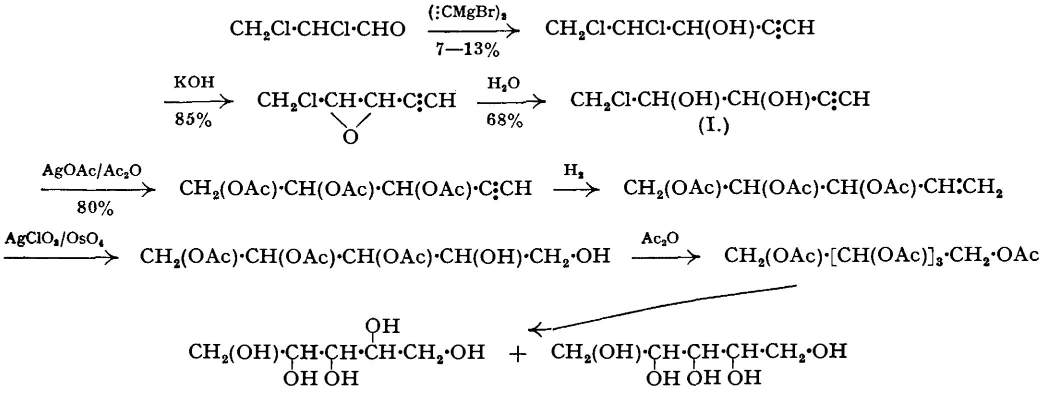
S 9. *Synthesis of Carbohydrates by Use of Acetylenic Precursors. Part I.* DL-erythro*Pent-4-yne-1 : 2 : 3-triol and its Conversion into* DL-*Arabitol and Ribitol.*

By R. A. Raphael.

The reaction of performic acid with the readily-available acetylenic alcohol, pent-2-en-4-yn-1-ol (IV) is shown to produce DL-*erythro*pent-4-yne-1 : 2 : 3-triol (V), the constitution and configuration of which are rigidly proved. The conversion of the triol into DL-arabitol and ribitol is demonstrated. The employment of *N*-bromosuccinimide in aqueous medium as an agent for the addition of the elements of hypobromous acid to a double bond is described.

The only recorded work envisaging the application of acetylenic compounds to the synthesis of sugars and their derivatives has been that of the French chemist Lespieau. In a number of papers published from 1928 to 1938 he described a series of experiments culminating in the successful synthesis of the hexitols, dulcitol and allitol (the latter hitherto unknown) and the pentitols, DL-arabitol (II), and ribitol (III). (Hexitol synthesis : Lespieau, *Compt. rend.*, 1921, **173**, 1367; 1927, **184**, 1329; 1930, **190**, 378; 1934, **198**, 183; *Bull. Soc. chim.*, 1928, **43**, 199; 1934, **1**, 1374. Pentitol synthesis : Lespieau, *Compt. rend.*, 1924, **179**, 1606; 1925, **181**, 557; 1936, **203**, 145; *Bull. Soc. chim.*, 1926, **39**, 991; 1928, **43**, 657; 1938, **5**, 1638. For summary see Lespieau, " Advances in Carbohydrate Chemistry," Vol. II, p. 107.)

The route adopted by Lespieau in the preparation of the pentitols may be briefly delineated as follows :



$$CH_2Cl{\cdot}CHCl{\cdot}CHO \xrightarrow[7-13\%]{(:CMgBr)_2} CH_2Cl{\cdot}CHCl{\cdot}CH(OH){\cdot}C{\vdots}CH$$

$$\xrightarrow[85\%]{KOH} CH_2Cl{\cdot}\underbrace{CH{\cdot}CH}_{O}{\cdot}C{\vdots}CH \xrightarrow[68\%]{H_2O} \underset{(I.)}{CH_2Cl{\cdot}CH(OH){\cdot}CH(OH){\cdot}C{\vdots}CH}$$

$$\xrightarrow[80\%]{AgOAc/Ac_2O} CH_2(OAc){\cdot}CH(OAc){\cdot}CH(OAc){\cdot}C{\vdots}CH \xrightarrow{H_2} CH_2(OAc){\cdot}CH(OAc){\cdot}CH(OAc){\cdot}CH{:}CH_2$$

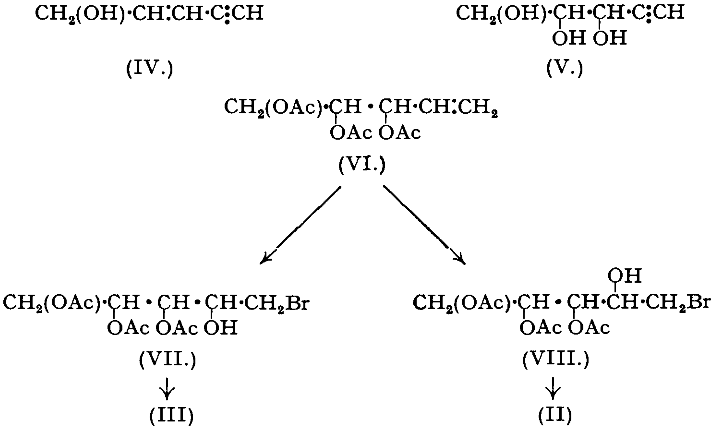
$$\xrightarrow{AgClO_3/OsO_4} CH_2(OAc){\cdot}CH(OAc){\cdot}CH(OAc){\cdot}CH(OH){\cdot}CH_2{\cdot}OH \xrightarrow{Ac_2O} CH_2(OAc){\cdot}[CH(OAc)]_3{\cdot}CH_2{\cdot}OAc$$

$$CH_2(OH){\cdot}\underset{OH}{CH}{\cdot}\underset{OH}{CH}{\cdot}\overset{OH}{CH}{\cdot}CH_2{\cdot}OH + CH_2(OH){\cdot}\underset{OH}{CH}{\cdot}\underset{OH}{CH}{\cdot}\underset{OH}{CH}{\cdot}CH_2{\cdot}OH$$

(II.) (III.)

The monochlorohydrin (I) was a pure, sharply-melting racemate and, since it gave rise to DL-arabitol and ribitol only, with no detectable amount of xylitol, Lespieau concluded that it possessed the *erythro*-configuration. As is seen, the route is long and difficult and it is doubtless this factor that has deterred other workers from employing similar methods.

With the advent of a convenient preparation of the acetylenic carbinol, pent-2-en-4-yn-1-ol (IV) (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583) a new approach to the problem immediately presented itself. It has been shown that the triple bond is remarkably resistant to the action of peracids and that a conjugated enyne under these conditions is attacked at the double bond only (Malenok and Sologub, *J. Gen. Chem. Russia*, 1936, **6**, 1904; 1940, **10**, 150; 1941, **11**, 983; Malenok, *ibid.*, 1939, **9**, 1947). Accordingly, pent-2-en-4-yn-1-ol was subjected to the action of the conveniently-prepared performic acid (Swern, Billen, Findley,. and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786); a smooth reaction took place with the formation of the *monoformate* of DL-*erythro*pent-4-yne-1 : 2 : 3-triol, steam distillation of which yielded the free triol (*tribenzoate*, trisphenylurethane) as a viscous, water-soluble liquid. The constitution of the triol was confirmed by fission with sodium periodate whereby propargylaldehyde (2 : 4-*dinitrophenylhydrazone*), formic acid, and formaldehyde were obtained. The stereochemical configuration of the compound was demonstrated in two ways; ozonolysis led to the formation of DL-erythronic acid (isolated as its phenylhydrazide), whilst oxidative degradation with nitric acid produced *meso*tartaric acid (characterised as its dimethyl ester and diamide).



$$\underset{(IV.)}{CH_2(OH){\cdot}CH{:}CH{\cdot}C{\vdots}CH} \qquad \underset{(V.)}{CH_2(OH){\cdot}\underset{OH}{CH}{\cdot}\underset{OH}{CH}{\cdot}C{\vdots}CH}$$

$$\underset{(VI.)}{CH_2(OAc){\cdot}\underset{OAc}{CH}\cdot\underset{OAc}{CH}{\cdot}CH{:}CH_2}$$

$$\underset{(VII.)}{CH_2(OAc){\cdot}\underset{OAc}{CH}\cdot\underset{OAc}{CH}\cdot\underset{OH}{CH}{\cdot}CH_2Br} \rightarrow (III) \qquad \underset{(VIII.)}{CH_2(OAc){\cdot}\underset{OAc}{CH}\cdot\underset{OAc}{CH}{\cdot}\overset{OH}{CH}{\cdot}CH_2Br} \rightarrow (II)$$

The production of an *erythro*-compound from pent-2-en-4-yn-1-ol (which almost certainly possesses the *trans*-configuration) by means of performic acid is a further example of the theoretically derived rule that *trans*-addition to a *trans*-double bond or *cis*-addition to a *cis*-double bond leads to a product with the *erythro*-spatial arrangement of the added groups, while *trans*-addition to a *cis*-double bond or *cis*-addition to a *trans*-double bond produces a compound with the *threo*-configuration. The validity of this conception is borne out by a great deal of experimental work (see below). Among the addenda to double bonds giving rise to *trans*-addition may be numbered the halogens (McKenzie, *J.*, 1912, **101**, 1196; Frankland, *J.*, 1912, **101**, 678; Terry and Eichelberger, *J. Amer. Chem. Soc.*, 1925, **47**, 1067; Roberts and Kimball, *ibid.*, 1937, **59**, 947; Lucas and Gould, *ibid.*, 1941, **63**, 2541; Prévost and Valette, *Compt. rend.*, 1946, **222**, 326), hypohalous acids (Swern, *J. Amer. Chem. Soc.*, 1948, **70**, 1235), peracids followed by fission of the epoxide ring produced (the actual epoxide formation involves a *cis*-addition but many authors have demonstrated that, with the breaking of the ring, inversion of configuration on one of the carbon atoms invariably occurs; the net effect, therefore, is that of a *trans*-addition) (King, *J.*, 1942, 387; 1943, 37; Swern, *loc. cit.*, references 6, 7, 8, 9), and the iodine–silver benzoate complex (Wittcoff and Miller, *J. Amer. Chem. Soc.*, 1947, **69**, 3138). Those producing *cis*-addition include alkaline potassium permanganate (*inter al.*, Böeseken, *Rec. Trav. chim.*, 1922, **41**, 199; Hunsdiecker, *Ber.*, 1944, **77**, 185; Prévost and Valette, *loc. cit.*), osmium tetroxide (Böeseken, *loc. cit.*; Criegee, *Annalen*, 1936, **522**, 75), osmium tetroxide-catalysed metal chlorates (Milas and Terry, *J. Amer. Chem. Soc.*, 1925, **47**, 1412; Glattfeld and Woodruff, *ibid.*, 1927, **49**, 2309; Braun, *ibid.*, 1929, **51**, 228), osmium tetroxide-, vanadium pentoxide-, and chromium trioxide-catalysed *tert.*-butyl hydroperoxide (Milas and co-workers, *ibid.*, 1936, **58**, 1302; 1937, **59**, 543, 2342, 2345; 1939, **61**, 1844), and hydrogen peroxide in the presence of ultra-violet light (Milas, Kurz, and Anslow, *ibid.*, 1937, **59**, 543).

Lespieau (*Bull. Soc. chim.*, 1928, **43**, 657) obtained a pentynetriol by hydrolysis of the monochlorohydrin (I) with an aqueous suspension of calcium carbonate. He made no speculation as to its configuration but the close correlation of its properties and the properties of its derivatives with those of the triol (V), obtained in the manner described above leaves little doubt that the two are identical.

Treatment of the triol (V) with acetic anhydride gave the corresponding triacetate as a distillable liquid solidifying on standing to a crystalline mass melting sharply at 53°; the physical constants of the liquid agreed with those recorded by Lespieau but he did not succeed in inducing crystallisation. Semihydrogenation of the acetylenic triacetate employing palladium–calcium carbonate as catalyst furnished a good yield of the corresponding ethylenic compound (VI). The double bond of this latter substance was remarkably resistant to additive reagents. Thus perbenzoic acid, perphthalic acid, *tert.*-butyl hydroperoxide, and the iodine–silver benzoate complex had practically no effect, while performic and peracetic acids gave small yields of impure products. The comparative inertness of terminal double bonds towards peracids has been noted by many workers (Böeseken and Blumberger, *Rec. Trav. chim.*, 1925, **44**, 90; Meerwein, Ogait, Prang, and Serini, *J. pr. Chem.*, 1926, **113**, 9; Stuurman, *Proc. Acad. Sci. Amsterdam*, 1935, **38**, 450; Findley, Swern, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 412; Swern, Billen, and Scanlan, *ibid.*, 1946, **68**, 1504) and a theoretical explanation has recently been proposed (Swern, *ibid.*, 1947, **69**, 1692). Lespieau (*loc. cit.*) employed osmium tetroxide-catalysed silver chlorate to effect the hydroxylation, but the method is tedious and inconvenient, a reaction time of three months being required.

Recourse was then had to a method widely used in the sterol field, namely reaction of the unsaturated compound with an aqueous solution of *N*-bromoacetamide; this has the effect of adding the elements of hypobromous acid across the double bond (*inter al.*, Schmidt, Knilling, and Ascherl, *Ber.*, 1926, **59**, 1279; Salamon and Reichstein, *Helv. Chim. Acta*, 1947, **30**, 1616). As *N*-bromoacetamide is rather inconvenient to prepare it was felt that the readily-available *N*-bromosuccinimide might well replace it in this reaction. Such proved to be the case; on shaking an aqueous suspension of (VI) with *N*-bromosuccinimide an excellent yield of a mixture of two racemic bromohydrins was obtained. The reaction was conveniently followed by the rate of dissolution of the *N*-bromosuccimide. Crystallisation of one of the racemates greatly facilitated their separation, the solid bromohydrin, m. p. 110—111°, being easily isolated by virtue of its insolubility in dry ether. Treatment of the solid with a solution of potassium acetate in glacial acetic acid–acetic anhydride furnished a viscous pentitol penta-acetate which was hydrolysed with methanolic hydrogen chloride to yield crystalline ribitol; further characterisation was provided by the preparation of the dibenzylidene derivative.

The ether-soluble liquid bromohydrin was readily purified by high-vacuum distillation; acetylation by means of the above mixture gave a good yield of the crystalline DL-arabitol penta-acetate. Alcoholysis, employing a catalytic amount of sodium methoxide in methanol, produced crystalline DL-arabitol in 45% yield.

EXPERIMENTAL.

DL-erythro*Pent-4-yne-*1 : 2 : 3-*triol* (V).—A solution of pent-2-en-4-yn-1-ol (IV) (50 g.) in formic acid (98%; 300 c.c.) was treated with hydrogen peroxide (100 vol.; 90 g.) added in one portion. The initially-purple mixture slowly decolorised and its temperature slowly rose to 50° at which point it was maintained by external cooling. After 16 hours the solution was evaporated under reduced pressure and the residual liquid distilled in a vacuum. The triol *monoformate* (59 g.) distilled as a mobile liquid, b. p. 108—110°/0·1 mm., $n_{\mathrm{D}}^{13^\circ}$ 1·4800; the ester was rapidly hydrolysed by water, even moist air sufficing to produce an acrid odour of formic acid in a very short time. For this reason the analyses were inaccurate (Found: C, 49·0; H, 5·3. $C_6H_8O_4$ requires C, 50·0; H, 5·55%).

The monoformate was steam distilled until the distillate was no longer acid to litmus. The distilland was evaporated under reduced pressure and the viscous residue fractionated in a vacuum. The triol (V) (42 g.; 59%) was obtained as a viscous pale-yellow liquid, b. p. 120—122°/0·1 mm., $n_{\mathrm{D}}^{14^\circ}$ 1·5000 (Lespieau, *Bull. Soc. chim.*, 1928, **43**, 657, gives b. p. 156—159°/4 mm., $n_{\mathrm{D}}^{25^\circ}$ 1·489) (Found: C, 52·0; H, 6·9. Calc. for $C_5H_8O_3$: C, 51·7; H, 6·95%).

The trisphenylurethane of the triol exhibited a curious melting-point phenomenon. The first crystallisation from alcohol yielded a product, m. p. 201—205° (Lespieau, *loc. cit.*, gives m. p. 204—206°), but on further crystallisation the derivative formed needles, m. p. 178—180° (Found: C, 66·0; H, 4·5; N, 9·1. Calc. for $C_{26}H_{23}O_6N_3$: C, 66·0; H, 4·85; N, 8·9%). The *tribenzoate* crystallised in rosettes from light petroleum (b. p. 80—100°) or alcohol; it melted first at 110° then resolidified and remelted at 118—119° (Found: C, 72·7; H, 4·6. $C_{26}H_{20}O_6$ requires C, 72·9; H, 4·7%).

Action of Sodium Metaperiodate on Triol (V).—(*a*) A solution of the triol (1·16 g.) in water (25 c.c.) was treated slowly with sodium metaperiodate (4·3 g.) in water (50 c.c.). After 16 hours at room temperature the mixture was steam distilled and the first 300 c.c. of the distillate treated with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate. The filtered, washed, and dried precipitate (3·4 g.; theory, 4·5 g.) was dissolved in benzene and chromatographed on alumina using benzene as the developing solvent; an upper brown and a lower yellow band were formed. Rather unexpectedly, elution of the *lower* band gave *propargylaldehyde* 2 : 4-*dinitrophenylhydrazone*, crystallising from alcohol in glistening orange-yellow needles, m. p. 121—122°, undepressed on admixture with an authentic specimen (Found: N, 23·8. $C_9H_6O_4N_4$ requires N, 23·95%). The upper band on elution yielded formaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 166—167°.

(*b*) To estimate the formic acid produced the method of Halsall, Hirst, and Jones (*J.*, 1947, 1427) was used. The triol (252 mg.) was dissolved in distilled water (100 c.c.) and sodium metaperiodate solution (20 c.c.; 0·2M) added. After 24 hours at room temperature ethylene glycol (250 mg.) was added and the solution titrated with 0·1N-NaOH using methyl-red as indicator; the volume used (19·8 c.c.) indicated the formation of 0·91 mol. of formic acid.

Ozonolysis of Triol (V).—The triol (2·3 g.) was dissolved in water (20 c.c.) and ozonised oxygen was passed through the solution for 72 hours. The solution was evaporated to dryness under reduced pressure and the residual viscous liquid dissolved in methanol (10 c.c.); phenylhydrazine (2·3 g.) was then added and the mixture allowed to stand for 16 hours at room temperature. The crystalline material formed (120 mg.) was filtered off and crystallised from methanol, forming plates, m. p. 175—176° (decomp.); the nature of this material was not further investigated. The filtrate was then treated with ethyl acetate until no more yellow solid was precipitated; the crude phenylhydrazide (2·59 g.; 58%) melted at 133—145°. Crystallisation from nitroethane yielded colourless prisms, m. p. 145—146° (Glattfeld and Hoen, *J. Amer. Chem. Soc.*, 1935, **57**, 1407, give m. p. 147·5° for DL-erythronic phenylhydrazide).

Nitric Acid Oxidation of Triol (V).—The triol (3 g.) was treated with nitric acid (*d* 1·2; 40 c.c.) and kept at 50—55° for 72 hours. The solution was evaporated to dryness under reduced pressure and then warmed with a little methanol to destroy any residual nitric acid. The residue was refluxed for 16 hours with methanolic hydrogen chloride (50 c.c.; 5%); the hydrogen chloride was removed with silver carbonate, the filtrate evaporated to dryness and the residual liquid distilled in a vacuum. The distillate (530 mg.), b. p. 145—160° (bath temp.)/0·01 mm., rapidly solidified; crystallisation from chloroform yielded needles of dimethyl *meso*tartrate, m. p. and mixed m. p. 113—114° (Heslop and Smith, *J.*, 1944, 582, give m. p. 114°). Treatment with alcoholic ammonia gave *meso*tartaric diamide, prisms, m. p. 184° (decomp.), from aqueous alcohol [Heslop and Smith, *loc. cit.*, give m. p. 184° (decomp.)].

DL-erythro*Pent-4-yne-*1 : 2 : 3-*triol Triacetate.*—The triol (V) (12 g.) was refluxed with acetic anhydride (50 g.) and anhydrous potassium acetate (1 g.) for three hours. The hot solution was poured into water and the precipitated oil isolated by means of ether. Distillation furnished the triacetate as a colourless, mobile liquid (20·2 g.; 81%), b. p. 120°/0·8 mm., $n_{\mathrm{D}}^{18^\circ}$ 1·4525 (Lespieau, *Bull. Soc. chim.*, 1938, **5**, 1638, gives 149·5—150°/9 mm., $n_{\mathrm{D}}^{25\cdot5^\circ}$ 1·4445). On standing, the ester set to a solid mass; crystallisation from a large volume of light petroleum (b. p. 60—80°) gave prisms, m. p. 52—53° (Found: C, 54·9, 54·65; H, 5·85, 6·1. Calc. for $C_{11}H_{14}O_6$: C, 54·55; H, 5·8%).

DL-erythro*Pent-4-ene-*1 : 2 : 3-*triol Triacetate* (VI).—The acetylenic triacetate (6 g.) was dissolved in ethyl acetate (50 c.c.) and the solution shaken with hydrogen at atmospheric pressure in the presence of palladium–calcium carbonate catalyst (200 mg.; 5%) until 1 mol. of hydrogen had been absorbed. Filtration, evaporation, and distillation furnished the *pentene-triol triacetate* as a colourless, mobile liquid (5·3 g.; 88%), b. p. 143—144°/11 mm., 86—88°/0·2 mm., $n_{\mathrm{D}}^{17^\circ}$ 1·4422 (Lespieau, *loc. cit.*, gives b. p. 148—149°/14 mm., $n_{\mathrm{D}}^{18\cdot5^\circ}$ 1·4418, but no analysis) (Found: C, 53·75; H, 6·3. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%).

Full hydrogenation, employing platinic oxide as catalyst yielded DL-erythro*pentane-*1 : 2 : 3-*triol triacetate*, b. p. 75—76°/0·1 mm., $n_{\mathrm{D}}^{20^\circ}$ 1·4285 (Found: C, 53·95; H, 7·25. $C_{11}H_{18}O_6$ requires C, 53·65; H, 7·35%).

Action of Aqueous N-*Bromosuccinimide on Triacetate* (VI).—The ethylenic triacetate (VI) (3·9 g.), freshly crystallised, finely-powdered *N*-bromosuccinimide (3·9 g.; 1 mol.), and water (50 c.c.) containing a few drops of glacial acetic acid were shaken at room temperature for 16 hours. Extraction with ether followed by washings with sodium metabisulphite solution, sodium hydrogen carbonate solution, and water yielded, after drying ($MgSO_4$) and evaporation, an oil which partly solidified on standing. Separation was easily effected by trituration with cold, dry ether, in which the solid was sparingly soluble. The solid *bromohydrin* (VII) (1 g.; 19%) crystallised from light petroleum (b. p. 80—100°) in sheaves of needles, m. p. 110—111°, with preliminary sintering at 103° (Found: C, 39·2; H, 4·95. $C_{11}H_{17}O_7Br$ requires C, 39·5; H, 4·9%). Evaporation of the ether washings and distillation furnished the liquid *bromohydrin* (VIII) (3·1 g.; 57%), b. p. 150° (bath temp.)/10^{-5} mm., $n_D^{20°}$ 1·4730 (Found: C, 38·7, 38·8; H, 5·0, 4·7. $C_{11}H_{17}O_7Br$ requires C, 39·5; H, 4·9%).

DL-*Arabitol* (II).—The liquid bromohydrin (VIII) (2·5 g.) was refluxed with glacial acetic acid (25 c.c.), acetic anhydride (5 c.c.), and anhydrous potassium acetate (2·5 g.) for 16 hours. The acetic acid and excess anhydride were removed under reduced pressure and the residue poured into water. Isolation by means of ether furnished an oil which rapidly solidified. Crystallisation from light petroleum (b. p. 80—100°) gave prisms, m. p. 97—98° (1·8 g.; 68%) (Lespieau, *loc. cit.*, gives m. p. 96—96·5° for DL-arabitol penta-acetate) (Found: C, 49·95; H, 6·35. Calc. for $C_{15}H_{22}O_{10}$: C, 49·7; H, 6·1%). The penta-acetate (1 g.) was dissolved in dry methanol (10 c.c.) containing a trace of sodium methoxide (from Na, 10 mg.) and the solution refluxed for 3 hours. The mixture was evaporated to half its bulk and allowed to stand overnight. The crystals separating were filtered off (190 mg.; 45%) and recrystallised from alcohol in prisms, m. p. 105° (Ruff, *Ber.*, 1899, **32**, 550, gives m. p. 104—105° for DL-arabitol) (Found: C, 39·65; H, 8·45. Calc. for $C_5H_{12}O_5$: C, 39·5; H, 7·95%).

Ribitol (III).—The solid bromohydrin (VII) (1 g.) was refluxed with glacial acetic acid (10 c.c.), acetic anhydride (1 c.c.), and potassium acetate (1 g.) for 16 hours. The solvents were evaporated under reduced pressure and the residue treated with water. Isolation by means of ether gave an oil which did not crystallise. This crude penta-acetate was dissolved in methanolic hydrogen chloride (10 c.c.; 3%) and the solution refluxed for 5 hours. The reaction mixture was evaporated to dryness and the residual syrup allowed to stand in a vacuum desiccator over solid potassium hydroxide. After 4 days it solidified; crystallisation from alcohol gave needles, m. p. 101—102° (110 mg.; 24%) (Fischer, *Ber.*, 1893, **26**, 633, gives m. p. 102° for ribitol) (Found: C, 39·6; H, 8·35. Calc. for $C_5H_{12}O_5$: C, 39·5; H, 7·95%). The dibenzylidene derivative, prepared in the manner described by Fischer (*loc. cit.*), crystallised from light petroleum (b. p. 80—100°) as a mass of felted needles, m. p. 164—165° (Fischer, *loc. cit.*, gives m. p. 164—165° for dibenzylideneribitol).

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