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Studies on Pyrimidine Derivatives and Related Compounds. LXI.[1] Reaction of Thiamine with Isocyanates. (2)[2]

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Thiamine (I) reacted with ethyl isocyanate to give three moles adduct (II) and four moles adduct (III). N-Ethylcarbamoylthiamine (VIII) reacted with ethyl isocyanate to afford a mixture of three moles adducts, and separation of these isomers revealed the formation of perhydrofurothiazole derivatives (IX, X). $NaBH_4$ reduction of these diastereomers gave dihydro (XIII) and tetrahydro (XV) compounds, respectively.

Previous paper[4] has described the reaction of thiamine (I) with phenylisocyanate revealing the spiro hydantoin formation at thiazolium C-2 position and the relative reactivity of thiazolium C-2 position, amino, and hydroxy function in thiamine molecule. This paper deals with the reaction of ethylisocyanate with thiamine (I).

After treatment of thiamine (I) with Et_3N in DMF, four mole equivalents of ethyl isocyanate was allowed to react to give the compound (II) (30.4%, mp 124—127° (decomp.)) and (III) (15.2%, mp 131—134°).

Elemental analysis of II was agreed with the value for three moles adduct of ethyl isocyanate to thiamine, and III showed the value agreed with four moles adduct of ethyl isocyanate to thiamine. On heating with EtOH–HCl, II gave diamine (IV) and N,N′-diethylparabanic acid (V). This result suggested the presence of hydantoin skeleton in II. Infrared (IR) spectra of II and III showed strong carbonyl bands at about 1770 and 1720 cm^{-1}, characteristic of hydantoin skeleton. Nuclear magnetic resonance (NMR) spectrum[5] ($CDCl_3$) of II showed three triplets and three quartets (J=6 cps) attributable to three ethyl groups, singlet at τ 8.23 due to the methyl group attached to the double bond, singlet at τ 7.53 due to the methyl group at pyrimidine 2-position, AB quartet attributable to the bridged methylene group at τ 6.40, 6.13, 5.93 and 5.67, broad signal at τ 4.27 due to the amino group, and singlet at τ 2.08 attributable to pyrimidine C-6 proton. And two triplets at τ 7.42 and 5.88 (J=6 cps) indicated the presence of the oxyethyl group attached to a double bond. Therefore, the structure of II was considered to be a spiro hydantointhiazoline having the carbamoyloxyethyl group.

On the other band, III showed no signal attributable to the amino group but two signals due to the NH group in urea system at τ 2.03 and 0.63. The latter appeared as broad triplet at the lowest field and was assigned to the signal due to the NH group adjacent to the ethyl group. Therefore, the structure of III was assigned as 2-(2-ethylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-ethylcarbamoylaminopyrimidin-5-ylmethyl)-6,8-diethyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione. Now, it was found that the reaction between ethyl isocyanate and the amino group in thiamine had proceeded even in the presence of rather weak

1) Part LX: A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 343 (1969).
2) A part of this work was presented at 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *Sagisu, Fukushima-ku, Osaka.*
4) A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 2130 (1968).
5) NMR spectra were recorded on a Varian A-60 spectrometer with TMS as an internal reference.

base triethylamine. This is in contrast to the reaction with phenyl isocyanate giving carbamoylamino compound only in the presence of strong base as methylsulfinyl carbanion.[4]

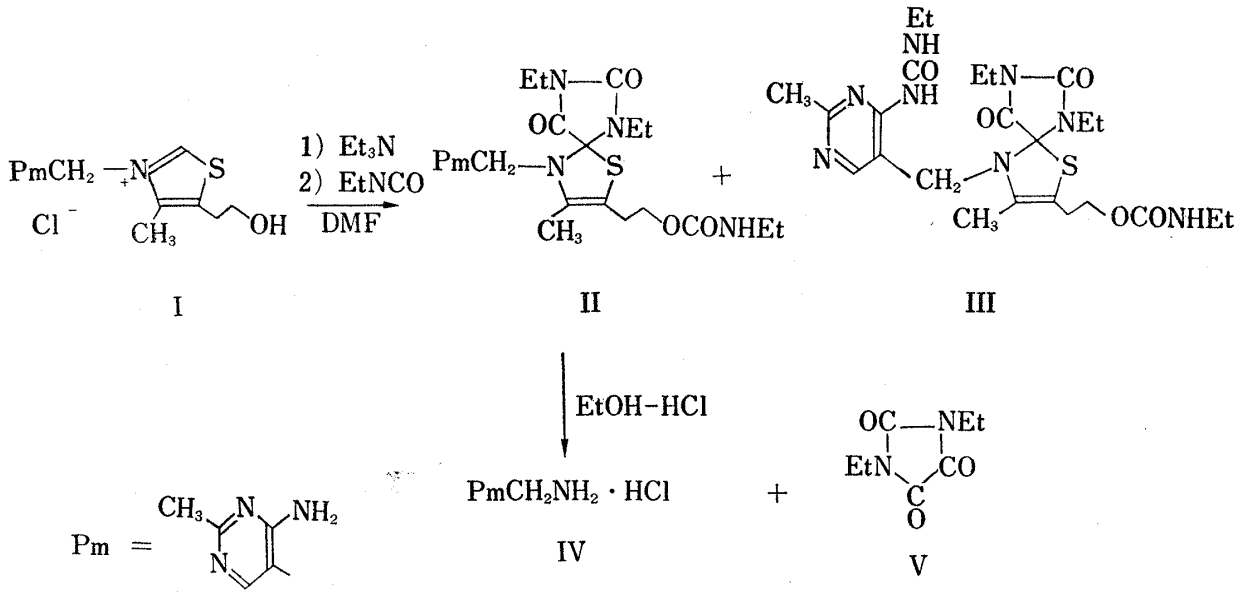

Chart 1

N-Ethylcarbamoylthiamine free base (VII) derived from thiamine free base (VI) was treated with HCl to give N-ethylcarbamoylthiamine chloride (VIII). After treatment of VIII with Et_3N in DMF, four mole equivalents of ethyl isocyanate was allowed to react to afford four moles adduct (III) (4.7%), compound (IX) (25.1%), and (X) (15.3%). Elemental analyses of IX and X showed the same value agreed with three moles adduct of ethyl isocyanate, but IR spectra differed from that of O-carbamoyl compound (II).

Interconversion between IX and X by acid suggested that these were diastereomer each other. IR spectra of IX and X showed characteristic pattern to hydantoin skeleton. In NMR spectra, both IX and X exhibited two NH signals attributable to urea system but no signal due to urethane NH signal. Besides, two triplets attributable to the oxyethyl group observed in urethane (II) had changed to appear as multiplets. These results indicated that the hydroxyethyl group in II transformed into the tetrahydrofuran ring, and IX and X were diastereomers arised from this tetrahydrofuran ring formation. This was the case in the reaction with phenyl isocyanate.[4] The phenyl analogue showed marked up field shift of C-CH_3 protons (0.65 ppm) by shielding effect of phenyl ring was assigned to *cis* configuration (XII) with respect to the C-CH_3 and the N-phenyl groups.

In the case of ethyl analogues, no significant difference of C-CH_3 chemical shifts between IX and X was observed. In *cis*-phenyl analogue (XII), however, one proton in the methylene group adjacent to the oxygen in the tetrahydro-

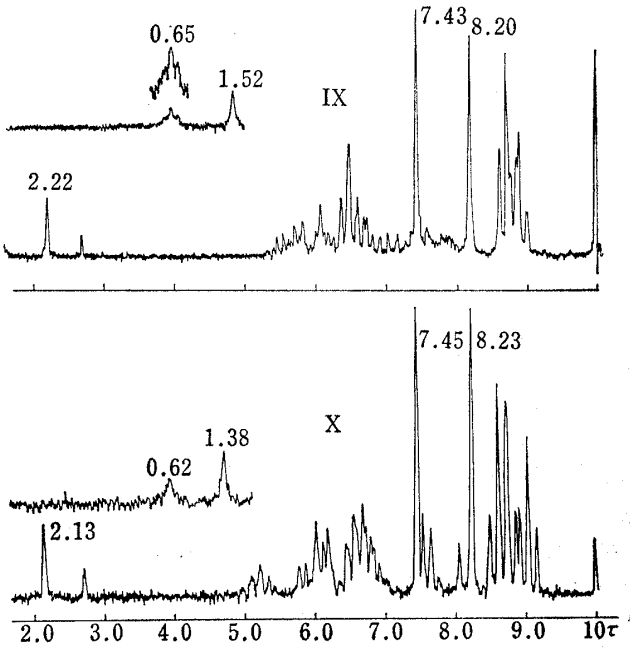

Fig. 1. NMR ($CDCl_3$, 60 Mc, τ)

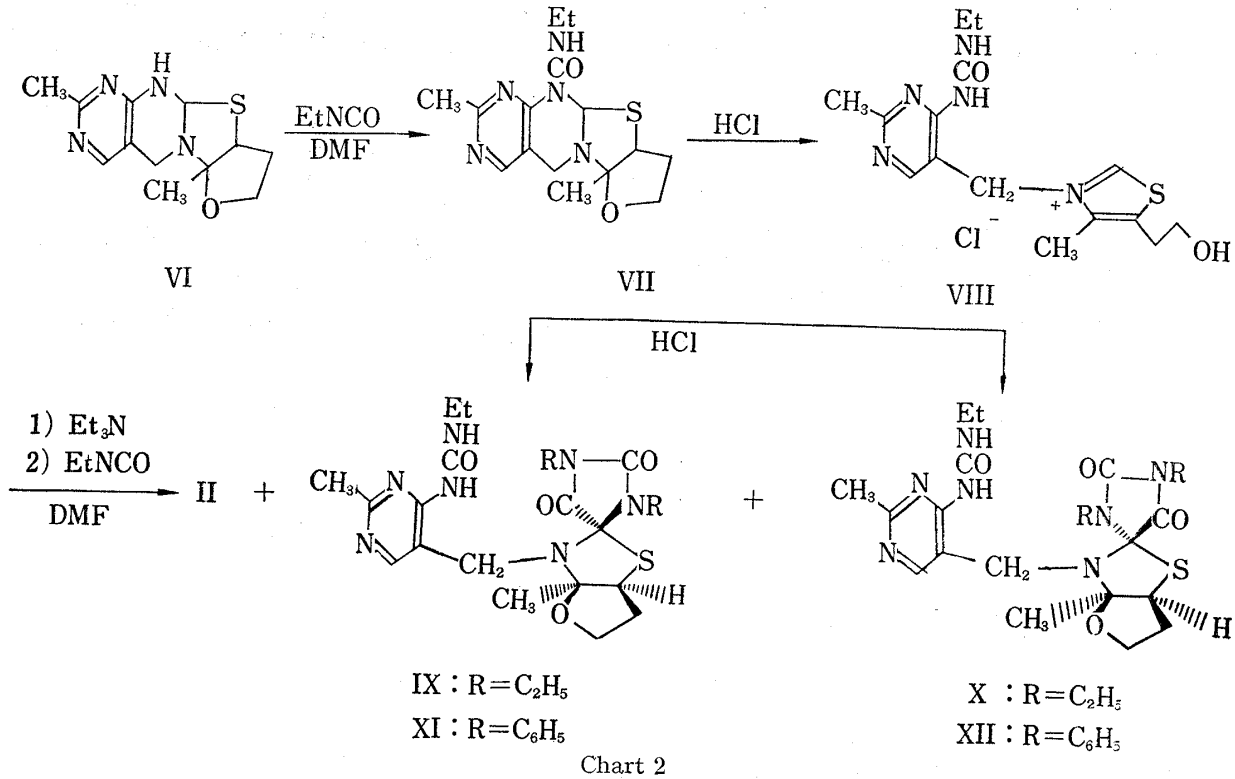

Chart 2

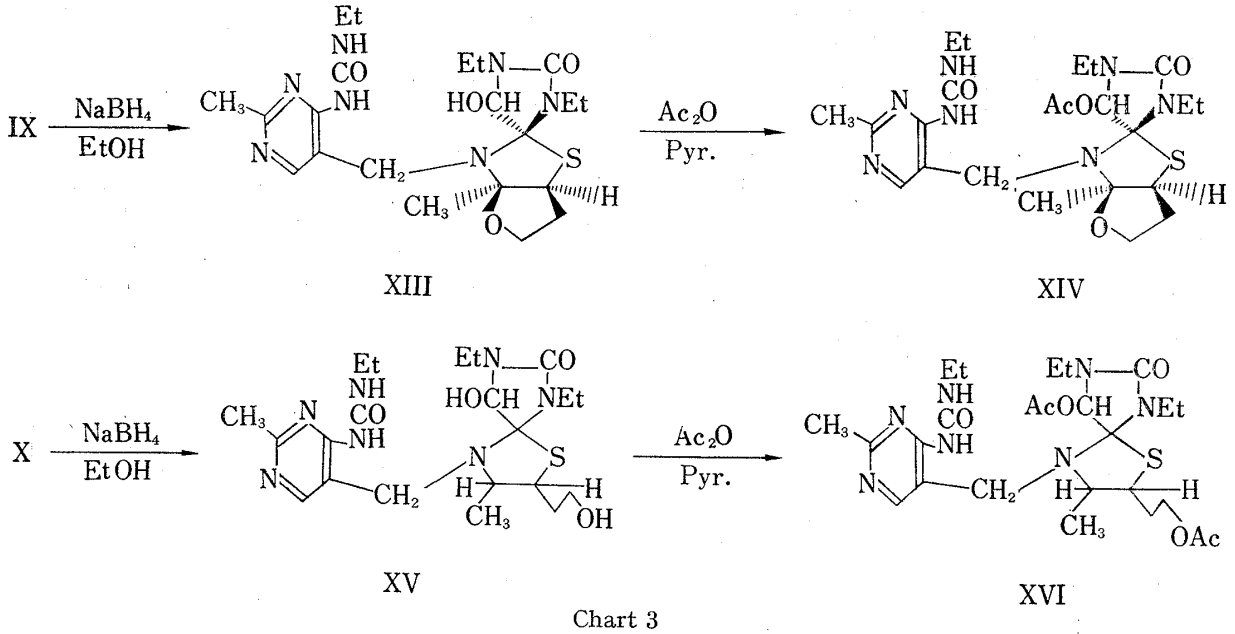

Chart 3

furan ring showed the signal shifted to lower field affected by the carbonyl group situated on the same side. Therefore, one may conclude that X showing the proton signal shifted to lower field has *cis* configuration, and as a result, IX has *trans* configuration.

Attempt to modify the hydantoin skeleton prompted us to investigate $NaBH_4$ reduction of both isomers. Treatment of *trans* isomer (IX) with $NaBH_4$ in EtOH at room temperature gave dihydro compound (XIII) in 86.4% yield. Acetylation of this product gave monoacetate (XIV). On the other hand, *cis* isomer (X) reacted with $NaBH_4$ to yield tetrahydro compound (XV) which gave diacetate (XVI) on acetylation. NMR spectrum of XIII showed two NH signals due to urea system, newly appeared OH signal at τ 3.75 and broad one proton signal at τ 4.65. On addition of D_2O to the solution examined, OH signal was disappeared and broad one proton signal changed to sharp singlet shifting 0.83 ppm to lower field. On

treatment of XIII with HCl gave two mole equivalents of ethyl urea. These result suggested that XIII had structure bearing secondary OH group arised from the reduction of carbonyl group at hydantoin 4-position.[6] Diacetate (XVI) also showed the singlet (τ 3.62) due to α-proton of secondary acetate indicating the carbonyl group at hydantoin 4-position was reduced. Moreover, angular C–CH_3 group in the perhydrofurothiazole ring showed the signal as a doublet at high field to overlap with the signal of the ethyl groups. This suggested that the C–O bond in the N–C–O grouping was cleavaged[7] to yield the tetrahydro compound. It has been known that hydantoin opened up to β-ureidoethanol and 5,5-diphenylhydantoin was resistant to hydrogenolysis by $NaBH_4$.[8] In our compounds, however, gave the result to yield secondary alcohol.[9]

Experimental[10]

2-(2-Ethylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-aminopyrimidin-5-ylmethyl)-6,8-diethyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione (II) and 2-(2-ethylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-ethyl-carbamoylaminopyrimidin-5-ylmethyl)-6,8-diethyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione (III) To a suspension of 9.0 g of thiamine chloride (I) in 90 ml of DMF, 3.3 g of Et_3N was added. After stirring for 1 hr at room temperature, 8.4 g of EtNCO was added and stirred for 6 hr at room temperature in a tube. After standing overnight at room temperature, the reaction mixture was stirred for 5 hr and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to a column chromatography on Al_2O_3 with AcOEt. First fraction gave oil (0.2 g) and second fraction afforded 1.7 g (15.2%) of III as colorless prisms, mp 131—134° (decomp.). IR ν_{max} cm^{-1}: 3452, 3364, 3311, 2270 ($CHCl_3$); 1777, 1717, 1680, 1600 (Nujol). NMR (τ, $CDCl_3$): 8.95^t (3H, J=7), 8.87^t (3H, J=7), 8.75^t (3H, J=7), 8.72^t (3H, J=7), 8.12^s (3H), 7.43^s (3H), 7.37^t (2H, J=6), 5.85^t (2H, J=6), 6.02, 5.55 (2H, ABq, J=16), 1.78^s (1H), 2.03^b (1H), 0.63^{b,t} (1H). *Anal.* Calcd. for $C_{24}H_{36}O_5N_8S\cdot 1/2H_2O$: C, 51.69; H, 6.69; O, 15.58; N, 20.09; S, 5.75. Found: C, 51.96; H, 6.74; O, 15.62; N, 19.77; S, 5.90.

Third fraction afforded 2.9 g (30.4%) of II as colorless prisms, mp 124—127° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1765, 1714, 1598. NMR (τ, $CDCl_3$): 8.83^t (3H, J=6); 8.75^t (3H, J=6), 8.65^t (3H, J=6), 8.23^s (3H), 7.53^s (3H), 7.42^t (2H, J=6), 5.88^t (2H, J=6), 4.27^b (2H), 2.08^s (1H),

Hydrolysis of II——A solution of 0.707 g of II in 4 ml of EtOH and 3 ml of 15% HCl was refluxed for 1 hr, and allowed to stand overnight at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was subjected to a column chromatography on silicagel with ether to give 0.18 g (70.5%) of N,N′-diethylparapanic acid (V) as colorless needles, mp 49—50°. *Anal.* Calcd. for $C_7H_{10}\cdot N_2O_3$: C, 49.40; H, 5.92; O, 28.21; N, 16.46. Found: C, 49.74; H, 5.97; O, 28.44; N, 16.37.

The H_2O layer was concentrated *in vacuo*, and the residue was treated with EtOH to give 0.27 g of 2-methyl-4-amino-5-aminomethylpyrimidine hydrochloride (IV).

N-Ethylcarbamoylthiamine Free Base (VII)——A solution of 5.3 g of thiamine free base in 100 ml of DMF was added 4.2 g of EtNCO and stirred at room temperature in a tube. After standing overnight at room temperature stirred for 6 hr, and the reaction mixture was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, the $CHCl_3$ extract was dried ($MgSO_4$), and evaporated. The residue was treated with ether to give 3 g (44.8%) of VII as colorless prisms, mp 125—127°. IR ν_{max}^{Nujol} cm^{-1}: 3240, 1670, 1595. *Anal.* Calcd. for $C_{15}H_{21}O_2N_5S$: C, 53.72; H, 6.31; O, 9.54; N, 20.89; S, 9.54. Found: C, 53.62; H, 6.27; O, 9.76; N, 20.60; S, 9.41.

N-Ethylcarbamoylthiamine Hydrochloride (VIII)——To a solution of 0.168 g of VII in 5 ml of EtOH, 1.2 g of 10% EtOH–HCl was added and stirred for 5 hr under ice cooling. Separated crystals were collected to give 0.135 g of VIII as colorless prisms, mp 161—164° (decomp.). Filtrate was concentrated and the residue was treated with EtOH to give 0.02 g of VIII. Yield 72%. IR ν_{max}^{Nujol} cm^{-1}: 1731, 1604. *Anal.* Calcd. for $C_{15}H_{22}O_2N_5Cl\cdot HCl\cdot H_2O$: C, 42.25; H, 5.91; N, 16.42; S, 7.52; Cl, 16.63. Found: C, 41.76; H, 5.35; N, 15.96; S, 7.61; Cl, 16.10.

3-(2-Methyl-4-ethylcarbamoylaminopyrimidin-5-ylmethyl)-3a-methylperhydrofuro[2,3-*d*]thiazole-2-spiro-5′-(1′-,3′-diethyl)imidazolidine-2′,3′-dione (IX, X)——To a suspension of 4.3 g of VIII in 40 ml of DMF,

6) NMR spectrum showed only one diastereomer was yielded; W.G. Panben, G.J. Fonken and D.S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
7) *cf.* $LiAlH_4$ reduction; N.G. Gaylord, *Experientia*, **10**, 351 (1950).
8) Y. Kondo and B. Witkop, *J. Org. Chem.*, **33**, 206 (1968).
9) Some imides gave secondary alcohols on treatment with $NaBH_4$; Z. Horii, C. Iwata and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961).
10) All melting points are uncorrected.

2.2 g of Et_3N was added, and stirred for 5 min at room temperature. To this solution, 2.8 g of EtNCO was added, stirred for 2 hr, and allowed to stand overnight at room temperature. The reaction mixture was extracted with $CHCl_3$, the $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and evaporated.

The residue was subjected to a column chromatography on Al_2O_3 with AcOEt. First fraction gave 1.2 g (25.1%) of IX as colorless prisms. IR ν_{max} cm^{-1}: 3300, 3257 ($CHCl_3$), 1765, 1711, 1700, 1600 (Nujol). NMR (τ, $CDCl_3$): 8.88^t (3H, J=7), 8.75^t (3H, J=7), 8.73^t (3H, J=7), 8.20^s (3H), 7.43^s (3H), 2.22^s (1H), 1.52^b (1H), 0.65^{b,t} (1H). *Anal.* Calcd. for $C_{21}H_{31}O_4N_7S$: C, 52.81; H, 6.54; O, 13.41; N, 20.53. Found: C, 52.90; H, 6.55; O, 13.54 N, 20.51;.

Second fraction afforded 0.78 g (15.3%) of X as colorless pillars, mp 175—178°. IR ν_{max} cm^{-1}: 3290, 3254 ($CHCl_3$), 1765, 1715, 1695, 1598 (Nujol). NMR (τ, $CDCl_3$): 9.03^t (3H, J=7), 8.75^t (J=7), 8.62^t (J=7), 8.23^s (3H), 7.45^s (3H), 2.13^s (1H), 1.38^b (1H), 0.62^{b,t} (1H). *Anal.* Calcd. for $C_{21}H_{31}O_4N_7S$: C, 52.81; H, 6.54; N, 20.53. Found: C, 52.38; H, 6.55; N, 20.30.

Third fraction afforded 0.26 g (4.65%) of III as colorless prisms, mp 131—134° (decomp.).

Isomerization between IX and X——a) To a solution of 0.35 g of IX in 4 ml of EtOH, 1.5 ml of 10% EtOH–HCl was added under ice-cooling. After stirring for 2 hr, allowed to stand overnight at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $NaHCO_3$ solution and H_2O successively, dried ($MgSO_4$), evaporated to give the residue, which was treated with ether and purified with Al_2O_3 column chromatography with AcOEt to give 0.165 g of IX and 0.11 g (31.5%) of X.

b) To a suspension of 0.25 g of X in 3 ml of EtOH–HCl, 1 ml of 10% EtOH–HCl was added under ice-cooling. After stirring for 4 hr and standing overnight at room temperature, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $NaHCO_3$ and H_2O successively, dried ($MgSO_4$), and evaporated. The residue was subjected to a column chromatography on Al_2O_3 with AcOEt to give 0.107 g (42.8%) of IX and 0.098 g of X.

3-(2-Methyl-4-ethylcarbamoylaminopyrimidin-5-ylmethyl)-3a-methylperhydrofuro[2,3-*d*]thiazole-2-spiro-5′-(1′,3′-diethyl)imidazolidine-2′-hydroxy-3′-one (XIII)——To a solution of 0.1 g of $NaBH_4$ in 10 ml of EtOH, 0.3 g of IX was added and stirred for 3 hr at room temperature and allowed to stand overnight. After adding acetone to the reaction mixture, concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and evaporated to give 0.26 g (86.4%) of XIII as colorless prisms, mp 149—151°. IR ν_{max} cm^{-1}: 3602, 3292, 3250 ($CHCl_3$), 1702, 1691, 1679, 1595, 1045 (Nujol). NMR (τ, $CDCl_3$): 8.86^t (3H, J=7), 8.85^t (3H, J=7), 8.75^t (3H, J=7), 8.47^s (3H), 7.42^s (3H), 4.65^b (1H), 3.75^b (1H), 1.85^s (1H), 0.78^b (1H), 0.40^{b,t} (1H). *Anal.* Calcd. for $C_{21}H_{33}O_4N_7S$: C, 52.60; H, 6.93; O, 13.09; N, 20.45; S, 6.67. Found: C, 53.13; H, 6.62; O, 13.09; N, 20.26; S, 6.56.

3-(2-Methyl-4-ethylcarbamoylaminopyrimidin-5-ylmethyl)-3a-methylperhydrofuro[2,3-*d*]thiazole-2-spiro-5′-(1′,3′-diethyl)imidazolidine-2′-acetoxy-3′-one (XIV)——To a solution of 0.16 g of XIII in 4 ml of pyridine, 0.17 g of Ac_2O was added, stirred for 3 hr, and allowed to stand overnight at room temperature. After evaporation, extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was subjected to a column chromatography on silica gel with acetone to give 0.035 g (20.1%) of XIV. Recrystallization from AcOEt–ether gave colorless prisms, mp 148—150° (decomp.). IR ν_{max} cm^{-1}: 3292, 3250 ($CHCl_3$), 1700, 1595 (Nujol). NMR (τ, $CDCl_3$): 9.02^t (3H, J=7), 8.78^t (6H, J=7), 8.30^s (3H), 7.85^s (3H), 7.42^s (3H), 3.84^s (1H), 2.03^s (1H), 1.35^b (1H), 0.48^{b-t} (1H). *Anal.* Calcd. for $C_{23}H_{35}O_4N_7S$: C, 52.96; H, 6.76; O, 15.34; N, 18.80; S, 6.15. Found: C, 53.08; H, 6.99; N, 18.64; S, 6.35.

2-(2-Hydroxyethyl)-3-methyl-4-(2-methyl-4-ethylcarbamoylaminopyrimidin-5-ylmethyl)-6,8-diethyl-1-thia-4,6,8-triazaspiro[4,4]non-9-hydroxy-7-one (XV)——To a solution of 0.2 g of $NaBH_4$ in 20 ml of EtOH, 0.6 g of X was added and stirred for 3 hr at room temperature. After standing overnight, acetone was added to the reaction mixture and evaporated *in vacuo*. The residue was extracted with $CHCl_3$, the $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was treated with ether to give 0.44 g (80.9%) of XV as colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 1700, 1683, 1073, 1598, 1042 (Nujol). *Anal.* Calcd. for $C_{21}H_{35}O_4N_7S$: C, 52.36; H, 7.32; N, 20.37. Found: C, 52.53; H, 7.37; N, 19.94.

2-(2-Acetoxyethyl)-3-methyl-4-(2-methyl-4-ethylcarbamoylaminopyrimidin-5-ylmethyl)-6,8-diethyl-1-thia-4,6,8-triazaspiro[4,4]non-9-acetoxy-7-one (XVI)——To a solution of 0.32 g of XV in 8 ml of pyridine, 0.34 g of Ac_2O was added under ice-cooling. After stirring for 3 hr and standing overnight at room temperature, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was subjected to a silica column chromatography with acetone to give 0.15 g (45%) of XVI. Recrystallization from ether gave colorless prisms, mp 140°. IR ν_{max} cm^{-1}: 3261 ($CHCl_3$), 1740, 1718, 1695, 1595 (Nujol). NMR (τ, $CDCl_3$): 8.88^t (3H, J=7), 8.77^t (3H, J=7), 8.72^t (3H, J=7), 8.95^d (3H, J=7), 8.00^s (3H), 7.88^s (3H), 7.43^s (3H), 1.62^b (1H), 0.87^{b-t} (1H). *Anal.* Calcd. for $C_{25}H_{36}O_6N_7S \cdot 1/2H_2O$: C, 52.47; H, 6.51; N, 17.12; S, 5.60. Found: C, 52.12; H, 7.12; N, 16.89; S, 5.76.

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