78. *Synthesis of Carbohydrates by Use of Acetylenic Precursors. Part II.* Addition Reactions of* cis- *and* trans-*But-2-ene-1 : 4-diol Diacetates. Synthesis of* DL-*Erythrulose.*

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The reactions of the above two diacetates with per-acids, osmium tetroxide-catalysed hydrogen peroxide, hypobromous acid, and bromine have been carried out. The stereochemistry of the conversion of the adducts into tetritol tetra-acetates has been investigated and interpreted. DL-Erythrulose has been obtained from the hypobromous acid adducts.

The acetylenic approach to the synthesis of carbohydrates frequently leads to compounds containing an ethylenic double bond flanked by carbon atoms each attached to an acetoxyl group. It was of obvious interest, therefore, to examine the stereochemical effect, if any, exercised by the acetoxyl groups on addition to the double bond and on the subsequent substitution of the added groups. The simplest representatives, *cis*- and *trans*-but-2-ene-1 : 4-diol diacetates, $AcO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OAc$ (I), were chosen for study; both possible end products, erythritol and DL-threitol, are well-characterised compounds.

The *trans*-diacetate (I) was prepared by interaction of *trans*-1 : 4-dibromobut-2-ene and potassium acetate in glacial acetic acid, and the *cis*-isomer by partial catalytic hydrogenation of but-2-yne-1 : 4-diol diacetate. From the latter reaction a small quantity of crystalline by-product was obtained which proved to be a dimer of the main product; as it appeared to be saturated it may be formulated as one of the stereoisomers of 1 : 2 : 3 : 4-tetrakisacetoxymethyl *cyclo*butane. Such dimerisation of ethylenic derivatives is well known to occur under the influence of light (*e.g.*, the formation of truxillic and truxinic acids) or heat (Dykstra, *J. Amer. Chem. Soc.*, 1934, **56**, 1625; Cupery and Carothers, *ibid.*, p. 1167) but formation of a *cyclo*butane ring during catalytic hydrogenation is new. An alternative constitution based on dimerisation to the acyclic

$$AcO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CH_2{\cdot}OAc){\cdot}C(CH_2{\cdot}OAc){:}CH{\cdot}CH_2{\cdot}OAc$$

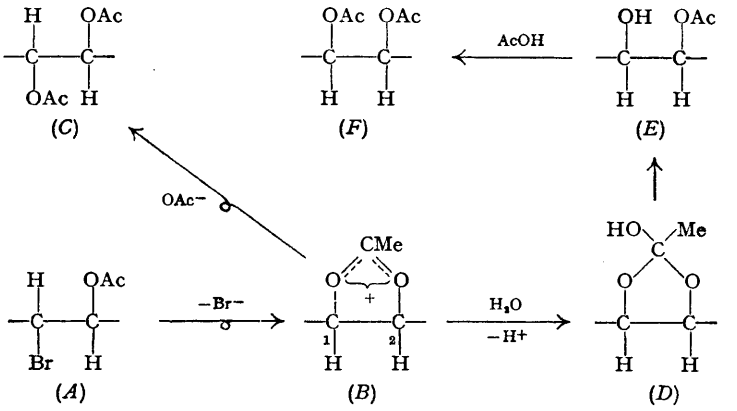
(cf. Bergmann, *Trans. Faraday Soc.*, 1939, **35**, 1025) and subsequent hydrogenation to the saturated compound is considered less likely.

The action of peracetic acid on the *trans*-diacetate (I) gave, after complete acetylation of the product, erythritol tetra-acetate; similar treatment of the *cis*-compound produced threitol tetra-acetate. Osmium tetroxide-catalysed *cis*-hydroxylation of the *cis*-diacetate with a *tert.*-butanol solution of hydrogen peroxide furnished crystalline erythritol 1 : 4-diacetate which gave erythritol tetra-acetate on complete acetylation. Under these conditions the *trans*-diacetate gave a liquid glycol converted on acetylation into threitol tetra-acetate. All these results are in full accord with stereochemical theory (see Part I).

trans-Addition of hypobromous acid to the *cis*- and *trans*-compounds (I) was smoothly effected by aqueous *N*-bromosuccinimide (Part I), to give homogeneous liquid bromohydrins which in view of the above precedents of " normal " addition were assigned the configurations *threo*- (II) and *erythro*-2-bromobutane-1 : 3 : 4-triol 1 : 4-diacetate respectively. The conversion of these compounds into tetritol tetra-acetates is of considerable stereochemical interest in view of the recent work of Winstein and his collaborators on the effect of vicinal substituents on the replacement of a bromine atom (for full references see Braude, *Ann. Reports*, 1949, **46**, 122). The relevant conclusions of the American workers may be briefly summarised with reference to the *threo*-bromo-acetate (*A*). Reaction with silver or potassium acetate results firstly in the removal of bromide ion with accompanying Walden inversion to give the cyclic acetoxonium ion (*B*). The subsequent reactions depend on the nature of the solvent. In dry acetic acid, (*B*) is attacked by acetate ion at the back of $C_{(1)}$ or $C_{(2)}$ (the examples studied gave symmetrical structures), with a second inversion that produces the *threo*-diacetate (*C*); thus there is overall retention of configuration. In moist acetic acid or ethanol, however, the predominating reaction is the attack of a water molecule with the expulsion of a proton, to give the unstable orthomonoacetate (*D*) the

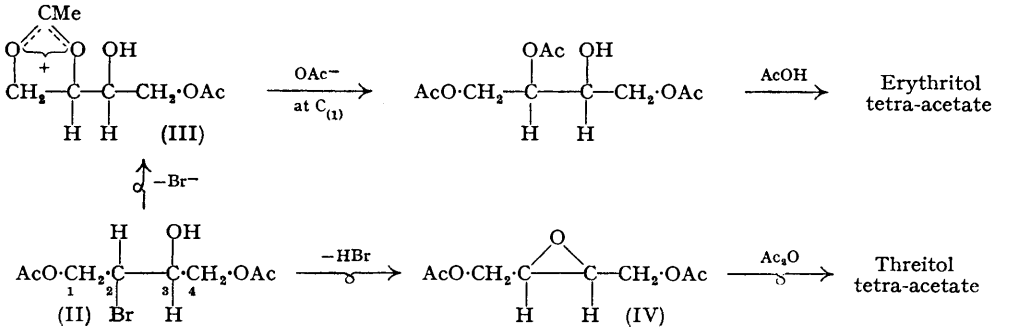
* Part I, *J.*, 1949, S 45.

ring of which then opens to yield the monoacetate (*E*), esterification furnishing finally the diacetate (*F*). Since none of these reactions involves a Walden inversion the diacetate (*F*) possesses the *erythro*-configuration, *i.e.*, overall inversion of configuration occurs. Analogous steric considerations apply to the *erythro*-isomer of (*A*).



The bromohydrins (II) represent more complex examples of this type of replacement since removal of bromide ion in this case allows of two possibilities, namely, the formation of an acetoxonium ring involving $C_{(1)}$ and $C_{(2)}$ or the formation of an epoxide between $C_{(2)}$ and $C_{(3)}$. The practical results of the replacement reactions were as follows.

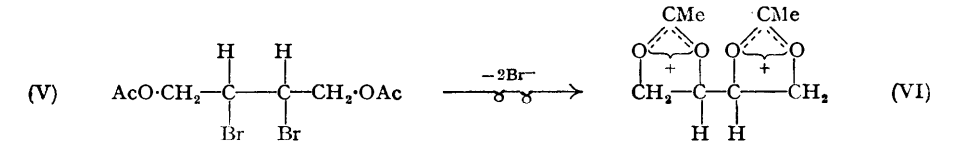
Treatment of the *erythro*-bromohydrin with potassium acetate in dry acetic acid gave exclusively threitol tetra-acetate; the same reagent in moist ethanol gave, after treatment with acetic anhydride, erythritol tetra-acetate only. Similar reactions involving the *threo*-bromohydrin (II) gave mainly erythritol tetra-acetate in dry acetic acid and threitol tetra-acetate in moist alcohol, although in this case the specificity was less clear-cut.



These results may be interpreted by the mechanism illustrated above for the case of the *threo*-bromohydrin (II); it seems to be the only explanation capable of fully so doing. Abstraction of the bromide ion by potassium acetate in dry acetic acid results in the formation of the cyclic acetoxonium ion (III) with inversion of configuration at $C_{(2)}$. Attack of acetate ion then takes place at the non-asymmetric $C_{(1)}$ which is considerably easier of access than the more sterically hindered $C_{(2)}$; overall inversion of configuration has thus occurred to give, after esterification, erythritol tetra-acetate. Reaction in moist alcohol, however, gives rise to the formation, with Walden inversion, of the epoxide (IV) which, on treatment with acetic anhydride, undergoes ring opening, again with Walden inversion, to threitol tetra-acetate; the overall effect is that of retention of configuration (for detailed mechanism of epoxide formation and fission see Winstein and Lucas, *J. Amer. Chem. Soc.*, 1939, **61**, 1576). In order to confirm the second mechanism an attempt was made to isolate the epoxide (IV). The oily product, however, proved to be inhomogeneous,

although it gave threitol tetra-acetate in high yield on acetylation; it was possibly a mixture of the required epoxide (IV) with threitol 1 : 2 : 4-triacetate, the latter being formed by interaction of (IV) with the acetic acid formed in the reaction. Exactly analogous arguments account for the results derived from the *erythro*-bromohydrin.

The addition of bromine to the *trans*-diacetate (I) has already been recorded by Griner (*Bull. Soc. chim.*, 1893, **9**, 219) and, in agreement with his results, the reaction gave the crystalline *erythro*-2 : 3-dibromobutane-1 : 4-diol diacetate (V). This compound gave the *same* product, erythritol tetra-acetate, on treatment with potassium acetate in either dry or moist acetic acid. This result may be readily interpreted on the basis of formation of a symmetrical dicyclic bisacetoxonium ion (VI) whence attack by either two acetate ions or two water molecules would give the same compound.



Bromination of the *cis*-diacetate (I) gave a liquid dibromide which, after distillation, largely solidified. The solid component proved to be the *erythro*-dibromide (V) while redistillation of the liquid again gave a distillate which partly solidified. From this it would seem that the expected *threo*-dibromide underwent thermal isomerisation to the *erythro*-isomer during distillation. Models show that in the stable, uniplanar, zig-zag *d* constellation of the four " backbone " carbon atoms (cf. Prelog, *J.*, 1950, 424) the two bromine atoms in the *erythro*-isomer are widely separated, whereas in the *threo*-dibromide there is strong steric interference.

Chromium trioxide oxidation of either the *erythro*- or the *threo*-bromohydrin (II) gave the same ketone, 2-bromo-1 : 4-diacetoxybutan-3-one which, by treatment with silver acetate in acetic acid, yielded DL-erythrulose triacetate. Hydrolysis with baryta then gave DL-erythrulose, characterised as its phenylosazone.

Experimental

trans-*But-2-ene*-1 : 4-*diol Diacetate* (I).—*trans*-1 : 4-Dibromobut-2-ene was heated with a solution of potassium acetate in glacial acetic acid according to the directions of Prevost (*Compt. rend.*, 1926, **183**, 1292). A solid bromine-containing impurity co-distilling with the main fraction was found to be 1 : 2 : 3 : 4-tetrabromobutane, m. p. 116—117°; for complete removal of this an alcoholic solution of the product had to be heated under reflux for 6 hours with zinc wool. The pure *trans*-diacetate had b. p. 120—121°/16 mm., m. p. 13—14°, n_D^{21} 1·4447.

cis-*But-2-ene*-1 : 4-*diol Diacetate* (I).—But-2-yne-1 : 4-diol diacetate was prepared from the glycol by acetic anhydride (Johnson, *J.*, 1946, 1009); it solidified to prismatic crystals, m.p. 27—29° (Found : C, 56·1; H, 5·8. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%). A solution of it (34 g.) in ethyl acetate (50 c.c.) was shaken under hydrogen with palladium–calcium carbonate (10%; 1 g.) until 1 mol. of hydrogen had been absorbed (4911 c.c. at 20°/754 mm.). Removal of catalyst and solvent and distillation gave the cis-*diacetate* (28 g.), b. p. 120—121°/18 mm., n_D^{19} 1·4435 (Found : C, 55·9; H, 7·2. $C_8H_{12}O_4$ requires C, 55·85; H, 7·05%).

The distillation residue solidified on cooling and was extracted with boiling ethanol. The extract on cooling deposited the *dimer* (1·2 g.) as stout needles, m. p. 104—105° [Found : C, 55·75; H, 6·7. *M* (ebullioscopic in acetone), 363. $(C_8H_{12}O_4)_2$ requires C, 55·85; H, 7·05%; *M*, 344]. Hydrolysis with a catalytic quantity of sodium methoxide furnished the parent glycol as a thick oil, Schotten–Baumann benzoylation of which gave the corresponding *benzoate* crystallising in needles, m. p. 149—150°, from *n*-butanol [Found : C, 72·85; H, 5·55. $(C_{18}H_{16}O_4)_2$ requires C, 72·95; H, 5·45%].

Action of Peracetic Acid on (I).—A solution of hydrogen peroxide (30%; 19 g.) in glacial acetic acid (25 c.c.) was heated to 85° for 1 hour and then cooled to 25° (Scanlan and Swern, *J. Amer. Chem. Soc.*, 1940, **62**, 2305). To this solution was added the *trans*-diacetate (I) (4·3 g.); as no exothermic reaction was observed the mixture was warmed to 50° and kept at this temperature for 16 hours. Evaporation under reduced pressure gave a viscous oil which was heated under reflux with acetic anhydride (10 c.c.) for 3 hours. The excess of anhydride was removed under reduced pressure, the residue treated with water, and the precipitated oil

extracted with ether. Washing with sodium hydrogen carbonate solution, drying ($MgSO_4$), and evaporation of the ether gave an oil which rapidly solidified; crystallisation from benzene–light petroleum (b. p. 60—80°) gave erythritol tetra-acetate (3·7 g., 51%) as prismatic needles, m. p. 89—90°, undepressed on admixture with an authentic specimen. The yield of product was found to be much improved (5·7 g., 79%) and the time of reaction considerably shortened if performic acid (18 c.c. of 98% formic acid and 7 g. of 30% H_2O_2) were used (Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786). The resulting reaction mixture was distilled in steam to hydrolyse the formoxy-group, and the residue left after evaporation to dryness was acetylated as above.

When the *cis*-diacetate (I) (4·3 g.) was treated with peracetic acid as described above, the only product consisted of DL-threitol tetra-acetate (4·1 g., 57%), crystallising in large prisms, m. p. 54—55°, after slow crystallisation from benzene–light petroleum (b. p. 60—80°) with preliminary seeding (Griner, *Compt. rend.*, 1893, **117**, 555 gives m. p. 53°). A small quantity of the product was catalytically deacetylated with sodium methoxide in methanol, and the residue after evaporation treated with concentrated hydrochloric acid and benzaldehyde; the resulting dibenzylidene compound crystallised in needles, m. p. 222°, from a large volume of ethanol (Maquenne and Bertrand, *Compt. rend.*, 1901, **132**, 1566, give m. p. 220° for dibenzylidene DL-threitol).

Action of Milas's Reagent on (I).—To a solution of hydrogen peroxide in *tert.*-butanol (6%; 20 c c.) was added the *trans*-diacetate (I) (4·3 g.), followed by a *tert.*-butanol solution of osmium tetroxide (1%; 1 c.c.). After 36 hours at room temperature the reaction mixture was evaporated under reduced pressure, to give a viscous oil which was acetylated by heating it with acetic anhydride (15 c.c.). Isolation and crystallisation as described above gave threitol tetra-acetate (5·3 g., 73%), m. p. and mixed m. p. 54—55°.

Treatment of the *cis*-diacetate (I) (4·3 g.) with the same reagent gave a viscous oil which rapidly solidified. Crystallisation from benzene gave *erythritol* 1 : 4-*diacetate* (3·9 g., 76%) as needles, m. p. 93—94° (Found: C, 46·3; H, 7·1. $C_8H_{14}O_6$ requires C, 46·6; H, 6·85%). This compound is possibly identical with the erythritol diacetate of unknown constitution, m. p. 89—91°, obtained by Fischer and Rund (*Ber.*, 1916, **49**, 98). Treatment of the product with acetic anhydride gave an almost quantitative yield of erythritol tetra-acetate, m. p. and mixed m. p. 89—90°.

threo- (II) *and* erythro-2-*Bromobutane*-1 : 3 : 4-*triol* 1 : 4-*Diacetate*.—A mixture of the *cis*-diacetate (I) (26 g.), powdered freshly crystallised *N*-bromosuccinimide (30 g.), water (50 c.c.), and acetic acid (0·2 c.c.) was shaken at room temperature for 16 hours. Water and ether were then added, and the ethereal layer was washed with sodium hydrogen carbonate solution and water and finally dried ($MgSO_4$). Evaporation and distillation gave threo-3-*bromobutane*-1 : 2 : 4-*triol* 1 : 4-*diacetate* (II) (33·6 g., 83%), b. p. 138—140°/2 × 10^{-2} mm., n_D^{15} 1·4796 (Found: C, 35·5; H, 5·0. $C_8H_{13}O_5Br$ requires C, 35·7; H, 4·9%).

Similarly the *trans*-diacetate (I) (17·2 g.) gave the erythro-*bromohydrin* (19·8 g., 74%), b. p. 130—132°/3 × 10^{-2} mm., n_D^{18} 1·4810 (Found: C, 35·55; H, 4·9%).

Action of Potassium Acetate on the Bromohydrins.—(a) *In dry acetic acid* (glacial acetic acid boiled for 1 hour with 5% of acetic anhydride). A mixture of the *erythro*-bromohydrin (1·7 g.), anhydrous potassium acetate (2 g.), and dry acetic acid (15 c.c.) was heated under reflux for 16 hours. The solvent was evaporated under reduced pressure, and water and ether were added to the residue. The ethereal layer was washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$); evaporation gave an oil which solidified. Slow crystallisation from benzene–light petroleum (b. p. 60—80°) gave threitol tetra-acetate (1·52 g., 83%), m. p. and mixed m. p. 53—54°.

Similarly the *threo*-bromohydrin (II) (2·1 g.) was treated with potassium acetate (2·5 g.) and dry acetic acid (25 c.c.); working up as above gave an oil which slowly solidified (2·1 g.). The product was dissolved in a small quantity of benzene (*ca.* 5 c.c.), and light petroleum (b. p. 60—80°) added slowly until a slight permanent turbidity was obtained. The solution was then seeded with a crystal of erythritol tetra-acetate and kept at room temperature for 24 hours. The precipitated crystalline mass (1·2 g.) had m. p. 85—87° undepressed on admixture with erythritol tetra-acetate. The mother-liquors were evaporated to dryness, the residue was dissolved in the minimum quantity of benzene, and the solution again treated to turbidity with light petroleum (b. p. 60—80°). The turbidity was removed with a drop of benzene, a seed of threitol tetra-acetate was introduced, and the solution cooled slowly to 0°, at which it was kept for 36 hours. The crystals thus obtained (0·24 g.) consisted of threitol tetra-acetate, m. p. and mixed m. p. 54—55°.

(b) *In moist alcohol* (95%). The *erythro*-bromohydrin (2·3 g.), potassium acetate (2·6 g.), and moist alcohol (25 c.c.) were heated under reflux for 16 hours. The solvent was removed under reduced pressure, leaving a residue smelling strongly of acetic acid; to this was added acetic anhydride (10 c.c.), and the mixture heated under reflux for 4 hours. Working up as already described gave erythritol tetra-acetate (1·8 g., 73%), m. p. and mixed m. p. 88—89°.

Similarly the *threo*-bromohydrin (II) (3·1 g.), potassium acetate (3·5 g.), and moist alcohol (30 c.c.) gave, after acetylation, a product (2·9 g.) from which threitol tetra-acetate (1·9 g.) and erythritol tetra-acetate (0·3 g.) were isolated. In one experiment the residue left after evaporation was treated with water and ether instead of acetic anhydride, in an attempt to isolate the intermediate epoxide. Evaporation of the washed and dried ethereal solution gave an oil which boiled continuously in the range 80—120°/5 × 10^{-3} mm.

Action of Bromine on (I).—To a solution of the *trans*-diacetate (I) (10 g.) in carbon tetrachloride (75 c.c.) was slowly added at room temperature a solution of bromine (9·1 g.) in carbon tetrachloride (25 c.c.). Evaporation of the solvent gave a crystalline mass which was crystallised from light petroleum (b. p. 60—80°) to give an almost quantitative yield of the *erythro*-dibromide (V), prisms, m. p. 87—88° (Griner, *loc. cit.*, gives m. p. 87°).

Similarly the *cis*-diacetate (I) (4·8 g.) in carbon tetrachloride (10 c.c.) was treated with a solution of bromine (5 g.) in carbon tetrachloride (15 c.c.). Evaporation gave an oil which was distilled at 102—104°/6 × 10^{-4} mm., n_D^{17} 1·5020. The distillate largely solidified; the liquid expressed from the solid was again distilled but again the distillate partly solidified. The solid products crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 87—88°, undepressed on admixture with the *erythro*-dibromide (V).

Action of Potassium Acetate on the erythro-*Dibromide* (V).—The dibromide (3·3 g.) was heated under reflux with dry acetic acid (25 c.c.) and potassium acetate (5 g.) for 16 hours. Working up by the usual procedure gave erythritol tetra-acetate (2·6 g., 66%), m. p. and mixed m. p. 86—88°.

When similar quantities of reactants were heated in moist (95%) acetic acid a similar yield of erythritol tetra-acetate was obtained.

DL-*Erythrulose*.—The *erythro*-bromohydrin (15 g.) was dissolved in acetic acid (15 c.c.), and a solution of chromium trioxide (8 g.) in acetic acid (95%; 50 c.c.) added slowly with cooling and shaking. The solution was kept for 16 hours at room temperature and the acetic acid then evaporated at 25°/0·1 mm. Water was added to the residue, and the precipitated oil isolated by means of ether. Distillation gave 1 : 4-*diacetoxy*-2-*bromobutan*-3-*one* (10·1 g.), b. p. 100—102°/10^{-4} mm., n_D^{17} 1·4795. A similar yield of the identical product was obtained from the *threo*-bromohydrin (II) (Found: C, 35·8; H, 4·35. $C_8H_{11}O_5Br$ requires C, 36·0; H, 4·15%).

The bromo-ketone (5·6 g.), silver acetate (6 g.), and glacial acetic acid (50 c.c.) were heated under reflux for 6 hours. The cooled reaction mixture was filtered and the solids washed with a little acetic acid. The combined filtrates were reheated with a further quantity of silver acetate (6 g.) for 3 hours longer. The cooled solution was filtered and the filtrate evaporated under reduced pressure. The residual oil was dissolved in ether, and the solution filtered, evaporated, and distilled.

DL-*Erythrulose triacetate* was obtained as a pale yellow oil (3·3 g.), b. p. 108—110°/10^{-4} mm., n_D^{18} 1·4545 (Found: C, 48·25; H, 5·7. $C_{10}H_{14}O_7$ requires C, 48·75; H, 5·75%).

To an ice-cold filtered solution of barium hydroxide octahydrate (8 g.) in water (80 c.c.) was added the ketose triacetate (2·5 g.), and the mixture kept at 0° with occasional shaking for 90 minutes (cf. Wolfrom, Brown, and Evans, *J. Amer. Chem. Soc.*, 1943, **65**, 1026). The solution was saturated with carbon dioxide, and the resulting barium carbonate filtered off. Dilute sulphuric acid (4N.) was then carefully added until a slight excess was present. The barium sulphate was centrifuged off, and the solution evaporated under reduced pressure to one-quarter of its bulk. This solution was then passed through a column of "Bio-Deminrolit," and the effluent evaporated to dryness under reduced pressure. DL-Erythrulose was obtained as a viscous syrup (0·8 g.) which did not solidify; it was dissolved in a small quantity of water and heated with an excess of a solution of phenylhydrazine in 50% acetic acid. The precipitated brown solid was filtered off, dried on porous tile, and purified by crystallisation from benzene, from which the DL-erythrulose phenylosazone separated in yellowish-brown needles, m. p. 166—168° (Fenton and Jackson, *J.*, 1899, **75**, 8, record m. p. 167° for erythrosazone obtained from the ferrous–peroxide oxidation of erythritol) (Found: N, 18·4. Calc. for $C_{16}H_{18}O_2N_4$: N, 18·8%).

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