SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-ARYL-1,3-BIS(DIALKYLAMINOMETHYL)-2-OXOINDOLINES

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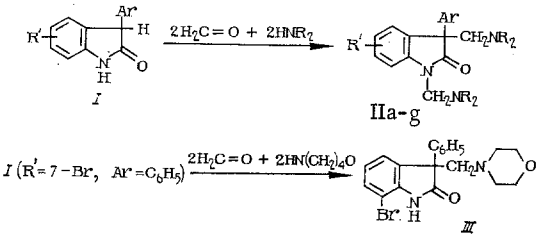
UDC 615.276:547.756].012.1

We have already shown [1, 2] that 3,3-diaryl-3-oxoindolines undergo aminomethylation at position 1 to form 1-aminomethyl-3-diaryl-2-oxoindolines with antiinflammatory activity. In the literature a case is described [3, 4] of aminomethylation at position 3 of 1,3-disubstituted derivatives of 2-oxoindolines. The case of simultaneous aminomethylation of derivatives of 2-oxoindolines at positions 1 and 3 has not been described in the literature. It was therefore interesting to carry out this reaction with 3-aryl-2-oxoindolines (I), which can be aminomethylated at positions 1 and 3, and also to study the antiinflammatory activity of the compounds obtained.

3-Aryl-1,3-bis(dialkylaminomethyl)-2-oxoindolines IIa-g were obtained by reacting compounds I with two equivalents of formaldehyde and secondary amines in an ethanol or DMFA medium.



IIa: Ar = C_6H_5; R′ = 5-Br; NR_2 = N $(CH_2)_4O$;
IIb: Ar = C_6H_5; R′ = 5-Br; NR_2 = N $(CH_2)_5$;
IIc: Ar = C_6H_5; R′ = 5-CH_3; NR_2 = N $(C_2H_5)_2$;
IId: Ar = C_6H_5; R′ = 5-CH_3; NR_2 = N $(CH_2)_4O$;
IIe: Ar = C_6H_5; R′ = H; NR_2 = N $(CH_2)_4O$;
IIf: Ar = C_6H_4-Br-p; R′ = H; NR_2 = N $(CH_2)_4O$;
IIg: Ar = C_6H_4Br-p; R′-H; NR_2 = N $(CH_2)_5$.

Compounds IIa-g (Table 1) are white crystalline substances, which are insoluble in water and readily soluble in ethanol, chloroform, hexane, and other organic solvents.

The structure of these compounds was confirmed by the data of elemental analysis and IR spectra, in which there are bands at 1720 cm^{-1} (ν C=O of the lactam ring), while bands characteristic of the NH groups are absent. In the IR spectra of compounds IIa, d-f, containing a morpholine residue, there is a band at 1120 cm^{-1} (ν C–O–C).

It should be noted that the aminomethylation of compound I(R′ = 7-Br; Ar = C_6H_5), in which there is a substituent at the 7-position of the annelated benzene ring, proceeds only into position 3 with the formation of 3-phenyl-3-morpholinomethyl-7-bromo-2-oxoindoline (III), because of steric hindrances due to this substituent (see literature data in [2]). In the IR spectrum of this compound there are bands at 3140 (ν NH), 1728 (ν CO) and 1110 (ν C–O–C) cm^{-1}. In contrast to compounds IIa, e-f, in which the intensity of bands of CO and C–O–C groups is almost the same, in compound III the intensity of the first group is nearly twice that of the second group.

EXPERIMENTAL PHARMACOLOGY

The antiinflammatory activity of compounds IIa-g was judged from their anti-exudative action, which was determined according to [5] on mice weighing 18-20 g each, in parallel

Kharkov Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 9, pp. 1060-1063, September, 1983. Original article submitted December 7, 1982.

 0091-150X/83/1709-0630$07.50

TABLE 1. 3-Aryl-1,3-bis(dialkylaminomethyl)-2-oxoindolines

Compound	Yield, %	mp, °C	Found, %	Empirical formula	Calculated, %
IIa	78	151—2	8,71	$C_{24}H_{28}BrN_3O_3$	8,64
IIb	71	82—4	8,59	$C_{26}H_{32}BrN_3O$	8,71
IIc	63	79—80	10,59	$C_{25}H_{35}N_3O$	10,68
IId	69	156—8	9,92	$C_{25}H_{31}N_3O_3$	9,97
IIe	75	100—2	10,02	$C_{24}H_{29}N_3O_3$	10,31
IIf	58	147—9	8,76	$C_{24}H_{28}BrN_3O_3$	8,64
IIg	61	82—4	8,63	$C_{26}H_{32}BrN_3O$	8,71

Note. Compounds IIa, c, e, g were recrystallized from ethanol, IIb from hexane, IId from benzene.

TABLE 2. Influence of 3-Aryl-1,3-bis(dialkylaminomethyl)-2-oxoindolines on Vasopermeability (M ± m)

Compound	Phlogogenic agent					
	formalin	serotonin	polyglucin	albumen	histamine	kaolin
	time until color appears in papule, min					
IId	12,2±0,3 <0,05	7,3±0,5 <0,01	5,9±0,6 <0,02	4,8±0,5 <0,01	6,9±0,4 <0,01	22,4±0,4 <0,01
IIg	16,4±2,0 <0,05	3,9±0,6 >0,4	4,9±0,2 <0,02	3,8±0,2 <0,1	5,0±1,0 >0,4	19,2±2,3 <0,02
Butadione	18,7±0,4 <0,01	12,8±2,5 <0,05	10,2±2,5 <0,05	9,2±2,3 <0,05	12,5±1,8 <0,01	16,0±2,0 <0,02
Control	9,0±1,7	3,5±0,7	3,5±0	2,0±0	2,8±0,3	8,8±1,6

Note. P was calculated with reference to control.

and in comparison with butadione. As the phlogogenic agent a 2.5% solution of formalin was used, 0.1 ml of which was introduced into the thigh. Compounds IIa-g were introduced orally in a dose of 150 mg/kg in the form of a 1% suspension, stabilized by Tween-80 (1 drop per 2 ml of suspension). The compounds were introduced 2 h before the introduction of formalin and 5 and 18 h after that. The corresponding volume of distilled water with Tween-80 was given to the control animals. The anti-exudative action was determined 24 h after the introduction of formalin. The activity of compounds IIa, b, d, g was found to be at the level of butadione activity, and that of the remaining compounds was lower by a factor of 1.5. Thus, the highest activity is exhibited by compounds containing piperidinomethyl and morpholinomethyl groups in combination with a bromine atom or the methyl group in the annelated benzene ring or bromine atom or the methyl group in the annelated benzene ring or bromine atom in the phenyl radical present at the 3-position of the heterocyclic ring.

To clarify the separate aspects of the antiinflammatory action mechanism of compounds II, we studied the influence of some of the most active among them (IIf, g) on the permeability of walls of vessels, intensified by various phlogogenic agents by the method described in [6]. As the phlogogenic agents, we used 0.1 ml portions of a 3% formalin solution, of a 0.01% solution of serotonin, polyglucin, undiluted egg albumen, and of a 10% suspension of kaolin. The rats received a 1% solution of Trypan blue (2 ml/kg) intravenously, and after 10 min phlogogenic agents were introduced into the abdominal cavity. The compounds studied were administered intraperitoneally in the form of a suspension prepared on an isotonic solution of sodium chloride (1 ml) in a dose of 0.1 LD_{50}. The control animals received 1 ml of the isotonic NaCl solution. In parallel, studies were carried out with butadione. The activity of the compounds was judged from the increase in time until a section of skin at the site where the phlogogenic compounds were introduced acquired a color. The results listed in Table 2 show that compounds IId, g, in comparison with the control, reliably decrease the permeability of walls of vessels upset by formalin, polyglucin, and kaolin, and in the case of compound IId, also by serotonin, albumen, and histamine. In the introduction of kaolin, the activity of compounds IId, g exceeds that of butadione by 1.4 and 1.2 times, respectively, but in the case of other phlogogenic agents, it is lower. The results obtained confirm the presence of antiinflammatory activity in the compounds studied.

If we consider that the compounds studied decrease the permeability of the walls of the

vessels, increased by polyglucin, albumen, serotonin, histamine and kaolin, and also take into account the literature data [7, 8] on the mechanism of the development of inflammatory reactions by the action of these phlogogenic agents, it can be assumed that the antiinflammatory properties of compounds IIa-g are due either to depletion under their influence of tissue reserves of endogenic inflammation mediators, or to their antagonism to these mediators (histamine, serotonin, quinins).

The LD_{50} of compounds IId, g, calculated by the method in [9], are 759 and 476 mg/kg, respectively.

The results of all the experiments were treated statistically [10].

EXPERIMENTAL CHEMISTRY

The IR spectra of the compounds were run on the UR-20 spectrophotometer (GDR) in mineral oil.

3-Aryl-11,3-bis(dialkylaminomethyl)-2-oxoindolines (IIa-g). Ethanol of DMFA (2 ml), 1.8 ml (0.02 mole) of 37% formaldehyde solution, and, with cooling, 0.02 mole of the corresponding secondary amine are added to 0.01 mole of the corresponding compound I. The reaction mixture is stirred for 15 min, heated on a boiling water bath for 15 min, and left to stand for 12 h. Water, 30 ml, is added to the reaction mixture, and the oil separating out is washed 2-3 times with water, and after crystallization of the oil, it is recrystallized from the corresponding solvent (see Table 1).

7-Bromo-3-phenyl-3-morpholinomethyl-2-oxoindoline (III). The compound is obtained from I (Ar = C_6H_5; R' = 7-Br) by the method described above in a DMFA medium. Yield 95%, mp 175-176°C (from ethanol). Found, %: N 7.02. $C_{19}H_{19}BrN_2O_2$. Calculated, %: N 7.24.

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