Convenient Synthesis of Mono and Cyclic Sulphates of Carbohydrates *via* Triflate Displacement

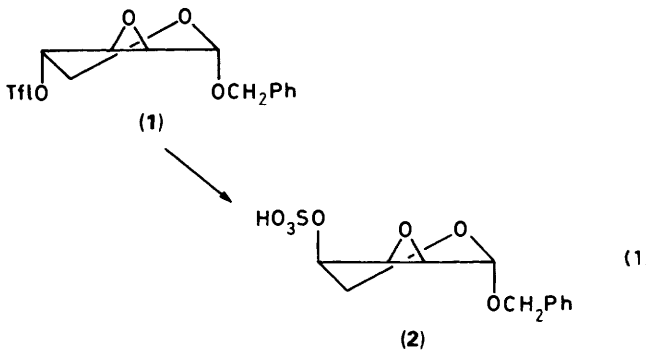
Farzana Latif,[a] Mohammed Saleh Shekhani,[b] and Wolfgang Voelter*[,a]
[a] *Abteilung für Physikalische Biochemie des Physiologisch-chemischen Instituts der Universität Tübingen, Hoppe-Seyler-Str. 1, D-7400 Tübingen, Federal Republic of Germany*
[b] *On leave from the H.E.J. Research Institute of Chemistry, University of Karachi, Karachi-32, Pakistan*

The 2,3-anhydropyranoside-4-triflates (**1**), (**3**), and (**6**) react with tetrabutylammonium hydrogen sulphate to afford the sulphate esters (**2**), (**4**), and (**7**) respectively. In the case of triflates (**3**) and (**6**) the cyclic sulphates (**5**) and (**8**) were obtained as major products. The benzyl pyranoside (**8**) was successfully deblocked to yield the free sugar cyclic sulphate (**9**). The ^{1}H NMR spectra of the newly synthesized sulphates have been discussed in detail. The ^{13}C NMR spectral data are also described.

The importance of sulphate esters of carbohydrates was recognized several years ago.[1] Biochemical studies are actively being performed on sulphated glycosaminoglycans, glycosphingolipids, and glycoproteins. Sulphated glycosaminoglycans from human tumour tissue have shown inhibition of DNA synthesis in virus-transformed cells.[2] The pronounced activity of synthetic sugar sulphate derivatives against peptic ulcers,[3,4] heptatitis,[4] skin wounds and burns,[4] their complementary inhibition[5] and modulation[6] activity, and their utility in wastewater treatment,[7] as well as in high quality electroplating,[8] has only highlighted the importance of this class of compounds. Chlorosulphonic acid,[1] or complexes of sulphur trioxide with pyridine,[1,9] dimethylformamide (DMF),[1] or triethylamine[5,6] have been used for the conversion of carbohydrates into their sulphate esters. More recently, approaches involving conversion of a sugar derivative into its sulphite ester followed by oxidation,[10] and reaction of suitably protected sugar[5] with an aryl chlorosulphate followed by hydrogenolysis,[11] have been used. These methods often have practical disadvantages due to the difficulties in isolation of the product and handling of the reagents, formation of complex mixtures, and poor yields. In all of those methods mentioned above the configuration at the carbon bearing the sulphate group remains the same as that in the parent sugar. We describe here a convenient and mild procedure for the introduction of the sulphate group into sugars with *inversion* of configuration at the reaction centre.

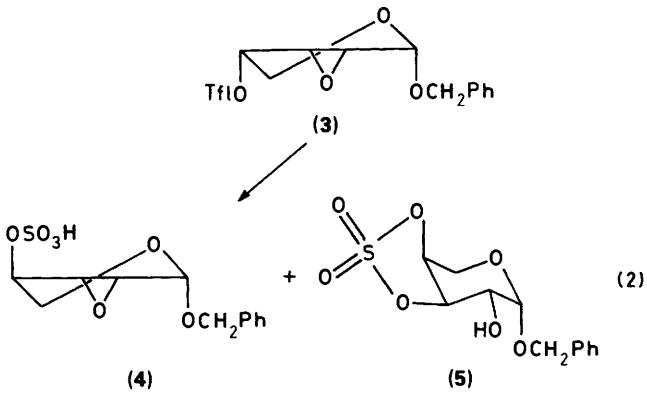
In continuation of our studies on carbohydrate triflates,[12] we wanted to investigate the displacement of a secondary triflyl group by a weak nucleophile. To this end we treated the known[12a] triflate (**1**) with tetrabutylammonium hydrogen sulphate in acetonitrile at room temperature. To our delight the crystalline sulphate (**2**) was isolated as the only product [equation(1)]. Reaction of the triflates (**3**) and (**6**)[12a] under the same conditions afforded the cyclic sulphates (**5**) and (**8**) in addition to the monosulphates (**4**) and (**7**) [equations (2) and (3)]. The ratio of the monosulphate to cyclic sulphate was *ca.* 1:2 in each case, and the products were conveniently separated by column chromatography (see Experimental section). Thus, this method also provides a convenient entry into the cyclic sulphates, a class of compounds prepared in the past by using the unpleasant sulphuryl chloride.[13]

Despite a literature report[14] that the sulphate group interferes with hydrogenolysis of the benzyl protecting group, we were able to hydrogenolyse the benzyl group from the cyclic



(1)

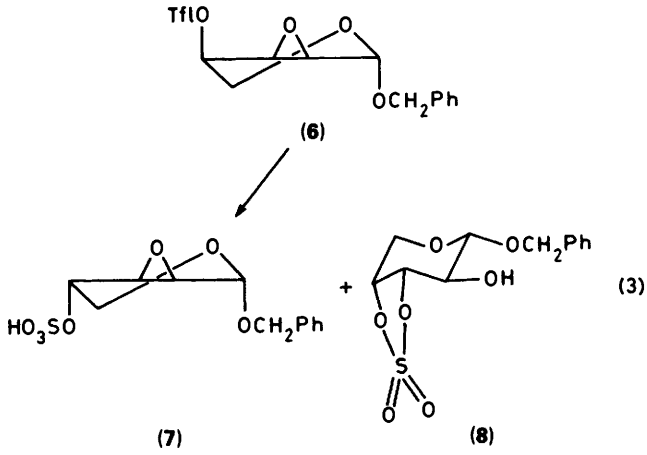
Reagents and conditions: $Bu^n_4N^+$ HSO_4^-, MeCN.



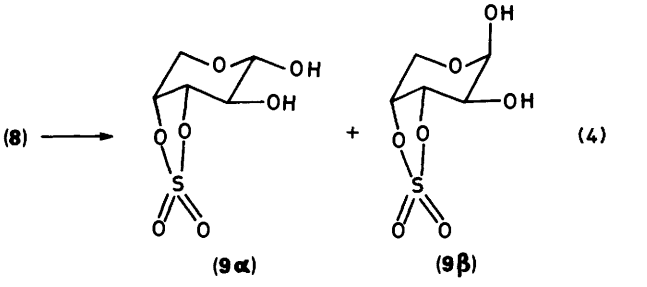
(2)

Reagents and conditions: $Bu^n_4N^+$ HSO_4^-, MeCN.

sulphate (**8**) [equation (4)]. Thus hydrogenolysis on 10% Pd–C in ethanol proceeded rather fast in the beginning, but slowed down and finally stopped roughly half-way through (TLC analysis). At this point the catalyst was changed, whereby the reaction was brought to completion to yield a *ca.* 2:3 equilibrium mixture of the α and the β-anomers (**9**). The ratio of the two anomers was determined on the basis of ^{1}H NMR integration. Interestingly, upon crystallization from ethyl acetate–ether almost all of the compound crystallized out as the β-anomer. The ^{1}H and ^{13}C NMR spectra of a freshly prepared solution of the crystalline compound in CD_3OD showed clearly the signals corresponding to the β-anomer. After *ca.* 30 min the



Reagents and conditions: $Bu^n_4N^+ HSO_4^-$, MeCN.



Reagents and conditions: H_2, Pd–C, EtOH.

Table 1. 400 MHz ^{1}H NMR spectra of compounds (4)–(9);[a] chemical shifts.

Compound	1-H	2-H	3-H	4-H	5-H	5-H′
(2)[b]	5.05	3.24	3.72	5.01	3.75	3.99
(4)[b]	5.08	3.42	3.55	4.94	4.02	3.79
(5)[c]	4.96	4.11	5.05	5.26	4.05	4.05
(7)[b]	4.98	3.21	3.51	4.83	3.75	3.75
(8)[c]	4.37	3.93	4.95	5.16	3.88	4.33
(9α)[c]	4.73	3.82	4.99	5.19	3.90	3.33
(9β)[c]	5.14	4.02	5.03	5.25	4.27	3.99

[a] The resonances corresponding to benzyl groups have been omitted. [b] In $CDCl_3$. [c] In CD_3OD.

Table 2. 400 MHz ^{1}H NMR spectra of compounds (4)–(9); coupling constants (Hz)

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
(2)	0	4.0	2.0	3.1	4.0	12.8
(4)	3.2	3.2	0	0	1.7	13.7
(5)	3.6	8.8	5.2	0	0	0
(7)	0	3.5	0	7.1	7.1	0
(8)	7.7	7.7	5.4	2.0	2.0	14.6
(9α)	8.0	8.0	5.3	2.0	0	14.1
(9β)[a]	3.5	8.7	5.2	2.3	0	14.3

[a] $J_{1,5'}$ = 0.6 Hz.

signals corresponding to the α-anomer started to appear, and after 24 h the solution again showed signals corresponding to a 2:3 mixture of the two anomers, which thereafter remained unchanged.

There is relatively little in the literature regarding the ^{1}H NMR spectra of sugar sulphates[15] and practically no information is available regarding the NMR spectra of cyclic sulphates. We therefore decided to study the ^{1}H NMR spectra of compounds (2), (4), (5), (7), (8), and (9) in detail. Table 1 lists the chemical shifts and Table 2 the coupling constants for these compounds. The spectrum of (9α) was obtained by subtracting the spectrum of (9β) from that of the mixture. The assignments were made on the basis of our previous experience with anhydro sugars,[12] reported[16] NMR studies on anhydro sugars, coupling patterns, and double-resonance experiments when necessary.

The relatively low values of $J_{4,5}$ and $J_{4,5'}$ in compounds (2) and (4), and the characteristic chemical shift of 1-H,[12,16] suggest that these two compounds exist in the $^0H_5$ conformation. The coupling constants $J_{1,2} = J_{2,3} = 7.7$ Hz in (8) show *trans* diaxial orientation of 2-H with both 1-H and 3-H, suggesting a $^1C_4$ conformation. In compound (5), the coupling constants $J_{1,2} = 3.6$ Hz and $J_{2,3} = 8.8$ Hz indicate an equatorial axial relationship between 1-H and 2-H, and *trans* diaxial relationship between 2-H and 3-H. The downfield chemical shift of 1-H in compound (5) compared with that in compound (8) also indicates the equatorial orientation of 1-H in (5). Thus conformation $^4C_1$ can be assigned to compound (5). The reason for the absence of any significant coupling between 4-H and 5-H and 5-H′ is not clear; so is the reason for the identical chemical shift of 5-H and 5-H′. As expected the chemical shift of 1-H is downfield in both anomers (9α) and (9β) compared with that in compound (8). $J_{1,2}$ (3.5 Hz) for (9β) and $J_{1,2}$ (8.0 Hz) for (9α), coupled with a relatively downfield resonance of 1-H in the former, support an equatorial orientation of 1-H in anomer (9β) and an axial one in anomer (9α). The facts that the coupling pattern in the rest of the molecule is about the same as that in (8) (*vide infra*), and that the values of the chemical shifts of 1-H in anomers (9α) and (9β) are consistent with those expected,[17] suggest that conformation $^1C_4$ can be assigned to both anomers of compound (9).

Table 3 lists the ^{13}C NMR data of compounds (2), (4), (5), (7), (8), and (9). Once again the values for anomer (9α) were obtained by subtraction of the values for anomer (9β) from those of the mixture of anomers. The resonances corresponding to the benzyl groups have been omitted for the sake of simplification.

Compounds (4), (7), (8), and (9) showed molecular ions in their field desorption mass spectra (FDMS). The IR spectra (KBr) of all the compounds showed characteristic (S=O) absorption at *ca.* 1 250 cm^{-1}, and S–O–C absorption between 810–860 cm^{-1}.

Further work on the biological activities of these sugar sulphates, as well as on other compounds derived from them, is in progress and will be reported in due course.

Experimental

General.—^{1}H NMR spectra were recorded at 400 MHz on a Bruker WM-400 machine and ^{13}C NMR spectra were recorded on the same machine at 100 MHz with Me_4Si as internal standard. Field desorption mass spectra were obtained on a Varian MAT 711, and IR spectra on a Perkin-Elmer 2021 instrument. Optical rotations were recorded on a Zeiss Old-5 polarimeter. Elemental analyses were performed on a Perkin-Elmer analyser Model 240.

Benzyl 2,3-*Anhydro*-β-L-ribo-*hexopyranoside* 4-(*Hydrogen Sulphate*) (2).—To a solution of the triflate (1)[12a] (300 mg, 0.85 mmol) in anhydrous acetonitrile (15 ml) at 0 °C was added tetrabutylammonium hydrogen sulphate (600 mg, 1.77 mmol) and the mixture was stirred at room temperature for 12 h, when no unchanged triflate could be observed by TLC. Evaporation of the solvent under reduced pressure afforded a gum, which upon crystallization from ether–light petroleum (40–60 °C)

Table 3. 100 MHz ^{13}C NMR spectra chemical shifts of compounds (**4**)–(**9**).

Compound	C-1	C-2	C-3	C-4	C-5
(**2**)[a]	93.4	51.4	48.5	75.3	58.4
(**4**)[a]	91.4	51.8	48.5	76.4	57.8
(**5**)[b]	99.3	71.2	86.1	82.6	58.3
(**7**)[a]	93.8	51.6	50.3	72.5	56.7
(**8**)[b]	102.1	71.6	87.2	81.6	62.5
(**9α**)[b]	97.2	73.0	87.9	82.2	62.8
(**9β**)[b]	93.9	69.6	86.4	82.7	57.5

[a] In $CDCl_3$. [b] In CD_3OD.

gave pure crystalline *monosulphate* (**2**) (151 mg, 59%), m.p. 92–93 °C (Found: C, 47.5; H, 4.6; S, 10.1. $C_{12}H_{14}O_7S$ requires C, 47.7; H, 4.6; S, 10.6%); $[\alpha]_D^{20}$ +10.8° (*c* 1 in $CHCl_3$).

Benzyl 2,3-*Anhydro*-β-L-lyxo-*hexopyranoside* 4-(*Hydrogen Sulphate*) (**4**) *and Benzyl* β-L-arabino-*Hexopyranoside* 3,4-(*Cyclic Sulphate*) (**5**).—The triflate (**3**)[12a] (600 mg, 1.7 mmol) and tetrabutylammonium hydrogen sulphate (1.33 g, 3.92 mmol) were allowed to react in anhydrous acetonitrile as described above. After 8 h the solvent was stripped off under reduced pressure, and the residue was chromatographed on a silica gel column with ethyl acetate–hexane (1:4) as eluant. The compound eluted first was recrystallized from ether–hexane to afford pure *monosulphate* (**4**) (130 mg, 25%), m.p. 110–112 °C (Found: C, 47.5; H, 4.55; S, 10.1. $C_{12}H_{14}O_7S$ requires C, 47.7; H, 4.6; S, 10.6%); $[\alpha]_D^{20}$ +30.5° (*c* 1 in $CHCl_3$).

The next compound eluted from the column was recrystallized from ethyl acetate–hexane to afford pure *cyclic sulphate* (**5**) (266 mg, 52%), m.p. 144–145 °C (Found: C, 47.6; H, 4.7; S, 10.1. $C_{12}H_{14}O_7S$ requires C, 47.7; H, 4.6; S, 10.6%); $[\alpha]_D^{20}$ 10.4° (*c* 1 in MeOH).

Benzyl 2,3-*Anhydro*-α-D-lyxo-*hexopyranoside* 4-(*Hydrogen Sulphate*) (**7**) *and Benzyl* α-D-arabino-*Hexopyranoside* 3,4-(*Cyclic Sulphate*) (**8**).—The triflate (**6**) (600 mg, 1.7 mmol) and tetrabutylammonium hydrogen sulphate (1.33 g, 3.92 mmol) were allowed to react in anhydrous acetonitrile (30 ml) as described above. After evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with ethyl acetate–hexane (1:4) as eluant to give two crystalline products. Both products were crystallized from ethyl acetate–hexane. The compound which was eluted first was found to be pure monosulphate (**7**) (130 mg, 25%), m.p. 72–73 °C (Found: C, 47.6; H, 4.6; S, 10.4. $C_{12}H_{14}O_7S$ requires C, 47.7; H, 4.6; S, 10.6%); $[\alpha]_D^{20}$ +30.5° (*c* 1 in $CHCl_3$).

The second compound eluted from the column was found to be pure *cyclic sulphate* (**8**) (304 mg, 59%), m.p. 114–116 °C (Found: C, 47.7; H, 4.7; S, 10.0. $C_{12}H_{14}O_7S$ requires C, 47.7; H, 4.6; S, 10.6%); $[\alpha]_D^{20}$ +20.5° (*c* 1 in MeOH).

α- *and* β-D-arabino-*Hexopyranose* 3,4-(*Cyclic Sulphates*) (**9α**) *and* (**9β**).—To a degassed solution of compound (**8**) (1.4 g, 4.67 mmol) in ethanol under N_2 was added 10% Pd–C (1.0 g), and the gas was replaced with H_2. After the mixture had been stirred for 4 h under H_2 (1 atm) the reaction did not appear to proceed any further (TLC). The solid was filtered off and fresh catalyst (400 mg) was added. The mixture was stirred for an additional period of 5 h under H_2 (1 atm), when no unchanged pyranoside (**8**) could be observed on TLC. The catalyst was removed by filtration and the solvent was evaporated off under reduced pressure to afford an off-white solid (0.59 g, 60%), which was found to be a 2:3 mixture of α and β anomers of compound (**9**) (see text). Recrystallization from ethyl acetate–hexane afforded pure β-D-arabino-*hexopyranose* 3,4-(*cyclic sulphate*) (**9β**) (0.472 g, 80% based on crude mixture), m.p. 92–93 °C (Found: C, 28.3; H, 3.8; S, 15.0. $C_5H_8O_7S$ requires C, 28.3; H, 3.8; S, 15.1%); $[\alpha]_D^{20}$ +80° (*c* 1 in MeOH).

References

1 For reviews see 'Carbohydrate Sulfates,' ACS Symposium Series 77, ed. R. W. Schweiger, American Chemical Society, Washington, DC, 1978; F. Egami and T. Yamagata, in Glycoconjugate Research Proceedings of the International Symposium, 4th, 1977, eds J. D. Gregory and R. W. Jeanloz, Academic Press, New York, 1979, pp. 427–440; D. A. Rees, *Annu. Rep. Prog. Chem.*, 1965, **62**, 469.

2 Y. Aoi, M. Yokota, I. Kato, and T. Hosokawa, *J. Med.*, (Westbury, N.Y.), 1981, **12**, 127.

3 Chugai Pharmaceutical Co. Ltd., Tokyo, Jap.P. 83,208,294 (*Chem. Abstr.*, 1984, **100**, 121 538u); R. Maeda, Jap.P. 76, 00,175 (*Chem. Abstr.*, 1976, **84**, 155 711r); H. Yokoi, T. Nojiri, and R. Maeda, Jap.P. 73, 15,830 (*Chem. Abstr.*, 1973, **79**, 79 129m).

4 A. Mizutani, T. Ogawa, and H. Hanai, Jap.P. 79, 163,526 (*Chem. Abstr.*, 1980, **93**, 8 452q).

5 V. G. Nair, J. P. Joseph, and S. Bernstein, G.P. 2,730 992 (*Chem. Abstr.*, 1978, **89**, 44 115h).

6 J. Upeslacis, R. E. Schaub, and S. Bernstein, U.S. P. 4 431 637 (*Chem. Abstr.*, 1984, **100**, 197 806e).

7 K.-W. Law, Ph.D. Dissertation, Univ. Oklahoma, Norman, Oklahoma, 1979 (*Diss. Abstr. B*, 1979, **40**, 1818).

8 G. Ya. Yakimenko, *Vestn. Kharkov, Politekh Inst.*, 1972, **70**, 211 (*Chem. Abstr.*, 1974, **80**, 77 460j).

9 E. E. Gilbert, *Chem. Rev.*, 1962, **62**, 549.

10 K. Takiura and S. Honda, *Chem. Pharm. Bull.*, 1970, **18**, 2125.

11 C. L. Penney and A. S. Perlin, *Carbohydr. Res.*, 1981, **93**, 241.

12 (*a*) R. Kimmich and W. Voelter, *Liebigs Ann. Chem.*, 1981, 1100; (*b*) F. Latif, A. Malik, and W. Voelter, *Z. Naturforsch.*, 1985, **40b**, 371; (*c*) N. Afza, A. Malik, F. Latif, and W. Voelter, *Liebigs Ann. Chem.*, 1985, 1929; (*d*) A. Malik, M. Roosz, and W. Voelter, *Z. Naturforsch.*, 1985, **40b**, 559; (*e*) W. Kowollik, A. Malik, N. Afza, and W. Voelter, *J. Org. Chem.*, 1985, **50**, 3325; (*f*) G. Janairo, A. Malik, and W. Voelter, *Liebigs Ann. Chem.*, 1985, 653.

13 B. Helferich, *Ber. Dtsch. Chem. Ces.*, 1921, **54**, 1082; B. Helferich, A. Lowa, W. Nippe, and H. Riedel; *ibid.*, 1923, **56**, 1083; B. Helferich, G. Sprock, and E. Besler, *ibid.*, 1925, **58**, 886; J. K. N. Jones, M. B. Perry, and J. C. Turner, *Can. J. Chem.*, 1969, **38**, 1122; P. D. Bragg, J. K. N. Jones, and J. C. Turner, *ibid.*, 1959, **37**, 1412; H. J. Jennings and J. K. N. Jones, *ibid.*, 1963, **41**, 1151.

14 J. R. Turvey and J. P. Williams, *J. Chem. Soc.*, 1962, 2119.

15 For ^1H NMR data of the monosulphates of D-galactose and D-glucose, see P. J. Archbald, M. D. Fenn, and A. B. Roy, *Carbohydr. Res.*, 1981, **93**, 177.

16 J. G. Buchanan, R. Fletcher, K. Parry, and W. A. Thomas, *J. Chem. Soc.* B, 1969, 377.

17 For the relationship between the chemical shifts and conformation in pyranosides, see R. U. Lemieux and J. D. Steven, *Can. J. Chem.*, 1965, **43**, 2059; B. Coxon, *Tetrahedron*, 1966, **22**, 2281.

Paper 8/03586E
Received 19*th September* 1988
Accepted 31*st July* 1989