UDC 547.778.07

70. Matao Kanaoka : Synthesis of Related Compounds of Thiosemicarbazide. IV.[1] 1-(1,3,4-Thiadiazol-2-yl)-2-pyrazolin-5-one and Tetrazolo[4,5-*a*]-1,3,4-thiadiazole Derivatives.

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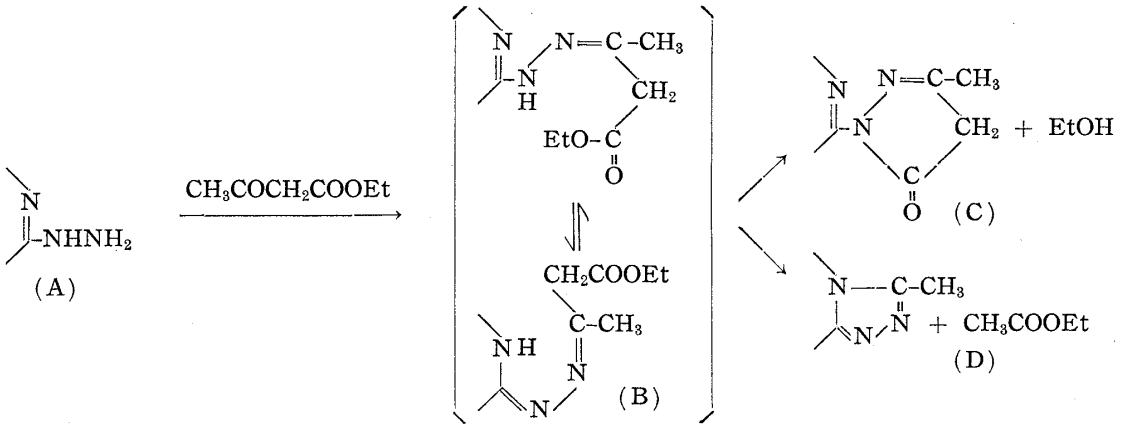
In a previous paper of this series, it was reported that s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (V), new skeleton compounds, were prepared from 5-substituted 2-hydrazino-1,3,4-thiadiazole (I) and ethyl orthoacylates.

This paper describes the reaction of hydrazino compounds (I) with ethyl ester of *β*-ketonic acid and nitrous acid.

According to the literature, the reaction of hydrazino derivatives of nitrogen-containing heterocyclic compounds (A), in which the hydrazino group is in the position *ortho* to ring nitrogen, with ethyl acetoacetate under various conditions affords 3-methyl-5-pyrazolone derivatives (C) or 3-methyl-s-triazolo derivatives (D) via ethyl acetoacetate hydrazone (B), and then either the separation of ethyl alcohol or ethyl acetate. The former examples are 2-hydrazinothiazole[2] and 2-hydrazinobenzothiazole,[3] and the latter 1-hydrazinophthalazine.[4]



However, the ethyl acetoacetate hydrazone (B) was not mentioned in the above two examples.

In the present series of experiments, 2-hydrazino-5-R-1,3,4-thiadiazoles (I : R=CH_3, C_2H_5, *n*-C_3H_7, *iso*-C_4H_9, C_6H_5) were reacted with equivalent moles of ethyl acetoacetate or ethyl 3-acetylisovalerate in alcohol solution and 1,3,4-thiadiazolylhydrazones (II) corresponding to (B) (Table I) were obtained. In the case of ethyl acetoacetate, however, the products were not the hydrazone (II : R′=H), but 1-(5-R-1,3,4-thiadiazol-2-yl)-3-methyl-2-pyrazolin-5-ones (III : R=alkyl, R′=H) when R was alkyl in hydrazino compounds (I).

Carrying out the foregoing reaction in glacial acetic acid solution, 5-pyrazolones (III) were obtained directly in excellent yield (Table I).

The cyclization reaction of the hydrazones (II), therefore, was effected by treating them with glacial acetic acid or heating at 180~190° under the separation of ethanol and this also produced 5-pyrazolones (III).

* Okuda, Toyama (金岡又雄).

1) Part III : This Bulletin, **5**, 385(1957).
2) H. Beyer, D. Stehwien : Arch. Pharm., **286**, 13(1953).
3) L. S. Efros, L. R. Davidenkov : Zhur. Obshcheĭ Khim., **21**, 2046(1951) (C. A., **46**, 8100(1952)).
4) J. Druey, B. H. Ringier : Helv. Chim. Acta, **34**, 195(1951).

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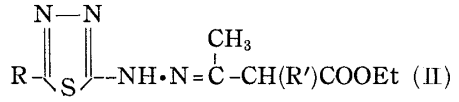
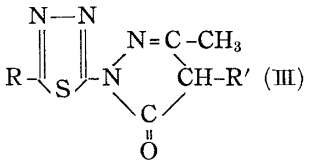
TABLE I.



(II)

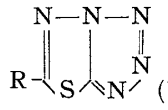
No.	R	R′	m.p.(°C)[a]	Appearance	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H	Yield (%)	$FeCl_3$[b]	P.N.D.A[c]	Recrystn. solvent
1	C_6H_5	H	164～165	Pale yellow leaflets	$C_{14}H_{16}O_2N_4S$	55.24	5.30	55.21	5.42	78	—		EtOH
2	CH_3	*iso*-C_3H_7	99～100	Colorless needles	$C_{12}H_{20}O_2N_4S$	50.68	7.09	50.77	7.23	64	—		hydr. EtOH
3	C_2H_5	*iso*-C_3H_7	64～65	Colorless needles	$C_{13}H_{22}O_2N_4S$	52.32	7.43	52.20	7.42	65	—		hydr. EtOH
4	*n*-C_3H_7	*iso*-C_3H_7	93～94	Colorless needles	$C_{14}H_{24}O_2N_4S$	53.82	7.74	53.72	7.81	65	—		hydr. EtOH
5	*iso*-C_4H_9	*iso*-C_3H_7	89～91	Colorless needles	$C_{15}H_{26}O_2N_4S$	55.18	8.03	54.99	8.08	70	—		hydr. EtOH
6	C_6H_5	*iso*-C_3H_7	153.5	Colorless needles	$C_{17}H_{22}O_2N_4S$	58.93	6.40	58.78	6.38	81	—		EtOH



(III)

7	CH_3	H	188～189	Pale yellow needles	$C_7H_8ON_4S$	42.84	4.11	42.77	4.18	74	v.dk.PB	dk.R	hydr. EtOH
8	C_2H_5	H	173～174	Pale yellow needles	$C_8H_{10}ON_4S$	45.70	4.79	45.81	4.85	72	v.dk.PB	dk.R	hydr. EtOH
9	*n*-C_3H_7	H	143～144	Pale yellow needles	$C_9H_{12}ON_4S$	48.19	5.39	48.02	4.43	76	v.dk.PB	dk.R	hydr. EtOH
10	*iso*-C_4H_9	H	156～157	Pale yellow needles	$C_{10}H_{14}ON_4S$	50.40	5.92	50.38	6.04	78	v.dk.PB	dk.R	hydr. EtOH
11	C_6H_5	H	241	Pale yellow needles	$C_{12}H_{10}ON_4S$	55.80	3.90	55.69	4.02	73	v.dk.PB	dk.R	EtOH
12	CH_3	*iso*-C_3H_7	163～164	Colorless needles	$C_{10}H_{14}ON_4S$	50.40	5.92	50.26	6.00	82	dk.B	—	hydr. EtOH
13	C_2H_5	*iso*-C_3H_7	113～115	Colorless needles	$C_{11}H_{16}ON_4S$	52.35	6.39	52.34	6.37	75	dk.B	—	hydr. EtOH
14	*n*-C_3H_7	*iso*-C_3H_7	106～107	Colorless needles	$C_{12}H_{18}ON_4S$	54.11	6.81	54.06	6.88	95	dk.B	—	hydr. EtOH
15	*iso*-C_4H_9	*iso*-C_3H_7	139～140	Colorless needles	$C_{13}H_{20}ON_4S$	55.68	7.19	55.72	7.20	92	dk.B	—	hydr. EtOH
16	C_6H_5	*iso*-C_3H_7	201～203	Pale yellow needles	$C_{15}H_{16}ON_4S$	59.97	5.37	59.88	5.35	90	v.dk.B	—	EtOH

TABLE II.



(VII)

No.	R	m.p. or b.p.(°C)	Appearance	Formula	Calcd. C	Calcd. H	Found C	Found H	Yield (%)	Recrystn. solvent
17	CH_3	92～93	Colorless needles	$C_3H_3N_5S$	25.52	2.14	25.42	2.21	54	ligroine
18	C_2H_5	b.p_2 70	Colorless oil	$C_4H_5N_5S$	30.96	3.25	30.86	3.36	52	ligroine
19	*n*-C_3H_7	b.p_1 77	Colorless oil	$C_5H_7N_5S$	35.49	4.17	35.32	4.23	60	
20	*iso*-C_4H_9	b.p_2 84	Colorless oil	$C_6H_9N_5S$	39.33	4.95	39.28	5.05	45	
21	C_6H_5	103～104	Colorless leaflets	$C_8H_5N_5S$	47.28	2.48	47.69	2.74	55	hydr. EtOH

a) All melting points are uncorrected
b) $FeCl_3$; $FeCl_3$ reaction, v.dk.PB; very dark purple blue, dk.B; dark blue, v.dk.B; very dark blue, —; negative
c) P.N.D.A; Coupling test with *p*-nitrosodimethylaniline, dk.R; dark red, —; negetive

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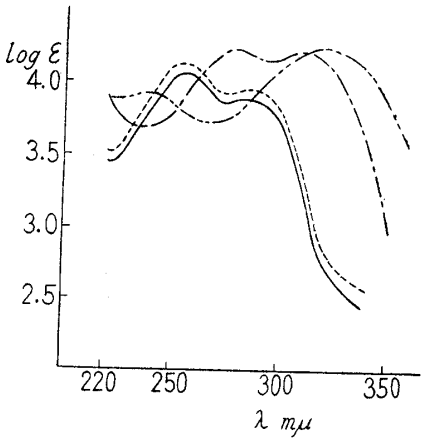


Fig. 1.

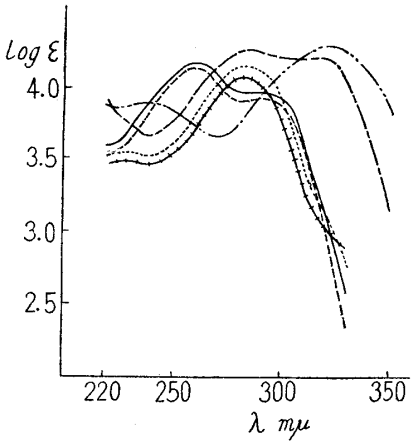


Fig. 2.

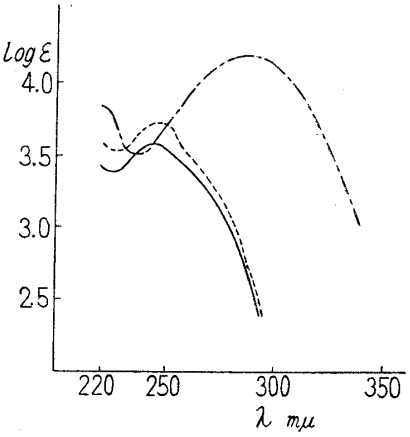
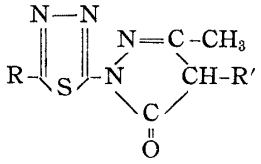
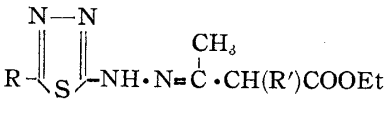


Fig. 3.





	R	λ_{max}^{EtOH} mμ	log ε	R	λ_{max}^{EtOH} mμ	log ε
Fig. 1. R′=H	CH_3	255.5	4.06			
	———	284.5	3.90			
	C_2H_5	255.5	4.12			
	----------	284.5	3.96			
	C_6H_5	277	4.24	C_6H_5	239	3.92
	—·—·—	309	4.32	—·—·—	322	4.27
Fig. 2. R′=*iso*-C_3H_7	CH_3	258	4.19	CH_3	282	4.10
	———	290	4.00	- - - - -		
	C_2H_5	258	4.16	C_2H_5	282.5	4.18
	----------	290	3.96	----------		
	C_6H_5	284	4.29	C_6H_5	239	3.89
	—·—·—	315	4.25	—·—·—	321	4.32

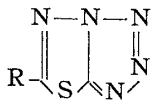


Fig. 3.	CH_3	246	3.60
	———		
	iso-C_4H_9	243	3.70

	C_6H_5	289	4.21
	—·—·—		

In order to encourage the condensation reaction of (D) type which gave s-triazolo compound, 2-hydrazino-5-phenyl-1,3,4-thiadiazole (I : R=C_6H_5) was heated with an excess of ethyl acetoacetate under reflux for 5 hours, but the s-triazolo compound was not obtained. In the above reaction, two molecules of ethyl acetoacetate condensed with hydrazino compound (I : R=C_6H_5) and a lactone-type pyrazolone (IV), m.p. 280~281°, was produced. This lactone-type pyrazolone (IV) was also obtained by the reaction of 5-pyrazolone (III : R=C_6H_5, R′=H) with an excess of boiling ethyl acetoacetate for 1.5 hours.

The results of ferric chloride reaction and coupling test with *p*-nitrosodimethylaniline[5] for 3-methyl-5-pyrazolones (III : R′=H) and 3-methyl-4-isopropyl-5-pyrazolones (III : R′=*iso*-C_3H_7) are shown in Table I. The reaction of the former with *p*-nitrosodimethylaniline resulted in change of the green color of the nitroso compound to deep

5) Sachs, Barschall : Ber., **35**, 1437(1902); Chem. Zentr., **1900** II, 1224; Friedländer, **6**, 1045; A. Weissberger, H.D. Porter : J. Am. Chem. Soc., **65**, 732(1943).

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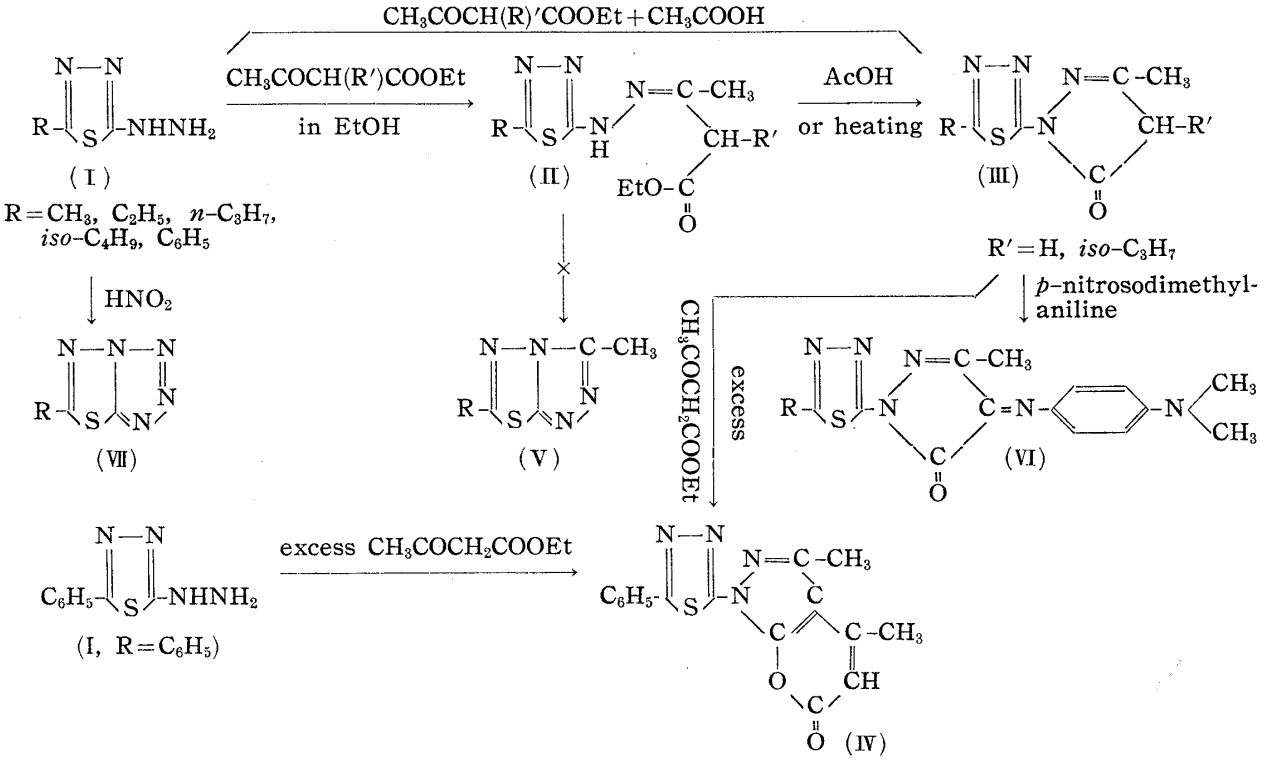
red, forming an azomethine dye (VI), but that of the latter kept the original green color on this coupling test, so that the former has active methylene groups.



Further attempt was made to prepare compounds analogous to 8-azaguanine, an antitumor agent, and 2-R-tetrazolo[4,5-*a*]-1,3,4-thiadiazoles (VII) shown in Table II were synthesized.[6]

The objective compounds were obtained by the reaction of (I) with sodium nitrite in diluted acetic acid.

Ultraviolet absorption spectra of some of the compounds prepared are shown in Figs. 1~3.

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

Experimental

1) Ethyl 3-Acetylisovalerate 5-R-1,3,4-Thiadiazolylhydrazone (II : R=*iso*-C_3H_7)—To a solution of 0.003 mole of (I) in 1 cc. of EtOH, 0.003 mole of ethyl acetylisovalerate was added and the mixture was warmed on a water bath for 2 hrs. After removal of EtOH under reduced pressure, the residue was recrystallized from hydr. EtOH (Table I, Nos. 2~6).

Ethyl Acetoacetate 5-Phenyl-1,3,4-thiadiazolylhydrazone (II : R=C_6H_5, R'=H)—To a suspension of 0.003 mole of (I : R=C_6H_5) in 3 cc. of EtOH, 0.003 mole of ethyl acetoacetate was added and the mixture was warmed on a water bath for 2 hrs. After cool, the separated precipitate was collected by filtration and recrystallized from EtOH (Table I, No. 1).

2) 1-(5-R-1,3,4-Thiadiazol-2-yl)-3-methyl-2-pyrazolin-5-one (III : R'=H)—i) Reaction in glacial AcOH solution : A mixture of 0.003 mole of (I) and 0.003 mole of ethyl acetoacetate was warmed on a water bath for a few mins. and 2 cc. of glacial AcOH was added. The mixture was warmed on a water bath for 2 hrs. and after romoval of glacial AcOH under reduced pressure, the residue was recrystallized from hydr. EtOH (Table I, Nos. 7~10).

In the case of (I : R=C_6H_5), after warming with glacial AcOH, the separated precipitate was collected by filtration and recrystallized from EtOH (Table I, No. 11).

6) R. G. Fargher, R. Furness : J. Chem. Soc., **107**, 688(1915); A. Mangini, M. Colonna : Gazz. chim. ital., **73**, 313(1943) (C. A., **41**, 1224(1947)).

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ii) Reaction in EtOH : To a solution of 0.003 mole of (I : R=alkyl) in 1 cc. of EtOH, 0.003 mole of ethyl acetoacetate was added and the mixture was warmed on a water bath for 2 hrs. After removal of EtOH under reduced pressure, the residue was recrystallized from hydr. EtOH (Table I, Nos. 7～10).

1-(5-R-1,3,4-Thiadiazol-2-yl)-3-methyl-4-isopropyl-2-pyrazolin-5-one (III : R′=*iso*-C_3H_7)—A mixture of 0.003 mole of (I) and 0.003 mole of ethyl 3-acetylisovalerate was warmed on a water bath for a few mins. and 2 cc. of glacial AcOH was added. The mixture was warmed on a water bath for 2 hrs. and after removal of glacial AcOH under reduced pressure, the residue was recrystallized from hydr. EtOH (Table I, Nos. 12～15).

In the case of (I : R=C_6H_5), after warming with glacial AcOH, the separated precipitate was collected by filtration and recrystallized from EtOH (Table I, No. 16).

Ring Closure of Ethyl Acetoacetate or Ethyl 3-Acetylisovelerate 5-R-1,3,4-Thiadiazolylhydrazone (II)—i) By AcOH : A mixture of 0.2 g. of the hydrazone (II) and 1 cc. of glacial AcOH was warmed on a water bath for 2 hrs. After removal of glacial AcOH, the residue was recrystallized from hydr. EtOH or EtOH. Yield 70～80%.

ii) By heating : 0.2 g. of the hydrazone (II) was heated in an oil bath at 180～190° for 1.5 hrs. After cool, the residue was recrystallized from hydr. EtOH or EtOH. Yield, 50～60%.

3) Lactone-type Pyrazolone (IV)—a) A mixture of 0.5 g. of 5-phenyl-2-hydrazino-1,3,4-thiadiazole (I : R=C_6H_5) and 5 cc. of ethyl acetoacetate was heated in an oil bath under reflux for 5 hrs. The yellow needle crystals which separated were collected by filtration, washed with MeOH, and recrystallized from BuOH or glacial AcOH. m.p. 280～281°. *Anal.* Calcd. for $C_{16}H_{12}O_2N_4S$: C, 59.24; H, 3.73. Found : C, 59.30; H, 4.03.

$FeCl_3$ reaction and coupling test with *p*-nitrosodimethylaniline were negative.

b) 0.5 g. of 1-(5-phenyl-1,3,4-thiadiazol-2-yl)-3-methyl-2-pyrazolin-5-one (III : R=C_6H_5, R′=H) was suspended in 3 cc. of ethyl acetoacetate and the mixture was refluxed in an oil bath. After 1.5 hrs.' boiling, the separated crystals were collected by filtration and recrystallized from BuOH or glacial AcOH. It was undepressed on admixture with the compound prepared by the above a) method.

4) 2-R-Tetrazolo[4,5-*a*]-1,3,4-thiadiazole—i) R=alkyl : To a solution of 0.003 mole of (I : R=alkyl) in 2 cc. of 12.5% AcOH, a solution of 0.0032 mole of $NaNO_2$ in 1 cc. of water was added dropwise under ice cooling, and the mixture was allowed to stand at room temperature for 5 hrs. The separated oily product was extracted with AcOEt, the extract was dried over anhyd. Na_2SO_4, and the solvent was distilled off. The residue was distilled under a reduced pressure (Table II, Nos. 17～20).

ii) R=C_6H_5 : To a suspension of 0.003 mole of (I : R=C_6H_5) in 15 cc. of 50% AcOH, a solution of 0.0032 mole of $NaNO_2$ in 1 cc. of H_2O was added dropwise under ice cooling, and the mixture was allowed to stand at room temperature for 5 hrs. The separated crystals were collected by filtration and recrystallized from hydr. EtOH (Table II, No. 21).

Summary

1) 1-(5-R-1,3,4-Thiadiazol-2-yl)-3-methyl-4-R′-2-pyrazolin-5-one (R′=H, *iso*-C_3H_7) (III) were synthesized starting with 2-hydrazino-5-R-1,3,4-thiadiazole (I : R=CH_3, C_2H_5, *n*-C_3H_7, *iso*-C_4H_9, C_6H_5), and reacting them with ethyl acetoacetate or ethyl 3-acetylisovalerate to form 5-R-1,3,4-thiadiazolylhydrazone (II).

2) 2-R-Tetrazolo[4,5-*a*]-1,3,4-thiadiazole, compound analogous to 8-azaguanine, were synthesized by the reaction of 2-hydrazino-5-R-1,3,4-thiadiazole (I) with sodium nitrite in diluted acetic acid.

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