1 hr. The reaction mixture was treated with 15 cc. of EtOH to decompose the excess of Na, diluted with water, and EtOH was evaporated *in vacuo*. The resulting aqueous solution was acidified with 10% HCl at −10° and extracted with Et_2O which was dried over Na_2SO_4 in an ice-box and evaporated *in vacuo*. 950 mg. of the oily residue was dissolved in Et_2O and extracted with 5% Na_2CO_3. 750 mg. of acidic oil was obtained from the alkaline solution by the same procedure as above and 200 mg. of neutral oil from the Et_2O solution.

By distillation and adsorption chromatography with SiO_2 (Mallinckrodt for chromatography, 100 mesh) and $CHCl_3$ as an elution solvent, 90 mg. of slightly yellow oil was obtained from the neutral fraction. *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; mol. wt., 196.28. Found : C, 73.49; H, 10.02, mol. wt., 200, 210, 210. IR $\nu_{max}^{liq.\ film}$ cm^{-1} : 1665, 1175, 1128, 980.

Distillation of the 750 mg. of acidic fraction afforded 500 mg. of neutral oil, whose IR spectrum was in good coincidence with that of the neutral fraction (Fig. 3).

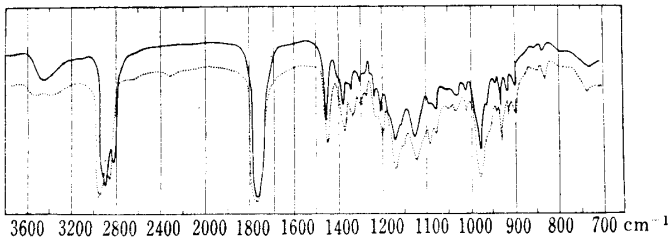

Fig. 3. Infrared Spectra of Reduction Products with Na and EtOH

—— Neutral fraction
------ Distilled from acid fraction

The authors express their gratitude to Mr. K. Narita of this Institute for the elemental analyses.

Summary

The structure of ligustilide was discussed upon the fact that sedanonic acid, 3-butylphthalide, and 2-valerylcyclohexanecarboxylic acid were obtained by catalytic hydrogenation. Tentative structures were proposed on the basis of available data. The position of double bonds, however, remains to be determined.

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22. Shun-ichi Yamada and Kazuo Achiwa : Studies on Thiamine Analogs; Synthesis of 3-[(2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)methyl]-4-methyl-5-(2-hydroxyethyl)thiazolium Nitrate.

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Many kinds of thiamine analogs have been synthesized and the relationship between their chemical structure and physiological actions has been studied in detail. From these results,[1] it has been shown that it is essential for the action of thiamine (I) to have the amino group in 4-position of the pyrimidine ring. It is also essential that one hydrogen be present in 2-, methyl in 4-, and hydroxyethyl in 5-positions of the thiazolium ring, and

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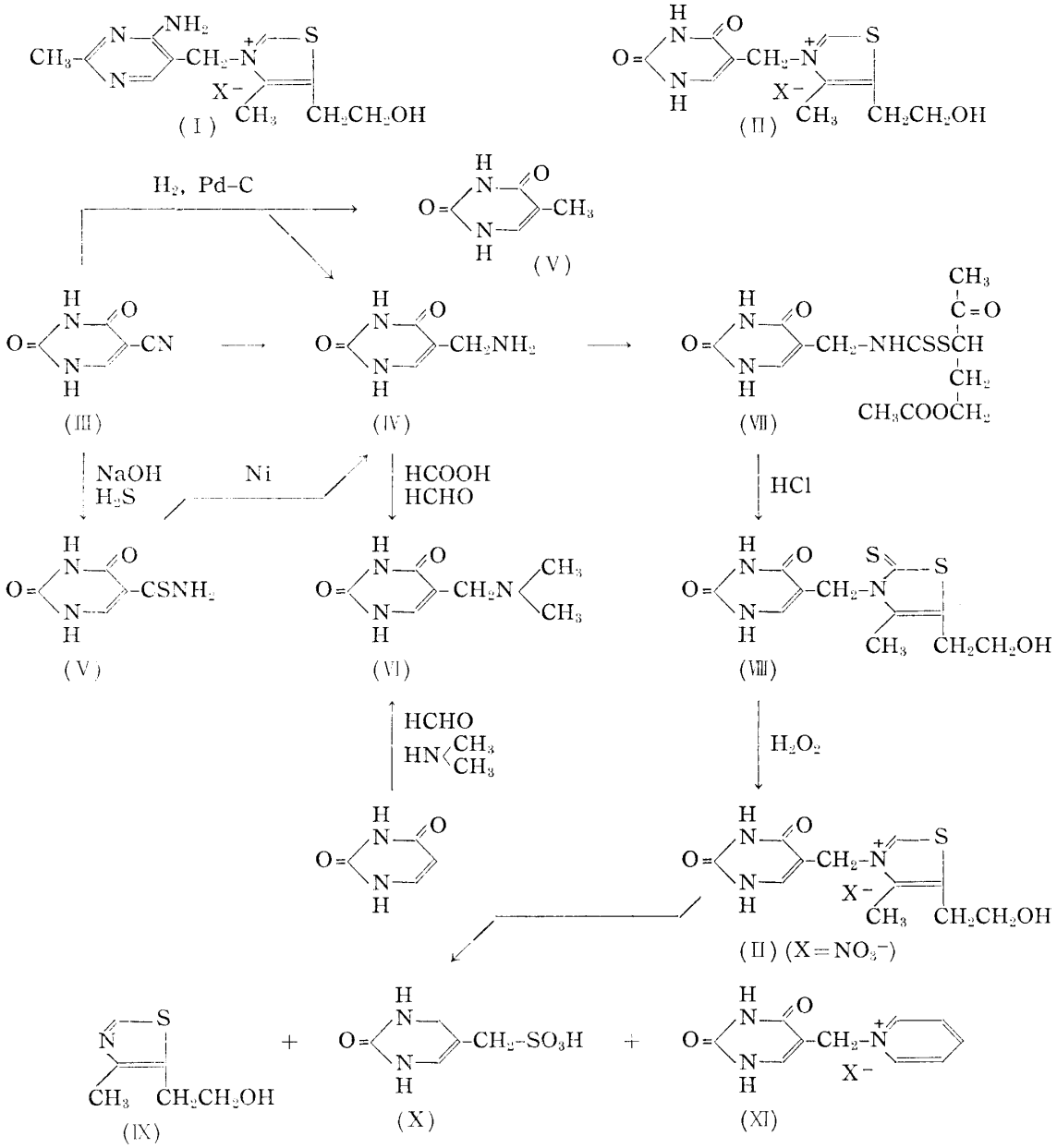
1) "Vitamin B_1," compiled by The Japanese Science Council, 69 (1948). Sogensha, Tokyo.



both rings, pyrimidine and thiazole, should be joined with $-CH_2-$ bridge in its molecule. As a result, it appears that the thiazole part of thiamine plays a still more important rôle in thiamine action.

On the other hand, oxythiamine[2] showed antithiamine action and recently it was reported that 5-substituted uracils, such as 5-fluorouracil,[3] showed remarkable antimetabolic action. A deep interest was felt on how the action of thiamine analog would appear when the pyrimidine ring was replaced by uracil, and the synthesis of such a compound (II) was carried out. It is considered that the compound (II) has the essential functional groups for the synthesis of protein and for the metabolism of carbohydrate in one molecule.

5-Cyanouracil[4] (III) was used as the starting material. It has been reported[5] that there is a resistance in the reduction of uracil by catalytic hydrogenation at room temperature to dihydrouracil, but when the temperature is raised to 70° the uracil is reduced to dihydrouracil. Therefore, the nitrile (III) was first reduced to the amine (IV) with 10% palladium charcoal in hydrochloric acid solution at room temperature, and the amine (IV) was obtained in 30.2% yield as its picrate, after the consumption of ca. 3 moles of hydrogen

during about 5 hours. It was interesting to note that besides the amine (IV), this reduction gave thymine*[2] (V) in 29.3% yield. When Raney nickel was used as the catalyst in ammonium hydroxide solution, at 50~60 atm. of initial hydrogen pressure at 100~120°, the amine (IV) was obtained in 57.5% yield.

Secondary amine was not obtained at all in these reductions. To find a new method for obtaining the amine (IV), (III) was treated with hydrogen sulfide in 5% sodium hydroxide solution and thioamide (VI) was obtained in 74.8% yield and the subsequent treatment of thioamide with Raney nickel in 28% ammonium hydroxide solution gave the amine (IV) in 60% yield. The amines (IV) obtained by these methods were all identical. The picrate of (IV) came as yellow needles with 2 moles of crystal water, melting at 125~130° and decomposing at 222~223° through a loss of crystal water. This picrate was converted to a hydrochloride, and the ultraviolet spectrum of this hydrochloride was very similar to that of thymine,[6] showing the maximum absorption (in water) at 261 mμ (log ε 3.86). Dihydrothymine[7] does not show the maximum absorption near 260 mμ. These results suggested that the uracil ring was not reduced. Further, for the chemical proof of the amine, this was converted to dimethylamino derivative (VI) by treatment with formic acid and formaldehyde, and (VI) was identified with authentic specimens prepared by Mannich reaction of uracil, dimethylamine, and formaldehyde. Under these conditions, the amine (IV) was successfully obtained without reduction of the uracil ring. Condensation of (IV) with 3-chloro-4-oxopentyl acetate, ammonia, and carbon disulfide, according to the method of Matsukawa,[8] produced (VII), which was treated with 10% hydrochloric acid solution and afforded thiothiazolone (VIII). This compound was oxidized with hydrogen peroxide and gave (II) in a good yield. Matsukawa and others[9] reported the action of hydrogen sulfite and pyridine on thiamine and the action of hydrogen sulfite on (II) was examined to prove the structure of (II). (II) was treated with a hydrogen sulfite solution and pyridine at 35° over night and 4-methyl-5-(2-hydroxyethyl)thiazole (IX) was obtained in a yield of 59.3% as its picrate, but the pyridine (XI) and sulfo derivatives were not obtained. Pharmacological tests of (II) are now being conducted in this laboratory.

Experimental*[3]

2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinecarbothionamide (V)—A solution of 0.5 g. of 5-cyanouracil dissolved in 13 cc. of 5% NaOH solution was saturated with H_2S and needle crystals appeared. The reaction mixture in a sealed tube was warmed in a water bath for 20 hr. and the crystals were collected. Yield, 0.46 g. (74.8%), m.p. 308~310° (decomp.). Recrystallization from water gave faint yellow sandy crystals, m.p. 310~312° (decomp.). *Anal.* Calcd. for $C_5H_5O_2N_3S$: C, 35.09; H, 2.95; N, 24.56; S, 18.70. Found : C, 35.61; H, 3.14; N, 24.92; S, 18.67.

5-Aminomethyluracil (IV)—a) To a solution of 2 g. of (III) in 70 cc. of 28% NH_4OH solution, Raney Ni catalyst prepared from 4 g. of W-7[10] was added. The mixture was shaken in an autoclave with the initial H_2 pressure of 55 atm. Between the temperatures of 100° and 120°, 680 cc. of H_2 was consumed during 2 hr. After removal of the catalyst by filtration, the solvent was evaporated from the filtrate *in vacuo*. Aqueous solution of picric acid was added to the residue and the picrate was obtained as yellow crystals, m.p. 220~222° (decomp.). Yield, 3.4 g. (57.4%). This was recrystallized

*[2] Recently it has been reported that thymine is obtained by reduction of 5-(4-morpholinylmethyl)-uracil with 10% palladium-charcoal in ethanol (J. H. Burckhalter, R. J. Seiwald, H. C. Scarborough : J. Am. Chem. Soc., **82**, 993 (1960)).

2) M. Soodak, L. R. Cerecedo : J. Am. Chem. Soc., **66**, 1988 (1944).
3) C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, J. Scheiner : Nature, **179**, 663 (1957).
4) T. B. Johnson : Am. Chem. J., **42**, 50 (1909).
5) E. B. Brown, T. B. Johnson : J. Am. Chem. Soc., **45**, 2702 (1923).
6) cf. M. M. Stimson : *Ibid.*, **71**, 1471 (1949).
7) R. D. Batt, J. K. Martin, J. M. Ploeser, J. Murray : *Ibid.*, **76**, 3663 (1941).
8) T. Matsukawa, T. Iwatsu : Yakugaku Zasshi, **71**, 455, 720 (1951); **72**, 354 (1952).
9) T. Matsukawa, S. Yurugi : *Ibid.*, **71**, 1423, 1450 (1951); **72**, 33 (1952).

from water to yellow needles, which melted at 125~130° with a loss of crystal water, solidified once, and decomposed at 222~223°. *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot C_6H_3O_7N_3 \cdot 2H_2O$: C, 32.98; H, 3.52; N, 20.98. Found : C, 33.32; H, 3.22; N, 20.81. IR : ν_{O-H} 3750 cm^{-1} (Nujol). This was dried in diminished pressure (120~130°/3 mm. Hg, 2 hr. over P_2O_5) and gave a yellow amorphous powder, m.p. 225~226° (decomp.). *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot C_6H_3O_7N_3$: C, 35.68; H, 2.72; N, 22.70. Found : C, 35.36; H, 2.66; N, 22.71.

The hydrochloride was obtained from the picrate by the usual method and recrystallized from H_2O and EtOH into colorless prisms, m.p. 250~251° (decomp.)*4. *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot HCl$: C, 33.81; H, 4.54; N, 23.66; Cl, 19.96. Found : C, 34.12; H, 4.88; N, 23.38; Cl, 18.94. UV : $\lambda_{max}^{H_2O}$ 261 mμ (log ε 3.86).

b) The compound (VI) (200 mg.) was dissolved in 30 cc. of 28% NH_4OH solution, Raney Ni (from 1.5 g. of alloy) was added, and the mixture was heated on a water bath for 2 hr. The reaction mixture was allowed to stand at room temperature overnight and filtered. The filtrate was treated to obtain the picrate as described in (a) and gave yellow needles, m.p. 125~130°, which decomposed at 223~224°, with a loss of crystal water. Yield, 285 mg. (60.0%). *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot C_6H_3O_7N_3 \cdot 2H_2O$: C, 32.98; H, 3.52; N, 20.98. Found : C, 32.99; H, 3.72; N, 20.48. IR : ν_{O-H} 3750 cm^{-1} (Nujol). This was dried in diminished pressure at 125~130°/2 mm. Hg (on P_2O_5) as yellow amorphous powder, m.p. 225~226° (decomp.). *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot C_6H_3O_7N_3$: C, 35.68; H, 2.72; N, 22.70. Found : C, 36.05; H, 2.53; N, 23.07.

Hydrochloride : Colorless prisms (from EtOH and H_2O), m.p. 250~251°*4 (decomp.). *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot HCl$: C, 33.81; H, 4.54; N, 23.66; Cl, 19.96. Found : C, 33.59; H, 4.40; N, 23.02; Cl, 19.72. UV : $\lambda_{max}^{H_2O}$ 261 mμ (log ε 3.86).

Admixture of the picrates obtained by these two methods (a and b) showed no depression and their IR curves were indentical. The hydrochloride also indicated the same results as the picrates.

Thymine (V) and 5-(Aminomethyl)uracil (IV)—The nitrile (III) (0.3 g.) was reduced by using 200 mg. of 10% Pd-C in a mixture of 50 cc. of H_2O and 8 cc. of conc. HCl at ordinary pressure. The amount of H_2 consumed was 140 cc. over a period of 5 hr. After removal of the catalyst by filtration, the solvent was evaporated from the filtrate *in vacuo*. Recrystallization of the residue from water gave (V) of m.p. 305~306° (decomp.). *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.64; H, 4.88; N, 22.23. Found : C, 47.50; H, 4.30; N, 21.89. It showed no depression when mixed with authentic sample of thymine and the IR absorption curves of both were completely identical.

The mother liquor left after removal of thymine was concentrated *in vacuo* to a small volume and aqueous solution of picric acid was added to it, the picrate was obtained as yellow needles, m.p. 216~218 (decomp.). Yield, 280 mg. (30.2%). Recrystallization from water gave yellow needles, m.p. 222~223 (decomp.). *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot C_6H_3O_7N_3 \cdot 2H_2O$: C, 32.98; H, 3.52; N, 20.98. Found: C, 33.31; H, 3.52; N, 20.86.

It showed no depression when mixed with the sample obtained by another method and the IR absorption curves of these compounds were completely identical.

5-(Dimethylaminomethyl)uracil (VI)—a) To 1 g. of the hydrochloride of (IV) dissolved in 1 cc. of water, 310 mg. of Na_2CO_3 and 2 cc. of water were added. After neutralization, the solution was mixed with 1.5 g. of 90% HCOOH and 1.2 g. of 30% HCHO, and allowed to stand at room temperature for 0.5 hr. The mixture was warmed on a water bath for 2 hr. and allowed to stand overnight. After the solvent was evaporated *in vacuo*, picric acid was added to the residue and recrystallization from water yielded yellow plates, m.p. 247~248°. Yield, 0.58 g. *Anal.* Calcd. for $C_7H_{11}O_2N_3 \cdot C_6H_3O_7N_3$: C, 39.30; H, 3.55; N, 21.15. Found : C, 39.47; H, 3.11; N, 20.88.

Hydrochloride : Colorless prisms (from EtOH and H_2O), m.p. 263~264°. *Anal.* Calcd. for $C_7H_{11}O_2N_3 \cdot HCl$: C, 40.85; H, 5.85; N, 20.43; Cl, 17.24. Found : C, 41.19; H, 5.68; N, 20.21; Cl, 16.53.

b) To a stirring solution of 0.5 g. of uracil in 3 cc. of water and 1 g. of Me_2NH, 0.5 g. of 30% HCHO was added in drops. After allowing this to stand overnight, the mixture was concentrated *in vacuo* into a small volume, H_2O was added, and the evaporation was repeated to remove Me_2NH completely. This mixture was treated as described above to give 1.15 g. of the picrate of (VI) as yellow crystals, m.p. 243~245° (decomp.). This was recrystallized from H_2O to yellow plates, m.p. 247~248° (decomp.). *Anal.* Calcd. for $C_7H_{11}O_2N_3 \cdot C_6H_3O_7N_3$: C, 39.30; H, 3.55; N, 21.15. Found : C, 39.57; H, 3.43; N, 21.53.

Hydrochloride : Colorless prisms (from EtOH and H_2O), m.p. 263~264°. *Anal.* Calcd. for $C_7H_{11}O_2N_3 \cdot HCl$: C, 40.85; H, 5.85; N, 20.43; Cl, 17.24. Found : C, 40.89; H, 5.48; N, 20.39; Cl, 16.95.

*3 All m.p.s are uncorrected.

*4 It has recently been reported that this compound is synthesized from 5-chlorouracil and melts at 252~253° (J. H. Burckhalter, R. J. Seiwald, H. C. Scarborough : J. Am. Chem. Soc., 88, 991 (1960)).

10) Org. Syntheses, Coll. Vol., **3**, 179 (1955).

1-Acetyl-3-(acetyloxy)propyl N-[(2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl) methyl]dithiocarbamate (VII)—To a solution of 310 mg. of hydrochloride of (IV) dissolved in 2 cc. of water, 0.3 cc. of 5% NH_4OH, 0.35 g. of 3-chloro-4-oxopentyl acetate and 2 cc. of MeOH were added with cooling and 0.2 cc. of CS_2 was dropped into this solution. This was stirred at room temperature and faint yellow crystals deposited. After standing overnight at room temperature, the crystals were collected by filtration, m.p. 204~205°; yield, 350 mg. (55.7%). Recrystallization from EtOH yielded colorless scales, m.p. 209~210°. *Anal.* Calcd. for $C_{13}H_{17}O_5N_3S_2$: C, 43.46; H, 4.77; N, 11.70; S, 17.81. Found: C, 43.43; H, 4.88; N, 11.75; S, 17.42.

3-[(2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)methyl]-4-methyl-5-(2-hydroxyethyl)-4-thiazoline-2-thione (VIII)—A solution of 1 g. of (VII) dissolved in 10 cc. of 10% HCl and 2 cc. of EtOH was warmed in a water bath for 1 hr. After the crystals dissolved, different kind of crystals deposited on liquid surface. The mixture was warmed on a water bath for 1 hr. and allowed to stand overnight in an ice box. The crystals (m.p. 220~222° (decomp.)) were collected (0.59 g. 70.5%) and recrystallized from water to colorless scales, m.p. 228~229°. *Anal.* Calcd. for $C_{11}H_{13}O_3N_3S_2$: C, 44.15; H, 4.38; N, 14.04; S, 21.39. Found : C, 44.05; H, 4.76; N, 14.08; S, 21.64.

3-[(2,4-Dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)methyl]-4-methyl-5-(2-hydroxyethyl)thiazolium Nitrate (II) (X=NO_3^-)—Under cooling, 1.5 g. of 30% H_2O_2 was added to 870 mg. of the compound (VIII) suspended in 15 cc. of water. This was warmed to 45° and the crystals disappeared. After standing overnight, $Ba(NO_3)_2$ was added to the reaction mixture until precipitation of $BaSO_4$ no longer occurred (approx. calcd. amount of $Ba(NO_3)_2$). $BaSO_4$ was removed by filtration, the filtrate was evaporated *in vacno*, and the residue was washed with EtOH, affording 802 mg. (83.6%) of faint orange crystals, m.p. 192~194° (decomp.). Recrystallization from hydr. EtOH and dioxane yielded colorless pillars, m.p. 196~197°. *Anal.* Calcd. for $C_{11}H_{14}O_6N_4S$: C, 40.00; H, 4.27; N, 16.97; S, 9.69. Found : C, 40.36; H, 3.97; N, 16.96; S, 9.76. UV : $\lambda_{max}^{H_2O}$ 261 mμ (log ε 3.99).

Reaction of H_2SO_3 and (II) (X=NO_3^-); Formation of 4-Methyl-5-thiazoleëthanol (IX)—A solution of 0.5 g. of (II) and 5 cc. of pyridine dissolved in 20 cc. of 1% H_2SO_3 solution and 5 cc. of H_2O (pH 6.0) was allowed to stand overnight at 35°. After evaporation of the reaction mixture *in vacuo*, the residue was extracted with 10 cc. of hot EtOH. EtOH was evaporated to a small volume, the residue was made alkaline with NaOH solution, and pyridine was removed completely by steam-distillation. The residue was extracted with $CHCl_3$. After evaporation of $CHCl_3$, EtOH was added, and EtOH solution of picric acid was added to it. The picrate (227 mg. or 59.3%) was obtained as yellow crystals, m.p. 160~161°. Recrystallization from EtOH yielded yellow needles, m.p. 162~163°. *Anal.* Calcd. for $C_6H_9ONS \cdot C_6H_3O_7N_3$: C, 38.69; H, 3.25; N, 15.06; S, 8.60. Found : C, 39.03; H, 3.34; N, 14.87; S, 8.05.

On admixture of this compound with 4-methyl-5-thiazoleëthanol picrate (m.p. 162~163°), obtained from thiamine by Matsukawa's method, no depression of the m.p. was observed and IR absorption curves of the two were identical. The part insoluble in hot EtOH (66 mg.) was purified, but sulfonic acid (X) and pyridinium (XI) derivatives could not be found.

The authors are thankful to Misses E. Kobayashi and N. Ninomiya for infrared spectral measurements, and to the members of the Analysis Room of this Faculty for the microanalysis.

Summary

A new thiamine analog, 3-(2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxyethyl)thiazolium nitrate (II) was synthesized from 5-cyanouracil (III). In the course of the reduction of (III), thymine was obtained besides the amine (IV). Further, a new method for obtaining (IV) was found.

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[Added in proof] After this paper was submitted for publication, J. A. Carbon (J. Org. Chem., **25**, 1731(1960)) reported the synthesis of 3-(2,4-dihydroxy-5-pyrimidylmethyl)-4-methyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide.