50. *The Synthesis of Pentaerythrose.*

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Pentaerythrose (trishydroxymethylacetaldehyde) has been obtained crystalline by two routes, one of which establishes its formation as an intermediate in the synthesis of pentaerythritol from acetaldehyde and formaldehyde in alkaline solution. The occurrence of pentaerythrose in a dimeric form in the solid state and in aqueous solution is discussed.

Pentaerythrose (I) has been postulated as an intermediate in the synthesis of pentaerythritol; it is assumed to be formed by three successive base-catalysed condensations of formaldehyde with acetaldehyde. This reaction is followed by a crossed Cannizzaro reaction to give pentaerythritol. Detection of pentaerythrose in this system has been claimed [1] and its preparation as a viscous liquid has been reported [2] when a weaker base, sodium carbonate, was used with the same reactants. Paper chromatography of the reaction mixture indicated that the latter method produced some pentaerythrose, together with other products.

During an investigation [3] of the course of pentaerythritol synthesis at 50—60°, portions of the reaction solution were removed at various times and, after demineralisation, were examined by paper chromatography. The products were identified by spraying the paper chromatograms with potassium periodatocuprate.[4] Unchanged starting materials were too volatile to be retained by this treatment. Other products, *i.e.*, formals and polypentaerythritols, were probably not detectable by the technique used.

Pentaerythritol (R_F 0·41) was found to be present after three minutes and a compound (R_F 0·52) was detected for up to 10-minutes' reaction time, with maximum formation after 3 minutes. The disappearance of this compound suggested it was a precursor of pentaerythritol. On reaction at 20°, pentaerythritol was detectable after 8 minutes while the unknown product was still present after 35 minutes. At 0°, pentaerythritol was not formed in the first hour, and the unknown product was detectable after 20 minutes and present, probably in a greater amount than pentaerythritol, after 2 hours. Using a much smaller quantity of sodium hydroxide at 0° gave other intermediates having still higher R_F values; these, together with the product of R_F 0·52, could be detected, unlike pentaerythritol, by means of 2,4-dinitrophenylhydrazine and thus were carbonyl compounds. No pentaerythritol was observed in the first 6 hours of the reaction and, although it was subsequently formed, all the intermediates were still present after 24 hours. The Cannizzaro reaction is evidently extremely slow under these conditions of low temperature and low sodium hydroxide concentration, and the main product is a compound of R_F 0·52.

This compound was isolated by demineralisation of the reaction mixture after 1 hour at 0°, removal of volatile constituents under diminished pressure, and separation on a Celite column. The column was developed with butan-1-ol saturated with water and the fractions containing only the component of R_F 0·52 were collected and concentrated. Crystals were deposited after a week. Recrystallisation gave a product with the empirical formula of pentaerythrose, $C_5H_{10}O_4$; a 2,4-dinitrophenylhydrazone of the correct composition was prepared from acidified dimethyl sulphoxide solution.

The infrared absorption spectrum of crystalline pentaerythrose in potassium bromide showed strong hydroxyl absorption at 3300 cm.$^{-1}$ and a very weak carbonyl absorption at 1730 cm.$^{-1}$. This virtual absence of carbonyl absorption is also found in 1,1,2-trishydroxymethylpropionaldehyde.[5] The abnormal depression of freezing point of camphor

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[1] Macleod, *Amer. Chem. J.*, 1907, **37**, 20.

[2] Fitsky, U.S.P. 2,275,586/1942.

[3] Bonner, Bourne, and Butler, *Chem. and Ind.*, 1961, 750.

[4] Bonner, *Chem. and Ind.*, 1960, 345.

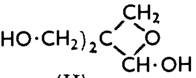
[5] Kuhn and Duckworth, *J. Org. Chem.*, 1959, **24**, 1005.

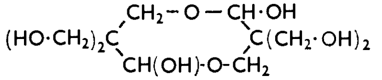
by pentaerythrose, corresponding to a molecular weight of 203 instead of the expected value of 134, suggested that the solute, in these conditions, existed wholly or partly in a hemiacetal form. The monomer (II) contains a strained ring, while the polymer (IV) would be unlikely either to be crystalline or to possess a sharp melting point. One probable hemiacetal form is the dimer (III) and models indicated the conformation (V) as the most stable. Another possible hemiacetal form is (VI). No decision can yet be made concerning which hemiacetal structure predominates.

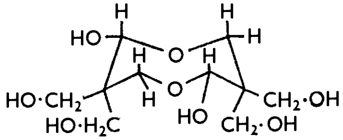
The nuclear magnetic resonance spectrum (see Table) in deuterium oxide and in dimethyl sulphoxide confirmed the presence of an aldehyde and a hemiacetal group. From the relative areas of the aldehyde- and methylenic-hydrogen peaks, it was concluded that in deuterium oxide the aldehyde form was present to the extent of about 25%, and that this proportion was slightly higher in dimethyl sulphoxide. Examination of the infrared spectrum of a 20—25% solution of pentaerythrose in deuterium oxide (calcium fluoride plates) revealed a strong carbonyl absorption at 1700 cm.$^{-1}$, and methine absorption at 2900 cm.$^{-1}$. The infrared spectrum of pentaerythrose in dimethyl sulphoxide (0·15 g./ml.), measured against a dimethyl sulphoxide control also showed the expected increase in carbonyl absorption at 1730 cm.$^{-1}$.

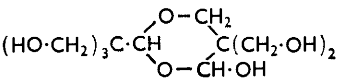
(I) $(HO{\cdot}CH_2)_3C{\cdot}CHO$

(IV) $[{\cdot}O{\cdot}CH_2{\cdot}C(CH_2{\cdot}OH)_2{\cdot}CH(OH){\cdot}]_n$


(II)


(III)


(V)


(VI)

It appears that in the crystalline state pentaerythrose is present almost entirely as a dimer, while in solutions of deuterium oxide and dimethyl sulphoxide it is present in the dimeric form to the extent of 70—75%.

Nuclear magnetic resonance spectra.

In deuterium oxide *		In dimethyl sulphoxide †	
Shift	Assignment	Shift	Assignment
6·31	Methylenic H in CH$_2$·OH	6·42 6·36	Methylenic H in CH$_2$·OH and CH$_2$·O
6·15	„ „ CH$_2$·O		
5·21	H in water and OH	5·88 5·36	Methine H in CH(OH)O and H in OH
4·95 4·81	Methine H in CH(OH)·O and possibly in CH(OH)$_2$		
0·23	H in CHO	0·28	H in CHO

Internal standards: * Bu^{t}OH, τ 8·78; † SiMe$_4$, τ 10·00.

An alternative synthesis of pentaerythrose was achieved by conversion of trishydroxymethylacetic acid into the acid chloride, followed by Rosenmund reduction; deacetylation with sodium methoxide in chloroform produced a detectable but not isolable product. Hydrolysis with dilute aqueous acid resulted in the formation of an amorphous white polymeric product (m. p. > 350°), whose formation was presumably due to traces of acid which remained after demineralisation. Hydrolysis was accomplished by heating an aqueous solution of the triacetate with a strong acid resin on a water-bath for several hours. After removal of the water by freeze-drying and trituration of the remaining syrup with butan-1-ol, a solid product slowly separated. Recrystallisation gave a product identical with the pentaerythrose isolated in the pentaerythritol reaction.

EXPERIMENTAL

Materials.—40% Aqueous formaldehyde and acetaldehyde were B.D.H. reagents. Trishydroxymethylacetic(β-hydroxy-αα-bishydroxymethylpropionic) acid was supplied by the Hercules Powder Co. and had m. p. 213—215° (lit.,[6] m. p. 210—213°).

Synthesis of Pentaerythrose.—(*a*) *Isolation during pentaerythritol preparation.* 40% Aqueous formaldehyde (15·5 ml.), acetaldehyde (2 ml.), sodium hydroxide (0·05 g.), and water (2 ml.) were allowed to react for 1 hr. at 0°. The reaction was stopped, the catalyst was removed by shaking the solution with Biodeminrolit (mixed-bed resin), and volatile constituents were removed under diminished pressure. The residual solution (*ca.* 15 ml.) was adsorbed on Celite (15 g.) and transferred to a Celite column (60 × 5 cm.) and the column was developed with water-saturated butan-1-ol. The flow rate was about 2 ml./min. and fractions of 25 ml. were collected and analysed on paper chromatograms with Whatman No. 1 paper and butan-1-ol–ethanol–water (40 : 11 : 19 v/v). Pentaerythrose was found free from other products in fractions 35—49. These were combined and the solvent was removed. The residue had R_F 0·52 (pentaerythritol, R_F 0·41) and was detected by potassium periodatocuprate, by 2,4-dinitrophenylhydrazine, by silver nitrate, and by *p*-anisidine hydrochloride reagents. A mixture of this residue and pentaerythritol was separated after running on paper in butanol–ethanol–water for 24 hr. After 1 week at room temperature crystals were deposited, having m. p. 127—129°. Recrystallisation from butan-1-ol gave material of m. p. 131—132·5°. Another specimen similarly obtained had m. p. 132—134° (Found: C, 44·95; H, 7·45. Calc. for $C_5H_{10}O_4$: C, 44·8; H, 7·5%).

Samples of pentaerythrose were subjected to the following reactions and the products examined by paper chromatography: (i) treatment with aqueous sodium hydroxide gave pentaerythritol and trishydroxymethylacetic acid by the Cannizzaro reaction; (ii) treatment with aqueous sodium hydroxide and formaldehyde gave pentaerythritol as the only detectable product; and (iii) reduction with potassium borohydride in water gave a small yield of pentaerythritol.

A solution of the product in dimethyl sulphoxide was added to one of 2,4-dinitrophenylhydrazine in dimethyl sulphoxide containing some aqueous hydrochloric acid. The original deep red colour changed slowly to yellow and after 3 days water was added. Yellow crystals of the *hydrazone* were deposited; recrystallised from water they had m. p. 197·5—198° (Found: C, 42·2; H, 4·6; N, 18·15. $C_{11}H_{14}N_4O_7$ requires C, 42·0; H, 4·5; N, 17·8%). A mixed m. p. with 2,4-dinitrophenylhydrazine was 170—190°.

(*b*) *Preparation from trishydroxymethylacetic acid.* Acetylation of trishydroxymethylacetic acid gave the triacetate, m. p. 85—88° (lit.,[7] 95°), which with thionyl chloride [7] gave trisacetoxymethylacetyl chloride, m. p. 72—74° (lit.,[7] 78°). The acid chloride (7·5 g.) was added to a suspension of palladium–barium sulphate (1·5 g.) in dry xylene (100 ml.) containing quinoline–sulphur " poison " (15 mg.).[8] Hydrogen was passed into the mixture with stirring for 15 min. then the mixture was heated at 140—150° and the reaction followed by absorbing in water the hydrogen chloride carried out by the hydrogen; the aqueous acid was titrated at intervals with N-sodium hydroxide. After 12 hr., analysis indicated that the amount of hydrogen chloride evolved corresponded to 96% conversion. The reaction mixture was allowed to cool to room temperature, the catalyst was removed by filtration through two sheets of Whatman No. 50 filter paper, and the solvent evaporated under diminished pressure. The residual oil crystallised, to give *trisacetoxymethylacetaldehyde* (5·8 g.), m. p. 40—42° (Found: C, 50·6; H, 5·9. $C_{11}H_{16}O_7$ requires C, 50·8; H, 6·2%).

A mixture of this aldehyde (3 g.), water (100 ml.), and Zeo-Karb 225 resin (5 g.) was heated on a boiling-water bath for 8 hr. with stirring, then cooled, filtered, and stirred with Biodeminrolit (to remove the acetic acid produced), and the water was removed by freeze-drying. A solution of the residue in methanol was filtered and evaporated, giving a syrup that on trituration with butan-1-ol solidified. The solid, m. p. 119—122°, recrystallised from butan-1-ol, to give pentaerythrose (0·5 g.), m. p. 127—128° (Found: C, 44·7; H, 7·4. Calc. for $C_5H_{10}O_4$: C, 44·8; H, 7·5%). The mixed m. p. with the sample obtained as in (*a*) was 128—132°, and

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[6] Heyns and Beck, *Chem. Ber.*, 1956, **89**, 1648.

[7] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.

[8] Mosettig and Mozingo, " Organic Reactions," John Wiley and Sons, Inc., New York, 1948, Vol. IV, p. 362.

the two compounds had the same R_F value and the same infrared spectrum in potassium bromide. The second sample gave a 2,4-dinitrophenylhydrazone, m. p. 191—192° [mixed m. p. with the 2,4-dinitrophenylhydrazone of pentaerythrose from (*a*) 193°].

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