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Syntheses of Thiazolo[3,2-*e*]purines

Hitoshi Uno, Akira Irie and Katsuhiko Hino

Research Laboratories, Dainippon Pharmaceutical Co., Ltd.[1]

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8-(Acetylmethyl)thioadenines, which have an amino group on 6-position of purine ring, were cyclized with condensing agents and thiazol[3,2-*e*]adenines, in which cyclization took place to 7-nitrogen of purine ring, were obtained. Structures of these thiazoladenines were determined by desulfurization with Raney Ni.

For a period, thiazolo[2,3-*f*]purine ring system was erroneously considered to be contained in thiochrome, an alkaline oxidation product of Vitamin B_1. Therefore the first thiazolopurine was synthesized in the effect to confirm the structure of thiochrome.[2] And afterwards some compounds were synthesized as purine-antagonists in the search for anticancer drugs.[3]

Most of these thiazolopurines were prepared by reactions of 8-mercaptopurines with α-halocarbonyl compounds and subsequent cyclizations of resulting intermediates with condensing agents such as phosphorous oxychloride or ethanolic hydrogen chloride. It is apparent that in the cyclization, the ring closure take place to either 7- and 9-position of purine ring. Most of these thiazolopurines, however, were described to be thiazolo[2,3-*f*]-purine without any definite evidences for excluding thiazolo[3,2-*e*]purine structure.

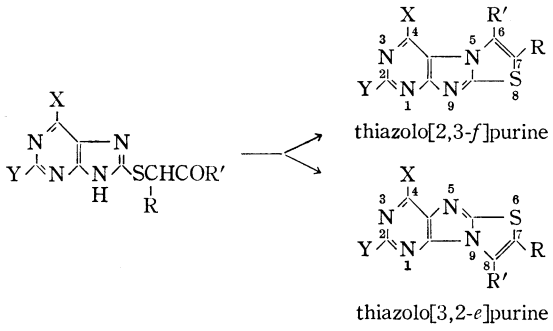


Chart 1

Since adenine is known to give 3- and 9-substituted derivatives by the alkylation and glycosilation, it was expected that 8-thioadenine derivatives might give thiazol[3,2-*e*]adenines when treated with α-halocarbonyl compounds. So, it was thought to be of interest to prepare a series of thiazoladenines starting from 8-thioadenines and to examine their structures.

In this paper, the synthesis of thiazol[3,2-*e*]adenine derivatives and the elucidation of their structures were described. As far as we are aware, no thiazolo[3,2-*e*]purine, except a 7,8-dihydrothiazolo-[3,2-*e*]purine[3c] and some 2',8-cyclonucleosides,[4] has been reported.

Syntheses of thiazolopurines were carried out as follows. Fusion of 4,5,6-triaminopyrimidines (I) with thiourea or carbon disulfide in pyridine afforded the starting materials, 8-thioadenine derivatives (II-a,[5] b,[6] c). 8-Thioadenine (II-a) was also prepared by direct

1) Location: *33-94, Enokicho, Suita City, Osaka.*
2) E. Ochiai, *Chem. Ber.*, **69**, 1650 (1936); A.R. Todd and F. Bergel, *J. Chem. Soc.*, **1936**, 1599.
3) *a*) M. Gordon, *J. Am. Chem. Soc.*, **73**, 984 (1951); *b*) R.C. Elderfield and R.N. Prasad, *J. Org. Chem.*, **24**, 1410 (1959); *c*) R.W. Balsinger, A.L. Fikes, T.P. Johnston and J.A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).
4) M. Ikehara, *Accounts of Chemical Research*, **2**, 47 (1969).
5) R.K. Robins, *J. Am. Chem. Soc.*, **80**, 6671 (1958).
6) J. Baddiley and B. Lythgoe, *J. Chem. Soc.*, **1943**, 383; G.M. Blackburn and A.W. Johnson, *J. Chem. Soc.*, **1960**, 4347.

thiation of adenine with sulfur in dimethylacetamide.[7] By adding α-halocarbonyl compounds in small portions to alkaline solutions of II, 8-(acylmethyl)thioadenine derivatives (III) were separated from reaction mixtures. Melting points and analytical data of III thus obtained, were summarized in Table I. Cyclizations were carried out at 140—150° in polyphosphoric acid or refluxing in ethanol with hydrogen chloride to give thiazoladenine derivatives (IV). Properties of IV were shown in Table II.

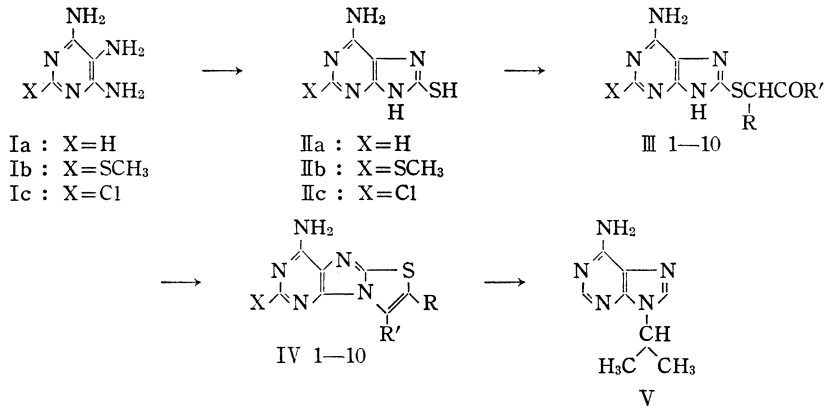
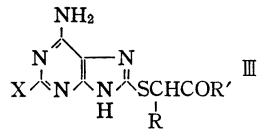


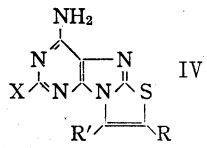
Chart 2

TABLE I.  III

No.	X	R	R′	mp °C (Solvent)	Yield	Formula	Analysis (%) Calcd. C	H	N	S	Cl	Found C	H	N	S	Cl
1	H	H	CH_3	224—226 (EtOH)	49	$C_8H_9ON_5S$	43.04	4.06	31.37	14.36		42.74	4.25	31.07	14.07	
2	H	H	C_2H_5	175—180 (EtOH)	51	$C_9H_{11}ON_5S$										
3	H	CH_3	CH_3	— (EtOH)	29	$C_9H_{11}ON_5S$										
4	H	H	$C(CH_3)_3$	250 (decomp) (EtOH)	59	$C_{11}H_{15}ON_5S$	48.15	5.88	25.53	11.69		48.28	5.74	25.52	12.22	
5	H	H	C_6H_5	220—225 (EtOH)	76.5	$C_{12}H_{13}ON_5S$										
6	H	$-(CH_2)_4-$		196—198 (EtOH)	42.8	$C_{11}H_{13}ON_5S$	50.17	4.97	26.60	12.18		50.16	4.97	26.32	11.99	
7	SCH_3	H	CH_3	201—202 (EtOH)	68.2	$C_9H_{11}ON_5S_2$	40.13	4.12	26.00	23.81		40.26	4.13	25.84	23.71	
8	SCH_3	H	C_2H_5	190—193 (EtOH)	52.8	$C_{10}H_{13}ON_5S_2$	42.40	4.63	24.73	22.60		42.30	4.56	24.42	22.82	
9	SCH_3	H	C_6H_5	225—227 (DMF+EtOH)	45.2	$C_{13}H_{15}ON_5S_2$										
10	Cl	H	CH_3	230—231 ($EtOH-H_2O$)	37	$C_8H_8ON_5SCl$	37.28	3.13	27.18	12.44	13.76	37.02	3.14	27.17	12.85	13.14

7) Ajinomoto, Japan Patent, 21515 (1970).

TABLE II



IV

No.	X	R	R′	mp °C (Solvent)	Method	Yield %
1[a]	H	H	CH_3	>300 (H_2O)	A	41.6
					B	65
2[a]	H	H	C_2H_5	290—300 (H_2O)	B	50.5
3[a]	H	CH_3	CH_3	>300 (EtOH+H_2O)	A	20.4
4[a]	H	H	$C(CH_3)_3$	250—275 (EtOH)	B	22
5[a]	H	H	C_6H_5	267—270 (EtOH+H_2O)	B	16.5
6[a]	H	$-(CH_2)_4-$		>300 (EtOH+H_2O)	B	35.4
7	SCH_3	H	CH_3	281—284 (DMF+EtOH)	B	53
8	SCH_3	H	C_2H_5	250—300 (DMF)	B	11.8
9	SCH_3	H	C_6H_5	264—267 (DMF)	B	44.6
10	Cl	H	CH_3	>300 (MeOH)	B	35.4

No.	Formula	Analysis (%) Calcd. C	H	N	S	Cl	Found C	H	N	S	Cl
1[a]	$C_8H_8N_5SCl$	39.75	3.33	28.98	13.27	14.67	40.08	3.07	28.74	13.09	14.58
2[a]	$C_9H_{10}N_5SCl$	42.27	3.94	27.39	12.54	13.87	41.97	3.97	27.43	12.52	13.81
3[a]	$C_9H_{10}N_5SCl$	42.27	3.94	27.39	12.54	13.87	42.51	3.66	27.32	12.27	13.87
4[a]	$C_{11}H_{14}N_5SCl$ $1/2H_2O$	45.12	5.16	23.92	10.95	12.11	44.89	4.93	23.88	10.53	11.97
5[a]	$C_{13}H_{10}N_5SCl$	51.40	3.32	23.06	10.56	11.67	51.27	3.02	22.07	10.37	11.43
6[a]	$C_{11}H_{12}N_5SCl$	46.88	4.29	24.86	11.38	12.58	47.05	4.25	24.90	11.35	12.47
7	$C_9H_9N_5S_2$	43.01	3.61	27.87	25.52		43.04	3.37	28.15	25.63	
8	$C_{10}H_{11}N_5S_2$	45.26	4.18	26.39	24.17		45.26	3.89	26.56	24.37	
9	$C_{14}H_{11}N_5S_2$	53.65	3.54	22.35	20.46		53.46	3.30	22.52	20.17	
10	$C_8H_6N_5SCl$	40.08	2.52	29.22	13.38	14.79	40.20	2.18	29.00	13.55	15.13

a) hydrochloride

Thiazoladenines (IV-1—10) gave single spot on thin-layer chromatography (TLC) and were not considered to be a mixture of two products from their physical data. When the cyclization was carried out in ethanolic hydrogen chloride, the reaction mixture was evaporated to dryness and the residue was examined on TLC, and only a single product was detected.

Heated in acetic anhydride, IV-1 gave diacetate and this diacetate was easily converted to monoacetate in 1N NaOH solution at room temperature. When IV-7 was heated in acetic anhydride, only monoacetate was obtained. IV-1 gave 6-hydroxy analogue, thiazolo[3,2-*e*]-hypoxanthine, after treating with barium nitrite in acetic acid. Although an atempt to displace 2-methylthio group of IV-7 by nucleophiles did not succeed, 2-chlorine atom of IV-10 could be displaced with piperidino group by heating in piperidine.

To determine the structure of thiazoladenines, IV-1, 7 and 10 were treated with Raney Ni in ethanol. Thiazolo[2,3-*f*]purine must give 7-substituted purine, and thiazolo[3,2-*e*]purine must give 9-isomer after desulfurization. Refluxing with Raney Ni in ethanol IV-1 gave a compound which was analyzed to give the empirical formula $C_8H_{11}N_5$ and had mp 127—130°.

Nuclear magnetic resonance (NMR) spectrum and infrared (IR) spectrum showed that this was an isopropyl adenine. Ultraviolet (UV) spectrum of this compound was very similar to that of 9-methyladenine[8] and different from that of 7-methyladenine.[9] Therefore this isopropyladenine must be 9-isopropyladenine derived from 8-methylthiazol[3,2-*e*]adenine. When IV-7 was treated with Raney Ni, the same compound, 9-isopropyladenine was obtained. After desulfurization, IV-10 gave 2-chlor-9-isopropyladenine which gave also 9-isopropyladenine by the reduction on palladium. These facts showed that all compounds, IV-1—10 contained the same ring system, thiazolo[3,2-*e*]purine.

TABLE III. UV Absorption Properties of Thiazolo[3,2-*e*]purines

No.	$\lambda_{max}^{0.1N\ HCl}$ mμ (ε)	$\lambda_{max}^{0.1N\ NaOH}$ mμ	λ_{max}^{EtOH}
IV-1	249 (24000)	241.5 (sh)	234
	292.5 (13700)	286	279 (sh)
		297.5	287
			298 (sh)
IV-2	249 (24300)	239	240
	292.5 (14100)	287	253
		297 (sh)	288
			298 (sh)
IV-3	252.5 (24300)	241	
	293 (12500)	288.5	
		300 (sh)	
IV-4	249.5 (22800)	238	
	293 (13800)	286.5	
		296 (sh)	
IV-5	252.5 (22000)	243.5	
	297 (14800)	290	
		300 (sh)	
IV-6	254 (17400)	244.5 (sh)	
	293.5 (7300)	285	
IV-7	257 (16600)	248 (sh)	
	298 (15400)	294	
		305 (sh)	
IV-8	260	247 (sh)	
	300	295	
IV-9	257	241.5	
	302		
IV-10	239.5 (11100)	242.5	
	246 (sh)	289	
	279 (sh)	300	
	290 (14900)		
	300 (sh)		

TABLE IV. Comparison of UV Absorption Properties of Isopropyladenine (V), 7-Methyladenine and 9-Methyladenine

Compound	$\lambda_{max}^{0.05N\ HCl}(\varepsilon \times 10^{-3})$	$\lambda_{max}^{0.05N\ NaOH}(\varepsilon \times 10^{-3})$
7-Methyladenine[9]	269 (14.6)	269 (14.4)
9-Methyladenine[9]	260 (14.2)	260 (14.7)
(V)	260.5 (14.0)	263

8) C. Temple and J.A. Montgomery, *J. Med. Pharm. Chem.*, **5**, 886 (1962).
9) J.M. Gulland and E.R. Holiday, *J. Chem. Soc.*, **1936**, 765.

The thiazolo derivatives of theophylline, guanine, hypoxanthine and xanthine are being synthesized in this laboratory and their structures are being elucidated. Some of the results have been reported in the previous paper[10a] and the rest will be reported in later communications.[10b]

Experimental[11]

General Procedure for the Synthesis of 8-(Acylmethyl)thioadenine Derivatives——8-Thioadenine derivatives (IIa, and IIb) (0.02 mole) was dissolved in 50 ml of 0.4N NaOH. To this solution was added dropwise α-halocarbonyl compound (0.02 mole) in 2 ml of EtOH under stirring at 5—10°. The reaction mixture was stirred for 3 hr at room temperature. Separated precipitates were collected, washed with H_2O, and recrystallized from suitable solvent (Table I, III-1—9).

2-Chloro-6-amino-8-(acetonylthio)purine (III-10)——2-Chloro-4,5,6-triaminopyrimidine (Ic) (4 g), pyridine (35 ml) and CS_2 (4.7 ml) were mixed and heated at 60—70° for 30 min under stirring. After excess CS_2 was evaporated *in vacuo*, the mixture was refluxed for 10 min and then evaporated *in vacuo*. The residue was dissolved in dil. NaOH and reprecipitated with AcOH. Yield of IIc (mp >300°) was 2.4 g.

IIc (1.7 g) was dissolved in NaOH (0.34 g) and H_2O (50 ml). Chloracetone (0.94 g) dissolved in EtOH (2 ml) was added to the solution under stirring. Precipitates separated were collected and recrystallized from dil. EtOH. Yield of III-10 (mp 230—231°) was 0.8 g. *Anal.* Calcd. for $C_8H_8N_5SCl$: C, 37.28; H, 3.13; N, 27.18; S, 12.44; Cl, 13.76. Found: C, 37.02; H, 3.14; N, 27.17; S, 12.85; Cl, 13.14.

General Procedure for the Synthesis of Thiazol[3,2-*e*]adenine Derivatives——Method A: III (0.025 mole) was suspended in EtOH (300 ml). Under cooling dry HCl was bubbled through the suspension for 1 hr. The reaction mixture was refluxed for 2 hr. After cooling precipitates were collected and recrystallized from suitable solvent (Table II). Method B: III (0.015 mole) was added to polyphosphoric acid (105%, 20 g). The reaction mixture was heated at 140—150° for 3 hr under stirring. After cooling, H_2O (100 ml) was added, Precipitates which separated were collected, and washed with dil. NaOH and H_2O. Dried product were converted into its hydrochloride in EtOH with dry HCl and recrystallized from suitable solvent (Table II).

2-Piperidino-6-amino-8-methylthiazolo[3,2-*e*]purine——IV-10 (0.4 g) was dissolved in piperidine (4 ml) and refluxed for 4 hr. After evaporation of the solvent *in vacuo*, the residue was added to cold H_2O. The precipitates were collected and recrystallized from dil. EtOH. White needles (0.25 g), mp 203—204°, were obtained. *Anal.* Calcd. for $C_{13}H_{16}N_6S$: C, 54.14; H, 5.59; N, 29.15; S, 11.12. Found: C, 54.08; H, 5.54; N, 29.16; S, 10.98.

N^6,N^6-Diacetyl-8-methylthiazol[3,2-*e*]adenine——IV-1 (2 g) was dissolved in Ac_2O (50 ml) and refluxed for 3 hr. After cooling, crystals separated were collected and recrystallized from EtOH. Yield of the diacetate (mp 192—197°) was 1.5 g. *Anal.* Calcd. for $C_{12}H_{11}O_2N_5S$: C, 49.82; H, 3.83; N, 24.21; S, 11.08. Found: C, 49.83; H, 3.91; N, 24.32; S, 11.33.

N^6-Acetyl-8-methylthiazol[3,2-*e*]adenine——The diacetate, obtained above, was dissolved in 1N NaOH and stirred for 1 hr at room temperature. The reaction mixture was neutralized with AcOH. Crystals separated were collected and recrystallized from EtOH, yielding 0.3 g of monoacetate, mp 202—204°. *Anal.* Calcd. for $C_{10}H_9ON_5S$: C, 48.57; H, 3.67; N, 28.32; S, 12.97. Found: C, 48.60; H, 3.64; N, 28.58; S, 13.19.

N^6-Acetyl-2-methylthio-6-amino-8-methylthiazolo[3,2-*e*]purine——III-7 (1 g) was dissolved in Ac_2O (10 ml) and refluxed for 4 hr. After cooling deposited crystals were collected, recrystallized from EtOH Yield of monoacetate (mp 183—185°) was 0.6 g. *Anal.* Calcd. for $C_{11}H_{11}ON_5S_2$: C, 45.04; H, 3.78; N, 23.87; S, 21.86. Found: C, 44.84; H, 3.75; N, 23.82; S, 21.77.

8-Methylthiazolo[3,2-*e*]hypoxanthine——IV-1 HCl (10 g) was dissolved in H_2O (300 ml) and to this solution was added barium nitrite (24 g) at 60—70°. After cooling, AcOH (20 ml) was added to the reaction mixture and stirred for 30 min. Precipitates were collected and extracted with hot dil. HCl. White precipitates separated from extracts were collected. This precipitate was identified with IV-1 HCl. The unextracted solid with hot dil. HCl of the precipitates was submitted to column chromatography on silica gel. Elution with $CHCl_3$–MeOH (90:6) gave starting material (0.6 g) and elution with $CHCl_3$–MeOH (90:10) gave 0.1 g of yellowish powder. Recrystallization from DMF gave 0.1 g of the product, mp >300°. *Anal.* Calcd. for $C_8H_6ON_4S$: C, 46.59; H, 2.93; N, 27.17; S, 15.55. Found: C, 46.36; H, 2.95; N, 26.90; S, 15.36. UV $\lambda_{max}^{0.1N\ NaOH}$ mμ (ε) 226.5 (17100), 282.5 (14800).

Desulfurization of IV-1——IV-1 (2 g), EtOH (300 ml), H_2O (50 ml) and Raney Ni (prepared from 20 g of Ni-alloy) were mixed and refluxed for 3 hr. After Ni was filtered off, the mixture was evaporated *in*

10) *a*) H. Uno, A. Irie and K. Hino, *Chem. Pharm. Bull.* (Tokyo), **20**, 2603 (1972); *b*) *Idem*, *ibid.*, **21**, in press.

11) All melting points were uncorrected. NMR spectra were taken with a Varian A-60 spectrometer using TMS as an internal standard, and UV spectra with a Hitachi EPS-2U spectrophotometer.

vacuo. The residue was recrystallized from ether–petroleum ether, and yield of V, mp 127—130°, was 350 mg. *Anal.* Calcd. for $C_8H_{11}N_5$: C, 54.22; H, 6.62; N, 39.52. Found: C, 54.11; H, 6.00; N, 39.51. UV $\lambda_{max}^{0.1N\ HCl}$ mμ (ε) 260.5 (13200), $\lambda_{max}^{0.1N\ NaOH}$ mμ 236. NMR ($CDCl_3$): 7.91 (1H, s), 6.64 (2H, broad), 4.88 (1H, double, q, $J=7$ Hz), 1.62 (6H, d, $J=7$ Hz).

V was converted into its hydrochloride in EtOH with dry HCl. Recrystallization from EtOH gave white crystals, mp 229—231°. *Anal.* Calcd. for $C_8H_{12}N_5Cl$: C, 44.96; H, 5.66; N, 32.78; Cl, 16.59. Found: C, 44.71; H, 5.61; N, 32.62; Cl, 16.86.

Desulfurization of IV-7——IV-7 (2 g), 80% EtOH (50 ml), and Raney Ni (prepared from Ni-alloy 20 g) were mixed and refluxed for 6 hr. After Ni was filtered off, the mixture was evaporated *in vacuo*, and the residue was recrystallized from EtOH–ether. 0.5 g of white powder was obtained. This product was converted into its hydrochloride, mp 227—229°. UV $\lambda_{max}^{1.0N\ HCl}$ 261 mμ. This hydrochloride was identical with V HCl obtained from IV-1, by mixed melting point and comparison of IR spectra.

Desulfurization of IV-10——IV-10 (1 g), EtOH (180 ml), H_2O (10 ml) and Raney Ni (prepared from Ni-alloy 10 g) were mixed and refluxed for 2 hr. After Ni was filtered off, the mixture was evaporated and the residue was recrystallized from EtOH. Yield of crystals, mp 250—252°, was 0.3 g. The crystals were dissolved in 90% EtOH (65 ml) and 5% Pd-C was added. The mixture was shaken in H_2 stream. After the catalyst was filtered off, the mixture was evaporated and the residue was dissolved in $CHCl_3$. The solution was chromatographed on silica gel column (3×10 cm). Elution with $CHCl_3$ gave 2-chloro-9-isopropyladenine (0.11 g, mp 255—258°). NMR (DMSO-d_6) δ: 8.36 (1H, s), 7.73 (2H, broad), 4.70 (1H, double q, $J=7$ Hz), 1.53 (6H, doublet, $J=7$ Hz). *Anal.* Calcd. for $C_8H_{10}N_5Cl$: C, 45.39; H, 4.76; N, 33.09; Cl, 16.75. Found: C, 45.70; H, 4.50; N, 33.02; Cl, 16.88.

Elution with $CHCl_3$–MeOH (90:1) gave 9-isopropyladenine (V), which was converted into its hydrochloride (30 mg, mp 229—231°). UV $\lambda_{max}^{0.1N\ HCl}$ 261 mμ. This hydrochloride was identical with V HCl obtained from IV-1 by mixed melting point and comparison of IR spectra.

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