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Syntheses of Thiazolo[2,3-*f*]guanine Derivatives

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Thiazolo[2,3-*f*]guanines were synthesized by the cyclization of 8-acylmethylthioguanines. Structure of these compounds were determined by desulfurization with Raney Ni.

In previous papers[2a-c] we have reported that ring closure of 8-(acylmethyl)thioadenines, which have an amino group at 6-position of purine ring, took place to N^9 of purine ring to give thiazolo[3,2-*e*]adenine derivatives, while in cases of 8-(acylmethyl)thiohypoxanthine, 8-(acylmethyl)thioxanthine and 8-(acylmethyl)thiotheophylline, which have an oxo group at 6-position of purine ring instead of an amino group, the ring closure took place to N^7 of purine ring to give thiazolo[2,3-*f*]purine derivatives.

These results seemed to suggest that the substituent at 6-position of purine ring controls the position to which the ring closure occurs. In this paper the ring closure of 8-(acylmethyl)-thioguanines, which have an oxo group at 6-position and an amino group at 2-position of purine ring, was described.

The starting material, 8-thioguanine[3] (I) was prepared by the fusion of 4-hydroxy-2,5,6-triaminopyrimidine[4,5] and thiourea. Addition of chloroacetone or phenacyl bromide in small portions to the alkaline solution of 8-thioguanine (I), gave 8-(acetylmethyl)-(II) and 8-(benzoylmethyl)-thioguanine (III) respectively. II was cyclized by refluxing with hydrogen chloride in anhydrous ethanol to give IV, $C_8H_7ON_5S$. III was not cyclized with the same reaction condition and the cyclization was carried out by heating in polyphosphoric acid to give V, $C_{13}H_9ON_5S$.

To determine the structures of the products thus obtained, IV was treated with Raney Ni in ethanol. The nuclear magnetic resonance (NMR) spectrum of the product VI of desulfurization of IV showed the presence of isopropenyl group; δ: 2.3 (3H, singlet, CH_3–), 5.1 and 5.3 (each 1H, singlet, $C{=}C\langle^{H}_{H}$). And the ultraviolet (UV) absorption spectra of VI was much same as those of 7-methyl-[6] and 7-ethyl-guanine[6] and different from those of 9-methyl-[7] and 9-*n*-propyl-guanine.[7] Since the UV spectra of 7-isopropenylhypoxanthine was similar to those of 7-methylhypoxanthine, as shown in the previous paper,[1c] VI was thought to be 7-isopropenylguanine. Thus it was concluded that 8-(acetylmethyl)thioguanine cyclized to N^7 of purine ring to give thiazolo[2,3-*f*]guanine.

Attempts to reduce the double bond of isopropenyl group of VI by catalytic reduction on platinum oxide or palladium were unsuccessful.

Although the structure of V was thought to be 6-phenylthiazolo[2,3-*f*]guanine by analogy, but the desulfurization of V was unsuccessful, because V was insoluble in organic solvents and water.

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Table I

Compounds	pH of medium	λ_{max} nm (ε)
VI	1	248 (9100), 273 (6500)
	11	284.5
7-Me guanine[6]	1	250 (10600), 270 (6900)
	12	280.5 (7300)
7-Et guanine[6]	1	250 (11100), 274 (7000)
	12	280 (7400)
9-Me guanine[7]	1	252 (12200), 278 (8800)
	11	268 (10900)
9-*n*-Pr guanine[7]	1	253 (15800), 279 (10200)
	11	269 (11100)

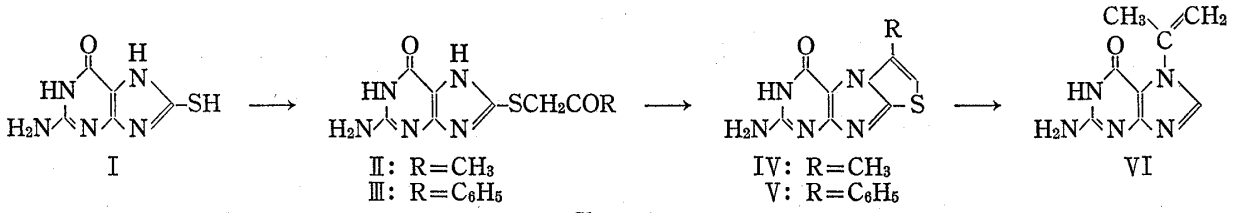

Chart 1

Experimental[8]

8-(Acetylmethyl)thioguanine (II)——8-Thioguanine[3] (I) (0.5 g) was dissolved in 20 ml of 0.4N NaOH. To this solution was added chloroacetone (1 g dissolved in 2 ml of EtOH) and the mixture was stirred at room temperature for 1 hr. Resulting yellow precipitate was collected and recrystallized from H_2O to give 0.1 g of II, mp>250°. *Anal.* Calcd. for $C_8H_9O_2N_5S$: C, 40.16; H, 3.79; N, 29.27; S, 13.40. Found: C, 40.06; H, 4.10; N, 28.98; S, 12.94.

8-(Benzoylmethyl)thioguanine (III)——I (3.66 g) was dissolved in 100 ml of 0.4N NaOH and phenacyl bromide (4 g dissolved in 15 ml of EtOH) was added to the solution. The mixture was stirred at room temperature for 1 hr. Resulting orange precipitate was collected and recrystallized from dimethylformamide (DMF) and H_2O to give 1.5 g of III, mp>250°. *Anal.* Calcd. for $C_{13}H_{11}O_2N_5S \cdot 1/8H_2O$: C, 51.43; H, 3.74; N, 23.07; S, 10.56. Found: C, 51.49; H, 4.23; N, 22.67; S, 10.18.

2-Amino-4-hydroxy-6-methylthiazolo[2,3-*f*]purine (IV)——II (1 g) was suspended in 60 ml of anhydrous EtOH. Dry HCl was passed into the solution for 10 min at room temperature and the solution was refluxed for 1 hr. Crystals separated were collected and recrystallized from DMF to give 0.6 g of IV, mp>250°. *Anal.* Calcd. for $C_8H_7ON_5S$: C, 43.43; H, 3.19; N, 31.66; S, 14.49. Found: C, 43.01; H, 3.61; N, 31.35; S, 14.33. $\lambda_{max}^{0.1N\ HCl}$ nm(ε): 239 (15300), 280 (sh) 288 (10800); $\lambda_{max}^{0.1N\ NaOH}$ nm: 240, 278.

2-Amino-4-hydroxy-6-phenylthiazolo[2,3-*f*]purine (V)——8-(Benzoylmethyl)thioguanine (III) (1.5 g) was mixed with polyphosphoric acid (20 g) and the mixture was heated under stirring at 130—140° for 2 hr. After cooled, cold H_2O was added to the mixture and resulting precipitate was collected. The product was recrystallized from DMF to give 0.5 g of V, mp>250°. *Anal.* Calcd. for $C_{13}H_9ON_5S$: C, 55.11; H, 3.20; N, 24.72; S, 11.32. Found: C, 55.13; H, 2.57; N, 24.40; S, 11.05. $\lambda_{max}^{0.1N\ HCl}$ nm: 244, 291 (sh); $\lambda_{max}^{0.1N\ NaOH}$ nm: 255.

Desulfurization of IV——IV (5 g) was dissolved in the mixture of 20 ml 1N NaOH and 100 ml EtOH. Raney Ni (prepared from 30 g Alloy) was added to the solution and the hot mixture was refluxed for 10 hr. The catalyst was filtered off and the filtrate was acidified with acetic acid and kept in a refrigerator overnight. Resulting precipitate was collected and recrystallized from H_2O to give white crystalline, 0.5 g of VI, mp>250°. *Anal.* Calcd. for $C_6H_9ON_5$: C, 50.25; H, 4.74; N, 36.63. Found: C, 50.42; H, 4.88; N, 37.23. NMR (δ in dimethyl sulfoxide-d_6): 2.3 (3H, singlet, $-CH_3$), 5.1, 5.34 (each 1H, singlet, $C{=}C\langle^{H}_{H}$), 6.38 (2H, broad, NH_2), 8.07 (1H, siglet, 8-H).

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