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SYNTHESIS, SOME REACTIONS, AND BIOLOGICAL PROPERTIES OF IMIDAZO[1,2-f]THIOPURIN-7-ONE DERIVATIVES*

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The thionation of 1,8-dimethyl-6-H-2-phenolimidazole[1,2-f]xanthine with the aid of P_2S_5 in γ-picoline leads to 1,8-dimethyl-2-phenyl-5-thioxoimidazo[1,2-f]purin-7-one. On alkylation with methyl iodide, the latter is converted into 1,8-dimethyl-5-methylthio-2-phenylimidazo-[1,2-f]purin-7-one. The reductive desulfuration of 1,8-dimethyl-5-methylthio-2-phenylimidazo[1,2-f]purin-7-one with Raney nickel in aqueous ethanol forms 1,8-dimethyl-2-phenyl-7,8-dihydroimidazo[1,2-f]purin-7-one; the actions of colamine and benzylamine on the same compounds form 5-(β-hydroxyethylamino)- and 5-benzylamino-1,8-dimethyl-2-phenylimidazo[1,2-f]purin-7-one, respectively. The thionation of 1,8-dimethyl-2-phenylimidazo[1,2-f]xanthine in γ-picoline with an excess of phosphorus pentasulfide leads to 1,8-dimethyl-2-phenyl-5,7-dithioxoimidazo[1,2-f]purine. Some results of biological trials are given. The UV, IR, PMR, and mass spectra of the compounds obtained are discussed.

In the present paper, which represents a continuation of the investigations of the chemical properties of the 6-H-imidazo[1,2-f]xanthine system [2], the direct thionation reaction of this system is described and the possibility is shown of performing a number of transformations on the basis of the 5-thioxo derivative obtained.

The interest in thio derivatives of imidazo[1,2-f]purin-7-one is due to the fact that in its biochemical properties it can be assigned to nucleotide analogs and, like them, exhibits a high physiological activity, including antitumoral activity [3, 4].

According to the literature [5-7], the thionation of uncondensed xanthenes and their derivatives leads to 6-thioxo derivatives. The thionation of 1,8-dimethyl-6H-2-phenylimidazo[1,2-f]xanthine (I) with the aid of phosphorus pentasulfide in γ-picoline gives 1,8-dimethyl-2-phenyl-5-thioxoimidazo[1,2-f]purin-7-one (II) or the 5,7-dithioxo derivative (VIII). The alkylation of (II) with methyl iodide in aqueous alcoholic caustic soda leads to the

*See [1].

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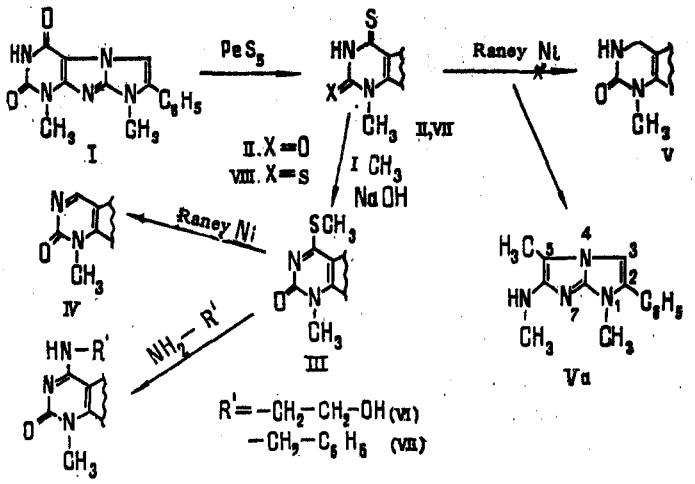
TABLE 1. Assignment of the Chemical Shifts in the PMR Spectra

Compound	Chemical shifts, ppm						
	C_3H	CH_{arom}	N_1-CH_3	N_8-CH_3,	$S-CH_3$	C_5H	N_6-H
II	7,26*	br. s 7,50 (5H)	s 3,76 (3H)	s 3,62 (3H)			s 8,79 (1H)
III	s 7,29 (1H)	br. s 7,51 (5H)	s 3,75 (3H)	s 3,70 (3H)	s 2,75 (3H)		
IV	s 7,29 (1H)	br. s 7,52 (5H)	s 3,75† (6H)			s 8,64 (1H)	

*The C_3H signal is superposed on the signal of the solvent $CDCl_3$.

†The N_1-CH_3 and N_8-CH_3 signals are superposed.

formation of the 5-methylthio derivative (III). The course of the transformations is shown in Scheme 1.



Scheme 1

The hydrodesulfuration of compound (III) with Raney nickel in aqueous ethanol yielded 1,8-dimethyl-2-phenyl-7,8-dihydroimidazole[1,2-f]purin-7-one (IV).

The authenticity of the transformations shown in the scheme has been confirmed with the aid of physicochemical methods of analysis.

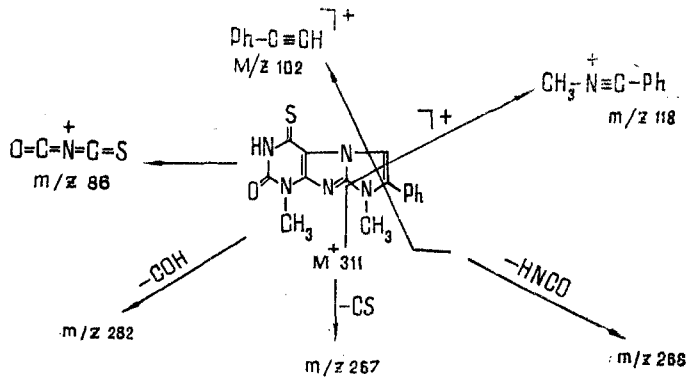
The presence of ill-defined absorption bands ν_{CH_3} = 2960 cm^{-1} in the spectra of compounds of (II), (III), and (IV) confirms the presence of $N-CH_3$ groupings in the molecules. A strong absorption band at ν 1640 cm^{-1} in compound (III) and at 1650 cm^{-1} in (IV) relates to the stretching vibrations of the amide grouping, and bands at 1580 and 1560 cm^{-1} are due to the $\nu_{C=C}$ and $\nu_{C=N}$ bonds in the imidazo[1,2-f]xanthine nuclei. A $\nu_{CH_{arom}}$ band is recorded in the IR spectra of compound (II), (III), and (IV), at 3030-3080 cm^{-1}.

More informative for confirming the compounds synthesized are the PMR and mass spectra. The chemical shifts of the protons of compounds (II)-(IV) are given in Table 1.

The mass spectra of compound (II) contain the peak of the molecular ion M^+ with m/z 311, corresponding to the suggested structure. The presence of a thiouracil ring in the structure of this compound is confirmed by the characteristic elimination of the particles CS and NHCO from M^+ with the formation of particles having m/z 267 and 268, respectively.

All the fragmentation processes are characteristic for mercaptopurines studied previously [8].

In the mass spectra of compound (III), a peak with m/z 325 corresponding to the molecular mass of the suggested structure. The presence of a 1-methyl-2-phenylimidazole moiety in the molecule, as in the preceding case, is confirmed by the following peaks of fragmentary ions (m/z): 77, 102, 103, and 118 (see the Experimental part).



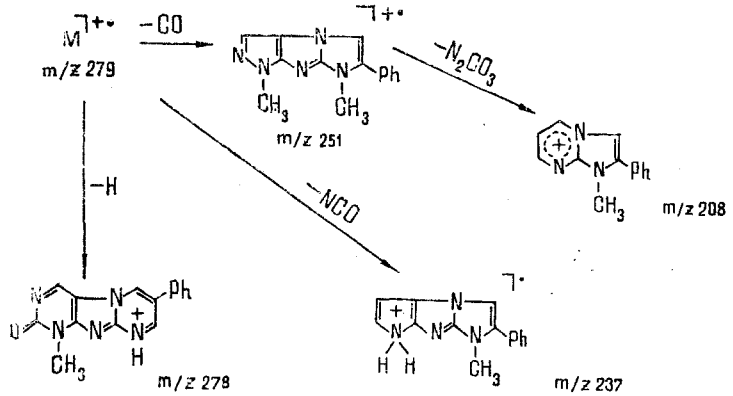
Scheme 2

The presence of a $S-CH_3$ grouping in the pyrimidine part of the molecule of (III) is evidenced by the following processes of the fragmentation of M^+: $M^+ \xrightarrow{-CH_3} (M-CH_3)^+$ m/z 310 (β decomposition relative to the heteryl nucleus); $M^+ \xrightarrow{-HS} (M-HS)^+$ m/z 292 (this process presupposes the migration of a methyl group to the adjacent nitrogen atom in the oxopyrimidine ring); and $M^+ \xrightarrow{-CH_2S} (M - CH_2S)^+$ 279 (a pseudomolecular ion having the structure of (IV)). In addition, the SCH_3 group itself is recorded in the mass spectrum (ion with m/z 47).

The oxopyrimidine moiety in the molecule of (III) is confirmed by a characteristic process of particle elimination: $(M - H) \xrightarrow{-CH_3NCO} [(M - (H) - CH_3NCO]^+$ m/z 267; $(M - SH) \xrightarrow{-NCO} (M - H) - NCO^+$ m/z 250 and $(M - CH_2S)^+ \xrightarrow{-CO} [M - CH_2S)-CO]^+$ m/z 251.

The aromatic (polynucleic) nature of structure (III) is shown by the peak of the doubly charged ion M^{2+} (m/z 162.5).

The fragmentation of M^+ of compound (IV) is shown in Scheme 3.



Scheme 3

The recorded peak of M^+ with m/z 279 corresponds to the molecular mass of the proposed structure (IV). In favor of the presence of an imidazole fragment in the molecule are the following ion peaks (m/z): $77 - C_6H_5^+$; $102 - C_6H_5C \equiv CH^+$; $103 - C_6H_5C \equiv N^+$; $118 - CH_3N^+ \equiv C-C_6H_5$. The presence of the oxopyrimidine moiety of the structure under consideration is confirmed by the process $M^+ \xrightarrow{-CO} (M - CO)^+$ m/z 251, $M^+ \xrightarrow{-NCO} (M - NCO)^+$ m/z 237 and $M^+ \xrightarrow{-CH_3NCO} (M - CH_3NCO)^+$ m/z 222 [9, 10]. The condensed structure of M^+ and of the fragmentary ions with m/z 251 and 250 explains the appearance of the doubly charged ions corresponding to them.

As is well known [11], purine derivatives are characterized by two strong absorption bands (λ_{max}) at 220 and 260 nm. A shift of both bands into the visible region is observed on the introduction of electron-donating substituents into the purine nucleus. In this connection it may be assumed that for compound (III) in an acid medium the protonation of the N_6 nitrogen atom takes place, which leads to a disturbance of the aromaticity of the pyrimidine part of the molecule. This fact is confirmed by the shift of the long-wave absorption maximum (see Table 2). In the UV spectrum of compound (IV), the same phenomenon leads to a hyp-

TABLE 2. Absorption Bands in the Electronic Spectra of the Compounds Synthesized

Compound	λ_{max}, nm (lg ε)		
	alkaline	neutral	acid
II	280 (4,39) 332 (4,35)	212 (4,33) 251 (4,26) 348 (4,43)	212 (4,36) 251 (4,29) 348 (4,45)
III	256 (4,47) 319 (4,35)	256 (4,45) 319 (4,36)	249 (4,42) 332 (4,37)
IV	262 (4,21) 328 (4,22)	262 (4,23) 328 (4,24)	253 (4,26) 312 (4,13)

sochromic shift of both bands. It is probable that in compound (III) the bathochromic shift of the long-wave maxima is due to the influence of the long-wave-S—CH_3 chromophore.

For compound (II), the action of an acid caused no change in the positions of the absorption bands. This fact additionally confirms the assumption that protonation takes place at the N_6 position in the nucleus and not at N_4 or N_9. The action of alkali on (II) caused a bathochromic shift of the short-wave λ_{max} and a hypsochromic shift of the long-wave λ_{max}. This phenomenon may be connected with processes of tautomerism (thione-thiol or lactim-lactam) in the structure (II) under consideration. The phenomenon of tautomerism is not realized for compounds (III) and (IV).

Attempts to reduce (II) with Raney nickel in an alkaline medium did not lead to the expected 1,8-dimethyl-2-phenyl-5,6,7,8-tetrahydroimidazo[1,2-f]purin-7-one (IV) but to a product which we identified as 1,5-dimethyl-6-methylamino-2-phenylimidazo[1,2-a]imidazole (Va).

In the PMR spectrum of compound (V) the signals of the following protons were recorded (ppm): 1.55 (s, 3 H), C_5—CH_3; 3.64 (s, 3 H), HN—CH_3; 3.76 (s, 3 H), N—CH_3; 7.29 (s, 1 H), C_3H; 7.52 (br. s, 5 H), CH_{arom}; 10.86 (s, 1 H), C_6NH.

A calculation of the PMR spectrum showed that compound (Va) was present in the form of a mixture with 20% of compound (II). (Similar results were obtained with the aid of liquid chromatography but are not given in the present paper.)

In the mass spectrum of compound (Va) the peak M^+ with m/z 240 is recorded, which corresponds to the molecular mass of the proposed compound. The elimination of the H atom and of a CH_3 group from M^+ (β decomposition) characterizes the presence of a 6-methylamino grouping in the molecule. The absence of an oxopyrimidine ring in the molecule of (Va) is confirmed by the absence of the ions $(M - HNCO)^+$ and $(M - CH_3NCO)^+$ in the mass spectrum.

Apparently, on desulfuration with Raney Ni in a strongly alkaline medium, the thiouracil ring opens with the subsequent reduction of the thioamide group to a methyl group. The mechanism of this process is being considered in more detail at the present time.

The sulfur atom in position 5 of compound (II) proved to be inert in relation to the action of nucleophilic reagents (amines) as compared with 4-thioxopteridine derivatives [12]. The sulfur atoms in (II) underwent no change when the compound was heated with amines under severe conditions (160-180°C). In compound (III), the methylmercapto group was mobile and was replaced by an amine residue on boiling in a high-boiling amine (monoethanolamine, benzylamine) which led to the formation of the corresponding amino derivatives (VI and VII).

In the IR spectrum of 5-(β-hydroxyethylamino)-1,8-dimethyl-2-phenylimidazole[1,2-f]-purin-7-one (VI), the stretching vibrations of an associated OH group are observed at 3310 cm^{-1}, and there are also the stretching vibration of a C—O grouping in the form of a strong band at 1250 cm^{-1}. The stretching vibrations of a NH group are shifted into the low-frequency region, ν_{NH} 3135 cm^{-1}, obviously because of the formation of an intramolecular hydrogen bond. In the PMR spectrum (60 MHz) of compound (IV) taken in trifluoroacetic acid appear the signals of the protons of methyl groups — N_1—CH_3 at δ 3.85 ppm (s, 3 H) and N_8—CH_3 at δ 3.88 ppm (s, 3H) — and of the phenyl substituent in the form of a singlet at 7.6 ppm. The signals of the protons of the methylene groups appear in the form of multiplets at 4.03 and 4.76 ppm.

In the IR spectrum of 5-benzylamino-1,8-dimethyl-2-phenylimidazo[1,2-f]purin-7-one (VII) is observed in the broad band of the stretching vibrations of an associated NH group at 3175 cm^{-1}. In the PMR spectrum of (VII) in trifluoroacetic acid, singlets of methyl groups (N_1

and N_8) are recorded at 3.85 and 3.88 ppm (3 H). The signals of the protons of the aromatic substituents appear in the form of a multiplet at 7.53-7.5 ppm (10 H). The signals of the protons of the methylene group form a triplet [13] with δ 5.06 ppm.

As the results of an investigation in a liquid nutrient medium of the antimicrobial and mycostatic activity of the compounds synthesized, it was established that some of them exhibit activity in a concentration of 200 μg/ml. At the same time, it was found that the compounds synthesized possess a highly selective action. Thus, compound (III) shows activity in relation to *Bac. anthracoides* while a compound with a similar structure but without the methylthio group (VI) was inactive in relation to this bacterium but exhibited an effect in relation to the bacterium *Staphylococcus aureus* and the fungus *Microsporum lanosum*. When a β-hydroxyethylamino group was present in the structure in position 5 (VI), only a mycostatic activity in relation to the fungi *Microsporum lanosum* and *Trichophyton mentagrophites* was exhibited.

The highly selective biological activity of this class of compounds creates definite prospects for the search among this series for effective cytostatic and antibacterial agents.

Thus, as our investigations have shown, imidazo[1,2-f]purin-7-one derivatives are an interesting class of basically new heteroaromatic compounds in relation to their physicochemical properties, reactivities, and biological effects.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (in KBr tablets); electronic spectra on a Specord UV-Vis spectrophotometer in CH_3OH at concentrations of the order 10^{-5} M.

The PMR spectra were recorded on a Bruker WH-90 spectrometer in $CDCl_3$ solutions with TMS as standard, and the results are given in the δ scale (ppm).

Mass spectra were recorded on a Varian MAT-311 A instrument with the direct introduction of the sample into the ion source. The recording conditions were the standard ones: accelerating voltage 3 kV, cathode emission current 300 μA, ionizing voltage 70 eV. The results of the elementary analyses of all the compounds synthesized corresponded to the calculated figures.

1,8-Dimethyl-2-phenyl-6H-imidazo[1,2-f]xanthine (I) was obtained as described previously [2].

1,8-Dimethyl-2-phenyl-5-thioimidazo[1,2-f]purin-7-one (II) [1]. A mixture of 11.2 g (0.04 mole) of (I) and 13.32 g (0.06 mole) of P_2S_5 was heated at the boil in 100 ml of γ-picoline for 10 h. Then it was cooled, treated with 200 ml of water, and boiled for another 3 h. After 24 h, the precipitate was filtered off and was washed successively with water and ether. Composition $C_{15}H_{13}N_5SO$, yield 10.7 g (92%). mp 326-328°C (decomp., from DMFA). Its main characteristics are given in the tables. Mass spectrum (temperature of evaporation of the sample 200°C), m/z: 55 (17.8); 56 (6.9); 57 (20.0); 63 (28.2); 67 (11.0); 69 (48.4); 71 (9.7); 77 (13.9); 79 (23.3); 81 (24.0); 86 (11.3); 87 (4.8); 95 (7.8); 97 (6.6); 102 (12.3); 103 (5.1); 116 (6.8); 118 (9.6); 134 (13.6); 240 (8.2); 267 (2.7); 268 (8.9); 282 (4.4); 311 (100.0); 312 (20.0).

1,8-Dimethyl-5-methylthio-2-phenyl[1,2-f]purin-7-one (III) [1]. A suspension of 6.22 g (0.02 mole) of (II) in 40 ml of 50% isopropanol containing 2.24 g (0.04 mole) of KOH was boiled while 2.64 ml of methyl iodide was added through the condenser, and the resulting mixture was boiled for another 5 min and was filtered in the hot state from insoluble impurities. The filtrate was left at 0°C for 48 h and the resulting precipitate was filtered off: $C_{16}H_{15}N_5SO$ — yield 65% (4.2 g), mp 283-284°C (decomp. from aqueous DMFA). The spectral characteristics are given in the tables.

Mass spectrum (temperature of evaporation of the sample 240°C), m/z: 47 (6.0); 55 (10.1); 57 (12.3); 64 (9.2); 69 (11.5); 71 (6.4); 76 (5.4); 77 (19.6); 83 (6.1); 86 (31.8); 89 (7.3); 91 (5.0); 102 (13.0); 103 (7.4); 116 (9.9); 117 (4.2); 118 (25.7); 141 (7.3); 155 (11.4); 162.5 (11.7); 173 (7.6); 212 (11.8); 223 (6.9); 250 (14.6); 251 (27.6); 252 (7.1); 267 (7.1); 279 (9.9); 292 (13.61); 309 (16.8); 310 (13.1); 324 (25.4); 325 (100.0); 326 (22.0).

1,8-Dimethyl-2-phenyl-7,8-dihydroimidazo[1,2-f]purin-7-one (IV) [1]. Raney nickel catalyst (prepared from 8.0 g of nickel—aluminum alloy) in the form of a suspension in 50 ml of methanol was added to 1.3 g (4 mmole) of (III) in 100 ml of water. The mixture was heated at the boil for 6 h and it was filtered in the hot state through a glass filter. The sol-

vent was distilled off in vacuum to 2/3 of the initial volume and the residue was left for 24 h. The precipitate ("needles") that deposited was filtered off: $C_{13}H_{13}N_5O$ — yield 0.75 g (67%), mp 281-282°C (decomposition, from water).

Mass spectrum (temperature of evaporation of the sample 180°C), m/z: 51 (11.4); 52 (7.5); 63 (4.7); 66 (5.0); 67 (7.2); 76 (7.5); 77 (30.8); 78 (4.6); 81 (6.7); 89 (8.9); 91 (7.3); 101 (4.1); 102 (13.1); 103 (8.1); 116 (14.5); 117 (15.4); 118 (23.5); 125 (3.4); 125.5 (3.2); 128 (7.1); 139.5 (15.5); 140 (5.0); 208 (5.0); 222 (6.1); 223 (9.5); 224 (7.4); 437 (14.9); 250 (82.8); 251 (32.7); 252 (9.0); 278 (16.4); 279 (100.0); 280 (20.6).

1,5-Dimethyl-6-methylamino-2-phenylimidazo[1,2-a]imidazole (Va). Raney nickel catalyst prepared from 8.0 g of nickel–aluminum alloy was added in the form of a suspension in 50 ml of methanol to 3.1 g (0.01 mole) of (II) in 100 ml of 5% aqueous KOH solution, and the mixture was heated at the boil for 2 h, filtered, and brought to neutrality by the addition of glacial acetic acid. The resulting precipitate was filtered off. Yield 2.5 g.

Mass spectrum (temperature of evaporation of the sample 300°C), m/z: 51 (6.3); 55 (13.0); 63 (8.9); 67 (11.3); 77 (15.3); 78 (6.3); 90 (15.1); 91 (19.3); 102 (51.3); 103 (27.1); 116 (15.6); 118 (30.2); 197 (24.7); 198 (12.4); 224 (7.3); 225 (12.5); 239 (31.8); 240 (100.0); 241 (21.3).

5-(β-Hydroxyamino)- and 5-Benzylamino-1,8-dimethyl-2-phenylimidazo[1,2-f]purin-7-one [(VI) and (VII), respectively]. A mixture of 0.01 mole of (III) and 10-15 ml of monoethanolamine or benzylamine were heated at the boil for 3-4 h (until the evolution of methyl mercaptan ceased). Then it was cooled and poured into 200 ml of water, and the precipitate was filtered off. In the case of (VI), the yield was 71%, mp 284-286°C (acetone—DMFA), $C_{17}H_{18}N_6O_2$. In the case of (VII) the yield was 47%, mp 300°C (H_2O—DMFA), $C_{22}H_{20}N_6O$.

1,8-Dimethyl-2-phenylimidazo[1,2-f]purine-5,7-dithione (VIII). A mixture of 11.2 g (0.04 mole), of (I) and 26.6 g (0.12 mole) of P_2S_5 was heated at the boil in 100 ml of γ-picoline for 24 h. Then it was cooled, 200 ml of water was added, and the new mixture was heated at the boil for another 3 h. After 24 h, the precipitate was filtered off and was washed with water and acetone: $C_{13}H_{13}N_5S_2$ — yield, %: 97.5 (12.1 g); mp > 360°C (decomp.).

SUMMARY

1. Direct thionation has been studied as a method of modifying the uracil fragment in 6H-imidazo[1,2-f]xanthine derivatives, leading to 5-thioxo derivatives.

2. It has been established that the hydrodesulfuration of a 5-thioxo derivative with the aid of Raney nickel leads to the corresponding imidazo[1,2-a]imidazole. A similar process applied to the 5-methylmercapto derivative led to 7,8-dihydroimidazo[1,2-f]purin-7-one.

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