537. 3 : 6-3′ : 6′-*Dianhydro-derivatives of* β-*Methylcellobioside and of* β-*Methylmaltoside.*

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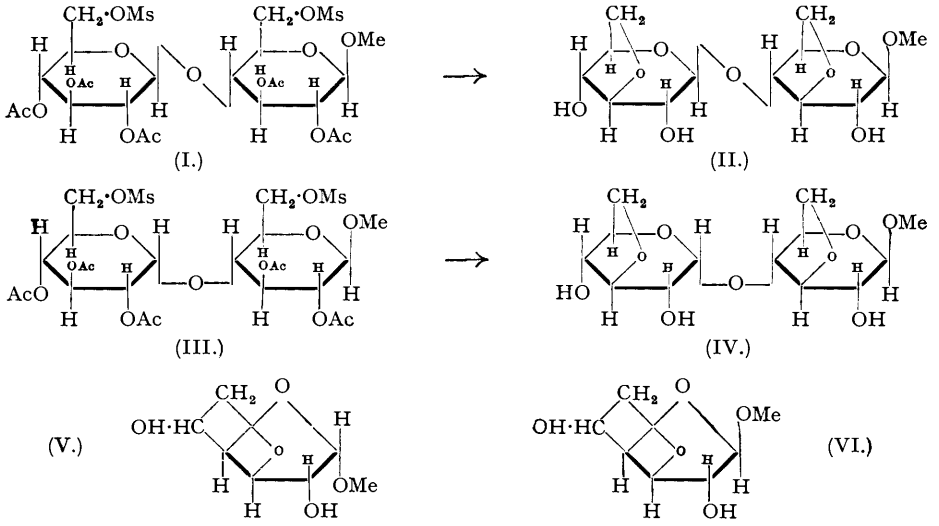
The 3 : 6-3′ : 6′-dianhydro-derivatives (II) and (IV) of β-methylcellobioside and of β-methylmaltoside, respectively, have been prepared by treatment of the corresponding 6 : 6′-dimethanesulphonates with alkali. The structure of these dianhydrides is deduced from the fact that treatment with boiling methyl-alcoholic hydrogen chloride gives rise in each case to a crystalline mixture of the α- (V) and the β-form (VI) of 3 : 6-anhydro-methyl-D-glucofuranoside which can be separated by fractional crystallisation. These dianhydro-compounds are sensitive to acidic reagents.

Previous studies on the 3 : 6-anhydro-derivatives of D-glucose (Haworth, Owen, and Smith, *J.*, 1941, 88) and D-galactose (Haworth, Jackson, and Smith, *J.*, 1940, 620; *Nature*, 1938, **142**, 1075; Smith and Rao, *J.*, 1944, 229) have demonstrated that the presence of the hydrofuranol or 3 : 6-anhydro-ring so governs the structure that it is undoubtedly responsible for the peculiar properties which these substances possess. The exceptional behaviour of 3 : 6-anhydro-compounds may be illustrated by the observation that the α- and the β-form of 3 : 6-anhydro-methyl-D-glucopyranoside can be directly converted into 3 : 6-anhydro-α- and -β-methyl-D-glucofuranoside, respectively; the change of the ring system from pyranoside to furanoside takes place without loss of the glycosidic methyl group. It was also established that direct transformation of 2 : 4-dimethyl 3 : 6-anhydro-α-methyl-D-glucopyranoside into the β-pyranoside can also be brought about by acidic reagents without loss of the glycosidic methyl group (Haworth, Owen, and Smith, *loc. cit.*). 2 : 4-Dimethyl 3 : 6-anhydro-α-methyl-D-galactopyranoside can be similarly transformed into the corresponding β-glycoside without cleavage of the methyl group at $C_{(1)}$ (Haworth, Jackson, and Smith, *loc. cit.*). An inspection of the structures of the 3 : 6-3′ : 6′-dianhydro-derivatives of the disaccharides shows that, if the anhydro-ring confers upon these substances properties analogous to those which it induces in the methyl-glucopyranosides, it is to be expected that suitable treatment of dianhydro-methylmaltoside with acidic reagents might result in a change of the 1 : 4-biose linkage from the α- to the β-type and also in a transformation of the ring system in the terminal or " non-reducing " glucose residue from the pyranose to the furanose form. By analogy it was expected that the 3 : 6-3′ : 6′-dianhydro-derivative of β-methylcellobioside might exhibit in acid solution a change in which the terminal or " non-reducing " glucopyranose unit would be converted into a furanose residue. It is apparent that the presence of the 1 : 4-biose linkage in these two dianhydro-disaccharides will prevent the " reducing " glucose residue changing from the pyranose to the furanose form, but it is possible, for both dianhydro-compounds, that the sugar ring of the " reducing " moiety may open as it does with 3 : 6-anhydro-derivatives of galactose (Haworth, Jackson, and Smith *loc. cit.*).

In order to test these possibilities the 3 : 6-3′ : 6′-dianhydro-derivative of β-methylmaltoside and of β-methylcellobioside have been synthesised. The procedure adopted for their preparation is similar to that by which the 3 : 6-anhydro-derivatives of glucose and galactose have been prepared from the 6-tosyl derivatives (Haworth, Owen, and Smith, *loc. cit.*; Haworth, Jackson, and Smith, *loc. cit.*; cf. Percival *et al.*, *Nature*, 1938, **142**, 1076; *ibid.*, p. 797; Hands and Peat, *ibid.*, p. 797; Valentin, *Coll. Czech. Chem. Comm.*, 1932, **4**, 364). 6 : 6′-Ditosyl penta-acetyl β-methylcellobioside was prepared by Compton (*J. Amer. Chem. Soc.*, 1938, **60**, 1203) but repetition of this work gave an amorphous product. The corresponding 6 : 6′-dimethanesulphonyl penta-acetyl β-methylcellobioside (I) was prepared in good yield from β-methylcellobioside by the method of Helferich and Stryk (*Ber.*, 1941, **74**, 1794). Catalytic deacetylation of (I) by the Zemplén method yielded 6 : 6′-dimethanesulphonyl β-methylcellobioside and treatment either of this compound or of (I) with an excess of sodium methoxide gave 3 : 6-3′ : 6′-*dianhydro*-β-*methylcellobioside* (II). (II) appeared to exist in two crystalline modifications, (A) m. p. 182—183° and (B) m. p. 209—210°. The two forms showed the same high negative rotation ($[\alpha]_D$ *ca.* −200° in water); they were interconvertible and were shown by the identity of their *X*-ray powder photographs to be crystallographically identical, and are thus the same chemical compound. Acetylation of either the A or the B form with acetic anhydride–pyridine afforded the same crystalline dianhydro-triacetate. Analysis of the dianhydride (II) and its triacetate showed that two anhydro-groups were present. The location of the anhydro-rings in the 3 : 6-position of each moiety of the disaccharide followed from the fact that when (II) was boiled with methyl-alcoholic hydrogen chloride, there was

formed a crystalline mixture of the α- (V) and β-form (VI) of 3 : 6-anhydromethyl-D-glucofuranoside. Fractional crystallisation of this mixture enabled the two forms (V) and (VI) to be separated; they proved to be identical with authentic specimens (Haworth, Owen, and Smith, *loc. cit.*; Ohle and Wilcke, *Ber.*, 1938, **71**, 2316).



(Ms = $CH_3 \cdot SO_2$)

3 : 6-3′ : 6′-Dianhydro-β-methylmaltoside was synthesised by a similar series of reactions. Maltose was acetylated with a mixture of acetic acid and acetic anhydride in the presence of catalytic amounts of perchloric acid. The acetylation reaction mixture was treated with glacial acetic acid saturated with hydrogen bromide, and the octa-acetyl maltose thus converted directly into α-acetobromomaltose (Nicholas and Smith, *Nature*, 1948, **161**, 349). The action of methyl alcohol upon the latter in the presence of silver carbonate yielded hepta-acetyl β-methylmaltoside (Irvine and Black, *J.*, 1926, 862; Schoch, Wilson and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 2871). When the β-methylmaltoside, obtained by catalytic deacetylation of the hepta-acetate, was allowed to react in pyridine with methanesulphonyl chloride at 0°, followed by acetic anhydride, 6 : 6′-*dimethanesulphonyl penta-acetyl* β-*methylmaltoside* (III) was obtained. This was deacetylated by the Zemplén method (*loc. cit.*) and the resultant 6 : 6′-dimethanesulphonyl β-methylmaltoside (an amorphous solid) treated with aqueous alkali to yield 3 : 6-3′ : 6′-*dianhydro*-β-*methylmaltoside* (IV). The first specimen of this product was amorphous, but when acetylated it afforded a crystalline *triacetate* and this upon deacetylation gave the dianhydro-β-methylmaltoside (IV) as a crystalline monohydrate. When (IV) was boiled with methyl-alcoholic hydrogen chloride more than half the theoretical amount of a mixture of the α- (V) and the β-form (VI) of 3 : 6-anhydro-methyl-D-glucofuranoside was obtained, thus proving the existence of the two 3 : 6-anhydro-rings in the maltose compound (IV). The two forms (V) and (VI) were separated by fractional crystallisation and characterised by comparison with authentic specimens.

When treated with methyl alcohol containing small amounts of hydrogen chloride, these dianhydro-disaccharide β-methylglycosides (III) and (IV) behaved in an analogous manner to 3 : 6-anhydromethylglucopyranosides, as indicated by a rapid change in optical rotation. The nature of this transformation is under investigation.

Experimental.

β-Methylcellobioside.—Octa-acetyl cellobiose (75 g.) obtained by the acetolysis of cotton linters was converted into α-acetobromocellobiose by the usual procedure. Yield, 38 g.; m. p. 175—180° (Fischer and Zemplén, *Ber.*, 1910, **43**, 2536, record m. p. 180°). From this, hepta-acetyl β-methylcellobioside (20 g.; m. p. 178—182°) was obtained according to the method of Zemplén and Gerecs (*Ber.*, 1930, **63**, 2720). Hepta-acetyl β-methylcellobioside (20 g.) was dissolved in hot methyl alcohol and to the cooled solution 0·2N-sodium methoxide in methyl alcohol (2 c.c.) was added. After being kept overnight the solution was evaporated and the residue recrystallised from alcohol. The β-methylcellobioside (9·7 g.) had m. p. 198° and showed $[\alpha]_D^{17}$ −30·0° in water (*c*, 1·2).

6 : 6′-*Dimethanesulphonyl Penta-acetyl β-Methylcellobioside* (I).—β-Methylcellobioside (11·7 g.), dissolved in pyridine (100 c.c.), was treated at 0° with methanesulphonyl chloride (7·4 g., 2 mols.) for 12 hours, followed by acetic anhydride (40 c.c.) for 4 hours at room temperature according to the method of Helferich and Stryk (*loc. cit.*). The dimethanesulphonyl penta-acetyl derivative (I) (19 g.) had m. p. 197—198° (after recrystallisation from alcohol). Helferich and Stryk (*loc. cit.*) record m. p. 196—198° for this compound.

3 : 6-3′ : 6′-*Dianhydro-β-methylcellobioside* (II).—(*a*) To an ice-cold solution of dimethanesulphonyl penta-acetyl β-methylcellobioside (5 g.) in chloroform (15 c.c.), dry methyl alcohol (15 c.c.) containing sodium (1·21 g.) was added. After the mixture had been kept overnight the excess of the alkali was removed by passing carbon dioxide into the solution, which was then evaporated to dryness. The residue was extracted exhaustively with boiling ethyl acetate, and evaporation of this extract gave a partly crystalline residue (2 g.). Recrystallisation of this residue from alcohol gave 3 : 6-3′ : 6′-*dianhydro-β-methylcellobioside* (0·5 g.) in the form of prismatic needles (A), m. p. 182—183°, $[\alpha]_D^{28}$ −201° in water (*c*, 1·4) (Found : OMe, 10·2. $C_{13}H_{20}O_9$ requires OMe, 9·7%). Evaporation of the mother-liquors gave a syrup from which no more crystals could be obtained.

(*b*) Dimethanesulphonyl penta-acetyl β-methylcellobioside (5 g.) was dissolved in chloroform (80 c.c.), and dry methyl alcohol (40 c.c.) containing sodium (5 mg.) added. After 17 hours the solution was evaporated to dryness. The deacetylated product was a water-soluble glass, which was treated for 48 hours at room temperature with N-sodium hydroxide solution (20 c.c.). When the excess of alkali was neutralised (phenolphthalein) with solid carbon dioxide, crystals (0·7 g.; m. p. 195—210°) separated, which upon recrystallisation from alcohol afforded 3 : 6-3′ : 6′-*dianhydro-β-methylcellobioside*, as rectangular plates (B), m. p. 209—210°, $[\alpha]_D^{28}$ −203° in water (*c*, 1·0) (Found : C, 48·8; H, 6·4. $C_{13}H_{20}O_9$ requires C, 48·7; H, 6·25%). Evaporation of the aqueous mother-liquors gave a further 0·9 g., m. p. 207—210°

The materials (A) (needles) and (B) (plates) are different forms of 3 : 6-3′ : 6′-dianhydro β-methylcellobioside (II). When crystals (A), m. p. 182—183° (m. p. unaltered after resolidification), were treated with methyl-alcoholic ammonia at 0° for 12 hours (cf. Micheel and Bischoff, *Annalen*, 1936, **525**, 66; Haworth, Hirst, Smith, and Wilson, *J.*, 1937, 829), they formed prismatic needles, m. p. 200—202°, and when treated with cold N-sodium hydroxide crystals (A) again yielded prismatic needles, m. p. 205—211°. Neither of the two specimens prepared from (A) by alkaline treatment depressed the m. p. of crystals (B). A mixture of (A) and (B) had m. p. 186—196°. When the crystals (B) were crystallised from alcohol, prismatic needles, m. p. 179°, were obtained which showed no depression of the m. p. in admixture with crystals (A). The *X*-ray powder diagrams of all the crystalline fractions were identical.

Triacetyl 3 : 6-3′ : 6′-*Dianhydro-β-methylcellobioside*.—Dianhydro-β-methylcellobioside (50 mg.) was dissolved in dry pyridine (5 c.c.), and acetic anhydride (1 c.c.) added. After being kept overnight the reaction mixture was poured into water, and the aqueous solution extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated, whereupon the resulting syrup crystallised spontaneously. When recrystallised from alcohol the *triacetyl* derivative formed prisms, m. p. 155—156°, $[\alpha]_D^{17}$ −127° in chloroform (*c*, 0·5) (Found : C, 51·1; H, 5·9. $C_{19}H_{26}O_{12}$ requires C, 51·1; H, 5·8%).

Treatment of Dianhydro-β-methylcellobioside with Methyl-alcoholic Hydrogen Chloride.—(*a*) When the dianhydride (0·30 g.) was boiled for 7 hours with 1% methyl-alcoholic hydrogen chloride (10 c.c.), the solution showed $[\alpha]_D$ +48° (constant). The acid was neutralised by means of diazomethane in ether, and the solution evaporated under diminished pressure. The syrup so obtained distilled [b. p. 140° (bath temp.)/0·03 mm.] as a colourless liquid (0·20 g.), n_D^{21} 1·4918, which crystallised on trituration with ether. Fractional crystallisation from alcohol–ether–light petroleum provided two fractions : (1) 3 : 6-anhydro-α-methylglucofuranoside (V) as needles (0·105 g.), m. p. 66—67° (alone or in admixture with an authentic specimen), $[\alpha]_D^{21}$ +169° in water (*c*, 1·45); and (2) 3 : 6-anhydro-β-methylglucofuranoside (VI) as plates (0·055 g.), m. p. 94—95° (alone or in admixture with an authentic specimen), $[\alpha]_D^{22}$ −48·2° in water (*c*, 1·45). The total yield of the 3 : 6-anhydromethylglucofuranosides was 0·16 g. In order to achieve the separation of the two components it was necessary to maintain anhydrous conditions.

(*b*) When the dianhydride (40 mg.) dissolved in methyl alcohol (4 c.c.) was treated at room temperature with 1% methyl-alcoholic hydrogen chloride (4 c.c.) the solution showed $[\alpha]_D$ −92° (after 2 minutes), −52° (5 minutes), −36° (10 minutes), −28° (15 minutes), −18° (20 minutes), −14° (25 minutes), −10° (30 minutes), −8° (35 minutes), −4° (40 minutes, constant value). When this solution was boiled for 8 hours a further increase in specific rotation was observed, the final value reaching +52° (*i.e.*, the equilibrium value for a mixture of 3 : 6-anhydro-α- and -β-methylglucofuranoside; Haworth, Owen, and Smith, *loc. cit.*).

Hepta-acetyl β-Methylmaltoside.—To a suspension of maltose (5 g.) in a mixture of acetic anhydride (12·5 c.c.) and glacial acetic acid (25 c.c.) perchloric acid (0·12 c.c., sp. gr. 1·54) was added. The maltose dissolved quickly and the temperature of the reaction mixture rose to 60—70°. After 1 hour the solution was cooled in ice and treated with a solution (20 c.c.) of hydrobromic acid in glacial acetic acid (saturated at 0°). After 30 minutes the ice-bath was removed, and after a further 30 minutes, the reaction mixture was poured into ice-water, and the solution extracted 3 times with chloroform. The combined chloroform extracts were washed with water, dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure. A solution of the resulting glassy solid in methyl alcohol (200 c.c.) was shaken for 12 hours with silver carbonate (8 g.). The reaction mixture was treated with a little charcoal and filtered, and the residue washed with chloroform. Evaporation of the combined filtrate and washings gave hepta-acetyl β-methylmaltoside (5·05 g.), m. p. 123—124° (after recrystallisation from absolute alcohol) (cf. Irvine and Black, *loc. cit.*; Schoch, Wilson, and Hudson, *loc. cit.*).

β-Methylmaltoside.—To a solution of hepta-acetyl β-methylmaltoside (14·7 g.) in dry methyl alcohol (90 c.c.) there was added 0·2N-sodium methoxide in methyl alcohol (4 c.c.), and the solution was boiled under reflux for 1 hour. After addition of charcoal, the solution was filtered and evaporated under reduced pressure to an amorphous solid which, crystallised from 95% alcohol, gave β-methylmaltoside

as the monohydrate (6·5 g.), m. p. 110—111°, $[\alpha]_D^{19}$ +81° in water (*c*, 2·0) (cf. Irvine and Black, *loc. cit.*; Schoch, Wilson, and Hudson, *loc. cit.*).

6 : 6′-*Dimethanesulphonyl Penta-acetyl β-Methylmaltoside* (III).—A solution of anhydrous β-methylmaltoside [prepared from the crystalline monohydrate (5·2 g.) by heating at 125° under reduced pressure] in dry pyridine (50 c.c.) was treated at 0° with a solution of methanesulphonyl chloride (2·1 c.c.) in dry pyridine (40 c.c.). After 16 hours at 0°, acetic anhydride (20 c.c.) was added and the mixture kept at room temperature overnight. The mixture was poured into ice-water and extracted 3 times with chloroform. The combined chloroform extracts were washed with dilute hydrochloric acid (to remove pyridine), sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated under reduced pressure. Recrystallisation of the residue from absolute alcohol gave 6 : 6′-*dimethanesulphonyl penta-acetyl β-methylmaltoside* (III), m. p. 175—176°, $[\alpha]_D^{20}$ +56·5° in chloroform (*c*, 1·5) (Found : C, 41·2; H, 5·2; S, 8·8; OMe, 4·3. $C_{25}H_{38}O_{20}S_2$ requires C, 41·5; H, 5·3; S, 8·8; OMe, 4·3%). From the mother-liquors there was obtained a small quantity of another substance, m. p. 153—156° (after crystallisation from ethyl alcohol), $[\alpha]_D^{21}$ +53·5° in chloroform (c, 0·7) (Found : C, 44·95; H, 5·6; S, 5·05; OMe, 4·7. Calc. for a monomethanesulphonyl hexa-acetyl β-methylmaltoside, $C_{26}H_{38}O_{19}S$: C, 45·4; H, 5·6; S, 4·7; OMe, 4·5%).

3 : 6-3′ : 6′-*Dianhydro-β-methylmaltoside* (IV).—(*a*) To a solution of 6 : 6′-dimethanesulphonyl penta-acetyl β-methylmaltoside (2 g.) in dry methyl alcohol (90 c.c.) 1 c.c. of 0·2N-sodium methoxide in methyl alcohol was added. After the solution had been kept for 12 hours at room temperature, the solvent was removed under reduced pressure to give 6 : 6′-dimethanesulphonyl β-methylmaltoside as a syrup which failed to crystallise. To a solution of this syrup in alcohol (5 c.c.) 12 c.c. of N-sodium hydroxide were added and the solution was heated for 3·5 hours at 60°. After neutralisation with carbon dioxide and filtration to remove inorganic matter the solution was evaporated to dryness under reduced pressure. Repeated extractions with ethyl acetate and evaporation of the extracts gave an amorphous solid which, crystallised from 95% ethyl alcohol, afforded 3 : 6-3′ : 6′-*dianhydro-β-methylmaltoside monohydrate* (0·45 g.), m. p. 95—101°, $[\alpha]_D^{17}$ −66° in water (*c*, 2·4) (Found : C, 46·4; H, 6·65; OMe, 9·3. $C_{13}H_{20}O_9,H_2O$ requires C, 46·2; H, 6·5; OMe, 9·2%).

(*b*) To a solution of triacetyl dianhydro-β-methylmaltoside (0·63 g.; see below) in methyl alcohol (140 c.c.) 0·108N-sodium methoxide in methyl alcohol (1·4 c.c.) was added. After 12 hours at room temperature removal of the solvent under reduced pressure gave dianhydro-β-methylmaltoside monohydrate (0·35 g.), m. p. 94—101° (after recrystallisation from 95% alcohol).

Triacetyl 3 : 6-3′ : 6′-*Dianhydro-β-methylmaltoside*.—A solution of amorphous dianhydro-β-methylmaltoside [prepared from 6 : 6′-dimethanesulphonyl penta-acetyl β-methylmaltoside (2 g.) as described above] in pyridine (10 c.c.) was treated for 2 hours at 60° with acetic anhydride (10 c.c.). The reaction mixture was poured into ice-water, and the solution saturated with sodium sulphate. The crystalline solid which separated was filtered off and washed with water. Recrystallisation from absolute alcohol gave *triacetyl dianhydro-β-methylmaltoside* (0·23 g.), m. p. 218—219°, $[\alpha]_D^{19}$ +25·4° in chloroform (*c*, 1·4). The aqueous filtrate and washings were extracted several times with chloroform. After washing the combined extracts with water and drying (Na_2SO_4), removal of the solvent afforded a further quantity of triacetyl dianhydro-β-methylmaltoside (0·56 g.) (Found : C, 51·0; H, 5·85; OMe, 7·4. $C_{19}H_{26}O_{12}$ requires C, 51·1; H, 5·9; OMe, 7·0%).

Treatment of Dianhydro-β-methylmaltoside with Methyl-alcoholic Hydrogen Chloride.—(*a*) Dianhydro-β-methylmaltoside monohydrate (0·28 g.) was dissolved in 1% methyl-alcoholic hydrogen chloride (10 c.c.), and the solution boiled for 6·5 hours by which time it showed $[\alpha]_D$ +53° (constant). The acid was neutralised by the addition of ethereal diazomethane, and the solution evaporated to dryness under diminished pressure. The syrup so obtained distilled [b. p. 160° (bath temp.)/0·08 mm.] as a colourless liquid (0·23 g.; n_D^{18} 1·4938) and crystallised on trituration with ether. From this mixture there were separated in the manner described above, 3 : 6-anhydro-α-methylglucofuranoside (V) (0·115 g.), m. p. and mixed m. p. 67°, and 3 : 6-anhydro-β-methylglucofuranoside (VI) (0·050 g.), m. p. and mixed m. p. 94—95°, the combined yield being 0·165 g.

(*b*) When a solution of the dianhydride (21·3 mg.) in methyl alcohol (1·5 c.c.), which showed $[\alpha]_D^{20}$ −67·7° (*c*, 1·4), was treated with 1% methyl-alcoholic hydrogen chloride (0·2 c.c.), the following changes in specific rotation were observed : $[\alpha]_D$ +0·6° (1 minute), +32° (1·5 minutes), +51° (3 minutes), +59° (5 minutes), +64° (7 minutes), +72° (10 minutes), +75° (20 minutes), +78° (30 minutes), +76° (45 minutes), +73° (129 minutes), +53° (202 minutes), +51° (24 hours, constant value).

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