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STUDIES IN THE SERIES OF 4(3H)-QUINAZOLONE. XVI. SYNTHESIS, STRUCTURE–ACTIVITY–TOXICITY RELATIONSHIP, AND ANTI-INFLAMMATORY ACTION OF 1-(3'-CHLOROBUT-2'-ENYL)-2-METHYL-3-ARYL-4(3H)-QUINAZOLONIUM PERCHLORATES

L. M. Korkodinova, M. I. Vakhrin, Yu. V. Kozhevnikov, V. S. Zalesov, L. G. Mardanova, and L. P. Drovosekova

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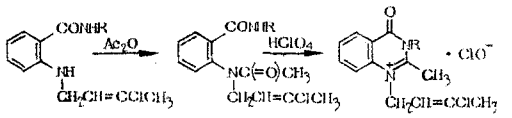
The synthesis of 4(3H)-quinazolinium perchlorates was described and their antispasmodic activity was shown in [3, 4, 8]. To study the influence of a substituent at the 1-position of the quinazoline ring on the biological activity and to show the structure–activity–toxicity relationship, we prepared a series of 1-(3'-chlorobut-2'-enyl)-2-methyl-3-aryl-4(3H)-quinazolinium perchlorates (IVa-d), starting from N-(3'-chlorobut-2'-enyl)anthranilic acid (I). The methyl ester of acid (I), obtained by esterification [2], was used to synthesize N-(3'-chlorobut-2'-enyl)-anthranilic acid arylamides (IIa-d) [5]. Acetylation of arylamides IIa-d leads to N-(3-chlorobut-2'-enyl)-N-acetylanthranilic acid arylamides (IIIa-d), which, when boiled in methanol with 50% perchloric acid, cyclize into perchlorates IVa-d



IIa-d IIIa-d IVa-d

IIa, IIIa, IVa: R = C_6H_5; IIb, IIIb, IVb: R = 2-$CH_3C_6H_4$; IIc, IIIc, IVc: R = 3-$CH_3C_6H_4$; IId, IIId, IVd: R = 4-$CH_3C_6H_4$.

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TABLE 1. Arylamides of N-(3'-chlorobut-2'-enyl)anthranilic Acid (IIa-d) and N-Acetylanthranilic Acid (IIIa-d)

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %	
			Cl	N		Cl	N
IIa	79	93—5	12,01	9,39	$C_{17}H_{17}ClN_2O$	11,79	9,31
IIб	68	110—2	11,00	8,60	$C_{18}H_{19}ClN_2O$	11,26	8,9
IIв	52	94—6	11,5	8,64	$C_{18}H_{19}ClN_2O$	11,26	8,9
IIг	77	113—5	10,98	8,95	$C_{18}H_{19}ClN_2O$	11,26	8,9
IIIa	68	154—5	10,18	8,41	$C_{19}H_{19}ClN_2O_2$	10,34	8,17
IIIб	57	129—31	9,65	7,91	$C_{20}H_{21}ClN_2O_2$	9,93	7,85
IIIв	53	152—4	9,70	8,00	$C_{20}H_{21}ClN_2O_2$	9,93	7,85
IIг	61	129—130	10,21	8,11	$C_{20}H_{21}ClN_2O_2$	9,93	7,85

Note. Compounds IIa-d and IIIa-d are crystallized from methanol.

TABLE 2. 1-(3'-Chlorobut-2'-enyl)-2-methyl-3-aryl-4(3H)-quinazolinium Perchlorates

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %		IR spectrum, ν_{max}, cm^{-1}
			Cl	N		Cl	N	
IVa	95	213—4	16,81	6,3	$C_{19}H_{18}Cl_2N_2O_5$	16,67	6,59	1720, 1620, 1500, 1550, 1460, 1290, 1100
IVб	78	215—7	16,32	6,51	$C_{20}H_{20}Cl_2N_2O_5$	16,14	6,38	1720, 1620, 1560, 1500, 1290, 1110
IVв	72	205—7	16,21	6,40	$C_{20}H_{20}Cl_2N_2O_5$	16,14	6,38	1730, 1620, 1555, 1495, 1460, 1300, 1110
IVг	77	233—5	16,18	6,40	$C_{20}H_{20}Cl_2N_2O_5$	16,14	6,38	1720, 1620, 1560, 1500, 1460, 1300, 1120

Note. Compounds IVa-d are crystallized from absolute ethanol.

TABLE 3. Structure—Activity—Toxicity Relationship in Compounds IVa-d

Compound	Concentration, mole %	Chemical shift of protons of 3-clorobut-2-enyl radical, Hz				Acute toxicity, mg/kg
		δ' (—CH_3)	δ'' (—CH=)	δ''' (—CH_2—)	δ'+δ''+δ'''	
IVa	0,95	134,6	346,4	311,3	792,3	570 (491—661)
IVb	0,97	135,3	347,1	315,0	797,4	350 (273—448)
IVc	0,95	134,6	345,7	311,6	791,9	300 (245—366)
IVd	0,99	134,7	346,3	311,7	792,7	450 (360—562)

Note. Here and in Table 4, the vibration limits are given in brackets.

TABLE 4. Anti-Inflammatory and Analgetic Activity of Compounds I, IVa-d

Compound	Acute toxicity: LD_{50}	Dose in experiment	Anti-inflammatory activity: increment in volume of rat's paw, % with respect to initial state		Analgetic action: duration of conditionally defensive reflex at peak of action, sec
	mg/kg		after 3 h	after 6 h	
I	230 (209—253)	46	94,4±3,8 P_1<0,5 P_2<0,001	94,0±3,8 P_1<0,5 P_2<0,001	16,0±1.8 P_1<0.25 P_2<0.001
IVa	570 (491—661)	115	110,2±14,7 P_1<0,1 P_2<0,001	100,8±11,6 P_1<0,5 P_2<0,001	15.1±1.9 P_1<0.01 P_2<0.002
IVb	350 (273—448)	70	101,9±11,3 P_1<0,1 P_2<0,001	90,8±7,3 P_1<0,5 P_2<0,001	13,5±0.8 P_1<0.5 P_2<0.001
IVc	300 (245—366)	60	60,2±4.5 P_1<0,01 P_2<0,01	49,6±4,9 P_1<0,001 P_2<0,05	14.0±1.9 P_1<0.1 P_2<0,001
IVd	450 (360—562)	90	97,5±3,9 P_1<0,5 P_2<0,001	83,5±2,1 P_1<0,1 P_2<0,001	12.3±2.0 P_1<0,5 P_2<0.001
Control (2% starch mucilage)		100	84,0±5,2	90,2±6,6	12.1±2.1
Reference standard (amidopyrine)		300	25.1±2,8	26,0±4,3	36,0±4.3

Note. P_1) Confidence limit compared with control, P_2) in comparison with standard (amidopyrine).

Perchlorates IVa-d are colorless crystalline compounds, sparingly soluble in ethanol, dioxane, and soluble un DMFA and DMSO. The composition and structure of the compounds were confirmed by IR and PMR spectra and data of elemental analysis. The following characteristic absorption bands were found in the IR spectra of perchlorates IVa-d: 1720-1730 (the Ar—C=O group), 1650-1660, 1550-1600, 1460-1500 (quinazolone bands), 1100-1120 cm^{-1} (intense band of perchlorate anion). Signals are observed in the PMR spectra of the compounds confirming their structure.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on a UR-20 spectrophotometer (GDR) in the form of a suspension in mineral oil, and the PMR spectra on a RYa-2310 spectrometer, using TMS as internal standard.

N-(3'-Chlorobut-2'-enyl)anthranilic acid (I). A 25 g porition (200 mmoles) of 1,3-dichloro-2-butene is added dropwise, with stirring, in the course of 3 h to a solution of 27.4 g (200 mmoles) of anthranilic acid. The precipitate is filtered, washed on the filter with 3 × 50 ml of cold water, and crystallized from methanol. Yellow needles mp 104-106°C.. Yield 51%. Calculated, %: NH 6.21; Cl 15.71. $C_{11}H_{12}ClNO_2$. Found, %: N 6.09; Cl 15.47. IR spectrum, λ_{max}, cm^{-1}: 3385, 3300, 1675, 1570, 1480, 1430, 1240, 1170.

N-(3'-Chlorobut-2'-enyl)anthranilic Acid Anilide(IIa). A 7 g portion (75 mmoles) of aniline in 15 ml of absolute ether is added to EtMgBr, prepared from 16.3 g (150 mmoles) of EtBr, 3.6 g (150 mmoles) of Mg in 50 ml of absolute ether. The mixture is heated for 30 min on a water bath, and then a solution of 12 g (50 mmoles) of acid I in 20 ml of absolute ether is added, and heating is continued for another 30 min. After completion of the reaction, the organomagnesium compound is decomposed by 10% CH_3COOH. The ether layer is separated, and the aqueous layer is extracted by 3 × 40 ml of ether. The solvent is steam-distilled from the ether extracts. Crystals, mp 93-95°C, Yield 68%. IR spectrum, λ_{max}, cm^{-1}: 3230, 1680, 1640, 1500, 1460, 1400, 1310. PMR spectrum (d_6-acetone), ppm: 1.93 t (CH_3); 3.77 d (CH_2); 5.5 m(—CH=); 6.17 ± 8.17 (10 H); 9.17 (NH). Compounds IIb-d (Table 1) were obtained in a similar way.

N-(3'-Chlorobut-2'-enyl)-N-acetylanthranilic Acid Anilide (IIIa). A solution of 3 g (10 mmoles) of IIa in 6 ml of Ac_2O is held at 80°C for 30 min. When cool, it is poured into 50 ml of water, and the excess Ac_2O is neutralized with Na_2CO_3 to pH 7.0-7.5. The precipitate that separated, is filtered, washed with 150 ml of water, and crystallized. mp 154-155°C. IR spectrum, λ_{max}, cm^{-1}: 3210, 1680, 1640, 1490, 1410, 1380, 1310, 1300.

Compounds IIIb-d (see Table 1) were obtained in a similar way.

1-(3'-Chlorobut-2'-enyl)-2-methyl-3-(4'-tolyl)-4(3H)-quinazolinium Perchlorate (IVd). A 2 g (10 mmoles) portion of 50% $HClO_4$ is added to a solution of 3.6 g (10 mmoles) of II in 20 ml of methanol, and the mixture is held on a water bath for 30 min. The precipitate that separates is filtered and crystallized. mp 233-235°C. Yield 77%. PMR spectrum (CF_3COOH); ppm: 2.2, 2.73 t (CH_3); 5.3 d (CH_2); 5.77 m (-CH=); 7.00-8.58 (8H).

Compounds IVa-c (Table 2) were obtained in a similar way.

PMR spectroscopy was used for studying the structure–activity–toxicity relationship and the biological activity. The PMR spectra were run in $AsCl_3$ at 25°C on a PS-60 spectrometer. The concentration of the compounds was kept constant, and was equal to (0.97 ± 0.02) mole %. Internal standard, TMS. The chemical shifts were measured by the method of lateral signals. An arithmetical mean of 4-6 measurements was taken as the observed chemical shift. The error of the determination did not exceeed ± 0.3 Hz (0.005 ppm). Table 3 shows that the overall chemical shift of protons of the 3'-chlorobut-2'-enyl radical at N(1) is smallest for compound IVc. In this case, the electron density on N(1) is highest. Compound IVc has a pronounced anti-inflammatory activity. With a decrease in the electron density on N(1), the toxicity of IVa,b,d, increases, and there is not anti-inflammatory activity.

EXPERIMENTAL (BIOLOGICAL)

Compounds I and IVa-d were studied for the presence of anti-inflammatory and analgetic activity. First, the acute toxicity (LD_{50}) was tested on nonpedigree white mice of both sexes, weighing 18-22 g each, with a single intraperitoneal administration and observation of the death of the animals in the course of 5 days. The anti-inflammatory action was studied on white rats of the Vistar line, weighing 160-220 g each obtained from "Stolbovaya" nursery, on a model of an aseptic formalin-induced inflammation. The value of the inflammatory reaction was determined oncometrically.

The analgetic activity was studied on mice weighing 18-20 g each, according to a "hot plate" test [9]. The effect was evaluated from the latent time of the defensive reflex 30 min, 1, 1½, 2, and 2½ h after administration. Amidopyrine in a dose of 1/3 LD_{50} (100 mg/kg) served as the reference standard for the anti-inflammatory and analgetic action. Compounds IVa-d were administered to the experimental animals in the form of a suspension with 2% starch mucilage in a dose of 1/5 LD_{50}. The control animals received the same volume of starch mucilage. The data obtained were treated statistically [1].

The LD_{50} for compounds IVa-d was within 300-600 mg/kg, hence they are considered to be slightly toxic [7]. The initial acid I is more toxic and has no anti-inflammatory activity. It was found that the introduction of phenyl, o- or p-tolyl radicals into the 3-position of the quinazolone ring does not lead to the appearance of activity; only IVc has an anti-inflammatory activity (Table 4).

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-ARYLIMINOBARBITURIC ACIDS

A. S. Zaks, S. B. Goncharenko,
V. G. Voronin, E. A. Usachev,
Yu. V. Portnov, Yu. M. Rabotnikov,
and L. E. Pchelintseva

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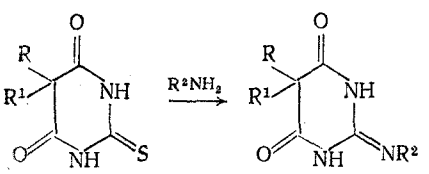
Derivatives of 2-thiobarbituric acid with their clearly marked soporific action occupy an important place among synthetic medicinal agents. The substitution of the thione group by the protected amino group leads to the appearance of new types of biological action [6]. We previously [1] accomplished the synthesis of a series of unknown 4-aryl(aralkyl)iminobarbituric acids among which compounds possessing antiphlogistic activity were found [2]. The aim of the present work was the synthesis and investigation of the anti-inflammatory and analgesic activity of the 2-aryliminobarbituric acids (II*a*-m) which are isomeric with them. Several methods for the synthesis of such compounds are known; these utilize both the methods of cycilization of malonic esters or the acid chlorides of malonic acids with substituted guanidines [8, 10] and the direct substitution of the thio, methylthio, or imino group by the substituted imino group [6, 7, 9]. The synthesis of the compounds II*a*-m was accomplished by us in the reaction of the 2-thiobarbituric acids (I*a*, b) with amines according to [1].



I*a*, b II*a*-m

I*a*, II*a*-h: R = R¹ = Et; Ib, III-m: E = Et, R¹ = Am-sec; II*a*, i: R² = Ph; IIb: R² = CH_2Ph; IIc, j: R² = C_6H_4Me-p; IId,k: R² = C_6H_4Me-m; IIe: R² = C_6H_4Cl-m; IIf,l: R² = C_6H_4OMe-p; IIg: R² = C_6H_4OMe-m; IIh,m: R² = C_6H_4OMe-o.

Heating the 2-thiobarbituric acids I*a*, b with an excess of the amine without a solvent at 160-180°C in the course of 6-12 h leads to the formation of the iminobarbituric acids IIa-m. The compounds obtained are white, high-melting, and crystalline substances. Their IR spectra contain absorption bands corresponding to the vibrations of the NH and the C=O, C=N, and C=C groups in the region of 3300-3000 and 1700-1500 cm^{-1} respectively.

EXPERIMENTAL (CHEMICAL)

The IR spectra were taken on a Perkin-Elmer 577 spectrophotometer for the suspensions in mineral oil. The control of the course of the reactions and the purity of the compounds obtained was performed using thin layer chromatography on plates of Silufol UV-254 in the

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