

The Addition of Diazomethane to 1,2-O-Isopropylidene-5-O-Trityl- α -D-erythro-pentos-3-ulose¹

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The reaction of 1,2-O-isopropylidene-5-O-trityl- α -D-erythro-pentos-3-ulose (**1c**) with excess diazomethane in methanol-ether affords a multicomponent mixture from which a tricyclic derivative and two epoxides, in addition to methyl trityl ether, were isolated on preparative tlc and identified. The structures of the epoxides were established from the corresponding products of reduction (LiAlH₄), 1,2-O-isopropylidene-3-C-methyl-5-O-trityl- α -D-xylofuranose (**3c**) and 4,5-dideoxy-1,2-O-isopropylidene-3-C-methyl-5-O-trityl- α -D-heptoseptanose (**10**). The presence of a seven-membered ring in **10** indicates that the homologation of **1c** first to a pyranos-3-ulose (**4c**) and then to a septanos-3-ulose (**8**) competes successfully with oxetane ring formation. The structure 3,5-anhydro-3-C-hydroxymethyl-1,2-O-isopropylidene- α -D-ribofuranose (**14a**), which was deduced from nmr spectral data, was assigned to the tricyclic derivative. It is proposed that **14a** arises from a cyclic oxonium ion (**13**), formed in turn by trityloxy-group participation in the expulsion of nitrogen from the initial addition intermediate (**12**) or as a two-step process involving prior loss of nitrogen. Attack of methanol on **13** provides **14a** and methyl trityl ether in about equal (35%) yield.

Overend and coworkers³ obtained a mixture of two epoxides in 85% yield from the interaction of diazomethane and 5-O-benzoyl-1,2-O-isopropylidene- α -D-erythro-pentos-3-ulose (**1a**) in methanol-ether (Scheme I). The major component (**5a**), a product of prior

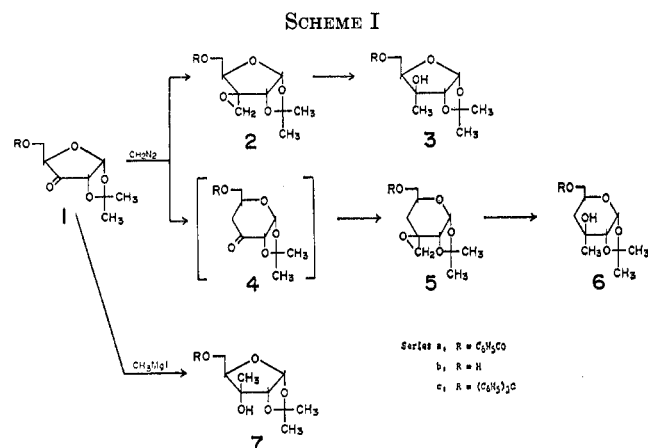
oxetane derivatives on treatment with diazomethane.^{5,6} Moreover, the "ribo-epoxide" is the preponderant isomer in both cases.

The present investigation was undertaken to examine more closely the apparent stereoselectivity of the reaction of **1** and diazomethane which leads (after reduction) to methyl branched chain sugars of a configuration opposite to those obtainable from corresponding reactions with methylmagnesium halides.^{7,8} In the current study, 1,2-O-isopropylidene-5-O-trityl- α -D-erythro-pentos-3-ulose (**1c**)⁹ was used rather than **1a** to avoid the loss of the blocking group at C-5 in the reduction step and thereby to facilitate the isolation of products.

The reaction mixture obtained following addition of excess diazomethane to **1c** in methanol-ether showed four spots^{10a} on tlc (silica gel, ether-petroleum ether) with *R_f* values of $\cong 0$ (A), 0.17 (B), 0.28 (C), and 0.61 (D). A separation of the four components was effected by preparative tlc (plc^{10b}) using the same system. Substance D, obtained in 36% yield, was readily identified as methyl trityl ether on the basis of spectral (ir and nmr) evidence together with mixture melting point.

Of the remaining components, only B and C gave a positive Ross test¹¹ for an epoxide. Moreover, the nmr spectrum of C, which was isolated as a foam (11% yield), showed a well-resolved AB system at high field consistent with an exocyclic methylene epoxide.¹² Reduction of C with lithium aluminum hydride gave a product which, on the basis of the evidence outlined below, was assigned the structure 1,2-O-isopropylidene-3-C-methyl-5-O-trityl- α -D-xylofuranose (**3c**).

Walton and coworkers⁷ have shown that the reaction of **1a** with methylmagnesium iodide is essentially stereospecific affording the 3-C-methyl- α -D-ribofuranose



ring expansion of **1a**, on treatment with excess lithium aluminum hydride in tetrahydrofuran, yielded a solid to which the structure 4-deoxy-1,2-O-isopropylidene-3-C-methyl- α -D-xylo-hexopyranose (**6b**) was assigned. The minor epoxide (**2a**) (20% yield), which incidentally was obtained in 70% yield when the addition of diazomethane to **1a** was carried out in ether alone, gave 1,2-O-isopropylidene-3-C-methyl- α -D-xylofuranose (**3b**) on reduction with lithium aluminum hydride.

The failure to detect products of the *ribo* configuration⁴ is perhaps somewhat surprising in view of the fact that the methyl 3,4-O-isopropylidene- β -(*D* and *L*)-*erythro*-pentosulopyranosides both give the isomeric

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(2) (a) To whom all inquiries should be addressed at the Michigan Cancer Foundation, 4811 John R. Street, Detroit, Mich. 48201. (b) Michigan Cancer Foundation Research Fellow.

(3) S. Nahar, W. G. Overend, and N. R. Williams, *Chem. Ind.* (London), 2114 (1967).

(4) It is conceivable that the direct precursor of the hexopyranos-3-ulose (**4a**) is an intermediate of the *ribo* configuration.

(5) W. G. Overend and N. R. Williams, *J. Chem. Soc.*, 3446 (1965).
(6) R. J. Ferrier, W. G. Overend, G. A. Rafferty, and N. R. Williams, *ibid.*, 1091 (1968).

(7) R. F. Nutt, M. J. Dickinson, F. W. Holly, and E. Walton, *J. Org. Chem.*, **33**, 1789 (1968).

(8) R. D. King, W. G. Overend, J. Wells, and N. R. Williams, *Chem. Commun.*, 726 (1967).

(9) W. Sowa, *Can. J. Chem.*, **46**, 1586 (1968).

(10) (a) The same reaction in ether alone gave rise to a multicomponent system, as judged by glpc, and was not further investigated. (b) Preparative layer chromatography.

(11) W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

(12) L. J. T. Andrews, J. M. Coxon, and M. P. Hartshorn, *J. Org. Chem.*, **34**, 1126 (1969).

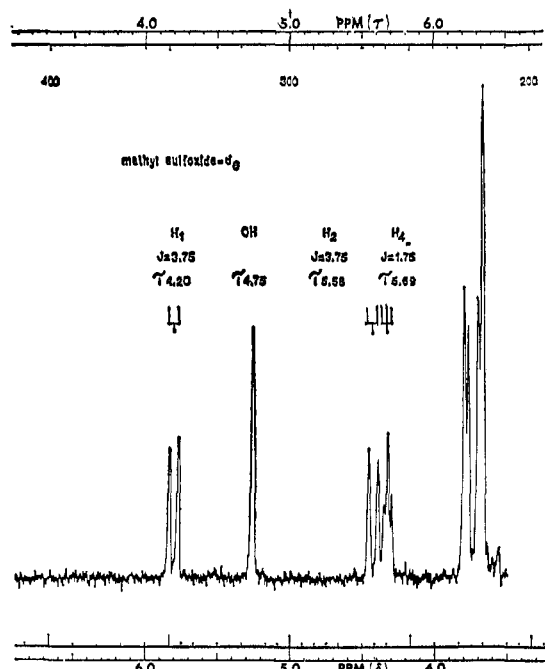
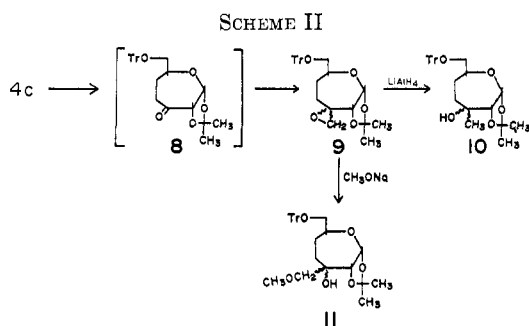


Figure 1.—A 60-MHz partial spectrum of substance A (14a) in methyl sulfoxide- d_6 .

derivative, 7a. Similarly, we observed that the action of the same Grignard reagent on 1c produced a single 3-C-methyl derivative (7c) in high yield but with properties different from those of the reduction product (3c).

Debenzylation of 7a with sodium methoxide and tritylation of the resulting intermediate, 7b, gave a product identical in every respect with 7c. Accordingly, the reduction product (3c) and the precursory oxetane (2c, substance C) are both of the *xylo* configuration.

Reduction (LiAlH_4) of the slower moving epoxide B, which appeared to be the major product, gave a crystalline solid though in relatively low yield to which the structure 4-deoxy-3-C-methyl-1,2-*O*-isopropylidene-5-*O*-trityl- α -D-hexopyranose (6c) was tentatively assigned on the basis of elemental analysis and a nmr spectrum. However, a molecular ion peak of 474 in the mass spectrum precludes 6c (mol wt 460) as a plausible structure. Moreover, an unambiguous (nmr) proton count of 34 exceeds by two the number required by 6c. These findings indicate a further homologation of the initial product of ring expansion, 4c, to a septanos-3-ulose (8, Scheme II) prior to oxetane formation (B, 9c).



Accordingly, the initial structural assignment (6c) was amended to a 4,5-dideoxy-1,2-*O*-isopropylidene-3-

C-methyl-5-*O*-trityl- α -D-heptoseptanose (10) as the product of reduction of B.

The location of the site of branching at C₃, ascertained initially for 6c, is consistent as well with 10. Thus, the nmr (CDCl_3) of the reaction product showed (*inter alia*) doublets at τ 4.5 and 5.9 ($J = 5.0$ Hz) which were assigned to the bridgehead protons of C₁ and C₂, respectively. These data then locate the site of branching at C₃ but the exact configuration remains in question. A strong absorption at 3570 cm^{-1} for the hydroxyl group was seen in the ir spectrum (carbon tetrachloride, c 0.005 *M*) of 10 which suggests¹³ possible hydrogen bonding with neighboring oxygen and therefore a *ribo* configuration at C-3. However, the present data on related structures are simply too limited to extend the method of Ferrier¹³ for the assignment of configuration at the site of branching to 10.

Additional evidence for the presence of a seven-membered ring in 10 was derived from alkaline methanolysis which afforded, though once more in low yield, a crystalline product with properties in accord with a 3-*C*-methoxymethyl- α -D-heptoseptanose (11). Again, the configuration at C-3 in 11 as well as the precursory oxetane 9 must remain unassigned.

Indirect support for structures 9–11 is derived from the findings of Overend and coworkers¹⁴ who obtained a branched-chain methyl α -D-heptoseptanoside derivative on reduction of one of two epoxides isolated following the addition of diazomethane to methyl 4,6-*O*-benzylidene-2-deoxy- α -D-*erythro*-hexopyranosid-3-ulose. The second epoxide, after treatment with lithium aluminum hydride, yielded methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl- α -D-*arabino*-hexopyranoside.

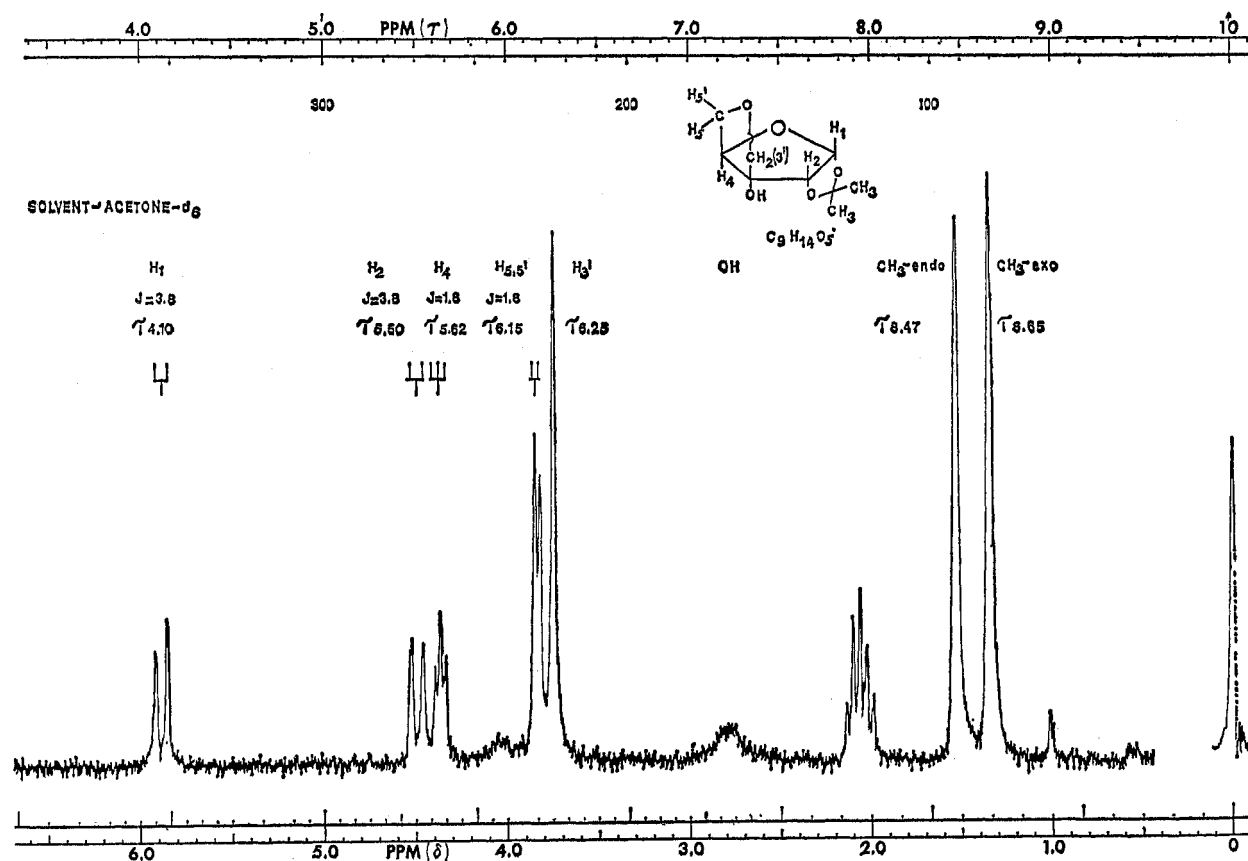
While no epoxide derivative of the pyranos-3-ulose, 4c, was isolated in the present work, glpc (Chromosorb W) indicated, contrary to tlc, that B was in fact a mixture of two minor components along with the principal spirooxetane 9. This would explain, in part, the relatively low yield of reduction and hydrolysis products 10 and 11, respectively.

The absence of an exocyclic methylene epoxide residue in the slowest moving component A was confirmed by nmr and ir spectra which revealed, in addition, the loss of the original trityl group. The latter observation, together with the isolation of methyl trityl ether, suggested the possibility of a prior detritylation of either 1c, or the direct precursor of A, induced by diazomethane. However, 5-*O*-trityl-1,2-*O*-isopropylidene- α -D-xylofuranose was recovered unchanged after treatment with diazomethane in methanol.

Substance A, a crystalline solid of the composition $\text{C}_9\text{H}_{14}\text{O}_5$, afforded a monoacetate on treatment with acetic anhydride in pyridine at room temperature but attempts to tritylate the hydroxyl group under the usual conditions were unsuccessful. The alcohol proton in A appears (Figure 1) as a clearly resolved singlet at τ 4.7 ppm in methyl sulfoxide- d_6 . The absence of spin-spin splitting of the hydroxyl proton together with the failure of A to tritylate point to the presence of a tertiary hydroxyl group. In fact, the structure of A was readily deduced by analysis of its nmr spectrum which is reproduced without the corresponding inte-

(13) R. J. Ferrier, W. G. Overend, G. A. Rafferty, H. M. Wall, and N. R. Williams, *Proc. Chem. Soc.*, 133 (1963).

(14) B. Flaherty, W. G. Overend, and N. R. Williams, *Chem. Commun.*, 434 (1966).

Figure 2.—The 60-MHz spectrum of substance A (14a) in CDCl_3 .

gration curve in Figure 2. The three-proton singlets at τ 8.49 and 8.66 are ascribed to the *endo*- and *exo*-methyl groups, respectively, of an *O*-isopropylidene residue.¹⁵ A pair of doublets that characterize the bridgehead hydrogen atoms H_1 and H_2 of the two *cis*-fused five-membered rings of a number of 1,2-*O*-isopropylidene- α -D-xylo-hexofuranose derivatives¹⁶ are seen at τ 4.10 and 5.50 ($J = 3.8$ Hz), respectively. The one-proton triplet at τ 5.62 ($J = 1.8$ Hz) and the two-proton doublet at τ 6.15 ($J = 1.8$ Hz) are assigned to the protons at C_4 and C_5 , respectively, which apparently comprise an AX_2 pattern in substance A.

The spectral patterns of H_4 and H_2 preclude the presence of a proton at C_3 . In fact, the patterns locate both the site of the branch as well as the (tertiary) hydroxyl group at C_3 of the furanose derivative. Finally, the two-proton singlet at τ 6.25, together with the other data, indicate that the branch involves a methylene group which is linked through oxygen to C_5 as part of a second, *cis*-fused five-membered ring. Accordingly, the structure 3,5-anhydro-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene- α -D-ribofuranose (14a) is assigned to substance A. The facile acetylation of the tertiary OH in 14a (to 14b) is in accord with the findings of Nutt, *et al.*,⁷ who effected the benzylation of 7a under mild conditions.

The formation of 14a requires that the addition of diazomethane to the furanos-3-ulose (1c) occurs at the side above the isopropylidene ring. The resulting intermediate (12) can lead to 14a via the cyclic oxonium ion (13), formed by either trityloxy-group participa-

tion in expulsion of nitrogen or a two-step process involving prior loss of nitrogen. Attack of methanol on the cyclic oxonium ion (13) provides compound 14 together with methyl trityl ether which, incidentally, were isolated in virtually identical (35%) yields.

Investigations by Winstein and coworkers^{17,18} as well as those by Capon¹⁹ have established that methoxy-group participation in solvolytic displacement reactions is substantial where such anchimeric assistance leads to a five- or six-membered ring. Recently, examples of both methoxy¹⁹⁻²¹ and benzyloxy^{22,23} assisted solvolysis of a sulfonate have been recorded in the carbohydrate literature and, therefore, evidence of trityloxy participation is not surprising, though it is to our knowledge the first such case described.

It is evident that 12 (see Scheme III) is also the requisite precursor of a "ribo-oxetane" (15) derivative of 1c. Moreover, the initial product of ring enlargement (4c) may, in part, evolve from 12. However, the extent of cyclization of 12 to 15 remains in question, since the corresponding product of reduction, 1,2-*O*-isopropylidene-3-*C*-methyl-5-*O*-trityl- α -D-ribofuranose, (7c), if indeed generated, remained undetected.

(17) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

(18) E. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 3991, 3998, 4008, 4012 (1967).

(19) B. Capon, *Quart. Rev. (London)*, **18**, 45 (1964).

(20) J. S. Brimacombe and O. A. Ching, *Carbohydr. Res.*, **9**, 287 (1969).

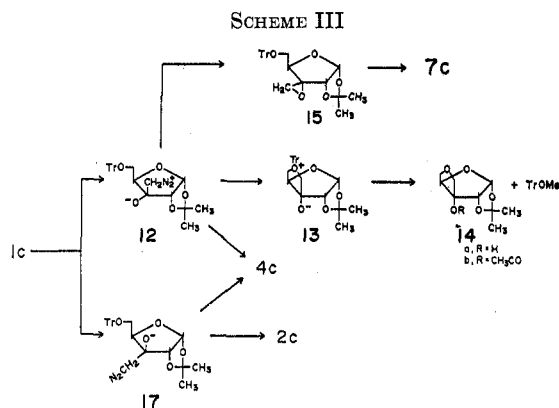
(21) Examples of methoxy-group participation have been reported in the carbohydrate field (see ref 20) but all have involved the migration of a methoxy group of an acetal ring.

(22) (a) J. S. Brimacombe and O. A. Ching, *ibid.*, **5**, 239 (1967); (b) *J. Chem. Soc., C*, 1842 (1968).

(23) (a) G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965); (b) J. S. Brimacombe and O. A. Ching, *Carbohydr. Res.*, **8**, 376 (1968).

(15) R. D. King and W. G. Overend, *Carbohydr. Res.*, **9**, 423 (1969).

(16) R. J. Abraham, L. D. Hall, L. Hough, and K. H. McLaughlan, *J. Chem. Soc.*, 3699 (1962).



The isomeric intermediate, 17, which originates from the addition of diazomethane to 1c at the side adjacent to the *O*-isopropylidene residue and which leads to the *xylo*-oxetane derivative, 2c, could as well account for the hexopyranos-3-ulose (4c). The possibility that this same intermediate could lead to a cyclic oxonium ion comprised of *trans*-fused five-membered rings appears remote from examination of molecular models. The uncertainties as to origin of 4c together with the failure to identify 15 preclude any firm conclusion as to the stereoselectivity attending the addition of diazomethane to 1c.

Experimental Section

General Procedures.—Evaporations were carried out *in vacuo* at bath temperatures below 45°. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Thin layer chromatography (tlc) was performed on silica gel GF (Merck); separated materials were detected by spraying with a 6% solution of ammonium molybdate in 10% sulfuric acid followed by heating at 100°. Preparative tlc was carried out on 20 × 20 cm glass plates coated with 1-mm layers of the same adsorbent. Optical rotations were determined in chloroform with a Perkin-Elmer Model 141 polarimeter. The ir spectra were measured in a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60A spectrometer with TMS as internal reference, and mass spectra using an A.E.I. MS-902 instrument with a direct inlet system and an ionizing voltage of 70 eV. Gas chromatography was carried out on a Barber-Colman Series No. 5000 with 6 ft × 1/8 in. glass U tubes packed with Chromosorb W (80–100 mesh) coated with 1.2% SE-30. Operation was isothermal at 225° with nitrogen as carrier gas and flame ionization detection. Petroleum ether used in recrystallizations was of a 30–60° range.

1,2-O-Isopropylidene-3-C-methyl-5-O-trityl- α -D-ribofuranose (7c).—To a stirred solution of methylmagnesium bromide, prepared from 0.243 g (0.01 g-atom) of magnesium shavings and 2.13 g (15 mmol) of methyl iodide in 10 ml of dry ether, and then cooled to 0°, was added, dropwise, a solution of 1.29 g (10 mmol) of 1c⁹ in 50 ml of dry ether. The addition complex, a heavy white precipitate, was carefully decomposed by addition of water. The water layer was separated and extracted with three 25-ml portions of ether. The extracts were combined, washed with 20 ml of saturated sodium chloride solution, and dried over magnesium sulfate. Evaporation of the solvent left a solid residue (1.29 g) which, on recrystallization from ether, gave 1.15 g (86% yield) of a crystalline solid: mp 152–153°; $[\alpha]^{27D} - 14.7^\circ$ (c 1.0); ir (CCl₄) 3660 cm⁻¹ (OH); nmr (CDCl₃) τ 3.68 (m, 15, aromatic), 4.23 (d, 1, $J_{1,2} = 3.6$ Hz, H-1), 5.96 (d, 1, H-2), 6.10 (m, 1, H-4), 6.73 (m, 2, H-5), 8.40 (s, 3, 3-C-CH₃), 8.67 (s, 3, isopropylidene, CH₃-endo), 9.05 (s, 3, isopropylidene, CH₃-exo); mass spectrum *m/e* 446 (M⁺).

Anal. Calcd for C₂₅H₃₀O₅: C, 75.31; H, 6.77. Found: C, 75.13; H, 6.80.

1,2-O-Isopropylidene-3-C-methyl- α -D-ribofuranose (7b).—A quantity (0.308 g, 1 mmol) of 7a, prepared according to the

procedure of Nutt, *et al.*,⁷ was dissolved in 10 ml of ethanol containing 1 mequiv of sodium ethoxide and the solution was refluxed for 0.75 hr. The dark reaction mixture was evaporated to dryness and the residue was dissolved in 10 ml of water. The solution was carefully neutralized with dilute acetic acid and then extracted with four 25-ml portions of ether. The combined dried extracts were concentrated to ca. 10 ml and the product, 0.105 g (50% yield), crystallized as a mat of colorless, fine needles: mp 92.5–93.5°; $[\alpha]^{26D} + 24.8^\circ$ (c 0.5); nmr (CDCl₃) τ 4.18 (d, 1, $J_{1,2} = 3.7$ Hz, H-1), 5.88 (d, 1, H-2), 8.40 (s, 3, 3-C-CH₃), 8.63 (s, 3, isopropylidene, CH₃-endo), 8.84 (s, 3, isopropylidene, CH₃-exo).

Anal. Calcd for C₉H₁₆O₅: C, 52.93; H, 7.9. Found: C, 53.02; H, 7.89.

To a solution of 25 mg (0.12 mmol) of 7b in 0.5 ml of dry pyridine was added 40 mg (0.14 mmol) of trityl chloride and the mixture, protected from moisture, was held at room temperature for 1 week. The reaction mixture was evaporated to dryness and the pyridine-free residue crystallized on trituration with water. The solid was collected and the air-dried product was recrystallized from ether-petroleum ether to give 25 mg (56% yield) of crystalline solid, mp and mmp (with 7c) 151–152°. The ir and nmr spectra of this material and the corresponding spectra of 7c were essentially superimposable.

Addition of Diazomethane to 1,2-O-Isopropylidene-5-O-trityl- α -D-erythro-pentose-3-ulose (1c).—To a solution of 4 g (9.3 mmol) of 1c in a mixture of 50 ml of dry ether and 50 ml of anhydrous methanol, cooled to 0°, was added, all at once, a solution of ~18 mmol of diazomethane in 50 ml of ether. The reaction mixture was gradually allowed to attain room temperature and then maintained at ambient temperatures for 2 days.²⁴ The colorless solution was evaporated to a syrup which amounted to ca. 4 g and which showed four spots on tlc [ether-petroleum ether, 2:5 (v/v)] with the following *R_f* values: (\cong 0 A), (0.17 B), (0.28 C), and (0.61 D). Preparative tlc was effected on a total of 20 plates using the same solvent system.

Methyl Trityl Ether (D).—The bands corresponding to the fastest moving spot were eluted with acetone and the combined filtered solutions on evaporation left a solid residue which crystallized from methanol: wt 0.890 g (35% yield), mp and mmp (with an authentic sample of methyl trityl ether) 82–84° (lit.²⁵ 82.6–82.9°). The ir and nmr spectra of D were identical in every respect with corresponding spectra of methyl trityl ether.

3,5-Anhydro-3-C-hydroxymethyl-1,2-O-isopropylidene- α -D-ribofuranose (14a).—The band corresponding to the slowest moving spot A was eluted from each plate with acetone and the combined, filtered eluents were evaporated to dryness. The residue crystallized from ether-petroleum ether as a colorless solid, wt 0.675 g (36% yield), mp 66–69°. An analytical sample, mp 72–73°, was obtained by sublimation of the recrystallized material at room temperature (5 × 10⁻² mm): $[\alpha]^{25D} + 51.4^\circ$, $[\alpha]^{2585} + 182^\circ$ (c 0.5); nmr (see Figures 1 and 2); mass spectrum *m/e* (M⁺ - CH₃) 187.

Anal. Calcd for C₉H₁₄O₅: C, 53.46; H, 6.93. Found: C, 53.58; H, 6.93.

To a solution of 0.2 g (1 mmol) of 14a in 6 ml of dry pyridine was added 3 ml of acetic anhydride, and the reaction mixture was stirred at room temperature for 16 hr. The solution was then chilled to -20°, while 10 ml of methanol was added dropwise with stirring and, after 1 hr at room temperature, the solution was evaporated to dryness. The last traces of pyridine were removed by evaporation from toluene. The residue was taken up in ether, and the solution was washed first with water and then dried over magnesium sulfate. The filtered solution was evaporated to dryness and the residue (14b) was crystallized from ether-petroleum ether as a colorless solid (0.112 g, 50% yield): mp 122–124°; $[\alpha]^{24D} + 78.8^\circ$, $[\alpha]^{2785} + 151.1^\circ$ (c 1); nmr (CDCl₃) τ 4.03 (d, 1, $J_{1,2} = 4.0$ Hz, H-1), 5.09 (d, 1, H-2), 5.27 (m, 1, H-4), 7.91 (s, 3, acetate, CH₃), 8.49 (s, 3, isopropylidene, CH₃-endo), 8.66 (s, 3, isopropylidene, CH₃-exo).

Anal. Calcd for C₁₁H₁₆O₆: C, 54.09; H, 6.60. Found: C, 54.29; H, 6.71.

1,2-O-Isopropylidene-3-C-methyl-5-O-trityl- α -D-xylofuranose (3c).—Substance C (2c), which was isolated as a foam (0.443 g, 11% yield), showed the following properties: $[\alpha]^{24D} - 2.4^\circ$, $[\alpha]^{2484} - 18.7^\circ$ (c 1); ir (KBr) 1220 cm⁻¹ (epoxy ring, sym

(24) The color of the diazomethane was not completely discharged until nearly 2 days had elapsed.

(25) J. F. Norris and A. Cresswell, *J. Amer. Chem. Soc.*, **55**, 4946 (1933).

stretch); nmr (CDCl_3) τ 2.73 (m, 15 (C_6H_5)₃C), 4.05 (d, 1, $J_{1,2} = 4.0$ Hz, H-1), 5.47 (t, H-4), 5.72 (d, 1, H-2), 6.78, 6.99 (q, 2, $J = 4.0$ Hz, epoxy, CH_2AB), 8.44 (s, 3, isopropylidene, $\text{CH}_3\text{-endo}$), 8.66 (s, 3, isopropylidene, $\text{CH}_3\text{-exo}$). A quantity of 2c (0.392 g, 0.9 mmol) and 0.190 g (5 mmol) of lithium aluminum hydride in 10 ml of dry ether was refluxed for 10 hr. Water (ca. 1.0 ml) was added dropwise to the reaction mixture, the ether layer was drawn off, and the aqueous phase was extracted with four 20-ml portions of ether. The combined extracts were dried over magnesium sulfate and the filtered solution was evaporated to dryness. The foamy residue (0.286 g) was judged to be ca. 90% pure on tlc (ethyl-acetate petroleum ether, (1:4) but could not be crystallized from the usual solvents. The material was applied to two plc plates and the mixture was resolved with the same solvent system. The major fraction (3c, 0.194 g) showed a single spot on tlc and readily crystallized from petroleum ether as a colorless solid: wt 0.130 g (33% yield); mp 130–131°; $[\alpha]_D^{25} + 70.4^\circ$, $[\alpha]_{2585}^{25} + 247.4^\circ$ (c 1); ir (CCl_4) 3510 cm^{-1} (OH) 1380 (geminal CH_3); nmr (pyridine d_5) τ 3.96 (d, 1, $J_{1,2} = 3.7$, H-1), 5.60 (d, 1, H-2), 5.67 (m, 1, H-4), 6.32 (m, 2, H-5, H-5'); mass spectrum m/e 446 (M^+).

Anal. Calcd for $\text{C}_{28}\text{H}_{30}\text{O}_6$: C, 75.31; H, 6.77. Found: C, 75.19; H, 6.83.

4,5-Dideoxy-1,2-O-isopropylidene-3-C-methyl-5-O-trityl- α -D-heptoseptanose (10).—Substance B, when subjected to glpc at a gas flow rate of 64.5 ml/min, was found to consist of one major and two minor components exhibiting retention times of 33, 27, and 23 min, respectively. A solution of 0.675 g of B in 10 ml of dry tetrahydrofuran containing 0.190 g (5 mmol) of lithium aluminum hydride was refluxed for 8 hr. The work-up of the reaction mixture was the same as that described for 3c. The product, obtained as a foam (0.507 g), was applied to two plc plates which were developed in ethyl acetate-petroleum ether (1:4). The principal band was eluted with acetone and the filtered solution was evaporated to dryness. The residue crystallized from petroleum ether to give 0.205 g of a colorless solid: mp 129–130°; $[\alpha]_D^{25} - 44.6^\circ$, $[\alpha]_{2585}^{25} - 138.3^\circ$ (c 1, CHCl_3); ir (KBr) 3420 (OH), 1380 cm^{-1} (geminal -CH_3); ir (CCl_4) 3570 cm^{-1} (OH); nmr (CDCl_3) τ 2.62 (m, 15, aromatic), 4.46 (d, 1, $J_{1,2} = 5.0$ Hz, H-1), 5.95 (d, 1, H-2), 6.70–8.22 (m, 6, CH_2

envelope), 8.35 (s, 3, -CH_3), 8.63 (s, 6, $(\text{CH}_3)_2\text{C-}$); mass spectrum m/e 474 (M^+), 416 ($\text{M}^+ - (\text{CH}_3)_2\text{CO}$).

Anal. Calcd for $\text{C}_{30}\text{H}_{34}\text{O}_6$ (mol wt 474):²⁶ C, 75.92; H, 7.22. Found: C, 75.77; H, 7.16.

4,5-Dideoxy-1,2-O-isopropylidene-3-C-methoxymethyl-5-O-trityl- α -D-heptoseptanose (11).—A solution of 0.309 g of B in 55 ml of methanol containing 6 ml of 10 N sodium hydroxide was refluxed for 3 hr. The cooled solution was neutralized (phenolphthalein) with dilute acetic acid and evaporated to dryness. The residue was dissolved in ether previously equilibrated with water and the ether layer was washed with a dilute solution of sodium bicarbonate, and then dried over magnesium sulfate. The filtered solution was evaporated to dryness and the residue was crystallized first from ether-petroleum ether and then from ethanol to give 0.253 g of the product: mp 145–147°; $[\alpha]_D^{25} - 47.2^\circ$, $[\alpha]_{2585}^{25} - 148^\circ$ (c 0.25); ir (CCl_4) 3550 cm^{-1} (OH); nmr (CDCl_3) τ 2.68 (m, 15, aromatic), 4.46 (d, 1, $J_{1,2} = 5.0$ Hz, H-1), 5.70 (d, 1, H-2), 6.60 (s, 3, CH_3O), 6.68–8.32 (m, 8, CH_2 envelope), 8.38 (s, 3, isopropylidene, $\text{CH}_3\text{-endo}$), 8.66 (s, 3, isopropylidene, $\text{CH}_3\text{-exo}$); mass spectrum m/e 504 (M^+), 489 ($\text{M}^+ - \text{CH}_3$).

Anal. Calcd for $\text{C}_{31}\text{H}_{36}\text{O}_6$ (mol wt 504):²⁷ C, 73.78; H, 7.19. Found: C, 73.99; H, 6.90.

Registry No.—Diazomethane, 334-88-3; 1c, 20590-54-9; 2c, 24515-45-5; 3c, 24467-32-1; 7b, 24467-33-2; 7c, 24467-36-5; 10, 24467-39-8; 11, 24467-40-1; 14a, 24467-37-6; 14b, 24467-38-7.

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(26) Calcd for $\text{C}_{28}\text{H}_{32}\text{O}_6$ (mol wt 460): C, 75.62; H, 7.00.

(27) Calcd for $\text{C}_{28}\text{H}_{34}\text{O}_6$ (mol wt 490): C, 73.44; H, 6.99.

The Synthesis and Birch Reduction of

2-Isoamyl-3-methyl-4-methoxy-2,3-dihydrobenzofurans and Related Compounds¹

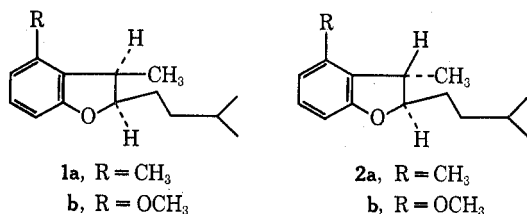
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Conditions have been found by which Birch reduction, followed by hydrolysis of *cis*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofuran (1a), gave 75% of α,β -unsaturated ketone. Stereospecific catalytic reduction of the carbon-carbon unsaturation could not be attained. 4-Methoxy-2-isoamyl-3-methyl-2,3-dihydrobenzofuran (9b) was prepared in good yield, and was converted into *cis*-2-isoamyl-3-methyl-4-keto-2,3,4,5,6,7-hexahydrobenzofuran in good yield. Mass spectral fragmentation patterns for perhydrobenzofurans and related compounds have been determined.

The synthesis and proof of configuration of *cis*- and *trans*-2-isoamyl-3,4-dimethyl-2,3-dihydrobenzofurans (1a and 2a), which were needed for syntheses in the fumagillin series, were reported recently.² The present



paper describes a study of the Birch reduction of the *cis* compounds 1a as well as the synthesis and Birch reduction of the corresponding 4-methoxy compound 1b; the *trans* compound 2b was also prepared.

The *cis* compound 1a was prepared by catalytic reduction of the corresponding 2-isoamyl-3,4-dimethylbenzofuran, using platinum and hydrogen in ethanol; the product, obtained in 92% yield, was 98% pure by vpc. Reduction of 1a with 16 g-atoms of lithium in liquid ammonia, *t*-butyl alcohol, and ether,^{3,4} followed by methanol, gave a product which showed no aromatic protons in the nmr, and showed a deficit of vinyl

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