The authors wish to thank Prof. T. Okada and Dr. A. Okazaki, Department of Physics of this University, for their kind guidance and help in X-ray measurements. The authors also wish to express their gratitudes to Prof. T. Oyama, Department of Applied Science of this University, for his kind advice and help in differential thermal analysis.

This work was partly supported by the Grant-in-aid for Scientific Research provided by Ministry of Education, to which they are also grateful.

Summary

It was definitely found that dehydroacetic acid had two kinds of crystals, one of which was α-form (monoclinic), stable at a low temperature, and the other was β-form (triclinic), stable at a high temperature. Transition from α-form to β-form occurred at 80°. Lattice constants and other crystal data of these two kinds of crystals were reported.

(Received August 27, 1962)

UDC 547.859.3.07

146. Yasuo Makisumi: Studies on Azaindolizine Compounds. XIV.*2 Transetherification in *s*-Triazolo[1,5-*a*]pyrimidines.

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

Oliverio[1] reported that *o*- or *p*-nitrophenyl methyl ether was transformed into *o*- or *p*-nitrophenethol by heating with ethanol in the presence of alkali and this reaction was reversible. The same reaction on 2,4-dinitrophenyl ethers was reported by Ogata and Okano.[2] Recently, such transetherification reaction was reported on the aromatic heterocyclic compounds *e.g.* benzothiazole,[3,4] benzodiazine,[5] and pyrimidine[6] fields. From the results of these papers, the transetherification reaction is considered to be the nucleophilic substitution by the alcoholate anions and also to be able to occur at the only position possessing high nucleophilic reactivity.

In the previous paper,[7] the author reported that 5- and 7-positions of the *s*-triazolo-[1,5-*a*]pyrimidine ring were very reactive towards the nucleophilc substitution and the 7-position was more reactive than the 5-position. In connection with these facts, the transetherification of the alkoxyl groups at the 5- and 7-positions in *s*-triazolo[1,5-*a*]-pyrimidines was investigated.

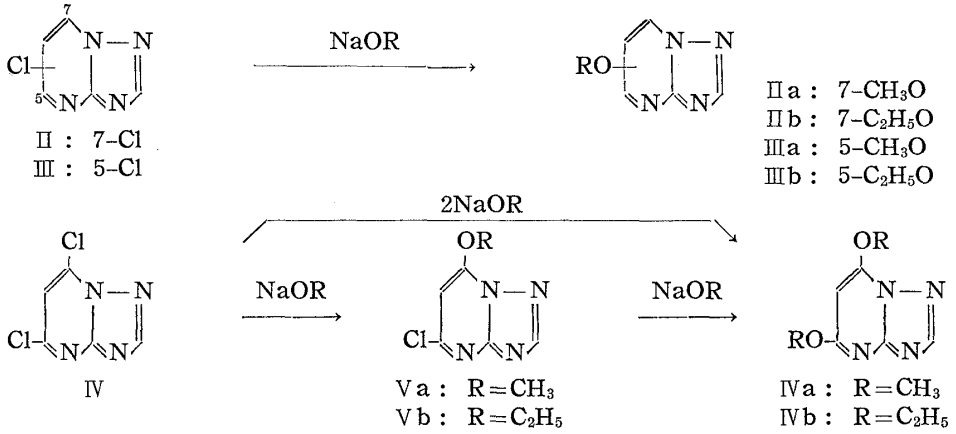
In the previous work,[8] 5-methyl-7-alkoxy-*s*-triazolo[1,5-*a*]pyrimidines (Ia and Ib) were synthesized by the reaction of the corresponding 5-methyl-7-chloro derivative (I) with an equimolar amount of sodium alkoxide at room temperature. By the same method,

*1 Fukushima-ku, Osaka (牧角徳夫).

*2 Y. Makisumi: This Bulletin, **11**, 129 (1963).

1) A. Oliverio: Atti X° congr. intern. chim., **3**, 258 (1939). (C. A., **33**, 9302 (1939)).
2) Y. Ogata, M. Okano: J. Am. Chem. Soc., **71**. 3211 (1949).
3) H. H. Fox, M. T. Bogert: *Ibid.*, **63**, 2996 (1941).
4) Y. Mizuno, K. Adachi: Yakugaku Zasshi, **72**, 269 (1952).
5) K. Adachi: *Ibid.*, **75**, 1426 (1955).
6) M. Watatani: Ann. Rept. Takamine Lab., **12**, 37 (1960).
7) Y. Makisumi: *Ibid*, **9**, 801 (1961).
8) Y. Makisumi, H. Kano: *Ibid.*, **11**, 67 (1963).

7-methoxy-(IIa), 7-ethoxy-(IIb), 5-methoxy-(IIIa), and 5-ethoxy-(IIIb) *s*-triazolo[1,5-*a*]-pyrimidines were prepared from the corresponding 7- and 5-chloro derivatives (II and III). Moreover, when 5,7-dichloro-*s*-triazolo[1,5-*a*]pyrimidine (IV) was treated with two moles of sodiumalkoxide at room temperature, 5,7-dimethoxy and 5,7-diethoxy derivatives (IVa and IVb) were obtained. In the case of using of an equimolar amount of sodium alkoxide, 5-chloro-7-methoxy and 5-chloro-7-ethoxy derivatives (Va and Vb) were obtained, which were also converted into IVa and IVb by the action of equimolar amount of sodium alkoxide, respectively. The structure of Va and Vb was confirmed by the results that the alkoxy derivatives prepared by dechlorination of Va and Vb by catalytic reduction, were identified with the above-mentioned samples (IIa and IIb), respectively.



Cahrt 1.

Transetherification reaction of the ten kinds of alkoxy-*s*-triazolo[1,5-*a*]pyrimidines obtained here, was examined by the treatment with ethanol or methanol in the presence of an equimolar amount of sodium alkoxide.

The 7-methoxy derivatives (Ia and IIa) were smoothly transformed into the 7-ethoxy derivatives (Ib and IIb) by the action of ethanol containing sodium ethoxide at room temperature and Ib and IIb were also converted into Ia and IIa respectively by the action of methanol containing sodium methoxide at the same condition. Similarly, the 5-methoxy derivative (IIIa) was transformed into the 5-ethoxy derivative (IIIb), but IIIb did not reacted at room temperature and IIIb was converted into IIIa by the reaction under heating.

In the case of 5,7-dialkoxy-*s*-triazolo[1,5-*a*]pyrimidines (IVa and IVb), only 7-alkoxyl group was exchanged at room temperature and both 5- and 7-alkoxyl groups reacted by the reaction under heating. Namely, the 5,7-dimethoxy derivative (IVa) was transformed into 5-methoxy-7-ethoxy-*s*-triazolo[1,5-*a*]pyrimidine (VIa) by the action of ethanol containing sodium ethoxide at room temperature and into the 5,7-diethoxy derivative (IVb) at refluxing temperature. VIa was also transformed into IVb by the same method at refluxing temperature. Similarly, IVb was transformed into 5-ethoxy-7-methoxy-*s*-triazolo[1,5-*a*]pyrimidine (VIb) by the action of methanol containing sodium methoxide at room temperature and IVb and VIb were also converted into IVa by the same method at refluxing temperature. The structure of the above monotransetherified compounds (VIa and VIb) was confirmed by the following experiments. VIa was converted by hydrolysis with aqueous sodium hydroxide into methoxy-hydroxy derivative (VIIa), which was further chlorinated to the corresponding methoxy-chloro derivative (VIIIa) by the action of phosphoryl chloride. The product which was dechlorinated from VIIIa by catalytic reduction, was identified with the 5-methoxy compound (IIIa). Accordingly, the starting compound (VIa) of these reactions is 5-methoxy-7-ethoxy-*s*-triazolo[1,5-*a*]pyrimidine and

the intermediates (VIIa and VIIIa) of the above reactions are 5-methoxy-7-hydroxy- and 5-methoxy-7-chloro-*s*-triazolo[1,5-*a*]pyrimidines, respectively. Similarly, VIb was converted into the 5-methoxy compound (IIIb) *via* VIIb and VIIIb. Accordingly, VIb is 5-ethoxy-7-methoxy-*s*-triazolo[1,5-*a*]pyrimidine and the intermediates (VIIb and VIIIb) which were obtained by the hydrolysis of VIb and the following chlorination, are 5-ethoxy-7-hydroxy- and 5-ethoxy-7-chloro-*s*-triazolo[1,5-*a*]pyrimidines.

From these results, it became clear that the 7-alkoxyl group was transetherified more easily than the 5-alkoxyl group in 5,7-dialkoxy-*s*-triazolo[1,5-*a*]pyrimidines. This fact was consistent with the following results of the alkali hydrolysis reaction of 5,7-dialkoxy-*s*-triazolo[1,5-*a*]pyrimidines. Namely, IVa and IVb were hydrolysed by heating with aqueous sodium hydroxide to the 5-alkoxy-7-hydroxy derivatives which were identified with VIIa and VIIb, respectively.

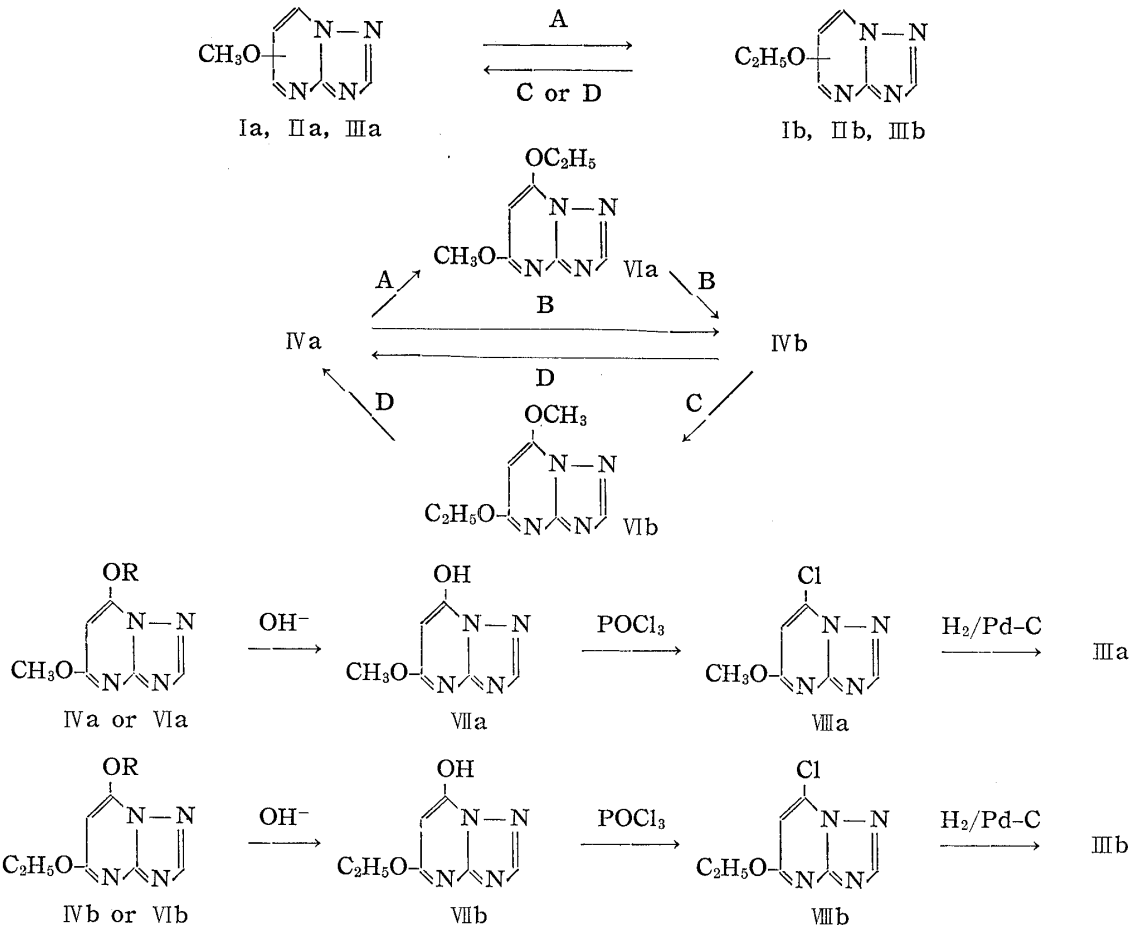
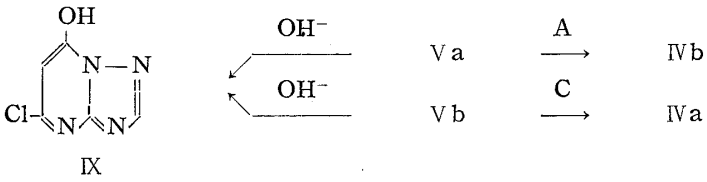


Chart 2.

On the other hand, reaction of 5-chloro-7-methoxy-*s*-triazolo[1,5-*a*]pyrimidine (Va) with ethanol in the presence of an equimolar amount of sodium ethoxide at room temperature gave the 5,7-diethoxy compound (IVb) and 5-chloro-7-ethoxy-*s*-triazolo[1,5-*a*]pyrimidine (Vb) was also converted into the 5,7-dimethoxy compound (IVa) by the action of methanol containing an equimolar amount of sodium methoxide in good yield, respectively. Because the transetherification of the alkoxyl group is able to occur only in the presence of alkali, the alkoxyl group at 7-position must be transetherified in the first step of the above reactions and the nucleophilic substitution of the chlorine atom at 5-position by the alcoholate anion must follow. This interpretation was supported by the following fact that the alkoxyl group at 7-position was more reactive than the chlorine

atom at 5-position in the alkali hydrolysis of 5-chloro-7-alkoxy-*s*-triazolo[1,5-*a*]pyrimidines. Both Va and Vb were converted into 5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-ol[7] (IX) by hydrolysis with aqueous sodium hydroxide.



IX

In the hydrolysis reaction of 5,7-dialkoxy- and 5-chloro-7-alkoxy-*s*-triazolo[1,5-*a*]-pyrimidines, all substituents at 5-position were inactive. This fact suggests that the polar effect of the ring-nitrogen at 4-position is reduced by the electron-repelling effect of the hydroxyl group at 7-position which produced by the hydrolysis.

Among alkoxy-*s*-triazolo[1,5-*a*]pyrimidines obtained here, all compounds possessing methoxyl group at 7-position were unstable towards heating and showed the double melting points. These properties suggest that the methyl radical of the 7-methoxyl group must easily migrate to the ring-nitrogens on heating as the alkyl rearrangement in the previous work.[8]

Table I. Transetherification of Alkoxy-*s*-triazolo[1,5-*a*]pyrimidines

Reactant	Reaction method	Product	Yield (%)	Reactant	Reaction method	Product	Yield (%)
I a	A	Ib	91.7	Ib	C	I a	73.2
II a	A	II b	73.2	II b	C	II a	50.0
III a	A	III b	87.3	III b	D	III a	90.1
IV a	A	VIa	95.2	IV b	C	VIb	97.5
IV a	B	IV b	92.0	IV b	D	IV a	92.0
V a	A	IV b	90.0	V b	C	IV a	89.5
VIa	B	IV b	90.5	VIb	D	IV a	91.0

Experimental*3

7-Methoxy-*s*-triazolo[1,5-*a*]pyrimidine (IIa)——To a solution of 0.23 g. of Na dissolved in 30 cc. of anhyd. MeOH, 1.5 g. of 7-chloro-*s*-triazolo[1,5-*a*]pyrimidine (II) was added under stirring and cooling. The mixture was stirred at room temperature for 2 hr., the separated NaCl was filtered off and washed with MeOH. The filtrate and the washing solution were combined and evaporated to dryness under reduced pressure. The resulting residue was diluted with H_2O, extracted with $CHCl_3$, the extract was dried over Na_2SO_4, and evaporated to give 1.25 g. of white crystals. Recrystallization from EtOH gave colorless needles which showed the double melting point at 164° and 200~214°. *Anal.* Calcd. for $C_6H_6ON_4$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.91; H, 4.33; N, 37.55.

7-Ethoxy-*s*-triazolo[1,5-*a*]pyrimidine (IIb)——This compound was prepared from 1.5 g. of II and 0.23 g. of Na in 30 cc. of anhyd. EtOH by the same method as above. The resulting crystals (1.35 g., m.p. 115~116°) were recrystallized from benzene to give colorless pillars, m.p. 116~117°. *Anal.* Calcd. for $C_7H_8ON_4$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.40; H, 5.14; N, 33.97.

5-Methoxy-*s*-triazolo[1,5-*a*]pyrimidine (IIIa)——This compound was prepared from 3.4 g. of 5-chloro-*s*-triazolo[1,5-*a*]pyrimidine (III) and 0.5 g. of Na in 80 cc. of anhyd. MeOH by the same method as above. The resulting crystals (3.1 g.) were recrystallized from benzene-petr. benzin to give colorless pillars, m.p. 201~202°. *Anal.* Calcd. for $C_6H_6ON_4$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.15; H, 4.08; N, 37.35.

5-Ethoxy-*s*-triazolo[1,5-*a*]pyrimidine (IIIb)——This compound was prepared from 3.4 g. of III and 0.5 g. of Na in 80 cc. of anhyd. EtOH by the same method as above. The resulting crystals (3.5 g.) were recrystallized from benzene to give colorless plates, m.p. 148~149°. *Anal.* Calcd. for $C_7H_8ON_4$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.28; H, 5.04; N, 34.10.

5-Chloro-7-methoxy-*s*-triazolo[1,5-*a*]pyrimidine (Va)——To a solution of 5.7 g. of 5,7-dichloro-*s*-triazolo[1,5-*a*]pyrimidine (IV) in 80 cc. of anhyd. MeOH, a solution of 0.7 g. of Na in 20 cc. of anhyd.

*3 All melting points are uncorrected.

MeOH was dropwise added under cooling and stirring. After the mixture was stirred at room temperature for 1 hr., the separated crystals were collected by filtration and the filtrate was evaporated to dryness under reduced pressure. The resulting both solids were combined, diluted with H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated under reduced pressure to give 5.3 g. of the crude product. Recrystallization from benzene-MeOH gave 4.9 g. of colorless needles which showed the double melting point at 159~160° and 203~207°. *Anal.* Calcd. for $C_6H_5ON_4Cl$: C, 39.04; H, 2.73; N, 30.35. Found : C, 39.28; H, 2.88; N, 30.20.

A solution of 0.5 g. of this compound in 100 cc. of MeOH was hydrogenated over 0.15 g. of 5% Pd-C and 0.22 g. of AcONa. One mole of H_2 was absorbed during 30 min. After removal of the catalyst, the filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in H_2O, and extracted with $CHCl_3$. Evaporation of the solvent gave 0.3 g. of white solid, which was recrystallized from EtOH to give colorless needles, m.p. 163~164° and 200~214°. This compound was identified with IIa by admixture and IR spectrum comparison.

5-Chloro-7-ethoxy-*s*-triazolo[1,5-*a*]pyrimidine (Vb)——This compound was prepared from 3.8 g. of IV and 0.45 g. of Na in anhyd. EtOH by the same method as above. The resulting crystals were recrystallized from benzene-ligroin to give 3.5 g. of colorless needles, m.p. 161~162°. *Anal.* Calcd. for $C_7H_7ON_4Cl$: C, 42.27; H, 3.55; N, 28.21. Found : C, 42.44; H, 3.53; N, 28.21.

This compound (0.5 g.) was hydrogenated over 5% Pd-C by the same method as above and the resulting product was recrystallized from benzene to give 0.28 g. of colorless pillars, m.p. 116~117° which was identified with IIb by admixture.

5,7-Dimethoxy-*s*-triazolo[1,5-*a*]pyrimidine (IVa)——a) To a solution of 0.46 g. of Na in 40 cc. of anhyd. MeOH, 1.9 g. of IV was added in small portions under stirring and cooling. The mixture was stirred for 2 hr. at room temperature and evaporated to dryness under reduced pressure. The residue was diluted with H_2O, extracted with $CHCl_3$, and the extract was washed with H_2O and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue (1.75 g.) was recrystallized from benzene to give colorless needles which showed the double melting point at 167° and 241~244°. *Anal.* Calcd. for $C_7H_8O_2N_4$: C, 46.66; H, 4.48; N, 31.10. Found : C, 46.45; H, 4.70; N, 31.22.

b) To a solution of 0.23 g. of Na in 40 cc. of anhyd. MeOH, 1.85 g. of Va was added and the mixture was treated as above giving 1.65 g. of colorless needles, m.p. 166~167° and 241~244°, undepressed on admixture with the sample IVa prepared by the method of a).

5,7-Diethoxy-*s*-triazolo[1,5-*a*]pyrimidine (IVb)——a) To a solution of 0.95 g. of Na in 50 cc. of anhyd. EtOH, 3.8 g. of IV was added and the mixture was treated as above giving 3.4 g. of the crude product, m.p. 156~158°, which was recrystallized from benzene-ligroin to give colorless needles, m.p. 161~162°. *Anal.* Calcd. for $C_9H_{12}ON_4$: C, 51.91; H, 5.81; N, 26.91. Found : C, 51.92; H, 5.80; N, 26.75.

b) To a solution of 0.23 g. of Na in 50 cc. of anhyd. EtOH, 1.99 g. of Vb was added and the mixture was treated as above giving 1.9 g. of colorless needles, m.p. 161~162°, undepressed on admixture with the sample (IVb) prepared by the method of a).

Transetherification of Alkoxyl of *s*-Triazolo[1,5-*a*]pyrimidines

Method A——To a solution of Na (0.01 mole) in 50 cc. of anhyd. EtOH, respective methoxy-*s*-triazolo-[1,5-*a*]pyrimidine (0.01 mole) was added. The mixture was stirred at room temperature for 1.5 hr. and evaporated to dryness at the same temperature under reduced pressure. The residue was diluted with H_2O, neutralized with 10% HCl, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness under reduced pressure. The resulting product was recrystallized from a suitable solvent to give the corresponding ethoxy-*s*-triazolo[1,5-*a*]pyrimidine.

Method B——In the method A, the reaction was carried out by heating for 15 min.

Method C——To a solution of Na (0.01 mole) in 50 cc. of anhyd. MeOH, respective ethoxy-*s*-triazolo-[1,5-*a*]pyrimidine (0.01 mole) was added and the mixture was treated as the method A to give the corresponding methoxy-*s*-triazolo[1,5-*a*]pyrimidine.

Method D——In the method C, the reaction was carried out by heating for 15 min.

The results are shown in Table I.

5-Methoxy-7-ethoxy-*s*-triazolo[1,5-*a*]pyrimidine (VIa)——This compound was obtained as colorless pillars, m.p. 181~182° by recrystallization from benzene. *Anal.* Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found : C, 49.68; H, 5.25; N, 29.11.

5-Ethoxy-7-methoxy-*s*-triazolo[1,5-*a*]pyrimidine (VIb)——This compound was obtained as colorless pillars, which showed the double melting point at 117° and 218~230°, by recrystallization from benzene-ligroin. *Anal.* Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found : C, 49.52; H, 5.22; N, 28.75.

5-Methoxy-*s*-triazolo[1,5-*a*]pyrimidin-7-ol (VIIa)——a) A mixture of 0.45 g. of VIa and 10 cc. of 2% NaOH was heated on a steam bath for 20 min, and acidified with 10% HCl. The precipitated crystals were collected by filtration, washed with H_2O, and recrystallized from H_2O to give 0.28 g. of colorless pillars, m.p. 244°(decomp.). *Anal.* Calcd. for $C_6H_6O_2N_4 \cdot \frac{1}{3}H_2O$: C, 42.32; H, 4.23; N, 32.45; H_2O, 3.48. Found : C, 42.16; H, 4.15; N, 32.43; H_2O, 3.67.

b) A mixture of 0.2 g. of IVa and 5 cc. of 2% NaOH was heated on a steam bath for 20 min. and the reaction mixture was treated as above to give 0.13 g. of colorless pillars, m.p. 244° (decomp.), which was identified with the sample (VIIa) described in a) by IR spectrum comparison.

5-Ethoxy-*s*-triazolo[1,5-*a*]pyrimidin-7-ol (VIIb)——a) A solution of 0.45 g. of VIb and 10 cc. of 2% NaOH was heated on a steam bath for 20 min. and the reaction mixture was treated as above. The resulting product was recrystallized from H_2O to give 0.26 g. of colorless needles, m.p. 253° (decomp.). *Anal.* Calcd. for $C_7H_8O_2N_4$: C, 46.66; H, 4.48; N, 31.10. Found : C, 46.72; H, 4.64; N, 30.97.

b) A solution of 0.3 g. of IVb and 7 cc. of 2% NaOH was treated as above to give 0.18 g. of colorless needles, m.p. 253° (decomp.), which was identified with the sample (VIIb) described in a) by IR spectrum comparison.

5-Methoxy-7-chloro-*s*-triazolo[1,5-*a*]pyrimidine (VIIIa)——A mixture of 6 g. of VIIa and 30 cc. of $POCl_3$ was refluxed for 2.5 hr. The excess of $POCl_3$ was removed under reduced pressure on a steam bath and the residual syrup was poured with stirring into ice-water. The solution was extracted with $CHCl_3$, the extract was washed with H_2O, dried over $CaCl_2$, and evaporated to dryness. The residue was dissolved in benzene-$CHCl_3$, purified by alumina chromatography, and recrystallized from benzene-petr. benzin to give 1.8 g. of colorless needles, m.p. 116~118°. *Anal.* Calcd. for $C_6H_5ON_4Cl$: C, 39.04; H, 2.73; N, 30.35. Found : C, 38.95; H, 2.85; N, 30.18.

5-Ethoxy-7-chloro-*s*-triazolo[1,5-*a*]pyrimidine (VIIIb)——A mixture of 2.5 g. of VIIb and 25cc. of $POCl_3$ was refluxed for 2.5 hr. and the reaction mixture was treated as above to give 1.4 g. of crude product (m.p. 125~127°), which was recrystallized from benzene-petr. benzin to give colorless pillars, m.p. 128~129°. *Anal.* Calcd. for $C_7H_7ON_4Cl$: C, 42.27; H, 3.55; N, 28.21. Found : C, 42.52; H, 3.70; N, 28.05.

Catalytic reduction of 5-Alkoxy-7-chloro-*s*-triazolo[1,5-*a*]pyrimidines——1) A solution of 0.6 g. of VIIIa in 50 cc. of anhyd. EtOH was hydrogenated over 0.2 g. of 5% Pd-C and 0.28 g. of AcONa. One mole of H_2 was absorbed during 40 min. After removal of the catalyst by filtration, the filtrate was evaporated to dryness under reduced pressure and the residue was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $CaCl_2$, and evaporated to dryness giving 0.25 g. of white crystals. Recrystallization from benzene gave colorless pillars, m.p. 201~202°, which was identified with IIIa by admixture and IR spectrum comparison.

2) One gram of VIIIb was hydrogenated by the same method as above and the resulting crystals (0.7 g.) were recrystallized from benzene to give colorless plates, m.p. 148~149°, which was identified with IIIb by admixture and IR spectrum comparison.

Hydrolysis of 5-Chloro-7-alkoxy-*s*-triazolo[1,5-*a*]pyrimidines——1) A mixture of 0.2 g. of Va and 10 cc. of 2% NaOH was heated on a steam bath for 30 min. and acidified with 10% HCl. The precipitated crystals were collected by filtration, washed with H_2O, and recrystallized from 60% EtOH to give 0.13 g. of colorless needles, m.p. 257° (decomp.). *Anal.* Calcd. for $C_5H_3ON_4Cl$: C, 35.19; H, 1.76; N, 32.85. Found : C, 35.35; H, 2.04; N, 32.95. This compound was identified with authentic sample of 5-chloro-*s*-triazolo[1,5-*a*]pyrimidin-7-ol[7] (IX) by IR spectrum comparison.

2) 0.2 g. of Vb was hydrolysed with 10 cc. of 2% NaOH as above and the resulting product was recrystallized from 60% EtOH to give 0.12 g. of colorless needles, m.p. 257° (decomp.), which was identified with IX by IR spectrum comparison.

The author expresses his gratitude to Dr. K. Takeda, Director of this Laboratory, and to Dr. H. Kano of this Laboratory, for their helpful advices and encouragements. Thanks are also due to the members of the Analysis Room of this Laboratory for elemental analysis.

Summary

Ten kinds of alkoxy-*s*-triazolo[1,5-*a*]pyrimidines were synthesized by reaction of the corresponding chloro derivatives with sodium alkoxides and the transetherification reaction of these compounds was investigated. It was clear that the alkoxyl group at 7-position was transetherified more easily than that at 5-position in *s*-triazolo[1,5-*a*]-pyrimidines.

(Received December 17, 1962)