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# Activation of Weak Organic Bases. VI.[1] The Alkylation of Thiol Esters by Triethyloxonium Salt and Diethoxycarbonium Salt ($\overset{+}{HC}(OC_2H_5)_2$, $\overset{-}{SbCl_6}$)

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The alkylation of thiol esters with effective alkylating reagents was studied. It was found that the process which afford products was in most cases thermodynamically controlled, which establishes the high susceptibility of the divalent sulfur in thiol esters to the alkylating reagents.

The chemistry of thiol esters(I) has attracted much attention of many investigators because of their well known importance in enzymatic reaction.[3] In continuation of the previous work[4a,b] relating to the activation of weak organic beases through alkylation or acylation, the alkylation of thiol esters was investigated. The protonation of thiol esters in $FSO_3H$-$SbCl_5$-$SO_2$ solution at low temperature has been proved to occur on carbonyl oxygen atom.[5] However, the possibility that the alkylation takes place on sulfur atom should seriously be considered because 1) electron releasing ability of sulfur is much less than that of oxygen[6] 2) the presence of the resonance form(II) which could serve to increase the sulfur basicity has been suggested[3] 3) based upon the HSAB principle[7] that "soft" bases prefer to bind to "soft" acid, it is expected that the affinity of sulfur to the alkylating agents is much stronger than to proton which is the hardest acid of all. If S-alkylation takes place, the sulfonium ion(III) would be formed and O-alkylation, the carbonium ion(IV) could be produced as shown in Chart 1. The syntheses of both salts by other routes and their reactions were discussed in

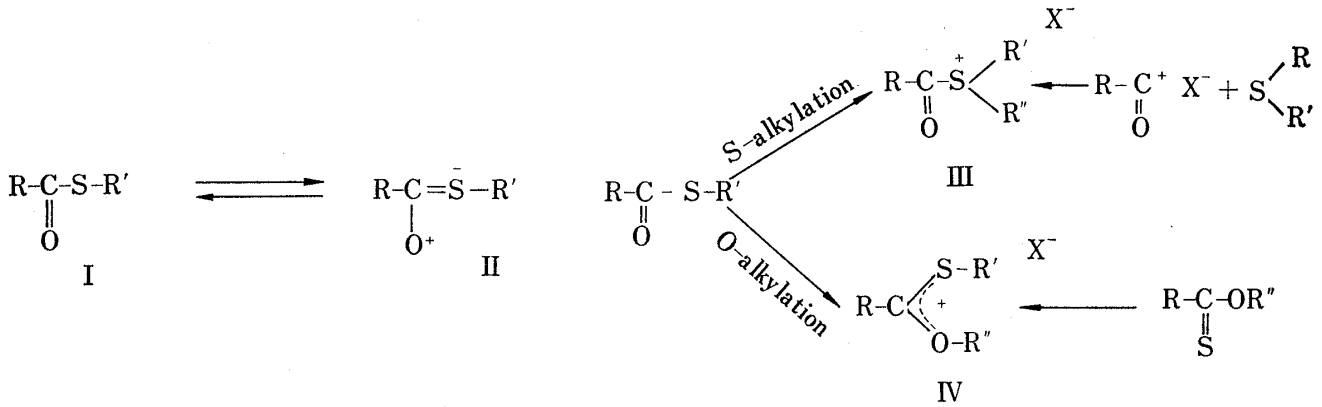


Chart 1

1) Part V: T. Oishi, M. Mori and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **19**, 1871 (1971).
2) Location: *Kita-12, Nishi-6, Sapporo.*
3) T.C. Bruice and S.J. Benkovic, "Bioorganic Mechanism," Vol. 1, ed. by W.A. Benjamin, Inc., New York, 1966, p. 254.
4) *a*) Part III: T. Oishi, M. Mori and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **19**, 1863 (1971); *b*) Part IV: T. Oishi, M. Mori and Y. Ban, *Tetrahedron Letters* **1971**, 1777.
5) G.A. Olah, A.T. Ku and A.M. White, *J. Org. Chem.*, **34**, 1827 (1967).
6) F.G. Bordwell, G.D. Cooper and H. Morita, *J. Am. Chem. Soc.*, **79**, 376 (1957); H. Bohme, H. Fischer and R. Frank, *Ann.*, **563**, 54 (1962); S. Oae, A. Ohno and W. Tagaki, *Bull. Chem. Soc. Japan*, **35**, 681 (1962).
7) R.G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967).

the previous reports in this series.[1,4a,b] Having obtained some informations on the nature of III and IV, we carried out the alkylation of the thiol esters(I) using effective reagents such as $Et_3\overset{+}{O}$, $\overset{-}{B}F_4$(V) or $HC(\overset{+}{OEt})(OEt)_2$ $\overset{-}{SbCl_6}$ (XIII).

**Alkylation by $Et_3\overset{+}{O}$, $\overset{-}{B}F_4$(V)[8]**

A readily available ethyl thiobenzoate (VI) was chosen as a thiol ester. The compound (VI) remained unaffected when it was refluxed in excess $CH_3I$ for 6 hr. Then, VI was treated with a molar equivalent of $Et_3\overset{+}{O}$, $\overset{-}{B}F_4$(V) and refluxed for 1.5 hr in $CH_2Cl_2$. The starting material was again recovered unchanged, which indicates that thiol esters were less susceptible than thion esters to the reagent(V).[4b] Alkylation took place when VI was treated with a large excess of V(4.0 molar equivalents) without solvent at 85—100°(bath temp.). After the mixture was digested with *n*-hexane, the *n*-hexane layer was separated and the solvent was evaporated to give ethyl benzoate(81%) and benzoic acid(15%). From the residual semi-solid, there was obtained the sulfonium salt($Et_3\overset{+}{S}$, $\overset{-}{B}F_4$, IX) in the yield of 82%. When an equimolar mixture of the reactants was treated in the same way as above, the reaction also occured but only 28% of IX and 16% of ethyl benzoate were obtained in this case. Moreover, the same reaction proceeded even in dichloroethane when an excess of V was used but the yield was much lower than in the previous case. The alkylation of ethyl β-phenylthiopropionate(X) was then carried out and the almost same result was obtained. The possible pathways of the above reaction were delineated in Chart 2.

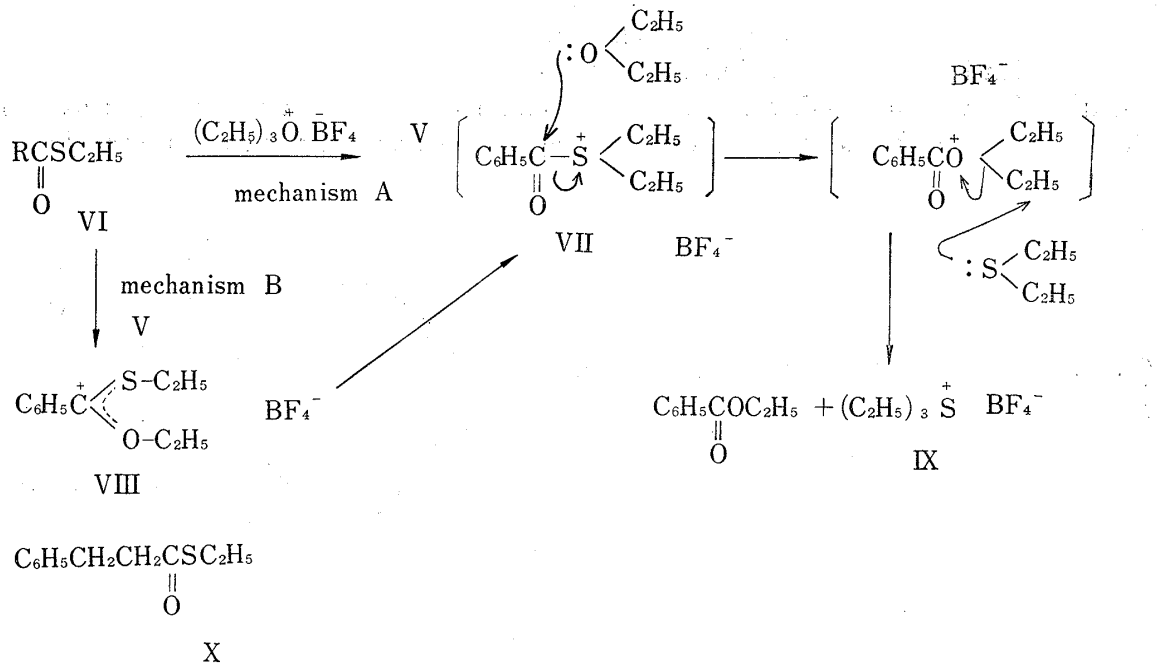


Chart 2

The reaction should proceed *via* the salt(VII), the conversion of which to ethyl benzoate and IX had been proved to occur in the presence of ether.[4a] However, two mechanisms may be considered for the formation of VII. One possibility is that the initial attack of the reagent occurs on sulfur atom of VI yielding the salt(VII) directely(mechanism A).

8) H. Meerwein, G. Hinz, P. Hofmann, E. Kroning and E. Pfeil, *J. Prakt. Chem.* (2), **147**, 17 (1937).

The other is that the alkylation occurs on carbonyl oxygen atom first and then the ethyl group of the resulting salt(VIII) migrate from oxygen to sulfur yielding the sulfonium ion(VII) (mechanism B). Further works aimed to clarify this ambiguity were carried out.

**Alkylation by $\overset{+}{HC}(OEt)_2$, $\bar{S}bCl_6$(XIII)[9]**

If the alkylation proceeds at low temperature and the reaction is carried out in the absence of ether, the isolation of the intermediary salts(XI or XII) could be expected. Therefore, diethoxycarbonium hexachloroantimonate(XIII), an effective alkylating reagent, was then used. The reaction proceeded at 0° expectedly but the salt was obtained as an oily material. However, this salt gave benzoic acid when it was treated with water[10] and ethyl benzoate, when it was treated with sodium ethoxide, which shows that the salt was mainly composed of the sulfonium salt(XI).

It may be assumed that the salt(XV) would be in equilibrium with the acylium salt(XVI) and methyl ethyl sulfide. Therefore, if XV is reacted with the reagent(XIII), the formation of the sulfonium salt(XVII) would be anticipated (see Chart 3). Thus, excess XIII was added

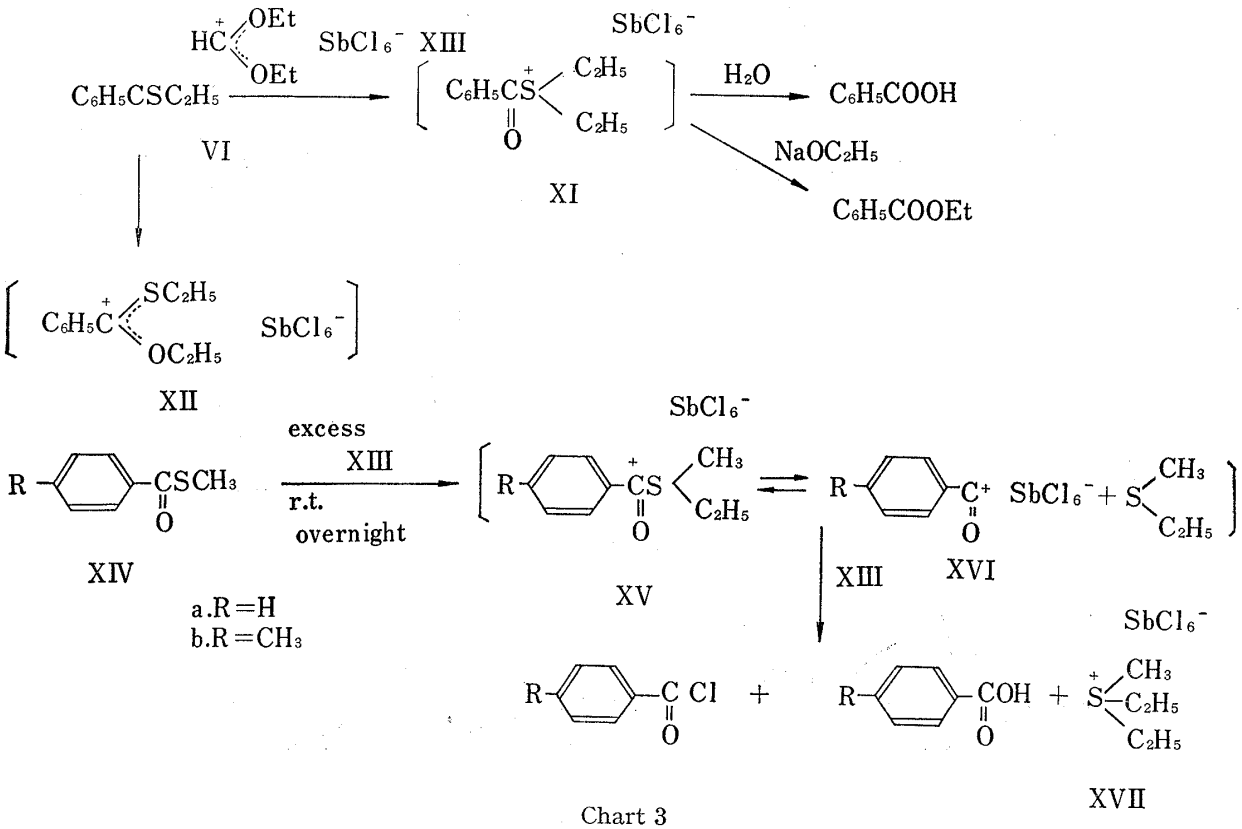


Chart 3

to methyl thiobenzoate (XIVa) in $CH_2Cl_2$ and the mixture was allowed to stand overnight at room temperature. After usual work-up, the expected sulfonium salt(XVII) was obtained in the yield of 27.1%. Similarly, the *p*-tolyl derivative(XIVb) reacted with excess XIII affording XVII. In the preceding paper, we reported[1] that when the carbonium ion(XII) obtainedby the alkylation of ethyl thionobenzoate was heated for 3 hr in dichloroethane at 50°, half of the XII was remained unchanged and the remainder decomposed into benzoyl chloride. Only trace of the sulfonium salt(XVIII) could be isolated. As to the mechanism,[1] the posibility

9) S. Kabuss, *Angew. Chem. Intern. Ed. Engl.*, **5**, 675 (1966); R.F. Borch, *J. Org. Chem.*, **34**, 627 (1969).
10) S.G. Smith and M. O'Leary, *J. Org. Chem.*, **28**, 2825 (1963); S.G. Smith and R.J. Feldt, *ibid.*, **33**, 1022 (1968).

that the decomposition of XII into benzoyl chloride proceeds *via* XI which was formed by the direct migration of ethyl group from oxygen to sulfur(mechanism B) may also be considered. However, if this sort of migration were take place, the appreciable amounts of the sulfonium salt(XVIII) should be obtained because the salt(XII) which works as an efficient alkylating agent is always involved in this system and would alkylate diethyl sulfide from XI to yield in the same manner as depicted in Chart 3. These data strongly suggest that the carbonium ion(XII) cannot be converted thermally to the sulfonium ion(XI) (Chart 4) and hence that the mechanism B (Chart 2) which involves direct conversion of VIII to VII or XII to XI (Chart 3) is not operative in the alkylation of thiol esters.

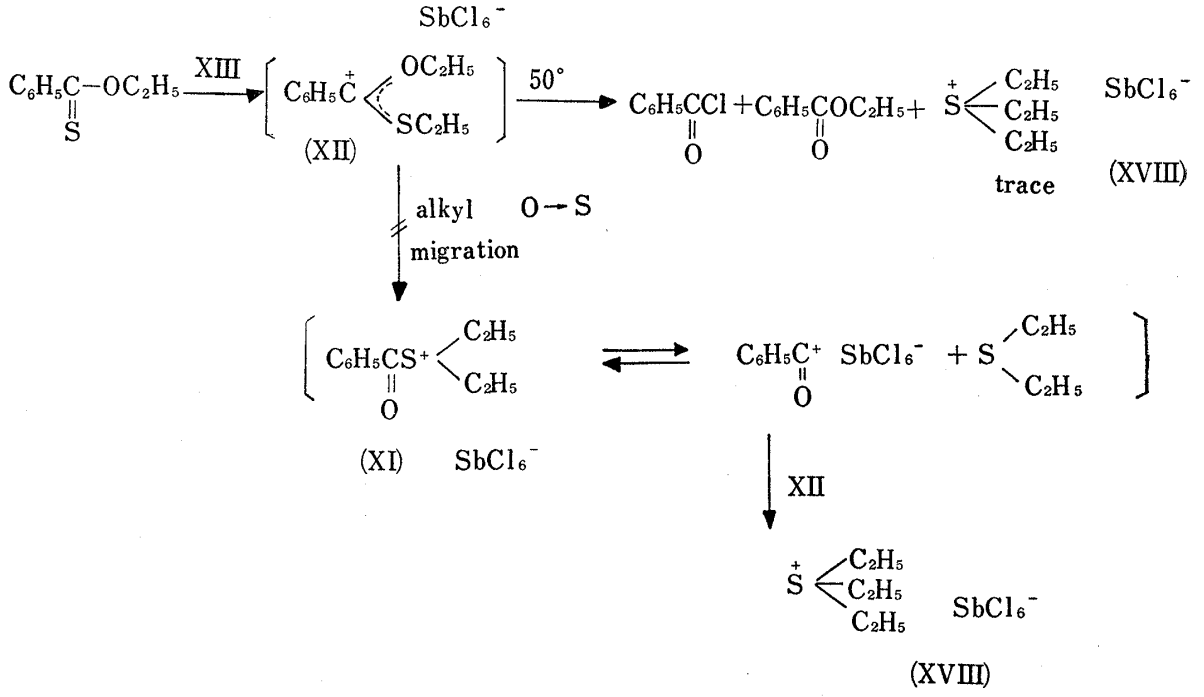

Chart 4

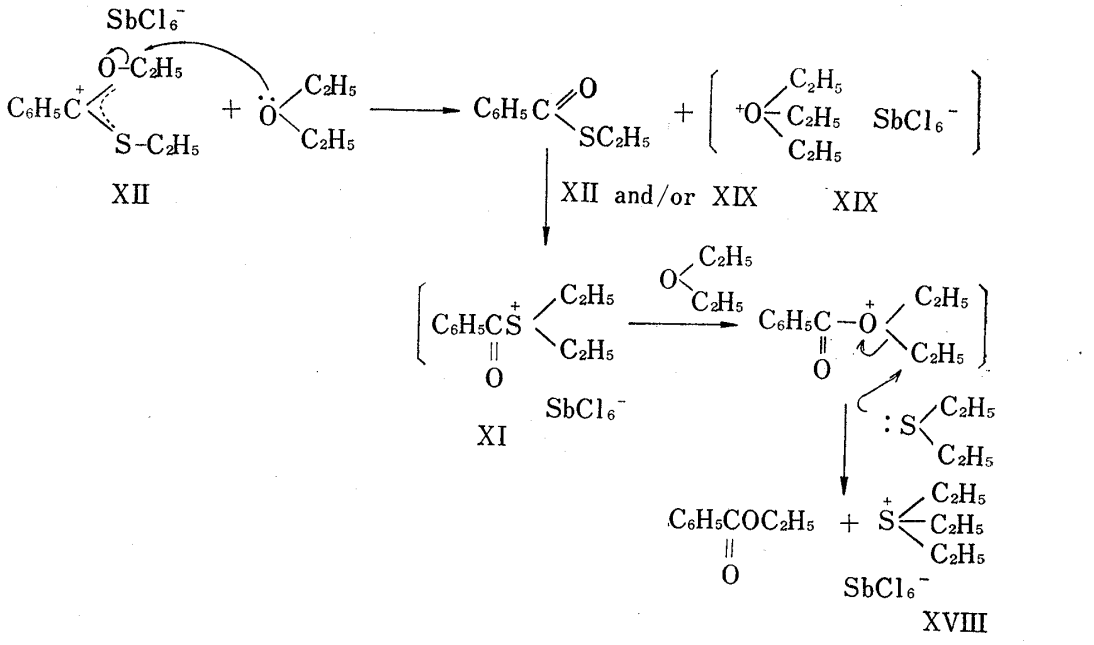

Chart 5

We also reported[1] that when XII was heated in $CH_2Cl_2$ with ether, a mixture of ethyl benzoate, ethyl thiobenzoate and the sulfonium salt(XVIII) were obtained. With the aid of the results presented above (Chart 3), the mechanism of this reaction can be assumed as illustrated in Chart 5.

Meerwein, *et al.*[11] have claimed that thio-$\gamma$-butyrolactone (XX) was alkylated on carbonyl oxygen by $Et_3\overset{+}{O}$, $\overset{-}{B}F_4$ affording the crystalline salt (XXIV) when the mixture was allowed to stand at room temperature for 2 days. Taking account of the afore-mentioned experiments that the sulfonium salt(IX) was obtained from VI, their reaction was reinvestigated. The alkylation was carried out in the same way as noted in the literature and the salt obtained (XXI) was treated with water and after usual work-up there were obtained the starting thiolactone(XX)(32.9%), the mercapto ester(XXII)(7.5%) and the sulfonium salt(XXIII) (8.9%). It is apparent that the compounds XX and XXII were liberated from the O-alkylated salt (XXIV) on hydrolysis whereas the salt(XXIII) was formed *via* S-alkylated salt(XXV). The reason why the O-alkylated species was trapped in this case is not known at present but may be partially attributed to the salt(XXIV) being stabilized by some factor. If this assumption is correct, the carbonium ion such as XXVII which is stabilized by the effect of the methyl group[12] would also be isolated. In fact, a similar result was obtained when $\beta$-phenylethyl thioacetate(XXVI) was alkylated with V.

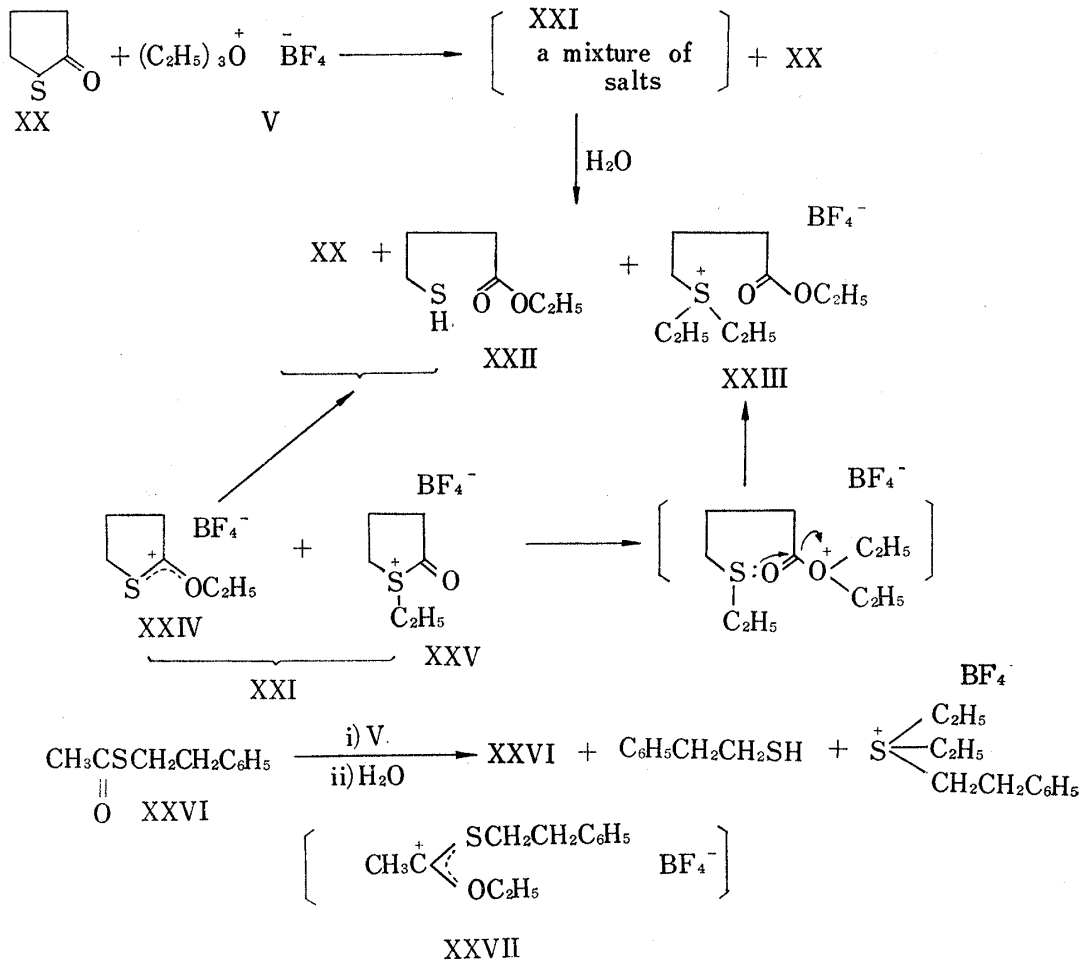


Chart 6

11) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt and J. Spille, *Chem. Ber.*, **89**, 2060 (1956).
12) T. Nakai and M. Okawara, The 23rd Annual Meeting of the Chemical Society of Japan, Abstructs of Papers, III, 1970, p. 1318.

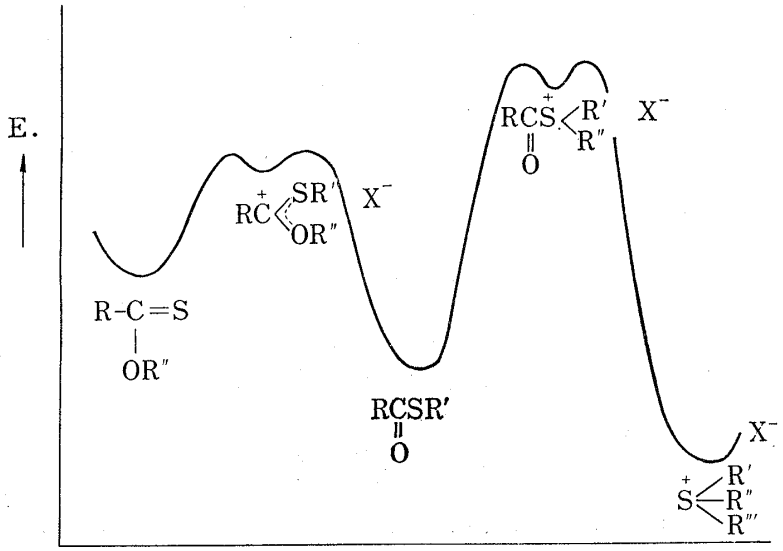


Fig. 1. Energy Diagram

Based on the data accumurated, the alkylation was found to occur both on sulfur and carbonyl oxygen of thiol ester. Generally, the final products were those derived from the S-alkylated species and the O-alkylated species were trapped only in the special cases where the carbonium ions(IV) are perhaps stabilized by some factor. The plausible mechanism for this product formation may be considered as follows: even if O-alkylated species are initially formed, they could be reconverted to the thiol ester (I) by the attack of ether and or the remaining starting thiol ester(I). While thiol ester and the O-alkylated species(IV) are in equilibrium, the alkylating reagents would find a chance to attack on sulfur in I yielding the S-alkylated species (III), which give the thermodynamically stable trialkylsulfonium salt (Chart 7). The energy diagram of these reactions could be shown as depicted in Fig. 1. The remarkable affinity of even the sulfur atoms in thiol esters to the alkylating reagents was thus verified. Further works aimed to activate sulfur containing compounds in connection with these significant characteristics of divalent sulfur are being continued.

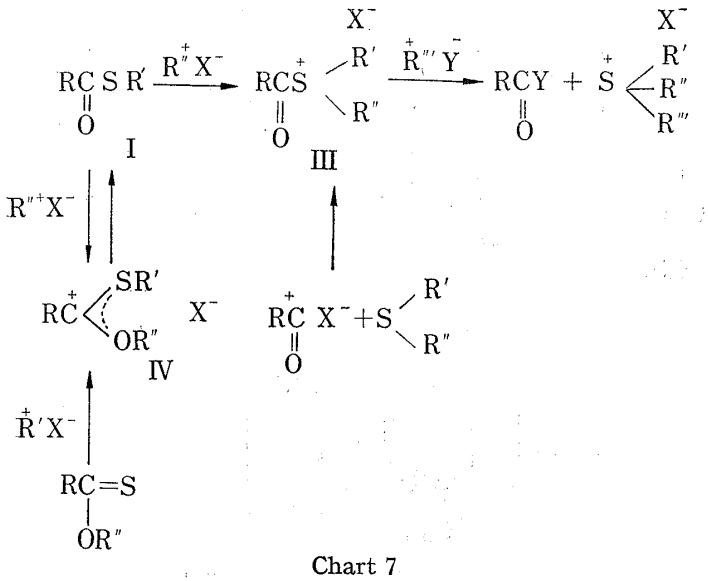


Chart 7

## Experimental[13]

**An Attempted Alkylation of Ethyl Thiobenzoate (VI) with $CH_3I$**——A mixture of 200 mg of VI and 771 mg of $CH_3I$ was refluxed for 6 hr. When excess of $CH_3I$ was evaporated off, VI was recovered in quantitative yield.

**Alkylation of VI with Triethyloxonium Tetrafluoroborate (V)**——a) A mixture of 1.0 g of VI and 1.0 g of V (a relative ratio, 1.2: 1) in 10 ml of $CH_2Cl_2$ was refluxed for 1.5 hr. After usual work-up, the starting

13) Melting points are uncorrected.

material (VI) was recovered quantitatively. b) A mixture of 1.3 g of VI and 6.02 g of V (a relative ratio, 1: 4) was stirred for 6 hr at 85—100° (bath temp.). The mixture was digested with *n*-hexane. The *n*-hexane layer was separated and the solvent was evaporated to give an oil which was treated with sat. $Na_2CO_3$ solution. The solution was extracted with ether twice. The combined ether extracts were dried and evaporated to give 725 mg of ethyl benzoate. The $Na_2CO_3$ solution was acidified and the precipitated benzoic acid (107 mg) was collected. The aforementioned *n*-hexane insoluble portion was digested with ether. The ether layer was washed well with water and the solvent was dried and evaporated to give 250 mg of ethyl benzoate and 43 mg of benzoic acid. The water extracts were treated with 3 g of sodium tetraphenylborate ($\overset{+}{Na}\ \overset{-}{B}(C_6H_5)_4$) and the precipitated compound was recrystallized with nitromethane to give 2.41 g of $Et_3\overset{+}{S},\ \overset{-}{B}(C_6H_5)_4$, mp 240—243°. *Anal.* Calcd. for $C_{30}H_{35}SB$: C, 82.26; H, 7.97; S, 7.19. Found: C, 82.18; H, 8.05; S, 7.31. The ether insoluble portion was dissolved in water. The aqueous solution was again treated with $\overset{+}{Na},\ \overset{-}{B}(C_6H_5)_4$ solution to give additional $Et_3\overset{+}{S},\ \overset{-}{B}(C_6H_5)_4$ (440 mg). c) A mixture of 1.47 g of VI and 6.72 g of V (a relative ratio, 1: 4) in 10 ml of dichloroethane was refluxed for 11.5 hr. The reaction mixture was treated in the same way as described in b) affording 16% of the starting material (VI), 58% of ethyl benzoate, 16% of benzoic acid and 49% of $Et_3\overset{+}{S},\ \overset{-}{B}(C_6H_5)_4$.

**Alkylation of Ethyl *β*-Phenylthiopropionate (X) with V**——A mixture of 1.59 g of X and 6.23 g of V (a relative ratio, 1: 4) was stirred for 6 hr at 85—90°. The reaction mixture was treated in the same way as described above affording 57% of ethyl *β*-phenylpropionate and 84% of $Et_3\overset{+}{S},\ \overset{-}{B}F_4$ along with small amounts of X.

**Alkylation of VI with Diethoxycarbonium Hexachloroantimonate (XIII)**——a) To a solution of 3.94 g of XIII in dichloroethane was added 1.5 g of VI in dichloroethane at −30°. After the mixture had been stirred for 1 hr at this temperature and for 2 hr at 0°, 10% $Na_2CO_3$ solution was added and the mixture was extracted with ether twice. When the water layer was made acidic by the addition of 10% HCl, 591 mg of benzoic acid (54%) separated out. The combined ether extracts were washed with water, dried and evaporated to yield 676 mg of an oil, which was found to be a mixture of ethyl benzoate and VI (a relative ratio, 1: 1.65, based on the gas chromatographic analysis). b) A mixture of 0.93 g of VI and 2.46 g of XIII was stirred for 1 hr at −17° then for 5 hr at 0°. After the same work-up described above, benzoic acid (66%) and ethyl benzoate (6%) was obtained.

**The Reaction of the Alkylated Ethyl Thiobenzoate with Sodium Alkoxide**——To a mixture of 1.2 g of VI and 3.4 g of XIII in 4 ml of $CH_2Cl_2$ was added an ethanolic sodium alkoxide which had been prepared from 1.6 g of sodium and 60 ml of abs. ethanol. The mixture was allowed to stand overnight at room temperature. After the precipitates had been removed centrifugally, the solvent was evaporated off under reduced pressure. The resulting semi-solid was diluted with ether. After filtration, the solvent was evaporated and the residue was distilled under reduced pressure to yield 333 mg (31%) of pure ethyl benzoate.

**Alkylation of Thiol Esters (XIVa,b) with a Excess of XIII**——a) A mixture of 535 mg of methyl thiobenzoate (XIVa) and 3.38 g of XIII in 2 ml of $CH_2Cl_2$ was kept at 0° for 2 hr in the sealed tube, then allowed to stand overnight at room temperature. When $CCl_4$ was added, a crystalline material deposited. The solid was collected and dissolved in $CH_2Cl_2$. The solvent was washed with water, dried and evaporated to give 421 mg (27.1%) of the sulfonium salt (XVII), which was recrystallized from ethanol, mp 213—214°. *Anal.* Calcd. for $C_5H_{13}SSbCl_6$: C, 13.65; H, 2.98; S, 7.29; Cl, 48.38. Found: C, 13.75; H, 2.95; S, 7.43; Cl, 48.12. The $CCl_4$ layer was dried and the solvent was evaporated to yield an oil, which was redissolved in $CH_2Cl_2$. The solvent was washed with water, dried and evaporated to give 402 mg of a semi-solid substance, which was found to be a mixture of benzoic acid and benzoyl chloride. b) A mixture of 600 mg of methyl *p*-tolylthiobenzoate (XIVb) and 3.46 g of XIII was treated in the same way as described above. After usual work-up, there were obtained 785 mg (32%) of XVII and 385 mg of a mixture of ether soluble materials, from which 58 mg of ethyl benzoate and 251 mg of benzoic acid was obtained after $Na_2CO_3$ treatment.

**Alkylation of Thio-γ-Butyrolactone (XX) with V**——To a solution of 900 mg of XX in 1 ml of dichloroethane was added 1.67 g of V (a relative ratio, 1: 1). After the solvent had been evaporated off, the whole was kept for 2 days at room temperature. The resulting material was dissolved in $CH_2Cl_2$ and reprecipitated by the addition of ether. This process was repeated thrice affording 1.67 g of crystalline material. The ether layer was washed with water and the solvent was evaporated off to afford an oil, which was purified by silica gel chromatography to yield 142 mg of the starting material (XX). The crystalline substance obtained above was dissolved in $CH_2Cl_2$ and the $CH_2Cl_2$ layer was washed with water, dried and evaporated to give an oil (849 mg), which was digested with ether. The ether extracts were evaporated to give an oil (461 mg) which was subjected to silica gel chromatography to yield 296 mg of XI (32.9%) and 97 mg of the mercapto ester (XXII) (7.5%). The ether insoluble fraction was subjected to silica gel chromatography. Elution with a mixture of $CH_2Cl_2$–MeOH afforded 230 mg of the sulfonium salt (XXIII) as an oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1735. The salt (XXIII) was characterized after it was converted into the corresponding tetraphenylborate, which was recrystallized from a mixture of acetone and ether, mp 165—166°. *Anal.* Calcd. for $C_{34}H_{41}O_2SB$: C, 77.83; H, 7.88; S, 6.11. Found: C, 77.67; H, 7.80; S, 6.27.

**Alkylation of β-Phenylethyl Thioacetate (XXVI) with V**——A mixture of 242 mg of XXVI and 300 mg of V (a relative ratio, 1: 1.2) in 1 ml of $CH_2Cl_2$ was allowed to stand overnight at room temperature. The reaction mixture was digested with *n*-hexane. From the *n*-hexane layer, there was obtained 82 mg (33.8%) of starting material (XXVI). The *n*-hexane insoluble portion was treated in the same way as described above to afford 92 mg of an oil, which was found to be a mixture of β-phenylethyl mercaptane and XXVI in a relative ratio of 1: 3.5 (based on the gas chromatographic analysis) and 87 mg of diethylphenethylsulfonium tetraphenylborate (initially formed $\bar{B}F_4$ anion was replaced by $(C_6H_5)_4\bar{B}$ anion in the same way as described above). *Anal.* Calcd. for $C_{36}H_{39}SB$: C, 84.03; H, 7.64; S, 6.23. Found: C, 84.07; H, 7.61; S, 6.16.