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

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2-Morpholino-, 2-piperidino-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole (VI, IX), and N,N′-bis{2-[3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]]thiazolyl}piperazine (X) were synthesized by the reaction of B_1 hydrochloride (I) or B_1-Na (II) with corresponding amines. Reactions of II with aniline and benzylamine were also undertaken to result in giving N-[1-methyl-2-phenylimino (or 2-oxo-)-4-hydroxybutyl]-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]-formamide (XIV, XVII). Brief reaction mechanisms are discussed.

Since the mechanism for thiamine (B_1) catalysis on the decarboxylation of pyruvic acid was proposed by Breslow,[3] much attention on the reactivity of B_1 thiazole C_2 position has been drawn. The authors also have been interested in the study of the reactivity at B_1 thiazole C_2 position and found as reported in the preceeding paper that the reaction of B_1 with aldehydes occurred at the thiazole C_2 position accompanying the cyclization of a hydroxyethyl group forming a tetrahydrofuran ring to give 2-acyl-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-d]thiazoles.

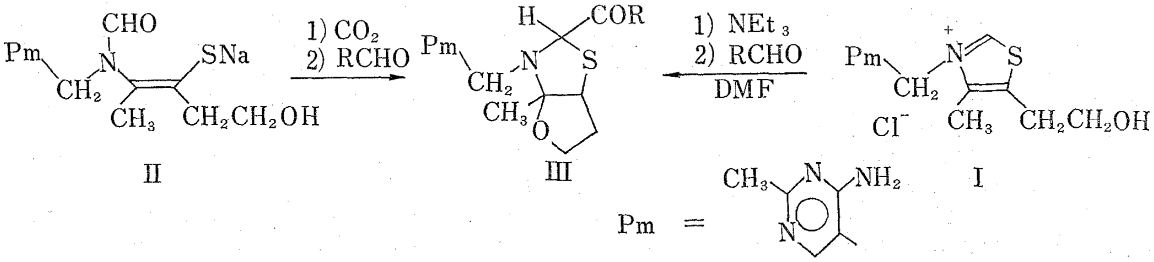

Chart 1

Recently, Metzger, *et al.*[4] reported that benzothiazolium salts reacted with piperidine to give C_2 substitution derivatives by way of ylid, carbene structure or its precursor of benzothiazolium salts. In view of the above fact it would be interesting to study the reaction of B_1 with amines. Reaction of thiol B_1 (B_1-Na) with various amines had already been investigated in details by Masuda,[5] whose reports described that amine substitution products such as N-(1-methyl-2-alkylamino-4-hydroxy-1-butenyl)-N-[(2-methyl-4-aminopyrimidin-5-yl)-methyl]formamide (IV) were obtained with primary amines, and 2-(2-hydroxyethyl)-3,8-dimethyl-4-formyl-4,5-dihydro-1H-pyrimido[4,5-e]-1,4-diazepine (V) by loss of hydrogen sulfide with secondary amines. Investigation on reaction of B_1-Na (II) with various amines has also been undertaken in our laboratory. This paper describes the new type of reaction of II

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[1] Part L: A. Takamizawa, K. Hirai, Y. Hamashima, and S. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1210 (1968).
[2] Location: *Sagisu, Fukushima-ku, Osaka.*
[3] R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958).
[4] J. Metzger, H. Larivé, R. Dennilauler, R. Baralle, and G. Gaurat, *Bull. Chim. Soc. France*, **1964**, 2857.
[5] K. Masuda, *Yakugaku Zasshi*, **81**, 533, 536, 540 (1961).

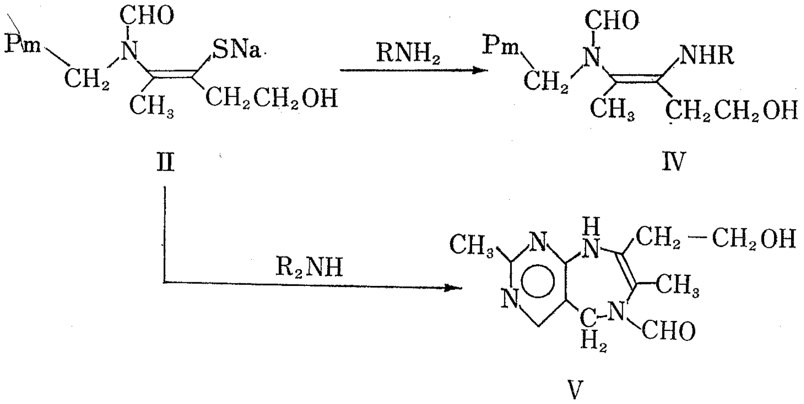
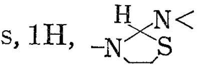
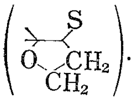


Chart 2

with amines. After being passed carbon dioxide into a toluene or ethanol suspension of II under cooling to adjust to about pH 8.0—7.5, two moles of morpholine were added and the mixture was stirred for 8 hours at room temperature. The light brown reaction mixture was concentrated and the residue was extracted with chloroform. From the extract there were obtained colorless crystals, mp 143—144°, in good yield, showing analytical data for $C_{16}H_{25}O_2N_5S$ corresponding to the 1 : 1 adduct of B_1 and morpholine. The ultraviolet (UV) spectrum showed maxima at 237 (ε 8,160) and 278.5 mμ (ε 5,580), suggesting that the pyrimidine nucleous might be a monocyclic system. The infrared (IR) absorption spectrum showed absorption bands at 3310, 3132, 1672 (NH_2), 1593, 1514 (characteristics), 1112 (morpholine–O–), and at 999 cm^{-1} which was anticipated to be due to an another ether band. Nuclear magnetic resonance (NMR) spectrum (Fig. 1) in deuterio chloroform (I) showed peaks at 8.42 (s) being attributed to the 3a–methyl group of perhydrofuro[2,3–*d*]thiazole nucleous, 7.65 and 6.35 (m, 8H, morpholine), 6.10 (s, 2H, Pm–C_5–CH_2–), 4.95(s, 1H, ), 3.72 (b, NH_2), 1.98 (s, 1H, Pm–C_6–H), and at 5.6—8.1 (m, 5H) indicating the presence of tetrahydrofuran ring system (). When an aqueous hydrochloric acid solution of VI was allowed to stand at room temperature, B_1–hydrochloride and morpholine hydrochloride were obtained in a quantitative yield. Action of picric acid to VI afforded 3–(2–methyl–4–aminopyrimidin–5–yl)methyl-3a-methyl-3a,5,6,6a-tetrahydrofuro[2,3-*d*]thiazolium picrate (VII) and morpholine picrate, VII was converted into B_1–dipicrate (VIII) by heating in ethanol. From the above data the structure of VI was determined to be 2–morpholino–3–(2–methyl–4–aminopyrimidin–5–yl)methyl–3a–methylperhydrofuro[2,3-*d*]thiazole. VI was also obtained in good yields either by reaction of II with dimethylformamide–phosgene complex[6] and successive treatment with morpholine or reaction of B_1–HCl (I) with triethylamine and successive treatment with morpholine, respectively. It was found that the reaction of I or II with piperidine proceeded quite analogously to give 2–piperidino–3–(2–methyl–4–aminopyrimidin–5–yl)methyl–3a–methylperhydrofuro[2,3-*d*]thiazole (IX), mp 145—147° (decomp.), in 76% yield. The structure of IX was confirmed on the basis of

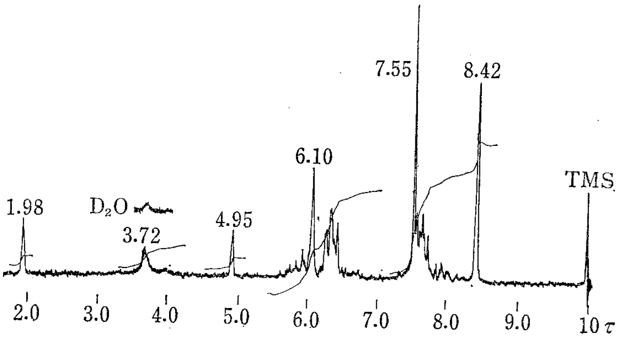


Fig. 1. Nuclear Magnetic Resonance Spectrum of VI in $CDCl_3$ (60 Mcps)

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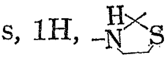
[6] Z. Arnold, *Collection Czech. Chem. Commun.*, 24, 4048 (1959).

the following data: UV λ_{max}^{EtOH}: 238.5 (ε 8,400), 280.5 mμ (ε 5,930), IR ν_{max}^{Nujol}: 3360, 1672, 1604, 1596, 1032 cm^{-1}, NMR (τ in CDCl$_3$): 1.96 (s, 1H, Pm–C$_6$–H), 3.76 (b, 2H, Pm–C$_4$–NH$_2$), 4.90 (s, 1H, ), 6.10 (s, 2H, Pm–C$_5$–C$\underline{H}_2$–), 7.55 (s, 3H, Pm–C$_2$–CH$_3$), 8.46 (s, 3H, 3a–CH$_3$), 5.65—8.1 (m, 5H, cyclic >CH–CH$_2$–CH$_2$–O–), 7.63 (m, 4H, piperidine –CH$_2$–N–CH$_2$–), 8.52 (m, 6H, piperidine –CH$_2$–CH$_2$–CH$_2$–). In the reaction of II with piperazine it was obtained N,N′-bis-{2-[3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro-[2,3-*d*]]thiazolyl}-piperazine (X), mp 147—150° (decomp.), in 78% yield. Physical data of X were described as follows, elemental analysis ($C_{28}H_{42}N_{10}O_2S_2$), UV [λ_{max}^{EtOH}: 235, 278 mμ], IR [ν_{max}^{Nujol}: 3340, 3170, 1671, 1596, 1026, 996 cm^{-1}], and NMR [τ (CDCl$_3$): 1.92 (s, 2H, Pm–C$_6$–H), 4.02 (b, 4H, Pm–C$_4$–NH$_2$), 4.91 (s, 2H, Th–C$_2$–H), 6.05 (s, 4H, Pm–CH$_2$–), 7.54 (s, 6H, Pm–C$_2$–CH$_3$), 8.47 (s, 6H, Th–C$_4$–CH$_3$)].

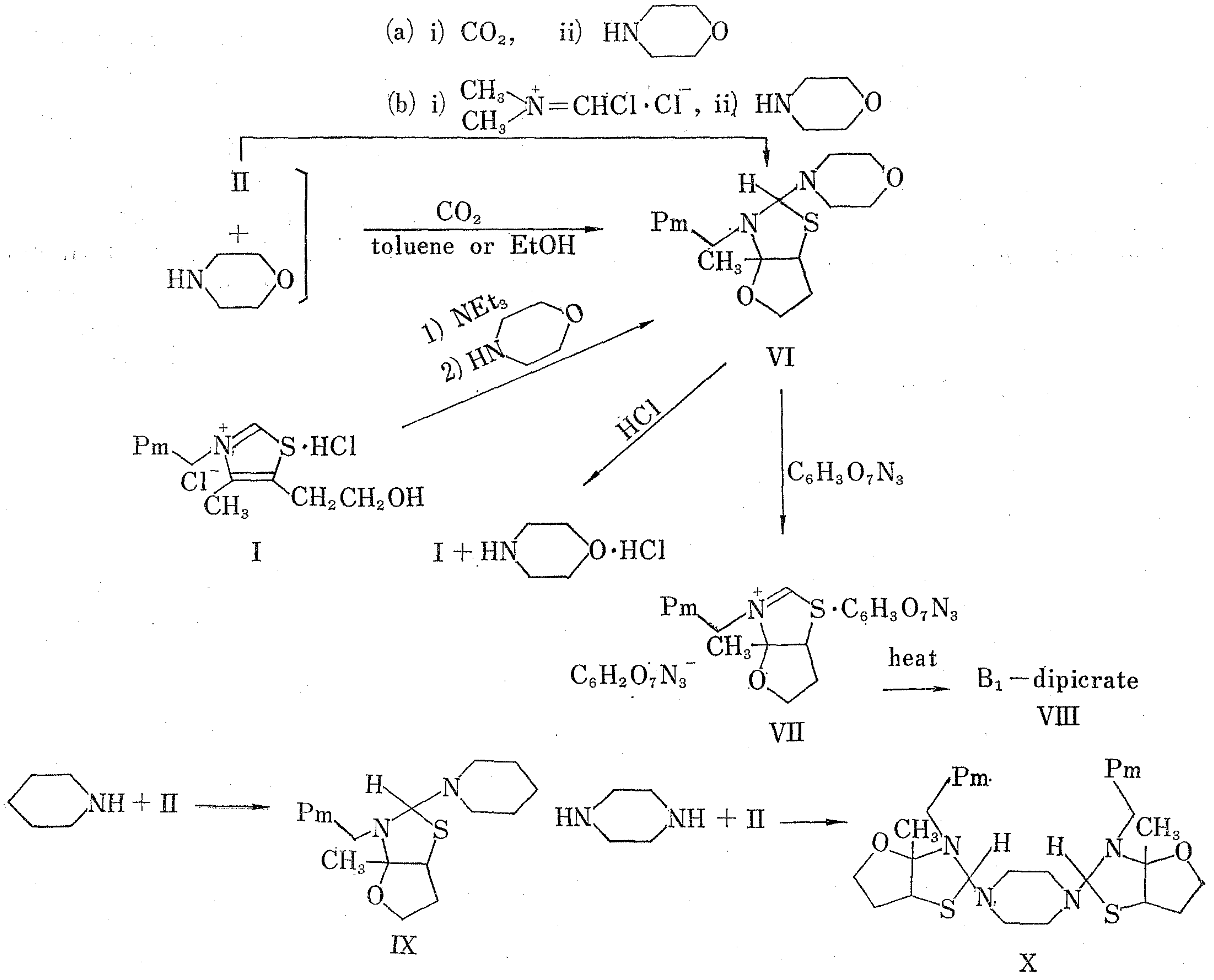


Chart 3

Next, reactions of II with aniline and benzylamine were undertaken. In these cases, on the contrary, no thiazole C$_2$-substitution products were obtained. It was found that the reaction of II with aniline gave 2,2-bis[4-methyl-5-(2-hydroxy)-ethyl]thiazole (XI),⁷⁾ thiothiamine (XII), N-(2-methyl-4-aminopyrimidin-5-yl)methylidenaniline (XIII), and N-(1-methyl-2-phenylimino-4-hydroxybutyl)-N-[(2-methyl-4-aminopyrimidin-5-yl)methyl]formamide (XIV), respectively. The structure of XIII was confirmed by the elemental analysis ($C_{12}H_{12}N_4$), UV (λ_{max}^{EtOH} 330 mμ), and NMR [(τ in CDCl$_3$) 2.19 (s, 1H, Pm–C$_6$–H, 2.22—2.60

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7) P. Karrer and M.C. Sanz, *Helv. Chim. Acta*, **27**, 619 (1944).

(m, 5H, C_6H_5), 3.22 (s, 1H, Pm–C$\underline{H}$=), 7.53 (s, 3H, Pm–C_2–CH_3)] spectral consideration. XIV contained no sulfur and corresponded to $C_{18}H_{23}O_2N_5$, and showed signals of typical CH_3–CH< system at 8.43 (d, 3H, $J=7.0$ cps) and 5.50 τ (q, 1H, $J=7.0$ cps) in its NMR spectrum. In the reaction of II with benzylamine XI, XII, small amount of thiamine anhydride (XV) and XVI, were obtained. XVI, mp 122—123°, having analytical data for $C_{12}H_{18}O_3N_4S$, showed absorption maxima at 238, and 277 mμ, and showed a strong carbonyl band at 1721 cm^{-1} in its IR spectrum. NMR spectrum showed signals at 1.78 (s, 1H, N–CHO), 2.08(s, 1H, Pm–C_6–H), 3.90 (b, 2H, NH_2), 7.45 (q, 1H, CH_3–C$\underline{H}$<, $J=7.2$ cps), and at 8.50 (d, 3H, C$\underline{H}_3$–CH<, $J=7.2$ cps). From the above mentioned data the structure of XVI was determined to be N–(1–methyl–2–oxo–4–hydroxybutyl)–N–[(2–methyl–4–aminopyrimidin–5–yl) methyl] formamide.[8] XVI might be produced by hydrolysis of N–(1–methyl–2–benzylimino–4–hydroxybutyl)–N–[(2–methyl–4–aminopyrimidin–5–yl)methyl]formamide (XVII),[5] which would be produced initially, during the column chromatographic separation.

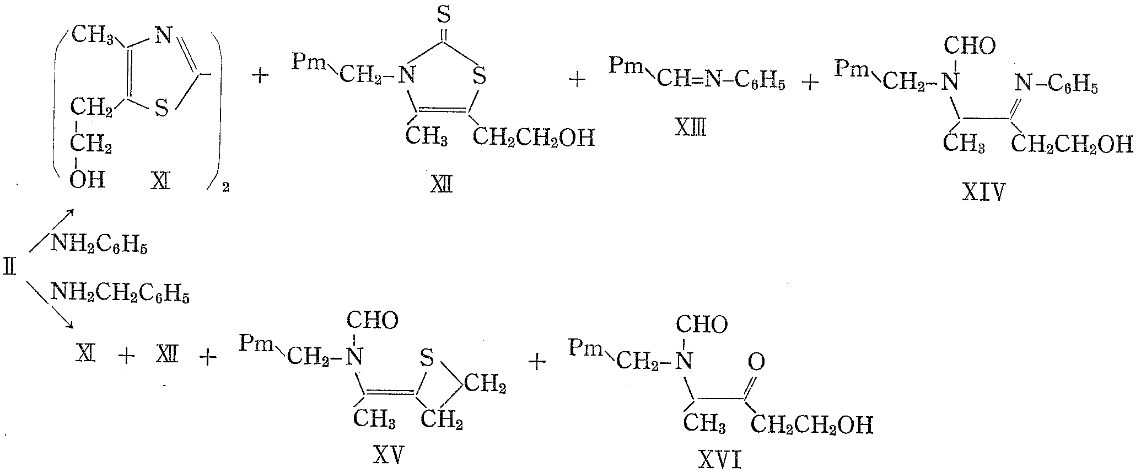

Chart 4

As mentioned above, the authors succeeded in obtaining new thiamine derivatives (VI, IX and X) substituted at the Th–C_2 position. Plausible mechanism for this reaction may be described as follows. It has been nearly clarified that reaction of B_1 with aldehydes proceeded by way of nucleophilic B_1 carbene as mentioned in preceeding report. Although it may be

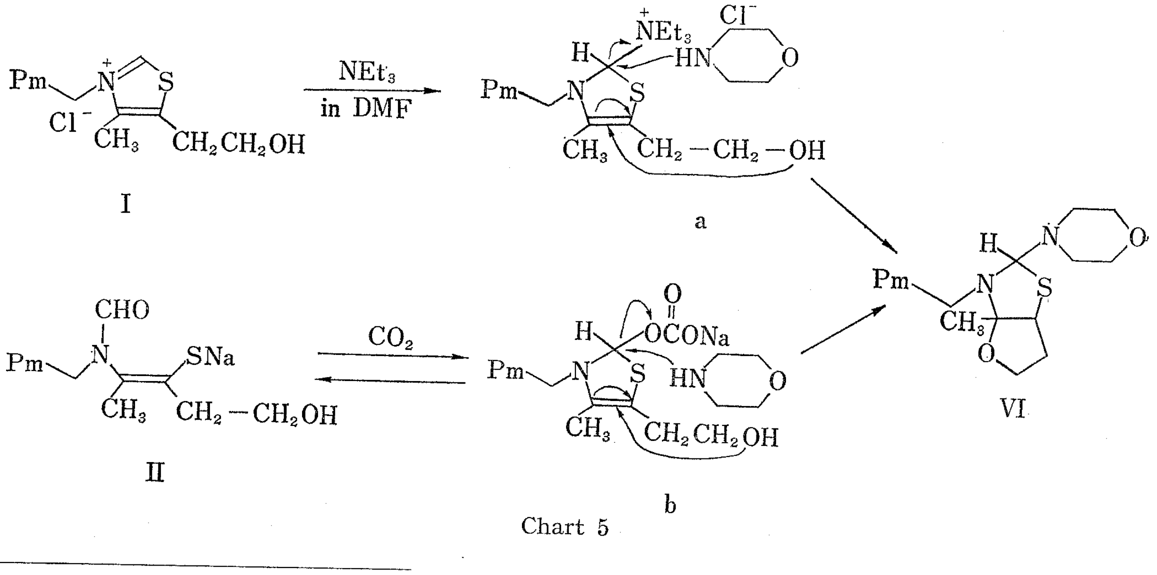

Chart 5

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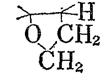
[8] G. Kurata, T. Sakai, R. Miyahara, and H. Yokoyama, *Vitamins* (Japan), **35**, 136 (1967).

considered in this case that the reaction proceeds *via* B_1 carbene in the similar manner, such a hypothesis will be rather improbable because of lower nucleophilicity of the carbene than that of amines. From this reason it seems to be reasonable to assume that it will firstly produce pseudothiamine type a by treatment of I with triethylamine and b by treatment of II with carbon dixoide, both a and b, considering as precursors of B_1 carbene, further proceed to give VI reacting with morpholine. This is the first case that amines were introduced at the Th–C_2 position of B_1. Now, in the reaction of II with aniline or benzylamine as mentioned above no such products as VI were obtained anyway. For this fact it may be considered that the nucleophilicity of aniline or benzylamine is not so strong as that of piperidine, morpholine or piperazine it can not be able to produce pseudothiamine type intermediate like a or b. For the reason obtaining different result against Masuda's report in the reaction of II with aniline, it seems to be due to a different reaction condition used. In our case, it may be considered that reactivity of pyrimidine C_4–amino group will be rather weakened and results in producing aniline substitution product. Details of these reactions are now in progress.

Experimental[9]

2-Morpholino-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole (VI)——a) To a suspension of 3.92 g of B_1–Na and 3 ml of morpholine in 25 ml of EtOH was passed through excess of CO_2 under ice–water cooling. After the mixture was allowed to stand at room temperature for 8 hr, the mixture was concentrated to dryness and extracted with $CHCl_3$. Evaporation of the solvent gave 2.5 g of colorless residue, which was recrystallized from acetone to give VI as colorless needles, mp 143—144° (decomp.). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3342, 3146, 1676 (NH_2), 1597, 1577. 1113 (–O–). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 237 (3.914), 278.5 (3.748).NMR (τ) in $CDCl_3$: 1.98 (s, 1H, Pm–C_6–H), 3.72 (b, 2H, NH_2), 4.95 (s, 1H, Th–C_2–H), 6.10 (s, 2H, Pm–C_5–CH_2–), 6.35 (m, 4H, –CH_2–O–CH_2–), 7.55 (s, 3H, Pm–C_2–CH_3), 7.65 (m, 4H, –CH_2–N–CH_2–), 8.42 (s, 3H, Th–3a–CH_3), 5.62—6.0, 6.5—6.78, 7.72—8.0 (m, 2H, 1H, 2H,  $\underset{\text{CH}_2}{\overset{\quad\text{H}}{\text{O}\;\text{CH}_2}}$). *Anal.* Calcd. for $C_{16}H_{25}O_2N_5S$: C, 54.67; H, 7.17; N, 19.92. Found: C, 54.87; H, 7.35; N, 19.41.

b) To 30 ml toluene solution containing 1.3 g of phosgene was added 4.25 g of B_1–Na under dry ice–acetone cooling and stirring. After 1hr, the temperature was rosen to room temperature during 20 hr. The solution was concentrated learing cololress powder, to which was added 5 ml of morpholine and 20 ml of EtOH. The mixture was stirred at room temperature for 2 hr, concentrated and extracted with $CHCl_3$. Removal of the solvent afforded VI as colorless crystals, which were recrystallized from acetone to give colorless needles, mp 143—144° (decomp.), which was identical with the sample obtained above. Yield, 2.5 g (71.2%).

c) To a suspension of B_1–HCl (3.37 g) in DMF (20 ml) was added NEt_3 (4.05 g) under ice–water cooling and stirring. After 30 min, 1.8 g of morpholine was added into the suspension to obtain rather liquid paste, which was reacted at room temperature for 20 hr resulting light brown suspension, filtered and the filtrate was concentrated and extracted with $CHCl_3$. Removal of the solvent afforded colorless needles, which was identified as VI by the IR comparison. Yield, 1.5 g (42.7%).

d) Addition of 0.64 g of N–chloromethylene dimethylammonium chloride in $CHCl_3$ to the suspension of 4.5 g of B_1–Na in 40 ml of $CHCl_3$ under ice–water cooling occurred vigorous reaction and obtained semi-transparent emulsion. After being stirred at the temperature for 30 min, the suspension was added 3.4 g of morpholine and the mixture was stirred at room temperature for 8 hr, washed and dried. Removal of the solvent gave VI as colorless crystals, which were identified with VI mentioned above by their IR comparison. Yield, 2.0 g (57%).

Acid Hydrolysis of VI——Fifty milligrams of VI was dissolved in 0.2 ml of 5% HCl and neutralized with 20% NaOH to became pH 8.5—9.0. Addition of NH_4SCN and AcOH to adjust pH 7.5—8.0, and allowed to stand overnight in a refrigerator. Precipitated crystals were collected (35 mg), which showed identical IR spectrum with that of B_1–rhodanate, mp 178—180°.

Addition of Picric Acid to VI——On addition of picric acid to 120 mg of VI in EtOH, yellow precipitates were liberated immediately. Filtration and washing the precipitate gave VII melting at 147—149°

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[9] 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. Multiplicities of signals are represented as s (singlet), d (doublet), t (triplet), b (broad), and m (multiplet).

(decomp.). Yield, 200 mg. *Anal.* Calcd. for $C_{24}H_{22}O_{15}N_{10}S$: C, 39.89; H, 3.07; N, 19.37. Found: C, 39.98; H, 3.35; N, 19.03. From the mother liquid 80 mg of yellow plates (mp 145—147°) were obtained, which was identical with morpholine picrate. Recrystallization of VII from EtOH gave B_1–picrate (VIII), mp 207—208° (decmp.), which was identified with an authentic B_1–picrate by IR comparison. Yield, 186 mg. *Anal.* Calcd. for $C_{24}H_{22}O_{15}N_{10}S$: C, 39.89; H, 3.07; N, 19.37. Found: C, 39.41; H, 3.42; N, 19.34.

2-Piperidino-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazole (IX)——To a suspension of B_1–Na (prepared from 1 mole of B_1–HCl and 3 mole of NaOH by an ordinary method) in 40 ml of EtOH was added 3.4 ml of piperidine, after that excess of CO_2 was passed into the suspension for 30 min. The mixture was stirred at room temperature for 2 days, concentrated and extracted with $CHCl_3$. The extract was washed, dried and evaporated to leave colorless crystals, which was recrystallized from acetone giving IX as colorless pillars, mp 145—147° (decomp.). Yield, 2.5 g (71.5%). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3360, 3056, 1672 (NH_2), 1604, 1090, 1032. UV $\lambda_{\max}^{\text{EtOH}}$ $m\mu$ (log ε): 238.5 (3.925), 280.5 (3.775). NMR (τ) in $CDCl_3$: 1.96 (s, 1H, Pm–C_6–H), 3.76 (b, 2H, Pm–C_4–NH_2), 4.90 (s, 1H, Th–C_2–H), 6.10 (s, 2H, Pm–CH_2–), 7.55 (s, 3H, Pm–C_2–CH_3), 8.46 (s, 3H, Th–3a–CH_3), 5.65—8.1 (m, 5H, cyclic $\rangle$CH–CH_2–CH_2–O–), 7.63 (m, 4H, Pip–CH_2–$\overset{|}{N}$–CH_2–), 8.52 (m, 6H, Pip–CH_2–CH_2–CH_2–). *Anal.* Calcd. for $C_{17}H_{27}ON_5S$: C, 58.42; H, 7.79; N, 20.04; O, 4.58; S, 9.17. Found: C, 58.63; H, 8.08; N, 20.15; O, 4.64; S, 9.40; mol. wt. 339 ($CHCl_3$). Calcd. 349.51.

N,N′-Bis[3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-*d*]thiazol-2-yl]piperazine (X)——After passing through CO_2 gas into a suspension of B_1–Na (4.25 g) in EtOH (45 ml) for 1.5 hr, piperazine hexahydrate (3.9 g) was added and stirred at room temperature for 2 hr, the reaction mixture was concentrated, extracted with $CHCl_3$. Evaporation of the solvent leaves 2.4 g of colorless crystals, which were recrystallized from acetone or EtOH giving X as colorless prisms, mp 147—150° (decomp.). TLC (SiO_2–acetone): *Rf* 0.22. *Anal.* Calcd. for $C_{28}H_{42}O_2N_{10}S_2$: C, 54.71; H, 6.89; N, 22.79; S, 10.41. Found: C, 54.68; H, 6.96; N, 22.36; S, 11.00.

Reaction of Aniline with B_1-Na——To a mixture of B_1–Na (4.5 g) and aniline (3.94 g) in 40 ml of EtOH was passed through excess CO_2 under ice–water cooling. After passing for 2 hr, the suspension was allowed to react at room temperature for 24 hr, concentrated and extracted with $CHCl_3$. Evaporation of the solvent and the residue was chromatographed over SiO_2, and eluated by acetone. First fraction contained aniline (2.1 g). Next fraction gave colorless crystals, which was recrystallized from acetone giving 2,2–bis[4–methyl–5–(2–hydroxy)ethyl]thiazole (XII), mp 180—181°, which was identified with authentic sample of XII by the melting point determination and IR comparison. Next fraction gave colorless crystals, which was recrystallized from MeOH to give thiothiamine as colorless needles, mp 240°. Yield, 0.52 g. The last fraction gave colorless crystals which were recrystallized from acetone giving XIII as colorless needles, mp 124—125°, which showed analytical data for $C_{18}H_{23}O_2N_5$: Calcd. C, 63.32; H, 6.79; N, 20.52; O, 9.37. Found: C, 63.42; H, 6.58; N, 20.53; O, 9.69. Picrate, yellow sticks, mp 177—178°. *Anal.* Calcd. for $C_{30}H_{29}O_{16}N_{11}$: C, 45.05; H, 3.66; N, 19.29; O, 32.05. Found: C, 44.83; H, 4.07; N, 19.50; O, 31.53.

NMR (τ) in $CDCl_3$: 1.60 (s, 1H, N–CHO), 1.95 (s, 1H, Pm–C_6–H), 2.47—3.35 (m, 5H, C_6H_5), 3.91 (b, 2H, NH_2), 5.50 (q, 1H, –$\overset{|}{C}\underline{H}$–$CH_3$, *J*=7.0), 5.55 (s, 2H, Pm–CH_2–), 6.45 (t, 2H, –O–$C\underline{H}_2$–CH_2, *J*=6.1), 7.56 (s, 3H, Pm–C_2–CH_3), 7.68 (t, 2H, –O–CH_2–$C\underline{H}_2$–, *J*=6.1), 8.43 (d, 3H, –N–CH–$C\underline{H}_3$, *J*=7.0).

Reaction of Benzylamine with B_1-Na——To a suspension of B_1–Na (9.0 g) in EtOH (80 ml) was passed through excess of CO_2, after that benzylamine (4.3 g) was added and the mixture was stirred at room temperature for 3 hr. Evaporation of the mixture left oily residue, which was extracted with $CHCl_3$. Removal of the solvent left oily residue partly precipitated. Acetone was added and the insoluble solids were filtered. It was recrystallized from MeOH gave colorless rhombs., mp 125—126° (decomp.), which showed analytical data for $C_{12}H_{16}ON_4S$ and was identified as anhydrothiamine (XIV) by the IR comparison. The filtrate was chromatographed over SiO_2 and eluated by acetone affording benzylamine as first fraction. Next fraction gave XI as colorless needles (0.32 g). Next fraction gave thiothiamine (0.16 g) as colorless solid. Elution solvent was exchanged by MeOH and obtained 320 mg of XV as colorless solid, which was recrystallized from MeOH to give colorless sticks, mp 122—123°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1721 (C=O). UV $\lambda_{\max}^{\text{EtOH}}$ $m\mu$: 238, 277. NMR (τ) in $CDCl_3$: 1.78 (s, 1H, N–CHO), 2.08 (s, 1H, Pm–C_6–H), 3.90 (b, 2H, NH_2), 5.66 (AB q, 2H, Pm–CH_2–), 6.21, 7.45 (t–t, 4H, –CH_2–CH_2–O–), 7.55 (s, 3H, Pm–C_2–CH_3), 8.50 (d, 3H, –N$\langle\underset{|}{\overset{|}{C}}$H–$C\underline{H}_3$). *Anal.* Calcd. for $C_{12}H_{18}O_3N_4$: C, 54.05; H, 6.81; N, 21.02; O, 18.01. Found: C, 53.60; H, 7.12; N, 20.49; O, 18.76.

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