

Figure 2. A projection of the thieno[3,4-*d*]thiopin 6,6-dioxide molecule down the *b* axis showing bond distances and angles. Estimated standard deviations are C-C = 0.006, C-S = 0.005, and S-O = 0.003 Å and 0.4° for angles. These have been obtained from coordinate standard deviations estimated from inverse elements of the inverse matrix after block diagonal anisotropic least-squares refinement.

bon bond distance has been determined with reasonable accuracy and appears to be predominantly single bonded in character ( $1.46 \pm 0.02$  Å).<sup>9</sup> The other bond lengths appear to be quite reasonable at this stage of refinement and will be reported in a subsequent communication.

Thiopin **3** forms transparent needles which are monoclinic,  $P2_1/c$ , with  $a = 8.897$ ,  $b = 11.295$ , and  $c = 9.504$  Å, and  $\beta = 121^\circ 13'$ . Intensity data were taken as described previously. Reflections (1384) were recorded to a maximum  $2\theta$  angle of  $130^\circ$ , representing about 75% of the data theoretically accessible in the Cu sphere. The structure was determined by the heavy-atom method. A sharpened three-dimensional Patterson function was calculated, and this revealed the positions of the sulfur atoms. Successive Fourier syntheses gave the complete structure. The structure was refined by block diagonal least-squares using individual isotropic temperature factors ( $R = 11.5\%$ ), and finally with individual anisotropic temperature parameters ( $R = 6.0\%$ ). Difference Fourier synthesis has revealed the positions of all of the hydrogen atoms.<sup>10</sup> Figure 2 shows the bond distances and angles of sulfone **3** as determined from this analysis. The seven-membered ring of this molecule exists in the boat conformation in much the same fashion as thiopin 1,1-dioxide.<sup>3</sup> The dihedral angles describing the ring puckering of sulfone **3** are  $45.2$  and  $19.8^\circ$ .<sup>11</sup>

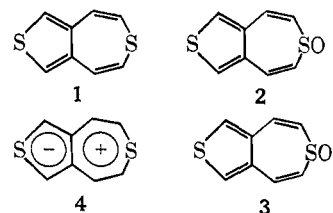
The crystal structure of thiopin **1** bears a striking resemblance to that of azulene. This result lends weight to our previous suggestion that **1** is an extensively delocalized aromatic system in which species such as **4** contribute significantly to the ground state.<sup>1</sup> The degree of ring puckering present in **3** does not, in our opinion,

(9) In azulene, this bond length is  $1.483$  Å after full-matrix least-squares refinement.

(10) The complete details of the structure analysis of **3** will be published elsewhere.

(11) Similar dihedral angles of  $44.6$  and  $22.8^\circ$  have been found for thiopin 1,1-dioxide. See ref 3, Figure 1.

indicate that any significant  $\pi$ -electron delocalization occurs in the seven-membered ring of this annulated thiopin sulfone.



Work on other annulated thiopins related to **1** is in progress and will be reported shortly.

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## Lithium Cyanohydridoborate, a Versatile New Reagent

Sir:

In connection with our work on the hydride reduction of imino esters,<sup>1</sup> we had occasion to examine the reducing power of a variety of hydride reagents. We wish to report here our results with lithium cyanohydridoborate; in contrast to a previous report,<sup>2</sup> this versatile reagent will reduce a variety of functional groups with remarkable selectivity.

The utility of lithium cyanohydridoborate<sup>3</sup> is enhanced by its two important chemical properties: (1) the reagent is stable in acid up to pH  $\sim 3$ , and at low pH the hydrogens can be readily exchanged;<sup>4</sup> (2) at pH  $< 7$ , the reduction of an iminium group is much faster than the reduction of a carbonyl group. Thus, functional groups sensitive to the high pH required in sodium borohydride reductions (*cf.* thiamine, Table I) are easily reduced at pH 7, and by prior exchange of the hydrogens for deuterium or tritium an efficient and economical route is available for deuteride or tritride reduction of aldehydes and ketones. The faster rate of reduction of the iminium moiety provides an excellent method for reductive amination of aldehydes and ketones under exceedingly mild conditions.

The reductions of some representative functional groups are summarized in Table I. It should be noted that the rates of reduction are much slower than with

(1) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).

(2) G. Drefahl and E. Keil, *J. Prakt. Chem.*, 6, 80 (1958).

(3) Available from Alfa Inorganics, Inc., Beverley, Mass.

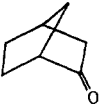
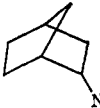
(4) M. M. Kreevoy and J. E. C. Hutchins, submitted for publication.

**Table I.** Reduction of Representative Functional Groups with Lithium Cyanohydridoborate in Methanol

Compound	Time, hr	Temp, °C	Product	Yield, %	
				Anal. <sup>a</sup>	Isolated
PhCHO	24	Reflux	PhCH <sub>2</sub> OH	>95	78
Farnesal	24	Reflux	Farnesol	>95	74
	24	Reflux	Farnesol-T <sub>1</sub> <sup>b</sup>	>95	70
Cyclohexanone	24	Reflux	Cyclohexanol	>95	77
Cyclohexanone-d <sub>4</sub>	72	Reflux	1,2,2,6,6-Pentadeuterio-cyclohexanol <sup>c</sup>		50
PhCOCH <sub>3</sub>	72	Reflux	PhCHOHCH <sub>3</sub>	38	36
2-Heptanone	72	Reflux	2-Heptanol	40	35
Ph <sub>2</sub> CO	72	Reflux	Ph <sub>2</sub> CHOH	<5	
PhCH=NCH <sub>2</sub> CH <sub>3</sub>	24	25	PhCH <sub>2</sub> NHCH <sub>2</sub> CH <sub>3</sub>	65 <sup>d</sup>	59
PhC(OEt)=NCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	25	25	PhCH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	>95	74
Thiamine <sup>e</sup>	6	25	Tetrahydrothiamine		55

<sup>a</sup> Obtained by gas chromatographic analysis. <sup>b</sup> Labeled >95% at C-1. <sup>c</sup> Isotopic purity >95% at C-1. <sup>d</sup> Some hydrolysis to benzaldehyde occurred. <sup>e</sup> Water used as solvent.

**Table II.** Representative Reductive Aminations with Lithium Cyanohydridoborate in Absolute Methanol (pH 5–6)<sup>a</sup> at 25°

Compound	Amine	Time, hr	Product	Yield, %	
				Anal. <sup>b</sup>	Isolated <sup>c</sup>
	NH <sub>3</sub>	36		63	48
PhCHO	CH <sub>3</sub> CH <sub>2</sub> NH <sub>2</sub>	72	PhCH <sub>2</sub> NHEt	91	80
Cyclohexanone	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	24	N-Propylcyclohexylamine	90	81
Cyclododecanone	CH <sub>3</sub> NHCH <sub>3</sub>	96	N,N-dimethylcyclo-dodecylamine	71	66
Sodium phenylpyruvate	NH <sub>3</sub>	36	d,l-Phenylalanine	49 <sup>d</sup>	41

<sup>a</sup> pH adjusted by using amine and amine hydrochloride or by passing anhydrous HCl into the solution until the appropriate pH was reached. <sup>b</sup> Obtained by gas chromatographic analysis. <sup>c</sup> Obtained as the hydrochlorides or picrates. Melting points of derivatives agreed with reported literature values in all cases. <sup>d</sup> Measured by the ninhydrin method.

sodium borohydride; this result is expected on the basis of the electron-withdrawing effect of the cyano group. Aldehydes and easily reduced ketones can be converted to alcohols in high yield. Aromatic and acyclic ketones, however, are not completely reduced under these conditions; the only other compound present is the starting ketone in each case. Introduction of deuterium or tritium is accomplished by prior exchange in D<sub>2</sub>O or T<sub>2</sub>O at pH 3, then carrying out the reduction by refluxing in methanol or THF at pH 7. It is interesting to note that there is a substantial isotope effect on the rate of reduction; when LiBD<sub>3</sub>CN is used, much longer reaction times are necessary.

Efficient reduction of imino esters and imines requires protonation of the nitrogen atom; at pH 10 the imino ester of N-propylbenzamide was recovered unchanged after 24 hr, whereas at pH 6 conversion to N-propylbenzylamine was complete. Because thiamine has an iminium moiety already present in the thiazolium ring, rapid reduction occurs at pH 7. Reduction proceeds to the tetrahydro compound, presumably because of the enamine-immonium equilibrium in the dihydrothiamine.

The reductive amination of aldehydes and ketones provides the most versatile application of the reagent. Existing methods normally require high-pressure hydrogenation conditions, and yields are often low.<sup>5</sup> Reaction of a variety of aldehydes and ketones with ammonia or primary or secondary amines at pH <7 in abso-

lute methanol in the presence of lithium cyanohydridoborate proceeds smoothly at room temperature to give good yields of the corresponding amine. Some representative reductions are listed in Table II. The exclusive by-product in these reactions is the alcohol which arises by reduction of the ketone. If the reduction is carried out with substituted sodium pyruvates and ammonium chloride, good yields of amino acids are obtained. Using ammonium chloride as the limiting reagent leads to comparable yields of amino acids, thus opening an efficient route for the synthesis of <sup>15</sup>N-labeled amino acids.

It should be noted that the reduction of aldehydes, ketones,<sup>6</sup> and amines<sup>7</sup> by structurally analogous amine-boranes has been reported. The amine-borane reduction of carbonyl compounds proceeds much faster than with lithium cyanohydridoborate, however. This fact, coupled with the problem of amine-amine-borane exchange, makes lithium cyanohydridoborate a more satisfactory reagent.

The scope of these reductions is currently under investigation and will be the subject of a forthcoming paper.

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(8) National Institutes of Health Predoctoral Fellow, 1968–present.

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(5) W. S. Emerson, *Org. Reactions*, **4**, 174 (1948).