Properties and Syntheses of Sweetening Agents

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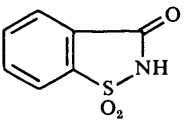
1 Introduction

Research for inexpensive non-toxic non-nutritive sweetening agents has been intensified since the withdrawal of cyclamate from the consumer's market in 1970. There is doubt whether the other commercial sweetener, saccharin, will continue to be marketed because of toxicological problems that have been encountered. Further, the increase in cost of sugar has also prompted a search for novel cheap sweeteners. The number of new sweeteners that have emerged for public consumption over the past decade has been severely restricted by the stringent requirements of the American Food and Drugs Administration (F.D.A.) and the British Food Standard Committee.

A major difficulty in the search for the ideal sweetener is that no satisfactory theory or mechanism has been elucidated to explain the relation of molecular structure to sweetness.

It is known, however, that sensory responses to sweet substances are related to chemical specificity. A very slight modification in the molecule's structure can result in a tasteless or even bitter product. For example saccharin (1) is very sweet but the *N*-methyl derivative (2) is tasteless.[1] Similarly, sodium cyclamate (3) is sweet, but the *N*-methyl derivative[2] (4) is tasteless. Dulcin, *p*-ethoxyphenylurea (5), is 250 times sweeter than sucrose, the ortho derivative (6) is tasteless, whereas the thiourea analogue (7) is bitter.



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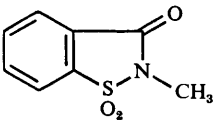

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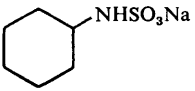

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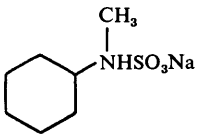
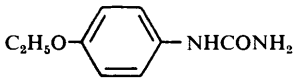
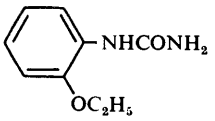


(4)

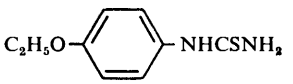
[1] A. F. Holleman, *Rec. Trav. chim.*, 1923, **42**, 839.
[2] R. J. Wicker, *Chem. and Ind.*, 1966, 1708.



(Sweet)
(5)



(Tasteless)
(6)



(Bitter)
(7)

Stereoisomers and anomers may have different tastes. For example L-glucose has a slightly salty taste whereas D-glucose is sweet. Similarly, the two anomers of D-mannose have different tastes, α-D-mannose is sweet whereas β-D-mannose is bitter (some sugars, for example cellobiose, are tasteless). Many of the D-isomers of amino acids are sweet, while the L-isomers generally are tasteless (L-isoleucine is bitter and D-isoleucine is sweet). These differences in taste are due to a change in the conformation of the molecule and indicate that discrimination between tastes is in part a recognition of the spatial structure of molecules.

So far none of the more promising sweeteners which have been tested in recent years have satisfied all the requirements for an ideal sweetener, hence the search for such a sweetener continues.

This review intends to survey the most recent trends in the search for sweetening agents. There have been other reviews[2–5] on sweeteners but they are not concerned with complete examination of all the classes of sweeteners now known.

2 Gustation

Taste or gustation is comprised of four basic taste sensations; sourness, saltiness, sweetness, and bitterness. Sourness is related to the concentration of hydrogen ions in the media. Saltiness is caused by the presence of Group I cations Li^+, Na^+, and K^+ (and only in a minor way to halogen anions such as the chlorine anion). Sweet and bitter sensations are more complex and their mechanism is not understood. There is no satisfactory explanation why, for example, in the non-nutritive sweeteners cyclamate (3) and saccharin (1) there should be a marked decrease in their sweetening potency as their concentration in aqueous solutions increases. Surprisingly, at high concentrations these sweeteners become bitter.[6] Magidson and Gorbatschow[7] showed, over 50 years ago, the comparative decrease in sweetness of saccharin with respect to sugar (Table 1). Later Sjoström and Cairncross[8] observed that the addition of 0.5% saline solution to a 5% sucrose solution increased the sweetening potency. Recently it has been reported by Seybold[9] that even salt can taste sweet at a sufficiently low concentration. Bitterness is often found in such natural products as alkaloids, bile salts, and glycosides such

[3] W. Herzog, *Fortschr. Chem. Ztg.*, 1929, **53**, 99.
[4] E. Newbrun, *Internat. Dental J.*, 1973, **23**, 328.
[5] G. A. Crosby, *CRC Rev. Food Sci. Nutrition*, 1976, **7**, 297.
[6] M. Brook, *Royal Soc. Health J.*, 1969, **89**, 140.
[7] O. J. Magidson and S. W. Gorbatschow, *Ber.*, 1923, **56B**, 1810.
[8] L. B. Sjoström and S. E. Cairncross, *Adv. Chem. Ser.*, 1955, **12**, 108.
[9] P. G. Seybold, *Chemistry*, 1975, **48**, 6.

Table 1

Concentration of Sucrose %	*Sweetness* *Concentration of sucrose solution/concentration of saccharin solution as sodium salt*
15	190
10.2	261
6.2	317
3.9	399
2.7	553
1.65	675

as the saponins. It will be seen in this review that only minor differences distinguish bitterness from sweetness and that in many cases a reversible relationship exists between them.

3 Natural Sweeteners

The earliest natural sweetener known to man was honey. Evidence from rock paintings indicates that it was used in the Neolithic period. The manna mentioned in the Bible was possibly the secretion of the insects *Trabutina mannipara* and *Naiacoccus serpentinus* which feed on desert Tamarisk trees. Analysis shows that this secretion contains sucrose and invert sugar as the principal ingredients.[10]

Table 2 shows the sweetness of a variety of sugars based on sucrose as the standard.[4,11–13] The discrepancies in the sweetness factor are due to differences in: (a) concentration of the sweetener, (b) temperature, (c) pH of the sugar solution, (d) nature of the medium, (e) sensitivity of the human taster.

The world sugar production has increased from 8 million metric tons in 1900 to 73 million metric tons in 1970. Sugar is by far the cheapest natural sweetener currently available and it will not be easy to replace it as an important food ingredient. It should be appreciated that sugar is not the panacea to man's sweet taste as it can have a detrimental effect on health (especially during pregnancy) and can cause (a) obesity, (b) dental diseases, particularly dental carries in man and (c) coronary diseases.[14,15] It is because of these serious side effects of sugar that the search for non-caloric sweetening agents has been dramatically intensified during the past decade.

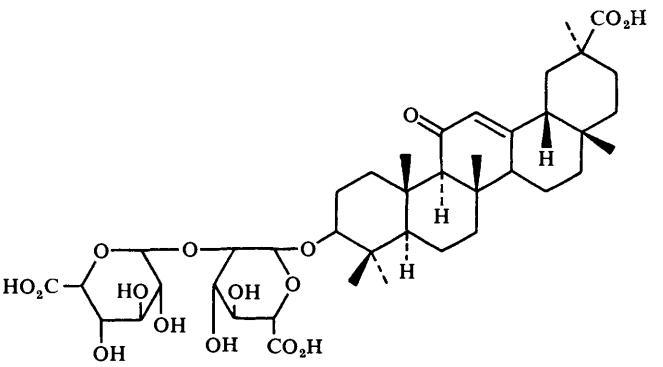
4 Glycyrrhizin

Glycyrrhizin, the potassium or calcium salt of glycyrrhizic acid (8) (3β,20β)-20-carboxy-11-oxo-30-norolean-12-en-3-yl 2-*O*-β-D-glucopyranosyl α-D-gluco-

[10] K. S. Brown, *Chem. Soc. Revs.*, 1975, **4**, 277.
[11] H. M rk, J. Mcketta, and D. Othmer *Encyclopedia of Chem. Technol.*, 1969, **19**, 594, John Wiley.
[12] L. W. Aurand and A. E. Woods *Food Chemistry, Carbohydrates*, 1973, 101.
[13] A. Biester, M. W. Wood, and C. S. Wahlin, *Amer. J. Physiol.*, 1925, **73**, 387.
[14] O. Paul, A. Macmillan, and H. Park, *Lancet*, 1968, **2**, 1049.
[15] W. E. Waters, S. Moore, and P. Sweltnam, *Lancet*, 1970, 1014.

Table 2

Sugar	*Sweetness based on sucrose* 100		
Raffinose	1[4]	23[13]	
α-Lactose	16[4,13]		
β-Lactose	32[4]	39[12]	40[11]
α-Mannose	32[4]		
α-Galactose	32[4,13]	63[11,12]	
Maltose	32[4,13]	46[12]	50[11]
Rhamnose	32[4,13]		
D-Xylose	40[4,13]	70[11]	
Xylitol	100[4]		
Mannitol	57[4]	70[11]	
Sorbitol (D-glucitol)	50[11]	54[4]	
Dulcitol	40[11]		
α-Glucose	70[11]	74[4,13]	
β-Glucose	82[4]		
Sucrose	100[4]		
Invert sugar (Glucose + Fructose)	65[12]	70—90[11]	130[4,13]
D-Fructose	110[11]	114[12]	
β-Fructose	173[4,13]	180[4]	



Glycyrrhizic acid

(8)

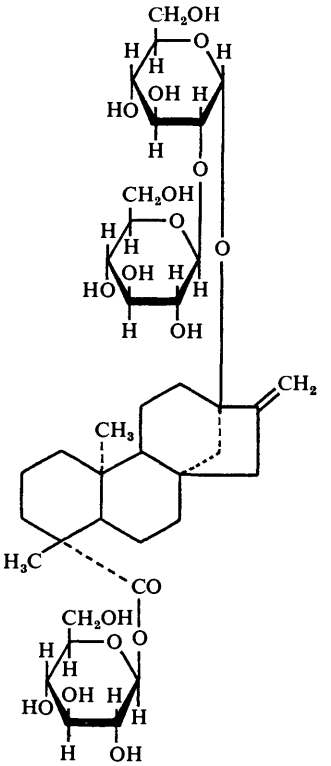
pyranosidouronic acid has been known for at least 4000 years. It is found in certain rhizomes and licorice roots such as *Glycyrrhiza glabra* L., *G. hersuta* and *G. Uralensis*. Glycyrrhizin is about 50 times sweeter than sucrose. The rhizomes contain from 3 to 23% of glycyrrhizic acid salts.[16] The ammonium salt of glycyrrhizic acid is also 50 times sweeter than sucrose and when it is mixed with

[16] A. Muravev, *Farm. Polska*, 1967 798.

sugar a potentiating effect occurs which doubles its sweetening potency. Ammonium glycyrrhizate is not suitable as a marketable sweetener because of its lingering licorice flavour, however, this lingering after taste is repressed by the presence of specific nucleotides such as 5′ inosinic acid or 5′ guanylic acid without any loss of sweetening power of the ammonium glycyrrhizate.[17]

5 Stevioside

Stevioside, [13-(2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]kaur-16-en-18-oic β-D-glucopyranosyl ester (9) was first isolated by two French chemists



Stevioside

(9)

Bridel and Lavielle[18] in 1931 from the leaves of the shrub *Stevia rebaudiana* Bertoni (also known as *Yerba dulce*) which grows wild in Paraguay. Stevioside is 230 to 300 times sweeter than sucrose.[4,5]

[17] MacAndrews and Forbes Co., Israel P. 42,862/1975.
[18] M. Bridal and R. Lavielles, *J. Pharm. Chim.*, 1931, **14**, 99.

6 Sweet Proteins

A. Monellin.—Monellin is an intensely sweet protein found in the red berries (known as 'serendipity berries' or 'guinea potatoes'[19]) of the tropical West African plant, *Dioscoreophyllum comminsii*.[19] It is a single polypeptide which, on a weight basis, is approximately 3000 times sweeter than sucrose. It is reputed to be the sweetest natural product known and is also the first protein known to exhibit the remarkable property of potent sweetness. It has an unusual sweetness which develops in a few seconds and lingers for a few minutes. Unfortunately its sweetening potency disappears within 24 hours at room temperature and it is therefore not suitable for use in foods and beverages. The complete structure of monellin has recently been elucidated.[20–22]

Subunit A

Arg-Glu-Ile-Lys-Gly-Tyr-Glu-Tyr-Gln-Leu-Tyr-Val-Tyr-Ala-Ser-Asp-Lys-Leu-Phe-Arg-Ala-Asn-Ile-Ser-Gln-Asn-Tyr-Lys-Thr-Arg-Gly-Arg-Lys-Leu-Leu-Arg-Phe-Asx-Gly-Pro-Val-Pro-Pro-Pro.

Subunit B

Gly-Glu-Trp-Glu-Ile-Ile-Asp-Ile-Gly-Pro-Phe-Thr-Gln-Asn-Leu-Gly-Lys-Phe-Ala-Val-Asp-Glu-Glu-Asn-Lys-Ile-Gly-Gln-Tyr-Gly-Arg-Leu-Thr-Phe-Asn-Lys-Val-Ile-Arg-Pro-Cys-Met-Lys-Lys-Thr-Ile-Tyr-Glu-Glu-Asn.

Complete structure of monellin

B. Thaumatin.—Thaumatin, another sweet-tasting protein has been isolated by van der Wel[23] from the fruit of *Thaumato coccus* Danielli Benth, a plant found in West Africa. Thaumatin is a basic protein with a molecular weight of about 14,000 and an iso-electric point of 12.0. It is 750 times as sweet as sucrose with a slight licorice after taste. It is also a single polypeptide chain, but about twice as long as the monellin molecule. Heat denaturation and the splitting of the disulphide bridges of thaumatin both result in the complete disappearance of sweetness implying the importance of the tertiary structure of the protein for its taste.[24]

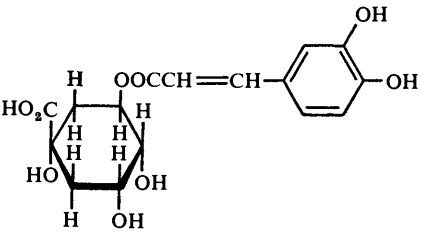
C. Miraculin.—A native shrub of Tropical West Africa yields a small red berry which, when chewed, causes sour substances to taste sweet.[19] This berry first came to European attention in 1852 when an English surgeon, Daniell, noted that the commander of a British fort in Dahomey enjoyed 'constant opportunities of testing the wonderful effects of this fruit'. The so-called 'miracle berry' was

[19] G. E. Inglett and J. F. May, *Econ. Bot.*, 1968, **22**, 326.
[20] G. Frank and H. Zuber, *Z. Physiol. Chem.*, 1976, **357**, 585.
[21] Z. Bohak and Shoei-Lung Li, *Biochim. Biophys. Acta*, 1976, **427**, 153.
[22] G. Hudson and K. Biemann, *Biochem. Biophys. Res. Comm.*, 1976, **71**, 212.
[23] H. van der Wel, *FEBS Letters*, 1972, **21**, 88.
[24] H. van der Wel and K. Loeve, *European J. Biochem.*, 1972, **31**, 221.

rediscovered in the 1920's by a U.S. Department of Agriculture collecting expedition. In 1968 Beidler and Kurihara[25] and independently van der Wel and coworkers[26] showed that the active constituent of miracle fruit, *Synsepalum dulcificum*, is a basic glycoprotein with an approximate molecular weight of 44,000. The modifying effect usually lasts from 1 to 2 hours. The sweetness of miraculin is gradually lost on being heated, which again implies a relationship between tertiary structure and taste. The approximate amino acid composition of miraculin is known but not its amino acid sequence.

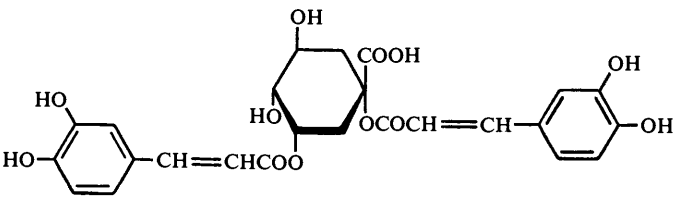
7 Chlorogenic Acid and Cynarin

The taste-modifying property of artichoke (*Cynara scolymus*) has been known for some time.[27] Tests have shown that solutions of different taste qualities (sucrose, citric acid, quinine hydrochloride and sodium chloride) are all sweetened to some degree by a prior mouth rinse with artichoke extract. The artichoke induced sweetness, however, lasts only for about 4 to 5 minutes. Chlorogenic acid (3-caffeoyl quinic acid) (10) and cynarin (1,5-dicaffeoylquinic acid) (11) have been



Chlorogenic acid

(10)



Cynarin

(11)

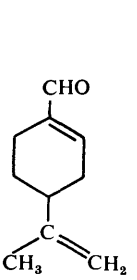
shown to be the two principal active compounds responsible for the taste-modifying property of artichoke. Cynarin also has a sweet taste. Artichokes

[25] L. Beidler and K. Kurihara, *Science*, 1968, **161**, 1241.
[26] H. van der Wel, J. N. Brouwer, A. Francke, and G. J. Henning, *Nature*, 1968, **220**, 373.
[27] L. M. Bartoshuk, C. H. Lee, and R. Scarpellino, *Science*, 1972, **178**, 988.

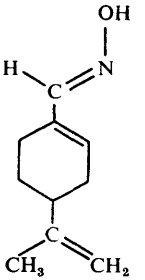
are on the G.R.A.S. (Generally Regarded As Safe) list of the F.D.A. and hence these two compounds may show promise as sugar substitutes.

8 Perillartine

1-Perillaldehyde (12) the essential oil of the plant *Perilla nankinensis* is 12 times sweeter than sucrose. On the other hand the *syn*-oxime of 1-perillaldehyde known as perillartine (13) is 2000 times sweeter than sucrose.[11] The isomer, originally believed to be the *β-anti*-oxime (14) was in fact the *tert*-chloride formed by the



(12)



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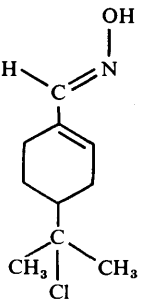


(14)

Markovnikov addition of HCl to the isopropenyl moiety of (12). Numerous analogues of perillartine have been synthesized by Acton and coworkers[28–30] and were found to be sweet. The most promising was 4-(methoxymethyl)-cyclohexa-1,4-diene-1-carboxaldehyde, *syn*-oxime (15) known as SRI oxime V. It is 450 times sweeter than sucrose and has no undesirable after taste of saccharin.[31] If kept above pH 3 this sweetener is stable in most foods and sweet concentrates. SRI oxime-V was synthesized[32] according to Scheme 1.

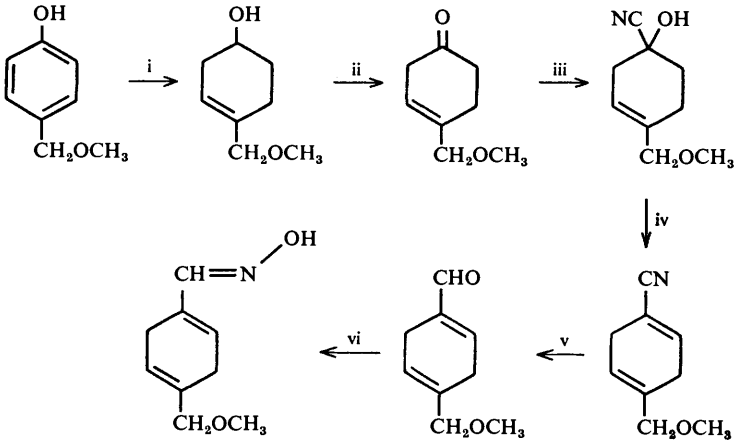
9 Osladin

Osladin (16), a steroidal saponin, has recently been isolated from the rhizomes of *Polypodium vulgare*, the first sweet substance isolated from the steroid group.[33] It is approximately 3000 times sweeter than sucrose. Osladin has recently been partially synthesized from solasodine to osladin aglycone.[34]

10 Phyllodulcin

Phyllodulcin (17) is a sweetener which was first isolated, in 1916, from the tea

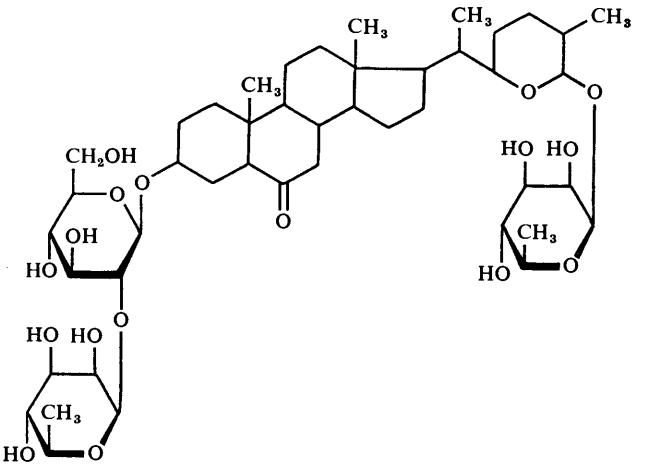
[28] E. M. Acton, K. Yamamoto, and H. Stone, U.S.P. 3,833,654/1974.
[29] E. M. Acton and H. Stone, *Science*, 1976, **193**, 584.
[30] E. M. Acton, M. W. Lerom, and H. Stone, U.S.P. 3,952,144/1976.
[31] *Chem. and Eng. News*, 1975, **53**, No. **34**, 27.
[32] E. M. Acton, M. W. Lerom, and H. Stone, U.S.P. 3,919,318/1975.
[33] J. Jizba, L. Dolejs, V. Herout, and F. Sörm, *Tetrahedron Letters*, 1971, **1329**.
[34] M. Havel and V. Cerny, *Coll. Czech. Chem. Comm.*, 1975, **40**, 1579.



(15)

Reagents: i, Li–$EtNH_2$; ii, oxidation–HNO_3 aq.; iii, KCN–H^+; iv, $-H_2O$; v, Bu^i_2AcH; vi, NH_2OH.

Scheme 1



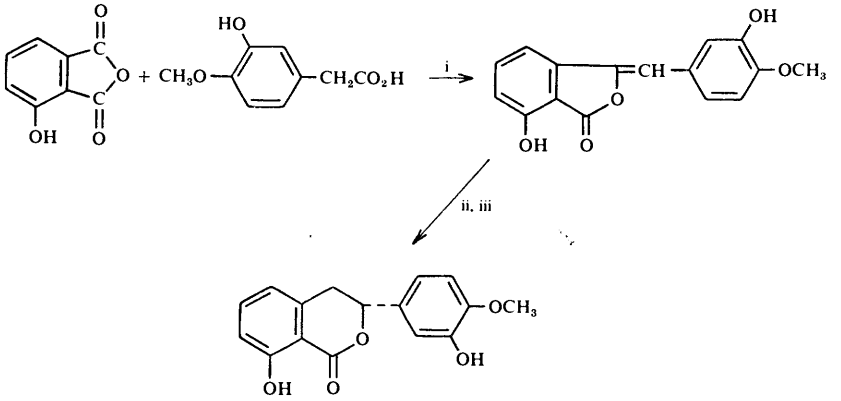
Osladin

(16)

leaves of *Hydraugea macrophylla* Seringe.[35] It is 200 to 300 times sweeter than sucrose.[36] Phyllodulcin may be synthesized by condensing 3-hydroxyphthalic

[35] Y. Asabina and S. Ueno, *J. Pharm. Soc. Japan*, 1916, 146.
[36] Y. Ariyoshi, *Kagaku To Seibutsu*, 1974, **12**, 274.

anhydride with homoisophthalic acid to 7,3′-dihydroxy-4′-methoxybenzalphthalide which undergoes simultaneous reduction and lactone ring expansion in the presence of ethanolic sodium borohydride and aqueous alkali.[37] Various Japanese workers have successfully synthesized phyllodulcin[38–40] (Scheme 2).



(17)

Reagents: i, KAc; ii, $NaBH_4$–EtOH; iii, OH^-

Scheme 2

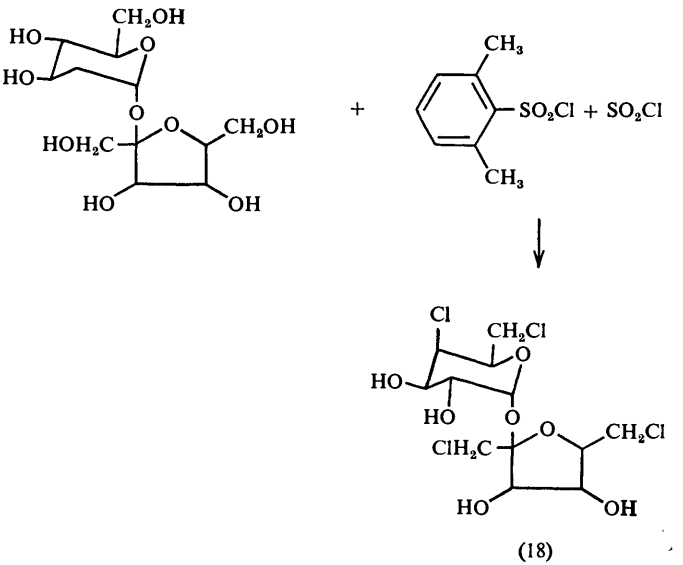
11 Sweetener from the Chineese Fruit 'Lo Han Kuo'

Recently a natural sweetener was isolated from the dried fruit (Lo Han Kuo) of *Momordica grosvenori* Swingle which grows in Southern China. This sweetener of unknown composition is about 150 times sweeter than sucrose with a licorice after taste similar to the after taste of stevioside and the dihydrochalcones. Preliminary studies indicate the sweetener to be a glycoside of a triterpene.[5]

12 Chlorinated Sucrose

A very sweet sucrose analogue was accidentally discovered by Hough and his coworkers of Queen Elizabeth College, London.[41] The analogue, 1,4,6,6′-tetrachloro-1′,4,6,6′-tetradeoxygalactosucrose (18) was obtained by chlorination of sucrose (Scheme 3). It was 500—600 times sweeter than sucrose without the licorice after taste associated with stevioside and aspartame or the bitter after taste of saccharin. In the reaction the glucose ring of sucrose inverts to a galactose

[37] Ternyo Tsuji, Jap. P. (Kokai) 74/110,667.
[38] Y. Naoi, S. Higuchi, H. Ito, T. Nakano, K. Sakai, T. Matsui, S. Wagatsuma, A. Nishi, and S. Sano. *Org. Repn. Proced. Int.*, 1975, **7**, 129.
[39] T. Nakano H. Ito, Y. Naoi, S. Higuchi, Y. Takahashi, K. Sakai, T. Matsui, A. Nishi, and S. Sano, Jap. P. (Kokai) 75/35,167.
[40] T. Nakano, M. Murase, K. Ochi, and S. Tobinaga, *Chem. Comm.*, 1976, **20**, 820.
[41] *Chem. Eng. News*, 1976, 30.



(18)

Scheme 3

ring. It is known that galactosucrose is tasteless and the reason is probably because of intramolecular hydrogen bonding on the 4-carbon hydroxy group. This bonding is not present in the conformational structure of sucrose or its chlorinated product.

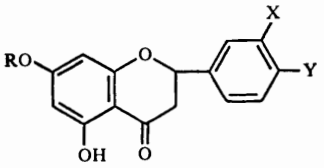
13 The Dihydrochalcones

It is known that citrus fruits contain bitter ingredients known as flavone glycosides. Naringin (19) is the bitter ingredient of grapefruit, neohesperidin (20) is the bitter ingredient of unripe Seville oranges and Prunin (21) is the bitter ingredient of Prunus wood.

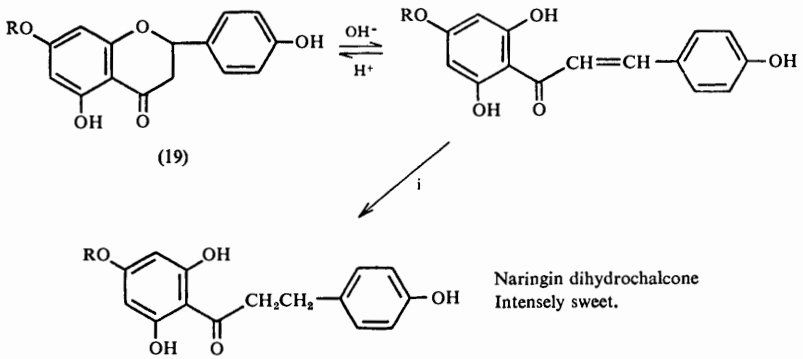
In 1963 Horowitz and Gentili accidentally found in the course of study on the structure–taste relations of citrus flavanones that catalytic reduction of naringin (19) and neohesperidin (20) gave dihydrochalcones (DHC) which were found to be surprisingly sweet[42] (Scheme 4). This discovery led to numerous analogues of dihydrochalcones being synthesized and one of them displayed particular promise as a highly potent non-nutritive sweetener, β-neohesperidin dihydrochalcone (23) which was 1500 times sweeter than sucrose.

The synthesis of dihydrochalcones from naringin has been reported[43,44] (Scheme 4).

[42] R. M. Horowitz and B. Gentili, *J. Agr. Food Chem.*, 1969, **17**, 696.
[43] L. Krbechek, G. Inglett, M. Holik, B. Dowling, R. Wagner, and R. Riter, *J. Agric. Food Chem.*, 1968, **16**, 108.
[44] L. Givandan and Co., B.P. 1,443,310/1976.



(19) Naringin R = β-neohesperidosyl* X = H Y = OH
(20) Neohesperidin R = β-neohesperidosyl X = OH Y = OCH_3
(21) Prunin R = β-D-glucosyl X = H Y = OH
*β-neohesperidosyl = 2-*O*-α-L-rhamnopyranosyl-D-glucopyranosyl

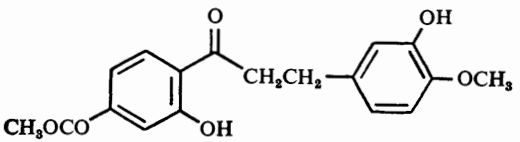


(19)

(22)

Reagent: i, H_2(Pd–C)

Scheme 4



(23)

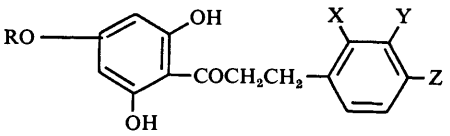
Although the intense sweetness of neohesperidin dihydrochalcone (22a) permits the use of extremely low amounts to be used as a non-caloric additive, the lingering menthol after taste presents some problems. It has been found that a mixture of (22a) with saccharin gives a more acceptable sweet taste.

The relative sweetness of some dihydrochalcone derivatives compared to sucrose are shown in Table 3.[43]

Dihydrochalcones are stable in acids at normal temperatures and can be used in fruit and carbonated beverage products.[45]

[45] G. E. Inglett, L. Krbechek, B. Dowling, and R. Wagner, *J. Food Sci.*, 1969, **34**, 101.

Table 3



R = β-Neohesperidosyl group

Compound	*Benzaldehyde substitute* X	Y	Z	*Relative sweetness sucrose* = 1
2,4,6,3-tetrahydroxy-dihydrochalcone 4′-β-neohesperidoside	H	OH	H	100
Naringin dihydrochalcone (22)	H	H	OH	100
Neohesperidin dihydrochalcone (22a)	H	OH	OMe	1500
Homoneohesperidin dihydrochalcone	H	OH	OEt	1000
2,4,6,3-Tetrahydroxy-4-n-propoxy-dihydrochalcone 4′-β-neohespidoside	H	OH	OPr^n	2000

Horowitz and Gentili[42] replaced the neohesperidosyl group of the dihydrochalcones of naringin and neohesperidin with other sugar moieties such as glucose, galactose, and xylose.[46] These dihydrochalcone glycosides were found to be sweet having 5 to 10% the sweetening power of (22a) and were found to be less soluble. Esaki and coworkers[47] further modified the sugar moieties of DHC and found that certain DHC glycosides such as β-sophorosyl DHC and β-D-glucosyl-(1-2)β-D-galactosyl DHC were devoid of any sweetness. This contradicts the hypothesis of Horowitz and Gentili[42] that in the DHC's of naringin and neohesperidin neither the C-2 or C-6 hydroxyl of the glucose molecule is essential for sweetness since the sweetness does not disappear when these groups are blocked with a 2-*O*-α-L-rhamnosyl group or the 6-*O*-methyl substituents. However, the C-3 and C-4 hydroxyl groups of glucose are necessary which suggests that the rhamnose moiety is essential for sweetness. The problem of lingering menthol after taste was overcome by a Hungarian company[48] who synthesized DHC analogue (23) which substituted a sugar moiety by an acetyl moiety (Table 4).

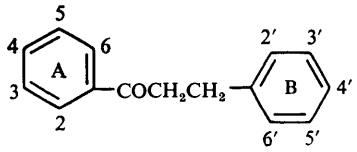
14 Synthetic Non-Nutritive Sweeteners

A. Sulphamic Acid Derivatives

Sodium cyclohexyl sulphamate (*sodium cyclamate*).—The sweetness of sodium cyclamate (3) was accidentally discovered by Michael Sveda of the University of Illinois in 1937 while he was investigating the antipyretic properties of sulphamic

[46] R. M. Horowitz and B. Gentili, U.S.P. 3,890,298/1975.
[47] S. Esaki, S. Kamya, and F. Konishi, *J. Agric. Biol. Chem.*, 1975, **39**, 1385.
[48] L. Farkas, M. Nogradi, A. Gottsegen, and S. Antus, G. P. (Offen.) 2,258,304/1973.

Table 4 *Relative sweetness of some dihydrochalcone analogues*



Compound—common name	2	4	6	2′	3′	4′	*Relative sweetness sucrose = 1*	*References*
Naringin DHC	OH	NeoH*	OH			OH	100	42, 43, 49, 50, 51
Neohesperidin DHC	OH	NeoH	OH		OH	OMe	1000	42, 43, 49, 50, 51
Neoeriocitrin DHC	OH	NeoH	OH		OH	OH	Slightly† sweet	42, 43, 49, 50, 51
	OH	NeoH	OH		OH		100	43
	OH	NeoH	OH		OH	OEt	1000	43
	OH	NeoH	OH		OH	OPr^n	2000	43
	OH	NeoH	OH		OH	OPr^i	1000	42
	OH	(a)	OH		OH	OMe	Sweet†	54
	OH	NeoH	OH	OH	OMe		Sweet†	50
	OH	NeoH			OH	OMe	Sweet†	55
	OMe	NeoH	OH		OH	OMe	Sweet†	51
	OH	(b)	OH		OH	OMe	80	42, 50, 51
	OH	(c)	OH		OH	OMe	160	51, 52
	OH	(d)	OH		OH	OMe	140 300—500[53]	51, 53
	OH	6-*O*-Me NeoH	OH		OH	OMe	1000	51
	OH	(e)	OH		OH	OMe	1	R. M. Horowitz Personal communication 1973

	OH	OCH_2CO_2H		OH	OMe	180	48
	OMe	NeoH	OH		OH	Sweet†	51
	OH	(f)	OH		OH	1000	51, 56
Hesperedin DHC	OH	OH	OH	OH	OMe	†	R. M. Horowitz Personal communication 1973
		$OCOCH_3$	OH	OH	OMe	180	48
		$O(CH_2)_3$— SO_3H	OH	OH	OMe	†	57

* NeoH = β-neohesperidosyl
† Not available

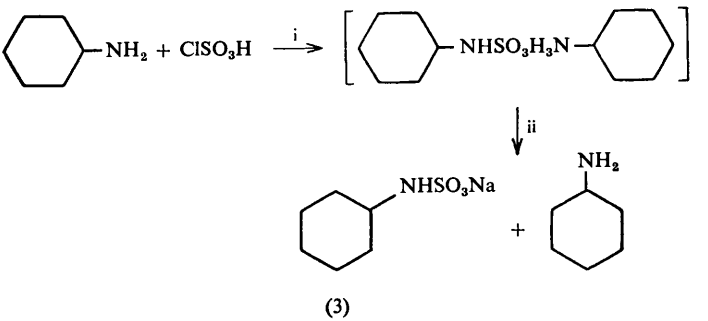
(a) 4-*O*-α-glucosyloxy
(b) β-D-glucosyloxy
(c) β-D-xylosyloxy
(d) β-D-galactosyloxy
(e) 6-*O*-α-L-rhamnosyl-NeoH
(f) 2-*O*-α-L-rhamnosyl-β-D-galactosyloxy

[49] R. M. Horowitz and B. Gentili, U.S.P. 3,087,821/1963.
[50] R. Horowitz and B. Gentili, in 'Sweetness and Sweeteners,' ed. G. G. Birch, L. F. Green, and C. B. Coulson, Applied Science Publishers, London, 1971.
[51] R. Horowitz and B. Gentili, in 'Sweeteners' Symposium, ed. G. E. Inglett, Avi Publishing, Westport, Conn., U.S.A., 1974, chapter 16.
[52] R. M. Horowitz and B. Gentili, U.S.P. 3,826,856/1974.
[53] R. M. Horowitz and B. Gentili, U.S.P. 3,890,296/1975.
[54] S. Okada, *Kagaku To Seibutsu*, 1974, **11**, 712.
[55] L. Farkas and M. Nogradi, Hung.P. 4026/1972.
[56] D. M. Van Niekerk and B. H. Koespen, *Experientia*, 1972, **28**, 123.
[57] L. Farkas, M. Nogradi, T. Pfliegel, S. Antus, and A. Gottsegen. G.P. (Offen.) 2,506,356/1975.
[58] L. F. Audrieth and M. Sveda, *J. Org. Chem.*, 1944, **9**, 89.
[59] L. F. Audrieth and M. Sveda (E. I. Du Pont de Nemours & Co., Inc.), U.S.P. 2,275,125/1942.

acid derivatives when he found that his cyclamate contaminated cigarette tasted sweet. The sodium salt of cyclohexyl sulphamate was found to be 30 times sweeter than sucrose. Aqueous solutions of sodium cyclamate are neutral whereas cyclamic acid, the free base of sodium cyclamate, has a sweet-sour taste and the pH of a 10% aqueous solution is between 0.8 and 1.6.

The cyclamates are stable under most conditions encountered in food processing. The sweetness of cyclamate salts, usually in the sodium or calcium form, relative to sucrose may vary from 25 to 140, depending on the type of food that is used. The potassium and magnesium salts were also found to be sweet but are not commercially used.

The syntheses usually involve sulfonation of cyclohexylamine in the presence of a base. Sulfonation is often carried out in excess cyclohexylamine in order to isolate the cyclohexylammonium cyclamate. This double salt is readily converted to the desired sodium or calcium salt by treating it with either NaOH or $Ca(OH)_2$, respectively. Audrieth and Sveda's original method used chlorosulfonic acid. This is a simple and nonexpensive method of synthesizing cyclamates[58,59] (Scheme 5).

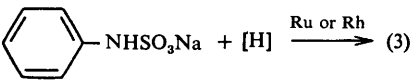


(3)

Reagents: i, CCl_4 @ 5 °C; ii, NaOH

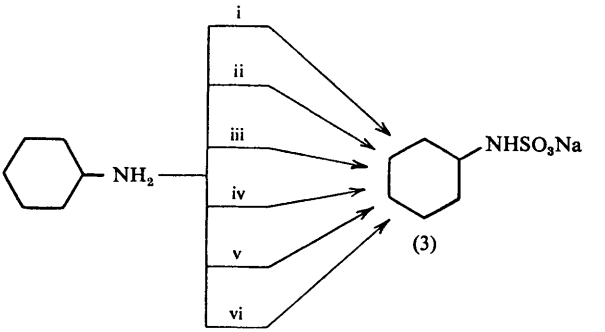
Scheme 5

Catalytic reduction[66] of the aromatic sulphamate was carried out by the Abbott Laboratories (Scheme 6). Various other processes for synthesizing (3) have been patented but none of them have any commercial prospects[60–67] (Scheme 7).



Scheme 6

[60] D. J. Lodger (E. I. Du Pont de Nemours & Co., Inc.), U.S.P. 2,804,472/1957.
[61] H. S. McQuaid (E. I. Du Pont de Nemours & Co., Inc.), U.S.P. 2,804,477/1957.
[62] Abbott Laboratories (USA); Israel P. 18,631/1965.
[63] P. Mueller and R. Trefzer (Ciba Corp.), U.S.P. 3,060,231/1962.
[64] O. G. Birsten and J. Rosin (Baldwin-Montrose), U.S.P. 3,366,670/1968.
[65] A. Calder and J. Whetstone (I.C.I. Ltd.), B.P. 1,395,497/1975.
[66] M. Freifelder and B. Meltsner (Abbott Laboratories), U.S.P. 3,194,833/1965.
[67] W. W. Thompson (E. I. Du Pont de Nemours & Co. Inc.), U.S.P. 2,800,501/1957.

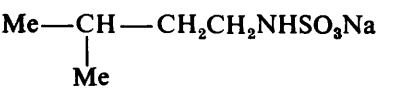


Reagents: i,[60] H_2NSO_3Na; ii,[61] $H_2NSO_3NH_4$; iii,[62] SO_3–N_2; iv,[63] H_2NSO_3H; v,[64] $ClSO_3H$, Et_3N; vi,[64,65] Me_2NSO_3

Scheme 7

In 1970 cyclamate was the cheapest non-nutritive sweetener on the market. On August 14, 1970 the sale of cyclamate was forbidden on the American market. The decision came about because certain experiments on the bladder of rats showed that it was possibly carcinogenic. Other countries including England and Canada followed the American decision to ban cyclamate. Various groups retested the initial findings and were convinced that cyclamate was not carcinogenic.[68,69] In March 1976 the National Cancer Institute Committee presented their findings to the F.D.A. and concluded that 'the evidence to date does not establish the carcinogenicity of cyclamates'.

Chemical structure and sweetness in certain sulphamates.—There are no specific rules or even explanations relating structure of certain sulphamate molecules to sweetness. Audrieth and Sveda[58] investigated cyclamate and its derivatives in order to determine which part of the molecule causes sweetness. They first determined whether the cyclohexane ring was essential for sweetness by synthesizing the normal straight chained hexyl analogue, n-hexyl sulphamate, which they found to be tasteless. Later the Nitto Labs[70] found a branched chain n-isoamyl sulphamate



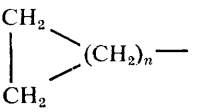
to be 10 times sweeter than cane sugar. Recently, Nofre[71] discovered that the

[68] F. Coulston, E. W. McChesney, and L. Goldberg, *Food Cosmet. Toxicol.*, 1975, **13(2)**, 297.
[69] B. L. Oser, S. Carson, G. E. Cox, E. E. Vogin, and S. S. Sternberg, *Toxicology*, 1975, **4(3)**, 315.
[70] H. Yamaguchi, Nitto Laboratories, Jap.P. (Kokai) 8815/1960.
[71] C. Nofre and F. Pautet, *Bull. Soc. chim. France*, 1975, **3-4**, 686.

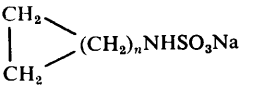
n-butyl derivative is 50 times sweeter than saccharose. Sveda *et al.* further found that the sweetness disappeared when the hydrogen atom on the sulphamyl moiety ($NHSO_3Na$) was replaced by a methyl, ethyl or a cyclohexyl group (Table 5). After preparing the benzene analogue and finding that it was tasteless,

Table 5 *Sodium sulphamate analogue non-sweeteners*

$R_1—\underset{\displaystyle R_2}{\underset{|}{N}}SO_3Na$

R_1	R_2	*Reference*
Phenyl	H	58
Cyclohexyl	Alkyl (C_{1-5}) or cyclohexyl	58
$Me(CH_2)_5$—	H	58
		
n = 1[72,75], 2[72], 10[72]	H	72, 75
Cyclohexylmethyl	H	72
Methyl	Bu^i	72
Cycloheptyl	Me	72
2-Methylcyclopent-1-yl	H	72
2-Methylcyclohexen-1-yl	H	72
Adamantyl	H	72
Piperidin-4-yl	H	72
Tetrahydropyran-4-yl	H	72
$Me(CH_2)_nCH$—(n = 4—16)	H	72
Isopropyl	H	72

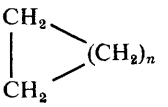
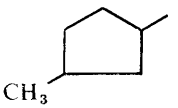
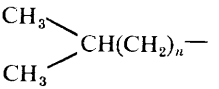
they decided that retention of the sulphamate moiety and the presence of a saturated cycloaliphatic ring was essential for sweetness in sulphamate molecules. Spillane[72] confirmed that various saturated cycloaliphatic rings did not destroy the sweetening power of these sulphamates. He prepared a number of sulphamates of the formula



and also showed that if these rings were substituted by methyl or dimethyl groups, the sweetness was retained (Table 6).

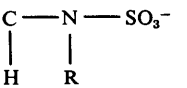
[72] G. A. Benson and W. J. Spillane, *J. Medicin, Chem.*, 1976, **19**, 869.
[73] B. Unterhalt and L. Böschemeyer, *Z. Lebensm.-Untersuch.-Forsch.*, 1971, **145**, 93.

Table 6 *Sodium alkyl and cycloalkyl sulphamate sweeteners*

R	R—$NHSO_3Na$ *Relative sweetness sucrose* = 1	*Reference*
		
$n = 2$	10*	72
$n = 3$	41*, 30	72
$n = 4$	34*	72
$n = 5$	28*	72
	30	73
$Me(CH_2)_nCH_2$—		
$n = 1$	0.5*	74
$n = 2$	3.5*	74
		
$n = 1$	2.9*	70
$n = 2$	10*	2

* The sulphamates were compared to a 3% w/v sucrose solution

A recent study of Benson and Spillane[72] concluded that in the structure–activity relationships of acyclic sulphamates sweetness appears to be present in the system



[73] K. M. Beck and A. W. Weston, U.S.P. 2,785,195/1957.
[71] B. Unterhalt and L. Böschemeyer, *Z. Lebensm.-Untersuch.-Forsch.*, 1972, **149**, 227.

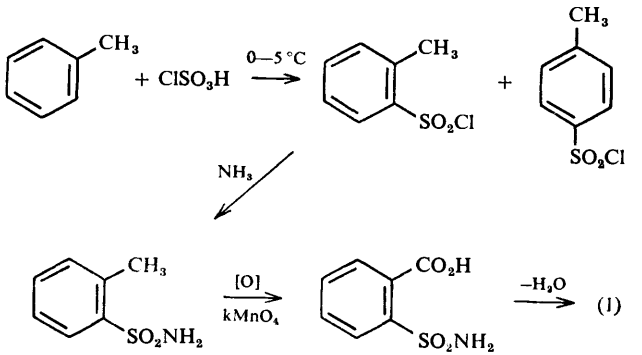
where there can be one or two α-hydrogens. They argued that the presence of this system is a necessary but not a sufficient condition for sweetness. *N*-n-Butylsulphamate was three and a half times sweeter than sucrose but *N*-n-propylsulphamate was only one fifth as sweet and other straight chain sulphamates were not sweet.

It appears that from the various examples in Table 5 that there is no relation between the hydrocarbyl moiety and sweetening power. Possibly the proton of the sulphamyl moiety —$NHSO_2$— is related to sweetening power in certain sulphamate molecules.

15 Cyclic Sulphamates

Saccharin.—The earliest known commercial synthetic sweetening agent was saccharin or 3-oxo-2,3-dihydro-1,2-benzisothiazol-1,1-dioxide (1).

Saccharin was discovered accidentally by Remsin and Fahlberg[76] at the Johns Hopkins University in 1879 during an academic study of the oxidation of *o*-toluene sulphonamides. Fahlberg noticed that during his evening meal his bread tasted sweet and he traced this the following day in his laboratory to a certain benzisothiazole derivative which was later known as saccharin. It has been employed as a non-nutritive sweetener for more than 80 years. The original synthesis used by Remsin and Fahlberg nearly 100 years ago is still the principal industrial process of today. The synthesis starts from toluene and it is shown in Scheme 8. An alternative method is used by Maumee Company in the U.S.A.[77] starting from anthranilic acid.



Scheme 8

Saccharin is approximately 300 to 550 times as sweet as cane sugar and has a bitter metallic after taste. The sweetness of saccharin and cyclamate relative to sugar is not constant. For example, as the concentration of saccharin in aqueous solution increases, the relative sweetness compared with sugar appears to decrease.

[76] I. Remsen and C. Fahlberg, *Amer. Chem. J.*, 1879, **1**, 426.
[77] Maumee Co., *Chem. Eng.*, 1954, **61**(7), 128.

Also the calcium salt is less sweet than the sodium salt. Bitterness becomes apparent with a saccharin solution as the concentration is increased. Furthermore, relative sweetness is affected by acidity, temperature, and the type of food in which it is being measured. So far 17 different reports have been published dealing with the mutagenicity of saccharin.[78] Mainly tested as its sodium salt, saccharin has shown mutagenic effects in Salmonella, Drosophila, and in mice. Saccharin was removed from the list of GRAS food additives after it was discovered that it can also cause bladder cancer in rats.[79]

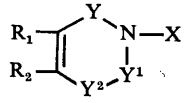
As with cyclamate, there have been detailed studies in order to find the effect of changes in the structure of saccharin on its sweetness. Saccharin forms salts, many of which are sweet, and it is reasonable to assume that the saccharin anion is an essential part of the structure required for the property of sweetness. This is supported by the fact that *N*-alkyl derivatives of saccharin are tasteless. Holleman and coworkers[1] carried out an intensive investigation into the effect of altering the saccharin molecule and discovered some interesting results. If the heterocyclic ring is opened to give the corresponding *o*-carboxy-benzenesulphonamide then the sweetness disappears. Further, if the sulphonyl group is replaced by a carbonyl group the product is the tasteless phthalimide analogue. On the other hand if the carbonyl group in saccharin is changed from a sulphonyl group to benzodithioimide then the sweetness is retained, but with a bitter after taste. Duplication of the heterocyclic ring on the other side of the benzene ring also causes loss of sweetness. Substitution in the benzene ring of saccharin with various substituents modifies the taste. In the case of electron donating halogen group, the change from sweetness to bitterness progresses as the change from F to Cl to I. Substitution with the NO_2 group and other electron withdrawing groups resulted in the disappearance of sweetness with the introduction of bitterness. The *p*-ethoxy group, essential for sweetness in the dulcin molecule, is not effective in the saccharin molecule. Since perillartine, which is the oxime of perillaldehyde, is sweeter than perillaldehyde, and the oximes are known to be sweet, it might be expected that the introduction of the oxime group on the carbonyl would modify the sweetness, but this is not so in the case of saccharin when sweetness disappears on oximation. Table 7 shows the relation of saccharin analogues and sweetening potency.

In the pursuit of other types of saccharin analogues Clauss and Jensen[80] accidentally discovered a different class of non-toxic sweetening agents, 1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxides (Table 7). Their alkaline salts were very soluble in water, and like the cyclamates, were stable to hydrolysis. They were prepared according to Schemes 9 and 10.

Very recently BASF[87] AG have discovered that the replacement of the benzene ring of saccharin with thiophene does not enhance its sweetening power. Further the 3 analogues (24, 25, 26) that were prepared were found to have no unpleasant taste and were non-toxic (Scheme 11).

[78] P. G. N. Kramers, *Mutation Research*, 1975, **32**, 81.
[79] G. T. Bryan and E. Ertürk, *Science*, 1970, **167**, 996.
[80] K. Clauss and H. Jensen, *Angew. Chem. Internat. Edn.*, 1973, **12**, 869.
[87] O. Hromatka and D. Binder (BASF AG.), G.P. (Offen). 2,534,689/1976.

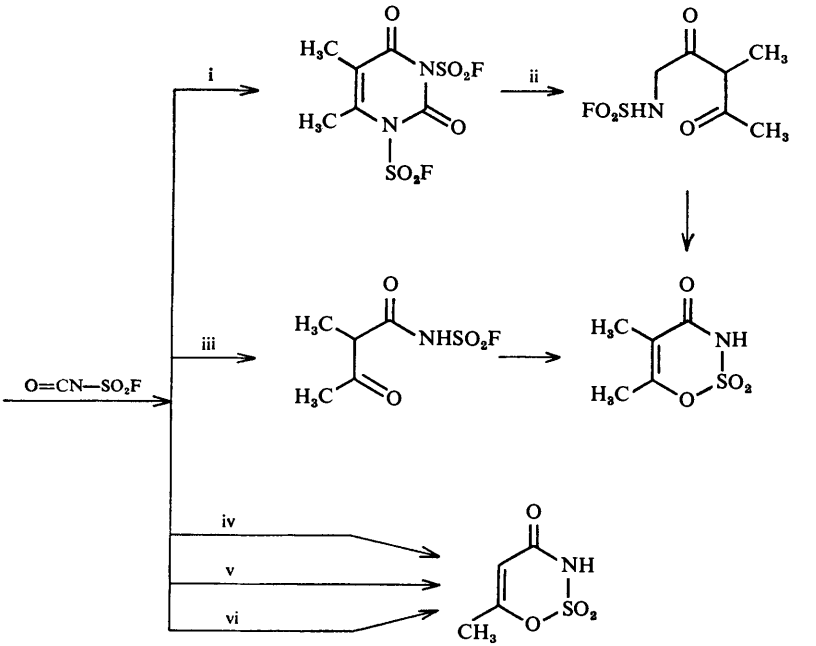
Table 7 *Saccharin and heteroazine analogues and their sweetening potency*



R_1	R_2	X	Y	Y^1	Y^2	*Relative sweetness sucrose = 1*	*Reference*
CH=CH—CH=CH		Na	CO	SO_2	O	50 Bitter after taste	5
CH=CH—CH=CH		H	CO	SO_2	NH	Tasteless	80
CH=CH—CH=CH		H	SO_2	CO	NH	Sweet	80
CH=CH—CH=CH		H	SO_2	CO	O	Tasteless	80
CH=CH—CH=CH		H	CO	SO_2	O	100	81
CH=CH—CH=CH		H	CO	SO_2	Bond	500	76
CH=CH—CH=CH		H	CO	CO	Bond	Tasteless	2
CH=CH—CH=CH		H	SO_2	SO_2	Bond	Sweet Bitter after taste	1
CH=CH—CH=CH		H	HC=N—OH	SO_2	Bond	Insipid taste	108
CH=CH—CH=CH Substituted by F, Cl, Me, NH_2		H	CO	SO_2	Bond	Sweet	1
H	H	Na	CH_2	SO_2	O	10	80
H	Me	Na	CH_2	SO_2	O	130	80
Me	H	Na	CH_2	SO_2	O	20	80
Me	Me	Na	CH_2	SO_2	O	130	80
H	Et	Na	CH_2	SO_2	O	150	80
Et	H	Na	CH_2	SO_2	O	20	80

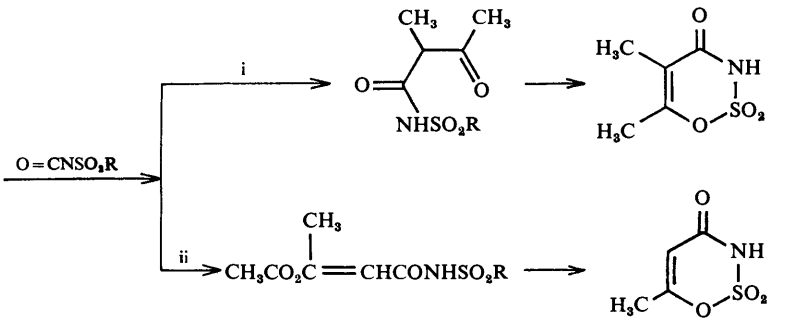
Me	Et	Na	CH_2	SO_2	O	130	80
Et	Me	Na	CH_2	SO_2	O	250	80
H	Bu^n	Na	CH_2	SO_2	O	30	80
Pr^n	Me	Na	CH_2	SO_2	O	30	80
Et	Pr^n	Na	CH_2	SO_2	O	70	80
Me	Me	Double Bond with Y	CHCOMe	SO_2	O	Tasteless	80
H	Me	Me	CO	SO_2	O	Tasteless	80
H	Me	H	CO	SO_2	NH	Tasteless	80
H	Me	H	CO	SO_2	NMe	Tasteless	80
H	H	H	CO	SO_2	O	10	81
Me	H	H	CO	SO_2	O	Sweet	82
Me	H	H	O	SO_2	CO	Sweet	83

[81] K. Clauss, H. Jensen, and H. Lück (Farb. Hoechst AG.), G.P. (Offen.) 2,228,423/1973.
[82] K. Clauss, H. Jensen, and H. Schnabel (Farb. Hoechst AG.), G.P. (Offen.) 2,237,804/1973.
[83] K. Clauss and H. Jensen (Farb. Hoechst AG.), G.P. (Offen.) 2,264,235/1974.
[108] A. Mannessier-Mameli, *Gazzetta.*, 1932, **62**, 1062.



Reagents: i,[80] MeCCMe; ii, H_2O; iii,[80] $MeCH_2COMe$; iv,[84] MeCOMe; v,[83] $MeCOCH_2COCOCMe_3$; v,[86] $MeCOCH_2CO_2H$

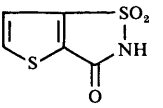
Scheme 9



Reagents: i,[80] EtCOMe; ii,[85] $MeCO_2C(Me)CH_2$

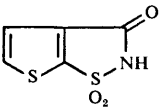
Scheme 10

[84] Farb. Hoechst AG., B.P. 1,340,911/1973.
[85] K. Clauss, H. Jensen, E. Schmidt, and H. Pietsch (Farb. Hoechst AG.), G.P. (Offen.) 2,434,547/1976.
[86] K. Clauss, E. Schmidt, H. Jensen, and H. Pietsch (Farb. Hoechst AG.), G.P. (Offen.) 2,434,549/1976.



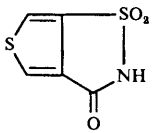
(24)

2,3-dihydro-3-oxothieno[2,3-*d*]isothiazole-1,1-dioxide



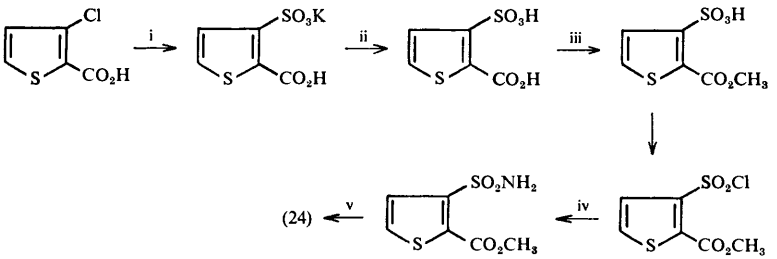
(25)

2,3-dihydro-3-oxothieno[3,2-*d*]isothiazole-1,1-dioxide



(26)

2,3-dihydro-3-oxothieno[3,4-*d*]isothiazole-1,1-dioxide



Reagents: i, $NaHSO_3$; ii, H^+; iii, MeOH; iv, NH_3; v, $NaOCH_3$

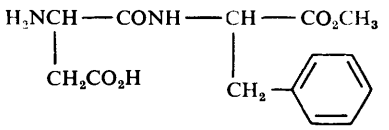
Scheme 11

16 Dipeptide Esters

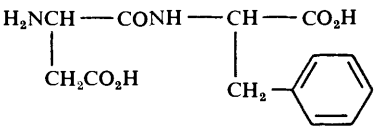
Aspartame.—Aspartame or L-aspartyl L-phenylalanine methyl ester (27) was also accidentally discovered by James Schlatter[88] of G. D. Searle in the early sixties, and in 1966 by Davey and coworkers of I.C.I.[89] while they were involved in the synthesis of gastrin and its tetrapeptide analogues, but the sweetness was unnoticed. The surprisingly potent sweet taste of this dipeptide is completely unexpected and could not have been predicted from its chemical structure. The

[88] R. H. Mazur, J. M. Schlatter and A. H. Goldkamp, *J. Amer. Chem. Soc.*, 1969, **91**, 2684.
[89] J. M. Davey, A. H. Laird, and J. S. Morley, *J. Chem. Soc.* (*C*), 1966, 555.

sweetness may be related to the polarity of the molecule since the free carboxylic acid (28) is tasteless.



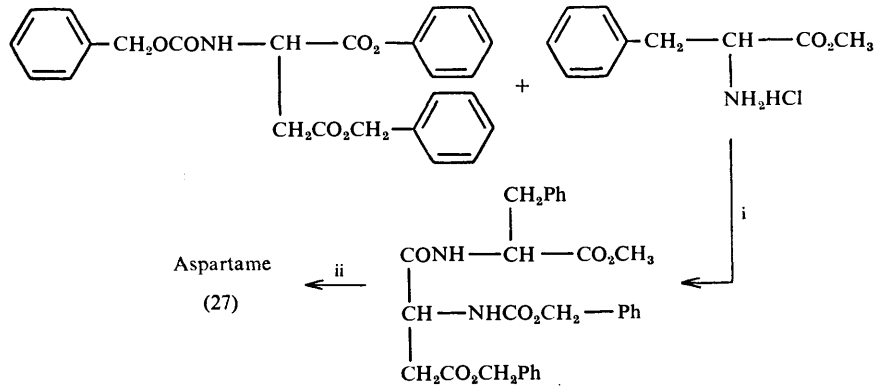
(27)



(28)

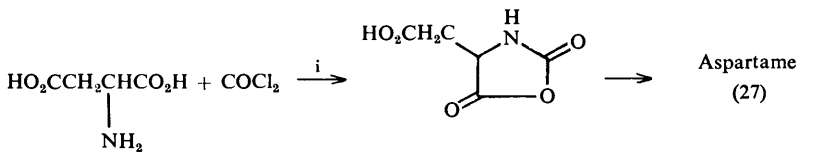
The sweetening property of (27) is dependent on the stereochemistry of the individual amino acids, *i.e.* the aspartyl and phenylalaninyl moieties from which it is derived. Each of the two amino acids can exist in two optically isomeric forms. Aspartame, the L,L optical isomer, is sweet whereas the corresponding D,D; D,L and L,D isomers are tasteless. The combination of isomers (racemates) which contain the L,L form *i.e.* DL-aspartyl-L-phenylalanine, L-aspartyl-DL-phenylalanine and DL-aspartyl-DL-phenylalanine are also sweet.

Aspartame is conveniently prepared by suitable processes involving the coupling of amino acids (Schemes 12 and 13) and a method for the large-scale manufacture of aspartame has been reported by Ariyoshi and coworkers.[90]



Reagents: i, 65 °C, 24 hr; ii, Pd–AcOH, H_2

Scheme 12



Reagents: i, THF, N_2 (< 0 °C); ii, $PhCH_2CH(NH_2)CO_2CH_3$, Et_3N–THF (< 0 °C)

Scheme 13

[90] Y Ariyoshi (Ajinomoto Co. Inc.), *Kagaku to Sebutsu*, 1974, **12**(3), 189.

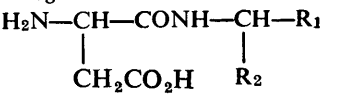
Aspartame has a sweetening potency of about 180 times that of sucrose. This is surprising since neither L-aspartic acid nor L-phenylalanine is sweet. In fact, while a number of small peptides are known to be bitter, aspartame is the only known peptide to elicit a sweet taste. The potency of aspartame relative to sucrose decreases with increasing concentrations of sucrose. It was found to be about 180 times sweeter than 2% sucrose solutions, but only 40 times sweeter than 30% sucrose. There is evidence of a synergistic increase in sweetening potency when it is combined with other ingredients in foods. The unpleasant after taste (*e.g.* bitter, metallic, saline) characteristic of saccharin and cyclamate does not occur with aspartame. It would be expected that as aspartame is derived from naturally occurring amino acids it would be devoid of any toxicity and extensive studies have shown this to be so,[91] except for persons affected by phenylketonurea.[92]

Like many sweeteners aspartame is more acceptable and relatively sweeter in low concentrations than in high concentrations. It is unstable in acidic solutions and therefore not suitable for use in carbonated beverages and fruit products: also, it decreases in sweetness during storage and during hot processing.[4]

Schlatter and coworkers investigated the aspartame molecule in order to specify the sweetening site of the molecule. They found that the C-terminal amino acid could be changed to a considerable degree even to the extent of replacing the methoxycarbonyl moiety by a methyl group without any significant loss in sweetness potency (Table 8). It appeared, however, that the presence of the free unsubstituted amino group and the carboxy group of the aspartamine moiety as well as the minimum distance between them, and the absolute configuration of the asymmetric carbon atom of the aspartyl moiety were necessary for sweetness. The L configuration of the phenylalaninyl moiety of aspartame was also an essential factor. It was shown (Table 8) that the sweetening potency decreased markedly with increasing size of the ester group. The ethyl ester of (27) had 25% sweetening potency whereas the n-propyl ester had only 1% sweetening potency. The sweetening potency was increased if the benzene ring was hydrogenated implying a conformational structural relationship between the non-planar cyclohexane ring and the planar benzene ring (Table 8). The problem of explaining the diversity of structure giving a sweet taste has not yet been satisfactorily solved. Various theories based on the assumption of a single complex receptor site have been made by Shallenberger[93] and more recently by Kier.[94] No prediction could have been made that the ester group could be replaced by alkyl groups without major change in biological activity. The essential requirement for sweetness appears to be an α-amide of L-aspartic acid in which the nitrogen atom of the amide group is attached to an asymmetric carbon bearing two unidentical groups. When the groups are identical no sweetness results. When the groups are

[91] S. L. Halpern, in 'Scientific Review of a New Sweetener,' American College of Nutrition, First Annual Interim meeting, II, November 16—18, 1974.
[92] 'Aspartame,' Technical Bulletin No. 600 (060473), Searle Biochemics, G. D. Searle, Arlington Heights, Ill., U.S.A.
[93] R. S. Shallenberger and T. E. Acree, *Nature*, 1967, **216**, 480.
[94] L. B. Kier, *J. Pharm. Sci.*, 1972, **61**, 1394.

Table 8 *Aspartame analogues*



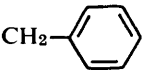
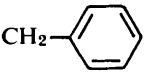
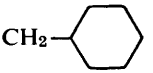
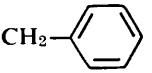
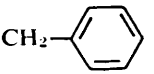
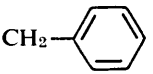
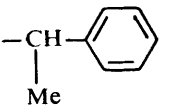
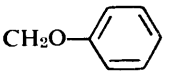
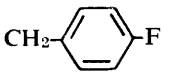
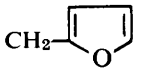
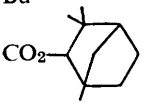
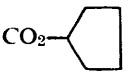
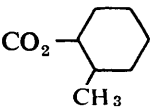
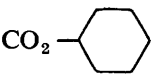
	R_1	R_2	*Relative sweetness sucrose* = 1	*Reference*
1	CO_2Me		100—200	95,96
2	CO_2Et		25—50	96
3	CO_2Me		225	97
4	Me (Laevo)		50	97
5	Me (Dextro)		0	97
6	H		0	97
7	H		Bitter	97
8	Me		10	97
9	Me		20	97
10	Me		10	97
11	Me	Bu^n	30	97
12	Me	$(CH_2)_4Me$	20	97
13	Me	$(CH_2)_4Me$ (Laevo)	50	97
14	Me (Laevo)	$(CH_2)_2CHMe_2$	100	97
15	Me	CH_2CH_2OEt	10	97
16	CO_2Me (Laevo)	Me	0	97

Table 8 (*continued*)

	R_1	R_2	*Relative sweetness sucrose* = 1	*Reference*
17	CO_2Me (Laevo)	$Me(CH_2)_5$	70	97
18	CO_2Pr^i	Me	125	97
19	CO_2Pr^i	Bu^n	0	97
20	CO_2Me	 (Fenchyl)	22,200—33,200	98, 99
21	CO_2Me		300—600	98
22	CO_2Me	 (*trans*)	5450—7300	98
23	CO_2Me		556—880	98

sufficiently different sterically then there is a definite possibility that one of the diastereoisomers will be sweet. The requirement of a particular absolute configuration follows from the fact that the receptor site is asymmetric. Compounds 16 and 17 (Table 8) show that amino acid methyl esters with alkyl side chains do not yield sweet derivatives until the receptor site contains an alkyl group of at least 4 carbon atoms (when R^2 = butyl, R^1 = CO_2Me the relative sweetness is 40). On the other hand isopropyl esters (R^1 = CO_2Pr^i) require C_{1-4} alkyl groups to ensure sweetness. The compound R^2 = n-pentyl, R^1 = CO_2Pr^i is tasteless because the bulky alkyl group of R^2 is too near to the ester moiety CO_2R^1 for sweetening potency. Appreciable potency is detected when the alkyl group for R^2 has no more than 3 carbon atoms.

The most intense sweeteners yet known were discovered by M. Fujino's Japanese group[98,99] working for Takeda Chemical Industries. The compounds were L-aspartyl amino malonic diesters with ester groups selected from alcohols such as fenchyl alcohol and cycloalkanols. The most potent sweetener, methyl

[95] R. H. Mazur, A. H. Goldkamp, P. A. James, and J. M. Schlatter, *J. Medicin. Chem.*, 1970, **13**, 1217.

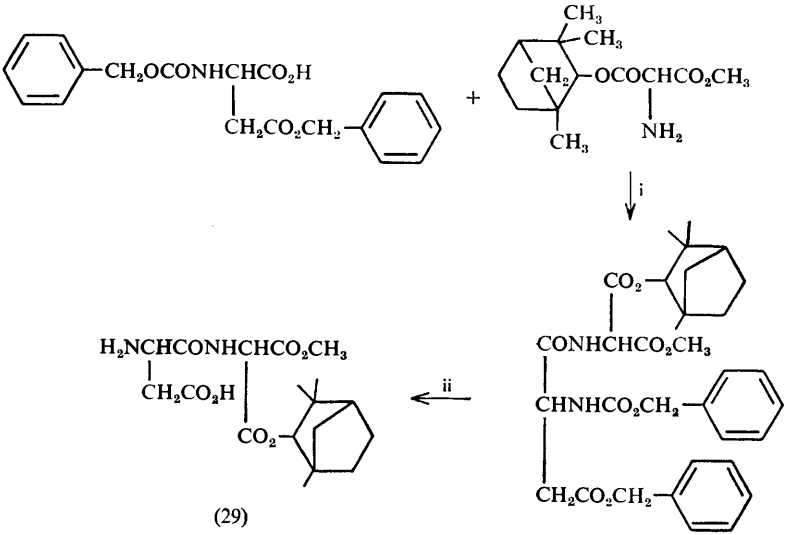
[96] J. M. Schlatter, G. D. Searle & Co., Israel P. 30,266/1972.

[97] R. H. Mazur, J. A. Reuter, K. A. Swiatek, and J. M. Schlatter, *J. Medicin. Chem.*, 1973, **16**, 1284.

[98] M. Fujino, M. Wakimasu, K. Tanaka, H. Aoki, and N. Nakajima, *Naturwiss*, 1973, **60**, 351.

[99] M. Fujino, M. Wakimasu, N. Nobuo, and H. Aoki, Takeda Chemical Industries, Japan B.P. 1,434,043/1976.

fenchyl L-aspartylaminomalonate (29), was synthesized in the same manner as aspartame (Scheme 14).

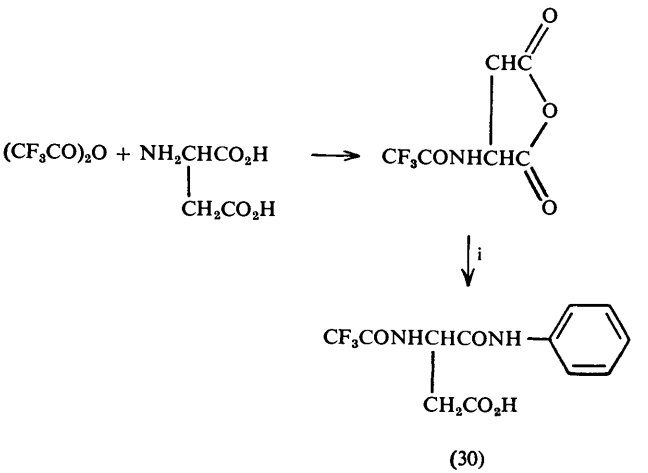


(29)

Reagents: i, DCCD; ii, Pd–AcOH

Scheme 14

Again by accident, Milton Lapidus of Wyeth Laboratories[100] tasted a peptide L-3-(2,2,2-trifluoroacetamido)-succinanilic acid (30) and found it to be 12 times sweeter than sugar. It was synthesized according to Scheme 15.



(30)

Reagent: i, $PhNH_2$

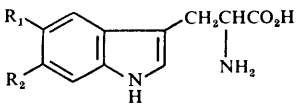
Scheme 15

[100] M. Lapidus and M. Sweeney, *J. Medicin. Chem.*, 1973, **16**, 136.

The L-form of (30) was tasteless. Furthermore the acetylation of aspartame by the trifluoroacetyl group yielded the trifluoroacetyl aspartame which was found to be 120 times sweeter than sugar. This derivative is slightly less sweet than aspartame but its potency invalidates Mazur's assumption that a free amino group is a necessary requirement for sweetness in the aspartyl dipeptide ester analogues.

17 The Tryptophanes

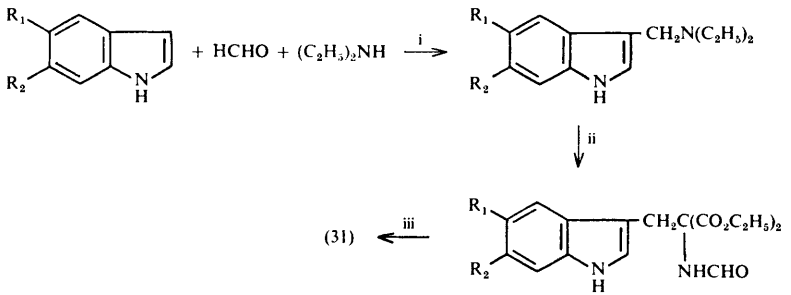
In 1968 Kornfeld and coworkers,[101] while working on pyrrolnitrin derivatives, accidentally discovered that *dl*-6-trifluoromethyltryptophane was intensely sweet. Like Horowitz and his coworkers who had prepared dihydrochalcone analogues, Kornfeld and his coworkers synthesized various tryptophane analogues in order to determine the sweetening site of the molecule. They found that substituting different groups[102] in position 6 of the *dl*-tryptophane molecule gave particularly good results (31). These tryptophane sweeteners were synthesized by well known methods, for example via the Mannich reaction (Scheme 16) or via the



R_1 = H and R_2 = CF_3, Cl, Br, F, CH_3O, or $(CH_3)_2CH$

R_1 = R_2 = CH_3 or Cl

(31)



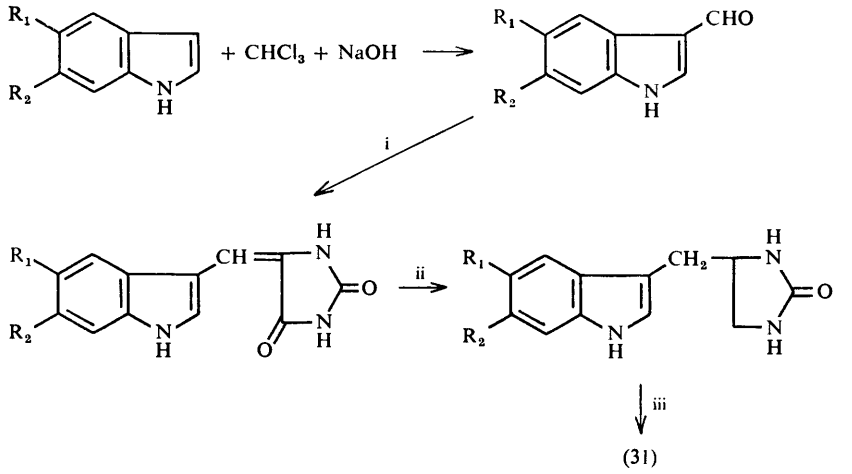
Reagents: i, AcOH; ii, $(C_2H_5CO_2)_2CHNHCHO$; iii, AcOH–HCl

Scheme 16

Reimer–Tiemann route (Scheme 17). Kornfeld and coworkers resolved these *dl*-tryptophanes into their *d* and *l* forms. It was found that D-6-chlorotryptophane was 1000 times sweeter than sugar. The L form, as expected, was tasteless but was

[101] E. C. Kornfeld, J. M. Sheneman, and T. Suarez, Eli Lilly and Co., G.P. (Offen.) 1,917,844/1969.

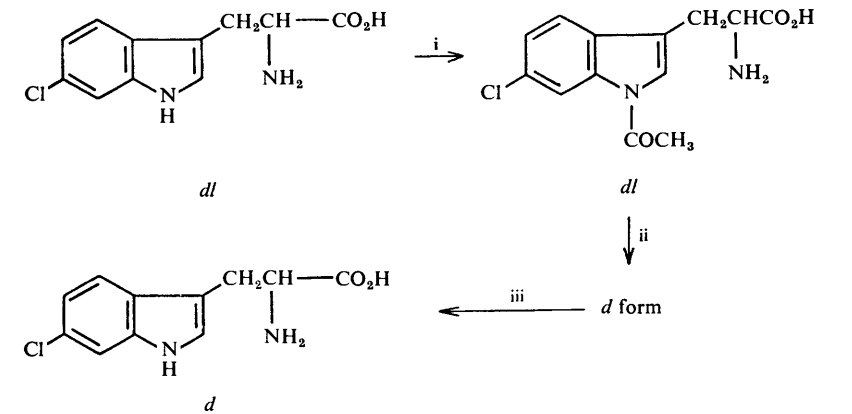
[102] E. C. Kornfeld, J. M. Sheneman, and T. Suarez, Eli Lilly & Co., B.P. 1,269,851/1972.



Reagents: i, Hydantoin–Ac_2O; ii, Na–Hg, [H]; iii, H^+

Scheme 17

found to have antidepressant activity instead. Chibata and coworkers successfully separated the D form of 6-chlorotryptophane from the racemic mixture by addition of an enzyme extract of wheat bran and $CoCl_2$, $6H_2O$[103] (Scheme 18). Various other heterocyclic compounds have been (accidentally) found to be sweet.



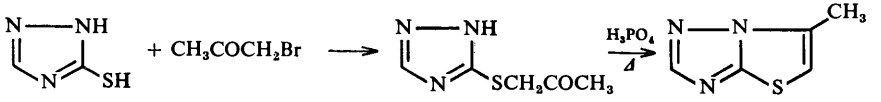
Reagents: i, AcOH; ii, enzyme extract of wheat bran and $CoCl_2$, $6H_2O$; iii, OH^-

Scheme 18

[103] I. Chibata, T. Tosa, T. Mori, and Y. Iwasawa, Jap.P. (Kokai) 75/58060.

18 Thiazolo[3,2-*b*]-*a*-Triazoles[104]

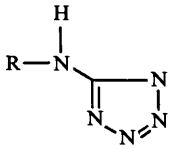
The 3-methyl derivative was prepared according to Scheme 19.



Scheme 19

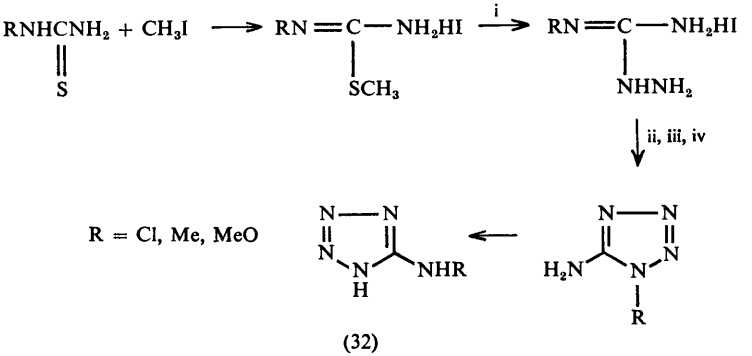
19 Tetrazole Derivatives

(a) 4-Amino tetrazoles[105] (32) were synthesized according to Scheme 20. (b) 5-(m-Hydroxyphenoxy)-tetrazole[106] (c) 5-Amino tetrazoles (33).



R = alkyl, phenyl or cycloalkyl

(33)



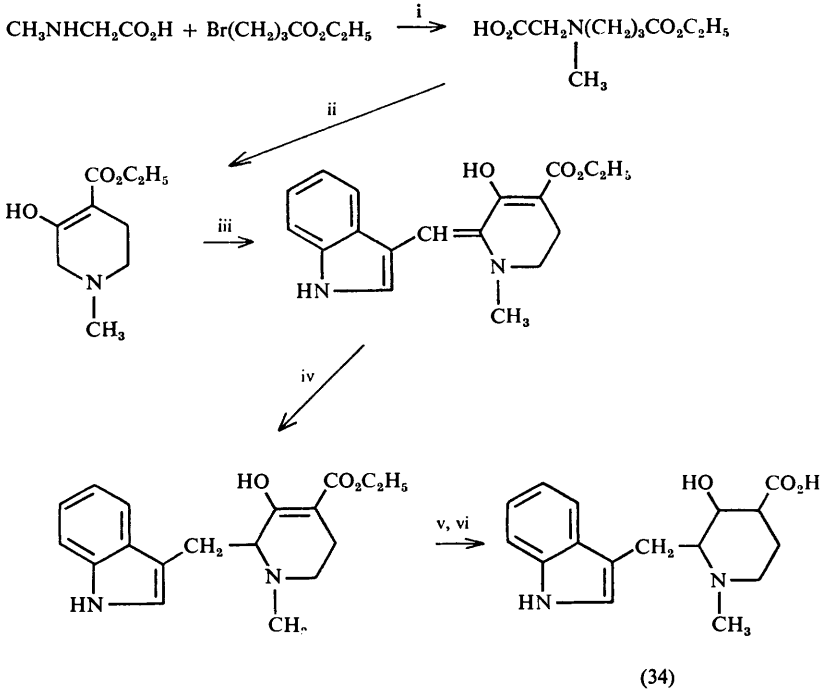
Reagents: i, N_2H_4, H_2O; ii, HNO_3; iii, $AgNO_3$; iv, $NaNO_2$; v, Reflux/xylene

Scheme 20

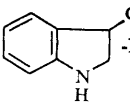
20 3,4-Dehydro-3-Hydroxy-2-(1*H*-indol-3-ylmethyl)-1-methylpiperidine-4-carboxylic acid (34)

Hauth and Hofmann[107] of Sandoz have found that (34) is 500 to 1000 times sweeter than cane sugar. It was synthesized according to Scheme 21.

[104] S. Kano, O. Nomura, and T. Taniguchi, Jap.P. (Kokai) 73/68589.
[105] R. M. Herbst, Eli Lilly & Co., B.P. 1,170,590/1969.
[106] W. L. Garbrecht, Eli Lilly & Co., B.P. 1,221,115/1971.
[107] H. Hauth and A. Hofmann (Sandoz Ltd.), Swiss P. 574,439/1976.



(34)

Reagents: i, Et_3N–C_6H_6; ii, NaOEt; iii,  -Pyridine-Piperidine; iv, H^+; v, Ac_2O; vi, hydrolysis

Scheme 21

21 Conclusions

The search for the ideal sweetener to replace sugar is primarily to satisfy the diabetic who desires a non-nutritive sweetener having no undesirable side effects such as obesity.

The ideal sweetener should satisfy the following requirements:

1 It must be reasonably sweet, at least as sweet as sugar, with no lingering after taste.

2 It must be economical to produce and be cheaper than sugar for the consumer market.

3 It should be preferably non-caloric and have no nutritive value.

4 It must be non-toxic with no dangerous side effects such as carcinogenicity or teratogenicity. It should not have any synergistic detrimental effects with drugs or in the presence of foods or beverages.

5 The metabolite must also be non-toxic with none of the side effects mentioned above.

6 It must be thermostable and not decompose during cooking or in the presence of sunlight.

7 It must be soluble in water.

So far no sweeteners satisfy all the above requirements. One of the main reasons for being unable to find the ideal sweetener is the lack of understanding of the mechanism responsible for causing the sensation of sweetness. Various theories and hypotheses have been proposed but the most satisfactory to date is Shallenberger's hydrogen bonding hypothesis. This hypothesis is based on the fact that sweetness depends on a lock–key fit of hydrogen bonds between the sweet molecule and a receptor site with a separation between them of 2.5 to 4 Å. For successful hydrogen bonding to take place a specific conformative and spatial arrangement of atoms must be present in the molecule. Such an arrangement is present in many sweeteners, natural and artificial, but cannot explain why such an arrangement is also found in non-sweetening molecules. The diversity of structures of sweet compounds suggests that the taste bud protein responsible for initiating a sweet sensation has more than one active receptor site.