The Action of Grignard Reagents on Anhydro-sugars of Ethylene Oxide Type. Part IV. The Behaviour of Methyl* 2 : 3-*Anhydro*-4 : 6-O-*benzylidene*-α-D-*mannoside towards Diphenylmagnesium.*

By G. N. Richards.

[Reprint Order No. 6045.]

Methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside with diphenylmagnesium in ether gives methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside. In boiling toluene the same reagent also causes racemisation of the benzylidene group. Theories of the reactions of Grignard reagents with epoxides are discussed.

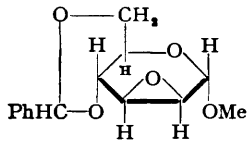
In Part III* reference was made to the reaction of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (I) with diphenylmagnesium and it was pointed out that the nature of the product, methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (II), indicated a different direction of ring opening from the corresponding reaction with diethylmagnesium (Foster, Overend, Stacey, and Vaughan, *J.*, 1953, 3308). We now report a more detailed study of the former reaction.

Treatment of the anhydro-mannoside (I) with ethereal phenylmagnesium iodide, from which the whole of the iodine had been precipitated as the dioxan complex (cf. Schlenk, *Ber.*, 1931, **64**, 734), followed by fractionation, yielded as sole product methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (II) (m. p. 163·5°). The structure of this compound was demonstrated by its partial acidic hydrolysis to methyl 2-deoxy-2-*C*-phenyl-α-D-glucoside (III), which reacted with 1 equivalent of lead tetra-acetate at a rate corresponding to the presence of a *trans*-α-glycol group. For comparison, methyl 2-*O*-toluene-*p*-sulphonyl-α-D-glucoside (IV) was prepared from its known 4 : 6-*O*-benzylidene derivative (Bollinger and Prins, *Helv. Chim. Acta*, 1945, **28**, 465) and shown to react with lead tetra-acetate in an analogous manner. The ultraviolet absorption spectrum confirmed the presence of a phenyl group in (III) and, if the assumption made in earlier papers of this series concerning the absence of rearrangement reactions, is accepted, its structure must be considered proved.

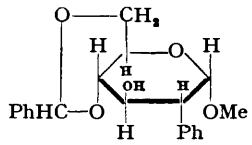
When the reaction with diphenylmagnesium was repeated under more drastic conditions, in boiling toluene solution for 3 or 6 hours, two compounds isomeric with (II) were also obtained (m. p. 144·5° and m. p. 194·5°). These compounds, which will be referred to as methyl 4 : 6-*O*-benzylidine-2-deoxy-2-*C*-phenyl-α-D-glucoside (A) and (B) respectively, differed in melting point and to a smaller extent in optical rotation from (II), but showed

* Part III, *J.*, 1954, 4511.

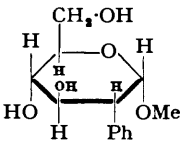
the same ultraviolet absorption spectrum and on partial acidic hydrolysis gave the same product (III); the differences in optical rotation of the hydrolysed solutions are probably due to the presence of optically active hemiacetals of benzaldehyde. It is concluded that compounds (A) and (B) are stereoisomeric with (II), differing only at the optical centre



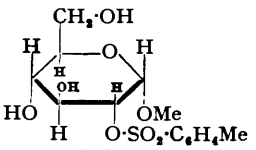
(I)



(II)

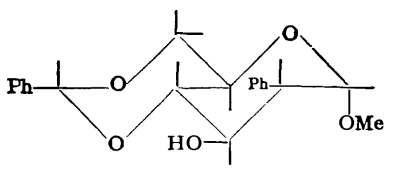


(III)

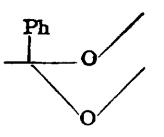


(IV)

introduced by the benzylidene group, and the optical activities indicate that (A) may be the racemate of (II) and (B). The behaviour of these compounds on recrystallisation, and in particular the difficulty experienced in obtaining a sample of sharp melting point from compound (A), is reminiscent of the results of Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1946, **68**, 1769; 1948, **70**, 765) with benzylidene derivatives of heptitols, but the racemisation of the glucoside derivatives seems to take place much less readily than with 1 : 3-*O*-benzylideneglycerol (Irvine, Macdonald, and Souter, *J.*, 1915, **107**, 344). This fact is rather unexpected, since in only one of the stereoisomers (V) is the bulky phenyl of the benzylidene group in the equatorial configuration, and the alternative form (VI) would be expected to be relatively unstable. Accordingly this type of isomerisation in the pyranoside series is normally found only in 5-membered benzylidene rings, such as methyl 2 : 3-4 : 6-di-*O*-benzylidene-α-D-mannoside (cf. Mills, *Chem. and Ind.*, 1954, 633), where the two forms do not differ greatly in stability. The racemisation would be assisted by the basic character of the diphenylmagnesium (cf. Ness, Hann, and Hudson, *loc. cit.*; Buchanan, *Chem. and Ind.*, 1954, 1484) and possibly also by the presence of the phenyl anion formed from it on ionisation. Racemisation by pyridine is demonstrated by its use as solvent in the benzoylation of the compound (II), yielding an ester which was purified with difficulty and on hydrolysis yielded compound (B). This suggests that the ease of racemisation may depend on the presence of the phenyl group in the pyranoside ring.

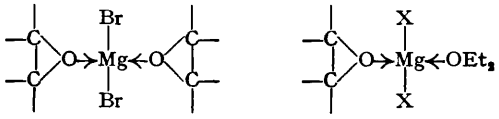


(V)



(VI)

The above results serve to emphasise the fact that in a Grignard reagent solution where the Schlenk equilibrium renders possible two different types of simple scission of an epoxide ring, the normal ring opening agent is MgX_2, while the products arising from reaction of MgR_2 are observed only when MgX_2 is removed from solution, *e.g.*, as the dioxan complex. This may perhaps be explained as due to the more complete ionisation of the magnesium halide as compared with the di-alkyl- or -aryl-magnesium, since the anion (X^- or R^-) would be the agent involved in attack on the carbon atoms of the epoxide ring. Or alternatively the greater polarity of the Mg–X bond compared with the Mg–R bond may assist complex formation in the former case and hence cause preferential reaction. Either of these possibilities would explain the increased reactivity of diphenyl- as compared with diethylmagnesium (cf. Foster *et al.*, *loc. cit.*), and in addition the results of Johnson and Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 1943) indicate that the concentration of the former will be the greater. In this connection Huston and Agett's isolation (*J. Org. Chem.*, 1941, **6**, 123) of the complex $C_4H_8O_2MgBr_2$ in the reaction of ethylene oxide with alkylmagnesium bromides is of interest and indicates that a complex of type (VII) or possibly (VIII) (cf. Part I, *J.*, 1950, 2356) is the reactive intermediate in this type of reaction, theoretically capable of *trans*-addition of either halide or alkyl anion (cf. Angyal, *Chem. and Ind.*, 1954, 1230).



(VII) (VIII)

The isolation of the stereoisomers described above must render less conclusive the tentative assignment of structure made in Part III of this Series (*loc. cit.*) to the supposed methyl 4 : 6-*O*-benzylidene-2-deoxy-2-iodo-α-D-glucoside.

Experimental

Methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside was prepared by the method of Bollinger and Prins (*loc. cit.*).

Reaction of Methyl 2 : 3-*Anhydro*-4 : 6-O-*benzylidene*-α-D-*mannoside with Diphenylmagnesium.*—(a) *In ether.* To the Grignard reagent prepared from iodobenzene (5·57 ml.) and magnesium (1·2 g.) in ether (20 ml.), dioxan (6 ml.) was added dropwise with stirring, and the resulting paste treated with a solution of the anhydro-sugar (1·36 g.) in ether (125 ml.). Thereafter the mixture was heated under reflux with vigorous stirring for 10 hr. and kept at room temperature for a further 12 hr. Water was next added cautiously, followed by a slight excess of dilute hydrochloric acid, the ether layer separated, and the aqueous phase further extracted with ether. The combined ethereal extracts were washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4), and evaporated to dryness. The partly crystalline residue (3·80 g.) was shaken at room temperature with ether (10 ml.) and light petroleum (5 ml.; b. p. 60—80°), the unchanged anhydromannoside (0·281 g.; m. p. and mixed m. p. 146—147°) remaining undissolved. The solution was then transferred to alumina (30 × 1 cm.) and eluted as follows: (i) Ether–light petroleum (b. p. 60—80°) (2 : 1) gave a colourless optically inactive liquid, which, when distilled at 115—120° (bath-temp.)/18 mm., yielded crystalline diphenyl, m. p. 68—70° (Found: C, 92·9; H, 6·3. Calc. for $C_{12}H_{10}$: C, 93·5; H, 6·5%). (ii) Further use of the same eluant yielded the unchanged anhydro-sugar (0·734 g., total recovery 74%) showing m. p. and mixed m. p. 146—147° when once recrystallised from ethanol. (iii) Elution with chloroform yielded methyl 4 : 6-O-*benzylidene*-2-*deoxy*-2-C-*phenyl*-α-D-*glucoside* (0·345 g., 19%), which, when recrystallised twice from benzene–light petroleum (b. p. 60—80°), had m. p. 162·5—163·5°, $[\alpha]_D^{21}$ +143° (*c*, 1 in $CHCl_3$) (Found: C, 69·9; H, 6·3. $C_{20}H_{22}O_5$ requires C, 70·1; H, 6·5%). Ultraviolet absorption: ε 506 at 2150 Å, 495 at 2550 Å.

(b) *In toluene.* The reagent was prepared in ether exactly as in the previous experiment. Ether was next removed from the resulting paste by slow distillation with vigorous stirring, while toluene (50 ml.) was slowly added. After the complete removal of ether, a solution of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-mannoside (1·37 g.) in toluene (25 ml.) was added and the mixture heated under reflux with vigorous stirring for 6 hr. The product, isolated as in the previous experiment, crystallised partly and the crystals when separated on sintered glass and recrystallised from light petroleum (b. p. 60—80°) had m. p. 162—163° alone or in admixture with the product from the previous experiment (0·80 g.). The remaining syrup was dissolved in light petroleum (5 ml.; b. p. 60—80°), transferred to alumina (30 × 1 cm.), and eluted as follows: (i) Ether–light petroleum (b. p. 60—80°) (2 : 1) yielded needles mixed with a liquid. The crystals, when separated on sintered glass, were methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (B) (0·183 g., 10%), and when once recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) had m. p. 193·5—194·5°, $[\alpha]_D^{19}$ +126° (*c*, 1 in $CHCl_3$) (Found: C, 69·9; H, 6·6%). Ultraviolet absorption, ε 498 at 2150 Å, 5·21 at 2550 Å. The liquid filtrate distilled at 115—120° (bath-temp.)/18 mm. to yield diphenyl (2·23 g.), m. p. and mixed m. p. 68—70°. (ii) Elution with chloroform yielded a further quantity of methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (0·34 g., total yield 64%).

A further experiment under conditions similar to (b) above, except that the reaction mixture was heated for only 3 hr., yielded, after chromatography on alumina, diphenyl (2·90 g.) and compound (B) (0·09 g., 5%), but later fractions gave in addition, methyl 4 : 6-*O*-benzylidene-2-deoxy-2-*C*-phenyl-α-D-glucoside (A) (1·60 g., 91%), m. p. 139—145°. Recrystallisation of this product from ethanol resulted in more diffuse m. p.s, but after several recrystallisations from benzene–light petroleum and later from ethyl acetate–light petroleum it had m. p. 144—144·5°, $[\alpha]_D^{22}$ + 132° (*c*, 1 in $CHCl_3$) (Found: C, 69·8; H, 6·4%). Ultraviolet absorption, ε 501 at 2150 Å, 521 at 2550 Å. The m. p. of this compound after 3 years was 150—160°.

Partial Acid Hydrolysis of Methyl 4 : 6-O-*Benzylidene*-2-*deoxy*-2-C-*phenyl*-α-D-*glucoside*.—A solution of the glucoside (0·319 g.) in ethanol (25 ml.) containing 0·1N-hydrochloric acid (1 ml.) was heated under reflux for 2·5 hr. $\{[\alpha]_D^{20} +119° \longrightarrow +50·5°$ (2 hr., const.)$\}$. After steam-distillation under reduced pressure to remove ethanol and benzaldehyde the solution was neutralised with silver carbonate, filtered, and evaporated to dryness. The residue was extracted with boiling light petroleum (5 ml.; b. p. 60—80°), and the insoluble portion recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving *methyl* 2-*deoxy*-2-C-*phenyl*-α-D-*glucoside* as colourless needles, m. p. 180·5—181·5°, $[\alpha]_D^{18} +175°$ (*c*, 0·5 in EtOH) (Found: C, 61·0; H, 7·1. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%). Ultraviolet absorption, ε 507 at 2100 Å, 278 at 2575 Å.

Compound (A) (0·873 g.), treated as in the preceding experiment $\{[\alpha]_D^{18} +107° \longrightarrow +37°$ (2 hr., const.)$\}$, yielded the same product, m. p. and mixed m. p. 180·5—181·5°. Similar treatment of compound (B) (0·183 g.) in ethanol (12·5 ml.) and 0·1N-hydrochloric acid (0·5 ml.) $\{[\alpha]_D^{16} +70° \longrightarrow +76°$ (0·5 hr., const.)$\}$ also yielded this product, m. p. and mixed m. p. 180·5—181·5°.

Partial Acid Hydrolysis of Methyl 4 : 6-O-*Benzylidene*-2-O-*toluene*-p-*sulphonyl*-α-D-*glucoside*.—The glucoside (0·494 g.) was heated under reflux for 6 hr. with acetone (25 ml.) and aqueous oxalic acid (0·9 g. of dihydrate in 3 ml.) ($[\alpha]_D +51° \longrightarrow +72°$). More oxalic acid (0·9 g.) was added and the whole was heated for 4 hr. ($[\alpha]_D \longrightarrow +80°$), and finally 2N-sulphuric acid (2 ml.) was added and the whole heated for a further 3 hr. ($[\alpha]_D \longrightarrow +80°$, const.). The solution was distilled in steam to remove benzaldehyde and acetone, and the remaining aqueous solution