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Formation and Conformation of Benzoyloxylated Sulfur-containing Heterocycles

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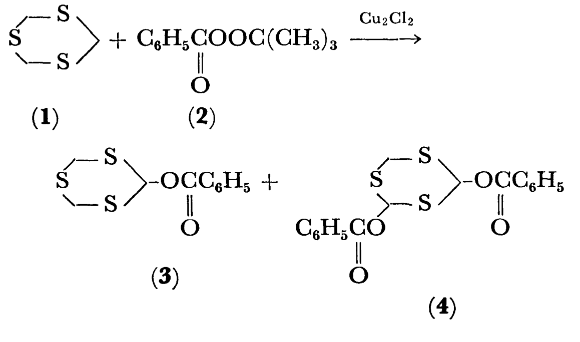
Thiane, 1,3-dithiane, and 1,3,5-trithiane were treated with *t*-butyl peroxybenzoate in the presence of cuprous chloride to yield benzoyloxylated products. Methylenes placed between two sulfur atoms were found to be more reactive than those next to one sulfur atom. Introduction of two benzoyloxy groups into 1,3,5-trithiane afforded *cis*-2,4-dibenzoyloxy-1,3,5-trithiane only. PMR spectra of benzoyloxylated products at various temperatures indicate that benzoyloxy-axial conformation is overwhelming for all the compounds investigated.

Some stereospecific reactions of anions derived from dithianes and trithianes have been reported.[1,2] As an extension of these works, it was thought of interest to study the reactions of sulfur-heterocycles taking place *via* carbonium ions. In order to carry out such studies, it is necessary to synthesize sulfur-heterocycles which carry electronegative substituents.

The synthesis of these compounds was found to be tedious halogenation of 1,3,5-trithiane under either basic or neutral conditions gave intractable materials, attempts to introduce a hydroxyl group being unsuccessful. Acyloxylation of ethers and sulfides by peroxy esters with the aid of cuprous salt is known.[3] The reaction should introduce a benzoyloxy group to the sulfur-heterocycles if *t*-butyl peroxybenzoate is used and the products could be used for the nucleophilic reactions. A benzoyloxy group itself is not a good leaving group in solvolytic reactions but the presence of sulfur atoms may enhance the reactivity of the compound. This paper concerns the benzoyloxylation of thiane, 1,3-dithiane, and 1,3,5-trithiane, the stereoselectivity of the reaction, and the conformation of the products.

Results and Discussion

Benzoyloxylation and Stereoselectivity. When 1,3,5-trithiane (**1**) was treated with *t*-butyl peroxybenzoate (**2**) in benzene, the number of benzoyloxy groups introduced into the trithiane skeleton was found to depend on the molar ratio of **1** to **2**. The results are summarized in Table 1.



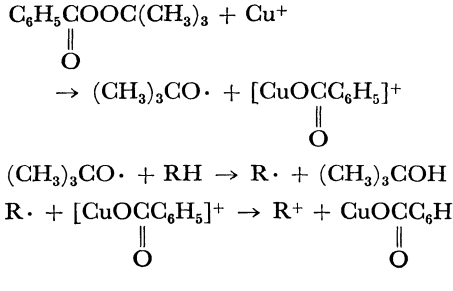
The highest yield (70—80% based on the unrecovered trithiane) of 2-benzoyloxy-1,3,5-trithiane (**3**) was obtained when 0.7 mol of the peroxy ester **2** was used per mole of **1**. When a mixture of 3.0 mol of the peroxy ester **2** and 1.0 mol of **1** was treated with cuprous chloride in benzene, *cis*-2,4-dibenzoyloxy-1,3,5-trithiane (**4**) was obtained as the main product.

Table 1. Distribution of products in the reaction between *t*-butyl peroxybenzoate and 1,3,5-trithiane or its derivatives

Substrate	Peroxy ester (mol/mol substrate)	Relative yield including recovery		
		1	**3**	**4**
1	0.5	1.5	1.0	—
1	0.7	0.4_5	1.0	0.1
1	1.0	1.0	1.0	0.25
1	2.0	0.01	1.0	1.5
1	3.0	—	1.0	4.0
3	1.0	—	1.0	1.2

Assignment of the stereochemistry of the product is straight-forward. The PMR spectrum of compound **4** in deuteriochloroform shows a quartet (δ 3.74 and 5.32, J=15.0 Hz) for the ring methylene group, indicating that the two protons are magnetically nonequivalent, and a singlet for the methine protons indicating that they are equivalent. The features are not significantly altered when the solution is cooled to −80 °C. If the compound were of *trans* form, the spectra would show sharp singlets for the methylene and methine protons at room temperature, and two kinds each of methylenes and methines would be observed at low temperatures as bis(phenylthio)trithiane did.[4]

The absence of 2,2-dibenzoyloxy-1,3,5-trithiane or other geminally disubstituted products and the sole formation of the *cis*-disubstituted isomer deserves special attention.[5] Benzoyloxylation with *t*-butyl peroxybenzoate has been extensively studied and the mechanism has been established as follows.[6] **2** is decomposed catalytically by cuprous ion to *t*-butoxy radical and cupric benzoate at the initial step. The *t*-butoxy radical thus formed abstracts a hydrogen from the substrate to form a radical R· and *t*-butyl alcohol. The radical R· is oxidized by cupric ion to the corresponding carbonium ion which then reacts with the benzoate ion to form a benzoate ester.

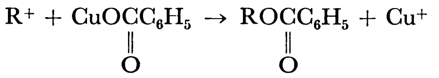


$$C_6H_5\underset{\overset{\|}{O}}{C}OOC(CH_3)_3 + Cu^+$$

$$\rightarrow (CH_3)_3CO\cdot + [CuO\underset{\overset{\|}{O}}{C}C_6H_5]^+ \qquad (1)$$

$$(CH_3)_3CO\cdot + RH \rightarrow R\cdot + (CH_3)_3COH \qquad (2)$$

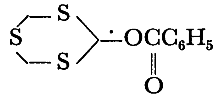
$$R\cdot + [CuO\underset{\overset{\|}{O}}{C}C_6H_5]^+ \rightarrow R^+ + CuO\underset{\overset{\|}{O}}{C}C_6H_5 \qquad (3)$$



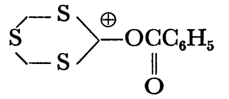
$$R^+ + CuOC(=O)C_6H_5 \rightarrow ROC(=O)C_6H_5 + Cu^+ \qquad (4)$$

Although the rate-determining step is generally step 2, if the free radical formed is reluctant to release an electron, the net reaction would hardly proceed at all.[7] Thus steps 2 and 3 are important in determining whether the reaction occurs easily or with difficulty. The lack of *gem*-dibenzoyloxy compound in the product may be interpreted by assuming either a slow step 2 due to the electron-defficient hydrogen to be removed by an electron-demanding *t*-butoxy radical or a slow step 3 because of the possible instability of a carbonium ion which possesses electronegative substituents. Either case seems possible but we prefer the former for the following reasons.

Firstly, if benzoyloxytrithianyl radical (**5**) is formed easily but step 3 is very slow, **5** may abstract hydrogen from other sources. This indicates that products like **4** have a strong possibility of existing as a *cis-trans* mixture but none of the isomers of **4** was detected.[8] Secondly, the carbonium ion (**6**) to be formed may not be too unstable because of the participation of p-electrons of oxygen and sulfur atoms. Nakai and Okawara reported such stable tri-hetero-substituted carbonium ions.[9]

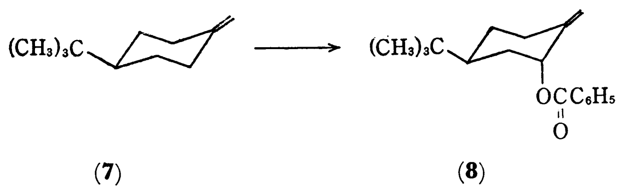


(**5**)



(**6**)

The stereoselectivity of the reaction may be explained on the basis of either thermodynamic or kinetic control. The thermodynamic control of the products cannot be ruled out because of the failure in an equilibration experiment. However, the authors are inclined to consider that the stereoselectivity is of the kinetic origin. The stereospecific formation of 2-methylene-*trans*-5-*t*-butylcyclohexyl benzoate (**8**) is known for the reaction between 4-*t*-butyl-1-methylenecyclohexane (**7**) and *t*-butyl peroxybenzoate and is interpreted by assuming the preferred axial-side attack with the benzoate anion on a carbonium ion produced by the oxidation of the radical.[10]



(**7**) (**8**)

Since the benzoyloxy group in 1,3,5-trithiane takes axial conformation as will be discussed later, the benzoate anion attacking from the axial side should form the *cis*-dibenzoate. It is not yet clear whether the cause for the preferred axial attack is the same in the cases of cyclohexane and trithiane series.

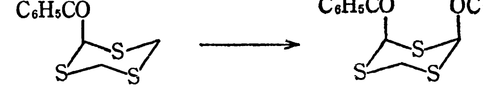
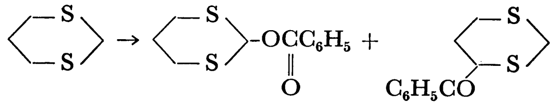


Table 2. Comparison of the reactivities of sulfides toward *t*-butyl peroxybenzoate[a)]

Substrate	Total yields of benzoates (%)	Half-Lives of peroxybenzoate[b)] (min)
1	70—80	2
9	70	8
12	50	75

a) Molar ratios were 0.5 and 0.07 for the peroxybenzoate and cuprous chloride, respectively, per mole of substrate. b) The half-lives were determined by iodometric titration.

Reaction of 1,3-dithiane (**9**) and thiane (**12**) with *t*-butyl peroxybenzoate was carried out as in the case of 1,3,5-trithiane. Yields and half-lives of the peroxy ester as revealed by iodometry are summarized in Table 2. It is evident that thiane is the least reactive among the compounds tested, and dithianes and trithianes react more easily. It was also noted that the reaction with thiane gave 15% methyl benzoate and 2—3% biphenyl in contrast to the absence of these by-products in the cases of dithiane and trithiane. This means that the methylene between two sulfur atoms is much more reactive than the others and the following product analysis is consistent with the idea.

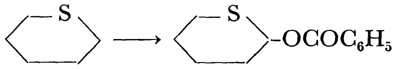


(**9**) (**10**) (**11**)

Since dithiane has three kinds of methylene groups, three kinds of mono-benzoyloxylated products are expected. The structural assignment for the isomers should be easy from the PMR spectra. 2-Benzoyloxy-1,3-dithiane (**10**) was too unstable to be isolated in the air. Thus the reaction mixture was treated with benzenethiol for conversion into 2-phenylthio-1,3-dithiane which was characterized. Identification and estimation of the yields of **10** were performed with a PMR signal at 6.68 ppm which is close to the chemical shift of the methine proton of 2-benzoyloxy-1,3,5-trithiane and thus is assigned to the proton at the foot of the benzoyloxy group. Similarly 4-benzoyloxy-1,3-dithiane was identified by a signal at 6.08 ppm; this chemical shift is close to that of the methine proton of 2-benzoyloxythiane.

The product ratio seems to reflect the reactivities of the methylenes[11] since the reverse of the final reaction, coupling of the ions, is assumed to be very slow. Thus, the relative reactivity of position 2 of 1,3-dithiane is found to be 10.0±1.0 after correction was made as regards the statistical factor, the reactivity of position 4 of 1,3-dithiane being taken as unity and that of 5 practically zero. Thus the methylene between two sulfur atoms is more reactive than the methylene next to one sulfur atom and the methylene beta to a sulfur atom is still less reactive. The smaller half-life of the peroxy ester, when mixed with trithiane, can be attributed to the presence of three methylene groups of the enhanced reactivity.

One of the reaction products from thiane (**12**) and *t*-butyl peroxybenzoate was found to be 2-benzoyloxythiane (**13**) and was purified by chromatography. However, the reaction gave another product which was not identified.



(**12**) (**13**)

Conformation of the Benzoyloxy Derivatives. The PMR spectrum of 2-benzoyloxythiane in carbon tetrachloride showed a near-triplet signal for the methine proton at position 2 at 5.98 ppm from the internal TMS. The half-band width of the signal was 7.2 Hz. These features of a methine proton in six-membered rings are characteristic of equatorially oriented ones.[12) The benzoyloxy group should be axial at least mainly at room temperature. The signal shape of the methine proton, as measured in a mixture of chloroform and carbon disulfide, was not altered even though the temperature was lowered from the ambient to −90 °C. The results are best interpreted by assuming that the conformation of 2-benzoyloxythiane is almost fixed in the benzoyloxy-axial form even at room temperature. No evidence for the presence of the benzoyloxy-equatorial form was obtained even though the spectra were determined in various solvents.

Studies were carried out on the anomeric effect in oxane derivatives. The alkoxy-equatorial form was reported by some authors to be present to the extent of 20—30%[13) but in very small amount by others.[14) The result presented here corresponds to an extreme case even in the oxane series and indicates that no significant difference is caused by replacing an oxygen atom by a sulfur in the heterocyclic system. The only report on the anomeric effect in thiane series also suggests that the alkoxy-axial form is present to the extent of *ca.* 80%.[15)

The PMR spectrum of 2-benzoyloxy-1,3,5-trithiane in deuteriochloroform at 34 °C is shown in Fig. 1 together with an expanded spectrum of the methylene region. The signals at the higher field, assigned to equatorial protons of the methyl groups,[16) appear as triplets with coupling constant of 0.9 Hz and are smaller in height than the counterparts of the AB signal. The phenomenon can be attributed to the W-letter coupling and may be taken as evidence supporting the view that this compound exists solely in the benzoyloxy-axial form, since if the ring were to invert rapidly, the small couplings would have been averaged out to disappear. Another piece of evidence for the assignment of the conformation is obtained by comparing the chemical shifts of the methylene protons: the chemical shift difference, 1.24 ppm, is much greater than that for the methylene protons of 1,3,5-trithiane, 0.76 ppm,[17) and this variation is only explainable by assuming the insertion of an axial benzoyloxy group to trithiane. Thus 2-benzoyloxy-1,3,5-trithiane is seen to exist in the benzoyloxy-axial conformation. The PMR spectrum of this compound in a mixture of deuteriochloroform and acetone-d_6 at −80 °C shows no significant variation from that at room temperature. Thus the conformation of 2-benzoyloxy-1,3,5-trithiane is almost exclusively the benzoyloxy-axial form. No evidence for the presence of the benzoyloxy-equatorial conformation was obtained.

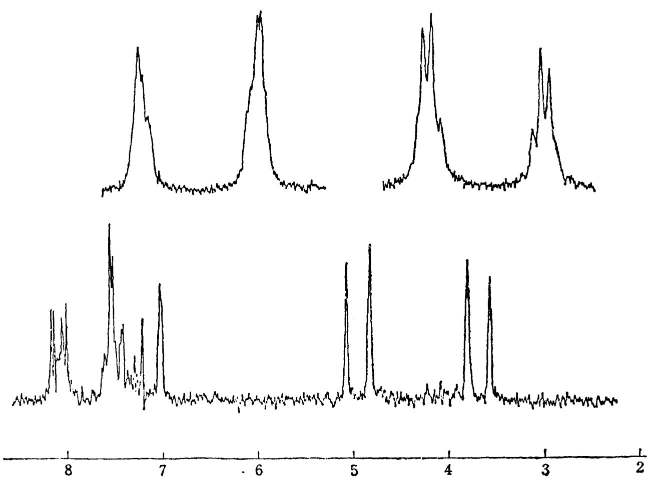


Fig. 1. Below: PMR spectrum of 2-benzoyloxy-1,3,5-trithiane in CDCl$_3$-CS$_2$ at 34 °C.
Above: Expanded (× 5) spectrum of the AB part for the ring methylenes.

PMR spectra of 2-benzoyloxy-1,3-dithiane in a mixture of deuteriochloroform and carbon disulfide showed a similar feature. A broad signal at 6.68 ppm, assigned to the methine proton at position 2, showed no temperature dependency. The expanded spectrum revealed that the signal was of triplet nature. These results suggest that this compound also exists in the benzoyloxy-axial conformation.

The methine proton signal of 4-benzoyloxy-1,3-dithiane appeared at 6.08 ppm as a near-triplet with a coupling constant of *ca.* 3 Hz and a half-band width of 9 Hz. These results can best be interpreted by assuming the equatorial proton at position 4. This indicates the predominance of the axial benzoyloxy group. The spectral feature was essentially unchanged, though the temperature was lowered to −80 °C.

The PMR spectrum of *cis*-2,4-dibenzoyloxy-1,3,5-trithiane showed similar features to those of the monobenzoyloxy compound. Two signals due to the equatorial proton of the methylene group showed a triplet nature, the coupling constant being estimated to be *ca.* 1 Hz. The spectrum was not significantly altered even at −80 °C. The shape of the signal was practically the same in various solvents. The difference in the chemical shift of the AB protons in deuteriochloroform was 1.58 ppm and greater than that for the methylene protons of 1,3,5-trithiane: compared with the difference between 2-benzoyloxy-1,3,5-trithiane, it almost doubles and the results are expected because two benzoyloxy groups are inserted to trithiane this time. Thus it is concluded that *cis*-2,4-dibenzoyloxy-1,3,5-trithiane exists solely in the benzoyloxy-axial form. The 1,3-diaxial conformation is strongly disfavored in cyclohexane series[18) but, in trithiane series, the diaxial interaction may be relieved to some extent because of the longer distance of the C-S than the C-C and also the strong anomeric effect.[19)

Experimental

Reaction of Cyclic Sulfides with t-*Butyl Peroxybenzoate.* To a refluxing solution of 0.04 mol of the substrate in 350 ml of anhydrous benzene was added an appropriate amount of a 50 vol% solution of *t*-butyl peroxybenzoate in benzene and 0.05—0.1 equivalent of cuprous chloride. The resulting mixture was heated under nitrogen. The reaction was monitored by checking the decrease in carbonyl absorption of the peroxybenzoate (1760 cm^{-1}) and was stopped when the carbonyl band disappeared. It took about 40 min for trithiane and dithiane, and about 4 hr for thiane. After the mixture had been cooled to room temperature, it was quickly filtered through a potassium carbonate layer to remove the cupric-cuprous salt and acidic materials. Evaporation of the solvent under reduced pressure below 40 °C gave a crude product which was purified by either chromatography or recrystallization.

2-Benzoyloxy-1,3,5-trithiane (**3**), mp 137—138 °C, was best prepared by treating 1,3,5-trithiane with 0.7 molar peroxy ester and was purified by recrystallization from 1 : 1 benzene–hexane. Found: C, 46.49; H, 3.90; S, 37.23%. Calcd for $C_{10}H_{10}O_2S_3$: C, 46.63; H, 3.86; S, 37.06%. IR (Nujol): 1720 cm^{-1}. NMR ($CDCl_3$, δ from TMS): 3.71 and 4.95 (quartet, $J=15.0$ Hz, 4H), 7.05 (broad singlet, 1H), 7.30—8.20 (multiplet, 5H).

The compound slowly deteriorated in the air unless stored in a desiccator.

cis-*2,4-Dibenzoyloxy-1,3,5-trithiane* (**4**), mp 156 °C, was best prepared by treating 1,3,5-trithiane with 3 molar peroxy ester and was purified by recrystallization from 7 : 3 benzene–hexane. Found: C, 53.92; H, 3.73%. Calcd for $C_{17}H_{14}O_4S_3$: C, 53.78; H, 3.93. IR (Nujol): 1720 cm^{-1}. NMR ($CDCl_3$, δ from TMS): 3.74 and 5.32 (quartet, $J=15.0$ Hz, 2H), 7.17 (broad singlet, 2H), 7.50—8.20 (multiplet, 10H).

2-Benzoyloxy-1,3-dithiane (**10**) was found to be labile. It decomposed in the air with a half-life of *ca.* 5 min at 20 °C, unless prevention against moisture was provided. The reaction mixture was therefore treated under a dry atmosphere. 1,3-Dithiane was treated with an equimolar peroxybenzoate and the mixture was treated as above. After evaporation of the solvent, the mixture was heated at 60 °C under 2 mmHg pressure to remove unchanged dithiane as far as possible. Thus **10** with a purity of *ca.* 80% was obtained, the main impurity being 4-benzoyloxy-1,3-dithiane (**11**). IR (neat): 1720 cm^{-1}. NMR(CCl_4, δ from TMS): 2.0—3.6 (multiplet, 6H), 6.68 (broad singlet, 1H), 7.30—8.20 (multiplet, 5H).

4-Benzoyloxy-1,3-dithiane (**11**) was obtained as a by-product of the reaction between 1,3-dithiane and the peroxy ester. IR (neat): 1720 cm^{-1}. NMR (CCl_4, δ from TMS): 4.41 and 3.40 (quartet, 2H), 6.01 (triplet, 1H), 7.30—8.20 (multiplet, 5H).

Since both **10** and **11** were unstable compounds, they were converted into phenylthiodithianes for the sake of confirmation by the following procedure. Three molar excess of benzenethiol was added to a freshly prepared solution of benzoyloxylated dithianes in benzene and the mixture was heated at 80 °C for 3 hr. After removal of the solvent, the residue was chromatographed on alumina. 2-Phenylthio-1,3-dithiane, mp 59—60 °C, was eluted with 3 : 7 benzene–hexane and 4-phenylthio-1,3-dithiane, a glass, was eluted with 1 : 1 benzene–hexane. 2-Phenylthio-1,3-dithiane: Found: C, 52.31; H, 5.29; S, 41.87%. 4-Phenylthio-1,3-dithiane: Found: C, 52.86; H, 5.28; S, 41.92%. Calcd for $C_{10}H_{12}S_3$: C, 52.58; H, 5.29; S, 42.11%.

2-Benzoyloxythiane (**13**) was obtained as the main product when an equimolar mixture of thiane and the peroxy ester was treated as above. The compound deteriorated unless chromatography was carried out on neutral alumina at low temperature (−4∼−6 °C). Elution with 2 : 8 benzene–hexane gave the desired compound as a colorless oil. IR (neat). 1720 cm^{-1}. NMR (CCl_4, δ from TMS): 5.98 (near triplet, 1H): 1.20—1.35 (multiplet, 8H), 7.20—8.12 (multiplet, 5H).

The compound was unstable and thus was converted into 2-phenylthiothiane, an oil, by the above procedure. The following analytical data were obtained for a substance after purification by chromatography. Found: C, 63.08; H, 6.42; S, 30.33%. Calcd for $C_{11}H_{14}S_2$: C, 62.80; H, 6.71; S, 30.48%.

PMR Measurement. The PMR spectra were recorded on a Hitachi R-20B spectrometer equipped with a temperature variation accessory operating at 60 MHz. Temperature was read by the difference in chemical shift of methyl and hydroxy protons of methanol.

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5) The lack of *gem*-dihalogenation is well known, an example being bromination of xylenes which gives bis(bromomethyl)benzene. However, dibenzoyloxylation under similar conditions has not been reported.

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8) There is a possibility that the *cis* isomer is thermodynamically so stable that the *trans*-form is not detected. Equilibration of *cis* and *trans* 2,4-dibenzoyloxy-1,3,5-trithiane should shed light on this problem. However, **4** is thermally unstable, giving only intractable materials on being treated with acids.

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