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HETEROCYCLIC PURINE DERIVATIVES. 2.* ELECTROPHILIC SUBSTITUTION

REACTIONS IN THE IMIDAZO [1, 2-f] XANTHINE SERIES

UDC 547.785'857

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Imidazo[1,2-f]xanthine derivatives have a diversified pharmacological activity [2,3]. Up to the present, the synthesis of such compounds has been effected via cyclization of 7-acylmethyl-8-bromotheophyllines with primary amines [3] or of 7-acylmethyl-8-aminotheophyllines in acid medium [4].

By analogy with the imidazo[1,2-a]benzimidazoles [5], it might have been supposed that imidazo[1,2-f]xanthines would also enter into electrophilic substitution reactions at the 3-position to form functional derivatives which it is not possible to obtain by direct synthesis

It turned out that the bromination of 1,2-disubstituted 6,8-dimethylimidazoxanthines Ib-d and Ig-k with bromine takes place smoothly in chloroform, dioxane, or acetic acid, to form the 3-bromo derivatives IIa-h. It is not possible to introduce a second bromine atom into the II molecule, even on heating in methanol, dioxane, or acetic acid with excess bromine. The bromine in the compounds of type II proved to be of low reactivity in nucleophilic substitution reactions, and was not replaced on reaction with alcoholic alkali, sodium butoxide, morpholine, piperidine, or sodium nitrite. On heating the bromides IIa and b with morpholine or piperidine in the presence of powdered copper at 200° in the Ullmann reaction, dehalogenation takes place, with formation of compounds Ib and Id in yields up to 80%.

On action of fuming nitric acid in acetic acid, or of fuming nitric acid or potassium nitrate in concentrated sulfuric acid, on the 2,6,8-trimethylimidazoxanthines (Ia, d, e) the nitro derivatives IIIa-c were obtained in yields up to 90%. It is known that the nitration of 2-arylimidazo[1,2-a]benzimidazoles [6], arylimidazoles [7], and of 2-phenylimidazo[1,2a]pyridine [8] takes place principally in the para position of the aryl substituent. However, on nitration of the 2-phenyl derivatives Ib and Ic in one equivalent of nitrating agent, we obtained a mixture of the mono (70-80%) and dinitro derivatives (7-15%). When two equivalents of nitrating agent were used, the yield of the dinitro derivatives IIIf and IIIg was increased to 90%.

*For communication No. 1, see [1].

Zaporozhe Medical Institute, Zaporozhe 330074. Dnepropetrovsk Engineering-Construction Institute, Dnepropetrovsk 320092. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1404-1410, October, 1979. Original article submitted June 19, 1978. We have assigned the structure of 3-nitro-2-phenylimidazoxanthines (IIId,e) to the mononitro derivatives. These compounds differ from the 2-p-nitrophenylimidazoxanthines (Ik, Il) prepared by an independent method. In the NMR spectrum of the 3-mononitro derivative IIId, the signal in the 7.41 ppm region which is characteristic of the proton in the 3-position of the starting compound Ib is lacking. Moreover, on the nitration of the p-nitrophenylimidazoxanthines Ik and Il and of the 3-mononitro derivatives IIId and IIIe, the very same dinitro derivatives, IIIf and IIIg, were obtained.



In the NMR spectrum of the dinitro derivative IIIf, a quartet of signals of an AB system of aromatic protons of a benzene ring is recorded, with a center at 8.00 ppm ($J_{AB} = 9$ Hz).

When there is a substituent in the 3-position, for example, the bromine atom in 3-bromo-2-phenylimidazoxanthines (IIa, b), as in the case of the 3-mononitro derivatives IIId, e, nitration takes place in the para position of the benzene ring, to form 3-bromo-2-p-nitrophenylimidazoxanthines (IIc, d), which are identical to those obtained by bromination of the 2-p-nitrophenyl derivatives Ik and I1.

The imidazoxanthines Ib, c, and m readily undergo the Vilsmeier reaction. The structure of the 3-formylimidazoxanthines formed (IVa-c) was demonstrated by Wolff-Kishner reduction, as a result of which the known [3] 3-methyl derivatives Va and Vb were obtained.



1a, 111a, V11, 1Xa $R = R^1 = CH_3$; Ib, 11a, 111d 1Va, Va, VIa, 1Xb $R = CH_3$, $R^1 = C_6H_5$; Ic, 11b, 111e, 1Vb Vb V1b 1Xc, $R = n \cdot C_4H_9$, $R^1 = C_6H_4$; Id, 11h 111b, $R = n \cdot C_4H_9$, $R^1 = CH_3$; Id 111c R = cyclohexy1, $R^1 = cH_3$; If, V111, $R = R^1 = C_6H_5$; Ig, 11e, $R = CH_3$, $R^1 = p \cdot BrC_6H_4$; Ih 11f $R = n \cdot C_4H_9$, $R^1 = p \cdot BrC_6H_4$; II, 11g, R = cyclohexy1, $R^1 = p \cdot BrC_6H_4$; Ik, 11c, 111f, $R = CH_3$, $R^1 = p \cdot NO_2C_6H_4$; II, 11d, 111g, $R = n \cdot C_4H_9$, $R^1 = p \cdot NO_2C_6H_4$; Im, 1Vc, $R = C_6H_5$, $R^1 = CH_3$

By reduction of the aldehydes IVa, b with sodium borohydride, the 3-hydroxylmethylimidazoxanthines (VIa, b) were synthesized; these were also obtained in the action of formalin in acetic acid on compounds Ib,c. Upon hydroxymethylation of compound Ia under analogous conditions, di(1,2,6,8-tetramethylimidazo[1,2-f]xanthinyl)methane (VII) is obtained. The Mannich reaction takes place just as easily in the imidazoxanthine series, to form 3-dialkylaminomethyl derivatives, compound VIII, for example.

By acetylation of compounds Ia-c with acetic anhydride in the presence of strong mineral acids, the ketones IXa-c are obtained. In the presence of anhydrous sodium acetic or pyridine, acetylation of I with acetic anhydride does not take place (the starting compounds are recovered). As is well-known [9], an acetyl group present on a carbon atom having an increased electron density is readily eliminated in acid medium. The 3-acetyl derivatives

		Ratio of integral				
Compound	X*	чКСН₃	⁰NCH₃	*NCH3	aromatic protons	signal intensities
1b 11a 111d 111f 1Va 1Xb	7,41 s 10,83 s 2,36 s	3,42 3,31 3,43 3,42 3,44 3,44	3,70 3,49 3,77 3,78 3,62 3,62 3,62	3,60 3,48 3,61 3,62 3,62 3,55	$7,61 \pm 0.057,49 \pm 0.067,58 \pm 0.108,00 \pm 0.067,50 \pm 0.137,53 \pm 0.12$	1:3:3:56:3:53:3:5:53:3:2:21:6:3:53:3:5:53:3:5:5

TABLE 1. Data from NMR Spectra of Imidazo[1,2-f]xanthine Derivatives

*X is the substituent in the 3-position.

which we obtained are stable both in acid and in alkaline medium. They easily undergo reactions which are characteristic of compounds of this type, the aldol condensation, for example, form dinitrophenylhydrazones, and so on.

We were not able to carry out for compounds of type I such typical electrophilic substitution reactions as nitrosation, azo-coupling, or heteroarylation with salts of N-acyl hetero-aromatic cations in situ.

The structures of compounds of type I-IX were confirmed by spectral methods. Thus, the signals of the protons in the N-methyl groups of compounds Ib, IIa, IIId, IIIf, IVa, and IXa were recorded in the NMR spectra in the form of singlets. Their chemical shifts depend but little on the nature of the substituent in the 3-position. The aromatic protons of the phenyl substituent in the 2-position are manifested in the form of a complex symmetrical multiplet having a clearly expressed maximum. The ratio of the integral intensities for the signals corresponds to the proposed structure in each case. Data from the NMR spectra are given in Table 1.

The decomposition of M^+ in the compounds Ib, IIa, IIId, IIIf, IVa, and IXa takes place in two directions - A and B (Table 2). The first of these is associated exclusively with decomposition of the oxopyrimidine part of the molecule; this process is very characteristic of hydroxy-substituted pyrimidines [10] and uracils [11]. The second direction is determined by the presence and character of the substituent in the 3-position. An analysis performed of the mass spectra shows that acceptor substituents inhibit fragmentation of M^+ by route A, while in the case of a donor substituent (IIa, X = Br), decomposition by route B essentially is not effected in the first stage. The general character of the fragmentation of imidazoxanthines is illustrated by scheme 1.



1b x=Y=H; II a x=Br, Y=H; III b x=NO21Y=H; III f x=Y=NO2; IV a X=CHO, Y=H; IX b x=COCH1, Y=H

Scheme 1

EXPERIMENTAL

IR spectra were recorded on a UR-10 spectrophotometer, using KBr disks or in the form of a suspension in mineral oil. NMR spectra were taken on a Bruker WH-90 instrument in CDCl, (tetramethylsilane as internal standard). The mass spectra were measured on a Varian MAT-311 instrument (3 kV,300 μ A, 70 mV), the source temperature was 180°, with direct introduction of the specimen into the ion source.

6,8-Dimethylmidazo[1,2-f]xanthines (Ia-m). A) As synthesized by reaction of 7-acylmethyl-8-bromotheophylline with primary amines [3], their constants conformed to the data of [3].

B) A mixture of 10 mmole of the 3-bromoimidazoxanthine (IIa or b), 5 ml of piperidine, and 0.75 g of powdered copper in 70 ml of methanol was heated for 10 h in a 150-ml autoclave at 200°. The autoclave was cooled, and the precipitate was filtered off and washed with water. The yield of Ib was 58%; of Ic, 78%. Data on the previously undescribed compounds Ii-k are given in Table 3.

<u>3-Bromo-6,8-dimethylimidazo[1,2-f]xanthines (IIa-h)</u>. To a solution of 5 mmole of the compounds Ib-d, g-k in chloroform, with stirring, was added 5 mmole of bromine, in 10 ml of chloroform, dropwise over a 1 h period, and stirring was continued for 2 h. The chloroform was evaporated, the residue was treated with water, the 3-bromo derivatives IIa-h were filtered off, and they were washed with water. Compounds IIa, b,e-h are colorless crystals, compounds IIc,d are yellow needles (Table 3).

<u>3-Nitro-6,8-dimethylimidazo[1,2-f]xanthines (IIIa-g)</u>. To a solution of 5 mmole of compound Ia-e,k, or 1 in acetic acid, with stirring, was added 5 mmole of concentrated HNO₃ (d 1.5), dropwise, and the mixture was stirred for 5 h at 20°, then it was poured into 100-150 ml of water, the IIIa-g was filtered off, and it was washed with water. The IIIa-g compounds were also synthesized by the action of equivalent amounts of conc. HNO₃ (d 1.5) or KNO₃ on a solution of Ia-e, k, or 1 in concentrated H₂SO₄ (d 1.83). Compounds IIIa-g are crystalline substances which are pale yellow to orange in color.

<u>3-Nitro-2-p-nitrophenyl-6,8-dimethylimidazo[1,2-f]xanthines (IIIe,g)</u> were also prepared by nitration of the 3-nitro derivatives IIId, e with 1 equivalent of KNO₃ or of the imidazoxanthines Ib,c with 2 equivalents of KNO₃ in concentrated H_2SO_4 , with the following yields: IIIe, 90% (from IIId or Ib), and IIIg, 93% (from IIIe) or 83% (from Ic).

<u>3-Bromo-2-p-nitrophenyl-6,8-dimethylimidazo[1,2-f]xanthines (IIc,d)</u>. To a solution of 5 mmole of the 3-bromoimidazoxanthine (IIa or b) in 25 ml of conc. H_2SO_4 , at 0-5°, with stirring, was slowly added a solution of 5 mmole of KNO₃ in 10 ml of H_2SO_4 , the mixture was stirred at this temperatured for 5 h, poured onto 150 g of ice, the solid was filtered off, and washed with water. Yield of Ic, 68%, of Id, 85%.

<u>3-Formyl-6,8-dimethylimidazo[1,2-f]xanthines (IVa-c)</u>. To 10 ml of dry dimethylformamide, at 0-5°, with stirring, was added dropwise 10 mmole of freshly distilled phosphorus oxychloride; the mixture was stirred for 30 min at 20°, and the solution was poured into a mixture of 10 mmole of compound Ib,c, or m in 20-40 ml of dimethylformamide. The mixture was heated for 4 h at 80°, then it was cooled and poured onto 75 g of ice. After 5 h the aldehyde (IVa-c) which had fallen as a precipitate was filtered off and washed with water. Compounds IVa-c are colorless prisms (Table 3).

The hydrazone of IVb was prepared by 2-h boiling of a mixture of 2.95 g (7.7 mmole) of aldehyde IVb, 1.6 ml (40 mmole) of 98% hydrazine hydrate, and 3 drops of concentrated HCl in 50 ml of methanol, with a yield of 91%. It forms yellow crystals having a mp of 280° (dec., from isopropyl alcohol). Found: C61.1; H5.8; N25.0%. $C_{20}H_{23}N_7O_2$. Calculated: C61.1; H5.9; N25.0%.

<u>2-Phenyl-3,6,8-trimethylimidazo[1,2-f]xanthines (Va,b).</u> A) A mixture of 10 mmole of the aldehyde (IVa or b), 8.5 ml of 98% hydrazine hydrate, and 2.24 g (40 mmole) of KOH in 100 ml of diethylene glycol was heated to 195°, distilling off water and hydrazine hydrate, and then was heated at this temperature for another 4 h. After cooling, the mixture was neutralized with concentrated HCl and the diethylene glycol was distilled off under vacuum to a volume of 25 ml; the mixture was cooled, and the solid was filtered off and washed with water and ether. The yield of Va was 82%, mp 233-234° (from ethanol). According to [3], the mp is 233-234°. The yield of Vb was 55%, mp 145-146° (from aqueous methanol). According to [3], to [3], the mp is 144-146°.

Characteristic ions	Peak intensity	(as % of maximum	ionpeaks;peaks with a	ın intensity ≥ 5% ar	e indicated)	
(or m/e)	1a	IIa	P111	J 111	IVa	qxi
+ (H+W	20,7 (310)	20,3 (390)	20,3 (355)	l	20,8 (338)	19,1 (352)
1+-	100,0 (309)	21,1 (388) 96,6 (389) 100,0 (387)	100,0 (354)	15,5 (399)	100,0 (337)	85,1 (351)
			Route A			
a) (M-CH ₃ NCO)+·	25,3 (252)	27,4 (332) 25,5 (330)	23,1 (297)	5,0 (342)	5,3 (280)	5,0 (294)
a-H) +	8,9 (251)	12,3 (331) 8,9 (329)	5,0 (296)]		8,1 (293)
a-HCN)+·	19,9 (225)	43,4 (303) 43,4 (303)	17,2 (270)	5,0 (315)	10,1 (253)	1
b) (a-CO)+·	28,2 (224)	31,1 (302)	26,2 (269)	8,1 (314)	49,5 (252)	5,0 (266)
c) (a-HNCH ₂)+·	25,3 (223)	43,4 (303) 30,9 (301) 50,0000	15,9 (268)	5,6 (313)	12,3 (251)	9,2 (265)
-CH ₃) +	8,3 (209)	5,0 (287)	1	l	ł	1
-HCN)+-	11,9 (197)	11.1 (277) 11.5 (275)	22,5 (242)	5,1 (287)	22,5 (225)	I
			Route B			
A = A + A + A + A + A + A + A + A + A +		5,0 (308)	10,9 (308)	100,0.(353)	18,5 (336) 5,2 (308) 7,3 (300)	5,0 (308) 5,0 (308) 0.9 (308)
$\int (U + v) - v$	1	11	12,4 (324)	5,0 (369)	(ene) c'+1	(enc) 7'e
M - X) - NOJ ⁺ M - X) - NO ₂]+		11	11	15,0 (307)		
+z (128) (118)	5,0 (154,5) 7,8 19,0	50,0 50,0	5,0 6,2	6,8 6,3	6,5 (108,5) 7,2 19,0	5,8 6,2 6,2
(36)	6,4 191	35,7 21.9	11,3	10,3	13,5	6,0 5,0

TABLE 2. Mass Spectra of Imidazo[1,2-f]xanthine Derivatives*

*Mass numbers of the corresponding ions are indicated in parentheses.

Com-	mp , ° C	Found, %				Empirical	Calculated, %				Yield,
pound		с	н	Br	N	formula	с	н	Br	N	%
li Ik Ila Ilb Ilc Ild Ilf Ilf Ilf Ilf Ilf Ilf Ilf Ilf Va Vib IVc Vib IXc	$\begin{array}{c} 209-210\\ 312-314\\ 262-263\\ \textbf{252}\\ 168-170\\ > 322\\ 241-242\\ 262\\ 219-221\\ 206-207\\ 190\\ 250\\ 190-191\\ 234-235\\ 285-287\\ 250-252\\ > 350\\ 295-296\\ 330-332\\ 211-212\\ > 323\\ 229-230\\ 147\\ 284-285\\ 232-233\\ 163-165\\ \end{array}$	$\begin{array}{c} 55,3\\ 54,1\\ 49,3\\ 53,2\\ 44,2\\ 48,3\\ 44,5\\ 44,8\\ 44,8\\ 44,8\\ 44,8\\ 44,8\\ 53,2\\ 44,2\\ 53,2\\ 44,2\\ 51,7\\ 60,6\\ 63,1\\ 54,9\\ 63,1\\ 54,0\\ 64,2\\ 51,7\\ 60,6\\ 63,1\\ 54,0\\ 64,4\\ 64,2\\ \end{array}$	$\begin{array}{c} 9,1\\ -34,3,1\\ 34,3,4,0\\ 55,8,8,0\\ 53,4,5,5,3,3,5,6,7,1,0,2,0\\ 55,6,0\\ \end{array}$	17,7 20,8 18,3 18,4 16,8 34,5 29,7 21,6 	$\begin{array}{c} 15,66\\ 24,00\\ 21,31\\ 16,3\\ 19,22\\ 17,55\\ 13,36\\ 13,33\\ 19,22\\ 23,4\\ 23,7\\ 22,12\\ 23,7\\ 24,7\\ 22,12\\ 23,7\\ 23,7\\ 22,12\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 23,7\\ 24,22\\ 23,7\\ 24,22\\ 23,7\\ 24,22\\ 22,12\\ 23,12\\ 24,3\\ 22,12\\ 23,12\\$	$\begin{array}{c} C_{21}H_{22}BrN_5O_2\\ C_{16}H_{14}N_6O_4\\ C_{19}H_{20}N_6O_4\\ C_{19}H_{20}N_6O_4\\ C_{19}H_{20}BrN_6O_2\\ C_{19}H_{19}BrN_6O_4\\ C_{19}H_{19}BrN_6O_4\\ C_{19}H_{19}BrN_6O_2\\ C_{19}H_{19}Br2N_5O_2\\ C_{19}H_{19}Br2N_5O_2\\ C_{19}H_{19}Br2N_5O_2\\ C_{11}H_{12}N_6O_4\\ C_{14}H_{18}N_6O_4\\ C_{14}H_{18}N_6O_4\\ C_{16}H_{40}N_6O_4\\ C_{16}H_{40}N_7O_6\\ C_{17}H_{15}N_5O_3\\ C_{20}H_{21}N_5O_3\\ C_{17}H_{15}N_5O_3\\ C_{11}H_{15}N_5O_3\\ C_{11}H_{15}N_5O_3\\ C_{11}H_{15}N_5O_3\\ C_{11}H_{15}N_5O_3\\ C_{21}H_{23}N_5O_3\\ C_{21}H_{23}N_5O_3\\ C_{21}H_{23}N_5O_3\\ \end{array}$	$\begin{array}{r} 55,3\\54,2\\49,5\\53,0\\44,4\\48,0\\41,1\\44,8\\47,1\\45,8\\47,1\\50,3\\53,4\\54,2\\57,6\\63,3\\60,6\\63,3\\60,6\\63,0\\64,1\\63,0\\64,1\\\end{array}$	$\begin{array}{c} 4,9\\ 4,0\\ -\\ 3,6\\ 4,7\\ 3,0\\ 4,8\\ 3,40\\ 4,8\\ 5,4\\ 5,3\\ 3,3\\ 5,5\\ 5,5\\ 5,9\\ 5,9\\ 5,9\\ 5,9\\ 5,9\\ 5,9$	17,5 	$\begin{array}{c} 15,4\\ 23,7\\ 21,2\\ 18,0\\ 16,3\\ 19,4\\ 17,7\\ 15,0\\ 13,8\\ 13,1\\ 19,1\\ 128,6\\ 25,1\\ 22,2\\ 24,6\\ 22,2\\ 20,8\\ 20,6\\ 18,4\\ 20,1\\ 17,8\\ 20,1\\ 17,8\\ \end{array}$	$\begin{array}{c} 66\\ 49\\ 46\\ 92\\ 63\\ 99\\ 98\\ 98\\ 98\\ 98\\ 99\\ 73\\ 75-84\\ 84-90\\ 85-87\\ 70-82\\ 70-81\\ 70\\ 93\\ 96\\ 90\\ 77\\ 83\\ 80\\ 68\\ 80\\ 68\\ 70\\ \end{array}$

TABLE 3. 6,8-Dimethylimidazo[1,2-f]xanthines

*Compounds II, IIb, IIh, IIIb and c, IVb, VIa, and IXb were recrystallized from methanol; VIb, from aqueous methanol; Ik, IIc,d,fand g, IIIa, d, f, and g from acetic acid; I1, IIa and e, and IIIe from dilute acetic acid; IVc and IXa, from dioxane; IVa, from dimethyl formamide; and IXc, from aqueous acetone.

B) The same compounds were obtained after 8-h heating of $7-[(\alpha-benzoy1)ethy1]-8-bromotheophyllin [3] with excess methyl- or n-butylamine in methanol in an autoclave at 140°, with yields of 65% (Va) or 55% (Vb).$

<u>3-Hydroxymethyl-2-phenyl-6,8-dimethylimidazo[1,2,f]xanthines (VIa,b).</u> A. To a suspension of 10 mmole of aldehyde IVa or b in 250 ml of dimethylformamide was added 20 mmole of sodium borohydride in small portions with stirring; the mixture was allowed to stand for 12 h, and the excess sodium borohydride was decomposed with a $25\% N_2SO_4$ solution. The dimethylformamide was distilled off under vacuum to a volume of 30 ml, the residue was poured into 100 ml of water, and the alcohols which separated as precipitates (VIa and b) were filtered off and washed with water.

A. A solution of 10 mmole of imidazoxanthine Ib or c in a mixture of 40-50 ml of 36% formalin and 15-20 ml of acetic acid was boiled for 5 h, the mixture was cooled and poured into 200 ml of water, and the precipitate which separated was filtered off and washed with water. Yield, VIa, 80%, VIb, 71% (Table 3).

<u>Di(1,2,6,8-tetramethylimidazo[1,2-f]xanthinyl)methane (VII)</u>. A solution of 2.42 g (10 mmole) of compound Ia in a mixture of 35 ml of 36% formalin and 25 ml of acetic acid was boiled for 3 h; after cooling the precipitate was filtered off and washed with water. Yield of VII, 55%. It forms colorless prisms, mp > 350° (dec., from CH₃COOH). IR frequencies: 1670, 1710 cm⁻¹. Found: C 54.6; H 5.1; N 27.8%. $C_{23}H_{26}N_{10}O_4$. Calculated: C 54.5; H 5.2; N 27.7%.

<u>3-Dimethylaminomethyl-1,2-diphenyl-6,8-dimethylimidazo[1,2-f]xanthine (VIII).</u> A mixture of 10.0 g (27 mmole) of compound If, 5.7 ml (40 mmole) of 33% aqueous dimethylamine solution, and 4 ml (40 mmole) of 36% formaline in 90 ml of acetic acid was boiled for 4 h. The acetic acid was distilled off under vacuum, the residue was treated with 300 ml of water, and it was neutralized with a 20% KOH solution to pH 8-9. Compound VIII which separated as a precipitate was filtered off and washed with water. Yield, 95%. It forms colorless needles, mp. 225-226° (from methanol). Found: C 67.3; H 5.7; N 19.7%. C₂₄H₂₄N₆O₂. Calculated: C 67.3; H 5.6; N 19.6%. <u>3-Acetyl-6,8-dimethylimidazo[1,2-f]xanthines (IXa-c)</u>. A mixture of 10 mmoles of compound Ia-c, 20-25 ml of freshly distilled acetic anhydride, and 1-2 ml of concentrated H_2SO_4 (d 1.83) or 57% HClO₄ was heated for 2 h on a boiling water bath. After cooling, the reaction mixture was poured onto 150 g of ice, and after 12 h the ketone (IXa-c) which had precipitated was filtered off and washed with water. The compounds IXa-c are colorless crystals (Table 3).

The 2,4-Dinitrophenylhydrazone of IXb was prepared in 95% yield. It formed wine-colored crystals having a mp of 275-276° (dec., from a dioxane-isopropyl alcohol mixture). Found: N 24.0%. $C_{24}H_{21}N_9O_6$. Calculated: N 23.7%.

<u>3-(p-Nitrocinnamoyl)-1-n-butyl-2-phenyl-6,8-dimethylimidazo[1,2-f]xanthine (X).</u> To a solution of 1.38 g (3.5 mmole) of ketone IXb and 0.6 g (4 mmole) of p-nitrobenzaldehyde in 20 ml of methanol was added 2 drops of 40% KOH solution. The mixture was heated for 3 h at 45-50° with stirring, then it was cooled, and the precipitate of compound X was filtered off, and was washed with water and methanol. Yield, 73%. It forms yellow crystals, mp 264-265° (from propanol). IR frequencies: 1670, 1695, 1718 (C=O); 1360, 1520 cm⁻¹ (NO₂). Found: C $64_{\circ}0$; H 5.6; N 15.8%. $C_{28}H_{26}N_6O_5$. Calculated: C 63.9; H 5.3; N 16.0%.

3-[p(N,N-Dimethylamino)cinnamoy1]-1-n-buty1-2-pheny1-6,8-dimethylimidazo[1,2-f]xanthine (XI) was prepared analogously to compound X using p-dimethylaminobenzaldehyde; yield, 45%. It forms yellow crystals, mp 220-222° (from methanol). IR frequencies: 1680, 1705, 1720 cm⁻¹ (C=0). Found: C 68.0; H 6.0; N 16.1%. C₃₀H₃₂N₆O₃. Calculated: C 63.9; H 5.3; N 16.0%.

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