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SYNTHESIS OF 3,5-DIALKYL-1,2,4-TRITHIOLANES
ASSIGNMENT OF CONFIGURATION AND CONFORMATIONAL ANALYSIS BY PMR

S. B. TJAN, J. C. HAAKMAN, C. J. TEUNIS and H. G. PEER
Unilever Research Duiven, Postbox 7, Zevenaar, The Netherlands

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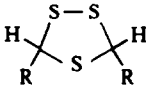
Abstract—3.5-Dialkyl-1.2.4-trithiolanes (I–IV) have been synthesized in reasonable yields by a new route



I: R = Me
II: R = Et
III: R = i-Pr
IV: R = t-Bu

involving chlorination of dialkyl disulfides to α-chloroalkyl sulfenyl chlorides, reaction with potassium iodide giving di-α-chloroalkyl disulfides and subsequent cyclization with sodium sulfide.

All dialkyltrithiolanes synthesized exist in two isomeric configurations (*cis*/*trans*), separable by preparative GLC or column chromatography over alumina.

We were able to assign unequivocally the *cis* and *trans* configurations by use of the Nuclear Overhauser Effect. From the temperature dependence of the PMR spectra and from Aromatic Solvent Induced Shifts in the spectra it appeared that all dialkyltrithiolanes show pseudorotation: the relative abundance of each conformer is dependent on the bulk of the alkyl groups. The energy barrier for pseudorotation was estimated to be smaller than 6 kcal/mole.

INTRODUCTION

DURING their investigations into components contributing to beef flavour, Brinkman *et al.*[1] isolated from beef broth two volatile isomers which were tentatively identified as the 3,5-dimethyl-1,2,4-trithiolanes (I). Chang *et al.*,[2] who also isolated two isomeric 3,5-dimethyl-1,2,4-trithiolanes from boiled beef, suggested that the isomers were *cis* and *trans* forms, but made no structural assignment.

To confirm this identification it was necessary to synthesize compound I and in view of the promising properties of the compounds as flavouring agents we investigated a more general synthesis for 3,5-dialkyl-1,2,4-trithiolanes.

Apart from the configuration of the two isomers, the question arises whether we are dealing with rigid or rapidly interconverting conformations. A detailed spectrometric investigation was undertaken in order to assign unequivocally *cis* and *trans* configurations to the isomeric dialkyltrithiolanes, and either to define the dominant conformation of the 3,5-dialkyl-1,2,4-trithiolanes (if one exists) or to determine whether rapid (on the PMR time scale) pseudorotation takes place.

For the assignment of the *cis* and *trans* configuration we applied the Nuclear Overhauser Effect[3,4] (NOE). Conformational analysis was carried out by studying the temperature dependence of the PMR spectra and by use of Aromatic Solvent Induced Shifts (ASIS) on the methine ring protons of the 3,5-dialkyl-1,2,4-trithiolanes.[5]

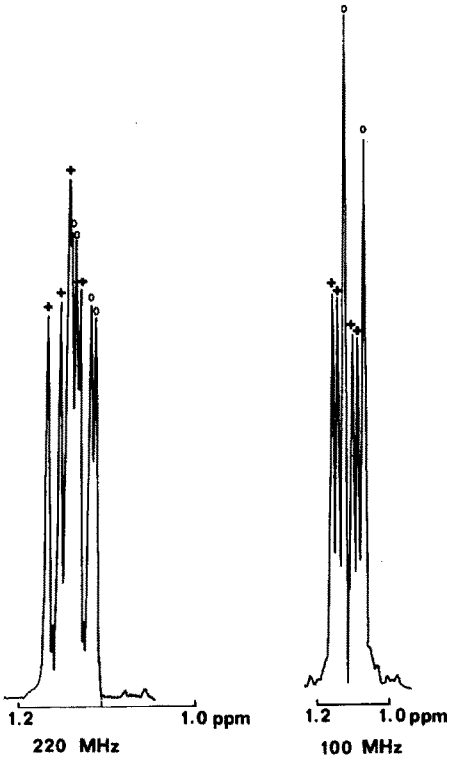
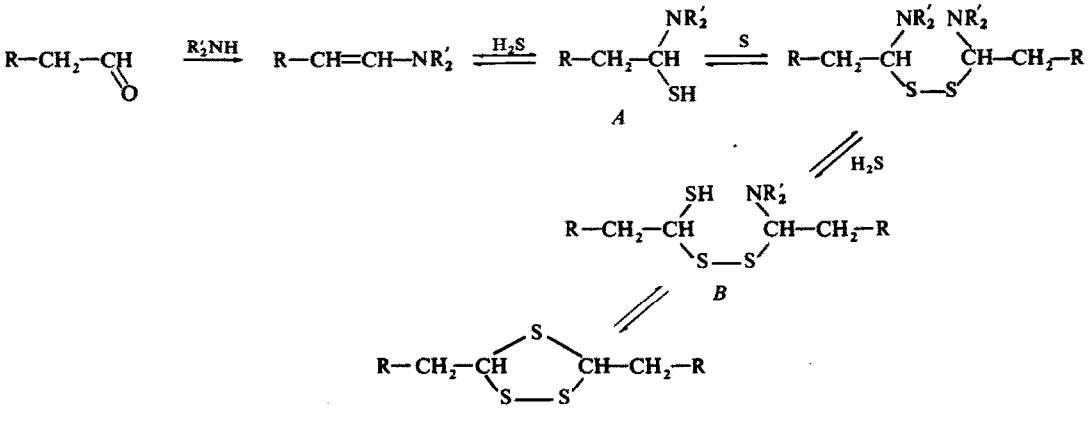


FIG 1. Methyl proton signals in the 100 and 220 MHz spectra of the 3,5-diisopropyl-1,2,4-trithiolanes III_1 (0) and III_2 (+). Synthetic mixture was dissolved in CCl_4.

Synthetic routes to 3,5-dialkyl-1,2,4-trithiolanes

Synthesis of trithiolanes from aldehydes. The literature on 1,2,4-trithiolanes was reviewed by Breslow.[6] It appears that Asinger *et al.*[7] are the only workers who obtained 3,5-dialkyl substituted derivatives: they developed the route illustrated in

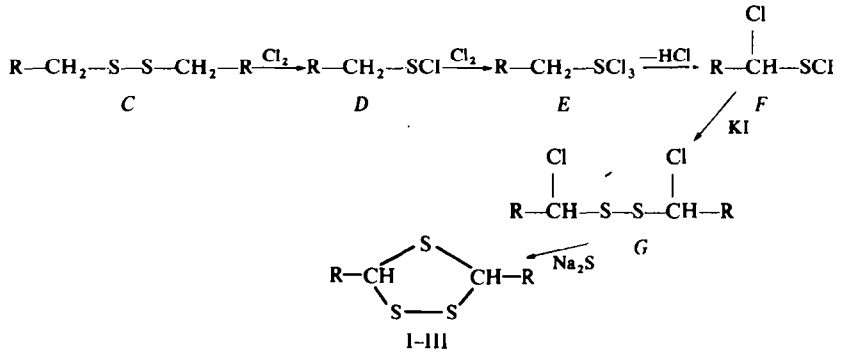
SCHEME 1. Asinger's route to 3,5-dialkyltrithiolanes.



Scheme 1. This route is completely unsuccessful with formaldehyde—no unsubstituted trithiolane is produced—and the yield is very low (5%) when the dimethyl homologue is produced by this route from acetaldehyde. Further, although the product which we obtained from acetaldehyde had the same physical constants as those given by Asinger, GLC of the product showed it to be very impure. The impurities included polymeric material which was probably formed by intermolecular reactions of the mercapto intermediates A and B (Scheme 1).

Synthesis of trithiolanes from disulfides. The poor results obtained by the above method prompted us to look for an alternative synthetic route to 3,5-dialkyltrithiolanes, in particular the dimethyl homologue. Our investigations resulted in the route illustrated in Scheme 2. As described by Brintzinger,[8–11] the disulfides (C; R = Me,

SCHEME 2. Route to 3,5-dialkyltrithiolanes from disulfides.



Et, and i-Pr) were chlorinated to sulfenyl chlorides (D) at temperatures between −10 and −30°. Prolonged chlorination (−10 to −30°)[12] gave solid sulfenyl chloride–chlorine complexes (E), which at higher temperatures (−10 to 0°) stabilized by elimination of HCl to yield α-chloro sulfenyl chlorides (F). The latter compounds were treated in CCl_4 with KI aq.,[10] liberated iodine being removed by titration with sodium thiosulfate aq. In this way di-α-chloroalkyl disulfides (G) were obtained: these could be cyclized with Na_2S to the 3,5-dialkyltrithiolanes with R = Me, Et, and i-Pr respectively. The best solvents for this final reaction step appeared to be dimethylformamide and 50% aqueous acetone. Polymerization reactions could be partly suppressed by using dilute solutions.

With the exception of the sulfenyl chloride–chlorine complexes, all intermediates could be isolated and purified by distillation, although good yields of the di-α-chloroalkyl disulfides were obtained without isolation of the intermediates. The cyclization reaction, however, has a low yield. The overall yields of the two synthetic routes to 3,5-dialkyl-1,2,4-trithiolanes are summarized in Table 1.

We were not able to synthesize unsubstituted 1,2,4-trithiolane starting with the chlorination of dimethyl disulfide. Douglas[13,14] noted the impossibility of synthesizing chloromethane sulfenyl chloride free from more highly chlorinated products, and this may be the explanation for our failure.

An attempt to synthesize 3,3,5,5-tetramethyl-1,2,4-trithiolane from diisopropyl disulfide failed. Chlorination of the disulfide yielded a product which Douglas[13]

TABLE 1. OVERALL YIELD IN THE SYNTHESIS OF 3,5-DIALKYL-1,2,4-TRITHIOLANES

Alkyl group	From aldehydes	From dialkyl disulfides
Me	4% (5%)*	21%
Et	40% (38%)*	29%
i-Pr	2·6%	57%
t-Bu	62%	not done

* Figures given by Asinger *et al.*[7].

stated to be α-chloroisopropyl sulfenyl chloride. However, upon reaction with KI the product which we had obtained underwent total decomposition.

Separation of isomeric 3,5-dialkyl-1,2,4-trithiolanes

GLC on Carbowax or Apiezon columns of compounds I–III, whether synthesized by our method or Asinger's, always revealed the presence of two components: di-t-butyltrithiolane, however, was eluted as a single peak. The two components of the trithiolanes I–III could be isolated by prep GLC. Separation could also be achieved by column chromatography over alumina with hexane or a 1:1 mixture of $CHCl_3$ and CCl_4 as eluant. Even di-t-butyltrithiolane could be separated into two components by the latter method. To facilitate discussion, the isomers with the shortest retention time on alumina will be denoted by the subscript 1.

PMR *spectral data.* The chemical shifts and coupling constants for the dialkyltrithiolanes are given in Table 2. The magnetic non-equivalence of the Me signals of the isopropyl group of compound III could be clearly seen in the 220 MHz spectrum (Fig. 1).

Assignment of the configuration by use of the NOE

From the IR, PMR, and mass spectra it is clear that the dialkyltrithiolanes exist as isomeric pairs. However, it is not possible to assign the *cis* and *trans* configurations on the basis of these spectral data alone.*

A powerful method for the precise assignments of PMR signals to particular protons or for molecular structure determinations in organic compounds has been recently developed, and is known as the intramolecular NOE.[3,4] An NOE is the change in integrated signal of proton A when a saturating r.f. field is applied at the frequency of proton B. An NOE will be observed only if the following additional conditions are met:

(1) Relaxation of the observed spin A by the (irradiated) spin B occurs by a dipole–dipole mechanism.
(2) Proton A and proton B are separated by no more than 3 Å.
(3) The compound to be studied is dissolved in a magnetically inert solvent i.e. not containing nuclei with high magnetic moments.

* The compound with both the alkyl substituents in either the equatorial or the axial positions in the envelope (C_s) conformation is called the *cis* isomer (Scheme 3).

TABLE 2. CHEMICAL SHIFTS AND COUPLING CONSTANTS OF THE 3,5-DIALKYL-1,2,4-TRITHIOLANES IN CCl_4 SOLUTION

Compound	δ (ppm)					J (Hz)				
	CH_3	$CH_3—CH_2—$	$(CH_3)_2CH—$	$(CH_3)_3C—$	$\diagdown\!\!\diagup CH$	$—\overset{\displaystyle H}{\underset{\displaystyle \vert}{C}}—CH_3$	$—\overset{\displaystyle H}{\underset{\displaystyle \vert}{C}}—CH_2—$	$—\overset{\displaystyle H}{\underset{\displaystyle \vert}{C}}—\overset{\displaystyle H}{\underset{\displaystyle \vert}{C}}—$	$—CH_2—CH_3$	$\overset{\displaystyle H}{\underset{\displaystyle \vert}{C}}—(CH_3)_2$
I_1	1·66 (d)				4·98 (q)	7·2				
I_2	1·75 (d)				4·80 (q)	7·2				
II_1		1·06 (t) 1·90* (m)			4·62 (t)		7·5		7·0	
II_2		1·12 (t) 2·05* (m)			4·56 (t)		7·5		7·0	
III_1			1·11 (d) 1·12 (d) 2·06* (m)		4·58 (d)			8·0		6·5
III_2			1·13 (d) 1·15 (d) 2·13* (m)		4·50 (d)			8·0		7·0
IV_1				1·15 (s)	4·80 (s)					
IV_2				1·13 (s)	4·60 (s)					

* Centre of multiplet

From Dreiding models we found that in the *trans* isomer, the alkyl group is 0·5–2·5 Å from the methine proton on the opposite ring carbon atom. This separation is more than 3 Å for the *cis* isomer. The distance between these groups on the same carbon atom is $\leqslant$0·5 Å for both isomers. From this consideration we may therefore expect that the methine proton in the *trans* isomer will possess a better relaxation path than in the *cis* isomer, and will consequently show a greater NOE. We can thus differentiate the *cis* from the *trans* configuration by use of the NOE. Our assignment, based on the NOE's, are listed in Table 3.

TABLE 3. ASSIGNMENT OF THE *cis* AND *trans* CONFIGURATIONS TO THE 3,5-DIALKYL-1,2,4-TRITHIOLANES BY USE OF NOE

Compound	δ Ring methine (ppm)	Percentage increase in ring methine signal upon irradiation of		Assignment
		CH_3-signal	CH_2- or >CH-signal	
I_1	4·98	21		*cis*
I_2	4·80	33		*trans*
II_1	4·60	9	10	*cis*
II_2	4·56	14	17	*trans*
III_1	4·58	31	10	*cis*
III_2	4·50	38	15	*trans*
IV_1	4·80	20[a]		*trans*
IV_2[b]	4·60	8[a]		*cis*

[a] Sample not degassed

[b] We are indebted to D. J. Frost (Unilever Research Vlaardingen) for measuring the NOE of this mixture.

Once the *cis* and *trans* configurations had been assigned we could draw the following conclusions:

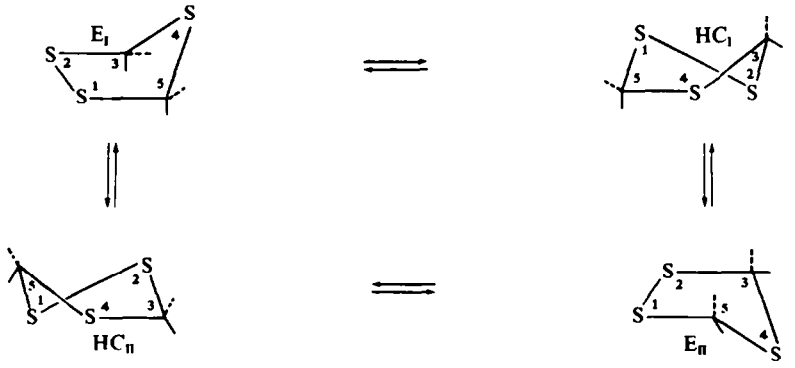
(1) The Me, Et and i-Pr groups exert a shielding effect on the opposite *cis* methine proton.

(2) The t-butyl group deshields the opposite *cis* methine proton.

Conformational analysis

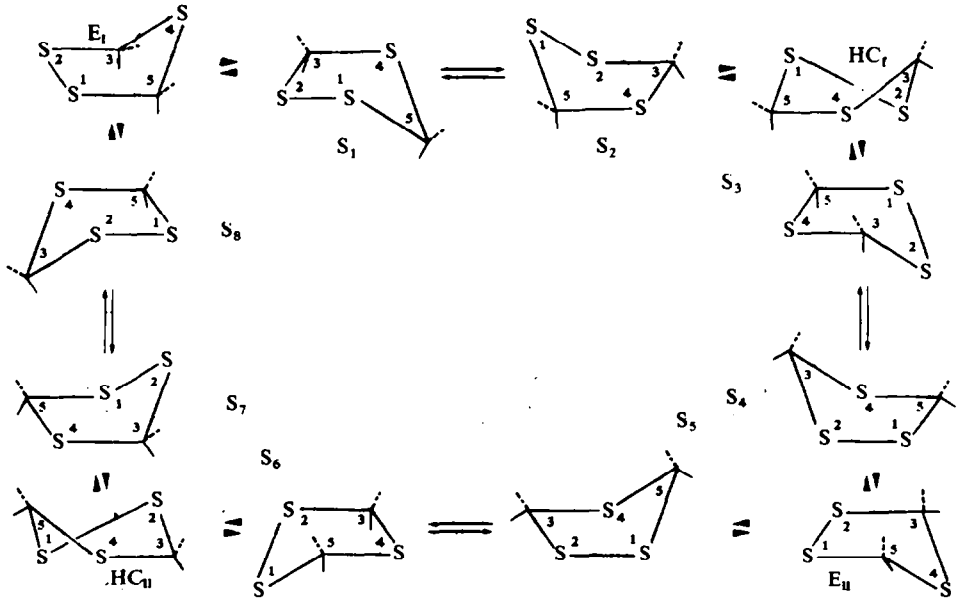
In general five-membered ring systems show low barriers for pseudorotation; this complicates the conformational analysis of such compounds.[15] Although relatively little is known about the barrier for five-membered sulfur-containing heterocyclics, we may expect that it will be low in such cases as well. The five-membered trithiolane ring can assume several conformations, two of which contain elements of symmetry *viz.* the C_2 or half-chair form (Scheme 3, HC_I and HC_{II}) and the C_s or envelope form (Scheme 3, E_I and E_{II}).

SCHEME 3. Half-chair (HC) and envelope (E) conformations of the 1,2,4-trithiolane ring.



From conformational energy calculations and electron diffraction investigations with the oxygen analogue of trithiolane, 1,2,4,-trioxolane, Náhlovska *et al.*[16] found that the C_2 form is more stable than the C_s form by 1·5–3·0 kcal/mole. On the PMR time scale the four hydrogen atoms are equivalent, which suggests a rapid interconversion between the C_2 and C_s forms. Further, these authors determined that the C_2 form for tetrahydrothiophene is more stable than the C_s form by 2·0–3·0 kcal/mole. It is therefore reasonable to assume that for the trithiolanes the C_2 form would also be the most stable conformation.

SCHEME 4. Pseudorotation sequences for the 1,2,4-trithiolane ring.



The PMR spectra of the dialkyltrithiolanes show that both the two alkyl groups and the two methine ring protons in the *cis* and *trans* isomer are mutually equivalent. This fact can be explained in three ways:

(1) The two envelope conformations (E_I and E_{II}, Scheme 3) interconvert rapidly:

$$E_I \leftrightarrows E_{II} \qquad \text{(i)}$$

(2) Both the *cis* and *trans* isomers pseudorotate by the following mechanism:

$$S_1 \leftrightarrows S_2 \leftrightarrows HC_I \leftrightarrows S_3 \leftrightarrows S_4 \qquad \text{(ii)}$$

$$S_5 \leftrightarrows S_6 \leftrightarrows HC_{II} \leftrightarrows S_7 \leftrightarrows S_8 \qquad \text{(iii)}$$

It can be seen that by this process S_2 and S_3, S_1 and S_4, S_8 and S_5, and S_7 and S_6 become equivalent (Scheme 4). There is however no reason to assume that no interconversion takes place between the HC_I and HC_{II} conformations.

(3) The *cis* and *trans* isomers are rigid conformers: the *cis* isomer exists exclusively in an envelope conformation in which the alkyl groups are both equatorial; the *trans* isomer on the contrary exists in either the HC_I or the HC_{II} conformation.

To distinguish between these possibilities we studied the temperature dependence of the PMR spectra of 1,2,4-trithiolane, 3,3,5,5-tetramethyl-1,2,4-trithiolane, and 3,5-di-t-butyl-1,2,4-trithiolane. Further we used the influence of benzene as solvent on the chemical shifts of the methine protons of the alkyltrithiolanes for the conformational analysis.

Temperature dependence of the PMR spectra of some trithiolanes. 1,2,4-Trithiolane and 3,3,5,5-tetramethyl-1,2,4-trithiolane show single resonance lines at $\delta = 4{\cdot}17$ and at $\delta = 1{\cdot}85$ ppm respectively (CCl_4). Thus we conclude that we are dealing with flexible conformations. It is more difficult to answer the question whether sequence (i) or sequences (ii) and (iii) are responsible for the magnetic equivalence of the four hydrogen atoms and four Me groups respectively. All three sequences are possible for 1,2,4-trithiolane. The singlet at $\delta = 4{\cdot}17$ ppm (CS_2) in the spectrum recorded at 30° did not change when the temperature was lowered to $-117°$, which suggests a low energy barrier for pseudorotation.[17]

For 3,3,5,5-tetramethyl-1,2,4-trithiolane a noticeable broadening of about 2 Hz was observed for the Me signal at $-155°$, which corresponds to an energy barrier for pseudorotation of less than 6 kcal/mole. It is not unreasonable to assume that sequence (ii) or (iii) holds for this compound on account of the steric hindrance of the Me groups in the envelope conformation.

The PMR spectrum of a mixture of *cis* and *trans* di-t-butyl-1,2,4-trithiolane did not change when the temperature was lowered to $-155°$.

Summarizing, we conclude that all the dialkyltrithiolanes are flexible conformers with an energy barrier for pseudorotation of less than 6 kcal/mole. Depending on the substituents, some conformations will be relatively more abundant than others, e.g. for the *cis* dialkyltrithiolanes we may expect that conformations in which the alkyl groups are situated in equatorial or pseudo-equatorial positions will be favoured. An indication for this supposition was found in the ASIS of the PMR spectra of these compounds.

TABLE 4. ASIS OF THE METHINE-RING PROTONS OF 3,5-DIALKYL-1,2,4-TRITHIOLANES [CONCENTRATIONS ≤ 5% (v/v)]

Compound	δ (ppm) CCl_4	δ (ppm) C_6D_6	$\Delta^{CCl_4}_{C_6D_6}$ (ppm)
I_1	4·98	4·58	0·40
I_2	4·80	4·52	0·28
II_1	4·62	4·34	0·28
II_2	4·56	4·41	0·15
III_1	4·58	4·41	0·17
III_2	4·50	4·41	0·09
IV_1	4·80	4·80	—
IV_2	4·60	4·60	—

ASIS of the PMR spectra. Table 4 contains data for the aromatic solvent induced shifts of the methine protons of the 3,5-dialkyl-1,2,4-trithiolanes.

The non-similarity of solvent shifts for the various dialkyltrithiolanes provided support for the hypothesis that the dominant conformation is dependent on the nature of the substituent.[5]

CONCLUSIONS

(1) Dialkyltrithiolanes exist as two configurational isomers.
(2) By use of the Nuclear Overhauser Effect the *cis* and *trans* configurations could be unequivocally assigned.
(3) The dialkyltrithiolanes exhibit pseudorotation and the relative abundance of each conformer is dependent on the nature of the substituent. The barrier for pseudorotation was estimated to be smaller than 6 kcal/mole.

EXPERIMENTAL

An AEI MS-9 instrument was used for the mass spectrometric analysis. Compounds were introduced into the ion source *via* the heated inlet system. IR spectra were recorded on a Perkin–Elmer 225 spectrometer using a Barnes ultramicro cavity cell. The PMR spectra were recorded on a Jeol C-60HL spectrometer, TMS as internal standard. Solvents were CCl_4, C_6D_6, CS_2, and CF_2Cl_2, the latter only for low temperature measurements.

NOE experiments. Spectra were recorded on a Jeol C-60HL spectrometer using the frequency-sweep mode. The second r.f. field was obtained by using a Jeol JNM-SD-50 Homo-Nuclear Spin Decoupler. Spectra were recorded in CS_2 solution; solutions were carefully degassed by three freeze-pump-thaw cycles, and sample tubes were sealed under a N_2 atmosphere; concentrations varied between 5 and 10% (v/v), CH_2Cl_2 ($\leq 5\%$) was added as internal reference. All values reported for NOE's are the average of at least three determinations. Each determination consisted of running five integrals (sweep speed: 1·8 Hz/sec.) with the oscillator tuned to the desired frequency, and five integrals with the oscillator tuned to a frequency well away from any proton absorption ($\geq$100 Hz). The frequency and the strength of the irradiation field were optimized to give a maximum area increase. After each area had been recorded the system was allowed to return to equilibrium by waiting from 2 to 5 min, depending on the proton being observed.

GLC separation of isomers. Analytical GLC was performed with an F & M model 5750 instrument. The 3 m × 2 mm column was packed with 10% Apiezon L and 1% Carbowax 20 M on Diatoport S, and was temperature programmed from 100–200° at 4°/min. The effluent was passed through a flame-ionization detector operating at 220°. The carrier gas (N_2) flow rate was 25 ml/min at a column temperature of 100°.

A Hupe APG 402 (modified by fitting of an all-glass system) was used for prep GLC. The 6 m × 10 mm column was packed with 10% Carbowax 20 M on 60–80 mesh Diatoport S, and was operated at a temperature of 150°. The carrier gas (N_2) input pressure was 1·4 atmospheres.

Column chromatographic separation of isomers. Separation of the isomers of 3,5-diethyl- and 3,5-diisopropyl-1,2,4-trithiolane was achieved on a 65 × 1·5 cm alumina column (Woelm neutral, activity grade I) with a 1:1 (v/v) mixture of $CHCl_3$ and CCl_4 as eluant. Di-t-butyltrithiolane isomers could be separated on a 15 × 1·5 cm alumina column with hexane as eluant.

Synthesis of 3,5-dialkyl-1,2,4-trithiolane from dialkyl disulfides. 3,5-Dimethyl-1,2,4-trithiolane. A solution of 33 g of diethyl disulfide (0·27 mole) in 75 ml CCl_4 was cooled in an ice-salt bath to − 20°. 57·5 g of chlorine (0·81 mole) was slowly introduced into the vessel. At the end of the reaction, the mixture was allowed to warm to room temperature. When HCl evolution stopped, solvent was evaporated. Distillation of the product at low pressure gave 45 g of α-chloroethyl sulfenyl chloride (64%). b.p. 42°/30 mm (Lit.[9] b.p. 38°/27 mm.).

This chloro compound (0·34 mole) was dissolved in 300 ml CCl_4. To the stirred solution was added at room temp 57 g of KI (0·34 mole) in water (300 ml). The mixture was stirred for 15 min and the liberated iodine removed by titration with sodium thiosulfate aq. The organic layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of solvent gave 26 g of di-α-chloroethyl disulfide (79%).

This product was cyclized, without further purification, by dissolving in 500 ml of DMF to which 32·7 g of $Na_2S.9H_2O$ (0·14 mole) was added. The reaction was complete after stirring for two hr at room temp. The product was extracted with light petroleum: this solution was washed with water, and dried ($MgSO_4$). Evaporation of solvent left 16 g of red oil. Distillation at low pressure yielded 8·7 g of 3,5-dimethyl-1,2,4-trithiolane (21% overall). b.p. 43–45°/0·7 mm; n_D^{20} 1·5925 (Lit.[7] b.p. 38°/0·3 mm; n_D^{20} 1·597).

IR. I_1 2980, 2965, 2920, 2890, 2860, 2800, 1440 sh, 1430, 1370, 1261 sh, 1257, 1187, 1160, 1150 sh, 1050, 1034, 1029, 972, 710 sh, 695, 670, 630, 620, 588, 520, 508, and 438 cm^{-1}.

I_2 2980, 2970 sh, 2925, 2890, 2860, 2810, 1450 sh, 1440, 1370, 1260, 1180, 1050, 1038, 972, 705, 669, 630, 605, 522, and 440 cm^{-1}.

Mass spectra.* I_1 154(14), 152(100), 137(1), 94(4), 93(4), 92(40), 91(1), 90(1), 89(3), 88(35), 87(10), 85(1), 83(1), 77(1), 76(5), 73(4), 66(3), 65(1), 64(30), 62(2), 61(10), 60(40), 59(57), 58(18), 57(8), 56(1), 55(16), 54(4), 53(1), 47(2), 46(2), 45(30), 44(1), and 41(1).

I_2 154(13), 152(100), 137(1), 94(4), 93(4), 92(44), 91(1), 90(1), 89(2), 88(36), 87(10), 85(1), 83(1), 77(1), 76(4), 73(3), 66(3), 65(1), 64(29), 62(1), 61(8), 60(36), 59(52), 58(16), 57(7), 56(1), 55(13), 54(4), 53(1), 47(2), 46(2), 45(30), 44(1), and 41(1).

3,5-*Diethyl*-1,2,4-*trithiolane*. This compound was synthesized according to the procedure described for the dimethyl homologue. A solution of 100 g of di-n-propyl disulfide (0·67 moles) was treated at − 25° with 142 g chlorine (2 mole) to give 111 g of α-chloropropyl sulfenyl chloride, b.p. 51°/22 mm. (Lit.[13] b.p. 62–64°/27 mm). Treatment of this product with an equivalent amount of KI aq yielded 101 g of di-α-chloropropyl disulfide. After work-up, the di-α-chloro compound was immediately cyclized with Na_2S giving 35·5 g of 3,5-diethyl-1,2,4-trithiolane (29%), b.p. 73–74° 0·5 mm; n_D^{20} 1·5659. (Lit.[7] b.p. 77°/1 mm n_D^{20} 1·567).

IR. II_1 2970, 2960, 2950, 2920, 2900, 2860, 2850, 1455, 1452, 1445, 1435, 1388, 1373, 1332, 1324, 1280, 1219, 1180, 1156 sh, 1152, 1143 sh, 1110, 1082, 1059, 1027, 998, 948, 900, 880, 805, 742, 720, 662, 640 sh, 632, 622, 519, 502, 485, and 432 cm^{-1}.

II_2 2970, 2960, 2930, 2918, 2900, 2865, 2850, 1460, 1440, 1435, 1380, 1375, 1332, 1326 sh, 1285, 1280, 1220, 1172, 1085, 1060, 1035, 1028, 950, 900, 880, 810, 800 sh, 767 sh, 752 sh, 732 sh, 720 sh, 662, 642, 618, 522, and 440 cm^{-1}.

Mass spectra: II_1 182(3), 180(26), 151(1), 118(1), 116(12), 115(10), 112(1), 111(2), 108(1), 107(1), 106(18), 101(2), 99(1), 97(1), 91(1), 88(1), 87(4), 85(3), 81(1), 78(2), 77(1), 76(4), 75(7), 74(80), 73(25), 72(3), 71(7), 70(1), 69(5), 68(1), 67(1), 66(1), 64(9), 61(1), 60(1), 59(18), 58(11), 57(4), 55(3), 49(1), 48(1), 46(10), 48(20), 45(66), 44(6), 43(1), 42(5), and 41(100).

II_2 182(3), 180(20), 151(1), 118(1), 116(10), 115(8), 112(2), 111(3), 108(1), 107(1), 106(15), 101(2), 99(1), 97(1), 91(1), 88(1), 87(3), 85(1), 81(1), 78(2), 77(1), 76(6), 75(6), 74(78), 73(22), 72(4), 71(8), 70(1), 69(6), 68(1), 67(1), 66(1), 64(8), 61(1), 60(2), 59(16), 58(11), 57(4), 55(3), 49(5), 48(1), 47(22), 46(20), 45(67), 44(4), 43(1), 42(4), and 41(100).

3,5-*Diisopropyl*-1,2,4-*trithiolane*. 24·8 g of diisobutyl disulfide (0·14 mole) was dissolved in 70 ml CCl_4.

* The underlined figures are the parent and base peaks.

The solution was cooled to −30°, and treated with 9·9 g of chlorine (0·14 mole). The temperature in the vessel was raised to −10°, and another 19·8 g chlorine (0·28 mole) introduced. The mixture was stirred for one hr at room temp and the liberated HCl stripped off under vacuum. 400 ml CCl_4 and 100 ml water were added to the mixture. KI (65 g) in water (250 ml) was added dropwise, the liberated iodine being removed by titration with sodium thiosulfate aq. Separation of the organic layer, washing with water, drying ($MgSO_4$) and evaporation, gave crude di-α-chloroisobutyl disulfide (41 g). The disulfide, without further purification, was dissolved in 250 ml of acetone. This solution was added dropwise, simultaneously with a solution of 41·7 g of $Na_2S.9H_2O$ in water (250 ml), to 500 ml of 50% aqueous acetone. After stirring for 90 min at room temp, acetone was evaporated. The resulting emulsion was extracted with light petroleum, the extract washed with water and dried ($MgSO_4$). Solvent evaporation and distillation of residue gave 16·5 g of 3,5-diisopropyl-1,2,4-trithiolane (57%). b.p. 80–82°/0·7 mm; n_D^{20} 1·5457.

IR. III_1 2978 sh, 2960, 2930, 2910, 2890, 2870, 1465, 1458, 1385, 1383, 1368, 1365, 1328, 1310, 1220, 1182, 1176, 1160, 1098, 1072, 960, 948, 935, 925 sh, 840, 820, 729, 698, 673, and 512 cm^{-1}.

III_2 2975 sh, 2960, 2930, 2910, 2900 sh, 2870, 1465, 1458, 1386, 1382, 1369, 1365, 1325, 1308, 1224, 1180 sh, 1172, 1160, 1110 sh, 1100, 1072, 960 sh, 948, 935, 925 sh, 839, 820, 735, 705, 695, 668, 520, and 515 cm^{-1}.

Mass spectra. III_1 210(2), 208(13), 165(3), 152(2), 145(1), 144(2), 143(13), 120(4), 109(5), 102(1), 101(2), 90(4), 89(8), 88(73), 87(20), 86(2), 85(3), 76(1), 75(1), 74(1), 73(21), 72(2), 71(9), 69(4), 64(1), 61(3), 60(15), 59(24), 58(4), 57(3), 56(13), 55(100), 54(11), 53(12), 52(1), 51(3), 50(2), 49(1), 48(2), 47(15), 46(12), 45(57), 43(19), 42(3), and 41(19).

III_2 210(2), 208(15), 174(1), 165(3), 152(2), 145(1), 144(3), 143(14), 142(2), 120(5), 111(1), 109(5), 102(1), 101(2), 99(2), 91(1), 90(4), 89(9), 88(73), 87(23), 86(3), 85(4), 83(1), 76(1), 75(1), 74(1), 73(20), 72(2), 71(9), 70(1), 69(5), 67(1), 64(1), 61(3), 60(14), 59(24), 58(4), 57(3), 56(14), 55(100), 54(16), 53(21), 52(1), 51(3), 50(2), 49(1), 48(2), 47(15), 46(10), 45(53), 43(18), 42(3), and 41(31).

Synthesis of 3,5-*dialkyl*-1,2,4-*trithiolanes from aldehydes: the route of Asinger* et al.[7] The reactions were performed in a three-necked flask fitted with a stirrer, gas inlet, and dropping funnel. During the procedure the flask atmosphere was kept saturated with H_2S. One equivalent of diisobutylamine was placed in the flask and cooled with stirring to 0 to 5° by immersing in an ice-salt bath. When a semi-solid mass of the amine-hydrogen sulfide salt was obtained, one equivalent of aldehyde was added at such a rate that the temperature remained below 5°. A half equivalent of sulfur was added in small portions, after which the mixture was stirred for one hr at 0–5°, then allowed to come to room temp. Stirring for 10–24 hr at room temp resulted in an amber to red-brown oil. The oil was acidified with 2 N AcOH aq and ether extracted. The ether solution was washed with water and, after phase separation, dried ($MgSO_4$). Evaporation of solvent gave light yellow oil, which on low pressure distillation yielded the trithiolane.

3,5-*Di-t-butyl*-1,2,4-*trithiolane*. The yellow oil obtained after reaction of 129 g of diisobutylamine (1 mole) with 86 g of 2,2-dimethylpropionaldehyde (1 mole) and 16 g of sulfur (0·5 mole) was worked up as above. Distillation at low pressure yielded 73 g of product (62%). b.p. 97–98°/0·5 mm; n_D^{23} 1·5334.

IR. IV_1 2965, 2955, 2940, 2930, 2900, 2862, 1473, 1460, 1392, 1389 sh, 1366, 1361, 1283, 1275, 1260, 1229, 1177, 1162, 1022, 935, 897, 799, 789, 769, 748, 692, and 495 cm^{-1}.

IV_2 2960, 2928, 2900, 2860, 1473, 1460, 1394, 1389, 1365, 1360, 1287, 1273, 1228, 1168, 1160 sh, 1022, 935, 897, 795, 772, 750, 705, 680, and 502 cm^{-1}.

Mass spectra. IV_1 238(5), 236(35), 206(2), 181(6), 180(5), 179(41), 173(1), 171(4), 168(1), 167(1), 166(5), 159(1), 157(2), 151(1), 140(3), 136(1), 135(1), 134(6), 133(1), 123(1), 122(1), 119(2), 117(1), 116(1), 115(5), 111(5), 110(2), 109(35), 105(1), 104(4), 103(17), 102(43), 101(39), 100(1), 99(1), 69(100), 68(4), 67(9), 65(2), 64(2), 62(1), 61(5), 60(6), 59(45), 58(4), 57(66), 56(10), 55(35), 54(3), 53(19), 52(1), 51(3), 50(2), 49(1), 48(1), 47(14), 46(4), 45(43), 44(10), 43(33), 42(14), and 41(97).

IV_2 238(6), 236(46), 221(3), 181(8), 180(8), 179(55), 172(3), 171(5), 167(8), 151(2), 135(2), 134(8), 119(3), 117(3), 116(2), 115(7), 111(5), 110(3), 109(33), 105(2), 104(4), 103(19), 102(64), 101(34), 89(2), 88(3), 87(22), 86(3), 85(4), 82(2), 79(2), 76(3), 75(3), 74(30), 73(3), 72(2), 71(6), 70(62), 69(100), 68(6), 67(9), 65(2), 64(2), 62(2), 61(5), 60(7), 59(56), 58(5), 57(61), 56(8), 55(34), 54(3), 53(22), 52(2), 51(4), 50(3), 49(2), 48(2), 47(12), 46(5), 45(48), 43(9), 42(11), and 41(89).

3,3,5,5-*Tetramethyl*-1,2,4-*trithiolane*. Reaction of 104 g of diisobutylamine (0·8 mole) with 58 g of acetone (1 mole) and 16 g of sulfur (0·5 mole) produced a yellow oil, which on distillation yielded 52·6 g of product (58·5%), b.p. 44°/1 mm; n_D^{20} 1·5462. (Lit.[7] b.p. 75°/10 mm; n_D^{20} 1·546).

IR. 2980, 2960, 2920, 2890, 2850, 1455, 1448 sh, 1430, 1378, 1360, 1150, 1145 sh, 1120, 1085, 940, 890, 690, 642, 550, and 405 cm^{-1}.

Mass spectrum. 182(3), 180(22), 116(6), 113(1), 112(1), 111(2), 108(4), 107(4), 106(13), 101(1), 97(1), 83(2), 78(1), 77(2), 76(7), 75(43), 74(82), 73(6), 72(1), 71(4), 69(4), 68(2), 66(4), 64(4), 61(8), 60(7), 59(100), 58(17), 57(5), 55(1), 47(6), 46(4), 45(22), 44(2), 43(3), 42(5), and 41(55).

1,2,4-*Trithiolane*. 1,2,4-Trithiolane was synthesized according to the procedure of Morita *et al.*[18]. To a solution of $Na_2S.9H_2O$ (300 g) and 60 g of sulfur in 1 litre of water was added CH_2Cl_2 (1 litre). The mixture was stirred vigorously overnight. The organic layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of solvent followed by distillation resulted in 10 g of 1,2,4-trithiolane. b.p. 102–103°/10 mm. (Lit.[18] 78–79°/3 mm).

Mass spectrum. 126(1), 124(95), 80(33), 79(10), 78(99), 77(4), 76(4), 74(1), 73(2), 71(1), 69(1), 64(4), 62(1), 61(5), 60(26), 57(5), 56(1), 55(1), 49(1), 48(3), 47(8), 46(62), 45(100), 43(3), 42(1), and 41(3).

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REFERENCES

[1] H. W. Brinkman, H. Copier, J. J. M. de Leuw and S. B. Tjan, *J. Agr. Food Chem.* **20**, 177 (1972)
[2] S. S. Chang, C. Hirai, B. R. Reddy, K. O. Herz, A. Kato and G. Sipma, *Chem. Ind. (London)* 1639(1968)
[3] G. Moreau, *Bull. Soc. Chim. France* 1770 (1969)
[4] P. D. Kennewell, *J. Chem. Educ.* **47**, 278 (1970)
[5] P. Laszlo, *Progress in NMR Spectroscopy* (Edited by J. W. Emsley, J. Feeney and L. H. Sutcliffe) p. 231, Vol. 3, Pergamon Press (1967)
[6] D. S. Breslow and H. Skolnic, *The Chemistry of Heterocyclic Compounds* (Edited by A. Weissberger) p. 67, Vol. 21 part 1, Wiley Interscience (1966)
[7] F. Asinger, M. Thiel and G. Lipfert, *Liebigs Ann. Chem.* **627**, 195 (1959)
[8] H. Brintzinger, K. Pfannstiel, H. Koddebusch and K. E. Kling, *Chem. Ber.* **83**, 87 (1950)
[9] H. Brintzinger and H. Ellwanger, *Ibid.* **87**, 300 (1954)
[10] H. Brintzinger and H. Schmall, *Ibid.* **87**, 314 (1954)
[11] H. Brintzinger and M. Langheck, *Ibid.* **87**, 325 (1954)
[12] I. B. Douglas, *J. Am. Chem. Soc.* **74**, 5770 (1952)
[13] I. B. Douglas and F. T. Martin, *J. Org. Chem.* **15**, 795 (1950)
[14] I. B. Douglas, F. T. Martin and R. Addor, *Ibid.* **16**, 1297 (1951)
[15] G. E. Wilson, Jr., Muh Guey Huang and F. A. Bovey, *J. Am. Chem. Soc.* **92**, 5907 (1970)
[16] Z. Náhlovska, B. Náhloský and H. M. Seip, *Acta Chem. Scand.* **23**, 3534 (1969)
[17] R. M. Moriarty, N. Ishibe, M. Kayser, K. C. Ramey and H. J. Gister Jr., *Tetrahedron Letters* 4883 (1969)
[18] K. Morita and S. Kobayashi, *Chem. Pharm. Bull.* **15**, 988 (1967)