Notes

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Organosulfur Chemistry. II. Use of Dimethyl Sulfoxide; a Facile Synthesis of Cyclic Sulfides[1)]

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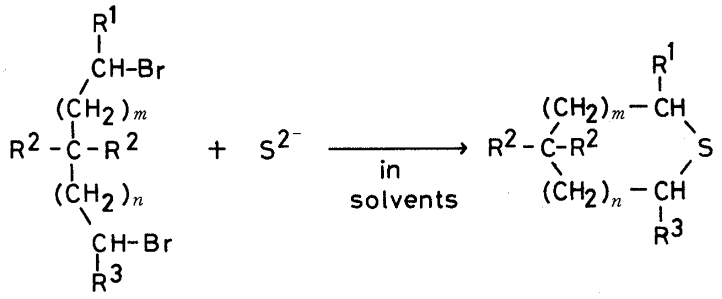
A versatile and short-reaction-time synthesis of twelve four-, five- and six-membered thiacycloalkanes (II_{a-l}) from the appropriate α,ω-dibromoalkanes (I_{a-l}) has been developed. Technical-grade dimethyl sulfoxide was proved to be by far the best for this cyclization. The pronounced effect for ring formation was recognized to be in order of five-membered ring (thiolanes) > six-membered ring (thianes) > four-membered ring (thietanes). Startling were 2-methylthiolane (II_f) and 2,5-dimethylthiolane (II_g; *cis,trans* mixture), both obtained in high yields although α-methyl- and α,α'-dimethyl substitution in general showing a remarkable retardation for cyclization. On the other hand, in both 3,3-dimethylthietane (II_d) and 4,4-dimethylthiane (II_l) cyclization was much more efficient than other counterparts in each series, which is referred to as the *gem*-dimethyl effect.

Keywords——thiacycloalkane; thietane; thiolane; thiane; dimethyl sulfoxide; cyclization; α,ω-dibromoalkane; sodium sulfide nonahydrate; refractive index

As part of a program in our laboratory on the chemistry of α,β-unsaturated cyclic sulfoxides, samples of some thietanes, thiolanes and thianes were required. However, none of those have been still satisfactory so far, although many synthetic methods on preparation of organic cyclic sulfides have appeared in the literature. This is because the major drawbacks lie in the followings; low yields, long reaction periods, readily inaccessible laboratory materials, tedious purification steps and so forth. Therefore we need an efficacious, short-reaction-time and large-scale synthesis, together with ease of work-up and high purity of the parent sulfides.

Since in 1916, thietane (II_a) was first prepared by a Russian chemist using 1,3-dibromopropane (I_a) with sodium sulfide in only 11% yield,[2a)] four other groups[2b−e)] have reported on the same compound; however, the yields have been seldom or never over 50%



Ia-l IIa-l

R^{1-3} = -H and -CH_3

$m = n = 0$; $m = 0, n = 1$; $m = n = 1$

Chart 1

except in the case of 3,3-disubstituted thietanes.[3,4] Thiolane (II_e) and thiane (II_i), both were produced in moderate yields when the reactions of 1,4-diiodobutane with potassium sulfide;[5] 1,4-dibromobutane (I_e)[2a,6] or 1,4-dichlorobutane[7,8] with sodium sulfide and of 1,5-dibromopentane (I_i) with sodium sulfide nonahydrate[6] were similarly performed at reflux temperature in aqueous alcoholic solution as illustrated in Chart 1, except in refs. 7 and 8.

It is likely that the majority responsible for such disadvantages are due to 1) rather high dilution condition, 2) base-catalyzed side reactions (the formation of polymeric sulfides in particular for a long-period reaction) and 3) an appreciable loss of the products as azeotropes with extracting solvents in a purification step and any solvent system other than aqueous alcohol, *N*,*N*-dimethylformamide (DMF) or ethylene glycol has been little investigated. Accordingly, using 1,5-dibromopentane (I_i) and 1 eq of sodium sulfide nonahydrate as reactants, a study was undertaken to determine the scope of this cyclization, varying both solvent and temperature. The results are summarized in Table I.

TABLE I. Preparation of Thiacyclohexane, II_i from 1,5-Dibromopentane, I_i with $Na_2S \cdot 9H_2O$ under Various Conditions[a]

	Solvent system										
	C_6H_6/H_2O[b]	THF/H_2O[b]	$EtOH/H_2O$[b]	H_2O	DMF	DMSO			HMPA		
Temp. (°C)	100	90	110	120	150	100	150	180	100	150	200
Time required for completion[c] (min)	300	240	100	150	60	40	20	20	70	40	30
Yield (%)[d]	30	43	55	68	62	75	80	65	60	55	33

a) Combination of 0.25 mol of each reactant and 100 ml of each solvent. *b*) Contained 50 ml of water as co-solvent for $Na_2S \cdot 9H_2O$. *c*) Checked by TLC (Merck, Silica gel 60 F_{254}, *n*-pentane) on disappearance of dibromide. *d*) Isolated after distillation.

In refluxing benzene–water mixture, reaction was complete in 300 min and gave 30% of pure thiane (II_i). The same reactions performed in tetrahydrofuran–water at 90 °C and in ethanol–water at 110 °C went to completion in 240 and 100 min to afford 43 and 55% yields of product, respectively. Furthermore, using DMF or hexamethylphosphoramide (HMPA) as solvent at higher temperatures, namely 150 and 200 °C, cyclization proceeded much faster but gave almost the same or a little bit better yields, 62, 55 and 33%, respectively. In all cases described here, prolonged or higher-temperature heating resulted in a lower yield, mainly due to considerable formation of polymeric products. In marked contrast, attempts to use dimethyl sulfoxide (DMSO)[9] as solvent were very successful, namely the cyclization at 150 °C was complete in only 20 min and the desired product was steam-distilled and obtained pure in 80% isolated yield after a usual work-up. Thus the procedure using DMSO as a solvent at 150 °C was applied to various kinds of α,ω-dibromoalkanes (I_{a-l}) with the results shown in Table II.

It has been found that the ease of ring formation for thiacycloalkanes is as follows; 5-membered > 6-membered > 4-membered ring as expected owing to ring strain as seen in Table II. Comparing in each series it is surprising that cyclization to both α-methyl- and α,α'-dimethyl-substituted thiolanes (II_f and II_g) in DMSO is by no means inferior but rather proceeds at least well though, in general, substitution on an α-carbon lowers the yields obtained from this type of cyclization, which presumably involves sulfide ion nucleophilic substitution at a saturated carbon atom as an S_N2 reaction. Therefore using DMSO seems to be the best approach to the synthesis of a diversity of 4-, 5- and 6-membered cyclic thiaalkanes bearing α- and/or α'-substituents, even though the yields leave much to be desired, especially in case of thietanes (II_a, II_b and II_c). Moreover, for 3,3-dimethylthietane (II_d), 3,3-

Table II. Physical Properties of Cyclic Sulfides,

Product	R^1	R^2	R^3	Yield (%)[b]	Reaction time (min)	bp (°C/760 Torr)[c] Found	Lit.
Thietanes ($m=n=0$)							
II_a	H	H	H	65.0	20	96	94—95[10]
II_b	CH_3	H	H	60.1	15	107	103—105[10]
II_c[e]	CH_3	H	CH_3	58.0	20	109—110	112.5—113.5[2a] (757 Torr)
II_d	H	CH_3	H	88.6	15	119—120	116[9]
Thiolanes ($m=0$, $n=1$)							
II_e	H	H	H	95.0	20	122—124	121.2[6]
II_f	CH_3	H	H	94.1	15	132—133	132.4[6]
II_g[e]	CH_3	H	CH_3	94.8	30	145—146	—
II_h	H	CH_3	H	95.0	15	150	—
Thianes ($m=n=1$)							
II_i	H	H	H	80.0	20	141—142	141.6[6]
II_j	CH_3	H	H	69.0	20	154	55.0[6] (26 Torr)
II_k[e]	CH_3	H	CH_3	65.0	30	168	—
II_l	H	CH_3	H	92.3	20	57—58 (15 Torr)	—

a) Refer to Chart 1. *b*) Isolated values after distillation. *c*) Uncorrected. *d*) For the parent compounds, II_a, II_e and II_i, tendency,[11] the complexity of signals (s, singlet; d, doublet; t, triplet; q, quartet) and $^1J_{C-H}$ (Hz) in the nuclear Overhauser effect mode.

dimethylthiolane (II_h) and 4,4-dimethylthiane (II_l) the "*gem*-dimethyl effect"[12] seemed to be in operation.

In conclusion, we believe that the simplicity, no special devices usually employed for the slow addition of the reagents into the reaction medium due to high dilution and significantly short reaction time of the method, together with ease of work-up and high purity and better yields of the products, combine to provide a useful alternative effecting such transformations.

Experimental

All melting points (a hot-stage microscope, Yanaco MP) and boiling points are uncorrected. Infrared (IR) spectra were recorded neat with a Hitachi IR-215 spectrometer. Low- or high-resolution mass spectra (MS) were determined with a Shimadzu-LKB 9000-B or a JEOL JMS-DX 300 mass spectrometer. ^{1}H- and ^{13}C-NMR were taken in $CDCl_3$ solution at 22±0.1 °C on a JEOL JNM-PMX 60 and on a JEOL JNM-FX 100 (25 MHz, pulse width 3 μs, repetition time 3 s, frequency range 5000 Hz and data points 8192), respectively. The chemical shifts are given in ppm relative to internal tetramethylsilane and coupling constants (J) in Hz. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Refractive indexes, n_D, were obtained at 20 °C on an Atago refractometer model NAR-1. Among the starting materials, the non-substituted dibromides (I_a, I_e and I_i) were purchased from Kanto Chemical Company Ltd. and were distilled briefly before use.

5-Oxohexanoic Acid——Following the procedure reported by Linstead and Rydon[13] with a slight modification, ethyl acetoacetate and methyl 3-chloropropionate, both were condensed in the presence of metallic sodium to afford 1-ethyl 5-methyl 2-acetylglutarate in 55.6%, bp 112—114 °C (1.5 Torr), n_D^{20} 1.4422. Next, a mixture of an ester and

II$_{a-1}$ Obtained from α,ω-Dibromoalkanes I$_{a-1}$$^{a)}$

n_D^{20} Found	n_D^{20} Lit.	^{13}C-NMR Spectral Data in CDCl$_3$$^{d)}$
1.5097	1.5096$^{9)}$	25.34 (C$_2$) 27.38 (C$_3$) (t, 146.50) (t, 136.73)
1.4896	1.4881$^{9)}$	37.43 (C$_2$) 35.57 (C$_3$) 21.05 (C$_4$) 25.05(CH$_3$) (d, 146.48) (t, 124.51) (t, 146.48) (q, 123.29)
1.4715	1.4502$^{2a)}$	32.41 (C$_2$ or C$_4$) 42.49 (C$_3$) 25.10 (CH$_3$) 32.60 (d, 142.83) 44.10 (t, 133.06) 25.39 (q, 126.96)
1.4730	1.4733$^{9)}$	38.11 (C$_2$) 41.18 (C$_3$) 29.58 (CH$_3$) (t, 145.26) (s) (q, 125.73)
1.5045	1.5047$^{6)}$	31.33 (C$_2$) 30.75 (C$_3$) (t, 137.95) (t, 128.21)
1.4912	1.4909$^{6)}$	42.98 (C$_2$) 39.23 (C$_3$) 30.12 (C$_4$) 32.60 (C$_5$) 22.51 (CH$_3$) (d, 140.38) (t, 129.39) (t, 129.39) (t, 140.38) (q, 129.39)
1.4786	—	44.25 (C$_2$ or C$_5$) 37.86 (C$_3$ or C$_4$) 22.66 (CH$_3$) 44.34 (d, 141.60) 39.47 (t, 126.95) 23.58 (q, 125.73)
1.4846	—	30.11 (C$_2$) 42.98 (C$_3$) 44.05 (C$_4$) 44.05 (C$_5$) 26.07 (CH$_3$) (t, 141.60) (s) (t, 124.51) (t, 136.72) (q, 125.73)
1.5066	1.5067$^{6)}$	28.80 (C$_2$) 27.48 (C$_3$) 26.22 (C$_4$) (t, 135.57) (t, 125.70) (t, 128.20)
1.4908	1.4905$^{6)}$	37.28 (C$_2$) 36.55 (C$_3$) 26.31 (C$_4$) 26.85 (C$_5$) 29.29 (C$_6$) 21.83 (CH$_3$) (d, 137.94) (t, 128.17) (t, 124.51) (t, 124.51) (t, 142.82) (q, 125.73)
1.4819	—	33.41 (C$_2$ or C$_6$) 34.82 (C$_3$ or C$_5$) 20.78 (C$_4$) 21.43 (CH$_3$) 38.34 (d, 154.42) 36.05 (t, 127.95) 27.07 (t, 126.48) 21.72 (q, 127.95)
1.4902	—	24.12 (C$_2$) 39.61 (C$_3$) 29.04 (C$_4$) 28.16 (CH$_3$) (t, 136.72) (t, 126.95) (s) (q, 124.51)

see also *Chem. Pharm. Bull.*, **30**, 4189 (1982). Assignments (ppm from internal tetramethylsilane) were performed based on the general
e) Mixture (*ca.* 1/1) of *cis*- and *trans*-components by ^{1}H-NMR.

35% aq. HCl was refluxed for 6 h to give viscous pale yellow 5-oxohexanoic acid in 85.9%, bp 123 °C (1.5 Torr), n_D^{20} 1.4462. ^{13}C-NMR δ: 18.32 (t, C$_3$), 29.47 (q, C$_6$), 32.58 (t, C$_2$), 41.98 (t, C$_4$), 178.25 (s, C$_1$), 208.60 (s, C$_5$). They report bp 130—131 °C (2.5 Torr).[13]

Heptane-2,6-dione——This substance was prepared by a modification of the literature method.[14b] A dry ether solution of 5,5-ethylenedioxyhexanoic acid, prepared from 5-oxohexanoic acid in three steps was allowed to react with fresh methyl lithium in ether at 5—10 °C for 16.5 h under argon to provide 6,6-ethylenedioxyheptan-2-one in 96.3%, bp 114—116 °C (10 Torr), n_D^{20} 1.4451. Deketalization of the ketal ketone was accomplished with 60% HClO$_4$ in ether at room temperature for 1 h to give the expected compound in 81.9%, bp 95—96 °C (10 Torr), mp 30 °C (lit.[14a] mp 34 °C), colorless leaflets (from *n*-pentane), n_D^{30} 1.4279. IR νcm^{-1}: 1710 (–$\underline{\text{C}}$OCH$_3$). ^{13}C-NMR δ: 17.44 (t, C$_4$), 29.65 (q, C$_1$ and C$_7$), 42.21 (t, C$_3$ and C$_5$), 208.00 (s, C$_2$ and C$_6$). MS *m/e*: 128 ($\overline{M^+}$). High-resolution MS *m/e*: Calcd for $C_7H_{12}O_2$: 128.0842. Found: 128.0840.

4,4-Dimethylthiane: A Representative——(1) Reduction: To a cold suspension of LiAlH$_4$ (7.6 g, 0.2 mol) in dry THF (350 ml) was dropwise added a THF (50 ml) solution of 3,3-dimethylglutaric acid (16.0 g 0.1 mol) in a period of 45 min and then the whole mixture was refluxed for 5 h with stirring. After cooling, H$_2$O (7.6 ml), 15% aq. NaOH (7.6 ml) and H$_2$O (22.8 ml) were carefully added in succession to this suspension. Removal of the solvent followed by distillation *in vacuo* of the residual oil presented colorless pure 3,3-dimethylpentane-1,5-diol (12 g, 0.091 mol, 91%), bp 114 °C (1 Torr), n_D^{20} 1.4585.

(2) Bromination: Direct addition of PBr$_3$ (54 g, 0.2 mol) with stirring in a period of 1 h resulted in an orange-red suspension and this was heated at 100 °C for 3 h. The orange emulsion was poured onto 50 ml of ice water after cooling and extracted with CH$_2$Cl$_2$ (3 × 30 ml), washed with 5% aq. NaOH followed by brine, dried (MgSO$_4$) and concentrated to dryness. Distillation *in vacuo* provided colorless pure 1,5-dibromo-3,3-dimethylpentane (I$_1$, 40 g, 0.155 mol, 77.5%), bp 78 °C (1 Torr), n_D^{20} 1.5098.

(3) Cyclization[15,16]: To a colorless solution of I$_1$ (12.9 g, 0.05 mol) in crude DMSO (30 ml) was added in small

portions finely ground $Na_2S \cdot 9H_2O$ (12.0 g, 0.05 mol) and then the whole mixture was heated at 150 °C for 20 min with extremely vigorous stirring, during which time the steam-distillate (*ca.* 8 ml) was collected. Distillation of the dried organic layer after separation from the H_2O which being first saturated with NaCl furnished colorless and glossy pure 4,4-dimethylthiane (6.0 g, 0.4615 mol, 92.3%), bp 57—58 °C (15 Torr), n_D^{20} 1.4902. ^1H-NMR δ: 0.95 (6H, s, $2\times C\underline{H}_3$–), 1.60 (4H, t, $J=6$ Hz, $2\times$–$C^2\underline{H}_2$–), 2.65 (4H, t, $J=6$ Hz, $2\times$–$C^3\underline{H}_2$–). Sulfilimines (sulfimides) were prepared for elementary analysis according to a reported method.[17)]

S,S-(3,3-Dimethylpentamethylene)-*N*-*p*-tosylsulfimide: mp 183—185 °C, colorless needles (from 95% aq. EtOH). *Anal.* Calcd for $C_{14}H_{21}NO_2S_2$: C, 56.16; H, 7.07; N, 4.68. Found: C, 55.87; H, 7.10; N, 4.40.

S,S-(2,2-Dimethyltetramethylene)-*N*-*p*-tosylsulfimide: mp 104 °C, colorless needles (from 95% aq. EtOH). *Anal.* Calcd for $C_{13}H_{19}NO_2S_2$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.56; H, 6.65; N, 4.89. The physical properties of other cyclic sulfides synthesized by the method described above are shown in Table II.

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References and Notes

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15) Even in case of the ten-time scale operation using mechanical stirring, the preparation could be run without any crucial disadvantages and reproducibly exhibited the same high yields recorded in Table II.
16) It is important to note that extraction with *n*-pentane, ether or benzene followed by evaporation caused the appreciable loss of the sulfides and also that no increase in yield was made when prepared in an aqueous DMSO.
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