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THE SYNTHESIS AND STEREOCHEMISTRY OF SYN-2,3-DITHIABICYCLO[3.2.1]OCTAN-8-OL

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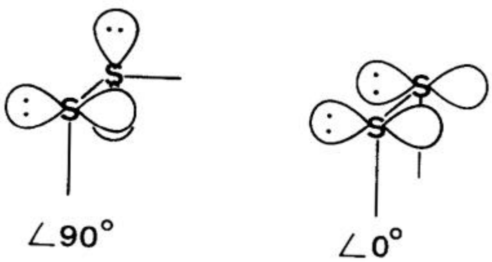
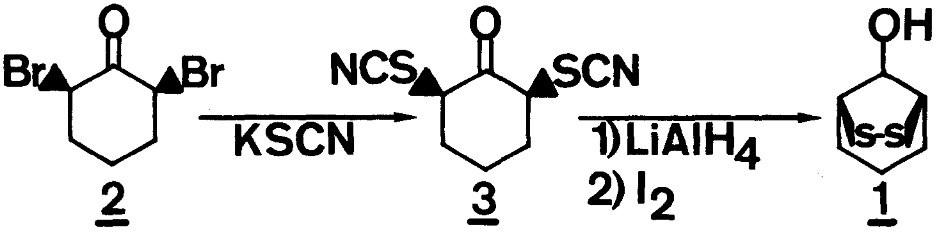
The nature of the disulfide linkage is quite significantly altered by changes in the dihedral angle between the two carbon-sulfur bonds.[1] As this angle is reduced from 90° to 0° the interaction between the two pairs of 3p nonbonding electrons on the sulfur atoms becomes much stronger. Thus, disulfides with small dihedral angles absorb light at longer wavelengths in the ultraviolet[2] and have lower ionization potentials[3] than do disulfides with larger dihedral angles. In order to more fully examine the nature of this interaction and its influence upon the chemistry of the disulfide linkage it would be most desirable to have easy access to simple bicyclic disulfides in which the ⟍S-S⟋ dihedral angle was of necessity very close to 0°. We would like to report a facile synthesis of such a system, syn-2,3-dithiabicyclo[3.2.1]octan-8-ol (1s).[4]



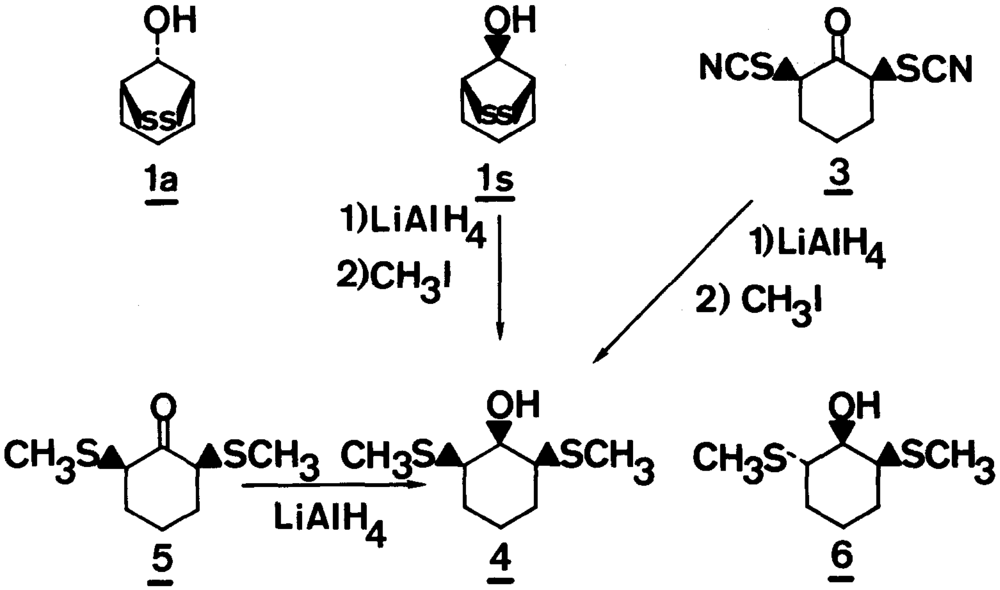
Reaction of cis-2,6-dibromocyclohexanone (2)[5] with KSCN dissolved in acetone yields cis-2,6-dithiocyanatocyclohexanone (3) (94%), m.p. 103-105°; i.r. 2265 (sharp) and 1725 cm^{-1}; Anal. Calcd. for $C_8H_8N_2OS_2$: C, 45.26; H, 3.80; N, 13.20; S, 30.21. Found: C, 45.22; H, 3.67; N, 13.00; S, 30.40. Reduction of 3 with $LiAlH_4$ in THF followed by oxidation of the intermediate dithiolate with I_2 yields a yellow oil which after chromatography on silica gel and recrystallization from methylene chloride-n-pentane affords the bicyclic disulfide 1 as yellow crystals, m.p. 235-236°[6] with rapid sublimation, loss of birefringence at 62°; n.m.r. (CCl_4) (δ) -O-CH⟨ 4.11 ppm (1H) doublet of triplets (J = 12 Hz and 1.8 Hz), bridgehead protons 3.86 ppm (2H) broad "singlet", -OH 2.22 ppm (1H) doublet (J = 12 Hz) exchangeable with D_2O, methylene protons 1.95-1.18 ppm (6H) complex; U.V. λ_{max}^{EtOH} 369 nm (ε = 65), 276 (23) [lit.^{4a} λ_{max}^{MeOH} 364 nm (ϵ = 51)]; Anal. Calcd. for $C_6H_{10}OS_2$: C, 44.43; H, 6.16; S, 39.54. Found: C, 44.45; H, 6.10; S, 39.69.



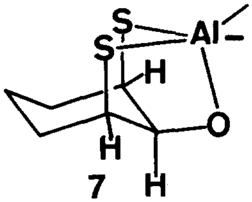
Yields in this oxidative cyclization can be highly variable (15-64%) due to polymerization or overoxidation of the disulfide **1** caused by too great an excess of I_2. However, reproducible yields of **1** (35%) are obtained by starting with 5 gm of **3** and operating under high dilution conditions during the oxidation step. These conditions consist of the simultaneous drop-wise addition of the quenched (ethyl acetate) $LiAlH_4$ reaction mixture and an ethereal solution of 1.25 equivalents of I_2 to 2.0 liters of refluxing ether. In contrast to the parent molecule, 1,2-dithiolane, **1** is quite stable and does not seem to polymerize appreciably even after storage for several months or exposure to light.

The question remains as to the orientation of the hydroxyl group in **1** which might exist in either the *anti* configuration, **1a**, or the *syn* configuration, **1s**. Even though a substantial amount of effort has been devoted to the detection of both of these isomers (**1a** and **1s**), only a single isomer has ever been observed. The stereochemistry of this isomer has been assigned on the basis of the following evidence. Reduction of **3** with $LiAlH_4$ followed by treatment of the dithiolate with methyl iodide yields a single alcohol **4** (59%). Under the same conditions **1** is also converted to **4** (83%). Both of these products were identical to the single alcohol obtained from the $LiAlH_4$ reduction of *cis*-2,6-dithiomethylcyclohexanone (**5**).[7] That this material is indeed *cis*-2,*cis*-6-dithiomethylcyclohexan-*r*-1-ol (**4**)[8] is readily determined from its n.m.r. spectrum which displays a triplet at 4.01 ppm, J = 2.0 Hz, due to the proton at C_1. This pattern confirms the expected plane of symmetry and the magnitude of the coupling constant indicates that the protons at C_1 and C_2 (C_6) bear an equatorial-axial relationship to each other.[9] The relative magnitudes of the equatorial-axial and the axial-axial coupling constants in systems of this type were obtained from *cis*-2,*trans*-6-dithiomethylcyclohexan-*r*-1-ol (**6**)[8] which was prepared by $LiAlH_4$ reduction of *trans*-2,6-dithiomethylcyclohexanone.[7] The n.m.r. spectrum of **6** displays the proton at C_1 at 3.70 ppm as a doublet of doublets with Jea = 3.6 Hz and Jaa = 7.5 Hz.

The $LiAlH_4$ reductions of **3** and **5** are quite interesting in that they are stereospecific or at least highly stereoselective, and in that the resulting alcohol **4** is the thermodynamically least stable isomer. A number of factors might serve to direct this stereo-



specificity, but steric control to approach of the hydride species is probably of major importance. Hydride reductions of 2-alkylcyclohexanones produce greater amounts of the thermodynamically less stable alcohol as the steric requirements of the 2-alkyl substituent are increased. Thus, the following ratio of cis and trans alcohols is observed in the $LiAlH_4$ reduction of 4-t-butylcyclohexanone (11:89)[10]; 2-methylcyclohexanone (25:75)[11]; 2-t-butylcyclohexanone (58:42)[11]. Furthermore, when THF is used as the solvent steric factors are accentuated through solvation effects.[12] The possibility also exists that chelates such as 7[13] play a role in directing the stereochemistry of these reductions, particularly in the case of 3. Further investigation of these factors might prove most interesting.



7

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REFERENCES

1. J. Linderberg and J. Michl, *J. Am. Chem. Soc.*, **92**, 2619 (1970).
2. J. A. Barltrop, P. M. Hayes, and M. Calvin, *ibid.*, **76**, 4348 (1954).
3. W. M. Moreau and K. Weiss, *ibid.*, **88**, 204 (1966).
4. The 2,3-dithiabicyclo[3.2.1]octane system has been prepared in certain steroid molecules: a) D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **35**, 3259 (1970); b) R. C. Tweit and R. M. Dodson, *J. Am. Chem. Soc.*, **81**, 4409 (1959).
5. O. Wallach, *Ann.*, **437**, 172 (1924).
6. The unusually high melting point of **1s** is attributed to the high symmetry of this molecule.
7. Both isomers prepared from **2** and potassium methyl thiolate. Previously reported by H. Brintzinger and M. Langheck, *Ber.*, **87**, 325 (1954).
8. Revised IUPAC nomenclature for Organic Chemistry, *J. Org. Chem.*, **35**, 2849 (1970).
9. F. A. L. Anet, *J. Am. Chem. Soc.*, **82**, 994 (1960); R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *ibid.*, **80**, 2237 (1958).
10. E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1367 (1960).
11. H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965).
12. H. Haubenstock and E. L. Eliel, *ibid.*, **84**, 2363 (1962).
13. E. L. Eliel and T. J. Brett, *J. Org. Chem.*, **28**, 1923 (1963); S. J. Angyal and K. P. Davis, *Chem. Commun.*, 500 (1971).