SYNTHESIS AND ANTIINFLAMMATORY PROPERTIES OF o-CARBOXYPHENYLAMINO PYRIMIDINES

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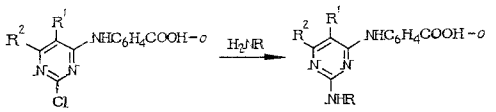
Pyrimidine derivstives substituted with an o-carboxyphenylamino group at the 2, 4, or 5 position of the pyrmidine ring are physiologically active compounds [1-5].

The aim of the present work is to synthesize new o-carboxyphenylaminopyridines, with a phenylamino-, hydrazino-, or o-carboxyphenylamino group in the 2 position (Ia-f) and to study their antiinflammatory activity.



Ia:R = C_6H_5, $R^1 = R^2 = H$; Ib.R = NH_2, $R^1 = R^2 = H$;
Ic:R^1 = Br, $R^2 = CH_3$; Id:$R^1 = H$, R^2 = COOH;
Ie:$R^1 = H$, R_2 = Cl; If:$R^1 = H$, $R^2 = CH_3$;
Ic-f:R = C_6H_4COOH-*o*

Compounds Ia-f were obtained by the reaction of 2-chloro-4-(o-carboxyphenylamino) pyrimidines [6] with aniline, hydrazine, or anthranilic acid. The pyrmidines Ic-f were isolated as the hydrochlorides.

The 4-(o-carboxyphenylamino)pyrimidines Ia-f are yellow, crystalline substances, soluble in DMFA, DMSO, dilute acids, and bases; their properties are given in Table 1. The purity of compounds Ia-f were checked by TLC on UV 254 Silufol plates (ChSSR). Two solvent systems were used as eluents: 1) n-butanol—acetic acid—water (4:1:5); 2) alcohol—25% aqueous ammonia (10:1).

The IR spectra of compounds Ia-f (KBr pellets) showed absorptions due to stretching vibrations at 3400 cm^{-1} (OH and NH), 1600-1620 cm^{-1} (C=O), and 1580 cm^{-1} (C=C and C=N of the pyrimidine ring), and absorptions due to deformation vibrations at 1450 cm^{-1} (NH and OH of the pyrimidine ring), 1220-1240 cm^{-1} (C=C), and 750 cm^{-1} (pyrimidine ring CH).

EXPERIMENTAL CHEMISTRY

Infrared spectra were taken on a Perkin-Elmer instrument (Sweden), UV spectra of ethanol solutions on an MPS-5000 spectrophotometer (Japan), c = $1 \cdot 10^{-5}$ moles/liter.

2-Phenylamino-4-(o-carboxyphenylamino) pyrimidine (Ia). To 4.6 g (0.2 moles) of metallic sodium dissolved in 50 ml of absolute methanol was added 18.6 g (0.2 moles) of aniline and 24.9 g (0.1 moles) of 2-chloro-4-(o-carboxyphenylamino)pyrimidine. The reaction mixture was heated in a sealed tube at 110°C for 6 h, cooled, the precipitated sodium chloride filtered off, the filtrate diluted with water and neutralized with 50% acetic acid to pH 6.0. The precipitate was filtered off, washed with water and ethyl alcohol, and recrystallized from ethanol.

2-Hydrazino-4-(o-carboxyphenylamino)pyrimidine (Ib). A stirred mixture of 24.9 g (0.1 moles) of 2-chloro-4-(o-carboxyphenylamino)pyrimidine and 10 g (0.2 moles) of hydrazine hydrate in 30 ml of methanol was heated under reflux on a water bath for 3 h. The precipitated material was filtered off and recrystallized from 50% aqueous ethanol.

Hydrochloride of 2,4-Di-(o-carboxyphenylamino)-5-bromo-6-methylpyrimidine (Ic). A mixture of 34.2 g (0.1 moles) of 2-chloro-4-(o-carboxyphenylamino)-5-bromo-6-methylpyrimidine

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TABLE 1. o-Carboxyphenylaminopyrimidines Ia-f

Compound	Yield, %	Melting point, °C	Found, %		Empirical formula	Calculated, %		$R_f \cdot 100$ in system		UV spectra λ_{max} in ethanol, nm
			N	Cl		N	Cl	1	2	
Ia	81	279—80	18,30	—	$C_{17}H_{14}N_4O_2$	18,28	—	41	74	214, 274, 328
Ib	80	229—31	18,82	—	$C_{11}H_{11}N_5O_2$	28,56	—	33	52	216, 242, 319
Ic	80	298—9	11,79	7,55	$C_{19}H_{15}BrN_4O_4HCl$	11,68	7,39	52	48	228, 283, 336
Id	84	260	12,83	8,21	$C_{19}H_{14}N_4O_6 \cdot HCl$	13,01	8,23	14	20	284, 348
Ie	76	210	14,30	8,86	$C_{18}H_{12}ClN_4O_4HCl$	14,58	9,22	64	52	234, 279, 336
If	80	285	14,16	8,58	$C_{19}H_{16}N_4O_4 \cdot HCl$	13,87	8,84	54	45	232, 280, 326

TABLE 2. Antiinflammatory Properties of the o-Carboxyphenylaminopyrimidines Ia-f

Compound	LD_{50}, mg/kg (intraperitoneally)	% decrease of formalin edema of the paw	Increase in threshold of pain sensitivity in mice, %	Antipyretic action in rats ($\Delta t°$)
Ia	1130	28,5±4,4	127,3±17,6	1,5±0,18
Ib	640	13,4±6,0	—	—
Ic	330	9±3,2	53±7,4	1,9±0,26
Id	460	48±6,0	62±4,6	2,0±0,13
Ie	550	34±4,9	54±7,7	2,3±0,9
If	400	45±3,2	74±6,0	1,3±0,22
Sodium mefenamate	150	30,6±7,8	55,1±5,0	1,5±0,22

and 13.85 g (0.11 moles) of anthranilic acid was heated on an oil bath at 100°C for 2 h. The precipitate formed was filtered off, washed with alcohol, and recrystallized from 50% acetic acid. Compounds Id-f were obtained in the same way from substituted 2-chloro-4-(o-carboxyphenylamino)pyrimidine and anthranilic acid.

EXPERIMENTAL BIOLOGY

A study was made of the acute toxicity, antiinflammatory, analgesic, and antipyretic activity of the 4-(o-carboxyphenylamino)pyrimidines Ia-f. The data obtained are given in Table 2.

Acute toxicity was determined by intraperitoneal injection into white mice of both sexes weighing 20-25 g; antiinflammatory and antipyretic action on rats of both sexes weighing 150-200 g.

Antiinflammatory action of the substances was determined from observations of edema of the rear paw of the rat, induced by the supplantar injection of 2% formalin. The test compounds were injected intraperitoneally as suspensions in starch at a dosage of 1/10 of the LD_{50} 30 min before the injection of formalin. The volume of the paw was measured plethymographically 4 h after the injection of the inflammatory agent.

The antipyretic activity of the compounds was studied in tests on rats with milk fever caused by the injection of boiled skimmed cow's milk heated to 37-40°C (intramuscularly; 1 ml per 100 g of body weight). Compounds Ia-f were injected at the peak of the fever and the antipyretic action monitored over a period of 3 h.

The analgesic activity was studied on white mice weighing 20-25 g by the method described in [7, 8] by determining the threshold of sensitivity of heat. Pyrimidines Ia-f have low toxicity with LD_{50} of 330-1130 mg/kg. The toxicity depends somewhat on chemical structure. The 2-(o-carboxyphenylamino)pyrimidines are more toxic than their analogs with an unsubstituted phenylamino or hydrazino group in the 2 position of the pyrimidine ring. The most toxic compound was Ic — 2,4-di(o-carboxyphenylamino)-5-bromo-6-methylpyrimidine.

Compounds Ia-f possess antiinflammatory properties and suppressed the development of formalin edema of the paw. The most active compounds were the 2,4-di(o-carboxyphenylamino)-pyrimidines Ic-f.

All the compounds also exhibited analgesic properties: The most active was 2-phenylamino-4-(o-carboxyphenylamino)pyrimidine Ia.

These compounds exhibited antipyretic action lowering the body temperature of a rat with milk fever. Most active were the 2,4-di(o-carboxyphenylamino)pyrimidines. In this group of compounds, preparation Ie — 2,4-di(o-carboxyphenylamino)-6-chloropyrimidine had the greatest antipyretic effect.

Thus, compounds Ia-f are less toxic than sodium mefenamate or brufen, and exhibit anti-inflammatory, analgesic, and antipyretic action.

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BROMINE ANALOGS OF QUINOXIDINE, DIOXIDINE, AND AMIDES OF DI-N-OXIDES OF 3-HYDROXYMETHYLQUINOXALINE-2-CARBOXYLIC ACID

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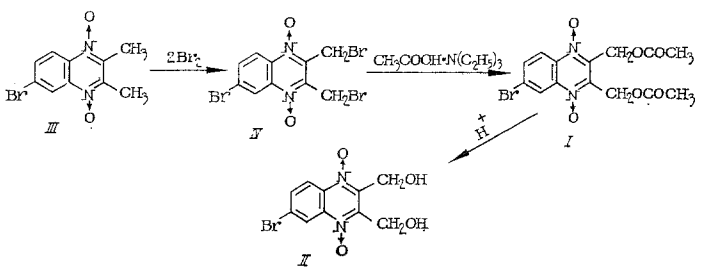
We investigated the synthesis of bromine analogs of the biologically-active quinoxaline derivatives quinoxidine, dioxidine, and amides of di-N-oxides of 3-hydroxymethylquinoxaline-2-carboxylic acid [1-3] in order to study their biological activity.

The bromine analogs of quinoxidine [2,3-bis(acetoxymethyl)-7-bromoquinoxaline-di-N-oxide (I)] and dioxidine [2,3-bis(hydroxymethyl)-7-bromoquinoxaline-di-N-oxide (II)] were synthesized as indicated in the scheme below from 2,3-dimethyl-7(6)-bromoquinoxaline-di-N-oxide (III) by means of the intermediate 2,3-bis(bromomethyl)-7(6)-bromoquinoxaline-di-N-oxide (IV).



Amides of 3-hydroxymethyl-7-bromoquinoxaline-2-carboxylic acid di-N-oxide (XXIIIa-i) were synthesized from 2-carbethoxy-3-methyl-7-bromoquinoxaline-di-N-oxide (V), which was in turn prepared by a known method: the reaction of 5(6)-bromobenzofuroxane (VI) with esters of acetoacetic acid in the presence of various basic reagents [4, 5]. These authors recommended the use of the 7- and 6-bromo isomers of 2-carbalkoxy-3-methylquinoxaline-di-N-oxide

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