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FLUORINATION OF TRI-O-ACETYL-D- AND L-ARABINALS BY LEAD TETRAFLUORIDE*

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Abstract—Diacetyl-D and L-arabinals reacted with lead tetraacetate and anhydrous hydrogen fluoride to give, after deacetylation, crystalline products identified as 2,5-anhydro-1-deoxy-1,1-difluoro-D and L-ribitols respectively. Each product was stable towards acids and alkali and on oxidation with chromic acid gave difluoroacetic acid. The difluoride (D-series) consumed 1 mole/mole of sodium metaperiodate and borohydride reduction of the oxidized product gave a stable, dextrorotatory diol, characterized as the crystalline bis-*p*-nitrobenzoate. The proposed structure of the difluoride is supported by proton and ^{19}F magnetic resonance and by optical rotatory measurements.

ADDITION of fluorine to steroid olefins has been smoothly accomplished giving *cis*-difluorides by the use of lead tetrafluoride generated *in situ* from lead dioxide[1,2] or lead tetraacetate[3] in liquid hydrogen fluoride at −70°. In the light of results of additions of mixed fluorine-halogens to glycals[4,5] where *cis* 2-haloglycosyl fluorides are formed, it is now of interest to explore the reaction of lead tetrafluoride with unsaturated sugars.

Reaction of diacetylarabinal (in both D and L series) with lead tetrafluoride led to fluorinated products, which after catalytic deacetylation gave a crystalline compound (in each series) which had the empirical formula expected for a 2-deoxy-2-fluoropentosyl fluoride. Unlike glycosyl fluorides however, the product (II, D series) was stable towards hot methanolic hydrogen chloride (1% w/v), 0·1N NaOMe and 0·2N H_2SO_4, at 100° for 18 hr. Each of these conditions is known to lead to rapid reaction in the cases of the 2-bromo and 2-iodoglycosyl fluorides.[4,5] Furthermore, the diacetate of difluoro-product (II) exhibited an IR spectrum markedly different from that of di-O-acetyl-2-bromo-2-deoxy-β-L-arabinopyranosyl fluoride, and was suggestive of a five-membered ring.

Subsequently the product (II) was identified as 2,5-anhydro-1-deoxy-1,1-difluoro-D-ribitol, on the basis of the following evidence. A preliminary examination of the NMR spectrum of the difluoride (II, as the diacetate) indicated the presence of the CHF_2 group. This was confirmed by chromic acid oxidation of the substance and distillation of the volatile acid product which was identified as difluoroacetic acid by formation of its crystalline S-benzylthiouronium salt. In a quantitative modification

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† This paper is dedicated to the memory of Professor H. Stephen.

[1] A. L. Henne and T. P. Waalkes, *J. Amer. Chem. Soc.* **67**, 1639 (1945); **68**, 496 (1946).

[2] A. L. Henne and T. H. Newby, *J. Amer. Chem. Soc.* **70**, 130 (1948).

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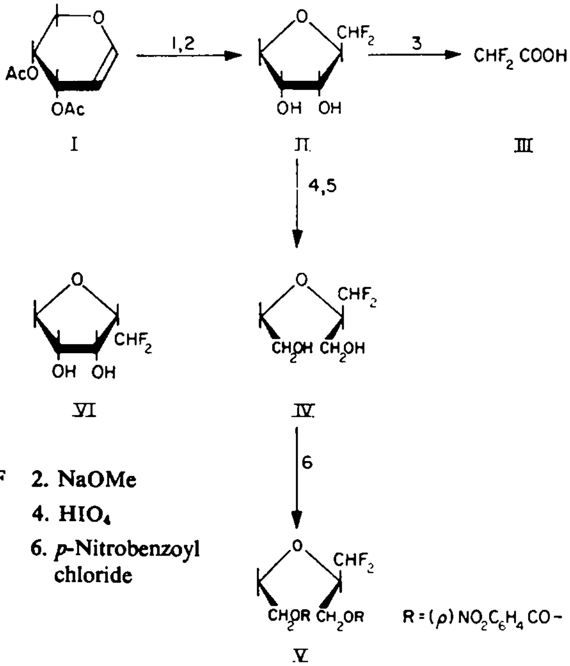
of the experiment, one mole of difluoroacetic acid was found to be formed from one mole of difluorosugar. Though Swartz[6] has reported traces of hydrogen fluoride to be



1. $Pb(OAc)_4$-HF 2. NaOMe
3. CrO_3-H^+ 4. HIO_4
5. KBH_4 6. p-Nitrobenzoyl chloride

formed in comparable oxidations of 2,2-difluoroethanol, no F^- could be detected in the distillate products of the present experiments.

The difluorosugar (II) consumed one mole per mole of potassium metaperiodate with great rapidity (10 min, 3×10^{-4} M IO_4^-) consistent with the presence of *cis*-hydroxyls. The structure of the difluoro compound is thus indicated as being either 2,5-anhydro-1-deoxy-1,1-difluoro-D-ribitol (II) or 2,5-anhydro-1-deoxy-1,1-difluoro-D-arabitol (VI) i.e. differing in configuration at C-2. Optically active 3,4-dihydroxy-tetrahydrofurans substituted at 2 but not at 5 have rarely been obtained.[7] Recently however, methyl β-D-erythrofuranoside has been synthesized,[8] having molecular rotation $[M]_D$ −19,600. The average molecular rotational difference[9] for methyl α- and β-glycosides is about 33,000. The rotational contribution of the glycoside portion of methyl β-D-erythrofuranoside is thus about −3,000, which is comparable with the molecular rotation (−3,900) of the difluoride (II) but these values are not sufficiently distinctive to decide between the *ribo* and *arabo* configurations.

Evidence in favour of the *ribo*-configuration (II) was obtained by periodate oxidation followed by borohydride reduction of the "dialdehyde" (Smith degradation).[10] This procedure resulted in the destruction of every optical in the molecule save

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[6] F. Swartz, *Bull. Classe Sci., Acad. roy. Belg.* 597 (1903).

[7] M. Cifonelli, J. A. Cifonelli, R. Montgomery and F. Smith, *J. Amer. Chem. Soc.* 77, 121 (1955).

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[9] F. J. Bates, *Polarimetry, Saccharimetry and the Sugars.* U.S. Government Printing Office, Washington (1942).

[10] F. Smith and J. W. Van Cleve, *J. Amer. Chem. Soc.* 77, 3091 (1955).

TABLE 1. MOLECULAR ROTATIONS OF PERIODATE OXIDATION AND BOROHYDRIDE REDUCTION PRODUCTS

$[\alpha]_D^{20}$	Methyl α-L-arabinoside[10]	Methyl β-L-arabinoside[10]	Difluoride (II) (D-series)
Sugar (H_2O)	+19·7°	+238°	−35°
"Dialdehyde" (H_2O)	−122·4	+122·7	−12·3
Diol (EtOH)	+6·8	−6·9	+2·5*
Bis-p-nitrobenzoate ($CHCl_3$)	+10·8	−10·2	+7·5

* in H_2O

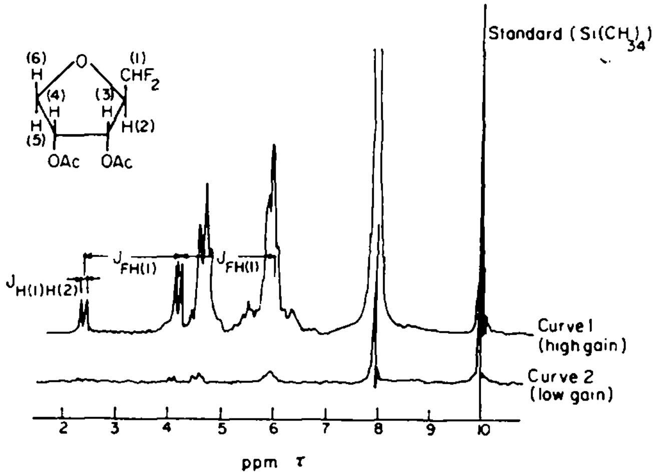

FIG. 1.

that in question, at C-2. The final diol (IV), characterized as the crystalline bis-p-nitrobenzoate (V), is a suitable form for the establishment of absolute configuration. Parallel degradative steps reported for methyl α- and β-L-arabinosides provide a basis of comparative rotational values (Table 1). It is apparent that a substantial measure of agreement exists between the values for the D-difluoride (II) and methyl α-L-arabinoside, thus supporting the *ribo* configuration at C-2.

The PMR spectrum of the difluoride (II) (as the di-O-acetate) was measured in deuterochloroform at 29·91 Mc/s (Fig. 1) using tetramethylsilane as standard. On the basis of published values[11] for acetylated sugars, the band at τ 8 ppm was ascribed to acetyl protons, those at τ 6 ppm to H(5) and H(6), while the hydrogens H(3) and H(4) were at τ 4·6 ppm. Comparison of the area of the doublet at τ 4·2 ppm with that of the acetyl groups (6 protons) showed that the former contained half a proton. The ratio of the area of the doublet τ 2·4 ppm to that at τ 4·2 ppm is 1: 2, indicating that a further doublet containing 1/4 proton is hidden, probably in the band at τ 6 ppm. The coupling between the doublets ($J_{FH(1)}$) is 54 c/s; the splitting of each doublet is 4 c/s ($J_{H(1)H(2)}$) as determined by the side-band technique. The observed bands are consistent with the presence of the —CHF_2 group which is a triplet containing only one proton with areas 1: 2: 1 and coupling J_{FH}, 54 c/s.[12] Each band is in turn split by coupling with

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[11] R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *J. Amer. Chem. Soc.* **80**, 6098 (1958).

[12] B. H. Arison, T. Y. Shen and N. R. Trenner, *J. Chem. Soc.* 3828 (1962).

the hydrogen H(2) into a doublet. These bands are not consistent with any other arrangement of fluorine atoms.

The ^{19}F magnetic resonance spectrum measured at 28·14 Mc/s (Fig. 2) revealed the expected doublet ($J_{FH(1)}$, 54 c/s) and confirms the presence of two identical fluorine atoms coupled to a single hydrogen atom. The fine structure (J_{FH}, 12 c/s) which indicates that two hydrogens are equally coupled to the difluoromethyl group, is more difficult to interpret in terms of the structure proposed. However, anomalous fluorine–hydrogen coupling constants have been previously observed (the coupling across the fluorocyclobutane molecule is much greater than between adjacent positions[13]). The observed splitting is assumed to be due to H(2) and H(3).

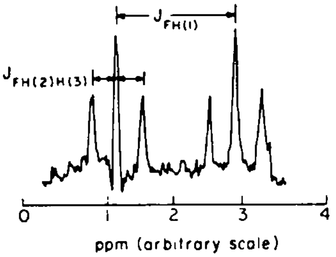
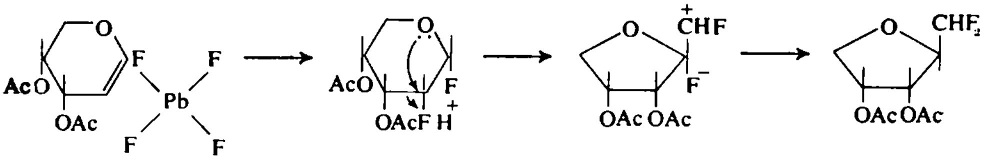


FIG. 2.

The unexpected structure of the difluoride indicates that in its formation from diacetylarabinal a rearrangement has occurred. Previous cases of rearrangements arising in reactions with lead tetrafluoride include the formation of 1,1-difluoro-1,2-diphenylethane from 1,1-diphenylethylene.[14] In a second instance,[3] the rearranged *gem*-difluoride was not conclusively identified. It is suggested that in the present work, the rearrangement occurs after the initial formation of a *vicinal* difluoro-adduct:



In the course of isolating the D-difluoro product, a crystalline monoacetate was isolated through the position of the ester group has not been established. Both ring contraction[15] and selective deacylation[16–18] have been observed in other carbohydrate reactions using hydrogen fluoride.

EXPERIMENTAL

Analytical methods were as described previously.[4,5]

Estimation of the —CHF$_2$ *group*. In view of the known stability of difluoroacetic acid under oxidizing conditions, it was possible to determine the CHF$_2$ content of compounds containing that grouping (in the absence of terminal CH$_3$ groups) by the following modification of the procedure for

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[13] C. M. Sharts and J. D. Roberts, *J. Amer. Chem. Soc.* **79**, 1008 (1957).

[14] J. Bornstein and M. R. Borden, *Chem. & Ind.*, 441 (1958).

[15] C. Pederson and H. G. Fletcher Jnr., *J. Amer. Chem. Soc.* **82**, 941 (1960).

[16] D. H. Brauns, *J. Amer. Chem. Soc.* **48**, 2776 (1926).

[17] C. Pederson and H. G. Fletcher Jnr., *J. Amer. Chem. Soc.* **82**, 945 (1960).

[18] C. Pederson, *Acta Chem. Scand.* **16**, 1831 (1962).

C-methyl group analysis. The sample (ca. 25 mg) accurately weighed, was added to 7 ml of oxidizing reagent [prepared from A.R. chromic acid (16·8 g), water (100 ml) and conc H_2SO_4 (20 ml)] and gently refluxed for 1 hr in an all-glass apparatus. Anhydrous $MgSO_4$ (7 g, A.R.) was added and the volatile acidic products (found to be F^- free[19]) were separated by steam distillation. The distillate (ca. 200 ml) was titrated (phenolphthalein) with 0·05N NaOH. In every case, a blank titration was performed. Control experiments using known quantities of sodium difluoroacetate gave reproducible recoveries (within 1 % of the expected value).

Periodate oxidation. Oxidations of compounds bearing *trans* or hindered *cis* glycol systems were performed by the method of Aspinall and Ferrier.[20] Other *cis* glycols and acylic polyols were oxidized and followed spectroscopically. Sufficient material (to consume two thirds of the oxidant) dissolved in water (50 ml) was mixed with 10 ml of 3×10^{-3} M potassium metaperiodate and made up to a final volume of 100 ml in an all-glass flask. The change in absorption at λ 247·5 mμ was measured in 1 cm quartz cells. The concentration of IO_4^- was calculated from standard solutions constructed by mixing known volumes of 3×10^{-3} M potassium metaperiodate and 3×10^{-3} M potassium iodate.

2,5-*Anhydro*-1-*deoxy*-1,1-*difluoro*-D-*ribitol* (II). Diacetyl-D-arabinal (I, 15 g) in dry CH_2Cl_2 (150 ml) was added to a solution of anhydrous HF (80 g) and lead tetraacetate (80 g) in dry CH_2Cl_2 (150 ml) at −70°. The reactants were stirred rapidly at that temp for 40 min and then were poured on to ice mixed with CH_2Cl_2 (200 ml). After neutralization (K_2CO_3) and filtration the separated organic layer was washed with $NaHCO_3$aq and with water and finally it was dried ($MgSO_4$). After filtration and removal of the solvent, a syrup (5·1 g) was obtained from which a crystalline *monoacetate* of 2,5-*anhydro*-1-*deoxy*-1,1-*difluoro*-D-*ribitol* (0·75 g) separated. After recrystallization from ether–light petroleum (60–80°) the acetate had m.p. 60·5°, $[\alpha]_D^{21.6}$ −24° (*c* 0·6 in $CHCl_3$), $[\alpha]_D^{20}$ −35° (*c* 0·4 in MeOH). (Found: C, 43·0; H, 5·3; F, 19·2. $C_7H_{10}F_2O_4$ requires: C, 42·8; H, 5·1; F, 19·1 %.) The IR spectrum showed strong peaks at 3500 cm^{-1} (OH) and 1740 cm^{-1} (carbonyl).

Ether extraction of the aqueous residues (after separation of the CH_2Cl_2 layer) gave a further crop of the crystalline monoacetate (2·7 g) while subsequent continuous extraction (18 hr) with ether gave 2,5-*anhydro*-1-*deoxy*-1,1-*difluoro*-D-*ribitol* (II, 200 mg) which after recrystallization from ether–light petroleum (60–80°) had m.p. 75° $[\alpha]_D^{20}$ −26° (*c* 1·44 in MeOH) R_f 0·68 in n-butanol:ethanol:water. (Found: C, 39·0; H, 5·2; F, 25·0: CHF_2, 31·0. $C_5H_8F_2O_3$ requires: C, 39·0; H, 5·2; F, 24·6; CHF_2, 33·1 %.)

The monoacetate (above) (1·1 g) dissolved in MeOH (50 ml) and N-NaOMe (0·5 ml) was kept at 20° for 1 hr. The solution was passed down a MeOH-washed Amberlite IR 120 (H^+) column (2 cm × 25 cm), concentrated to dryness and the residue was extracted with ethyl acetate (4 × 20 ml). After filtration and evaporation of the solvent, the difluoro compound (II, 0·73 g) was obtained and which after recrystallization as before had m.p. 75° alone or mixed with the preceding specimen.

2,5-*Anhydro*-1-*deoxy*-1,1-*difluoro*-L-*ribitol*. Diacetyl-L-arabinal (4 g) in CH_2Cl_2 (150 ml) was treated with HF (21 g) and lead tetraacetate (22 g) in CH_2Cl_2 (150 ml) as in the previous experiment. The monoacetate (2 g $[\alpha]_D^{20}$ +58° in MeOH, n_D^{20} 1·4430) did not crystallize immediately and was deacetylated as before giving 2,5-*anhydro*-1-*deoxy*-1,1-*difluoro*-L-*ribitol* m.p. 73–74° $[\alpha]_D^{20}$ +25° (*c* 0·84 in MeOH), R_f 0·68. (Found: C, 39·0; H, 4·8; F, 25·0. $C_5H_8F_2O_3$ requires: C, 39·0; H, 5·2; F, 24·6 %.) The compound on oxidation consumed 0·96 moles sodium metaperiodate per mole of sugar.

Chromic acid oxidation of the difluoride (II). The difluoride (II, 250 mg) was dissolved in chromic acid (30 ml) and was refluxed for 1 hr. $MgSO_4$ (30 g) was added to the cooled mixture which was then submitted to steam distillation. The distillate (300 ml) was neutralized (phenolphthalein) by titration with 0·5N NaOH (CO_2-free conditions), 2·2 ml of the alkali being required. The neutral solution decolourized with charcoal, was filtered and evaporated to dryness, giving sodium difluoroacetate. (The product gave negative tests for F^-). The salt was dissolved in water (0·4 ml) and to it was added 0·4 ml of a solution of S-benzylthiouronium chloride [made from 1 g of the chloride in water (5 ml) acidified with 0·1N HCl (0·2 ml)].

S-Benzylthiouronium difluoroacetate (22 mg) separated at 0° and after recrystallization from water had m.p. 161–163° alone or mixed with an authentic specimen. (Found: C, 45·9; H, 4·9; F, 13·8. $C_{10}H_{12}F_2N_2O_2S$ requires: C, 45·9; H, 4·6; F, 14·5 %.) The product gave depression of m.ps with the

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[19] R. Belcher, M. A. Leonard and T. S. West, *J. Chem. Soc.* 3577 (1959).

[20] G. O. Aspinall and R. J. Ferrier, *Chem. & Ind.*, 1216 (1957).

S-benzylthiouronium acetate (m.p. 136°), monofluoroacetate (m.p. 160–162°) and trifluoroacetate (m.p. 166–170°).

Smith degradation of the difluoride (II). The difluoride (II, 66 mg) was dissolved in water (2 ml) containing periodic acid (150 mg). After 3 hr the optical rotation became constant ($[\alpha]_D^{20}$ $-12{\cdot}3°$ calc. for the "dialdehyde"). The solution, deionized by Dowex 1 (CO_3^{2-} form) was made up to 5 ml and KBH_4 (20 mg was added). The optical rotation which at once became positive and was constant after 2 hr, was not changed by addition of more KBH_4 (20 mg) $[\alpha]_D^{20}$ $+2{\cdot}5°$ (calc. for the diol IV). The aqueous solution was neutralized (CO_2) and was frozen dried; the final traces of water being removed at 1·5 mm and 50°. The diol (IV) was separated from the dry solid extract with dry EtOH (3 × 10 ml). Evaporation of the solvent gave a syrup (IV, 40 mg) which was dissolved in dry pyridine (2 ml). *p*-Nitrobenzoyl chloride (180 mg) was added to the mixture which was heated at 90° for 40 min. The solid, which separated when the reaction mixture was poured into $NaHCO_3$aq (6 ml) was filtered and recrystallized from chloroform–light petroleum (60–80°). The resulting product *bis*-p-*nitrobenzoyl*-1,1-*difluoro*-2-0-(2'-*hydroxyethyl*)-D-*propane*-2,3-*diol* (V) had m.p. 86–87° $[\alpha]_D^{20}$ $+7{\cdot}5°$ (*c* 0·67 in $CHCl_3$). (Found: C, 50·5; H, 3·4; F, 8·4; $C_{19}H_{16}N_2F_2O_9$ requires: C, 50·2; H, 3·5; F, 8·4%.)

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