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Enhancement in the sweetness of sucrose

THERE is considerable interest in the relationship between chemical structure, both configurational and conformational and the sweet response¹ particularly in the case of sucrose (1) since, of all the sweetening agents it is the most widely used. Hitherto, no derivative of sucrose nor any other carbohydrate has shown sweetness substantially greater than that of sucrose, indeed to the contrary sucrose octa-acetate is very bitter, sucrose monoesters are much less sweet and *galacto*-sucrose (2), a C4 epimer of sucrose, is greatly diminished in sweetness². Nevertheless, one of the objectives in our studies on the chemistry of sucrose has been to modify its structure, by chemical means in order to enhance its natural sweetness and in the process prevent metabolism by inhibiting breakdown by invertase. We have now been greatly encouraged by the surprising discovery that a *galacto*-sucrose derivative, namely 1',4,6,6'-tetrachloro-*galacto*-sucrose (3) is intensely sweet, comparable with saccharin but without an unpleasant after-taste.

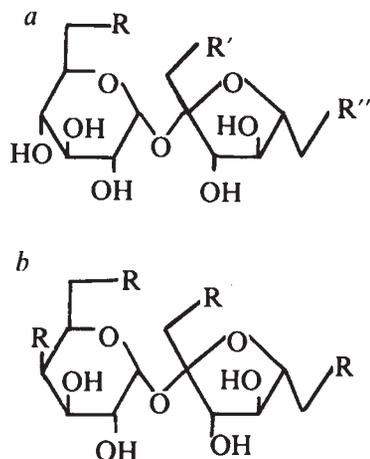


Fig. 1 *a*, Sucrose (1; R = R' = R'' = OH) and its 6,6'-dichloro (4; R = R'' = Cl, R' = OH) and 1',6'-dichloro (5; R = R'' = Cl, R = OH) derivatives; *b*, *galacto*-sucrose (2; R = OH) and its tetrachloro derivative (3; R = Cl).

Lindley, Birch and Khan² suggested from studies on methyl ethers of sucrose that the equatorial 4-hydroxyl group of sucrose (1) interacts with the taste buds of the tongue by intermolecular hydrogen bonding and that loss of sweetness in *galacto*-sucrose (2) is due to the axial 4-hydroxyl group being masked by an intramolecular hydrogen bond to the ring oxygen. Whilst our tetrachloro derivative (3) is not in disagreement with the latter observation, the 4-chloro substituent could only act as a hydrogen bond acceptor on the taste bud. Likewise they suggested the importance of the 1'-hydroxyl group of sucrose which is supported by our own observations in that 6,6'-dichloro-sucrose³ (4) is less sweet than sucrose, implying that in (3) the 1',4-dichloro substituents are enhancing its sweetness. On the other hand 1',6,6'-trichloro⁴ and 4,6,6'-trichloro⁵ derivatives are more than 10 times sweeter than sucrose but not as intensely sweet as the aforementioned tetrachloro derivative (3). It is highly significant that 1',6'-dichlorosucrose (5) is intensely sweet, like the tetrachloro derivative (3), which

pinpoints the importance of the chloro substituent at the 1'-position on the molecule of sucrose.

If the Shallenberger theory of sugar sweetness⁶ is correct, where two electronegative atoms A and B separated by 2.5-4.0 Å initiate the sweet taste by intermolecular hydrogen bonding between A-H and B and similar groups on the receptor site, then it would seem that the 1'-chloro substituent is the proton acceptor B and the 2-hydroxyl on the glucosyl moiety is A-H, the proton donor. The intense sweetness of the chloro compounds 3 and 5 could also be due in part to their greater lipophilic character than sucrose. The subtle interplay of intramolecular bonding in the sucrose molecule has an important role and the introduction of chloro substituents seems to have reinforced the effect. The sucrose derivatives in which a 6-hydroxyl of the fructofuranosyl unit of sucrose has been replaced by a chloro substituent are resistant to the action of invertase, a β -D-fructofuranosidase (J. Chapman, unpublished results). Hence in the development of alternative sweeteners from sucrose, as for example for application in dietetic food, combining high sweetness with low calorie content, the chloro derivatives are worthy of further evaluation.

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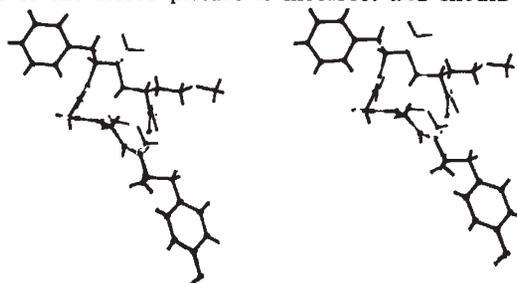
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Erratum

In the article "Conformation of met⁵-enkephalin determined by high field PMR spectroscopy" by B. P. Roques *et al.* (*Nature*, **262**, 778; 1976) the legends to Figs 2 and 3 are transposed. The Figs are in the correct positions. The alignment of the stereo picture is incorrect and should be as below.



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