Comparison of the toxic properties of (XI) and (XII) (Table 2) shows that the introduction of a formyl group into the benzene ring of the pyrroloindole (X) quantitatively enhances its biocial activity.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SOME 6,8-DIMETHYLIMIDAZO[1,2-f]XANTHINE DERIVATIVES

B. A. Priimenko, B. A. Samura, E. A. Skul'skaya, D. A. Troshin, S. N. Garmash, and N. P. Milonova

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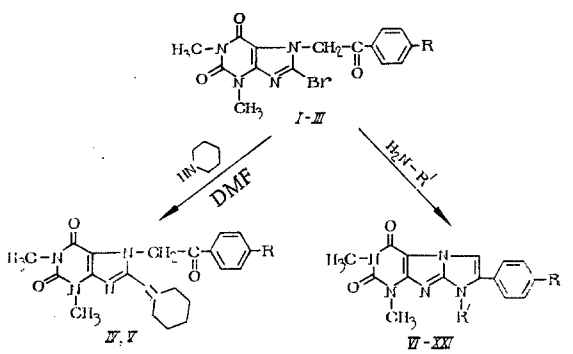
Xanthine derivatives have found extensive applications in medicine (theophyllin, theobromine, caffeine, and diprophyllin) [8]. 6H,8-methylimidazo[1,2-f]xanthines display high diuretic and neuroleptic activity [3]. There have been literature reports of the biological activity of some 6,8-dimethylimidazo[1,2-f]xanthines [5].

We have obtained some hitherto undescribed derivatives of 6,8-dimethylimidazo[1,2-f]xanthine, and examined their pharmacological properties.

The starting materials were 7-acylmethyl-8-bromotheophyllins (I-III) [9], which were reacted with primary and secondary amines to give the 6,8-dimethylimidazo[1,2-f]xanthines (VI-XXI) or 7-acylalkyl-8-cycloalkylaminotheophyllins (IV, V).



I:R = OCH_3; II:R = CH_3; III:R = C_2H_5; IV:R = OCH_3; V:R = CH_3; VI:R′ = $CH_2C_6H_5$; R = CH_3; VII:R′ = n-C_4H_9; R = C_2H_5; VIII:R′ = $C_6H_4OCH_3$-p; R = CH_3; IX:R′ = cyclohexyl; R = CH_3; X:R′ = $(CH_2)_2OH$; R = CH_3, XI:R′ = $(CH_2)_3OH$; R = CH_3; XII:P = R^I = CH_3; XIII:R^I = n-C_4H_9; R = CH_3; XIV:R = n-C_4H_9; R = OCH_3; XV:R′ = C_6H_5; R = C_2H_5; XVI:R′ = cyclohexyl; R = C_2H_5; XVII:R, = $C_6H_4CH_3$-n; R = CH_3; XVIII:R′ = $C_6H_4OC_2H_5$-p; R = OCH_3; XIX:R′ = $C_6H_4OCH_3$-p; R = C_2H_5; XX:R′ = $C_6H_4OCH_3$-p; R = OCH_3; XXI:R′ = C_6H_5; R = CH_3.

Zaporozhe Medical Institute.

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TABLE 1. 6,8-Dimethylimidazo[1,2-f]xanthines

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			LD_{50}, mg/kg
			C	H	N		C	H	N	
VI	78	224—226	69,3	5,7	16,47	$C_{23}H_{21}N_5O_2 \cdot H_2O$	69,15	5,3	16,78	515,0±15,9
VII	56	108—110	66,97	8,82	18,50	$C_{21}H_{21}N_5O_2$	67,18	5,64	18,66	730,0±31,8
VIII	83	306—307	66,65	5,35	16,90	$C_{23}H_{21}N_5O_3$	66,49	5,09	16,86	1880,0±32,1
IX	78	158—160	67,52	6,63	18,20	$C_{22}H_{25}N_5O_2$	67,32	6,42	17,85	1204,0—33,7
X	56	220—221	61,37	3,17	20,01	$C_{18}H_{19}N_5O_3$	61,17	5,42	19,82	142,5±9,3
XI	62	172—174	62,32	5,41	19,45	$C_{19}H_{21}N_5O_3$	62,1	5,76	19,06	215,0±16,6
XII	53	201—203	66,0	5,32	21,47	$C_{17}H_{17}N_5O_2$	65,6	5,47	21,14	218,0±13,6
XIII	63	229—231	—	—	19,33	$C_{20}H_{19}N_5O_2$	—	—	19,38	265,0±16,1
XIV	67	251—253	—	—	18,29	$C_{20}H_{19}N_5O_3$	—	—	18,56	220,0±15,9
XV	92	270—272	69,25	5,50	17,70	$C_{23}H_{21}N_5O_2$	69,15	5,29	17,53	655,0±16,1
XVI	76	116—118	—	—	17,31	$C_{23}H_{27}N_5O_2$	—	—	17,27	720,0±14,1
XVII	88	352—354	70,25	5,47	17,78	$C_{23}H_{21}N_5O_2$	69,11	5,23	17,53	1370,0±42,2
XVIII	73	276—280	65,0	5,49	16,0	$C_{24}H_{23}N_5O_2$	64,7	5,2	15,72	1430,0±31,8
XIX	92	244—246	67,45	5,57	16,53	$C_{24}H_{23}N_5O_3$	67,12	5,39	16,31	315,0±15,9
XX	87	290—292	64,48	5,18	16,47	$C_{28}H_{21}N_5O_4$	64,02	4,9	16,23	300,0±19,3
XXI	91	304—306	68,75	5,03	18,20	$C_{22}H_{19}N_5O_2$	68,55	4,96	18,17	1870,0±31,8

The structures of the compounds obtained were confirmed by their elemental analysses and IR spectra. The IR spectrum of (IV) and (V) showed absorption for the amide carbonyl groups at 1710-1690 cm^{-1}; absorption of the ketone carbonyl was shifted to higher frequencies (1725-1715 cm^{-1}). Absorption for the methyl and methylene groups occurred at 2985-1975 and 2855-2845 cm^{-1}, respectively. The IR spectra of (VI-XXXI) showed absorption typical of these systems [10, 11], confirming the presence of the imidazo[1,2-f]xanthine system. The presence of two carbonyl groups in the uracil moiety of tricycles (VI-XXI) was confirmed by the presence in their IR spectra of typical strong absorption at 1715-1700 and 6765-1665 cm^{-1}. The IR spectra of (VIII), (XIV), and (XVIII-XX) were also characterized by the occurrence of a series of strong absorption bands at 1260-1215 and 1120-1070 cm^{-1}, confirming the presence of alkoxyaryl groups.

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a UR-20 instrument (East Germany) in KBr disks. p-Toluoylmethyl-8-bromo- (II) and p-methoxybenzoylmethyl-8-bromotheophyllins (I) were obtained as described in [9].

p-Ethylbenzoylmethyl-8-bromotheophyllin (III). The potassium salt of 8-bromotheophyllin (5.94 g, 0.02 mole) and 4.54 g (0.02 mole) of p-ethyl-α-bromoacetophenone were heated at the boil in 50 ml of DMF for 1 h, cooled, diluted with an equal volume of water, and the solid filtered off to give 6.2 g (76.5%), mp 179-180°C. Found %: C 50.50; H 4.65; N 14.00; Br 20.1; $C_{17}H_{17}N_4BrO_3$. Calculated, %: C 50.38; H 4.23; N 13.83; Br 19.72.

7-p-Methoxybenzoylmethyl- (IV) and 7-p-Toluoylmethyl-8-N-piperidinotheophyllin (V). A mixture of 0.01 mole of (I) or (II) and 0.02-0.03 mole of piperidine in 50 ml of DMF was heated at the boil for 4 h. The mixture was then cooled, diluted with an equal volume of water, and the solid filtered off to give 76% of (IV) and 83% of (V). mp of (IV), 230-232°C (from water—DMF). Found %: C 70.31; H 6.43; N 17.44; $C_{21}H_{25}N_5O_4$. Calculated, %: C 70.22; H 6.12; N 17.02; mp of (V), 219-221°C. Found, %: C 63.87; H 6.58; N 18.0. $C_{21}H_{25}N_5O_3$. Calculated, %: C 63.77; H 6.37; N 17.71.

6,8-Dimethylimidazo[1,2-f]xanthines (VI-XXI) were obtained by literature methods [6]. For constants, see Table 1.

EXPERIMENTAL PHARMACOLOGY

The acute toxicities and the antiinflammatory, diuretic, and neurotropic activity of the compounds were examined in laboratory animals.

Acute toxicities were determined in white mongrel mice of both sexes, weighing 18-27 g. The compounds were administered intraperitoneally as 3-5% finely divided aqueous suspensions stabilized by Tween-80. Each dose was tested in 5-7 animals. The animals were kept under observation for 10 days, and the LD_{50} values were calculated by Kerber's method [1] (Table 1).

Administration of toxic doses of the drugs resulted in the deaths of the animals by respiratory arrest and the cessation of cardiac activity. Treatment of the animals with tolerated doses, with the exception of (IV), caused adynamia and general depression. Compound (IV) gave rise to increased motor activity and faster respiratory movements, and in toxic doses it resulted in clonic—tonic convulsions.

Examination of the acylalkyl compounds (III-V) showed them to be of low toxicity, the LD_{50} values being 740 ± 46.9 mg/kg (III), 1730 ± 31.7 mg/kg (IV), and 1380 ± 32.0 mg/kg (V).

Tricyclic compounds containing an aryl substituent in the 1 position were less toxic (according to the LD_{50} values) than compounds containing alkyl substituents (Table 1).

Examination of the antiinflammatory activity of the compounds was carried out by a modified method [7] in two models (formalin and dextran) of aseptic exudative inflammation in white rats.

The animals were treated beneath the aponeurosis plantaris with 0.1 ml of the phlogogenic agent (2% formalin or 6% dextran solution). The intensity of the inflammatory reaction was estimated by the change in volume of the inflamed extremity of the animal (volumetrically). The volume of the extremity was measured at the beginning of the experiment, and 1, 3, and 5 h after the introduction of the phologenic agent. The increase in volume of the paw over the original volume before administration of the phlogogen was estimated.

TABLE 2. Antiinflammatory Activity of the Compounds Obtained

Compound	Increase in volume of the extremities, %								
	after 1 h			after 3 h			after 5 h		
	$M \pm m$	% of controls	P	$M \pm m$	% of controls	P	$M \pm m$	% of controls	P
Formalin model									
Control	35,0±3,9	—	—	48,2±5,4	—	—	49,1±7,8	—	—
Butadione[1]	24,0±4,0	63,1	<0,05	37,0±4,9	71,1	<0,05	31,0±4,0	40,8	<0,001
Butadione[2]	21,9±4,1	62,6	<0,05	32,1±8,4	66,6	>0,1	35,2±9,0	71,7	>0,25
Dimedrol	6,8±2,1	19,4	<0,001	15,6±5,2	32,4	<0,01	16,3±8,0	33,2	<0,01
IV	16,5±5,8	47,1	<0,02	42,5±5,5	38,2	<0,25	13,6±4,4	27,7	<0,001
VI	30,3±4,8	85,7	<0,25	31,0±5,9	63,3	<0,05	14,9±4,3	30,3	<0,002
VII	29,9±4,9	85,4	>0,5	34,7±8,1	72,0	<0,1	23,9±4,9	48,7	<0,02
VIII	37,4±5,7	106,8	>0,5	44,5±8,4	92,3	>0,5	32,4±6,2	66,0	>0,05
IX	21,1±4,7	60,3	<0,02	23,1±7,6	47,9	<0,02	13,1±3,6	24,6	<0,01
X	19,1±2,1	54,6	<0,01	27,2±3,9	56,4	<0,01	16,3±2,7	33,2	<0,001
Dextran model									
Control	48,8±8,2	—	—	68,4±9,1	—	—	74,7±10,7	—	—
Butadione[3]	89,0±9,1	150,8	>0,05	60,0±12,0	88,2	>0,5	33,0±6,9	49,2	<0,001
Butadione[2]	40,5±8,8	86,5	>0,5	30,9±6,6	45,2	<0,01	39,5±7,5	52,9	<0,02
Dimedrol	22,7±5,5	48,5	<0,05	26,1±7,1	38,2	>0,002	26,6±6,2	35,6	<0,002
IV	31,3±10,2	66,9	>0,05	28,2±8,7	41,2	>0,01	18,6±7,9	25,9	<0,001
VI	18,2±5,3	38,9	<0,01	29,7±4,4	43,4	<0,002	6,5±3,4	8,7	<0,001
VII	31,6±7,8	67,5	<0,1	34,4±5,7	50,3	<0,01	41,4±6,7	55,4	<0,02
VIII	27,5±6,6	58,8	>0,05	37,0±6,0	54,1	<0,01	30,0±6,2	40,2	<0,002
IX	25,6±3,9	54,7	<0,05	17,5±3,5	25,6	<0,001	13,8±3,6	18,5	<0,001
X	15,4±3,4	32,9	<0,01	24,0±2,0	35,1	<0,001	19,2±2,3	25,7	<0,001

[1] Introduced into the stomach.
[2] Intraperitoneal.
[3] Subcutaneous.

TABLE 3. Effects of the Test Compounds on Diuresis and the Duration of Narcotic Sleep in White Rats

Compound	Dose, mg/kg	Diuresis		Duration of narcotic sleep	
		ml over 6 h	% of controls	min	% of controls
Control	—	7,6±0,25	100	81,3±4,84	100
IV	20	10,76±0,43	141,57	—	—
	30	—	—	67,7±2,8	83,27
	40	12,8±0,64	168,42	—	—
	45	—	—	57,7±2,8	70,97
	60	9,63±0,31	126,71	76,5±3,5	94,1
V	50	3,78±0,57	49,73	165,0±14,01	202,95
	100	7,93±0,89	104,43	151,7±14,44	186,59
XI	10	9,28±0,18	122,11	—	—
	30	11,02±0,31	145,0	—	—
	50	8,87±0,25	111,67	—	—
XII	10	8,43±0,43	110,92	124,1±3,19	152,64
	20	8,57±0,15	112,76	136,7±5,13	168,14
	30	8,61±0,22	113,28	157,6±9,58	193,8
XIV	10	9,02±0,22	118,68	—	—
	30	8,9±0,26	117,1	—	—
	50	9,28±0,25	122,11	—	—
XV	15	8,54±0,45	112,37	—	—
	30	10,67±0,74	140,39	—	—
	45	9,77±0,6	128,55	—	—
XVI	25	—	—	110,1±4,6	135,42
	50	—	—	140,1±4,64	172,32
	75	—	—	123,7±3,84	152,15
XVII	25	—	—	107,3±3,35	131,98
	50	—	—	128,8±4,6	158,42
	75	—	—	121,7±4,37	149,69
Euphyllin	10	8,6±0,16	113,15	—	—
Chlorpromazine	5	—	—	112,14±4,7	137,93
Caffeine	10	—	—	68,0±6,44	83,64

The test compounds were administered in a single dose subcutaneously in a dose of 0.1 of the LD_{50} per 1 kg of animal weight. The antiinflammatory properties of the compounds were compared with the activity of butadione, administered intragastrically in a dose of 100 mg/kg and intraperitoneally in a dose of 50 mg/kg, and with the activity of the antihistamine drug dimedrol, administered subcutaneously in a dose of 2 mg/kg. Each phlogogen (control series), standards, and test compounds were tested in ten animals.

The effects was expressed as the percentage increase in the volume of the inflamed extremity, and as a percentage of the reaction of intact animals (taken as 100%). The significance of the difference was assessed from the P value. The results are shown in Table 2.

It will be seen from Table 2 that (IV), (VI), and (IX) display high antiinflammatory activity in both models of the inflammatory process. Since the compounds showed high activity in experimental dextran inflammation, it may be assumed that an antihistamine component is present in the mechanism of their antiexudative effects. This does not, however, exclude the possibility of a nonspecific effect on the permeability of the cell membranes.

The effects of some of the test compounds on diuresis was studied in intact white male Wistar rats of weight 220-370 g, as described in [2], in doses averaging 1/10-1/20 of the LD_{50}. Each dose was tested in seven animals (Table 3). The diuretic activity of the test compounds was compared with that of euphyllin. The most active compound was (IV), which in a dose of 40 mg/kg stimulated diuresis by 68% in comparison with euphyllin.

Compound (V) possesses antidiuretic activity, and in a dose of 50 mg/kg it decreased diuresis by 50% over the controls.

Neurotropic activity was assessed by the prolongation of the effects of subnarcotic doses of barbiturates [4]. The effects of the most active compounds on the duration of pentobarbital-sodium sleep in Wistar white rats are shown in Table 3. Each dose of the drug was tested in seven animals. The duration of narcotic sleep was measured by the time during which the animals remained in the lateral position, i.e., from the time of loss of the turnover reflex.

According to these results, most of the compounds display high neuroleptic activity, extending the duration of narcotic sleep by an average of 32-103% over the controls in doses of 10-75 mg/kg. Compound (IV) displayed analeptic activity, reducing the duration of sleep by 29% in a dose of 45 mg/kg.

These studies thereofore show that a search for novel biologically active compounds with antiinflammatory, diuretic, and neurotropic activity in the 6,8-dimethylimidazo[1,2-f]xanthine series holds promise. Of special interest is a search for antiinflammatory compounds in this series. 6,8-Dimethylimidazo[1,2-f]xanthines could obviously constitute a new class of nonsteroidal antiinflammatory agents.

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