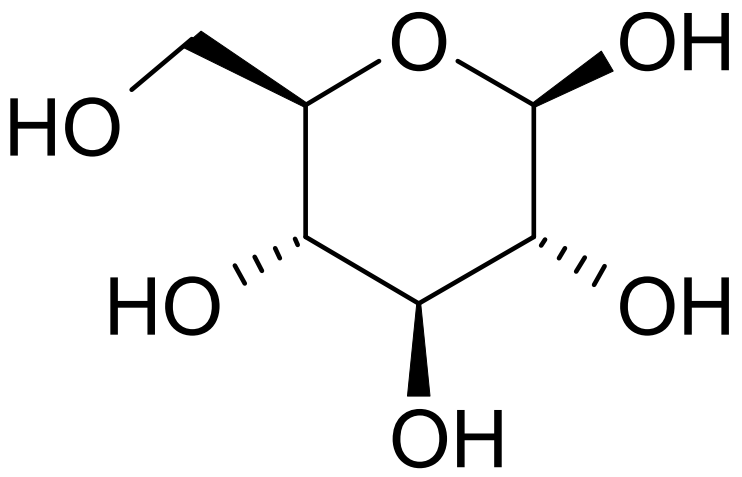
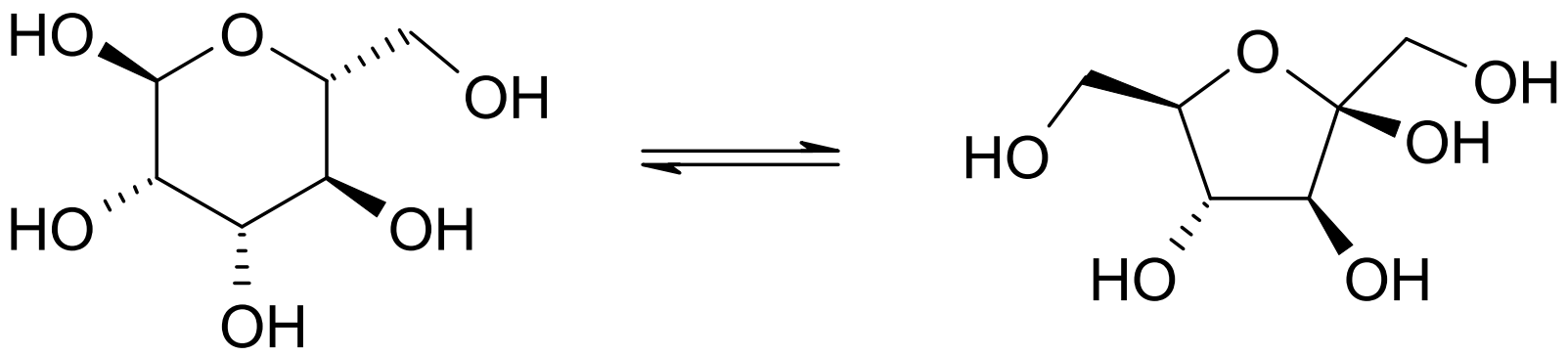
Taste corrigents – sweeteners

1. **Saccharides**
2. **Polyols = „sugar alcohols “**
3. **Glycosides**
4. **Proteins**
5. **(Short) peptides**
6. **Compounds with sulfamic acid fragment**
7. **Urea derivatives**

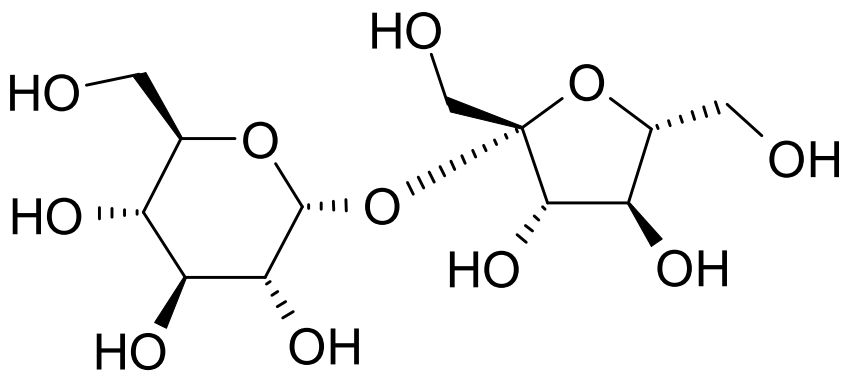


D-glucose
α-D-(+)-glucopyranose (monohydrate)
[5996-10-1]
PhEur: Glucosum monohydricum
USPNF: Dextrose
•sweetener, diluent of content of capsules, isotonizer, medicine
•5% aqueous solution is isotonic and serves as a vehicle for *i.v.* infusion administration of drugs (an alternative to isotonic solution = 0.9% NaCl)
•„liquid glucose“ = glucose syrup: PhEur: Glucosum liquidum; a mixture: glucose, fructosa, maltose, dextrin and other oligo- a polysacharides

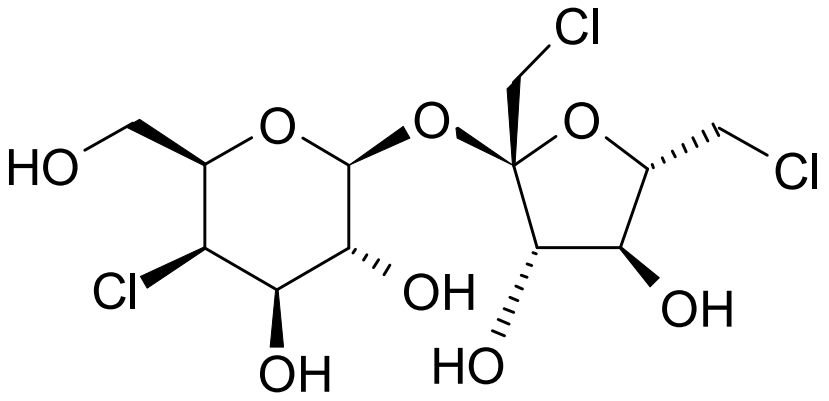


D-fructose, levulose
[57-48-7]
PhEur: Fructosum
•sweetener, „amplifier of taste“, masking of unpleasant tastes, its sweet taste is perceived faster than in glucose and sucrose
•avoids „freezing of bottle caps“ of syrups, i.e. crystallization of a sugar around the cap

1. Saccharides (continued)

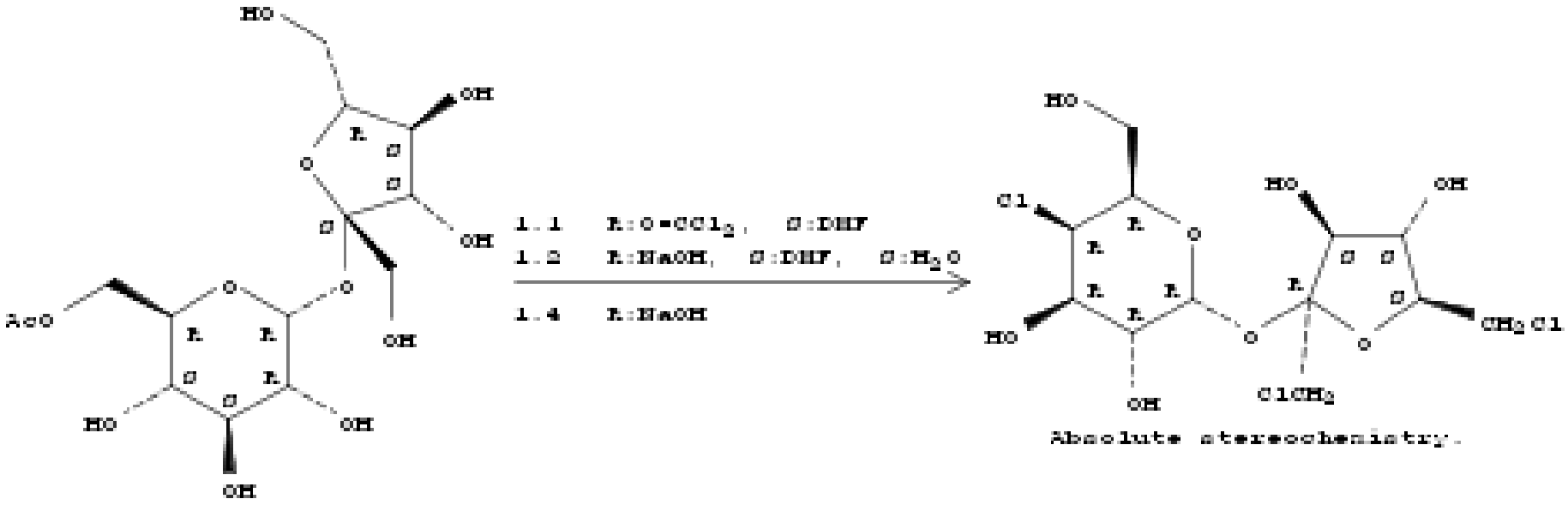


sucrose
β-D-fructofuranosyl-α-D-glucopyranoside
[57-50-1]
PhEur: Saccharum
(beet, cane) sugar
•sweetener, coating compound, viscosificant
•*Sir. simplex*

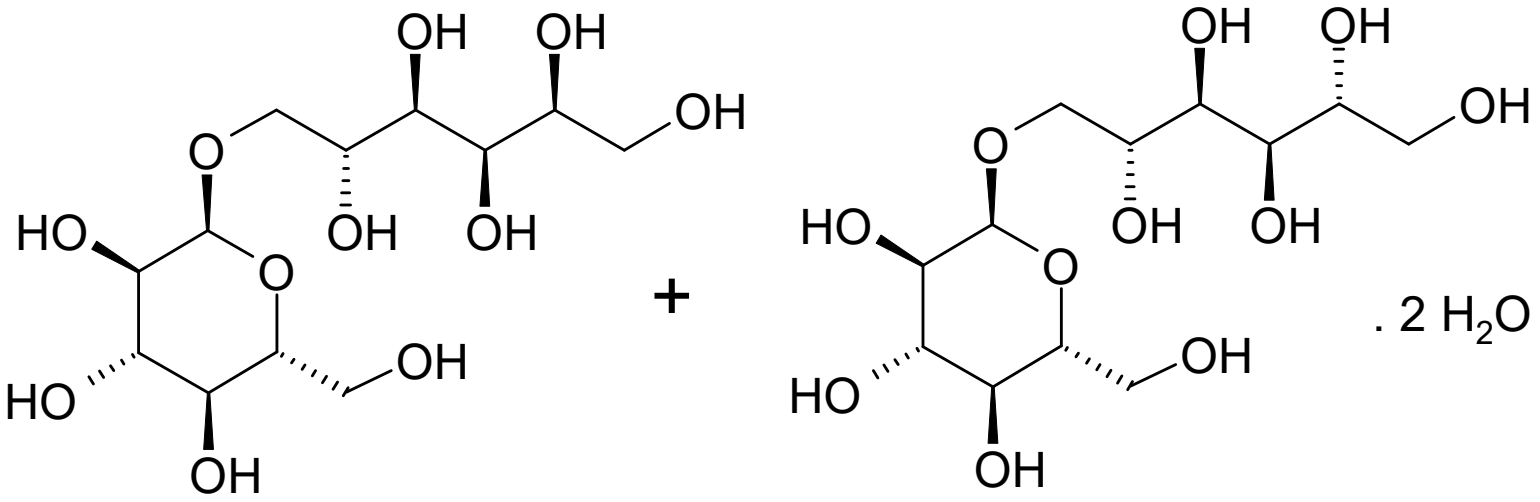


sucralose
1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chlor-4-deoxy-α-D-galactopyranoside
[56038-13-2]
USPNF: Sucralose
•sweetener of foods, beverages, drug forms
•300 – 1000x sweeter than sucrose
•LD_{50}>10g/kg
•acceptable daily intake after WHO 15mg/kg

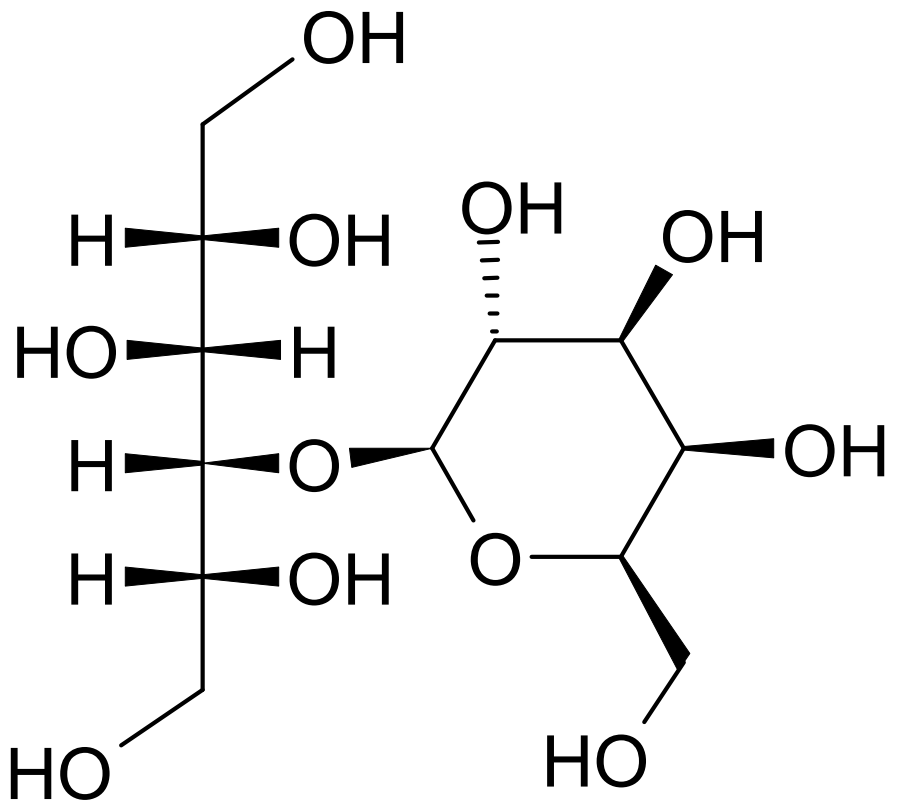
Sythesis of sucralose



NOTE: 2nd step is dual stream quench; 3rd step is DMF removal by steam stripping; 4th step at pH 11.5,
Reactants: 1, Reagents: 2, Solvents: 2,
Steps: 1, Stages: 4

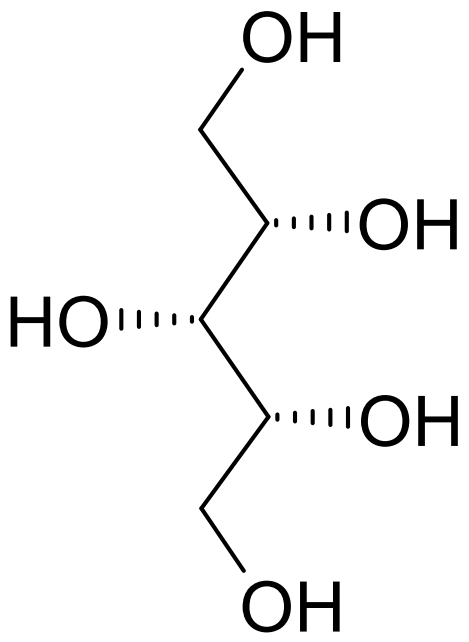


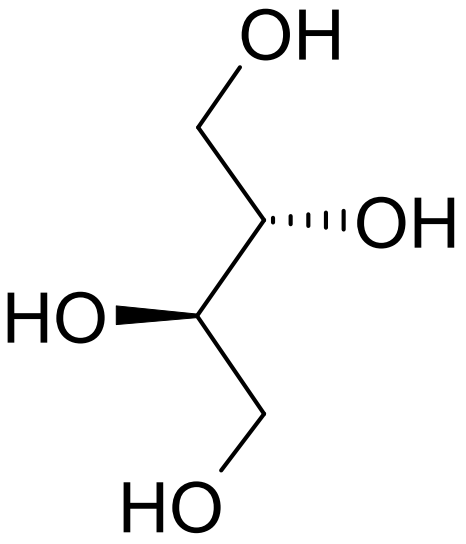
isomalt
[64519-82-0]
PhEur: Isomaltum
•mixture of 2 stereoisomers:
6-*O*-α-D-glucopyranosyl-D-sorbitol (1,6-GPS) [534-73-6]
1-*O*-α-D-glucopyranosyl-D-mannitol dihydrate (1,1-GPM) [20942-99-8]
•non-cariogenic sweetener, a compound for tablets coating, diluent of content of tablets and capsules, substance for both direct compression and dry granulation



lactitol
4-*O*-(β-D-galactopyranosyl)-D-sorbitol
[585-86-4]
PhEur: Lactitolum monohydricum
E 966
•non-cariogenic sweetener, diluent of content of tbl and cps
•drug: laxans, medicine for hepatic encphalopathy

2. Polyols – „sugar alcohols“ or „alcoholic sugars“

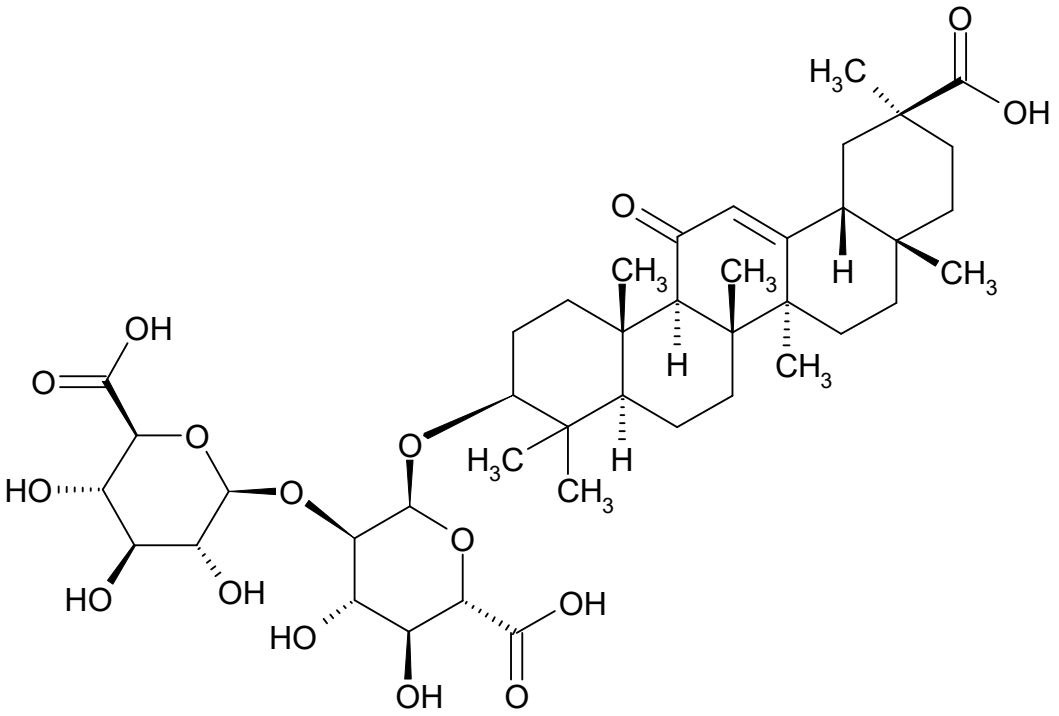




xylitol
xylo-pentane-1,2,3,4,5-pentaol
[87-99-0]
PhEur: Xylitolum
•humectant, compound for coating tbl
•lowers incidence of caries by inhibition of growth of cariogenic *Streptococcus mutans*
•potetiates the activity of antimicrobial preservatives
•non-caloric sweeteners, diluents of content of tbl and cps

erythritol
(2*R*,3*S*)-butane-1,2,3,4-tetraol
[149-32-6]
PhEur: Erythritolum
•compoud for masking of unpleasant taste

3. Glycosides

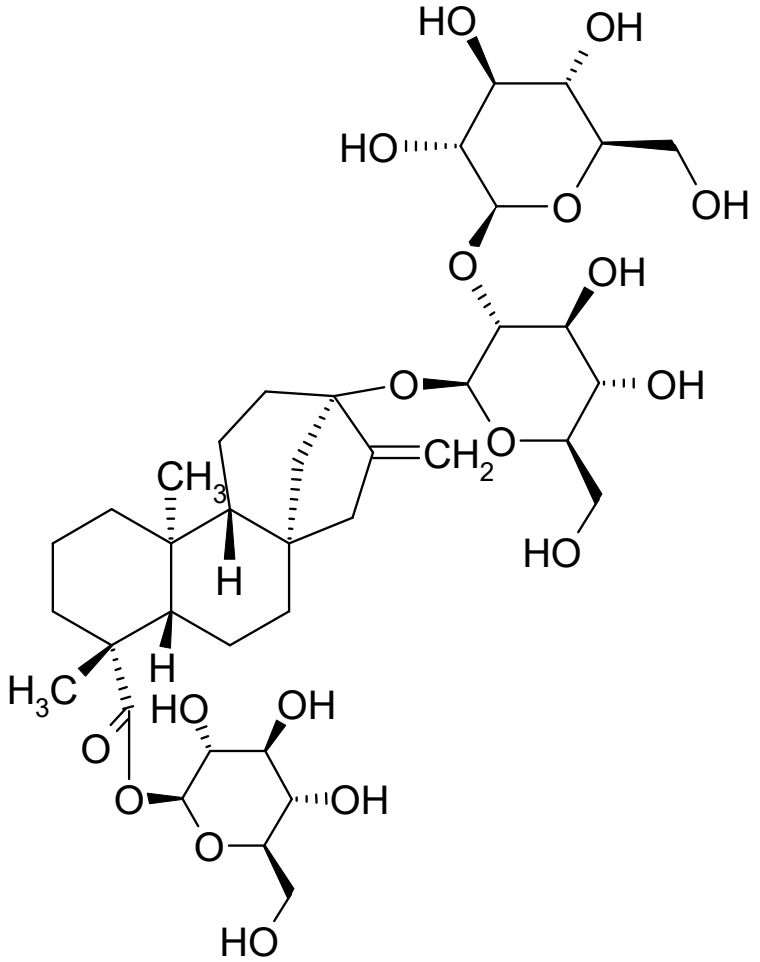


glycyrrhizine
syn. glycyrrhizinic acid

3β-[(5S)5-carboxy-O^2-((5S)-5-carboxy-β-D-xylopyranosyl)-α-D-xylopyranosyloxy]-11-oxoolean-12-en-30-oic acid
[1405-86-3]
LD_{50} (*p.o.* mouse) = 4.32 mg/kg

Steviol glycosides E 960

•mixture should contain not less than 95 % stevioside, rebaudiosides A, B, C, D, E and F, steviolbioside, rubusoside and dulcoside



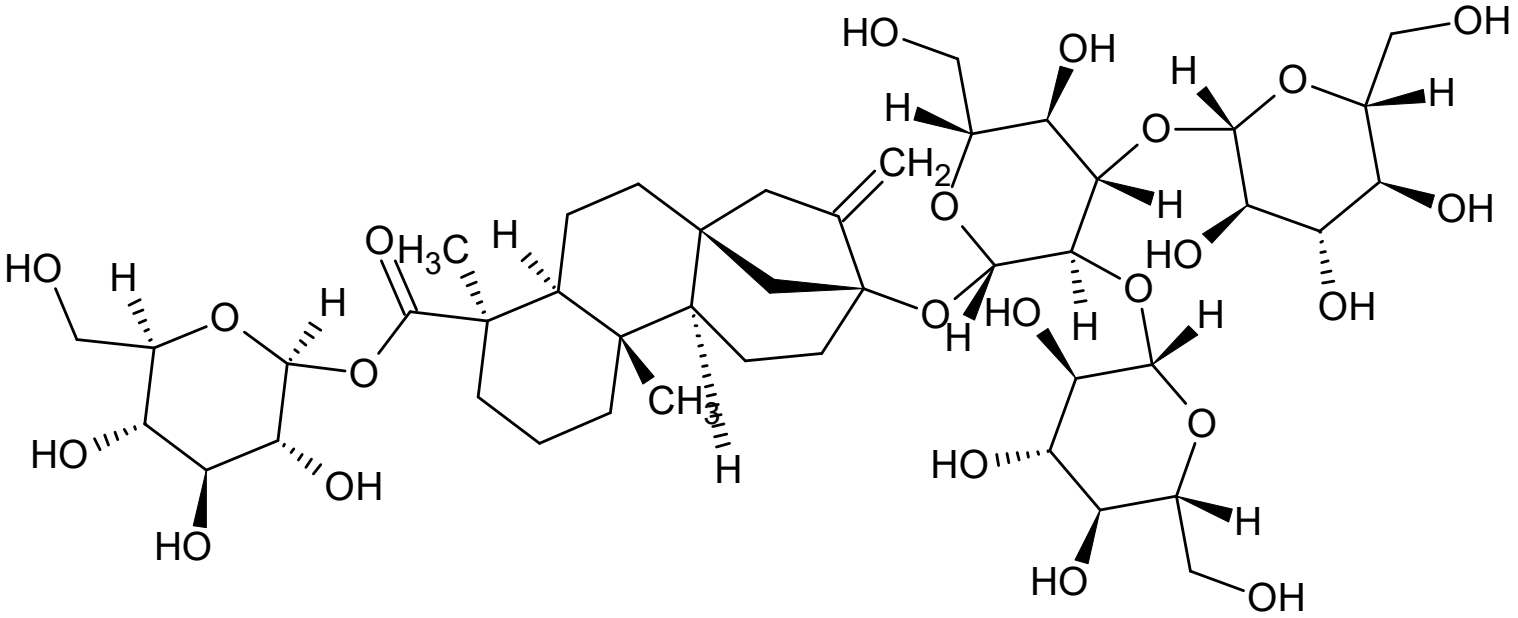
stevioside

(10S)-13-(O^2-β-D-glucopyranosyl-β-D-glucopyranosyloxy)kaur-16-en-19-oic acid β-D-glucopyranosyl ester

•from leaves of *Stevia rebaudiana Bertoni*

•300x sweeter than sucrose

LD_{50} (*p.o.*) = 8.2 – 17 g/kg



rebaudioside A

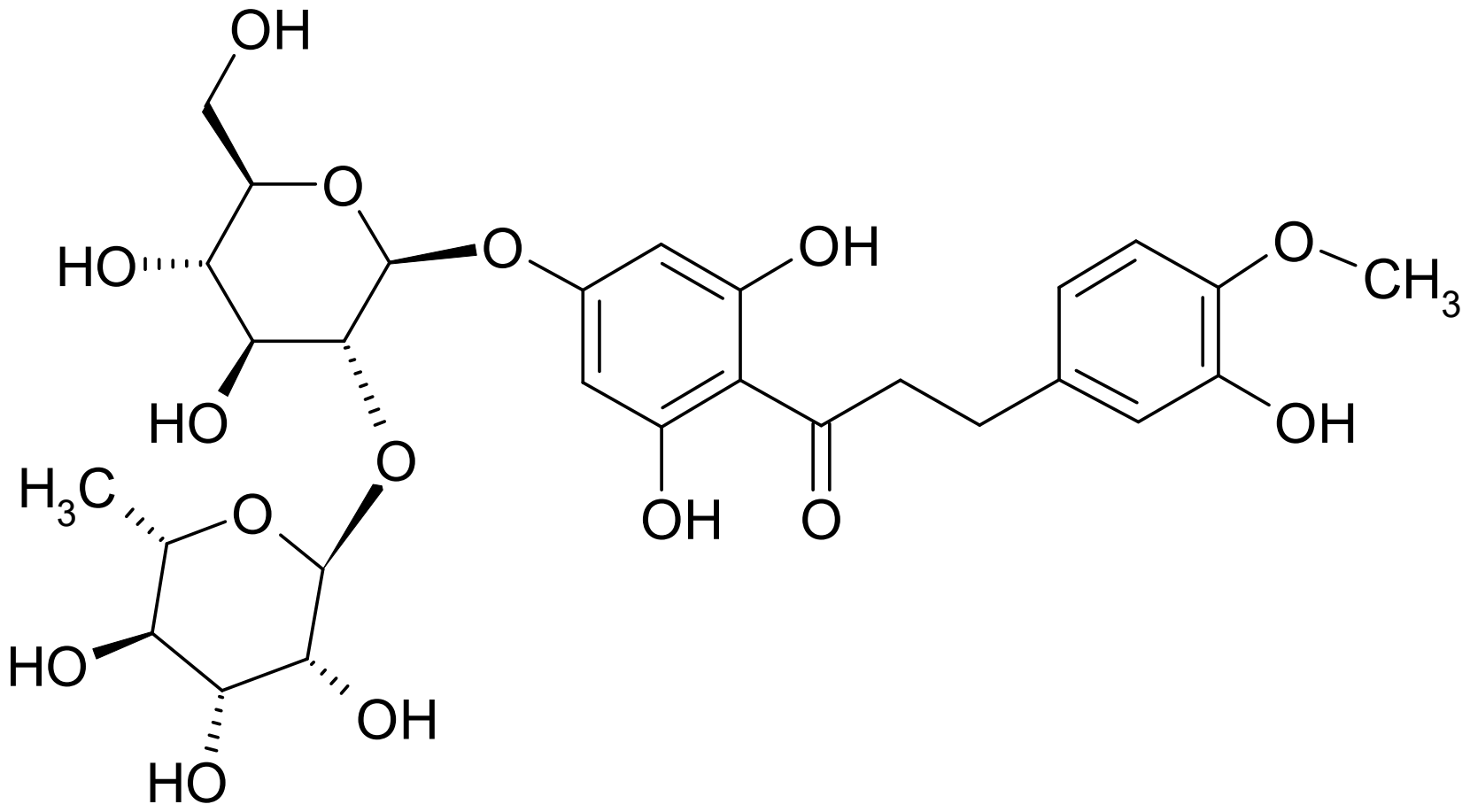
•sweeter than stevioside

•the mixture 200 - 300x sweeter than sucrose

The manufacturing process comprises two main phases:

•the first involving water extraction of the leaves of the *Stevia rebaudiana* Bertoni plant and preliminary purification of the extract by employing ion exchange chromatography to yield a steviol glycoside primary extract

•the second involving recrystallisation of the steviol glycosides from methanol or aqueous ethanol resulting in a final product consisting mainly (at least 75 %) of stevioside and/or rebaudioside A.



neohesperidin dihydrochalcone

1-[4-[[2-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,6-dihydroxyphenyl]-3-(3-hydroxy-4-methoxyphenyl)propan-1-on

[20702-77-6]

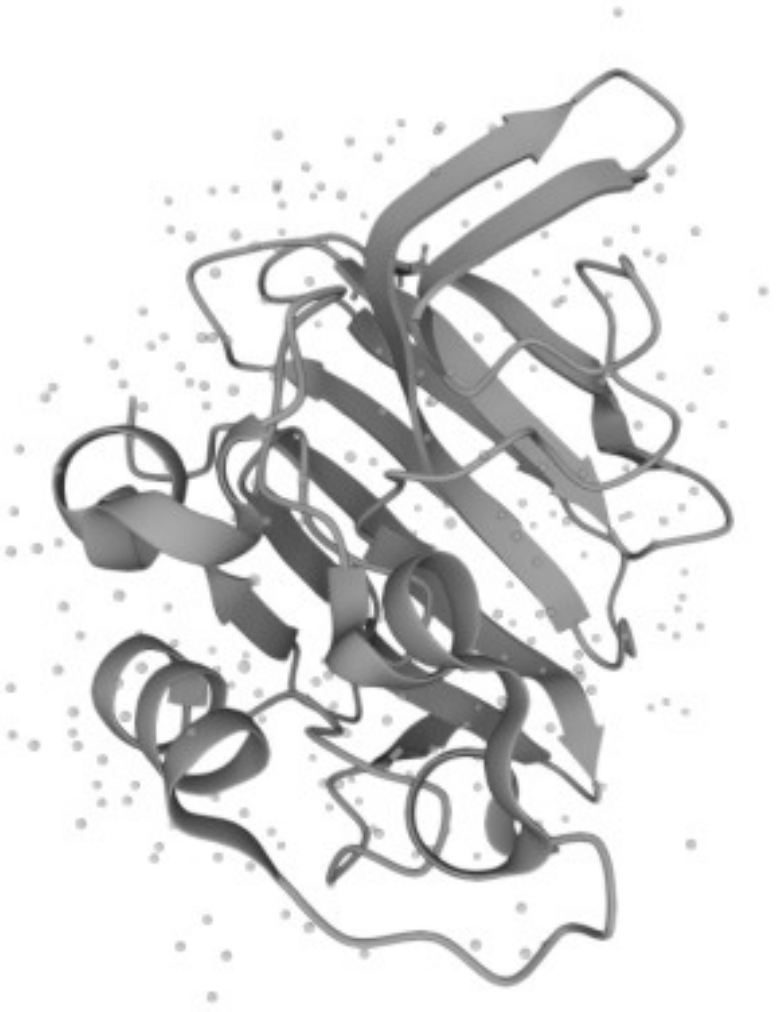
- sweetener, „taste amplifier“
- 1500 – 1800x sweeter than sucrose; 20x sweeter than sacharine
- acceptable daily intake up to 5 mg/kg

Thaumatin E 957

- sweet tasting protein mixture from fruit of *Thaumatococcus daniellie Benth*, a plant from tropical Africa.
- mixture of thaumatin I and II 2 : 1 (both 207 AA, M_r cca 22 000, 90 % homology)
- approx. 10^5 times sweeter than sucrose (on molar basis)

```
         10                  20                  30                  40                  50
MAATTCFFFL FPFLLLLTLS RAATFEIVNR CSYTVWAAAS KGDAALDAGG
                60                  70                  80                  90                 100
RQLNSGESWT INVEPGTNGG KIWARTDCYF DDSGSGICKT GDCGGLLRCK
               110                 120                 130                 140                 150
RFGRPPTTLA EFSLNQYGKD YIDISNIKGF NVPMDFSPTT RGCRGVRCAA
               160                 170                 180                 190                 200
DIVGQCPAKL KAPGGGCNDA CTVFQTSEYC CTTGKCGPTE YSRFFKRLCP
               210                 220                 230
DAFSYVLDKP TTVTCPGSSN YRVTFCPTAL ELEDE
```

thaumatin I precursor: 1-22 signal sequence, 23-229 **thaumatin I**, 230-235 propeptide removed in mature



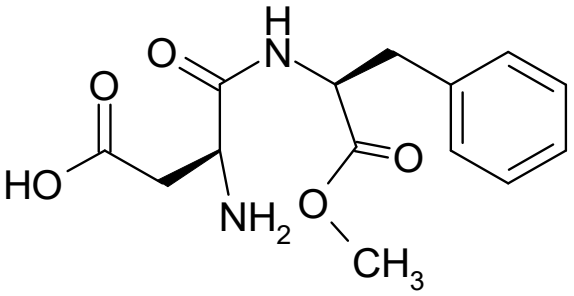
Tertiary structure of thaumatin I based on X-ray diffraction

Artificial (substitute) sweeteners

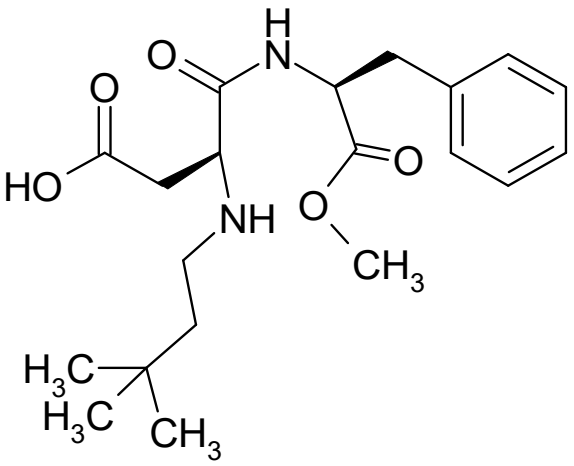
- correction of unpleasant taste of drugs
- substitute sweetening agents for patients with diabetes or obesity (minimal caloric value and influence to blood glucose level)

5. Peptides
6. Compounds with sulfamic acid fragment

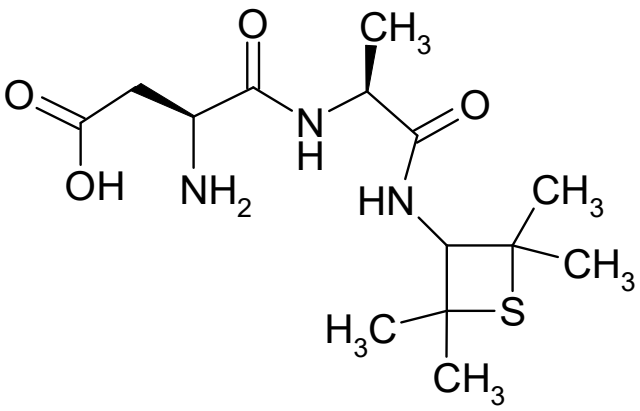
5. Peptides



aspartam
[22839-47-0]
E 951
•180 – 200x sweeter than sucrose
•LD_{50} (*p.o. mouse*, rat) > 10 g/kg
•m.p. 246-247°C
•stable for 250 days at pH 4 – 5 and 25°C in water solution

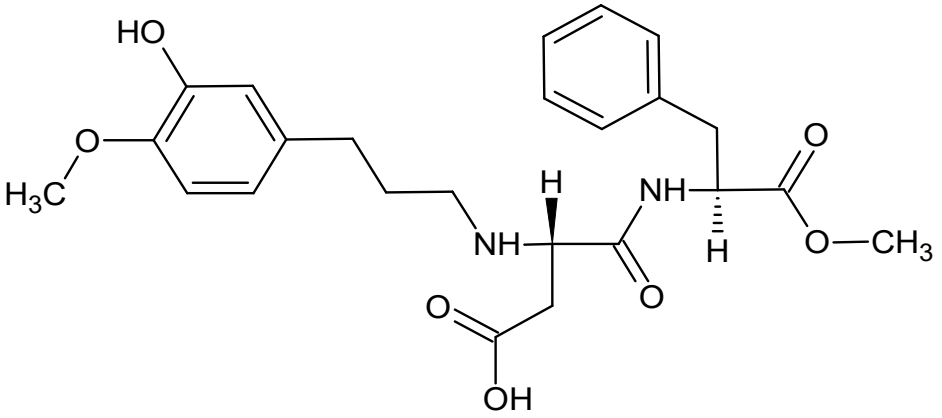


neotam
[165450-17-9]
•also for phenyleketonurics



alitam
[80863-62-3]
•2000x sweeter than sucrose
•LD_{50} (*p.o.* mouse, rat) > 5 g/kg
•m.p. 136-137°C
•at pH 5 - 8 half-time 4 years at 23°C

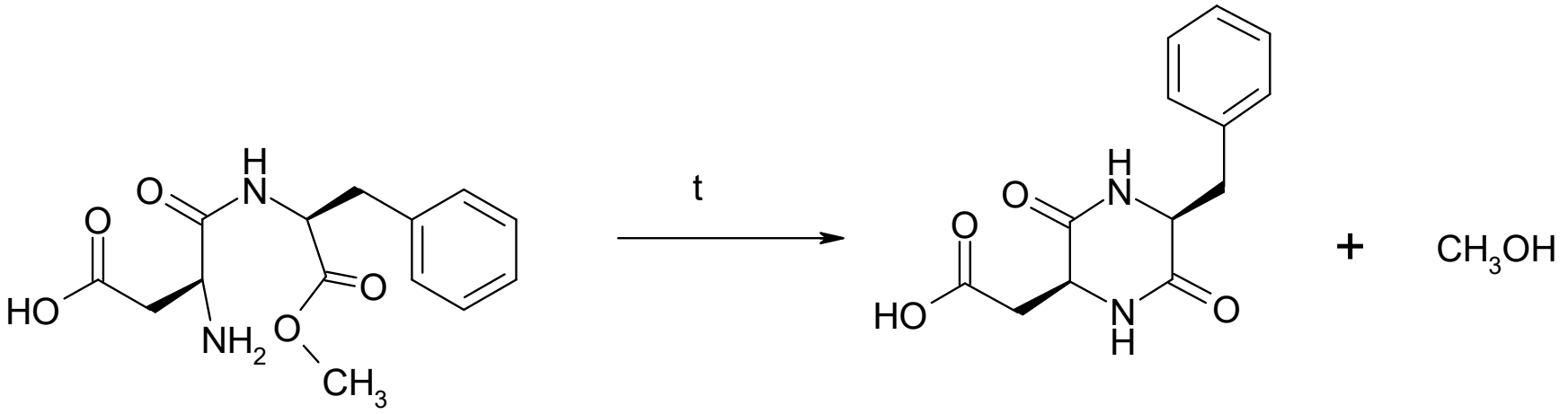
5. Peptides



advantame E 969

- maximum concentration 10 mg / l (or kg)
- low toxicity
- well tolerated in humans and animals (except for high doses in rabbits where it caused GIT disturbances

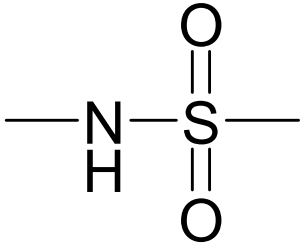
Thermal „decomposition“ of aspartam

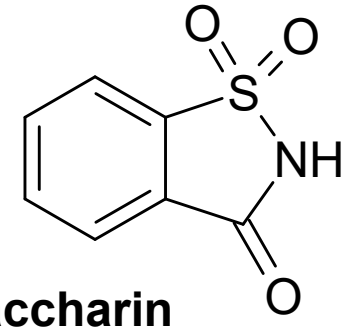


aspartam

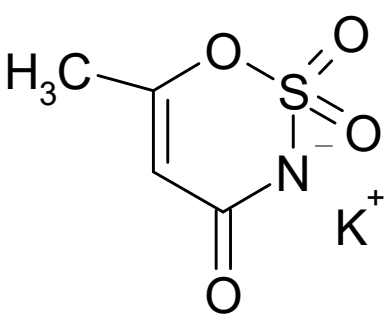
2-(5-benzyl-3,6-dioxopiperazine-5-yl)acetic acid

Compounds with sulfamic acid fragment

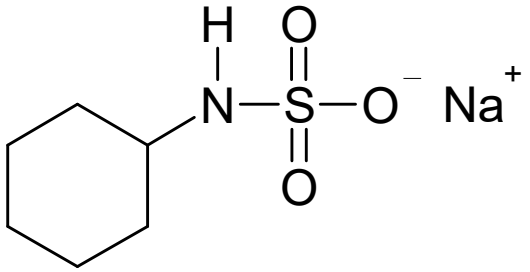




saccharin
1,2-benzothiazolin-3-one-1,1-dioxide
o-sulfobenzoic acid imide
[81-07-2]
E 954
PhEur: Saccharinum
•often as Na^+, Ca^{2+}, NH_4^+ salt
•about 500x sweeter than sucrose
•in drug forms conc. 0,02 – 0,5 %
•LD_{50} (*p.o., rat*): 14,2 g/kg
•m.p. 228-229°C
•decomposes in solutions at pH<2 at 125°C

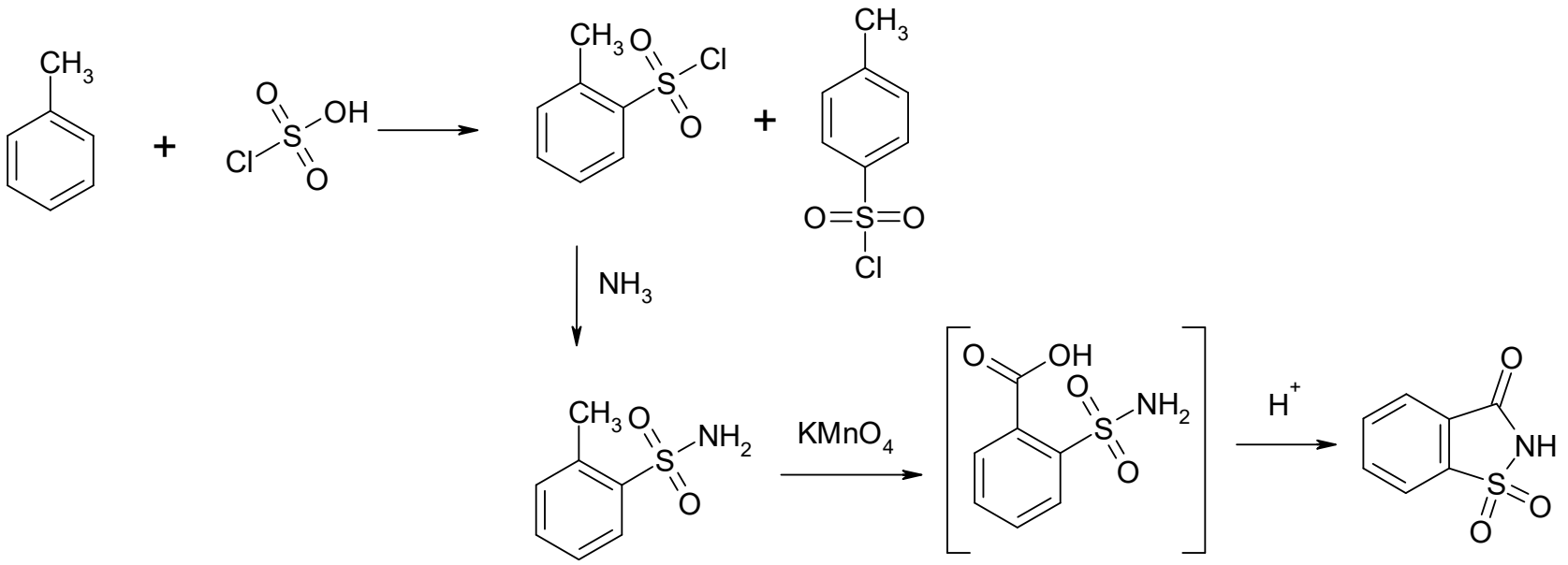


acesulfame K
6-methyl-1,2,3-oxathiazine-4(3*H*)-one-2,2-dioxide potassium salt
[55589-62-3]
E 950
•PhEur: Acesulfamum kalicum
•180 – 200x sweeter than sucrose
•LD_{50} (*p.o.*, rat): 6,9–8,0 g/kg
•m.p. 250°C
•sterilization or pasteurisation does not affect taste of its dispersions



sodium cyclamate
sodium N-cyclohexylsulfamate
[139-05-9]
E 952
PhEur: Natrii cyclamas
•about 30x sweeter than sucrose in concentrations up to 0,17 % m/V, in higher ones sweeting ability decreases and from 0,5 % m/V up bitter taste
LD_{50} *(p.o.*, rat): 15,25 g/kg
•m.p. 169-170°C
•not permitted as food additive in EU

Preparation of sacharine



Fahlberg and Remsen 1879; patented by Fahlberg and List's heir 1884

Title page of the original patent of saccharin preparation

KAISERLICHES PATENTAMT.

AUSGEGEBEN DEN 30. APRIL 1886.

PATENTSCHRIFT

— № 35211 —

KLASSE 12: CHEMISCHE APPARATE UND PROCESSE.

DR. CONSTANTIN FAHLBERG IN NEW-YORK
UND DIE ERBEN DES KAUFMANNS ADOLPH LIST IN LEIPZIG,
NÄMLICH: 1. SEINE EHEFRAU FLORA LIST GEB. FASS,
2. SEINE KINDER:
A) GEORG ADOLF LIST,
B) OTTO JULIUS LIST,
C) ADOLF MORITZ LIST,
D) SOPHIE BERTHA VEREH. BECKER GEB. LIST,
E) AUGUST ROBERT BRUNO LIST,
F) MADLEINE ANTONIE AUGUSTE LIST,
ZU E) UND F) NOCH MINORENN UND VERTRETEN DURCH IHRE MUTTER ALS VORMÜNDERIN.

Verfahren der Fabrikation von Benzoësäuresulfinid, auch Anhydroorthosulfaminbenzoësäure oder Saccharin genannt.

Patentirt im Deutschen Reiche vom 16. August 1884 ab.

Durch die Untersuchungen des Dr. Fahlberg über die Oxydationsproducte der Amide der Toluolsulfosäuren ist in die chemische Wissenschaft ein Körper eingeführt worden, der, sich von der Orthotoluolsulfosäure ableitend, mit dem Namen Benzoësäuresulfinid oder Anhydroorthosulfaminbenzoësäure belegt worden ist.

Dieser Körper, in den Ber. der deutsch. chem. Ges., XII., 469 u. f. beschrieben, zeichnet sich durch eine aufserordentliche Süfsigkeit aus, ferner durch antiseptische Einwirkungen, und haben diese Eigenschaften den Gedanken nahe gelegt, den Versuch zu machen, das besagte Product als Artikel der Grofstechnik zu gewinnen und zu versuchen, den genannten Stoff als Versüfsungsmittel, z. B. für Stärkezucker, und als Medicament einzuführen.

Bisher scheiterte die Verwirklichung jener Ideen an den völlig ungenügenden Ausbeuten, welche das von Fahlberg und Remsen eingeschlagene Verfahren zur Darstellung des betreffenden Körpers erzielen liefs. Es wurden aus 1 kg Toluol ungefähr 25 g der Anhydroorthosulfaminbenzoësäure erhalten, ein Umstand, der jede technische Verwerthung des Products unmöglich erscheinen liefs. Es kam daher darauf an, festzustellen, ob jene geringe Ausbeute wirklich unter allen Umständen den Gesammtprocefs charakterisire, oder aber, ob bestimmte Arbeitsbedingungen die Quantität der Ausbeute angemessen zu erhöhen im Stande seien. Infolge dieser Untersuchungen ist das Darstellungsverfahren des Benzoësäuresulfinids derart vervollkommnet, dafs heute aus 1 kg Toluol ca. $1\frac{1}{2}$ kg des Benzoësäuresulfinids, also das etwa Sechzigfache der früheren Ausbeute erzielt wird, und gestaltet sich hierdurch das in Rede stehende Product in der That zu

(2. Auflage, ausgegeben am 22. Dezember 1897.)

Preparation of acesulfame K

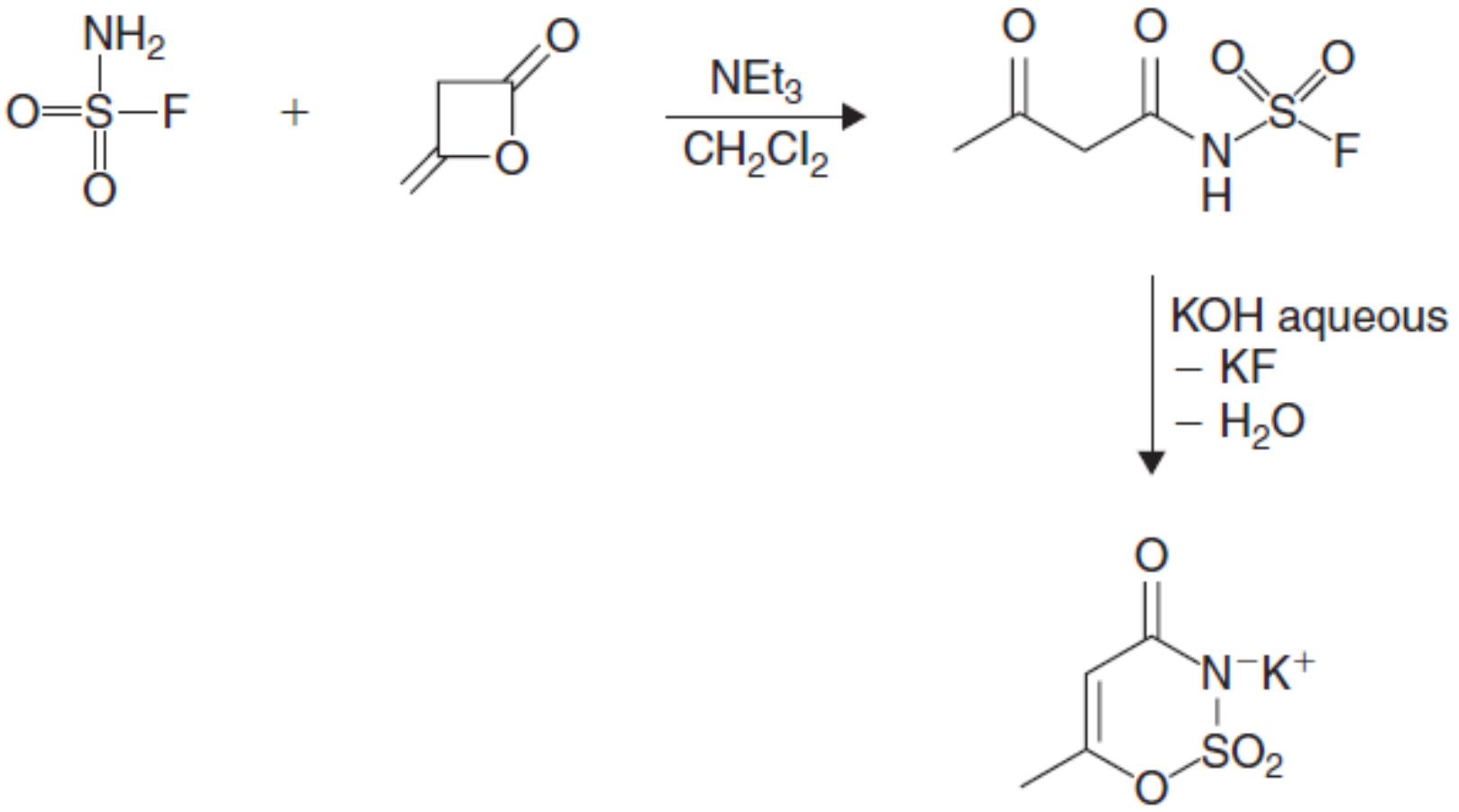
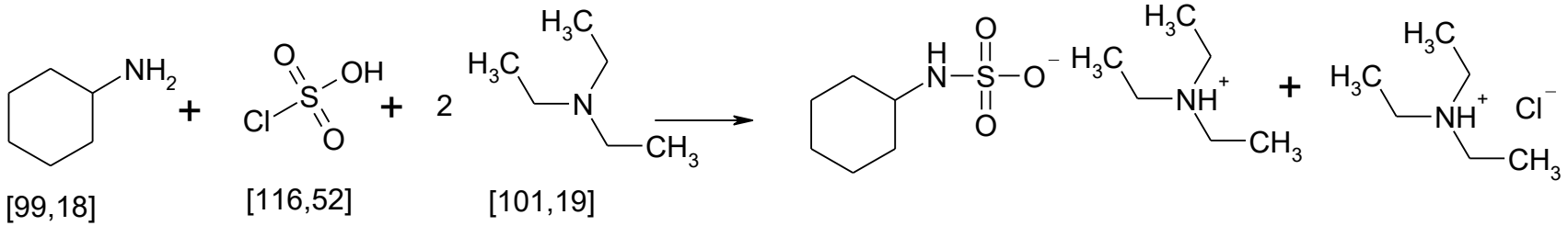
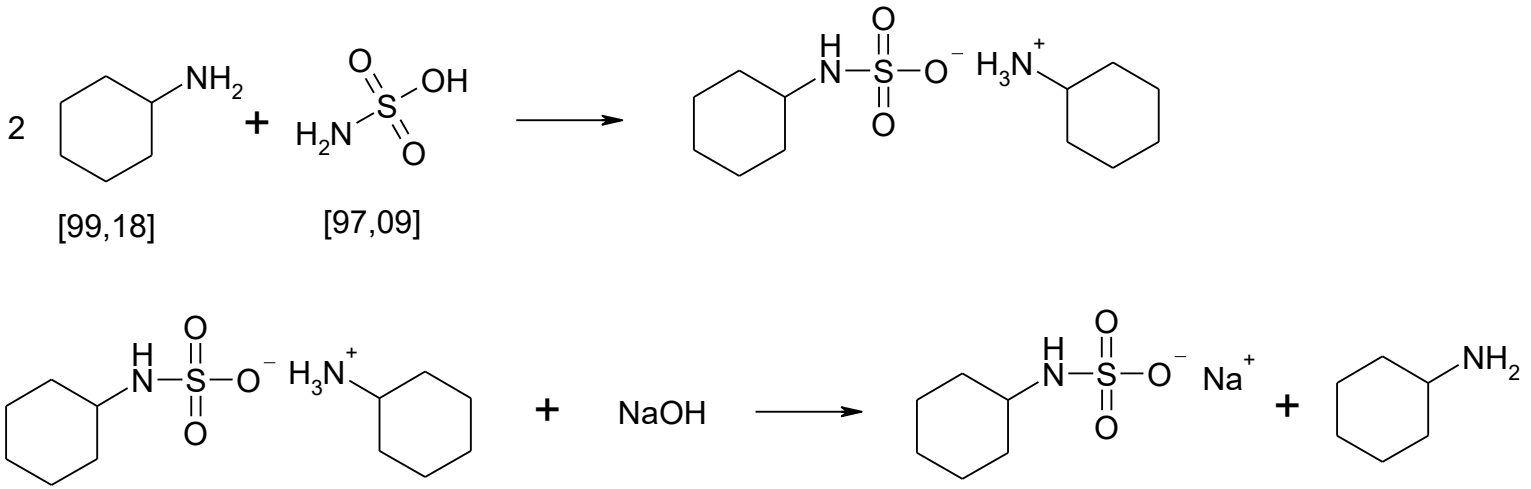


Fig. 5.2 Synthesis of acesulfame K according to the 'sulphur trioxide process'.[2]

Preparation of sodium cyclamate



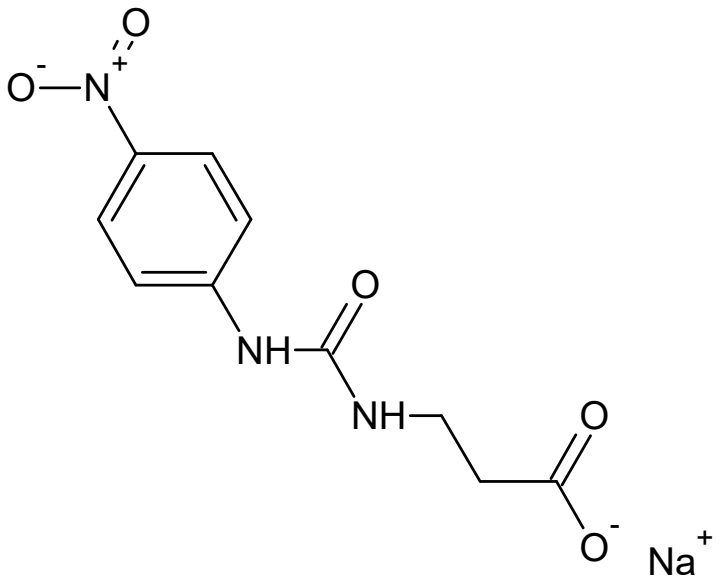
GB 669200



GB 662 800

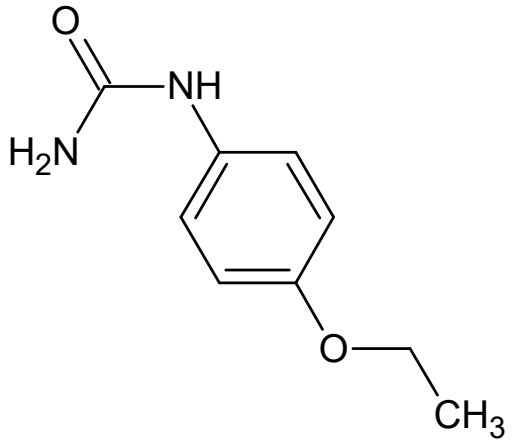
7. Urea derivatives

- not approved



suosan

LD_{50} I.*p.*, rat = 1 g / kg



dulcin

LD_{50}*p.o.*, rat = 3.2 g/kg

LDLo child = 400 mg / kg

- muscle weakeness
- nauzea and vomiting
- hallucinations, distorted perceptions

Structure-sweetness relationships main facts

1. polyhydroxylated or polyhalogenated alkans are usually sweet (glycerol, chloroform)
2. the sweet taste decreases in increasing homologous series (along with water solubility)
3. some aldehydes (or oximes of some aldehydes) or ketons are sweet
4. aromatic nitro compounds are sweet
5. some sulfo compounds are sweet
6. a symmetry within the molecule leads to sweet taste loss or optionally into a bitter taste
7. introduction of phenyl into the molecule leads to a bitter taste or taste loss

Overview of sweetness of selected compounds of natural and synthetic origin

sweetener	sweetness equivalent	sweetener	sweetness equivalent
lactose	0.27	acesulfam	200
palatinitol (isomalt)	0.4	aspartam	180-200
D-glucitol (sorbitol)	0.48	dulcin	250
glucose	0.5-0.6	stevioside	200-300
glycerol	0.5	suosan	350
erythritol	0.6-0.7	saccharin	400-550
tagatose	0,9	sucralose	500-650
sucrose	**1.0**	neohesperidin dihydrochalcon	1000
xylitol	1.0	perillaldehyde *anti*oxim	2000
fructose	0.7-1.8	alitam	2000
glycin	1.5	monellin	3000
sodium cyclamate	30-60	1-methoxy-2-amino-4-nitrobenzen	4000
D-tryptophan	35	thaumatin I and II	3000
glycyrrhizin	50-100	neotam	8000