PARAMAGNETIC DERIVATIVES OF HEXAHYDROIMIDAZO[1,5-c]PYRIMIDINE

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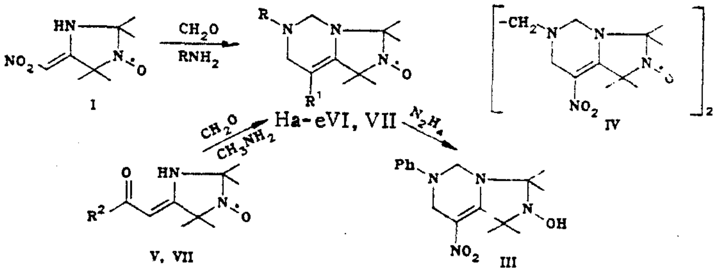
Paramagnetic derivatives of hexahydroimidazo[1,5-c]pyrimidine were obtained by the reaction of 2,2,5,5-tetramethyl-4-nitromethyleneimidazolidin-1-oxyl with formaldehyde and primary amines, ethylenediamine, or ammonia. It was shown that the intracyclic C=C bond in these compounds can be reduced selectively by the action of sodium borohydride.

It is known that derivatives of tetrahydropyrimidine can be obtained by the reaction of the simplest acyclic nitroenamines with formaldehyde and primary amines [1]. In the present work we studied the possibility of realizing this reaction for heterocyclic nitroenamines (imidazolidinoxyl derivatives) and the annellation of the imidazolidine and pyrimidine rings.

The reaction of 2,2,5,5-tetramethyl-4-nitromethyleneimidazolidin-1-oxyl with formaldehyde and aniline gives a high yield of compound (IIa). The IR spectrum of the product contains an absorption band at 1555 cm^{-1}, corresponding to the vibrations of the nitroenamine group, and bands at 3020 and 3040 cm^{-1} for the vibrations of the hydrogen atoms of the aromatic ring. The UV spectrum is characterized by absorption at λ_{max} 240 (log ε 4.13) and 372 nm (log ε 4.21). In the PMR spectrum of its diamagnetic analog (III), produced by the reduction of (IIa) with hydrazine hydrate, there are signals for the two gem-dimethyl groups at 1.12 (6H) and 1.40 (6H) ppm, multiplets centered at 4.34 (2H) and 4.80 (2H) ppm, a multiplet for the protons of the phenyl group centered at 7.1 (5H), and a singlet for the proton of the OH group at 8.04 ppm. On the basis of these data, compound (IIa) was assigned the structure of 1,2,4,5,6,7-hexahydro-1,1,3,3-tetramethyl-8-nitro-6-phenylimidazo[1,5-c]pyrimidin-2-oxyl (see below).



IIa–e $R^1=NO_2$; a $R=C_6H_5$; b $R=CH_3$; c $R=C(CH_3)_3$; d $R=H$; e $R=CH(CH_3)_2$;
V $R^2=C_6H_5$; VI $R=CH_3$, $R^1=C_6H_5CO$; VII $R^2=CF_3$; VIII $R=CH_3$, $R^1=H$

The reaction of the nitroenamine (I) with formaldehyde and methylamine, tert-butylamine, isopropylamine, or ammonia also leads to the respective derivatives of imidazo[1,5-c]pyrimidine (IIb-e). The reaction with formaldehyde and ethylenediamine gives the biradical (IV), i.e., the product from the addition of two molecules of the nitroenamine and four molecules of formaldehyde to the ethylenediamine molecule. It should be noted that the cyclocondensation of the nitroenamine (I) can only be realized with formaldehyde and primary amines. Other aldehydes do not enter into condensation, while a condensation product of the crotonic type [2] is formed in the reaction with formaldehyde and secondary amines.

We found that enamino ketones with similar structures also enter into cyclocondensation. Thus, the pyrimidine derivative (VI) is formed in the reaction of the enamino ketone (V) with methylamine and formaldehyde (cf. [3]). In contrast to this, the reaction of the enamino ketone (VII) with formaldehyde and methylamine is accompanied by the removal of the trifluoroacetyl group and leads to compound (VIII).

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	T_{mp}, °C[a]	IR spectrum[b] (KBr), cm^{-1}	UV spectrum (ethanol) λ_{max}, nm (lg ε)	Found, %			Molecular formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
IIa	144—146	1555	240 (4,13), 372 (4,21)	60,2	6,6	17,4	$C_{16}H_{21}N_4O_3$	60,6	6,7	17,7	63
IIb	170—172	1570	368 (4,29)	48,8	7,5	20,8	$C_{11}H_{19}N_4O_3 \cdot H_2O$	48,4	7,7	20,5	88
IIc	142—143	1560	374 (4,32)	56,4	8,6	18,6	$C_{14}H_{25}N_4O_3$	56,6	8,4	18,9	100
IId	183—184	1575, 1600, 3275	356 (4,11)	49,5	6,9	22,9	$C_{10}H_{17}N_4O_3$	49,8	7,1	23,2	83
IIe	140—141	1580	346 (4,14)	55,0	8,0	20,0	$C_{13}H_{23}N_4O_3$	55,2	8,1	19,8	86
III	164—166	1530, 1545, 3560[c]	242 (4,06), 376 (4,28)	60,4	6,9	17,6	$C_{16}H_{22}N_4O_3$	60,4	6,9	17,6	90
IV[d]	226—228	1575	372 (4,08)	51,7	7,2	22,0	$C_{22}H_{36}N_8O_6$	51,9	7,1	22,1	40
VI	142—144	1605	244 (3,97), 334 (4,27)	69,2	7,7	13,4	$C_{18}H_{24}N_3O_2$	69,0	7,6	13,4	83
VIII	81—83	1625		62,6	9,9	20,3	$C_{11}H_{20}N_3O$	62,8	9,6	20,0	60
Xa	118—120	1550		60,0	7,0	17,2	$C_{16}H_{23}N_4O_3$	60,2	7,2	17,6	53
Xb	109—112	1560		51,5	8,6	21,8	$C_{11}H_{21}N_4O_3$	51,4	8,2	21,8	90
Xc	98—100	1560		61,3	9,3	19,0	$C_{14}H_{27}N_4O_3$	61,9	9,7	18,8	40
Xd	129—131	1565, 3295		49,4	7,9	22,7	$C_{10}H_{19}N_4O_3$	49,4	7,8	23,1	5
XI	149—151	1570, 2300, 2380		48,9	9,2	21,0	$C_{11}H_{21}N_4O_3 \cdot BH_3$	48,9	8,9	18,4	71

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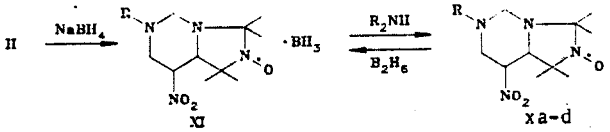
[a] Compounds (IIa, c, e, III, VI, Xb, XI) were purified by recrystallization from a mixture of ethyl acetate and hexane, (IIb) from ethyl acetate, (IId, IV) from DMFA, (VIII) from hexane, (Xa) from heptane, and (Xc, d) from cyclohexane.

[b] The absorption bands of the symmetrical vibrations of the NO_2 group were not assigned, since a large number of bands are observed for compounds (II, X) in the IR spectrum in the region of 1300-1400 cm^{-1}.

[c] The spectrum in the region of 2800-3600 cm^{-1} was recorded in carbon tetrachloride.

[d] EPR spectrum, quintet, a_N = 14.4 Oe.

It is known that the reduction of nitroenamines can be realized either by catalytic hydrogenation or by the action of lithium aluminum hydride. Here the C=C bond and the nitro group are reduced at the same time with the formation of the saturated diamines [4]. In reaction with lithium aluminum hydride the nitroenamine (I) forms the oxime 1-hydroxy-4-hydroxyiminomethyl-2,2,5,5-tetramethyl-3-imidazoline (IX), which was isolated in the form of the corresponding nitroxyl radical (IXa), but it does not react with sodium borohydride. However, the reaction of imidazo[1,5-c]pyrimidine (IIa) with sodium borohydride in alcohol leads to selective reduction of the C=C bond with the formation of compound (Xa). Two compounds (Xb) and (XI) are formed during the reduction of (IIb) under analogous conditions in THF. Their IR spectra contain absorption bands for the asymmetric vibrations of the unconjugated nitro groups at 1560 and 1570 cm^{-1}, respectively. For compound (XI) there are also bands at 2300 and 2380 cm^{-1}, typical of the vibrations of B—H bonds [5]. If a solution of (XI) in chloroform is kept in the presence of diethylamine, it is converted quantitatively into compound (Xb), on the basis of which it was assigned the structure of the adduct of the reduction product (Xb) with borane. This is also confirmed by the data from elemental analysis and by the fact that the adduct (XI) can be obtained by the action of diborane on compound (Xb). The reaction of (IIc) with sodium borohydride in THF followed by treatment of the reaction mixture with diethylamine leads to the formation of the corresponding reduction product (Xc) and also compound (Xd), the IR spectrum of which is close to the IR spectra of compounds (Xa-c). However, it contains a band for the vibrations of the N—H bond at 3295 cm^{-1}, on the basis of which this compound was assigned the structure of the product from reductive de-tert-butylation.



X a R=C_6H_5, b R=CH_3, c R=$C(CH_3)_3$, d R=H; XI R=CH_3

EXPERIMENTAL

The IR spectra were obtained on a UR-20 instrument for tablets with potassium bromide (c 0.25%) and solutions in carbon tetrachloride (c 5%). The UV spectra were obtained in alcohol on a Specord UV-vis instrument. The PMR spectrum was recorded on a Varian A-56-60A instrument in deuterodimethyl sulfoxide (c 10%).

The characteristics of the obtained compounds are given in Table 1. The synthesis and spectral characteristics of (I) were described in [6], and those of (V, VII) were described in [7].

1,2,4,5,6,7-Hexahydro-1,1,3,3,6-pentamethyl-8-nitroimidazo[1,5-c]pyrimidin-2-oxyl (IIb). To a suspension of 0.3 g (1.5 mmole) of the nitroenamine (I) in 5 ml of methanol, while stirring, we added 0.9 ml of a 30% solution of formalin and then 0.75 ml of a 20% solution of methylamine in water. The initial compound dissolved, and compound (IIb) was precipitated. The product was filtered off and washed with water.

Compounds (IIa, c-e, IV) were obtained similarly in the reaction of the nitroenamine (I) with formaldehyde and aniline, tert-butylamine, isopropylamine, ammonia, or ethylenediamine.

1,2,4,5,6,7-Hexahydro-2-hydroxy-1,1,3,3-tetramethyl-8-nitro-6-phenylimidazo[1,5-c]pyrimidine (III). A solution of 0.1 g (0.32 mmole) of (IIa) and 0.2 ml of 85% hydrazine hydrate in methanol was kept at 20°C for 12 h and evaporated. The residue was diluted with water and extracted with chloroform. The extract was dried with magnesium sulfate, the solution was evaporated, the residue was treated with dry ether, and the precipitated compound (III) was filtered off.

8-Benzoyl-1,2,4,5,6,7-hexahydro-1,1,3,3,6-pentamethylimidazo[1,5-c]pyrimidin-2-oxyl (VI). A solution of 0.3 g (1.16 mmole) of the enamino ketone (V), 0.8 ml of a 20% solution of methylamine, and 0.9 ml of 30% formalin in 10 ml of methanol was kept at 20°C for 15 days, evaporated, and diluted with water. The precipitated compound (VI) was filtered off.

Imidazo[1,5-c]pyrimidine (VIII) was obtained similarly from the enamino ketone (VII). The product was isolated by column chromatography on silica gel with a 25:1 mixture of chloroform and methanol as eluant.

4-Hydroxyiminomethyl-2,2,5,5-tetramethyl-3-imidazolin-1-oxyl (IXa). A solution of 0.4 g (2 mmole) of the nitroenamine (I) in dry THF was stirred with 0.4 g (12 mmole) of lithium aluminum hydride at 20°C for 24 h. The mixture was diluted with water, acidified to pH 6 with 5% hydrochloric acid, and extracted with chloroform. The extract was dried with magnesium sulfate, the drying agent was filtered off, 1 g (11.5 mmole) of manganese dioxide was added to the solution, and the mixture was stirred for 3 h. The excess of the oxidizing agent was filtered off, and the mixture of the initial nitroenamine (I) and the oxime (IXa) was separated by column chromatography on silica gel. The initial nitroenamine (I) was eluted first with chloroform, and the oxime (IXa) was then eluted with a 20:1 mixture of chloroform and methanol. The yield was 0.2 g (45%); mp 162-164°C. Published data [6]: mp 163-164°C.

1,1,3,3-Tetramethyl-8-nitro-6-phenylperhydroimidazo[1,5-c]pyrimidin-2-oxyl (Xa). A suspension of 0.2 g (0.63 mmole) of (IIa) and 0.2 g (5.3 mmole) of sodium borohydride in ethanol was stirred at 20°C for 15 min. The solution was evaporated, and the residue was diluted with chloroform and washed with 10 ml of water which had been acidified to pH 4 with 5% hydrochloric acid. The chloroform extract was separated and dried with magnesium sulfate, and the solution was evaporated. Compound (Xa) was isolated by column chromatography on silica gel with chloroform as eluant.

1,1,3,3,6-Pentamethyl-8-nitroperhydroimidazo[1,5-c]pyrimidin-2-oxyl (Xb) and Its Adduct with Borane (XI). The compounds were obtained similarly to compound (Xa), but the reaction was carried out in dry THF. The mixture was separated by column chromatography on silica gel with a 1:1 mixture of ether and hexane as eluant. Compound (Xb) was obtained with a yield of 20%, and the adduct (XI) was obtained with a yield of 70%. To produce compound (Xb) from the adduct (XI) 0.5 g (1.85 mmole) of the latter was dissolved in the smallest amount of chloroform, and 2 ml of diethylamine was added. After 15 min the solution was evaporated, the residue was washed with hexane, and the precipitated compound (Xb) was filtered off. In order to obtain compound (Xb) alone, the reaction mixture after reduction was treated with diethylamine and evaporated. Compound (Xb) was isolated with a yield of 90% by column chromatography on silica gel with a 1:1 mixture of ether and hexane as eluant.

A mixture of 1,1,3,3-tetramethyl-6-tert-butyl- and 1,1,3,3-tetramethyl-8-nitroperhydroimidazo[1,5-c]pyrimidin-2-oxyl (Xc, d) was obtained similarly by the action of sodium borohydride on compound (IIc) and subsequent treatment of the reaction mixture. The products were separated by column chromatography on silica gel with a 1:1 mixture of ether and hexane as eluant.

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

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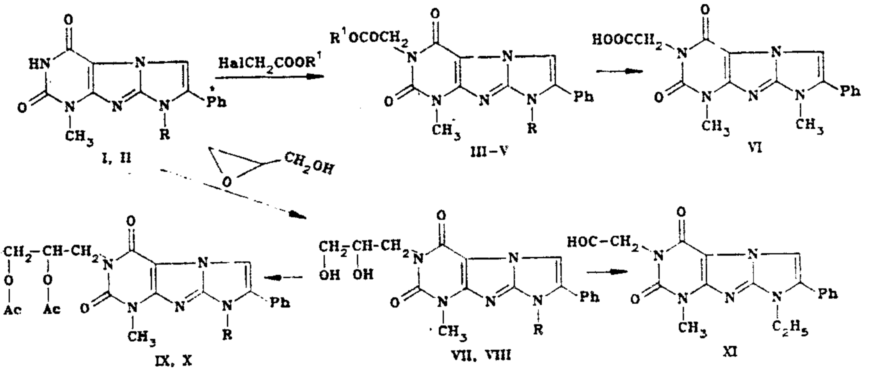
Alkylation at the $N_{(6)}$ atom of 6H-1-ethylethyl(methyl-2-phenylimidazo[1,2-f]xanthenes was realized with α-halogenoacetic esters. The alkylation of these compounds with glycidyl alcohol in the presence of organic bases also leads to 6-(dihydroxypropyl) derivatives.

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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