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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 3-FORMYL-8-METHYL-6H-IMIDAZO[1,2-f]XANTHINES

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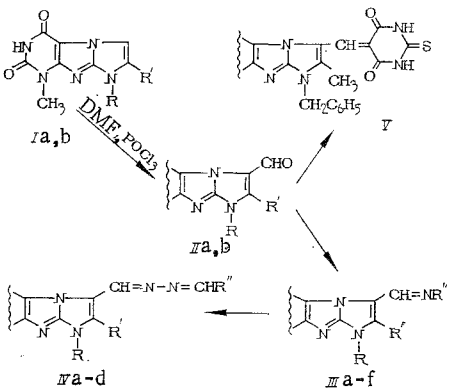
Xanthines annelated at side f by the imidazole ring display various types of biological activity [1-4]. Imidazo[1,2-f]xanthines undergo electrophilic substitution to give a variety of functional derivatives [5]. This communication describes an examination of the formulation of 1,8-dimethyl-2-phenyl- and 1-benzyl-2,8-dimethyl-6H-imidazo[1,2-f]xanthine (Ia, b) and nucleophilic addition reactions of the resulting aldehydes (IIa, b), together with a study of the biological activities of the compounds obtained.

Heating the tricyclic compounds (Ia, b) in a mixture of DMF and phosphoryl chloride (the Vilsmeier reaction) [5] affords the 3-formyl derivatives (IIa, b), the structures of which were confirmed by PMR spectroscopy (disappearance of the C_8 proton). The PMR spectrum of (IIa) (in CF_3COOH) contained signals for the following protons: N_1 and N_8 methyl groups (3.87 and 3.93 ppm, s, 3H), the phenyl substituent (7.7-7.83 ppm, m, 5H), and the formyl group (9.3 ppm, s, 1H). The presence of the formyl group resulted in a low-field shift of the PMR signals in comparison with those of the original compound (Ia) [6].



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Ia, IIa: $R = CH_3$, $R' = C_6H_5$; Ib, IIb: $R = C_6H_5CH_2$, $R' = CH_3$;
IIIa: $R = C_6H_5CH_2$, $R' = CH_3$, $R'' = NH_2$; IIIb: $R = CH_3$, $R' = C_6H_5$,
$R'' = HNC_6H_3(NO_2)_2$-o, p; IIIc: $R = CH_3$, $R' = C_6H_5$, $R'' = NH_2$;
IIId: $R = CH_3$, $R' = C_6H_5$, $R'' = \overline{NCH{=}N{-}N{=}CH}$; IIIe: $R = CH_3$,
$R' = C_6H_5$, $R'' = C_6H_4N(C_2H_5)_2$-p; IIIf: $R = C_6H_5CH_2$, $R' = CH_3$,
$R'' = HNC_6H_3(NO_2)_2$ o, p; IVa: $R = C_6H_5CH_2$, $R' = CH_3$,
$R'' = C_6H_4NO_2$-p; IVb: $R = CH_3$, $R' = C_6H_5$,
$R'' = C_6H_4NO_2$-p; IVc: $R = CH_3$, $R' = C_6H_5$,
$R'' = C(Cl) = CHC_6H_4NO_2$-p; IVd: $R = CH_3$, $R' = C_6H_5$,
R'' = 2-nitro-5-furyl

The aldehydes (IIa, b) are quite reactive compounds which undergo nucleophilic addition to hydrazines, p-diethylaminoaniline, and thiobarbituric acid to give the hydrazones (IIIa-d, f), Schiff's base (IIIe), and hetarylidene derivative (V). The hydrazones (IIIa, c) undergo further condensation with aldehydes to give the aldazones (IVa-d).

The structures of the compounds obtained were confirmed by their elemental analyses and IR spectra. The IR spectra of all the compounds contained bands typical of the imidazoxanthine nucleus [6, 7]. In addition, the IR spectra of (IIIb, f) and (IVa-d) contained strong absorption at 1590-1530 and 1385-1305 cm^{-1}, corresponding to the antisymmetrical and symmetrical vibrations of the NO_2 group. The NH absorption of the uracil moiety occurred at 3175-3150 cm^{-1}. Absorptions for the amide carbonyl groups were present in the usual range of 1720-1690 cm^{-1} [8].

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a UR-20 instrument (East Germany) as pastes in vaseline oil. PMR spectra were recorded on a Tesla BS 487C spectrometer (80 MHz), solvent CF_3COOH. Chemical shifts are given on the δ-scale relative to TMS.

1,8-Dimethyl-2-phenylimidazo[1,2-f]xanthine (Ia). This was obtained as described in [6].

1-Benzyl-2,8-dimethylimidazo[1,2-f]xanthine (Ib). A mixture of 5.12 g (0.02 mole) of 3-methylacetonyl-8-chloroxanthine [9] and 4.28 g (0.04 mole) of benzylamine in 20 ml of DMF was boiled for 10-15 min. The mixture was then cooled, and the solid which separated was suspended in 150 ml of water and filtered off. It was washed with 100 ml of acetone and dried to give (Ib) (see Table 1).

1,8-Dimethyl-2-phenyl- and 1-benzyl-2,8-dimethyl-3-formylimidazo[1,2-f]xanthines (IIa, b). To 20-30 ml of dry DMF was added dropwise with cooling to 0-5°C and stirring 0.015 mole of freshly-distilled phosphoryl chloride. The resulting solution was added to a suspension of 0.01 mole of (Ia) or (Ib) in 20-30 ml of DMF, and the mixture was heated on a boiling water bath for 4 h. After cooling, the mixture was poured into 100 g of finely crushed ice, and neutralized with ammonium hydroxide solution and sodium bicarbonate. After 12 h, the solid was filtered off, washed with water, and dried to give (IIa, b) (see Table 1).

3-Formyl-8-methyl-6H-imidazo[1,2-f]xanthine Hydrazones and Azomethines (IIIa-f). Obtained in the usual way by reacting (IIa, b) with hydrazine hydrate, 2,4-dinitrophenylhydrazine, or p-N,N-diethylaminoaniline in DMF or acetic acid (see Table 1).

3-Formyl-8-methyl-6H-imidazo[1,2-f]xanthine Aldazines (IVa-d). To a solution of 0.002 mole of (IIIa) or (IIIf) in 100 ml of DMF was added 0.002 mole of the aldehyde in 100 ml of DMF and 1 ml of concentrated acetic acid. The mixture was heated at boiling for 10 min, then the solid was filtered off or the mixture was poured into an equal volume of water and filtered to give (IVa-d) (see Table 1).

1-Benzyl-2,8-dimethylimidazo[1,2-f]xanthylidene-3-thiobarbituric Acid (V). A mixture of 3.37 g (0.01 mole) of (IIb), 0.015 mole of thiobarbituric acid, and 0.015 mole of anhydrous sodium acetate in 60 ml of glacial acetic acid was heated at boiling for 5 h. After cooling, the solid was filtered off and washed with water to give (V) (see Table 1).

EXPERIMENTAL BIOLOGY

Some of the compounds were tested for the following types of biological activity: acute toxicity (LD_{50}), neurotropic and diuretic activity, and bacteriostatic and mycostatic activity.

TABLE 1. 3-Formyl-6H-imidazo[1,2-f]xanthines

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Ib	284—285	62,5	5,2	22,84	$C_{16}H_{15}N_5O_2$	62,12	4,9	22,64	92
IIb	280 (decomp.)	60,93	4,48	20,76	$C_{17}H_{15}N_5O_3$	60,52	4,48	20,76	88
IIa	301—302	50,95	4,0	21,78	$C_{16}H_{13}N_5O_3$	59,43	4,05	21,66	91
IIIa	350(decomp.)	58,5	5,1	28,2	$C_{17}H_{17}N_7O_2$	58,1	4,87	27,9	73
IIIb	300 (decomp.)	48,2	3,5	23,01	$C_{22}H_{17}N_9O_6$	47,9	3,1	22,86	98
IIIc	348—349	56,8	4,78	29,0	$C_{16}H_{15}N_7O_2$	56,96	4,48	29,07	93
IIId	333—335	55,3	4,0	32,67	$C_{18}H_{15}N_9O_2$	55,52	3,88	32,38	—
IIIe	307—309	66,35	5,43	21,1	$C_{26}H_{27}N_7O_2$	66,5	5,8	20,88	—
IIIf	283—285	52,95	4,0	24,97	$C_{23}H_{19}N_9O_6$	53,38	3,7	24,36	93
IVa	300(decomp.)	60,0	4,65	23,42	$C_{24}H_{20}N_8O_4$	59,5	4,16	23,13	87
IVb	355—356	58,4	4,1	24,2	$C_{23}H_{18}N_8O_4$	58,71	3,85	23,8	95
IVc	346—348	56,9	4,02	21,5	$C_{25}H_{19}ClN_8O_4$	56,55	3,6	21,1	87
IVd	274—276	54,26	3,8	24,75	$C_{21}H_{16}N_8O_5$	54,68	3,5	24,39	62
V	>250(decomp.)	53,52	3,83	22,1	$C_{20}H_{17}N_7O_4$	53,8	3,79	21,7	81

Note. Compounds (Ib), (IIa, b), (IIIa), and (IIIb-e) were crystallized from DMF or DMF-alcohol; (IIIf), (IVa-d), and (V) were recrystallized from glacial acetic acid or aqueous acetic acid.

The acute toxicities (LD_{50}) of the new compounds were determined in white mice of both sexes weighing 18-25 g. The compounds were administered intraperitoneally as 3-5% fine aqueous suspensions stabilized by Tween-80. Each dose was tested in 5-7 animals. Observations were carried out for 14 days following treatment, and the LD_{50} values were calculated by Kerber's method [10] (see Table 2).

These studies showed that these imidoxanthines were of moderate or low toxicity, the LD_{50} values being in the range 405-1430 mg/kg.

Following large doses of the test compounds (in excess of 500-1500 mg/kg), the symptoms of intoxication took the form of a reduction in the respiratory activity of the animals, and the occurrence of dyspnea and periodic clonic and tonic convulsions.

Neurotropic activity was studied by the prolongation of the effects of subnarcotic doses of barbiturates [11]. The effects of the xanthine derivatives on the duration of pentobarbital-sodium sleep in white rats of the Wistar strain are shown in Table 2. Each dose level was tested in seven animals. The duration of narcotic sleep was taken as the time during which the animal took up a lateral position, i.e., from the moment of loss of the turnover reflex. In doses of 20-105 mg/kg, all the test compounds showed high potentiation of the soporific effects of pentobarbital-sodium, being 8.32-103.67% on average greater than the controls. The greatest neurotropic activity was shown by (IVc) (see Table 2), which contains a halogen atom in the side chain.

These findings give grounds for suggesting that these imidoxanthines, in producing a neurotropic effect, modify the functional state of the nervous system, and act synergistically with the narcotics. It may be that the mode of action of these xanthine derivatives which are considerably metabolitotropic, involves effects on biochemical processes in different areas of the cerebral cortex, which as shown by G. E. Batrak [12], play an important part in the dynamics of narcosis.

The effects of the test compounds on kidney function were examined in intact male Wistar white rate weighing 250-300 g as described in [13], in doses averaging 1/10 to 1/20 of the LD_{50}. Each dose was tested in seven animals. The results are shown in Table 2.

The diuretic activities of the test compounds were compared with those of an analogous xanthine, euphyllin. It follows from the results that in doses of 20-140 mg/kg these new 8-methyl-6H-imidazo[1,2-f]xanthines cause a slight increase in the excretion of urea, averaging 14.05-47.21% over the controls.

The antimicrobial and mycostatic activities of the compounds were examined by twofold serial dilution in a liquid nutrient medium [14] on a spectrum including 11 strains of microorganisms. Hottinger bouillon (pH 7.2-7.4) was used to culture the bacteria. The microbial

TABLE 2. Effects of (IIIb, c), (IVb-d), and (V) on the Duration of Narcotic Sleep in White Rats

Compound (LD_{50}, mg/kg)	Dose, mg/kg	Diuresis		Duration of narcotic sleep	
		ml per 6 h	as % of controls	min	as % of control
Control	—	7,54±0,44	100	81,7±2,13	100
IIIb	35	—	—	97,0±3,14	118,73
(1430,0±32,2)	70	10,0±0,49	132,63	122,1±3,96	149,45
	105	—	—	137,0±5,6	167,68
	140	8,5±0,38	112,73	—	—
IIIc	25	—	—	88,3±4,1	108,08
(778,0±18,9)	39	9,7±0,53	128,65	—	—
	50	—	—	114,3±4,44	139,90
	75	—	—	143,2±4,23	164,29
	78	10,7±0,54	141,91	—	—
IVb	45	10,0±0,35	132,63	—	—
(898,0±24,68)	50	—	—	88,5±2,52	108,32
	70	—	—	99,4±4,18	121,66
	90	8,60±0,32	114,05	107,4±5,47	131,45
IVc	40	—	—	94,4±5,76	115,54
(848,0±14,4)	42	9,2±0,44	122,06	—	—
	60	—	—	135,7±6,8	166,095
	85	11,1±0,48	147,21	166,4±5,85	203,67
IVd	40	—	—	9,21±3,70	112,73
(845,0±16,45)	43	9,1±0,21	120,69	—	—
	80	—	—	106,1±5,3	129,86
	85	9,7±0,31	128,65	—	—
V	20	9,3±0,19	123,34	90,8±4,7	111,14
(405,0±16,2)	30	—	—	109,0±2,97	133,41
	40	9,8±0,89	129,97	103,7±2,27	126,93
Euphyllin	20	9,25±0,49	122,67	—	—
Chlorpromazine	5	—	—	112,14±4,70	137,26

loading of the bacteria was $2.5 \cdot 10^5$ cells of an 18 h agar culture in 1 ml of medium. Sabouraud's medium (pH 6.0-6.8) was used to grow the fungi (loading 500,000 reproductive bodies per ml).

The antimicrobial activity of the compounds was assessed from the minimum bacteriostatic (MBC) or mycostatic (MMC) concentrations, expressed in μg/ml. All the compounds were dissolved in DMSO followed by dilution with sterile distilled water. The MBC values of the test compounds for *Staphylococcus aureus* and *anthracoid* fell within the range 25-200 μg/ml. The MMC values for the fungi *Microsporoum lanosum* and *Frichophiton menthagrophites* lay within the range of the test compounds, most of them being active against one or two strains of microorganisms, and only (IVd), which contains and α-nitrofuryl group in the side chain, and to some extent (V), have a sufficiently broad effect on the viability of microorganisms.

Hence, these studies have yet again shown the promising nature of a search for new drugs and biologically active compounds amongst imidazo[1,2-f]xanthine derivatives.

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SYNTHESIS AND EFFECTS ON THE CENTRAL NERVOUS SYSTEM OF SALTS OF 3-HYDROXYMETHYLPYRIDINE

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Most syntheses of 3-hydroxymethylpyridine (I) involve the reduction of nicotinic acid derivatives [1-3]. Methods have also been described for the synthesis of (I) by the reduction of 3-pyridinaldehyde (II) with sodium borohydride [4] or with hydrogen in the presence of nickel and palladium catalysts [5, 6]. We here describe a method for the reduction of (II) to (I) using thiourea dioxide, which has been used with success for the reduction of both aliphatic and aromatic ketones [7].

The reduction of (II) with thiourea dioxide was studied with initial concentrations of aldehyde and dioxide of 0.3-2.3 mole/liter in aqueous and aqueous-alcoholic media (Table 1). The reaction rates increase considerably in the presence of NaOH.

The yield of (I) dependes on the type of solvent, increasing with increasing dielectric constant from isopropyl alcohol (ε = 26) to water (ε = 80). The optimum initial concentration of (II) was 0.9 mole/liter, further increases in concentration resulting in a decrease in the

TABLE 1. Reduction of 3-Pyridinaldehyde (II) with Thiourea Dioxide at 90°C

Solvent	Initial concentration, mole/liter			Reaction time, h	Yield of (I),* %
	II	thiourea dioxide	NaOH		
Water	0,30	0,30	—	3	17,0
»	0,30	0,30	0,6	3	64,3
»	0,91	0,91	1,8	3	80,0
»	1,52	1,52	3,0	3	62,7
»	2,30	2,30	4,6	3	30,2
»	0,91	0,91	0,3	5	33,7
»	0,91	0,45	0,9	5	5,8
Isopropyl alcohol–water (1.5:1) (1,5 : 1)	0,91	0,91	1,8	5	58,1
Isopropyl alcohol	0,91	0,91	1,8	5	45,1
Ethyl alcohol– water (1,5 : 1)	0,91	0,91	1,8	5	27,5

*Yield determined by GLC.

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