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

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Thiamine ylid formed by the treatment of thiamine hydrochloride with triethylamine reacted with two moles of phenylisocyanate at the thiazolium C-2 position to give the cycloaddition product followed by the carbamoylation of the hydroxyl group. On the other hand, on treatment with strong base as methylsulfinyl carbanion or *t*-BuOK followed by the reaction with phenylisocyanate, carbamoylation of the amino group proceeded preferentially, then the cycloaddition of two moles of phenylisocyanate at the thiazolium C-2 position occurred, and finally the hydroxyl group was carbamoylated. Diastereoisomers of perhydrofurothiazole derivatives were isolated and the configurations were decided.

The importance of the thiazolium C-2 position in the mechanism of thiamine action[3] has received considerable supports in recent years.[4] In continuing our investigation[5] on the reactivity at the thiazolium C-2 position of thiamine, the reaction of phenylisocyanate with thiamine was carried out.

After treatment of thiamine hydrochloride (I) in dimethylformamide (DMF), phenylisocyanate was allowed to react to give the compound II, mp 166—168° (decomp.), in 42% yield. An elemental analysis was consistent with the constitution of three moles adduct of phenylisocyanate to thiamine ($C_{33}H_{31}O_4N_7S$). The ultraviolet (UV) spectrum showed the maxima at 234 and 271 mμ (log ε 4.61, 3.91), and infrared (IR) spectrum showed NH bands at 3420, 3300, and 3150 cm^{-1}, and strong carbonyl bands at 1780 and 1730 cm^{-1}. Nuclear magnetic resonance (NMR) spectrum[6] (d_6-DMSO) showed the following signals: τ 8.38 ($CH_3\text{-}\overset{|}{C}\text{=}$), 7.70 (pyrimidine $C_2\text{-}CH_3$), 6.42^t ($O\text{-}C\underline{H}_2\text{-}CH_2$, $J=6$), 5.57 (pyrimidine $C_5\text{-}CH_2$), 3.30 (NH_2), 1.97 (pyrimidine C_6-H), 0.55 (NH). On treatment of II with dil. EtOH–HCl, *o*-phenylcarbamoylthiamine hydrochloride (III), mp 218—220° (decomp.), N,N′-diphenylurea (IV), and 1,3-diphenylparabanic acid (V) were obtained. III was identified with the product obtained from *o*-chlorocarbonylthiamine[7] and aniline.

Treatment of II with dil. EtOH–KOH gave III and IV. From these results, the structure of II was assigned as 2-(2-phenylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-aminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione. Analogous cyclo-

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[1] Part LV: *Vitamin*, **37**, 483(1968).

[2] Location: *Sagisu, Fukushima-ku, Osaka.*

[3] R. Breslow, *J. Am. Chem. Soc.*, 79, 1762 (1957).

[4] L.O. Krampitz, G. Greull, C.S. Miller, J. Bicking, H.R. Skeggs, and J.M. Sprague, *J. Am. Chem. Soc.*, **80**, 5893 (1958); C.S. Miller, J.M. Sprague, and L.O. Krampitz, *Ann. N. Y. Acad. Sci.*, **98**, 401 (1962); G.L. Carlson and G.M. Brown, *J. Biol. Chem.*, 236, 2099 (1961).

[5] A. Takamizawa, K. Hirai, Y. Hamashima, and S. Matsumoto, *Tetrahedron Letters*, **1967**, 5071; A. Takamizawa, K. Hirai, and Y. Hamashima, *ibid.*, **1967**, 5077, 5081; A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *ibid.*, submitted.

[6] NMR spectra were recorded on a Varian A-60 spectrometer with TMS as an internal reference: chemical shifts (τ), coupling constants (J, cps). Peak multiplicities are presented by s (singlet), d (doublet), t (triplet), and b (broad).

[7] A. Takamizawa, K. Hirai, and Y. Hamashima, *Chem. Pharm. Bull.* (Tokyo), **11**, 882 (1963).

adducts (VIIa,b) were obtained from *o*-methylphenylcarbamoylthiamine (VIa) and *o*-benzoylthiamine (VIb).

Reduction of II with $NaBH_4$ in EtOH gave *o*-phenylcarbamoyldihydrothiamine (VIII), mp 136—140° (decomp.), which was also obtained from III by the reduction with $NaBH_4$ in EtOH after treatment with two moles of NaOEt. In aqueous EtOH, however, $NaBH_4$ reduction of II, III, or VIII gave tetrahydro derivative IX, respectively. Structure IX was confirmed by elemental analysis, as well as NMR spectral data. The signal of thiazolidine C-4 methyl protons appeared at τ 8.73 as doublet (J=6) and C-4, 5 protons at τ 6.6–7.3 as multiplet. Clark and Sykes[8] reported that the reduciton of a number of substituted thiazolium salts yielded diastereometric mixtures of thiazolidines. But thiazolidine IX obtained here was found to be single product from NMR spectrum.

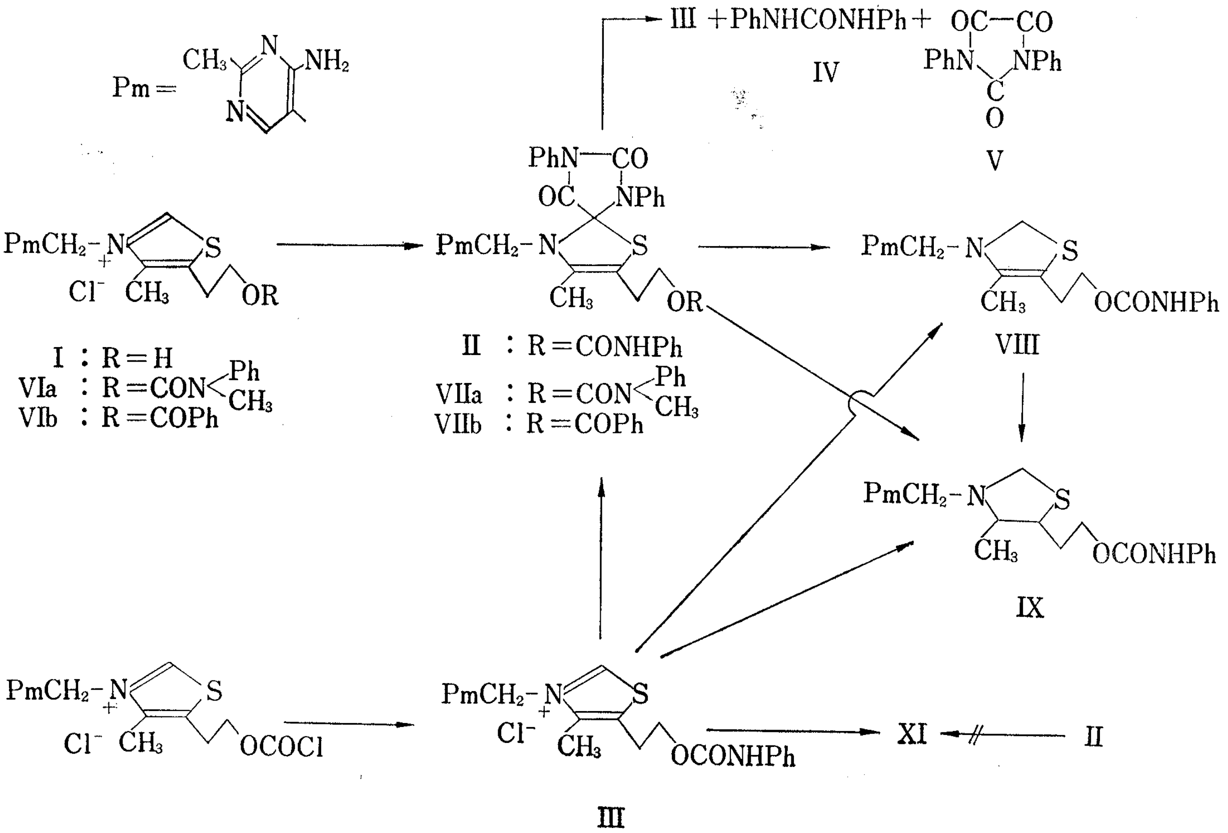

Chart 1

On the other hand, after treatment of I with methylsulfinyl carbanion or *t*-BuOK, phenylisocyanate was allowed to react to give the compound X, mp 155—158° (decomp.), and XI, mp 150—151° (decomp.), in 29.8 and 22.4% yield, respectively. An elemental analysis of X was consistent with the constitution of three moles adduct of phenylisocyanate to thiamine. UV spectrum showed the maxima at 225 and 275 mμ (log ε 4.51, 4.20), and IR spectrum showed strong carbonyl bands at 1782 and 1730 cm^{-1}. NMR spectrum ($CDCl_3$) showed two methyl proton signals at τ 8.37 and 7.45, two methylene proton signals at τ 7.73 and 6.67 as triplets (J=6.0), and two NH proton signals at τ 1.90 and −1.83, and the signal due to pyrimidine C_4–NH_2 group was disappeared. Therefore, the structure of X was assigned as 2-(2-hydroxyethyl)-3-methyl-4-(2-methyl-4-phenylcarbamoylaminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione. Treatment of X with dil. EtOH–HCl yielded I, IV, V, and N-phenylcarbamoylthiamine (XII), mp 194—197° (decomp.),

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[8] G.M. Clark and P. Sykes, *J. Chem. Soc.* (*C*), **1967**, **1411**.

which was identified with the product from thiamine free base (XIII)⁹⁾ and phenylisocyanate followed by hydrolysis.

Treatment of XII with methylsulfinylcarbanion followed by the reaction with phenylisocyanate afforded X and XI. Treatment of X with AcOH in acetone gave the compound XVI, mp 188—189° (decomp.), and the compound XVII, mp 198—199° (decomp.). These compounds have the same constitution as X. XVI was isomerized readily to XVII by acid. IR spectrum of XVI and XVII showed similar carbonyl bands as X. NMR spectrum showed two NH signals due to NHCONHPh at τ 1.65 and -1.67 (XVI) and at τ 1.05 and -1.85 (XVII), but the signals of methylene protons of the hydroxyethyl group in X was changed into multiplets indicating the formation of tetrahydrofuran rings. The angular methyl proton signal of XVII appeared at higher field (τ 8.77) than XVI (τ 8.12). Therefore, XVII was supposed to take the configuration as an anisotropy of phenyl ring in thiazolidinedione effected to the angular methyl group (*cis*), and XVI took the configuration as this effect was free (*trans*). An elemental analysis of the compound XI was consistent with the constitution of four moles adduct of phenylisocyanate to thiamine, and the structure of XI was considered to be 2-(2-phenylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-phenylcarbamoylaminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione. The structure was confirmed by the reaction of phenylisocyanate with X giving XI.

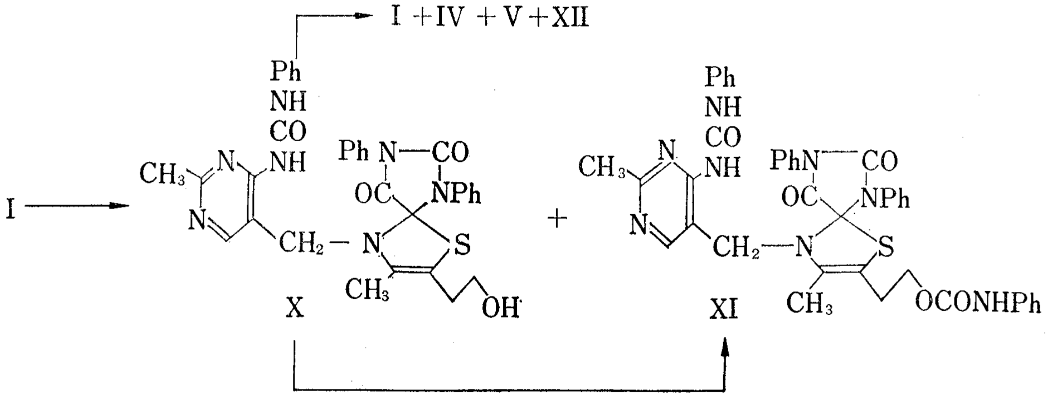

Chart 2

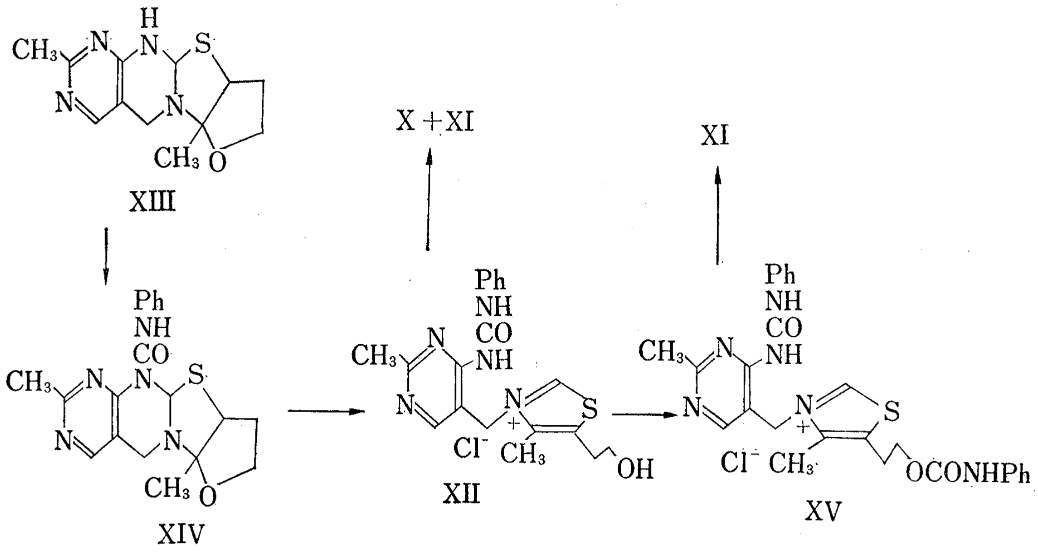

Chart 3

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[9] A. Takamizawa, K. Hirai, and Y. Hamashima, *Vitamin*, **34**, 280 (1966).

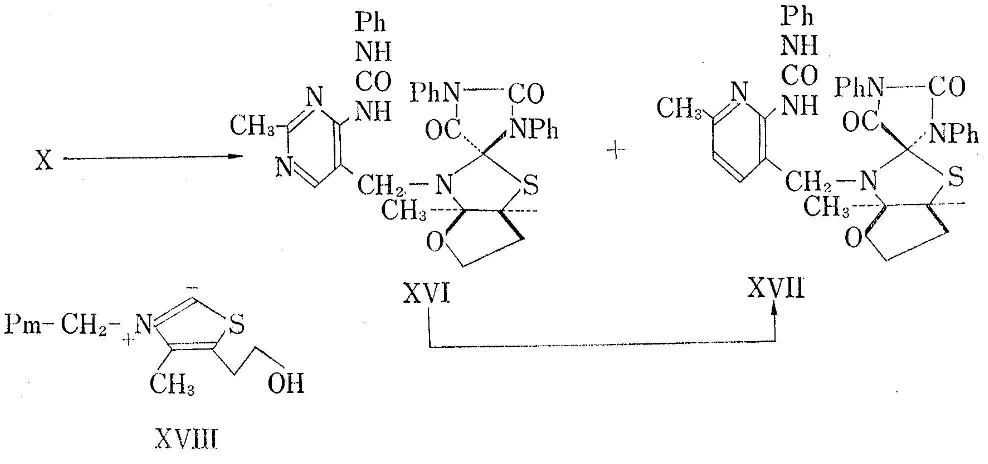

Chart 4

In order to examine the relative reactivity of thiazolium C-2, amino, and OH group in thiamine, toward carbamoylation, following reactions were carried out. N-Phenylcarbamoylthiamine (XII) was allowed to react with phenylisocyanate in the presence of Et_3N giving X and XI in 23.3 and 28.8% yield, respectively. Next, analogous reaction of *o*-phenylcarbamoylthiamine (III) with phenylisocyanate gave XI as major product and II as minor product with decreased overall yield. O,N-Bisphenylcarbamoylthiamine (XV), mp 135—137° (decomp), obtained from XII gave XI in 55.4% yield. However, II failed to give XI by the reaction of phenylisocyanate in the same reaction condition. XI was also obtained from III by the reaction of phenylisocyanate after treatment with methylsulfinylcarbanion in 23.6% yield.

Now it has been revealed that thiamine ylid (XVIII) formed by the treatment of I with Et_3N reacted with two moles of phenylisocyanate at the thiazolium C-2 position to give the cycloaddition product followed by the carbamoylation of the hydroxyl group yielding II. On the other hand, on treatment with strong bases as methylsulfinylcarbanion or *t*-BuOK followed by the reaction with phenylisocyanate, carbamoylation of the amino group proceeded preferentially, then the cycloaddition of two moles of phenylisocyanate at the thiazolium C-2 position occurred, and finally the hydroxyl group was carbamoylated.

Isocyanate forms readily dimer or trimer and the formation of 1,3-diaryl-5,5-diethoxyhydantoin by the reaction of arylisocyanate with ethyl orthoformate was reported,[10] but it will be noted that this novel cycloaddition at thiazolium C-2 position giving the spiro[thiazoline-2,4'-imidazolidine]derivatives is expectable to obtain the biologically active compounds. The biological tests are now in progress.

Experimental[11]

2-(2-Phenylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-aminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione (II)——a) To a suspension of 3.37 g of thiamine hydrochloride (I) in 40 ml of DMF, 2.2 g of Et_3N was added. After stirring for 2 hr, 4.8 g of phenylisocyanate was added to become clear solution. After 3 hr, the solvent was removed *in vacuo*, the residue was extracted with $CHCl_3$, washed with H_2O, and separated diphenylurea was removed. The $CHCl_3$ extract was dried ($MgSO_4$), evaporated, and the residue was treated with AcOEt to give 2.5 g of II. Recrystallization from EtOH gave colorless prisms, mp 166—168° (decomp). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3300, 3150, 1780, 1730. UV λ_{max}^{EtOH} $m\mu$ (log ε): 234, 271 (4.61, 3.91). NMR (τ, d_6-DMSO): 8.38^{s} (3H), 7.70^{s} (3H), 6.42^{t} (2H, J=*ca.* 6), 5.57^{s} (2H), 3.30^{b} (2H), 1.97^{s} (1H), 0.55^{s} (1H). *Anal.* Calcd. for $C_{33}H_{31}O_4N_7S$: C, 63.75; H, 5.02; O, 10.29; N, 15.81; S, 5.16. Found: C, 63.51; H, 5.12; O, 10.70; N, 15.49; S, 5.23.

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[10] C.W. Whitehead and J. Traverso, *J. Am. Chem. Soc.*, **80**, 962 (1958).

[11] All melting points are uncorrected.

b) A suspension of 2.23 g of *o*-phenylcarbamoylthiamine hydrochloride (III) in 30 ml of DMF was worked up as above to give 2.0 g of II.

***o*-Phenylcarbamoylthiamine Hydrochloride (III)**——To a suspension of 10.92 g of *o*-chlorocarbonylthiamine[7] in 120 ml of CH_3CN, 8.4 g of aniline was added under stirring and ice cooling. After standing overnight at room temperature, the separated crystals were collected, washed with EtOH, and recrystallized from dil. EtOH to give 9.4 g of colorless needles, mp 218—220° (decomp.). *Anal.* Calcd. for $C_{17}H_{23}O_2N_5SCl_2 \cdot H_2O$: C, 48.10; H, 5.32; O, 10.12; N, 14.77; S, 7.76; Cl, 14.95. Found: C, 47.62; H, 5.25; O, 9.71; N, 14.73; S, 6.72; Cl, 14.80.

HCl Decomposition of II——A mixture of 0.623 g of II, 4 ml of EtOH, and 4 ml of 15% HCl was refluxed for 6 hr. After evaporation *in vacuo*, the residue was treated with $CHCl_3$ and H_2O. The separated diphenylurea (0.05 g) was removed, H_2O layer was concentrated *in vacuo*, and the residue was recrystallized from dil. EtOH to give 0.25 g of III. The $CHCl_3$ layer was dried ($MgSO_4$), evaporated, and the residue was recrystallized from acetone to give V as colorless needles, mp 180—182°, which was identified with the sample obtained from diphenylurea and oxalyl chloride.[12] *Anal.* Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.66; H, 3.79; O, 18.03; N, 10.52. Found: C, 68.15; H, 3.99; N, 10.57; O, 18.03.

KOH Decomposition of II——A mixture of 0.624 g of II, 3.5 ml of 15% KOH, 4 ml of EtOH was allowed to stand overnight at room temperature. Separated IV (0.202 g) was removed, the filtrate was concentrated *in vacuo*, and made acidic by HCl to give 0.25 g of III.

2-(2-Methylphenylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-aminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione (VIIa)——To a suspension of 2.35 g of methylphenylcarbamoylthiamine hydrochloride (VIa) in 20 ml of DMF, 1.1 g of Et_3N was added. After stirring for 0.5 hr, 2.4 g of phenylisocyanate was added. After stirring for 2 hr, reaction mixture was concentrated *in vacuo*, the residue was extracted with $CHCl_3$, washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography with acetone to give 0.85 g of colorless prisms, mp 144—147° (decomp). UV λ_{max}^{EtOH} mμ (log ε): 229, 273 (4.51, 3.86). *Anal.* Calcd. for $C_{34}H_{33}O_4N_7S$: C, 64.23; H, 5.23; O, 10.07; N, 15.42; S, 5.04. Found: C, 64.21; H, 5.41; O, 10.21; N, 15.40; S, 5.19.

2-(2-Benzoyloxyethyl)-3-methyl-4-(2-methyl-4-aminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione (VIIb)——To a suspension of 4.6 g of *o*-benzoylthiamine hydrochloride (VIb) in 40 ml of DMF, 2.2 g of Et_3N was added. After stirring for 0.5 hr, 3.6 g of phenylisocyanate was added and stirred for 8 hr. Treatment as above gave 1.4 g of colorless prisms, mp 114—115° (decomp). UV λ_{max}^{EtOH} mμ (log ε): 229, 270 (4.59, 3.91). *Anal.* Calcd. for $C_{33}H_{30}O_4N_6S$: C, 65.33; H, 4.98; O, 10.75; N, 13.86; S, 5.28. Found: C, 64.94; H, 4.86; O, 10.65; N, 13.54; S, 5.74.

***o*-Phenylcarbamoyldihydrothiamine (VIII)**——a) To a solution of 0.604 g of $NaBH_4$ in 60 ml of EtOH, 1.244 g of II was added and stirred for 5 hr at room temperature. After addition of acetone the reaction mixture was concentrated *in vacuo*, extracted with $CHCl_3$, washed with H_2O, and the separated diphenylurea (0.325 g) was removed. The $CHCl_3$ layer was dried ($MgSO_4$), evaporated and acetone was added to the residue to give 0.33 g of colorless prisms, mp 136—140° (decomp). IR ν_{max}^{Nujol} cm^{-1}: 1740, 1223. UV λ_{max}^{EtOH} mμ (log ε): 236, 275 (4.41, 3.82). NMR (τ, $CDCl_3$): 8.15^s (3H), 7.50^s (3H), 7.35^t (2H, $J=6$), 6.20^s (2H), 5.78^s (2H), 5.73^t (2,H $J=6$), 4.17^b (2H), 2.02^s (1H). *Anal.* Calcd. for $C_{19}H_{23}O_2N_5S$: C, 59.21; H, 6.02; N, 18.17; S, 8.31. Found: C, 59.64; H, 6.10; N, 17.69; S, 7.98.

b) Sodium (0.092 g) was dissolved in 20 ml of EtOH, and 0.949 g of III was added to this solution under ice cooling. After stirring for 0.5 hr, 0.20 g of $NaBH_4$ was added, stirred for 1 hr at room temperature, allowed to stand overnight at room temperature. Acetone was added to the reaction mixture and concentrated *in vacuo*, the residue was extracted with $CHCl_3$, washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was added acetone to give 0.205 g of VIII.

***o*-Phenylcarbamoyltetrahydrothiamine (IX)**——a) To a mixture of 0.304 g of $NaBH_4$ and 30 ml of 50% EtOH, 0.622 g of II was added and stirred for 6 hr. After standing overnight at room temperature, acetone was added and evaporated *in vacuo*. The residue was treated with $CHCl_3$ and H_2O, the separated diphenylurea (0.19 g) was removed, $CHCl_3$ layer was dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography with acetone to give 0.30 g of colorless prisms, mp 176—177°. UV λ_{max}^{EtOH} mμ (log ε): 235.5, 274 (4.42, 3.82). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1605, 1225, 1065. NMR (τ, $CDCl_3$): 8.73^d (3H, $J=6$), 7.85^q (2H, $J=6$), 7.51^s (3H), 7.3–6.6^m (2H), 6.38^b (2H), 6.17^d (2H, $J=1.2$), 5.73^{t-d} (2H, $J=6.0$), 4.05^b (2H), 2.03^s (1H). *Anal.* Calcd. for $C_{19}H_{25}O_2N_5S$: C, 58.90; H, 6.50; N, 18.08; S, 8.26. Found: C, 59.04; H, 6.56; N, 17.94; S, 8.35.

b) To a suspension of 0.20 g of VIII in 10 ml of EtOH, 0.05 g of $NaBH_4$ was added. After stirring for 8 hr, 4 ml of H_2O and 0.05 g of $NaBH_4$ was added, stirred for 8 hr, and worked up as above to give 0.025 g of IX.

c) To a solution of 0.20 g of NaOH in 2.5 ml of H_2O, 1.14 g of III and 2.5 ml of EtOH was added. After addition of 0.115 g of $NaBH_4$, stirred for 4 hr, and the reaction mixture was worked up as above to give 0.51 g of IX.

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[12] H. Beltz and E. Topp, *Chem. Ber.*, **46**, 1399 (1913).

The Reaction of Thiamine and Its Derivatives with Phenylisocyanate in the Presence of Methylsulfinylcarbanion, *t*-BuOK, or Et_3N——a) To a solution of methylsulfinylcarbanion[13] prepared under nitrogen from 1.224 g (1.2 eq. mole) of sodium hydride (47% oil dispersion) and 30 ml of dimethylsulfoxide (DMSO), 6.9 g of thiamine monobromide was added with stirring under ice cooling, and 9.6 g of phenylisocyanate was added. After stirring for 6 hr and standing overnight at room temperature, the reaction mixture was concentrated *in vacuo.* The residue was treated with $CHCl_3$ and H_2O, $CHCl_3$ layer was dried ($MgSO_4$), evaporated and residue was chromatographed on silica gel with AcOEt to give 3.4 g of XI, 0.25 g of diphenylurea, and 3.7 g of X.

Recrystallization of X from acetone gave 2-(2-hydroxyethyl)-3-methyl-4-(2-methyl-4-phenylcarbamoylaminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione as colorless prisms, mp 155—158° (decomp). UV λ_{max}^{EtOH} mμ (log ε): 225, 275 (4.51, 4.20). IR ν_{max}^{Nujol} cm^{-1}: 1782, 1730, 1220, 1150. NMR (τ, $CDCl_3$): 8.37^{s} (3H), 7.73^{t} (2H, $J=6$), 7.45^{s} (3H), 6.70^{t} (2H, $J=6$), 5.45^{b} (2H), 1.90^{s} (1H), 1.57^{s} (1H), -1.83^{s} (1H). *Anal.* Calcd. for $C_{33}H_{31}O_4N_7S$: C, 63.69; H, 5.19; O, 10.28; N, 15.79; S, 5.15. Found: C, 63.83; H, 5.09; O, 10.02; N, 15.69; S, 5.24.

Recrystallization of XI from acetone–ether gave 2-(2-phenylcarbamoyloxyethyl)-3-methyl-4-(2-methyl-4-phenylcarbamoylaminopyrimidin-5-ylmethyl)-6,8-diphenyl-1-thia-4,6,8-triazaspiro[4,4]non-2-ene-7,9-dione as colorless prisms, mp 150—151° (decomp). UV λ_{max}^{EtOH} mμ (log ε): 233, 275 (4.60, 4.23). IR ν_{max}^{Nujol} cm^{-1}: 1787, 1720, 1230. NMR (τ, $CDCl_3$): 8.20^{s} (3H), 7.50^{t} (2H, $J=6$), 7.42^{s} (3H), 5.98^{t} (2H, $J=6$), 5.55^{b} (2H), 2.35^{s} (1H), 1.66^{s} (1H), -1.68^{s} (1H). *Anal.* Calcd. for $C_{40}H_{36}O_5N_8S\cdot\frac{1}{2}EtOH$: C, 64.48; H, 5.15; O, 11.52; N, 14.63; S, 4.20. Found: C, 64.45; H, 5.08; O, 11.37; N, 14.66; S, 4.42.

b) To a suspension of 1.5 g of thiamine monochloride in 20 ml of DMF, 0.67 g of *t*-BuOK was added and stirred for 0.5 hr. Phenylisocyanate (2.4 g) was added and allowed to stand overnight, worked up as above to give 1.25 g of XI, 0.3 g of diphenylurea, and 0.09 g of II.

c) To a solution of methylsulfinylcarbanion prepared under nitrogen from 0.511 g of sodium hydride (47% oil dispersion) and 20 ml of DMSO, 2.28 g of III was added with stirring and ice cooling, and 2.4 g of phenylisocyanate was added. After standing overnight at room temperature, the reaction mixture was worked up as above to give 0.1 g of phenylisocyanate trimer,[14] 0.909 g of XI, 0.059 g of diphenylurea, and 0.07 g of II.

d) To a solution of methylsulfinylcarbanion prepared under nitrogen from 0.011 g of sodium hydride (47% oil dispersion), and 5 ml of DMSO, 0.622 g of II and 0.24 g of phenylisocyanate was added and worked up as above to give 0.125 g of trimer, 0.02 g of diphenylurea, and 0.25 g of II.

e) To a suspension of 0.916 g of XII in 10 ml of DMF, 0.44 g of Et_3N and 0.72 g of phenylisocyanate were added and worked up as above to give 0.44 g of XI and 0.29 g of X.

f) To a solution of methylsulfinylcarbanion prepared under nitrogen from 0.051 g of sodium hydride (47% oil dispersion) and 5 ml of DMSO, 0.485 g of XV and 0.480 g of phenylisocyanate were added and worked up as above to give 0.050 g of trimer, 0.37 g of XI, and 0.005 g of diphenylurea.

g) To a solution of methylsulfinylcarbanion prepared from 0.011 g of sodium hydride (47%) and 5 ml of DMSO, 0.622 g of X, 0.24 g of phenylisocyanate was added and worked up as above to give 0.163 g of XI, 0.185 g of X, and 0.018 g of diphenylurea.

N-Phenylcarbamoylthiamine Free Base (XIV)——To a solution of 0.53 g of thiamine free base in 10 ml of DMF, 0.72 g of phenylisocyanate was added and stirred for 1.5 hr. After concentration of the reaction mixture *in vacuo,* extracted with $CHCl_3$, washed with H_2O, dried ($MgSO_4$), and evaporated to give 0.6 g of crystals.

Recrystallization from acetone gave colorless prisms, mp 175—178° (decomp). UV λ_{max}^{EtOH} mμ: 233, 255, 291. IR ν_{max}^{Nujol} cm^{-1}: 1678, 1600, 1217, 1025. *Anal.* Calcd. for $C_{19}H_{21}O_2N_5S$: C, 59.52; H, 5.52; O, 8.34; N, 18.27; S, 8.35. Found: C, 59.25; H, 5.61; O, 8.59; N, 17.95; S, 8.46.

N-Phenylcarbamoylthiamine Hydrochloride (XII)——To a solution of 0.10 g of XIV in 5 ml of EtOH, 0.7 ml of 5% EtOH–HCl was added. After becoming clear solution, crystals were separated, which were collected to give 0.12 g of colorless prisms, mp 194—197° (decomp). UV λ_{max}^{EtOH} mμ: 230, 271. IR ν_{max}^{Nujol} cm^{-1}: 1723, 1220. NMR (τ, d_6-DMSO); 7.48^{s} (3H), 7.28^{s} (3H), 6.95^{t} (2H, $J=6$), 6.50^{t} (2H, $J=6$), 4.18^{s} (2H), 2.33—3.17^{m} (5H), 1.35^{s} (1H), -0.30^{s} (1H), -1.12^{s} (1H). *Anal.* Calcd. for $C_{19}H_{25}O_2N_5SCl_2$: C, 49.78; H, 5.50; O, 6.98; N, 15.28; S, 7.00; Cl, 15.47. Found: C, 49.53; H, 5.12; O, 7.86; N, 15.08; S, 6.78; Cl, 15.15.

O,N-Bisphenylcarbamoylthiamine (XV)——To a solution of 2.1 g of XII monochloride in 20 ml of DMF, 2.4 g of phenylisocyanate was added and allowed to stand overnight. After concentration *in vacuo*, the residue was treated with acetone–MeOH to give 1.8 g of crude XV, which was recrystallized from EtOH to give colorless prisms, mp 135—137°(decomp). UV λ_{max}^{EtOH} mμ: 235, 261. IR ν_{max}^{Nujol} cm^{-1}: 1708, 1240. *Anal.* Calcd. for $C_{26}H_{27}O_3N_6SCl\cdot H_2O$: C, 56.05; H, 5.25; O, 11.51; N, 15.09; S, 5.76; Cl, 6.38. Found: C, 55.22; H, 5.00; O, 12.53; N, 14.91; S, 6.12; Cl, 6.47.

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3-(2-Methyl-4-phenylcarbamoylamino-5-pyrimidin-5-ylmethyl)-3a-methylperhydrofuro[2,3-*d*]thiazole-2-spiro-5′-(1′,3′-diphenyl)imidazolidine-2′,3′-dione (XVI, XVII)——a) A mixture of 0.311 g of X, 15 ml of acetone and 0.15 g of AcOH was refluxed for 8 hr. After concentration, acetone was added, and separated crystals were collected. The AcOEt filtrate was evaporated and chromatographed on Al_2O_3 with $CHCl_3$ to give 0.035 g of IX, 0.215 g of X, and 0.05 g of X.

Recrystallization of XVI from AcOEt gave colorless prisms, mp 188—189°. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 228, 279 (4.43, 4.13). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1778, 1722, 1232. *Anal.* Calcd. for $C_{33}H_{31}N_7SO_4 \cdot \frac{1}{2}CH_3COOC_2H_5$: C, 63.14; H, 5.30; O, 12.01; N, 14.73; S, 4.85. Found: C, 63.20; H, 5.20; O, 12.17; N, 14.93; S, 5.23.

Recrystallization of XVII from AcOEt gave colorless prisms, mp 198—199°. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 223, 275 (4.43, 4.18). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1780, 1733, 1240. *Anal.* Calcd. for $C_{33}H_{31}N_7SO_4$: C, 63.69; H, 5.19; O, 10.28; N, 15.79; S, 5.15. Found: C, 63.90; H, 4.99; O, 10.52; N, 15.81; S, 5.30.

b) A mixture of 0.04 g of XVI, 4 ml of acetone 0.06 g of AcOH was refluxed for 13 hr. After concentration of the reaction mixture *in vacuo*, acetone-ether was added to give 0.029 g of XVII.