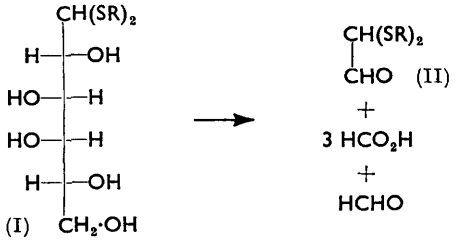
792. *The Periodate Oxidation of Some Thioacetals and Sulphones.*

By L. Hough and Mahmoud I. Taha.

Evidence has been obtained for the cleavage by periodate oxidation of the linkage between adjacent carbon atoms carrying respectively an ethyl thioacetal group and a hydroxy-, amino-, or acetamido-function. The diethyl dithioacetals of acetaldehyde and 2-deoxy-D-*arabino*hexose are similarly split giving methanol and formaldehyde respectively from $C_{(2)}$. Oxidation of D-galactose dibenzyl dithioacetal afforded dibenzylthioacetaldehyde.

Sulphur derivatives of carbohydrates show abnormal behaviour towards oxidation with periodate.[1-4] Thus Okui[3] found that ethyl thioglycosides and aldose diethyl dithioacetals always consume more periodate than that required by the Malaprade reaction, the quantity varying with the concentration of oxidant. The over-consumption of the reagent is generally attributed[1-3] to the oxidation of the sulphur atoms to sulphoxides and sulphones. However, our previous results[4] provided evidence for the periodate oxidation, at room temperature and in the dark, of certain compounds containing an α-hydroxy-β-thioalkyl structure [·CH(OH)·CHSR·] in a way similar to that of glycols or α-hydroxy-β-amino-derivatives, since 2 : 2-diethylthioethanol (glycollaldehyde diethyl dithioacetal) rapidly consumed 1 mol. of the oxidant with the simultaneous liberation of 1 mol. of formaldehyde, and D-galactose diethyl dithioacetal (I; R = Et) readily consumed 5 mol. of periodate liberating 4 equivalents of titratable acid and 1 mol. of formaldehyde. Under the same conditions, 2-amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride and its *N*-acetyl derivative rapidly consumed 6 mol. of periodate each, with the formation of 3 and 4 mol. of titratable acid respectively and 1 mol. of formaldehyde, thus suggesting that α-amino-β-thioalkyl and α-acetamido-β-thioalkyl groups are attacked by periodate. Comparison of the uptake of periodate by methyl 2-acetamido-2-deoxy-α-D-glucopyranoside and the α- and the β-isomer of 2-acetamido-2-deoxy-D-glucopyranosylthioethane support this conclusion.[4] Furthermore, 2-acetamido-3 : 4 : 5 : 6-tetra-*O*-acetyl-2-deoxy-D-glucose diethyl dithioacetal and 2-acetamido-1-acetoxy-1-ethylthioethane[5] rapidly consumed 1 mol. of periodate, whereas 2 : 3 : 4 : 5 : 6-penta-*O*-acetyl-D-galactose diethyl dithioacetal was only slowly oxidised. Participation of sulphur in these reactions was confirmed by the resistance of 2-acetamido-1-acetoxyethane[5] and 2-acetamidoethanol to periodate oxidation.



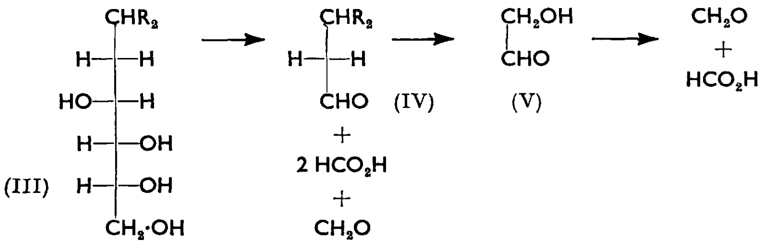
(I) (II)

When D-galactose dibenzyl dithioacetal (I; R = CH_2Ph) was treated with 5 mol. of sodium metaperiodate at room temperature, a chloroform extract gave, in high yield, a crystalline product identified as dibenzylthioacetaldehyde (II; R = CH_2Ph). That this aldehyde was associated in chloroform was indicated by molecular-weight estimation in that solvent by Menzies and Wright's method.[6] This compound (II; R = CH_2Ph) was

[1] Nicolet and Shinn, *J. Biol. Chem.*, 1942, **142**, 139.
[2] Bonner and Drisko, *J. Amer. Chem. Soc.*, 1951, **73**, 3699.
[3] Okui, *J. Pharm. Soc. Japan*, 1955, **75**, 1262.
[4] Hough and Taha, *J.*, 1956, 2042.
[5] *Idem*, *J.*, 1957, 3311.
[6] Menzies and Wright, *J. Amer. Chem. Soc.*, 1921, **43**, 2309, 2314.

surprisingly stable to periodate oxidation. In agreement with this observation, D-galactose dibenzyl dithioacetal (I; $R = CH_2Ph$) rapidly consumed 4 mol. of periodate, whereas under the same conditions the diethyl dithioacetal (I; R = Et) consumed 5. In contrast lead tetra-acetate in glacial acetic acid oxidises dibenzyl dithioacetals faster than diethyl dithioacetals[7, 8] although it is clear from the periodate oxidations that the mechanisms are different.

Okui[3] reported that 2-deoxy-D-*arabino*hexose (2-deoxy-D-glucose) diethyl dithioacetal (III; R = SEt) consumed 5—7 mol. of periodate (according to the concentration of the oxidant), liberating 3 mol. of titratable acid. He suggested that the products were 1 mol. of formaldehyde, 2 of formic acid, and 1 of the disulphone (IV; $R = SO_2Et$) which he incorrectly assumed would titrate as a monobasic acid. In agreement we found that the dithioacetal (III; R = SEt) consumed 6 mol. of periodate liberating 3 equiv. of acid, but 2 mol. of formaldehyde were also formed. Okui's conclusion therefore requires modification since during this oxidation fission of the $C_{(1)}$–$C_{(2)}$ bond occurred with oxidation of the methylene group to formaldehyde. Presumably oxidative cleavage of the $C_{(1)}$–$C_{(2)}$ bond of the dithioacetal (III; R = SEt) gives rise to glycollaldehyde (V) which would be further oxidised to 1 mol. each of formaldehyde and formic acid. This view gains considerable support from the fact that acetaldehyde diethyl dithioacetal readily consumed 2 mol. of periodate with formation of about 1 mol. of methanol. Under the same conditions, 1 : 1-diethylsulphonylethane was not oxidised. Oxidation of 1 : 1-diethylsulphonyl-D-*arabo*-3 : 4 : 5 : 6-tetrahydroxyhexane (III; $R = SO_2Et$) with sodium metaperiodate (3 mol. consumed) gave as expected 1 mol. of formaldehyde and 2 equivalents of titratable acid, thus invalidating the suggestion that the aldehydo-disulphone (IV; $R = SO_2Et$) would titrate as a monobasic acid.



EXPERIMENTAL

Paper chromatography was on Whatman No. 1 filter paper by the descending method with ethyl acetate–acetic acid–water (9 : 2 : 2 v/v) as mobile phase. The separated substances were detected with a *ca.* 4% solution of silver nitrate containing excess of ammonia. Solutions were evaporated under reduced pressure.

2-Acetamidoethanol.—Acetic anhydride (50 ml.) was added dropwise to 2-aminoethanol (5 g.) at 0° with shaking. After 4 hr. at room temperature the mixture was concentrated to a yellow syrup (*ca.* 8 g.) which slowly crystallised at 0°. After two recrystallisations from acetone the N-*acetyl derivative* had m. p. 8° (approx.) (Found: C, 46·7; H, 8·6; N, 13·9; Ac, 43·4. $C_4H_9O_2N$ requires C, 46·6; H, 8·7; N, 13·6; Ac, 41·7%). The compound did not give a colour with ninhydrin or react with nitrous acid.

D-*Galactose Dibenzyl Dithioacetal.*—D-Galactose (15 g.) was shaken with toluene-ω-thiol (25 g.) and concentrated hydrochloric acid (50 ml.) for 2 hr. The product (35 g.) had m. p. 138°, R_F 0·91, after 2 crystallisations from aqueous acetone.

Dibenzylthioacetaldehyde.—Sodium metaperiodate (5 g.) in water (100 ml.) was added with stirring to a suspension of D-galactose dibenzyl dithioacetal (5 g.) in water (500 ml.) at 0°. After 3 hr. the oily product was extracted with chloroform (100 ml.), washed with 1% sodium thiosulphate solution (2 × 100 ml.), and then with water, dried ($MgSO_4$), and concentrated to a syrup (3 g.), which slowly crystallised at 0°. *Dibenzylthioacetaldehyde* formed needles (from

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[7] Baker, *J. Amer. Chem. Soc.*, 1952, **74**, 827.

[8] Bourne, Corbett, Stacey, and Stephens, *Chem. and Ind.*, 1954, 106.

methanol), m. p. 73° (Found: C, 66·8; H, 5·8; S, 23·0%; *M*, 410. $C_{16}H_{16}OS_2$ requires C, 66·7; H, 5·56; S, 22·3%; *M*, 288).

The 2 : 4-*dinitrophenylhydrazone* was prepared by heating the aldehyde (0·5 g.) and 2 : 4-dinitrophenylhydrazine (0·5 g.) in ethanol (50 ml.) under reflux for 5 min., after which the mixture was cooled and concentrated hydrochloric acid (*ca.* 3 ml.) added. The product (*ca.* 1 g.) formed needles (from ethanol), m. p. 87° (Found: C, 56·3; H, 5·0; N, 12·2; S, 13·1. $C_{22}H_{20}O_4N_4S_2$ requires C, 56·4; H, 4·3; N, 11·95; S, 13·7%).

Acetaldehyde Diethyl Dithioacetal.—A mixture of acetaldehyde (*ca.* 2 g.), concentrated hydrochloric acid (20 ml.), and ethanethiol (*ca.* 10 ml.) was shaken for 24 hr. and then diluted with water (*ca.* 200 ml.), and the product extracted with ether (3 × 50 ml.). The combined extracts were washed with sodium hydrogen carbonate solution (3 × 50 ml.) and water, and dried ($MgSO_4$). Concentration gave the thioacetal as an oil (*ca.* 5 g.), b. p. 180° (bath temp.)/15 mm. (Found: S, 43·7. Calc. for $C_6H_{14}S_2$: S, 42·6%).

1 : 1-*Diethylsulphonylethane.*—The diethyl dithioacetal (2·0 g.) in methanol (20 ml.) was cooled to −10° (acetone–solid carbon dioxide) and an excess of cold aqueous peroxypropionic acid [9] (150% of theory for 4 mol., based on propionic anhydride) was added with shaking. After 1 hr. at room temperature the solution was concentrated yielding crystals (*ca.* 2·2 g.), m. p. 64—65° [from ether–light petroleum (b. p. 40—60°)] (Found: C, 33·9; H, 6·9; S, 27·0. Calc. for $C_6H_{14}O_4S_2$: C, 33·7; H, 6·5; S, 29·9%).

2-*Deoxy*-D-*glucose Diethyl Dithioacetal.*—2-Deoxy-D-glucose (0·8 g.) was shaken overnight with concentrated hydrochloric acid (*ca.* 5 ml.) and ethanethiol (*ca.* 2 ml.). The solution was diluted with ethanol (50 ml.), neutralised with lead carbonate, and the insoluble lead salts filtered off and washed with ethanol (20 ml.). Concentration of the combined filtrate and washings yielded a syrup (0·5 g.) which slowly crystallised. Recrystallisation from acetone–ether gave needles, m. p. 132°, $[\alpha]_D^{20}$ −8·8° (*c*, 2·5 in MeOH) (Found: C, 44·3; H, 7·9; S, 22·95. Calc. for $C_{10}H_{22}O_4S_2$: C, 44·5; H, 8·1; S, 23·7%). Hughes, Overend, and Stacey [10] record m. p. 133·5°, $[\alpha]_D^{20}$ −10° (in MeOH).

1 : 1-*Diethylsulphonyl*-D-arabo-3 : 4 : 5 : 6-*tetrahydroxyhexane.*—Oxidation of the dithioacetal (0·2 g.) gave the *sulphone* (0·22 g.), m. p. 162—163°, $[\alpha]_D^{20}$ +27·2° (*c*, 1·36 in H_2O) [from acetone–light petroleum (b. p. 40—60°)] (Found: C, 35·6; H, 6·6; S, 18·6. $C_{10}H_{22}O_8S_2$ requires C, 35·9; H, 6·6; S, 19·2%).

Periodate Oxidation Experiments.—(i) *Estimation of the uptake of periodate and of acid liberated.* In each case, 0·3M-aqueous sodium metaperiodate (5 ml.) was added to the compound (25—30 mg. accurately weighed) in water or ethanol (15 ml.), and the solution made up to 25 ml. with water and stored in the dark. A blank was worked concurrently. At intervals, samples (2 ml.) were transferred into mixtures of phosphate buffer (pH 6·98; 25 ml.) and 20% potassium iodide solution (1 ml.), and the liberated iodine titrated (starch indicator) with 0·01N-sodium thiosulphate solution. Acid liberated during the oxidation was determined in samples (2 ml.) by adding ethylene glycol (1 ml.) and, after 10 min., titrating them with 0·01N-sodium hydroxide with methyl-red, screened with methylene-blue as indicator.

(ii) *Estimation* [11] *of formaldehyde liberated.* Sodium metaperiodate (0·015M) in sulphuric acid (0·045N) was mixed with an equal volume of N-sodium hydrogen carbonate. The solution (5 ml.) was added to the compound to be oxidised (*ca.* 0·5 mg., accurately weighed) in water (5 ml.) and the mixture set aside in the dark at room temperature. After 24 hr., a portion (1 ml.) was pipetted into a centrifuge tube containing lead dithionate solution (10% in water; 1 ml.). After mixing and centrifugation a portion (1 ml.) of the supernatant liquor was placed in a second tube (50 ml.). Chromotropic acid reagent [10 ml.; sodium salt (1 g.) in 55% sulphuric acid (600 ml.)] was added; this and all further operations were carried out away from direct light. After 30 min., lead sulphate was removed on the centrifuge and the supernatant liquor heated for 30 min. (boiling-water bath) and then diluted to 30 ml. with water. The absorption at 570 mμ was read on a colorimeter (E.E.L. filter 626). The formaldehyde liberated from known amounts of D-glucose was used for the preparation of the standard curve.

(iii) *Characterisation* [12] *of methanol liberated from the oxidation of acetaldehyde diethyl dithioacetal.* A mixture of 0·3M-aqueous sodium periodate (5 ml.) and acetaldehyde diethyl dithioacetal (0·1 g.) in water (5 ml.) was stored in the dark for 2 hr. Pyridine (1 ml.), benzene (1 ml.),

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[9] Hough and Taylor, *J.*, 1955, 1212.

[10] Hughes, Overend, and Stacey, *J.*, 1949, 2846.

[11] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

Results of periodate oxidations.

Compound		½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	9 hr.	CH_2O *
D-Galactose dibenzyl dithioacetal [a]	uptake *	—	3·1	3·4	3·8	4·0	4·5	—
Acetaldehyde diethyl dithioacetal [a]	uptake	1·85	1·97	1·97	1·99	2·05	2·13	nil
	acid *	0·0	0·0	0·0	0·0	0·0	0·0	
2-Deoxy-D-glucose diethyl dithioacetal [b]	uptake	4·63	5·02	5·47	5·8	6·03	6·27	1·95
	acid	2·10	2·20	2·38	2·55	2·60	3·01	
1 : 1-Diethylsulphonyl-D-*arabo*-3 : 4 : 5 : 6-tetrahydroxyhexane [b]	uptake	3·1	3·1	3·1	3·1	3·15	3·3	
	acid	1·7	1·9	2·1	2·1	2·1	2·1	
2-Amino-2-deoxy-D-glucose diethyl dithioacetal hydrochloride [b]	uptake	5·1	5·7	5·9	5·97	6·1	6·35	
	acid	3·16	3·5	3·55	3·6	3·77	3·94	
2-Acetamido-2-deoxy-3 : 4 : 5 : 6-tetra-*O*-acetyl-D-glucose diethyl dithioacetal [a]	uptake	0·82	0·89	1·06	1·17	1·2	1·22	nil
	acid	0·0	0·0	0·0	0·0	0·0	0·0	
2-Acetamido-1-acetoxy-1-ethylthioethane [a]	uptake	0·6	0·91	1·0	1·1	1·14	1·17	nil
	acid	0·0	0·0	0·0	0·0	0·0	0·0	

* Mol. [a] In aqueous ethanol. [b] In water.

and anhydrous potassium carbonate (*ca.* 100 g. in small portions) were added at 0° followed by 3 : 5-dinitrobenzoyl chloride (0·5 g.) in benzene (2 ml.). After 3 min., the 3 : 5-dinitrobenzoate was extracted with sodium-dried ether (3 × 30 ml.), the combined extracts dried (K_2CO_3) and concentrated, and the crystalline product (0·2 g.) recrystallised twice from ether–light petroleum (b. p. 40—60°). It had m. p. and mixed m. p. 108° (Found: N, 12·1. Calc. for $C_8H_6N_2O_6$: N, 12·4%). An *X*-ray powder photograph was identical with that of an authentic specimen of methyl 3 : 5-dinitrobenzoate.

THE UNIVERSITY, BRISTOL.

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[13] Holley and Holley, *Analyt. Chem.*, 1952, **24**, 216.