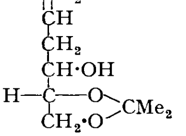
610. *A Synthesis of 2-Deoxy-*D*-ribose.*

By L. Hough.

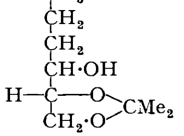
Allylmagnesium bromide and 2 : 3-*O*-*iso*propylidene-D-glyceraldehyde give 1 : 2-*iso*propylidenedioxyhex-5-en-3-ol, apparently containing largely the *erythro*-isomer. Hydroxylation of this, followed by periodate oxidation and hydrolysis, gave 2-deoxy-D-ribose, isolated *via* the aniline derivative in poor overall yield (cf. *Chem. and Ind.*, 1951, 406).

Fischer (*Ber.*, 1914, **47**, 186) described the first synthesis of 2-deoxy-D-ribose from D-arabinal, albeit the yield was poor, and the method has been re-investigated by other workers (Meischeimer and Jung, *Ber.*, 1927, **60**, 1462; Levene and Mori, *J. Biol. Chem.*, 1929, **83**, 803; Levene, Mikeska, and Mori, *ibid.*, 1930, **85**, 785; Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836; Ohta and Makino, *Science*, 1951, **113**, 273). Attempts to prepare this sugar in improved yield showed that methyl 2 : 3-anhydro-β-D-riboside with hydrogen bromide (Kent, Stacey, and Wiggins, *J.*, 1949, 1232), hydrogen chloride, or lithium aluminium hydride (Allerton and Overend, *J.*, 1951, 1480) gives mainly derivatives of 3-deoxy-D-xylose rather than of 2-deoxy-D-ribose. Similar results were obtained in the L-series by Mukherjee and Todd (*J.*, 1947, 969). A novel synthesis involving condensation of D-erythrose with nitromethane was described by Overend, Stacey, and Wiggins (*J.*, 1949, 1358) and by Sowden (*J. Amer. Chem. Soc.*, 1949, **71**, 1897; 1950, **72**, 808; *Adv. Carbohydrate Chem.*, 1951, **6**, 315), the last author claiming an improved overall yield. Recently, Matsushima and Imanaga have synthesised 2-deoxy-D-ribose from D-ribulose through the 2-amino-2-deoxypentitol, the overall yield being about 3% (*Nature*, 1953, **171**, 475). Overend and Stacey (*J. Sci. Food Agric.*, 1950, **1**, 168) have reviewed the methods available for the synthesis of 2-deoxy-D-ribose and its derivatives and the difficulties involved.

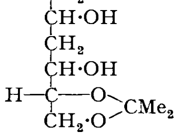
This communication is concerned with a synthesis of 2-deoxy-D-ribose from 2 : 3-*O*-*iso*propylidene-D-glyceraldehyde and allylmagnesium bromide. The condensation, in ether, gave syrupy 1 : 2-*iso*propylidenedioxyhex-5-en-3-ol (I); on catalytic hydrogenation this gave (II), which after hydrolysis yielded a crystalline 1 : 2 : 3-trideoxyhexitol in high yield, thus suggesting asymmetric synthesis in the Grignard reaction. Since 2-deoxy-D-ribose was finally obtained it seems probable that (II) has the D-*erythro*-configuration and that (I) contains largely the D-*erythro*-isomer. Hydroxylation of (I) by means of hydrogen peroxide in the presence of *tert.*-butanol and osmium tetroxide gave a mixture from which syrupy 3-deoxy-5 : 6-*O*-*iso*propylidenehexitol (III) was isolated in low yield. Raphael (*J.*, 1949, 544) has indicated the difficulty of hydroxylating terminal double bonds. Periodate oxidation of (III), followed by hydrolysis afforded a syrup which gave positive tests for 2-deoxypentose; paper chromatography suggested the presence of mainly 2-deoxyribose



(I)



(II)



(III)

with a little 2-deoxyxylose. The syrup gave a crystalline aniline derivative, identical with 2-deoxy-*N*-phenyl-D-ribosylamine, from which 2-deoxy-D-ribose was isolated. The poor overall yield renders the synthesis, in its present form, valueless as a preparative method.

EXPERIMENTAL

Unless stated otherwise, distillations were under reduced pressure, paper chromatography was performed at 17° on Whatman No. 1 filter paper with *n*-butanol–ethanol–water (4 : 1 : 5 v/v) as mobile phase, and ammoniacal silver nitrate was used for the detection of polyhydric compounds on paper chromatograms (Hough, *loc. cit.*).

1 : 2-iso*Propylidenedioxyhex-5-en-3-ol.*—Allylmagnesium bromide was formed as described by Gilman and McGlumphy (*Bull. Soc. chim.*, 1928, **43**, 1322; see also Henze, Allen, and Leslie, *J. Org. Chem.*, 1942, **7**, 326) by slow addition of dry, redistilled allyl bromide (15·7 g.) to magnesium (15 g.) in dry ether (300 c.c.). The ethereal solution was rapidly filtered through a cotton-wool plug and to the filtrate was added an ethereal solution (50 c.c.) of freshly distilled 1 : 2-*O*-*iso*-propylidene-D-glyceraldehyde (Baer and Fischer, *J. Biol. Chem.*, 1939, **128**, 463) (8·3 g.). After 1 hour's stirring, ice and water (*ca.* 250 c.c.) were added, followed by 0·5N-sulphuric acid, dropwise with vigorous shaking, until the solution was faintly acid. The ethereal layer was separated, the aqueous phase was extracted with ether (2 × 250 c.c.), and the combined ethereal extracts were dried (Na_2CO_3) and evaporated, to give a pale yellow liquid (10·1 g.), n_D^{15} 1·4520 (Found: C, 62·9; H, 9·3. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). Hydrolysis of a portion (2·56 g.) with 0·1N-sulphuric acid for 1 hr. at 95—100°, followed by neutralisation with barium carbonate and evaporation, gave syrupy *hex-5-ene-*1 : 2 : 3-*triol* (1·72 g.), n_D^{20} 1·4835, $[\alpha]_D^{17}$ +4° (*c*, 2·46 in $CHCl_3$) (Found: C, 54·4; H, 9·0. $C_6H_{12}O_3$ requires C, 54·5; H, 9·1%). On oxidation with sodium metaperiodate, this consumed 2 mols. of periodate, forming one mol. of formic acid. It travelled as a single round spot (R_F 0·72) on the paper chromatogram.

Hydrogenation of the syrupy *iso*propylidenedioxy-compound (0·43 g.) in methanol (20 c.c.) in the presence of Adams platinum catalyst (0·02 g.) at room temperature was complete in 5 hr. (1·06 H_2 consumed). The mixture was evaporated to a viscous syrup (0·48 g.), $[\alpha]_D^{17}$ +4° (*c*, 1·9 in H_2O). A portion (0·29 g.) was hydrolysed in 0·1N-sulphuric acid (15 c.c.) at 95—100° for 1 hr. and the mixture was neutralised with barium carbonate, filtered, and evaporated to a syrup, 1 : 2 : 3-*trideoxyhexitol* (0·22 g.), which crystallised spontaneously. The crystals, isolated on a tile and then recrystallised from ethanol, had m. p. 82°, $[\alpha]_D^{17}$ −4·5° (*c*, 1·8 in H_2O) (Found: C, 53·7; H, 10·4. $C_6H_{14}O_3$ requires C, 53·7; H, 10·4%). It gave one discrete spot (R_F 0·76) on the paper chromatogram.

3-*Deoxy*-5 : 6-O-iso*propylidenehexitol* (III).—1 : 2-*iso*Propylidenedioxyhex-5-en-3-ol (I) (2·79 g.) was dissolved in *tert.*-butanol (30 c.c.), cooled to 0°, and mixed with a 0·5% solution of osmium tetroxide in *tert.*-butanol (1 c.c.). A 6·4% solution of hydrogen peroxide in *tert.*-butanol (10 c.c.) was added dropwise and the whole stored at 0° for 18 hr. (cf. Hackett, Sapp, and Millman, *J. Amer. Chem. Soc.*, 1941, **63**, 2051). The solution was evaporated in the presence of a little potassium carbonate, the residue was extracted with acetone (3 × 50 c.c.), and the extracts were evaporated to a dark brown syrup (3·16 g.). Paper chromatography showed it to be a mixture of at least four components (R_F 0·85, 0·77, 0·66, and 0·03). Chromatography on a cellulose column with *n*-butanol–light petroleum (b. p. 80—100°) (40 : 60 v/v) as mobile phase (Hough, Jones, and Wadman, *J.*, 1950, 1702) gave a syrupy mixture of 3-deoxy-5 : 6-*O*-*iso*-propylidenehexitols {R_F 0·77 and 0·66; 0·602 g.; $[\alpha]_D$ 0° (*c*, 3·4 in H_2O)} (Found: C, 52·6; H, 8·5. Calc. for $C_9H_{18}O_5$: C, 52·4; H, 8·7%). Examination on the paper chromatogram of the hydrolysis products of a little of the foregoing syrup revealed only one spot corresponding in position to that occupied by deoxyhexitols (R_F 0·26).

2-*Deoxy*-D-*ribose.*—The deoxy-*O*-*iso*propylidenehexitols (III) (0·6 g.) were oxidised with sodium metaperiodate (20 c.c.; 0·17M) in a phosphate buffer (pH 7·4; 25 c.c.) at room temperature in the dark. After 2 hr., the solution was extracted with chloroform (3 × 75 c.c.), and the extract dried (K_2CO_3), filtered, and evaporated, to give a pale yellow syrup {0·34 g.; $[\alpha]_D^{17}$ −1° (*c*, 0·93 in H_2O)}. A portion (0·185 g.) was hydrolysed in 0·01N-sulphuric acid (25 c.c.) at 100° for 1 hr., whereafter $[\alpha]_D$ was constant (−19°). The solution was neutralised with barium carbonate, filtered, and evaporated to a syrup {0·134 g.; $[\alpha]_D^{17}$ −24·5° (*c*, 1·34 in H_2O)}, which gave positive tests for 2-deoxypentose with the Dische reagent (Dische, *Microchem. Acta*, 1930, **8**, 4; Deriaz, Stacey, Teece, and Wiggins, *J.*, 1949, 1222; Overend, Shafidazeh, and Stacey, *J.*, 1950, 1027) and the Feulgen reagent (Feulgen, *Z. phys. Chem.*, 1923, **128**, 154;

1924, **135**, 203; Overend, *J.*, 1950, 2769). On the paper chromatogram it gave two spots corresponding to 2-deoxyribose (R_F 0·32, strong spot) and 2-deoxyxylose (R_F 0·36, weak spot).

After 5 hours' heating under reflux with alcoholic aniline (3·5%; 3 c.c.), the syrup (0·13 g.) gave 2-deoxy-*N*-phenylribosylamine (m. p. 161°) which on recrystallisation thrice from alcohol–ether had m. p. and mixed m. p. 171—172°, $[\alpha]_D^{17}$ +164° (*c*, 0·5 in pyridine; 10 min.) ⟶ + 64° (20 hr., const.) (63 mg.) (Found: C, 63·2; H, 6·9; N, 7·0. Calc. for $C_{11}H_{15}O_3N$: C, 63·2; H, 7·2; N, 6·7%). An *X*-ray powder photograph of the crystals was identical with that of an authentic specimen.

Hydrolysis of the aniline derivative (0·18 g.) (Overend, Stacey, and Wiggins, *J.*, 1949, 1358) gave a syrup {48 mg.; $[\alpha]_D$ −49° (*c*, 2·1)} which gave only one spot corresponding to 2-deoxyribose on the paper chromatogram; crystallised from *iso*propanol, it had m. p. 83—85°, $[\alpha]_D^{17}$ −55° (*c*, 0·96 in H_2O).

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