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The Reactions of α-Substituted Carbonyl-stabilized Sulfonium Ylides with Succinic Anhydride

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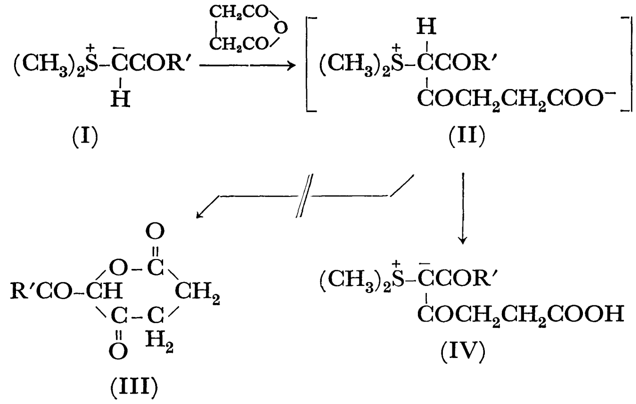
It was found that various kinds of α-substituted carbonyl-stabilized sulfonium ylides were conveniently prepared from the corresponding sulfonium salts by treating with 50% aqueous sodium hydroxide. The reactions of sulfonium ylides with succinic anhydride afforded furofuran derivative by one step procedure in yields ranging these from 5 to 14%. The structures of furofuran derivatives were confirmed by IR spectrum, NMR sepctrum, degradation, and its behavior toward alkali and acid.

It has been recently reported that 3-hydroxyfuran derivatives were obtained in good yields by the reactions of α-unsubstituted carbonyl-stabilized sulfonium ylides with ketene dimer.[1]

In the present experiment, the reactions of carbonyl-stabilized ylides (I) with succinic anhydride were tried with the expectation that the six-membered lactone derivatives (III) would be formed by way of an intramolecular nucleophilic attack of carboxylate anion to α-carbon of the sulfonium compound (II). In the reactions of α-unsubstituted carbonyl-stabilized sulfonium ylides with succinic anhydride, it was found that the stable adducts (IV) were obtained in good yields instead of the expected six-membered lactone derivatives. These results indicate that the sulfonium ylide (II) is converted to the more stable tautomer (IV) by an intramolecular proton transfer from α-carbon to carboxylate anion.



It was established that, unexpectedly, furofuran derivatives were obtained instead of six-membered lactone derivatives or stable adducts by the reactions of α-substituted carbonyl-stabilized sulfonium ylides with succinic anhydride.

Concerning to the preparation of α-substituted carbonyl-stabilized sulfonium ylides, there are few papers, except the cyclic ylide, dimethylsulfonium 2,6-diacetyl-

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[1] H. Takei, M. Higo, K. Saito, and T. Mukaiyama, This Bulletin **41**, 1738 (1968).

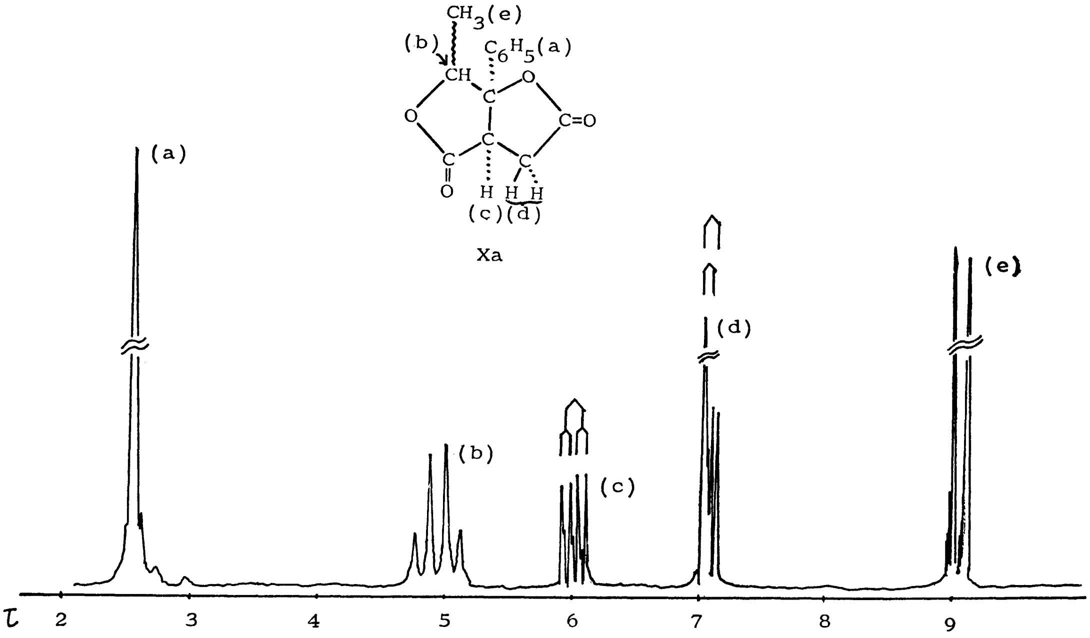
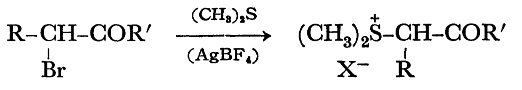


Fig. 1. NMR spectrum of Xa.

2,6-dimethyl-4-oxo-1,3-dioxan-5-ylide.[2] According to this procedure, the preparation of α-substituted sulfonium ylides were tried. When α-bromopropiophenone and dimethyl sulfide were mixed in acetone and allowed to stand for a week at room temperature, the crystalline sulfonium salt (IXa) was obtained in 76% yield. On the other hand, in the case of 3-bromo-2-oxobutane, the reaction took place very slowly and, even after ten days, the sulfonium salt (IXb) was produced only in 40% yield as syrup. When an equimolar amount of silver tetrafluoroborate was added to the resulting reaction mixture of 3-bromo-2-oxobutane and dimethyl sulfide in acetone, the sulfonium salt (IXb′) was obtained in almost quantitative yield within 16 hr. In a similar way, the sulfonium salts, IXc and IXd, were obtained in excellent yields from the corresponding bromides, VIIIc and VIIId. The desired sulfonium ylides (Va—d) were conveniently prepared from the corresponding sulfonium salts in chloroform by the action of 50% aqueous. sodium hydroxide according to the method of Payne.[3] The IR spectra of ylides (Va—d) show bands at 1500, 1505, 1555, and 1560 cm^{-1} attributable to carbonyl groups of sulfonium ylides respectively.

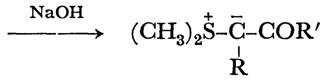


$$\underset{\text{Br}}{\text{R-CH-COR}'} \xrightarrow[\text{(AgBF}_4\text{)}]{(\text{CH}_3)_2\text{S}} (\text{CH}_3)_2\overset{+}{\text{S}}\text{-}\underset{\text{X}^- \ \text{R}}{\text{CH-COR}'}$$

VIII IX

VIIIa $R=CH_3$, $R'=C_6H_5$
b $R=CH_3$, $R'=CH_3$
c $R=C_2H_5$, $R'=H$
d $R=n\text{-}C_4H_9$, $R'=H$

IXa $R=CH_3$, $R'=C_6H_5$, $X=Br$
b $R=CH_3$, $R'=CH_3$, $X=Br$
b′ $R=CH_3$, $R'=CH_3$, $X=BF_4$
c $R=C_2H_5$, $R'=H$, $X=BF_4$
d $R=n\text{-}C_4H_9$, $R'=H$, $X=BF_4$



$$\xrightarrow{\text{NaOH}} (\text{CH}_3)_2\overset{+}{\text{S}}\text{-}\underset{\text{R}}{\overset{-}{\text{C}}}\text{-COR}'$$

V

Va $R=CH_3$, $R'=C_6H_5$
b $R=CH_3$, $R'=CH_3$
c $R=C_2H_5$, $R'=H$
d $R=n\text{-}C_4H_9$, $R'=H$

Next, the reaction of the sulfonium ylide with succinic anhydride was tried. When a mixture of the ylide (Va) and succinic anhydride in tetrahydrofuran (THF) was refluxed for 5 hr, evolution of dimethyl sulfide was observed by its characteristic odor and tarry residue remained after the solvent was evaporated. The crystals (Xa), mp 148—149°C, $C_{13}H_{12}O_4$, were isolated from the tarry residue by silica gel column chromatography. The IR spectrum of this compound shows bands at 1795 and 1775 cm^{-1} assigned to a five-membered lactone, and its NMR spectrum shows a singlet at 2.53 τ (5H), a quartet at 4.97 τ (1H), a double doublet at 6.09 τ (1H), a double doublet at 7.05 τ and 7.08 τ (2H) and a doublet at 8.95 τ (3H) (Fig. 1). This compound was stable toward hydrolysis in refluxing concentrated hydrochloric acid-ethanol (1 : 1). On the other hand, this affords acetaldehyde and ketoalcohol (XII) by reducing with lithium aluminum hydride in THF, followed by oxidation with sodium metaperiodate in aqueous ethanol. Acetaldehyde was identified by deriving to its 2,4-dinitrophenylhydrazone. The oily ketoalcohol (XII) reacted with *p*-nitrobenzoyl chloride to give the syrupy ketoester (XIII), which was confirmed by elemental analysis, IR spectrum showing bands at 1730 and 1682 cm^{-1}, and its NMR spectrum having a multiplet at 1.27—2.70 τ (13H), a doublet at 5.28 τ (2H), a triplet at 5.38 τ (2H), a multiplet at 5.72 τ (1H) and a multiplet at about 7.6 τ (2H). From these results, it seems reasonable to conclude that Xa is a furofuran derivative. In this case, Xa is a single product, but the configuration of a methyl group at C_6 in Xa can not be elucidated. Perhaps, a methyl group at C_6 exists in *trans* relation to a phenyl group at C_{6a}

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[2] G. B. Payne, *J. Org. Chem.*, **33**, 3517 (1968).

[3] G. B. Payne, *ibid.*, **32**, 3351 (1967).

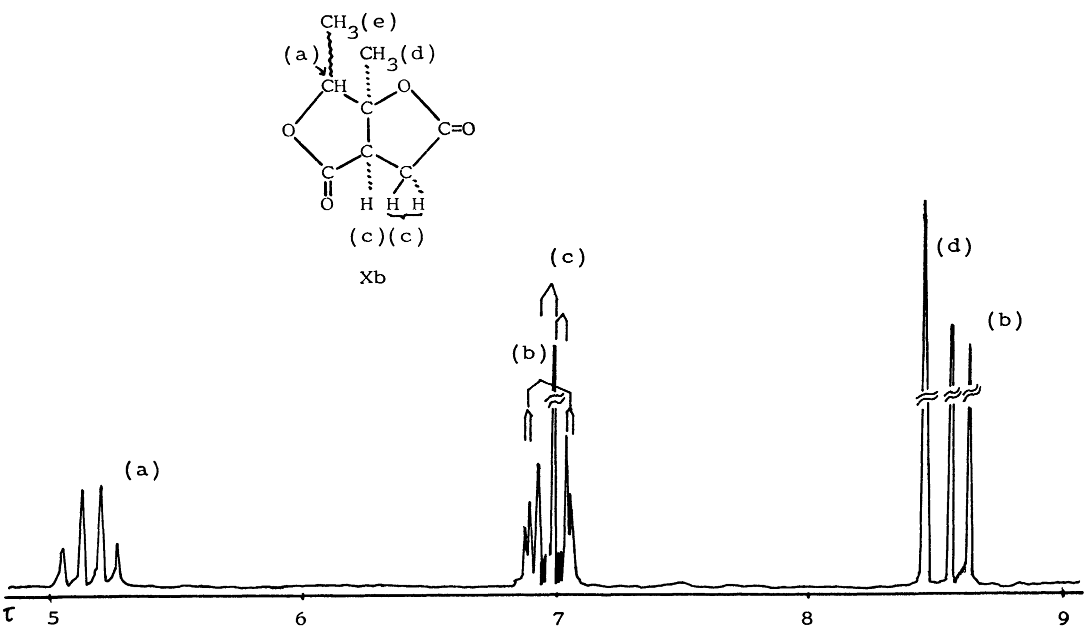
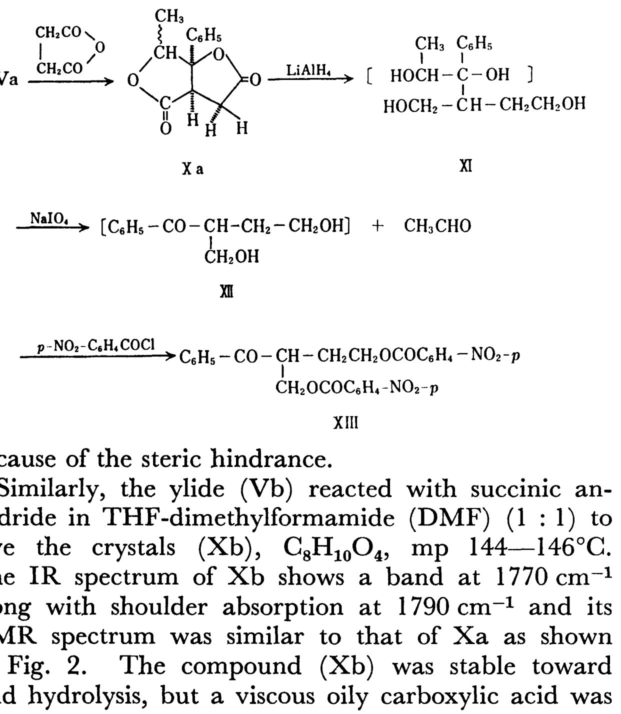
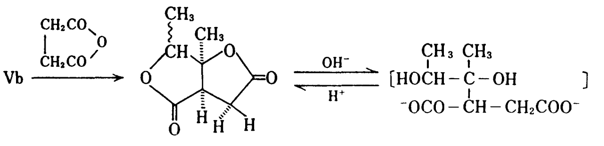


Fig. 2. NMR spectrum of Xb.



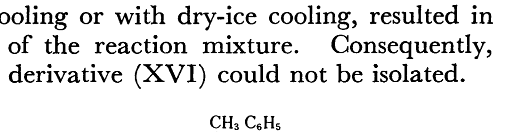
because of the steric hindrance.

Similarly, the ylide (Vb) reacted with succinic anhydride in THF-dimethylformamide (DMF) (1 : 1) to give the crystals (Xb), $C_8H_{10}O_4$, mp 144—146°C. The IR spectrum of Xb shows a band at 1770 cm^{-1} along with shoulder absorption at 1790 cm^{-1} and its NMR spectrum was similar to that of Xa as shown in Fig. 2. The compound (Xb) was stable toward acid hydrolysis, but a viscous oily carboxylic acid was obtained by hydrolysis of Xb with aqueous sodium hydroxide. This carboxylic acid is transformed to the original compound (Xb) by the treatment with acid. Based on these results, the structure of Xb was confirmed to be a furofuran derivative.



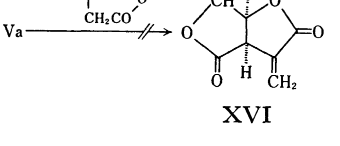
Xb XIV

In the cases of the ylides, Vc and Vd, the reactions with succinic anhydride in THF-DMF (1 : 1) gave the furofuran derivatives, Xc, mp 107—108°C, $C_8H_{10}O_4$, and Xd, mp 86—87°C, $C_{10}H_{14}O_4$, in 10% and 5% yields respectively. The IR and NMR spectra of Xc and Xd were similar to those of Xb as shown in Figs. 3 and 4. The coupling constant between H_d and H_e (J_{de}=0 H_z) indicates that these protons have a *trans* relationship.



Xc $R=C_2H_5$ d $R=n\text{-}C_4H_9$

The reaction of Va and itaconic anhydride was tried in order to apply this reaction to the synthesis of the furofuran derivative[4] having an exocyclic double bond. However, the reaction under various conditions, such as with ice cooling or with dry-ice cooling, resulted in resinification of the reaction mixture. Consequently, the furofuran derivative (XVI) could not be isolated.



XVI

On the other hand, 2-methylsuccinic anhydride reacted with the ylide (Va) in THF-DMF (1 : 1) to give the furofuran derivative (XVII), mp 103—104°C, $C_{14}H_{14}O_4$, in only 10% yield. The IR spectrum of

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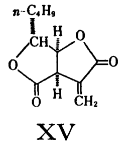
[4] These types of the skeletal structures exist in natural products, as Canadensolide (XV) which is one of metabolites produced by the fungi P. C.



XV

N. J. McCorkindale, J. L. C. Wright, P. W. Brain, S. M. Clarke, and S. A. Hutihinson, *Tetrahedron Lett.*, **1968**, 727.

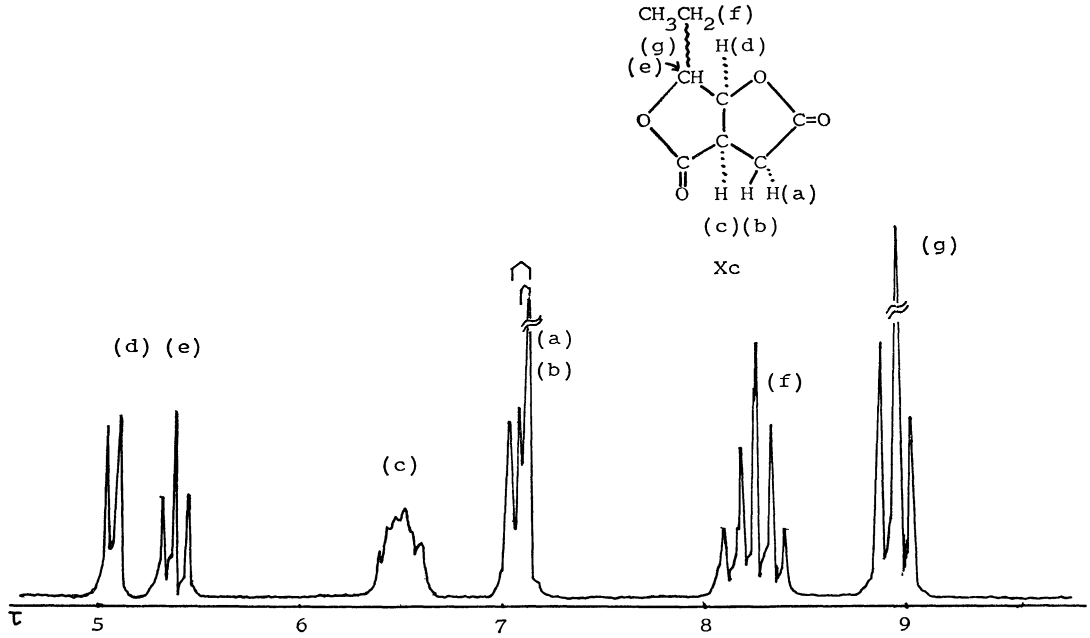


Fig. 3. NMR spectrum of Xc.

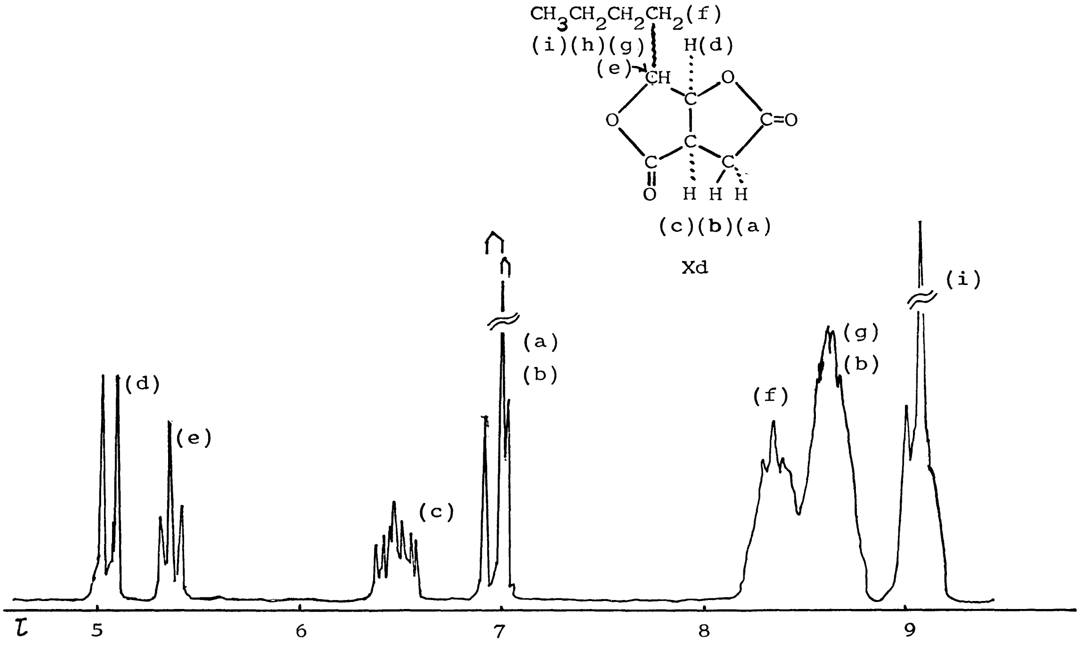
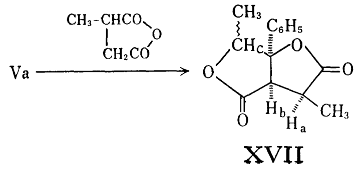


Fig. 4. NMR spectrum of Xd.

XVII shows a band at 1770 cm^{-1} along with shoulder absorption at 1790 cm^{-1} assigned to a five-membered lactone. The NMR spectrum of XVII shows a singlet at 2.55 τ (5H, C_6H_5), a quartet at 5.08 τ (1H, Hc), a doublet at 6.14 τ (1H, Hb), a quintet at 7.02 τ (1H, Ha), a doublet at 8.53 τ (3H, C_2-CH_3), and a doublet at 8.97 τ (3H, C_6-CH_3) (Fig. 5). From the coupling constant between Ha and Hb, it is concluded that Ha and Hb have a *cis* relationship.



XVII

Experimental

All melting points are uncorrected.

Sulfonium Salts. The sulfonium salts were prepared by the following two methods, (A) and (B).

Method (A): A solution of α-bromopropiophenone (21.3 g, 0.1 mol) and dimethyl sulfide (6.8 g, 0.11 mol) in acetone (50 m*l*) was allowed to stand for a week. Filtration gave the sulfonium salt (IXa), 19.2 g (73%), mp 135—137°C (dec.). Recrystallization from ethanol gave colorless microcrystals, mp 138—139°C (dec.).

Method (B): A mixture of 3-bromo-2-oxobutane (11.7 g, 0.08 mol), dimethyl sulfide (9.3 g, 0.15 mol) and silver tetrafluoroborate (15.5 g, 0.08 mol) in acetone (50 m*l*) was stirred for 16 hr at room temperature. Silver bromide was filtered off and washed with ethanol. The combined filtrate was

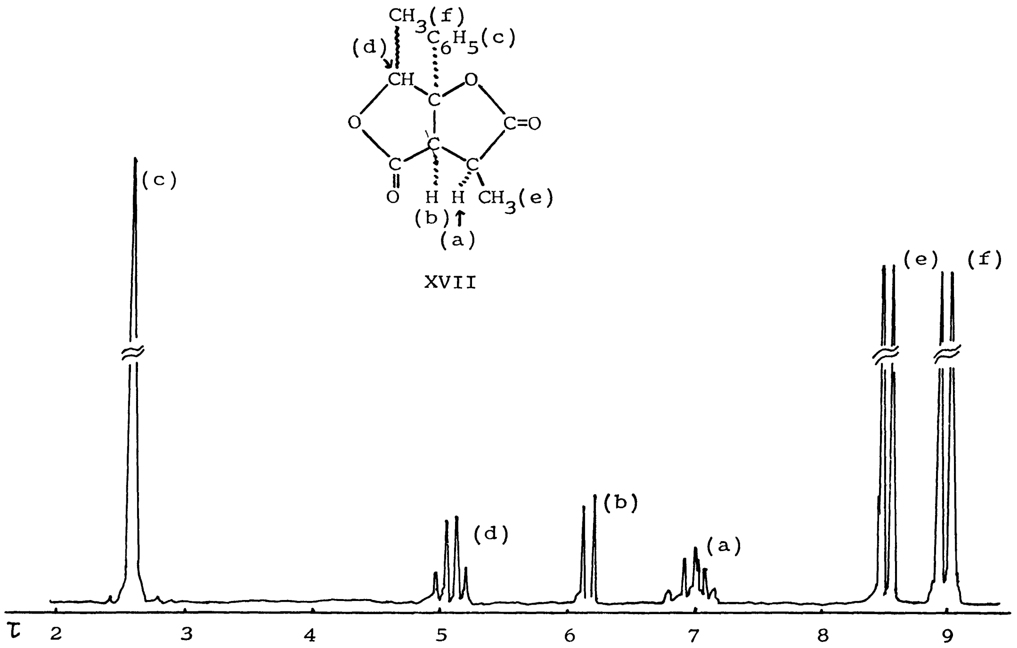


Fig. 5. NMR spectrum of XVII.

evaporated under reduced pressure to give an oily residue. After washing the residue with ether, evaporation of the ether under reduced pressure gave the sulfonium tetrafluoroborate (IXb′) as dark hygroscopic syrup with constant weight of 17.09 g (quantitative yield).

Similarly, various sulfonium salts were obtained by the reactions of α-bromoaldehydes with dimethyl sulfide. The results are listed in Table 1.

TABLE 1. PREPARATION OF SULFONIUM SALT

Sulfonium salt	IXa	IXb	IXb′	IXc	IXd
Time	1 week	10 days	16 hr	15 hr	2 weeks
Yield (%)	73	40	quant.	quant.	quant.
Mp (°C)	135—137	(syrup)	(syrup)	(syrup)	(syrup)
Method	A	A[a]	B	B	B

a) After removal of supernatant liquid by decantation, the residue was washed with ether and dried under reduced pressure.

Sulfonium Ylides. The sulfonium ylides were prepared according to the method of Payne.[3] The results are listed in Table 2.

TABLE 2. PREPARATION OF SULFONIUM YLIDE

Ylide	Va	Vb	Vb′	Vc	Vd
Yield (%)	96	59	68	38	50
Mp (°C)	110 (dec.) (sint. 60)	—	—	—	—
IR ($\nu_{C=O}$) cm^{-1}	1500	1505 a)	1505 b)	1555	1560

a) From the sulfonium salt (IXb)
b) From the sulfonium salt (IXb′)

The ylide was washed with ether, dried under reduced pressure, and used for the reaction with succinic anhydride without further purification.

6-Methyl-6a-phenyl-perhydrofuro[3,4-b]furan-2,4-dione (Xa). To a mixture of the ylide (Va) (10.8 g, 0.055 mol) and THF (50 m*l*) was added a solution of succinic anhydride (4.15 g, 0.41 mol) in THF (50 m*l*) with stirring at room temperature, and the reaction mixture was stirred for additional two hours. After refluxing for five hours (evolution of dimethyl sulfide was observed by its characteristic odor), removal of the solvent gave a tarry residue. The solution of the tarry residue in

TABLE 3. REACTION OF SULFONIUM YLIDE WITH SUCCINIC ANHYDRIDE OR 2-METHYLSUCCINIC ANHYDRIDE

Furofuran	Xa	Xb	Xc	Xd	XII
Ylide	Va	Vb	Vc	Vd	Va
Anhydride	succinic anhydride	succinic anhydride	succinic anhydride	succinic anhydride	2-methylsuccinic anhydride
Solvent	THF	THF-DMF (1 : 1)	THF-DMF (1 : 1)	THF-DMF (1 : 1)	THF-DMF (1 : 1)
Temp. and time	2 hr at r.t. and refl. for 5 hr	2 hr at r.t. and refl. for 2 hr	2 hr at r.t. and refl. for 2 hr	2 hr at r.t. and refl. for 2 hr	1 hr at r.t. and refl. for 3 hr
Yield (%)	44	29	10	5	10
Mp (°C)	148—149	144—146	107—108	86—87	103—104
Solvent of recrystallization	ethanol	ethanol	carbon tetrachloride	carbon tetrachloride	cyclohexane
	C H	C H	C H	C H	C H
Anal. Found	67.34 5.46	56.52 5.75	56.77 5.64	60.59 7.20	67.98 5.73
Calcd	67.23 5.21	56.46 5.92	56.46 5.92	60.55 7.12	68.28 5.73

ethyl acetate was washed with aqueous sodium hydrogen carbonate followed by water, and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel, and elution with methylene chloride gave a yellow oil, which was crystallized from ether, and filtration gave colorless crystals, mp 146—148°C. Recrystallization from ethanol gave Xa, 4.22 g (44%), as colorless needles.

Similarly, various furofurans were obtained by the reaction of ylides with succinic anhydride or 2-methylsuccinic anhydride. The results are listed in Table 3.

Degradation of Xa. To a solution of lithium aluminum hydride (0.74 g) in dry THF (20 m*l*) was added a solution of Xa (1.70 g) in dry THF (10 m*l*). After refluxing for two hours, excess lithium aluminum hydride was decomposed by addition of small amount of water and the mixture was filtered. Evaporation of the solvent gave alcohol (XI), 1.45 g (81%), as syrup. A solution of XI (1.45 g) and sodium metaperiodate (1.33 g) in aqueous ethanol (1 : 1) (30 m*l*) was stirred in bubbling nitrogen atmosphere at room temperature for five hours. Evolved acetaldehyde was led into a solution of 2,4-dinitrophenylhydrazine in ethanol to give 2,4-dinitrophenylhydrazone, 1.04 g (75%), which was recrystallized from ethanol, mp 144—145°C. This hydrazone was identical with an authentic sample by comparing IR spectrum. The reaction mixture was extracted with ether. Evaporation of ether gave ketoalcohol (XII), 1.20 g (quantitative yield), as colorless oil, $\nu_{C=O}$ 1680 cm^{-1}. To a solution of XII (0.75 g) in pyridine (10 m*l*) was added *p*-nitrobenzoyl chloride (1.50 g) with stirring and heated at 70°C for fifteen minutes. After evaporation of pyridine, the reaction mixture was poured into water and extracted with methylene chloride which was washed with dilute hydrochloric acid and water. After evaporation of the solvent, the residue was chromatographed on silica gel, and elution with methylene chloride gave ketoester (XIII), 1.05 g (61%), as viscous syrup: $\nu_{C=O}$ 1730 and 1682 cm^{-1}; NMR (in $CDCl_3$): 1.27—2.70 τ (13H, multiplet), 5.28 τ (2H, doublet), 5.38 τ (2H, triplet), 5.72 τ (1H, multiplet), and 7.60 τ (2H, multiplet).

Found: C, 60.70; H, 3.86; N, 5.50% Calcd for $C_{25}H_{20}O_9N_2$: C, 60.97; H, 4.09; N, 5.69%.

Hydrolysis of Xb and Cyclization of XIV. A suspension of Xb (0.54 g) in 10% sodium hydroxide (40 m*l*) was heated at 70°C for two hours to give a clear solution, which was then cooled, washed with ether, acidified with hydrochloric acid, and immediately extracted with ethyl acetate. Removal of the ethyl acetate gave an oily carboxylic acid (XIV), 0.52 g, ν_{OH} 3430 cm^{-1} (broad) and $\nu_{C=O}$ 1705 cm^{-1}. A solution of 200 mg of the carboxylic acid (XIV) and one drop of conc. hydrochloric acid in ethyl acetate was refluxed for five hours. After removal of the ethyl acetate, the oily residue was crystallized from ether to give Xb; 120 mg, mp 142—144°C, which was identified by IR spectrum.