191 *The Nucleophilic Degradation of Diethylsulphonylglycopyranosylmethane Derivatives.*[1]

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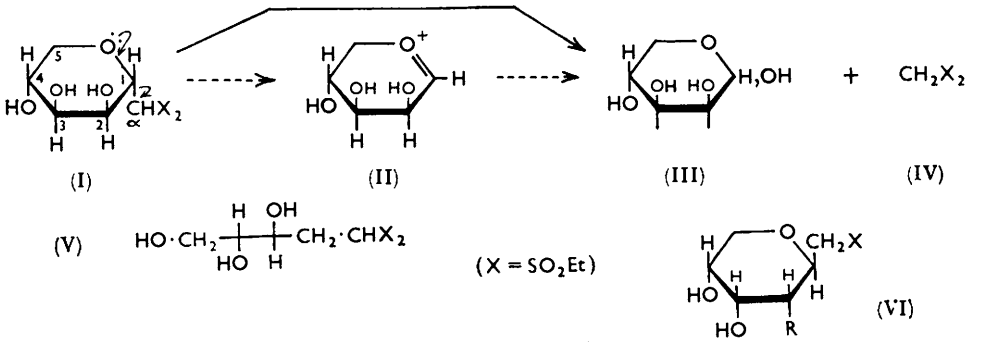
The nucleophilic hydrolysis of diethylsulphonylglycopyranosylmethanes into aldopentose and diethylsulphonylmethane has been investigated. Participation by the ring oxygen atom is essential for the reaction to occur. The reaction showed neither first- nor second-order kinetics, the measurement of which was complicated by various factors including the acidity of the disulphones and side reactions at high pH values.

PREVIOUS work [2,3] has indicated that the hydrolysis of diethylsulphonylglycopyranosylmethane derivatives with dilute ammonia solution proceeds by a nucleophilic mechanism in which the diethylsulphonylmethyl group is replaced by a hydroxyl group, yielding the corresponding aldopentose and diethylsulphonylmethane (IV). Theoretical considerations favour the S_N1 mechanism since the S_N2 transition state would lead to severe steric compression whereas in the S_N1 reaction considerable steric relief would result from the ejection of the large diethylsulphonylmethyl group which constitutes about half of the size of the original molecule. A study of the kinetics of the uncatalysed solvolysis of *O*-acylglycosyl halides by Newth and Phillips [4] revealed that the S_N1 mechanism was operative and that the intermediate carbonium ion was resonance-stabilised by interaction of a lone pair of electrons on the ring oxygen atom, thus forming an oxonium cation (II). This participation explained the exceptional reactivity of the halogen substituents of various α-halogeno-ethers.[5] If ring-oxygen participation were operative in the heterolysis of diethylsulphonylglycopyranosylmethanes, then derivatives in which there is no similarly placed oxygen substituent, as in 1,1-diethylsulphonyl-D-*threo*-3,4,5-trihydroxypentane (V) and 1,1-diethylsulphonylethane, should be stable in ammonia solution. In fact these two

[1] For a preliminary communication see Hough and Richardson, *Proc. Chem. Soc.*, 1959, 193.
[2] Hough and Taylor, *J.*, 1956, 970.
[3] Hough and Taha, *J.*, 1957, 3564.
[4] Newth and Philips, *J.*, 1953, 2896.
[5] Newth and Philips, *J.*, 1953, 2900.

derivatives were not degraded, thus showing that the ring oxygen participates in the elimination of the diethylsulphonylmethyl anion from diethylsulphonylglycopyranosylmethanes. However, Ballinger, de la Mare, Kohnstam, and Prestt [6] have shown that electron-donating groups can also increase the rate of an S_N2 reaction, mainly it would seem, by conjugative rather than inductive processes. The replacement of the hydroxyl group at $C_{(2)}$ of diethylsulphonyl-β-D-ribopyranosylmethane (VI; R = OH) by an



acetamido-group (VI; R = NHAc) reduced [7] its rate of heterolysis by a non-conjugative electron-withdrawing effect. Further evidence was sought by kinetic studies of the reaction of diethylsulphonyl-α-D-lyxopyranosylmethane (I) with base.

Its rate of reaction in varying concentrations of ammonia solution was determined by polarimetry. In experiment 3 (Table 1) the rate constant was also measured by Bailey's colorimetric method,[8] and the results were compatible with those obtained by the polarimetric method. The pseudo-unimolecular rate constants (k) were calculated from a plot of $2{\cdot}303 \log_{10}(\alpha - \alpha_\infty)$ against time (t), where α = observed rotation at t and α_∞ is the final rotation at $t = \infty$; it follows that $k = -2{\cdot}303 \times$ slope of the line. The concentrations of hydroxyl ions were determined from the pH of the reaction mixtures since the mildly acidic disulphone (pK_A 10·1) depressed the pH of the ammonia solution. As can be seen from Table 1, the reaction obeyed neither first- nor second-order kinetics.

TABLE 1.

Reaction rates of diethylsulphonyl-α-D-lyxopyranosylmethane with ammonia solution at 25° ([disulphone] ≃ 0·065M).

Experiment	1	2	3	4	5	6	7
$[NH_4OH]$ (N)	0·049	0·074	0·29	0·39	0·45	0·74	1·47
10^6k (25°) (sec.$^{-1}$)	3·92	5·23	8·49	11·1	12·1	16·9	17·8
$[\alpha]_\infty$, lyxose	−13·5°	−13·8°	−27·8°	−29·2°	−30·3°	−30·6°	−37·2°
pH	9·8	10·0	10·4	10·5	10·6	10·8	11·1
$10^3[OH^\ominus]$	6·3	9·3	25·1	31·6	38·9	60·3	120

A simple correlation between the order of a reaction and its mechanism is not always observed [9a] and consequently other criteria of the mechanisms were investigated. Since α-D-arabinopyranosyldiethylsulphonylmethane underwent solvolysis in boiling aqueous solution,[2] the rate of solvolysis of the D-*lyxo*-isomer (I) was examined at pH 6·6 and 25°. A slow solvolysis [$10^6k(25°) = 0{\cdot}028$ sec.$^{-1}$] was observed by polarimetry, and paper chromatography of the reaction mixture revealed that approximately 10% degradation had

[6] Ballinger, de la Mare, Kohnstam, and Prestt, *J.*, 1955, 3641.
[7] Coxon and Hough, unpublished results.
[8] Bailey, *Biochem. J.*, 1958, **68**, 669.
[9] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, (*a*) p. 314, (*b*) p. 347.

occurred after 12 days, a much more rapid reaction than that expected for second-order kinetics. The rate of nucleophilic degradation of the cyclic disulphone (I) was decreased in the presence of methanol (Table 2) due to the reduction in the polarity of the solvent, an effect which usually enhances the rate of S_N2 reactions.[9b]

TABLE 2.

The effect of methanol on the rate of degradation of the sulphone (I) ([sulphone] = 0·066M).

Solvent	[NH_4·OH] (N)	pH	10^6k (25°) (sec.$^{-1}$)
Water	0·29	10·4	8·5
80% Methanol	0·29	10·9	2·8
Water	0·74	10·8	16·9

Equivalent concentrations (0·29N) of ammonia in water and in aqueous methanol had pH 11·25 and 11·15, respectively, which on the addition of the sulphone (0·006M) fell to 10·4 and 10·9 (Table 2). The higher pH of the sulphone in aqueous methanol–ammonia is attributed to the smaller degree of ionisation of the sulphone under these conditions. An aqueous solution of the sulphone of similar pH is included for comparison.

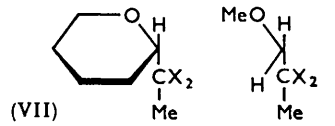
During the above experiments (Table 1) it was observed that the final specific rotations, calculated on the assumption that D-lyxose was the sole optically active product, were not all in accord with the accepted value of −13·8° in water for the pentose. The value decreased progressively from −13·5° to −37·2° as [NH_4·OH] was increased. D-Lyxose was the sole product detected on paper chromatograms, and upon recovery from a reaction mixture (expt. 7) the pentose had an optical rotation which was in good agreement with that of authentic D-lyxose. When the crystalline pentose was dissolved in ammonia solution a slow reversible decrease in optical rotation was observed which was complete within 24 hr., and the final values were in good agreement with those obtained previously in the corresponding reaction mixtures (expts. 3 and 7); upon neutralisation with acetic acid, the optical rotations changed rapidly to the authentic value for D-lyxose. The changes in the optical rotation of D-lyxose in ammonia are probably due to alterations in either the proportions of the various molecular species present in the mutarotated mixture or their conformations. Under the same conditions, D-ribose was unaffected by ammonia solution.[7] Reeves and Blouin [10] have observed relatively large reversible changes in the optical rotations of certain glycopyranosides in aqueous sodium hydroxide, due to changes in the conformations of the pyranosides.

If the electron-withdrawing power of the sulphone groups in (I) increases progressively with pH owing to the slight polarisation of the doubly covalent [11] sulphur-to-oxygen linkages the kinetics could be interpreted by the S_N1 mechanism. It seemed possible that the reaction would become independent of base concentration at sufficiently high values of pH and consequently the use of sodium hydroxide was investigated. Chromatographic examination of the reaction mixtures containing 0·10—0·025N-sodium hydroxide indicated that lyxose was the sole product of the sulphone (I) and that little degradation or anomerisation of the pentose has occurred. Unfortunately the small differences in the initial and final rotations (<0·30°) and the orange-red colours which slowly developed did not permit accurate determination of the rate constants. Furthermore, the pH of the reaction mixtures varied considerably during the reactions, thus invalidating the kinetic results. It was significant, however, that the addition of methanol (50% v/v) resulted in a three-fold reduction in the rate of heterolysis of the sulphone (I) under the same conditions in the presence of 0·1N-sodium hydroxide. Complete inhibition of the reaction occurred in 0·1N-ethanolic sodium hydroxide, no pentose being detected after several months, whereas some degradation would have been expected if the S_N2 mechanism were operative. It is

[10] Reeves and Blouin, *J. Amer. Chem. Soc.*, 1957, **79**, 2261.
[11] Barnard, Fabian, and Koch, *J.*, 1949, 3442; Gillespie and Passerini, *J.*, 1956, 3850.

regarded as unlikely that under these conditions the sulphone (I) would have been completely converted into the unreactive anion by removal of the hydrogen substituent at $C_{(\alpha)}$. Re-investigation of the behaviour of α-D-arabinopyranosyldiethylsulphonylmethane in methanolic sodium methoxide at room temperature failed to reveal any nucleophilic substitution, contrary to the results of Hough and Taha.[3]

In the following paper we report finding no reaction of 1,1-diethylsulphonyl-1-pentopyranosylethane (VII) and 2,2-diethylsulphonyl-1-methoxypropane (VIII) with ammonia solution and this effect has been attributed to the electron-donating inductive effect of the methyl group attached to the carbon atom carrying the sulphone groups. Electronic effects are usually smaller for S_N2 displacements at a saturated carbon atom than for S_N1 reactions.[6,12] The possibility of steric inhibition of the S_N2 transition state in the hindered cyclic sulphone (VII) would appear to be ruled out by the stability of the smaller open-chain disulphone (VIII).



(VII) (VIII)

Experimental

Paper chromatography was carried out on Whatman No. 1 filter paper by the descending method at room temperature with either (i) butan-1-ol–ethanol–water (40 : 11 : 9 v/v) or (ii) butan-1-ol–pyridine–water (10 : 3 : 3 v/v) as mobile phase. *p*-Anisidine hydrochloride was used for the detection of reducing sugars. Polyhydroxy-compounds were detected either by ammoniacal silver nitrate or, where the latter was unsatisfactory, the dried paper was thinly and evenly sprayed with 0·02M-sodium metaperiodate, followed 3 min. later by ammoniacal silver nitrate. M. p.s were determined on a Kofler micro-heating stage. Solutions were evaporated under reduced pressure. Optical rotations were determined at 25°. The pH values of the reaction mixtures and the pK_A of the disulphone (I) were determined by use of an E.I.L. direct-reading pH meter. In the latter case, the disulphone (*ca.* 0·3 g.) in water (10 ml.) was titrated with 0·1N-sodium hydroxide, and the pK_A was taken as the pH at half-neutralisation.

Determination of the Rate of Reaction of Diethylsulphonyl-α-D-lyxopyranosylmethane (I) *with Aqueous Ammonia.*—The disulphone (0·2—0·25 g.; accurately weighed) was dissolved in aqueous ammonia (10 ml.) of known concentration, transferred to a Pyrex polarimeter tube (1 dm.), and kept at 25°. At intervals of time (*t*) the optical rotation (α) was measured until it attained a constant value. The rate constants are listed in Table 1 and an individual experiment is illustrated below:

t (hr.)	¼	1	2	3	4½	5½	6½	8¼	25	29½	32	49	∞
α °	0·14	0·12	0·10	0·07	0·04	0·02	−0·01	−0·03	−0·19	−0·23	−0·24	−0·27	−0·3

c, 2·18; *l*, 1; $[NH_4{\cdot}OH]$ = 0·74N; 10^6k = 16·9 sec.$^{-1}$.

In experiment 3 (see Table 1), portions (1 ml.) were removed at various intervals of time and acidified with 0·01N-sulphuric acid so that solutions were obtained containing 20—100 μg./ml. of lyxose. The concentration of pentose was then determined by the anthrone colorimetric method of Bailey,[5] and the results of the two methods compared:

t (hr.)	2	4	7	24	50
% D-Lyxose (polarimetric)	6	11	19	51	78
% D-Lyxose (colorimetric)	5	8	18	60	75

D-*Lyxose* (III).—After 72 hr., the mixture from experiment 7 (Table 1) had $[\alpha]_D$ −37° based on a 100% conversion of the disulphone (I) into D-lyxose. The aqueous solution was extracted

[12] Hine, " Physical Organic Chemistry," McGraw-Hill Book Co. Inc., New York, 1956, p. 152.

continuously with chloroform for 6 hr. to remove diethylsulphonylmethane and then concentrated to a pale syrup of D-lyxose (0·09 g.; 90%), $[\alpha]_D$ −11·9° (*c* 4·5 in water). This pentose was identical with an authentic sample of lyxose on paper chromatograms.

Solvolysis of the Sulphone (I) *at* pH 6·6.—The disulphone (271 mg.) was dissolved in 0·17M-phosphate buffer at pH 6·6 (20 ml.). One portion of the solution was stored in a tightly stoppered polarimeter tube at 25°, and a separate portion was kept for chromatographic examination. The rotation of the solution was measured at intervals in a 1-dm. tube and the following results were obtained:

t (days)	0	9	12	16	33	40	43	73	81
α °	0·16	0·12	0·12	0·11	0·08	0·07	0·06	0·03	0·01

It was assumed that the final value would be that of D-lyxose (*i.e.*, −0·065°) and from this the rate constant was calculated to be $2{\cdot}8 \times 10^{-8}$ sec.$^{-1}$.

A paper-chromatographic examination of the reaction mixture showed that D-lyxose was the only reducing sugar produced, and by using standard solutions of D-lyxose it was calculated that approximately 10% degradation had occurred after 12 days, which was in accord with the rate constant obtained.

The Effect of Aqueous Ammonia on the Specific Rotation of D-*Lyxose* (III).—A solution of D-lyxose (0·1 g.) in 1·47N-ammonia solution (10 ml.) was kept in a Pyrex polarimeter tube (1 dm.). The specific rotation $[\alpha]_D$ was determined at intervals:

t (hr.)	0	2	5	22	48
$[\alpha]_D$	−14·0°	−20·5°	−23·5°	−37·5°	−37·5°

The calculated specific rotation from the corresponding reaction mixture (expt. 7), based on a quantitative conversion of the disulphone into D-lyxose, was −37·2°.

In another experiment in which $c = 1$ and $[NH_4{\cdot}OH] = 0{\cdot}29$N, the following results were obtained:

t (hr.)	0	3	6	24	48
$[\alpha]_D$	−13·0°	−16·5°	−19·0°	−26·5°	−27·0°

The corresponding reaction mixture had $[\alpha]_D$ −27·7°. Neutralisation of this ammoniacal solution with acetic acid caused the specific rotation to increase to −14° within ½ hr.

*Treatment of Diethylsulphonyl-*α-D-*lyxopyranosylmethane* (I) *with Sodium Methoxide.*—A solution of the disulphone (0·68 g.) in 0·165N-sodium methoxide (10 ml.) was kept at room temperature. After 8 days, large, thick prisms of starting material, m. p. and mixed m. p. 193—195°, separated. Chromatography indicated that, apart from starting material, lyxose (a faint trace) was the only other compound present in the mother liquors. Neutralisation with Amberlite IR-120 (H) resin yielded crystals after concentration. Recrystallisation from ethanol gave more diethylsulphonyl-α-D-lyxopyranosylmethane, m. p. and mixed m. p. 193—195°. The total recovery of starting material was 0·52 g. (76%).

Treatment of α-D-*Arabinopyranosyldiethylsulphonylmethane with Sodium Methoxide.*—The disulphone (0·38 g.) was dissolved in 0·1N-sodium methoxide (10 ml.). After 3 months, chromatography indicated the presence of starting material, a faint trace of arabinose, and a very faint trace of an unknown compound [R_{Rh} 1·05; solvent (i)] which reacted with the ammoniacal silver nitrate spray only. The solution was de-ionised as above and concentrated to a syrup which had $[\alpha]_D$ −14° (*c* 3·3 in methanol). Hough and Taylor [2] report $[\alpha]_D$ −11·5° for α-D-arabinopyranosyldiethylsulphonylmethane.

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