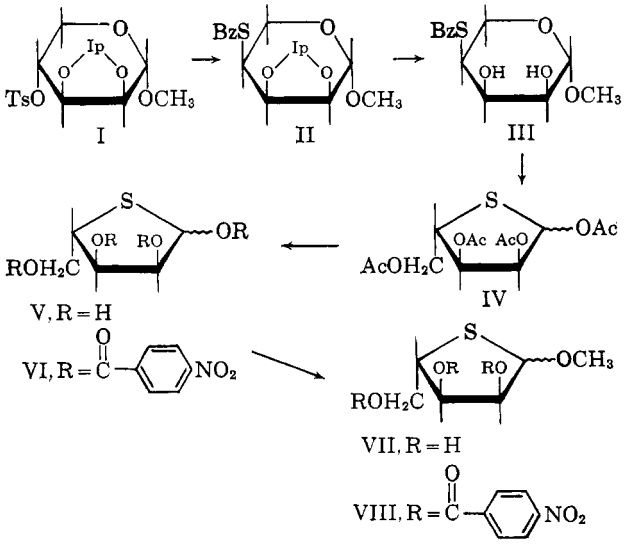
4-Thio-L-ribose: A Thiofuranose Sugar[1]

Sir:

There has been a considerable interest in recent years in the synthesis of thio sugars in which the ring oxygen atom has been replaced by sulfur. Thus, 5-thio-D-xylose,[2] 5-thio-D-ribose,[3] and 5-thio-D-glucose[4] have been synthesized. In all cases the sulfur atom assumed the ring position to give a thiopyranose configuration rather than the isomeric furanose in which the ring closed on oxygen. The biological importance of D-ribofuranose in the nucleic acids prompted us to investigate the synthesis of 4-thio-ribose with the hope that the sulfur atom would again assume the ring position to give a thiofuranose. The synthesis of 4-thio-L-ribofuranose[5] is the subject of the present communication.

Methyl 2,3-O-isopropylidene-4-O-(*p*-tolylsulfonyl)-α-D-lyxopyranoside (I) was prepared from D-lyxose by essentially the same method described by Kent and Ward.[6]



Treatment of I with potassium thiobenzoate in N,N-dimethylformamide (DMF) gave methyl 4-S-benzoyl-2,3-O-isopropylidene-4-thio-L-ribopyranoside (II) as a sirup. Deacetonation of II with aqueous acetic acid yielded crystalline methyl 4-S-benzoyl-4-thio-L-ribopyranoside (III), m.p. 148–149.5°. *Anal.* Found: C, 54.9; H, 5.64; S, 11.3. Acetolysis of III with acetic anhydride and sulfuric acid gave a chromatographically homogeneous analytically pure sirup which showed no thiol ester absorption in the infrared and which must be the thiofuranose tetra-O-acetate[7] (IV), $[\alpha]^{25}D$ +56° (1.3% in chloroform). *Anal.* Found: C, 46.5; H, 5.22; S, 9.81. Deacetylation of IV with methanolic sodium methoxide gave 4-thio-L-ribofuranose (V) as an analytically pure sirup (*Anal.* Found: C, 36.2; H, 6.3; S, 19.1) characterized as the tetra-*p*-nitrobenzoate (VI), m.p. 216–217°; $[\alpha]^{25}D$ +30° (1.36% in chloroform). *Anal.* Found: C, 52.0; H, 2.95; N, 7.28; S, 4.16.

Sirupy 4-thio-L-ribose reacted rapidly with aqueous iodine solution at room temperature to about the theoretical uptake for one thiol group, after which there was a relatively slow additional iodine consumption. This contrasts with the behavior of 5-thio-D-xylopyranose[2b] and 5-thio-D-ribopyranose,[3] which reacted only slowly with aqueous iodine solution with intermittent heating.[2b] Titration of V with silver nitrate[8] showed one equivalent of thiol. That the sirupy 4-thio-L-ribose exists primarily in the furanose form was decided from spectral evidence. The absence of significant amounts of absorption at 5.75 and 3.90 μ indicative of the carbonyl and free thiol,[9] respectively, eliminated both the open-chain sugar and the 4-thio-L-ribopyranose as major structural contributors, although small quantities of either would probably not be detected.

Treatment of V with methanolic hydrogen chloride gave the glycoside (VII) as a sirup which was characterized as the crystalline tris-*p*-nitrobenzoate hydrate (VIII), m.p. 107–108.5°, resolidified at 110°, remelted 195–195.5°, $[\alpha]^{24}D$ −89° (1% in chloroform). *Anal.* Found: C, 50.2; H, 3.38; N, 6.04; S, 4.85. A nitroprusside test on the glycoside (VII) was negative, indicating that ring formation was exclusively on sulfur. This was further established by the infrared spectrum of the *p*-nitrobenzoate (VIII) which showed no evidence for a thiol ester.

It is interesting to note that reactions which involved C-1 of 4-thioribose (V) gave thiofuranose products in which the ring closed on sulfur (*e.g.*, IV and VII) rather than the isomeric pyranoses in which the ring must close on oxygen.

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(2) (a) J. C. P. Schwarz and K. C. Yule, *Proc. Chem. Soc.*, 417 (1961); (b) T. J. Adley and L. N. Owen, *ibid.*, 418 (1961); (c) R. L. Whistler, M. S. Feather, and D. L. Ingles, *J. Am. Chem. Soc.*, **84**, 122 (1962).

(3) C. J. Clayton and N. A. Hughes, *Chem. Ind.* (London), 1795 (1962).

(4) M. S. Feather and R. L. Whistler, *Tetrahedron Letters*, 667 (1962).

(5) The commercial availability of D-lyxose for a starting material suggested the model synthesis of 4-thio-L-ribose, rather than the biologically significant 4-thio-D-ribose which would require L-lyxose for a starting material.

(6) P. W. Kent and P. F. V. Ward, *J. Chem. Soc.*, 416 (1953).

(7) A similar reaction was described by Feather and Whistler[4] where the acetolysis of 1,2-O-isopropylidene 3,5,6-O,S,O-triacetyl-5-thio-D-glucofuranose resulted in ring expansion to give 1,2,3,4,6-penta-O-acetyl-5-thio-D-glucopyranose.

(8) B. Saville, *Analyst*, **86**, 29 (1961).

(9) Debenzoylation of III with methanolic sodium methoxide gave methyl 4-thio-β-L-ribopyranoside in which there was thiol absorption at 3.90 μ. Thus the absence of absorption at 3.90 μ in V is indicative of the absence of a free thiol.

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Isomerization of Cyclononatrienes

Sir:

In a recent communication concerning base-catalyzed isomerization of medium ring dienes and trienes, Gardner and co-workers[1] reported the conversion of 1,2,6-cyclononatriene (I) to a mixture of 4,7-dihydroindane (II) and an isomeric bicyclic material, either III or IV, by potassium *t*-butoxide (KOBu) in dimethyl sulfoxide (DMSO) in 2 hr. at 70°. Two intermediates in the isomerization sequence were observed after reaction for 2 hr. at 27°, and these appeared also to be bicyclo[4.3.0]nonadienes. A sample of 1,3,6-cyclononatriene, obtained from 9,9-dibromo[6.1.0]non-2-ene, was recovered unchanged after being subjected to the isomerizing conditions for 144 hr. at 70°. Thus, it was concluded that 1,3,6-cyclononatriene is not an intermediate in the bridging isomerization I to II. In this communication we report some pertinent observations regarding cyclononatriene isomerizations made while examining *cis-cis-cis*-1,4,7-cyclononatriene[2] (V) out of curiosity about the nature and behavior of carbanions derived from this hydrocarbon.

As summarized in Table I, in 1.2 *M* solution in DMSO, 0.7 *M* in KOBu, 1,4,7-cyclononatriene (V) at

(1) D. Devaprabhakara, C. G. Cardenas, and P. D. Gardner, *J. Am. Chem. Soc.*, **85**, 1553 (1963).

(2) P. Radlick and S. Winstein, *ibid.*, **85**, 344 (1963).