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SYNTHESIS, TRANSFORMATIONS, AND BIOLOGICAL PROPERTIES OF 7,8-DISUBSTITUTED XANTHINES

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Derivatives of xanthine are valuable medicinal compounds having, in particular, pronounced bronchiolytic properties [1]. Theophylline and euphylline, used for prophylaxis and curing of bronchospasms in bronchial asthma [7], block phosphodiesterase in lung tissues and cause the accumulation of cyclic adenosine triphosphate [9].

Based on the above considerations, and in view of the urgency of finding new broncholytic preparations, we investigated the synthesis of several 7,8-disubstituted xanthines in order to study their broncholytic activity.

7-(2,3-Dihydroxypropyl)-8-bromotheophylline (II) was obtained by the reaction of 8-bromotheophylline (I) with glycidol in the presence of catalytic quantities of pyridine. The previously described [3, 8] 6,8-dimethyl-2-hydroxymethyloxazolino[3,2-f]xanthine (III) was obtained by the action of an equimolar amount of an alcoholic solution of alkali on the dihydroxy derivative II.

The derivatives of 7-(2,3-dihydroxypropyl)-8-aminotheophylline (IV-VIII) were synthesized by aminolysis of compounds II and III. It should be noted that the preparation of amines from oxazolinoxanthine III by cleaving the oxazoline ring proceeds much more easily than by substitution of the bromine atom in the bromo derivative II.

8-Bromotheophyllinyl-7-acetaldehyde (IX) was obtained by glycolic cleaving of compound II by periodic acid. In the case of the oxidation of amino alcohols, for example VII and VIII, the amino-aldehydes (X, XI) could not be isolated, since they undergo cyclization into the derivatives of imidazo[1,2-f]xanthine (XIII, XV). To confirm the above scheme of transformations, we prepared a series of derivatives of imidazo[1,2-f]xanthine XII-XV by the reaction of aldehyde IX with primary amines.

The structure of the synthesized compounds II-XV was confirmed by the data of IR and PMR spectroscopy. (See Scheme at top of next page.)

EXPERIMENTAL CHEMICAL

The IR spectra were run on an UR-20 spectrophotometer (GDR) in KBr tablets and in mineral oil. The PMR spectra were obtained on a "Tesla-487C" spectrometer (80 MHz) at 20°C, using HMDS as internal standard.

7-(2,3-Dihydroxypropyl)-8-bromotheophylline (II). A mixture of 25.9 g (0.1 mole) of 8-bromotheophylline (I), 8.15 g (0.11 mole) of glycidol, and 1.5 ml of pyridine in 150 ml of propanol was heated at the boiling point for 90 min. It was then cooled and the precipitate was filtered. The data on the compounds synthesized are given in Table 1.

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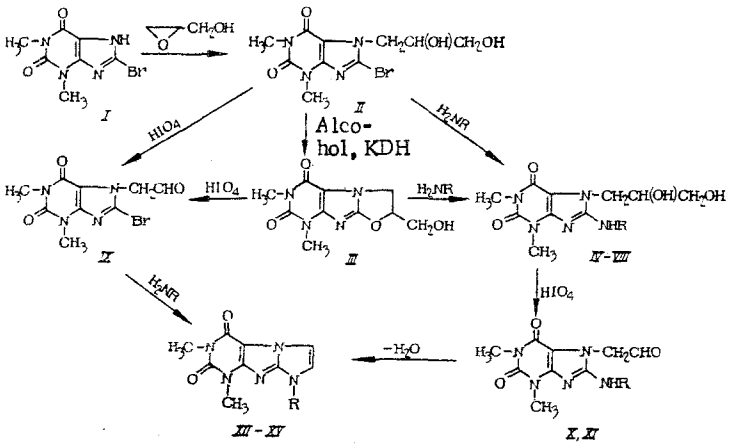

R = H (IV); CH_3 (V); CH_2CH_2OH (VI, XII); n-C_4H_9 (VII, X, XIII) $CH_2C_6H_5$ H (VIII, XI, XV); cyclohexyl (XIV).

TABLE 1. Physicochemical Properties of 7,8-Disubstituted Xanthine II-VIII and Derivatives of Imidazo[1,2-f]xanthine

Compound	Yield, %		Melting point, °C	Found, %				Empirical formula	Calculated, %			
	method A	method B		C	H	N	Br		C	H	N	Br
II	83	—	152—154	36.0	3.8	17.0	24.0	$C_{10}H_{13}BrO_4$	36.1	3.9	16.8	24.0
III	71	—	258—260	...	...	22.3	—	$C_{10}H_{11}N_5O_3$	...	...	22.3	—
IV	54	—	242—243	44.5	5.7	26.0	—	$C_{10}H_{15}N_5O_4$	44.6	5.6	26.0	—
V	54	—	212	46.4	6.3	24.6	—	$C_{11}H_{17}N_5O_4$	46.6	6.0	24.7	—
VI	51	83	164—166	46.2	6.3	22.3	—	$C_{12}H_{19}N_5O_5$	46.0	6.1	22.4	—
VII	65	80	152—153	51.6	7.0	21.7	—	$C_{14}H_{23}N_5O_4$	51.7	7.1	21.5	—
VIII	58	74	143—145	56.8	5.8	19.1	—	$C_{17}H_{21}N_5O_4$	56.8	5.9	19.5	—
IX	70	—	189—191	35.7	3.3	18.9	26.7	$C_9H_9BrN_4O_3$	35.9	3.3	18.6	26.5
XII	—	45	250—251	49.9	5.1	26.7	—	$C_{11}H_{18}N_6O_3$	50.2	5.0	26.6	—
XIII	39	47	227—229	57.0	6.4	25.6	—	$C_{13}H_{17}N_5O_2$	56.7	6.2	25.4	—
XIV	55	66	208—210	60.1	6.5	23.0	—	$C_{16}H_{19}N_5O_2$	59.8	6.4	23.2	—
XV	60	65	180—181	62.2	4.7	22.4	—	$C_{16}H_{15}N_5O_2$	62.1	4.9	22.6	—

Note. Compounds IX and XII were recrystallized from water, II-VI from absolute methanol, VII and VIII from absolute acetone, XIII-XV from 50% alcohol.

2-Hydroxymethyl-6,8-dimethyloxazolino[2,3-f]xanthine (III). A mixture of 2.6 g (0.01 mole) of I, 0.4 g (0.01 mole) of NaOH, and 0.82 g (0.11 mole) of glycidol in 40 ml of 80% alcohol was heated at the boiling point for 90 min, then was evaporated to half its volume, and poured into 50 ml of water. The crystalline precipitate that separated was filtered.

7-(2,3-Dihydroxypropyl)-8-β-hydroxyethylaminotheophylline (VI). Method A. A mixture of 3.83 g (0.01 mole) of II and 1.83 g (0.603 mole) of monoethanolamine in 50 ml of ethanol was heated in an autoclave (150 ml) at 160-170°C for 6-7 h. After opening the autoclave, the reaction mixture was evaporated to dryness and crystallized twice from absolute methanol or acetone. Compounds VII and VIII were obtained in a similar way. To obtain compounds IV and V, 50-ml portions of 10% solutions of ammonia and methylamine, respectively, were used. Method B. A 1.22-g (0.02 mole) portion of monoethanolamine was added to a warm solution of 2.5 g (0.01 mole) of III in 40 ml ethylene glycol monoethyl ether, and the mixture was heated at the boiling point for 7-8 h. After cooling, the precipitate was separated.

Compounds VII and VIII were obtained in a similar way.

8-Bromotheophyllinyl-7-acetaldehyde (IX). Periodic acid dihydrate (4.9 g, 0.022 mole) was added in small portions in the course of 1 h and with stirring to a solution of 0.66 g (0.02 mole) of II in 90 ml of water. Thirty minutes from the beginning of the addition of periodic acid, an abundant flake-like precipitate began to separate from the solution. The reaction mixture was allowed to stand for 10 h, and then the precipitate was filtered and washed with cold water.

1-Benzyl-6,8-dimethylimidazo[1,2-f]xanthine (XV). Method A. Periodic acid dihydrate (4.9 g, 0.022 mole) was added in small portions in the course of 30 min, with stirring, to

TABLE 2. Influence of 7,8-Disubstituted Xanthines on Tonus of Bronchi in Cats

Compound	LD_{50}	Decrease in tonus of bronchi, %
IX	341,7±3,1	27,0±6,16
VII	345,0±28,1	22,0±6,2
VIII	555,0±19,0	28,0±10,9
IV	605,0±18,8	51,0±11,2
V	641,7±27,0	25,0±10,7
II	1330,0±16,8	—
VI	2947,5±141	16,0±11,5
Euphylline	194±13,6	47,7±5,2

a solution of 3.6 g (0.01 mole) of VIII in 80 ml of water. The reaction mixture was allowed to stand for 10 h. The precipitate that separated was filtered and washed with water.

Compounds XIII and XIV were obtained in a similar way.

Method B. A mixture of 3.6 g (0.01 mole) of IX and 3.2 g (0.03 mole) of benzylamine in 60 ml of ethanol was heated in an autoclave (150 ml) at 140°C for 8 h. After cooling, the precipitate of compound XV was filtered.

Compounds XII-XIV were obtained in a similar way.

EXPERIMENTAL PHARMACOLOGICAL

The bronchiolytic activity of the compounds synthesized was studied on narcotized (Nembutal, 40 mg/kg, intraperitoneally) and curare-treated (myorelaxin, 1 mg/kg, intravenously) cats, each weighing 1.5-2.6 kg. The tonus of bronchi was recorded by the Koncett and Rosler procedure in the T. M. Turpaev modification [6]. The experimental biospasm was induced by proserine (0.25 mg/kg) and (or) carbocholine (5 μg/kg). The compounds studied and euphylline, used for comparison, were introduced in a dose of 8 mg/kg in the form of aqueous solutions. The data obtained were statistically processed by means of the R. B. Strelkov tables [5].

The acute toxicity of the compounds studied was determined by intraperitoneal administration to white mice of both sexes, weighing 21-27 g each, and was calculated according to Kerber [4].

The prophylactic broncholytic action of 7-(2,3-dihydroxypropyl)-8-aminotheophylline IV was studied using doses of 2 and 4 mg/kg with intramuscular administration during serotonin (10 μg/kg) and histamine (10 μg/kg) induced bronchospasm in guinea pigs by the method of M. É. Kaminka [2].

The acute toxicity and the influence on the tonus of bronchi of the compounds studied are given in Table 2.

Analysis of the data obtained on the broncholytic activity of xanthine derivatives shows that 7-(2,3-dihydroxypropyl)-8-aminotheophylline IV has the greatest activity. This compound somewhat surpasses euphylline in its bronchiolytic activity, and it is three times less toxic than the latter compound. Moreover, in doses of 2 and 4 mg/kg, the compound prevents histamine bronchiospasm in guinea pigs, 3 min after the introduction by 28 ± 4.1 and 41.4 ± 7.6%, respectively, and after 20 min, the similar effect is equal to 13.7 ± 7.6 and 19.3 ± 4.1%. Decrease in the serotonin-induced bronchiospasm by the action of compound IV was less pronounced (by 26.3 ± 8.6%) and was observed 3 min after the introduction of the preparation in a dose of 4 mg/kg. This shows that compound IV has a noncompetitive antihistamine and antiserotonin action, and hence also a myotropic and spasmolytic effect.

In several derivatives of 7-(2,3-dihydroxypropyl)-8-aminotheophylline, the replacement of the hydrogen atom by alkyl, hydroxyalkyl, and aralkyl groups leads to weakening of the bronchiolytic action, and when the amino group at the 8-position is replaced by a bromine atom, this action disappears in general, while introduction of the dihydroxypropyl group

into the 7-position in place of the aldehyde residue results in the bronchiolytic activity reappearing.

Continued search for new 7,8-disubstituted derivatives of xanthine having a bronchiolytic activity appears to be promising.

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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF ACYLATED BENZOXA- AND BENZODIOXAHETEROCYCLES AND THEIR ACYCLIC ANALOGS

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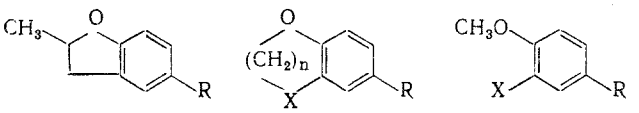
Some benzoylated benzoxa- and benzodioxaheterocycles have been found to possess antiinflammatory activity [5]. With the aim, therefore, of investigating structure–activity relationships and of identifying novel antiinflammatory drugs, we have synthesized and tested benzoxa- and benzodioxaheterocycles and their acyclic analogs, containing an acyl substituent of the aliphatic series (Ib-f, i, IIc, i, IIIc, i, IVc, i, Vc, f-j, VIc, i, VIIi, VIIIi, IXc, f, i) or cinnamoyl (IIk-VIIk, IXk) which have either not previously been reported, or the antiinflammatory activity of which was not known.



I II — VII VIII, IX

II, V: $n = 1$; III, VI: $n = 2$; IV, VII: $n = 3$; II — IV $X = CH_2$; V — VII: $X = O$; VIII: $X = C_2H_5$; IX: $X = OCH_3$; Ia — IXa: $R = H$; Ib — IXb: $R = COCH_3$; Ic — IXc: $R = COCH_2CH_3$; Id — IXd: $R = CO(CH_2)_2CH_3$; Ie — IXe: $R = COCH(CH_3)_2$; If — IXf: $R = CO(CH_2)_2Cl$; Ig — IXg: $R = CO(CH_2)_3Cl$; Ih — IXh: $R = COCH_2N(CH_3)_2 \cdot HCl$; Ii — IXi: $R = CO(CH_2)_2N(CH_3)_2 \cdot HCl$; Ij — IXj: $R = CO(CH_2)_3N(CH_3)_2 \cdot HCl$; Ik — Ik: $R = COCH{=}CHC_6H_5$.

The ketones and chloroketones (Ib-f), (IIc, k), (IIIc, k), (IVc, k), (Vc, f, g, k), (VIc, k), (VIIk), (IXc, f, k) were obtained by the Friedel–Crafts acylation of the benzoxa- or benzodioxaheterocycles (Ia-VIIa) or 1,2-dimethoxybenzene (IXa) with acid chlorides in the presence of anhydrous $AlCl_3$ of $SnCl_4$, the β-aminoketone hydrochlorides (Ii-IXi) by the Mannich reaction of the appropriate acetyl compounds (Ib-IXb) with dimethylamine hydrochloride and paraformaldehyde, and the γ-aminoketone (Vj) by treatment of the chloroketone (Vg) with dimethylamine.

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