Organosulfur Chemistry. II. Highly Stereoselective Reactions of 1,3-Dithianes. "Contrathermodynamic" Formation of Unstable Diastereoisomers[1]

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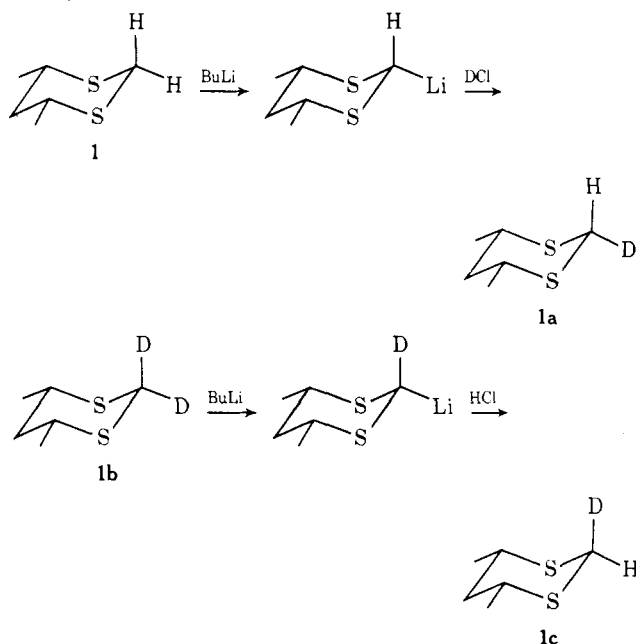
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Abstract: Treatment of the lithium derivative of *cis*-4,6-dimethyl-1,3-dithiane (**1**) with DCl gives nearly exclusively (over 99%) the equatorial 2-deuterio compound (**1a**), treatment with methyl iodide gives exclusively the equatorial methyl compound (*r*-2,*cis*-6,*cis*-4-trimethyl-1,3-dithiane, **2**), and treatment with carbonyl compounds (formaldehyde, acetone, and pivalic aldehyde) gives the equatorial carbinols (**4**) in at least 99.8% isomeric purity. Treatment of the lithium derivative of the equatorial 2-methyl compound **2** with HCl yields exclusively the corresponding axial isomer **3** (*r*-2,*trans*-4,*trans*-6-trimethyl-1,3-dithiane); a similar "contrathermodynamic" equilibration occurs with the equatorial carbinols mentioned above, with *r*-2-*tert*-butyl-*cis*-4,*cis*-6-dimethyl-1,3-dithiane and with *cis*-2,4,4,6-tetramethyl-1,3-dithiane, suggesting a very large preference of the intermediate 2-dithianyllithium compound to have the metal in the equatorial position. The high degree of this preference (over 6 kcal/mol) suggests operation of a stereoelectronic rather than a simple steric effect. Carboxylation of the lithium derivative of **2** gives exclusively the equatorial carboxy derivative, *r*-2,*cis*-4,*cis*-6-dimethyl-1,3-dithianecarboxylic acid (**6**), whereas methylation of the lithium derivative of 2-carbomethoxy-*cis*-4,6-dimethyl-1,3-dithiane with methyl iodide leads exclusively to the diastereoisomer **7**. Lithiation followed by methylation of the two diastereoisomeric 2-deuterio-*cis*-4,6-dimethyl-1,3-dithianes indicates that the *kinetic* stereoselectivity of the lithiation is only by a factor of 8.6 ± 1.3 with an isotope effect of 2.5 ± 0.1. The preference of the lithium derivative or carbanion to be equatorial is thus largely thermodynamically controlled.

Some years ago, Corey and Seebach[2] discovered that the lithium derivative of 1,3-dithiane is a very useful intermediate for a wide variety of syntheses.[3] It occurred to us that study of the lithium derivative of a conformationally locked ("anancomeric")[4] 1,3-dithiane might be of interest for comparison with anancomeric cyclohexyllithium derivatives (4-*tert*-butylcyclohexyllithium, menthyllithium) whose reactions (deuteronation, carbonation, and bromination) proceed with 95–97% stereoselectivity.[5] Treatment of the anancomeric[6,7] *cis*-4,6-dimethyl-1,3-dithiane (**1**) with butyllithium in tetrahydrofuran (THF) at −25°, followed by quenching with D₂O–DCl, rather surprisingly gave rise virtually exclusively to the equatorial deuterium compound **1a**. Similar treatment of the 2,2-dideuterio analog **1b**[8] with butyllithium followed by quenching with H₂O–HCl gave the axial deuterium compound **1c**

(1) (a) Paper I: O. Hofer and E. L. Eliel, *J. Amer. Chem. Soc.*, **95**, 8045 (1973); (b) for preliminary publication of the present work, see A. A. Hartmann and E. L. Eliel, *J. Amer. Chem. Soc.*, **93**, 2572 (1971); E. L. Eliel, A. Abatjoglou, and A. A. Hartmann, *ibid.*, **94**, 4786 (1972); presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 11, 1973; taken, in part, from the Ph.D. thesis of A. A. Hartmann, University of Notre Dame, 1971.
(2) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075, 1077 (1965).
(3) *Cf.* D. Seebach, *Synthesis*, **1**, 17 (1969).
(4) *Cf.* M. Anteunis, D. Tavernier, and F. Borremans, *Bull. Soc. Chim. Belg.*, **75**, 396 (1966).
(5) W. H. Glaze and C. M. Selman, *J. Organometal. Chem.*, **11**, P3 (1958); *J. Org. Chem.*, **33**, 1987 (1968); W. H. Glaze, C. M. Selman, A. L. Ball, Jr., and L. E. Bray, *ibid.*, **34**, 641 (1969).
(6) *syn*-Axial methyl groups destabilize the chair by over 5 kcal/mol: N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, **83**, 2145 (1961).
(7) Escape of the dithiane into the twist form would require an investment of over 3 kcal/mol: E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, **91**, 2703 (1969).
(8) Prepared either from diethyl formal-*d₂* or exchange of **1** with dimethyl-*d₆* sulfoxide and lithiodimethyl-*d₅* sulfoxide (see Experimental Section).

(Scheme I). The nmr spectra of **1**, **1a**, and **1c** are shown, in part, in Figure 1.

Scheme I

The AB pattern (H-2) of **1** shows broadening of the two upfield lines, due to long-range (J^5) coupling with the equatorial proton at C-5[9] (zig-zag coupling). Thus the upfield proton at C-2 is equatorial, contrary to the situation in cyclohexane but in agreement with previous

(9) K. C. Ramey and J. Messick, *Tetrahedron Lett.*, 4423 (1965); J. Gelan and M. Anteunis, *Bull. Soc. Chim. Belg.*, **77**, 447 (1968); the broadening is also evident in H₅ₑ in **1** and **1c** which disappears in **1a** and **1b**.
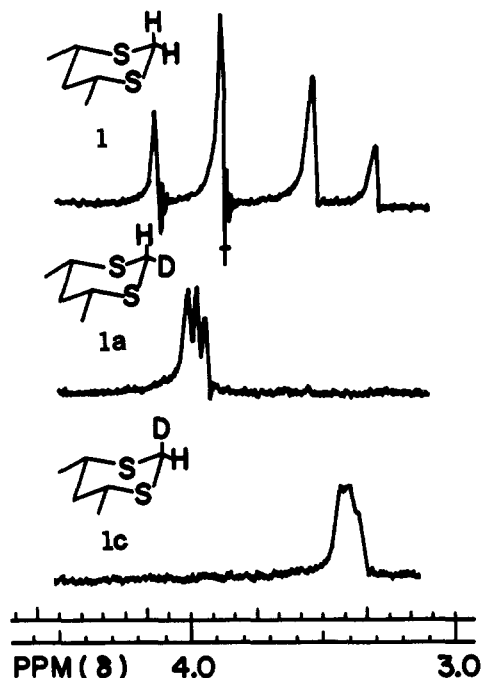
Figure 1. Nmr spectra (3.2–4.2-ppm region) of cis-4,6-dimethyl-1,3-dithiane (1) and its epimeric 2-deuterio analogs (1a and 1c).

findings on epimeric 2-substituted 1,3-dithianes.[7] Compound 1a as formed from the lithio derivative displays complete absence of the equatorial proton; the axial proton is a triplet, narrowly split by the geminal deuterium. In 1c formed from the lithio derivative of 1b the low-field axial proton is absent; the high-field equatorial proton at C-2 is now broadened by a combination of geminal deuterium and long-range coupling. It is clear from Figure 1 that there is very little cross-contamination of 1a and 1c. Examination of nmr spectra of mixtures of 1a and 1c indicated that such cross-contamination could have been clearly detected at the 1% level. The stereoselectivity of the lithiation–deuteronation (or protonation) sequence is thus of the order of 100:1 corresponding to a free energy difference of 2.3 kcal/mol at $-25°$. The origin of this stereoselectivity is not totally defined by the experiments, but it is tempting to assume that it is the intermediate 2-dithianyllithium compound (1-Li) which exists in one greatly preferred stereoisomeric form and that the subsequent protonation or deuteronation is diffusion controlled and proceeds with retention of configuration.[5,10] If this hypothesis is accepted, it follows that the lithium moiety of the intermediate (whether this be a covalent monomeric compound, an oligomeric cluster, an ion pair, or an ionized species) occupies the equatorial position.

We have not yet examined the intermediate lithium derivative[11] but we have established[11] that the high stereoselectivity of the overall lithiation–protonation sequence is independent of solvent. Thus the lithiation–deuteronation sequence is highly stereoselective in n-hexane, diethyl ether, 1,2-dimethoxyethane, tetramethylethylenediamine (TMEDA), and hexamethylphosphoramide (HMPA) as well as in THF. This finding suggests, though it does not prove, that the

(10) Cf. R. Viau and T. Durst, J. Amer. Chem. Soc., 95, 1346 (1973).
(11) Work in progress with A. G. Abatjoglou.

intermediate which gives rise stereoselectively to the equatorial deuterium compound 1a is a carbanion or carbanion pair rather than a covalent lithium compound or oligomer thereof.

Reaction of the lithio derivative of 1 (1-Li) with methyl iodide was studied next and found to give rise exclusively to the equatorial 2-methyl compound 2. (Since analysis of 2 was carried out by gas chromatography, the presence of more than 0.3% of the epimeric axial compound 3 could certainly have been detected.)
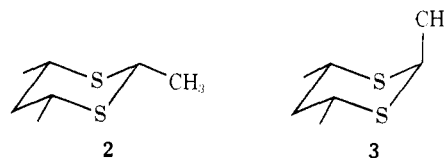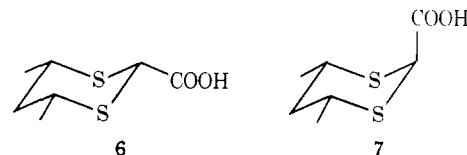

This result, in conjunction with the assumption that the stereochemical purity of the product reflects the stereochemical purity of the intermediate lithium compound, raises the estimate of that purity from 100:1 to over 300:1 ($\Delta G°_{-25} > 2.8$ kcal/mol).

Reaction of 1-Li with formaldehyde, acetone, trimethylacetaldehyde, or cyclohexanone gave exclusively the equatorial carbinols 4a–d. Compound 4a was crystalline and, when the mother liquor from its crystallization was subjected to gas chromatography, a small amount of the epimer 5a was detected; calculation
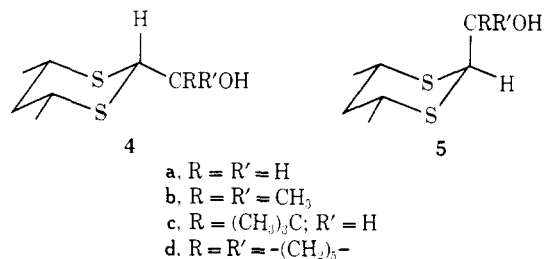
a. R = R' = H
b. R = R' = CH₃
c. R = (CH₃)₃C; R' = H
d. R = R' = -(CH₂)₅-

showed that this was present in the originally formed 4a to the extent of 0.2%.[12] No epimeric impurity was detected in 4b or 4c.

The only reaction of 1-Li studied by us which did not proceed highly stereospecifically was carboxylation which yielded a mixture containing only 20% of the equatorial carboxylic acid 6 along with 80% of the axial epimer 7. Since equilibration of 6 would be ex-

pected[13] to yield 7 and since the acidity of the α (C-2) hydrogen in 6 is enhanced by the carboxylate function to the extent that epimerization during quenching with CO_2 is very likely, it appeared that the outcome of the carboxylation experiment was at least partially thermodynamically controlled. To avoid epimerization sub-

(12) This does not necessarily imply that the stereoselectivity of formation of 4a was only 99.8%. Since 4a is initially formed as its lithium derivative RCH₂OLi, it is possible that a small amount of transfer of lithium to the C-2 position of the 1,3-dithiane followed by epimerization occurred; see the following text.

(13) The methyl ester of 7 is favored over the methyl ester of 6 at equilibrium; $\Delta G° = 1.31$ kcal/mol in methanol, 0.81 kcal/mol in chloroform: A. A. Hartmann, Ph.D. Dissertation, University of Notre Dame, Notre Dame, Indiana, 1971.

sequent to introduction of the COOLi group, we carboxylated the lithium derivative of the 2-methyl compound **3** (see below regarding formation of **3**-Li). Either treatment of **3**-Li with CO_2 followed by acidification and esterification of the acid formed or direct carbomethoxylation with methyl chloroformate yielded the gas chromatographically pure equatorial methyl ester **8**-Me (Scheme II). Again the stereoselectivity of this reaction exceeded 99.7%.

Scheme II
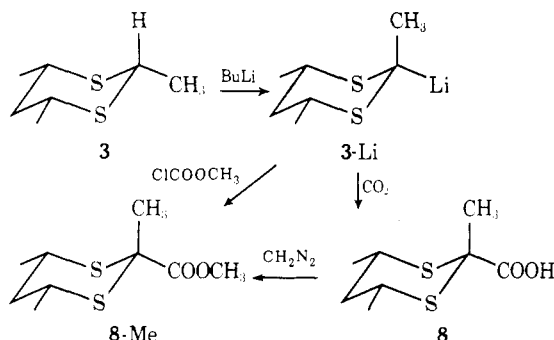
We next turned to an investigation of the lithium derivatives of 2-monosubstituted 1,3-dithianes. Since the corresponding carbanions (or ion pairs) are tertiary rather than secondary, these derivatives are expectedly[14] somewhat less readily formed than **1**-Li. The result of lithiation of **2** or **3** with BuLi followed by quenching with DCl–D_2O is shown in Scheme III. In either case,

Scheme III
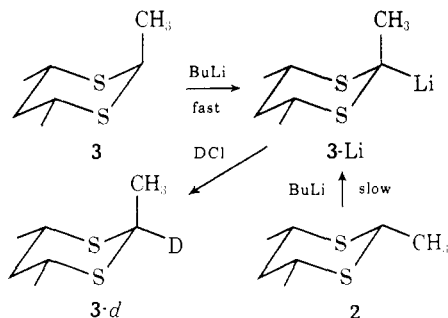
the only product of the reaction is the equatorially deuterated derivative **3**-*d*. When the precursor is the axial methyl compound **3**, lithiation with BuLi proceeds relatively readily and the only chemical species found at the end of the reaction is the original axial methyl compound. However, deuterium analysis showed that, when lithiation was allowed to proceed for 2.5 hr at $-25°$, 80% of the product was **3**-*d* which was evidently formed *via* **3**-Li whereas 20% was unchanged **3** which had escaped lithiation. When the precursor is the equatorial isomer, **2**, the rate of butane evolution indicated a much more sluggish lithiation with BuLi. Quenching after 24 hr at $-20°$ gave a mixture whose chemical composition was 75% **3**-**3**-*d* and 25% **2** as indicated by gas chromatography. The two chemical species were separated by preparative glpc and each was analyzed for deuterium by mass spectrometry. The mass spectrum of recovered **2** was identical with that of the starting material; *i.e.*, the material had never been converted to the lithium derivative in the first place. The trans

(14) *Cf.* D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 21.

species (**3**), on the other hand, was the deuterated **3**-*d* evidently formed *via* **3**-Li. The conclusion is that quenching of **3**-Li gives only the axial methyl compound **3** and none of the equatorial compound **2**; the most likely interpretation is that **3**-Li itself has axial methyl and equatorial lithium. If, once again, one ascribes a lower limit of 99% to the stereoselectivity of the process shown in Scheme III, and keeping in mind that the equilibrium of the 2-methyl group in the parent 2,*cis*-4,-6-trimethyl-1,3-dithiane strongly favors the equatorial isomer **2** $(\Delta G_{2\rightarrow 3}° = 1.7$ kcal/mol[7]), the minimum preference of the lithium moiety for the equatorial position in **3**-Li is 4 kcal/mol (2.3 + 1.7). (This value is approximative, since the assumption that the conformational energy of methyl is the same in **3**-Li as in **3** may not be entirely justified.)

Subsequently, we succeeded in converting **2** quantitatively to **3** by lithiating **2** with BuLi in TMEDA[15] at room temperature and then quenching with HCl–H_2O. In this way a cleanly "contrathermodynamic" process was effected.[16] In similar fashion, *r*-2-*tert*-butyl-*cis*-4,-*cis*-6-dimethyl-1,3-dithiane (**9**) was converted to the corresponding trans isomer **10** and *cis*-2,4,4,6-tetramethyl-1,3-dithiane (**11**) was converted to the trans isomer **12** (Scheme IV). In the equilibration of **9** to

Scheme IV
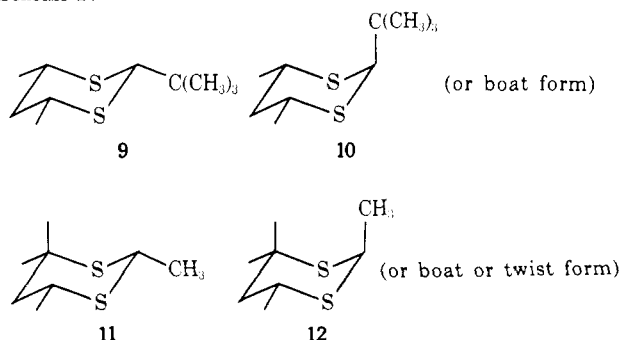
10, the use of TMEDA proved essential, for whereas **10** was converted to its lithium derivative by BuLi in THF, isomer **9** was inert to this combination.

The conversion of **9** to **10** and **11** to **12** proceeded to the extent of at least 99.7% at room temperature corresponding to a stereoselectivity of *ca.* 3.4 kcal/mol. Since **10** is unstable, *vis-à-vis* **9** by 2.7 kcal/mol,[7] this raises the equatorial preference of the lithium in the intermediate to *ca.* 3.4 + 2.7 or >6 kcal/mol.[17]

Treatment of the carbinols **4a**, **4b**, and **4c** with 2 mol

(15) This combination is known to be a more powerful anion generator than BuLi in ether solvents, *e.g.*, in ethylene polymerization: A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, 741 (1966).

(16) The term "contrathermodynamic" was first coined by H. C. Brown and M. V. Bhatt; *cf.* H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972, p 305. Of course, there are no truly contrathermodynamic processes; in the present case the equilibrium of the lithium salts (2-Li, 3-Li) appears to be almost entirely on the side of the latter whereas the equilibrium of **2** and **3** is known[7] to be largely on the side of the former.

(17) An upper limit is hard to define. Compound **10** probably exists in a rigid boat form.[7] However, in this conformation, H-2 does not have an "equatorial-like" disposition with respect to the two sulfur atoms and the conformation is probably not hospitable to the formation of a stable lithium derivative. That derivative may well exist in a twist form, or in the chair form, in which additional nonbonded interaction would be engendered; thus the 2.7 kcal/mol value for the instability of **10** *vs.* **9** represents a minimum value when applied to the corresponding lithium derivatives. The instability of **12** *vis-à-vis* **11** is not known but is probably considerable; the nmr spectrum of **12** suggests that it exists as a twist form. Whether the lithium derivative of **12** can exist in the same twist form is an open question.

of butyllithium followed by treatment with HCl–H$_2$O led to quantitative conversion to the corresponding axial carbinols 5a, 5b, and 5c. The first mole of BuLi undoubtedly converts the carbinols to the lithium carbinolates, but the latter species are still reactive to butyllithium and apparently form a dilithium complex in which, once again, the lithium is placed equatorially, at equilibrium, and the CRR'OLi group axially.

A similar conversion to the equatorial metal–axial COOCH$_3$ intermediate appears to occur when the methyl esters of either 6 or 7 are treated with butyllithium (Scheme V). Because of anticipated epimeriza-

Scheme V

COOCH$_3$

6-Me   BuLi or NaH   COOCH$_3$ ··· Li(Na)

↓ CH$_3$I

COOCH$_3$

7-Me   COOCH$_3$ 13-Me   CH$_3$
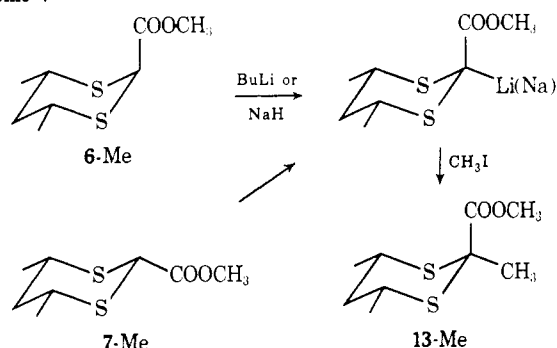
tion difficulties during quenching with acid, we treated the intermediate with methyl iodide and isolated exclusively the axial ester 13-Me. Since the α hydrogen in 6-Me and 7-Me is considerably more acidic than the C-2 hydrogen in any of the other 1,3-dithianes studied, it may be abstracted with sodium hydride without ensuing decomposition;[18] methylation of the resulting sodio derivative is equally as stereoselective as the methylation via the lithio analog.

Configurational Assignments

The basis of configurational assignment of 1a and 1c has already been discussed. The configurations of 2 and 3 have been assigned previously[7] on the basis of pmr study and equilibration results; the more stable epimer may confidently be assigned the all-equatorial configuration 2. The configuration of 4a was established by reducing it, via the tosylate, to 2 by means of lithium aluminum hydride. Comparison of the pmr spectra of 4a and 5a confirms this assignment; 4a has the downfield (axial) hydrogen at C-2 (4.36 ppm) and 5a the upfield one (3.76 ppm). Of significance, also, is the fact that the extent of intramolecular hydrogen bonding differs[19] in 4a and 5a, the stretching frequency of the bonded hydroxyl being 3600 cm^{-1} in 5a. Configurations of the pairs 4b–5b and 4c–5c were assigned by analogy in the infrared and nmr spectra: 4b, ir 3571 cm^{-1}, nmr, H-2, 4.18 ppm; 5b, ir, 3535 cm^{-1}, nmr, H-2, 3.63 ppm; 4c, ir, 3588 cm^{-1}, nmr, H-2, 4.48 ppm; 5c, ir, 3449 cm^{-1}, nmr, H-2, 3.82 ppm. The configuration of the acids 6 and 7 followed from their reduction, with lithium aluminum hydride, to the carbinols 4a and 5a, respectively.
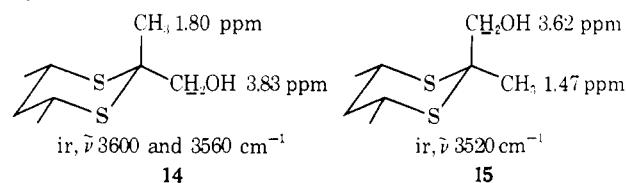
The only configurational assignment of any difficulty

(18) Cf. E. L. Eliel and A. A. Hartmann, J. Org. Chem., 37, 505 (1972); see also D. Seebach, Angew. Chem., Int. Ed. Engl., 8, 639 (1969).

(19) The infrared spectra of these and other compounds will be discussed in detail in a subsequent publication. It is somewhat surprising that the equatorial CH$_2$OH group in 4a (3.89 ppm) is downfield from the axial one in 5a (3.76 ppm); we believe this reflects the stronger hydrogen bond in 5a.

was that of the carboxylic acids 8 and 13 effected via their respective methyl esters, 8-Me and 13-Me. The slightly lower field COOCH$_3$ signal in 8-Me (3.83 ppm) compared to 13-Me (3.73 ppm) is in accord with the difference between 6-Me (3.79 ppm) and 7-Me (3.72 ppm). However, the difference is too small to permit a confident assignment of configuration. The higher field (equatorial) 2-methyl group in 13-Me (1.72 ppm) as compared to the axial one in 8-Me (2.05 ppm) is also in accordance with expectation (cf. 2 and 3 above), but we felt it could not be relied on because of the presence of a potentially disturbing anisotropy effect caused by the geminal carbomethoxy group. Therefore, 8-Me and 13-Me were correlated with 14 and 15, respectively, whose salient ir and nmr spectral data are shown in Scheme VI. Here the downfield position of the CH$_2$OH

Scheme VI

CH$_3$ 1.80 ppm   CH$_2$OH 3.62 ppm

CH$_2$OH 3.83 ppm   CH$_3$ 1.47 ppm

ir, ν 3600 and 3560 cm^{-1} ir, ν 3520 cm^{-1}
14   15

protons of 14,[19] the downfield position of its methyl group (as compared to 15), and the higher wave number of its bonded OH stretching frequency are all compatible with the assigned structure with equatorial CH$_2$OH. Since all assignments are consistent, the configurations of 8-Me and 13-Me may confidently be accepted as shown.

Kinetic vs. Thermodynamic Control

Since the very high stereoselectivity of a wide variety of reactions proceeding via dithianyllithium derivatives seems to involve an equatorial preference of the lithium moiety itself (vide supra), it became of interest to find out whether this preference was kinetic (i.e., whether the equatorial hydrogen was replaced by lithium much more rapidly than the axial) or whether it is thermodynamic, involving formation of a more stable equatorial lithium compound regardless of which proton is abstracted in the first instance. To answer this question we resorted to a technique originally suggested by Curtin and Kellom[20] in which two stereospecifically labeled and otherwise identical substrates are allowed to undergo the reaction in question, following which the products are analyzed for retention or loss of the isotopic label. The application of the method to the present case is shown in Scheme VII. Treatment of 1a or 1c with butyllithium followed by methyl iodide (methylation was used to distinguish material which had undergone lithiation from unreacted starting material) gave either 2 or 2-d (Scheme VII). If the lithiation had been totally stereoselective for the equatorial hydrogen, 1a should have given 2 and 1c should have given 2-d. Conversely, exclusive axial lithiation would have given 2-d from 1a and 2 from 1c. In the event, neither course was followed but the results turned out to be as shown in Table I. It is clear that both equatorial and axial hydrogen abstraction occur, with the equatorial mode the preferred one. When the starting material is 1c, the preference for equatorial abstraction and the iso-

(20) D. Y. Curtin and D. B. Kellom, J. Amer. Chem. Soc., 75, 6011 (1953).

Scheme VII

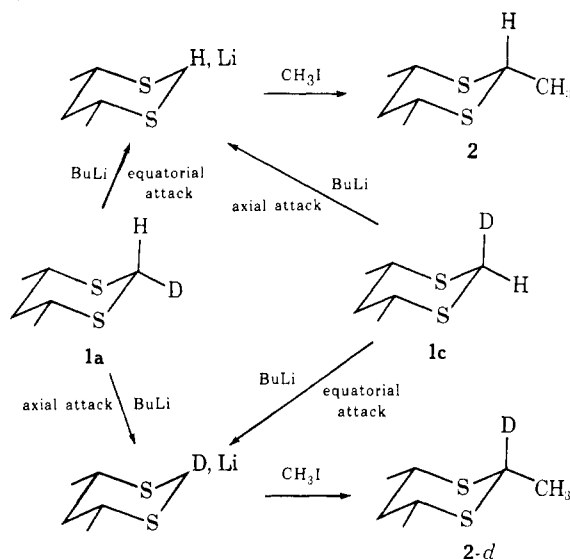
Table I. Lithiation–Methylation of **1a** and **1c**

Run	Starting material	Product 2		k_e:k_a	IE[a]
		d_0, %	d_1, %		
1	1c	3.2	96.8		
	1a	84.3	15.7	12.9	2.41
2	1c	4.4	95.6		
	1a	73.5	26.5	9.9	3.73
3	1c	6.8	93.2		
	1a	74.85	25.15	7.3	2.55
4	1c	6.42	93.58		
	1a	77.2	22.7	8.5	2.57

[a] Isotope effect.

tope effect work in the same direction and the equatorial hydrogen is abstracted nearly exclusively with formation of **2-d** (93.2–96.8%). In contrast, when **1a** is the substrate, the equatorial preference and the isotope effect work against each other and appreciable axial abstraction (16–26%) occurs, leading to a like amount of **2-d** along with the predominant undeuterated **2**. If the intrinsic rate of attack on H_e is k_e and that on H_a is k_a, and if it is assumed (of necessity, in the absence of knowledge on this point) that the isotope effect (IE) is the same for equatorial and axial abstraction, the following equations[23] apply

$$\text{for } \mathbf{1c} \quad (k_H/k_D)_c = k_e\text{IE}/k_a$$

$$\text{for } \mathbf{1a} \quad (k_H/k_D)_a = k_a\text{IE}/k_e$$

where k_H/k_D is the ratio of **2-d** to **2** obtained from the appropriate starting material.

From these equations it follows by multiplication that

$$\text{IE} = (k_H/k_D)_c^{1/2}(k_H/k_D)_a^{1/2}$$

$$= (2\text{-}d/2)_c^{1/2}(2\text{-}d/2)_a^{1/2}$$

and by division that

$$k_e/k_a = (k_H/k_D)_c^{1/2}/(k_H/k_D)_a^{1/2}$$

$$= (2\text{-}d/2)_c^{1/2}/(2\text{-}d/2)_a^{1/2}$$

The values for k_e:k_a in Table I were calculated in this manner; if one rejects the extreme value in each in-

stance and averages the remainder, one obtains k_e:k_a = (8.6 ± 1.3):1 and IE = 2.5 ± 0.1.

The relatively low isotope effect is what one might expect in the reaction of a very strong base (butyllithium) to give a much weaker one (**1-Li**), since the transition state for such a proton transfer should involve bond formation and bond breaking to a very uneven extent.[21]

It is interesting that the reaction of butyllithium with an anacomeric 1,3-dithiane is not very highly stereoselective at all, far less so, for example, than the H–D exhange of 2-norbornanone at C-3 (Scheme VIII).[22]

Scheme VIII

$$k_{exo}/k_{endo} = 715:1^{26}$$
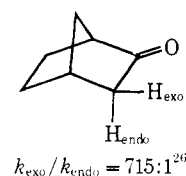
Thus, the extraordinary stereoselectivity of the subsequent protonation, alkylation, carbonylation, and carboxylation reactions rests on a thermodynamic rather than a kinetic base. However, there is some kinetic stereoselectivity even in the original proton abstraction, and it operates in the same sense as the reprotonation of the intermediate lithium compound formed by proton abstraction. This is in accord with some recent similar observations concerning α-hydrogen exchange in sulfoxides[10] and not with others;[23,24] the two systems may not be closely analogous. More significant is the finding that the proton abstraction–(with BuLi) reprotonation sequence may occur with either overall retention (89%) or overall inversion (11%) of configuration. There are two ways of interpreting the experimental finding, depending on whether one assumes the reprotonation to involve retention or inversion. Assuming retention, the overall sequence is retention–retention (89%) and inversion–retention (11%). Assuming inversion in reprotonation, the overall sequence would be inversion–inversion (89%) and retention–inversion (11%). To us, the assumption of overall retention appears more plausible, but the point remains to be established.[11]

Discussion

Highly stereoselective nonenzymatic H–D exchanges have been previously observed in sulfoxides,[25–28] such as **16** and **17**, and in s-trithianes[29] and have been claimed in five-membered sulfonium salt, such as **18**.[30]

(21) Cf. J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 241.

(22) T. T. Tidwell, J. Amer. Chem. Soc., **92**, 1448 (1970).

(23) K. Nishihata and M. Nishio, Chem. Commun., 958 (1971); J. Chem. Soc., Perkin Trans. 2, 1730 (1972).

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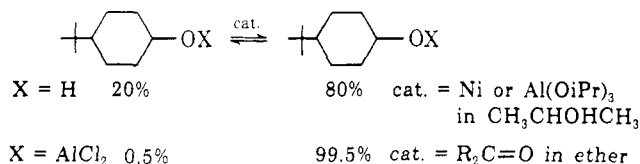(28) K. Nishihata and M. Nishio, Tetrahedron Lett., 4839 (1972).

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16   17   18
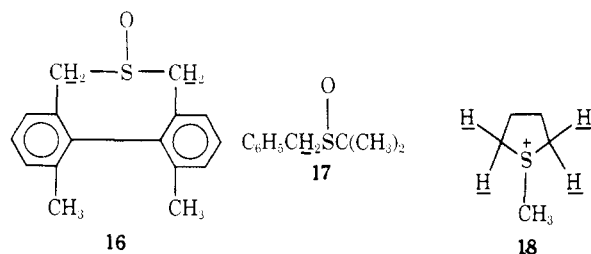
In the sulfoxide case, the effects may be quite solvent dependent.[27] The sulfonium salt case, originally claimed[30] to have a stereoselectivity of over 400 :1, is in fact only mildly stereoselective[1,31] (12 :1 to 29 :1). Stereoselectivity of this magnitude is also found in H–D exchanges of the benzyl group in benzyl methyl sulfoxide.[23,26,32] Perhaps the more striking aspect of our work is the "contrathermodynamic" interconversion of more stable isomers into less stable ones in nearly quantitative conversion (see Schemes III and IV). Thus (Scheme III), while **3** is converted to **2** in about 95% conversion at equilibrium,[7] **2** may be converted quantitatively to **3** via 3-Li using BuLi in TMEDA. The situation is even more extreme for the cases in Scheme IV where **9** may be quantitatively converted to **10** and **11** to **12** even though the **9–10** equilibrium[7] and presumably also that between **11** and **12** lies all the way in the opposite direction, favoring **9** and **11** essentially quantitatively. Cases where formation of a metal complex completely reverses the thermodynamics of an equilibrium between two diastereomers are uncommon, one example being the formation of terminal from nonterminal olefins via organoboranes.[33] One of us has previously described[34] a situation (Scheme IX) where

Scheme IX

X = H   20%   80%   cat. = Ni or Al(OiPr)₃
                          in CH₃CHOHCH₃

X = AlCl₂ 0.5%   99.5% cat. = R₂C=O in ether

complex formation (probably also involving solvation forces) shifts an equilibrium from 80 :20 to 99.5 :0.5. The technique of exploring metal complex or chelate formation for reversing positions of equilibrium may recommend itself in other contexts.

In view of our lack of knowledge about the nature of the intermediate lithium compound, attempts to account for the equatorial preference must necessarily be speculative. Steric factors alone can presumably not account for this preference, for similar factors should be operative in cyclohexyllithium derivatives which, however, as mentioned earlier, are less stereoselective in their reactions. A more plausible cause might be a high equatorial preference of an anion or ion pair in the 1,3-dithiane. Such a preference, if real, may, in turn,

be caused by a stereoelectronically favorable p–d overlap[35,36] or by the "gauche effect."[37] The latter effect is depicted in Scheme X; the equatorial carbanion is

Scheme X
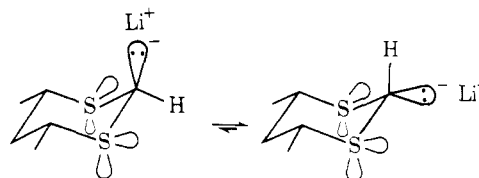
favored because the C(2)–H bond is gauche to the S–C(4) and S–C(6) bonds, whereas it would be anti in the conformation where the lithium is axial.

This explanation does, however, leave something to be desired. The gauche effect is derived from calculations on the HS–CH₂⁻ anion[38] which apply to the gas phase. It has already been shown[27] that the nature of the solvent greatly affects the relative rate of exchange to the protons next to the sulfoxide function in compound **16**; we suspect that ion pairing phenomena likely to occur in organolithium compounds may easily override the kind of stabilization calculated in a gas-phase ion.

It may be significant that protonation, alkylation, carboxylation, and carbonyl reactions of the dithianyl-lithium moiety all occur with the same stereochemistry, probably retention. In other instances studied,[22,26] alkylation follows the opposite stereochemical course (presumably inversion) from protonation and reaction with carbonyl compounds[39] (presumed to involve retention). One might surmise that the equatorial approach of all the various reagents is enforced by steric approach control, but this, also, seems unlikely, since no correspondingly high steric approach control is found in cyclohexyl derivatives.[40]

It would appear that both the presence of the sulfur atoms and the presence of the lithium moiety are responsible for the very high degree of steric control we have observed. Perhaps the picture shown in Scheme XI, wherein the lithium ion is held equatorially by the

Scheme XI
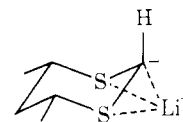
cooperative effect of the carbanion and one of the unshared electron pairs on sulfur, best accounts for the overwhelming equatorial preference of all the reactions here studied.

Experimental Section

Nmr spectra were recorded on Varian A60-A or XL-100 and Jeolco C-60HL instruments using TMS as internal standard and

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(40) Despite differences in geometry, a profound difference in steric factors between cyclohexyl and 1,3-dithianyl should not be expected; for example, axial–equatorial equilibria of alkyl groups at C(2) in 1,3-dithianes are similar to corresponding conformational equilibria in cyclohexanes.[7]

approximately 20% w/v solutions. Analytical gas chromatography was carried out on an F & M Scientific Corp. Model 810-29 dual thermal conductivity analytical research chromatograph equipped with a Honeywell Brown Elektronik Model 15 1.0 mV recorder or a Hewlett-Packard Model 5750 equipped with a Hewlett-Packard 7127-A recorder both equipped with Disc Instrument Co. peak area integrators. The injector block was at 225° and the detector block at 295°. Stainless steel columns (i.d. $^1/_8$ in.) were used for the analytical work with helium as a carrier gas, at 50 psi and a flow rate of 60 ml/min. Preparative gas chromatography was carried out on Varian Aerograph Series 1520 and Series 2700 chromatographs using aluminum columns (i.d. $^3/_8$ in.) with helium used as carrier gas. The traps were cooled in an ice bath. Analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind., and Galbraith Laboratories, Knoxville, Tenn. The hydrogen bonding studies were carried out on Perkin-Elmer Model 421 or 521 grating infrared spectrophotometers using matched pairs of 1- or 10-cm infrasil cells. Mass spectra were recorded on a Consolidated Electrodynamic Corp. Model 902 or a Hitachi Perkin-Elmer RMU-6E instrument.

meso-2,4-Pentanediol Ditosylate. The previous procedure[7] was modified as follows. The mixture of *meso-* and *dl*-diol obtained by either borohydride reduction of 2,4-pentanedione or catalytic hydrogenation[41] (*ca.* 66% meso isomer) was converted to the tosylate with *p*-toluenesulfonyl chloride and pyridine.[7] The crude product was successively recrystallized from ethanol-chloroform (2:1) until the melting point reached 136° (usually 5-6 recrystallizations). On the average, 100 g of mixed diol afforded 200 g of nearly pure *meso*-ditosylate (76% yield based on meso content of starting material).

meso-2,4-Pentanedithiol. Thiolacetic acid (1.2 mol) was added to a solution of potassium hydroxide (1.2 mol) in 1.5 l. of absolute ethanol contained in a three-necked 5-l. flask equipped with a mechanical stirrer and reflux condenser. The ditosylate (240 g, 0.58 mol) was dissolved in 1.5 l. of hot acetone and added with stirring to the homogeneous alcoholic solution of potassium thiolacetate. The solution was refluxed (*ca.* 24 hr) until an abundant precipitate of potassium tosylate appeared. At this time, the reaction was complete, the reflux condenser was reset for downward distillation and the solvent was distilled until 2 l. of distillate had been collected. The residue was allowed to cool to room temperature and transferred to a 2-l. separatory funnel, with the aid of 1000 ml of water and 200 ml of chloroform used to rinse the flask. The chloroform layer was separated and the aqueous layer once more extracted with 200 ml of chloroform and then discarded. The combined chloroform layers were washed several times with 200-ml portions of water and then dried over MgSO₄, filtered, and concentrated by means of a rotary evaporator at reduced pressure as far as possible. The crude residual dithioacetate could be used directly for the next step or distilled to give 85 g (67%) of mainly *meso*-2,4-pentanedithiol diacetate, bp 72-78° (0.25 mm). Glpc analysis indicated the material to be 90% *meso*-diacetate, 3% *dl*-diacetate (this corresponded to the amount of *dl*-dithiane obtained, see below), and 7% other impurities, possibly monothiolacetate-monoacetate.

The product (85 g, 0.4 mol) was dissolved in 350 ml of absolute ethanol in a 1000-ml round-bottom flask cooled in an ice bath and flushed with nitrogen. Ethylenediamine (36 g, 0.6 mol) was slowly added to the alcoholic solution while swirling the flask in the ice bath. After the exothermic reaction subsided (5-10 min) the flask was closed with a stopper and left standing at room temperature overnight. It was then concentrated to a paste on the rotary evaporator and transferred to a 250-ml separatory funnel by rinsing the flask with 100 ml of water followed by 80 ml of chloroform. The organic layer was separated and the aqueous layer once again extracted with 80 ml of chloroform and discarded. The combined chloroform extracts were washed with 50 ml of water, dried over 5 g of magnesium sulfate, filtered, concentrated, and distilled to give 37 g (70%) of *meso*-2,4-pentanedithiol, bp 68-72° (13 mm), $n^{20}\text{D}$ 1.5062 (lit.[7] bp 72.5° (12 mm), $n^{25}\text{D}$ 1.5052); ir and nmr spectra identical with those previously recorded.[7]
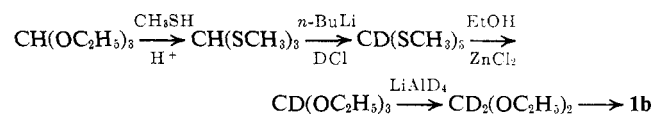
cis-4,6-Dimethyl-1,3-dithiane (1). The procedure of Seebach[3] was followed. A solution of 4 g (0.029 mol) of the above dithiol (*ca.* 95% meso isomer) and 2.25 g (0.03 mol) of dimethoxymethane dissolved in 6 ml of chloroform was added dropwise to a refluxing solution of 7.4 ml (0.06 mol) of boron trifluoride etherate in 20 ml of

chloroform over a period of 15 min. Boiling was contined for 30 min; the solution was cooled to room temperature, transferred to a separatory funnel, and washed successively with 50 ml of water, 50 ml of 20% aqueous potassium carbonate, and twice with 50 ml of water. The solution was dried over magnesium sulfate, filtered, concentrated at reduced pressure, and distilled to give 4.2 g (97%) of product which, after recrystallization from methanol, melted at 81-82.5°: ir (CCl₄) 900 (m), 1025 (s), 1090 (m), 1145 (s), 1195 (s), 1240 (s), 1310 (m), 1375 (s), 1380 (s), 1405 (m), 1440 (s), 1445 (s), 2890 (s), 2920 (s), 2990 (s) cm⁻¹; nmr 1.19 (d, $J = 6.5$ Hz, 6 H), 1.41, 1.59 (part of A part of AB), 1.94, 2.16 (B part of AB, $J_{\text{gem}} = -14$ Hz, $J_{\text{vic}} = 2.5$ Hz, 1 H), 2.44-3.7 (m, 2 H), 3.41, 4.03 ppm (AB, $J_{\text{gem}} = -14$ Hz, 2 H). The analytical sample was sublimed.[42]

Gas chromatography of the crude material showed it to contain about 3-5% of a close-boiling impurity, presumably the *dl* isomer (see above).

***r*-2-Deuterio-*cis*-4,*cis*-6-dimethyl-1,3-dithiane (1a).** The lithiation procedure of Seebach[3] was followed. To 3 g (0.02 mol) of **1** in 40 ml of tetrahydrofuran (THF) dried over molecular sieves[43] cooled to −30° in a container flushed with dry nitrogen and then capped with a rubber septum is added 0.022 mol of a solution of *n*-butyllithium in hexane by means of a syringe while the solution is stirred with a magnetic stirrer. Stirring was continued for 1.5 hr at −20 to −25° and the lithium derivative was then quenched with an equimolar solution of DCl in D₂O (prepared by dissolving 0.02 mol, 1.6 g, of acetyl chloride in 3 ml of deuterium oxide) added by means of the syringe. Stirring was continued for 5 min and the solution was then concentrated on a rotary evaporator at reduced pressure. The residue was transferred to a separatory funnel with the aid of 25 ml of chloroform, washed twice with 25 ml of water, dried over MgSO₄, and concentrated. The residual solid was crystallized and sublimed as above: yield 2.8 g (92%); mp 80°; deuterium content (nmr), 98+%; ir (CCl₄) 892 (s), 1030 (s), 1150 (s), 1180 (s), 1240 (m), 1250 (s), 1315 (m), 1375 (s), 1420 (m), 1440 (s), 1455 (s), 2820 (m), 2900 (s), 2940 (s), 2980 (s) cm⁻¹; nmr (see Figure 1) 3.96 ppm (t, $J_{\text{HD}} = 2.2$ Hz, 1 H), the C-4,5,6, region was similar to that of **1**.

2,2-Dideuterio-*cis*-4,6-dimethyl-1,3-dithiane (1b). (a) The sequence used was

$$\text{CH(OC}_2\text{H}_5)_3 \xrightarrow[\text{H}^+]{\text{CH}_3\text{SH}} \text{CH(SCH}_3)_3 \xrightarrow[\text{DCl}]{n\text{-BuLi}} \text{CD(SCH}_3)_3 \xrightarrow[\text{ZnCl}_2]{\text{EtOH}}$$

$$\text{CD(OC}_2\text{H}_5)_3 \xrightarrow{\text{LiAlD}_4} \text{CD}_2\text{(OC}_2\text{H}_5)_2 \longrightarrow \textbf{1b}$$

Trithiomethyl Orthoformate. The literature[44] procedure was modified as follows. Trimethyl orthoformate (18 g, 0.17 mol) and 25 g (0.52 mol) of methyl mercaptan were placed in a flask cooled in an ice bath and equipped with a Dry Ice–acetone cooled condenser and a magnetic stirrer. To the cooled solution was added 0.5 g of *p*-toluenesulfonic acid and stirring was continued for 2 hr at 5° and then for 12 hr at room temperature. The product was diluted with 20 ml of ether and washed with 20 ml of water and several times with 5% aqueous sodium carbonate. The residue was dried over MgSO₄, filtered, concentrated, and distilled to give 23 g (90%) of product, bp 102° (15 mm), $n^{20}\text{D}$ 1.5769, mp 17-18° (lit.[45] bp 96° (9 mm), mp 16°). Gas chromatography on several columns showed only a single peak.

Trithiomethyl Deuterioorthoformate. The above material was metalated with a 10% excess of *n*-butyllithium as described earlier for **1**. After 1 hr the lithium derivative was quenched with DCl–D₂O and the product worked up as described above for the protio analog. Recovery was 75% of material: bp 100° (12 mm), $n^{20}\text{D}$ 1.5738, mp 17°; nmr 2.18 ppm (s). The nmr spectrum suggested that over 99% of the methine position was deuterated.

Triethyl Deuterioorthoformate.[46] A solution of 12 g of the trithiomethyl deuterioorthoformate (*vide supra*) in 15 ml of absolute ethanol was refluxed in the presence of 1.5 g of fused zinc chloride for 36 hr. The product was distilled and the fraction boiling at

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(42) Elemental analyses of all new compounds were within normal limits; see paragraph at end of paper regarding supplementary material.

(43) For smaller runs it is advisable to distil the THF over lithium aluminum hydride (with the usual precaution of leaving about 30% of the solvent behind) and to degas it.

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144–146° (760 mm) collected, yield 6.3 g (55%). The infrared and nmr spectra were in accord with those reported in the literature.[35]

2,2-Dideuterio-*cis*-4,6-dimethyl-1,3-dithiane (1b). (a) The compound obtained in the previous step, 6.3 g (0.042 mol), was reduced in benzene by means of lithium aluminum deuteride.[47] The solution was worked up as described,[47] but the product was kept in the benzene solution to which, after drying, 6.7 g (0.05 mol) of *meso*-2,4-pentanedithiol was added. The procedure from this point was the same as for the undeuterated material (*vide supra*) except that benzene took the place of chloroform as the solvent. The yield of product was 3 g (48% based on triethyl deuterioorthoformate): mp 80–81°; ir (CCl₄) 935 (s), 1035 (m), 1040 (m), 1150 (m), 1250 (s), 1375 (s), 1415 (m), 1445 (s), 1455 (s), 2150 (m), 2900 (s), 2940 (s), 2990 (s) cm⁻¹; nmr 1.12 (t, $J = 7.2$ Hz, 3 H), 3.49 ppm (q, $J = 7.2$ Hz, 2 H).

(b) **By Exchange with DMSO-*d₆*.** A solution of 148 mg (1 mmol) of **1** in 5 ml of purified[43] THF was placed in a dry 50-ml round-bottom flask containing a magnetic stirring bar and capped with a rubber septum. The solution was cooled to −25° in a Dry Ice–acetone bath while dry nitrogen was flushed through the flask by means of hypodermic needles. *n*-Butyllithium in hexane (0.65 ml, 1.2 mmol, 1.9 *M*) was added slowly by means of a syringe. After 2 hr of stirring, 1.5 ml of dimethyl-*d₆* sulfoxide was added by syringe, stirring was continued for 0.5 hr at room temperature (after removal of the cooling bath), and 1 ml of D₂O was added. The mixture was diluted with an additional 20 ml of ordinary water and extracted three times with 25 ml of ether. The combined ether extracts were washed three times with 25 ml of water, dried over magnesium sulfate, and concentrated and the residual solid was recrystallized from methanol, mp 80–81°. The nmr spectrum showed a small amount of *d₁* compound (*cf.* Figure 1). Mass spectral analysis at 8 V ionizing voltage indicated 92.5% *d₂* and 7.5% *d₁* material. (The latter could presumably be removed by repeating the exchange.)

r-2-Deuterio-*trans*-4,*trans*-6-dimethyl-1,3-dithiane (1c). The preparation was carried out similar to that of **1a**, but using as starting material **1b**, extending the reaction time for lithiation to 26 hr, and quenching with 6 N hydrochloric acid. The product melted at 79–80° and, according to relative integration of the peaks, contained 71% *d₁* and 29% residual *d₂* material. The nmr spectrum (at C-2) of the material is shown in Figure 1.

r-2-*cis*-4,*cis*-6-Trimethyl-1,3-dithiane (2). A solution of **1** (0.296 g, 0.002 mol) in 5 ml of dry benzene containing 1 drop of TMEDA was allowed to react under N₂ with 1 ml of butyllithium 2.2 *M* in hexane (0.0022 mol) at 25° with stirring. After 30 min stirring was stopped and the lithium salt of **1**, in the form of a white precipitate, was allowed to settle. The supernatant liquid was removed by means of a syringe and discarded, the solid was stirred with 5 ml of benzene for 1 min, and after discarding the solvent the product was dissolved in 5 ml of dry THF at −25° in a Dry Ice–acetone bath. To this, 0.15 ml (0.0024 mol) of methyl iodide was added; the resulting solution was stirred at 25° for 15 min and rotary evaporated. The product was partitioned between 5 ml of water and 5 ml of CHCl₃, the aqueous portion was extracted again with 5 ml of CHCl₃, and the combined organic extracts were washed with 5 ml of water, dried over sodium sulfate, filtered, and distilled in a kugelrohr. The product, bp 110° (2 mm Hg), consisted of a mixture of 90–93% of **2** and 7–10% of a mixture of starting material (*ca.* 6%) and 2-*n*-butyl-4,6-dimethyl-1,3-dithiane (*ca.* 4%, probably formed from **1** and butyl iodide resulting from metathesis of residual *n*-butyllithium and methyl iodide), as shown by glc and mass spectrometry, yield 0.213 g (65%). After purification by preparative glc[7] the product **2** was identical in ir and nmr spectrum with an authentic sample.[7]

When the same procedure was applied to **1a** or **1c**, the samples of **2** obtained were partially deuterated. Deuterium analysis was carried out at 15 V. The results are summarized in Table I.

r-2,*trans*-4,*trans*-6-Trimethyl-1,3-dithiane (3). A mixture of **2** (90%) and **3** (10%) (1.62 g) was dissolved in 20 ml of TMEDA and converted to the lithium derivative by means of 10.5 ml of 1.9 *M n*-butyllithium in hexane. The procedure was the same as described below for the 2-*tert*-butyl compound (**10**). The final material was recrystallized from methanol, mp 65–66° (lit.[7] 64–64.5°); recovery was 1.3 g (80%). Gas chromatographic analysis on the same column used for **10** (*vide infra*) at 90° showed a single compound whose retention time corresponded to that of **3**; no recovered **2**

could be detected. The sample was purified by preparative gas chromatography (see **10** for column); its nmr spectrum was identical with that of an authentic sample[7] of **3**.

In preliminary experiments, using butyllithium in THF at −20° as described above, it was found that **2**, after 24 hr reaction time followed by quenching with DCl-D₂O, yielded only *ca.* 75% **3** along with 25% unreacted **2**. Mass spectrometry indicated that recovered **2** had picked up no deuterium, whereas **3**, according to its nmr spectrum (singlet methyl group at C-2), was entirely deuterated. When the same experiment was carried out using **3** as starting material, the metalation appeared to proceed faster and the product was worked up after 2.5 hr at −25°. The product was chemically pure **3**; no **2** was formed, as indicated by gas chromatography. Mass spectroscopy (comparison with the 70-V spectrum of **3**-*d* obtained from **2**) and nmr spectroscopy indicated that the recovered sample was approximately 80% **3**-*d* and 20% **3**.

r-2-*tert*-Butyl-*trans*-4,*trans*-6-dimethyl-1,3-dithiane (10). A mixture of *cis*- and *trans*-2-*tert*-butyl-*cis*-4,6-dimethyl-1,3-dithiane (**9, 10**, from condensation of pivalic aldehyde with *meso*-pentane-2,4-dithiol[7]), 2.04 g (0.01 mol), was dissolved in 20 ml of TMEDA (distilled over calcium hydride before use) in a dry 50-ml flask containing a magnetic stirring bar and capped with a rubber septum. The solution was cooled to −25° while dry nitrogen was flushed through the flask by means of two hypodermic needles. *n*-Butyllithium in hexane (10.5 ml of 1.9 *M* solution, 0.02 mol) was then added slowly by syringe; the solution was warmed up to room temperature and stirring was continued for 48 hr. The solution was removed from the flask by means of a syringe and added slowly to a flask containing 30 ml of water which was stirred rapidly to ensure good mixing and blanketed with nitrogen to prevent oxidation of the lithium derivative. After quenching the product was extracted with three 25-ml portions of ether and the combined ether extracts washed with three 25-ml portions of 5% aqueous hydrochloric acid and two 25-ml portions of water. After drying over MgSO₄ and concentrating the material was distilled in a kugelrohr (bulb-to-bulb) at 0.5 Torr and 80° air bath temperature to give 1.5 g (75%) of **10**. Gas chromatographic analysis on a 25 ft, ⅛ in. 25% QF-1 on 80–100 mesh Chromosorb W column at 120° indicated 99.7% of the material whose retention time corresponded to that of **10** and about 0.3% corresponding to **9**. Pure **10** was obtained by preparative gas chromatography (⅜ in. column as above but on 60–80 mesh Chromosorb W at 150°) and had an nmr spectrum identical with that of an authentic sample.[7]

***cis*-2,4,4,6-Tetramethyl-1,3-dithiane (11). 4-Benzylthio-4-methylpentan-2-ol.** 4-Benzylthio-4-methylpentan-2-one was prepared as described[48] from mesityl oxide and benzyl mercaptan in the presence of sodium ethoxide: bp 118° (0.25 mm) (lit.[48] 137–138.5° (4 mm)); ir 710 (s), 770 (m), 940 (w), 1030 (m), 1072 (m), 1145 (s), 1360 (s), 1380 (m), 1455 (m), 1495 (m), 1600 (w), 1710 (s), 2965 (m), 2983 (s), 3013 (m), 3030 (w) cm⁻¹; nmr 1.37 (s, 6 H), 1.98 (s, 3 H), 2.53 (s, 2 H), 3.66 (s, 2 H), 7.18 ppm (m, 5 H).

A solution of 102 g (0.46 mol) of the above ketone in 200 ml of absolute ether was added dropwise to a well-stirred dispersion of 6.75 g (0.18 mol) of lithium aluminum hydride in 600 ml of ether contained in a 2-l. three-necked flask equipped with a mechanical stirrer, reflux condenser, and pressure-equalized dropping funnel. When addition was complete, the mixture was boiled for 2 hr and then hydrolyzed by successive addition of 6.75 ml of water, 6.75 ml of 15% NaOH solution, and 13.5 ml of water. After 1 hr more of stirring the solution was filtered by mild suction and the residue washed with 300 ml of ether. The combined ether solutions were dried (MgSO₄) and concentrated and the residue distilled to yield 100 g (90%) of product: bp 120–122° (0.5 mm), n^{25}D 1.5402; ir 925 (m), 1045 (m), 1070 (m), 1140 (s), 1365 (m), 1382 (m), 1455 (s), 1494 (m), 1600 (w), 2960 (s), 2982 (s), 3013 (w), 3030 (w), 3400 cm⁻¹ (s, broad); nmr 1.1 (d, $J = 6.3$ Hz, 3 H), 1.31 (s, 6 H), 1.18–1.98 (AB, each leg split, $J_{gem} = -13.6$ Hz, $J_{vic} = 2.9, 8.7$ Hz, 2 H), 3.4 (s, 1 H), 3.7 (s, 2 H), 4.05 (m, 1 H), 7.28 ppm (m, 5 H).

The tosylate was prepared by slowly adding a solution of 70 g (0.37 mol) of *p*-toluenesulfonyl chloride in 100 ml of dry pyridine to a solution of 80 g (0.36 mol) of 4-benzylthio-4-methylpentan-2-ol in 150 ml of pyridine with good stirring at 0°. Stirring at the same temperature was continued for 5 hr and the solution was kept in the refrigerator for an additional 20 hr. Pyridine hydrochloride precipitated. The mixture was poured into 350 ml of concentrated hydro-

(47) C. J. Claus and J. L. Morgenthau, *J. Amer. Chem. Soc.*, **73**, 5005 (1951).

(48) H. J. Backer and G. J. deJong, *Recl. Trav. Chim. Pays-Bas*, **70**, 377 (1951).

chloric acid mixed with 500 g of ice. The oily tosylate was extracted with three 200-ml portions of chloroform and the chloroform extracts washed three times with 150-ml portions of water, dried over $MgSO_4$, filtered, and concentrated. The residue crystallized on standing and was recrystallized from 95% ethanol: yield 100 g (74%); mp 78–80°;[42] nmr 1.17 (d, $J = 4.5$ Hz), 1.25 (s, two signals combined, 9 H), 1.37–2.1 (AB, each leg split, $J_{gem} = -14.7$ Hz, $J_{vic} = 4.8$, 6.2 Hz, 2 H), 2.4 (s, 3 H), 3.6 (s, 2 H), 4.85 (m, 1 H), 7.2–7.9 ppm (m, 9 H).

2,4-Bisbenzylthio-2-methylpentane. A solution of 94 g (0.25 mol) of the above tosylate in 200 ml of warm ethanol was added, under nitrogen, to a refluxing solution of potassium benzylmercaptide which was prepared by addition of 31 g (0.25 mol) of benzyl mercaptan to a solution of 14 g (0.25 mol) of potassium hydroxide in 200 ml of ethanol. After a few hours, benzyl mercaptan consumption stopped, as indicated by iodometric titration. Reflux was continued for a total of 24 hr. Upon cooling, potassium tosylate precipitated. The solution was concentrated by vacuum distillation and 300 ml of water was added to dissolve the salts. The solution was extracted three times with 100-ml portions of ether which were combined, cleared three times with 50-ml portions of water, dried over $MgSO_4$, and concentrated. Part of the material was distilled to give two major fractions, bp 75° (0.22 mm) and 95–98° (0.3 mm), plus a high-boiling residue. Gas chromatography of the distilled material revealed three components, each of which had m/e 206 in the mass spectrum and which must thus be positional isomers, of the elimination products of the tosylate. The desired compound remained in the high-boiling residue as a minor reaction product.

2-Methyl-2,4-pentanedithiol. The crude product obtained above, 45 g, was added to 1.5 l of liquid ammonia contained in a three-necked flask equipped with Dry Ice–acetone condenser and mechanical stirrer. Small pieces of sodium were added with fast stirring until the solution became permanently blue. Ammonium chloride (15 g) was added and the ammonia was allowed to evaporate. Water (300 ml) was added to the residue and the mixture acidified with 5% hydrochloric acid and extracted with three 100-ml portions of ether. The combined ether extracts were washed twice with 100 ml of water, dried over magnesium sulfate, and concentrated. Distillation of the residue through a Vigreux column gave material boiling at 39–40° (1 mm) which appeared to be a mixture of mercaptan and disulfide. The material was reduced by means of lithium aluminum hydride following the procedure of Arnold, et al.,[49] to give, eventually, 5 g of the dithiol, bp 40° (1 mm), which appeared to be pure according to gas chromatographic analysis on the column described earlier (QF-1) at 100°: ir 855 (w), 1050 (w), 1136 (m), 1215 (m), 1369 (m), 1384 (m), 1455 (s), 2550 (w), 2860 (m), 2920 (s), 2960 cm^{-1} (s); nmr 1.47 (d, $J = 7.2$ Hz), 1.45 (s, total of two peaks, 9 H), 1.60 (d, $J = 5.8$ Hz), 1.65 (s, combined peaks, 2 H), 1.88 (d, $J = 5.8$ Hz, 2 H), 3.2 ppm (m, 1 H). The material was purified for analysis through the corresponding preparative column.[42]

Synthesis of 11. The procedure of Seebach[3] was modified[14] to condense 3 g (0.02 mol) of the above dithiol with 2.36 g (0.02 mol) of diethyl acetal. The product was distilled in a kugelrohr at 0.5 Torr, air bath temperature 80°, to give 2.5 g (60%) of dithiane which appeared, from glpc analysis at 100° on the above described QF-1 column, to contain 90% of the major and 10% of a minor component. Preparative glc (150°) yielded the desired cis-2,4,4,6-tetramethyl-1,3-dithiane as indicated by the nmr spectrum:[42] ir 725 (m), 1060 (m), 1150 (w), 1128 (w), 1170 (m), 1190 (m), 1225 (m), 1368 (m), 1384 (m), 1448 (s), 2905 (w), 2935 (s), 2963 (s), 2983 cm^{-1} (s); nmr 1.16 (d, $J = 6.8$ Hz), 1.24 (s), 1.30 (s), 1.39 ($J = 6.7$ Hz, total of four peaks plus a small overlapped signal, 13 H), 1.48 (B part of AB), 1.75, 1.89 (A part of AB, each d, $J_{gem} = -13.7$ Hz, $J_{vic} = 2.6$ Hz, 1 H), 2.9–3.1 (m, 1 H), 4.12 ppm (q, $J = 6.8$ Hz, 1 H).

trans-2,4,4,6-Tetramethyl-1,3-dithiane (12). The procedure described above for **10** was applied to a mixture of **11** (see above) and **12** containing over 90% of **11**. Gas chromatographic analysis of the product of the QF-1 column described above at 100° revealed only one compound whose retention time was different from that of **11** and was the same as that of the minor component (ca. 10%) contained in the starting material. The material was isolated on the preparative column at 140°;[42] ir 715 (w), 1047 (w), 1057 (w), 1125 (w), 1165 (w), 1190 (w), 1224 (m), 1368 (m), 1383

(m), 1448 (s), 2910 (w), 2934 (m), 2963 (s), 2982 cm^{-1} (s); nmr 1.25 (d, $J = 6.8$ Hz), 1.32 (s), 1.34 (s, total of three peaks, 9 H), 1.56 (d, $J = 7$ Hz, ca. 4 Hz including overlapping peaks), 1.70 (part B of AB), 1.74, 1.88 (A part of AB, $J_{gem} = -13.6$ Hz, $J_{vic} = 3.5$ Hz), 3.0–3.35 (m, 1 H), 4.10 ppm (q, $J = 7$ Hz, 1 H).

Methyl cis-4,cis-6- **(6-Me) and** trans-4,trans-6-Dimethyl-1,3-dithiane-r-2-carboxylate (7-Me). Condensation of 5 g (0.036 mol) of meso-2,4-pentanedithiol with 7 g (0.07 mol) of glyoxylic acid sesquihydrate in 50 ml of benzene containing 0.5 g of p-toluenesulfonic acid was effected by boiling at reflux with a Dean-Stark trap until no more water was formed (2–3 hr). The acid which crystallized (6.2 g, 89.6%) was dissolved in 150 ml of methanol containing 3% gaseous HCl to which 15 ml of methyl orthoformate was added as a water scavenger. The solution was boiled at reflux for 12 hr and concentrated on a rotary evaporator at reduced pressure to yield a yellowish oil which was taken up in 20 ml of chloroform and washed with water until the washings were neutral and the chloroform solution dried over $MgSO_4$, filtered, and concentrated. The product boiled at 80–85° (0.07 mm), yield 4.5 g (60%) of a mixture of 70% 6-Me and 30% 7-Me as indicated by gas chromatography on the QF-1 column (see above) at 185°. The compounds were separated by preparative gas chromatography (QF-1, 130°).

Cis-isomer, 6-Me: mp 26.5–27.5° (stored in a plastic vial since epimerization seems to occur in a glass container);[42] ir (CCl$_4$) 902 (m), 1010 (m), 1030 (m), 1145 (s), 1180 (m), 1250 (s), 1285 (s), 1375 (m), 1430 (s), 1445 (s), 1450 (s), 1740 (s), 2845 (s), 2940 (m), 2970 (s) cm^{-1}; nmr 1.28 (d, $J = 6.8$ Hz, 6 H), 1.41, 1.61 (part of A part of AB), 2.03, 2.26 (B part of AB, $J_{gem} = -14$ Hz, $J_{vic} = 2.5$ Hz, 1 H), 2.65–3.32 (m, 2 H), 3.78 (s, 3 H), 4.97 ppm (s, 1 H).

Trans isomer, 7-Me: mp 49–50° after recrystallization from hexane;[42] ir (CCl$_4$) 892 (w), 1005 (m), 1030 (m), 1140 (s), 1185 (m), 1245 (m), 1280 (s), 1370 (m), 1420 (m), 1445 (m), 1735 (s), 2870 (m), 2980 (s) cm^{-1}; nmr 1.22 (d, $J = 6.8$ Hz, 6 H), 1.37, 1.42, 1.62 (part A part of AB), 2.06, 2.28 (part B of AB, $J_{gem} = -14$ Hz, 1 H), 3.18–3.80 (m, 2 H), 3.76 (s, 3 H), 4.30 ppm (s, 1 H).

r-2-Hydroxymethyl-cis-4,cis-6-dimethyl-1,3-dithiane (4a). (a) The lithium derivative of **1** was prepared as described above from 1.48 g (0.01 mol) of **1** in 15 ml of THF at −25° (under nitrogen) by means of 5.0 ml of 2.2 M BuLi in hexane. After 2 hr of stirring, a solution of 0.33 g of formaldehyde gas (generated by sweeping the equivalent amount of paraformaldehyde, heated to 190°, with dry nitrogen) in 2 ml of THF was added and stirring was continued for 1 hr at −20°. The mixture was let stand for 12 hr at room temperature, diluted with an equal volume of ether, and washed with a 10-ml portion of saturated aqueous ammonium chloride followed by three 10-ml portions of water. The solution was concentrated and the residue crystallized from hexane: yield 1.45 g (82%); mp 60–60.5°;[42] ir (5 × 10^{-3} M in CCl$_4$) 3600 cm^{-1}, chloroform solution (ca. 10%) 902 (m), 975 (m), 1020 (s), 1030 (s), 1055 (s), 1100 (m), 1155 (m), 1250 (s), 1380 (s), 1455 (m), 2900 (s), 2950 (s), 2995 (s), 3450 (m), 3680 (m) cm^{-1}; nmr 1.28 (d, $J = 6.8$ Hz, 6 H), 1.42 (part of A part of AB), 2.03, 2.18 (B part of AB, $J_{gem} = -14$ Hz, $J_{vic} = 2$ Hz, 1 H), 2.50 (s, 1 H), 2.68–3.08 (m, 2 H), 3.85 (d, $J = 6$ Hz, 2 H), 4.34 ppm (t, $J = 6$ Hz, 1 H).

In one instance, the mother liquor from recrystallization of **4a** was subjected to gas chromatography and an amount of **5a** equivalent to 0.2% of the total original material was found. It is possible that **5a** was formed from **4a** by lithiation on the ring and epimerization (see below).

(b) The same material, as indicated by infrared and nmr spectrum, was obtained in 95% yield from 6-Me by reduction with ethereal lithium aluminum hydride in the usual way.

p-Toluenesulfonate of 4a. Treatment of **4a** with p-toluenesulfonyl chloride in pyridine in the usual way[50] gave the tosylate, characterized by its ir (CHCl$_3$): 810, 845, 940, 970, 1025, 1095, 1180, 1190, 1250, 1365, 1445, 1592, 2860, 2915, 2970 cm^{-1}.

Reduction of the tosylate with lithium aluminum hydride in tetrahydrofuran gave the equatorial (cis) methyl compound **2** as evidenced by infrared and nmr spectral comparison.

Other Equatorial Carbinols. Compounds **4b**, **4c**, and **4d** were prepared in the same fashion as **4a** but using equivalent amounts (0.011 mol) of dry acetone, pivalic aldehyde, and cyclohexanone, respectively, as reagents. In some cases it was necessary to chromatograph the products on silica, using hexane–acetone (2:1) to elute contaminants and chloroform to elute the product.

Product **4b**: mp 58–61°;[42] ir (5 × 10^{-3} M in CCl$_4$) 3571 cm^{-1};

(49) R. C. Arnold, A. P. Lien, and R. M. Alm, *J. Amer. Chem. Soc.*, **72**, 731 (1950).

(50) L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses," Wiley, New York, N. Y., 1967, p 1180.

nmr 1.30 (d, J = 6.5 Hz, 6 H), 1.42 (s, 6 H), 1.51, 1.74 (part of A part of AB), 2.02, 2.25 (part B of AB, J_{gem} = −14 Hz, J_{vic} = 2.5 Hz, 1 H), 2.36 (s, 1 H), 2.60–3.23 (m, 2 H), 4.18 ppm (s, 1 H).

Product 4c: mp 80–82°;[42] ir (5 × 10⁻³ M in CCl_4) 3588 cm⁻¹; nmr 1.06 (s, 9 H), 1.26 (d, J = 6.5 Hz, 6 H), 1.49, 1.66 (part of A part of AB), 1.97 (part of B of AB), 2.15 (d, J = 5.30 Hz, 1 H), 2.65–3.25 (m, 2 H), 3.53 (d, d, J = 5.30, 2.25 Hz, 1 H), 4.46 ppm (d, J = 2.25 Hz, 1 H).

Product 4d: mp 90–93°;[42] ir (5 × 10⁻³ M in CCl_4) 3568 cm⁻¹; nmr 1.28 (d, J = 6.5 Hz, 6 H), 1.10–1.85 (m, 6 H), 2.00, 2.23 (B part of AB, J_{gem} = −14 Hz, J_{vic} = 2.5 Hz, 1 H), 2.10 (s, 1 H), 2.58–3.18 (m, 2 H), 4.23 ppm (s, 1 H).

Gas chromatographic analysis of 4b, 4c, and 4d showed no detectable amount of 5b, 5c, or 5d.

r-2-Hydroxymethyl-trans-4,trans-6-dimethyl-1,3-dithiane (5a). (a) The lithium alkoxide was prepared as indicated above for 4a, but instead of the solution being treated with ammonium chloride it was treated with an additional 6 ml of BuLi (2.2 M in hexane). The solution was kept in the refrigerator at 0° for 24 to 40 hr and was then worked up as indicated for 4a. The product melted at 91–92° after recrystallization from hexane:[42] ir (5 × 10⁻³ M in CCl_4) 3529, chloroform solution (ca. 10%) 901 (w), 962 (m), 1020 (s), 1030 (m), 1055 (s), 1145 (m), 1170 (m), 1245 (s), 1315 (m), 1325 (m), 1375 (s), 1445 (s), 2880 (s), 2940 (s), 2970 (s), 3550 (m) cm⁻¹; nmr 1.22 (d, J = 6.5 Hz, 6 H), 1.36, 1.48 (part of A part of AB), 2.00, 2.14 (B part of AB, J_{gem} = −14 Hz, J_{vic} = 2.5 Hz, 1H), 1.58 (s, 1 H), 2.78–3.18 (m, 2 H), 3.80 ppm (s, 3 H).

(b) Compound 5a is also obtained by treating a solution of 1.78 g (0.01 mol) of 4a in 15 ml of THF with 11.0 ml of 2.2 M BuLi in hexane and then proceeding as indicated above.

(c) Lithium aluminum hydride reduction of 7-Me gave 5a, identical in ir and nmr spectrum with the above described samples, in 95% yield.

Other axial carbinols were prepared in the same manner.

Compound 5b, liquid, $n^{25}D$ 1.535;[42] ir (5 × 10⁻³ M, CCl_4) 3619 (w), 3535, (5 × 10⁻³ M, CCl_4) 3619 (w), 3535 cm⁻¹; nmr 1.21 (d, J = 6.7 Hz, 6 H), 1.40 (s, 6 H), 1.51 (part of A part of AB), 1.99, 2.28 (B part of AB, J_{gem} = −14 Hz, J_{vic} 2.5, 1 H), 2.02 (s, 1 H), 2.82–3.40 (m, 2 H), 3.12 (s, 1 H).

Compound 5c: mp 55–58°;[42] ir (5 × 10⁻³ M, CCl_4) 3642 (w), 3449, (5 × 10⁻³ M, CCl_4) 3642 (w), 3449 cm⁻¹; nmr 1.00 (s, 9 H), 1.20 (d, J = 6.75 Hz, 6 H), 1.36, 1.55 (part of A part of AB), 1.95, 2.17 (B part of AB, J_{gem} = −13.7), 2.18 (d, J = 6 Hz, 1 H), 2.90–3.30 (m, 2 H), 3.61 (d, d, J = 6, 6 Hz, 1 H), 3.82 (d, J = 6 Hz, 1 H).

Compound 5d was not isolated in pure form.

Gas chromatographic analysis of 5a, 5b, and 5c showed no evidence for the presence of 4a, 4b, and 4c.

r-2-Carbomethoxy-2,cis-4,cis-6-trimethyl-1,3-dithiane (8-Me). (a) A solution of 0.8 g (0.005 mol) of 3 in 10 ml of THF at −20° was allowed to react with 2.4 ml of BuLi in hexane (2.2 M). The mixture was left standing for 12 hr as previously described. A piece of Dry Ice, weighing ca. 1 g, was wiped dry with a cloth and added to the solution which was stirred for 10 min and then allowed to warm to room temperature for 30 min. The product was diluted with an equal volume of ether and extracted with 10 ml of 20% aqueous KOH. The alkaline layer was cleared three times with 10-ml portions of ether, acidified with 5% hydrochloric acid, and extracted twice with 10-ml portions of ether. The combined ether layers were washed with water until no more hydrochloric acid was extracted, dried over $MgSO_4$, filtered and cooled to 0°. An ethereal solution of diazomethane prepared from 4 g of N-nitrosomethylurea[51] was gradually added to the solution of the acid until the yellow color of diazomethane persisted. The solution was allowed to warm to room temperature resulting in the deposition of some insoluble oil. After 2 hr the ether layer was decanted, dried over $MgSO_4$, filtered, and concentrated. Addition of hexane led to crystallization of the residue. The material was collected, sublimed, recrystallized from hexane, and resublimed, mp 82–84°. The gas chromatogram showed a single peak; examination of the gas chromatogram of the mother liquor showed absence of the peak of the epimer:[42] ir (CCl_4) 860, 965, 1025, 1080, 1115, 1150, 1250, 1375, 1445, 1730, 2860, 2920, 2950 cm⁻¹; nmr 1.25 (d, J = 6.75 Hz, 6 H), 1.55 (part of A part of AB), 2.05 (s, 3 H), 2.20, 2.24, 2.28 (part of B part of AB), 2.80–3.45 (m, 2 H), 3.82 ppm (s, 3 H).

(b) Compound 8-Me was also prepared by quenching the lithium derivative of 0.5 g (0.0025 mol) of 3 (prepared as above) with an

equimolar amount of methyl chloroformate (0.26 mol) dissolved in 2 ml of THF at 0°. The product was diluted with 20 ml of ether, washed with 20 ml of H_2O, and worked up as in the previous procedure. However, the desired material failed to crystallize due to the presence of an unidentified impurity. Glc analysis of the crude reaction product showed it to contain ca. 50% of 8-Me and none of the epimeric compound 13-Me.

r-2-Hydroxymethyl-2,cis-4,cis-6-trimethyl-1,3-dithiane (14). To a solution of 3.24 g (0.02 mol) of a mixture of 2 and 3 in 30 ml of THF cooled, under nitrogen, to −25° was added 10 ml of 2.2 M n-butyllithium in hexane. The solution was stirred at −20° for 2 hr, following which 0.75 g (0.024 mol) of gaseous formaldehyde (vide supra) was swept into the reaction mixture. Stirring was continued for 1 hr at −20° and the solution left to stand at room temperature for 12 hr. The solution was diluted with 30 ml of ether, washed with 20 ml of saturated aqueous ammonium chloride, washed three times with 50-ml portions of water, dried over $MgSO_4$, and concentrated to give 2.8 g of crude product which was purified by column chromatography on silica gel, eluting impurities with hexane and the main product with hexane–acetone (9:1). Gas chromatography showed this material to be different from the epimer described below. The material is liquid at room temperature; solvent was removed by prolonged pumping:[42] ir (10⁻⁴ M in CCl_4) 3600, 3560 cm⁻¹; nmr 1.17 (d of t, J_{gem} = −13.8 Hz, J_{vic} = 11.8 Hz, 1 H), 1.26 (d, J = 6.75, 6 H), 1.80 (s, 3 H), 2.17 (d of t, J_{gem} = −13.8 Hz, J_{vic} = 2.25 Hz), 2.71 (s, 1 H), 3.18 (m, 2 H), 3.83 ppm (s, 2 H).

r-2-Carbomethoxy-2,trans-4,trans-6-trimethyl-1,3-trithiane (13-Me). Either 6-Me or 7-Me (2.06 g, 0.01 mol) was dissolved in 5 ml of THF and added to a well-stirred solution of either 0.012 mol of BuLi (5.5 ml of 2.2 M solution in hexane) or NaH (0.29 g, as 57% suspension in mineral oil) in 15 ml of THF at −30°. After 3 min 2.2 g (0.015 mol) of CH_3I in 2 ml of THF were added with stirring for 1 hr at −20° followed by standing 12 hr at room temperature. The work-up was identical with that described for 4a above; yield 1.54–1.76 g (70–80%); mp 54–54.5° after recrystallization from hexane. Gas chromatographic analysis of the mother liquor showed absence of the peak for the epimeric 8-Me:[42] ir 850, 970, 1030, 1090, 1145, 1235, 1370, 1440, 1720, 2860, 2910, 2940 cm⁻¹; nmr 1.20 (d, J = 6.75 Hz, 6 H), 1.44 (part of A part of AB), 1.72 (s, 3 H), 2.02, 2.25 (part B of AB, J_{gem} = −14 Hz, 1 H), 3.1–3.65 (m, 2 H), 3.72 ppm (s, 3 H).

r-2-Hydroxymethyl-2,trans-4,trans-6-trimethyl-1,3-dithiane (15). Reduction of 1.1 g (0.005 mol) of 13-Me with lithium aluminum hydride by the standard technique gave 15 in 91% yield (0.87 g). The material was purified by column chromatography on silica gel using hexane to elute impurities and 95:5 hexane–acetone to elute product. The liquid was freed of solvent by pumping:[42] ir (10⁻⁴ M in CCl_4) 3520 cm⁻¹; nmr 1.13 (d of t, J_{gem} = −13.5 Hz, J_{vic} = 11.3 Hz, 1 H), 1.225 (d, J = 6.75 Hz, 6 H), 1.47 (s, 3 H), 2.11 (d of t, J_{gem} = −13.5 Hz, J = 2.25 Hz), 2.43 (t, J = 6.0 Hz, 1 H), 3.0 (m, 2 H), 3.62 ppm (d, J = 6.0 Hz, 2 H).

(51) F. Arndt, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 165.