SYNTHESIS AND ANALGESIC ACTIVITY OF SUBSTITUTED 1-ARYL-2-ACYLAMINOINDOLES

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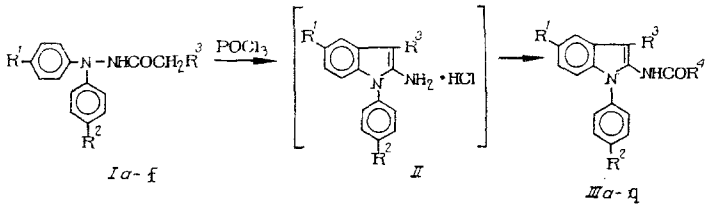
UDC 615.212.3:547.556.8]012.1.07

Substituted aminoacyl derivatives of 1-alkyl-2-aminoindole exhibit pharmacological activity, and are reported to possess analgesic and antiinflammatory properties [1].

In a search for new physiologically active compounds, we have synthesized some aminoacyl derivatives of 1-aryl-2-aminoindoles (III).



Ia-f II IIIa-q

R^1=H(Ia-c, e; IIIa, b, d, e, g-j, m-q), Me (If, IIIf, k)
OMe (Id, IIIc, ℓ); R^2=H (Ia-c, b, g-i, m-q), NO_2 (Id-f; IIIc-f, j-ℓ);
R^3=Me (Ia, d-f; IIIa-f; i-ℓ, n-q), Et (Ib, IIIg, m), i-Pr (Ic, IIIh);
R^4= Me (IIIj-m), p-C_6H_4Cl (IIIo), CH=CHPh (IIIn), CH_2Cl (IIIq),
$(CH_2)_6NH_2$ ·HCl (IIIi), CH_2NEt_2 (IIIp), $(CH_2)_5NPht$ (IIIa, d, f), $(CH_2)_6NPht$ (IIIb, c, d, g, h).

The N,N-diaryl-N'-acylhydrazides (Ia-f) were used as starting compounds. The hydrazides Ia-c were obtained by the reaction of diphenylhydrazine hydrochloride with the anhydride or acid chloride of the acid in the presence of Et_3N, and the hydrazides Id-f by the arylation of the corresponding N-aryl-N'-acylhydrazides with arylhalides in the presence of CuI and base [2]. The reaction of the hydrazides Ia-f with a small excess of $POCl_3$ gave the hydrochlorides of the corresponding 1-aryl-2-aminoindoles (II) [3].

As noted in [4], the rearrangement of the substituted N,N-diarylhydrazides of carboxylic acids with the conditions of the Kost reaction [4] is regiospecific and in the case of the hydrazides with different aromatic substituents at the nitrogen atom (compound Id and j) gave isomers involving the N-aryl ring with an electron-donor substituent. As a rule, the process of indolization of the diarylhydrazides is accompanied by the formation of derivatives resulting from phosphorylation at the amino group. Furthermore this is most marked in the heterocyclization of N,N-diaryl-N'-acylhydrazides which have an electron acceptor substitutent in one of the phenyl rings (compound Id-f).

However, this is not reflected in the acylation reaction, which results in the substitution of the phosphoryl group by an acyl group. Because of this, the hydrochloride of the 1-aryl-2-aminoindoles II was acylated without further purification with the anhydride or acid chloride of the corresponding carboxylic acids in the presence of Et_3 or NaOAc. The reaction produced the monoacyl derivatives III.

The acid chloride of the N-phthalyl-ω-amino acids were obtained by the reaction of the corresponding carboxylic acids with excess $SOCl_2$ in the presence of catalytic amounts of DMFA. The acid chlorides were used for subsequent reactions without further purification.

The protective phthalyl group in compound IIIb was removed by hydrazinolysis followed by conversion of the free base to the hydrochloride IIIi. The structure of compound IIIi

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 11, pp. 18-21, November, 1991. Original article submitted November 20, 1990.

0091-150X/91/2511-0771$12.50

TABLE 1. 1-Aryl-2-acylaminoindoles (IIIa-q)

Compound	Yield, %	Mp, °C	Empirical formula
IIIa	59	165—6	$C_{29}H_{27}N_3O_4$
IIIb	60	129—31	$C_{30}H_{29}N_3O_4$
IIIc	74	185—7	$C_{31}H_{30}N_4O_4$
IIId	58	197—9	$C_{29}H_{26}N_4O_5$
IIIe	53	199—200	$C_{30}H_{28}N_4O_5$
IIIf	67	191—3	$C_{30}H_{28}N_4O_5$
IIIg	59	165,5—6	$C_{31}H_{31}N_3O_4$
IIIh	62	178—9	$C_{32}H_{33}N_3O_4$
IIIi	89	145—6	$C_{29}H_{26}N_3OCl$
IIIj	52	239—40	$C_{17}H_{15}N_3O_4$
IIIk	72	242—3	$C_{18}H_{17}N_3O_4$
IIIℓ	62	245—6	$C_{18}H_{17}N_3O_4$
IIIm	79	143—5	$C_{18}H_{18}N_2O$
IIIn	72	228,5—9,5	$C_{24}H_{20}N_2O$
IIIo	69	229—30	$C_{22}H_{17}N_2OCl$
IIIp	55	96—6,5	$C_{21}H_{28}N_4O$
IIIq	59	134,5—5	$C_{17}H_{15}N_2OCl$

was confirmed by physicochemical methods of analysis. In the IR spectrum, peaks at 1770 and 1705 cm^{-1} characteristic of the phthalimide C=O group, give way to broad absorption bands at 3200-2300 cm^{-1} corresponding to the salt-forming ammonium group. The mass spectrum of the compounds contains a peak due to the molecular ion $(M+H)^+$ with m/z 350.

Compound IIIp was obtained by the amination of 3-methyl-1-phenyl-2-(chloroacetylamino)indole IIIq with excess Et_2NH in boiling acetonitrile. The PMR spectrum of the indole IIIp contains, in addition to other signals, a triplet and a quartet characteristic of protons of the diethylamino group.

The structures of the N,N-diaryl-N'-acylhydrazides Ia-f and 1-aryl-2-acylaminoindoles IIIa-q were confirmed by a combination of physicochemical methods and elemental analysis.

EXPERIMENTAL (CHEMICAL)

IR Spectra were taken on a Specord IR-75 (Germany), compounds were prepared as mulls with mineral oil; PMR spectra were obtained using a Tesla BS-587 A spectrometer (Czechoslovak Federal Republic), solent DMSO-d_6. Mass spectra were obtained on an MX-1321 A, ionization energy 70 eV, and also on an MI 1201 E by the method of BUA. The course of the reaction and the purity of the products were monitored using thin layer chromatography (TLC) on Silufol UV-254 plates or on Al_2O_3 (activity II). Data for the compounds synthesized are given in Table 1. Elemental analysis data were in good agreement with calculated values.

N,N-Diphenyl-N'-propionylhydrazide (Ia). To a vigorously stirred suspension of N,N-diphenylhydrazine hydrochloride (4.41 g, 0.02 mole), benzene (50 ml) and Et_3N (2.02 g, 0.02 mole) at 20-25°C was added dropwise $(EtCO)_2O$ (2.8 ml, 0.022 mole) and the reaction mixture stirred until TLC indicated that no starting N,N-propionylhydrazine was present (benzene-acetone, 2:1). The precipitated material was filtered off, washed with water, and recrystallized from i-PrOH. Yield of Ia, 62.5%, mp 176-177°C. Literature value: mp 178°C [5].

N,N-diphenyl-N'-butanoylhydrazide (Ib) was obtained by the reaction of N,N-diphenylhydrazine hydrochloride with the acid chloride of butyric acid and a 2.5-fold excess of Et_3N. Yield of compound Ib, 68%.

N,N-diphenyl-N'-isopentanoylhydrazide (Ic) was obtained by the same method. Yield of compound Ic, 63%.

Substitute N,N-diaryl-N'-propionylhydrazines (Id-f) were prepared by the arylation of the corresponding N-aryl-N'-propionylhydrazines as described in [2].

1-Aryl-2-(ω-phthalimidoacylamino)indoles (IIIa-h) (General Method). N-phthalyl-ω-aminocarboxylic acid (0.01 mole), $SOCl_2$ (0.02 mole) and DMFA (1 drop) in absolute CH_2Cl_2 (20 ml) was refluxed for 2 hours, the solvent then distilled off under vacuum leaving the acid chloride which was dissolved in absolute CH_2Cl_2 (10 ml). To this was added dropwise a mixture of the appropriate 2-aminoindole hydrochloride (0.01 mole) and Et_3N (0.02 mole) in absolute CH_2Cl_2 (30 ml) at ≤5°C and stirring was continued until no 2-aminoindole was present (TLC). The reaction mixture was washed with water, dried with Na_2SO_4, evaporated to dryness, and the residue triturated with hexane, and recrystallized from alcohol (Table 1).

TABLE 2. Analgesic Activity and Acute Toxicity of the 1-Aryl-2-acylaminoindoles

Compound III	LD_{50} mg/kg, I/P	Supression of AcOH-induced convulsions, ED_{50}, mg/kg				Latent period of pain reaction on heat stimulation, % of control	
		I/P	RA	intravenously	RA	IP (200 mg/kg)	intravenously (100 mg/kg)
a	>800	70	0,49	30	1,83	160*	126
b	>800	40	0,85	70	0,79	114	202*
c	>800	15	2,27	20	2,75	132	
d	>800	10	3,49	37	1,49	200	
e	>800	20	1,7	22	2,5	119	130
f	>800	10	3,40	17	3,24	160*	117
g	>800	5	6,8	52	1,06	161*	244*
h	>800	10	3,40			160*	
i	150	5	6,8				
m	600	20	1,7	63	0,87	535*	190*
n	>1000	15	2,27	32	1,72	108	149
o	>800	10	3,40			160*	
p	100	5	6,8	18	3,06		(30 mg/kg) 141
Analgin	1667	34	1,0	56	1,0	(100mg/kg) 164* (150 mg/kg) 228*	195*
Amidopyrine	320	64	0,53	95	0,58	(100mg/kg) 217 (150 mg/kg) 453*	230*

Notes. RA) relative activity; I/P) intraperitoneally asterisk – $p < 0.05$.

Substituted 1-Aryl-2-acetylaminoindoles (III j-ℓ) (General Method). A mixture of the corresponding substituded N,N-diphenyl-N'-propionylhydrazine (0.003 mole)[2], $POCl_3$ 0.6 g, 0.0039 mole) and dry dioxane (5 ml) were heated at 65-70°C until TLC indicated that there was no longer any hydrazine present. The reaction mixture was evaporated under vacuum, to the residue was added absolute ether, and the insoluble material filtered off. To the 2-aminoindole hydrochloride obtained was added Et_3N (0.25 g, 0.003 mole) and Ac_2O (4 ml), and the mixture stirred at 20°C until no 2-aminoindole was present (TLC). The reaction mixture was evaporated to dryness, the residue dissolved in $CHCl_3$, washed successively with water, $NaHCO_3$ solution, and again with water. It was then dried with potassium hydroxide, and evaporated to dryness. Hexane was added to the residue, the precipitated material filtered off and recrystallized from alcohol (see Table 1).

2-Acetylamino-1-phenyl-3-ethylindole (IIIm). A mixture of N,N-diphenyl-N'-butanoylhydrazine (3.6 g, 0.014 mole), $POCl_3$ (2.82 g, 0.018 mole) and dry dioxane (15 ml) was refluxed until no more diarylhydrazide was present (TLC). The reaction mixture was evaporated to dryness under vacuum, and absolute ether added to the residue. The insoluble 2-amino-1-phenyl-3-ethylindole hydrochloride obtained was dissolved in CH_2Cl_2 (30 ml) and without further purification Ac_2O (1.57 g, 0.015 mole) added, followed by Et_3N (3.04 g, 0.03 mole). After 16 hours at 20°C, the reaction mixture was washed with water (2 × 100 ml). The organic layer was dried over Na_2SO_4, filtered, evaporated, the residue triturated with hexane and recrystallized from aqueous alcohol (see Table 1).

N-acyl Derivatives of 2-Amino-3-methyl-1-phenylindole (IIIn, p, q). To a stirred mixture of 2-amino-3-methyl-1-phenyldinole hydrochloride (0.5 g, 1.9 mmole) and Et_3N (0.79 ml, 5.57 mmole) in CH_2Cl_2 (10 ml) at 5°C was added the acid chloride of the corresponding acid (2.1 mmole). Stirring was continued at 20°C until no more 2-aminoindole was present. The reaction mixture was evaporated to dryness, water (10 ml) added, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried with potassium hydroxide, and evaporated to dryness. The residue was triturated with hexane, and recrystallized from benzene (see Table 1).

2-(Diethylamino)acetylamino-3-methyl-1-phenylindole (IIIp). To a solution of 3-methyl-1-phenyl-2-(chloroacetylamino)indole IIIq in acetonitrile (15 ml) was added Et_2NH (1.8 g, 2.56 ml, 0.024 mole). After refluxing for 35-40 minutes, the mixture was cooled, the precipitate filtered off, and the filtrate evaporated to dryness in vacuum. The oily residue was chromatographed on a silica gel column (30 × 110 mm) in $CHCl_3$. The fraction containing the desired product was evaporated, hexane added, and the precipitated material filtered off (see Table 1).

Hydrochloride of 2-(7-aminoheptanoylamino)-3-methyl-1-phenylinode (IIIi). A mixture of 3-methyl-1-phenyl-2-(7-phthalimidoheptanoyl)aminoindole (IIIb) (2.85 g, 5.8 mmole) in

alcohol (20 ml) and hydrazine hydrate (0.34 g, 0.33 ml, 6.8 mmole) was refluxed for 2 hours. The alcohol was then evaporated, NaOH (40 ml, 2N) added to the residue, and extracted with $CHCl_3$. The $CHCl_3$ solution was evaporated, and the residue dissolved in alcohol. Ether was added, saturated with HCl, and the precipitated filtered off (see Table 1).

EXPERIMENTAL (BIOLOGICAL)

Experiments were conducted on white male mice weighing 18-24 g. Acute toxicity was measured by a single intraperioneal injection of the compound: observations were made over a period of 4 days. Analgesic activity was studied on models of chemical [6] and heat pain stimulation [7], compounds were administered intravenously and intraperitoneally. Each dose was tested on 10 mice. As a result of tests on models of convulsions induced by the injections of AcOH, and ED_{50} was calculated by the method of Litchfield and Wilcoxon [8]. Analgin and amidopyrine were used as standards for comparison of activities; the activity of analgin was taken as a unit measure. Test compounds were administered intraperitoneally at 30 minutes, intravenously at 1 hour before the AcOH. Results were treated statistically, and Student's criteria were calculated.

Results of the study of analgesic activity and acute toxicity are presented in Table 2. As can be seen from the table, compounds IIIa-h, n, o according to K. K. Siderov's classification [9] were slightly toxic or almost non-toxic (LD_{50} exceeded 800 and 1000 mg/kg). These compounds did not show significant effect on the behavior of the animals, but in doses of 200 and 800 mg/kg they had a slight sedative action. Compounds IIIi, m, p were more toxic (LD_{50} from 100 to 600 mg/kg). They caused a noticeable depression of activity, and in toxic doses, convulsions.

All the compounds tested exhibited analgesic action on chemically-stimulated pain. Compounds IIIa, g-h, m, o injected intraperitoneally increased the latent period of thermally-stimulated pain, while compounds IIIb, g, m raised the threshold of pain sensitivity when injected intravenously (100 mg/kg). For analgesic action, compounds IIIb, g, m did not exceed analgin, while compounds IIIc-d, n, p were more effective. Compounds IIIc-d, n, o, having low toxicity, are worth further study. Analysis of the structure vs. pharmacological action in this series clarified the effect of the substituent R^4 on the acute toxicity. Thus, the introduction of $(CH_2)_6NH_2$, CH_2NEt_2, and Me groups led to an increase in toxicity. No substantial regularity in the variation in pain-relieving properties depending on the change in molecular structure of the phthalimide derivatives of indole was observed. The introduction of a nitro group into the phenyl ring ($R^3 = NO_2$) slightly increased the analgesic action on the model of chemically-stimulated pain.

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