*The Degradation of Carbohydrates by Alkali. Part VII.** 5-O-*Benzyl- and* 3 : 5-O-*Benzylidene*-2-*deoxy*-D-*ribose.*

By J. KENNER and G. N. RICHARDS.

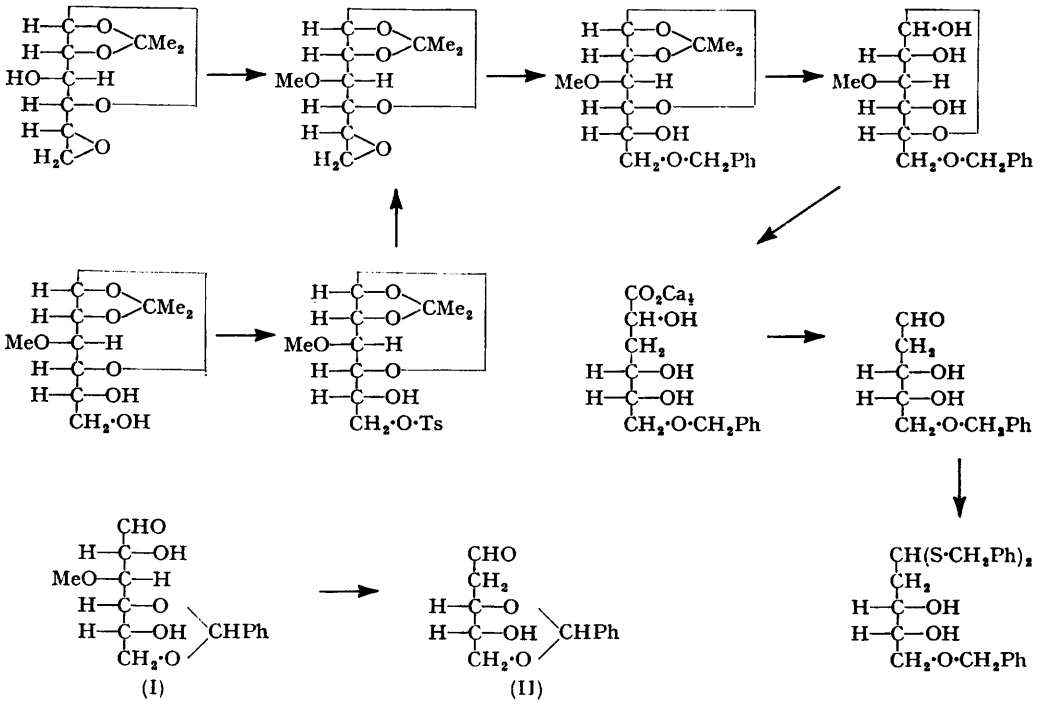
[Reprint Order No. 5366.]

Preparation of 5-*O*-benzyl- and of 3 : 5-*O*-benzylidene-2-deoxy-D-ribose is described.

THE generalisation in Parts III and IV of this series (Kenner and Richards, *J.*, 1954, 278, 1784) indicates that a desired derivative of either a meta- or an *iso*-glucosaccharinic acid will be accessible, uncontaminated by isomerides, from the corresponding derivative of respectively a 3- or a 4-*O*-alkylglucose. Furthermore, although 2-deoxy-D-ribose is now easily accessible (Richards, *J.*, 1954, this issue) some of its 5-*O*-derivatives are desirable for use in incorporation of the 2-deoxy-D-ribofuranosyl grouping into molecular structures, *e.g.*, deoxynucleosides (cf. G. W. Kenner, Taylor, and Todd, *J.*, 1949, 1620). Accordingly we have applied our principles to the preparation of 5-*O*-benzyl-2-deoxy-D-ribose from 3-*O*-methyl-6-*O*-benzyl-D-glucose through the corresponding 6-*O*-benzyl-D-glucometasaccharinic acid. The annexed scheme exhibits the alternative series of reactions involved, starting from the 6-*O*-toluene-*p*-sulphonyl derivative of either 1 : 2-*O*-*iso*propylidene-D-glucose or its 3-*O*-methyl derivative. Similarly the 4 : 6-*O*-benzylidene derivative of 3-*O*-methyl-D-glucose (I) has been converted into 3 : 5-*O*-benzylidene-2-deoxy-D-ribose (II). In this case it was possible to correlate one of the intermediate 4 : 6-*O*-benzylidenemeta-

* Part VI, preceding paper.

saccharinic acids with authentic 3-deoxy-γ-D-mannonolactone, and also to convert the benzylideneribose derivative into 2-deoxy-D-ribose itself.



Experimental

6-O-*Benzyl*-3-O-*methyl*-D-*glucose*.—(a) **5 : 6-*Anhydro*-3-O-*methyl*-1 : 2-O-iso*propylidene*-α-D-*glucose*.** 5 : 6-Anhydro-1 : 2-*O*-*iso*propylidene-α-D-glucose (30·0 g.) (Ohle and Vargha, *Ber.*, 1929, **62**, 2435) was methylated thrice with silver oxide and methyl iodide, and the resulting 3-O-*methyl ether* distilled at 98°/0·3 mm. The distillate (29·54 g., 92%) showed n_D^{17} 1·4586, $[\alpha]_D^{21}$ −69·6° (*c*, 2·5 in $CHCl_3$) (Found: C, 55·5; H, 7·6. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·5%).

6-O-*Benzyl*-3-O-*methyl*-1 : 2-O-iso*propylidene*-α-D-*glucose*. The above anhydro-sugar (18·64 g.) and sodium benzyloxide (from 10 g. of sodium) in oxygen-free benzyl alcohol (150 ml.) were kept for 2 days at 35°. After acidification with 20% acetic acid (250 ml.) the mixture was extracted with ether, and the extracts were washed with aqueous sodium hydrogen carbonate and with water and then evaporated under reduced pressure. After removal of benzyl alcohol at 0·1 mm., the residual syrupy *product* distilled at 185—190° (bath-temp.)/0·1 mm. It showed n_D^{19} 1·5062, $[\alpha]_D^{21}$ −37° (*c*, 2 in $CHCl_3$) (Found: C, 62·7; H, 7·4. $C_{17}H_{24}O_6$ requires C, 62·9; H, 7·5%).

(b) A solution of 3-*O*-methyl-1 : 2-5 : 6-di-*O*-*iso*propylidene-α-D-glucose (9·96 g.; Glen, Myers, and Grant, *J.*, 1951, 2568) in a mixture of acetic acid (400 ml.) and water (100 ml.) was kept at 20° ± 1° for 48 hr. and then concentrated to a syrup at 40° under reduced pressure. The residual syrup was diluted with ethanol (100 ml.), neutralised with barium carbonate, and further diluted with ether (100 ml.). After removal of solvent from the filtered solution, 3-*O*-methyl-1 : 2-*O*-*iso*propylidene-α-D-glucose (6·4 g., 75%) distilled at 170—180° (bath-temp.)/0·1 mm. and had n_D^{17} 1·4720, $[\alpha]_D^{20}$ −36·8° (*c*, 4 in EtOH) (Found: C, 51·4; H, 7·5. Calc. for $C_{10}H_{18}O_6$: C, 51·3; H, 7·7%) [Freudenberg, Dürr, and Hochstetter (*Ber.*, 1928, **61**, 1735) reported b. p. 173—175°/1 mm.]. A solution of this product (9·98 g.) in dry pyridine (50 ml.) was treated with toluene-*p*-sulphonyl chloride (8·9 g.) at room temperature for 24 hr. and subsequently poured into ice-water. The product was extracted with chloroform and treated in the usual way, to yield crude 3-*O*-methyl-1 : 2-*O*-*iso*propylidene-6-*O*-toluene-*p*-sulphonyl-α-D-glucose as a pale yellow syrup. This was dried (P_2O_5 at 50°/0·1 mm.) (16·37 g., 99%), dissolved in a solution of sodium (6 g.) in oxygen-free benzyl alcohol (75 ml.) and kept

at 25° for 4 days (cf. Levene and Raymond, *J. Biol. Chem.*, 1932, **97**, 751). After acidification with 20% acetic acid (200 ml.) the 6-*O*-benzyl ether was isolated as described above and distilled at 180—190° (bath-temp.)/0·1 mm. The product (7·69 g., 46·5%), n_D^{19} 1·5070, $[\alpha]_D^{21}$ −37° (*c*, 2 in $CHCl_3$), was clearly identical with the benzyl ether described above (Found: C, 63·2; H, 7·8%).

Hydrolysis of 6-O-*benzyl*-3-O-*methyl*-1 : 2-O-iso*propylidene*-α-D-*glucose*. The above derivative (18·63 g.) was refluxed in dioxan (150 ml.) and 0·2N-sulphuric acid (150 ml.) until its rotatory power was constant {$[\alpha]_D^{20}$ +21·6° (15 min.) ⟶ +36·7° (1 hr.)}. After neutralisation with barium carbonate the solution was filtered, adjusted to pH 5·5 with acetic acid, and evaporated to dryness, yielding 6-O-*benzyl*-3-O-*methyl*-D-*glucose* as a colourless syrup (16·05 g., 98%), $[\alpha]_D^{20}$ +38° (*c*, 1·5 in EtOH) (Found: C, 58·8; H, 7·6. $C_{14}H_{20}O_6$ requires C, 59·1; H, 7·1%). This gave a single spot on paper chromatography [R_F 0·71 in butanol–light petroleum (b. p. 80—100°), (1 : 1), saturated with water]. The *phenylosazone* had m. p. 137—139° (from aqueous ethanol) (Found: N, 12·0. $C_{26}H_{30}O_4N_4$ requires N, 12·1%). The same osazone was obtained from material whether prepared by route (a) or route (b).

Action of Lime-water on 6-O-*Benzyl*-3-O-*methyl*-D-*glucose*.—(*a*) A solution of the glucose derivative in oxygen-free lime-water (50 ml.; 0·04N) was kept at 25° under nitrogen and the formation of saccharinic acid followed as in the case of 3-*O*-methyl-D-glucose (Part III, *loc. cit.*) :

Time (hr.)	1·0	4·0	7·0	100	150	200	250
Sacc. acid (equiv./mole)	0·12	0·41	0·575	0·90	0·98	0·99	0·99

Paper-chromatographic analysis of intermediate fractions (solvent as above) showed the slow disappearance of the glucose derivative accompanied by the formation of an acid (R_F <0·05) and the intermediate formation of a ketose (R_F 0·72), probably 6-*O*-benzyl-3-*O*-methyl-D-fructose.

(*b*) A solution of 6-*O*-benzyl-3-*O*-methyl-D-glucose (16·05 g.) in oxygen-free water (400 ml.) was treated with calcium hydroxide (15 g.) with occasional shaking at 35° for 4 days. The resulting solution was filtered from excess of calcium hydroxide, saturated with carbon dioxide, boiled for a few minutes, and again filtered. The filtrate was evaporated to dryness, to yield the mixed calcium 6-*O*-benzyl-D-glucometasaccharinates as a pale yellow syrup (12·77 g., 78%). These were dissolved in warm ethanol (100 ml.) and kept at room temperature overnight; the β-*isomer* separated (8·07 g.). After crystallisation, from hot water, in fine colourless needles it had $[\alpha]_D^{20}$ −6·5° (*c*, 3 in H_2O) (Found: C, 53·6; H, 6·3; Ca, 6·8. $C_{13}H_{17}O_6Ca_{\frac{1}{2}}$ requires C, 53·9; H, 5·9; Ca, 6·9%). The crude α-isomer (4·50 g.) obtained by evaporation of the mother-liquors from the above reaction, was dissolved in ethanol (50 ml.) and water (10 ml.). Fractional precipitation by ether ultimately yielded pure *calcium* 6-O-*benzyl*-α-D-*glucometasaccharinate* as a white powder, $[\alpha]_D^{20}$ −1·8° (*c*, 4 in H_2O) (Found: C, 63·2; H, 7·8; Ca, 7·4%).

In later experiments yields of up to 95% of the crude mixture of calcium salts were obtained and this material was suitable for the next stage.

5-O-*Benzyl*-2-*deoxy*-D-*ribose*.—Barium acetate (0·40 g.) and ferric sulphate (0·20 g.) were added to a solution of the mixed calcium salts (4·35 g. from the previous reaction) in water (50 ml.). Hydrogen peroxide (2·5 ml.; 30%) was added to the boiled and filtered mixture after cooling to 40° and the resulting solution was then warmed to 60° to initiate the reaction. When this had subsided and the temperature of the solution had fallen to 40°, more hydrogen peroxide (2·5 ml.) was added and the procedure repeated. The resultant solution was filtered and extracted with ether (5 × 25 ml.), and the extracts were dried (Na_2SO_4) and evaporated to dryness to yield 5-O-*benzyl*-2-*deoxy*-D-*ribose* as a colourless syrup (0·701 g.), $[\alpha]_D^{20}$ +9·4° (*c*, 4 in EtOH) (Found: C, 64·8; H, 7·2. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2%). Continuous extraction of the residual aqueous solution with ether for 24 hr. yielded a further quantity (0·880 g., total 47%) of the same compound (Found: C, 64·7; H, 7·5%), and the product from both extractions gave only a single spot on paper chromatography (R_F 0·78; solvent as above).

5-*O*-Benzyl-2-deoxy-D-ribose (2·23 g.) and toluene-ω-thiol (3 ml.) were cooled to 0°, mixed with concentrated hydrochloric acid (6 ml.), and shaken at room temperature for 30 min. The resultant emulsion was diluted with chloroform (50 ml.) and poured into water (50 ml.), the chloroform extract being subsequently washed with saturated sodium hydrogen carbonate solution and then with water, dried (Na_2SO_4), and evaporated to dryness. 5-O-*Benzyl*-2-*deoxy*-D-*ribose dibenzyl mercaptal* crystallised slowly on trituration with ether–light petroleum and when recrystallised from a mixture of the same solvents had m. p. 71—71·5°, $[\alpha]_D^{20}$ +3·1° (*c*, 3 in $CHCl_3$) (4·11 g., 91%) (Found: C, 68·4; H, 6·6; S, 13·8. $C_{26}H_{30}O_3S_2$ requires C, 68·7; H, 6·7; S, 14·1%).

Preparation of 3 : 5-O-*Benzylidene*-2-*deoxy*-D-*ribose*.—4 : 6-O-*Benzylidene*-3-O-*methyl*-D-*glucose*. 3-*O*-Methyl-D-glucose (20·0 g.; Glen, Myers, and Grant, *J.*, 1951, 2568) was shaken in nitrogen with freshly distilled benzaldehyde (50 ml.) and powdered zinc chloride (18 g.) for 24 hr., and the resulting solution poured into ice-water (200 ml.) and stirred vigorously for 10 min. After decantation of the aqueous solution the amorphous precipitate was triturated with light petroleum (100 ml.; b. p. 60—80°), filtered, and washed repeatedly with light petroleum until free from the odour of benzaldehyde, and with ice-water until the washings were free from chloride ions. The *product*, dried over phosphoric oxide (yield, 12·3 g., 42%), had m. p. 128—132°, and, after one crystallisation from methanol–water, m. p. 130—133°, $[\alpha]_D^{20}$ +55° ⟶ +16° (7 days; *c*, 1 in MeOH) (Found: C, 59·3; H, 6·5; OMe, 11·1. $C_{14}H_{18}O_6$ requires C, 59·5; H, 6·4; OMe, 11·0%). The 2 : 4-*dinitrophenylhydrazone* was prepared by boiling a solution of the glucose derivative (0·56 g.) in ethanol (15 ml.) with powdered 2 : 4-dinitrophenylhydrazine (0·40 g.) for 1½ hr. After cooling to room temperature and filtration from a small amount of the unchanged base, the hydrazone was precipitated by the addition of water (20 ml.). It separated from ethanol–water as fine yellow needles, m. p. 167—167·5° (Found: N, 12·3; OMe, 6·3. $C_{20}H_{22}O_9N_4$ requires N, 12·1; OMe, 6·7%).

Action of lime-water on 4 : 6-O-*benzylidene*-3-O-*methyl*-D-*glucose*. This sugar (20·15 g.) and calcium hydroxide (20 g.) in oxygen-free water (1 l.) were stirred in a sealed flask at 20° ± 1°. At intervals, samples (5 ml.) of the filtered solution were shaken with Amberlite resin IR-120 (*ca.* 1 g.) and filtered. The filtrate and resin washings (20 ml.) titrated with 0·025N-potassium hydroxide furnished the following results:

Time (hr.)	1·3	18	24	95
Acidity (equiv./mole)	0·70	0·81	0·83	0·88

Examination of the resin-treated solution at this stage by paper chromatography (solvent as above) indicated the presence of a ketose (R_F 0·80; staining relatively slowly with alkaline silver nitrate and probably 4 : 6-*O*-benzylidene-3-*O*-methyl-D-fructose), and a trace of the original glucose derivative (R_F 0·76). The filtered solution, after saturation with carbon dioxide, was boiled, filtered again, and concentrated at 40°. The solution (200 ml.) at room temperature overnight deposited fine, white crystals of *calcium* 4 : 6-O-*benzylidene*-3-*deoxy*-D-*mannonate* (6·05 g., 29·5%) which, recrystallised once from hot water, showed $[\alpha]_D^{20}$ −58° (*c*, 1 in H_2O) [Found: C, 53·9; H, 5·4. $(C_{13}H_{15}O_6)_2Ca$ requires C, 54·4; H, 5·3%]. The filtrate was evaporated to a yellow syrup which crystallised on trituration with warm acetone, the acetone extract yielding on evaporation a brown syrup (0·44 g.) which was not examined further.

Part of the mixed calcium salts (5·05 g. from 13·09 g.; 64%) was dissolved in hot ethanol (30 ml.); fractional precipitation by ether then yielded *calcium* 4 : 6-O-*benzylidene*-3-*deoxy*-D-*gluconate dihydrate*, $[\alpha]_D^{20}$ −34° (*c*, 1 in H_2O) [Found: C, 50·8; H, 5·6. $(C_{13}H_{15}O_6)_2Ca,2H_2O$ requires C, 51·1; H, 5·6%].

Acidic hydrolysis of calcium 4 : 6-O-*benzylidene*-3-*deoxy*-D-*mannonate*. The mannonate (0·10 g.) was stirred with Amberlite resin IR-120 (1 g.) in water (10 ml.) at 60° for 2 hr., and subsequently filtered and evaporated to dryness. The residue crystallised readily and when recrystallised once from acetone had m. p. 86—88°, alone or in admixture with authentic 3-deoxy-γ-D-mannonolactone (Richards, *loc. cit.*).

3 : 5-O-*Benzylidene*-2-*deoxy*-D-*ribose*. Barium acetate (0·36 g.) and ferric sulphate (0·18 g.) were added to an aqueous solution of the mixed calcium salts of 4 : 6-*O*-benzylidene-3-deoxy-D-mannonic and -gluconic acids (5·05 g.). The solution was then boiled for a few minutes, filtered, cooled to 40°, and treated with hydrogen peroxide (2·5 ml.; 30%), with subsequent warming to initiate the reaction. When the temperature had fallen to 40° more hydrogen peroxide (2·5 ml.) was added and the procedure repeated. The resulting solution was filtered and extracted with ether (2 × 50 ml.), and the extracts were dried (Na_2SO_4) and evaporated, to yield 3 : 5-O-*benzylidene*-2-*deoxy*-D-*ribose* as a colourless syrup (0·771 g.), $[\alpha]_D^{21}$ −61° (*c*, 2 in EtOH) (Found: C, 65·2; H, 6·3. $C_{12}H_{14}O_4$ requires C, 65·0; H, 6·3%). This gave a single spot on paper chromatography (R_F 0·82; solvent as above). Further continuous extraction of the aqueous solution with ether for 24 hr. yielded a further quantity (0·429 g.) of the same compound. More barium acetate (0·2 g.) and ferric sulphate (0·1 g.) were then added to the remaining aqueous solution which was boiled, filtered, and treated with more hydrogen peroxide (2 × 2 ml.) as described above. Continuous extraction of the resulting solution with ether for 24 hr. yielded a further quantity of 3 : 5-*O*-benzylidene-2-deoxy-D-ribose (0·429 g.; total yield 41·8%). The 2 : 4-*dinitrophenylhydrazone* was prepared by boiling an ethanolic solution (10 ml.) of this product (0·32 g.) with 2 : 4-dinitrophenylhydrazine (0·25 g.) for 1 hr. Addition of water precipitated

the hydrazone (0·40 g.) which separated from its ethanol–water solution as fine yellow needles, m. p. 132—134° (Found : N, 14·3. $C_{18}H_{18}O_7N_4$ requires N, 13·9%).

Acid hydrolysis. The ribose derivative (0·090 g.) was stirred with Amberlite resin IR-120 (0·5 g.) in water (10 ml.) at room temperature for 18 hr. and the resulting solution, after filtration, washed with chloroform and evaporated to dryness. The residual syrup was dissolved in methanol (1 ml.) containing freshly distilled aniline (0·02 g.) and the solution heated under reflux for 2 hr. Concentration of the resulting solution then yielded colourless needles of *N*-2-deoxy-D-ribosylaniline, m. p. and mixed m. p. 170—173°.

THE BRITISH RAYON RESEARCH ASSOCIATION, HEALD GREEN LABORATORIES,
WYTHENSHAWE, MANCHESTER. [*Received, May 5th,* 1954.]