N-Methylation of the Ketal-lactam (XLI)——A mixture of the ketal-lactam (XLI) (100 mg.) and NaH (80 mg.) (50% in mineral oil) in dry benzene (30 ml.) was heated under reflux for 2 hr. After cooling, methyl iodide (1 ml.) was added to the benzene solution which was refluxed for 1 hr. The reaction mixture was washed with H_2O, dried and evaporated to dryness to give the N-methyl-ketal-lactam (XLII) (85 mg.) which was crystallized from acetone-ether as prisms, m.p. 179~180°. IR ν_{max}^{KBr} cm^{-1}: 1640 (amide C=O). *Anal.* Calcd. for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.79; H, 6.80; N, 4.07.

Tetrahydrooxocrinine Methine (XLIII)——A solution of the N-methyl-ketal-lactam (XLII) (70 mg.) and $LiAlH_4$ (80 mg.) in tetrahydrofuran (30 ml.) was heated under reflux for 5 hr. The excess reagent was decomposed by addition of a small amount of H_2O and the precipitate which formed was removed by filtration. The filtrate was concentrated to dryness to give a solid which was taken up in $CHCl_3$. The $CHCl_3$ solution was extracted with diluted HCl and the aqueous layer was basified with aqueous NH_3, and extracted with ether. The ethereal extract was washed with H_2O, dried and evaporated to dryness to afford tetrahydrooxocrinine methine (XLIII) (50 mg.) which crystallized from EtOH-ether as prisms, m.p. 147~148°, identical in all respects with an authentic sample. UV λ_{max}^{EtOH} mμ (log ε): 242 (3.62), 290 (3.58). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O). *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.33; H, 7.45; N, 4.93.

Summary

Tetrahydrooxocrinine methine (XLIII) has been synthesized by a sequence of reactions including ring enlargement of a tetralone (XXXVI) to a seven-membered nitrogenous ring compound (XXXVIII) by the use of Schmidt reaction.

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UDC 547.918 : 615.711.5

56. Toshio Kawasaki, Itsuo Nishioka, Tatsuo Yamauchi, Kazumoto Miyahara, and Miyoko Enbutsu: Digitalis Saponins. III.*1 Enzymatic Hydrolysis of Leaf Saponins of *Digitalis purpurea* L.

(*Faculty of Pharmaceutical Sciences, Kyushu University**2)

In the preceding paper*1 of this series it was reported that the crude saponin of *Digitalis purpurea* leaves precipitated by cholesterol from the butanol extracts of the remainings from the manufacture of cardiac glycosides contained two saponins (I and II). I was composed of tigogenin- and gitogenin-tetraglycosides (desgalactotigonin and F-gitonin) and II was a mixture of three pairs of more polar oligosides each of which seemed also to consist of tigogenin- and gitogenin-glycosides. Since I and its component saponins had[1] the greater capacity than II and commercial "digitonin" in forming molecular compound of great insolubility with cholesterol, it was desired to obtain enough amount of I in order to investigate the structures and properties of its component saponins in detail. This paper concerns a convenient method to prepare I, and subsequently the component saponins, from the crude saponin and more efficiently from the original butanol extract by a specific partial hydrolysis of II with commercially available enzyme preparations.

*1 Presented at the 84th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 5, 1964. Part II. T. Kawasaki, I. Nishioka: This Bulletin, **12**, 1311 (1964).

*2 Katakasu, Fukuoka (川崎敏男, 西岡五夫, 山内辰郎, 宮原一元, 円仏美代子).

1) Presented at the 82nd Annual Meeting of Pharmaceutical Society of Japan, Shizuoka, Nov. 3, 1962.

The content of I in the crude saponin*1 was less than that of II, the isolation of I by alumina chromatography as reported*1 is not always practical for a large scale experiment, and I has remained relatively inaccessible. However, co-existence of I and II suggests that the former might be the prosapogenin of the latter and II could be converted enzymatically*3 into I. As a preliminary experiment, when II obtained by alumina chromatography was treated in aqueous alcohol with emulsin, snail enzyme, hemicellulase and amylase and the products were examined by paper chromatography, II was found to be cleaved to give a saponin (tentatively represented as FSE) corresponding to I and glucose. The experiment was then conducted in a larger scale and a considerable amount of amorphous precipitates*3 was obtained as a product. The product was extracted with chloroform-methanol (1:1) mixture, the solution was concentrated and left to stand to give a crystalline solid which revealed one spot of FSE on paper chromatograms and was shown on thin-layer of silica gel G to be composed of two saponins (FSE-1 and -2) which correspond very likely to desgalactotigonin and F-gitonin (Fig. 1). The mixture was separated on cellulose powder impregnated with formamide*1 or preferably on silica gel column*4 into FSE-1, fine needles, m.p. 284~286° (decomp.), $[\alpha]_D^{28}$ −68° (c=0.50, pyridine), and FSE-2, fine needles, m.p. 251~255° (decomp.), $[\alpha]_D^{28}$ −66° (c=0.50, pyridine).

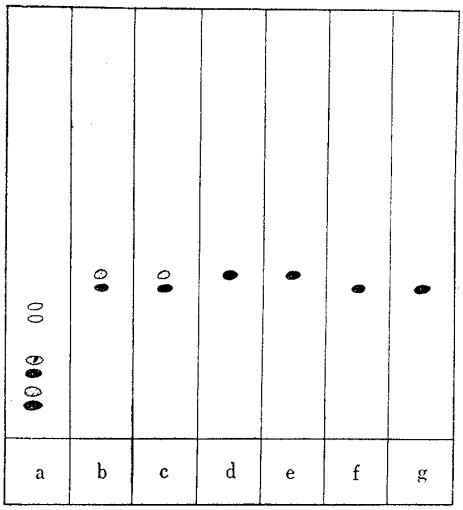

Fig. 1. Thin-layer Chromatorams on Silica Gel G

Solvent: $CHCl_3$-MeOH-H_2O (65:35:10)
a: Saponin II*1 e: Desgalactotigonin*1
b: FSE f: FSE-2
c: Saponin I*1 g: F-Gitonin*1
d: FSE-1

By acid hydrolysis followed by qualitative and quantitative determinations of the products they were found to be tigogenin- and gitogenin-glycosides both of which had the same kind and number of monosaccharide units (2 glucose+galactose+xylose) and were identified with desgalactotigonin and F-gitonin, respectively, by direct comparisons with the authentic samples.*1 Accordingly it was proved that FSE is nothing but I and that desgalactotigonin and F-gitonin are the prosapogenins of II and selectively yielded by enzymatic cleavage from the corresponding parent saponins.

In the above experiment it was noted that the tetraglycosides formed were not likely to undergo further degradation*3,*5 and the method seemed applicable to a mix-

*3 M. M. Krider, J. R. Branaman, M. E. Wall (J. Am. Chem. Soc., **77**, 1238 (1955)) have reported that the partial hydrolysis of steroid saponin of *Yucca schidigera* (water-soluble) with native enzymes or dil. HCl or H_2SO_4 produced water-insoluble prosapogenins, and that the products of enzymatic cleavage (consisting primarily of sarsasapogenin linked to glucose-galactose oligosides) were obtained in the crystalline form. An attempted partial hydrolysis of II with acid resulted in providing less polar compounds together with I and II. Kikuba-saponin (diosgenin + 3 glucose + rhamnose) of *Dioscorea septemloba* Thunb. was cleaved with emulsin to give gracillin (diosgenin + 2 glucose + rhamnose) as precipitates from the reaction mixture (T. Kawasaki, T. Yamauchi, R. Yamauchi: This Bulletin, **10**, 698 (1962)).

*4 Chromatography on silica gel was advantageous over that on formamide-impregnated cellulose powder in easiness of the procedure and in resolving power of the component saponins. According to the private communication (March 6, 1964) from Prof. Tschesche, some saponin mixtures were successfully separated by silica gel chromatography also in his laboratory.

*5 In part, at least, it may be due to the insolubility of the product. The BuOH extract and the crude saponin from the leaves harvested in September contained originally a trace amount of less polar compound (substance (x)) besides I and II (cf. Fig. 2a, b, c).

ture of I and II. Hence the hydrolysis of the crude saponin was carried out in the same way and I was successfully obtained in 27～53% yield.*6

Meanwhile, a treatment of the original butanol extract with decolorizing carbon in methanol provided a highly hygroscopic (giving a clear aqueous solution) yellowish-brown powder (Ex) which showed a thin-layer chromatogram (Fig. 2c) quite similar*5,*7 to that (Fig. 2b) of the crude saponin. Therefor the direct use of the extract was thought to offer a more efficient and economical method for the preparation of I. When an aqueous solution of Ex was allowed to stand with a commercial amylase or cellulase preparation, the reaction mixture yielded precipitates quite analogously to the above experiment for the crude saponin. They were extracted with chloroform-methanol (extract: TLC, Fig. 2d; yield, 24～40%) and recrystallized to give I revealing only two spots of the expected teraglycosides on thin-layer (Fig. 2e).

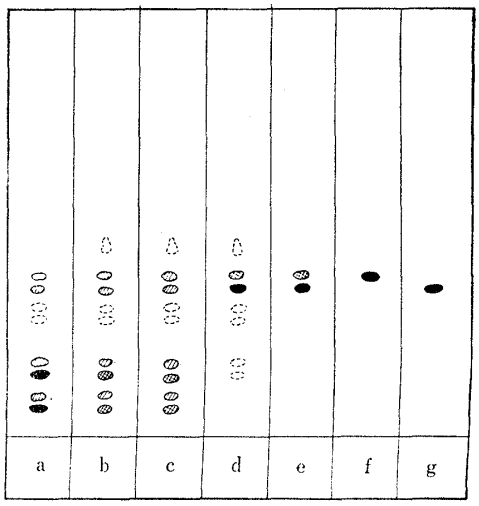

Fig. 2. Thin-layer Chromatograms on Silica Gel G

Solvent: $CHCl_3$-MeOH-H_2O (65:35:10)
a: Crude saponin (Oct.-Nov.)*1,8
b: Crude saponin (Sept.)*5,8
c: BuOH extract (Sept.)*5,8 treated with carbon in MeOH (Ex)
d: $CHCl_3$-MeOH extract of a product of enzymatic cleavage of (b) or (c)
e: FSE=Saponin I
f: FSE-1=Desgalactotigonin
g: FSE-2=F-Gitonin

I thus obtained from the crude saponin or from the butanol extract was fractionated into desgalactotigonin and F-gitonin by silica gel chromatography as mentioned afore, and when the latter is contained in I about 85%,*8 pure F-gitonin was provided only by repeated recrystallization of I from dilute ethanol and from butanol saturated with water.

Thereby saponin (I) in the *Digitalis purpurea* leaves, accordingly also the two component tetraglycosides, particularly F-gitonin, became available in large amounts.

Recently Tschesche and Wulff have reported[2] that the hydrolyses of "digitonin" (Merck) (seed saponins of *Digitalis purpurea*) in water with four kinds of enzyme preparations resulted in a slight spliting (by β-glucosidase and "Luizyme") of xylose, glucose and galactose. The difference in behaviors of seed- and leaf-saponins against enzyme is worth of note.

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*6 In one case when a sample was cleaved in H_2O, I was obtained in up to 60% yield (cf. experimental part).

*7 Several unknown substances*1 detected on paper chromatograms of the original BuOH extract were almost removed by the treatment with carbon in MeOH. The relative amounts of the tetraglycosides (*vs.* the polar oligosides) in Ex was apparently less than those in the crude saponin (cf. preceding paper*1).

*8 The content (purity) was calculated from the yields of gitogenin and tigogenin obtained by hydrolysis of a saponin mixture followed by alumina chromatographic separation of the sapogenin fraction. The yield of gitogenin from the BuOH extract or Ex was almost same as those from crude saponin*1 precipitated by cholesterol and from enzymatically prepared I (=FSE), while it varied to a considerable extent depending on the harvest time of the leaves: leaves harvested in September, gitogenin ca. 60%; those harvested in October～November, ca. 85% (cf. Fig. 2a, b). F. Weiss and O. Manns (Pharm. Zentralhalle, **98**, 437 (1959)) have reported that "tigonin" was the major component of a leaf saponin (yield of sapogenin: tigogenin, 40～70%; gitogenin, 20～30%).

2) R. Tschesche, G. Wulff: Tetrahedron, **19**, 621 (1963).

Experimental*9

Enzymatic Hydrolysis of Saponin (II)——As a preliminary experiment, II (50 mg.) was incubated with an enzyme, the reaction mixture was diluted with H_2O, extracted with BuOH, and BuOH and H_2O layers were respectively evaporated *in vacuo* and examined by the conventional paper chromatography (PC). The results are summarized in Table I.

Table I. Enzymatic Hydrolysis of Saponin (II) (50 mg.)

Medium (ml.)	Enzyme (mg.)	Time (days)	Temp. (°C)	Products: BuOH layer (saponin)	Products: H_2O layer (sugar)
30% EtOH 100 AcOH 0.2	emulsin[a] 500	5	25	FSE[e] II (trace)	glucose[f]
30% EtOH 100	snail enzyme[b] 200	5	25	FSE	glucose
20% EtOH 50 AcOH 0.1	hemicellulase[c] 100	7	25	〃	〃
20% EtOH 50 AcOH 0.1	"takadiastase-A"[d] 100	7	30	〃	〃

a) Prepared from the apricot seeds according to the Helferich's procedure (B. Helferich, *et al.*: Z. physiol. Chem., **208**, 91 (1932); **209**, 369 (1932); **215**, 277 (1933).
b) Kindly furnished by Dr. M. Shimizu of Daiichi Seiyaku Co., Ltd., to whom the authors are grateful.
c) Commercical preparation (Tokyo Kasei Co., Ltd.).
d) Kindly furnished by Dr. M. Iwai of Sankyo Co., Ltd., to whom the authors are grateful.
e) Stand for the product of Rf 0.45 on paper chromatograms*1 (solv., BuOH-AcOH-H_2O (4:1:5); Rf values of reference compounds, saponin (I) 0.45, saponin (II) 0.24).
f) Examined by paper chromatography.*1

Subsequently II (gitogenin glycoside content: ca. 85%)*8 (2 g.) was dissolved in 20% EtOH (500 ml.), and AcOH (0.2 ml.), toluene (0.3 ml.) and hemicellulase or "takadiastase-A" (4 g.) were added. The mixture was allowed to stand at 30° for 7 days. The amorphous precipitates formed were collected by filtration, dried, extracted with $CHCl_3$–MeOH (1:1) and the solution was concentrated and left stand to give a crystalline solid (FSE) (gitogenin glycoside: ca. 85%) (yield, 930 mg.; PC Rf 0.45; TLC, Fig. 1). From another sample of II (gitogenin glycoside: ca. 60%)*8 FSE (gitogenin glycoside: ca. 60%) was similarly obtained.

Fractionation of the Product (FSE) into the Component Saponins (FSE-1 and -2)——Cellulose powder chromatography: FSE (150 mg.) above obtained (gitogenin glycoside: ca. 60%) was separated into four fractions by chromatography on cellulose powder impregnated with formamide in the same way as reported before*1 using $CHCl_3$–tetrahydrofuran–pyridine (10:10:2)/formamide (4) as the solvent. Fr. 2 (TLC; FSE-1 +, FSE-2 −) was recrystallized from CH_2Cl_2–MeOH to give a crystalline powder (12 mg.). Further recrystallization from $CHCl_3$ (or CH_2Cl_2)–MeOH afforded thin-layer chromatographically pure FSE-1 as a crystalline powder, m.p. 284~286° (decomp.). Fr. 4 (TLC; FSE-1 −, FSE-2 +) was recrystallized from CH_2Cl_2–MeOH and from BuOH saturated with H_2O (BuOH–H_2O) to give pure (TLC) FSE-2 as fine needles (18 mg.), m.p. 252~255° (decomp.).

Silica gel chromatography: FSE (500 mg.) in $CHCl_3$–MeOH–H_2O (7:3:1) (bottom layer) (3 ml.) was placed on a silica gel (Kantō Kagaku Co., Ltd., 100~200 mesh, 250 g.) column (diameter, 5 cm.), eluted with the same solvent, fractionated into 416 portions and each portion (ca. 5 ml.) was examined by TLC: Fr. 1~240, none; Fr. 241~260, 3 mg., unknown substance (x);*5 Fr. 261~265, 25 mg., x ±, FSE-1 +; Fr. 266~300, 116 mg., FSE-1; Fr. 301~310, 29 mg., FSE-1 +, FSE-2 ±; Fr. 311~325, 27 mg., FSE-1 +, FSE-2 +; Fr. 326~337, 62 mg., FSE-1 ±, FSE-2 +; Fr. 338~390, 178 mg., FSE-2; Fr. 391~416, 47 mg., FSE-2 +, polar substance ±. Fr. 266~300 was recrystallized from dil. MeOH to give thin-layer chromatographically pure FSE-1 as fine needles, m.p. 284~286° (decomp.), $[\alpha]_D^{28}$ −68° (c=0.5, pyridine). Fr. 338~390 was recrystallized from dil. MeOH or BuOH–H_2O to afford pure (TLC) FSE-2 as fine needless, m.p. 251~255° (decomp.), $[\alpha]_D^{28}$ −66° (c=0.5, pyridine).

*9 Paper chromatography (PC) of saponins, sopogenins and sugars, thin-layer chromatography (TLC) of saponins, hydrolysis of saponins and qualitative and quantitative determinations of the products were all carried out in the same ways as described before.*1 All melting points were taken on a Kofler block and are uncorrected.

FSE-1——Acid hydrolysis of FSE-1 (6.6 mg.) yielded tigogenin (2.6 mg.), and xylose, glucose and galactose in a ratio of 1:1.7:1 (calcd. for desgalactotigonin dihydrate : tigogenin, 2.64 mg.; sugar ratio, xylose-glucose-galactose=1:2:1). Indentified with desgalactotigonin*1 by mixed melting point, comparisons of $[\alpha]_D$ and IR spectra and co-chromatography on thin-layer.

FSE-2——Acid hydrolysis of FSE-2 (10.0 mg.) yielded gitogenin (4.3 mg.), and xylose, gluose and galactose in a ratio of 1:1.8:0.9 (calcd. for F-gitonin dihydrate : gitogenin, 3.98 mg.; sugar ratio, xylose-glucose-galactose=1:2:1). Identical with F-gitonin*1 in every respect.

Enzymatic Hydrolysis of the Crude Saponin (a Mixture of Saponins (I and II))——Crude saponin (gitogenin glycoside : ca. 85%) (TLC, Fig. 2a) (10 g.) obtained *via* molecular compound with cholesterol was dissolved in 20% EtOH (3 L.) containing AcOH (3 ml.) and toluene (2 ml.) and the solution was treated with "takadiastase-A" or hemicellulase (20 g.) at 30° for 8 days. The reaction mixture (amorphous substances being deposited) was diluted with H_2O (1 L.) and the precipitates were collected by filtration, extracted with $CHCl_3$-MeOH and the solution was concentrated and left stand to give FSE (=I) as a crystalline powder (3.9 g.), PC, Rf 0.45; TLC, Fig. 2e. In several runs the yields were in the range of 27~53%. Another sample of crude saponin (gitogenin glycoside : ca. 60%) (TLC, Fig. 2b) provided FSE in 45% yield in the same way as above, and the same sample in H_2O (1%) with "takadiastase-A" (half amount as much as that of the saponin) gave FSE in about 60% yield.

Enzymatic Hydrolysis of the Butanol Extract of the Remainings from the Manufacture of Cardiac Glycosides——BuOH extract (25 g.) in 90% MeOH (250 ml.) was refluxed with decolorizing carbon (5 g.) for 1 hr., carbon was filtered off and the filtrate was evaporated *in vacuo* to provide an yellowish-brown, highly hygroscopic powder (Ex) (21 g.). It gave a clear aqueous solution and the thin-layer chromatogram as shown in Fig. 2c. An aq. solution of Ex was subjected to enzymatic hydrolyses at 37° in various conditions : concentration of Ex, 0.5~10%; kind and amount of enzyme preparation, "takadiastase-A," "-B,"*10 hemicellulase, "sanactase"*11 and "meicelase,"*12 twice~one-twentieth weight as mucn as that of Ex; incubation time, 1~4 days. The precipitates separated out from the reaction mixture were collected by centrifugation, washed with H_2O (again centrifuged), dried *in vacuo*, and extracted with $CHCl_3$-MeOH (1:1). The solution was evaporated to dryness *in vacuo*, weighed and examined by TLC. Satisfactory results were obtained by incubation of 0.5~2% Ex solution with twice~one-fourth amount of any enzyme used (except for hemicellulase) as much as that of Ex for 4 days. Some examples are as follows : Ex (gitogenin glycoside : ca. 60%) (TLC, Fig. 2c), 2 g.; H_2O, 200 ml.; "takadiastase-B," 0.5 g., 1 g., 2 g., 4 g.; at 37° for 4 days; yield of $CHCl_3$-MeOH extract (TLC, Fig. 2d), 0.54 g., 0.52 g., 0.5 g., 0.48 g., respectively. In larger scale experiments, above Ex (40 g.) and "takadiastase-B" (10 g.) in H_2O (4 L.) at 37° for 4 days gave FSE (10.6 g.) as a crystalline solid (recrystallized from CH_2Cl_2-MeOH) (TLC, Fig. 2e), while another Ex (gitogenin glycoside : ca. 85%) (30 g.) and "takadiastase-B" (60 g.) afforded FSE (12 g.) as needles (recrystallized from BuOH-H_2O).

Preparation of F-Gitonin and Desgalactotigonin——FSE thus obtained from the crude saponin or from the BuOH extract was separated into pure F-gitonin and desgalactotigonin in a larger scale by silica gel chromatography as described for that from I.

In the case when FSE contained ca. 85% F-gitonin, the sample (9.2 g.) was recrystallized from 70% EtOH and then from BuOH-H_2O to give F-gitonin (6.2 g.) of ca. 94% purity*8 as fine needles, m.p. 246~252° (decomp.), and further recrystallization (8 times) from BuOH-H_2O afforded that of almost 100% purity as fine needles, m.p. 243~252° (decomp.). However, in another sample of FSE (F-gitonin : ca. 60%) of which solubility in BuOH-H_2O was relatively high, it was hard to obtain pure F-gitonin only by recrystallization. Thus, the sample (500 mg.) gave a crystalline powder (200 mg.) (F-gitonin : ca. 60%), m.p. 256~258° (decomp.) (from dil. MeOH and MeOH or CH_2Cl_2-MeOH), or needles (120 mg.) (F-gitonin : ca. 70%), m.p. 256~260° (decomp.) (from BuOH-H_2O (twice)).

The authors thank Shionogi & Co., Ltd. for the butanol extracts of the digitalis leaves, Prof. T. Momose and Dr. Mukai for the kind advices and helps in the micro determination of sugars, and Miss N. Nasu for technical assistance.

*10 Commercial preparation (Sankyo Co., Ltd.).

*11 Commercial preparation (Meiji Seika Co., Ltd.). An enzyme mixture (α- and β-amylases (main) and protease, lypase, cellulase, etc.) from *Aspergillus niger*. Kindly furnished by Dr. S. Kawaji of Meiji Seika Co., Ltd., to whom the authors are grateful.

*12 Commercial preparation (Meiji Seika Co., Ltd.). An enzyme mixture (cellulase (main) and cellobiase, xylanase, amylase, etc.) from *Trichoderma koningi*. Kindly furnished by Dr. S. Kawaji of Meiji Seika Co., Ltd., to whom the authors are grateful.

Summary

Saponin (II) (a mixture of polar oligosides), the major component of the leaf saponins of *Digitalis purpurea* L., was found to be enzymatically cleaved to yield solely the minor component, saponin (I) (a mixture of two tetraglycosides, desgalactotigonin and F-gitonin).

Saponin (I), subsequently the component two tetraglycosides, were conveniently prepared from the crude leaf saponins precipitated by cholesterol and more efficiently from the butanol extract of the leaves by the specific partial hydrolysis of saponin (II) with some commercial enzyme preparations.

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UDC 577.164.11 : 543.422.25

57. Keishi Kotera : The Conformational Studies of Vitamin B_1 Analogues by the Proton Magnetic Resonance Spectroscopy.

(*Osaka Research Laboratory, Tanabe Seiyaku Co., Ltd.*[*1])

Recently, Vitamin B_1 has been improved to provide maintainable efficiency, higher absorbability and inertness to Thiaminase. Vitamine B_1 analogues can be classified into two groups as regards the thiazole ring cyclizing or not, and the latter case can be divided into the symmetric disulfide type and other sulfide derivatives.

In the present paper, the chemical shifts and the temperature dependence of the proton magnetic resonance spectra were studied to obtain the conformational relation between pyrimidine ring and thiazole ring or N-formyl group.

Experimental

For the following various vitamin B_1, either recrystallized from the commercial reagents or synthesised by the usual method, the proton magnetic resonance (NMR) spectra were measured on Japan Electron Co. J. N. M-C60 spectrometer at 60 Mc. About 15% solutions of the samples, in *N*/2 HCl acidic deuterium oxide added a few drops of dioxane as internal standard, or in $CDCl_3$ with TMS, were prepared. The temperature of these sample was changed over the range from −2° to 80° by Japan Electron Co. JES-VT-2 Temperature Controller.

Samples :

Thiamine	[T]	O-Benzoylthiamine	[OBT]
Thiothiamine	[TT]	S-Benzoylthiamine monophosphate	[BTMP]
S-Methylthiamine	[MT]	Thiamine disulfide	[TDS]
Thiamine diphosphate	[TDP]	Thiamine disulfide monophosphate	[TDMP]
		O-Benzoylthiamine disulfide	[BTDS]

Results and Discussion

The proton chemical shifts of various vitamin B_1 are shown in Chart 1. Further the influence of substituted oxyethyl group and cyclization of thiazole ring are described in Table I.

*1 Kashima-cho, Higashiyodogawa-ku, Osaka (小寺啓司).