Studies on Pyrimidine Derivatives and Related Compounds. XLI.[1] Reaction of Diethyl Benzoylphosphonate with Thiamine (Takamizawa Reaction 3)

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Detailed investigation of the reaction of thiamine (I) (Chart I) with diethyl benzoylphosphonate (II) revealed that 1-phenyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′,4,5]pyrimido[2,3-*c*][1,4]thiazine (III) was obtained in about 90% yield from zwitterion-type thiamine (XIV) through a novel reaction. The tricyclic compound (III) was hydrolyzed to give 2-phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine (VI). In this reaction, deuterioamino-O-benzoylthiamine (X) produced the reaction product XI substituted by deuterium at the 1 position. The tricyclic compound (VIII) was synthesized by alternative route and the structure of this compound was confirmed. Possible mechanisms of this reaction are described.

In the previous communication,[2] we reported that 2-phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine (VI) was obtained from the reaction of "neutral form thiamine" with diethyl benzoylphosphonate (II). This reaction involved a novel conversion of thiazolium salt into 1,4-thiazine derivatives. Subsequent detailed investigation of this reaction has now revealed that "zwitterion type thiamine"[3] (XIV) should be considered instead of "neutral form thiamine" to react with II giving tricyclic structural compound, 1-phenyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′,-4,5]pyrimido[2,3-*c*][1,4]thiazine (III), followed by ring fission to VI. Therefore VI was the secondary product in this reaction. This paper deals with the results that led to the above conclusion.

To the suspension of thiamine hydrochloride (I) in dry dimethylformamide, three molar amounts of triethylamine were added, and an equimolar amount of II was allowed to react with cooling. The ultraviolet absorption spectrum of this reaction mixture begin to show a maximum at 373 mμ. This differed markedly from the spectrum of VI which gave maxima at 230 and 277 mμ. The intensity of this maximum at 373 mμ was increased with the time. At the end of the reaction, the reaction mixture was treated as described in the Experimental Section; the yellow crystals of III, mp 207–208° dec, were obtained in a good yield (86%). The value of the elemental analysis of III agreed with that for $C_{19}H_{20}N_4OS$, ultraviolet spectrum exhibited the maximum at 373 mμ, and no NH and carbonyl bands were observed in its infrared spectrum.

This would indicate that III has a similar structure to thiochrome (XIII)[4] [λ_{max}^{EtOH} 370 mμ (log ε 4.27)]. Acetylation of III gave monoacetate VIII, mp 149–150° dec, which showed C=O band at 1741 cm^{-1} and COC band at 1246 cm^{-1} in its infrared spectrum. Proton magnetic resonance (pmr) spectrum[5] of this acetate showed the signals as follows: τ 1.83 (singlet, 1 H) (pyrimidine C-6), 2.75 (singlet, 5 H) (phenyl), 4.95 and 5.12 (AB-type quartet, 2 H), 5.17 (singlet, 1 H), 6.18 (multiplet, 2 H), 7.37 (singlet, 3 H) (pyrimidine C-2-methyl), 8.00 (singlet, 3 H), 8.15 (singlet, 3H) (acetyl), 7.37 (overlapping multiplet, 2 H) (Figure 1). These results indicate that the structure of VIII should be the cyclized form of 2-phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-acetoxy)-ethyl-2,3-dihydro-4H-1,4-thiazine (VII). Then, VII was treated with phosphoryl chloride and VIII obtained as expected. The identity was confirmed by the comparison of infrared spectra between both products.

When VIII was heated in 50% ethanol VII was obtained, and in NaOH–ethanol VI was yielded. From these results, the structure of VIII was confirmed to be 1-phenyl-3-(2-acetoxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′,4,5]pyrimido[2,3-*c*][1,4]thiazine (Chart I).

Two equimolar amounts of II were allowed to react with I under anhydrous condition in the same manner as mentioned above to give III in 55.5% yield accompanied by the yellow crystals of IV, mp 196–198° dec.

The constitution of IV was $C_{26}H_{24}N_4O_2S$, ultraviolet spectrum showed the same pattern as III showed (absorption maximum was 372 mμ), and the infrared spectrum exhibited C=O and COC bands at 1719 and 1276 cm^{-1}, respectively, but no NH band was observed. On heating IV in 50% ethanol V was obtained, and in NaOH–ethanol VI was found. From these results, IV was formulated as 1-phenyl-3-(2-benzoyloxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′,4,5]pyrimido-[2,3-*c*][1,4]thiazine. The yield of IV was 34.1%.

In order to see the influence of water, O-benzoylthiamine (IX) was subjected to the same reaction with the addition of ten molar amounts of water; IV was obtained in 57% yield, but V was not isolated.

When a part of the reaction mixture was heated, the intensity of the ultraviolet spectral maximum at about 370 mμ slowly decreased and the maxima at 230 and 277 mμ appeared.

It was now found that the reaction of I with II, either under dry or hydrous condition, first formed III. A reasonable route for the formation of III might involve the initial attack of benzoyl group in II on the carbanion of zwitterion-type thiamine (XIV) which produced from I by the addition of triethylamine to give XV, and abstraction of oxygen by producing diethyl phosphite followed by the rearrangement of thiazole into 1,4-thiazine derivative. To find a clue to this reaction mechanism, we considered the origin of the hydrogen at the 1 position in III.

(1) Part XL: *Chem. Pharm. Bull.* (Tokyo), in press.

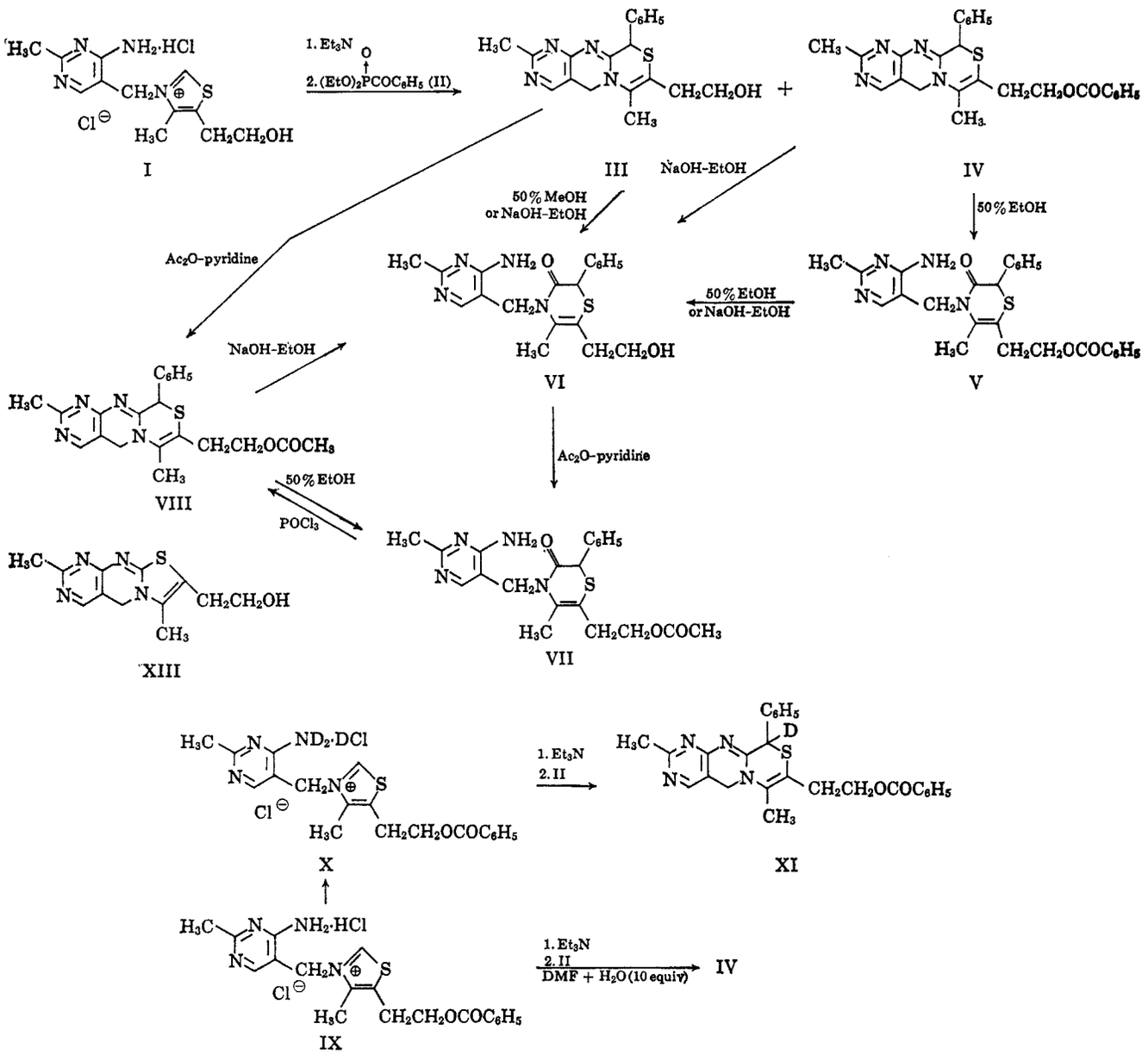
(2) A. Takamizawa, Y. Sato, S. Tanaka, and H. Itoh, *Tetrahedron Letters*, 3599 (1964).

(3) R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958).

(4) A. R. Todd and F. Bergel, *J. Chem. Soc.*, 1601 (1936).

(5) All of the nmr spectra were taken with a Varian A-60 spectrometer on the solution in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed in τ values and coupling constants are in cycles per second.

CHART I



No other protons beside the amino protons in I should be ruled out in this case. Thus, deuterioamino-O-benzoylthiamine (X) was prepared and the purity of this product was checked by infrared spectrum (Figure 2, Table I); X was allowed to react with II in a dry-box to give the product XI. From the comparison of nmr spectra (Figure 3) between XI and IV, it was found that the hydrogen at the 1 position of XI was, as expected, deuterated in about 80%.

TABLE I
EXCHANGE DATA OF NH TO ND IN O-BENZOYLTHIAMINE HYDROCHLORIDE

ν_{NH}, cm^{-1}	ν_{ND}, cm^{-1}	ν_{NH}/ν_{ND}
3150	2470	1.28
	2270	
2630	2110	1.27
	2060	1.29

The fact that about 20% of IV was contained in this product is probably due to the exchange of deuterioamino group with the proton of triethylamine hydrochloride produced by the treatment of X with triethylamine.

To give the chemical evidence for the structure of VIII which has new ring system, VIII was synthesized by alternative route as shown in Chart II.

2-Methyl-4-amino-5-(2-chlorophenylacetyl)aminomethylpyrimidine (XIV) was obtained as the crystals of mp 201° from the reaction of 2-methyl-4-amino-5-aminomethylpyrimidine (XII) with chlorophenylacetyl chloride (XIII). Then XIV was allowed to react with benzyl mercaptan in EtOH–EtONa solution to give S-benzyl-N-(2-methyl-4-amino-5-pyrimidyl)methylthiomandelylamide (XV) as the crystals of mp 135–136°. After treatment of XV with metallic sodium in liquid ammonia, 3-acetyl-3-chloropropanol acetate (XVI) was allowed to react. The product obtained was purified with alumina column chromatography to give S-[1-acetyl-3-(2-acetoxy)]propyl-N-(2-methyl-4-amino-5-pyrimidyl)methylthiomandelylamide (XIX) as the crystals of mp 150–151°.

From the value of elemental analysis and ultraviolet, infrared, and nmr spectra, the structure of XIX was

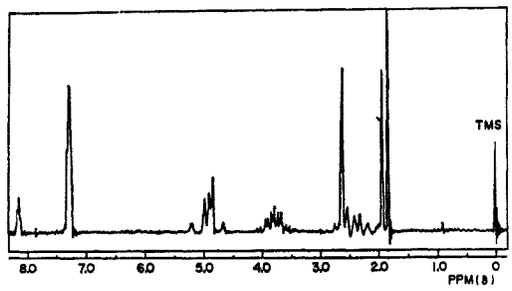


Figure 1.—Nmr spectrum of VIII.

confirmed. In this reaction, the crystals of mp 170° were obtained at the same time. The value of elemental analysis and the physical properties of this product suggest that the structure is 2-methyl-4-amino-5-pyrimidylmethylbenzylamide (XVIII). The structure of XVIII was confirmed by identification with authentic sample synthesized from XII and phenylacetyl chloride. The treatment of XIX with dilute HCl gave S-[1-acetyl-3-(2-hydroxy)]propyl-N-(2-methyl-4-amino-5-pyrimidylmethyl)thiomandelylamide (XXI) as the crystals of mp 142°. The structure of XXI was confirmed from the value of elemental analysis, ultraviolet, infrared, and nmr spectra, and giving XIX by acetylation of XXI with acetic anhydride in pyridine.

On the other hand, after treatment of XV with metallic sodium in liquid ammonia, 1-acetyl-1-chloro-O-tetrahydropyranylpropanol (XVII) was allowed to react to give the crystals of mp 136–137° accompanied by XXVIII.

This product was formulated as S-[1-acetyl-3-(2-tetrahydropyranyloxy)]propyl-N-(2-methyl-4-amino-5-pyrimidyl)methylthiomandelylamide (XX) based on physical properties and the fact that XXI was obtained from XX by acid treatment.

The similarity between XX, XIX, and XXI as shown above gave conclusive confirmation for the structure of XIX. The treatment of XIX with phosphoryl chloride gave VIII. The identity was confirmed by infrared comparison.

Previously,[6] it was reported that the treatment of VI with concentrated HCl gave S-[(1-acetyl-3-(2-chloropropyl)-N-(2-methyl-4-amino-5-pyrimidyl]methylthiomandelylamide (XXII). When XXI was treated with concentrated HCl, the crystals of mp 165–166° were obtained and these crystals were identified with XXII. It was now found that the treatment of XIX with phosphoryl chloride afforded tricyclic compound VIII and this result also gave the chemical evidence for the structure of VIII. At the same time, the chemical evidence for the structure of XXII derived from VI has now been gained.

From these results, two possible routes in this "Takamizawa reaction" may be considered as shown in Chart III. Further studies leading to the clarification of this reaction mechanism are being continued.

Experimental Section

1-Phenyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido-[4′,5′,4,5]pyrimido[2,3-*c*][1,4]thiazine (III).—To a suspension of 10.1 g (30 mmoles) of thiamine hydrochloride (I) in 50 ml of dimethylformamide was added dropwise 9.1 g (90 mmoles) of triethylamine under ice cooling with stirring. The temperature of the mixture was maintained for 1 hr below 10°, after which 7.3 g (30 mmoles) of diethyl benzoylphosphonate (II) was added dropwise and the cooling continued for 1 hr with stirring.

Then the mixture was allowed to stand overnight at room temperature. After evaporation of the dimethylformamide *in vacuo* at 40°, the resulting oil was dissolved in chloroform, washed repeatedly with 1 *N* sodium bicarbonate and water, and dried over anhydrous sodium sulfate.

The residue after removal of the solvent *in vacuo* was washed with ether to give 9.1 g (86.3%) of yellow crystals which were recrystallized from methanol to give needles: mp 207–208° dec; λ_{max}^{EtOH} 373 mμ (log ε 4.05).

Anal. Calcd for $C_{19}H_{20}N_4OS$: C, 64.76; H, 5.72; N, 15.90; S, 9.08. Found: C, 64.83; H, 5.95; N, 15.95; S, 9.37.

1-Phenyl-3-(2-benzoyloxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′,4,5]pyrimido[2,3-*c*][1,4]thiazine (IV).—To a suspension of 6.7 g (19.9 mmoles) of I in 30 ml of dry dimethylformamide was added dropwise 8.1 g (80.1 mmoles) of triethylamine under ice cooling with stirring. The temperature of the mixture was maintained for 1 hr below 10°, after which 9.7 g (40 mmoles) of II was added dropwise and the cooling continued for 2 hr with stirring. Then the mixture was allowed to stand overnight at room temperature and then heated at 70° for 4 hr with stirring. After evaporation of the dimethylformamide *in vacuo* the resulting oil was dissolved in chloroform, washed repeatedly with 1 *N* sodium bicarbonate and water, and dried over anhydrous sodium sulfate. The residue after removal of the solvent was washed with ether and ethyl acetate to give 7.0 g of yellow crystals which were a mixture of two components: R_f 0.12 (identified with III) and R_f 0.47 on the thin layer chromatogram of alumina using ethylacetate. This mixture was dissolved in chloroform and subjected to the alumina column chromatography.

Elution with ethylacetate gave 3.1 g (34.1%) of yellow crystals (R_f 0.47) which were recrystallized from ethyl acetate to give needles: mp 196–198° dec; λ_{max}^{EtOH} 372 mμ (log ε 4.08). Continuous elution with 5% methanol in chloroform yielded yellow crystals of III, but quantitative elution was difficult due to tailing; yield of III, 3.9 g (55.5%).

Anal. Calcd for $C_{25}H_{24}N_4O_2S$: C, 68.41; H, 5.30; N, 12.27; S, 7.02. Found: C, 67.95; H, 5.46; N, 12.32; S, 7.52.

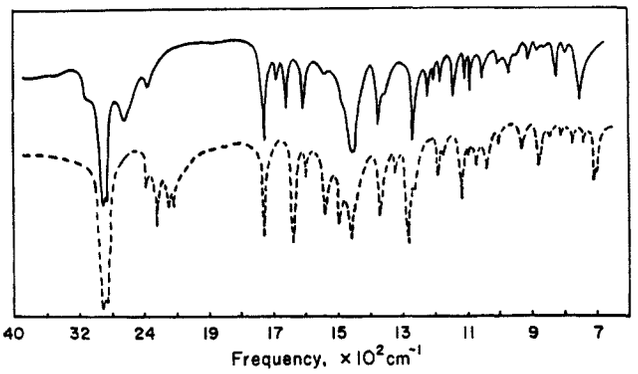


Figure 2.—Infrared spectra of O-benzoylthiamine hydrochloride (IX) (———) and deuterated O-benzoylthiamine hydrochloride (X) (- - -).

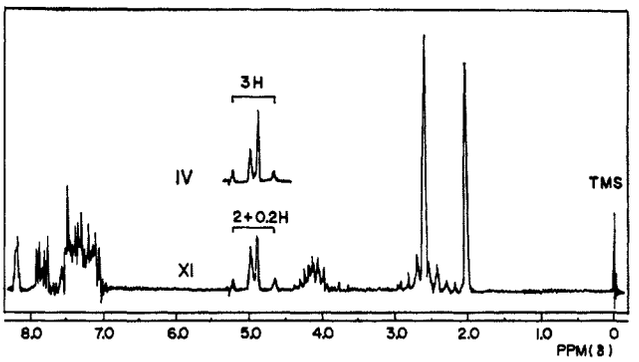
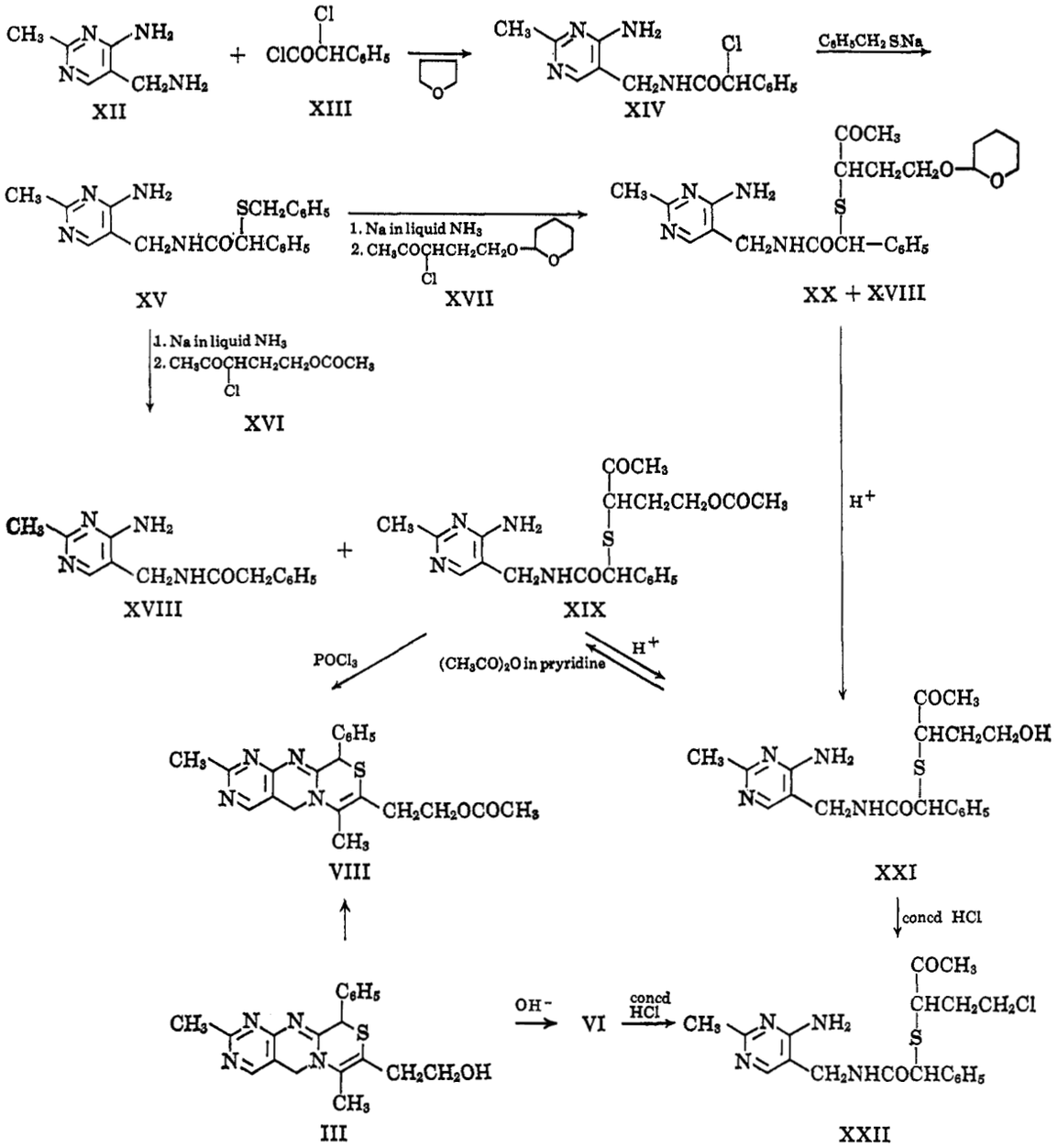


Figure 3.—Nmr spectra of IV and XI.

(6) A. Takamizawa, Y. Sato, S. Tanaka, and H. Ito, *Chem. Pharm. Bull.* (Tokyo), in press.

CHART II



1-Phenyl-3-(2-acetoxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido-[4′,5′,4,5]pyrimdo[2,3-*c*][1,4]thiazine (VIII).—(a) A mixture of 1.0 g of III and 5 ml of acetic anhydride in 10 ml of pyridine was stirred until the mixture had become clear. The solution was concentrated and the residue was extracted with chloroform. The chloroform extract was washed successively with sodium carbonate and water and dried over magnesium sulfate. Evaporation of the solvent gave yellow solid, which was recrystallized from methanol–ether to give VIII as yellow rhombics: mp 149–151° dec; λ_{max}^{EtOH} 372 mμ (log ε 4.04); ν_{max}^{Nujol} 1742 (C=O) and 1240 (COC) cm^{-1}; nmr, τ 1.83 (C-7 H, singlet), 2.72 (C-1 C_6H_5, singlet), 4.95 and 5.12 (C-6 H_2, AB-type quartet, J = 11.2 cps), 5.17 (C-1 H, singlet), 7.37 (C-9 CH_3, singlet), 8.00 (C-4 CH_3, singlet), and 8.05 ($COCH_3$, singlet).

Anal. Calcd for $C_{21}H_{22}N_4O_2S$: C, 63.94; H, 5.62; N, 14.21; S, 8.12. Found: C, 63.72; H, 5.82; N, 14.31; S, 8.23.

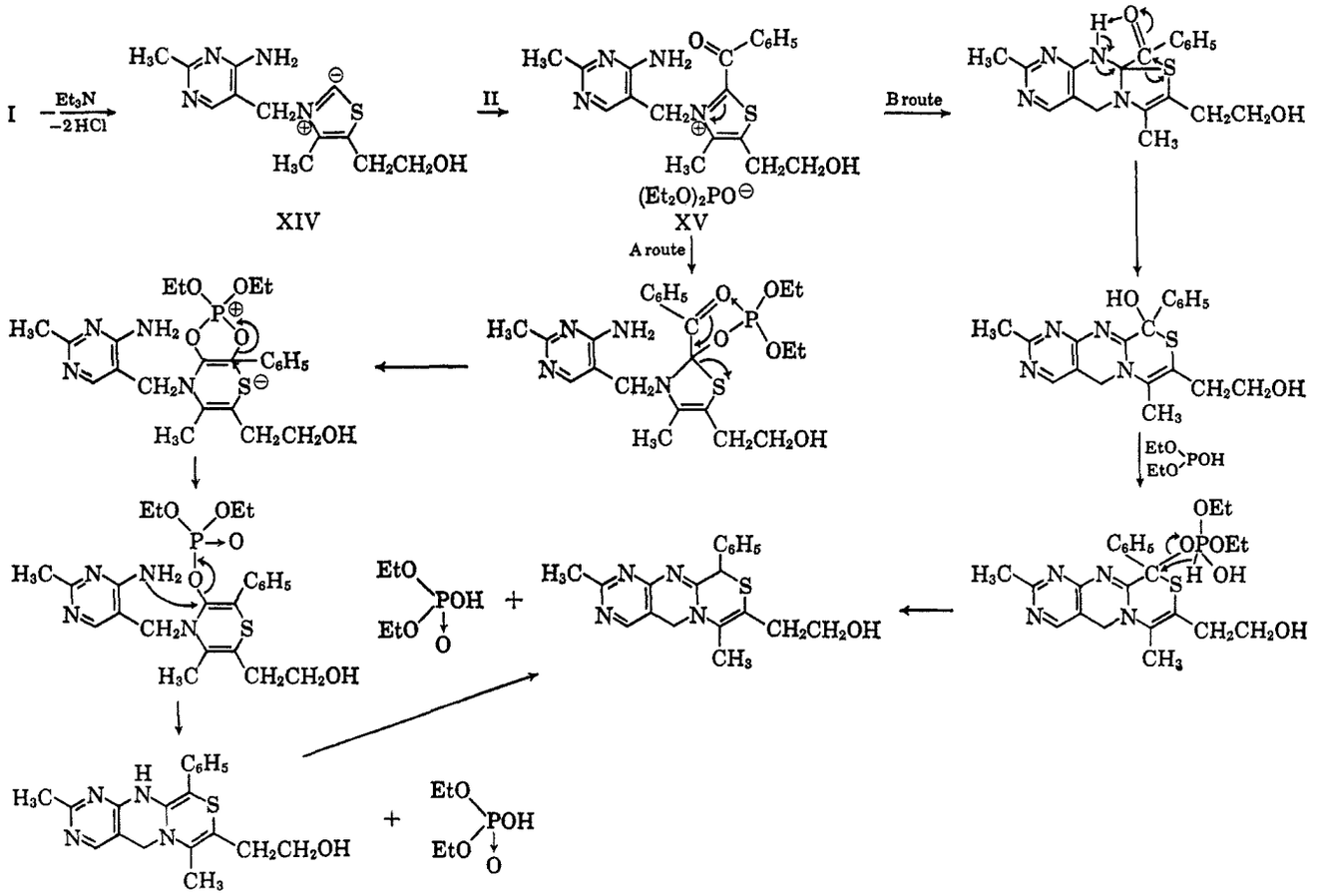
(b) A mixture of 2.4 g of VII and 20.9 g of phosphoryl chloride was heated at 95–100° for 18 hr under N_2. The excess phosphoryl chloride was removed by distillation, and the residue was decomposed with crushed ice, neutralized with sodium bicarbonate, and extracted with chloroform. The chloroform extract after being dried was concentrated to leave yellow residues, which were chromatographed over alumina. Elution with ethyl acetate gave the yellow product, which was identified as VIII by infrared comparison; yield, 0.78 g (34%).

2-Phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimdyl)methyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (V).[7] —A suspension of 0.50 g of IV in 20 ml of 50% ethanol was heated to reflux for 20 hr on a steam bath until an absorption at 372 mμ had disappeared.

The resulting light brown solution was concentrated and extracted with chloroform. Evaporation of the dried chloroform solution gave 0.35 g (67.2%) or light brown precipitates. Recrystallization from acetone–ethyl acetate gave V as colorless rhombics: mp 163°; λ_{max}^{EtOH} 230, 277 mμ (log ε 4.47, 3.90); ν_{max}^{Nujol} 3310, 3220 (NH), 1717 (OCO), 1667 (CO), and 1642 (NH) cm^{-1}; nmr, τ 1.98 (pyrimidine C-6 H, singlet), 2.6–2.8 (5 H, benzoyl-type multiplet), 2.78 (5 H, singlet) 3.9 (NH_2, broad), 4.95 and 5.28 (bridged CH_2, AB type quartet, J = 15.4 cps), 5.45 (C-2 H, singlet), 5.85 (C-6 CH_2, doublet of triplets), 7.5 (C-6 CH_2O, triplet doublet), 7.53 (pyrimidine C-2 CH_3, singlet), and 7.92 (C-5 CH_3, singlet).

(7) A. Takamizawa, Y. Sato, and S. Tanaka, *Yakugaku Zasshi*, **85**, 298 (1965).

CHART III



Anal. Calcd for $C_{26}H_{26}N_4O_3S \cdot H_2O$: C, 63.39; H, 5.73; N, 11.38; S, 6.51. Found: C, 63.71; H, 5.92; N, 11.64; S, 6.14.

2-Phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine (VI).[7]—(a) To 5 ml of 75% ethanol containing 5% sodium hydroxide was added 0.3 g of VIII, and the mixture was heated to reflux on a steam bath until an absorption at 372 mμ had disappeared. The brown solution was concentated and extracted with chloroform; the extract was washed with water and dried. Evaporation of the solvent gave 0.23 g (63.1%) of light brown precipitates. Recrystallization from chloroform gave colorless rhombics, mp 102–104°, which proved to be identical with an authentic sample of VI, which was cited as compound X in the previous paper,[7] by infrared comparison.

(b) Treatment of 0.1 g of III by the similar method described above to give VI as colorless rhombics: mp 101–103°; yield 0.08 g (56.1%).

(c) A solution of 0.05 g of IV in 10 ml of 5% NaOH–ethanol was warmed at 60° for 1 hr. The mixture was concentrated and extracted with chloroform. The extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 0.035 g (53.9%) of VI as colorless rhombics, mp 103°.

2-Phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-acetoxy)ethyl-2,3-dihydro-4H-1,4-thiazine (VII).[7]—A solution of 0.35 g of VIII in 16 ml of 50% ethanol was heated to reflux for 9.5 hr. The reaction mixture was concentrated to leave the light brown residue which gradually solidified. The solid was recrystallized from ethyl acetate to give VII as colorless needles: mp 91–92°; yield, 0.32 g (87.5%).

Reaction of O-Benzoylthiamine (IX) with Diethyl Benzoylphosphonate (Wet Condition).—To a stirred suspension of 4.41 g (0.01 mole) of IX in 15 ml of dimethyl formamide containing 1.8 g (0.1 mole) of water was added 3.1 g (0.03 mole) of triethylamine under ice–water cooling. Stirring was continued for 15 min after triethylamine had been added. To the solution was added 2.42 g (0.01 mole) of diethyl benzoylphosphonate dropwise under ice–water cooling. After being stirred for 2 hr under cooling, it was brought to room temperature and left overnight. The reaction mixture was concentrated under reduced pressure to leave a yellow-brown precipitate. The material was extracted with chloroform and the chloroform extract was washed with sodium carbonate solution, water, and dried. The residue after removal of the solvent was washed with ethyl acetate–ether to become yellow crystals, mp 194–196°, which proved to be identical with IV obtained above by infrared comparison; yield, 2.6 g (57%).

Deuteration of O-Benzoylthiamine (IX).—Compound IX (2 g) was dissolved in 6 ml of D_2O and the solution was concentrated *in vacuo* at room temperature. The residue was dried over P_2O_5 overnight, and heated at 110° for 4 hr over P_2O_5. Deuterium oxide was added to this product and above procedure repeated to give X. Sampling for infrared measurement was carried out under dry nitrogen in a drybox. Infrared spectral data are listed in Table I and Figure 2.

Reaction of Deuterio-O-benzoylthiamine (X) with Diethyl Benzoylphosphonate (II).—The deuterated product X (2.08 g) was added dropwise to 10 ml of triethylamine with ice cooling for 15 min and 1.0 ml of II was added to give solidified product. These operations were carried out under dry nitrogen in a drybox. After standing overnight at room temperature, triethylamine was decanted; the residue was made alkaline with sodium carbonate and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and the solvent was removed to give 2.2 g of the residue, which was chromatographed on alumina (3% hydrous, neutral, 30 g) with the mixture of benzene and ethyl acetate (1:1). The product obtained was recrystallized from ethyl acetate to give 1.56 g of the crystals (mp 198–198.5° dec) and 0.9 g (mp 196–197° dec) of the crystals. The nmr spectrum of IV showed the signal of the proton at 1 position overlapping with C-6-methylene protons, but that of above product showed the signal peaks at this field with the area corresponding to 2.2 H proton as shown in Figure 2.

2-Methyl-4-amino-5-(2-chlorophenylacetylamino)methylpyrimidine (XIV).—To the solution of 4.4 g of 2-methyl-4-amino-5-aminomethylpyrimidine (XII) in 130 ml of tetrahydrofuran, 3.0 g of chlorophenylacetyl chloride was added dropwise at 10–15°. After stirring for 3 hr at room temperature, separated crystals were collected and the filtrate was concentrated. The residue

was extracted with ethyl acetate and ethyl acetate extract was washed with cold dilute NaOH, then with water, dried over anhydrous sodium sulfate, and evaporated. The residue combined with the crystals obtained above and recrystallized from ethyl acetate to give colorless plates: mp 201°; yield 3.85 g (83.6%); λ_{max}^{EtOH} 229 and 274 mμ (log ε 4.09 and 3.73); ν_{max}^{Nujol} 3350, 3320, 3120 (NH), and 1658 (C=O) cm^{-1}.

Anal. Calcd for $C_{14}H_{13}ClN_4O$: C, 57.90; H, 5.21; Cl, 12.21; N, 19.25. Found: C, 58.01; H, 5.45; Cl, 12.31; N, 19.34.

S-Benzyl-N-(2-methyl-4-amino-5-pyrimidylmethyl)thiomandelylamide (XV).—To the solution of 30 ml of ethanol containing 0.23 g of sodium, 1.24 g of benzylmeraptan was added, and after a few minutes 2.9 g of XIV was added and warmed to react separating sodium chloride. After refluxing for 1 hr, the reaction mixture was concentrated *in vacuo*. The residue was extracted with chloroform; the chloroform extract was washed with dilute NaOH and water. After drying over anhydrous sodium sulfate, the solvent was removed and the residue was recrystallized from acetone to give colorless needles: mp 135–136°; yield, 3.3 g (87.2%); λ_{max}^{EtOH} 236, 275 mμ (log ε 4.03 shoulder and 3.73); ν_{max}^{Nujol} 3332, 3280, 3100, 654 cm^{-1}; nmr, τ 2.31 (pyrimidine C-6 H, singlet), 2.50 (NH), 2.73, 2.80 (phenyls, singlets) 3.93 (NH_2, broad), 5.58 (C_6H_5CHS, singlet), 5.86 (CH_2N, doublet, J = 6.0 cps), 6.34 (center, 6.24, 6.44, quartet, J = 13 cps), and 7.60 (CH_3, singlet).

Anal. Calcd for $C_{21}H_{22}N_4OS$: C, 66.65; H, 5.86; N, 14.81; S, 8.46. Found: C, 66.79; H, 6.10; N, 14.61; S, 8.29.

S-[1-Acetyl-3-(2-acetoxy)]propyl-N-(2-methyl-4-amino-5-pyrimidylmethyl)thiomandelylamide (XIX).—To a suspension of 3.37 g of IV in 120 ml of liquid ammonia, 0.425 g of metallic sodium in small pieces was added. The reaction mixture became a pale violet-pink solution. After 5 min of disappearance of sodium, 3.3 g of V was added to become an almost clean solution. After removing ammonia and adding ice to the residue, it was extracted with chloroform. The chloroform extract was washed with water, dried, and solvent was removed. Oily residue was chromatographed over alumina (standardized, E, Merck) to recover 0.295 g of starting material from the first fraction. Next fraction contained two components, and this mixture was chromatographed on SiO_2 (Davison) and eluted by acetone to give 0.35 g of colorless plates at first. Recrystallization from acetone or ethyl acetate gave XIX as the crystals of mp 150–151°; λ_{max}^{EtOH} 229, 275 mμ (log ε 4.09 and 3.76); ν_{max}^{Nujol} 3280, 3140, 1739, 1701, and 1238 cm^{-1}; nmr, τ 2.32 (pyrimidine C-6 H, singlet), 2.3 (NH, broad), 2.70 (phenyl, singlet), 3.97 (NH_2, broad), 5.57 (C_6H_5CHS, singlet), 5.80 (CH_2N, doublet, J = 6.2 cps), 5.95 (OCH_2, triplet, J = 6.0 cps), 6.75 (SCH, triplet), 7.62, 7.85, and 8.07 (three CH_3, singlets).

Anal. Calcd for $C_{21}H_{26}N_4O_4S$: C, 58.55; H, 6.09; N, 13.02; O, 14.85; S, 7.44. Found: C, 58.73; H, 6.38; N, 13.00; O, 15.25; S, 7.54.

Next fraction left 0.075 g of XVIII, which was recrystallized from acetone to give colorless plates: mp 170°; λ_{max}^{EtOH} 235.5 and 275.5 mμ (log ε 3.92 and 3.74); ν_{max}^{Nujol} 3290, 3215, 3100, 1676, and 1659 cm^{-1}; nmr, τ 2.37 (pyrimidine C-6 H, singlet), 2.77 (phenyl, singlet), 3.36 (NH, broad), 3.93 (NH_2, broad), 5.83 (CH_2N, doublet, J = 6.0 cps), 6.43 ($C_6H_5CH_2$, singlet), and 7.60 (CH_3, singlet). Identification of XVIII with authentic sample was confirmed.

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.60; H, 6.29; N, 21.86; O, 6.26. Found: C, 65.79; H, 6.59; N, 21.49; O, 6.46.

S-[1-Acetyl-3-(2-tetrahydropyranyloxy)]propyl-N-(2-methyl-4-amino-5-pyrimidylmethyl)thiomandelylamide (XX).—To a suspension of 8.0 g of XV in 200 ml of liquid ammonia, 0.972 g of sodium was added bit by bit with stirring. After 5–10 min of disappearance of sodium, 9.33 g of 1-acetyl-1-chloro-O-tetrahydropyranylpropanol (XVII) was added. After 1 hr, 1.0 g of NH_4Cl was added, ammonia removed, and ice added to the residue and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and the solvent was removed. The residue was chromatographed on alumina and eluted with ethylacetate to give following four fractions: first fraction left 1.3 g of starting material, second fraction left 1.2 g of mixture of starting matrial and XX, third fraction gave 1.22 g of XX, and fourth fraction gave 0.2 g of XVIII.

The crystals obtained from third fraction were recrystallized from ether–ethyl acetate to give colorless rhombics: mp 136–137°; λ_{max}^{EtOH} 228, 276 mμ (log ε 4.10 and 3.76); ν_{max}^{Nujol} 3440, 3165, 1703, 1661 cm^{-1}; nmr, τ 2.27 (pyrimidine C-6 H, singlet), 2.1 (NH, broad triplet), 2.70 (phenyl, singlet), 3.83 (NH_2, broad), 5.55 (C_6H_5CHS, singlet), and 5.78 (CH_2N, doublet, J = 6.0 cps).

Anal. Calcd for $C_{24}H_{32}N_4O_4S$: C, 60.99; H, 6.83; N, 11.86; O, 13.54; S, 6.78. Found: C, 61.22; H, 7.00; N, 11.73; O, 13.22; S, 6.87.

Hydrolyses of XIX and XX.—To a solution of 1 ml of concentrated HCl and 2 ml of H_2O, 0.1 g of XIX was added under cooling to give a solution. After stirring at room temperature for 2 hr, the reaction mixture was washed with chloroform, neutralized with sodium bicarbonate, and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and the solvent removed to leave 0.083 g of crystals, which were recrystallized from ethyl acetate to give XXI as colorless rhombics: mp 142°; λ_{max}^{EtOH} 228 and 275 mμ (log ε 4.09 and 3.77); ν_{max}^{Nujol} 3350, 3295, 3120, 1701, 1664 cm^{-1}; nmr τ 2.13 (NH, broad triplet), 2.20 (pyrimidine C-6 H, singlet), 2.68 (phenyl, singlet), 3.83 (NH_2, broad), 5.48 (C_6H_5CHS, singlet), 5.78 (CH_2N, doublet, J = 5.7 cps), 5.97 (OH, singlet), 6.35 (OCH_2, triplet), 6.93 (SCH, triplet), 7.63 (CH_3, singlet), 7.85 (CH_3, singlet), and 7.97 (CH_2, triplet).

Anal. Calcd for $C_{19}H_{24}N_4O_3S$: C, 58.75; H, 6.23; N, 14.43; O, 12.34; S, 8.26. Found: C, 58.41; H, 6.45; N, 14.00; O, 12.87; S, 8.46.

To a solution of 4 ml of concentrated HCl and 8 ml of H_2O, 0.36 g of IX was added under cooling to become a solution, stirred for 30 min at room temperature, and washed with chloroform. The aqueous layer was neutralized with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried and evaporated to give 0.257 g of crystalline residue. Recrystallization from ethyl acetate gave colorless rhombics, mp 142°, identical with XXI obtained above.

Acetylation of XXI.—To a suspension of 0.1 g of XXI in 1 ml of pyridine, 0.5 g of acetic anhydride was added and stirred at room temperature for 1 hr. The reaction mixture was concentrated *in vacuo* and ether was added to the residue to give the crystals. Recrystallization from ethyl acetate gave 0.083 g of colorless plates, mp 149–150°, identified with XIX by infrared comparison.

The Cyclization of XIX with Phosphoryl Chloride.—The suspension of 1.0 g of XIX in 30 ml of phosphoryl chloride was heated at 100° for 7.5 hr under N_2 stream. The reaction mixture was concentrated *in vacuo*, ice was added to the residue, and it was neutralized with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried and evaporated. The residue was chromatographed on SiO_2 (Darison), eluted with acetone, then chromatographed on alumina (standardized, E. Merck), and eluted with ethyl acetate. Removal of ethyl acetate left the crystals, which were recrystallized from ethyl acetate–ether to give 0.12 g of yellow rhombics, mp 149–150° dec. Infrared spectrum of this product was identical with that of VIII obtained from acetylation of III.

Anal. Calcd for $C_{21}H_{22}N_4O_2S$: C, 63.94; H, 5.62; N, 14.21; S, 8.12. Found: C, 63.87; H, 5.81; N, 13.88; S, 8.24.

S-(1-Acetyl-3-chloro)propyl-N-(2-methyl-4-amino-5-pyrimidylmethyl)thiomandelylamide (XXII).—The solution of 0.05 g of XXI in 1 ml of concentrated HCl was stirred for 3 hr at room temperature. After standing overnight, 2 ml of H_2O was added, and extracted with chloroform. The chloroform extract was washed with aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. Removal of the solvent left 0.025 g of crystalline residue, which was recrystallized from ethyl acetate to give colorless rhombics: mp 165–166°; ν_{max}^{Nujol} 3340, 3160, 1709, 1668, 1022 cm^{-1}; nmr, τ 2.28 (pyrimidine C-6 H, singlet), 2.47 (NH, broad), 2.67 (phenyl, singlet), 4.0 (NH_2, broad), 5.52 (C_6H_5CHS, singlet), 5.80 (CH_2N, doublet, J = 6.2 cps), 6.45 (CH_2, multiplet), 7.60 (CH_3, singlet), and 7.80 (CH_3, singlet). The aqueous layer was neutralized with sodium bicarbonate and extracted with chloroform to recover 0.012 g of starting material.

Anal. Calcd for $C_{19}H_{23}ClN_4O_2S$: C, 56.07; H, 5.69; Cl, 8.71; N, 13.77; O, 7.86; S, 7.88. Found: C, 55.83; H, 5.89; Cl, 8.67; N, 13.83; O, 8.54; S, 7.53.

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