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SYNTHESIS AND BIOLOGICAL PROPERTIES OF ANALOGS OF DIPROPHYLLINE

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The aim of the present work was to develop methods for synthesizing analogs of diprophylline containing various functional groupings in position 8 of the bicyclic xanthine nucleus and also the study of their biological properties. We have developed several preparative methods for synthesizing the amino alcohols (IX-XVIII). The first method is based on the reaction of derivatives of 8-aminotheophylline (I-VIII) with glycidol and glycidol ethers in the presence of catalytic amounts of pyridine. The second synthetic route consisted in the ammonolysis of derivatives of 2-hydroxymethyloxazolino [3,2-f]xanthine (XXXII-XXIII) synthesized by a known method [2]. The desired products (IX-XVIII) were also obtained by the hydrolysis of 8-amino-7-(2,3-epoxypropyl)theophyllines (XIX, XX), which were synthesized from the 8-aminotheophyllines (I and VIII) and epichlorohydrin in propanol in the presence of equivalent amounts of sodium propanolate.

It is known that the introduction of a hydrazine group into the position 8 of the bicyclic xanthine system leads to the appearance of broncholytic [3], analeptic [4], hypotensive, and other forms of activity [5, 6]. We therefore obtained a number of derivatives of diprophylline (XIV, XXV) containing a hydrazine residue in position 8. The synthesis of these compounds was carried out by the hydrazinolysis of compounds (XXII) and (XXIII). To prove the presence of a free hydrazine grouping the hydrazones (XXVI-XXXV) were obtained by the condensation of the 8-hydrazino derivatives (XXIV) and (XXV) with aldehydes and with isatin. The structures of the compounds synthesized were confirmed by IR and mass spectrometry.

EXPERIMENTAL (PHARMACOLOGICAL)

We studied the acute toxicity, neurotopic action, diuretic effect, and bacteriostatic and fungistatic activities of some of the compounds synthesized. Acute toxicities were determined in experiments on white mice of both sexes weighing 18-20 g. The compounds were introduced intraperitoneally in physiological solution or in the form of suspensions in Tween-80. Each dose was tested on 5-6 animals. The LD_{50} values were calculated by Kerber's method [7]. The LD_{50} for compound (X) was 655.0 ± 19.4 mg/kg, for (XIV) 485.0 ± 19.1 mg/kg, for (XV) 1150.0 ± 18.0 mg/kg, for (XXVIII) 221.0 ± 9.5 mg/kg, for (XXIX) 219.0 ± 9.6 mg/kg, for (XXX) 187.0 ± 11.0 mg/kg, and for (XXXIV) 201.0 ± 9.6 mg/kg.

The neurotropic activities were studied by means of the test for the potentiation of the action of barbiturates [8]. The influence of (X), (XIV), and (XV) on the duration of ethaminal-sodium sleep was studied on ten groups of white rats of the Wistar line (7 rats in each group). The duration of the narcotic effect was studied from the time during which the animals were present in the lateral position, i.e., from the moment of loss of the righting reflex. The results of the experiments are given in Table 1.

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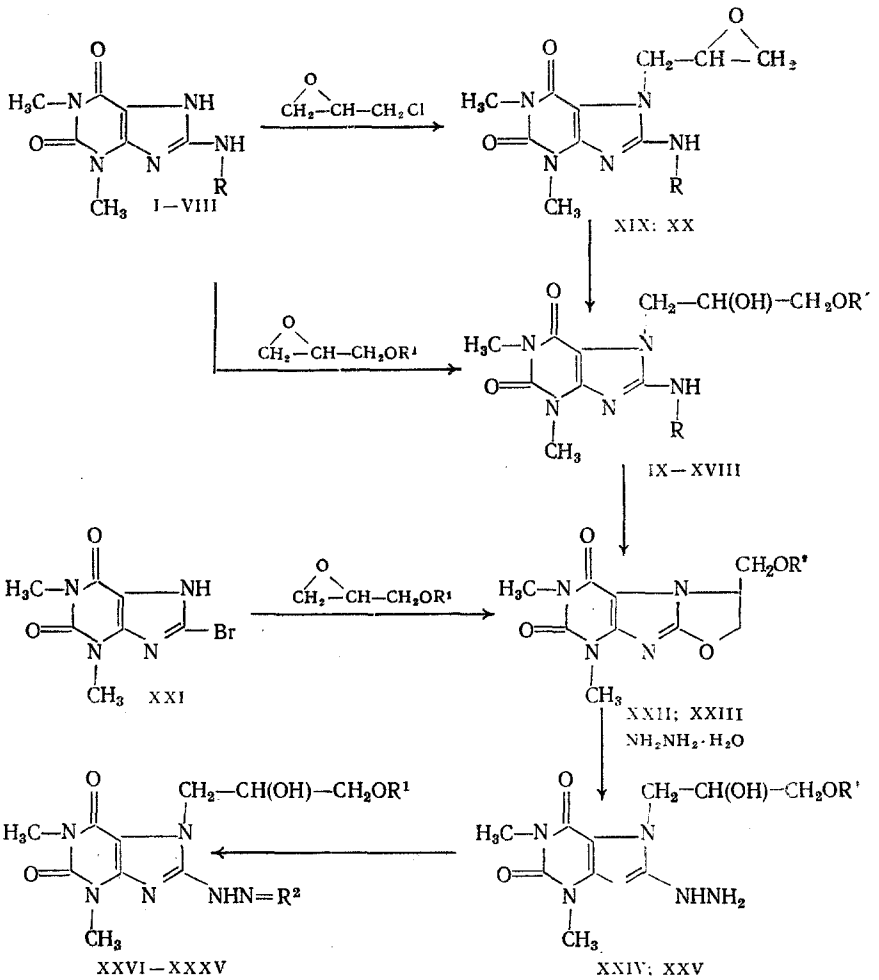
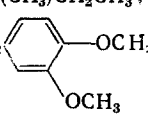
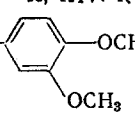


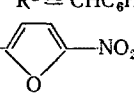
I: R = C_2H_5; II: R = CH_2—CH=CH_2; III: R = CH_2CH_2OH;
IV: R = $CH(CH_3)CH_2CH_2CH_2OH$; V: R = $CH(CH_3)CH_2CH(CH_3)CH_2CH_3$;

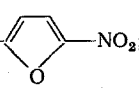
VI: R = cyclohexyl; VII: R = C_6H_5; VIII: R = CH_2CH_2— 

IX: R = C_2H_5, R^1=H; X: R = CH_2—CH=CH_2, R^1 = H;
XI: R = $CH(CH_3)CH_2CH_2OH$, R^1 = H; XII: R = $CH(CH_3)CH_2CH(CH_3)CH_2CH_3$, R^1 = H;
XIII: R = cyclohexyl, R^1 = H; XIV: R = C_6H_5, R^1 = H;

XV: R = CH_2CH_2—  , R^1 = H;

XVI: R = $CH(CH_3)CH_2CH_2CH_2OH$, R^1 = C_4H_9-n; XVII: R = CH_2CH_2OH, R^1 = C_6H_5;
XVIII: R = R^1 = C_6H_5; XIX: R = C_2H_5; XX: R = C_6H_5; XXII: R^1 = H;
XXIII: R^1 = C_6H_5; XXIV: R^1 = H, XXV: R^1 = C_6H_5; XXVI: R^1 = H,
R^2 = CHC_6H_4—NO_2-p, XXVII: R^1 = H, R^2 = $CHC_6H_4N(CH_3)_2$-p;

XXVIII: R^1 = H, R^2 = CH—  ;

XXIX: R^1 = H, R^2 = CH—CH=CH—  ;

XXX: R^1 = H, R^2 = isatin residue; XXXI: R^1 = C_6H_5; R^2 = CH—C_6H_4—NO_2-p
XXXII: R^1 = C_6H_5, R^2 = CH—C_6H_4—NO_2-m XXXIII: R^1 = C_6H_5,
R^2 = CH—C_6H_4—$N(CH_3)_2$-p; XXXIV: R^1 = C_6H_5,

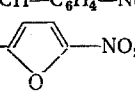
R^2 = CH—CH=CH—  ; XXXV: R^1 = C_6H_5, R^2 = isatin residue

TABLE 1. Influence of Diprophylline Analogs on Diuresis and the Duration of Narcotic Sleep of White Rats

Compound	Dose, mg/kg	Diuresis		Duration of narcotic sleep	
		ml in 6 h (M ± m)	% on control	min (M ± m)	% on control
Control		7,81±0,32	100	82,6±5,67	100
X	10	9,45±0,32	120,9	107,3±6,48	129,9
	25	11,81±0,57	151,2	108,8±8,82	131,7
	50	10,28±0,37	131,6	93,3±5,56	112,9
XIV	10	9,54±0,43	122,1	88,9±5,28	107,6
	25	11,20±0,78	143,4	106,3±4,50	128,6
	50	10,55±0,46	135,1	135,1±6,42	163,5
XV	25	9,67±0,51	123,8	115,1±4,07	139,3
	50	11,25±0,93	144,0	141,8±5,51	171,6
	75	10,60±0,52	135,7	145,1±6,93	175,6

As can be seen from the figures given, compounds (X), (XIV), and (XV) increased the duration of narcotic sleep, exhibiting a neuroleptic effect. Compound (XV) proved to be the most active, in doses of 50 and 75 mg/kg increasing the duration of sleep by 71.6% and 75.6%, respectively on an average.

The influence of compounds (X), (XIV), and (XV) on diuresis was studied in intact male white rats of the Wistar line weighing 200-300 g by Berkhin's method [9]. A total of 70 experiments was performed. The results of the investigations are given in Table 1. They showed that compounds (X), (XIV), and (XV) cause a statistically significant increase in diuresis by an average of 20.9-51.2%.

Thus, the search for pharmacologically active compounds among 8-amino derivatives of diprophylline is promising for their study as neuroleptic and diuretic agents.

The bacteriostatic and fungistatic activities of the compounds synthesized (XXV-XXXV) with respect to several types of bacteria and fungi were determined by the method of serial dilutions in liquid nutrient medium. The minimum bacteriostatic concentration of the compounds studied with respect to *Staph. aureus* and *B. anthracis* was between 15.6 and 250 μg/ml, and for *E. coli* and *Ps. aeruginosa* it was between 15.6 and 500 μg/ml. The fungicidal action of the compounds investigated with respect to yeast-like fungi of the type *Candida albicans* was shown in concentrations of 31.25-250 μg/ml.

It must be mentioned that the compounds synthesized possess a moderate activity in relation to Gram-positive and Gram-negative microorganisms.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a UR-10 instrument (GDR) in KBr tablets. Mass spectra were recorded on a Varian MAT 311 instrument (USA) (3 kV, 300 μA, 70 mV, temperature of the source 180°C, with direct introduction of the sample into the ion source). The 8-aminotheophyllines (I-VIII) were obtained by the method of Cacace and Masironi [11]. 8-Bromotheophylline (XXI) was obtained by the method of Eckstein et al. [12].

7-(2,3-Dihydroxypropyl)-8-ethylaminotheophylline (IX). Method A. A mixture of 2.23 g (0.01 mole) of 8-ethylaminotheophylline, 0.74 g (0.01 mole) of glycidol and 4 drops of dry pyridine in 50 ml of propanol was heated for 4 h, the solution was filtered, and the filtrate was evaporated under reduced pressure to dryness. This gave (IX). Mass spectrum of (IX), m/e: 51 (33.9), 53 (19.8), 54 (10.5), 55 (5.0), 55.5 (43.6), 56 (10.1), 67 (43.5), 68 (24.3), 69.5 (29.9), 70.5 (5.0), 71 (16.5), 81 (33.4), 82 (93.9), 83 (27.7), 84 (7.2), 94 (13.9), 95 (9.6), 109 (18.4), 110 (24.5), 111 (13.6), 122 (11.0), 123 (9.8), 137 (18.1), 138 (17.0), 139 (10.2), 141 (5.6), 151 (14.7), 152 (13.3), 165 (10.8), 166 (10.3), 167 (9.9), 179 (22.4), 181 (13.6), 194 (14.4), 195 (48.8), 208 (65.8), 209 (29.6), 222 (48.2), 223 (82.4), 224 (44.6), 236 (37.1), 237 (34.6), 238 (5.6), 253 (5.1), 268 (5.0), 270 (37.8), 271 (7.1), 279 (7.0), 297 (100.0), 298 (14.5). W_M = 6.9 Compounds (X-XVIII) were obtained similarly.

TABLE 2. Constants of the 7,8-Disubstituted Theophyllines Synthesized

Compound	Yield, % (method)	°C	Found, %			Empirical formula	Calculated, %			Features of the IR spectra, ν, cm^{-1}					
			C	H	N		C	H	N	C=O	C=N	OH	NH	NO_2 sym.	NO_2 asym.
IX	82 (A) 61 (B) 76 (C)	191—3	48,5	6,5	23,6	$C_{12}H_{19}N_5O_4$	48,5	6,5	23,6	—	—	—	—	—	—
X	79	115—6	—	—	22,5	$C_{13}H_{19}N_5O_4$	—	—	22,6	1700 1670	1625	3450—3280	3195	—	—
XI	80	258—9	50,6	7,2	20,2	$C_{15}H_{25}N_5O_5$	50,7	7,1	19,7	1720 1660	1615	3550—3280	3210	—	—
XII	69	207—8	—	—	19,3	$C_{17}H_{29}N_5O_4$	—	—	19,1	1700 1600	1630	3320—3250	3170	—	—
XIII	70	106—7	55,0	7,0	20,3	$C_{16}H_{25}N_5O_4$	54,7	7,2	19,9	1700 1665	1630	3430—3300	3170	—	—
XIV	87 (A) 68 (B) 74 (C)	251—2	55,8	5,7	20,5	$C_{16}H_{19}N_5O_4$	55,6	5,6	20,3	1685	1610	3440—3320	3180	—	—
XV	72	155—6	—	—	16,4	$C_{20}H_{27}N_5O_6$	—	—	16,2	—	—	—	—	—	—
XVI	40	300	55,5	8,1	17,0	$C_{19}H_{33}N_5O_5$	55,5	8,1	17,0	—	—	—	—	—	—
XVII	71 (A) 59 (B)	187—8	55,7	6,1	18,2	$C_{18}H_{23}N_5O_5$	55,5	6,0	18,0	1680 1650	1615	3450—3320	3200	—	—
XVIII	54 (A) 73 (B)	177—8	—	—	16,7	$C_{23}H_{23}N_5O_4$	—	—	16,6	—	—	—	—	—	—
XIX	69	>300	51,2	6,0	24,9	$C_{12}H_{17}N_5O_3$	51,6	6,1	25,1	—	—	—	—	—	—
XX	70	225—6	—	—	21,1	$C_{16}H_{17}N_5O_3$	58,7	5,2	21,4	—	—	—	—	—	—
XXIII	86	214—5	58,7	4,6	17,1	$C_{16}H_{15}N_4O_4$	58,7	4,6	17,1	—	—	—	—	—	—
XXIV	72	204—5	42,3	5,5	29,8	$C_{10}H_{16}N_6O_4$	42,2	5,7	29,6	1700 1660	1615	3450—3380	3230— 3150	—	—
XXV	98	169—70	—	—	23,6	$C_{16}H_{20}N_6O_4$	—	—	23,3	—	—	—	—	—	—
XXVI	92	260	49,2	4,6	23,5	$C_{17}H_{19}N_7O_6$	48,9	4,6	23,5	1697 1667	1650 1632	3450—3150	3115	1520	1347
XXVII	85	234—5	—	—	23,9	$C_{19}H_{25}N_7O_4$	—	—	23,6	1695 1650	1620 1600	3450—3350	3190	—	—
XXVIII	94	215—6	43,8	4,1	24,4	$C_{15}H_{17}N_7O_7$	44,2	4,2	24,1	1695 1665	1650 1635	3450—3370	3120	—	—
XXIX	98	>820	47,1	4,2	22,7	$C_{17}H_{19}N_7O_7$	47,1	4,4	22,6	1695 1665	1645 1625	3400—3325	3180	1510	1355
XXX	97	304—5	52,6	5,0	24,1	$C_{18}H_{19}N_7O_5$	52,3	4,6	23,7	1712 1695 1650	1620 1580	3550—3450	3270 3170	—	—
XXXI	75	239—40	—	—	19,6	$C_{23}H_{23}N_7O_6$	—	—	19,9	1700 1660	1640 1620	3400—3300	3230	1520	1340
XXXII	33	253—4	56,1	4,7	20,3	$C_{23}H_{23}N_7O_6$	56,0	4,7	19,9	—	—	—	—	—	—
XXXIII	64	104—5	61,0	5,8	20,1	$C_{25}H_{29}N_7O_4$	61,0	5,9	19,9	1695 1665	1630 1610	3500—3300	3220	—	—
XXXIV	92	197—8	53,5	4,9	19,4	$C_{22}H_{23}N_7O_7$	53,1	4,7	19,7	—	—	—	—	—	—
XXXV	51	284—5	—	—	19,7	$C_{24}H_{23}N_7O_5$	—	—	20,0	—	—	—	—	—	—

Note. Compounds (IX, XIV, XVI, XVIII, and XXV) were crystallized from propanol, (XI and XII) from methanol, (XV, XXX, XX, and XXIII) from propan-2-ol, (XXVI, XXVII, and XXXII-XXXV) from dioxane, (XXVIII-XXXI) from DMFA, (X) from water, (XIII) from water—methanol (1:5), (XVII) from water—methanol (1:1) and (XXIV) from water—propanol (1:1).

Method B. A mixture of 2.5 g (0.01 mole) of (XXII) and 40 ml of 20% ethanolic ethylamine was heated in an autoclave with a capacity of 0.15 liter at 150-160°C for 6 h, and the solution was filtered. After cooling, the white crystalline precipitate of (IX) that had deposited was filtered off. Compounds (XIV), (XVII), and (XVIII) were obtained similarly from (XXII) and (XXII) by reaction with the corresponding primary amines.

Method C. A mixture of 2.8 g (0.01 mole) of (XIX), 2 ml of triethylamine, 2 ml of water, and 40 ml of 2-metnoxyethanol was boiled for 12 h, and the solution was filtered and cooled. The precipitate (IX) that deposited was filtered off. Compound (XIV) was obtained from (XX) similarly.

7-(2,3-Dihydroxypropyl)-8-hydrazinotheophylline (XXIV). A mixture of 2.5 g (0.01 mole) of compound (XXII) and 5 ml of 98% hydrazine hydrate in 40 ml 2-methoxyethanol was boiled for 5 h. Then it was cooled and the precipitate of (XXIV) that had deposited was filtered off. Compound (XXV) was obtained from (XXIII) similarly.

7-(2,3-Dihydroxypropyl)-8-p-nitrobenzylidenehydrazinotheophylline (XXIV). A mixture of 0.57 g (0.002 mole) of (XXIV), 0.3 g (0.002 mole) of p-nitrobenzaldehyde, and 2 drops of hydrochloric acid was boiled for 1 h and cooled, and the precipitate of (XXIV) was filtered off and was washed with propanol. Compounds (XVII-XXXV) were obtained similarly from (XXIV) and (XXV) with the corresponding aldehydes. Mass spectrum of (XXXII), m/e: 51 (21.4), 53 (9.7), 55 (30.9), 65 (19.1), 66 (12.8), 67 (15.6), 68 (12.7), 73 (7.6), 77 (58.2), 78 (12.2), 79 (24.8), 81 (16.4), 82 (54.3), 83 (9.8), 91 (17.1), 94 (50.1), 95 (8.4), 104 (12.4), 105 (35.5), 107 (20.3), 109 (18.7), 110 (8.4), 111 (8.9), 118 (8.4), 119 (19.9), 120 (24.1), 121 (11.6), 122 (8.4), 131 (13.9), 132 (12.9), 133 (86.4), 134 (17.8), 138 (12.6), 145 (70.3), 146 (45.6), 147 (100.0), 148, (87.9), 149 (44.8), 151 (17.8), 152 (11.9), 181 (11,4), 194 (12,4), 195 (36.7), 196 (39.4), 208 (70.6), 209 (36.9), 234 (23.2), 238 (88.7), 239 (13.7), 251 (9.1), 252 (18.6), 328 (5.6), 340 (6.5), 344 (5.1), 345 (29.7), 346 (5.4), 354 (6.1), 384 (5.2), 397 (5.5), 491 (83.6), 492 (28.9). $W_M = 4.3$.

The constants of the compounds synthesized are given in Table 2.

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