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# Substitution Reaction of 3-Thiacycloalkyl Derivatives

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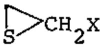
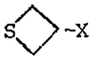
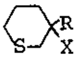
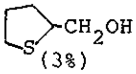
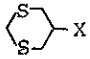
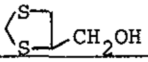
The reactivities of cycloalkyl derivatives in the displacement reaction have been extensively investigated and the effect of the ring size on the reactivity has been explained in terms of I-strain or by the σ-bond participation.[1] However, the reactivities of 3-thiacycloalkyl derivatives have rarely studied[2]. We have examined the reactivities of 3-thiacycloalkyl derivatives both in $S_N1$ and $S_N2$ conditions in order to scrutinize the effect of the ring size on the neighboring group participation of the β-sulfur atom to the reaction center.

Reaction Products The products in the hydrolyses of some 3-thiacycloalkyl derivatives in 50% aqueous dioxane are summarized at Table 1. In the hydrolyses of 3-thiacycloalkyl derivatives the main or only products obtained were the ring enlarged alcohols, or secondary alcohols which are considered to be formed through the more stable carbonium ion, a secondary carbonium ions.

In the case of 1,3-dithiane derivatives, however the main product was the ring contracted product, 2,4-dithiacyclopentyl carbinol, which would be less strained than the six membered ring because of the presence of rather large two sulfur atoms in the ring system.

In the $S_N2$ substitution reaction of 2a and 4a the distributions

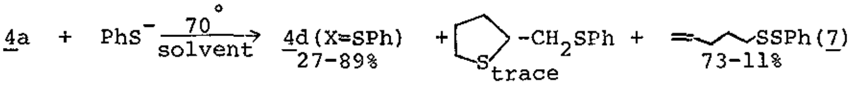
Table 1. The Reaction Products of 3-Thiacycloalkyl Derivatives in the Hydrolyses*

| Compound | | Product | |
|---|---|---|---|
|  | 1a, X=Cl | 1b, X=OH<br>(0%) | 2c, X=OH<br>(100%) |
|  | 2a, X=Cl<br>2b, X=ODNB[a] | 1b<br>(0%) | 2c<br>(100%) |
|  | 3a, X=Cl, R=H<br>3b, X=ODNB, R=H | 3c (100%), X=OH | |
| | 3'b, X=ODNB, R=Me | - | |
|  | 4a, X=Cl[b], R=H<br>4b, X=ODNB, R=H | 4c, X=OH<br>(97%) |  (3%) |
| | 4'b, X=ODNB, R=Me | - | - |
|  | 5a, X=Cl | - | - |
| | 5b, X=ODNB | 5cX=OH (42%) |  (58%) |

*, slightly excess urea added.
a, DNB=3,5-dinitrobenzoyl.
b, about 10% 3-thiacyclopentyl methylchloride is contained which cannot remove.

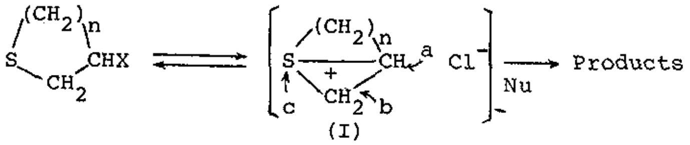
of products were somewhat different from those in the $S_N1$ hydrolyses, especially when thiophilic nucleophiles, for instance thiophenoxide anion, were used as shown below.

$$\underset{\sim}{2}a + PhS^- \xrightarrow[\text{solvent}]{70^\circ} \underset{28\text{-}65\%}{2d(X{=}SPh)} + \underset{\text{trace}}{1c(X{=}SPh)} + \underset{72\text{-}35\%}{\text{AllylSSPh}(6)}$$



$$\underset{\sim}{4}a + PhS^- \xrightarrow[\text{solvent}]{70^\circ} \underset{27\text{-}89\%}{4d(X{=}SPh)} + \underset{\text{trace}}{\text{-}CH_2SPh} + \underset{73\text{-}11\%}{\text{SSPh}(7)}$$

In these two cases the abnormal product ratio was changed by the solvent used. But in the reaction of 5-membered derivatives the disulfide such as 6 or 7 was not obtained. These results would suggest that the reaction proceeds through the bicyclic episulfonium salt (I), of which three probable reaction centers ( a, b and c ) are attacked by nucleophile to give the three different products as shown in Sheme I.



Scheme I

However, when amines, such as aniline, morpholine, pyrolidine and piperidine, were used as nucleophiles no these open-chained products, sulfenamides, were obtained. This difference could be explained by the concept of the thiophilicity$^{3)}$.

Reactivities on $S_N1$ and $S_N2$ Conditions The relative rates of 3-thiacycloalkyl chloride of the hydrolyses in 50% aqueous dioxane and the aminolyses in piperidine are listed in Table 2.

Table 2. The Relative Rates of 3-Thiacycloalkyl Chloride

| Compd. | r. rate[a] | r. rate[b] |
|---|---|---|
| $EtSCH_2CH_2Cl$ | $3x10^3$ | 1.8 |
| 1a | $2x10^2$ | 7.2 |
| 2a | $6x10^6$ | too fast |
| 3a | 1 | 1 |
| Cyclopentyl Chloride | 7.8 | - |
| 4a | $1x10^4$ | 1.3 |

a: relative rate of the hydrolyses in 50% aqueous dioxane.
b: relative rate of the aminolyses in piperidine.

The relative rates of 3-thiacycloalkyl 3,5-dinitrobenzoates of the hydrolyses in 50% aqueous dioxane are also summarized at Table 3. The reactivity of 3-thiacycloalkyl chloride and 3,5-dinitrobenzoates with the ring size in the $S_N1$ type solvolyses falls in the following order, i.e., $4 > 6 > 3 \gg 5$ as shown in Table 2 and 3, contrary to that of cycloalkyl derivatives, i.e., $5 \geq 4 > 6$.

In the $S_N2$ condition, the similar sequence is observed as shown in Table 2( see the relative rate$^{b)}$), and is quite different from that of cycloalkyl derivative which is: $5 > 6 > 4$ in the Finkelstein reaction4). Among the 3-thiacycloalkyl derivatives, the 5-membered *compound is the least reactive,* perhaps due to its strainless structure as compared to cyclopentyl derivatives because of the presence of a large sulfur atom in the ring, while the five membered carbon ring system is strained by the forced flat structure.

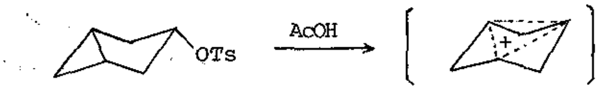
Table 3. The Relative Rates of 3-Thiacycloalkyl 3,5-dinitrobenzoate of the Hydrolyses in 50% Aqueous Dioxane

| Compd. | r. rate | $k_{Me}/K_H$ * |
|---|---|---|
| 2b | $1.2 \times 10^5$ | |
| 3b | 1 | 550 |
| 3'b | $5.5 \times 10^2$ | |
| 4b | $1.0 \times 10^4$ | 42 |
| 4'b | $4.2 \times 10^5$ | |
| 5b | $3.0 \times 10^3$ | |

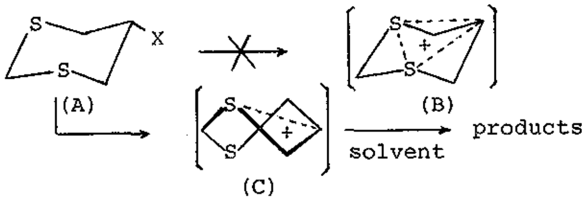
*: $k_{Me}/k_H$= 175,000, in the solvolysis of cyclopentyl derivative.5)

It has been reported that $k_{Me}/k_H$ value is generally very large in the *absence of the anchimeric assistance*5). We examined the effect of α-methyl substituent, expecting a relatively large value of $k_{Me}/k_H$ in the 5-membered thiacycloalkyl 3,5-dinitrobenzoate. However, a fairly large value ($k_{Me}/k_H$ =550) was observed as compared to that of the six-membered cyclic system($k_{Me}/k_H$=42).

Another interesting problem is to see if there is any additivity in the neighboring group participation when two or more sulfur atoms are present at β-positions. Winstein et al, reported that the tris homopropenyl cation is involved in the solvolysis of [3,1,0$^{3,5}$] bicyclohexyl tosylate6).



However, in the solvolysis of $\underline{5}$b we did not observe the rate enhancement, instead 3 - 10 fold retardation, ( $k_{\underline{4}b}/k_{\underline{5}b}=3$ in Table 3, $k_{\underline{4}a}/k_{\underline{5}a}=10$ in formolysis at 70°C). This result could be explained by " rabit ear effect "[7)] as shown in Scheme II. Two lone pair in (A) cannot participate to the reaction center at the same time by the repulsion of two lone pairs but the reaction proceeds through the transition state (C), in which only one sulfur atom can participate at a time. The rather small retardation of the rate as compaired to $\underline{4}$b may due to the inductive effect of another sulfur atom.



Scheme II

### $^{18}$O Tracer Experiment of Carbonyl-Oxygen Labeled m-Chlorobenzoate

The large rate enhancement in the solvolysis of 3-thiacycloalkyl derivatives, except 5-membered system, seems to be due to neighboring group participation of sulfur atom. In fact we can correlate the reactivities of 3-thiacycloalkyl derivatives with the distance of S···C , distance between the reaction center and sulfur atom, which can be estimated from the molecular model.

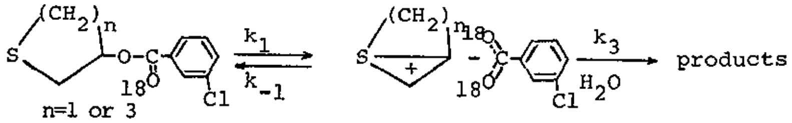
There is a possibility that internal return of the intermediate(I) in Scheme I is also fast. Thus, we have examined the $^{18}$O scrambling in the carbonyl group of 3-thiacylobutyl m-chlorobenzoate and 3-thiacyclohexyl m-chlorobenzoate which would rapidly form the bicyclic-episulfonium intermediate in view of their high reactivities.

The preliminary results of the $^{18}O$ experiment are shown below.

| Compd. | Exess Atom%[a]<br>Starting Ester | Recovered Ester[b] |
|---|---|---|
| 2d,X= m-ClPhCO$_2$- | 0.978 | 0.978 |
| 4d,X= m-ClPhCO$_2$- | 0.928 | 1.075 |

a, measurement value after routine work( the carbonyl oxygen).
b, recovered after 20 - 25% conversion of reaction.

These $^{18}O$ experiments, however unexpectedly revealed that there is practically no loss of $^{18}O$-content after a few % conversion of reaction. Thus, it is clear that $k_{-1}$ is not so rapid than $k_3$ and $k_1$ is the rate-determining step in this reaction.



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5. evaluated value, for example, see the reference, I. Moritani, " Solvolytic Displacement Reaction" Tokyo Kagaku Dojin,1966.
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