Thio-sugars with Sulphur in a Seven-membered Ring

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THERE are very few monocyclic sugar derivatives containing a seven-membered ring (excluding oxidised or reduced systems).[1] Recent attempts to obtain analogous compounds with sulphur[2] or nitrogen[3] as the hetero-atom have been unsuccessful, but we have now obtained the first example of a glycoside having a "thiaseptanose" structure. Reaction of 6-deoxy-6-iodo-2,3 : 4,5-di-*O*-isopropylidene-D-galactose dibenzyl dithioacetal[4] (I) with benzyl sodium sulphide in boiling methanol gave the 6-benzylthio-compound (II), $[\alpha]_D^{27}$ $-90°$ (C_6H_6), which on hydrolysis with aqueous-ethanolic sulphuric acid yielded 6-benzylthio-6-deoxy-D-galactose dibenzyl dithioacetal (III), m.p. 130°, $[\alpha]_D^{25}$ $+49°$ ($CHCl_3$). Methylation with sodium hydroxide and dimethyl sulphate in tetrahydrofuran then gave the tetramethyl ether (IV), m.p. 82—83°, $[\alpha]_D^{28}$ $+73°$ ($CHCl_3$), which on treatment with mercuric chloride, cadmium carbonate, and ethylene glycol was converted into the ethylene acetal (V), m.p. 110°, $[\alpha]_D^{24}$ $-63°$ ($CHCl_3$), and thence, with sodium and liquid ammonia, into the thiol (VI), m.p. 55—58°, b.p. 116°/10^{-4} mm., $[\alpha]_D^{21}$ $-22°$ ($CHCl_3$). When this was boiled with ethanolic hydrogen chloride it gave a mixture, separated by chromatography on silica into a minor ketonic component (not yet identified) and ethyl 6-deoxy-6-mercapto-2,3,4,5-tetra-*O*-methyl-$\alpha\beta$-D-galactoseptanoside (VII), b.p. 90—100° (bath) /10^{-4} mm., n_D^{20} 1·4820, $[\alpha]_D^{24}$ $-117°$ ($CHCl_3$); the elemental analysis, molecular weight, and n.m.r. spectrum of the latter compound, and the absence of free thiol, are in agreement with the assigned structure. By treatment of the thiol (VI) with hydrogen chloride in ether, followed by reaction of the resulting crude 1-chloro-compound with ethanol and silver carbonate, a similar mixture of ketone and glycoside was obtained. The glycoside

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[1] F. Micheel and F. Suckfüll, *Annalen*, 1933, **502**, 85; 1933, **507**, 138; F. Micheel and W. Spruck, *Ber.*, 1934, **67**, 1665; E. Bayer and R. Widder, *Annalen*, 1965, **686**, 181, 197.

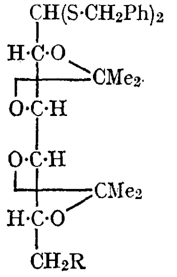
[2] R. L. Whistler and B. Urbas, *J. Org. Chem.*, 1965, **30**, 2721.

[3] W. A. Szarek and J. K. N. Jones, *Canad. J. Chem.*, 1965, **43**, 2345.

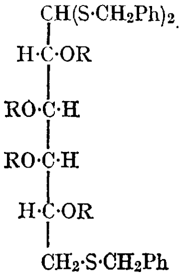
[4] N. K. Kochetkov and A. I. Usov, *Bull. Acad. Sci. U.S.S.R.* (English translation), **1962**, **977**; *Tetrahedron*, 1963, **19**, 973.

fraction, b.p. *ca.* 90° (bath)/10^{-4} mm., n_D^{20} 1·4840, $[\alpha]_D^{24}$ −183° ($CHCl_3$), clearly contained a higher proportion of the β-form than was present in the first preparation, but it was still an anomeric mixture; the n.m.r. spectra of both samples showed two peaks (τ 5·48 and 5·75) due to the proton at C-1, but, whereas in the first sample their intensities were approximately equal, the high-field signal given by the second sample had gained in intensity at the expense of the lower one.

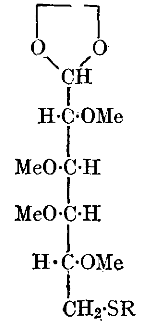
1,6-Anhydro-sugars exemplify bicyclic sugar derivatives in which a septanose ring is present in addition to the normal furanose or pyranose ring. To the two recently reported examples of 1,6-thioanhydro-sugars, *viz.* 1,6-anhydro-6-deoxy-6-mercapto-β-D-glucopyranose[5] and 1,6-anhydro-5,6-dideoxy-6-mercapto-β-D-*xylo*-hexofuranose,[2] we can now add a crystalline compound of the latter type. Methylation of 1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose[6] with methyl iodide and



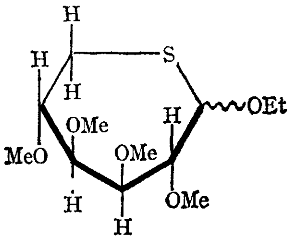
(I; R=I)
(II; R=S·CH₂Ph)



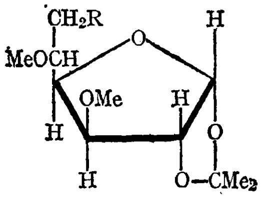
(III R=H)
(IV; R=Me)



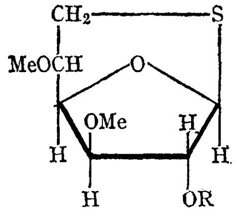
(V; R=CH₂Ph)
(VI; R=H)



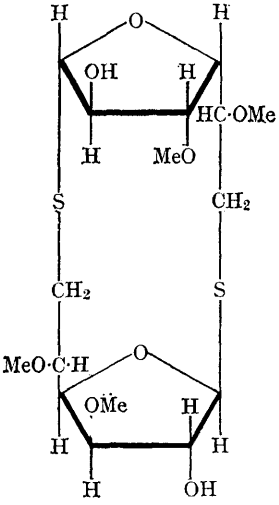
(VII)



(VIII; R=OTs)
(IX;R=SAc)
(X; R=SH)
(XI;R=S·CH₂Ph)



(XII. R=H)
(XIII; R=Me)



(XIV)

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[5] M. Akagi, S. Tejima, and M. Haga, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 58.
[6] K. Freudenberg and K. Oertzen, *Annalen*, 1951, **574**, 37.

silver oxide gave the liquid dimethyl ether (VIII), $[\alpha]_{\text{D}}^{25}$ $-15°$ ($CHCl_3$) which reacted with potassium thiolacetate to give the thiolacetate (IX), b.p. 123—125°/10^{-4} mm., n_{D}^{19} 1·4809, $[\alpha]_{\text{D}}^{21}$ $-12°$ ($CHCl_3$); deacetylation with sodium methoxide in methanol then afforded the thiol (X), b.p. 96°/10^{-4} mm., n_{D}^{23} 1·4710, $[\alpha]_{\text{D}}^{24}$ $-38°$ ($CHCl_3$). Alternatively, reaction of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose[7] with benzyl sodium sulphide gave 6-benzylthio-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose, m.p. 81·5—82·5°, $[\alpha]_{\text{D}}^{23}$ $-4°$ ($CHCl_3$), converted by methylation with dimethyl sulphate and sodium hydroxide in tetrahydrofuran into the dimethyl ether (XI), b.p. 160°/10^{-4} mm., n_{D}^{17} 1·5211, $[\alpha]_{\text{D}}^{24}$ $-75°$ ($CHCl_3$), from which the same thiol (X) was obtained by treatment with sodium and liquid ammonia. Hydrolysis of this thiol with sulphuric acid in aqueous acetic acid gave 1,6-anhydro-6-deoxy-6-mercapto-3,5-di-*O*-methyl-β-D-glucofuranose (XII), m.p. 107°, $[\alpha]_{\text{D}}^{24}$ $-117°$ ($CHCl_3$); the molecular weight, and other analytical and spectral characteristics, were in accordance with this structure, and on further methylation the product gave the trimethyl ether (XIII), b.p. 93°/10^{-4} mm., n_{D}^{19} 1·5043, $[\alpha]_{\text{D}}^{23}$ $-106°$ ($CHCl_3$). A by-product of the hydrolysis was a sparingly-soluble compound (1% yield), m.p. 260—270° (decomp.), for which the mass spectrum and analytical figures indicate the dimeric structure (XIV).

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Addendum: Hydrolysis of the acetal (VI) with sulphuric acid in aqueous acetic acid gave the thioseptanose (VII: OH replacing OEt), b.p. 120—130° (bath)/10^{-4} mm., n_{D}^{19} 1·4996, $[\alpha]_{\text{D}}^{22}$ $-112°$ (H_2O, unchanged after 24 hr.): elemental analyses and spectra were consistent with this structure. The sugar reacted with one equivalent of iodine in 5 min. at room temperature,[8] indicating that the ring is labile compared with that of the thiopyranose system.

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[7] H. Ohle and L. Vargha, *Ber.*, 1929, **62**, 2435.

[8] J. C. P. Schwarz and K. C. Yule, *Proc. Chem. Soc.*, 1961, 417; T. J. Adley and L. N. Owen, *ibid.*, p. 418.