was crystallized from methylene chloride–methanol. In this way N-acetylated **10b** gave material with mp 212–214°, identical in every respect with a known sample of 1-amino-3-methoxyestra-1,3,5(10)-trien-17-one (**10b**). The main product afforded colorless crystals (2.40 g) of 1,11α-imino-3-methoxy-estra-1,3,5(10)-trien-17-one (**14**), mp 199–201°. Material of comparable purity, obtained from another run, had the following properties: $\lambda_{max}$ 212, 235 (sh), 293 mμ (ε 28,000, 5800, 3550); $[\alpha]D$ +164°; $\nu_{max}^{KBr}$ 3300, 1130, 824, 794, and 667 $cm^{-1}$; nmr, 6.20 (s, C-2 + C-4 H), 3.72 (s, $OCH_3$), 0.98 ppm (s, C-18 $CH_3$).

*Anal.* Calcd for $C_{19}H_{23}NO_2$ (297.38): C, 76.73; H, 7.80; N, 4.71. Found: C, 76.81; H, 7.70; N, 4.66.

**Method B.**—The second half of the crude product was warmed and stirred with 125 ml of 1 *N* hydrochloric acid. The aqueous solution was decanted from some dark insoluble material, extracted with ether, and made basic with 30 ml of 5 *N* sodium hydroxide solution. The mixture was extracted with methylene chloride, the extract washed with water, dried over sodium sulfate, and evaporated to 2.85 g of tan solid. This material was acetylated as in method A and the product crystallized from methylene chloride–methanol to furnish 2.82 g (68%) pale tan crystals, mp 249–253°, which was pure N-acetylated **14** by infrared and tlc analysis. Hydrolysis of the product, as in method A, followed by a single crystallization from methylene chloride–methanol, gave 2.26 g of 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**), mp 199–200°.

**1,11α-Deuterioimino-3-methoxyestra-1,3,5(10)-trien-17-one.**—1-Butanol (5 ml) was shaken with three 5-ml portions of heavy water (Matheson Coleman and Bell, 99.5 mole %) taking 2–3 min for each equilibration. The resulting deuterated 1-butanol was dried over anhydrous sodium sulfate, filtered, and warmed for a few minutes on the steam bath with 200 mg of 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**) (mp 199–201°). The solution was allowed to stand overnight at room temperature, then evaporated to give 194 mg of colorless crystals, mp 198–202°, which were completely N-deuterated as shown by nmr analysis.

**1,11-Imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (15).**—A mixture of 892 mg (3.0 mmoles) of 1,11α-imino-3-methoxyestra-1,3,5(10)-trien-17-one (**14**) and 300 mg of 10% palladium on carbon (Baker) in 45 ml of xylene was stirred and refluxed for 1 hr. After cooling to room temperature, the mixture was filtered through 18 g of Magnesol which was washed with *n*-hexane to remove the xylene and the product desorbed with 250 ml of methylene chloride. Evaporation of the methylene chloride filtrate gave 847 mg (95% yield) of white crystalline product, mp 197–201°. Crystallization from methanol in the presence of 1 drop of pyridine gave 739 mg, mp 202–204°, plus a second crop of 56 mg, mp 199–203°. Hence, the total yield of crystallized product was 794 mg (90%).

A single recrystallization from methanol gave an analytical sample: mp 203–205°; $\lambda_{max}$ 229, 272, 298 mμ (ε 34,000, 5470, 3690); $[\alpha]D$ +225°; $\nu_{max}^{KBr}$ 3344, 1730, 1289, 1185, 1135, 819, and 802 $cm^{-1}$; nmr, 6.53 (s, C-2 + C-4 H), 3.75 (s, $OCH_3$), 1.15 ppm (s, C-18 $CH_3$).

*Anal.* Calcd for $C_{19}H_{21}NO_2$ (295.37): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.33; H, 7.28; N, 4.85.

**3-Hydroxy-1,11-iminoestra-1,3,5(10),9(11)-tetraen-17-one (1).**—To 25.0 g of pyridine hydrochloride at 200° was added 1.1 g (3.72 mmoles) of 1,11-imino-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**15**) and the mixture was heated at 200–210° for 10 min in an atmosphere of argon. The mixture was cooled and dissolved in 75 ml of water. The tan precipitate (0.73 g) was filtered off and the filtrate was extracted with chloroform. Work-up of the extract gave an additional 0.23 g of crude product. The total product (0.96 g) was crystallized from methanol to give 851 mg (81% yield) of off-white crystals decomposing over the range 290–300°.

A single recrystallization from methanol gave material of analytical purity and unchanged decomposition point: $\lambda_{max}$ 229, 270, 301 mμ (ε 32,000, 5080, 3530); $[\alpha]D$ +331° (pyridine); $\nu_{max}^{KBr}$ 3380, 1725, 1133, 1062, and 828 $cm^{-1}$; nmr (in $d_6$-DMSO), 6.47 (m, C-2 H), 6.27 (m, C-4 H), 4.58 (m, OH), 1.12 ppm (s, C-18 $CH_3$).

*Anal.* Calcd for $C_{18}H_{19}NO_2$ (281.34): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.67; H, 7.06; N, 5.31.

**Registry No.**—**1**, 13211-86-4; **2**, 5976-62-5; **3**, 13871-33-5; **6**, 6654-12-2; **8**, 13871-34-6; **9**, 6654-39-3; **10a**, 6770-02-1; **10b**, 6654-42-8; **12**, 13871-38-0; **13**, 6654-40-6; **14**, 13871-40-4; **15**, 13211-82-0.

**Acknowledgment.**—We wish to thank Professor Howard E. Zimmerman, University of Wisconsin, for some stimulating discussions and invaluable suggestions on this work.

# Syntheses with Partially Benzylated Sugars. X.[1] A New Method for the Synthesis of Ketoses

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*Received June 6, 1967*

A sequence of reactions which involves the reduction of C-1 in a partially benzylated aldose and subsequent oxidation at C-4 or C-5 has been studied as a means of converting aldoses into ketoses. In the hexopyranose series the following transformations were carried out (Scheme I): 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) → 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**2**) → 2,3,4,6-tetra-*O*-benzyl-1-*O*-triphenylmethyl-D-glucitol (**3**) → 1,3,4,5-tetra-*O*-benzyl-6-*O*-triphenylmethyl-*keto*-L-sorbose (**5**) → 1,3,4,5-tetra-*O*-benzyl-L-sorbopyranose (**6**) → L-sorbose (**7**); the over-all yield from **1** to **7** was 33%. In the pentofuranose series an analogous procedure was applied to the synthesis of D-*threo*-pentulose (D-xylulose, Scheme II, **17**). 2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**8**) was reduced to 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**) from which both 2,3,5-tri-*O*-benzyl-1-*O*-triphenylmethyl-D-arabinitol (**11**) and 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinitol (**13**) were prepared. Oxidation of **11** and **13** with dimethyl sulfoxide–acetic anhydride gave 1,3,4-tri-*O*-benzyl-5-*O*-triphenylmethyl-*keto*-D-*threo*-pentulose (**14**) and 5-*O*-benzoyl-1,3,4-tri-*O*-benzyl-*keto*-D-*threo*-pentulose (**15**), respectively; removal of the masking groups from **14** or from **15** gave D-*threo*-pentulose (**17**). The potential utility of this general synthetic approach for the synthesis of substituted or otherwise difficultly accessible ketoses is pointed out. In pyridine solution at room temperature tosyl chloride converts 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**) into 1,4-anhydro-2,3,5-tri-*O*-benzyl-D-arabinitol (Scheme III, **18**). Two crystalline derivatives of **8**, namely, 2,3,5-tri-*O*-benzyl-D-arabinono-1,4-lactone (**21**) and *N*-benzyl-2,3,5-tri-*O*-benzyl-D-arabinonamide (**22**), are described.

Compared with the aldoses, the ketoses are less frequently encountered in nature and the methods available for their synthesis are both fewer and often either laborious or of limited applicability. For these reasons, our knowledge of the chemistry of the ketoses is rather narrower than that of the aldoses. The

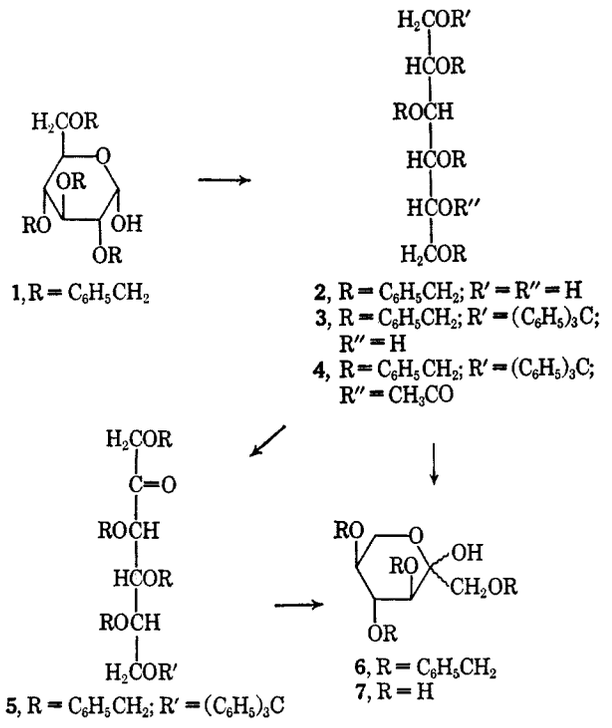
(1) Paper IX of this series: H. Kuzuhara and H. G. Fletcher, Jr., *J. Org. Chem.*, **32**, 2535 (1967).

(2) Chemical Foundation Fellow, 1966–1967; on leave from the Weizmann Institute of Science, Rehovoth, Israel.

objective of the research to be described here was to develop a new method for the synthesis of the ketoses which would complement existing methods and which might be of relatively general applicability.

As demonstrated in earlier papers of this series,[3-5] as well as in communications from other researchers,[6-8] aldopyranoses and aldofuranoses, fully benzylated save at C-1 and at the other carbon atom involved in the hemiacetal ring (C-4 or C-5), are readily accessible substances. In principle, any such benzylated aldohexopyranose or aldopentofuranose could be reduced to the corresponding partially benzylated alditol, the primary hydroxy group at C-1 in the latter could be selectively substituted, and the remaining hydroxyl function at C-4 or C-5 could be oxidized to a carbonyl group; subsequent removal of masking groups would then give a sugar in which C-4 or C-5 of the original aldose had become C-2 of a ketose.[9] In order to explore the feasibility of this synthetic pathway, we initially turned our attention to the readily accessible 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[6] (Scheme I, **1**).

SCHEME I

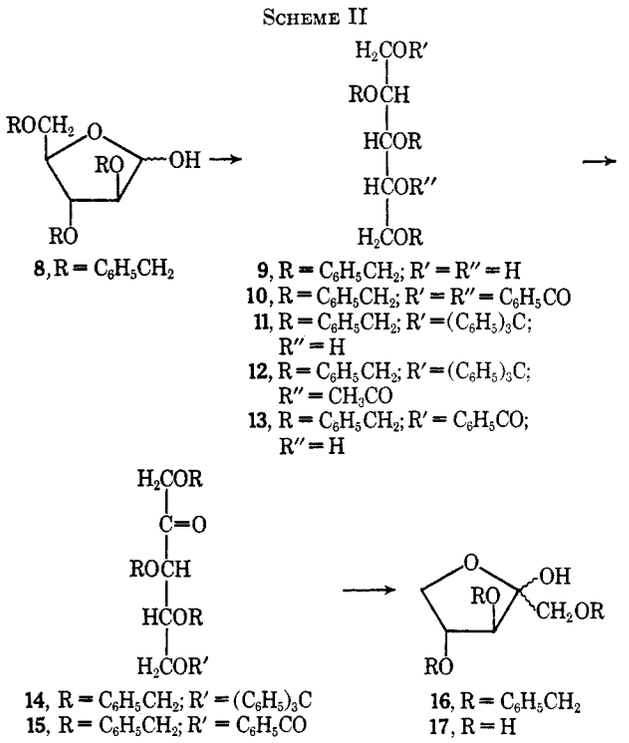



Reduction of this substance with lithium aluminum hydride gave 2,3,4,6-tetra-*O*-benzyl-D-glucitol (**2**) as a chromatographically homogenous syrup. Monotritylation of **2** afforded an amorphous trityl derivative in good yield; that attack had occurred at the primary position to give 2,3,4,6-tetra-*O*-benzyl-1-*O*-triphenylmethyl-D-glucitol (**3**) appeared a reasonable assumption which subsequently proved to be correct. A 5-*O*-acetyl derivative (**4**), made from the trityl ether (**3**), also proved to be amorphous.

Oxidation of **3** with dimethyl sulfoxide–acetic anhydride[10] at room temperature gave 1,3,4,5-tetra-*O*-benzyl-6-*O*-triphenylmethyl-*keto*-L-sorbose (**5**) in 79% yield, together with a small quantity of the acetate **4**; acidic detritylation of **5** led to the isolation of 1,3,4,5-tetra-*O*-benzyl-L-sorbopyranose (**6**) as a low-melting, crystalline solid. The masking groups in **5** or in **6** could be removed by catalytic hydrogenolysis over palladium to give L-sorbose (**7**). Although no particular attempt was made to maximize yields, the overall yield of L-sorbose (**7**) from **1** was 33%.

Having shown the apparent feasibility of this approach to the synthesis of ketoses, we then turned to the synthesis of a pentulose; of these we chose xylulose (*threo*-pentulose), first, because both enantiomorphic forms of this ketose are of biochemical importance[11,12] and, second, because the requisite starting materials, the 2,3,5-tri-*O*-benzylarabinofuranoses, are readily preparable[3,4] and, indeed, both enantiomorphs of this ether are currently available commercially.[13] Reduction of the D isomer (Scheme II, **8**) with sodium

SCHEME II




borohydride gave 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**) which was isolated in crystalline form. From this substituted pentitol were obtained a 1,4-di-*O*-benzoyl derivative (**10**), a 1-*O*-triphenylmethyl derivative (**11**), a 4-*O*-acetyl-1-*O*-triphenylmethyl derivative (**12**), and a 1-*O*-benzoyl derivative (**13**); all save the last were

(3) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).
(4) S. Tejima and H. G. Fletcher, Jr., *ibid.*, **28**, 2999 (1963).
(5) R. Harrison and H. G. Fletcher, Jr., *ibid.*, **30**, 2317 (1965).
(6) O. T. Schmidt, T. Auer, and H. Schmadel, *Ber.*, **93**, 556 (1960).
(7) P. W. Austin, F. E. Hardy, J. G. Buchanan, and J. Baddiley, *J. Chem. Soc.*, 1419 (1965).
(8) J. Gigg and R. Gigg, *ibid., Sect. C*, 82 (1966).
(9) Obviously, such a scheme could be applied to a benzylated aldopentopyranose to exchange its terminal functions although, with the ribose and xylose series, racemic products would be formed owing to the symmetry of the 2,3,4-tri-*O*-benzylpentitols involved. Application to a benzylated aldohexofuranose would lead to the synthesis of a 3-hexulose.
(10) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965); **89**, 2416 (1967).
(11) See, for instance, G. Ashwell, J. Kanfer, J. D. Smiley, and J. J. Burns, *Ann. N. Y. Acad. Sci.*, **92**, 105 (1961), and other papers in article 1 of that volume.
(12) The preparation of both enantiomorphic forms of xylulose has been studied extensively: *cf.* L. Hough and R. S. Theobald, *Methods Carbohydrate Chem.*, **1**, 94 (1962), and O. Touster, *ibid.*, **1**, 98 (1962).
(13) Pfanstiehl Laboratories, Inc., Waukegan, Ill. 60086.

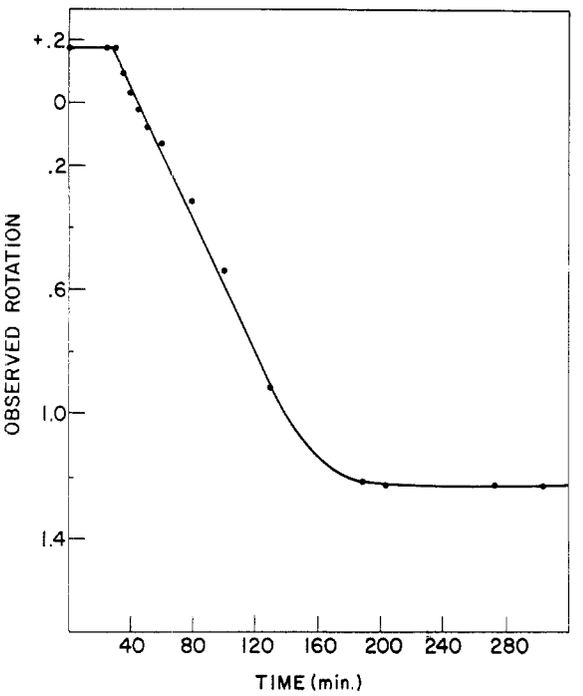
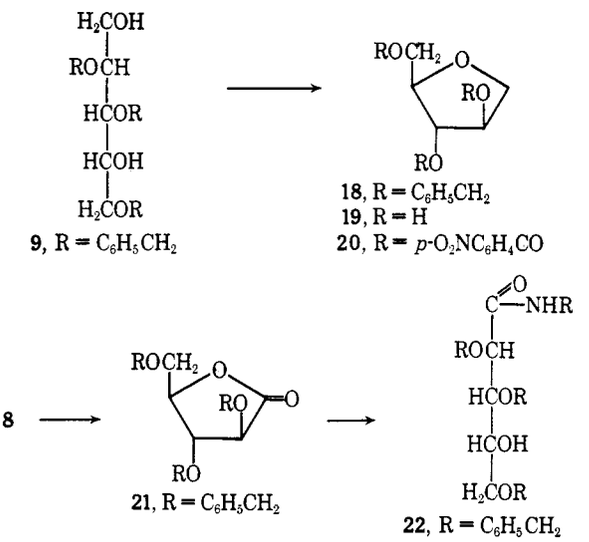



Figure 1.—Plot of rotation against time in oxidation of 2,3,5-tri-*O*-benzyl-1-*O*-triphenylmethyl-D-arabinitol (**11**) with dimethyl sulfoxide–acetic anhydride.

crystalline substances. The oxidation of 2,3,5-tri-*O*-benzyl-1-*O*-triphenylmethyl-D-arabinitol (**11**) with dimethyl sulfoxide–acetic anhydride was studied polarimetrically; as with the oxidation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1**) studied earlier,[14] an induction period was observed, followed by a reaction showing zero-order kinetics (Figure 1). The product, 1,3,4-tri-*O*-benzyl-5-*O*-triphenylmethyl-*keto*-D-*threo*-pentulose (**14**) was obtained as a chromatographically homogeneous syrup. In an analogous oxidation, 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinitol (**13**) was converted to amorphous 5-*O*-benzoyl-1,3,4-tri-*O*-benzyl-*keto*-D-*threo*-pentulose (**15**). Acidic detritylation of **14** or alkaline debenzoylation of **15** gave syrupy 1,3,4-tri-*O*-benzyl-D-*threo*-pentulose having an infrared spectrum with hydroxyl but no carbonyl absorption, indicating the furanose structure **16**. Removal of the benzyl groups from **16** by catalytic hydrogenolysis afforded D-*threo*-pentulose (**17**, D-xylulose) as a syrup which was chromatographically indistinguishable from authentic material.[15] Confirmation of the identity of the product was obtained through the preparation of 2,3-*O*-isopropylidene-D-*threo*-pentulofuranose[16] and of D-*threo*-pentulose *p*-bromophenylhydrazone.[17]

The technique for synthesizing ketoses which has been described here would appear to be potentially suitable for the preparation of terminally substituted ketose derivatives. Instead of masking C-1 in **2** or **9** with a trityl group, one might, for instance, introduce either the substituent eventually desired (phosphate, acetylated glycosyl group, etc.) at C-5 or C-6 or, alternatively, another masking group which could subsequently be replaced with the desired substituent. In this connection, it is relevant to describe an experiment with 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**) which was carried out in the course of the present research. An attempted monotosylation of this substance under conventional conditions gave a sulfur-free syrup with an infrared spectrum which showed no hydroxyl absorption; the elemental composition of the product indicated it to be an anhydrotri-*O*-benzylpentitol. On catalytic debenzylation it gave a syrup with the specific rotation of 1,4-anhydro-D-arabinitol[18] (Scheme III, **19** = 2,5-anhydro-D-lyxitol). Confirmation of the identity of this material was made through the preparation of 1,4-anhydro-2,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinitol (**20**); both **20**[18] and its enantiomorph[3] have been described in the literature.

SCHEME III




The intramolecular formation of ethers under forcing conditions of tosylation (excess tosyl chloride, elevated temperature) is not unknown. Treatment of 1,2-*O*-isopropylidene-α-D-glucofuranose with 3.3 molar equiv of tosyl chloride in boiling pyridine–chloroform for 8 hr has given 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose[19] while some of an anhydro-di-*O*-*O*-benzoyl-di-*O*-*p*-tolylsulfonylhexitol is formed during the prolonged tosylation of 1,6-di-*O*-benzoyl-D-mannitol.[20] However, anhydride formation at room temperature and in the absence of a large excess of tosyl chloride has not, as far as we are aware, been observed before.[20a] If 2,3,5-tri-*O*-benzyl-1-*O*-*p*-tolylsulfonyl-D-arabinitol is postulated as a not unreasonable intermediate, we must assume that, despite the presumed steric shielding provided by the benzyloxy groups at C-3 and C-5, the hydroxyl group at C-4 is readily accessible for nucleophilic attack on C-1.

In the course of this research, 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**8**) was oxidized with dimethyl sulfoxide–acetic anhydride to 2,3,5-tri-*O*-benzyl-D-arab-

(14) H. Kuzuhara and H. G. Fletcher, Jr., *J. Org. Chem.*, **32**, 2531 (1967).

(15) We are indebted to Dr. G. Gilbert Ashwell of this institute for the gift of an authentic specimen of D-xylulose. As of this writing, neither enantiomorph of this sugar has been obtained in crystalline form.

(16) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **120**, 607 (1937).

(17) O. T. Schmidt and R. Treiber, *Ber.*, **66**, 1765 (1933).

(18) J. Defaye, *Bull. Soc. Chim. France*, 2686 (1964).

(19) H. Ohle and E. Dickhäuser, *Ber.*, **58**, 2593 (1925); H. Ohle, L. von Vargha, and H. Erlbach, *ibid.*, **61**, 1211 (1928).

(20) A. Müller, *Ber.*, **65**, 1051, 1055 (1932); A. Müller and L. von Vargha, *ibid.*, **66**, 1165 (1933); P. Brigl and H. Grüner, *ibid.*, **66**, 1945 (1933); A. Müller, *ibid.*, **67**, 830 (1934).

(20a) NOTE ADDED IN PROOF.—J. M. Cox and L. N. Owen [*J. Chem. Soc., Sect. C*, 1121 (1967)] have found that the tosylation of D-galactose dibenzyl dithioacetal in pyridine at room temperature yields only 3,6-anhydro-D-galactose dibenzyl dithioacetal.

inono-1,4-lactone (21) and this substance was converted to *N*-benzyl-2,3,5-tri-*O*-benzyl-D-arabinonamide (22); the preparation and properties of these substances are described.

## Experimental Section[21]

**2,3,4,6-Tetra-*O*-benzyl-D-glucitol (2).**—Preliminary experiments appeared to indicate that the very low solubility of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**)[6,22] in methanol made its reduction by methanolic sodium borohydride impracticable. To a cooled suspension of lithium aluminum hydride (1.2 g) in dry tetrahydrofuran (200 ml) a solution of **1** (10.8 g) in dry tetrahydrofuran (100 ml) was added dropwise. After the mixture had been stirred at 10° for 1 hr, a small sample was removed, treated with hydrochloric acid, and extracted with dichloromethane. Examination of the extract (tlc, benzene–ether, 3:2, v/v) showed the absence of **1**. The excess of lithium aluminum hydride was decomposed through the addition of ethyl acetate and the mixture was added slowly, with stirring, to a mixture of ice and dilute hydrochloric acid. Dichloromethane was used to extract the crude product and the extract, after being washed with water, was dried over magnesium sulfate. Concentration of the extract gave a colorless syrup which could not be induced to crystallize. It was chromatographed on a column of silica gel using benzene–ether (3:2, v/v) to give 9.4 g (87%) of syrupy but chromatographically homogeneous product, $[\alpha]^{19}D$ +10.3 ± 0.2° (*c* 4.54, chloroform).

*Anal.* Calcd for $C_{34}H_{38}O_6$ (542.67): C, 75.25; H, 7.06. Found: C, 75.22; H, 6.82.

**2,3,4,6-Tetra-*O*-benzyl-1-*O*-triphenylmethyl-D-glucitol (3).**—2,3,4,6-Tetra-*O*-benzyl-D-glucitol (**2**, 4.0 g) and chlorotriphenylmethane (2.0 g) were dissolved in dry pyridine (20 ml) and the solution was stored at room temperature for 2 days. The mixture was poured into ice-cold water, stirred for 1 hr, and then cooled in the refrigerator for several hours. The clear supernatant solution was decanted and the syrup was dissolved in dichloromethane. After being washed successively with cold 5% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and water, the solution was dried over magnesium sulfate and concentrated *in vacuo* to a syrup which was chromatographed on silica gel (150 g) using benzene–ether (19:1, v/v). Fractions 47–61 contained homogeneous material (tlc) and, on pooling and concentration, gave 4.7 g (81%) of an amorphous product which could not be induced to crystallize, $[\alpha]^{20}D$ +12.1 ± 0.5° (*c* 3.54, chloroform).

*Anal.* Calcd for $C_{53}H_{52}O_6$ (785.00): C, 81.09; H, 6.68. Found: C, 80.95; H, 6.65.

**5-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-1-*O*-triphenylmethyl-D-glucitol (4).**—A sample of **3** (640 mg) was acetylated with a mixture of acetic anhydride (2 ml) and pyridine (5 ml) at room temperature overnight. The product was chromatographed on silica gel using chloroform–ether (97:3, v/v) to give a colorless, viscous syrup: yield, 510 mg (76%); $[\alpha]^{20}D$ +2.6 ± 0.3° (*c* 3.28, chloroform). The infrared spectrum of the substance showed absorption at 1240 and 1735 $cm^{-1}$ (OAc).

*Anal.* Calcd for $C_{55}H_{54}O_7$ (827.04): C, 79.88; H, 6.58. Found: C, 80.17; H, 6.54.

**1,3,4,5-Tetra-*O*-benzyl-6-*O*-triphenylmethyl-*keto*-L-sorbose (5).**—The trityl ether **3** (5.3 g) was dissolved in a mixture (50 ml) of dimethyl sulfoxide–acetic anhydride (3:2, v/v) and the solution was stored at room temperature overnight. Ice-cold water was added and the mixture was stirred for 1 hr, the aqueous phase was decanted, and the syrup residue was again washed with water. The washing was repeated three times and the crude product was then dissolved in dichloromethane and again washed with water. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* to a syrup which was chromatographed on a column of silica gel using benzene–ether (19:1, v/v) as eluent. The product (4.2 g, 79%) was obtained as a chromatographically homogeneous syrup, $[\alpha]^{20}D$ −4.2 ± 0.4° (*c* 2.87, chloroform); its infrared spectrum showed absorption at 1740 $cm^{-1}$ (CO) but no hydroxyl absorption.

*Anal.* Calcd for $C_{53}H_{50}O_6$ (782.98); C, 81.30; H, 6.44. Found: C, 80.98; H, 6.54.

**1,3,4,5-Tetra-*O*-benzyl-L-sorbopyranose (6).**—A solution of **5** (3.6 g) in aqueous acetic acid (100 ml, 70%, v/v) was heated at 65–70° for 2.5 hr. The solution was then cooled, ice was added, and the product was extracted with three 100-ml portions of chloroform; after being washed with water, the combined extracts were dried with magnesium sulfate and concentrated to dryness. The residue was chromatographed on a column of silica gel (200 g) using benzene–ether (85:15, v/v) for elution. Fractions 28–49 contained chromatographically homogeneous material and were pooled and concentrated to yield 1.85 g (74%) of crystalline **6**: mp 48–51°; $[\alpha]^{20}D$ −12.9 ± 0.3° (*c* 3.03, chloroform). The infrared spectrum showed hydroxyl absorption but no carbonyl absorption. Attempts to recrystallize the substance from a variety of solvent were unsuccessful.

*Anal.* Calcd for $C_{34}H_{36}O_6$ (540.63): C, 75.53; H, 6.71. Found: C, 75.43; H, 6.59.

**L-Sorbose (7). A. From 1,3,4,5-Tetra-*O*-benzyl-L-sorbopyranose (6).**—1,3,4,5-Tetra-*O*-benzyl-L-sorbopyranose (**6**, 1.0 g) was dissolved in aqueous dioxane (90%, v/v, 50 ml), palladium black, freshly made through the reduction of palladium chloride (150 mg), was added, and the suspension was shaken with hydrogen until absorption of the gas had ceased (*ca.* 3 hr). The catalyst was removed by filtration, washed with warm water, and the combined filtrate and washings were concentrated *in vacuo* (40° bath) to give 270 mg (81%) of L-sorbose: mp 157–159°; mmp (with authentic L-sorbose) 160–162°; $[\alpha]^{20}D$ −42.8 ± 0.3° (*c* 2.01, water).

**B. From 1,3,4,5-Tetra-*O*-benzyl-6-*O*-triphenylmethyl-*keto*-L-sorbose (5).**—The trityl ether **5** (5.0 g) was dissolved in aqueous dioxane (90%, v/v, 100 ml), palladium black (500 mg) and palladium chloride (50 mg) were added, and the suspension was shaken with hydrogen until absorption of the gas had ceased (4 hr). After removal of the catalyst, the solution was concentrated to a small volume, diluted with water (10 ml), and the triphenylmethane removed by filtration. The filtrate was stirred with Duolite A-4 until neutral and the resin was removed by filtration and thoroughly washed with water. After treatment of the combined filtrate and washings with decolorizing carbon (Darco X), the clear solution was concentrated *in vacuo* to a dry residue which was crystallized from a little water: yield, 600 mg (52%); mp 158–159°.

**2,3,5-Tri-*O*-benzyl-D-arabinitol (9).**—A solution of 2,3,5-tri-*O*-benzyl-D-arabinofuranose[13] (**8**, 5.0 g) in methanol (100 ml) was cooled to 5° and stirred while a solution of sodium borohydride (1 g) in methanol (30 ml) was added dropwise. The reaction mixture was stored at room temperature overnight, made slightly acidic through the addition of acetic acid, and then concentrated *in vacuo* at 35° (bath) to a small volume. The residue was dissolved in dichloromethane and the solution was washed with water; moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* to dryness. Dissolved in a mixture of ether (20 ml) and pentane (15 ml) and seeded,[23] the residue gave 4.1 g (82%) of crude 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**), mp 53–54°. After recrystallization from the same mixture of solvents, **9** had mp 54–55° and $[\alpha]^{22}D$ +1.3° (*c* 4.12, chloroform).

*Anal.* Calcd for $C_{26}H_{30}O_5$ (422.53): C, 73.91; H, 7.16. Found: C, 73.75; H, 7.15.

**1,4-Di-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinitol (10).**—A solution of 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**, 1.0 g) in a mixture of pyridine (10 ml) and benzoyl chloride (0.8 ml) was stored at room temperature for 2 days and then worked up in conventional fashion to yield a product which was crystallized from isopropyl alcohol (10 ml): yield, 1.22 g (82%); mp 85–86°. After recrystallization from isopropyl alcohol, the material had mp 86–87° and $[\alpha]^{22}D$ −8.5° (*c* 2.05, chloroform).

*Anal.* Calcd for $C_{40}H_{38}O_7$ (630.70): C, 76.17; H, 6.07. Found: C, 76.39; H, 5.91.

**2,3,5-Tri-*O*-benzyl-1-*O*-triphenylmethyl-D-arabinitol (11).**—2,3,5-Tri-*O*-benzyl-D-arabinitol (**9**, 5.0 g) was dissolved in anhydrous pyridine (20 ml) and a solution of chlorotriphenylmethane (3.46 g) in pyridine (8 ml) was added. The mixture was stored at room temperature for 48 hr, at 80° (bath) for 1 hr,

(21) Melting points are corrected. Thin layer chromatography was conducted on Silica Gel G (E. Merck AG, Darmstadt) using the solvent systems specified, components being detected by spraying with 10% sulfuric acid and heating at 100°. Column chromatography was carried out on silica gel (0.05–0.20 mm, E. Merck AG), 15-ml fractions being collected.

(22) For an improved procedure for the preparation of this substance, see T. D. Perrine, C. P. J. Glaudemans, R. K. Ness, J. Kyle, and H. G. Fletcher, Jr., *J. Org. Chem.*, **32**, 664 (1967).

(23) Seeds were originally obtained by chromatography of a crude preparation on a column of silica gel using benzene–ether (1:1, v/v) and crystallization from ether–pentane.

and it was then concentrated *in vacuo* to half its original volume. The cooled solution was poured into ice-cold water and stirred, the aqueous layer being decanted and the nonaqueous layer being washed with fresh water. The crude product was extracted with dichloromethane and the extract, after washing with water, was dried over magnesium sulfate and concentrated *in vacuo* to dryness. Dissolved in hot isopropyl alcohol (40 ml), the product crystallized on cooling: yield, 6.0 g (76%); mp 98–101°. Recrystallized from the same solvent, the product had mp 103–104° and $[\alpha]^{22}D \pm 0°$ (*c* 4.0, chloroform); a third crystallization failed to change its melting point further.

*Anal.* Calcd for $C_{45}H_{44}O_5$ (664.85): C, 81.29; H, 6.67. Found: C, 81.37; H, 6.64.

**4-*O*-Acetyl-2,3,5-tri-*O*-benzyl-1-*O*-triphenylmethyl-D-arabinitol (12).**—A portion (500 mg) of **11** was dissolved in a mixture of acetic anhydride (5 ml) and dry pyridine (7 ml) and the solution was stored at room temperature overnight. It was then poured into ice water and the precipitated syrup rubbed until it crystallized. After removal by filtration, the crude product was dissolved in ether and the solution was washed with water. Moisture was removed with sodium sulfate and the solution was concentrated *in vacuo* to yield a viscous syrup which was crystallized from its solution in ethanol: yield, 385 mg (72%); mp 63–64°. After recrystallization from ethanol, the product had mp 64.5–65° and $[\alpha]^{22}D -12.6°$ (*c* 1.0, chloroform)

*Anal.* Calcd for $C_{47}H_{46}O_6$ (706.89): C, 79.86; H, 6.56. Found: C, 79.78; H, 6.39.

**1-*O*-Benzoyl-2,3,5-tri-*O*-benzyl-D-arabinitol (13).**—2,3,5-Tri-*O*-benzyl-D-arabinitol (**9**, 8.5 g) was dissolved in dry pyridine (80 ml) and the solution, cooled to −10°, stirred while a solution of benzoyl chloride (3.0 g) in dry benzene (25 ml) was added dropwise over the course of 30 min. The mixture was stirred for 2 hr at −10° and then overnight at room temperature. A little ice was added and the mixture was stirred at room temperature for 1 hr and the diluted with ether. The solution was washed successively with cold 5% sulfuric acid, saturated aqueous sodium bicarbonate solution, and water. Moisture was removed with magnesium sulfate and the solution was then concentrated *in vacuo* to a syrup; examination (tlc, benzene–ether, 85:15, v/v) showed the presence of a main product, a component which moved faster than this (presumably the dibenzoate), a material with a migration rate close to that of the main product (4-*O*-benzoyl-2,3,5-tri-*O*-benzyl-D-arabinitol?), and a little unreacted **9**. The mixture was chromatographed on a column of silica gel using benzene–ether (85:15, v/v) to give 7.3 g (69%) of a chromatographically homogeneous syrup with $[\alpha]^{20}D -8.6 \pm 0.5°$ (*c* 1.92, chloroform).

*Anal.* Calcd for $C_{33}H_{34}O_6$ (526.63): C, 75.26; H, 6.51. Found: C, 75.45; H, 6.31.

**1,3,4-Tri-*O*-benzyl-5-*O*-triphenylmethyl-*keto*-D-*threo*-pentulose (14).**—In a preliminary experiment, **11** (500 mg) was dissolved in a mixture of dimethyl sulfoxide (9 ml) and acetic anhydride (6 ml) and the optical rotation of the solution was observed at 22° in a 1-dm polarimeter tube. The data thus obtained are plotted in Figure 1.

Compound **11** (5 g) was dissolved in dimethyl sulfoxide–acetic anhydride (30 ml, 3:2, v/v) and the solution was stored at room temperature for 18 hr. Cold water (120 ml) was added and the mixture was stirred for 30 min, the aqueous phase was decanted, and the yellowish, oily residue was washed twice more with water. The crude product was extracted with hexane and the extract was shaken many times with water; it was then washed with a 10% solution of silver nitrate and again with water; and, finally, it was dried with magnesium sulfate. Concentration of the solution *in vacuo* afforded a syrup (4.9 g) which was examined by tlc using benzene–ether (9:1, v/v). A major component ($R_f$ *ca.* 0.4) was found to be accompanied by a very minor one having a slightly higher mobility. The syrup was applied to a column of silica gel (250 g) and the column was washed with benzene (500 ml). Elution was then carried out with benzene–ether (19:1, v/v). Fractions 37–39 contained a mixture (200 mg) of the two components. Fractions 41–49 yielded a chromatographically homogeneous syrup: yield, 4.3 g (86%); $[\alpha]^{21}D -26.2°$ (*c* 2.1, chloroform). Attempts to crystallize the material were unsuccessful although it appeared to crystallize partially on prolonged storage.

*Anal.* Calcd for $C_{45}H_{42}O_5$ (662.84): C, 81.54; H, 6.39. Found: C, 81.35; H, 6.46.

The infrared spectrum of the substance showed a peak at 1735 $cm^{-1}$ (CO) but no hydroxyl absorption. Rechromatography of fractions 37–39 led to the isolation of **12**, identified by its melting point and by comparison of its infrared spectrum and chromatographic properties with those of an authentic specimen. The yield of **12** in this reaction varied from run to run, approaching 10% in some cases.

In one experiment, **11** was oxidized with dimethyl sulfoxide–pyridine–trifloroacetic acid–*N*,*N*-dicyclohexylcarbodiimide;[24] this combination of reagents proved to be less convenient, four products being detected by tlc, although column chromatography gave **14** in 61% yield.

**5-*O*-Benzoyl-1,3,4-tri-*O*-benzyl-*keto*-D-*threo*-pentulose (15).**—The monobenzoate **13** (5.0 g) was dissolved in dimethyl sulfoxide–acetic anhydride (50 ml, 3:2, v/v) and the solution, after storage at room temperature overnight, was worked up as described in the preparation of **14**. The crude product contained a major component (tlc, benzene–ether, 9:1, v/v), contaminated with faint traces of a faster moving substance. Column chromatography on silica gel using benzene–ether (9:1, v/v) afforded a chromatographically homogeneous syrup (4.2 g, 84%) which showed $[\alpha]^{20}D -38.8 \pm 0.5°$ (*c* 2.2 chloroform).

*Anal.* Calcd for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.46; H, 5.92.

**1,3,4-Tri-*O*-benzyl-D-*threo*-pentulose (16). A. From 1,3,4-Tri-*O*-benzyl-5-*O*-triphenylmethyl-*keto*-D-*threo*-pentulose (14).**—The trityl ether **14** (8.0 g) was dissolved in glacial acetic acid (60 ml) and the solution was diluted with water (40 ml). The turbid solution was then heated in a water bath at 60–65°, being stirred until the turbidity disappeared. Thin layer chromatography (benzene–ether, 9:1, v/v) was used to monitor the course of the reaction and showed, after 2 hr, that no starting material remained. Water (100 ml) was added and the product extracted with dichloromethane; the extract was washed successively with aqueous sodium bicarbonate solution and water, dried with magnesium sulfate, and concentrated *in vacuo*. Chromatography of the residual syrup on a column of silica gel using benzene–ether (85:15, v/v) afforded 4.4 g (87%) of pure product, $[\alpha]^{21}D -11 \pm 0.5°$ (*c* 1.96, chloroform, unchanged after 4 days).

*Anal.* Calcd for $C_{26}H_{28}O_5$ (420.48): C, 74.26; H, 6.71. Found: C, 74.26; H, 6.63.

The infrared spectrum of the substance showed hydroxyl absorption (3570 $cm^{-1}$) but no carbonyl absorption.

**B. From 5-*O*-Benzoyl-1,3,4-tri-*O*-benzyl-*keto*-D-*threo*-pentulose (15).**—To a solution of **15** (3.5 g) in dry methanol (60 ml) were added a few drops of methanolic sodium methoxide and the mixture was left at room temperature for 4 hr. It was then acidified slightly with acetic acid and concentrated *in vacuo;* the residue was extracted with dichloromethane and the extract was washed with water. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* to a syrup which was chromatographed on silica gel using benzene–ether (85:15, v/v) to give 2.1 g (75%) of pure **16**, $[\alpha]^{20}D -12 \pm 0.5°$ (*c* 2.03, chloroform). The infrared spectrum and chromatographic behavior of this product were indistinguishable from those of **16** prepared from **14**.

**D-*threo*-Pentulose (17).**—1,3,4-Tri-*O*-benzyl-D-*threo*-pentulose (**16**, 6.3 g) was dissolved in dioxane–water (9:1, v/v, 100 ml), and palladium black, freshly made by the reduction of palladium chloride (1 g) in methanol, was added. The suspension was shaken with hydrogen at room temperature until absorption of the gas had ceased, The catalyst was removed by filtration and washed with water; combined, the filtrate and washings were stirred with Duolite A-4 to ensure the removal of any traces of acid which may have been present. The solution was concentrated *in vacuo* and the residue dissolved in a little water, the resulting solution being passed through a small column of decolorizing carbon. The solution and aqueous washings from the column were combined and freeze-dried to give a colorless syrup: yield, 1.95 g. With descending paper chromatography, using butyl alcohol–pyridine–water (6:4:3, v/v) or ethyl acetate–acetic acid–formic acid–water (18:3:1:4, v/v), and either orcinol–hydrochloric acid or ammoniacal silver nitrate for development, the product was found to migrate at a rate which was indistinguishable from that of an authentic sample of D-*threo*-pentulose.[15] A trace of an unidentified, faster moving component was detected.

A sample (1.02 g) of the syrupy D-*threo*-pentulose was treated with acetone, anhydrous copper sulfate, and sulfuric acid as described for the preparation of 2,3-*O*-isopropylidene-D-*threo*-

(24) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5670 (1965).

pentulofuranose.[16] Recrystallized twice from ether–pentane (1:1, v/v), the derivative (300 mg, 23%) had mp 68°; 2,3-*O*-isopropylidene-D-*threo*-pentulofuranose is recorded as having mp 67–68°.[16] Another sample of **17** was converted into the *p*-bromophenylhydrazone which was recrystallized from ethyl acetate: mp 126–128°, $[\alpha]^{20}D$ +20.2 ± 1.0° (15 min) → −30.8 ± 1.0° (7 days, *c* 0.83, pyridine). For the *p*-bromophenylhydrazone of D-*threo*-pentulose, mp 128–129° and $[\alpha]^{20}D$ +24° (15 min) → −31° (pyridine) have been reported.[17]

**1,4-Anhydro-D-arabinitol (19) from 2,3,5-Tri-*O*-benzyl-D-arabinitol (9).**—To a solution of 2,3,5-tri-*O*-benzyl-D-arabinitol (**9**, 4.22 g, 10 mmoles) in dry pyridine (25 ml) was added dropwise a solution of *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmoles) in chloroform (15 ml) which was held at 0°. The solution was stirred at 0° for 2 hr and at room temperature overnight; water was then added and the product was extracted with dichloromethane. The extract was washed with cold 5% sulfuric acid and with water; moisture was removed with sodium sulfate and the solution was concentrated *in vacuo*. The residual syrup was chromatographed on a column of silica gel using benzene–ether (9:1, v/v) to give 1,4-anhydro-2,3,5-tri-*O*-benzyl-D-arabinitol (**18**, 3.0 g, 74%) as a chromatographically homogeneous syrup, $[\alpha]^{20}D$ +0.6° (*c* 3.17, chloroform). The product was sulfur free and its infrared spectrum showed no hydroxyl absorption.

*Anal.* Calcd for $C_{26}H_{28}O_4$ (404.51): C, 77.20; H, 6.98. Found: C, 76.88; H, 6.78.

A sample of **18** (5.0 g) was dissolved in methanol, palladium chloride (0.6 g) was added, and the suspension was shaken with hydrogen at room temperature until absorption of the gas had ceased. After removal of the catalyst, the solution was stirred with Duolite A-4, filtered through a layer of decolorizing carbon, and concentrated *in vacuo* to a colorless syrup, $[\alpha]^{25}D$ +23.7 ± 0.5° (*c* 2.95, methanol). Defaye[18] reported $[\alpha]^{25}D$ +25.3° (*c* 1.583, methanol) for 2,5-anhydro-D-lyxitol (**19** = 1,4-anhydro-D-arabinitol).

*Anal.* Calcd for $C_5H_{10}O_4$ (134.14): C, 44.77; H, 7.51. Found: C, 44.55; H, 7.47.

Acylation of **19** (1.1 g) with *p*-nitrobenzoyl chloride in conventional fashion yielded 3.7 g (78%) of 1,4-anhydro-2,3,5-tri-*O*-*p*-nitrobenzoyl-D-arabinitol (**20**): mp 78–80°; $[\alpha]^{20}D$ −84.3 ± 0.5° (*c* 1.01, chloroform). After recrystallization from benzene, the substance had mp 80–82°; Defaye[18] reported mp 80–81° and $[\alpha]^{25}D$ −85° (chloroform) for this substance while Barker and Fletcher[8] recorded mp 80–82° and $[\alpha]^{20}D$ +85.1° (chloroform) for its enantiomorph.

**2,3,5-Tri-*O*-benzyl-D-arabinono-1,4-lactone (21).**—2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**8**, 2.0 g) was dissolved in a mixture of dimethyl sulfoxide (6 ml) and acetic anhydride (4 ml) and the resulting solution was stored overnight at room temperature. The reaction mixture was poured into ice water (100 ml) and the mixture stirred for 1 hr, the precipitated solid then being removed by filtration, washed thoroughly with water, and dried: yield, 1.9 g (95%); mp 63–65°. The product thus obtained was homogeneous by tlc (benzene–ether, 9:1, v/v). It was recrystallized from cyclohexane (25 ml) to give 1.66 g of fine needles: mp 67°; $[\alpha]^{22}D$ +6.8° (*c* 1.1, chloroform). The infrared spectrum of the substance showed the absorption at 1775 $cm^{-1}$ characteristic of a γ-lactone.

*Anal.* Calcd for $C_{26}H_{26}O_5$ (418.50): C, 74.62; H, 6.26. Found: C, 74.91; H, 6.54.

***N*-Benzyl-2,3,5-tri-*O*-benzyl-D-arabinonamide (22).**—The lactone (**21**, 2 g) was dissolved in benzene (35 ml), benzylamine (5 ml) was added, and the mixture was stirred at room temperature for 2 hr and, finally, boiled gently under reflux for 1 hr. The cooled solution was diluted with benzene and washed successively with 5% hydrochloric acid, aqueous sodium bicarbonate solution, and water. Moisture was removed with magnesium sulfate and the solution was concentrated to give a crystalline residue (2.4 g). Tlc, using benzene–ether (9:1, v/v), showed that the product was contaminated with two faster moving components; no **21** was detected. The crude amide was chromatographed on a column of silica gel using benzene–ether (7:3, v/v), giving, in fractions 35–58, a chromatographically homogeneous material: yield, 2.1 g (84%); mp 91–93°. Recrystallization from ethyl acetate–pentane afforded 1.85 g of the pure amide (**22**): mp 95–96°; $[\alpha]^{20}D$ +37.6 ± 0.5° (*c* 1.78, chloroform).

*Anal.* Calcd for $C_{33}H_{35}NO_5$ (525.65): C, 75.40; H, 6.71; N, 2.66. Found: C, 75.24; H, 6.68; N, 2.70.

**Registry No.**—**2**, 14233-48-8; **3**, 14233-49-9; **4**, 14233-50-2; **5**, 14233-51-3; **6**, 14233-52-4; **7**, 87-79-6; **9**, 14233-53-5; **10**, 14233-54-6; **11**, 14233-55-7; **12**, 14233-56-8; **13**, 14233-57-9; **14**, 14233-58-0; **15**, 14233-59-1; **16**, 14233-60-4; **17**, 14233-61-5; **18**, 14233-62-6; **19**, 14233-63-7; **21**, 14233-64-8; **22**, 14233-65-9.

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# Photoinduced Reactions. VIII.[1,2] Photosensitized Oxidation of 3,5-Dihalogenophloretic Acids

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In order to elucidate the mechanism by which 3,5-diiodophloretic acid (I) is autoxided to 3,5,3′,5′-tetraiodothyropropionic acid (II), compound I was oxidized with various oxidizing agents, some of which are known to be one-electron transfer oxidizing agents. A small amount of II was detected in the reaction product in one case, while in others only polymers were formed. However, photooxidation of I in the presence of a sensitizer as well as oxidation with hypochlorite or with N-bromosuccinimide did not lead to dimerization or polymerization but to the formation of a spirolactone, 7,9-diiodo-1-oxaspiro[4,5]deca-6,9-diene-2,8-dione. Similar results were obtained with 3,5-dibromo- and 3,5-dichlorophloretic acid. Possible mechanisms for the formation of the spirolactone are discussed.

The last step in the biosynthesis of thyroxine is the conversion of 3,5-diiodotyrosine to thyroxine. Since an elucidation of the mechanism by which this conversion takes place is rendered difficult by the fact that the enzyme systems involved are not sufficiently known, nonenzymic model reactions have been investigated by several workers. These may be classified into two types. One of these, first described by von Mutzenbecher,[3] is the formation of thyroxine by incubation of diiodotyrosine at a slightly alkaline pH. The second kind of model reaction was first proposed by Hillmann[4] and later successfully carried out by Meltzer and Stana-

(1) Part VII: T. Matsuura and K. Ogura, *J. Am. Chem. Soc.*, **89**, 3850 (1967).

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(3) P. von Mutzenbecher, *Z. Physiol. Chem.*, **261**, 253 (1939).

(4) G. Hillmann, *Z. Naturforsch.*, **11B**, 424 (1956).