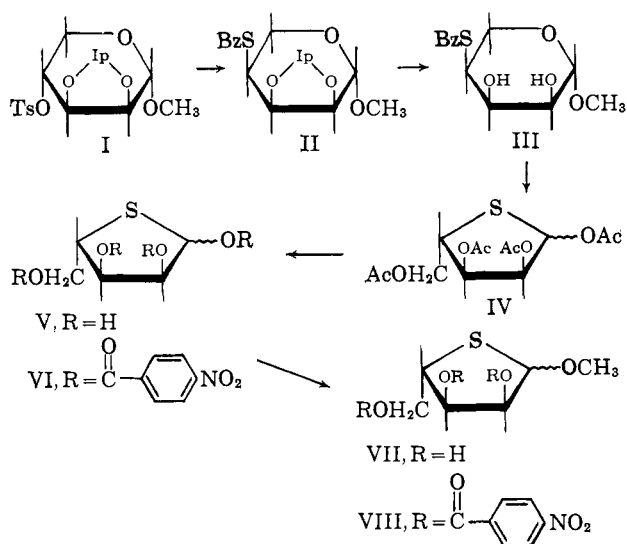## 4-Thio-L-ribose: A Thiofuranose Sugar[1]

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has been a considerable interest in recent years in the synthesis of thio sugars in which the ring oxygen atom has been replaced by sulfur.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 es-

sentially 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:

(1) The work reported in this communication was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center.

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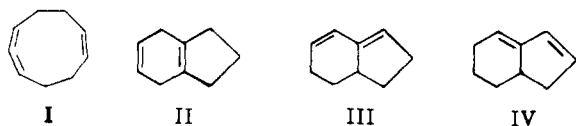
(3) C. J. Clayton and N. A. Hughes, *Chem. Ind.* (London), 1795 (1962).

(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.

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.

(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).
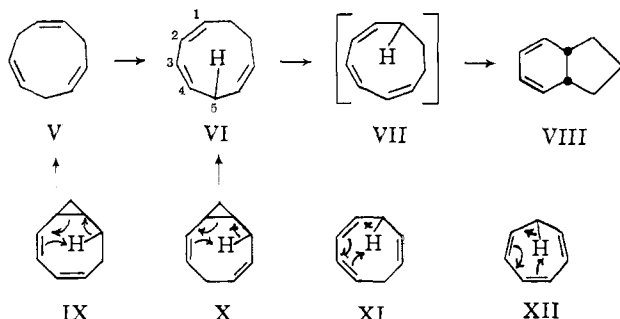
I   II   III   IV

25–50° is relatively rapidly converted first to A and then to B, these materials being distinguished by v.p.c. More vigorous treatment at 75° gives rise to one or more additional materials in a new v.p.c. fraction C. Pure fractions A and B were obtained most simply by preparative v.p.c. of isomerization mixtures after 7 min. at 25° or 25 min. at 50°, respectively.

TABLE I

ISOMERIZATION OF V BY POTASSIUM t-BUTOXIDE IN DMSO

Time, min.	T, °C.	V	A	B	C
5	25	45	52	3	
7	25	12	77	10	1
5	50		51	46	3
25	50		8	86	6
60	75		5	42	53

Examination of material A showed it to be cis-cis-cis-1,3,6-cyclononatriene (VI). Its n.m.r. spectrum showed proton signals at 4.23 τ (vinyl), 7.4 (bisallylic), and 7.96 (allylic) with relative areas of 3.02:1.00:1.98, respectively. In its infrared spectrum, it displayed bands at 1645 and 1627 cm.$^{-1}$ for isolated and conjugated olefinic stretching vibrations, strong bands at 670 and 717 for cis-olefinic C–H out-of-plane deformation, and no bands corresponding to C–H deformation characteristic of trans-olefins. In 95% ethanol solvent, VI displays an ultraviolet absorption band at 223 mμ (ε 3890) with strong absorption at longer wave lengths (ε 2090 at 240 mμ.) The ultraviolet, infrared, and n.m.r. spectra of VI agree very well with those observed by Roth[3] on a 1,3,6-cyclononatriene sample obtained by thermal isomerization of the 1,3,6-cyclooctatriene monomethylene adduct(X).

V   VI   VII   VIII

IX   X   XI   XII

Examination of material B showed it to be cis-bicyclo-[4.3.0]nona-2,4-diene (VIII). Its infrared spectrum was essentially identical with the spectrum of VIII published by Alder and Dortmann.[4] It contained none of the bands unique to the trans isomer of VIII, also reported by these authors.[4] The ultraviolet spectrum of B ($\lambda^{95\% \text{ EtOH}}_{\text{max}}$ 263 mμ (ε 3000)) and its n.m.r. spectrum (4.00:2.04:2.10:4.09 ratio of vinyl:allylic: methylene: methylene protons at 4.37, 7.34, 7.92, and 8.56 τ, respectively) are consistent with the cis-bicyclo-[4.3.0]nona-2,4-diene structure VIII.

From Table I, it is clear that 1,3,6-cyclononatriene (VI), the first isomerization product derived by removal of an allylic proton from 1,4,7-cyclononatriene and re-addition to a new carbanionic carbon atom, is an intermediate on the way to the bicyclic isomer (VIII). Consistently, treatment of isolated VI with 1.2 M KOBu in DMSO for 60 min. at 25° in a separate experi-

(3) W. Roth, private communication; Ann., in press.
(4) K. Alder and H. A. Dortmann, Ber., 87, 1905 (1954).

ment converted ca. 75% of it to VIII, together with a small proportion of C.

The most likely route between VI and VIII, but not the only conceivable one, involves further isomerization of VI to cis-cis-cis-1,3,5-cyclononatriene (VII) and rapid conversion of the latter to its valency tautomer[5] (VIII). The failure to detect the 1,3,5-isomer (VII) during the isomerizations does not militate against it as an intermediate since the isomerization was followed only by v.p.c. and the valency isomerization of VII to VIII could be expected to be quite rapid and very complete, judging by rates and equilibrium in the analogous valency tautomerism between 1,3,5-cyclooctatriene and its bicyclic isomer.[7,8]

It seems most probable that the isomerizations of 1,2,6-cyclononatriene observed by Gardner[1] also proceed by way of cis-cis-cis-1,3,6-cyclononatriene (VI) as the first intermediate and then follow the course observed in the present work with 1,4,7-cyclononatriene.[9] With 1,2,6-cyclononatriene, Gardner followed the isomerization to later stages than was done with the 1,4,7-isomer. Under these conditions, VIII presumably gives rise to II by way of at least one other isomer.

It is interesting that isomerization of 1,3,6-cyclononatriene (VI) to bicyclic isomer can also be accomplished thermally. While this thermal isomerization has been examined only in a preliminary way, the indications are that it occurs at a convenient rate at 200°. Presumably this involves a dienyl 1,5-hydrogen shift leading to 1,3,5-cyclononatriene, the latter undergoing valency isomerization. The dienyl 1,5-shift is analogous to dienyl and homodienyl 1,5-shifts in 1,3,6-octatriene[8] (XI), tropilidene[10] (XII), 1,3,5-cyclooctatriene monomethylene adduct[3,8] (IX), and the 1,3,6-cyclooctatriene monomethylene adduct[3] (X).

(5) Analogously, cis-cis-trans-1,3,5-cyclononatriene was presumed by Alder[4] to be the precursor of the trans VIII obtained from Hofmann degradation on 1-dimethylamino-2,4-cyclononadiene. As Vogel[6] has pointed out, the evidence for the presumed valency isomerization is far from compelling, since a transannular elimination route is conceivable.

(6) E. Vogel, Angew. Chem., 74, 829 (1962).

(7) A. C. Cope, et al., J. Am. Chem. Soc., 72, 2515 (1950); 74, 4867 (1952).

(8) D. S. Glass, J. Zirner, and S. Winstein, Proc. Chem. Soc., 276 (1963).

(9) Gardner, et al. (private communication, September 30, 1963), have now re-examined the material previously described[1] as 1,3,6-cyclononatriene and have found none of its chemistry consistent with data reported earlier.[1] Thus, the material which proved not to be an intermediate in the isomerization of 1,2,6-cyclononatriene was not the 1,3,6-isomer. Gardner, et al., have now also identified VIII as one of the "short-lived intermediates" in the isomerization of 1,2,6-cyclononatriene.

(10) A. P. ter Borg, H. Kloosterziel, and N. Van Meurs, Proc. Chem. Soc., 359 (1962).

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Effects of Millimolar Concentrations of Silver(I) Ion upon the γ-Radiolysis of Crystalline Potassium Nitrate

Sir:

The kinetics of formation of "equivalent nitrite," $M(NO_2^-)$, have been determined in pure and in silver-doped KNO_3, prepared by cocrystallizing mixtures of $AgNO_3$ and KNO_3, containing 0.04, 0.10, 0.4, and 1.0 mole % of Ag^+. Samples were irradiated in equipment described elsewhere[1] and products determined by dissolution at 20° in aerated water, followed by Shinn's analysis for nitrite.[2] Dissociation fragments, NO_2^-, NO_2, or NO, could each contribute to the observed total product,[3] which is expressed as moles of

(1) J. Cunningham, J. Phys. Chem., 65, 628 (1961).
(2) M. B. Shinn, Ind. Eng. Chem., Anal. Ed., 13, 33 (1941).
(3) J. Cunningham, J. Phys. Chem., 67, 1772 (1963).