TETRAPHENYL-5,5'-BIS[2-OXOINDOLINE-1-ACETIC ACIDS]

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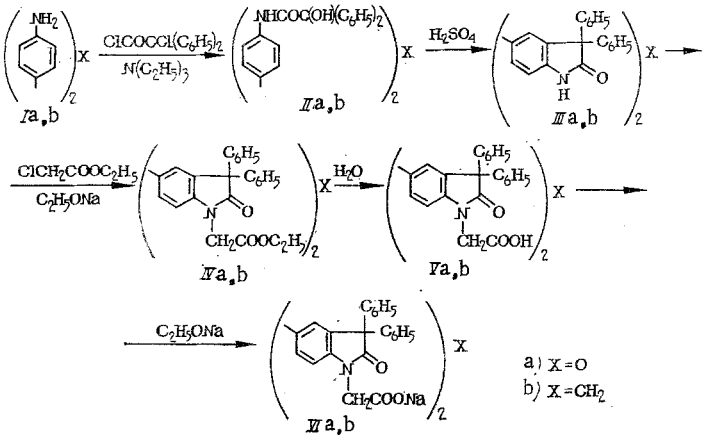
The 2-oxoindoline carboxylic acids and their derivatives include compounds which possess antiinflammatory and hypotensive activity [1, 2]. Continuing these studies, it was of interest to synthesize and examine the biological activity of 3,3,3',3'-tetraphenyl-5,5'-bis(2-oxoindoline-1-acetic acids) (Va, b). The 3,3,3',3'-tetraphenyl-5,5'-bis(2-oxoindolines) (IIIa, b) required for the synthesis of these compounds were obtained by the intramolecular cyclodehydration of the 4,4'-bis(benzilic acid amides) (IIa, b) with concentrated sulfuric acid, as described in [3]. The latter compounds were obtained by acylating 4,4'-bis(anilines) (Ia, b) with diphenylchloroacetyl chloride.



Compounds (IIa, b) were obtained as colorless, crystalline solids, insoluble in water, but soluble in organic solvents. Addition of concentrated sulfuric acid to acetic acid solutions of these compounds gave a fugitive brown halochromic coloration due to the formation of the biscarbocations C (cf. [4]).

The bis(2-oxoindolines) (IIIa, b) were colorless crystalline solids, sparingly soluble in the usual organic solvents, but soluble in dimethylformamide. Their melting points were considerably higher than those of the original (IIa, b).

Reaction of (IIIa, b) with ethyl chloroacetate in the presence of sodium ethoxide gave the diethyl 3,3,3',3'-tetraphenyl-5,5'-bis-(2-oxoindoline-1-acetates)(IVa, b). Hydrolysis of these compounds with 20% sodium hydroxide afforded the acids (Va, b) as colorless crystalline solids, soluble in organic solvents (dioxane and acetic acid) and aqueous solutions of caustic alkalies. Reaction of (Va, b) with sodium ethoxide gave the disodium salts (VIa, b).

The structures of the compounds obtained were confirmed by their elemental analyses (Tables 1 and 2) and IR spectra. The IR spectra of (IIIa, b) contained the following bands (cm^{-1}); 3250 (ν_{NH}), 1720-1710 ($\nu_{C=O}$), 1680-1670 (δ_{NH}). The IR spectra of esters (IVa, b) differed in the absence of NH absorption, and the presence of a band at 1725-1720 cm^{-1}($\nu_{C=O}$ in ring), with an inflection on the high-frequency side of the band at ~1730 cm^{-1} (ester $\nu_{C=O}$). The IR spectra of the acids (Va, b) contained broad bands at 3300-3200 (associated OH) and 1720 cm^{-1}, with an inflection on the low-frequency side at ~1700 cm^{-1}) ($\nu_{C=O}$).

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TABLE 1. Benzilic Acid 4,4'-Bisamides (II)

Compound	X	Yield, %	mp, °C	Found, N, %	Empirical formula	Calculated, N, %
IIa	None	78	231—2	4,51	$C_{40}H_{32}N_2O_4$	4,63
IIb	CH_2	81	232—5	4,81	$C_{41}H_{34}N_2O_4$	4,53

Note. Compound (IIa) was recrystallized from acetic acid, and (IIb) from dioxane.

TABLE 2. 3,3,3',3'-Tetraphenyl-5,5'-bis-(2-oxoindolines)

Compound	X	Yield, %	mp, °C	Found, N, %	Empirical formula	Calculated, N, %
IIIa	None	82	400	5,14	$C_{40}H_{28}N_2O_2$	4,93
IIIb	CH_2	73	283—6	4,94	$C_{41}H_{30}N_2O_2$	4,81
IVa	None	69	235—7	3,86	$C_{44}H_{33}N_2O_4$	3,78
IVb	CH_2	70	180—2	3,93	$C_{45}H_{35}N_2O_4$	3,71
Va	None	89	256—9	4,15	$C_{42}H_{29}N_2O_4$	3,93
Vb	CH_2	81	295—7	4,14	$C_{43}H_{31}N_2O_4$	3,85

Note. Compounds (IIIa, b) were recrystallized from dimethylformamide, (IVa) from ethanol, (IVb) from acetone, and (Va, b) from acetic acid.

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a UR-20 spectrophotometer (East Germany) in KBr disks (concentration of compound, 1%).

Benzylic Acid Benzidide (IIa). To a solution of 9.21 g (0.05 mole) of benzidine in 50 ml of acetic acid was added 14.1 ml (0.1 mole) of triethylamine, and in small portions 26.52 g (0.1 mole) of diphenylchloroacetyl chloride. The mixture was kept for 30 min, heated to the boil, left to cool, 2-3 ml of 5% sodium hydroxide solution added, and again heated to the boil, cooled, poured into water, and the solid filtered off and crystallized.

Compound (IIb) was obtained similarly from 4,4'-diaminodiphenylmethane.

3,3,3',3'-Tetraphenyl-5,5'-bis-(2-oxoindoline) (IIIa). To a solution of 3 g of (IIa) in 90 ml of acetic acid was added in small portions concentrated sulfuric acid, until the halochromic coloration ceased to appear (approximately 75 ml). The resulting solution was poured into 200 ml of water, the solid which separated filtered off, washed with water and ammonia solution, dried and crystallized from dimethylformamide.

Compound (IIIb) was obtained similarly from (IIb).

Diethyl 3,3,3',3'-Tetraphenyl-5,5'-bis-(2-oxoindoline-1-acetate) (IVa). To a solution of 0.23 g (0.01 mole) of sodium in 15 ml of absolute ethanol was added 2.84 g (0.005 mole) of (IIIa) and 30 ml of dry toluene. The excess ethanol was distilled off until the boiling point reached 110°C. The solution was cooled, and 1.1 ml (0.011 mole) of ethyl chloroacetate and a few crystals of phenolphthalein were added. The solution was boiled until the color of the phenolphthalein had disappeared (1.5 h). The toluene was distilled off, and the residue washed with water and crystallized.

(IVb) was obtained similarly.

3,3,3',3'-Tetraphenyl-5,5'-bis-(2-oxoindoline-1-acetic Acid) (Va). Compound (IVa) (1 g) was boiled for 2 h with 10 ml of 20% sodium hydroxide solution prepared using a mixture of ethanol and water (1:1). The solution was cooled and poured into 50 ml of water acidified with hydrochloric acid. The solid which separated was filtered off, washed with water, and crystallized from acetic acid or dioxane.

Compound (Vb) was obtained similarly.

The disodium salts of (VIa, b) were obtained by mixing solutions of 0.0025 moles of the acid (Va or b) in 20 ml of dioxane and 0.005 moles of sodium ethoxide in 5 ml of ethanol.

EXPERIMENTAL PHARMACOLOGY

Acids (Va, b) and their salts (VIa, b) were tested for antiinflammatory and hypotensive activity.

Antiinflammatory activity was assessed by their antiexudative effects, as measured in mice weighing 18-20 g, using the method described in [5]. Edema was induced by introducing a 2.5% formalin solution into the thickness of the femur. Experiments were carried out in parallel, and in comparisom with indomethacin. Indomethacin and (Va, b) were administered internally in equimolar doses (10 and 20 mg/kg, respectively) as 1% suspensions stabilized with Tween-80 (one drop per two ml of suspension). The control animals were treated with the same volumes of distilled water containing Tween-80. The compounds were introduced 2 h before and 5 and 18 h after treatment with formalin. Antiexudative activity was assessed 24 h after introduction of the phlogogenic agent.

Acid (Va) was virtually inactive, and the antiexudative activity of (Vb) was half that of indomethacin. The sodium salts (VIa, b) showed similar activity.

The latter were also tested for hypotensive activity. Tests were carried out on 12 white rats of both sexes weighing 200-300 g. The test compounds were administered intravenously as the 1% aqueous solutions in doses of 5, 10, and 20 mg/kg. The hypotensive activity of the compounds was assessed from their effects on the arterial pressure (AP) of untreated rats in an acute experiment. The AP was measured as described in [6].

The most pronounced hypotensive activity was displayed by (VIb) in a dose of 20 mg/kg. It reduced the AP of healthy rats by 33% (from 105 to 70 mm Hg) for 10 sec following administration. Over a period of 1.5-2 min, the AP gradually rose and returned to its original level.

In the same dose, (VIa) reduced the AP by 20%, the AP returned to its original level over a period of 40-60 sec. The acute toxicity (LD_{50}) of the more active compound (VIb) by the intraperitoneal route in white mice, by the method described in [7], was 2600 mg/kg.

These compounds therefore possess, in several cases, antiinflammatory activity which is as high as in the previously-described [1] 3,3-diaryl-2-oxoindoline-1-acetic acids, together with a short-lived hypotensive effect, and their toxicity is low. It must be pointed out that both types of pharmacological activity were greater in compounds in which the 2-oxoindoline system is directly linked (Va, VIa) than in systems in which this linkage is via a methylene group (Vb, VIb).

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