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65. Matao Kanaoka : Synthesis of Related Compounds of Thiosemicarbazide. III[1] *s*-Triazolo[3,4-*b*]-1,3,4-thiadiazole Derivatives. (2).

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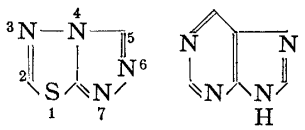
In the recent years, various structural change of the naturally-occuring purines have resulted in several potent antagonist in biological systems. Of special interest are the antitumor agents, 8-azaguanine[2] and 6-mercaptopurine.[3]

The synthesis of the *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole ring system (A) was undertaken to provide new compounds analogous to various biologically active purine —— the thiadiazole ring taking place of the pyrimidine ring in the purine system —— in the hope that a new antitumor agent might be discovered.



(A) Purine

In the preceding paper of this series,[1] it had been reported that 2-substituted 5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (V : R=phenyl) was synthesized from 3-phenyl-4-amino-5-mercapto-1,2,4-triazole, reacting it with fatty and aromatic acid chlorides to form 3-phenyl-4-acylamido-5-mercapto-1,2,4-triazole, and dehydrative cyclization with phosphoryl chloride.

The author had reported that 2-amino-1,3,4-thiadiazole was synthesized by a new method[4] of reacting ethyl orthoformate with thiosemicarbazide to form ethyl thiosemicarbazonoformate and its cyclization with acetic acid.

Using this method of cyclization, ethyl N'-(5-substituted-1,3,4-thiadiazol-2-yl)hydrazonoacylates (IV) were isolated as intermediate product of reaction between 5-substituted 2-hydrazino-1,3,4-thiadiazoles (III) and ethyl orthoacylate or ethyl acylimidate hydrochloride, and these intermediates were cyclized to yield 2,5-disubstituted *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles.

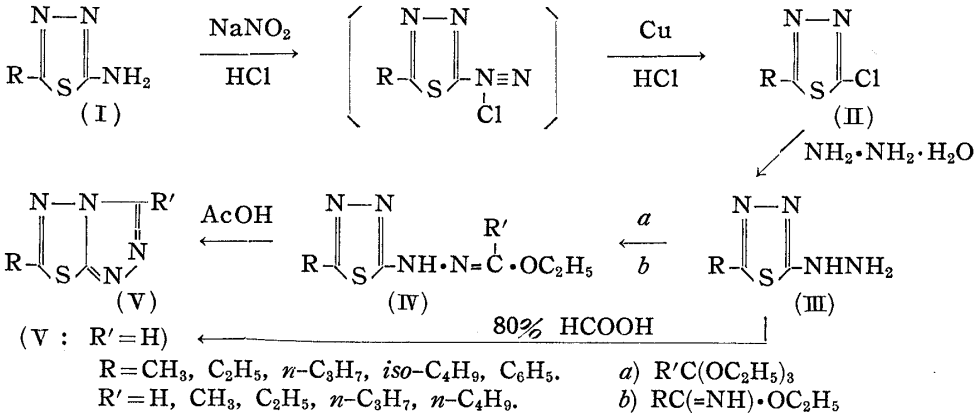
The key intermediate in the present work was (III), which was prepared by reaction of hydrazine hydrate, in methanol solution, with 2-chloro-5-alkyl-1,3,4-thiadiazoles (II), obtained by the diazotization of 2-amino-5-alkyl-1,3,4-thiadiazoles with sodium nitrite and followed by decompostion with copper powder in 25% hydrochloric acid. 2-Hydrazino-5-phenyl-1,3,4-thiadiazole (III : R=phenyl) was obtained by the reaction of 2-methylsulfonyl-5-phenyl-1,3,4-thiadiazole[5] with hydrazine hydrate in methanol. (III) was reacted with *p*-nitrobenzaldehyde to form 2-*p*-nitrobenzylidenehydrazino-1,3,4-thiadiazole (Table IV).

In the reaction of (III) with ethyl orthoacylates, when R was phenyl, the reaction proceeded at 120~130°, while the reaction proceeded only by warming at 60~70° when

* Okuda, Toyama (金岡又雄).

1) Part II : J. Pharm. Soc. Japan, **76**, 1133(1956).
2) C.W. Kidder, *et al.* : Science, **109**, 511(1949) (C.A., **43**, 9251(1949)).
3) H.E. Skipper, *et al.* : Cancer Research, **14**, 294(1954) (C.A., **48**, 12316(1954)).
4) M. Kanaoka : J. Pharm. Soc. Japan, **75**, 1149(1955).
5) K. Fujii, *et al.* : *Ibid.*, **74**, 1056(1954).

R was alkyl. In the reaction with ethyl acylimidate hydrochlorides, however, corresponding (IV) were not obtained when R was phenyl, but were obtained when R was alkyl.



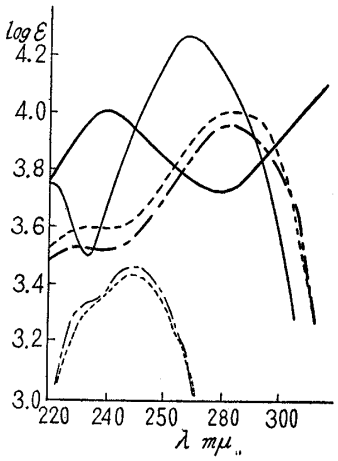
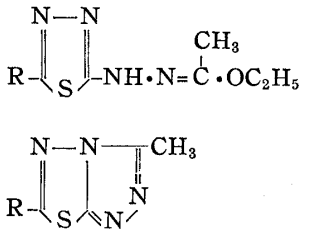
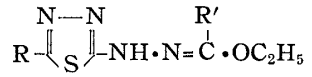


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)



R	λ_{max}^{EtOH} mμ	log ε
CH_3	281	4.02
C_2H_5	281	3.96
C_6H_5	240	4.01
CH_3	251	3.45
C_2H_5	251	3.47
C_6H_5	269	4.26

TABLE I. 

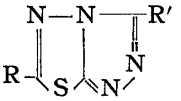
R	R′	m.p. or b.p. (C°)	Appearance	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H	Recrystn. solvent
CH_3	CH_3	159.5	Coloress needles	$C_7H_{12}N_4SO$	41.98	6.04	41.86	6.25	Hydr. EtOH Ligroine
C_2H_5	〃	97	〃	prisms	$C_8H_{14}N_4SO$	44.84	6.59	44.67	6.61	Hydr. EtOH
n-C_3H_7	〃	109	〃	〃	$C_9H_{16}N_4SO$	47.34	7.06	47.30	7.15	〃
iso-C_4H_9	〃	95	〃	〃	$C_{10}H_{18}N_4SO$	49.56	7.49	49.47	7.52	〃
C_6H_5	〃	173	〃	needles	$C_{12}H_{14}N_4SO$	54.94	5.38	54.92	5.43	Benzene
CH_3	C_2H_5	113	〃	leaflets	$C_8H_{14}N_4SO$	44.84	6.59	44.79	6.68	Hydr. EtOH
C_2H_5	〃	102	〃	〃	$C_9H_{16}N_4SO$	47.34	7.06	47.26	7.12	〃
n-C_3H_7	〃	90~92	〃	〃	$C_{10}H_{18}N_4SO$	49.56	7.49	49.37	7.56	〃
iso-C_4H_9	〃	60~61	〃	〃	$C_{11}H_{20}N_4SO$	51.53	7.86	51.48	7.91	〃
C_6H_5	〃	153	〃	needles	$C_{13}H_{16}N_4SO$	56.50	5.84	56.33	5.98	EtOH
CH_3	n-C_3H_7	147	〃	〃	$C_9H_{16}N_4SO$	47.34	7.06	47.12	7.16	Ligroine
C_2H_5	〃	141	〃	〃	$C_{10}H_{18}N_4SO$	49.56	7.48	49.50	7.52	〃
n-C_3H_7	〃	107	〃	〃	$C_{11}H_{20}N_4SO$	51.53	7.86	51.26	7.96	〃
iso-C_4H_9	〃	100	〃	〃	$C_{12}H_{22}N_4SO$	53.30	8.20	53.17	8.32	〃
CH_3	n-C_4H_9	102	〃	〃	$C_{10}H_{18}N_4SO$	49.56	7.49	49.29	7.63	Hydr. EtOH
C_2H_5	〃	50	〃	〃	$C_{11}H_{20}N_4SO$	51.53	7.86	51.39	7.92	〃
n-C_3H_7	〃	41	〃	〃	$C_{12}H_{22}N_4SO$	53.30	8.20	53.28	8.21	〃
iso-C_4H_9	〃	67	〃	leaflets	$C_{13}H_{24}N_4SO$	54.89	8.50	54.68	8.63	〃
C_6H_5	〃	133	〃	〃	$C_{15}H_{20}N_4SO$	59.18	6.62	59.10	6.65	〃
iso-C_4H_9	C_6H_5	161	〃	needles	$C_{15}H_{20}N_4SO$	59.18	6.62	58.93	6.71	EtOH

(III) was reacted with ethyl orthoformate to give a mixture of (V : R′=H) and red viscous oily product and this mixture was treated with glacial acetic acid to form (V: R′=H), which was also obtained by the reaction of (III) with 80% formic acid.

Moreover, 2-isobutyl-5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole reported in the preceding paper[1] was identified with the product obtained by the reaction of (III : R=*iso*-C_4H_9) with ethyl benzimidate hydrochloride (R′=phenyl).

Ultraviolet absorption spectra of some of the compounds prepared are shown in Fig. 1.

TABLE II.



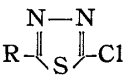
R	R′	m.p. or b.p. (°C)	Appearance	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H	Recrystn. solvent
CH_3	H	144	Colorless needles	$C_4H_4N_4S$	34.27	2.88	34.19	2.98	Ligroine
C_2H_5	〃	62	〃 〃	$C_5H_6N_4S$	38.94	3.92	38.66	4.01	Benzene
n-C_3H_7	〃	b.p_2 143～144		$C_6H_8N_4S$	42.84	4.79	42.68	4.88	
	Picrate	135～136	Yellow leaflets	$C_{12}H_{11}N_7SO_7$	48.47	3.73	48.36	3.82	EtOH
iso-C_4H_9	〃	b.p_2 146		$C_7H_{10}N_4S$	46.13	5.53	46.05	5.60	
	〃	132.5	Yellow needles	$C_{13}H_{13}N_7SO_7$	50.15	4.21	50.12	4.43	EtOH
C_6H_5	H	191.5	Colorless 〃	$C_9H_6N_4S$	53.40	2.99	53.17	3.07	Hot water
CH_3	CH_3	102	〃 〃	$C_5H_6N_4S$	38.94	3.92	38.83	3.99	Ligroine
C_2H_5	〃	104	〃 〃	$C_6H_8N_4S$	42.84	4.79	42.80	4.83	〃
n-C_3H_7	〃	67	〃 〃	$C_7H_{10}N_4S$	46.13	5.53	46.02	5.62	〃
iso-C_4H_9	〃	77～78	〃 〃	$C_8H_{12}N_4S$	48.95	6.16	48.77	6.25	〃
C_6H_5	〃	176～177	〃 〃	$C_{10}H_8N_4S$	55.53	3.73	55.23	3.92	〃
CH_3	C_2H_5	79	〃 pillars	$C_6H_8N_4S$	42.84	4.79	42.58	4.86	〃
C_2H_5	〃	81	〃 〃	$C_7H_{10}N_4S$	46.13	5.53	46.09	5.56	〃
n-C_3H_7	〃	28	〃 〃	$C_8H_{12}N_4S$	48.95	6.16	48.68	6.28	〃
iso-C_4H_9	〃	b.p_2 166～169		$C_9H_{14}N_4S$	51.40	6.71	51.23	6.94	
	Picrate	116～117	Yellow needles	$C_{15}H_{17}N_7SO_7$	53.08	5.05	52.79	5.21	EtOH
C_6H_5	C_2H_5	121～122	Colorless 〃	$C_{11}H_{10}N_4S$	57.37	4.38	57.16	4.50	Hydr. EtOH hot water
CH_3	*n*-C_3H_7	b.p_1 142～144		$C_7H_{10}N_4S$	46.13	5.53	45.89	5.65	
	Picrate	157～159	Yellow needles	$C_{13}H_{13}N_7SO_7$	50.15	4.21	49.96	4.33	EtOH
C_2H_5	*n*-C_3H_7	b.p_1 150～152		$C_8H_{12}N_4S$	48.95	6.16	48.62	6.32	
	Picrate	140～141	Yellow neeldes	$C_{14}H_{15}N_7SO_7$	51.67	4.65	51.48	4.68	EtOH
n-C_3H_7	*n*-C_3H_7	b.p_1 145		$C_9H_{14}N_4S$	51.40	6.71	51.28	6.84	
	Picrate	97～98	Yellow needles	$C_{15}H_{17}N_7SO_7$	53.08	5.05	52.94	5.18	EtOH
iso-C_4H_9	*n*-C_3H_7	b.p_2 156～157		$C_{10}H_{16}N_4S$	53.54	7.19	53.39	7.23	
	Picrate	109～107	Yellow needles	$C_{16}H_{19}N_7SO_7$	54.37	5.42	54.12	5.56	EtOH
CH_3	*n*-C_4H_9	57	Colorless 〃	$C_8H_{12}N_4S$	48.95	6.16	48.78	6.24	Ligroine
C_2H_5	〃	b.p_2 156～158		$C_9H_{14}N_4S$	51.40	6.71	51.36	6.80	
	Picrate	122～123	Yellow leaflets	$C_{15}H_{17}N_7SO_7$	53.08	5.05	52.91	5.23	EtOH
n-C_3H_7	*n*-C_4H_9	b.p_2 172		$C_{10}H_{16}N_4S$	53.54	7.19	53.21	7.33	
	Picrate	89～90	Yellow needles	$C_{16}H_{19}N_7SO_7$	54.37	5.42	54.23	5.66	EtOH
iso-C_4H_9	*n*-C_4H_9	b.p_3 169		$C_{11}H_{18}N_4S$	55.43	7.61	55.37	7.68	
	Picrate	120～121	Yellow needles	$C_{17}H_{21}N_7SO_7$	55.56	5.76	55.48	5.95	EtOH
C_6H_5	*n*-C_4H_9	118.5	Colorless 〃	$C_{13}H_{14}N_4S$	60.44	5.46	60.25	5.51	Hydr. EtOH
iso-C_4H_9	C_6H_5	104	〃 pillars	$C_{13}H_{14}N_4S$	60.44	5.46	60.38	5.60	〃 [4]

The author wishes to thank Prof. H. Saikachi, University of Kyushu, and Dr. D. Shiho, Professor of this Faculty, for their kind advices and continued encouragements. The microanalyses were carried out by Miss T. Ishiguro of this Faculty, to whom the author is indebted.

Experimental

5-Substituted 2-Chloro-1,3,4-thiadiazole (II)—Prepared according to the method described in the previous paper[4] and following compounds were synthesized in the present work.

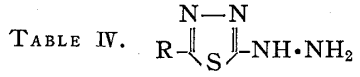
TABLE III.



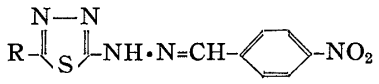
R	b.p. (°C/mm. Hg)	Yield (%)	Appearance	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H
C_2H_5	98~99/15	50~60	Colorless oil	$C_4H_5N_2SCl$	32.32	3.39	32.05	3.42
n-C_3H_7	121~122/20	75~80	〃	$C_5H_7N_2SCl$	36.92	4.34	36.84	4.48
iso-C_4H_9	120~121/15	〃	〃	$C_6H_9N_2SCl$	40.79	5.14	40.66	5.31

5-Substituted 2-Hydrazino-1,3,4-thiadiazole (III)—To a solution of 0.1 mole of (II) in 25 cc. of MeOH 0.5 mole of hydrazine hydrate (80%) was added dropwise and the mixture was warmed on a water bath for 2.5 hrs. After removal of MeOH under reduced pressure, residual crystalline mass was recrystallized from benzene or hot water (Table IV).

TABLE IV.



R	m.p.(°C)	Yield	Appearance	Formula	Recrystn. solvent
C_2H_5	113~114	70~80	Colorless needles	$C_4H_8N_4S$	Benzene
n-C_3H_7	72	80~90	〃	$C_5H_{10}N_4S$	Hot water
iso-C_4H_9	60	80~85	〃	$C_6H_{12}N_4S$	



R	m.p. (°C)	Appearence		Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H	Recrystn. solvent
C_2H_5	237.5	Yellow	leaflets	$C_{11}H_{11}O_2N_5S$	47.64	4.00	47.52	4.13	MeOH
n-C_3H_7	232	〃	〃	$C_{12}H_{13}O_2N_5S$	49.47	4.50	49.41	4.60	〃
iso-C_4H_9	215	〃	〃	$C_{13}H_{15}O_2N_5S$	51.13	4.95	51.08	5.23	〃
C_6H_5	277	〃	prisms	$C_{15}H_{11}O_2N_5S$	55.39	3.41	55.21	3.67	Dioxane

2-Hydrazino-5-phenyl-1,3,4-thiadiazole (III : R=phenyl)—Obtained by the method of Fujii, *et al.*[5]

5-Substituted 2-*p*-Nitrobenzylidenehydrazino-1,3,4-thiadiazole—To a solution of 0.001 mole of (III) in 1 cc. of water, containing 2 drops of 50% AcOH, a solution of 0.001 mole of *p*-nitrobenzaldehyde in MeOH was added and warmed on a water bath for a few mins. The resulting yellow precipitate was collected and purified from MeOH or dioxane (Table IV). Yield, 90~95%.

Ethyl N′-(5-Substituted-1,3,4-thiadiazol-2-yl)hydrazonoacylate (IV)—a) Reaction of Ethyl Orthoacylate with (III) : A mixture of 0.01 mole of (III) and 8 cc. of ethyl orthoacylate was heated on a water bath for 4 hrs. at 60~70°. In the case of (III, R=phenyl) reaction temperature was kept at 120~130° in an oil bath. After removal of excess ethyl orthoacylate under reduced pressure, crystalline residue was collected and recrystallized from ligroine or hydr. EtOH. Yield, 80~90% (Table I).

b) Reaction of Ethyl Acylimidate Hydrochloride with (III) : To a solution of 0.005 mole of (III)-HCl salt in 2 cc. of water was added a solution of 0.005 mole of ethyl acylimidate, whose hydrochloride had been neutralized with a solution of 0.005 mole of K_2CO_3 in ether under ice cooling. The reaction mixture was allowed to stand over night in an ice chamber. The ether layer was separated, dried, evaporated, and the residue was recrystallized from ligroine or hydr. EtOH. Yield, 40~60%.

2,5-Disubstituted *s*-Triazolo[3,4-*b*]-1,3,4-thiadiazole (V)—A mixture of 0.01 mole of (IV) and 5 cc. of glacial AcOH was heated on a water bath for 1.5 hrs. After removal of excess AcOH under reduced pressure, the residue was recrystallized from ligroine or EtOH (Table I). Yield, 70~80%.

2-Isobutyl-5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole : Ethyl N′-(5-isobutyl-1,3,4-thiadiazol-2-yl)hydrazonobenzoate (IV : R=*iso*-C_4H_9, R′=phenyl), m.p. 161°, obtained by the foregoing method (b), was cyclized by the same procedure as described above. It was undepressed on admixture with an authentic sample[4] (Table II).

2-Substituted *s*-Triazolo[3,4-*b*]-1,3,4-thiadiazole (V : R′=H)—a) Reaction of Ethyl Orthoformate with (III) : A mixture of 0.005 mole of (III) and 8 cc. of ethyl orthoformate was heated on a water bath for 5 hrs. After removal of excess ethyl orthoformate under diminished pressure, the red

viscous oily residue was immediately dissolved in glacial AcOH and warmed on a water bath for 2 hrs. Excess of AcOH was removed under reduced pressure and the residue was recrystallized from EtOH or hydr. EtOH. Yield, 70~80%.

b) Reaction of 80% Formic Acid with (III): A mixture of 0.005 mole of (III) and 6 cc. of 80% formic acid was heated in an oil bath for 5 hrs. at 110~120°. After removal of excess formic acid under pressure, crystalline residue was collected and recrystallized from EtOH. These compounds were undepressed on admixture with the compounds prepared by the above a) method.

Summary

2-R-5-R′-*s*-Triazolo[3,4-*b*]-1,3,4-thiadiazoles (V) were synthesized starting with 2-hydrazino-5-R-1,3,4-thiadiazole (III : R=CH_3, C_2H_5, *n*-C_3H_7, *iso*-C_4H_9, C_6H_5), reacting them with either ethyl orthoacylate or ethyl acylimidate (R′=H, CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9) to form ethyl N′-(5-R-1,3,4-thiadiazol-2-yl)hydrazonoacylate (IV), and cyclization with acetic acid. Treatment of (III) by heating with 80% formic acid produced 2-R-*s*-triazolo-[3,4-*b*]-1,3,4-thiadiazole (V, R′=H).

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UDC 547.869.2

66. Hideo Kano and Manabu Fujimoto: Phenothiazine Derivatives. I. Synthesis of Sulfoxide and Sulfone Homologs of Chlorpromazine.

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Chlorpromazine was shown to be very effective agent as a potent tranquilizer, antiemetic, analgesic, spasmolytic, neuroleptic, or ganglioplegic. Many workers have recently reported the formation *in vivo* and the elimination in urine of chlorpromazine sulfoxide after chlorpromazine administration.[1]

Therefore, we decided to prepare chemically further compounds of this type, e.g., chlorpromazine sulfone. The free base of chlorpromazine (II) has been usually prepared by the condensation of 2-chlorophenothiazine**(Ia)[2] and N,N-dimethyl-3-chloropropylamine in the presence of sodium amide.[3] The same pattern was repeated with N,N-dimethyl-3-chloropropylamine (DMCPA) and 2-chlorophenothiazine 5-oxide (IV) or 5-dioxide (IXa), obtained by the oxidation of (Ia) or 2-chloro-10-acetylphenothiazine (VIIa), but the yield of the free bases of chlorpromazine sulfoxide (V) and sulfone (X) was relatively low,[4] as shown in Chart 1.

Whereas the sulfoxide derivatives, (V) and (VI), could be prepared by the direct oxidation of (II) or (III), the sulfone analogs (X and XI) were derived only from sulfone-type phenothiazine (IX). In view of this, the synthesis of 2(or 4)-chlorophenothiazine 5-dioxide (IX) was attempted, although it was realized that 10-acylated phenothiazine might be suitable.

The physicochemical properties of (II), (V), (VI), (X), and (XI) are recorded in Table I and Figs. 1~4.

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** The nomenclature of phenothiazines conforms to the style of the Ring Index (1940).

1) N.P. Salzman, *et al.*: Nature, **176**, 1122(1955); Kopf: Klin. Wochschr., **15/16**, 455(1956); B. Kinberger, *et al.*: Svenska Läkart, **53**, (9) 501(1956).
2) French Pat. 1,029,987(1953).
3) French Pat. 1,075,117(1954).
4) cf. H. Gilman, J. Eisch: J. Am. Chem. Soc., **77**, 3862(1955).