[Chem. Pharm. Bull. 21(2) 256—259 (1973)]

UDC 547.857.4.04 : 547.789.057

Syntheses of Thiazolo[2,3-*f*]xanthine and Thiazolo[2,3-*f*]hypoxanthine

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(Received April 24, 1972)

Thiazolo[2,3-*f*]xanthine and thiazolo[2,3-*f*]hypoxanthine were synthesized from 8-thioxanthine and 8-thiohypoxanthine *via* 8-acetonylthio derivatives. Structures of these compounds were determined by desulfurization with Raney Ni and by comparisons of physical data and spectrometrical data with those of thiazolo[3,2-*e*]purines.

In the studies of purine derivatives, relative reactivities of nitrogens of purine ring, especially at 7- and 9-position, were interesting. Relative reactivities of nitrogens have been assumed to depend on the structure of purine and the condition of the reaction.

The ring closure of 8-(acylmethyl)thiopurines might occure to 7- and/or 9-nitrogen and would give some informations on the structural feature of purine ring that controls relative reactivities of 7- and 9-nitrogen of purine ring.

In the previous papers[2] we reported that ring closure of 8-(acylmethyl)thioadenines, which have an amino group at 6-position of purine ring, took place to 9-nitrogen and gave thiazol[3,2-*e*]adenines while it took place to 7-nitrogen to give thiazolo[2,3-*f*]theophyllines in the case of 8-(acylmethyl)thiotheophyllines. In this paper the ring closure of 8-acetonylthioxanthin and 8-acetonylthiohypoxanthine, which have an oxo group at 6-position of purine ring instesad of an amino group, and the structural elucidations of obtained thiazolopurines were described.

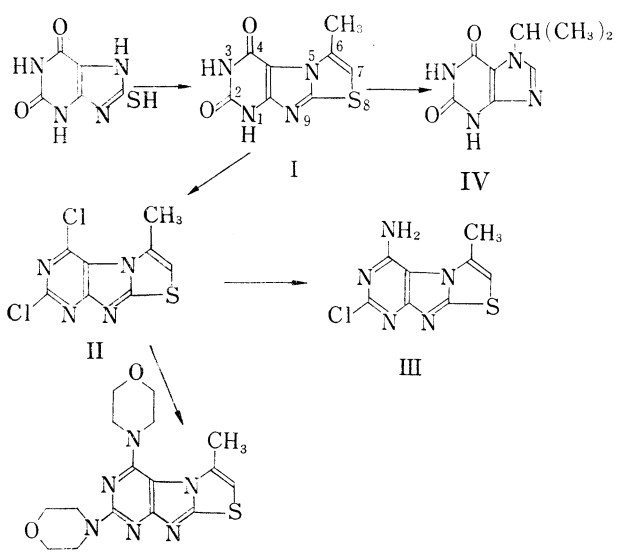

Chart 1

Thiazolo[2,3-*f*]xanthine

6-Methylthiazolo[2,3-*f*]xanthine (I) was first synthesized by Todd, *et al.*[3] in the effort to confirm the structure of thiochrome. They reported the structure of this compound as thiazolo[2,3-*f*]purine but any proof on this structure was not described. Therefore I was synthesized according to the direction of Todd, *et al.*[3] and its structure was reinvestigated.

8-Thioxanthine was heated in the excess of monochloracetone to give I. When heated in phosphorous oxychloride, I gave 2,4-dichloro-6-methylthiazolo[2,3-*f*]purine (II). II was converted to 2-chloro-6-methylthiazol[2,3-*f*]adenine (III) when reacted with ammonia in

1) Location: *33-94, Enokicho, Suita City, Osaka.*

2) H. Uno, A. Irie, and K. Hino, *Chem. Pharm. Bull.* (Tokyo), **21**, 34 (1973); *idem, ibid.*, **20**, 2603 (1972).

3) A.R. Todd and F. Bergel, *J. Chem. Soc.*, **1936**, 1559.

ethanol at room temperature. Physical data of III were not consistent with those of 2-chloro-6-methylthiazol[3,2-*e*]adenine[2] obtained by the ring closure of 2-chloro-6-amino-8-acetonylthiopurine. Desulfurization of I gave 7-isopropylxanthine (IV). Ultraviolet (UV) spectral data of IV were very similar to those of 7-methylxanthine.[4] These facts supported the structure of 6-methylthiazolo[2,3-*f*]xanthine described by Todd, *et al.*[3] and it was apparent that in the case of 8-acetonylthioxanthine, ring closure took place to 7-nitrogen of purine ring.

TABLE I. Comparisons of UV-Absorption Properties of Isopropylxanthine, 7- and 9-Substituted Xanthines

Compounds	Solvent	λ_{max} mμ ($\varepsilon \times 10^{-3}$)
7-Glucopyranosyl-	0.1N NaOH	290
	0.1N HCl	267
7-Methyl[5]	pH 10	290
	pH 5	269 (9.6)
9-Methyl-[5]	pH 10	278 (9.3), 247 (9.3)
	pH 5	264 (9.3), 235 (7.3)
9-Ribofuranosyl-[5]	pH 10	278 (7.4), 247 (8.6)
	pH 5	264 (8.4), 238 (7.8)
Isopropyl- (IV)	0.1N NaOH	290 (8.6)
	0.1N HCl	263 (7.4)

When heated in morpholine, II gave 2,4-dimorpholino-6-methylthiazolo[2,3-*f*]xanthine.

Thiazolo[2,3-*f*]hypoxanthine

Starting material, 8-thiohypoxanthine (V) was prepared by fusion of 4,5-diamino-6-hydroxypyrimidine with thiourea, according to the direction of Robins.[5] To the alkaline solution of V monochloracetone was added portionwise to give 8-acetonylthiohypoxanthine (VI). Ring closure of VI was carried out in ethanol with hydrogen chloride to give 6-methylthiazolo[2,3-*f*]hypoxanthine (VII).

Physical data of VII were not consistent with those of 8-methylthiazolo[3,2-*e*]hypoxanthine[2] derived from 8-methylthiazolo[3,2-*e*]-adenine. And it was suggested that in the case of 8-acetonylthiohypoxanthine, the ring closure occured to 7-nitrogen of purine ring and gave 6-methylthiazolo-[2,3-*f*]hypoxanthine. When heated in phosphorous oxychloride, VII gave 4-chloro-6-methylthiazolo-[2,3-*f*]purine (VIII), which gave 6-methylthiazol[2,3-*f*]adenine (IX) when heated with ammonia in ethanol. Physical data of IX were different from those of 8-methyl-

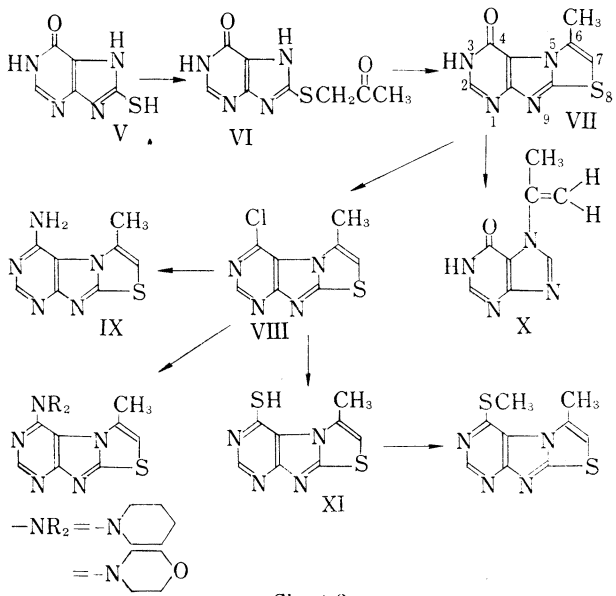

Chart 2

4) J.M. Gulland, E.R. Holiday, and T.F. Macrae, *J. Chem. Soc.*, **1934**, 1639.
5) R.K. Robins, *J. Am. Chem. Soc.*, **80**, 6671 (1958).

thiazol[3,2-*e*]adenine,[2] which was obtained by the ring closure of 8-acetonylthioadenine. This fact supported the structure of VII to be 6-methylthiazolo[2,3-*f*]hypoxanthine.

Desulfurization of VII with Raney Ni gave desulfurized compound (X), which was shown to be isopropenylhypoxanthine from its analytical data and nuclear magnetic resonance (NMR) spectrum. UV spectrum of X was similar to that of 7-methylhypoxanthine[6] and different from that of 9-methylhypoxanthine.[6] This result suggested that X was 7-isopropenylhypoxanthine derived from 6-methylthiazolo[2,3-*f*]hypoxanthine.

4-Chlorine atom of VIII was easily converted to piperidino- or morpholino-group by heating with corresponding amine. When VIII was heated with thiourea in ethanol, 4-thio-6-methylthiazolo[2,3-*f*]purine (XI) was obtained. XI was methylated with methyliodide to give 4-methylthio-6-methylthiazolo[2,3-*f*]purine.

Experimental[7]

6-Methylthiazolo[2,3-*f*]xanthine (I)[3]——8-Thioxanthine (1.2 g) was dissolved in monochloracetone (4 ml) and the reaction mixture was refluxed for 30 min. After cooling, ether was added to the reaction mixture and precipitates separated were collected and washed with acetone. The product was dissolved in dil. NH_4OH and reprecipitated with AcOH. After one more reprecipitation slightly brown powder (0.6 g), mp >300°, was obtained. *Anal.* Calcd. for $C_8H_4N_4S$: C, 43.23; H, 2.72; N, 25.21; S, 14.43. Found: C, 43.48; H, 2.57; N, 25.46; S, 14.14. UV $\lambda_{max}^{0.1N\ NaOH}$ mμ (ε): 231.5 (24600), 282 (13300).

2,4-Dichloro-6-methylthiazolo[2,3-*f*]purine (II)——I (1.1 g) was added to $POCl_3$ (50 ml) and the reaction mixture was refluxed for 7 hr under stirring. After the excess $POCl_3$ was evaporated off *in vacuo*, the residue was poured into ice-water. Brown precipitates were collected and extracted with hot $CHCl_3$ (50 ml × 2). $CHCl_3$ extracts were evaporated *in vacuo* and the residue was recrystallized from EtOH. White prisms (0.6 g), mp 255—260°, were obtained. *Anal.* Calcd. for $C_8H_4N_4SCl_2$: C, 37.08; H, 1.56; N, 21.62; S, 12.37; Cl, 27.37. Found: C, 37.10; H, 1.76; N, 21.85; S, 12.45; Cl, 27.43. UV λ_{max}^{EtOH} mμ (ε): 252 (25000), 293 (7000), 307 (sh).

2-Chloro-6-methylthiazol[2,3-*f*]adenine (III)——II (0.3 g) was dissolved in $CHCl_3$ (50 ml) and EtOH (20 ml). To this solution was added EtOH saturated with NH_3 (20 ml). The reaction mixture was allowed to stand for 5 days. Precipitates separated were collected and recrystallized from MeOH. White needles (55 mg), mp>300°, were obtained. *Anal.* Calcd. for $C_8H_6N_5SCl$: C, 40.08; H, 2.52; N, 29.22; S, 13.38; Cl, 14.79. Found: C, 40.23; H, 2.42; N, 29.44; S, 13.66; Cl, 14.81. UV $\lambda_{max}^{0.1N\ HCl}$ mμ (ε): 248 (23200), 278 (12700).

2,4-Dimorpholinothiazolo[2,3-*f*]purine——II (150 mg) was added to morpholine (3 ml) and the mixture was refluxed for 1 hr. After the excess morpholine was evaporated *in vacuo*, the yellow residue was dissolved in $CHCl_3$ (5 ml) and the product was isolated by column chromatography on silica gel. Elution with $CHCl_3$–MeOH (100:1) gave white needles, which was recrystallized from $CHCl_3$–EtOH. White needles (80 mg), mp 194°, were obtained. *Anal.* Calcd. for $C_{16}H_{20}O_2N_6S$: C, 53.32; H, 5.59; N, 23.32; S, 8.90. Found: C, 53.48; H, 5.29; N, 23.26; S, 8.83. UV $\lambda_{max}^{0.1N\ HCl}$ mμ (ε): 232 (17000), 255.5 (18900), 280 (13300), 321 (19000).

6-Methylthiazolo[2,3-*f*]hypoxanthine (VII)——8-Thiohypoxanthine (20 g), NaOH (9.6 g) and H_2O (200 ml) were mixed. And to this solution was added monochloracetone (13.2 g) in EtOH (10 ml) under stirring. After 30 min, precipitates which separated were collected, washed with H_2O and recrystallized from dimethylformamide (DMF)–EtOH. Yield of VI, mp 240°, was 24 g. *Anal.* Calcd. for $C_8H_8O_2N_4S$: C, 42.85; H, 3.59; N, 24.99; S, 14.30. Found: C, 42.56; H, 3.41; N, 24.80; S, 13.99.

VI (5 g) was suspended in EtOH (100 ml). Under cooling dry HCl was bubbled through the suspension for 10 min. The reaction mixture was refluxed for 3 hr. After cooling precipitates separated were collected and recrystallized from MeOH. Slightly yellow crystals (3.5 g), mp >300° were obtained. *Anal.* Calcd. for $C_8H_6ON_4S$ 1/2 H_2O: C, 45.95; H, 3.63; N, 25.21; S, 14.43. Found: C, 45.91; H, 3.43; N, 25.39; S, 14.80. UV λ_{max}^{EtOH} mμ (ε): 240.5 (20300), 247 (sh), 276 (10200).

4-Chloro-6-methylthiazolo[2,3-*f*]purine (VIII)——VII (2 g) was dissolved in $POCl_3$ (20 ml) and the solution was refluxed for 4 hr. After the excess $POCl_3$ was removed, the residue was poured into H_2O and precipitates were collected and recrystallized from EtOH. Colorless needles (1.1 g), mp 221—224°, were obtained. *Anal.* Calcd. for $C_8H_5N_4SCl$: C, 42.76; H, 2.24; N, 24.94; S, 14.27; Cl, 15.78. Found: C, 42.76; H, 2.43; N, 24.72; S, 14.01; Cl, 15.91. UV λ_{max}^{EtOH} mμ (ε): 246.5 (21200), 287.5 (6600).

6-Methylthiazol[2,3-*f*]adenine (IX) Hydrochloride——VIII (1 g) was dissolved in EtOH (20 ml) and NH_3 was saturated in the solution. The mixture was heated at 120—125° in a sealed tube. After EtOH

6) J. Masson and E.R. Holiday, *J. Chem. Soc.*, **1936**, 765.

7) All melting points were uncorrected. NMR spectra were taken with a Varian A-60 Spectrometer using tetramethylsilane (TMS) as internal standard and UV spectra with a Hitachi EPS-2U Spectrometer.

was removed *in vacuo*, the residue was triturated with H_2O and the solid was collected. Recrystallization from 0.2N HCl gave colorless needles (0.4 g), mp>300°. *Anal.* Calcd. for $C_8H_7N_5S$ HCl: C, 39.75; H, 3.33; N, 28.98; S, 13.27; Cl, 14.67. Found: C, 39.54; H, 3.48; N, 28.92; S, 13.09; Cl, 14.44. UV $\lambda_{max}^{0.1N\ HCl}$ mμ (ε): 249 (17200), 281 (11400).

4-Piperidino-6-methylthiazolo[2,3-*f*]purine——VIII (0.5 g), piperidine (2 g) and EtOH (20 ml) were mixed and the mixture was refluxed for 2.5 hr. After EtOH and excess piperidine were removed *in vacuo*, the residue was triturated with H_2O and extracted with $CHCl_3$. The $CHCl_3$-extract were dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene and hexane. Yellow crystals (0.3 g), mp 150—152°, were obtained. *Anal.* Calcd. for $C_{13}H_{15}N_5S$: C, 57.12; H, 5.53; N, 25.62; S, 11.73. Found: C, 56.84; H, 5.39; N, 13.09; S, 11.73. UV λ_{max}^{EtOH} mμ (ε): 225 (15500), 267 (15600), 291 (13900).

4-Morpholino-6-methylthiazolo[2,3-*f*]purine——VIII (1.9 g), morpholine (5 g) and EtOH (60 ml) were reacted as mentioned above. Recrystallization from EtOH gave colorless needles (1.4 g), mp 189—191°. *Anal.* Calcd. for $C_{12}H_{13}ON_5S$: C, 52.34; H, 4.76; N, 25.44; S, 11.65. Found: C, 52.36; H, 4.60; N, 25.56; S, 11.73. UV λ_{max}^{EtOH} mμ (ε): 227 (16300), 263 (15200), 290 (13100).

Desulfurization of I——I (0.5 g) was dissolved in 1% NaOH (40 ml). To this solution was added Raney Ni[3] (prepared from Ni-alloy 5 g) and the mixture was refluxed for 30 min. After Ni was filtered off, the filtrate was acidified with AcOH and crystals separated were collected. The recrystallization from EtOH gave 0.2 g of 7-isopropylxanthine, mp >300°. *Anal.* Calcd. for $C_8H_{11}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.71; H, 5.05; N, 28.70. UV $\lambda_{max}^{0.1N\ NaOH}$ mμ (ε): 290 (8600); $\lambda_{max}^{0.1N\ HCl}$ mμ (ε): 263 (7400). NMR (DMSO-d_6) δ: 1.50 (6H, doublet, J=7 Hz, $(CH_3)_2$), 4.86 (1H, septet, J=7 Hz, -CH(Me)$_2$), 8.10 (1H, s, C_8-H).

Desulfurization of VII——VII (3.5 g) was dissolved in MeOH (300 ml) and to this solution was added Raney Ni[3] (prepared from Ni-alloy 20 g) and the mixture was refluxed for 4 hr. After Ni was removed, the filtrate was evaporated *in vacuo* and the residue was extracted with MeOH. After MeOH was evaporated, the residue was recrystallized from EtOH and 0.2 g of needles, mp 243—246°, were obtained. *Anal.* Calcd. for $C_8H_8ON_4$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.82; H, 4.73; N, 31.73. UV $\lambda_{max}^{0.1N\ NaOH}$ mμ (ε): 263 (8800); $\lambda_{max}^{0.1N\ HCl}$ mμ (ε): 253 (9400). NMR (DMSO-d_6)δ 2.33 (3H, s, CH_3), 5.27 (1H, d, J=1.5 Hz, C=CH), 5.35 (1H, d, J=1.5 Hz, C=CH), 8.1 (1H, s, C_8-H), 8.33 (1H, s, C_2-H).

Acknowledgement The authors are grateful to Prof. M. Ikehara, Department of Pharmacy, Osaka University, for his helpful advices and to Drs. H. Takamatsu, H. Kaneko, S. Minami, and H. Nishimura for their encouragement throughout this work. Thanks are also due to the staffs of analytical section of this laboratories for the spectral measurement and elemental analyses.