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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 6H- and 6-ALKYL-8-METHYLIMIDAZO[1,2-f]XANTHINES

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There have been reported the synthesis [1-3] and studies of the chemical properties and reactivities [4] of 6,8-dimethylimidazo[1,2-f]xanthines. The compounds obtained included representatives with considerable pharmacological activity [3].

With the aim of discovering new neurotropic and diuretic drugs, we have examined the pharmacological activity of imidazo[1,2-f]xanthines with an acidic NH group or an alkyl radical in the 6-position.

The starting material for these synthetic studies was the potassium salt of 8-chloro-3-methylxanthine (I) [5], which on alkylation in DMF with acetonyl or phenacyl halides gave the corresponding 7-acetonyl (II) or 7-phenacyl- (III) derivatives.

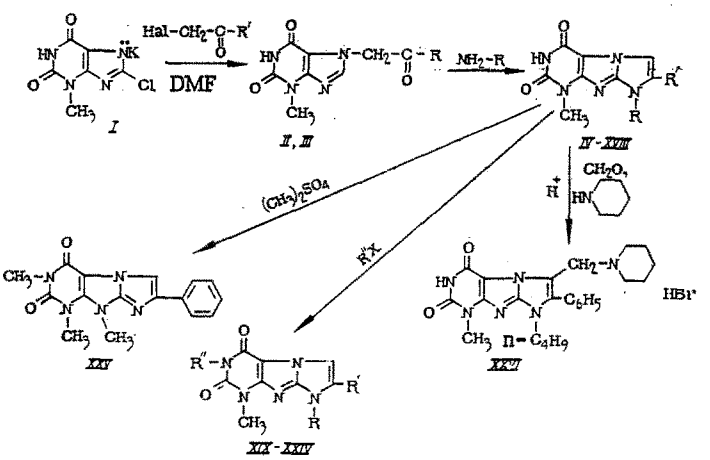
Reaction of 7-acylalkyl-8-halo-3-methylxanthines [5] with primary amines afforded 6H,-8-methylimidazo[1,2-f]xanthines (IV-XVIII).

Reaction of imidazo[1,2-f]xanthines (IV), (VI), (IX), (XVII) with alkyl halides in DMF in the presence of potassium carbonate afforded the 6-alkyl compounds (XIX-XXIV).

It is noteworthy that alkylation with dimethyl sulfate in aqueous-alcoholic solution in the presence of alkali, or with methyl iodide in DMF (K_2CO_3) gave the above-mentioned 6,8-dimethylimidazo[1,2-f]xanthines (XXII-XXIV).

Reaction of 2-phenyl-8-methylimidazo[1,2-f]xanthine (V) with dimethyl sulfate in acidic media gave 6,8,9-trimethyl-2-phenylimidazo[1,2-f]xanthine (XXV).

The Mannich reaction with (VII) gave the corresponding 3-aminomethyl derivative (XXVI).



(II): R' = CH_3COCH_2; (III): R' = $C_6H_5COCH_2$; (IV): R = CH_3, R' = C_6H_5; (V): R = H, R' = C_6H_5; (VII): R = R' = C_6H_5; (VIII): R = n-C_4H_9, R' = C_6H_5; (VIII): R = allyl, R' = CH_3; (IX): R = $HOCH_2CH_2$, R' = C_6H_5; (X): R = $C_6H_5CH_2$, R' = C_6H_5; (XI): R = cyclohexyl, R' = C_6H_5; (XII): R = homoveratryl; (XIII): R = p-$CH_3C_6H_5$, R' = C_6H_5; (XIV): R = p-$C_2H_5OCOC_6H_4$, R' = C_6H_5; (XV): R = C_6H_5, R' = CH_3; (XVI): R = R' = CH_3; (XVII): R = $HOCH_2CH_2$, R' = CH_3;

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(XVIII): R = p-anisyl, R' = C_6H_5; XIX: R = CH_3, R' = C_6H_5, R'' = $CH_2CH(OH)CH_2OH$; XX: R = $HOCH_2CH_2$, R' = C_6H_5, R'' = OCH_2CHCH_2; XXI: R = $HOCH_2CH_2$, R' = C_6H_5, R'' = $CH_2CH(OH)CH_3$; XXII: R = R' = C_6H_5, R'' = CH_3; XXIII: R = R'' = CH_3, R' = C_6H_5; XXIV: R = $HOCH_2CH_2$, R' = R'' = CH_3.

The IR spectra of 6H,8-methylimidazo[1,2-f]xanthines (IV-XVIII) showed characteristic absorptions over the range 1720-1690 cm^{-1} due to stretching vibrations of the amide carbonyl groups (amide I bands). Absorption at 1680-1610 cm^{-1} is attributed to stretching vibrations of the azomethine group, although amide II bands appear in this region together with stretching vibrations of the conjugated C=Cbond [6].

In the PMR spectrum of 1,2-diphenyl-6H,8-methylimidazo[1,2-f]xanthine (VI), obtained in trifluoroacetic acid, the phenyl group protons appear as a multiplet at 7.26-7.66 ppm (10H) centered at 7.33 ppm, and the signal for the C_3 proton is seen at 7.93 ppm (1H), the signal for the methyl group at N_8 appearing at 3.73 ppm (3H). The PMR spectra of the remaining compounds (IV-XVIII) were in accordance with the proposed structures [5].

The UV spectra of (IV-XVIII) showed three strong maxima at 202-206 nm (log ε 4.3-4.4), 222-227 nm (log ε 4.22-4.31), and 273-281 nm (log ε 4.28-4.32). There was no absorption at 222-227 nm in the UV spectra of (II) and (III), and its appearance may therefore be related to annelation of the imidazole moiety.

The UV spectrum of (XXV) showed two strong maxima at 208 nm (log ε 4.26) and 272 nm (log ε 4.33). In acidic media, a bathochromic shift of the short-wavelength maximum by 7 nm was seen, without any significant change in the intensity of absorption.

EXPERIMENTAL CHEMICAL SECTION

The IR spectra of the compounds were obtained on UR-10 and UR-20 instruments (East Germany), in KBr disks or as suspensions in vaseline oil. UV spectra were obtained on a Specord UV-VIS instrument in methanol or ethanol. PMR spectra were recorded on a Bruker WH-90 instrument (δ scale, standard TMS).

The potassium salts of 8-chloro-3-methylxanthine (I) and 7-acylalkyl-8-chloro-3-methylxanthines (II) and (III) were prepared as described in [5].

6H,8-Methylimidazo[1,2-f]xanthines (IV-XVIII). A. Compounds (IV), (V), (VII), and (XVII) were obtained as described in [5].

B. A mixture of 0.02 mole of the 7-acylalkyl-8-chloro-methylxanthine (II) or (III) and 0.04 mole of the aliphatic, aromatic, or araliphatic amine was heated in 150-200 ml of DMF at the boil for 2-5 h. The reaction mixture was diluted with an equal volume of water, and the solid filtered off to give (VI), (VIII), (IX-XV), (XVII), and (XVIII) (recrystallized from aqueous DMF).

The sodium salt of 1,2,8-trimethylimidazo[1,2-f]xanthine (XVIa) was obtained by reacting equimolar amounts if (XVI) and NaOH in water.

6,8-Dialkylimidazo[1,2-f]xanthines (XIX-XXIV). A mixture of 0.01 mole of the 6H,8-methylimidazo[1,2-f]xanthine (IV), (IX), or (XVII), 0.011 mole of glycerin α-monochlorohydrin (or epichlorohydrin, α-chloroisopropanol, or 0.02 mole of methyl iodide) and 0.011 mole of anhydrous potassium carbonate in 50-100 ml of DMF was boiled for 30 min. The mixture was cooled, diluted with twice its volume of water, and the solid filtered off to give (XIX-XXIV) (recrystallized from aqueous DMF). The properties of (IV-XVIII) and (XIX-XXIV) are given in Tables 1 and 2 respectively.

6,8,9-Trimethyl-2-phenylimidazo[1,2-f]xanthine (XXV). A mixture of 2.81 g (0.01 mole) of (V) and 70 ml of $(CH_3)_2SO_4$ was heated at 150-170°C for 30 min (until the solid had dissolved completely). The reaction mixture was kept for 12 h, then poured into 200 ml of water, and neutralized with solid NaOH followed by concentrated aqueous ammonia. After 6 h, the solid was filtered off and washed with acetone. Yield 1.8 g (61%). Crystallized from a mixture of alcohol and DMF, mp 320-321°C. Found, %: C 61.9; H 4.5; N 23.0. $C_{16}H_{15}N_5O_2$. Calculated, %: C 62.12; H 4.88; N 22.64.

PMR spectrum (DMSO-d_6), ppm: 3.52 (s, 3H) N_9-CH_3; 3.68 (s, 3H) N_8—CH_3; 3.98 (s, 3H) N_6—CH_3; 7.13-7.93 (m, 5H) C_6H_5; 7.95 (s, 1H) C_3H.

1-n-Butyl-2-phenyl-3-N-piperidinomethyl-8-methylimidazo[1,2-f]xanthine (XXVI). A

TABLE 1. 8-Methyl-6H-imidazo[1,2-f]xanthines

Compound	Yield, %	mp, °C	Found, %			Molecular formula	Found, %		
			C	H	N		C	H	N
IV	74	339—340	61,1	4,4	23,6	$C_{15}H_{13}N_5O_2$	61,0	4,44	23,7
V	60	360	59,8	4,4	25,6	$C_{14}H_{11}N_5O_2$	59,8	3,9	24,9
VI	72	344—345	67,0	4,7	20,0	$C_{20}H_{15}N_5O_3$	67,2	4,43	19,6
VII	68	243—244	64,1	5,5	20,8	$C_{18}H_{19}N_5O_2$	64,0	5,7	20,76
VIII	76	246—248	55,7	5,1	27,2	$C_{12}H_{13}N_5O_2$	55,58	5,05	27,0
IX	63	283—285	62,0	5,2	22,9	$C_{16}H_{15}N_6O_3$	62,12	4,95	22,6
X	93	246—247	65,3	4,3	18,01	$C_{21}H_{17}N_5O_2 \cdot H_2O$	65,6	4,45	17,96
XI	71	284—285	67,5	6,1	19,86	$C_{20}H_{21}N_5O_2$	66,0	5,32	19,27
XII	89	271—272	60,0	5,6	18,43	$C_{19}H_{21}N_5O_4$	59,52	5,5	18,27
XIII	85	344—345	67,5	5,1	18,86	$C_{21}H_{18}N_5O_2$	67,9	4,88	18,85
XIV	91	295—297	63,9	4,0	16,18	$C_{22}H_{19}N_5O_4$	64,3	4,5	16,3
XV	93	301—302	60,9	3,9	23,9	$C_{15}H_{13}N_5O_2$	61,0	4,4	23,7
XVI	81	310	51,7	4,4	29,8	$C_{10}H_{11}N_5O_2$	51,5	4,75	30,03
XVII	93	290—291	50,2	5,1	26,4	$C_{11}H_{13}N_5O_3$	50,18	4,9	26,6
XVIII	81	299—301	65,1	4,82	18,39	$C_{21}H_{17}N_5O_3$	65,11	4,42	18,0

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

Compound	Yield, %	mp, °C	Found, %			Molecular formula	Calculated, %		
			C	H	N		C	H	N
XIX	58	198—200	58,23	5,2	19,0	$C_{18}H_{19}N_5O_4$	58,52	5,2	18,9
XX	67	205—207	59,72	5,4	18,21	$C_{19}H_{19}N_5O_4$	59,83	5,02	18,36
XXI	59	275—277	60,0	5,2	18,4	$C_{19}H_{21}N_5O_4$	60,0	5,5	18,27
XXII	78	257—259	70,75	5,1	19,9	$C_{21}H_{17}N_5O_2$	70,96	4,82	19,7
XXIII	53	232—233	62,0	4,65	22,83	$C_{16}H_{15}N_5O_2$	62,12	4,88	22,64
XXIV	58	249—250	53,6	6,0	24,4	$C_{13}H_{17}N_5O_3$	53,6	5,9	24,0

TABLE 3. Neuroleptic and Diuretic Activity of the Compounds

Compound	Dose, mg/kg	Diuresis		Duration of narcotic sleep	
		ml over 6 h	as % of controls	min	as % of controls
Control	—	7,31±0,21	100	8,67±2,23	100
VIII	10	9,3±0,33	127,22	91,5±2,44	105,53
	20	10,47±0,31	143,23	100,7±2,76	116,14
	30	9,51±0,26	130,1	90,5±2,98	104,3
XVIa	25	—	—	117,3±11,24	135,29
	50	—	—	164,4±10,87	189,62
	75	—	—	135,7±6,68	156,5
XXI	10	9,05±0,30	123,8	120,3±5,84	138,75
	25	9,5±0,64	130,0	—	—
	40	8,87±0,33	121,34	—	—
	5	—	—	93,1±4,58	107,38
	20	—	—	107,4±4,14	123,87
	30	—	—	75,7±3,34	87,33
XXVI	10	9,43±0,12	129,0	124,8±6,72	149,94
	20	—	—	135,1±5,44	155,82
	30	10,36±0,17	141,72	123,14±7,0	142,02
	50	9,61±0,17	131,46	—	—
Euphyllin	10	8,82±0,46	120,66	—	—
Chlorpromazine	5	—	—	118,14±4,7	136,26

mixture of 0.01 mole of (VII), 0.02 mole of piperidine, and 0.02 mole of 37% aqueous formaldehyde in 20-30 ml of glacial acetic acid was boiled for 2 h, cooled, the mixture poured into 200 ml of water, filtered, and neutralized with aqueous ammonia. The solid was filtered off, washed with water, dried, dissolved in 30 ml of 48% hydrobromic acid, 100 ml of alcohol and 100 ml of acetone added, and evaporated to dryness in vacuo. The dry residue was suspended in 100 ml of dry diethyl ether, and filtered. Yield quantitative (calculated on base obtained). mp 170°C (decomp.). Found %: N 17.0; Br 15.63. $C_{23}H_{31}N_6BrO_2$. Calculated, %: N 16.7, Br 15.87.

EXPERIMENTAL PHARMACOLOGICAL SECTION

Laboratory animals were used to determine the acute toxicities of the compounds, and their effects on the duration of nembutal sleep and the urinary excretory function of the kidneys.

Acute toxicities were determined in intact white mice of both sexes weighing 18-25 g. The compounds were administered intraperitoneally as a fine 3-5% aqueous suspension stabilized with Tween-80. The animals were observed for 10 days. The results were treated by Kerber's method [7]. The LD_{50} values were: (IV) 1085.0 ± 15.9 mg/kg, V 132.0 ± 6.63 mg/kg, VI 1670.0 ± 17.3 mg/kg, VII 365.0 ± 18.4 mg/kg, VIII 195.0 ± 18.4 mg/kg, IX 1090.0 ± 37.7 mg/kg, XII 470.0 ± 31.9 mg/kg, XV 392.0 ± 7.96 mg/kg, XVIa 552.0 ± 9.27 mg/kg, XVII 1690.0 ± 18.2 mg/kg, XIX 485.0 ± 15.9 mg/kg, XX 415.0 ± 15.75 mg/kg, XXI 245.0 ± 3.22 mg/kg, XXVI 166.0 ± 15.02 mg/kg.

Assessment of neurotropic activity was carried out by the prolongation of the narcotic effects of barbiturates (nembutal sodium, 30 mg/kg) [8] (results are given here for the most active compounds). The experiments were carried out on 15 groups of Wistar strain white rats weighing 210-280 g (7 individuals per group). The duration of narcotic sleep was determined by the time during which the turn-over reflex was lost. The results showed that the highest neurotropic activity was possessed by (VIII), (XVI), (XXI), and (XXVI) (Table 3). The highest neuroleptic activity was shown by (XVI), which in a dose of 50 mg/kg increased the duration of nembutal-induced sleep by 89.6% as compared with the controls.

The effects of (VIII), (XXI), and (XXVI) on diuresis were studied in male white rats of the Wistar strain weighing 200-260 g, by the method described in [9]. In all, 77 experiments were carried out (cf. Table 3). The results showed that the compounds had a stimulant effect on the urinary excretory function of the kidneys, statistically increasing diuresis by 21-43% as compared with the controls.

The results of these studies therefore show that these compounds are of relatively low toxicity, and they possess neuroleptic and activity comparable with that of euphyllin and chlorpromazine.

For this reason, a search for neurotropic and diuretic drugs in this series holds promise.

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