CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 15 No. 6 June 1967

[Chem. Pharm. Bull. 15(6) 731~739 (1967)]

UDC 547.859.07

88. Akira Takamizawa, Kentaro Hirai, Teruyuki Ishiba, and Yoshihiro Matsumoto: Studies on Pyrimidine Derivatives and Related Compounds. XLIV.*1 Syntheses of Thiazolo[3,2-*a*]pyrimidine Derivatives.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**2)

Ethyl 2-thio-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Ⅷ) and 2-thio-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (XXⅢ) were used for various kinds of condensation reactions. From the reaction with ethylene dibromide, Ⅷ gave biscompound Ⅸ, and with phenacylbromide and *p*-chlorophenacylbromide thiazolo[3,2-*a*]pyrimidine derivatives were obtained. In this reaction, 5*H*-thiazolo[3,2-*a*]pyrimidine derivative (XⅢ, XⅦ, XXV) and the 7*H*-isomer (XIV, XⅧ, XXVI) were obtained separately. The structures of these isomers were assigned from NMR and UV spectra.

In this thiazolo[3,2-*a*]pyrimidine syntheses, 3-hydroxy compounds (Ⅻ, XVI, XXIV) were considered to be the key intermediates.

(Received July 11, 1966)

We have previously[1~5] reported on the condensation reactions of 2-methoxymethylene-3-ethoxypropionitrile (I) and ethyl 2-methoxymethylene-3-ethoxypropionate (Ⅱ) with urea and thiourea derivatives. It has also been described that 2-thio-1,2,3,4-tetrahydropyrimidine derivatives were readily obtained by the rearrangement of 2-amino-1,3-thiazine derivatives.[5]

Attempt to obtain the biologically active compounds led to a investigation about the syntheses of the cyclized compounds derived from 2-thio-1,2,3,4-tetrahydropyrimidine derivatives.

Gill, *et al.*[6] reported that 2-thio-4,4,6-trimethyl-1,4-dihydropyrimidine (Ⅲ) easily condensed with ethylenedibromide to give 5,7,7-trimethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]-pyrimidine (Ⅳ), but with phenacylbromide it gave 2-amino-4-phenylthiazole (Ⅴ) and mesityl oxide (Ⅵ).

Ethyl 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Ⅶ)[2] was converted into 2-thio-derivative Ⅷ by the reaction with phosphorus pentasulfide in pyridine, and Ⅷ

---

*1 Part XLⅢ: A. Takamizawa, K. Hirai, M. Ishihara (*neé* Hata), T. Ishiba, A. Takase, S. Sumimoto: Yakugaku Zasshi, **87**, 274 (1967).

*2 Sagisu, Fukushima-ku, Osaka (高見沢 映, 平井健太郎, 石破暉之, 松本至博).

1) A. Takamizawa, K. Hirai, Y. Sato, K. Tori: J. Org. Chem., **29**, 1740 (1964).
2) A. Takamizawa, K. Hirai: This Bulletin, **12**, 804 (1964).
3) *Idem*: *Ibid.*, **12**, 1418 (1964).
4) *Idem*: *Ibid.*, **13**, 681 (1965).
5) *Idem*: J. Org. Chem., **30**, 2290 (1965).
6) N. Gill, N. K. Ralhan, H. S. Sacholev, K. S. Narang: J. Org. Chem., **26**, 968 (1961).

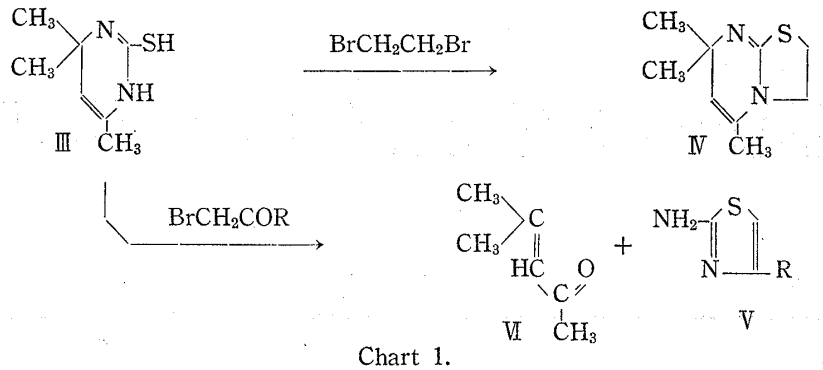

Chart 1.

was allowed to react with ethylenedibromide to afford the bis-compound IX instead of the cyclized compound. IX exhibited NH band in infrared spectrum, acetylation of IX with acetic anhydride in pyridine gave acetate X, and the reaction with sodium hydride and methyl *p*-tosylate in dimethylformamide afforded the methylation product XI. Structural assignments of these compounds were made from the value of their elemental analyses and molecular weight determination.

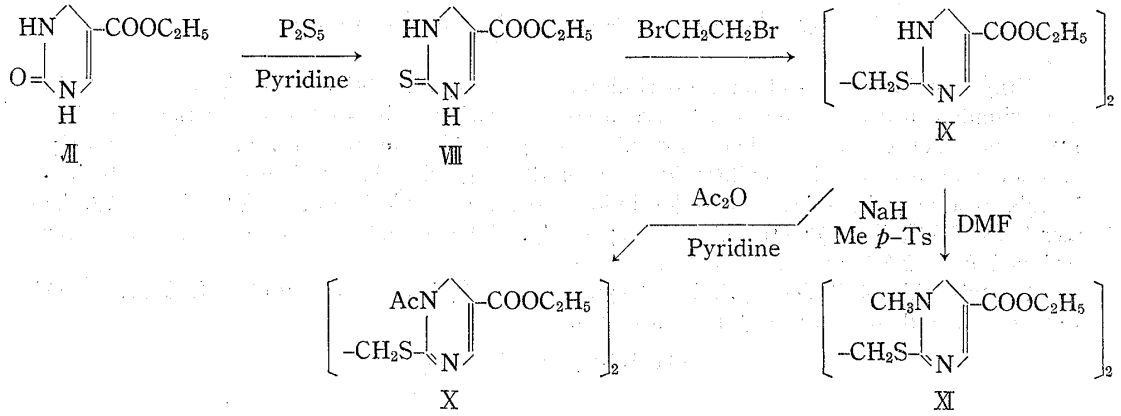

Chart 2.

The reaction of VIII with phenacylbromide in ethanol for a short time gave the compound XII in good yield, while the yellow crystals of m.p. 125~127° (decomp.) were obtained from the reaction in glacial acetic acid. These yellow crystals were found later to be a mixture of ethyl 3-phenyl-5*H*-thiazolo-[3,2-*a*]pyrimidine-6-carboxylate (XIII) and the 7*H*-isomer XIV. The elemental analysis of XII showed the value having one mole of water more than those of XIII or XIV. When XII was refluxed in glacial acetic acid, a mixture of XIII and XIV was obtained. These facts suggested that XII would be a precursor of XIII and XIV. Actually, in some cases, XII and a mixture of XIII and XIV were obtained together. After refluxing VIII and phenacylbromide in ethanol for 8.5 hours, the reaction mixture was subjected to column chromatography on alumina with ethyl acetate to afford XII in 12% and a mixture of XIII and XIV in 11% yields. Similarly, heating in glacial acetic acid for 2 hours also gave XII in 8% and a mixture of XIII and XIV in 18% yields. Infrared spectrum of XII exhibited no carbonyl band due to benzoyl group, but broad OH band was shown. The structure of XII was best considered to be ethyl 3-hydroxy-3-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate from above observation.

The yellow crystals of m.p. 125~127° (decomp.) showed two spots on alumina thin-layer chromatogram, and NMR*[3] spectrum of these crystals also exhibited that these

*[3] NMR spectra were taken in $CDCl_3$ solution at 60 Mc. by Varian A-60 NMR Spectrometer. Tetramethylsilane was used as an internal reference.

were a mixture of two isomers in a ratio of about 2:1. This mixture was subjected to column chromatography on alumina with chloroform to afford two crystalline products, m.p. 140° (decomp.) (XIII) and m.p. 119° (decomp.) (XIV), separately. The assignments of the structures of these compounds were made as follows. NMR spectrum of XIII showed the signals of methylene and methylidyne protons at 5.40 and 3.73τ, respectively. On the other hand, those of XIV were seen at 5.52 and 4.18τ, respectively (Fig. 1). If the thiazolo[3,2-*a*]pyrimidine rings of these compounds are situated at the co-plane to the benzene rings, the signal of C-5-methylene protons of ethyl 3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XIII) should be at a lower field than that of C-7-methylene protons of the 7*H*-isomer XIV owing to the anisotropic effect of the benzene ring, and C-2-methylidyne protons of XIII, which are located at a more extended conjugation system than those of XIV, also should resonate at a lower field than that of XIV does. Therefore, compound XIII, whose nuclear magnetic resonance (NMR) spectrum showed the signals of methylene and methylidyne protons at a low field than those of XIV, was formulated as ethyl 3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate, and also, XIV was assigned to the 7*H*-isomer.

On heating XII with polyphosphoric acid, XIII was readily obtained. This dehydration reaction was also carried out smoothly by the action of thionyl chloride in pyridine to give XIII. In order to confirm the structure of XIII, II condensed with 2-amino-4-phenylthiazole (V) in ethanol in the presence of hydrochloric acid to give XIII. Hydrolysis of XIII with ethanolic potassium hydroxide afforded the acid XV.

Similar reaction of VIII with *p*-chlorophenacylbromide in ethanol afforded ethyl 3-*p*-chlorophenyl-3-hydroxy-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XVI), while in glacial acetic acid XVI and a mixture of XVII and XVIII were obtained together. This mixture was subjected to the column chromatography on alumina and yellow

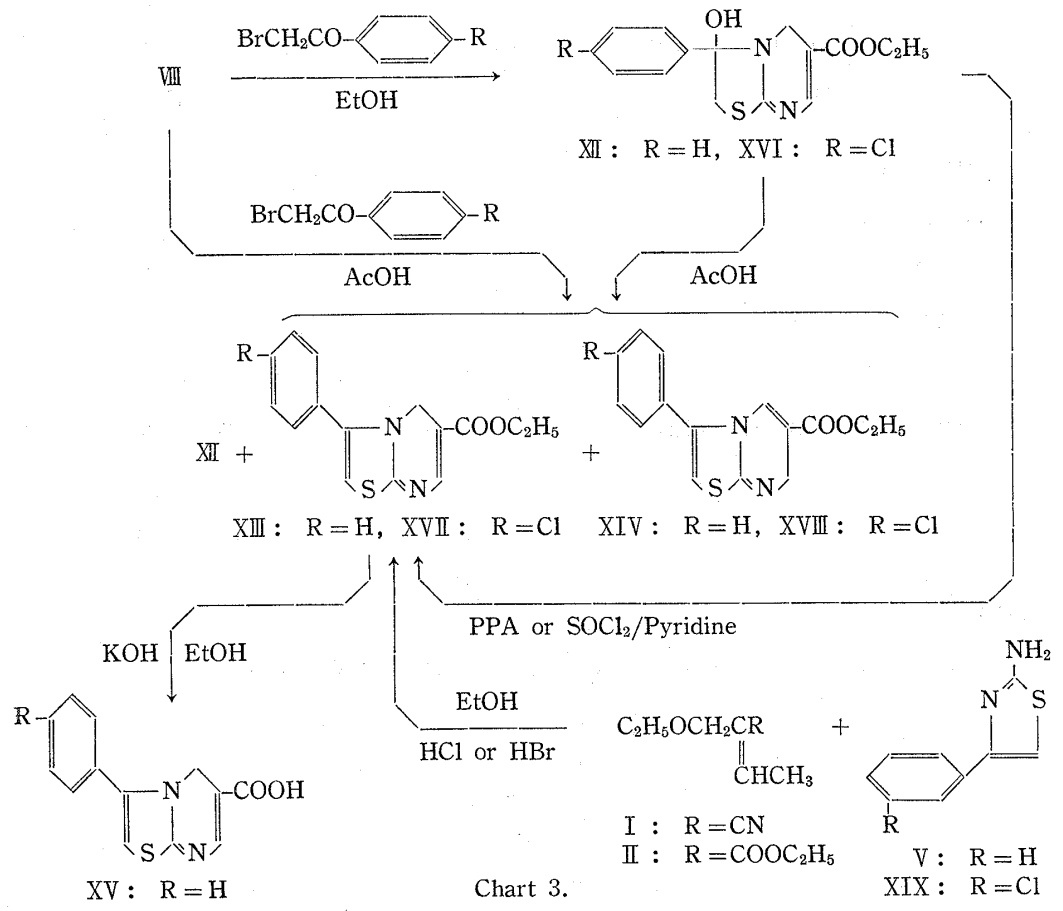

Chart 3.

crystals of m.p. 141~142° (decomp.) (XVII) and pale yellow crystals of m.p. 118~120° (decomp.) (XVIII) were obtained separately. NMR spectrum of XVII showed the signals of methylene and methylidyne protons at 5.38 and 3.72τ, respectively, while XVIII showed those at 5.50 and 4.13τ, respectively. Based on the reason described above, XVII was formulated as ethyl 3-*p*-chlorophenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate, and XVIII was assigned to the 7*H*-isomer. On heating XVI in glacial acetic acid under reflux, a mixture of XVII and XVIII was yielded. Dehydration reaction of XVI proceeded smoothly by heating with polyphosphoric acid to give XVII in good yield. XVII was also obtained by the condensation reaction of II with 2-amino-4-*p*-chlorophenylthiazole (XIX) in ethanol in the presence of hydrochloric acid. When VIII reacted with chloroacetone in glacial acetic acid, the condensation product XX was obtained as a sole product. The condensation reaction of II with 2-amino-4-methylthiazole (XXI) also gave the same product XX.

This synthetic reaction for obtaining thiazolo[3,2-*a*]pyrimidine derivatives was applied to 2-thio-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (XXIII). XXIII was prepared from 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (XXII).[1] The reaction of XXIII with phenacylbromide in ethanol proceeded analogously to the ester VIII to give 3-hydroxy-3-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (XXIV). In glacial acetic acid, however, XXIII reacted with phenacylbromide to afford XXIV and a mixture of XXV and XXVI. This mixture of XXV and XXVI was also obtained by the heating XXIV in glacial acetic acid, and after column chromatography on alumina, XXV and XXVI was obtained separately. NMR spectrum of XXV exhibited the methylene and methylidyne protons at 5.43 and 3.68τ, respectively, while XXVI exhibited those at 5.13 and 4.13τ, respectively. On the basis of the reason described above, XXV was formul-

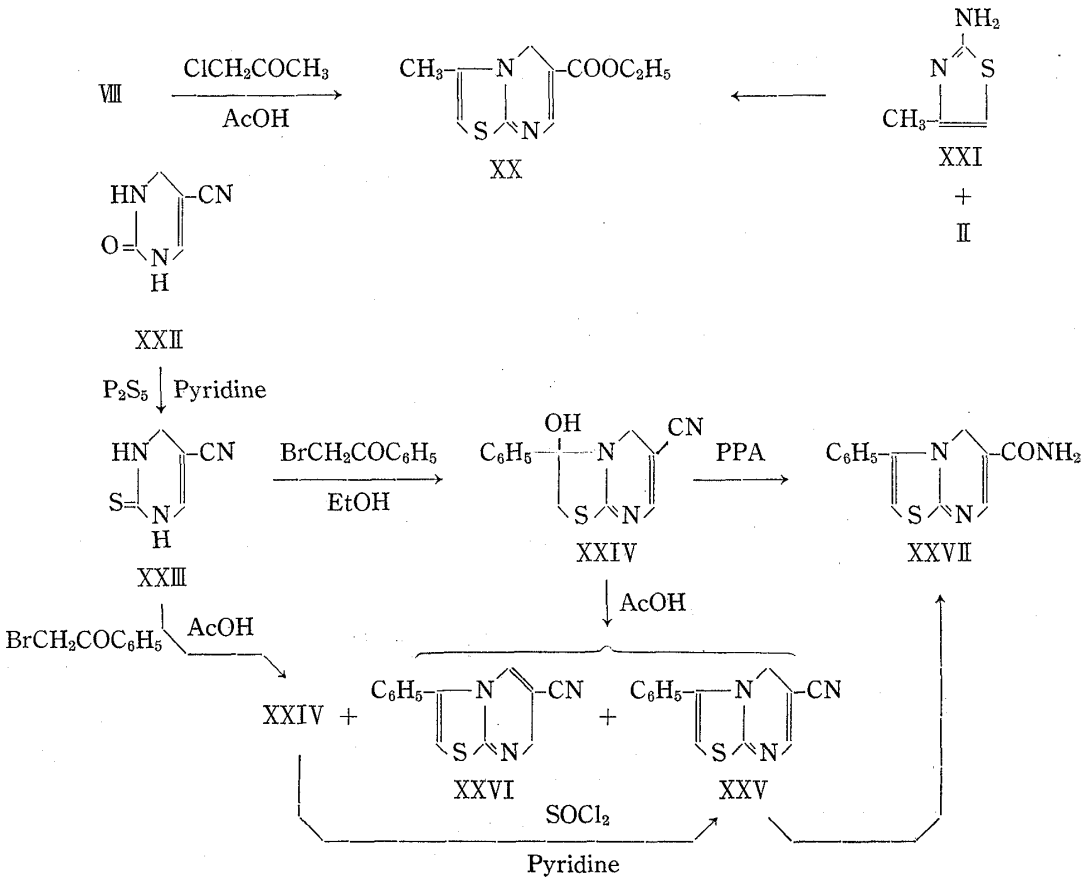

Chart 4.

ated as 3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile, and XXVI was assigned to the 7*H*-isomer.

When XXIV was heated with polyphosphoric acid, the amide XXVII was obtained. But the action of thionylchloride on XXIV in pyridine solution afforded the dehydration product XXV. Further treatment of XXV with polyphosphoric acid and water gave the amide XXVII. Then, it was now found that on heating XXIV with polyphosphoric acid the nitrile XXV was first formed and followed by the saponification of nitrile group with phosphoric acid to give the amide XXVII.

A possible route to yield 5*H*-thiazolo[3,2-*a*]pyrimidine and the 7*H*-isomer by the reaction of 2-thiotetrahydropyrimidine derivatives and phenacylbromide would be shown as in Chart 5. In this route, the hydroxy compounds XII, XVI and XXIV are considered to be the key intermediates. The fact that no interconversion between 5*H*-thiazolo[3,2-*a*]pyrimidine and the 7*H*-isomer was seen under the same condition as the condensation reaction was carried out also supports this route.

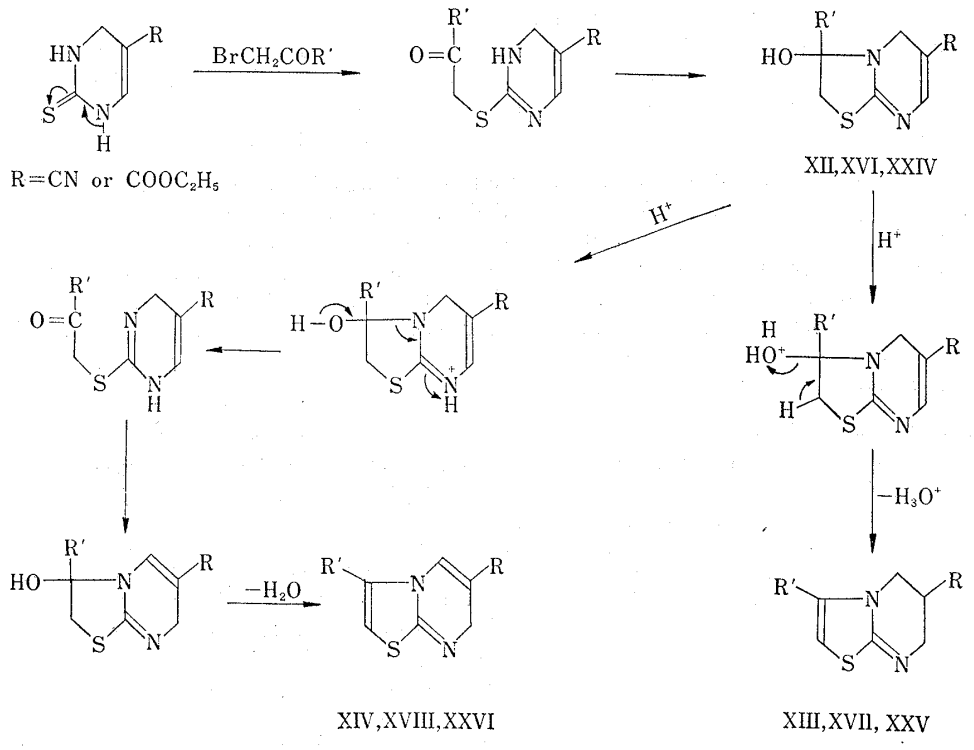

Chart 5.

Investigation of the ultraviolet spectra of thiazolo[3,2-*a*]pyrimidine derivatives obtained here revealed that 5*H*-compounds showed the strong absorption band at about 400 mμ, on the contrary, the 7*H*-isomers did not (Fig. 2, 3). These results would be ascribed to the more extended conjugation system caused by electron releasing conjugative effect of the lone pair of sulfur in 5*H*-compounds. Therefore, it is easy to distinguish the 5*H*-compounds from 7*H*-isomers by their ultraviolet spectra.

The biological test of these compounds obtained here is now in progress.

Experimental*4

Ethyl 2-Thio-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VIII)——To a solution of 1.0 g. of ethyl 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (VII)[2] in 10 ml. of pyridine, 1.0 g. of phosphorus pentasulfide was added, and refluxed for 3.5 hr. in an oil bath. After concentration of the reaction mixture *in*

*4 All melting points are uncorrected.

vacuo, H_2O was added to the residue, and 0.92 g. of the separated crystals were collected. Recrystallization from EtOH gave pale brown prisms, m.p. 224° (decomp.). *Anal.* Calcd. for $C_7H_{10}O_2N_2S$: C, 45.16; H, 5.41; N, 15.05; S, 17.22. Found: C, 45.14; H, 5.44; N, 15.13; S, 17.23. UV λ_{max}^{EtOH} mμ (log ε): 312 (4.10).

Diethyl 2,2′-(1,2-Dithioethano)bis(3,4-dihydropyrimidine-6-carboxylate) (IX)——A mixture of 0.23 g. of Ⅷ and 0.25 g. of ethylenedibromide was heated in an oil bath at 150° for 30 min. The reaction mixture was cooled and treated with dil. $NaHCO_3$. The solid so obtained was collected, washed with H_2O, and dried to yield 0.18 g. of crystals. Recrystallization from EtOH gave colorless prisms, m.p. 174° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_4N_4S_2$: C, 48.24; H, 5.57; N, 14.07; S, 16.07. Found: C, 47.99; H, 5.61; N, 13.80; S, 16.24. UV λ_{max}^{EtOH} mμ (log ε): 250, 313 (3.92, 4.10).

Diethyl 2,2′-(1,2-Dithioethano)bis(3-acetyl-3,4-dihydropyrimidine-6-carboxylate) (X)——To a solution of 0.1 g. of Ⅷ in 1.0 ml. of pyridine, 1.0 ml. of Ac_2O was added, and refluxed for 2 hr., in an oil bath. After concentration of the reaction mixture *in vacuo*, the residue was treated with ether to give 0.095 g. of yellow needles. Recrystallization from EtOH–AcOEt gave yellow needles, m.p. 165° (decomp.). *Anal.* Calcd. for $C_{20}H_{26}O_6N_4S_2$: C, 49.79; H, 5.43; N, 11.61; S, 13.26; mol. wt., 482.4. Found: C, 49.66; H, 5.76; N, 11.85; S, 13.75; mol. wt., 473 (vapor pressure osmometer method).

Diethyl 2,2′-(1,2-Dithioethano)bis(3-methyl-3,4-dihydropyrimidine-6-carboxylate) (XI)——To a solution of 0.20 g. of Ⅷ in 4 ml. of DMF, 0.08 g. of NaH (50% oil suspension) and 0.20 g. of methyl *p*-tosylate were added, and warmed at 60° for 10 min. The reaction mixture was poured into 70 ml. of H_2O, and the separated crystals were collected to yield 0.124 g. of crystals. Recrystallization from EtOH gave pale yellow prisms, m.p. 142~145° (decomp.). *Anal.* Calcd. for $C_{18}H_{26}O_4N_4S_2$: C, 50.70; H, 6.15; N, 13.14. Found: C, 50.70; H, 6.34; N, 12.79. UV λ_{max}^{EtOH} mμ (log ε): 232, 328 (4.23, 4.07).

Ethyl 3-Hydroxy-3-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XII)——To a solution of 1.035 g. of Ⅷ in 20 ml. of 95% EtOH, 1.385 g. of phenacylbromide was added, and refluxed for 45 min. The reaction mixture was concentrated *in vacuo*, the residue was treated with 10% K_2CO_3, and the separated pale yellow crystals were collected. After washing with H_2O, the crystals were dried to yield 1.67 g. (98.7%) of crystals, which was recrystallized from EtOH to give 1.45 g. (86%) of pale yellow needles, m.p. 144~145° (decomp.). *Anal.* Calcd. for $C_{15}H_{16}O_3N_2S$: C, 59.20; H, 5.30; N, 9.21; S, 10.54. Found: C, 59.06; H, 5.40; N, 9.47; S, 10.49. UV λ_{max}^{EtOH} mμ (log ε): 255, 355 (3.66, 3.81). IR ν_{max}^{Nujol} cm^{-1}: 3100~2700 (OH, broad).

XII·Hydrochloride——Free XII (0.10 g.) was dissolved in 1.0 ml. of conc. HCl to give a clear solution, after that immediately the crystals were separated. Collected crystals were recrystallized from EtOH–AcOEt to give colorless needles, m.p. 168°. *Anal.* Calcd. for $C_{15}H_{16}O_3N_2S\cdot HCl$: C, 52.86; H, 5.03; N, 8.22; S, 9.41; Cl, 10.41. Found: C, 52.52; H, 5.16; N, 8.33; S, 9.49; Cl, 10.85.

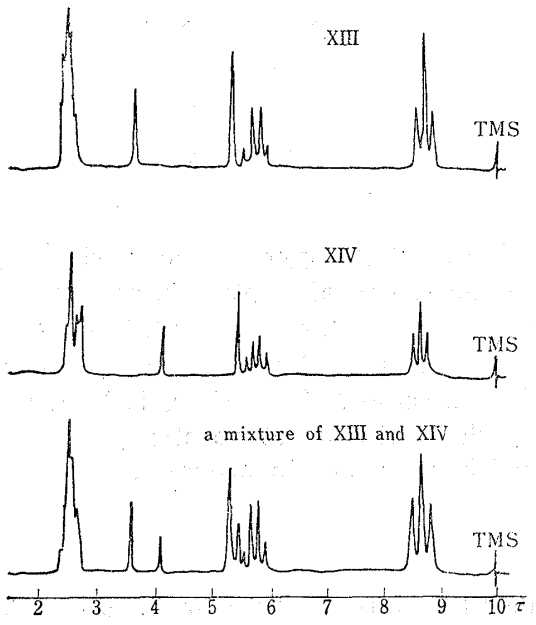

Fig. 1. NMR Spectra of XIII, XIV, and a Mixture of XIII and XIV in $CDCl_3$ at 60 Mc.

Ethyl 3-Phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XIII) and Ethyl 3-Phenyl-7*H*-thiazolo[3,2-*a*]-pyrimidine-6-carboxylate (XIV)——i) A solution of 1.40 g. of Ⅷ and 1.60 g. of phenacylbromide in 15 ml. of glacial AcOH was heated on the steam bath for 3.5 hr. The reaction mixture was concentrated *in vacuo*, and the residue was treated with ether to give 2.40 g. (87%) of yellow solid. Recrystallization from EtOH gave colorless needles, m.p. 219~223° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}O_2N_2S\cdot HBr$: C, 49.07; H, 4.12; N, 7.63; S, 8.74; Br, 21.77. Found: C, 48.93; H, 4.44; N, 7.81; S, 8.50; Br, 21.53.

Hydrobromide was treated with dil. $NaHCO_3$ and the separated crystals were collected. Recrystallization from EtOH gave yellow prisms, m.p. 125~127° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}O_2N_2S$: C, 62.93; H, 4.93; N, 9.79; S, 11.20. Found: C, 62.77; H, 5.22; N, 9.77; S, 11.04. TLC (Al_2O_3, $CHCl_3$) showed two spots. NMR spectrum also exhibited that these were a mixture of two isomers (Fig. 1). This product was subjected to alumina column chromatography with $CHCl_3$ and two fractions corresponding to the spots on TLC were obtained. The fraction corresponding to upper spot on TLC afforded pale yellow prisms (XIV), m.p. 121~123° (decomp.). *Anal.* Found: C, 62.50; H, 4.77; N, 9.55; S, 11.99. UV λ_{max}^{EtOH} mμ (log ε): 238, 360 (4.27, 3.76). NMR (τ) in $CDCl_3$: 5.52 (C-7-H_2), 4.18 (C-2-H).

The fraction corresponding to lower spot afforded yellow plates (XIII), m.p. 140~142° (decomp.).*5 *Anal.* Found: C, 63.03; H, 5.15; N, 9.64; S, 11.24. UV λ_{max}^{EtOH} mμ (log ε): 398 (3.91). NMR (τ) in $CDCl_3$: 5.40 (C-5-H_2), 3.73 (C-2-H).

ii) A mixture of 0.383 g. of VIII and 0.410 g. of phenacylbromide in 20 ml. of abs. EtOH was refluxed for 8.5 hr. The reaction mixture was concentrated *in vacuo*, the residue was added 10% K_2CO_3, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, evaporated, and the residue was recrystallized from EtOH–AcOH to give 0.078 g. (12%) of XII. The filtrate was concentrated to give 0.067 g. (11%) of orange yellow prisms (a mixture of XIII and XIV). Identification was made by comparison of IR spectra with those of the compounds obtained above.

iii) A mixture of 0.40 g. of VIII and 0.43 g. of phenacylbromide in 2 ml. of glacial AcOH was heated on a steam bath for 2 hr. The reaction mixture was concentrated *in vacuo*, the residue was added 10% K_2CO_3, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, evaporated, and the residue was subjected to the column chromatography on Al_2O_3 with $CHCl_3$. The crystals obtained from first fraction were recrystallized from benzene–petroleum ether to give 0.11 g. (18%) of orange yellow prisms, m.p. 120~123° (a mixture of XIII and XIV). The crystals obtained from the MeOH elute was recrystallized from EtOH to give 0.05 g. (8%) of pale yellow needles (VIII).

iv) A solution of 0.15 g. of XII hydrobromide in 2 ml. of glacial AcOH was heated on a steam bath for 1 hr. The reaction mixture was concentrated *in vacuo*, the residue was added dil. K_2CO_3, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, evaporated, and the residue was subjected to the column chromatography on Al_2O_3 to give a mixture of XIII and XIV.

Ethyl 3-Phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XIII)——i) A mixture of 0.2 g. of XII and 5.0 g. of polyphosphoric acid (PPA) was heated on a steam bath for 10 min. To the reaction mixture, H_2O was added, neutralized with NaOH and K_2CO_3 solution, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, and evaporated *in vacuo* to leave orange red solid. Treatment of this residue with petroleum ether gave 0.145 g. (78%) of orange red crystals. Recrystallization from benzene–petroleum ether gave pale yellow needles, which were confirmed to be XIII by the comparison of IR spectrum with that of the product obtained above.

ii) To a suspension of 1.45 g. of XII and 2.2 g. of pyridine in 20 ml. of $CHCl_3$, 0.82 g. of $SOCl_2$ was added dropwise with stirring in an ice bath.

Stirring was continued for 15 min., and the reaction mixture was filtered on charcoal. The filtrate was

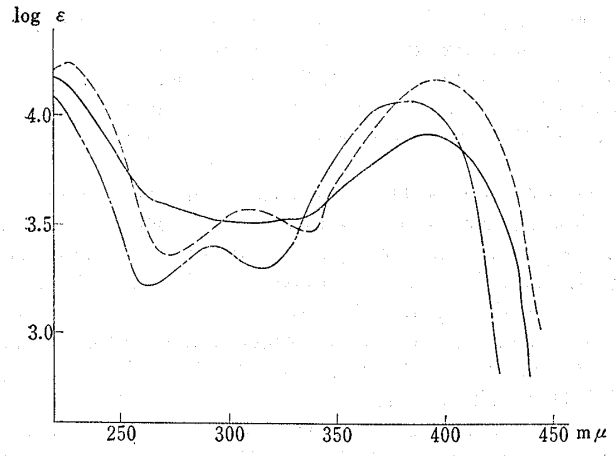

Fig. 2. UV Spectra of XIII, XVII, and XXV in EtOH.

XIII -------- XVII
XXV

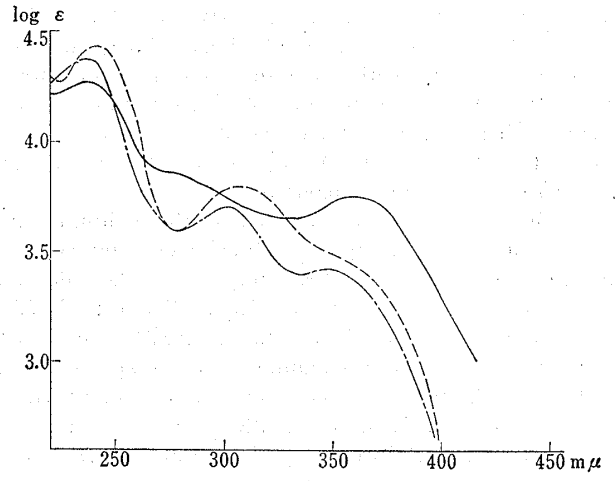

Fig. 3. UV Spectra of XIV, XVIII, and XXVI.

XIV -------- XVIII
XXVI

evaporated *in vacuo* to leave the yellow needles, 1.22 g. (89%), which were proved to be identical with XIII by the comparison of IR spectra and thin-layer chromatograms.

iii) The solution of 1.2 g. of 2-amino-4-phenylthiazole, 1.3 g. of II, and 1 ml. of conc. HCl in 150 ml. of EtOH was refluxed for 10 hr. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in $CHCl_3$, and washed with dil. K_2CO_3. The $CHCl_3$ layer was dried over $MgSO_4$, evaporated, and the residue was purified with Al_2O_3 column chromatography to give 0.40 g. (20%) of yellow needles, which were proved to be identical with XIII by the comparison of IR spectra and thin-layer chromatograms.

iv) A solution of 4.8 g. of 2-amino-4-phenylthiazole (V), 5.2 g. of II, and 4 ml. of conc. HBr in 600 ml.

*5 On recrystallization from ether pale yellow needles, m.p. 121~122° (decomp.), were obtained. These showed different IR spectrum in Nujol mull, while in $CHCl_3$ solution these showed the same spectrum as the crystals of m.p. 140~142° (decomp.).

of EtOH was refluxed for 15 hr. The reaction mixture was concentrated *in vacuo*, the residue was treated with ether, and recrystallized from EtOH to give 1.65 g. of colorless needles, m.p. 238~239° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}O_2N_2S \cdot HBr$: C, 49.05; H, 4.12; N, 7.62; S, 8.73; Br, 21.77. Found: C, 49.34; H, 4.37; N, 7.59; S, 8.85; Br, 22.05.

The solution of 1.0 g. of XIII • HBr in 20 ml. of glacial AcOH was refluxed in an oil bath for 2.5 hr. After cooling, separated crystals were collected to recover the starting material. No isomer was detected on thin-layer chromatography (TLC).

3-Phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic Acid (XV)——To a solution of 2.0 g. of XIII in 150 ml. of 70% EtOH, 2.8 g. of KOH was added, and refluxed for 40 min. The reaction mixture was treated with active charcoal and concentrated. The residue was dissolved in 100 ml. of H_2O, washed with $CHCl_3$, and filtered on charcoal. The filtrate was neutralized with 20% AcOH to separate the crystals, which were collected and dried to give 1.1 g. of yellow prisms, m.p. 125~126° (decomp.). *Anal.* Calcd. for $C_{13}H_{10}O_2N_2S \cdot H_2O$: C, 56.52; H, 4.38; N, 10.14; S, 11.58; H_2O, 6.53. Found: C, 57.19; H, 4.50; N, 10.42; S, 12.07; H_2O, 6.73.

Ethyl 3-*p*-Chlorophenyl-3-hydroxy-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XVI)——A solution of 2.0 g. of VIII and 3.0 g. of *p*-chlorophenacylbromide in 30 ml. of 90% EtOH was refluxed for 20 min. The reaction mixture was concentrated *in vacuo*, the residue was added dil. $NaHCO_3$ solution, and the separated crystals were collected, yield 4.2 g. Recrystallization from EtOH gave hydrobromide as colorless needles, m.p. 226° (decomp.). *Anal.* Calcd. for $C_{15}H_{15}O_3N_2SCl \cdot HBr$: C, 42.90; H, 3.84; N, 6.67; S, 7.64. Found: C, 42.96; H, 3.94; N, 6.64; S, 7.90.

Above hydrobromide was treated with dil. KOH to give yellow crystals, which were recrystallized from EtOH to give yellow needles, m.p. 147~148° (decomp.). *Anal.* Calcd. for $C_{15}H_{15}O_3N_2SCl$: C, 53.17; H, 4.46; N, 8.26; S, 9.46; Cl, 10.47. Found: C, 52.85; H, 4.66; N, 7.98; S, 9.46; Cl, 10.64. UV λ_{max}^{EtOH} mμ (log ε): 222, 255, 352 (4.21, 3.81, 3.95).

Ethyl 3-*p*-Chlorophenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XVII) and Ethyl 3-*p*-Chlorophenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XVIII)——i) A mixture of 1.5 g. of VIII and 2.0 g. of *p*-chlorophenacylbromide in 30 ml. of glacial AcOH was heated in a steam bath for 4 hr. After cooling, separated crystals were collected, and washed with ether to give 2.2 g. of XVI·HBr. The filtrate was concentrated *in vacuo*, and the residue was treated with ether and Me_2CO to give 0.80 g. of crystals, which were recrystallized from EtOH to give a mixture of XVII·HBr and XVIII·HBr as yellow needles, m.p. 242~243° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_2N_2SCl \cdot HBr$: C, 44.84; H, 3.51; N, 6.97; S, 7.98; Cl, 8.83; Br, 19.89. Found: C, 44.74; H, 3.34; N, 6.91; S, 8.20; Cl, 9.10; Br, 20.08.

ii) A mixture of 1.5 g. of VIII and 2.0 g. of *p*-chlorophenacylbromide in 30 ml. of glacial AcOH was refluxed in an oil bath for 1 hr. The reaction mixture was concentrated *in vacuo*, the residue was treated with ether to give a mixture of XVII·HBr and XVIII · HBr as yellow needles, m.p. 241~242° (decomp.). Yield 2.1 g. These hydrobromides were neutralized with $NaHCO_3$ to give free base as yellow crystals, m.p. 125~130° (decomp.). TLC (Al_2O_3, $CHCl_3$) showed two spots. NMR showed this product was a mixture of XVII and XVIII in a ratio of about 3:1.

This mixture was subjected to the column chromatography on Al_2O_3 with $CHCl_3$ and two fractions corresponding to the spots on TLC were obtained. The fraction corresponding to upper spot afforded 0.25g. of pale yellow pillars (XVIII), m.p. 118~120° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_2N_2SCl$: C, 56.16; H, 4.09; N, 8.73; S, 10.00; Cl, 11.05. Found: C, 56.14; H, 4.16; N, 8.84; S, 10.08; Cl, 11.07. UV λ_{max}^{EtOH} mμ (log ε): 243, 309 (4.44, 3.81). NMR (τ) in $CDCl_3$: 5.50 (C-7-H_2), 4.13 (C-2-H).

The fraction corresponding to lower spot on TLC afforded 0.58 g. of yellow orange pillars (XXII), m.p. 141~142° (decomp.). *Anal.* Found: C, 56.18; H, 4.12; N, 8.57; S, 10.02; Cl, 11.21. UV λ_{max}^{EtOH} mμ (log ε): 310, 400 (3.57, 4.16). NMR (τ) in $CDCl_3$: 5.38 (C-5-H_2); 3.72 (C-2-H).

Ethyl 3-*p*-Chlorophenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XVII)——i) XVI·HBr (2.2 g.) was neutralized with 2% KOH, the separated crystals were collected, washed with H_2O and Me_2CO, and dried. This free base was added 15 g. of PPA and warmed on a steam bath for 10 min. to become clear solution. To the reaction mixture, 50 ml. of H_2O was added and neutralized with $NaHCO_3$ to separate crystals. Collected crystals were washed with H_2O and dried to give 1.6 g. of yellow crystals, which was recrystallized from EtOH to give yellow orange pillars, m.p. 141~142° (decomp.). These crystals were proved to be identical with XVII obtained above from the comparison of IR spectra and TLC.

ii) A solution of 21 g. of XIX, 1.7 g. of II, 1.0 ml. of conc. HCl in 100 ml. of EtOH was refluxed for 18 hr. The reaction mixture was concentrated *in vacuo*, the residue was treated with Me_2CO to give 1.2 g. of the crystals, which was neutralized with $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, evaporated, and the residue was recrystallized from benzene-petroleum ether to give 0.245 g. of yellow plates, m.p. 140~142° (decomp.), which showed the spot at the same Rf value as above XVII. IR spectrum in Nujol mull showed slightly different, but in $CHCl_3$ identical spectrum with that of above XVII. It was considered to be ascribed to the polymorphism.

Ethyl 3-Methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (XX)——i) A solution of 0.327 g. of VIII and 0.185 g. of $ClCH_2COCH_3$ in 1 ml. of glacial AcOH was heated on a steam bath for 5.5 hr. The reaction mixture was concentrated *in vacuo*, the residue was washed with ether to give 0.52 g. of crystals, which

were recrystallized from EtOH to give 0.32 g. of pale yellow crystals, m.p. 199~201° (decomp.). *Anal.* Calcd. for $C_{10}H_{12}O_2N_2S \cdot HCl$: C, 46.07; H, 5.02; N, 10.74; S, 12.30; Cl, 13.60. Found: C, 45.97; H, 5.31; N, 10.66; S, 12.45; Cl, 13.34. UV λ_{max}^{EtOH} mμ (log ε): 354, 403 (3.87, 3.75). This hydrochloride was neutralized with K_2CO_3 to give yellow prisms, m.p. 80~83° (after solidifying melted at 95~98°). *Anal.* Calcd. for $C_{10}H_{12}O_2N_2S$: C, 53.75; H, 5.39; N, 12.50; S, 14.27. Found: C, 53.82; H, 5.69; N, 12.53; S, 13.97. UV λ_{max}^{EtOH} mμ (log ε): 229, 402 (3.73, 4.15). NMR (τ) in $CDCl_3$: 7.85[d] (C-3-CH_3, J*[6] =1.0), 5.17[d] (C-5-H_2, J =0.6), 4.03[q] (C-2-H, J =1.0), 2.55[t] (C-7-H, J =0.6).

ii) A solution of 2.3 g. of 2-amino-4-methylthiazole, 3.8 g. of II, and 2.5 ml. of conc. HCl in 140 ml. of EtOH was refluxed for 13 hr. The reaction mixture was concentrated *in vacuo*, and the residue was washed with ether to give 5.2 g. of crystals. Recrystallization from EtOH gave 1.2 g. of pale yellow crystals, whose IR spectrum was identical with that of the sample obtained above i).

2-Thio-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (XXIII)——To a suspension of 6.16 g. of XXII[1] in 60 ml. of pyridine, 6.2 g. of P_2S_5 was added and refluxed in an oil bath for 3 hr. The reaction mixture was concentrated *in vacuo*, and the residue was added ice water. The separated crystals were collected, dissolved in DMF, added EtOH, and the separated crystalline powder (1.7 g.) was collected.

The filtrate was concentrated *in vacuo* and the residue was treated with EtOH to give 3.2 g. of brown powder. Since this product was hard to purify by recrystallization, it was used without further purification.

3-Hydroxy-3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-5-carbonitrile (XXIV)——To a suspension of 2.4 g. of crude XXIII in 60 ml. of 90% EtOH, 4.0 g. of phenacylbromide was added, refluxed for 3 hr., and the reaction mixture was concentrated *in vacuo*. A part of the residue was recrystallized from dil. EtOH to give pale yellow prisms, m.p. 245° (decomp.). *Anal.* Calcd. for $C_{13}H_{11}ON_3S \cdot HBr$: C, 46.16; H, 3.58; N, 12.42; S, 9.48; Br, 23.62. Found: C, 46.16; H, 3.74; N, 12.52; S, 9.71; Br, 23.33.

Above crude hydrobromide was neutralized with dil. K_2CO_3, washed, and dried. Recrystallization from dil. EtOH gave 1.05 g. of colorless pillars, m.p. 213° (decomp.) (shrinked from about 160°). *Anal.* Calcd. for $C_{13}H_{11}ON_3S$: C, 60.68; H, 4.31; N, 16.33; S, 12.44. Found: C, 60.70; H, 4.63; N, 16.08; S, 12.29.

3-Phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (XXV)——To a solution of 1.0 g. of XXIV in 20 ml. of anhyd. pyridine, 1.5 g. of $SOCl_2$ was added dropwise in ice cooling. Stirring was continued for 5 min. in an ice bath, ice water was added to the reaction mixture, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and the residue was treated with ether to give 0.54 g. of yellow prisms, which were recrystallized from EtOH to give pale yellow pillars, m.p. 123° (decomp.). *Anal.* Calcd. for $C_{13}H_9N_3S$: C, 65.25; H, 3.79; N, 17.57; S, 13.38. Found: C, 65.32; H, 3.78, N, 17.17; S, 13.13. UV λ_{max}^{EtOH} mμ (log ε): 298, 397 (3.37, 4.07). IR ν_{max}^{Nujol} (cm^{-1}): 2193 (C≡N), 1596 (C=N). NMR (τ) in $CDCl_3$: 5.43 (C-5-H_2), 3.68 (C-2-H). TLC (Al_2O_3, $CHCl_3$): Rf 0.51.

3-Phenyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide (XXVII)——i) A mixture of 1.9 g. of XXIV and 25 g. of PPA was heated on a steam bath for 15 min. to be a clear solution. To the reaction mixture, dil. NaOH was added to separate yellow crystals, which were recrystallized from dil. EtOH to give 1.15 g. of yellow needles, m.p. 197~202° (decomp.). *Anal.* Calcd. for $C_{13}H_{11}ON_3S$: C, 60.68; H, 4.31; N, 16.33; S, 12.43. Found: C, 60.75; H, 4.75; N, 16.61; S, 12.31. UV λ_{max}^{EtOH} mμ (log ε): 310, 394 (3.76, 4.06). IR spectrum showed no C≡N band.

ii) XXV (0.20 g.) and 5.0 g. of PPA was treated as above to give 0.203 g. of crystals, which were proved to be identical with XXVII obtained above by comparison of IR spectra.

XXV and 3-Phenyl-7*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (XXVI)——i) A mixture of 2.4 g. of XXIII, 4.0 g. of phenacylbromide, and 28 ml. of glacial AcOH was heated on a steam bath for 5 hr. The reaction mixture was concentrated *in vacuo*, the residue was neutralized with dil. K_2CO_3, and extracted with $CHCl_3$. Undissolved material was filtered off to give 1.5 g. of XXIV. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, and the residue was treated with ether to give yellow crystals, m.p. 118~122° (decomp.). TLC (Al_2O_3, $CHCl_3$) showed two spots at Rf 0.70 and 0.51. NMR spectrum showed that this product was a mixture of XXV and XXVI in a ratio of about 3.5:1. This mixture was subjected to the column chromatography. From the first fraction corresponding to the upper spot on TLC, 0.215 g. of yellow prisms (XXVI), m.p. 156° (decomp.), was obtained. *Anal.* Calcd. for $C_{13}H_9N_3S$: C, 65.25; H, 3.79; N, 7.57; S, 13.38. Found: C, 65.28; H, 3.86; N, 17.83; S, 13.86. UV λ_{max}^{EtOH} mμ (log ε): 237, 301 (4.39, 3.74). TLC (Al_2O_3, $CHCl_3$): Rf 0.70. NMR (τ) in $CDCl_3$: 5.62 (C-7-H_2), 4.13 (C-2-H), 3.07 (C-5-H).

From the fraction corresponding to lower spot, 0.82 g. of yellow prisms, m.p. 124° (decomp.) was obtained. Identity with XXV obtained above was proved by the comparison of TLC and IR spectra.

ii) A solution of 1.0 g. of XXIV·HBr in 20 ml. of glacial AcOH was refluxed in an oil bath for 2 hr. The reaction mixture was concentrated *in vacuo*, the residue was neutralized by dil. K_2CO_3, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, evaporated, and the residue was subjected to the column chromatography on Al_2O_3 with $CHCl_3$ to give 0.218 g. of XXV and 0.081 g. of XXVI.

The authors are grateful to Dr. K. Takeda, Director of this laboratory, for his encouragement throughout this work. Thanks are also due to members of analytical room of this laboratory for elementary analyses.

*[6] Coupling constants are expressed in c.p.s.