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SYNTHESIS OF DERIVATIVES OF THIAZOLO[2,3-*i*]PURINE

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Thiazolo[2,3-i]purine and its 7,8-alkyl(aryl, heteryl)derivatives were obtained by the cyclodehydration of 7-hydroxy-7,8-dihydrothiazolo[2,3-i]purine and 6-β-oxoalkyl(aryl, heteryl)thiopurines in the presence of phosphoryl chloride, sulfuric, and polyphosphoric acids.

The interest in condensed purine systems containing a nitrogen atom at a ring junction arises from compounds with a range of biological activities among such substances [1].

Methods for the preparation and some properties of derivatives of thiazolo[2,3-*f*]purine have been reported [2-8] as has also the synthesis of a series of 6-β-oxoalkyl(aryl, heteryl)thiopurines and 7-hydroxy-7,8-dihydrothiazolo[2,3-*i*]purines [9, 10] from which thiazolo[2,3-*i*]purine and a few of its alkyl(aryl, heteryl)derivatives were obtained [11, 12].

The present paper is concerned with a study of cyclodehydration of 7-hydroxy-7,8-dihydrothiazolo[2,3-*i*]purine (I) and 6-β-oxoalkyl(aryl, heteryl)thiopurines II-XV to give derivatives of thiazolo[2,3-*i*]purine XVI-XXX (Table 1). Phosphorus oxychloride, concentrated sulfuric acid and polyphosphoric acid were used as dehydrating media.

The best results were obtained with $POCl_3$ and heating. During the reaction, both compound I and compounds II-XV dissolved progressively, followed by their dehydration to give the tricyclic compounds XVI-XXX in generally satisfactory yields (62-86%). The exception was 6-pinacolinylthiopurine (V) which gave only 32% of 7-*tert*-butylthiazolo[2,3-*i*]purine (XX) despite prolonged boiling (12 h) in $POCl_3$, probably because of steric factors.

Cyclization of compounds I-XV was prolonged and depended to a considerable extent on the structure of the group adjacent to the carbonyl group in the thioether starting material.

The reaction also occurred on heating in concentrated sulfuric acid or polyphosphoric acid (40-95°C), but the yields of the tricyclic products were considerably less (9-14%).

The cyclization of compounds I-XV might occur theoretically at positions 1 or 7 of the purine bicycle to give derivatives of thiazolo[2,3-*i*]purine [1, 4], thiazino[2,3,4-*g,h*]purine or a mixture of these. In all cases we isolated a single substance, confirmed by chromatography.

Taking into account the smaller strain in the five-membered thiazole ring in comparison with the six-membered *para*-thiazine ring, we proposed that the cyclodehydration of compounds I-XV gave derivatives of thiazolopurine XVI-XXX.

The structure of the products XVI-XXX as derivatives of thiazolo[2,3-*i*]purine was confirmed by physicochemical and chemical methods. The IR spectra of the products contained no bands due to the CO, OH, and NH groups which were present in the starting materials I-XV. Compounds XVII, XVIII and XXIX have two maxima in the 243.3-251.6 and 325.7-327.6 nm regions of their UV spectra, which represents a bathochromic shift from UV spectra of the starting materials. Signals of the heteroaromatic protons 2, 5, 7, and 8 were observed at 8.39, 9.28, 7.94, and 7.68 ppm in the ^1H NMR spectrum of the unsubstituted tricycle XVI. The ^1H NMR spectra of the other products are given in Table 2.

Compounds XVI-XXX have an unusual distribution of double bonds in the imidazole ring in which both nitrogens are tertiary.

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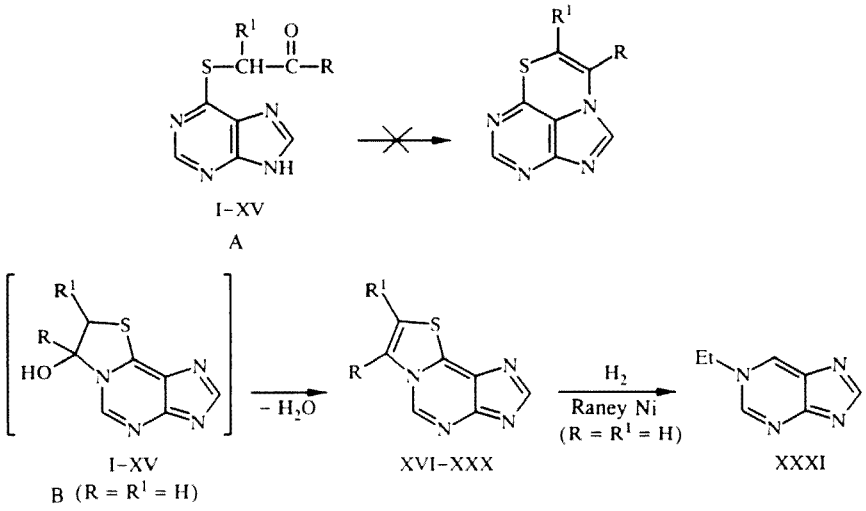

I, XVI R = H; II, III, XVII, XVIII R = CH_3; IV, XIX R = C_2H_5; V, XX R = $C(CH_3)_3$; VI, VII, XXI, XXII R = C_6H_5; VIII, XXIII R = $C_6H_4OCH_3$-*p*; IX, XXIV R = $C_6H_4C_6H_{11}$-*p*; X, XXV R = C_6H_4—C_6H_5-*p*; XI, XXVI R = C_6H_4Cl-*p*; XII, XXVII R = C_6H_4Br-*p*; XIII, XXVIII R = $C_6H_4NO_2$-*m*; XIV, XIX R = $C_6H_4NO_2$-*p*; XV, XXX R = 2-C_5H_4N; I, II IV—VI, VIII—XVII, XIX—XXI, XXIII—XXX R^1 = H; III, VII, XVIII, XXII R^1 = CH_3

The mass spectra of compounds XVII, XVIII, XXII, and XXIX contain intense molecular ion peaks, M^+.

An important indicator of the tricycle XVI is its desulphurization by Raney nickel in ethanol solution to give 1-ethylpurine (XXXI), which was characterized as its more stable picrate. Amine XXXI had an identical UV spectrum and melting point of its picrate to 1-ethylpurine, described earlier [13]. The structures of the other thiazolopurines XVII-XXX were established by analogy.

The mechanism of the closing of the thiazole ring was established earlier for the synthesis of derivatives of imidazolo[2,1-*b*]thiazole [14], thiazolo[3,2-*a*]benzimidazole [15] and thiazolo[2,3-*f*]purine [2, 5]. It is likely that closure of the thiazole ring in the formation of thiazolo[2,3-*i*]purines occurs analogously. The first step, as shown with 6-formylmethylthiopurine [10, 12], is the conversion of the initial aldehyde or ketone I-XV (structure A) into the cyclic tautomers, the 7-hydroxy-7,8-dihydrothiazolo[2,3-*i*]purines (structure B, ring-chain tautomerism). Dehydration of the latter in the dehydrating medium causes formation of a double bond and aromatization of the whole thiazolopurine tricycle.

EXPERIMENTAL

IR spectra of Nujol mulls were recorded with a Specord IR-75 spectrometer and UV spectra with a Perkin-Elmer 402 machine. ^1H NMR spectra were obtained with a Tesla BS-587 AC (80 MHz) with TMS as internal standard. Mass spectra were obtained by direct injection into the ion source of an MX-1321A mass spectrometer with an ionizing voltage of 70 eV and with the ionizing chamber at about 170°C. Progress of reactions and purity of the products were monitored by TLC on Silufol UV-254 strips with eluting systems *a*) *n*-butanol—water—ethanoic acid, 5:3:2, and b) isopropanol—water—25% aqueous ammonia, 15:4:1. Spots were revealed in UV light or with iodine vapor.

Elemental analyses for C, H, N, S, Cl, and Br corresponded to calculated values.

7-Hydroxy-7,8-dihydrothiazolo[2,3-*i*]purine (I) was obtained according to [10], and the 6-β-oxoalkyl(aryl, heteryl)-thiopurines (II-XV) according to [9, 10].

Thiazolo[2,3-*i*]purines XVI-XXX (Table 1). Method A. A suspension of compounds I-XV (0.02 mol) in freshly distilled $POCl_3$ (30-50 cm^3) was boiled for 2 h (compound I), 6 h (XVIII), 8-10 h (XVII, XIX), 12 h (XX-XIV), 14 h (XXVI-XXVIII, XXX), 16 h (XXIX) or 18 h (XXV). At the end of the reaction, residual $POCl_3$ was removed in vacuum and the residue was decomposed with water, the mixture was neutralized with aqueous ammonia to pH 8-10, and the precipitate was filtered off, washed with water and acetone, and dried to give compounds XVI-XXX (Table 1). Samples for analysis were purified by recrystallization from ethanol (XVII, XXXI), aqueous ethanol (XVIII, XVI), aqueous isopropanol (XIX), a mixture

TABLE 1. Characteristics of the Synthesized Compounds XVI-XXX

Compound	Molecular formula	mp, °C (dec.)	Yield, %
XVI	$C_7H_4N_4S$	*	47
XVII	$C_8H_6N_4S$	>300 †	81
XVIII	$C_9H_8N_4S$	292...294	73
XIX	$C_9H_8N_4S$	>300	70
XX	$C_{11}H_{12}N_4S$	265...267	32
XXI	$C_{13}H_8N_4S$	>300 †	86
XXII	$C_{14}H_{10}N_4S$	258...260	74
XXIII	$C_{14}H_{10}N_4OS$	>300 †	85
XXIV	$C_{19}H_{18}N_4S$	296...298	79
XXV	$C_{19}H_{12}N_4S$	>300	77
XXVI	$C_{13}H_7ClN_4S$	>300	64
XXVII	$C_{13}H_7BrN_4S$	>300	78
XXVIII	$C_{13}H_7N_5O_2S$	273...275	62
XXIX	$C_{13}H_7N_5O_2S$	281...283	81
XXX	$C_{12}H_7N_5S$	>300	66

*Picrate with mp 268-270°C (dec.), lit. datum 268-270°C [12].
†mp >300°C [12].

TABLE 2. ^1H NMR Spectra of Compounds XVI, XVIIa, XVIII, XXII, XXV and XXIX

Compound	δ, ppm*
XVI	7,68 (1H, d, 8-H), 7,94 (1H, d, 7-H), 8,39 (1H, s, 2-H), 9,28 (1H, s, 5-H)
XVIIa	2,92 (3H, s, CH_3), 7,92 (1H, s, 8-H), 8,83 (1H, s, 2-H), 9,71 (1H, s, 5-H)
XVIII	2,53 (3H, s, 8-CH_3), 2,64 (3H, s, 7-CH_3), 8,33 (1H, s, 2-H), 9,28 (1H, s, 5-H)
XXII	2,41 (3H, s, 8-CH_3), 7,70 (5H, br. s, C_6H_5), 8,37 (1H, s, 2-H), 8,97 (1H, s, 5-H)
XXV	7,67...7,94 (9H, m, H_{ar}), 8,32 (1H, s, 8-H), 9,02 (1H, s, 2-H), 9,45 (1H, s, 5-H)
XXIX	8,05, 8,67 (4H, d.d, H_{ar}), 8,31 (1H, s, 8-H), 9,22 (1H, s, 2-H), 9,59 (1H, s, 5-H)

*Spectra of compounds XVI, XVIII, and XXII were obtained in DMSO-D_6, XVIIa in D_2O, and compounds XXV and XXIX in CF_3COOD.

TABLE 3. Mass and UV Spectra of Compounds XVII, XVIII, XXII, and XXIX

Compound	Mass spectrum, *m/z*, (relative intensity, %*)	UV spectrum, λ_{max} (lg ε), nm (in 50% ethanol).
XVII	191 (18), 190 (100, $M^{\cdot+}$), 189 (10), 163 (10), 136 (12), 119 (18), 91 (12), 71 (74), 57 (12), 45 (18)	243,3 (4,03), 327,4 (4,19)
XVIII	205 (16), 204 (95, $M^{\cdot+}$), 203 (24), 171 (13), 149 (18), 129 (26), 111 (23), 97 (46), 91 (28), 83 (63), 71 (100), 69 (84), 59 (90), 53 (70)	244,2 (4,07), 327,6 (4,20)
XXII	267 (22), 266 (100, $M^{\cdot+}$), 265 (83), 185 (16), 147 (18), 129 (19), 115 (28), 98 (26), 84 (26), 72 (59), 55 (46)	—
XXIX	298 (18), 297 (100, $M^{\cdot+}$), 296 (29), 251 (25, $[M-NO_2]^+$), 250 (43, $[M-NO_2-H]^+$), 149 (22), 133 (20), 121 (31), 101 (22), 97 (33), 83 (42), 69 (59), 55 (60)	251,6 (4,16), 325,7 (4,28)

*Peaks with intensities ≥10% are given.

TABLE 4. Microanalysis Results for Compounds XVIII-XX, XXII-XXX

Compound	Molecular formula	(Found, %) (Calculated, %)			
		C	H	N	S
XVIII	$C_9H_8N_4S$	52,64 52,92	3,76 3,95	27,08 27,43	15,63 15,70
XIX	$C_9H_8N_4S$	52,83 52,92	3,91 3,95	27,66 27,43	15,54 15,70
XX	$C_{11}H_{12}N_4S$	57,00 56,87	5,50 5,21	24,20 24,12	13,76 13,80
XXII	$C_{14}H_{10}N_4S$	63,22 63,14	3,74 3,78	21,42 21,04	11,81 12,04
XXIII	$C_{14}H_{10}N_4OS$	59,24 59,56	3,35 3,57	19,40 19,84	10,91 11,36
XXIV	$C_{19}H_{18}N_4S$	68,28 68,24	5,50 5,42	16,78 16,75	9,63 9,59
XXV	$C_{19}H_{12}N_4S$	69,83 69,49	3,69 3,68	17,16 17,06	9,47 9,76
XXVI	$C_{13}H_7ClN_4S$*	54,02 54,45	1,98 2,46	18,91 19,54	10,82 11,18
XXVII	$C_{13}H_7BrN_4S$ †	47,45 47,14	2,37 2,13	17,09 16,92	9,38 9,68
XXVIII	$C_{13}H_7N_5O_2S$	52,45 52,52	2,31 2,37	23,42 23,56	11,01 10,78
XXIX	$C_{13}H_7N_5O_2S$	52,50 52,52	2,37 2,37	23,38 23,56	10,90 10,78
XXX	$C_{12}H_7N_5S$	57,03 56,91	2,63 2,79	27,51 27,65	12,79 12,66

*Found, %: Cl 12.12. Calculated, %: Cl 12.36

†Found, %: Br 24.27. Calculated, %: Br 24.13

of isopropanol and acetone (XX), aqueous methanol (XXII, XXIII, XXV, XXIX, XXX), a mixture of methanol and acetone (XXIV), DMF (XXVII, XVIII), while compound XVI was submitted as the picrate.

Properties of compounds XVI-XXX: amorphous (XVI) or crystalline (XVII-XXX) high melting substances of light beige (XVII-XXIV, XXVI, XXVII), beige (XXI, XXX), cinnamon (XXV), or deep yellow (XXVIII, XXIX) color, poorly soluble in water and most organic solvents, which form picrates and salts with mineral and organic acids.

7-Methylthiazolo[2,3-*i*]purine (XVII). Hydrochloride (XVIIa), mp > 300°C (from aqueous acetone). Found, %: Cl 14.18. Calc. for $C_8H_6N_4S \cdot HCl \cdot H_2O$, %; Cl 14.49.

Succinate (XVIIb). mp 138-140°C (from aqueous ethanol). Found, %: N 17.05. Calc. for $C_8H_6N_4S \cdot C_4H_6O_4 \cdot H_2O$, %: N 17.17.

N-Acetylglutamate (XVIIc): mp 172-174°C (from water). Found, %: N 17.29. Calc. for $C_8H_6N_4S \cdot C_7H_{11}NO_5 \cdot H_2O$, %: N 17.62.

N,N-Succinyldiglutamate (XVIId): mp 188-189°C (from water). Found, %: 16.86. Calc. for $C_8H_6N_4S \cdot C_{17}H_{20}N_2O_{10} \cdot H_2O$, %: N 17.02.

7,8-Dimethylthiazolo[2,3-*i*]purine (XVIII). N-Acetylglutamate (XVIIIa). mp 169-171°C (from water). Found, %: N 16.86, Calc for $C_9H_8N_4S \cdot C_7H_{11}NO_5 \cdot H_2O$, %: N 17.02.

Method B. A solution of compound IV (2.2 g) in 96% H_2SO_4 (10 cm_3) was heated for 4 h at 35-40°C, cooled, kept at 20-22°C for 24 h, poured over ice and neutralized to pH 8-9 with sodium carbonate. The precipitate was filtered off, washed with water, and crystallized from ethanol to give compound XIX (0.26 g, 13%), mp >300°C. A mixed melting point with a sample made by method A gave no depression of the melting point.

Method C. A solution of II or III (0.01 mol) in polyphosphoric acid (20 cm^3) was heated on a boiling water bath for 12 h, cooled, poured into water, and neutralized with aqueous ammonia. The precipitate was purified as in method A. The yields of compounds XVII and XVIII were 9 and 14% respectively. Mixed melting points with the corresponding materials made by method A gave no depressions of the melting points.

1-Ethylpurine (XXXI). Raney nickel paste (6 g) was added in two portions to a solution of compound XVI (1 g) in ethanol (400 cm^3). The mixture was boiled for 8 h, the catalyst was filtered off and extracted with hot ethanol (2 × 50 cm^3). The combined ethanol solutions were treated with charcoal, evaporated in vacuum, and the residue was extracted with acetone. The acetone was evaporated in vacuum to give the base XXXI (0.2 g, 24%) as a sticky oil. Half (0.1 g) was chromatographed on a silica gel column with isopropanol as eluant to give pure XXXI (0.032 g). mp 198-199°C, R_f 0.12 (system A). UV spectrum (in ethanol): λ_{max} (log ε): 221.3 (4.19), 273.4 (3.54) nm. Picrate mp 172-174°C (dec., from aqueous ethanol). Found, %: N 26.18. Calc. for $C_7H_8N_4 \cdot C_6H_3N_3O_7$, %: N 25.99.

Amine XXXI was obtained analogously from 7,8-dihydrothiazolo[2,3-*i*]purine [13] in 26% yield, mp 198-199°C (from isopropanol). Picrate mp 172-174°C (dec., from aqueous ethanol. A mixed melting point with samples of the picrate gave no depression. According to [13], melting point of amine XXXI is 198°C.

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