UDC 615.771.7 : 547.859.3

137. Yasuo Makisumi: Synthesis of Potential Anticancer Agents. IX.*2 Condensation of some 2-, 5-, and 7-Methyl-*s*-triazolo-[2,3-*a*]pyrimidines with Benzaldehyde.

(*Research Laboratory, Shionogi & Co., Ltd.**1)

It is well known that, because the methyl group at 2- and 4-position in the pyridine ring is activated by the polar effect of C=N group in its ring, 2- and 4-methylpyridines are reactive to benzaldehyde and produce 2- and 4-styrylpyridines by condensation.[1] The same fact is known in other heterocyclic compounds containing nitrogen, such as quinoline,[2] pyrimidine,[3] thiazole,[4] and benzothiazole.[5]

In the present work, the reactivity of the methyl group in *s*-triazolo[2,3-*a*]pyrimidine was investigated for the study of polarization in *s*-triazolo[2,3-*a*]pyrimidine ring.

According to the above fact, it was assumed that the methyl group at 2-, 5-, and 7-positions of *s*-triazolo[2,3-*a*]pyrimidine ring would also be active. Therefore, various kinds of *s*-triazolo[2,3-*a*]pyrimidine derivatives containing methyl group at 2-, 5-, or 7-position were synthesized. 2-Methyl[6] (I), 5-methyl[7] (II), 7-methyl[8] (III), 5,7-dimethyl[6,9] (VI), and 2,5,7-trimethyl[6,10] (VII) derivatives have already been reported, and 2-, 5-dimethyl (IV) and 2,7-dimethyl (V) derivatives were newly synthesized. (IV) was prepared by dehalogenation of 2,5-dimethyl-7-chloro derivative (IX) by means of catalytic reduction using palladium-charcoal. (IX) was obtained by the reaction of phosphoryl chloride with 2,5-dimethyl-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine[10,11] (VIII).

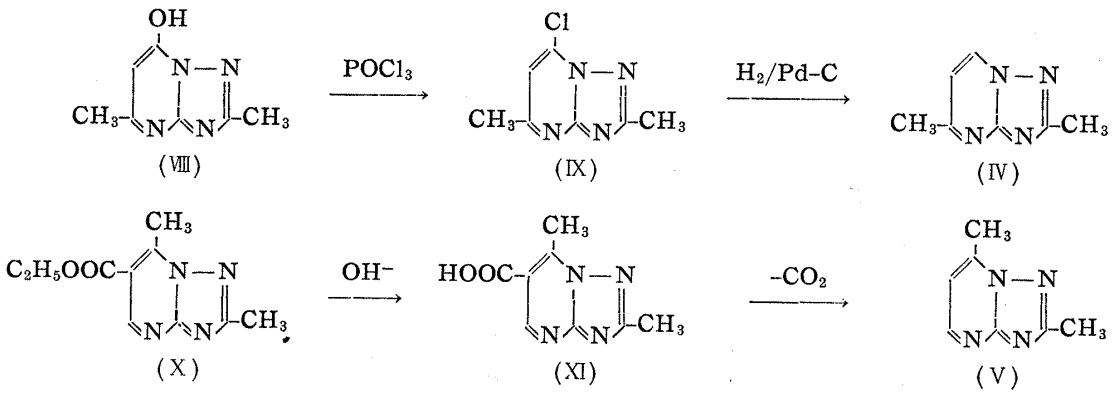


Chart 1.

*1 Fukushima-ku, Osaka (牧角徳夫).
*2 Part VII: This Bulletin, **9**, 878 (1961).

1) H. Baurath: Ber., **20**, 2719 (1887); **21**, 818 (1888); C. Friedländer: *Ibid.*, **38**, 159, 2838 (1905).
2) E. Jacobsen, C.L. Reimer: *Ibid.*, **16**, 2602 (1883); B.D. Shaw, E.A. Wagstaff: J. Chem. Soc., **1933**, 77; C.F. Kaslow, R.D. Stayner: J. Am. Chem. Soc., **67**, 1716 (1945).
3) S. Gabriel, J. Colman: Ber., **36**, 3379 (1903); H. Kondo, M. Yanai: Yakugaku Zasshi, **57**, 747 (1937).
4) W.H. Mills, J.L.B. Smith: J. Chem. Soc., **121**, 2724 (1922); H. Kondo, F. Nakazawa: Yakugaku Zasshi, **57**, 909 (1937).
5) E. Ochiai, T. Nishizawa: Yakugaku Zasshi, **60**, 132 (1940).
6) K. Shirakawa: *Ibid.*, **79**, 903 (1959).
7) H. Kano, Y. Makisumi, S. Takahashi, M. Ogata: This Bulletin, **7**, 903 (1959).
8) K. Shirakawa: Yakugaku Zasshi, **79**, 1482 (1959).
9) C. Bülow, K. Haas: Ber., **42**, 4638 (1909).
10) *Idem*: *Ibid.*, **43**, 375 (1910).
11) K. Shirakawa: Yakugaku Zasshi, **79**, 899 (1959); C.F.H. Allen, *et al.*: J. Org. Chem., **24**, 793 (1959).

(V) was prepared by decarboxylation of 6-carboxy derivative (XI) by heating in 40% sulfuric acid. The acid (XI) was obtained by hydrolysis of ethyl 2,7-dimethyl-*s*-triazolo-[2,3-*a*]pyrimidine-6-carboxylate[8] (X).

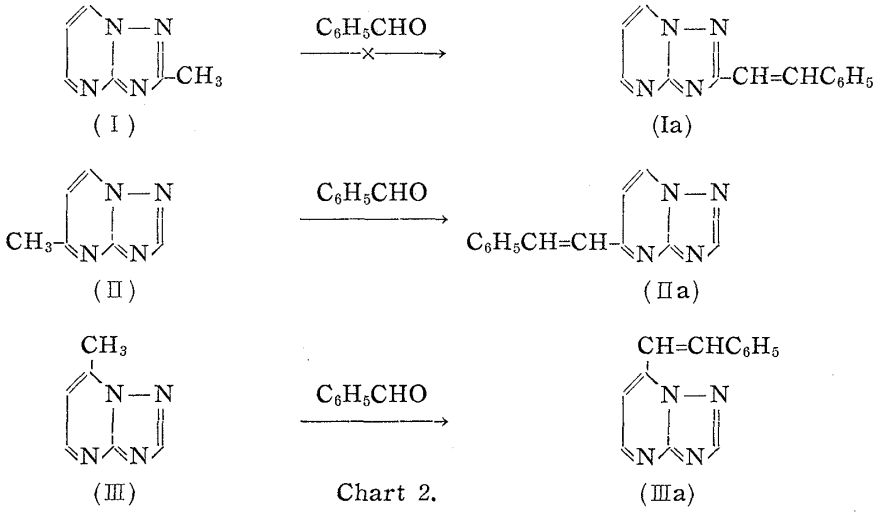
The ultraviolet spectra of these methyl derivatives of *s*-triazolo[2,3-*a*]pyrimidine were measured. These spectra all showed one absorption maximum in the region of 270~280 mμ.

Table I. Ultraviolet Absorption of some *s*-Triazolo[2,3-*a*]pyrimidines

Compd. No.	Substituent	m.p. (°C)	λ_{max}^{EtOH}	mμ (log ε)
	none[a]	144~145	273	(3.57)
(I)	2-CH_3	132~133	280	(3.63)
(II)	5-CH_3	184~185	272	(3.59)
(III)	7-CH_3	136~138	275	(3.66)
(IV)	2,5-di-CH_3	86~88[b]	278.5	(3.66)
(V)	2,7-di-CH_3	161~162	278.5	(3.71)
(VI)	5,7-di-CH_3	136~138	271	(3.70)
(VII)	2,5,7-tri-CH_3	144~145	276	(3.72)

a) Y. Makisumi, H. Kanō: This Bulletin, **7**, 907 (1959).
b) Monohydrate.

Treatment of monomethyl derivatives (I, II, and III) with 1.2 moles of benzaldehyde in the presence of zinc chloride at 160~170° gave 5- and 7-styryl derivatives (IIa and IIIa), but the 2-styryl derivative (Ia) was not obtained even by reaction at higher temperatures.



(I) (Ia) (II) (IIa) (III) (IIIa)

Chart 2.

By a similar reaction, the dimethyl derivatives (IV, V, and VI) were converted into monostyryl derivatives (IVa, Va, and VIa), and in the case of using 2.5~3 moles of benzaldehyde at 190~195°, only (VI) was converted into 5,7-distyryl derivative (VIb). (IV) and (V) were converted into the monostyryl derivative (IVa and Vb) and distyryl derivatives (IVb and Vb) were not obtained.

In order to compare the structural difference among these products, their ultraviolet spectra were carefully examined. 5-Styryl derivative (IIa) and 7-styryl derivative (IIIa) were taken as the standard compounds. The comparative absortpion of the two types is shown in Figs. 1 and 2. The 5-styryl derivative shows three maxima at 232.5, 269, and 336 mμ, and the 7-styryl derivative shows two maxima at 231 and 352 mμ in each curve. The spectra of (IVa) and (VIa) show three maxima and these curves are similar to the spectrum of (IIa) in Fig. 1. In contrast, there are two maxima in the spectrum of (Va), similar to that of (IIIa) in Fig. 2.

Oxidation of the two methyl-styryl compounds (IVa and Va) with potassium permanganate gave methyl-carboxyl derivatives (XII and XIII), which were both converted into the same methyl derivative, m.p. 132~133°, by decarboxylation. This compound was identical with (I). Hydrolysis of (IVa) and (Va) with concentrated hydrogen bromide gave 3-methyl-5-amino-*s*-triazole (XIV). Thus, it was proved that the structures of (IVa) and (Va) are 2-methyl-5-styryl- and 2-methyl-7-styryl-*s*-triazolo[2,3-*a*]pyrimidines, respectively. Similarly, another methyl-styryl compound (VIa) was oxidized with potassium permanganate into a methyl-carboxyl derivative (XV), which was identical with 7-methyl-*s*-triazolo[2,3-*a*]pyrimidine-5-carboxylic acid,[8] and decarboxylation of (XV) gave the 7-methyl derivative (III). Consequently, the structure of (VIa) was proved to be 5-styryl-7-methyl-*s*-triazolo[2,3-*a*]pyrimidine.

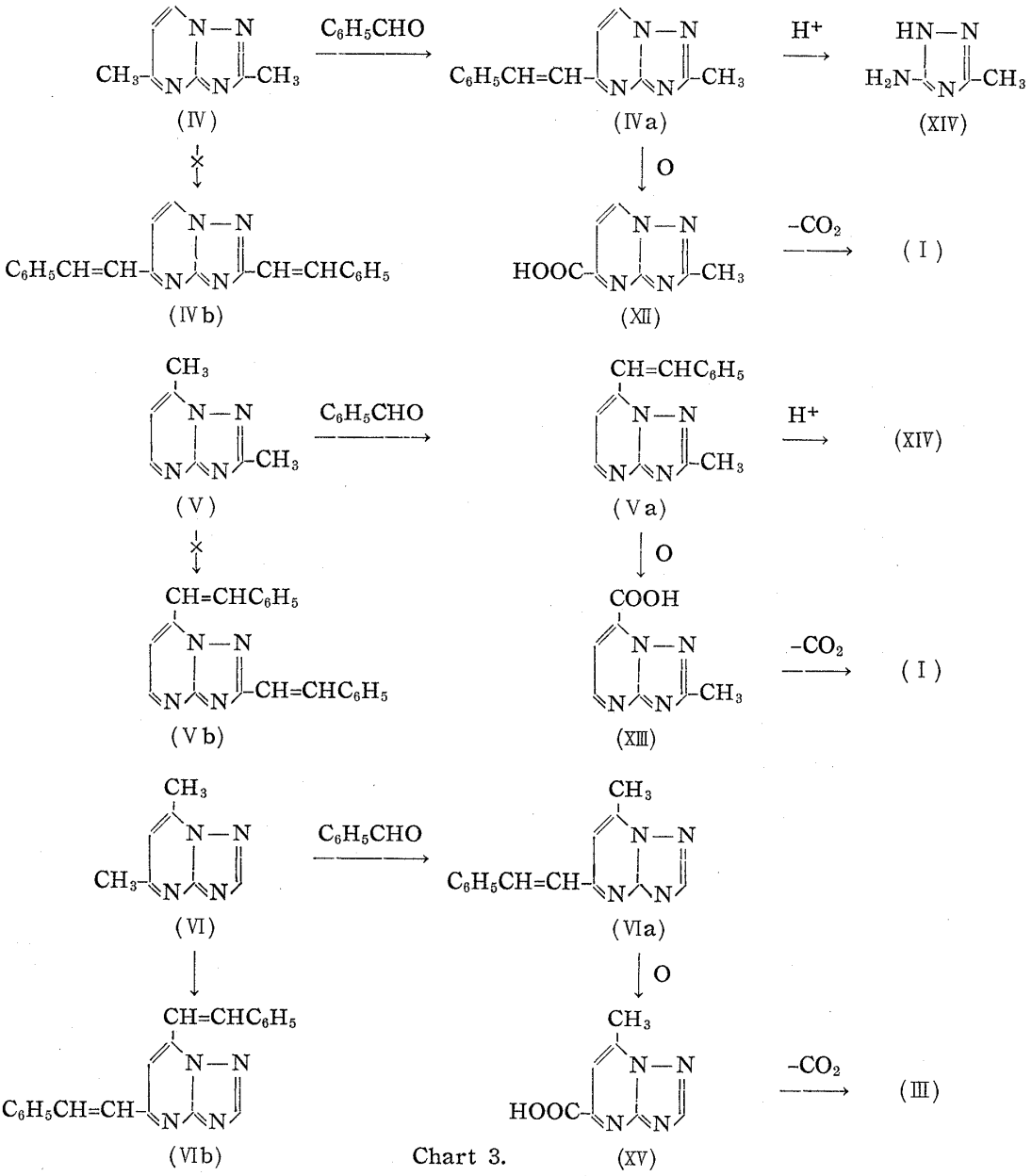


Chart 3.

Treatment of the trimethyl derivative (VII) with benzaldehyde under various reaction conditions gave only distyryl derivative (VIIa). Ultraviolet spectrum of this compound was compared with that of the 5,7-distyryl derivative (VIb). The latter compound shows two

maxima at 299 and 365 mμ in its curve and there are two maxima in the spectrum of (VIIa), similar to that of (VIb) in Fig. 3.

Oxidation of the methyl-distyryl compound (VIIa) with potassium permanganate gave a methyl-dicarboxyl derivative (XVI), whose decarboxylation afforded a monomethyl derivative. This compound was identical with (I). From these results, the structure of (VIIa) was determined as 2-methyl-5,7-distyryl-*s*-triazolo[2,3-*a*]pyrimidine.

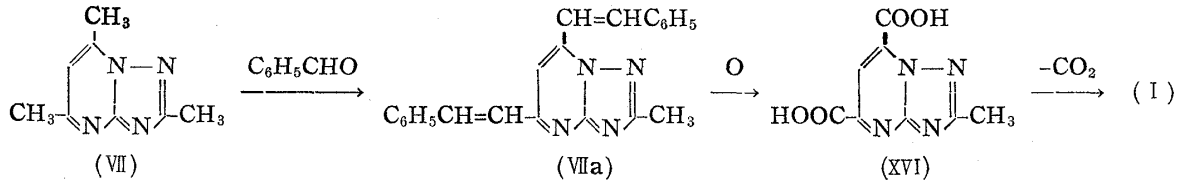


Chart 4.

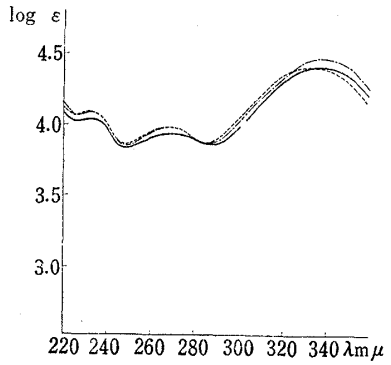
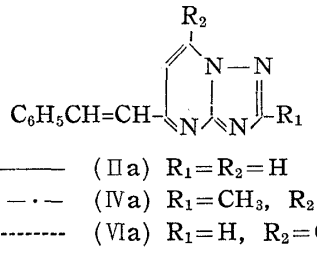


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)



——— (IIa) $R_1=R_2=H$
—·—·— (IVa) $R_1=CH_3$, $R_2=H$
---------- (VIa) $R_1=H$, $R_2=CH_3$

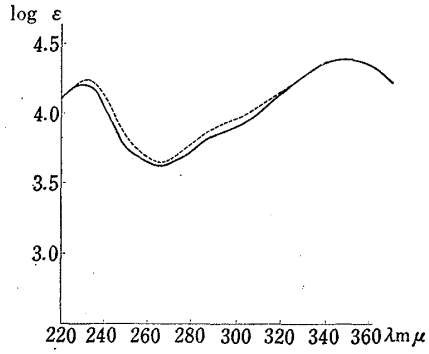
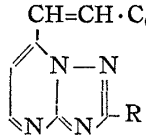


Fig. 2. Ultraviolet Absorption Spectra (in EtOH)



——— (IIIa) R=H
---------- (Va) $R=CH_3$

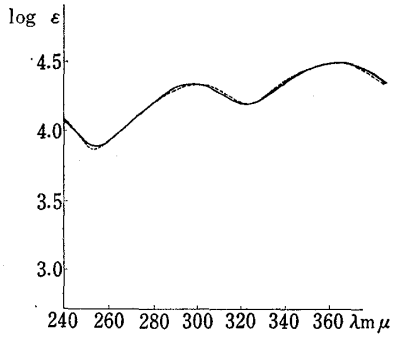
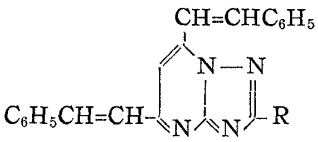


Fig. 3. Ultraviolet Absorption Spectra (in EtOH)



——— (VIb) R=H
---------- (VIIa) $R=CH_3$

Consequently, it became evident that the methyl groups at 5- and 7-positions of *s*-triazolo[2,3-*a*]pyrimidine ring are both active, with the methyl group at 5-position slightly more active than that at 7-position while the methyl group at 2-position is not active. From these facts, it was considered that the methyl groups at 5- and 7-positions were

activated by the polar effect of C=N group, but not that at 2-position, because the polar effect of C=N group in triazole ring is reduced by the −M effect of ring-nitrogen at 8-position.

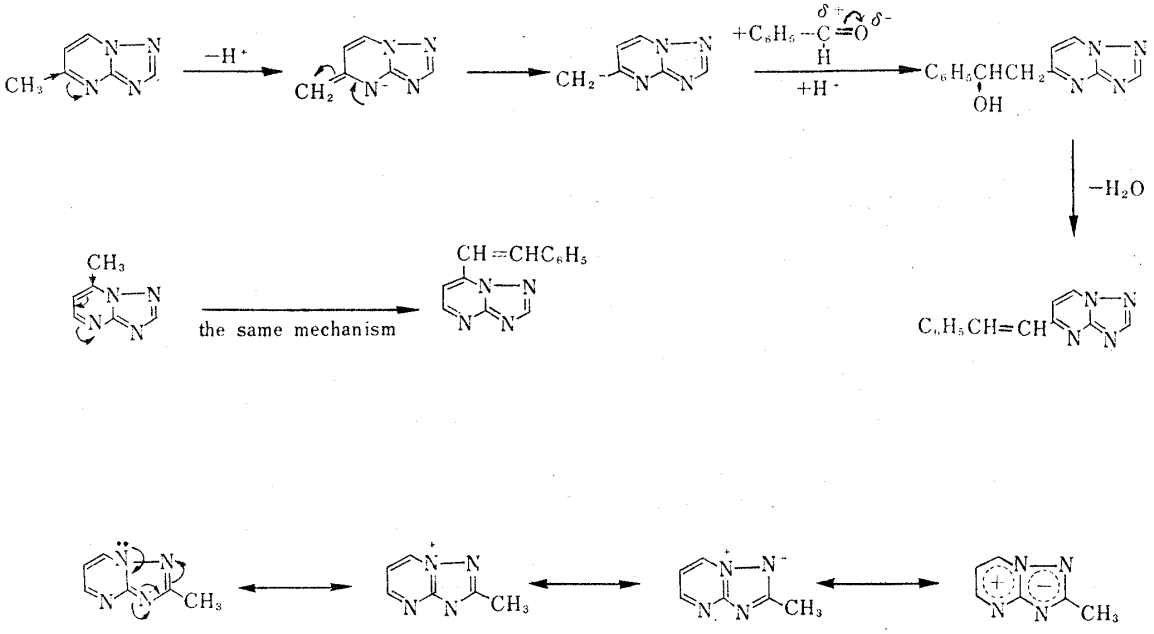


Chart 5.

Experimental*3

2,5-Dimethyl-7-chloro-*s*-triazolo[2,3-*a*]pyrimidine (IX)——A mixture of 9.5 g. of 2,5-dimethyl-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (Ⅷ) and 28 cc. of $POCl_3$ was refluxed for 2 hr. The excess $POCl_3$ was removed in a reduced pressure on a steam bath and the residual syrup was poured with stirring into ice water. The solution was neutralized with conc. NH_4OH and the resulting precipitate was collected by filtration. This filtrate was extracted with $CHCl_3$ and the extract was evaporated to leave slightly yellow crystals. The resulting combined crystals were purified by Al_2O_3 chromatography with $CHCl_3$ to 10.5 g. of white crystals and were recrystallized from benzene-ligroine (1:1) to colorless needles, m.p. 151~152°. *Anal.* Calcd. for $C_7H_7N_4Cl$: C, 46.04; H, 3.81; N, 30.68. Found : C, 46.19; H, 3.92; N, 30.60.

2,5-Dimethyl-*s*-triazolo[2,3-*a*]pyrimidine (IV)——A solution of 9.1 g. of (IX) in 160 cc. of dehyd. EtOH containing 3 cc. of conc. NH_4OH was hydrogenated over 2.0 g. of 5% Pd-C. Onemole of H_2 was absorbed during 2 hr. After removal of the catalyst, the filtrate was evaporated to dryness and the residue was extracted with hot benzene. The extract was concentrated and the residue was recrystallized from benzene-ligroine to 6.0 g. of colorless needles, m.p. 86~88°. *Anal.* Calcd. for $C_7H_8N_4 \cdot H_2O$: C, 50.59; H, 6.07; N, 33.72. Found : C, 50.87; H, 6.13; N, 33.84.

2,7-Dimethyl-*s*-triazolo[2,3-*a*]pyrimidine (V)——A mixture of 3 g. of 2,7-dimethyl-*s*-triazolo[2,3-*a*]pyrimidine-6-carboxylic acid (XI) and 15 cc. of 40% H_2SO_4 was refluxed for 10 hr. The reaction mixture was neutralized with 20% NaOH and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from benzene to 1.2 g. of colorless scales, m.p. 161~162°. *Anal.* Calcd. for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.82. Found : C, 56.95; H, 5.35; N, 37.69.

5-Styryl-*s*-triazolo[2,3-*a*]pyrimidine (IIa)——A mixture of 0.4 g. of (Ⅱ), 0.38 g. of benzaldehyde, and 0.2 g. of $ZnCl_2$ was heated at 160° for 3 hr. After cool, the resulting solid was powdered, suspended in H_2O, basified with NH_4OH, and extracted with $CHCl_3$. The extract was washed with aqueous $NaHSO_3$ solution and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from hydr. EtOH to 0.5 g. of colorless scales, m.p. 219.5~220.5°. *Anal.* Calcd. for $C_{13}H_{10}N_4$: C, 70.25 ; H, 4.54 ; N, 25.21. Found : C, 70.18; H, 4.75 ; N, 24.93. UV λ_{max}^{EtOH} mμ (log ε) : 232.5 (4.09), 269 (4.00), 336 (4.46).

*3 All melting points are uncorrected. Ultraviolet spectra were measured with the Hitachi Recording Spectrophotometer, EPS-2.

7-Styryl-*s*-triazolo[2,3-*a*]pyrimidine (IIIa)——A mixture of 0.2 g. of (III), 0.19 g. of benzaldehyde, and 0.1 g. of $ZnCl_2$ was heated at 160° for 2 hr. The reaction mixture was treated as described above and the resulting product was recrystallized from hydr. EtOH to 0.3 g. of colorless needles, m.p. 195~196°. *Anal.* Calcd. for $C_{13}H_{10}N_4$: C, 70.25; H, 4.54; N, 25.21. Found : C, 70.22; H, 4.68; N, 24.81. UV λ_{max}^{EtOH} mμ (log ε) : 231 (4.20), 352 (4.40).

2-Methyl-5-styryl-*s*-triazolo[2,3-*a*]pyrimidine (IVa)——A mixture of 0.8 g. of (IV), 0.6 g. of benzaldehyde, and 0.5 g. of $ZnCl_2$ was heated at 160~170° for 3 hr. The reaction mixture was treated as above and the resulting product was recrystallized from Me_2CO to 1.0 g. of colorless needles, m. p. 203.5~204°. *Anal.* Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found : C, 71.18; H, 5.28; N, 23.75. UV λ_{max}^{EtOH} mμ (log ε) : 231 (4.13), 268 (4.00), 339 (4.50).

2-Methyl-7-styryl-*s*-triazolo[2,3-*a*]pyrimidine (Va)——A mixture of 0.2 g. of (V), 0.15 g. of benzaldehyde, and 0.1 g. of $ZnCl_2$ was heated at 160~170° for 3 hr. The reaction mixture was treated as above, and the resulting product was recrystallized from benzene to 0.2 g. of colorless scales, m.p. 181~182°. *Anal.* Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found : C, 71.33; H, 5.35; N, 23.52. UV λ_{max}^{EtOH} mμ (log ε) : 232.5 (4.23), 352 (4.39).

5-Styryl-7-methyl-*s*-triazolo[2,3-*a*]pyrimidine (VIa)——A mixture of 0.75 g. of (VI), 0.6 g. of benzaldehyde, and 0.4 g. of $ZnCl_2$ was heated at 160~170° for 2 hr. The reaction mixture was treated as above and the resulting product was recrystallized from benzene to 0.4 g. of slightly yellow needles, m.p. 195~196°. *Anal.* Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.12; N, 23.72. Found : C, 71.37; H, 5.35; N, 23.62. UV λ_{max}^{EtOH} mμ (log ε) : 231.5 (4.14), 268 (4.03), 333 (4.45).

5,7-Distyryl-*s*-triazolo[2,3-*a*]pyrimidine (VIb)——A mixture of 0.74 g. of (VI), 1.3 g. of benzaldehyde, and 0.8 g. of $ZnCl_2$ was heated at 190° for 3 hr. The reaction mixture was treated as above and the resulting product was recrystallized from EtOH to 0.9 g. of yellow needles, m.p. 179~180°. *Anal.*Calcd. for $C_{21}H_{16}N_4$: C, 77.75; H, 4.97; N, 17.27. Found : C, 77.87; H, 5.13; N, 17.21. UV λ_{max}^{EtOH} mμ (log ε) : 299 (4.44), 365 (4,59).

2-Methyl-5,7-distyryl-*s*-triazolo[2,3-*a*]pyrimidine (VIIa)——A mixture of 0.8 g. of (VII), 1.3 g. of benzaldehyde, and 0.5 g. of $ZnCl_2$ was heated at 170° for 3 hr. The reaction mixture was treated as above and the resulting product was recrystallized from benzene to 0.6 g. of yellow needles, m.p. 224.5~225.5°. *Anal.* Calcd. for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56. Found : C, 78.04; H, 5.45; N, 16.54. UV λ_{max}^{EtOH} mμ (log ε) : 301 (4.46), 365 (4.56).

Hydrolysis of (IVa) and (Va)——a) A mixture of 0.3 g. of (IVa) and 15 cc. of HBr (sp. gr., 1.48) was refluxed for 4 hr. The reaction mixture was concentrated to dryness in a reduced pressure, the residue was dissolved in H_2O, and filtered. To the filtrate, a saturated aqueous solution of picric acid was added, the resulting yellow precipitate was collected, and recrystallized from H_2O to yellow needles, m.p. 231~232°(decomp.). *Anal.* Calcd. for $C_3H_6N_4 \cdot C_6H_3O_7N_3$: C, 33.03; H, 2.77; N, 29.97. Found : C, 33.05; H, 2.80; N, 29.85. This was identified with the picrate of (XIV).
b) 0.3 g. of (Va) was treated with 15 cc. of HBr by the same method as above. The picrate of yellow needles, m.p. 231~232°(decomp.), was obtained and identified with the picrate of (XIV).

Oxidation of (IVa) with Potassium Permanganate——To a solution of 2 g. of (IVa) in 100 cc. of 50% pyridine, 3.5 g. of finely powdered $KMnO_4$ was added in small portions with stirring at 10~15° and the mixture was stirred for further 2 hr. The precipitated MnO_2 was filtered off and washed with H_2O. The filtrate and the washing solution were combined, concentrated in a reduced pressure, and acidified with dil. H_2SO_4. The resulting white crystals were collected by filtration, washed with benzene, and the benzene-insoluble crystals were recrystallized from hydr. EtOH to 1.2 g. of 2-methyl-*s*-triazolo[2,3-*a*]pyrimidine-5-carboxylic acid (XII) as white needles, m.p. 243~243.5°(decomp.). *Anal.* Calcd. for $C_7H_6O_2N_4$: C, 47.19; H, 3.39; N, 31.45. Found : C, 47.56; H, 3.81 N, 31.33.

This compound was heated at 250~260° for 5 min., by which the crystals were decomposed and liquefied completely. After cool, the resulting product was recrystallized from benzene to colorless needles, m.p. 132~133°, which was identified with (I) by mixed melting point.

Oxidation of (Va) with Potassium Permanganate——To a solution of 1.5 g. of (Va) in 80 cc. of 50% pyridine, 2.6 g. of finely powdered $KMnO_4$ was added in small portions with stirring and the mixture was treated as above. The resulting benzene-insoluble crystals were purified by reprecipitation with acid and alkali to 0.9 g. of 2-methyl-*s*-triazolo[2,3-*a*]pyrimidine-7-carboxylic acid (XIII), which was recrystallized from hydr. EtOH to colorless needles, m.p. 194°(decomp.). *Anal.* Calcd. for $C_7H_6O_2N_4$: C, 47.19; H, 3.39; N, 31.45. Found : C, 47.37; H, 3.58; N, 31.38.

This compound was heated at 200° for 5~10 min. After cool, the resulting product was recrystallized from benzene to colorless needles, m.p. 132~133°, which was identified with (I) by mixed melting point.

Oxidation of (VIa) with Potassinm Permanganate——To a solution of 2 g. of (VIa) in 60 cc. of 50% pyridine, 3.5 g. of finely powdered $KMnO_4$ was added dropwise with stirring at 10~15° and the mixture was treated as above. The white crystals (benzoic acid) precipitated by acidification

with dil. H_2SO_4 were filtered off and the filtrate was allowed to stand overnight. The crystals that separated in the filtrate were collected and recrystallized from H_2O to 0.5 g. of 7-methyl-*s*-triazolo[2,3-*a*]pyrimidine-5-carboxylic acid (XV) as colorless needles, m.p. 243°(decomp.), which was identified with the authentic sample.[8]

This compound was heated at 250° for 10 min. After cool, the reaction product was recrystallized from benzene-ligroine to colorless needles, m.p. 136~138°, which was identified with (III).

Oxidation of (VIIa) with Potassium Permanganate——To a solution of 2.4 g. of (VIIa) in a mixture of 120 cc. of pyridine and 50 cc. of H_2O, 8.4 g. of finely powdered $KMnO_4$ was added in small portions with stirring at room temperature, and the mixture was stirred for further 8 hr. The reaction mixture was treated as above. The resulting benzene-insoluble crystals were purified by reprecipitation with acid and alkali to 0.5 g. of 2-methyl-*s*-triazolo[2,3-*a*]pyrimidine-5,7-dicarboxylic acid (XVI), which was recrystallized from hydr. EtOH to colorless pillars, m.p. 300°(decomp.). *Anal.* Calcd. for $C_8H_6O_4N_4 \cdot \frac{1}{2}H_2O$: C, 40.00; H, 3.36; N, 23.33. Found : C, 39.89; H, 3.59; N, 23.40.

This compound was heated at 240~290° under reduced pressure. After cool, the product was recrystallized from benzene to colorless needles, m.p. 132~133°, which was identified with (I) by mixed melting point.

The author is grateful to Dr. K. Takeda, Director of this Laboratory, and to Dr. H. Kanō of this Laboratory, for their continued guidance and encouragement. Thanks are also due to Mr. I. Tanaka for ultraviolet spectra measurement and to the members of the Analysis Room of this Laboratory for elemental analysis.

Summary

Various kinds of *s*-triazolo[2,3-*a*]pyrimidine derivatives containing methyl group at 2-, 5-, and 7-positions were synthesized and the condensation of these compound with benzaldehyde was investigated. Five kinds of monostyryl derivatives and two kinds of distyryl derivatives were obtained. The structure of these styryl derivatives was confirmed by chemical methods and ultraviolet spectral measurement, and it was clarified that the methyl groups at 5- and 7-positions are active while that at 2-position was not active.

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UDC 547.94 : 582.675.7

136. Tsutomu Sugasawa*1 : Aconitum-Alkaloide. XXV.[1] Über die Konstitution des Songorins. (2).[2]

(*Pharmazeutische Fakultät, Universität Tokio*)

In der Fortsetzung der Versuche zur Konstitutionsermittlung des Songorins wurde nun die Selen-Dehydrierung des Isodesoxosongorin-Hydrochlorids (II), das aus Songorin (I) durch Reduktion nach Huang-Minlon und anschließende Wasserstoff-Umlagerung mittels mit Wasserstoff gesättigter Palladium-Kohle abgeleitet wurde, durchgeführt[3] (Schema 1).

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1) XXIV. Mitt. E. Ochiai, T. Okamoto : Dieses Bulletin, **7**, 556 (1959).

2) I. Mitt : *Ibid.*, **4**, 6 (1956). Shimoburobase-I erwies sich mit Songorin bzw. Napellonin[6] als identisch, darnach wurden Shimoburobase-I sowie Napellonin Songorin genannt.

3) Kurze Mitt. E. Ochiai, T. Okamoto, S. Sakai, T. Sugasawa, T. Onouchi : Dieses Bulletin, **7**, 542 (1959).