[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF MARYLAND]

Sugar Alcohols. V. Chemical Constitution and Sweet Taste[1]

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The relationship between chemical constitution and sweet taste has not been elucidated satisfactorily. In a series of investigations[2–5] on the metabolism of sugar alcohols and their anhydrides a large number of these substances were prepared and the authors decided to study the relationship between their chemical constitution and sweet taste. The relative sweet tastes of the simple sugars have been investigated repeatedly, although comparative studies of the sugar alcohols and their anhydrides have not been reported. McGuigan[6] suggests a relationship between intensity of sweet taste and the number of hydroxyl groups in the molecule. This series affords an excellent opportunity to test this hypothesis. In addition, the response of animals and microorganisms to the sugar alcohols is so strikingly different from their response to their anhydrides that this investigation was initiated.

Experimental

Substances of C. P. quality were employed. The mannitol and sorbitol were supplied by the Atlas Powder Co. of Wilmington, Del. The anhydrides were prepared in this Laboratory and their purity and identity established as has been described previously.[2–5,7]

The polygalitol was extracted from *Polygala Amara* by the method of Picard[8] and occurred as colorless crystals, m. p. 142°; $[\alpha]^{16}\text{D} + 47.5$. All of the substances were dried in a desiccator for a period of several months and the threshold quantities represent anhydrous material.

Six carefully standardized individuals were used for the determinations and not more than three or four substances were tested on any one day. The threshold quantity of sucrose was determined before each test. After rinsing the mouth with water, 5 cc. of the standard solution was placed on the tongue which was brought in contact with the roof of the mouth and the sensation noted within half a minute. The minimal concentration just producing a sweet taste within one-half to one minute was considered the threshold quantity. Freshly distilled water was used in preparing all solutions. The average of the results for the sugar alcohols is shown in Table I and is compared with sucrose as a standard.

TABLE I

RELATIVE SWEETNESS OF THE SUGAR ALCOHOLS, SUCROSE TAKEN AS 100

Product	Carbon atoms number	OH groups number	Mol. wt.	Ratio
Sucrose	..	..	...	100
Ethylene glycol	2	2	62	130
Glycerol	3	3	92	108
i-Erythritol	4	4	122	238
Pentaerythritol	5	4	136	110
l-Arabitol	5	5	152	100
d-Mannitol	6	6	182	57
d,l-Sorbitol	6	6	182	54
i-Dulcitol	6	6	182	74
Inositol	6	6	180	50

Discussion

The results show no significant relationship between the number of carbon atoms or hydroxyl groups in the molecule and sweet taste. The anhydrides of several of these sugar alcohols, namely, ethylene oxide, epihydrin alcohol, mannitan, mannide, isomannide and dulcitan were devoid of a sweet taste and in most instances exhibited a decidedly bitter taste. It is of interest that these sugar alcohols are metabolized and produce gas with many members of the colon aerogenes group and their anhydrides do not.

Erythritan and polygalitol are the 1,4- and 1,5-anhydrides, respectively, of erythritol and mannitol. These substances possess a sweet taste and polygalitol produces gas and acid with many members of the colon aerogenes group of organisms.

There appears to be no relationship between spatial structure and sweet or bitter taste in this class of compounds. While α- and β-glucose have exactly the same degree of sweetness (ratio of 75), the derivatives of β-glucose are reported to be

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(1) The expense of this investigation was defrayed in part by a grant from the Committee on Therapeutics of the Council of Pharmacy and Chemistry of the American Medical Association.

(2) Carr, Musser, Schmidt and Krantz, *J. Biol. Chem.*, **102**, 721 (1933).

(3) Carr and Krantz, *ibid.*, **107**, 371 (1934).

(4) Krantz, Carr and Evans, *J. Pharmacy and Pharmacol.*, **8**, 213 (1935).

(5) Dozois, Hachtel, Carr and Krantz, *J. Bact.*, **30**, 189 (1935).

(6) McGuigan, "An Introduction to Chemical Pharmacology," P. Blakiston Sons, Philadelphia, Pa., 1921, pp. 28, 30.

(7) Dozois, Hachtel, Carr and Krantz, in press.

(8) Picard, *Bull. soc. chim. biol.*, **9**, 692 (1927).

uniformly more bitter than those of α-glucose.[9] The isomeric substances mannitol, sorbitol and dulcitol have approximately the same degree of sweetness while the two anhydrides mannide and isomannide are also of about the same degree of bitterness.

Summary

1. The removal of water from a sugar alcohol with the formation of the anhydride as a rule destroys the sweet taste of the former.

2. Erythritan, the first anhydride of erythritol, possesses a bitter taste in high concentrations but a sweet taste in threshold quantities.

3. Polygalitol, the 1,5-anhydride of mannitol, possesses a sweet taste in high concentration and an astringency in high dilution.

4. No relationship between the number of carbon atoms or hydroxyl groups in the molecule or the molecular weight or spatial configuration and sweet taste has been observed in this class of compounds.

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[9] Brigl and Scheyer, *Z. physiol. Chem.*, **160**, 214 (1926); *C. A.*, **21**, 418 (1927).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Some Derivatives of 1,3-Diketohydrindene

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Degradation of 2-acyl-1,3-diketohydrindenes by hydrolysis cannot be carried out successfully, and although these substances are converted by oxidation into a monocarboxylic acid and phthalic acid, the reaction does not always proceed smoothly. In connection with studies on the nitration of acyl diketohydrindenes we have found that bromination in acetic acid offers a superior method of degradation, the triketone being cleaved into 2,2-dibromo-1,3-diketohydrindene and a monocarboxylic acid. For example, 2-benzoyl-1,3-diketohydrindene yields dibromodiketohydrindene and benzoic acid. It is noteworthy that this cleavage, otherwise quite similar to the haloform reaction,[2] takes place in the absence of alkalies.

By means of this reaction it has been found that the nitration of 2-benzoyl-1,3-diketohydrindene yields 2-*m*-nitrobenzoyl-1,3-diketohydrindene, since bromination of the product yields dibromodiketohydrindene and *m*-nitrobenzoic acid.

Although the products obtained are too unstable to withstand the hydrolyzing action of the nitrating mixture, it is noteworthy that the O-acetate of 2-carbethoxy-1,3-diketohydrindene may be obtained by the action of acetyl chloride on either the sodium or the silver salt of the diketo ester, while the O-benzoate may be obtained only from benzoyl chloride and the silver salt.[3] The use of the sodium salt in the latter instance gives rise to an as yet unidentified substance, which is not the isomeric C-benzoate.

Experimental

Cleavage of 2-Benzoyl-1,3-diketohydrindene.—A solution of the triketone[4] (3 g.) and bromine (6 g.) in acetic acid (60 ml.) is warmed on a water-bath for two hours. After the bromine color has disappeared the mixture is cooled and diluted. The crystalline product separating melts at 178–179° and is 2,2-dibromo-1,3-diketohydrindene.[5]

Anal. Calcd. for $C_9H_4O_2Br_2$: Br, 52.7. Found: Br, 52.3, 52.7.

Evaporation of the mother liquor yields benzoic acid, purified by sublimation and identified by nitration.

Nitration of 2-Benzoyl-1,3-diketohydrindene.—The triketone (5 g.) is dissolved in sulfuric acid (40 ml.) at −5°, and treated at this temperature with a mixture of fuming nitric acid (1.5 g.) in sulfuric acid. After thirty minutes the solution is poured onto ice. The solid is washed with water and with much hot alcohol and crystallized from chloroform. The product forms microscopic needles that melt with decomposition at 228–229°; yield 70%.

Anal. Calcd. for $C_{16}H_9O_5N$: N, 4.74. Found: N, 4.73, 4.65.

On bromination in acetic acid, the nitrotriketone yields dibromodiketohydrindene and *m*-nitrobenzoic acid, identified by mixed melting points.

Acetylation of Ethyl 1,3-Diketohydrindene-2-carboxylate.—The sodium salt of the diketo ester[6] may be purified by crystallization from water with the aid of charcoal, and

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[1] The work presented in this paper is taken from a thesis by E. C. Yackel presented to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, October, 1929.—C. F. KOELSCH.

[2] *Cf.* Fuson, *Chem. Rev.*, **15**, 299 (1934).

[3] Hantzsch and Gajewski, *Ann.*, **392**, 306 (1912).

[4] Schwerin, *Ber.*, **27**, 106 (1894).

[5] Kronfeld, *ibid.*, **17**, 720 (1884).

[6] Wislicenus, *ibid.*, **20**, 594 (1887).