Chem. Pharm. Bull. 16(9)1764—1772(1968)

UDC 547.853.04 : 615.356.011.5 : 577.164.11

Studies on Pyrimidine Derivatives and Related Compounds. LII.[1] Reaction of Thiamine with Phosphites. (1)

Akira Takamizawa, Kentaro Hirai, Yoshio Hamashima, Yoshihiro Matsumoto, and Sachiko Tanaka

Shionogi Research Laboratory, Shionogi & Co., Ltd.[2]

(Received January 5, 1968)

Syntheses of dialkyl 2-{3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro-[2,3-*d*]-thiazole}phosphonates (Va–f), and their thermal isomerization affording dialkyl 7-[2,9*a*-dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]-thiazolo[3,4-*a*]pyrimidine]phosphonates (VIIa–f) are described. Transesterification was occurred in the reaction of thiamine (B_1) with diphenyl hydrogen phosphite in methanol. Regeneration of V from VII was also detected. O-allyl 7-[2,9*a*-dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphinic acid (IX), O-allyl 2-[3-(2-methyl-4-aminopyrimidin-5-yl) methyl-4-methyl-5-(2-hydroxyethyl)thiazoline (4)]phosphinic acid (X), methyl and ethyl 2-[3-(2-methyl-4-aminopyrimidin-5-yl) methyl-3 a-methylperhydrofuro [2, 3-*d*] thiazole] phenylphosphonate (XIIa–b) were obtained. Brief reaction mechanisms are discussed.

Thiamine (B_1) pyrophosphate (Ib)[3] is recognized as cocarboxylase, B_1 monophosphate (Ia), and B_1 triphosphate (Ic) are also well known. Recently B_1 dialkylphosphates[4] or B_1 dialkyl phosphate disulfides[5] were synthesized based on a pharmacological interest. However, nothing has yet been reported on the B_1 phosphorous derivatives substituted at the other positions excepting hydroxyethyl group. In the preceeding papers,[6] the authors reported that the reaction of B_1 with aldehydes or amines occurred at the B_1 thiazole (Th) C_2-position, in

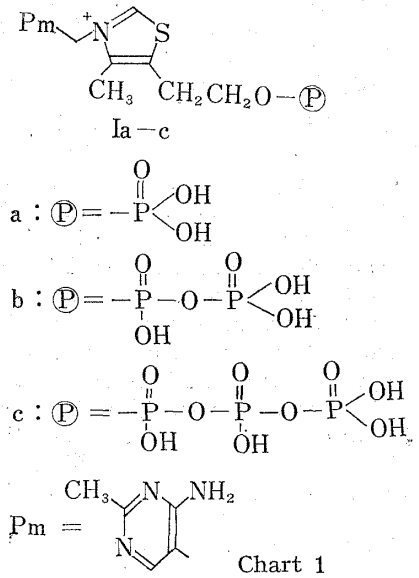

Chart 1

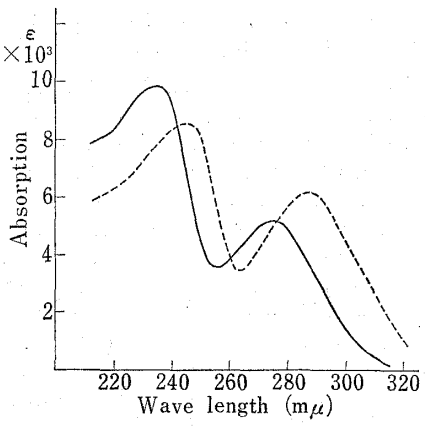

Fig. 1. Ultraviolet Absorption Spectra of Va (——) and VIIa (------)

1) Part LI: A. Takamizawa, K. Hirai, and Y. Hamashima, *Chem. Pharm. Bull.* (Tokyo), **16**, 1758 (1968).
2) Location: *Sagisu, Fukushima-ku, Osaka.*
3) K. Lohmann and P. Schuster, *Biochem. Z.*, **294**, 188 (1937).
4) M. Kataoka and H. Ito, *Ann. Takamine Lab.* (Japan), **13**, 24 (1961).
5) Y. Mushika and T. Fujita, *Yakugaku Zasshi*, **87**, 33 (1967).
6) A. Takamizawa, K. Hirai, Y. Hamashima, and S. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1210 (1968); A. Takamizawa, K. Hirai, and Y. Hamashima, *Chem. Pharm. Bull.* (Tokyo), **16**, 1758 (1968).

different modes from HET[7] type adducts, *via* nucleophilic B_1 carbene or pseudo B_1 type intermediate, respectively. Ramirez, *et al.*[8] reported that the unique acyloxycarbene was held responsible for the formation of the phthalide from phthalic anhydride and triethyl phosphite, and added diethyl hydrogen phosphite captured the acyloxycarbene to give diethyl phthalide phosphonate. This paper deals with the description of the reaction of B_1 with dialkyl hydrogen phosphites obtaining dialkyl 2-[3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methyl-perhydrofuro[2,3-*d*]thiazole]phosphonates and their thermal isomerization. After being passed carbon dioxide into a toluene or ethanol suspension of B_1 sodium salt (B_1-Na) to adjust to about pH 8.0—7.5 under cooling, diethyl hydrogen phosphite (IVa) was added affording colorless crystals (Va), mp 133—135°. Va was also obtained by the reaction of B_1-chloride (III) with IVa in the presence of triethylamine or other suitable bases. Va showed analytical data for $C_{16}H_{27}O_4N_4PS$ corresponding to the 1: 1 adduct of B_1 and IVa. The ultraviolet (UV) spectrum (Fig. 1) showed absorption maxima at 234.5 (ε 9875) and 275 (ε 5250) mμ suggesting that 2-methyl-4-aminopyrimidin-5-yl group might still remain. The infrared (IR) spectrum (Fig. 2) showed absorption bands at 3390, 3375, 1668 (NH_2), 1252 (P-O), and at 1042 cm^{-1} (P-O-C). The nuclear magnetic resonance (NMR) spectrum (τ values) showed peaks at 2.00 (singlet, 1H, pyrimidine=Pm-C_6-H), 3.72 (broad, 2H, Pm-C_4-NH_2), 7.51 (singlet, 3H, Pm-C_2-CH_3), and at 8.34 (singlet, 3H, 3a-CH_3) which was extremely higher than that expected as Th-C_4-CH_3 signal, in addition, typical signals corresponding to the hydroxyethyl group were deformed and shifted (Fig. 3). From the above spectral con-

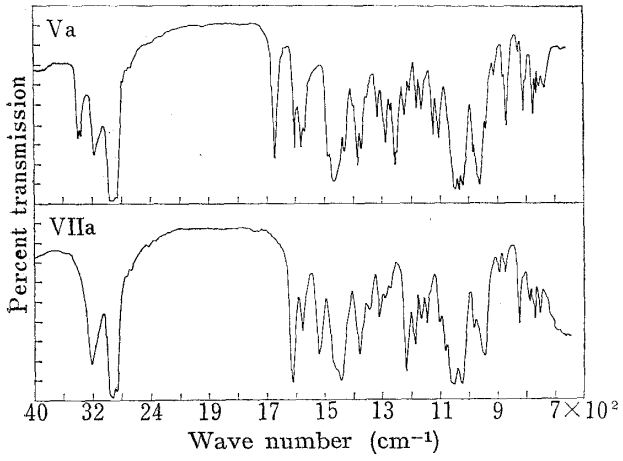

Fig. 2. Infrared Absorption Spectra of Va and VIIa in Nujol Mull

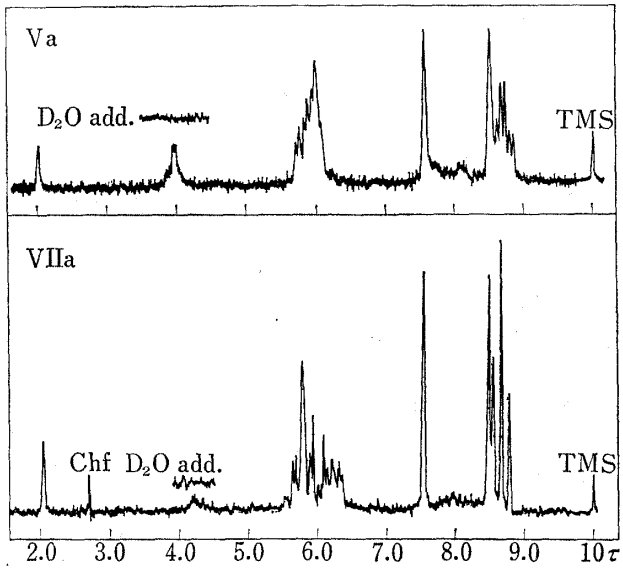

Fig. 3. Nuclear Magnetic Resonance Spectra of Va and VIIa in $CDCl_3$ (60 Mcps)

siderations, it was supported that the cyclization occurred quite similarly to the case of preceding aldehydes or amines to form tetrahydrofuran ring by the reaction of the hydroxyethyl group with Th-C_4-C_5 double bond. Accordingly, the structure of Va was confirmed to be diethyl 2-[3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate. When aqueous hydrochloric acid solution of Va was allowed to stand at room temperature B_1 hydrochloride was obtained in a quantitative yield. Benzoylation of Va afforded monobenzoate (VI), mp 114°. Physicochemical data of VI [λ_{max}^{EtOH} mμ (ε): 229 (19900), 273 (6090); ν_{max}^{Nujol} cm^{-1}: 1675 (C=O); τ in $CDCl_3$: 1.90 (singlet, 1H,

7) 2-(1-hydroxyethyl)thiamine.
8) F. Ramirez, H. Hamanaka, and O.H. Basedow, *J. Am. Chem. Soc.*, **83**, 173 (1961).

Pm–C_6–H), 3.15 (broad, 1H, C_4–NH), 7.47 (singlet, 3H, Pm–C_2–CH_3), 8.45 (singlet, 3H, 3a–CH_3)] indicated the structure to be diethyl 2-[3-(2-methyl-4-benzoylaminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate. The fact was provided for the chemical proof that Va has a tetrahydrofuran ring in the molecule. On heating to reflux in ethanol, Va afforded VIIa, mp 160—162°, in good yield, which showed analytical data for $C_{16}H_{27}O_4N_4PS$ corresponding to that of Va and so it was an isomer of Va. VIIa showed absorption maxima (Fig. 1) at 244 (ε 8,450) and 287 mμ (ε 6,250). Accordingly, the structure of VIIa was assumed to be taking a tricyclic form like dihydrothiochrome. The IR spectrum (Fig. 2) of VIIa showed bands at 3180, 1610 (NH), 1221 (P=O), and at 1022 cm^{-1} (P–O–C) indicating the existence of diethoxyphosphinyl group. The NMR spectrum showed peaks at 2.06 (singlet, 1H, Pm–C_6–H), 4.20 (broad, 1H, NH), 7.56 (singlet, 3H, Pm–C_2–CH_3), and at 8.50 (singlet, 3H, Th–C_4–CH_3) indicating that the Th–C_4–carbon was still saturated. In view of the above facts the structure of VIIa was assured to be diethyl 7-[2,9a-dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphonate, which was produced from the result of the cyclization between Pm–C_4–amino group and Th–C_4–C_5 double bond regenerated by the cleavage of the tetrahydrofuran ring. Benzoylation of VIIa with benzoylchloride in pyridine afforded monobenzoate (VIII), mp 107°, which showed bands at 1717, 1273 (O–C=O), and at 1612 cm^{-1} (NH) in the IR spectrum. It was clear that the benzoylation occured in a hydroxyethyl group but not in an amino group. The NMR spectrum also showed appropriate signals at 2.05 (singlet, 1H, Pm–C_6–H), 4.31 (broad, 1H, NH), 7.55 (singlet, 3H, Pm–C_2–CH_3), 8.48 (singlet, 3H, Th–C_4–CH_3), and at 1.82—2.60 (multiplet, 5H, COC_6H_5). Accordingly, the structure of VIIa was confirmed. Condensation and isomerization reaction of B_1 with dimethyl–, di-*n*-propyl, di-*n*-butyl, diallyl, and dibenzyl hydrogen phosphite (IVb–f) proceeded quite similar way to that of diethyl hydrogen phosphite (see experimental section). Reaction of III with diphenyl hydrogen phosphite (IVg) did not occur in acetonitrile. Although the reaction between III and IVg occurred in methanol, the product was not a diphenyl ester but Vb. In this case it was sure that transesterification between IVg and methanol occurred at first and resulted to give Vb as a product. The gaschromatographic analysis indicated that the transesterification between IVg and methanol occurred very fast. VIIb was decomposed to give B_1 accompanied with Vb but in very small quantities (<2%) when it was warmed with acetic acid. Treatment of VIIc or VIIe with sodium ethoxide in ethanol resulted in simple transesterification as in the case of the reaction of B_1 with diphenyl hydrogen phosphite. Now, following interesting facts were found as described below. The authors tried to obtain phosphoramide by the reaction of VIIe with benzylmethylamine in the presence of sodium hydride as a catalyst in dioxane, but obtained IX in 69.5% yield as an amorphous powder. The structure of IX was confirmed by elemental analysis ($C_{14}H_{22}O_4N_4PS$), UV [λ_{max}^{EtOH}: 247, 287 mμ], and NMR [2.15 (singlet, 1H, Pm–C_6–H), 3.07 (broad, 1H, NH), 3.76—4.41, 4.73—5.22, 5.47—5.70 (multiplet, 5H, O–CH_2–CH=CH), 5.92—6.03 (multiplet, 1H, C_7–H), 6.25—6.81 (multiplet, 5H), 7.71 (singlet, 3H, Pm–C_2–CH_3), 7.92—8.32 (multiplet, 2H, >CH–$\underline{CH_2}$–CH_2O–), 8.67 (singlet, 3H, 9a–CH_3)] spectral consideration. IX was also obtained by similar treatment of Ve with benzylmethylamine. It was much interested that IX afforded O-allyl 2-[3-(2-methyl-4-aminopyrimidin-5-yl)methyl-4-methyl-5-(2-hydroxyethyl)-4-thiazoline]phosphinic acid (X), mp 180—183°, by treatment with alcoholic hydrochloric acid, while it gave B_1–HCl with aqueous hydrochloric acid. X is the isomer of IX, because both of them have same component. X showed absorption maxima at 234 and 278 mμ. NMR spectrum showed signals at 2.18 (singlet, 1H, Pm–C_6–H),4.18 (broad, NH_2), 4.87 (singlet, 2H, Pm–CH_2–), 3.91—5.82 (multiplet, 5H, –CH_2–CH=CH_2), 6.37,7.05 (triplet–triplet, 4H, –O–CH_2–CH_2–, J=6.0 cps), 7.70 (singlet, 3H, Pm–C_2–CH_3), and at 7.78 (singlet, 3H, Th–C_4–CH_3). Further treatment of X with hydrochloric acid decomposed to give B_1–HCl.

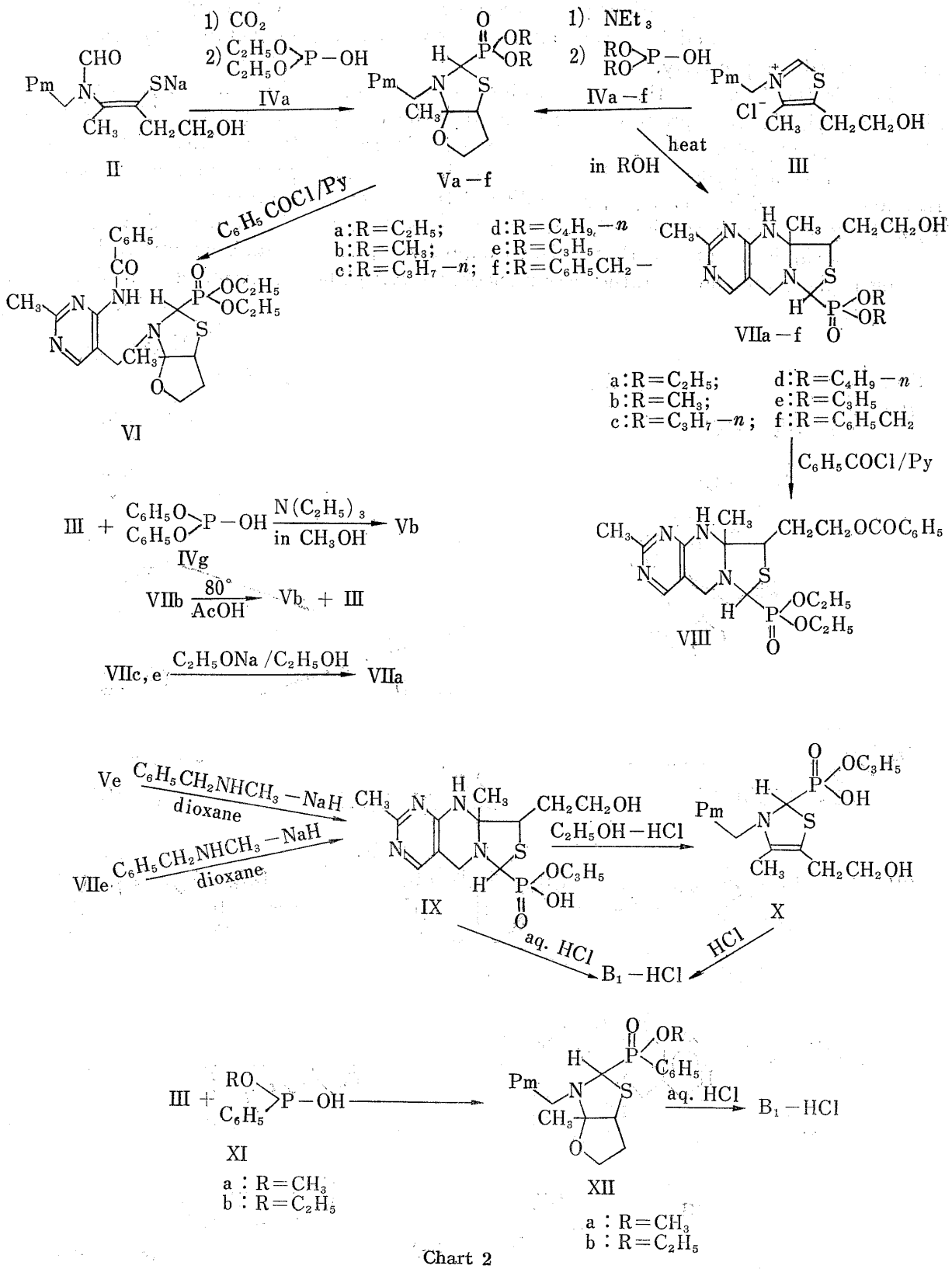

Chart 2

Reaction of B_1 with methyl or ethyl hydrogen phenylphosphonite (XIa or XIb) proceeded quite similarly to give Th–C_2 substituent products, methyl or ethyl 2-{3-(2-methyl-4-aminopyrimidin-5-yl) methyl-3a-methylperhydrofuro [2,3-*d*] thiazole}-phenylphosphinate (XIIa, XIIb), respectively. These structures were confirmed by elemental analysis, UV,

and NMR spectral considerations (see experimental section). When aqueous hydrochloric acid solutions of XIIa and XIIb were allowed to stand at room temperature B_1 hydrochloride was obtained, respectively.

This is the first time that organic phosphorous groups such as dialkoxyphosphinyl- or alkoxyphenylphosphinyl group were introduced at the Th–C_2 position of B_1. The possibilities of obtaining many other Th–C_2 substituent compounds are expected from this success including the reaction of aldehydes or amines described in previous papers. On the mechanism of reactions described in this paper, possibility of the concerted reaction mechanism as that of B_1 with amines may be considered, however, it seems more probable to proceed *via* B_1 carbene or ylidein a similar manner as that of B_1 with aldehydes, since it has been known that dialkyl hydrogen phosphite showed rather less nucleophilicity.[9] Thermal isomerization of V to VII

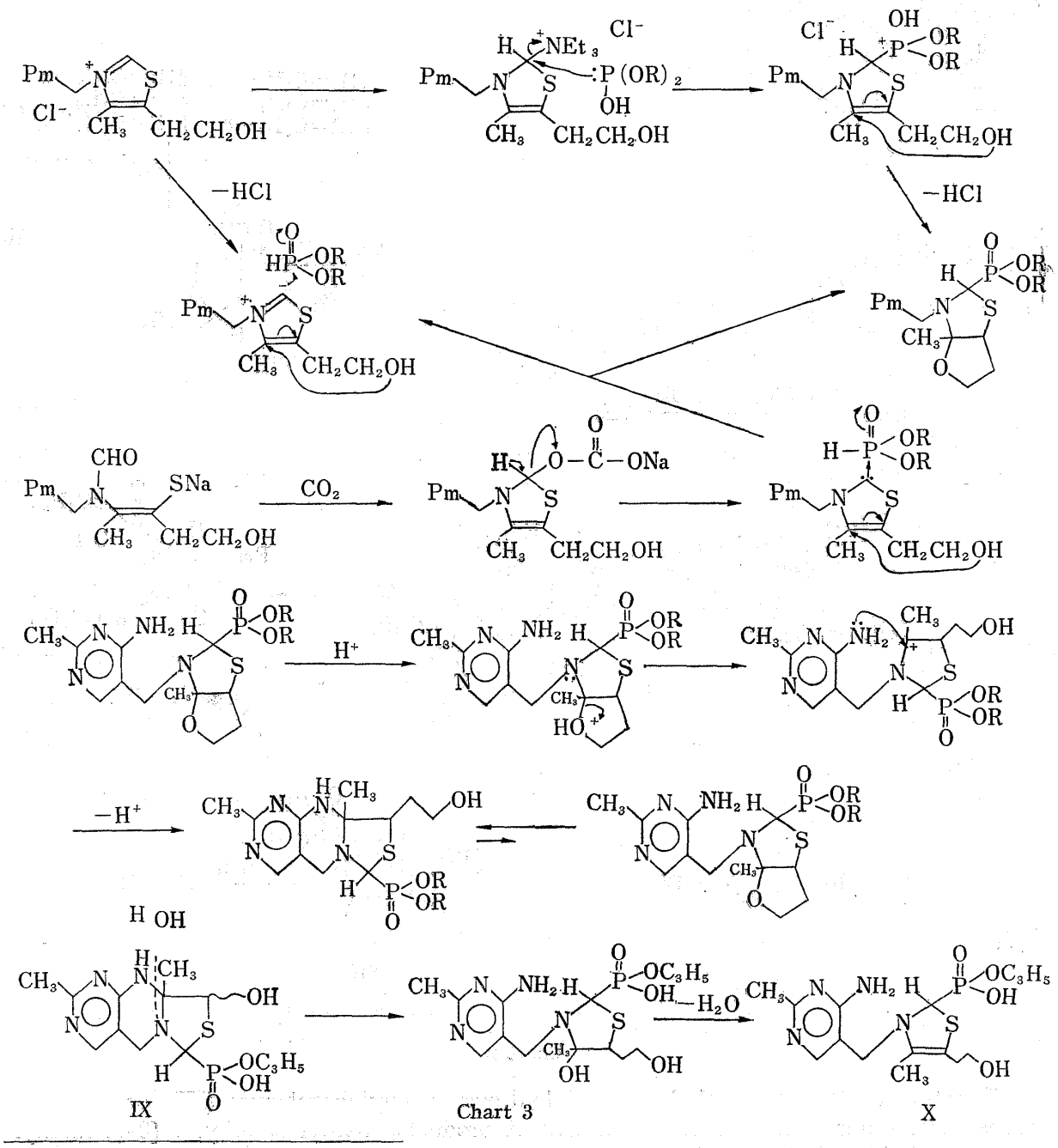

Chart 3

9) *a*) Z. Luz and B. Silver, *J. Am. Chem. Soc.*, **83**, 4518 (1961); *b*) W.J. Bailey and R.B. Fox, *J. Org. Chem.*, **28**, 531 (1963).

in alcohol occurs more quickly on addition of weak acid such as acetic acid. Accordingly, the process of the isomerization may be considered as follows: Protonation may be occurred at tetrahydrofuran oxygen to produce the oxonium salt, which will be expected ring opening on the Th–C_4–carbon and the carbonium ion formed will yield VII by an internal nucleophilic attack of amino group at Pm–C_4. Thermal conversion of VII to V is only a little if any as shown in the case of VIIb. Accordingly, it appears that VII is thermodinamically favored structure than V, and the equilibrium inclines towards VII. Hydrolytic decomposition of IX with strong acid such as aqueous hydrochloric acid proceeds to B_1 without stopping at the stage of X, however, X is obtained conveniently under weaker acidic condition such as alcoholic–hydrochloric acid.

Experimental[10]

Diethyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate (Va)——a) To a suspension of II (9.0 g) in EtOH (40 ml) was passed through carbon dioxide for 1.5 hr, after that 3.0 g of diethyl hydrogen phosphite (IVa) was added and the mixture was stirred at room temperature for 6 hr, concentrated and extracted with $CHCl_3$. Removal of the solvent after being dried gave colorless solid, which was recrystallized from acetone to give Va as colorless needles, mp 133—135°. Yield, 22%. ν_{max}^{Nujol} cm^{-1}: 3390, 3375, 1668 (NH_2), 1252 (P=O), 1042, 1030, 1016, 960 (P–O–C). λ_{max}^{EtOH} mμ (ε): 234.5 (9,875), 275 (5,250). *Anal.* Calcd. for $C_{16}H_{27}O_4N_4PS$: C, 47.74; H, 6.76; N, 13.96; S, 7.97. Found: C, 47.56; H, 6.87; N, 14.07; S, 7.63.

b) To a suspension of 6.0 g of B_1 chloride (III) in 40 ml of EtOH was added 2.3 g of NEt_3 and stirred for 1.5 hr. The brown suspension was added 3.0 g of IVa and stirred at 60° for 6 hr, cocentrated and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried, and concentrated to leave light brown residue, which was recrystallized from acetone giving colorless needles, mp 133—135°, which were confirmed to be Va by the IR comparison with that of the product obtained above a).

Each of Va–e was easily hydrolyzed to give III hydrochloride by treating with dil–HCl at room temperature for several hours.

Diethyl 2-[3(2-Methyl-4-benzoylaminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate (VI)——To a solution of Va (200 mg) in pyridine (5 ml) was added benzoyl chloride (120 mg) under ice water cooling, then the mixture was stirred at room temperature for 3 hr. The residue after removal of the solvent was extracted with $CHCl_3$. The extract was washed dried and evaporated to leave colorless solid, which was recrystallized from acetone–ether to give VI as colorless needles, mp 114°. ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1675(C=O), 1250 (P=O), 1040, 1025, 965 (P–O–C). λ_{max}^{EtOH} mμ (ε): 229 (19,900), 273 (6,090). τ (in $CDCl_3$): 1.90 (singlet, 1H, Pm–C_6–H), 1.81—2.62 (multiplet, 5H, C_6H_5CO), 3.15 (broad, 1H, NH), 5.52—6.20 (multiplet, 10H), 7.47 (singlet, 3H, Pm–C_2–CH_3), 7.86 (multiplet, 2H, >CH–CH_2–CH_2–O–), 8.45 (singlet, 3H, 3a–CH_3), 8.62, 8.68 (triplet, triplet, 6H, O–CH_2–CH_3 × 2, J = 7.0 cps). *Anal.* Calcd. for $C_{23}H_{31}O_5N_4PS$: C, 54.53; H, 6.17; N, 11.09; S, 6.33. Found: C, 54.68; H, 6.46; N, 11.28; S, 6.08.

Diethyl 7-[2,9a-Dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphonate (VIIa)——Ethanol (10 ml) solution of Va (500 mg) was heated to reflux on a steam bath for 15 hr. To the residue after removal of the solvent was added EtOAc to precipitate colorless solid, which was recrystallized from EtOAc giving VIIa as colorless sticks, mp 160—162°. Yield, 313 mg. *Anal.* Calcd. for $C_{16}H_{27}O_4N_4PS$: C, 47.74; H, 6.76; N, 13.96; S, 7.97. Found: C, 47.86; H, 6.93; N, 13.82; S, 7.81.

Diethyl 7-[2,9a-Dimethyl-9-(2-benzoyloxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]-pyrimidine]phosphonate (VIII)——Benzoylation of VIIa was treated by a similar method as that of Va using 100 mg of VIIa and 100 mg of benzoyl chloride in pyridine. Recrystallization from ether gave VIII as colorless rhombs, mp 107°. ν_{max}^{Nujol} cm^{-1}: 3420, 1603 (NH), 1717, 1273 (O–C=O), 1210 (P=O), 1049, 1023, 970 (P–O–C). τ (in $CDCl_3$): 2.05 (singlet, 1H, Pm–C_6–H), 1.82—2.60 (multiplet, 5H, C_6H_5CO), 4.31 (broad, 1H, NH), 5.48—6.60 (multiplet, 10H), 7.55 (singlet, 3H, Pm–C_2–CH_3), 7.76 (multiplet, 2H, >CH–CH_2–CH_2O–), 8.48 (singlet, 3H, 9a–CH_3), 8.72 (triplet, 6H, –O–CH_2–CH_3 × 2, J = 7.0 cps). *Anal.* Calcd. for $C_{23}H_{31}O_5N_4PS \cdot H_2O$: C, 52.67; H, 5.96; N, 10.68; S, 6.11. Found: C, 52.43; H, 6.18; N, 10.73; S, 6.01.

Dimethyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate (Vb)——To a suspension of III (18.6 g) in MeOH (75 ml) was added added NEt_3 (7.5 g) and stirred at room temperature for 2.5 hr. The colorless suspension was added IVb(7.5 g) at room temperature, after that the mixture was heated on a steam bath at 80° for 7 hr, concentrated and extracted with $CHCl_3$. The $CHCl_3$

10) All melting points are uncorrected. All of the NMR were taken with a Varian A-60 spectrometer on the solution in deuteriochloroform containing tetramethylsilane as an internal reference. Chemical shifts are expressed in τ values and coupling constants are in cycles per second.

extract was washed, dried and evaporated leaving oily residue (14.0 g). It was chromatographed over Al_2O_3–$CHCl_3$. From the first fraction was obtained Vb as colorless rhombs., mp 168—169° (acetone). Yield, 36%. ν_{max}^{Nujol} cm^{-1}: 3410, 3320, 3285, 1637 (NH_2), 1234 (P=O), 1058, 1027 (P–O–C). λ_{max}^{EtOH} mμ (ε): 235 (9,975), 275.5 (5,360). τ (in $CDCl_3$): 2.01 (singlet, 1H, Pm–C_6–H), 4.00 (broad, 2H, NH_2), 5.70—6.38 (multiplet, 6H), 6.17 (double doublet, 6H, $OCH_3 \times 2$, J=10.0, 4.0), 7.52 (singlet, 3H, Pm–C_2–CH_3), 7.90 (multiplet, 2H, >CH–CH_2–O–), 8.45 (singlet, 3H, 3a–CH_3). *Anal.* Calcd. for $C_{14}H_{23}O_4N_4PS$: C, 44.95; H, 6.22; N, 14.96; P, 8.26; S, 8.59. Found: C, 45.08; H, 6.36; N, 14.58; P, 8.10; S, 9.13.

Di-*n*-propyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate (Vc)——Vc was obtained by the similar method mentioned above using III (80 g), *n*-propyl alcohol (160 ml), NEt_3 (13.5 g), and dipropyl hydrogen phosphite (35.7 g). Colorless needles (ether), mp 93—96°. Yield, 10 g (11.5%). ν_{max}^{Nujol} cm^{-1}: 3330, 3275, 3050, 1674 (NH_2), 1241 (P=O), 1065, 1000, 980 (P–O–C). λ_{max}^{EtOH} mμ (ε): 234.5 (9,880), 274.5 (5,260). τ (in $CDCl_3$): 1.98 (singlet, 1H, Pm–C_6–H), 3.88 (broad, 2H, NH_2), 5.67—6.25 (multiplet, 10H), 7.53 (singlet, 3H, Pm–C_2–CH_3), 7.63–8.43 (multiplet, 6H), 8.43 (singlet, 3H, 3a–CH_3), 9.05, 9.07 (triplet, triplet, 6H, O–CH_2–$CH_2CH_3 \times 2$). *Anal.* Calcd. for $C_{18}H_{31}O_4N_4PS$: C, 50.22; H, 7.26; N, 13.01; P, 7.21; S, 7.45. Found: C, 50.40; H, 7.52; N, 12.93; P, 7.49; S, 7.68.

Di-*n*-butyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate (Vd)——To a suspension of III (6.2 g) in *n*-butanol (25 ml), was added NEt_3 (2.5 g) and stirred at room temperature for 2.5 hr. To the suspension was added 4.2 g of di-*n*-butylhydrogen phosphite (IVd), the mixture reacted at 60° for 15 hr. Concentration of the mixture gave brown oil, which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried, and evaporated. The light brown oily residue was chromatographed over SiO_2, and eluated with acetone. From the first fraction was obtained Vd as colorless oil (1.3 g). λ_{max}^{EtOH}: 235, 275 mμ. τ (in $CDCl_3$): 1.95 (singlet, 1H, Pm–C_6–H), 3.62 (broad, 2H, NH_2), 5.23 (multiplet, 1H, Th–C_2–H), 5.67—6.25 (multiplet, 9H), 7.50 (singlet, 3H, Pm–C_2–CH_3), 8.49 (singlet, 3H, 3a–CH_3), 7.62—9.16 (multiplet, 16H). From the second fraction was obtained VIId as colorless oil (0.4 g). λ_{max}^{EtOH}: 245, 278.5 mμ. $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390, 1599 (NH), 1242 (P=O), 1060, 1023, 993 (P–O–C).

Diallyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiozole]phosphonate (Ve)——Ve was obtained by the similar method mentioned above using III (24 g), allyl alcohol (80 ml), NEt_3 (8.25 g), and diallyl hydrogen phosphite (12.5 g). Colorless needles, mp 90—91°. Yield, 3.9 g (11.9%). ν_{max}^{Nujol} cm^{-1}: 3335, 3275, 3090, 1660 (NH_2), 1241 (P=O), 1025, 987 (P–O–C). λ_{max}^{EtOH}: 235, 276.5 mμ. τ (in $CDCl_3$): 2.00 (singlet, 1H, Pm–C_6–H), 3.97 (broad, 2H, NH_2), 4.00—4.40, 4.56—4.87, 5.28—5.57 (multiplet, 10H, –O–CH_2–CH=$CH_2 \times 2$), about 5.50 (multiplet, 2H, Pm–CH_2–), 5.37 (doublet, 1H, Th–C_2–H, J=7.6 cps), 5.68—6.19 (multiplet, 3H, >CH–CH_2–CH_2–O–), 7.55 (singlet, 3H, Pm–C_2–CH_3), 7.62—8.18 (multiplet, 2H, >CH–CH_2–CH_2O–), 8.48 (singlet, 3H, 3a–CH_3). *Anal.* Calcd. for $C_{17}H_{26}O_4N_4PS$: C, 50.69; H, 6.38; N, 13.14; P, 7.28; S, 7.52. Found: C, 51.08; H, 6.65; N, 12.84; P, 7.59; S, 8.16.

Dibenzyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phosphonate (Vf) and Dibenzyl 7-[2,9a-Dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphonate (VIIf)——To a suspension of III (6 g) in acetonitrile (20 ml) was added 2.06 g of NEt_3 at room temperature, then the suspension was added 5.05 g of dibenzyl hydrogen phosphite (IVf) and stirred for 4 hr. The residue after removal of the solvent was extracted with $CHCl_3$, and $CHCl_3$ extract was washed and dried (Na_2SO_4). The oily residue was column chromatographed over SiO_2 and eluated with acetone. From the first fraction was obtained colorless oil (0.2 g), which was confirmed as Vf by the following spectral considerations: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 3300, 3180, 1630 (NH_2), 1220 (P=O), 1021, 995, 968 (P–O–C). λ_{max}^{EtOH}: 238, 278 mμ. τ (in $CDCl_3$): 2.20 (singlet, 1H, Pm–C_6–H), 2.67 (singlet, 10H, $C_6H_5 \times 2$), 4.07 (broad, 2H, NH_2), 7.57 (singlet, 3H, Pm–C_2–CH_3), 8.53 (singlet, 3H, 3a–CH_3).

From the next fraction was obtained VIIf as colorless viscous oil, the structure was confirmed by the following data: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3365, 1600 (NH), 1220 (P=O), 1038, 995, 967 (P–O–C). λ_{max}^{EtOH}: 246, 289 mμ. τ (in $CDCl_3$): 2.18 (singlet, 1H, Pm–C_6–H), 2.67 (singlet, 10H, $C_6H_5 \times 2$), 5.95 (center, AB quartet, 2H, Pm–CH_2), 7.57 (singlet, 3H, Pm–C_2–CH_3), 8.60 (singlet, 3H, 9a–CH_3).

Dimethyl 7-[2,9a-Dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphonate (VIIb)——A MeOH (50 ml) solution of Vb (1.0 g) was heated to reflux for 24 hr, the mixture was concentrated leaving a mixture of Vb and VIIb. They were chromatographed over Al_2O_3 and eluated with $CHCl_3$. From the first fraction was recovered 0.3 g of Vb. From the following fraction was obtained VIIb as colorless needles, mp 173—175° (acetone). Yield, 0.38 g. ν_{max}^{Nujol} cm^{-1}: 3200, 1614 (NH), 1224 (P=O), 1061, 1040 (P–O–C). λ_{max}^{EtOH} mμ (ε): 244 (8,560), 287 (6,370). τ (in $CDCl_3$): 2.03 (singlet, 1H, Pm–C_6–H), 4.18 (broad, 1H, NH), 5.80 (singlet, 2H, Pm–CH_2–), 7.55 (singlet, 3H, Pm–C_2–CH_3), 8.48 (singlet, 3H, 9a–CH_3). *Anal.* Calcd. for $C_{14}H_{23}O_4N_4PS$: C, 44.91; H, 6.22; N, 14.96; P, 8.26; S, 8.59. Found: C, 44.95; H, 6.67; N, 15.14; P, 8.73; S, 9.01.

Di-*n*-propyl 7-[2,9a-Dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphonate (VIIc)——To a solution of Vc (7 g) in propyl alcohol (50 ml) was added 0.7 ml of AcOH, and the solution was heated at 75° for 2 hr. The oily residue after removal of the solvent was washed with pet. ether and extracted with $CHCl_3$. The extract was dried and evaporated to leave colorless oil (4.35 g), which was chromatographed over SiO_2 (acetone) and obtained colorless oil (2 g, 26%). Structural

identification was determined by the following spectral data: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370, 3300, 1603 (NH), 1210 (P=O), 1057, 1003 (P–O–C). λ_{max}^{EtOH}: 245, 288 mμ.

Conversion of VIIc to VIIa by Transesterification——The oil (VIIc, 100 mg) was dissolved in EtOH (6 ml) contading 2 mg of NaOEt, the solution was allowed to stand at room temperature for overnight. Evaporated the solvent, the residue was extracted with $CHCl_3$, the $CHCl_3$ extract was washed, dried, and evaporated to leave crystalline residue, which was proved to be identical with VIIa by the IR comparison and melting point determination. Yield, 52 mg.

Diallyl 7-[2,9a-Dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphonate (VIIe)——VIIe was obtained as an oil (16%) by the similar method described above. $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 3318, 1603 (NH), 1220 (P=O), 1028, 990, 937 (P–O–C). λ_{max}^{EtOH}: 240, 282.5 mμ. τ (in $CDCl_3$): 2.70 (singlet, 1H, Pm–C_6–H), 3.75—4.33, 4.50—4.88, 5.23—5.52 (multiplet, 1H–2H–2H, –O–CH_2–CH=CH_2 ×2), about 4.1 (broad, 1H, NH), 5.82 (singlet, 2H, Pm–CH_2–), 5.97 (doublet, 1H, C_7–H, J=9.0 cps), 6.12—6.37 (multiplet, 3H, >CH–CH_2–CH_2O–), 7.55 (singlet, 3H, Pm–C_2–CH_3), about 8.05 (multiplet, 2H, >CH–CH_2–CH_2O–), 8.50 (singlet, 3H, 9a–CH_3).

Conversion of VIIe to VIIa——VIIe (100 mg) was dissolved in 6 ml of EtOH containing 2 mg of EtONa and allowed to stand at room temperature for 20 hr. The mixture was concentrated and extracted with $CHCl_3$. From the extract was obtained colorless crystals (40 mg), which were proved to be identical with VIIa by IR comparison.

Reaction of III with Diphenyl Hydrogen Phosphite in Methanol——To a mixture of III (3 g) and NEt_3 (1.1 g) in MeOH (15 ml) after stirring at room temperature for 2.5 hr was added diphenyl hydrogen phosphite (2.35 g), the mixture was stirred for 1.7 hr until the mixture became clear. The residue after removal of the solvent was extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated leaving colorless oil, which was chromatographed on Al_2O_3 and eluated with $CHCl_3$ to give 0.3 g of cololress crystals, mp 155—158°, undepressed by admixture with Vb. Direct comparison of their IR spectra also showed them to be identical.

Regeneration of Vb from VIIb——VIIb (500 mg) was dissolved in 1 ml of AcOH, the mixture was heated at 80° for 9 hr. The brown mixture was concentrated and extracted with $CHCl_3$. The $CHCl_3$ extract was chromatographed over SiO_2 and eluated with acetone giving about 5 mg of Vb, which was identified with authentic sample by IR comparison. Aqueous layer was neutralized with $NaHCO_3$ to pH 5.8. NH_4SCN was added and obtained B_1–SCN as colorless crystals, 120 mg (29.9%).

O-Allyl 7-[2,9a-dimethyl-9-(2-hydroxyethyl)-5,6,7,9,9a,10-hexahydropyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine]phosphinic Acid (IX)——a) To a solution of Ve (1.75 g) in dioxane (35 ml) was added benzyl methyl amine (2.16 g) and sodium hydride (0.165 g), the mixture was heated at 100° for 8.5 hr. The solvent was removed and the residue was washed (ether) and chromatographed over SiO_2. Eluation with MeOH gave amorphous powder (1.1 g, 69.5%), which was confirmed as IX by the following spectral consideration: ν_{max}^{Nujol} cm^{-1}: 3220 (broad), 1605 (NH), 1210 (P–O), 1080, 1031, 995 (P–O–C). λ_{max}^{EtOH}: 247, 287 mμ. τ (in d_6–DMSO): 2.15 (singelt, 1H, Pm–C_6–H), 3.07 (broad, 1H, NH), 3.76—4.41, 4.73—5.22, 5.47—5.70 (multiplet, 1H–2H–2H, O–CH_2–CH=CH_2), 5.92—6.03 (multiplet, 1H, C_7–H), 6.25—6.81 (multiplet, 5H), 7.71 (singlet, 3H, Pm–C_2–CH_3), 7.92—8.32 (multiplet, 2H, >CH–CH_2–CH_2–O–), 8.67 (singelt, 3H, 9a–CH_3).

b) A mixture of 650 mg of VIIe, 802 mg of benzyl methyl amine, and 61 mg of sodium hydride in dioxane (13 ml) was heated at 100° for 11 hr. Similar treatment of the reaction mixture gave IX as an amorphous powder, (110 mg, 18.8%) accompanied with 124 mg of VIIe. These compounds were identified with authentic sample by their IR comparisons.

O-Allyl 2-[3-(2-methyl-4-aminopyrimidin-5-yl)methlyl-4-methyl-5-(2-hydroxyethyl)thiazoline (4)]phosphinic Aicd (X)——An amorphous powder of IX (300 mg) was dissolved in 10% HCl–EtOH, and allowed to stand at room temperature for 2 days. The solution was concentrated, neutralized ($NaHCO_3$) and extracted with $CHCl_3$. The residue after being evaporated the solvent was chromatographed over SiO_2 and eluated with MeOH. From the first fraction recovered IX (54 mg). The following fraction gave colorless crystals, which were recrystallized from EtOH affording X as colorless needles, mp 180—183°. Yield, 88 mg (29.4%). ν_{max}^{Nujol} cm^{-1}: 3240, 3120, 1673 (NH_2), 1273 (P=O), 1105, 1020, 1003 (P–O–C). λ_{max}^{EtOH}: 234, 278 mμ. τ (in d_6–DMSO): 2.18 (singlet, 1H, Pm–C_6–H), 4.18 (braod, 2H, NH_2), 3.91—4.36, 4.71—5.04, 5.60—5.82 (multiplet, 1H–2H–2H, –O–CH_2–CH=CH_2), 4.87 (singlet, 2H, Pm–CH_2–), 6.37, 7.05 (triplet–triplet, 4H, –CH_2–CH_2–O–, J=6.0 cps), 7.70 (singlet, 3H, Pm–C_2–CH_3), 7.78 (singlet, 3H, Th–C_4–CH_3).,

Methyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole]phenylphosphinate (XIIa)——A mixture of III (3 g) and NEt_3 (1.03 g) in MeOH (12 ml) was stirred at room temperature for 2 hr. Methylphenylphosphonite (XIa) (1.56 g) was added to the solution, the mixture was stirred at room temperature for 3 hr to become yellow clear solution. The residue after being evaporated the solvent was extracted with $CHCl_3$, and $CHCl_3$ extract was washed, dried and evaporated leaving colorless solids, which were recrystallized from MeOH to give XIIa as colorless prisms, mp 157—161° (decomp.). Yield, 0.92 g (21.9%). ν_{max}^{Nujol} cm^{-1}: 3395, 3290, 3230, 1631 (NH_2), 1225 (P=O), 1017 (P–O–C–). λ_{max}^{EtOH}: 219, 235, 268, 275 mμ. τ (in $CDCl_3$): 2.07 (singlet, 1H, Pm–C_6–H), 1.99—2.59 (multiplet; 5H, C_6H_5), 3.77 (broad, 2H, NH_2), 5.58 (doublet, 1H, Th–C_2–H, J=8.0 cps), 5.72, 6.17 (AB quartet, 2H, Pm–CH_2–, J=15.0 cps), 5.99—6.48 (multiplet, 2H, >CH–CH_2–CH_2–O–), 6.40 (doublet, 3H, OCH_3, J=11.0 cps), 6.73 (triplet, 1H,

>CH–CH_2–CH_2–O–), 7.53 (singlet, 3H, Pm–C_2–CH_3), 7.75—8.26 (multiplet, 2H, >CH–CH_2–CH_2–O–), 8.52 (singlet, 3H, 3a–CH_3).

Ethyl 2-[3-(2-Methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thaizole]phenylphosphinate (XIIb)——XIIb was obtained as colorless crystals by the similar method described above using III (9 g), NEt_3 (3.09 g), and XIb (5.2 g) in EtOH (30 ml), mp 143—146° (acetone–EtOAc). Yield, 0.32 g (2.45%). ν_{max}^{Nujol} cm^{-1}: 3395, 3275., 3210, 1620(NH_2), 1220 (P=O), 1020, 949 (P–O–C). λ_{max}^{EtOH}: 218, 236, 268, 275 mμ. τ (in $CDCl_3$): 2.13 (singlet, 1H, Pm–C_6–H), 2.0—2.70 (multiplet, 5H, C_6H_5), 3.81 (broad, NH_2), 5.63 (doublet 1H, Th–C_2–H, J=8.5 cps), 7.57 (singlet, 3H, Pm–C_2–CH_3), 8.55 (singlet, 3H, 3a–CH_3), 8.750 (triplet, 3H, O–CH_2–CH_3, J=7.0 cps).

Acknowledgement The authors are grateful to Prof. Emeritus E. Ochiai and Prof. S. Nagakura of Tokyo University for their valuable discussions. Thanks are also due to Dr. K. Tori for his helpful discussion on the NMR spectra.