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SUGARS WITH POTENTIAL ANTIVIRAL ACTIVITY—I

A NEW METHOD FOR THE PREPARATION OF GLYCOFURANOSYL CHLORIDES AND THE SYNTHESIS OF A MANNOSYL NUCLEOSIDE

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Abstract—A method for rapid preparation of a glycosyl halide is described. The halide may be isolated or used *in situ* in nucleoside synthesis. Use of di-isopinocampheyl borane for conversion of γ-lactone to furano-sugar is discussed.

AMONG the most useful intermediates for synthesis in the carbohydrate field are the O-substituted glycosyl halides. In most cases syntheses have employed pyranose forms. The less available and more unstable furanosyl halides have received less attention.[1] Relatively few have been obtained in crystalline form.[2-4]

Syntheses in the nucleoside field have often employed substituted glycosyl halides;[5] since the natural nucleosides contain the sugars in the furanose form, it has been of interest, when preparing analogues for studies of their physiological activity, to synthesize glycofuranosyl nucleosides. Essentially the problem falls into three stages; (a) Preparation of the sugar in some suitably protected furanose form, (b) conversion to halide, (c) condensation with some suitable derivative (e.g. a mercuric salt)[6] of the hererocyclic base. In some cases, stages (a) and (b) involve long time-consuming processes.[7]

We describe here a method for the preparation of glycofuranosyl chlorides and their subsequent condensation, in this instance with an adenine derivative but potentially with a variety of materials, which promises to speed up and simplify these procedures.

[1] L. J. Haynes and F. H. Newth, *Adv. in Carbohydrate Chem.* **10**, 207 (1955).
[2] C. S. Hudson and J. M. Johnson, *J. Am. Chem. Soc.* **38**, 1223 (1916); J. Compton and M. L. Wolfrom, *Ibid.* **56**, 1157 (1934); H. H. Schlubach and K. Meisenheimer, *Ber. Dtsch. Chem. Ges.* **67**, 429 (1934).
[3] J. C. Irvine and E. T. Stiller, *J. Am. Chem. Soc.* **54**, 1079 (1932); W. W. Binkley and M. L. Wolfrom, *Ibid.* **68**, 2171 (1946).
[4] R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.* **80**, 2007 (1958).
[5] Eg. *inter alia* E. Fischer and B. Helferich, *Ber. Dtsch. Chem. Ges.* **47**, 210 (1914); J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.* 967, 1685 (1948); G. A. Howard, B. Lythgoe and A. R. Todd, *Ibid.* 1052 (1947); B. Lythgoe and A. R. Todd, *Ibid.* 592 (1944); N. W. Bristow and B. Lythgoe, *Ibid.* 2306 (1949); J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.* **74**, 1563 (1952); H. Zinner, *Chem. Ber.* **83**, 153 (1950).
[6] J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.* **73**, 1650 (1951); G. Bruhns, *Z. physiol. Chem.* **14** 533 (1890); M. Krüger, *Ibid.* **18**, 423 (1894); J. J. Fox, N. Yung, J. Davoll and G. B. Brown, *J. Am. Chem. Soc.* **78**, 2117 (1956); M. Hoffer, R. Duschinsky, J. J. Fox and N. Yung, *Ibid.* **81**, 4112 (1959).
[7] N. Yung and J. J. Fox, *Methods of Carbohydrate Chemistry*, (Edited by R. L. Whistler and M. L. Wolfrom), p. 108. Acad. Press, New York, N.Y. (1963).

Preparation of substituted furanose compounds

The preparation of suitable furanose derivatives of sugars is in many cases tedious. In contrast, the lactones of the sugar acids show reversed stability in ring size and the preparation of substituted γ-lactones is readily accomplished.

Since Brown and Bigley[8] have shown that lactones are reduced to aldehydes by di-isoamyl borane, the use of this reagent to convert sugar lactones to the corresponding sugar hemiacetal seemed feasible. However since di-isopinocampheyl borane is more easily prepared and handled than the di-isoamyl borane, and since it appears to have rather similar steric properties, we investigated the use of this reagent with a sugar lactone.

As a model reaction 2,3;5,6-di-O-isopropylidene-D-mannonolactone was treated with di-isopinocampheyl borane in diglyme. From the reaction mixture, 2,3;5,6-di-O-isopropylidene-D-mannofuranose was isolated.

In this case the furanose sugar is more readily available by direct synthesis, but the application of the reaction to other examples could prove fruitful, since it was shown[8] that ester groups were stable to di-isoamyl borane under conditions in which lactones reacted, and poly-acyl glyconolactones are readily available.

Preparation of glycosyl chlorides

Crofts and Downie[9] described the reaction of triethyl phosphite, ethanol, and CX_4(X = chlorine or bromine) to give ethyl halide, triethyl phosphate and haloform. A scheme involving successive phosphonium ions (I and II) seemed adequate to account for their observations:—

$$\text{I} \quad (EtO)_3P + CCl_4 \longrightarrow [(EtO)_3PCCl_3]^+Cl^-$$

$$\downarrow EtOH$$

$$\text{II} \quad (EtO)_3PO + EtCl \longleftarrow [(EtO)_4P]^+Cl^- + CHCl_3$$

While Crofts and Downie did not investigate the reaction further, it is obviously capable of wider variation leading for example to phosphonium ions of the type III

$$ROH + CCl_4 + (R'O)_3P \longrightarrow [(RO)P(OR')_3]^+Cl^- + CHCl_3$$

$$\text{III} \longrightarrow (RO)PO(OR')_2 + R'Cl \text{ or } (R'O)_3PO + RCl$$

in which competition will occur in the final Arbusov-type stage[10] to give the halides RCl and R'Cl in relation to their relative competitive ability. We have confirmed this in a number of cases.

As a method for conversion of ROH to RCl the process as written is limited by this competition. We considered that the use of a tertiary phosphine in place of the phosphite should lead to formation of an ion IV finally, in which decomposition in the last Arbusov stage can proceed in one direction only.

$$\text{IV} \quad R_3P(OR')^+Cl^- \longrightarrow R_3PO + R'Cl \text{ only}$$

We have shown[11] that with simple alcohols reaction proceeds very rapidly under mild conditions, the conversion of alcohol to halide by triphenyl phosphine in carbon

[8] H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.* **83**, 486 (1961).
[9] P. C. Crofts and I. M. Downie, *J. Chem. Soc.* 2559 (1963).
[10] B. A. Arbusov, *Zh. Russ. Riz. Khim. Obshsh.* **38**, 687 (1906).
[11] I. M. Downie, I. B. Holmes and J. B. Lee, *Chem. Ind.* 900 (1966).

tetrahalide being essentially complete within a few minutes at 80°. The neutral, anhydrous conditions should ensure the stability of protecting groups during reaction.

Wishing to prepare a number of nucleosides, we investigated whether this method could be utilized for the synthesis of a glycofuranosyl chloride. As our first model we choose the readily available 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose (V). We found that treatment of the anhydrous V with an equimolar amount of triphenyl phosphine in anhydrous carbon tetrachloride at the reflux temperature gave a rapid reaction to form chloroform, triphenyl phosphine oxide, and 2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl chloride (VI) in good yield. The identity of VI was confirmed[12] by examination of its IR spectrum, chemical tests, and elementary analysis.

Examination of this compound (VI) by PMR spectroscopy confirmed the overall structure and further enabled us to assign the α-configuration to it, as follows:

In a *planar* 5-membered ring the projected valency angle between adjacent *cis* hydrogens is 0°, and that between adjacent *trans* hydrogens is 120°. According to the Karplus equation[13] as modified for furanose systems[14] these angles are associated with coupling constants of 9 c/s and 2 c/s (approximately) for *cis* and *trans* hydrogens respectively.

The PMR spectrum of 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose shows a singlet absorption (4·63 τ) for the low-field anomeric proton, which is consistent with the known *trans* arrangement of H_1 and H_2, the furanose ring being twisted[15] slightly out of plane. The signal for H_1 in the 2,3:5,6-di-O-isopropylidene mannofuranosyl halide appears at still lower field (3·90 τ) as is expected, since a more electronegative group has been introduced nearby, but more significant is its appearance as a singlet absorption.

J values less than 3 c/s have been observed for *cis* hydrogens in furanose systems[14] representing a projected valency angle of almost 50°, but since a singlet absorption would require an angle greater than 70°, which in this case would be a highly strained arrangement, H_1 and H_2 must be considered to be *trans*, and we therefore consider that retention of configuration has occurred. Since examination of some other systems suggests that a bimolecular nucleophilic substitution is usual in the method employed to synthesize the chloride, retention of configuration must imply some form of SNi mechanism.

Condensation of compound VI *with adenine*

A variety of routes are available for the synthesis of nucleosides; of those which involve glycosyl halides, the mercuri procedure[16] has been investigated and shown to be generally applicable.[17] In this method anhydrous mixtures of the mercuri

[12] As far as the authors are aware, no physical data other than b.p. have been recorded for this compound; see K. Freudenberg and A. Wolf, *Ber. Dtsch. Chem. Ges.* **60B**, 232 (1927).

[13] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

[14] A. J. Abraham, L. D. Hall, L. Hough and K. A. McLaughlan, *J. Chem. Soc.* 3699 (1962).

[15] Cf. also R. U. Lemieux, *Canad. J. Chem.* **39**, 116 (1961); L. D. Hall, *Chem. Ind.* 950 (1963); *Adv. Carbohydrate Chem.* **19**, 75 (1964).

[16] J. Davoll and B. A. Lowry, *J. Am. Chem. Soc.* **73**, 1650 (1951).

[17] Eg. see J. A. Montgomery and H. J. Thomas, *Adv. Carbohydrate Chem.* **17**, 301 (1962); J. J. Fox and I. Wempen, *Ibid.* **14**, 283 (1959).

derivative of the base and glycosyl halide react in an inert solvent (usually xylene) under reflux.

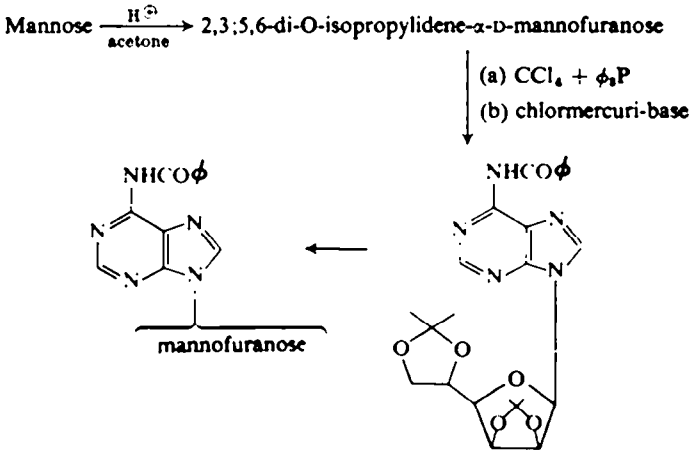
Since the glycofuranosyl halides in particular are rather unstable, it would be convenient, to avoid losses in isolating material, and to further shorten the reaction time, if the halide could be prepared and condensed *in situ*.

In the above described preparation of the glycosyl chloride (VI), the only additional materials present, formally, apart from the required halide, are solvent and the unreactive triphenylphosphine oxide. We find that the condensation of mercuri compounds with the hydroxy compound V *via* the chloro-compound VI can be readily accomplished in one stage.

In this case, when 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose (V) was reacted with triphenylphosphine and carbon tetrachloride as described above, and then reacted directly with chloromercuri-6-benzamidopurine[18] in xylene, under conditions similar to those used by Davoll and Lowry,[16] a product was obtained, which, after removal of the protecting groups, gave 9-D-mannofuranosyladenine (VII).

The structure of this compound was confirmed by elemental analysis, oxidation with periodate, (when extensive over-oxidation occurred, but formaldehyde (1 mole approx) was set free) and spectroscopic examination.

In the case of condensations of glycosyl halides having an acetyl group in the C(2) position, it is well known[19] that the product obtained in these nucleoside syntheses has the *trans* arrangement of the C(1) and C(2) substituents, whereas this is not necessarily the case where groups incapable of participation in the reaction are substituted on C(2).[20] In the case in question the *trans* rule[19] will not operate. The overall reaction may be represented as follows:



EXPERIMENTAL

CCl_4 was kept over $CaCl_2$, filtered, and distilled, rejecting the first 25% approx of distillate.

Triphenyl phosphine, recrystallized, was dried by dissolution in anhyd toluene with subsequent removal of solvent under reduced press.

[18] R. S. Wright, G. M. Tener and H. G. Khorana, *J. Am. Chem. Soc.* **80**, 2004 (1958).

[19] R. S. Tipson, *J. Biol. Chem.* **130**, 55 (1939); B. R. Baker, *Ciba Foundation Symposium Chem. and Biol. of Purines* 120 (1957).

[20] B. R. Baker, R. E. Schaub and H. M. Kissman, *J. Am. Chem. Soc.* **77**, 5911 (1955); R. S. Wright, G. M. Tener and H. G. Khorana, *Ibid.* **80**, 2004 (1958).

Acetone was dried and purified by treatment under reflux with $KMnO_4$, distillation, and storage for several days with anhyd K_2CO_3, followed by filtration and distillation.

2,3:5,6-*Di*-O-*isopropylidene*-α-D-*mannofuranose* (V). To a soln of 15 ml conc H_2SO_4 in 1 l. acetone was added 22 g anhyd mannose and the soln was stirred vigorously, with exclusion of moisture, for 5 hr. Anhyd Na_2CO_3 was added until the soln was neutral, the soln was filtered and the residues extracted with several lots of hot acetone. The combined filtrate and extracts were evaporated on a rotary evaporator and the residue dissolved in Na-dried ether, filtered, and precipitated with thrice the volume of pet. ether. The ppt was separated, and the mother liquor partially evaporated to give a further crop of crystals. After recrystallization from hot pet. ether, 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose was obtained (25 g, 90%), m.p. 121–122°, $[\alpha]_D^{20}$ +16·6° (*c*, 2·0 in EtOH) [cf. lit.[21] m. 122–123°, $[\alpha]_D^{14}$ +17° (*c*, 1·0 in acetone)]. This material reduced alkaline permanganate but not Fehling's soln.

2,3:5,6-*Di*-O-*isopropylidene*-α-D-*mannofuranosyl chloride* (VI). To a soln of 19·5 g 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose in 100 ml CCl_4 was added 19·65 g triphenylphosphine, and the mixture was heated under reflux, with exclusion of water. Triphenyl phosphine oxide commenced to separate from the mixture after 15 min, and, after 45 min, 2 g anhyd $PbCO_3$ and some powdered charcoal were added. The cooled soln was filtered through Kieselguhr, concentrated and strongly cooled. A further portion of triphenyl-phosphine oxide which deposited was separated. The soln was then distilled in a short path distillation apparatus. The fraction boiling at 112–122° (bath temp)/0·1 mm was collected (10·4 g), $n_D^{19\cdot6}$ 1·4679, $[\alpha]_D^{19\cdot6}$ +2·75° (*c*, 8·3 in acetone). (Lit.[18] b.p. 119° at 1 mm.) This material gave a white ppt with $AgNO_3$ in HNO_3, and showed bands in the IR at 665(m), 720(s), 765(m), 825(s), 850(s), 900(s), 950(m), 975(m), 985(m), 1020(m), 1070(s), 1100(s), 1125(s), 1170(s), 1220(s), 1270(s), 1315(m), 1380(s), 1390(s), 1460(s), 2890(sh), 2910(s), 2940(s), 2960(sh), 2995(s). GLC[23] showed a single peak: Column A,[25] R_t 18·06 min; R_v 1084 ml: Column B,[24] R_t 15·13 min; R_v 330 ml. (Found: C, 51·70, 51·64; H, 6·85, 6·71; Cl, 12·60, 12·47. $C_{12}H_{19}O_5Cl$ requires: C, 51·71; H, 6·82; Cl, 12·75%.)

PMR spectra of V *and* VI. Compound V showed signals at 4·73 τ (singlet, one proton) 5·1–6·0 τ (complex, 6 protons), 6·3 τ (one proton, absent on deuteration), 8·54 and 8·64 τ (singlet and doublet, 12 protons).

Compound VI showed signals at 3·92 τ (singlet, one proton) 4·98–6·0 τ (complex, 6 protons), 8·54 and 8·64 τ (singlet and doublet, 12 protons).

The downward shift of the low field proton is as expected for H_1. Some slight downfield shift of H_3 probably accounts for the slight difference in the group of signals corresponding to the remaining 6 sugar chain protons. The lack of change in the Me signals confirms the retention of basic ring structure. Some alteration might also have been expected if a β-chloro group was introduced.

Preparation of 6-*amino*-9-D-*mannofuranosyl-purine*. To a soln of 2·5 g 1,2:5,6-di-O-isopropylidene α-D-mannofuranose in 100 ml CCl_4 was added 2·5 g triphenyl phosphine, and the soln was then heated under reflux for 20 min. Some of the solvent was removed by direct distillation, the mixture was cooled slightly, and the remainder was removed under reduced press.

A suspension of 5 g Celite and 4·8 g chloromercuri-6-benzamido purine[18] in Na-dried redistilled xylene (approx 350 ml) was partially distilled under slightly reduced press, and when reduced to about ⅓ volume, the residue from the triphenyl phosphine reaction (slurried with dry xylene) was then added. The mixture was then refluxed gently for several hr, with exclusion of moisture. Charcoal was added, and the hot soln was then filtered, the residues were washed with chf, and the combined washings and filtrate were evaporated, using a rotary evaporator, to small bulk. The residues were dissolved in chf, washed with several portions of KIaq, then with water. The solvent was then removed under reduced press. A soln of Na in MeOH was added, and the mixture heated under reflux for 1 hr. Solvent was removed and the mixture stirred with a mixture of 30 ml water and 10 ml glacial AcOH on a steam bath for 4 hr, and then solvent was removed at 1 mm press. The residues were extracted with benzene and then aqueous EtOH. From the aqueous extract were obtained white needles (650 mg)

[21] J. C. Irvine and A. F. Skinner, *J. Chem. Soc.* 1089 (1926).

[23] C. T. Bishop, *Adv. Carbohydrate Chem.* **19**, (1964).

[25] Pye 104 Chromatograph, Apiezon L on firebrick, 200°, 60 ml per min H_2 flow.

[24] Perkin–Elmer 452 Chromatograph, silicone oil on firebrick, 195°, 21·8 ml per min N_2 flow.

m.p. 225–226° (dec); after recrystallization from aqueous EtOH, the material gave only one spot on TLC, with a variety of eluting solvents. This showed absorption in the UV λ_{max}^{water} 262 mμ; (ϵ_{max} 13,900), and in the IR at 3440, 1505, 1585, 1090, 1060 cm^{-1}.

Periodate oxidation of this material (100 mg) with unbuffered sodium metaperiodate (0·1M, 50 ml) at room temp proceeded rapidly with uptake of considerably more than 2 moles of oxidant; Formaldehyde (0·88 mole approx) was obtained. Overoxidation is not surprising in view of the expected production of a substituted malon-dialdehyde as the primary product of oxidation.