CCCXCVI.—*Synthesis of a New Disaccharide,* neo*Trehalose.*

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BY the additive union of triacetyl glucose 1 : 2-anhydride (Brigl, *Z. physiol. Chem.*, 1922, **122**, 257) and tetra-acetyl glucose in benzene solution we have prepared the *hepta-acetate* of a non-reducing disaccharide to which we have given the name of neo*trehalose*. It yields a crystalline *octa-acetate* on further acetylation and is easily deprived of its acetyl groups by dry ammonia to give the free crystalline sugar *neo*trehalose (*α-glucosidyl-β-glucoside*). The rotational values of all these substances are given in a comparative table below.

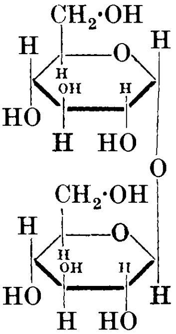
So far as it is possible to deduce ring structures from the chemical behaviour of partly acetylated sugar derivatives it would seem that both the reagents used in this synthesis should be regarded as derivatives of glucopyranose. Brigl (*loc. cit.*) showed that the triacetyl glucose 1 : 2-anhydride combines additively with methyl alcohol to yield a triacetyl derivative of β-methylglucoside which passes on de-acetylation to β-methylglucopyranoside. It is also the case that, since tetra-acetyl glucose is obtained direct from tetra-acetyl glucosidyl bromide, which itself gives rise to β-methylglucoside on condensation with methyl alcohol, followed by acetylation, it seems reasonable to allocate a pyranose structure to this tetra-acetyl glucose. The union of both these reagents which has been carried out in the present synthesis may be expected, therefore, to give rise to a disaccharide which can be formulated as a diglucopyranose, and this is the constitution which we tentatively allocate to *neo*trehalose.

One may, however, reserve judgment on this question until sufficient of the disaccharide has been prepared for the purpose of a study of its constitution by methylation methods. There is no real ground for doubting the constitution here assigned beyond the fact that instances of the migration of acetyl groups in partly acetylated hexoses have already been observed (compare Haworth, Hirst, and Teece, J., 1930, 1405). Theoretically there can exist three non-reducing disaccharides of the type of trehalose according as two glucopyranose units are united through the reducing positions as the αα-, αβ-, and ββ-forms. Of these the first is known as the naturally occurring sugar trehalose (Berthelot, *Ann. Chim. Phys.*, 1859, **55**, 272; von Lippman, *Ber.*, 1921, **45**, 3431; Schukov, *Z. ver. Rübenzuck. Ind.*, 1900, 818), the rotations of which are given below side by side with those exhibited by *neo*trehalose. In addition, figures are given for the synthetic *iso*trehalose obtained by Fischer and Delbrück (*Ber.*, 1909, **42**, 2783) by the condensation of tetra-acetyl glucosidyl bromide in the presence of silver carbonate.

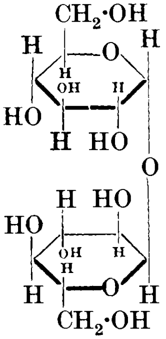
	$[\alpha]_D$.
Trehalose	+178° (hydrate); +197° (anhydrous)
Octa-acetyl trehalose	+162° (in chloroform)
*neo*Trehalose	+ 95° (hydrate); +100° (anhydrous)
Octa-acetyl *neo*trehalose	+ 82° (in chloroform) + 90° (in benzene)
*iso*Trehalose ($\beta\beta$)	− 39° (anhydrous)
Octa-acetyl *iso*trehalose	− 17° (in benzene)

From the mode of synthesis it would appear that *neo*trehalose is the hitherto unknown αβ-form of glucosidylglucose. The rotational values are, however, in disagreement with those foreshadowed by Hudson (*J. Amer. Chem. Soc.*, 1916, **38**, 1571) inasmuch as according to the statistical rules elaborated by him the rotation of an αβ-1 : 1-diglucose should be of the order $[\alpha]_D$ + 70°. Vogel and Debowska-Kurnicka (*Helv. Chim. Acta*, 1928, **11**, 910) claim to have prepared a disaccharide (and its octa-acetate), which is described as αβ-trehalose, having the rotation $[\alpha]_D$ + 67° in close agreement with that calculated by Hudson. The properties of their product differ from those of *neo*trehalose and it is to be noted that the octa-acetyl derivative, m. p. 68—70°, $[\alpha]_D$ + 68° (in chloroform), is also totally different from that now described. The constitution of *neo*trehalose may be provisionally indicated by the formula (I).

(I.)



(II.)



It can be inferred from the work of Schlubach and Maurer (*Ber.*, 1925, **58**, 1178) that trehalose should be given the constitution (II).

EXPERIMENTAL.

Union of 3 : 4 : 6-*Triacetyl Glucose* 1 : 2-*Anhydride and* 2 : 3 : 4 : 6-*Tetra-acetyl* β-*Glucose.*—The above crystalline substances (5·2 g. and 9·2 g. respectively) were mixed, covered with 2—3 c.c. of dry benzene, and kept at 90—100° for 37 hours, moisture being excluded.

The product, a viscid amber-coloured gum, was extracted repeatedly with hot water, and from the cooled extract globular aggregates of slender needles (1 g.) were deposited. The same product was also obtained by a similar treatment of the above triacetyl glucose 1 : 2-anhydride (1·5 g.) and the equilibrium mixture of α- and β-forms of 2 : 3 : 4 : 6-tetra-acetyl glucose (7 g.). Yield, 0·2 g. The *hepta-acetyl* neo*trehalose*, recrystallised from water and then from carbon tetrachloride, was obtained in slender needles, m. p. 155—156°, $[\alpha]_D^{20^\circ}$ + 78° in acetone (*c*, 2·4) (Found : C, 48·9, 49·05; H, 5·8, 5·7. $C_{26}H_{36}O_{18}$ requires C, 49·05; H, 5·7%).

Hepta-acetyl *neo*trehalose is not readily soluble in ether or benzene, but it crystallises from water as the *monohydrate* (Found : H_2O, 2·6. $C_{26}H_{36}O_{18},H_2O$ requires H_2O, 2·75%), which, when the temperature is gradually raised, shows the same m. p. (155—156°) as the above anhydrous form. If the hydrate, contained in a capillary tube, is suddenly plunged into a bath at 130° it melts immediately; if it is initially and suddenly heated to 120° and the temperature is gradually raised, it melts at 122—125° to an almost clear liquid.

Octa-acetyl neo*Trehalose*.—Hepta-acetyl *neo*trehalose (0·24 g.) was acetylated in pyridine (1 c.c.) by the addition of 0·8 g. of acetic anhydride. After being kept at room temperature for 48 hours, the mixture was diluted with water. The white turbidity thus produced gave place, gradually, to a deposit of the octa-acetyl compound in small nodular masses. A further quantity was obtained by extracting the aqueous portion with chloroform or a large volume of ether.

Octa-acetyl neo*trehalose* separates from warm alcohol in clusters of prismatic needles, m. p. 140—141° [Found : C, 49·1; H, 5·9; *M* (Rast), 638. $C_{28}H_{38}O_{19}$ requires C, 49·5; H, 5·65%; *M*, 678]. $[\alpha]_D^{20^\circ}$ + 90° (in benzene; *c* 1·14, *l* 0·5 dm.), + 82° (in chloroform; *c* 5). It is very sparingly soluble in cold water, but sufficiently soluble in boiling water to enable small quantities to be recrystallised from this medium. In cold ethyl alcohol its solubility at room temperature is approximately 0·7—0·8%. It is more soluble in benzene, ethyl acetate, chloroform, or warm ethyl alcohol.

neo*Trehalose* (*α-Glucosidyl-β-glucoside*).—A solution of hepta-acetyl αβ-trehalose (0·36 g.) in 25 c.c. of warm absolute alcohol was saturated at room temperature with dry ammonia. After 18 hours the solvent was removed under diminished pressure; the gummy residue crystallised after trituration with alcohol, and the pure sugar was obtained by dissolving it in a small volume of water, adding absolute alcohol, and keeping the mixture in a desiccator. neo*Trehalose monohydrate* was deposited in concentrically grouped clusters of small plate-like crystals (Found : C, 40·1, 39·9; H, 7·0, 6·9; *M*, in water, 329. $C_{12}H_{22}O_{11},H_2O$ requires C, 40·0; H, 6·7%; *M*, 342).

When heated in a capillary tube, the substance softens at about 145—150° and then swells to an opaque mass. As the temperature is raised, the mass gradually diminishes in bulk until at about 210—220° it has become an almost transparent syrup with a faint brown tint. $[\alpha]_D + 95°$ (*c*, 3·55 in water; *l*, 0·5 dm.) (calc. for anhydrous sugar, $[\alpha]_D + 100°$). The sugar is readily soluble in cold water, sparingly in absolute alcohol. It has a slight sweet taste. It has no apparent action on Fehling's solution even after prolonged boiling. It is hydrolysed to glucose by warm dilute hydrochloric acid.

A solution of *neo*trehalose in *ca.* 5% hydrochloric acid was heated at 90—100°. Initially $[\alpha]_D + 96·6°$ (*c*, 2·95), the specific rotation fell to + 52·2° after 2·6 hours. There was no change in rotation on further heating. In the hydrolysis products the presence of glucose was confirmed by the isolation of glucosephenylosazone, and by the formation of β-penta-acetyl glucose.

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