The CO streching frequency of N-acetylsulfonamide group showed a large shift to a shorter wave-length region.

Synthesis of some benzenesulfonamide derivatives was also described.

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135. **Shoji Inoue**: Studies on Pyrimidine Derivatives. VII.[1] Synthesis of Thiazolo[5,4-*d*]pyrimidines and Related Compounds. (7)

(*Pharmaceutical Faculty, Nagoya City University**)

In Part III[2] of this series, it was shown that 2-methyl-5-chlorothiazolo[5,4-*d*]pyrimidine was obtained from 2-chloro-4-mercapto-5-aminopyrimidine (I) by the action of acetic anhydride. Since then two kinds of thiazolo[5,4-*d*]pyrimidine derivatives have been prepared from (I). 5-Chlorothiazolo[5,4-*d*]pyrimidine (II) was obtained in a good yield by the treatment of (I) with ethyl orthoformate and 2-hydroxy-5-chlorothiazolo[5,4-*d*]pyrimidine (VI) was prepared by heating (I) with phosgene in dioxane.

The chlorine in (II) is reactive and by the action of sodium ethoxide, sodium ethanethioxide or sodium phenoxide, (II) was converted into 5-ethoxythiazolo[5,4-*d*]pyrimidine (III), 5-ethylthio-thiazolo[5,4-*d*]pyrimidine (IV), and 5-phenoxythiazolo[5,4-*d*]pyrimidine (V), respectively. In these operations, however, a small amount of alkali-soluble by-product was formed in each case. The products thus obtained were assumed to be formed by the cleavage of the C-S bond in (II).

The reactivity of the chlorine in (VI) was decreased owing to the strong influence of the 2-hydroxyl substituent and the condensation product (VII) was obtained from (VI) by refluxing with sodium ethanethioxide for 16 hours under conditions similar to the formation of (IV) from (II). Compound (VII) was also produced by the treatment of 2-hydroxy-5-mercapto-thiazolo[5,4-*d*]pyrimidine (IX) with ethyl bromide and (IX) was prepared from 2,4-dimercapto-5-aminopyrimidine (VIII)[3] and phosgene.

It has already been shown in part IV[3] of this series that 2,5-dimercaptothiazolo[5,4-*d*]-pyrimidine (X) may be prepared from (VIII) and potassium methylxanthate, and that (X) could be converted into the corresponding diethylthio derivative in the usual manner.

On the other hand, when only one mole of ethyl bromide was allowed to react with the dimercapto compound (X), a smooth reaction occurred and the monoethylthio compound, 2-mercapto-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (XI) was obtained. In order to determine the position of substitution in (XI), the remaining group in (XI) was oxidized to the corresponding hydroxyl group by the addition of hydrogen peroxide to the sodium salt of (XI), and the resulting product was found to be identical with 2-hydroxy-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (VII) obtained by the above-mentioned process.

Similarly, the reaction of 2,7-dimercaptothiazolo[5,4-*d*]pyrimidine (XIII),[1] prepared from (XII) by the action of one mole of ethyl bromide, afforded the 7-substituted monoethylthio compound (XIV), and this was oxidized to 2-hydroxy-7-ethylthio-thiazolo[5,4-*d*]pyrimidine (XV) by a method identical to the reaction of (XI) with hydrogen peroxide.

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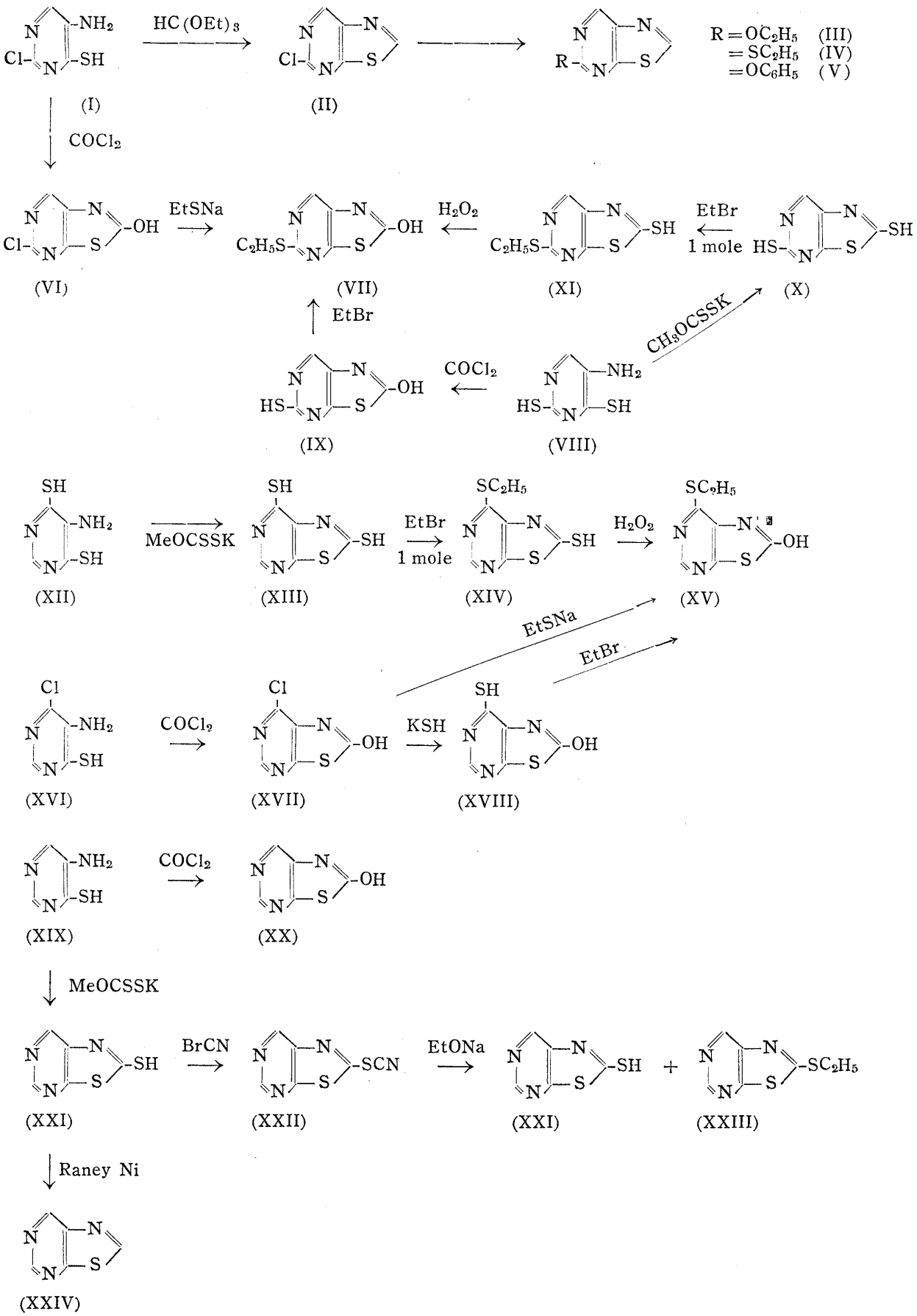
* Hagiyama-cho, Mizuho-ku, Nagoya (井上昭二).

1) Part VI: This Bulletin, **6**, 352(1958).

2) Part III: *Ibid.*, **6**, 343(1958).

3) Part IV: *Ibid.*, **6**, 346(1958).



2-Hydroxy-7-chlorothiazolo[5,4-*d*]pyrimidine (XVII) was prepared from (XVI)[4] and phosgene by methods similar to the preparation of (VI). (XVII) was then smoothly converted into 2-hydroxy-7-mercaptothiazolo[5,4-*d*]pyrimidine (XVIII) by the action of potassium hydrosulfide, but, (XVIII) underwent a change during purification and accordingly it was immediately converted into 2-hydroxy-7-ethylthio-thiazolo[5,4-*d*]pyrimidine (XV). Furthermore, (XV) was also obtained by the direct condensation of (XVII) with sodium ethanethioxide by refluxing for a short period (3 hours), and this contrasted with the difficulty encountered in preparing (VII) from (VI).

2-Hydroxythiazolo[5,4-*d*]pyrimidine (XX) was prepared from (XIX)[4] in the same way as in the case of (VI).

In 1944, Davis, *et al.*[5] reported the reaction of benzothiazole derivatives, and they observed that 2-thiocyanobenzothiazole reacted with sodium ethoxide in ethanol to give 2-mercaptobenzothiazole and 2-ethylthio-benzothiazole. Similarly to their case, 2-thiocyanothiazolo-[5,4-*d*]pyrimidine (XXII), prepared from 2-mercaptothiazolo[5,4-*d*]pyrimidine (XXI)[4] and cyanogen bromide, was converted into 2-mercaptothiazolo[5,4-*d*]pyrimidine (XXI) and a by-product, 2-ethylthio-thiazolo[5,4-*d*]pyrimidine (XXIII). Finally, the desulfurization of (XXI) with Raney nickel in ammonia solution gave thiazolo[5,4-*d*]pyrimidine (XXIV) which was identical with a specimen prepared from cyclization of 4-mercapto-5-aminopyrimidine with formic acid.

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Experimental[6]

5-Chlorothiazolo[5,4-*d*]pyrimidine (II)—A mixture of 2 g. of (I) and 20 cc. of ethyl orthoformate was refluxed for 2 hrs., during which the solid dissolved to form a clear yellow solution. After cool, the separated crystals were collected and combined with another crop of crystals obtained from the filtrate. Recrystallization from EtOH gave white plates, m.p. 126°. The yield was almost quantitative. *Anal.* Calcd. for $C_5H_2N_3SCl$: C, 34.99; H, 1.17. Found: C, 34.90; H, 1.45.

5-Ethoxythiazolo[5,4-*d*]pyrimidine (III)—To a solution of 30 cc. of dehyd. EtOH containing 0.05 g. of Na, 0.34 g. of (II) was added. After refluxing for 1 hr., the solvent was removed. To the residue, a small amount of H_2O was added and extracted with ether, which was dried and evaporated to give an oily product which was recrystallized from petr. ether to colorless prisms, m.p. 95°, undepressed on admixture with a sample prepared as described in part I.[7]

5-Ethylthio-thiazolo[5,4-*d*]pyrimidine (IV)—A solution of EtSNa was prepared from 0.03 g. of Na in 20 cc. of EtOH and 0.07 g. of EtSH. To this solution, 0.17 g. of (II) was added and refluxed for 1 hr. The product was obtained by the same manner as in the case of (III) as colorless needles, m.p. 82°, undepressed on admixture with a sample prepared as described in part IV.[1]

5-Phenoxythiazolo[5,4-*d*]pyrimidine (V)—A solution of 0.13 g. of sodium phenoxide in 20 cc. of EtOH and 0.17 g. of (II) was refluxed for 1 hr. The mixture was worked up as in the case of (III). White plates from benzene, m.p. 163~164°. *Anal.* Calcd. for $C_{11}H_7ON_3S$: C, 57.63; H, 3.08. Found: C, 58.26; H, 3.29.

2-Hydroxy-5-chlorothiazolo[5,4-*d*]pyrimidine (VI)—(I) (2 g.) was suspended in 100 cc. of dioxane, and $COCl_2$ gas was introduced for 15 mins. under heating. After the solvent was removed by distillation, the residue was dissolved in 30 cc. of dil. NH_4OH, decolorized with charcoal, filtered, the filtrate was acidified with AcOH, and the separated crystals were collected. Recrystallization from EtOH gave white prisms, m.p. 247~248° (decomp.). Yield, 1.8 g. A small amount of the product was obtained from the above filtrate. *Anal.* Calcd. for $C_5H_2ON_3ClS$: C, 32.00; H, 1.07. Found. C, 32.29; H, 1.16.

2-Hydroxy-5-ethylthio-thiazolo[5,4-*d*]pyrimidine (VII)—To a solution of 0.05 g. of Na in 30 cc. of dehyd. EtOH and 0.14 g. of EtSH, 0.19 g. of (VI) was added and the reaction mixture was refluxed for 16 hrs. After removal of the solvent, a small amount of H_2O was added to the residue which was acidified with AcOH, the separated crystals were collected, and recrystallized from EtOH to white

4) Part V: This Bulletin, **6**, 349(1958).
5) W. H. Daivis, *et al.*: J. Chem. Soc., **1944**, 11.
6) All m.p.s are uncorrected.
7) Part I: This Bulletin, **6**, 334(1958).

prisms, m.p. 222°. Yield, 0.15 g. *Anal.* Calcd. for $C_7H_7ON_3S_2$: C, 39.42; H, 3.29. Found. C, 39.93; H, 3.43.

2-Hydroxy-5-mercaptothiazolo[5,4-*d*] pyrmidine (IX)—Phosgene gas was introduced into a suspension of 3.3 g. of (VIII) in 150 cc. of dioxane under heating to form a red solution. This was worked up as in the case of (VI) and then directly converted into the ethylthio derivative owing to the difficulty in purifying (IX).

5-Ethylthio Derivative—This was prepared from 0.37 g. of (IX) in hydr. EtOH containing 0.23 g. of KOH and 0.22 g. of EtBr. The reaction mixture was warmed for a short time and after standing for 1 hr., the reaction mixture was concentrated. The residue was treated with 10 cc. of H_2O and acidified with AcOH. The product thus obtained was recrystallized from EtOH to white prisms, undepressed on admixture with (VII), m.p. 222°. Yield, 0.33 g.

Reaction of 2,5-Dimercaptothiazolo[5,4-*d*] pyrimidine (X) with 1 Mole of EtBr—(X) (0.2 g.) was dissolved in a solution of 0.12 g. of KOH in 20 cc. of hydr. EtOH, 0.11 g. of EtBr was added, and the reaction mixture was warmed for a short time. After concentrating the reaction mixture, the residue was treated with 15 cc. of H_2O, the minute amount of insoluble product was removed by extraction with ether, the rest was decolorized with charcoal, and the filtrate was acidified with AcOH to give golden yellow crystals. The product was 2-mercapto-5-ethylthio-thiazolo[5,4-*d*] pyrimidine (XI) which was determined by the following experiment. It was recrystallized from EtOH to light yellow prisms, m.p. 218~219°. Yield, 0.19 g. *Anal.* Calcd. for $C_7H_7N_3S_3$: C, 36.65; H, 3.07. Found: C, 37.29; H, 3.25.

Oxidation of (XI) with H_2O_2—(XI) (0.3 g.) was dissolved in 5 cc. of 0.5*N* KOH and this was treated with H_2O_2 under cooling. After standing for a short time, the deposited white crystals were collected and recrystallized from EtOH to white prisms; this was identical with 2-hydroxy-5-ethylthio-thiazolo[5,4-*d*] pyrimidine (VII). Yield, 0.18 g.

Reaction of 2,7-Dimercaptothiazolo[5,4-*d*]pyrimidine (XIII) with 1 Mole of EtBr—The reaction was carried out by the same way as in the case of (XI). The product thus obtained was 2-mercapto-7-ethylthio-thiazolo[5,4-*d*]pyrimidine (XIV) and owing to the unstability of the product, it was derived to the next product without purification.

Oxidation of (XIV) with H_2O_2—The operation was carried out as in the above-mentioned process. The product was recrystallized from EtOH to colorless needles or scales, m.p. 209~210°. This was 2-hydroxy-7-ethylthio-thiazolo[5,4-*d*] pyrimidine (XV). *Anal.* Calcd. for $C_7H_7ON_3S_2$: C, 39.42; H, 3.29. Found: C, 39.74; H, 3.46.

2-Hydroxy-7-chlorothiazolo[5,4-*d*] pyrimidine (XVII)—Prepared by the same way from (XVI) and $COCl_2$ as in the case of (VI). White prisms (from EtOH), m.p. 225° (decomp.). *Anal.* Calcd. for $C_5H_2ON_3ClS$: C, 32.00; H, 1.07. Found: C, 32.41; H, 1.23.

2-Hydroxy-7-mercaptothiazolo[5,4-*d*] pyrimidine (XVIII)—A mixture of 0.19 g. of (XVII) and 0.25 g. of KSH was warmed at 50° for 2 hrs. with stirring, the reaction mixture was acidified with AcOH and the separated precipitate was collected. The crude product was dissolved in dil. NH_4OH, decolorized with charcoal, filtered, and the filtrate was acidified with AcOH. The product underwent change during purification.

Preparation of 2-Hydroxy-7-ethylthio-thiazolo[5,4-*d*] pyrimidine (XV) by Another Route—i) 0.18 g. of (XVIII) was converted into (XV) by treatment with 0.1 g. of EtBr in alkaline medium in a manner similar to the preparation of (VII) from (IX). The product, m.p. 209°, was identical with the sample obtained by the oxidation of (XIV).

ii) A method similar to the preparation of (VII) from (VI) was followed. By refluxing 0.19 g. of (XVII) in 30 cc. of EtOH containing 0.05 g. of Na and 0.14 g. of EtSH for 3 hrs., there was obtained a product which was the same as that prepared as in i). Yield, 0.15 g.

2-Hydroxythiazolo[5,4-*d*] pyrimidine (XX)—(XIX) (0.5 g.) was cyclized by introducing $COCl_2$ gas into dioxane solution under heating and the resulting product was collected by filtration. The salt was neutralized by dissolving in 50 cc. of dehyd. EtOH and adding a slight excess of $NaHCO_3$. The mixture was filtered and the filtrate was evaporated. Recrystallization from acetone gave white grains (prism-like), m.p. 211~212°. Yield, 0.48 g. *Anal.* Calcd. for $C_5H_3ON_3S$: C, 39.21; H, 1.97. Found: C, 39.59; H, 2.29.

2-Thiocyanothiazolo[5,4-*d*] pyrimidine (XXII)—To a solution of 0.35 g. of (XXI) in 20 cc. of H_2O containing 0.12 g. of KOH, there was added dropwise 0.22 g. of BrCN in 150 cc. of H_2O under stirring. After a continued stirring of 30 mins. at room temp., the separated white precipitate was collected and recrystallized from benzene to slightly colored needles (green-yellow); on heating it gradually decomposed above 190°. Yield, almost theoretical. *Anal.* Calcd. for $C_6H_2N_4S_2$: C, 37.10; H, 1.04. Found: C, 37.57; H, 1.07.

Reaction of 2-Thiocyanothiazolo[5,4-*d*] pyrimidine (XXII) with Sodium Ethoxide—(XXII) (0.6 g.) was added at once to a stirred solution of EtONa (0.15 g. of Na in 20 cc. of EtOH) under ice cooling. After further 1 hr. at 0°, the reaction mixture was evaporated, 10 cc. of H_2O was added to the residue, and the separated insoluble fraction was extracted with ether. The oily product from the extract was

2-ethylthio-thiazolo[5,4-*d*]pyrimidine (XXIII), colorless needles (from petr. ether), m.p. 60°; yield, 0.05~0.15 g. *Anal.* Calcd. for $C_7H_7N_3S_2$: C, 42.51; H, 3.72. Found: C, 42.82; H, 3.81.

Acidification of the aqueous layer with AcOH gave yellow needles which was identified as 2-mercaptothiazolo[5,4-*d*]pyrimidine (XXI), m.p. and mixed m.p. with a specimen prepared in Part V[4] of this series, ca.287° (decomp.). Yield, 0.28~0.4 g. When less than 2 moles of EtONa was used, the yield of (XXI) was rather increased.

Desulfurization of 2-Mercaptothiazolo[5,4-*d*]pyrimidine (XXI)—To 0.2 g. of (XXI), 10 cc. of H_2O, 2 cc. of conc. NH_4OH, and 2 g. of Raney Ni catalyst were added, this mixture was refluxed for 2 hrs. with stirring, and then filtered. The residual Ni was washed with boiling H_2O. The washings and the filtrate from the reaction mixture were combined and extracted with ether. From the dried extract there were obtained white needles which melted at 143~144°, which was identical with thiazolo[5,4-*d*]-pyrimidine reported in Part V.[4]

Summary

5-Chlorothiazolo[5,4-*d*]pyrimidine was prepared from 2-chloro-4-mercapto-5-aminopyrimidine (I) and ethyl orthoformate. Ring closure occurred by the reaction of (I), 2,4-dimercapto-5-aminopyrimidine, 4-mercapto-5-amino-6-chloropyrimidine, or 4-mercapto-5-aminopyrimidine with phosgene, and the corresponding 2-hydroxythiazolo[5,4-*d*]pyrimidine derivatives (5-chloro-, 5-mercapto-, 7-chloro-) and 2-hydroxythiazolo[5,4-*d*]pyrimidine itself were respectively obtained.

When dimercaptothiazolo[5,4-*d*]pyrimidines possessing substituents in 2- and 5-positions or in 2- and 7-, were reacted with one mole of ethyl bromide in alkali, substitution occurred only in positions 5- and 7- of the thiazolo[5,4-*d*]pyrimidine ring. 2-Thiocyanothiazolo[5,4-*d*]-pyrimidine reacted with sodium ethoxide to give 2-mercaptothiazolo[5,4-*d*]pyrimidine. Thiazolo[5,4-*d*]pyrimidine was obtained by desulfurization of 2-mercaptothiazolo[5,4-*d*]-pyrimidine with Raney nickel.

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