SYNTHESIS AND ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF SOME ARYLAMIDES OF N-SUBSTITUTED ANTHRANILIC ACIDS

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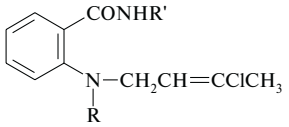
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 35, No. 4, pp. 17 – 19, April, 2001.

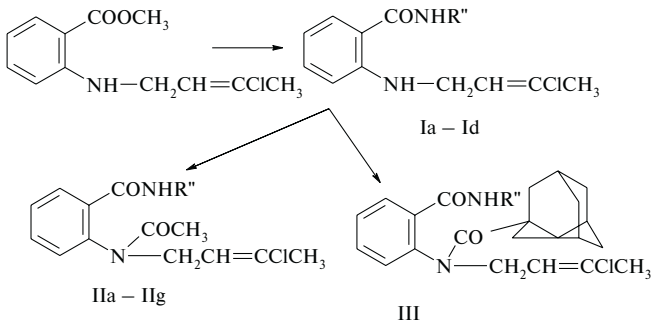
Original article submitted July 18, 2000

Our previous analysis [1] of the structure – antiinflammatory activity – toxicity relationship in a series of 1-(3′-chlorobuten-2′-yl)-2-methyl-3-aryl-4(3H)-quinazolinonium perchlorates obtained from N-acetyl-N-(3′-chlorobuten-2′-yl)anthranilic acid arylamides was not complemented by a study of the antiinflammatory properties of the latter compounds. To fill the gap, we have synthesized and characterized a series of N-alkenylanthranilic acid arylamides with the general formula



I – III

Compounds I – III were synthesized according to the scheme



I: R′ = $C_6H_4CH_3$-4 (a); $C_6H_4OCH_3$-4 (b); C_6H_4Br-4 (c); 2-PyBr-5 (d);
II: R′ = $C_6H_4CH_3$-4 (a); $C_6H_4OCH_3$-4 (b); C_6H_4Br-4 (c); 2-PyBr-5 (d); $C_6H_4CH_3$-3 (e); $C_6H_4CH_3$-2 (f); C_6H_5 (g);
III: R′ = C_6H_4Br-4.

The methyl ether of N-(3′-chlorobuten-2′-yl)anthranilic acid, synthesized by esterification of this acid with methanol in the presence of concentrated sulfuric acid [1], was treated with a mixture of ethylmagnesium bromide and arylamine to obtain compounds I. Compounds II were obtained by acetylation of the corresponding N-(3′-chlorobuten-2′-yl)anthranilic acid arylamides. Compound III was synthesized by acylating bromoanilide Ic with adamantanecarboxylic acid anhydride.

The synthesized compounds are white, sometimes with a yellowish tint, crystalline substances insoluble in water and soluble in ethanol, DMSO, and DMF.

EXPERIMENTAL CHEMICAL PART

The IR spectra were recorded on a UR-20 spectrophotometer (Germany) using samples prepared as nujol mulls. The ^{1}H NMR spectra were measured on an RYa-2310 spectrometer operated at a working frequency of 60 Hz. The chemical shifts were calculated relative to HMDS internal standard and expressed on the δ (ppm) scale.

N-(3′-chlorobuten-2′-yl)anthranilic acid 4-bromoanilide (Ic). To a solution of ethylmagnesium bromide, obtained from 16.3 g (150 mmole) of ethyl bromide and 3.6 g (150 mmole) Mg in 50 ml of anhydrous diethyl ether, were added 9.6 g (75 mmole) of 4-bromoaniline in 20 ml of anhydrous ether and the mixture was heated for 30 min on a water bath. Then a solution of 12 g (50 mmole) of N-(3′-chlorobuten-2′-yl)anthranilic acid methyl ester was added dropwise and the mixture was heated for another 30 min. Upon termination of the reaction, the organomagnesium compound was decomposed by treatment with a 10% CH_3COOH. The ether layer was decanted and the aqueous layer was extracted with ether (3 × 40 ml). Finally, solvent was distilled off from the ether extracts with aqueous vapor. Yield of compound Ic, 75%.

Analogous procedures were used to obtain compounds Ia, Ib, and Id.

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TABLE 1. Yields, Physicochemical Characteristics, and Parameters of the IR and ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Empirical formula	Yield, %	M.p., °C	IR spectrum: ν_{max}, cm^{-1}	^{1}H NMR spectrum (solvent): δ, ppm
Ia	$C_{18}H_{19}ClN_2O$	77	113 – 115	1320, 1370, 1390, 1460, 1510, 1590, 1640, 3120, 3150, 3320, 3380	$CDCl_3$, 2.1 (d, 6H, $2CH_3$), 3.76 (m, 2H, CH_2), 5.4 (m, H, CH=), 6.26 – 7.50 (m, arom. H), 7.6 (s, 2H, NH, CONH)
Ib	$C_{18}H_{19}ClN_2O_2$	62	120 – 121	1310, 1450, 1570, 1640, 3200, 3350	$(CD_3)_2SO$, 2.03 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 3.87 (d, 2H, CH_2), 5.57 (t, H, CH=), 6.07 – 7.87 (m, arom. H, NH, 9H), 9.1 (s, H, CONH)
Ic	$C_{17}H_{16}BrClN_2O$	75	122 – 124	1340, 1450, 1520, 1590, 1630, 3220	$CDCl_3$, 1.96 (s, 3H, CH_3), 3.8 (d, 2H, CH_2), 5.43 (m, H, CH=), 6.7 – 7.5 (m, arom. H), 7.7 (s, 2H, NH, CONH)
Id	$C_{15}H_{15}BrClN_3O$	45	71 – 73	1370, 1460, 1520, 1560, 1580, 1650, 3340	CF_3COOH, 2.0 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 5.53 (d, H, CH=), 6.5 (d, 3H, Py), 6.8 – 8.47 (m, arom. H), 10.3 (s, 2H, NH, CONH)
IIa	$C_{20}H_{21}ClN_2O_2$	77	129 – 130	…	$CDCl_3$, 1.78 (d, 6H, $2CH_3$), 2.23 (d, 3H, $COCH_3$), 4.26 (m, 2H, CH_2), 5.53 (m, H, CH=), 6.63 – 8.1 (m, arom. H), 8.5 (s, H, CONH)
IIb	$C_{20}H_{21}ClN_2O_3$	67	113 – 115	1310, 1410, 1450, 1640, 1680, 3200	$CDCl_3$, 1.7 (s, 3H, CH_3), 2.06 (d, 3H, $COCH_3$), 3.72 (s, 3H, OCH_3), 4.25 (t, 2H, CH_2), 5.56 (m, H, CH=), 6.3 – 7.8 (m, arom. H), 8.03 (s, H, CONH)
IIc	$C_{19}H_{18}BrClN_2O_2$	69	179 – 181	1320, 1400, 1440, 1510, 1570, 1610	CF_3COOH, 2.1 (s, 3H, CH_3), 2.93 (d, 3H, $COCH_3$), 5.38 (d, 2H, CH_2), 5.78 (m, H, CH=), 7.1 – 8.3 (m, arom. H), 8.96 (s, H, CONH)
IId	$C_{17}H_{17}BrClN_3O_2$	51	159 – 161	1300, 1380, 1400, 1450, 1470, 1490, 1520, 1580, 1590, 1680, 3080, 3230	CF_3COOH, 1.87 (s, $3H_3$, CH_3), 3.60 (d, 3H, $COCH_3$), 4.03 (d, 2H, CH_2), 5.53 (m, H, CH=), 6.93 – 8.43 (m, arom. H), 10.7 (s, H, CONH)
IIe	$C_{20}H_{21}ClN_2O_2$	52	152 – 154	1320, 1380, 1470, 1610, 3250	$CDCl_3$, 2.0 (d, 9H, $2CH_3$, $COCH_3$), 4.03 (m, 2H, CH_2), 5.4 (m, H, CH=), 6.4 – 7.73 (m, arom. H), 7.8 (s, H, CONH)
IIf	$C_{20}H_{21}ClN_2O_2$	57	129 – 131	1330, 1460, 1510, 1560, 1610, 3200	$CDCl_3$, 1.87 (s, 6H, $2CH_3$), 2.1 (d, 3H, $COCH_3$), 4.31 (m, 2H, CH_2), 5.58 (m, H, CH=), 6.9 – 8.1 (m, arom. H, CONH, 9H)
IIg	$C_{19}H_{19}ClN_2O_2$	79	154 – 155	1300, 1310, 1380, 1410, 1450, 1490, 1640, 1680, 3210	…
III	$C_{28}H_{30}BrClN_2O_2$	49	187 – 188	1390, 1460, 1530, 1590, 1610, 1670, 3250	CF_3COOH, 1.7 (s, 3H, CH_3), 1.9 – 2.6 (d, 15H 1-adamantyl), 4.27 (d, 2H, CH_2), 5.7 (m, H, CH=), 7.1 – 8.2 (m, arom. H), 9.3 (s, H, CONH)

N-(3′-chlorobuten-2′-yl)-N-acetylanthranilic acid 4-anisidide (IIb). A solution of 3.31 g (10 mmole) of compound Ib in 6 ml of acetic anhydride was heated for 35 min on a water bath and allowed to cool. Then the reaction mass was diluted with 50 ml of water and neutralized with sodium carbonate. The precipitate was separated by filtration and recrystallized from ethanol; yield of compound IIb, 67%.

Analogous procedures were used to obtain compounds IIa and IIc – IIg.

N-(3′-chlorobuten-2′-yl)-N-(adamant-1″-yl)anthranilic acid 4-bromoanilide (III). To a solution of 3.79 g (10 mmole) of N-(3′-chlorobuten-2′-yl)anthranilic acid 4-bromoanilide (Ic) in 10 ml of benzene was added 1.98 g (10 mmole) of adamantane-1-carboxylic acid anhydride and the mixture was heated for 30 min at 80°C. Then benzene was distilled off and the reaction mass was diluted with 20 ml of methanol and neutralized by sodium carbonate. The precipitate was recrystallized from a methanol – DMF mixture (1 : 1); yield of compound III, 49%.

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity of the synthesized compounds was studied on white mongrel rats weighing 180 – 220 g, bearing a carrageenan-induced foot edema model. The compounds to be tested (in a dose of 50 mg/kg) and the reference drug ortophen (10 mg/kg) were intraperitoneally injected with a 2% starch jelly 1 h before inducing inflammation. The degree of edema development was evaluated oncometrically, by measuring the inflamed foot volume 4 h after carrageenan injection (0.1 ml of an 1% aqueous solution) [2].

The analgesic activity was studied by the “hot plate” test on white mongrel mice weighing 18 – 23 g [3]. Here, the compounds studied were introduced in a dose of 50 mg/kg perorally 30 min before placing the animal onto a metal plate heated to 53.5°C. The change in the pain reaction was evaluated by measuring the time of animal staying on the hot plate

TABLE 2. Antiinflammatory and Analgesic Activity and Acute Toxicity of Compounds Ia – Id, IIa – IIg, and III

Compound	Dose, mg/kg (i.p.)	Carrageenan foot edema growth inhibition in rats, % of control	Latent period for defensive reflex in mice, sec	LD_{50}, mg/kg
Ia	50	40.5*	14.6 ± 1.2	> 2000
Ib	50	38.8*	10.8 ± 0.8	> 2000
Ic	50	18.3	15.3 ± 1.3	> 1500
Id	50	17.5	21.0 ± 2.4**	…
IIa	50	45.4*	15.2 ± 1.7	> 1500
IIb	50	42.4*	18.8 ± 1.6**	> 1500
IIc	50	35.4*	14.1 ± 0.9	> 1500
IId	50	40.4*	21.0 ± 2.2**	…
IIe	50	49.7*	22.0 ± 2.6**	> 1500
IIf	50	50.1*	19.8 ± 1.8**	> 1500
IIg	50	57.3*	15.2 ± 1.5	> 3000
III	50	15.9	19.0 ± 1.7**	1000 (840 – 1190)
Ortophen	10	61.3*	17.4 ± 0.7**	74.0 (48.8 – 124.8)
Control (2% starch jelly)	–	–	11.0 ± 0.5	…

* $p < 0.05$, ** $p < 0.001$ relative to control.

before the onset of a protective reaction (hind paw licking). Each compound was tested in a group of ten animals.

The acute toxicity of the synthesized compounds upon single intraperitoneal injection was studied on white mice weighing 17 – 22 g. The LD_{50} values were determined taking into account the loss of animals within 24 h after injection [4]. All experimental data were statistically processed by conventional methods [5].

It was established that most of the synthesized compounds possess antiinflammatory and analgesic properties (Table 2). The most pronounced antiinflammatory effect was observed for compounds IIg and IIf and the analgesic action, for compounds Id, IIb, IId – IIf, and III, which were comparable in activity with the reference drug (ortophen).

Thus, N-substituted anthranilic acid amides represent a promising group of compounds in the search for new antiinflammatory and analgesic substances.

REFERENCES

1. L. M. Korkodinova, M. I. Vakhrin, Yu. V. Kozhevnikov, et al., *Khim.-Farm. Zh.*, **20**(5), 553 – 556 (1986).
2. R. S. Salyamon, *Drug Control of the Inflammation Process* [in Russian], Medgiz, Leningrad (1958), pp. 11 – 43.
3. N. B. Eddy and D. J. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 – 393 (1953).
4. V. B. Prozorovskii, *Practical Guide to Accelerated Determination of Mean Effective Doses and Concentrations of Biologically Active Substances* [in Russian], NPP-Nauka, St. Petersburg (1992).
5. M. L. Belen'kii, *Elements of Quantitative Assessment of the Pharmacological Effect* [in Russian], Medgiz, Leningrad (1963).