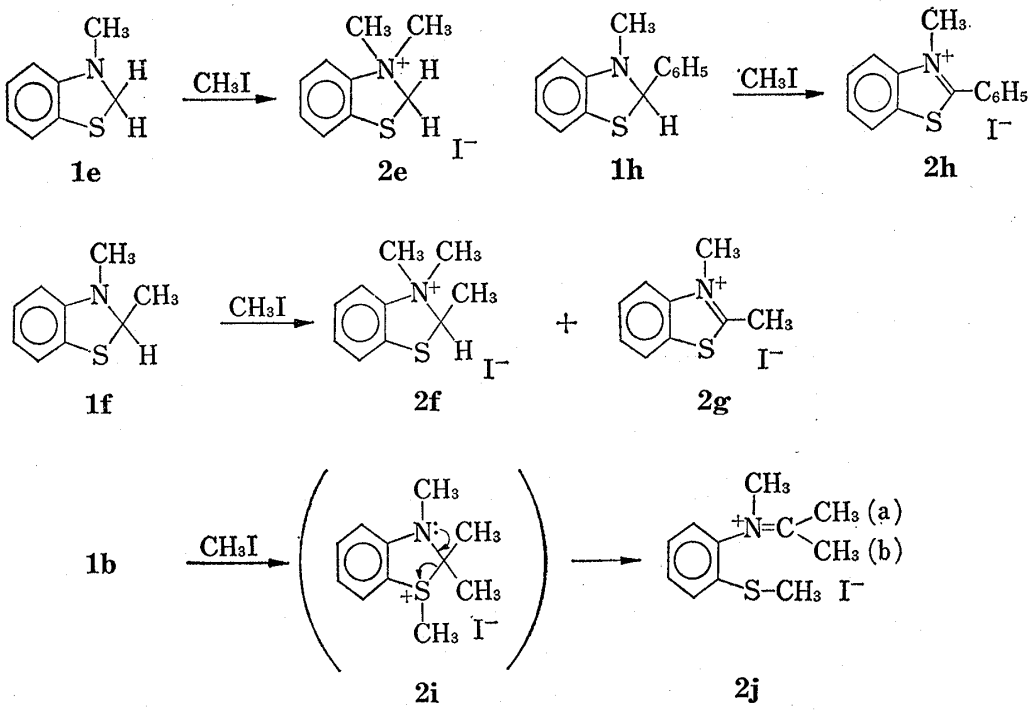

Chart 2

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Chemical Structure and Sweet Taste of Isocoumarins and Related Compounds[1] Synthesis of 5-Hydroxyflavanones and Related Dihydrochalcones

On the basis of the information obtained from our previous studies on relationship between structure and sweet taste of 3,4-dihydroisocoumarins, 5-hydroxyflavanones and related dihydrochalcones were synthesized. Compounds (**2**, **3**, **4**, and **7**) had a sweet taste while the others were tasteless. The relationship of structure-sweet taste of 5-hydroxyflavanones was similar to that of 3,4-dihydroisocoumarins.

Keywords——structure-sweet relationship; 3,4-dihydroisocoumarin; flavanone; dihydrochalcone; phyllodulcin

The taste of flavanones, chalcones, and dihydrochalcones were reported by Horowitz, *et al.*[2] Subsequently, Krbechek, *et al.* clarified the relationship between sweet taste and the substituent in B ring of the dihydrochalcone-4′-glycosides.[3] According to their reports,

1) M. Yamato, K. Sato, K. Hashigaki, and T. Koyama, *Chem. Pharm. Bull.* (Tokyo), **25**, 706 (1977).
2) R.M. Horowitz and B. Gentli, U.S. patent 3087821 (1963).
3) L. Krbechek, G. Inglett, M. Holik, B. Dowling, R. Wagner, and R. Riter, *J. Agr. Food Chem.*, **16**, 108 (1968); G. Inglett, L. Krbechek, B. Dowling, and R. Wagner, *J. Food Sci.*, **34**, 101 (1969).

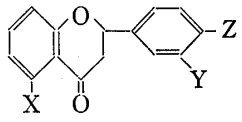
hesperetin is the only sweet flavanone, its sweetness being faint, and the other flavanones are bitter or tasteless. On the other hand, several dihydrochalcones reveal a strong sweet taste, and the sweetness of dihydrochalcones were summarized by krbechek, *et al.*[3]

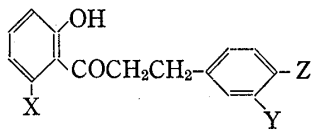
Recently, Crosby, *et al.*[4] and Farkas, *et al.*[5] synthesized acylphenoxypropanesulfonic acids having a strong sweet taste.

We have been interested in the difference between structure-sweetness relationship of dihydrochalcones and that of 3,4-dihydroisocoumarins. For example, the 3,4-dihydro isocoumarins reveal sweetness in spite of the lack of 6-glycoside group in the isocoumarin skeleton.[6] Most of the sweet 3,4-dihydroisocoumarins and related compounds have hydroxyl and methoxyl groups at 3- and 4-positions in the phenyl moiety corresponding to B ring of dihydrochalcones. Replacement of the methoxyl group with ethoxyl or *n*-propoxyl groups resulted in the decrease or loss of sweetness.[7] In view of the fact that the level of sweetness of phyllodulcin is stronger than that of 8-deoxyphyllodulcin,[8] 3-(3-hydroxy-4-methoxyphenyl)-3,4-dihydroisocarbostyril and 3-(3-hydroxy-4-methoxyphenyl)-8-hydroxy-3,4-dihydroisocarbostyril were synthesized to confirm the effect of the 8-hydroxyl group.[8] The former is tasteless while the latter reveals only a faintly sweet taste. In addition, it was clarified that the presence of a substituent at 4-position of the phenyl moiety resulted in the loss of sweetness,[1] by the molecular modification of β-(3-hydroxy-4-methoxyphenyl)ethylbenzene, essential structure of phyllodulcin.

In this study, it was attempted to apply the information obtained from previous studies of 3,4-dihydroisocoumarins to design sweet flavanones and dihydrochalcones. Namely, the information suggested that the sweet flavanones and dihydrochalcones may also be required the presence of a hydroxyl group forming hydrogen bonding with the carbonyl group. The compounds (**1**—**12**) were synthesized and these taste were summarized in Table I. The flavanones (**2**, **3**, and **4**) had a sweet taste, all of which had the 5-hydroxyl group forming a hydrogen bonding with the carbonyl group and 4-alkoxy-3-hydroxyphenyl moiety at the 2-position. The level of sweetness of **2**, **3**, and **4** decreased with the increasing number of methylenes in the alkoxyl group, and the order agreed with that of dihydroisocoumarins rather than that of dihydrochalcones.[2] Among them, the sweetest compound (**2**) was found

Table I. Sweetness of Flavanones and Dihydrochalcones





Compd. No.	X	Y	Z	Sweetness[a]	Compd. No.	X	Y	Z	Sweetness[a]
1[b]	H	OH	OCH_3	0	**7**	H	OH	OCH_3	100
2	OH	OH	OCH_3	350	**8**	OH	OH	OCH_3	0
3	OH	OH	OC_2H_5	150	**9**	OH	OH	OC_2H_5	0
4	OH	OH	O-*n*-C_3H_7	60	**10**	OH	OH	O-*n*-C_3H_7	0
5	OH	OCH_3	OH	0	**11**	OH	OCH_3	OH	0
6	OH	H	OH	0	**12**	OH	H	OH	0

a) Sucrose=1.
b) L. Hoerhammer, H. Wagner, H. Roesler, M. Keckeisen, and L. Farkas, *Tetrahedron*, 21, 967 (1965).

4) G.A. Crosby, G.E. Dubois, and N.M. Weinshenke, U.S. patent 3974299; G.A. Crosby and G.E. Dubois, *ibid*, 3976687 (1976).
5) L. Farkas, M. Nogradi, A. Gottsegen, and S. Antus, Hung. *Teljes*, **1976**, 10931.
6) M. Yamato, K. Hashigaki, Y. Kuwano, and T. Koyama, *Yakugaku Zasshi*, **92**, 535 (1972).
7) M. Yamato, K. Hashigaki, A. Tsukioka, and T. Koyama, *Chem. Pharm. Bull.* (Tokyo), **25**, 700 (1977).
8) M. Yamato, K. Hashigaki, E. Honda, K. Sato, and T. Koyama, *Chem. Pharm. Bull.* (Tokyo), **25**, 695 (1977).

to be 350 times sweeter than sucrose, and its sweet level was comparable to that of phyllodulcin.

From these results, it may be concluded that the relationship between sweet taste and structure of 5-hydroxyflavanones lacking 7-glycoside moiety is similar to that of 3,4-dihydroisocoumarins.

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Synthesis of the Nonatetracontapeptide corresponding to the Sequence proposed for Thymopoietin II[1)]

First total synthesis of a nonatetracontapeptide corresponding to the entire amino acid sequence of thymopoietin II, a T cell differentiating hormone isolated from bovine thymus, was described. Toward the synthesis of this hormone, two relatively large fragments corresponding to the sequence 1—27 and 28—49 were prepared and the fragments were served as the building blocks for the final construction of the entire amino acid sequence of the hormone. The final deprotection of the fully protected nonatetracontapeptide was achieved by the treatment with methanesulfonic acid or hydrogen fluoride, and the purification of the synthetic peptide was effected by a column chromatography on Sephadex G-50, Biogel P-2 and CM-cellulose. The physicochemical and biological properties of the synthetic peptide were also described.

Keywords——thymopoietin II; thymocyte differentiation; nonatetracontapeptide; fragment condensation; methanesulfonic acid

The entire amino acid sequence of bovine thymopoietin II (Tp), a T cell differentiating hormone of the thymus, was recently elucidated by Schlesinger and Goldstein.[2)] We have synthesized the nonatetracontapeptide corresponding to the entire sequence of this unique hormone. To date only partial synthesis of Tp, tridecapeptide (29—41), by the solid phase method has been described.[3)]

In our present synthesis of Tp in solution (Fig. 1), amino acid derivatives bearing protecting groups, *e.g.*, Z, OBzl and MBS, finally removable by the treatment with methanesulfonic acid (MSA)[4)] were employed. Among these protecting groups, the MBS group was recently

1) Amino acids, peptides and their derivatives in this communication are the L-configuration. The following abbreviations are used: Z=benzyloxycarbonyl, BOC=*tert*-butoxycarbonyl, MBS=*p*-methoxybenzenesulfonyl, OBzl=benzyl ester, OBu^t=*tert*-butyl ester, HONB=N-hydroxy-5-norbornene-2,3-dicarboximide, DCC=N,N′-dicyclohexylcarbodiimide, DMF=N,N′-dimethylformamide, TEA=triethylamine, TFA=trifluoroacetic acid. Solvent systems for thin-layer (silica gel, Merck 60 F-254 plate) chromatography are: Rf^1=$CHCl_3$–MeOH–AcOH (9:1:0.5), Rf^2=$CHCl_3$–MeOH–AcOH (8:2:0.5), Rf^3=$CHCl_3$–MeOH–AcOH (8:3:1), Rf^4=AcOEt–pyridine–AcOH–H_2O (60:20:6:10), Rf^5=*n*-BuOH–AcOH–H_2O (4:1:1), Rf^6=*n*-BuOH–AcOEt–AcOH–H_2O (1:1:1:1), Rf^7=*n*-BuOH–pyridine–AcOH–H_2O (30:20:6:24).

2) D.H Schlesinger and G. Goldstein, *Cell*, **5**, 361 (1975).
3) D.H. Schlesinger and G. Goldstein, M.P. Scheid and E.A. Boyse, *Cell*, **5**, 367 (1975).
4) H. Yajima, Y. Kiso, H. Ogawa, N. Fujii, and H. Irie, *Chem. Pharm. Bull.* (Tokyo), **23**, 1164 (1975).