acetates and their melting points, optical rotation, coloration reaction, and paper partition chromatography have been described, together with those of the acetates of known digitalis glycosides and various aglycone acetates.

Oral administration of gitoxin acetate and purpurea glycoside-B acetate showed them to be more toxic than their respective glycosides and their lethal dose in rats was found to have been much lowered.

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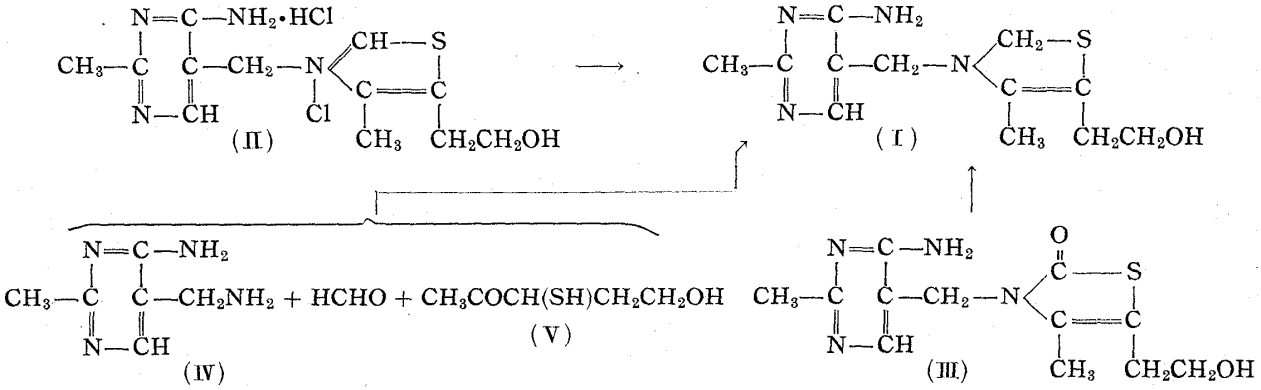
30. Shigeru Yoshida and Mitsuru Kataoka : Studies on the Allied Compounds of Vitamin B_1. XX.[1] The Structure of Dihydrothiamine. (1.)*

(*Takamine Research Laboratory, Sankyo Co., Ltd.***)

Dihydrothiamine (I) was synthesized for the first time by Karrer and others[2] by the reduction of thiamine (II) or thiamine-thiazolone (III) with lithium aluminum hydride and they reported its melting point as 138°. Hennessy and others[3] also carried out the reduction of thiamine but with sodium trimethoxyborohydride and obtained dihydrothiamine of m.p. 151°, which they found to change to an isomer of m.p. 175° by recrystallization from hot water. They surmised that this isomer is formed by the addition of the alcohol group to the double bond of the thiazoline ring. Iwatsu[4] studied new synthetic procedures for dihydrothiamine and found that it is formed in a good yield by the condensation of 2-methyl-4-amino-5-aminomethylpyrimidine (IV), formaldehyde, and 3-acetyl-3-mercaptopropanol (V). He also found that the compound of m.p. 150° changed to that of m.p. 160° by alkali treatment and designated the compounds of m.p. 150°, 160°, and 175° respectively as normal-, iso-, and pseudo-dihydrothiamine.



The present writers entertained some doubts about the structure of dihydrothiamine (I) from these experimental evidences, synthesized three kinds of isomer by the method

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1) Part XIX. W. Ishizuka : J. Pharm. Soc. Japan, **75**, 1392(1955).
2) P. Karrer, H. Krishna : Helv. Chim. Acta, **33**, 555(1950); **35**, 459(1952).
3) G.E. Bonuicino, D.J. Hennessy : Abstracts of Papers, 117th Meeting of the American Chemical Society, Philadelphia, April, 1950, 48c; *ibid.*, 122nd Meeting of the American Chemical Society, Atlantic City, September, 1952, 7c.
4) T. Iwatsu : J. Pharm. Soc. Japan, **75**, 677(1955).

of Karrer and of Iwatsu, and examined their infrared absorption spectra in detail. The spectra of normal and iso compounds, as a solid and chloroform solution, were almost identical, showing no specific difference. Their ultraviolet absorption was also identical, being λ_{max}^{EtOH} 235 mμ (ε 9500) and 275(5020). As shown in Table I and Fig. 1, their spectra in the region of 3000 cm^{-1} exhibits following absorptions : ν_{max}^{Nujol} 3375, 3144 cm^{-1}, $\nu_{max}^{CHCl_3}$ 3490, 3310, 3160(w) cm^{-1}. These absorptions, according to the work of Angyal,[5] are the N–H stretching vibration of the amino group in 4-position of the pyrimidine ring and there is no O–H stretching vibration. OH group should show an absorption in chloroform solution at around 3600 cm^{-1}. It follows, therefore, that normal- and iso-dihydrothiamine possess an amino group but not a hydroxyl, so that its structure would not be the hitherto assigned (I) but a compound with the hydroxyl added to the double bond in the thiazoline ring, i.e. 3-(2-methyl-4-amino-5-pyrimidylmethyl)-3a-methyl-perhydrofuro[2, 3-*d*]thiazole (VI). In order to prove this hypothesis, a dihydrothiamine analog possessing a benzene ring in place of the pyrimidine ring was prepared by the methods of Karrer[2] and Iwatsu.[4] The compound was obtained either by the condensation of benzylamine (or its *o*-nitro or *p*-nitro derivative), formaldehyde, and 3-acetyl-3-mercaptopropanol (V) or by the reduction of benzylthiazolium derivative (VIII).[6] The compounds thus obtained exhibited no absorption of a hydroxyl, so that its structure is not as represented by (VII′) but would be 3-(benzyl, *p*-nitrobenzyl, or *o*-nitrobenzyl)-3a-methyl-perhydrofuro[2, 3-*d*]thiazole (VII : a) X=H, b) X=*p*-NO_2, c) X=*o*-NO_2).

This assumption may be supported from the infrared absorption spectra of normal- (VI) and iso-dihydrothiamine (VI) in the finger print region. These compounds exhibit an extremely strong, characteristic absorptions in the region of 1030 and 840 cm^{-1} (Figs. 1 and 2, Table I). According to the infrared spectral studies on steroidal sapogenins by Jones and others,[7] these absorptions cannot be due only to the ring vibration of tetrahydrofuran ring in (VI) and (VII), and are more likely to be the absorption specific to a ring system formed by the coupling of ether vibration with perhydrofurothiazole ring as a whole.

It seems appropriate to assume that the difference in the melting points of normal- and iso-dihydrothiamine is due to polymorphism, because their infrared and ultraviolet absorption spectra are almost identical and because there are no isomeric structures for (VII). As for the likelihood of a steric isomerism, the fusion of the thiazolidine and tetrahydrofuran rings cannot be other than *cis*-fusion[8] from the identity of the infrared

Table I. Infrared Absorption Spectra of Dihydrothiamine and Related Compounds

Compound	Nujol(N) or $CHCl_3$(C)	Streching frequencies of NH_2 (cm^{-1})	Ring vibrations of perhydrofurothiazolidine (cm^{-1})
Normal-Dihydrothiamine	N	3375, 3145	1036, 844
	C	3490, 3310, 3160	1030, 840
Iso-Dihydrothiamine	N	3375, 3140	1035, 842
	C	3520, 3340, 3175	1032, 842
(VIIa : X=H)	N		1033, 1028, 835
	C		1035, 1024, 838
(VIIb : X=*p*-NO_2)	N		1027, 833
	C		1035, 838
(VIIc : X=*o*-NO_2)	N		1028, 834
	C		1035, 838

5) C. A. Angyal, R. L. Werner : J. Chem. Soc., **1952**, 2911; J. D. S. Goulden : *Ibid.*, **1952**, 2939; I. A. Brownlie : *Ibid.*, **1950**, 3062; L. N. Short, H. W. Thompson : *Ibid.*, **1952**, 168; H. Hirano, H. Yonemoto, H, Kamio : J. Pharm. Soc. Japan, **76**, 239(1956).
6) A. H. Livermore, R. R. Sealock : J. Biol. Chem., **167**, 699(1947).
7) R. N. Jones, E. Katzenellenbogen, K. Dobriner : J. Am. Chem. Soc., **75**, 158(1953).
8) If a *tanas*-fusion, the foregoing absorptions at 1030 and 840 cm^{-1} should differ due to the strain of the tetrahydrofuran ring.

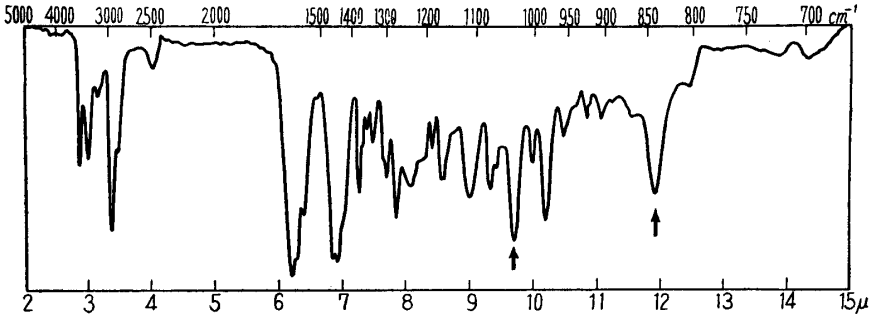


Fig. 1. Normal-Dihydrothiamine in 10% $CHCl_3$ solution (cell thickness, 0.1 mm.)

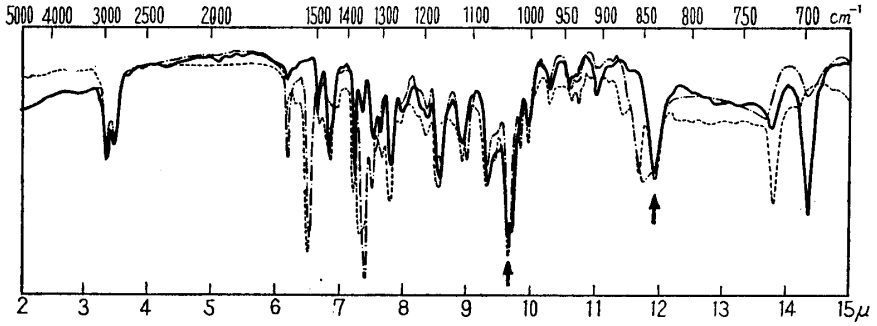
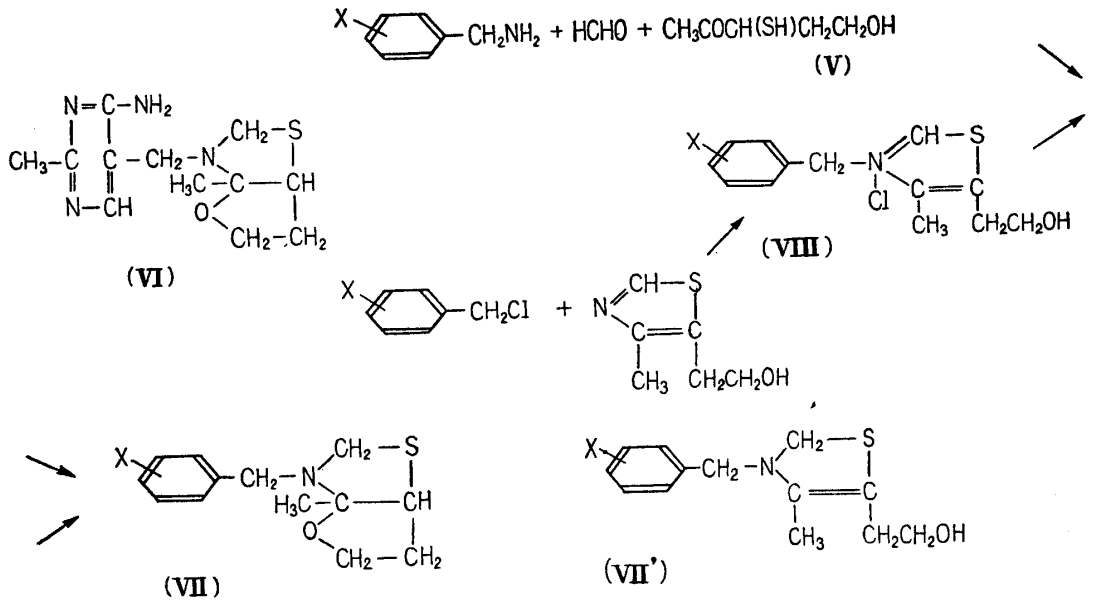


Fig. 2.

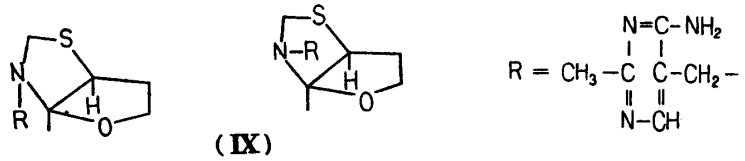
——— 3-Benzyl-3a-methyl-tetrahydrofuro[2,3-*d*]thiazolidine (X=H)
– – – – 3-*p*-Nitrobenzyl-3a-methyl-tetrahydrofuro[2,3-*d*]thiazolidine (VIIb : X=*p*-NO_2)
····· 3-*o*-Nitrobenzyl-3a-methyl-tetrahydrofuro[2,3-*d*]thiazolidine (VIIc : X=*o*-NO_2)
about 7.5% $CHCl_3$ solution (cell thickness 0.1 mm.)



absorption spectra and the S_N1 reaction assumed from the formation mechanism of these compounds to be described later. It would be possible to assume structures (IX) with the pyrimidine portion bonded to nitrogen in *cis* or *trans* to the methyl group,[9] but this seems very unlikely. If such isomerism were to exist, similar isomers should be obtained

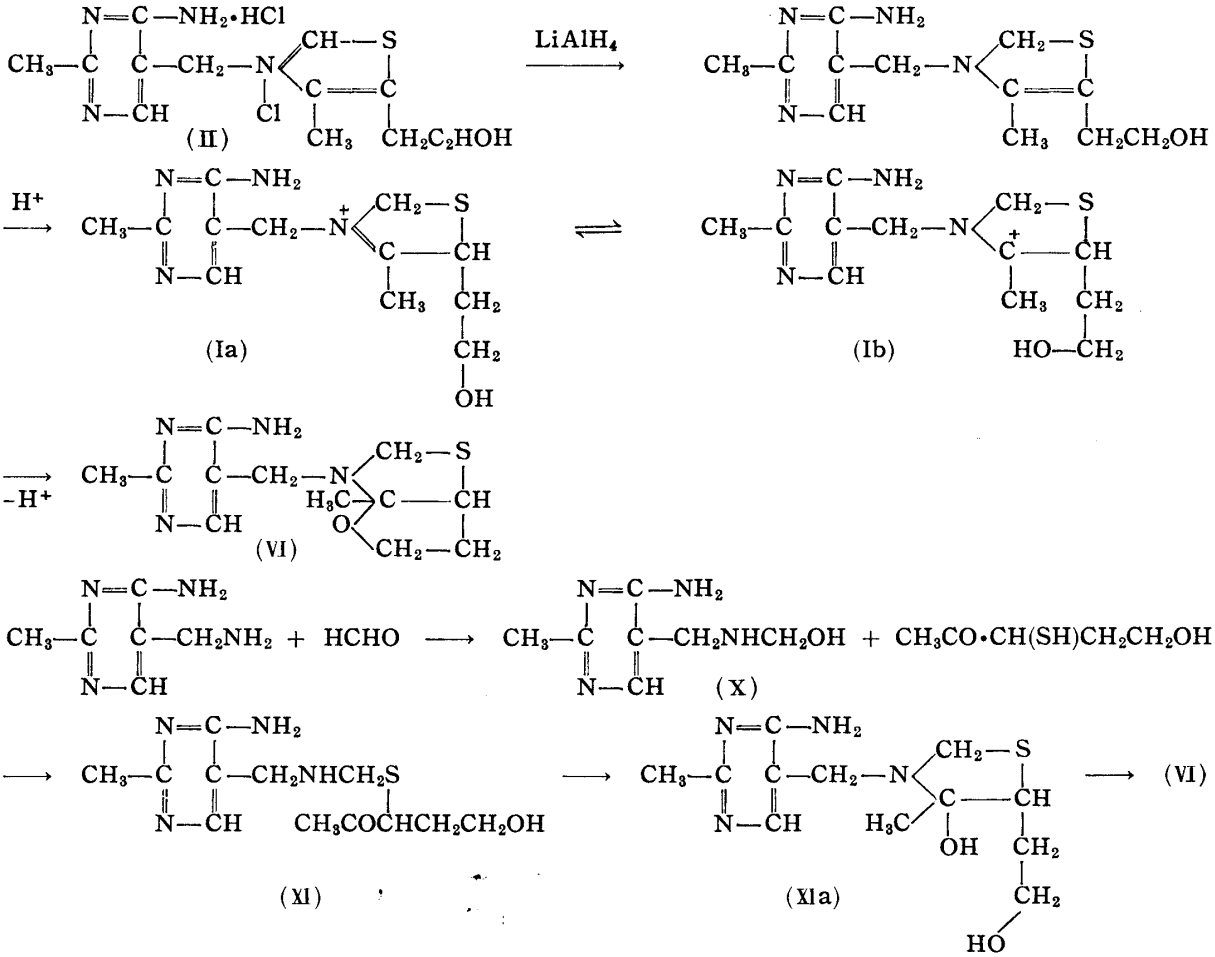
9) cf. Stereochemistry of 2,6-diaryl-*cis*-3,7-dioxabicyclo[3.3.0]octane (M. Beroza : J. Am. Chem. Soc., **78**, 5082(1956); **77**, 3332(1955)) and on tropane alkaloids (review by A. Heusner : Arzneimittel-Forsch., **6**, 105(1956)).

from (Ⅶ) but no such compounds have been isolated.



(Ⅸ)

The mechanism of the formation of normal- and iso-dihydrothiamine (Ⅵ) by reduction of thiamine (Ⅱ) is assumed to be in the following manner. (Ⅰ), formed by the reduction of thiamine, is an imine-enamine system[10] and easily undergoes transition of the double bond by the attack of a proton to (Ia) and, since (Ia) and (Ib) are tautomers, (Ⅵ) is easily formed from (Ib) by the liberation of a proton. In the Iwatsu method, hydroxymethyl compound (X) would be formed as an intermediate from 2-methyl-4-amino-5-aminomethylpyrimidine (Ⅳ) and formaldehyde, and the condensation[11] of (X) and 3-acetyl-3-mercaptopropanol (Ⅴ) would form (XI) which would take the structure (XIa) or (Ib) by tautomerism, thereby producing (Ⅵ).



(NOTE) After announcement of the present studies, a communication of Hirano and others (J. Pharm. Soc. Japan, **76**, 1332(1956)) on dihydrothiamine was published.

The writers are indebted to Mr. M. Matsui, Director of the Laboratory, to Messrs. Hideyo Shindo and Osamu Amakasu for infrared spectral measurements, and to Misses Chizu Furukawa and Hiro Ohtsuka for elemental analyses.

10) N. J. Leonard, *et al.*: J. Am. Chem. Soc., **76**, 2781(1954), **77**, 437, 439(1955), *et seq.*; B. Witkop: *Ibid.*, **78**, 2873(1956).
11) J. Graymore, *et al.*: J. Chem. Soc., **1953**, 208; **1953**, 143, 4089.

Experimental

Infrared absorption spectra were measured with the Perkin-Elmer Model 21 spectrophotometer.

3-Benzyl-3a-methyl-perhydrofuro[2,3-*d*]thiazole (VIIa : X=H)—Prepared by the method of Iwatsu.[4] A mixture of 30 g. of 2-acetyl-2-chlorobutyrolactone and 90 cc. of 5% HCl was warmed for 1.5 hrs. on a water bath, cooled, neutralized with $NaHCO_3$, and 60 cc. of EtOH added. A solution of NaHS was prepared by the saturation of H_2S in 88 cc. of 10% NaOH solution and this was added to the foregoing reaction mixture, by which 3-acetyl-3-mercaptopropanol formed with slight evolution of heat. To this solution, 32 g. of benzylamine was added, chilled in ice, and 15 cc. of HCHO solution was added gradually. On standing, an oily layer separated out, which soon crystallized. Two recrystallizations from EtOH afforded 15 g. of crystals, m.p. 71°. *Anal.* Calcd. for $C_{13}H_{17}ONS$: C, 66.38; H, 7.23; N, 5.91. Found : C, 66.45; H, 7.00; N, 5.85.

3-*p*-Nitrobenzyl-3a-methyl-perhydrofuro[2,3-*d*]thiazole (VIIb : X=*p*-NO_2)—Prepared by the same method as for (VIIb). m.p. 93~94°. Yield, 2.6 g. from 5 g. of *p*-nitrobenzylamine. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2S$: C, 55.71; H, 5.71; N, 10.00. Found : C, 55.40; H, 5.70; N, 10.23.

3-*o*-Nitrobenzyl-3a-methyl-perhydrofuro[2,3-*d*]thiazole (VIIc : X=*o*-NO_2)—Prepared by the same method as the foregoing and 5 g. of m.p. 63~64° obtained from 30 g. of *o*-nitrobenzylamine. *Anal.* Calcd. for $C_{13}H_{16}O_3N_2S$: C, 55.71; H, 5.71; N, 10.00. Found : C, 55.36; H, 5.15; N, 10.40.

Benzylthiazolium Compounds (VIII)—Prepared by the method of Livermore.[6] (VIIIb : X=*p*-NO_2), m.p. 177~178°. (VIIIc : X=*o*-NO_2), m.p. 206~207°. Both m.p.s are higher than those reported in the literature respectively as m.p. 172~173° and 199.5~200.5°.

Reduction of the Benzylthiazolium Compounds (VIII)—a) A mixture of 4.2 g. of 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (VIIIa : X=H) and 10 cc. of tetrahydrofuran was added to a mixture of 2.5 g. of $LiAlH_4$ and 100 cc. of tetrahydrofuran and the mixture was agitated for 6 hrs. at room temperature. On completion of the reaction, 4 cc. of water was cautiously added to the reaction mixture, insoluble matter was filtered off, and the filtrate was evaporated under a diminished pressure by which crystals precipitated out. Recrystallization from EtOH afforded crystals of m.p. 71°, undepressed on admixture with (VIIa) described above.

b) A mixture of 2 g. of 3-*p*-nitrobenzyl-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (VIIIb : X=*p*-NO_2), 0.5 g. of $NaBH_4$, and 25 cc. of MeOH was heated for 4 hrs. on a water bath, excess of $NaBH_4$ was decomposed by the addition of a small amount of AcOH, and the solvent was distilled off under a reduced pressure. The residue was repeatedly recystallized from EtOH to 0.3 g. of crystals, m.p. 93°, undepressed on admixture with (VIIb) described earlier.

c) 3-*o*-Nitrobenzyl-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (VIIIc : X=*o*-NO_2) was reduced with $NaBH_4$ as in (b) and the product of m.p. 63~64° showed no depression on admixture with (VIIc) described earlier.

Summary

1) From the infrared absorption spectral examination of normal- and iso-dihydrothiamine and related compounds (VII), it was confirmed that the structure of normal- and iso-dihydrothiamine should not be represented by the hitherto used structural formula (I) but by (II) from the fact that these compounds show absorption of an amino group but not of hydroxyl group and absorptions at 1030 and 840 cm^{-1} of characteristic ring vibration.

2) 3-Benzyl-3a-methyl-perhydrofuro[2,3-*d*]thiazole compounds (VII) were synthesized by the reduction of benzylthiazolium compounds (VIII) with lithium aluminum hydride or sodium borohydride, or by the condensation of benzylamine, formaldehyde, and 3-acetyl-3-mercaptopropanol.

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