from solution. The crystals were filtered, washed with water and air dried on the filter pad. Recrystallization from either hot ethanol or hot ethyl acetate gave 0.858 g (80%): mp 205–206; $[\alpha]^{20}D$ +85.9 (*c* 1.92, chloroform); R_f 0.64 in solvent A.

Anal. Calcd for $C_{16}H_{22}O_{12}S$: C, 43.8; H, 5.02; S, 7.32. Found: C, 44.0; H, 4.90; S, 7.10.

The sulfone, dissolved in chloroform, showed peaks in the infrared spectrum at 1330 and 1145 cm^{-1} which are characteristic for asymmetric and symmetric sulfone stretching vibrations in $C-SO_2-C$ type compounds.

The sulfone can also be made from the sulfoxide as follows. To a mixture of 6 ml of glacial acetic acid and 3 ml of 30% hydrogen peroxide was added 1 g of the sulfoxide V. The mixture was allowed to stand at 25° for 48 hr then worked up as described above. Recrystallization from hot ethyl acetate gave 0.856 (83%), mp 205–206°.

Alicyclic Carbohydrates. XXIX.[1,2] The Synthesis of a Pseudo-Hexose (2,3,4,5-Tetrahydroxycyclohexanemethanol)

G. E. McCasland,[3] Stanley Furuta,

Department of Chemistry and Institute of Chemical Biology, University of San Francisco, San Francisco, California 94117

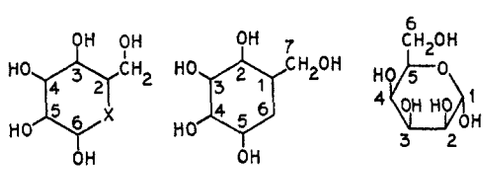
and Lois J. Durham

Department of Chemistry, Stanford University, Stanford, California 94305

Received October 18, 1965

The expression "pseudo-sugar" is proposed to designate any alicyclic analog of a cyclic monosaccharide, in which the usual ring-oxygen atom is replaced by methylene. A compound, 2,3,4,5-tetrahydroxycyclohexanemethanol, has been synthesized and appears to be the first known pseudo-hexose. It has the α-DL-talopyranose configuration. It was obtained by reduction of the corresponding tetraacetoxycyclohexanecarboxylic acid methyl ester which had been prepared by a Diels–Alder synthesis from 2-acetoxyfuran and maleic anhydride. Pentaacetate and trityl ether tetraacetate derivatives were also prepared. With the aid of nmr spectroscopy, it was established that the conformation with side chain equatorial was preferred for the pseudo-hexose and its derivatives. Conformational assignments were based upon spin–spin coupling patterns and comparisons with other spectra in the same series.

Recently several research groups have synthesized sugar analogs (**2** and **3**) in which the ring-oxygen atoms were replaced by other atoms, such as sulfur[4] or nitrogen (NH or NCOR).[5] Continuing our studies on alicyclic carbohydrates,[2] we have now synthesized a monosaccharide analog (**4**) in which the ring oxygen is replaced by *carbon* (CH_2). The term "pseudo-sugar"



1, X = O
2, X = S
3, X = NH or NCOR

4

5

has been coined to designate any such analog. It is hoped that pseudo-sugars may be found acceptable in place of corresponding true sugars to some but not all enzymes or biological systems, and thus might serve to inhibit growth of malignant or pathogenic cells.[6] Only aldohexopyranose analogs are here considered.[7]

Thirty-two stereoisomers (including anomers) are predicted for a true or pseudo-aldohexopyranose (**1** or **4**). The stereoisomer now reported has the α-DL-talopyranose or DL(1234/5) configuration[8a,8c] **5** or **11**. Syntheses of biologically more interesting analogs, *e.g.*, of glucose, mannose, and galactose, are in progress. In order to help increase the application of nmr spectroscopy in carbohydrate chemistry,[9] our numerous intermediates and products were characterized by nmr.

Synthesis of Pseudo-Talose

It appeared that pseudo-talose **11** would be the most readily accessible pseudo-hexose, since it might be

(1) Presented to the American Chemical Society (Division of Carbohydrate Chemistry), at the Winter Meeting, Phoenix, Ariz., Jan 1966, and (in part) at the 148th National Meeting, Chicago, Ill., Sept 1964.

(2) For preceding paper, see G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **29**, 2354 (1964). The combined series "Alicyclic Carbohydrates" incorporates papers I–XVIII in the series previously entitled "Stereochemistry of the Cyclitols," and also ten publications on hydroxylated cyclohexanes by G. E. McCasland and co-workers from the period 1949–1965 which were not assigned numbers at the time of publication. A complete list is available on request.

(3) To whom any correspondence should be addressed.

(4) Regarding sulfur-in-ring sugars, see (a) *Chem. Eng. News*, **41**, 70 (Sept 16, 1963); (b) R. L. Whistler, W. E. Dick, T. R. Ingle, R. M. Powell, and B. Urbas, *J. Org. Chem.*, **29**, 3723 (1964); (c) earlier work cited in these references.

(5) Regarding nitrogen-in-ring sugars, see A. J. Dick and J. K. N. Jones, *Can. J. Chem.*, **43**, 977 (1965), also earlier work of various authors there cited.

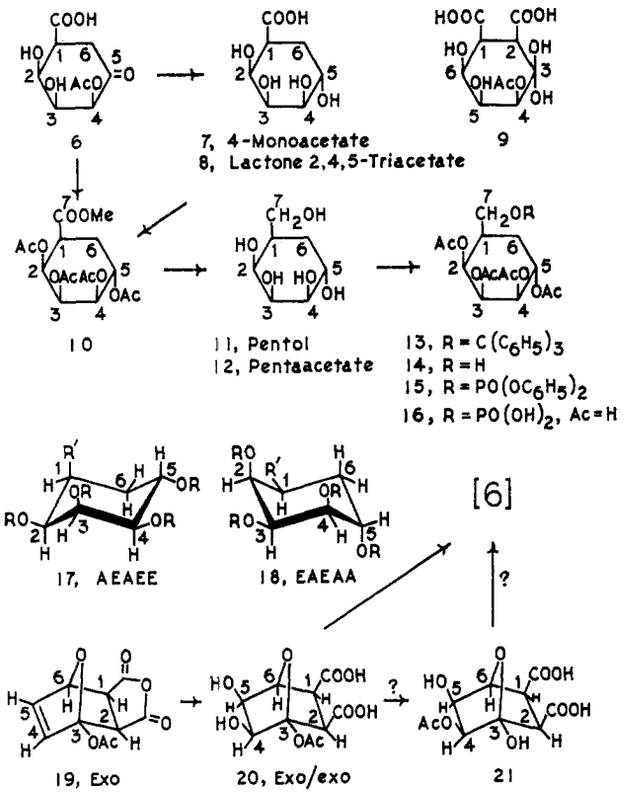
(6) P. A. J. Gorin, K. Horitsu, and J. F. T. Spencer in studies on certain inositols and sugars found that the absence of pyranose ring oxygen had little effect on the activity of certain glycosyl transfer enzymes [*ibid.*, **43**, 2259 (1965)].

(7) Pseudo-analogs of other aldoses or ketoses can similarly be defined. Thus certain (known) cyclohexanetetrols would correspond to pentopyranoses; certain hydroxymethylcyclopentanetriols to pentofuranoses; certain dihydroxyethylcyclopentanetriols to hexofuranoses; and certain cycloheptanepentols to hexoseptanoses. Pseudo-D-fructofuranose would be a certain isomer of trihydroxycyclopentanedimethanol.

(8) (a) For explanation of the fractional notation here used to designate stereoisomers, *e.g.*, DL(1234/5), see G. E. McCasland, *Advan. Carbohydrate Chem.*, **20**, 13 (1965). (b) The fractional notation for the two derivatives of 3-acetoxy-3,6-epoxycyclohexane presents a special problem, since neither "group" at position 3 is a hydrogen atom. According to a priority rule proposed by G. E. McCasland in 1953, the group *O–CH* comes alphabetically before the group *O–CO*, and is therefore the basis for fractional notation. Since in the stereoisomers **19** and **20**, the group *O–CH* at position 3 is *cis* to groups at 1, 2, and 6, or 1, 2, 4, 5, and 6, the fractional notation chosen is DL(1236/0) and DL(123456/0), respectively. (c) The organic compounds in this article are numbered and named as *cyclohexane* derivatives, according to *Chemical Abstracts* rules, *e.g.*, 2,3,4,5-tetrahydroxycyclohexanemethanol. Some chemists may prefer to use *carbohydrate* numbering and nomenclature, according to which the tertiary ring-carbon atom would be numbered 5 and the side-chain carbon atom 6, and the sixth ring-carbon atom would remain unnumbered (see formulas **5** and **11**).

(9) For reviews on the applications of nmr to carbohydrates, see L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964); G. E. McCasland, *ibid.*, **20**, 11 (1965).

CHART I



obtained from the methyl ester tetraacetate **10** recently employed by Daniels, Doshi, and Smissman in their synthesis of shikimic acid.[10-13] They prepared this ester from the lactone triacetate **8**. We now find it more expedient to treat the keto acid **6** successively with sodium borohydride, methanol–trifluoroacetic acid, and acetic anhydride (intermediates not isolated), giving an over-all yield of 41% (lit.[10b] 17%).

The crude product obtained by reduction of the ester **10** was acetylated, giving the crystalline pentaacetate, **12**. On acidic hydrolysis, there was obtained a high yield of the desired pseudo-α-DL-talopyranose (**11**), mp 162°.

This pentol was converted to its trityl ether tetraacetate **13**. Efforts to convert this trityl ether to the 2,3,4,5-tetraacetate **14**, and thus to the pseudo-hexose 7-phosphate **16**, for use in biological studies, are still in progress.

Nmr Evidence for Conformations.—The methyl ester tetraacetate was assigned the structure and configuration **10** by Daniels, Doshi, and Smissman.[10] Since no rearrangements or stereoinversions were probable in the reactions used, our pseudo-hexose and its pentaacetate and trityl ether tetraacetate would be expected to have the corresponding structures and configurations **11**, **12**, and **13**. The assignments are supported by analytic and spectroscopic data.

For each of these four compounds (**10–13**), two principal conformations were considered, AEAEE (**17**) or EAEAA (**18**). It was not easy to predict the

(10) R. Daniels, M. Doshi, and E. E. Smissman, (a) Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 36-O; (b) personal communication, March 1964.

(11) See also (a) E. E. Smissman, J. T. Suh, M. Oxman, and R. Daniels, *J. Am. Chem. Soc.*, **84**, 1040 (1962); (b) *ibid.*, **81**, 2909 (1959).

(12) See also E. E. Smissman and M. Oxman, *ibid.*, **85**, 2184 (1963).

(13) See also R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960).

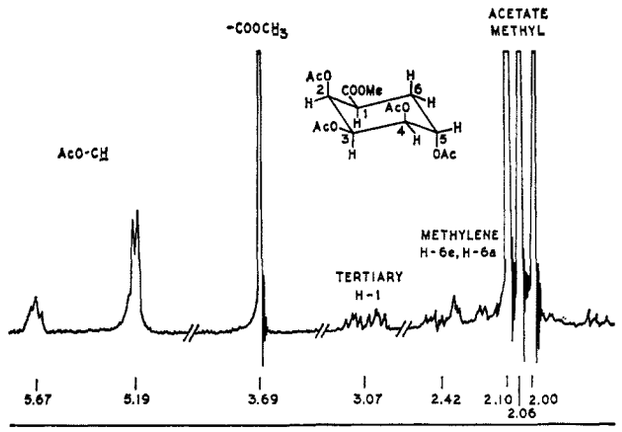


Figure 1.—Proton magnetic resonance spectrum at 100 Mc/sec of the DL(1234/5) diastereomer of methyl 2,3,4,5-tetraacetoxycyclohexanecarboxylate in chloroform-*d*.

actual conformations, since in each case the (otherwise favored) diaxial-triequatorial conformation would require the relatively large side chain to assume an unfavored axial orientation.

Experimentally, the pmr spectra of **10**, **12**, and **13** each were found to have one downfield and three upfield ring-proton signals in the AcO–C*H* region, as shown by integration. (See Experimental Section for nmr details.) This might once have been taken to indicate predominance in each case of the axial side-chain conformation **17**, which has one axial and three equatorial acetoxy groups.[14-16] However, recent refinements[14b,c] of rules for prediction of ring-proton chemical shifts lead to the opposite conclusion, now confirmed by further analysis of the spectra.

Methyl Ester Tetraacetate.—The acetate methyl pattern (Figure 1) of this compound (**10**) consisted of sharp singlets at 2.10, 2.06, and 2.00 ppm (six, three, and three protons, respectively). This pattern seemed more compatible with the presence of three axial (low-field) and one equatorial (high-field) acetate groups, as in formula **18**.

Conclusive evidence for this conformation was found in the spin–spin coupling pattern of the tertiary ring-proton H-1 of compound **10** at 60 and 100 Mc/sec. This eight-line pattern, centered at 3.07 ppm, seems well enough separated from neighboring signals to permit application of first-order theory, even at 60 Mc/sec. An axial orientation for H-1 is indicated by the presence of a large axial–axial coupling ($J_{1a,6a}$ = 11 cps), and two smaller axial–equatorial couplings ($J_{1a,6e}$ = 5 cps, $J_{1a,2e}$ = 3 cps). The side chain then must be equatorial, as it usually is in true pyranose sugars and their simple derivatives. Although all four acetate methyl groups give signals in the usual axial range for cyclitol acetates, as mentioned above, it

(14) (a) In 1958, it was suggested by R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider that, in six-membered ring compounds, axial *ring*-proton signals tend to appear upfield, and axial *acetate methyl* proton signals tend to appear downfield, compared to corresponding equatorial proton signals [*J. Am. Chem. Soc.*, **80**, 6098 (1958)]. (b) Improved rules for predicting chemical shifts of ring protons, especially in pyranose sugars, recently were proposed by R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965). (c) See also N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, pp 183–190.

(15) L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964); see especially pp 63 and 67.

(16) The reader should keep in mind that each axial substituent corresponds to an equatorial ring proton, and *vice versa*.

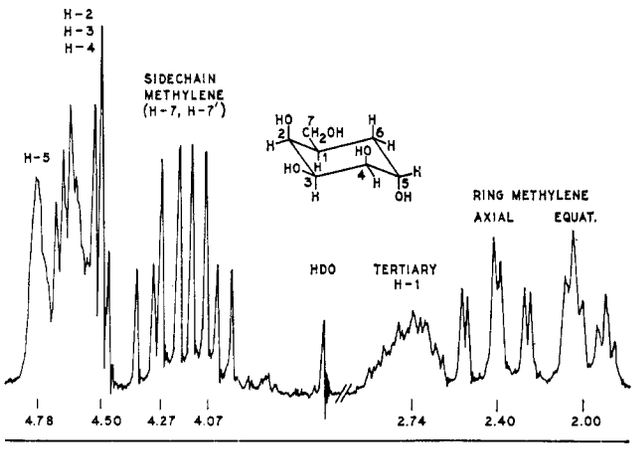


Figure 2.—Proton magnetic resonance spectrum at 100 Mc/sec of pseudo-α-DL-talopyranose in pyridine.

now appears that three of the groups are axial, and the remaining one (probably at 2.00 ppm) is equatorial.

The spectrum for the compound **10** thus appears to obey the "axial downfield" rule[14,15] for acetate methyl protons, as do also the spectra for compounds **12** and **13** (see below). However, the spectrum of **10** (and also of **12** and **13**) is an apparent exception to the once widely accepted "axial upfield" rule[14,15] for *ring* protons in cyclitols or sugars. The observed ring-proton chemical shifts are in conformity with more refined rules recently proposed.[14b,c]

Since the compound **10** (conformation **18**) has one axial and three equatorial (AcO–C*H*) ring protons, either two equatorial protons are shielded more than the third, causing their signals to move upfield near the axial signal,[17] or, alternatively, the single axial proton is deshielded more than any of the equatorial protons.

Pseudo-Hexose Pentaacetate.—The spectrum of compound **12** contained the expected[15] downfield singlets for axial acetate methyl groups at 2.08 and 2.07 ppm (three and six protons, respectively) and upfield singlets for the equatorial and side-chain groups at 2.03 and 2.01 ppm (three protons each).

The conformation **18** is also suggested by similarity of the AcO–C*H* ring-proton spectrum of **12** to that of **10** (low-field one-proton triplet and a higher field three-proton multiplet). The triplet (J = 2–3 cps) was centered at 5.38 ppm.

The tertiary proton H-1 in compound **12** was not as readily observed as in **10**, due to additional coupling with the side-chain methylene protons, which produced a broad complex multiplet. Analysis of this multiplet was difficult, even at 100 Mc/sec. However, simultaneous irradiation[18,19] of the two side-chain methylene protons of compound **12** (nuclear magnetic triple resonance) collapsed the multiplet into a pair of triplets. These triplets, although not too well resolved, appear to result from an axial–axial coupling ($J_{1a,6a}$ = 11–12 cps), plus two axial–equatorial couplings (about 6 cps each), further supporting the conformation **18** for compound **12**.

Trityl Ether Tetraacetate.—This compound **13** is believed also to have a favored conformation **18**, as indicated by the similarity of its ring-proton (AcO–C*H*) spectrum to that of compounds **10** and **12**. The AcO–C*H* spectrum once again consisted of a low-field one-proton triplet, and a higher field three-proton multiplet. The multiplet this time was much broader, presumably due to long-range shielding by the trityl group of one or more of the three protons. The acetate methyl singlets of **13** are more widely separated (2.10, 2.01, 1.92, and 1.83 ppm), due also to long-range shielding by the bulky trityl group. The tertiary proton (H-1) multiplet of this compound was very difficult to observe (at 60 Mc/sec), but it is believed to be centered at about 2.5 ppm, based on the degree of perturbation of the doublet (3.08 ppm) of the two neighboring side-chain methylene protons.

Pseudo-Hexose Free Pentol.—When the spectrum of pseudo-talose itself (**11**) was recorded in deuterium oxide, the tertiary proton H-1 signals were difficult to observe, even at 100 Mc/sec. However, in pyridine (see Figure 2) the resolution was strikingly improved. The axial nature of H-1 was then confirmed by the broadness of its pattern, resulting from axial–axial coupling with the neighboring axial ring proton at position 6 (formula **18**), plus couplings with the two neighboring equatorial ring protons, and with the side-chain methylene protons. In pyridine solution, the signals of the ring methylene and side-chain methylene protons themselves also were well resolved. Once again, the side chain of **11** must be equatorial, as it is in compounds **10**, **12**, and **13**.

Synthesis of the Keto Acid

The keto acid **6** needed for our pseudo-talose synthesis was prepared from 2-acetoxyfuran[20–22] by the ingenious route (see Chart I) developed recently by Daniels, Doshi, and Smissman[10] for their synthesis of shikimic acid. Using this route, the Diels–Alder adduct[20,23] **19** from 2-acetoxyfuran and maleic anhydride is hydroxylated and hydrolyzed, to give the diol diacid[23] **20**. The latter, on prolonged reaction with water at room temperature, undergoes a remarkable series of transformations—acetyl migration, opening of the 1,4-epoxide ring, carbonyl liberation, and decarboxylation—to produce the keto acid **6**.[10]

The previous workers proposed structures and configurations for each of these products, but in view of the numerous alternative structures possible, it appeared that more complete characterization of the

(17) If the axial proton signal is contained in the upfield three-proton pattern, it is possible that at extremely high resolution signals of the two upfield equatorial protons would be found to be *slightly* downfield from it. The compound would then still obey the axial upfield rule in a formal sense, but not in a useful sense.

(18) L. F. Johnson, "Technical Information Bulletin," Vol. III, No. 3, Varian Associates, Palo Alto, Calif., 1962, p 5.

(19) See also R. Freeman and D. H. Whiffen, *Mol. Phys.*, **4**, 321 (1961).

(20) (a) N. Clauson-Kaas and N. Elming, *Acta Chem. Scand.*, **6**, 535 (1952). (b) By the "lead tetraacetate" method of these authors we were able to obtain only about a 25% yield of 2,5-diacetoxy-2,5-dihydrofuran.

(21) (a) M. P. Cava, C. L. Wilson, and C. J. Williams, *J. Am. Chem. Soc.*, **78**, 2303 (1956). (b) By the procedure of these authors, we prepared eight batches of 2-acetoxyfuran with yields of 26–29 g (60–69%), reported 82%. Our products were collected over a 1–2° range at about 22° (1.5 mm), or 29° (2 mm); lit. bp 30–40° (3 mm). This product turns orange and polymerizes on long standing at room temperature.

(22) (a) N. Clauson-Kaas, S-O. Li, and N. Elming, *Acta Chem. Scand.*, **4**, 1233 (1950). (b) By the "bromine" procedure of these authors we prepared eight batches of 2,5-diacetoxy-2,5-dihydrofuran, with yields of 68–82% (reported 83%). Our products were collected over a 1 or 2° range at about 91° (0.7 mm) or 107° (3 mm); lit. bp 130–140° (10–15 mm).

(23) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).

synthetic intermediates, especially by nmr,[24] would be desirable. The new evidence obtained will now be described; in general, it supports the conclusions of Daniels, Doshi, and Smissman.

The spectrum for the anhydride **19** contained a sharp AB pattern produced by the protons H-1 and H-2. The near-zero coupling between H-1 and the bridgehead proton H-6 supports the *exo* configuration, in which the dihedral angle between H-1 and H-6 is about 90°.[25] If the configuration were *endo*, this angle would be about 30–40°, and an observable coupling effect would be expected. The bridgehead proton shows only a small coupling to the neighboring vinyl proton H-5.

The spectrum of the diol diacid **20** in dimethyl-d_6 sulfoxide contained a sharp singlet produced by the bridgehead proton H-6. The lack of coupling between H-6 and the neighboring protons H-1 and H-5 confirms the *exo-exo* configuration, in which both of the dihedral angles would be about 90°. The spectrum also contains two AB patterns, one produced by the pair of α-carboxylic protons H-1 and H-2, the other at lower field by the pair of α-hydroxylic protons H-4 and H-5. The vicinal coupling between H-1 and H-2 (J = 10 cps) is somewhat larger than that between H-4 and H-5 (J = 6 cps). The difference seems to be greater than would be predicted from electronegativities.[26]

Daniels, Doshi, and Smissman[10] reported that the diol diacid is obtained as a *monohydrate* (mp 156°) after one recrystallization (but not after four) from methanol–isoamyl acetate. This structure (hydrate of **20**) apparently is now confirmed. Other structures considered by us included the *gem*-diol (carbonyl hydrate) **9** in which the acetate group conceivably might be at position 4, 5, or 6, instead of 3.

It is also possible that the *anhydrous* diol diacid, mp 171° dec (which might be a ketone but not a *gem*-diol), has the acetate group at position 4, 5, or 6; we did not examine this compound.

The spectrum of the diol diacid in water (deuterium oxide) showed continuous changes when recorded at intervals up to 24 hr after solution. These changes no doubt reflect the previously reported[10] reactions of acetyl migration, epoxide opening, etc., but have not been analyzed in detail.

The reported[10] structure **6** for the keto acid monoacetate appeared to need verification, because (1) the acetate group conceivably might be at position 2, 3, or 5 (enol acetate), instead of 4; and (2) the carbonyl group might actually exist as a hemiketal owing to interaction with the position-2 hydroxyl group. (The reported acetonation[10] of the keto acid monoacetate seemingly would exclude the 3-monoacetate, but not the 2- or 4-monoacetate.)

The spectrum of the keto acid **6** was first observed in deuterium oxide and contained signals suggesting the presence of some lactone at equilibrium. Analysis had shown that the *crystalline* keto acid monoacetate is not a lactone. The carboxyl group, which possibly is equatorial in the free acid, must become axial in the lactone.

When the spectrum of **6** was observed in *pyridine*, however, no lactone was observed, and the spectrum confirmed the previously assigned structure **6** in every respect.[27]

The lactone triacetate **8** conceivably might have a β- or δ-lactone ring; the nmr spectrum, however, supports the γ structure previously assigned.[10]

Experimental Section[8]

All melting and boiling points have been corrected. Melting points unless otherwise noted were measured on a Nalge-Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Darco G-60 brand[28] of decolorizing charcoal was used. Petroleum ether of bp 30–60° was used.

Proton magnetic resonance spectra were recorded on a Varian A-60 or HR-100 spectrometer. Field-swept double-resonance experiments were conducted on the HR-100 after the method of Johnson,[18] using the fixed frequency of a V-3521-A nmr integrator and a variable frequency from a Hewlett-Packard hp-200-J audio oscillator, monitored by a hp-521-C frequency counter. Chemical shifts are reported as parts per million (ppm) on the δ scale. Internal tetramethylsilane (TMS) was used as zero reference in chloroform-*d*, dimethyl-d_6 sulfoxide, and pyridine solutions. External TMS or internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used in deuterium oxide solutions.

DL(1236/0) or *exo/cis* Diastereomer[9b] of 3-Acetoxy-3,6-epoxy-4-cyclohexene-1,2-dicarboxylic Acid Anhydride (19).—In six experiments, from 12 to 28 g of 2-acetoxyfuran[20,21] was treated with maleic anhydride by the procedure of Clauson-Kaas and Elming,[20] giving the anhydride product, mp 132–133°, in yields of from 67 to 90% (lit.[20] mp 132–133°, 67%).

The 60-Mc/sec pmr spectrum in chloroform-*d* showed a three-proton acetate methyl singlet at 2.27 ppm and a sharp AB pattern consisting of doublets centered at 3.44 (H-1) and 3.77 ppm (H-2). It contained also an ABX pattern, with the X or H-6 portion a poorly resolved doublet (J about 1.5 cps) centered at 5.36 ppm, and the very closely coupled AB portion (H-4 and H-5) centered at 6.74 ppm (J_{AB} about 6 cps). The H-1 signal showed slightly less ringing than H-2, which may indicate a very small, nearly zero, coupling with H-6.

DL(123456/0) or *exo-cis/exo-cis* Diastereomer of 3-Acetoxy-4,5-dihydroxy-3,6-epoxy-1,2-cyclohexanedicarboxylic Acid (20).—In five experiments by the procedure of Daniels and Fischer,[23] using up to 34 g of the anhydride **19**, from 50 to 69% of the once-recrystallized product was obtained (lit.[23] 54%). Our preparations melted at 156–157° dec (lit.[23] mp 155–156° dec, for the monohydrate; 171° dec, anhydrous).

The 60-Mc/sec pmr spectrum was recorded immediately after solution in deuterium oxide (external TMS). A three-proton acetate methyl singlet was observed at 2.86 ppm. Two AB patterns were present, the first with doublets (J = 10 cps) centered at 3.77 and 4.19 ppm, the second with doublets (J = 6.5 cps) centered at 4.64 and 4.86 ppm. The bridgehead proton (H-6) signal presumably was hidden in the HDO signal at 5.2 ppm, along with the exchangeable proton signals. A shoulder on the HDO signal became visible at 100 Mc/sec. After standing 24 hr in the refrigerator, the deuterium oxide solution was again observed. The spectrum had changed completely, indicating that reaction had taken place (see introductory section).

In dimethyl-d_6 sulfoxide solution, the ring proton signals were distinct and stable, despite traces of water in the solvent (signal at 4.85 ppm) which exchanged with the carboxylic and hydroxylic protons. The bridgehead proton H-6 was now visible as a sharp singlet at 4.37 ppm (little or no coupling with H-1 or H-5). One AB pattern (for H-1 and H-2) now had doublets

(24) The nmr spectrum of the keto acid **6** reportedly was observed by Daniels, *et al.*,[10] but no details were given.

(25) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(26) See ref 14c, p 52 ff.

(27) If the keto acid monoacetate had a 2-acetate or 3-acetate structure, a triplet or pair of doublets should be observed at low field. If it had a hemiketal structure, the spectrum should show greater resemblance to the spectrum of the diol diacid **20** than it actually does. If it had an enol acetate structure, the one vinyl proton should produce a low-field signal showing spin-coupling with one of the other ring protons, whose signals would appear at higher field.

(28) A product of Darco Division, Atlas Powder Co., Wilmington, Del.

centered at 3.02 and 3.35 ppm (J = 10 cps). The other AB pattern (for H-4 and H-5) was now at 4.08 and 3.90 ppm (J about 6 cps), and showed some broadening due to residual coupling with the hydroxyl protons (broadening removed by adding a little deuterium oxide). The acetate methyl singlet now appeared at 2.04 ppm.

DL(1234/0) **Diastereomer of 4-Acetoxy-2,3-dihydroxy-5-oxocyclohexanecarboxylic Acid (6).**—In eight experiments, the diol diacid **20** was treated by the procedure of Daniels, *et al.*,[10] giving the product, mp 146–147°, in yields of from 58 to 88% (lit.[10] mp 146–147°, 51%).

In deuterium oxide, the 60-Mc/sec pmr spectrum[24] indicated the presence of more than one compound (or conformation) even within 1 min of the solution time; the spectrum showed no further change up to 24 hr. The spectrum contained two different acetate methyl signals (2.63 and 2.68 ppm) and two different H-4 doublets (J = 3–4 cps), centered at 5.60 and 5.97 ppm. The high-field portion of the eight-line H-1 signal was partly covered by an interfering signal.

In pyridine at 60 or 100 Mc/sec, however, the typical spectrum of a pure substance, consistent with the structure **6**, was obtained. The acetate methyl produced a sharp singlet at 2.04 ppm. The proton H-4 produced a doublet centered at 5.82 ppm (J = 3 cps). The protons H-2 and H-3 produced a nonresolved pattern in the region 4.8–5.0 ppm. Multiplets attributed to H-1, H-6_e, and H-6_a were centered approximately at 3.5, 3.39, and 2.78 ppm, respectively. Although the H-1 signal was complicated by coupling with H-2, and badly overlapped by the signal of H-6_e, the coupling constants were estimated roughly to be $J_{6a,6e}$ = 16 cps, $J_{1a,6a}$ = 8 cps.

DL(1234/5) **Diastereomer of 2,4,5-Triacetoxy-3-hydroxycyclohexanecarboxylic Acid Lactone (8).**—An 11.4-g portion of the keto acid monoacetate **6** was reduced and acetylated essentially by the procedure of Daniels, Doshi, and Smissman.[10] The crude product (an oil), however, was purified by chromatography, using an 8 × 80 mm column of basic Woelm aluminum oxide,[29] and benzene as eluting solvent. The eluate was still an oil, but crystallized on treatment with absolute ethanol, giving colorless product, mp 152–156°. This material was recrystallized, giving 3.6 g (24%) of product melting at 162–163° (lit.[10] 29%, mp 158–159°).

The pmr spectrum at 60 and 100 Mc/sec in chloroform-*d* contained sharp acetate methyl singlets at 2.12 (six protons) and 2.05 ppm (three protons). Narrow multiplets at 2.82 and 4.82 ppm were attributed to the equatorial protons H-1 and H-3, respectively. An unresolved three-proton pattern in the region 4.9–5.3 ppm was assigned to H-2, H-4, and H-5. The ring methylene protons produced complex multiplets at 1.82 (H-6_e) and 2.45 ppm (H-6_a).

DL(1234/5) **Diastereomer of Methyl 2,3,4,5-Tetraacetoxycyclohexanecarboxylate (10). A. From the Lactone Triacetate.**—The method was essentially that of Daniels, *et al.*[10] From 300 mg of the lactone triacetate boiled 2 hr (instead of standing 18 hr) with methanolic hydrogen chloride, there was obtained 190 mg (51%) of product melting at 109–111° (lit.[10] 57%, mp 108–110°).

B. From the Keto Acid.—To 3.1 g of keto acid monoacetate in 30 ml of water was added dropwise with stirring 1.6 g of sodium borohydride in 30 ml of water. After stirring overnight, 25 ml of 12 M hydrochloric acid was added, and the solution boiled 2 hr under reflux, and then evaporated.

The residue was dried over potassium hydroxide *in vacuo*. Methanol (40 ml) and 1.0 ml of trifluoroacetic acid were added, and the mixture was boiled for 3 hr under reflux, stirred at 25° overnight, and evaporated. To the residue was added 25 ml of acetic anhydride containing 2 drops of 18 M sulfuric acid, and the mixture was heated 1 hr at 90–100°. The cooled mixture was evaporated, giving a viscous orange syrup, which was taken up in chloroform and processed in the usual manner. The crude product was crystallized from anhydrous diethyl ether–petroleum ether, giving 3.1 g of product, mp 106–109°. This material was recrystallized, giving 2.2 g (44%) of pure product, mp 111–112°.

The pmr spectra at 60 and 100 Mc/sec in chloroform-*d* contained sharp acetate methyl singlets at 2.10 (six protons), 2.06, and 2.00 ppm (three protons each). The carbomethoxy group gave a three-proton signal at 3.69 ppm. The AcO–C*H* spectrum consisted of a one-proton triplet at 5.67 ppm (sum of J = 5–6 cps), and a narrow three-proton multiplet at 5.19 ppm, which had a width at half-height of about 5–6 cps at either 60 or 100 Mc/sec. Complex multiplets at about 2.42 and 2.0 ppm were produced by the two ring methylene protons (latter multiplet obscured by acetate methyl signals). An eight-line pattern at about 3.08 ppm was assigned to the tertiary proton H-1 (J = about 11, 5, and 3 cps). (See introductory section.)

DL(1234/5) **Diastereomer of 2,3,4,5-Tetraacetoxycyclohexanemethanol Acetate (Pseudo-α-DL-talopyranose Pentaacetate) (12).**—To a boiling mixture of 0.500 g of lithium aluminum hydride and 25 ml of dry tetrahydrofuran under reflux was slowly added a solution of 0.900 g of the methyl ester tetraacetate in 15 ml of the same solvent. The mixture was boiled 2 hr longer, then stirred at 25° overnight.

Excess hydride was carefully decomposed at 0° by dropwise addition of water (hydrogen evolved). The pH was adjusted to 1 by addition of 12 M hydrochloric acid, and the resulting mixture was evaporated. The residue was taken up in 25 ml of water (treat with charcoal), and the solution was evaporated. Traces of water in the residue were removed by repeated additions and evaporations of absolute ethanol. The residue was dried over phosphorus pentoxide and potassium hydroxide.

Acetic anhydride (25 ml) and 1 drop of 18 M sulfuric acid were added, and the mixture was boiled 30 min under reflux, then evaporated. The residue was taken up in chloroform (filter) and further processed in the usual manner. The syrup obtained was taken up in 3.0 ml of ethyl acetate (treat with charcoal), and petroleum ether was added. The colorless crystals which separated were collected, giving 550 mg (59%) of product, mp 109–110°. Nonidentity with the starting material (mp 111–112°) was established by a mixture melting point and by infrared and nmr spectra.

A sample was recrystallized for analysis (mp 111–112°).

Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.56; H, 6.28.

The pmr spectrum at 60 and 100 Mc/sec in chloroform-*d* showed acetate methyl signals at 2.08, 2.07 (probably axial), 2.03, and 2.01 ppm (equatorial and side chain), with areas corresponding to three, six, three, and three protons, respectively. The tertiary proton H-1 produced a very complex pattern centered at about 2.35 ppm. The ring-methylene protons appeared as an unresolved multiplet at about 1.8 ppm. The two nonequivalent side-chain methylene protons produced the AB part of what to a first approximation might be described as an ABX pattern, with the A and B patterns apparently centered at 3.95 and 4.12 ppm, although the inner lines were not completely separated even at 100 Mc/sec. The coupling constants J_{AB}, J_{AX}, and J_{BX} had magnitudes of about 11, 7, and 8 cps, respectively. The remaining ring protons (H-2, H-3, H-4, and H-5) produced a one-proton triplet at 5.38 ppm and a three-proton pattern at about 5.15 ppm. The latter three protons had slightly different chemical shifts, since the pattern width increased on going from 60 to 100 Mc/sec. The similarity of this AcO–C*H* spectrum to that of the methyl ester tetraacetate **10** suggests that each compound has one equatorial and three axial acetate groups.

The broad multiplet of H-1 (2.35 ppm) was sharpened when either side-chain methylene proton was irradiated (nuclear magnetic double resonance)[18,19] using a frequency difference of 160 or 180 cps. By simultaneous irradiation of both side-chain methylene protons (triple resonance), the multiplet was transformed into a pair of triplets, not too well resolved, with one large and two small couplings (see introductory section.)

DL(1234/5) **Diastereomer of 2,3,4,5-Tetrahydroxycyclohexanemethanol (Pseudo-α-DL-talopyranose) (11).**—To 850 mg of the pentaacetate was added 5.0 ml of 2M hydrochloric acid and 5.0 ml of absolute ethanol. The mixture was boiled for 3 hr under reflux, then evaporated. The residue was purified by repeated additions and evaporations of isobutyl alcohol (5.0 ml each time). The residue was recrystallized from isobutyl alcohol (treated with charcoal), giving 340 mg (87%) of colorless product, mp 160–162°. A portion was recrystallized for analysis, melting point unchanged.

Anal. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.81; H, 8.05.

When the pmr spectrum at 60 and 100 Mc/sec was observed in deuterium oxide, using internal DSS reference, the tertiary proton H-1 appeared as a very complex multiplet centered at 2.0–2.1 ppm. The equatorial ring-methylene proton produced a pair of triplets centered at 1.5 ppm (J_{gem} = 11–12 cps, $J_{1a,6e}$ = 3 cps). The axial ring-methylene proton produced a multiplet

(29) A product of Alupharm Chemicals, New Orleans, La.

centered at 1.8 ppm (J_{gem} = 11–12 cps, $J_{1a,6a}$ = 9 cps). The remaining ring protons and the side-chain methylene protons produced an overlapping series of patterns downfield (3.3–4.2 ppm) which have not been analyzed, but appeared to contain a badly perturbed one-proton triplet (3.85 ppm, sum of J = 5–6 cps), and a two-proton narrow multiplet at about 4.04 ppm (not appreciably broadened at 100 Mc/sec).

The spectrum in pyridine (internal TMS) at 60 and 100 Mc proved more useful (see Figure 2); a trace of deuterium oxide was added to cause exchange of hydroxylic protons. The multiplet of the tertiary proton H-1 was now cleanly separated from the ring-methylene proton signals at 100 Mc/sec, but not at 60 Mc/sec (see introductory section.) The equatorial ring-methylene proton produced a pair of triplets at 2.0 ppm (J_{gem} = 12 cps, J_{vic} = 3 to 4 cps). The axial ring-methylene proton produced a pattern centered at 2.40 ppm, consisting of a trio of doublets, on which two additional low-intensity lines were superimposed near the central lines (J_{gem} = 12 cps, J_{aa} = 12–13 cps, J_{ae} = 2.0–2.5 cps). The side-chain methylene spectrum (protons not equivalent) was observed as an eight-line pattern, consisting of two perturbed sets of four lines centered at 4.07 (J_{gem} = 10 cps, J_{vic} = 5.5 cps) and 4.27 ppm (J_{gem} = 10 cps, J_{vic} = 7 cps).

The remaining pyridine spectrum (4.4–4.9 ppm) has not been fully analyzed, but appears to include (1) a quartet at 4.68 ppm, shown by double resonance[18,19] experiments to correspond to H-5; (2) a perturbed triplet probably due to H-3 or H-4 at 4.5 ppm (J about 3 cps); and (3) an unresolved multiplet at 4.78 ppm probably broadened by long-range couplings (width at half-height about 6 cps), which may be produced by an equatorial proton (H-2 or H-4).

DL(1234/5) Diastereomer of 1-Triphenylmethoxymethyl-2,3,4,5-cyclohexanetetrol Tetraacetate (Pseudo-α-DL-talopyranose Trityl Ether Tetraacetate) (13).—A solution of 50 mg of the pentol and 80 mg of triphenylmethyl chloride in 1.5 ml of dry pyridine was kept at 25° for 36 hr. Acetic anhydride (0.15 ml) was added, and the solution was again kept for 36 hr. The orange solution was poured into a mixture of ice and water (stir 30 min). The precipitate was collected and dried.

This material was recrystallized from 2-propanol–petroleum ether, giving an 80-mg (50%) yield of colorless product, mp 174–175°. This product was recrystallized for analysis from 2-propanol–ethanol (3:1), giving 60 mg of product, mp 175–176°.

Anal. Calcd for $C_{34}H_{36}O_9$: C, 69.37; H, 6.16. Found: C, 69.01; H, 6.06.

Similar treatment of 0.6 g of the pentol gave a 1.5-g (76%) yield of once-recrystallized product, mp 174–175°.

The pmr spectrum was observed at 60 Mc/sec in chloroform-*d*. Aromatic signals (15 protons) were observed at 7.1–7.5 ppm. Acetate methyl singlets appeared at 2.10, 2.01, 1.92, and 1.83 ppm (three protons each). The side-chain methylene protons produced a doublet at 3.08 ppm (J about 7 cps), whose degree of perturbation indicated location of the tertiary proton H-1 signal at about 2.5 ppm. The ring-methylene protons produced a pattern at 1.55–1.80 ppm. The AcO–C*H* spectrum (H-2, H-3, H-4, and H-5) resembled that of compounds **10** and **12** (see above), and consisted of a poorly defined one-proton triplet at 5.52 ppm (J about 3 cps), and a three-proton pattern at 4.8–5.3 ppm.

Infrared Spectra.—The spectrum for each intermediate and product, using potassium bromide pellets, was recorded with a Perkin-Elmer Model 137 Infracord spectrometer, and in each case was consistent with the assigned structure.

Acknowledgment.—This research was made possible by a generous grant (CA-07250) to the University of San Francisco from the National Cancer Institute, Public Health Service. We wish to thank Professor Edward E. Smissman, University of Kansas, and Professor Henry Z. Sable, Western Reserve University, for helpful discussions.

Compounds of Phosphorus and Fluorine. III. Preparation of Mono- and Diphosphonate Derivatives from Tetraethyl 3,3,4,4,5,5-Hexafluoro-1-cyclopenten-1,2-ylenediphosphonate[1]

ARLEN W. FRANK

Research Center, Hooker Chemical Corporation, Niagara Falls, New York 14302

Received December 1, 1965

A diphosphonic acid, 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonic acid (II), and a monophosphonic acid, 2-chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonic acid (V), were prepared from a common intermediate, the title compound Ia, and converted to various derivatives. Noteworthy reactions were (1) a C–P bond cleavage which occurred when Ia was treated with phosphorus pentachloride and which provided the access to the monophosphonate derivatives; (2) an ester dealkylation which occurred when Ia was refluxed in ethanol; and (3) the preparation of an unsymmetrical diphosphonate (Ib) by the reaction of diethyl 2-chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonate (VI) with tributyl phosphite.

The preparation of tetraalkyl perfluoro-1-cycloalken-1,2-ylenediphosphonates from trialkyl phosphites and 1,2-dichloroperfluorocycloalkenes was described in part II of this series.[1] The present paper is concerned with their reactions. A key step in this work was a reaction in which a cleavage of one of the C–P bonds occurred, providing an entry to a class of compounds, the 2-chloroperfluoro-1-cycloalken-1-ylphosphonates, which were not directly accessible from the 1,2-dichloroperfluorocycloalkenes.

The relationships between the various compounds described in this paper are sketched in Chart I.

An attempt to prepare 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonic tetrachloride (III) directly from tetraethyl 3,3,4,4,5,5-hexafluoro-1-cyclopenten-1,2-ylenediphosphonate (Ia) by reaction with phosphorus pentachloride, a reaction often used for the preparation of dichlorides of phosphonic acids,[2] gave a single product identified by its analyses and chemical reactions as 2-chloro-3,3,4,4,5,5-hexafluoro-1-cyclopenten-1-ylphosphonic dichloride (IV), a product containing only one C–P bond. Fairly forcing conditions were used, but under milder conditions the reaction was incomplete. If III had indeed been formed, it must have reacted further with the phosphorus pentachloride, probably through an exchange of chlorine for oxygen and thermal decomposition of the resulting tetrachlorophosphorane.[3] The presence of phosphorus trichloride in the distillate confirmed this.

(1) Part II: A. W. Frank, *J. Org. Chem.*, **30**, 3663 (1965).

(2) See, *e.g.*, its use with diethyl ω-hydroperfluoroalkylphosphonates: N. O. Brace, *ibid.*, **26**, 3197 (1961).

(3) For recent examples of the thermal cleavage of fluoroalkyl tetrachlorophosphoranes, see G. M. Burch, H. Goldwhite, and R. N. Haszeldine, *J. Chem. Soc.*, 1083 (1963).