SYNTHESIS AND BIOLOGICAL ACTIVITY OF ACYL DERIVATIVES OF 4-AMINOANTIPYRINE

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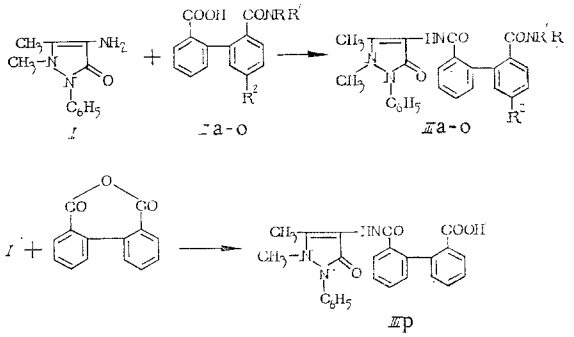
The present work was carried out in the development of preceding investigations on the synthesis and study of potentially biologically active compounds [1]. It was interesting to obtain new antipyryl amides of 2,2'-diphenic and 4-nitrodiphenic acids, and to study their biological activity in dependence on the character of the substituents bound to the amide nitrogen atom.

The antipyryl amides of diphenic and 4-nitrodiphenic acids (IIIa-p) were obtained by the reaction of 4-aminoantipyrine (I) with monoamides of diphenic (IIa-m) and 4-nitrodiphenic acid (IIn, o), and also of I with diphenic anhydride.



IIa, IIIa: R = R¹ = CH_3; IIb, IIIb: R = R¹ = C_2H_5;
IIc, IIIc: R = H, R¹ + C_3H_7; IId, IIId: R = H, R = iso-C_3H_7;
IIe, IIIe: R = H, R¹ = C_4H_9; IIf, IIIf: R = H, R¹ = iso-C_4H_9;
IIg, IIIg: R = R¹ = C_4H_9; IIh, IIIh: R = H, R¹ = $CH_2C_6H_5$;
IIi, IIIi: R = H, R¹ = C_6H_5; IIj, IIIj: R = H, R¹ = $C_6H_4CH_3$-p;
IIk, IIIk: R = H, R¹ = C_6H_4I-p; IIl, IIIl: R = H, R¹ = $C_6H_4NO_2$-p;
IIm, IIIm: R = H, R¹ = antipyryl; IIn, IIIn: R = H,
R¹ = C_6H_4I-p, R² = NO_2; IIo, IIIo: R = H, R¹ = iso-C_3H_7, R² = NO_2;
IIa-m, IIIa-m: R² = H.

EXPERIMENTAL CHEMISTRY

The monoamides of diphenic and 4-nitrodiphenic acids (IIa-p) were obtained by the reaction of the acid anhydrides with the corresponding amines [2]. The acylation of 4-aminoantipyrine (I) was carried out in a medium of boiling dry benzene in the presence of PCl_3 [1]. The IR spectra of the compounds were run on the UR-20 spectrophotometer (GDR) in the 400-4000 cm^{-1} region in mineral oil.

Antipyryl amides IIIa-p (Table 1) are crystalline colorless substances, which are insoluble in water and ether, but soluble in most organic solvents (acetone, alcohol, acetic acid, DMFA, etc.). They are identified according to the data of elemental analysis and IR spectra.

The IR spectra of antipyryl amides IIIa-p are characterized by the presence of absorption bands corresponding to the stretching vibrations of the N–H bond of secondary amides (3220-3070 cm^{-1}), bands of amide-I (1735-1680 cm^{-1}), amide-II (1540-1490 cm^{-1}), amide-III (1310-1220 cm^{-1}) of secondary amides, and also groups of absorption bands of biphenyl (1110-1000 cm^{-1}) [3, 4].

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TABLE 1. Characteristics of Acyl Derivatives of 4-Aminoantipyrine IIIa-p

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IIIa	38	233—4	72,92	5,83	12,71	$C_{26}H_{26}N_4O_3$	72,85	5,88	12,67
IIIb	35	187—7,5	72,25	5,97	11,53	$C_{29}H_{30}N_4O_3$	72,2	6,42	11,61
IIIc	52	228—30	71,82	6,21	11,42	$C_{28}H_{28}N_4O_3$	71,80	5,98	11,97
IIId	43	157—9	72,03	6,42	12,40	$C_{28}H_{28}N_4O_3$	71,80	5,98	11,97
IIIe	50	199—201	72,73	6,02	12,21	$C_{29}H_{30}N_4O_3$	72,20	6,22	11,62
IIIf	46	207—9	72,40	6,59	11,40	$C_{29}H_{30}N_4O_3$	72,20	6,22	11,62
IIIg	43	157—8,5	73,47	7,53	10,63	$C_{33}H_{38}N_4O_3$	73,60	7,10	10,41
IIIh	50	184—5,5	74,29	6,01	10,47	$C_{32}H_{28}N_4O_3$	74,42	5,43	10,85
IIIi	73	121—2	73,97	5,08	11,32	$C_{31}H_{26}N_4O_3$	74,1	5,18	11,60
IIIj	44	129—31	74,23	5,12	11,05	$C_{32}H_{28}N_4O_3$	74,41	5,42	10,80
IIIk	65	133—5	59,87	4,29	9,15	$C_{31}H_{25}N_4O_3$	59,24	3,98	8,93
IIIl	41	220—1	68,55	4,62	13,39	$C_{31}H_{25}N_5O_5$	67,89	4,57	12,93
IIIm	40	256—8	70,82	5,47	13,6	$C_{36}H_{32}N_6O_4$	70,58	5,22	13,72
IIIn	60	240—1	55,01	3,82	10,22	$C_{31}H_{24}N_5O_5$	55,27	3,57	10,40
IIIo	57	198—200	72,20	5,80	11,80	$C_{28}H_{28}N_4O_3$	71,80	5,98	11,96
IIIp	35	221—2	70,26	4,96	9,73	$C_{25}H_{21}N_3O_4$	70,31	4,99	9,21

Note. Compound IIIa, b, g, h, o were recrystallized from toluene, IIIn from acetic acid, and remaining compounds from xylene.

TABLE 2. Antiinflammatory Activity of Acyl Derivatives of 4-Aminoantipyrene

Compound	Capillary reactivity, sec (M ± m)	P
IIIa	86,9±7,3	0,110
IIIb	82,4±13,4	0,172
IIId	77,9±8,2	0,032
IIIg	104,2±8,7	0,069
IIIh	99,4±7,8	0,128
IIIk	113,6±6,0	0,264
IIIl	98,0±4,5	0,035
IIIp	105,9±8,8	0,044
IIIm	99,7±3,8	0,50
Butadione	100,6±2,3	0,003
Control	84,9±2,9	—

EXPERIMENTAL BIOLOGY

The antiinflammatory activity of the compounds was studied on white rats weighing 150-180 g each by carrying out screening tests: capillary reactivity [5] and aseptic peritonitis, induced by the introduction of silver nitrate [6], in comparison with butadione. In experiments on capillary permeability, the preparations were administered orally 1 h before injection of a dye. The intensity of the acute exudative inflammation was evaluated from the amount of exudate in the abdominal cavity of the animals of the control and experimental groups.

The antispasmodic activity was studied on white mice weighing 18-24 g each in maximum electrical shock tests [7] and corazole "titration" [8]. The ED_{50} value was determined by using probe analysis [9].

In all the experiments the preparations were administered orally in the form of a suspension in 1% starch mucilage. The statistical treatment of the data was carried out by the method of indirect differences [10].

The results of the study of the biological activity of the compounds investigated are listed in Table 2.

Table 2 shows that most of the compounds that we synthesized have no antiinflammatory activity in a dose of 100 mg/kg, except for compounds III [sic] and IIIp, which reliably increase the stability of the capillaries to the harmful action of xylene, and which are close to butadione in activity.

On a model of an acute inflammation with exudative peritonitis, the preparations studied showed inappreciable differences: The amount of the exudate in the control was 1.6 ± 0.3 ml, and in the experiment it was 1.0 ± 0.3 to 2.0 ± 0.3 ml.

The compounds obtained were also tested for antispasmodic activity, whose marked character depends to a certain extent on the structure of the compounds. Thus, the anticonvulsive effect of antipyrylamides is higher than in the case of diphenic acid amides. Antipyrylalkyl amides IIIa-g, o showed a higher antispasmodic activity (according to the maximal electrical shock test) than antipyrylaryl amides IIIh-n. With increase in the molecular weight of the alkyl radical attached to the amide group nitrogen atom, the activity of the preparation increases (IIIa, b, g). In antipyrylaryl amides, antispasmodic properties (according to corazole-spasms test) increase somewhat on transition from unsubstituted N-aryl-antipyryl amides (IIIh, i) to substituted ones (IIIj-l).

The introduction of the NO_2 group into the molecule of diphenic acid leads to intensification of the antispasmodic effect of compounds (IIIn, o), compared with that of analogous derivatives of unsubstituted diphenic acid (IIId, k).

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-AMINOALKYL(ARYL)-3-PHENYL-5-NITROINDOLES

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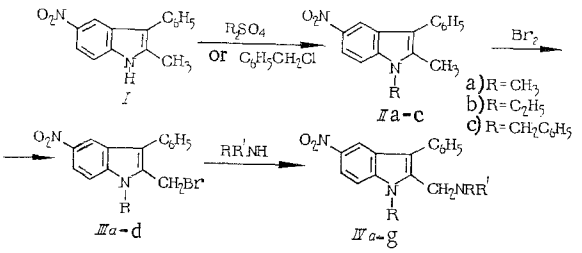
In conncetion with the search for biologically active compounds among the analogs of the alkaloid gramine, its structural analogs were obtained by reacting secondary amines with derivatives of 2-bromomethyl-3-phenyl-5-nitroindole [1]. The reaction of the latter compounds with other nucleophilic agents was also studied.



III: a) R = H; b) R = CH_3; c) R = C_2H_5; d) R = $CH_2C_6H_5$.

IV: a) R = H, $R^1 = R^2 = C_2H_5$; b) R = H, $R^1 = R^2 = CH_2C_6H_5$;
c) R = H, $R^1 + R^2 = -(CH_2)_4-$; d) R = H, $R^1 + R^2 = -(CH_2)_5-$;
e) R = H, $R^1 + R^2 = -(CH_2)_2O(CH_2)_2-$; f) R = CH_3, $R^1 = R^2 = C_2H_5$;
g) R = CH_3 $R^1 = R^2 = CH_2C_6H_5$; h) R + CH_3, $R^1 + R^2 = -(CH_2)_4-$;
i) R = CH_3, $R^1 + R^2 = -(CH_2)_5-$; j) R = CH_3, $R^1 + R^2 = -(CH_2)_2O(CH_2)_2-$;
k) R = CH_3, $R^1 + R^2 = -(CH_2)_2N(CH_3)(CH_2)_2-$; l) $R = R^1 = R^2 = CH_3$;
m) R = CH_3, R^1 = H, $R^2 = CH_2C_6H_5$;
n) R = CH_3, R^1 = H, R^2 = adamantyl; o) $R = CH_2C_6H_5$, $R^1 = R^2 = C_2H_5$;
p) $R = CH_2C_6H_5$, $R^1 + R^2 = -(CH_2)_5$; q) $R = CH_2C_6H_5$;
$R^1 + R^2 = -(CH_2)_2O(CH_2)_2-$.

2-Methyl-3-phenyl-5-nitroindole (I), previously obtained by the Fischer reaction in a low yield [2, 3], served as the starting material. However, by changing the conditions of the indolization reaction of p-nitrophenylhydrazone of benzyl methyl ketone, we were able to increase the yield of compound I to 70%.

1-Alkyl(aralkyl)-2-methyl-3-phenyl-5-nitroindoles (IIa-c) were synthesized in an 80-97% yield by alkylation of I by dimethyl and diethyl sulfate and benzylation with benzyl chloride.

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