249. *The Chemistry of* D-*Ribose and its Derivatives. Part VI.** iso*Propylidene and Benzylidene Derivatives.*

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The properties of *O*-*iso*propylideneribose anhydride are consistent with the structure proposed by Levene and Stiller. Condensation of ribose with benzaldehyde yields 2 : 3-*O*-benzylidene-D-ribose and what is believed to be 1 : 5-2 : 3-di-*O*-benzylidene-D-ribose. No anhydride is formed. Similarly 2 : 3-*O*-*iso*propylidene-D-ribose and benzaldehyde yield 1 : 5-*O*-benzylidene-2 : 3-*O*-*iso*propylidene-D-ribose. The difference in the course of the reactions with acetone and benzaldehyde is attributed to steric factors.

Condensation of D-ribose with acetone leads to 2 : 3-*O*-*iso*propylidene-D-ribose and an *iso*propylideneribose anhydride which was formulated by Levene and Stiller as 1 : 5-anhydro-2 : 3-*O*-*iso*propylidene-D-ribofuranose.[1] No rigorous proof of the constitution of this anhydride was offered but the molecular weight, determined in boiling benzene, was in agreement with the proposed structure. Since we had previously found that the diacetyl anhydride of ribose was dimeric,[2] as opposed to the structure originally proposed,[3] it seemed possible that the *iso*propylideneribose anhydride might be dimeric and that it decomposed in boiling benzene. We have prepared the latter anhydride by an improved method and have redetermined its molecular weight by depression of the freezing point of benzene and by isothermal distillation.[4] These measurements confirmed the monomeric nature of the material and we have therefore sought chemical evidence to support the bicyclic system proposed by Levene and Stiller.

Since hydrolytic conditions which are sufficient to remove the *iso*propylidene residue also destroy the anhydride structure, it was decided to attempt to prepare the analogous 2 : 3-*O*-benzylideneribose anhydride and to remove the benzylidene residue by hydrogenolysis. However, condensation of ribose with benzaldehyde yielded no anhydride but a mono- and a di-*O*-benzylidene-D-ribose. The former we designate as 2 : 3-*O*-benzylidene-D-ribose, since it reduces Fehling's solution and on methylation and hydrolysis yields 5-*O*-methyl-D-ribose. It is not oxidised by sodium metaperiodate in 50% aqueous dioxan, and, since it gives rise to 5-*O*-methyl-D-ribose, appears to exist in the furanose form. The same may be said of 2 : 3-*O*-*iso*propylidene-D-ribose which we find is also resistant to sodium metaperiodate and yields 5-*O*-methyl-D-ribose. It is of interest that 2 : 3-di-*O*-methyl-D-ribose is exceptional in being oxidised stoicheiometrically,[5] presumably reacting in the acyclic form.

The dibenzylideneribose possesses no free hydroxyl group, as shown by its infrared spectrum in the region 3700—3400 cm.$^{-1}$, and on hydrolysis with dilute mineral acid yields 2 mols. of benzaldehyde. After boiling with Raney nickel in ethanol for 45 min., hydrogenolysis of the benzylidene residues is complete since on paper chromatograms only one spot, corresponding to ribose, is observed. The dibenzylideneribose was treated with

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* Part V, *J.*, 1955, 1327.

[1] Levene and Stiller, *J. Biol. Chem.*, 1933, **102**, 187.

[2] G. R. Barker and Lock, *J.*, 1950, 23; G. R. Barker, Jeanloz, and Lock, *Nature*, 1951, **167**, 42.

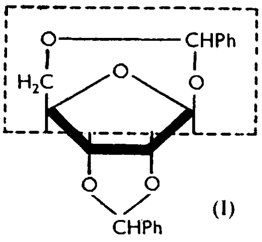
[3] Bredereck, Köthnig, and Berger, *Ber.*, 1940, **73**, 956.

[4] Niederl, Kasanof, Kisch, and Rao, *Mikrochem. Microchim. Acta*, 1949, **34**, 132.

[5] G. R. Barker and Smith, *J.*, 1955, 1323.

Raney nickel for 15 min. and the total product was methylated with methyl iodide and silver oxide. Hydrolysis and paper chromatography of the methylated material yielded, besides ribose, tri-*O*-methyl-D-ribose, a trace of di-*O*-methyl-D-ribose, and a mono-*O*-methyl-D-ribose which consisted only of 5-*O*-methyl-D-ribose.[6] It thus seems probable that on partial hydrogenolysis the dibenzylideneribose is converted into 2 : 3-*O*-benzylidene-D-ribose, and the dibenzylideneribose is therefore believed to be either 1 : 5-2 : 3-di-*O*-benzylidene-D-ribose or 1 : 4-2 : 3-di-*O*-benzylidene-D-ribose. No final choice can be made between these two possibilities at the moment. Infrared spectra have been used recently to distinguish between furanose and pyranose rings,[7] but the method is not applicable in this case since the bands of most diagnostic value lie too close to those due to the monosubstituted benzene ring. The furanose structure appears to be more likely since the alternative structure involves the adoption of the boat-form by the ribopyranose ring. However, it must be borne in mind that a boat-form six-membered ring is present also in the 2 : 3-*O*-*iso*propylideneribose anhydride. The latter can conceivably be formed by elimination of water either between the 1- and the 4-position of 2 : 3-*O*-*iso*propylidene-D-ribopyranose or between the 1- and the 5-position of 2 : 3-*O*-*iso*propylidene-D-ribofuranose. The latter mode of formation seems to be more likely since 2 : 3-*O*-*iso*propylidene-D-ribose appears to exist in the furanose form (see above). 2 : 3-*O*-Benzylidene-D-ribose under similar conditions also yields only 5-*O*-methyl-D-ribose and appears also to exist in the furanose form. In that case, it would seem more likely that the formation of di-*O*-benzylidene-D-ribose involves condensation with hydroxyl groups at positions 1 and 5.

Whichever of the two structures is adopted for the di-*O*-benzylidene-D-ribose, it remains to be considered why ribose behaves differently in its condensations with acetone and benzaldehyde. We believe this to be due to the inability of the *iso*propylidene residue to bridge the 1 : 5- or 1 : 4-positions, rather than to any effect produced by the group at the 2 : 3-positions. 2 : 3-*O*-*iso*Propylidene-D-ribose condenses readily with benzaldehyde, to give a product which we formulate as 1 : 5-*O*-benzylidene-2 : 3-*O*-*iso*propylidene-D-ribose. Since the condensation is carried out in presence of an excess of benzaldehyde any change in the location of the *iso*propylidene residue must be *via* an intramolecular rearrangement. We do not believe that this occurs, however, since on hydrogenolysis the compound is reconverted into 2 : 3-*O*-*iso*propylidene-D-ribose. Models of 2 : 3-1 : 4- and 2 : 3-1 : 5-di-*O*-benzylidene-D-ribose reveal that the hydrogen atom attached to the acetal carbon atom of the 1 : 4- or 1 : 5-*O*-benzylidene residue is very crowded and cannot be replaced by a methyl group. It thus appears that the formation of a 1 : 4- or 1 : 5-*O*-*iso*propylidene derivative is sterically prevented. This is found to be the case whichever conformation is adopted for the seven-membered ring indicated in (I). Further, models show that a change from one of the stable conformations of this seven-membered ring to the other necessitates changing also the 1 : 4- or 1 : 5-*O*-benzylidene residue from one geometrical form to the other. We have, in fact, obtained two forms of the *O*-benzylidene-*O*-*iso*propylidene-D-ribose which, although direct proof is not at the moment possible, we believe to be geometrical isomers.



(I)

EXPERIMENTAL

1 : 5-*Anhydro*-2 : 3-O-iso*propylidene*-D-*ribofuranose*.—D-Ribose (3·2 g.) was shaken at approx. 18° for 18 hr. with acetone (150 c.c.), powdered anhydrous zinc chloride (3 g.), and 80% phosphoric acid (1 c.c.). The mixture was neutralised with 20% aqueous sodium hydroxide and extracted repeatedly with chloroform. The extract was washed with water (2 × 50 c.c.) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual gum (4·5 g.) was dissolved in benzene and percolated through a column (18 × 3·5 cm.) of neutral alumina (Grade H; Peter Spence). Elution with 1 : 1 benzene–ether yielded, after removal of the solvent, 1 : 5-anhydro-2 : 3-*O*-*iso*propylidene-D-ribofuranose (0·9 g.) [Found : C, 56·0;

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[6] G. R. Barker, Noone, Smith, and Spoors, *J.*, 1955, 1327.

[7] S. A. Barker and Stephens, *J.*, 1954, 4550.

H, 7·4; *M* (cryoscopic in benzene), 169; *M* (isothermal distillation), 183. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%; *M*, 172]. Subsequent elution with ether containing 20% of methanol yielded, after removal of solvent, 2 : 3-*O*-*iso*propylidene-D-ribose (3·1 g.).

Condensation of Ribose with Benzaldehyde.—D-Ribose (3 g.) was shaken at approx. 18° for 20 hr. with freshly distilled benzaldehyde (37 g.) and powdered anhydrous zinc chloride (5 g.). Chloroform (50 c.c.) was added to the mixture which was washed with saturated aqueous sodium hydrogen carbonate, and the chloroform layer was washed with water (2 × 25 c.c.), dried ($MgSO_4$), and concentrated to dryness under reduced pressure. The residue was dissolved in benzene (200 c.c.) and percolated through a column (15 × 3·5 cm.) of alumina (Grade O; Peter Spence). Elution with ether and removal of the solvent yielded 1 : 5-2 : 3-*di*-O-*benzylidene*-D-*ribose* (1·4 g.) which separated from methanol in needles, m. p. 117—119°, $[\alpha]_D^{19}$ +7·3° (*c* 1·6 in $CHCl_3$) (Found: C, 70·05; H, 5·3. $C_{19}H_{18}O_5$ requires C, 69·92; H, 5·5%). Elution of the column with methanol yielded, after removal of solvent, 2 : 3-O-*benzylidene*-D-*ribose* (0·06 g.) which separated from pentane–chloroform (3 : 1) in needles, m. p. 98—101°, $[\alpha]_D^{19}$ −16·5° (*c* 0·605 in MeOH) (Found: C, 60·45; H, 5·6. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). A solution containing 1 : 5-2 : 3-di-*O*-benzylidene-D-ribose (0·0037 g.) and N-hydrochloric acid (2 c.c.) was diluted to 50 c.c. with ethanol and kept at approx. 18°. At intervals, the optical density of the solution at 245·5 mμ was measured. After 30 hr., the optical density had a constant value of 0·26 which corresponds to the formation of 2·04 moles of benzaldehyde per mole of dibenzylideneribose.

Methylation and Hydrolysis of 2 : 3-O-*Benzylidene*-D-*ribose.*—The material (0·065 g.) was refluxed and stirred for 6 hr. with methyl iodide (30 c.c.) and silver oxide (0·25 g.), further quantities of silver oxide (0·25 g.) being added every 0·5 hr. Refluxing and stirring were continued for a further 2 hr., silver salts were removed and washed with ether, and the combined filtrates were concentrated to dryness under reduced pressure. The residual gum was percolated in 1 : 1 benzene–ether through alumina (Grade H, Peter Spence) (10 g.). The eluate was concentrated under reduced pressure to a syrup which was kept at 60° for 2 hr. with 0·1N-hydrochloric acid (25 c.c.). Chloride ions were removed with silver carbonate, the silver salts being washed with methanol. The combined filtrates were concentrated under reduced pressure to a syrup (0·015 g.). A portion (approx. 3 mg.) of this was chromatographed on a large sheet of paper (Whatman No. 1) in butan-1-ol–water. Test strips were sprayed with the aniline phthalate spray reagent and the zone of R_F 0·41 was eluted. The eluate was chromatographed in butan-1-ol–saturated aqueous boric acid and had an R_F value (0·22) identical with that of authentic 5-*O*-methyl-D-ribose.[8] A further portion (0·0086 g.) of the syrup was oxidised with sodium metaperiodate (0·0504 g.) in water (10 c.c.). The material consumed 3 moles of sodium metaperiodate per mole of sugar.

Hydrogenolysis of 1 : 5-2 : 3-*Di*-O-*benzylidene*-D-*ribose.*—The material (0·13 g.) was refluxed for 15 min. in ethanol (30 c.c.) with Raney nickel (1·5 g.). After removal of the catalyst, the solution was concentrated to dryness under reduced pressure. The residual gum was refluxed and stirred with methyl iodide (20 c.c.) and silver oxide (0·25 g.) for 6 hr., further quantities of silver oxide (0·25 g.) being added at intervals of 0·5 hr. Silver salts were removed and washed with ether and the combined filtrates were concentrated to dryness under reduced pressure. The residual gum was boiled with 0·04N-hydrochloric acid (10 c.c.) for 1 hr., freed from chloride ions with silver carbonate, and the solution, after being concentrated to a small volume under reduced pressure, was chromatographed on a large sheet of paper (Whatman No. 1) in butan-1-ol–water. A test strip was sprayed with the aniline phthalate spray reagent and the zone containing a fraction at R_F 0·41 was eluted. This material had an R_F value (0·22) identical with authentic 5-*O*-methyl-D-ribose when chromatographed in butan-1-ol–saturated aqueous boric acid.[8]

1 : 5-O-*Benzylidene*-2 : 3-O-iso*propylidene*-D-*ribose.*—2 : 3-*O*-*iso*Propylidene-D-ribose (1·0 g.) was shaken at approx. 19° for 48 hr. with freshly distilled benzaldehyde (25 c.c.) and powdered anhydrous zinc chloride (1·5 g.). The product was isolated by the method used in the condensation of ribose with benzaldehyde and was chromatographed on a column (10 × 3·5 cm.) of alumina (Grade O, Peter Spence). Elution with benzene containing 15% of ether yielded, after removal of solvent, a *benzylidene*iso*propylideneribose* (0·065 g.) which separated from light petroleum in needles, m. p. 134—135°, $[\alpha]_D^{18}$ −59·6° (*c* 0·5 in $CHCl_3$) (Found: C, 64·6; H, 5·6. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%). Elution with benzene containing 50% of ether yielded, after removal of solvent, an (?) isomeric *form* (0·78 g.) which separated from ethanol in needles, m. p.

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[8] G. R. Barker and Smith, *Chem. and Ind.*, 1954, 19.

198—200°, $[\alpha]_D^{18}$ −40° (*c* 0·725 in $CHCl_3$) (Found : C, 64·8 ; H, 5·6. $C_{15}H_{18}O_5$ requires C, 64·7 ; H, 6·5%).

Treatment of both the above materials with Raney nickel as described above for the hydrogenolysis of di-*O*-benzylidene-D-ribose yielded a product which had an R_F value (0·8) in butan-1-ol–water identical with that of 2 : 3-*O*-*iso*propylidene-D-ribose.

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