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SYNTHESIS, PROPERTIES, AND MASS-SPECTROMETRIC BEHAVIOR OF 6-SUBSTITUTED IMIDAZO[1,2-f]XANTHINES

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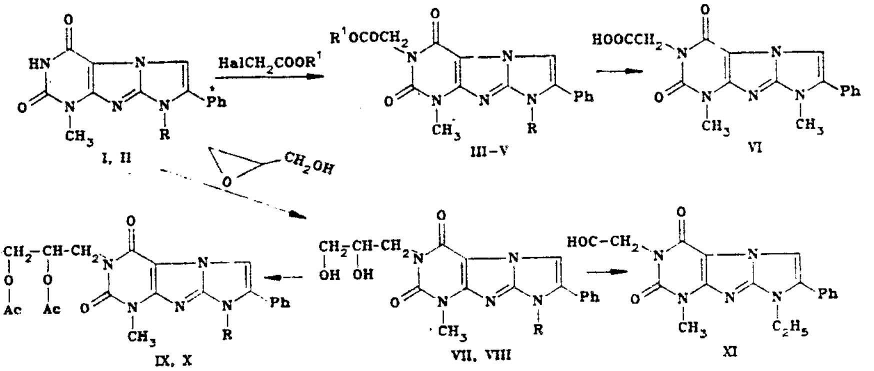
Alkylation at the $N_{(6)}$ atom of 6H-1-ethyl ethyl(methyl-2-phenylimidazo[1,2-f]xanthenes was realized with α-halogenoacetic esters. The alkylation of these compounds with glycidyl alcohol in the presence of organic bases also leads to 6-(dihydroxypropyl) derivatives.

Earlier we demonstrated the possibility of the alkylation of 6H-imidazo[1,2-f]xanthines at the free NH group of the uracil fragment with methyl iodide and obtained authentic derivatives of 6,8-dimethylimidazo[1,2-f]xanthine [1]. In the present communication we describe the synthesis of 6-(dihydroxyalkyl)-, 6-(alkoxycarbonylalkyl)-, and 6-(carboxyalkyl) derivatives and consider their behavior under electron impact.(see below).



I, III, VIII, X R=CH_3; II, IV, V, VII, IX R=C_2H_5; V R'=CH_3; III, IV R'=C_2H_5

During the alkylation of 6H-1,8-dimethyl- and 6H-8-methyl-1-ethyl-2-phenylimidazo[1,2-f]xanthine (I, II) with methyl bromoacetate and ethyl iodoacetate in DMFA in the presence of anhydrous potassium carbonate the corresponding (imidazo[1,2-f]xanthine-6-yl)acetic esters (III-V) are formed. Under the conditions of alkaline hydrolysis ethyl (1,8-dimethyl-2-phenylimidazo[1,2-f]xanthin-6-yl)acetate gives the acid (VI).

The alkylation of (I) and (II) with glycidyl alcohol in the presence of triethylamine leads to the 6-(β,γ-dihydroxypropyl) derivatives (VII) and (VIII). The O,O-diacetyl derivatives (IX) and (X) were obtained by briefly boiling these alcohols in acetic anhydride. 8-Methyl(1-ethyl-2-phenylimidazo[1,2-f]xanthin-6-yl)ethanol (XI) was obtained by the cleavage of the diol (VII) with periodic acid in an aqueous medium (Table 1).

The IR spectra of compounds (III-V) contain two strong characteristic absorption bands (C=O and C-O) for the ester fragment (1750 and 1315-1300 cm^{-1}, respectively). The bands for the carbonyl groups of the uracil fragment in these compounds appear at 1715-1705 and 1695-1670 cm^{-1}. The absorption bands belonging to the stretching vibrations of the C=N bonds lie in the region of 1625-1615 cm^{-1}.

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TABLE 1. Characteristics of the Synthesized Compounds II-XII

Compound	T_{mp}, °C	Found, %			Molecular formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
II	>300	62,0	5,0	22,9	$C_{16}H_{15}N_5O_2$	62,1	4,9	22,6	58
III	140—141	60,0	5,1	18,4	$C_{19}H_{19}N_5O_4$	59,8	5,0	18,4	83
IV	161—162	—	—	17,8	$C_{20}H_{21}N_5O_4$	60,7	5,4	17,7	75
V	184—186	59,7	5,2	18,6	$C_{19}H_{19}N_5O_4$	59,8	5,0	18,4	54
VI	268—270	57,6	4,3	20,0	$C_{17}H_{15}N_5O_4$	57,8	4,3	19,8	87
VII	141—142	60,0	5,9	18,5	$C_{19}H_{21}N_5O_4$	59,5	5,5	18,3	59
VIII	198—200	58,2	5,2	19,0	$C_{18}H_{19}N_5O_4$	58,5	5,2	18,9	58
IX	128—129	59,5	5,5	15,3	$C_{23}H_{24}N_5O_6$	59,2	5,2	15,1	95
X	173—174	56,0	5,7	16,7	$C_{20}H_{23}N_5O_6$	55,9	5,4	16,3	93
XI	215—217	—	—	18,5	$C_{18}H_{17}N_5O_3 \cdot H_2O$	58,5	5,2	18,9	67
XII	255—257	—	—	24,1	$C_{24}H_{21}N_9O_6$	54,2	4,0	23,7	76

TABLE 2. PMR Spectra of Compounds (III, VI, X, XI)

Compound	Chemical shifts, δ, ppm								
	ethyl substituent		$N_{(8)}-CH_3$	$N_{(1)}-CH_3$	CH_2	C_6H_5	C_5H	CH	CH_3
	CH_2	CH_3							
III	4,18 (q, 2H)	1,21 (t, 3H)[a]	3,50 (s, 3H)	3,72 (s, 3H)	4,62 (s, 2H)	7,50—7,70 (wm, 5H)	7,78 (s, 1H)		
VI			3,48 (s, 3H)	3,72 (s, 3H)	4,52 (s, 2H)	7,48—7,70 (wm, 5H)	7,73 (s, 1H)		
X			3,66 (s, 3H)	3,75 (s, 3H)	4,42 (m, 4H)	7,41 (bs, 5H)	7,71 (s, 1H)	5,53 (m, H)	2.03 (s, 3H) 2,13 (s, 3H)
XI	3,99 (q, 2H)	1,22 (t, 3H)[b]	3,50 (s, 3H)		4,72 (s, 2H)	7,50—7,61 (wm, 5H)	7,67 (s, 1H)	9,61 (s, 1H)	

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[a] $J_{1,2} = J_{2,1} = 8.2$ Hz.
[b] $J_{1,2} = J_{2,1} = 8.0$ Hz.

TABLE 3. Mass Spectra of the Synthesized Compounds

Compound	m/z values (peak intensities as % of maximum)[a]
II	77 (13), 102 (10), 128 (10), 209 (6), 210 (12), 211 (10), 237 (15), 238 (11), 239 (5), 265 (5), 266 (15), 309 (100), 310 (20). $W_M = 25$
III	45 (16), 73 (27), 77 (26), 102 (17), 118 (31), 196 (10), 197 (10), 223 (26), 224 (26), 225 (14), 251 (29), 266 (18), 309 (11), 322 (63), 350 (9), 395 (100), 396 (23). $W_M = 8$
IV	73 (8), 102 (5), 128 (10), 349 (11), 350 (10), 209 (5), 210 (10), 211 (5), 237 (7), 238 (6), 239 (11), 265 (7), 266 (18), 309 (11), 322 (63), 350 (9), 395 (100), 396 (23). $W_M = 20$
VI	45 (10), 77 (25), 102 (18), 118 (30), 197 (14), 223 (33), 224 (35), 225 (23), 251 (16), 252 (46), 295 (18), 308 (24), 309 (79), 353 (100), 354 (22). $W_M = 9$
VII	77 (10), 102 (11), 128 (10), 132 (10), 210 (11), 211 (7), 237 (10), 238 (11), 239 (7), 265 (5), 266 (14), 309 (100), 322 (11), 352 (10), 383 (50), 384 (11). $W_M = 10$
IX	43 (100), 128 (11), 209 (5), 210 (10), 237 (10), 265 (10), 266 (12), 309 (64), 322 (57), 365 (25), 467 (66), 468 (18). $W_M = 10$

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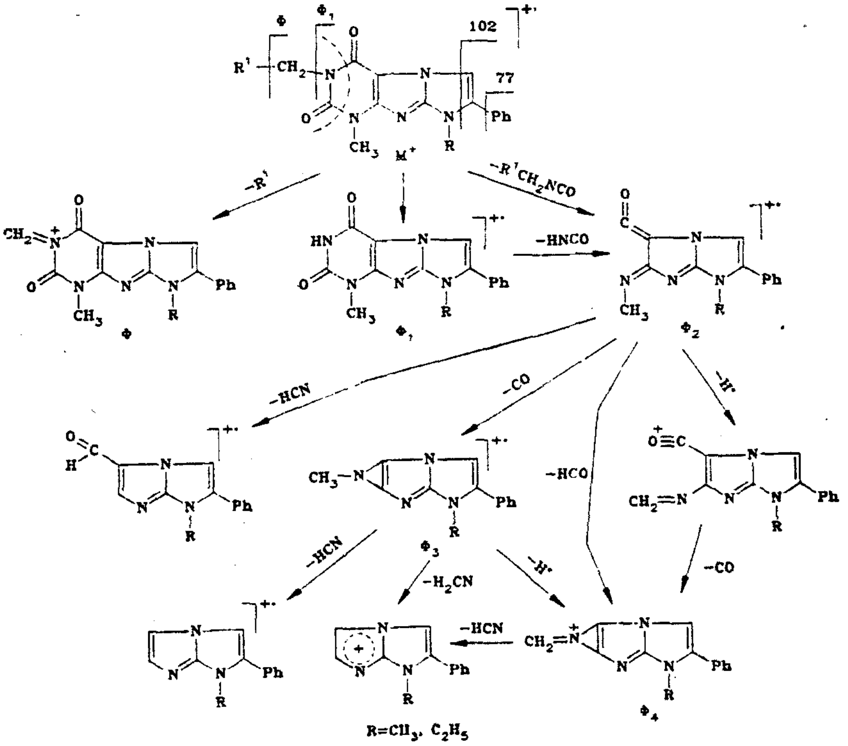
[a] Ion peaks with intensities of ≥5% are given.

The IR spectrum of the acid (VI) shows that it exists in the form of a dimer, as demonstrated by the strong broad band for the stretching vibrations of the hydroxy group at 3400 cm^{-1}; the absorption band of the acid carbonyl group is shifted toward lower frequencies (1712 cm^{-1}). The bands at 1280 and 1388 cm^{-1} correspond to the stretching vibrations of the C—O group and to the deformation vibrations of the hydroxy groups. A characteristic band in the spectrum of the acid (VI), which confirms its dimeric structure, is the strong band at 925 cm^{-1}, due to the out-of-plane deformation vibrations of the combined hydroxyl group [2]. In the IR spectra of (VII) and (VIII) there are broad absorption bands for the stretching vibrations of the hydroxy groups at 3500-3340 cm^{-1} and a series of strong absorption bands for the stretching vibrations of the C–O group (1255-1010 cm^{-1}). In the IR spectra of (IX) and (X) the stretching vibrations of the acetate group C–C(=O)–O appear at 1238 cm^{-1}, and the stretching vibrations of the C–C–O group appear in the form of a series of bands at 1212-1012 cm^{-1}. The IR spectra of these compounds contain $\delta^{s}_{CH_3}$ bands at 1375 cm^{-1} and $\delta^{as}_{CH_3}$ bands at 1450 cm^{-1}. The asymmetric and symmetric stretching vibrations of the methyl and methylene groups appear near 2968 and 2912 cm^{-1}, respectively [2, 3]. All the compounds are characterized by bands in the IR spectra at 3055-3065 cm^{-1} (CH of the aryl substituents).

The structures of compounds (III, IV, X, XI) (Table 2) are confirmed convincingly by their PMR spectra. In each case the integral intensity ratio of the signals corresponds to the proposed structure.

The structure of the synthesized compounds was confirmed in greater detail by mass spectrometry. The molecular ion peaks M^+ are recorded in the mass spectra of compounds (I-IV, VI, VII, IX) (Table 3). [The mass spectrum of (I) was given in [7].] Almost all the M^+ peaks have maximum intensity, and their stability to electron impact (W_M) lies in the range of 8-25% of the total ion current. (see below).



The presence of functional substituents at position 6 somewhat reduces the value of W_M in connection with the appearance of additional dissociation paths. The fragmentation of M^+ in compounds (I-IV, VI, VII, IX) begins with the retrodiene dissociation of the uracil part of the molecule (the Φ_2 ion) followed by elimination of the CO (Φ_3) or HCO$^\cdot$ (Φ_4) particles. This is followed by the elimination of the HCN molecule from the Φ_2 and Φ_3 ions. The observed dissociation events are typical of compounds containing a uracil fragment [4-7].

The presence of the substituent R^1 gives rise to the appearance of the Φ and Φ_1 ions on account of α- and β-cleavage in relation to the heterosystem. There are also certain other ions due to the characteristic features in the structure of the substituent R^1. Thus, removal of the CH_2OH particle from M^+ is observed for compound (VII), elimination of the OC_2H_5 and HOC_2H_5 particles from M^+ for compound (VI), while in the case of compound (IX) the dissociation of the substituent R^1 competes with the elimination of the HC≡C–Ph particle from the imidazole ring of the heteroaryl nucleus. The characteristic peak of the $[COCH_3]^+$ ion is found in the mass spectrum of this compound and has the maximum intensity. After the destruction of the uracil ring the terminal imidazole ring begins to dissociate. Its dissociation gives ions with m/z 77 – $[Ph]^+$, 102 – $[HC{\equiv}C{-}Ph]^+$, 118 – $[CH_3{-}N^+{\equiv}C{-}Ph]$ for compounds (I, III, VI) and 128 – $[HC{\equiv}C{-}N^+{\equiv}C{-}Ph]$ and 132 – $[C_2H_5{-}N^+{\equiv}C{-}Ph]$ for compounds (II, IV, VII, IX), confirming the structure of the imidazole part of the molecules.

The discovered relationships in the mass-spectral dissociation of the imidazo[1,2-f]xanthine derivatives can be used for the identification of compounds of such a type and determination of their structure.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer for tablets with potassium bromide. The PMR spectra were obtained on Tesla BS-467 (60 MHz) and Bruker M-250 (internal standard TMS) instruments for solutions in DMSO-D_6 and trifluoroacetic acid. The mass spectra were obtained on a Varian MAT-311A spectrometer with direct injection into the ion source (evaporation temperature 100-150°C, accelerating potential 3 kV, cathode emission current 1 mA, 70-eV electrons).

1,8-Dimethyl-2-phenyl-6H-imidazo[1,2-f]xanthine (I) was obtained by the method in [7].

1-Ethyl-8-methyl-2-phenyl-6H-imidazo[1,2-f]xanthine (II). A mixture of 18.16 g (50 mmole) of 7-phenacyl-8-bromo-3-methylxanthine [8], 24.5 g (300 mmole) of ethylamine hydrochloride, and 16.8 g (300 mmole) of potassium hydroxide in 150 ml of propanol was heated in a sealed tube at 175°C for 8 h. The mixture was cooled, and the precipitate was filtered off, dried, and recrystallized from acetic acid.

Substituted (Imidazo[1,2-f]xanthin-6-yl)acetic Esters (III-V). A mixture of equimolar amounts (10 mmole) of compound (I) or (II), methyl bromoacetate or ethyl iodoacetate, and anhydrous potassium carbonate in 70-100 ml of DMFA was boiled for 30-40 min and filtered while hot. The reaction mixture was diluted with 20-40 ml of water and left for 24 h. The precipitate was filtered off, washed with water and with acetone, dried, and recrystallized from a mixture of ethanol and DMFA.

(1,8-Dimethyl-2-phenylimidazo[1,2-f]xanthin-6-yl)acetic Acid (VI). A mixture of 11.43 g (30 mmole) of the ester (III) and 3.36 g (60 mmole) of potassium hydroxide in 100 ml of water was boiled for 10-15 min. The solution was filtered while hot and neutralized to a weakly acidic reaction with acetic acid. The precipitate was filtered off and washed with water. The product was purified by reprecipitation and treatment with sodium bicarbonate. The acid (VI) was crystallized from 2-propanol.

6-(β,γ-Dihydroxypropyl)-2-phenylimidazo[1,2-f]xanthines (VII, VIII). A mixture of 3.0 g (10 mmole) of compound (II) or 2.95 g (10 mmole) of compound (I), 1 ml of glycidyl alcohol, and 1 ml of triethylamine in 50 ml of propanol was boiled for 2 h, filtered while hot, and left at 20°C for 12 h. The precipitate was filtered off, washed with alcohol, dried, and crystallized from propanol.

1-Ethyl-6-(β,γ-diacetoxypropyl)-8-methyl-2-phenyl- and 1.8-Dimethyl-6-(β,γ-diacetoxypropyl)2-phenylimidazo[1,2-f]xanthine (IX, X). A 3.8-g sample (10 mmole) of (VII) or 3.7 g (10 mmole) of (VIII) was boiled in 20 ml of acetic anhydride for 40-60 min. The mixture was poured into 250 ml of water and left for 24 h. The precipitate was filtered off and crystallized from aqueous DMFA.

(8-Methyl-1-ethyl-2-phenylimidazo[1,2-f]xanthin-6-yl)ethanal (XI). To a suspension of 2.0 g (5 mmole) of (VII) in 100 ml of water at 60°C we added a solution of 2.3 g (10 mmole) of periodic acid in 20 ml of water. The mixture was stirred for 10 min, 200 ml of water was added, and the mixture was heated to boiling. It was then cooled to 20°C, and the precipitate was filtered off, dried, and crystallized from DMFA. The 2,4-dinitrophenylhydrazone (XII) was obtained in glacial acetic acid.

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CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES.

23.* ELECTROCHEMICAL CRITERIA FOR ELECTROPHILICITY IN 1,4-DIAZINIUM CATIONS AND THEIR PARTICIPATION IN CYCLIZATIONS WITH ACETOACETAMIDE

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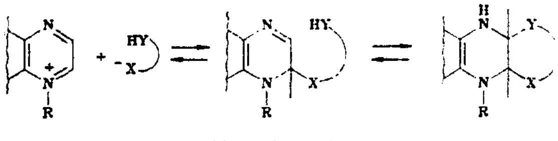
The polarographic reduction potentials $E_{\frac{1}{2}}$ of the pyrazinium, quinoxalinium, benzoquinoxalinium, pyrido[2,3-b]pyrazinium, and pteridinium cations were determined. Annellation of a benzene ring increases the electrophilicity of the diazinium cations to a greater degree than the introduction of such electron acceptors as aza, aminocarbonyl, or methoxycarbonyl groups. The boundary between the active and inactive 1,4-diazinium salts was determined; cations with $E_{\frac{1}{2}}$ values more negative than −0.50 V do not form either stable covalent adducts or cyclic diadducts through annellation of the dinucleophiles to the pyrazine ring.

The reactions of N-alkyl-substituted pyrazinium, quinoxalinium, pyrido[2,3-b]pyrazinium, and pteridinium cations with bifunctional nucleophiles can lead to the formation of cyclic adducts [2-4]. Cyclizations of this type include two consecutive reversible nucleophilic addition reactions, i.e., addition of the carbon and heteroatomic anionic centers of the dinucleophile X and Y to the $C_{(2)}$ and $C_{(3)}$ carbon atoms of the pyrazine ring. In the first stage the positively charged 1,4-diazinium cation takes part in the reaction, while the second can be regarded as intramolecular addition to the C=N bond of the pyrazine ring.



X, Y=CH, N, O, S

The outcome of the reactions is determined by a whole series of factors such as the basicity and nucleophilicity of the anionic centers X and Y, the electrophilicity of the 1,4-diazinium ions, the stability of the monoaddition products, the size of the HX—YH linking unit, the geometry of the obtained ring, the electrophilicity of the C=N bond in the 1,2-dihydropyrazines, and others. The structure of the diazines affects the nucleophilic addition

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