are grateful to the National Institutes of Health for financial assistance under Grants No. 5T01GM-00718 (to the Department of Biophysical Sciences, State University of New York at Buffalo) and GM-15787 (to R. Parthasarathy). Computer time was made available by Roswell Park and by the Health Sciences Faculty of the State University of New York at Buffalo, to whom our thanks are due.

Supplementary Material Available. A list of $|F_o|$ and $|F_c|$ and a diagram of the geometry of crystal I will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-1925.

Communications to the Editor

Alkylated Disulfides. A Degenerate Rearrangement

Sir:

Alkylated disulfide salts of the type $R_2S^+SR\ X^-$ are often encountered as intermediates in cleavage reactions of S–S bonds assisted by electrophiles.[1,2] Although they are not generally isolable, dimethylmethylthiosulfonium fluoroborate (I) is relatively stable and can be prepared by the methylation of methyl disulfide with trimethyloxonium fluoroborate.[3] The ease with which the S–S bond of I is cleaved is evident in the rapid exchange reaction it undergoes with methyl sulfide (eq 1).[4–6] We find, however, that an irreversible reaction

$$CH_3SCH_3 + CH_3\overset{+}{S}(CH_3)SCH_3 \xrightarrow[\text{or } CH_3CN]{CH_3NO_2} CH_3\overset{+}{S}(CH_3)SCH_3 + CH_3SCH_3 \quad (1)$$

I

intervenes on prolonged standing or heating of these reagents which leads to trimethylsulfonium fluoroborate and methyl disulfide (eq 2). This reaction appears to be

$$\underset{\text{IIa, R = CH}_3;\ \text{b, R = C}_6\text{H}_5\text{CHCH}_3}{RSCH_3} + CH_3\overset{+}{S}(CH_3)SCH_3 \xrightarrow{CH_3NO_2} R\overset{+}{S}(CH_3)_2 + CH_3SSCH_3 \quad (2)$$

$$\underset{\text{IIIa, R = CH}_3;\ \text{b, R = C}_6\text{H}_5\text{CHCH}_3}{}$$

a straightforward displacement at methyl carbon of I by methyl sulfide. 1-Phenylethyl methyl sulfide (IIb) also reacts with I in nitromethane to give the sulfonium salt IIIb, but, in contrast to IIa, we find this reaction is not a simple SN2 displacement and involves an alkylated disulfide intermediate that rapidly undergoes a degenerate carbon-to-sulfur rearrangement. The evidence for this follows. (1) Using $RSCD_3$ where R = 1-phenylethyl, the deuterium label was found in the disulfide and *not* in the salt IIIb.[7–9] This means that the reaction of eq 2 is not in this case a simple methyl transfer from I to IIb but involves C–S cleavage of the sulfide. (2) The disulfide obtained from $RSCD_3$ and I was found by mass spectral analysis to be a mixture of CH_3SSCH_3, CH_3SSCD_3, and CD_3SSCD_3.[10] Furthermore, unreacted sulfide recovered from the reaction of a twofold excess of $RSCD_3$ with I showed that extensive methyl exchange had occurred. The ratio of $RSCH_3$ to $RSCD_3$ was determined by nmr as 1:2. (3) The (−)-enantiomer of $RSCH_3$, IIb,[11] gave *racemic* salt IIIb on reaction with I. Control reactions showed that IIIb was configurationally stable under the reaction conditions[12] and that IIb was likewise stable except in the presence of I. (4) Nmr spectra and optical rotations recorded as frequently as possible after mixing the reagents showed that reaction was substantially complete within 15 min at room temperature. Resonances due to products were immediately apparent;[9] some methyl sulfide was also evident but disappeared as the reaction proceeded. (5) Most significantly, the sulfide is evidently racemized during reaction since nitromethane solutions of a 2:1 mole ratio of (−)-IIb to I lost almost 80% of its activity within minutes of mixing and thereafter slowly decayed to zero (see Figure 1); since the product salt is racemic, the residual activity of the sulfide would be 50% of its initial value had no racemization occurred.

The foregoing results can be explained by the mechanistic sequence of Scheme I. Rapid S–S cleavage of I is shown to occur *reversibly* in the *first step* by nucleophilic attack of II at dicoordinate sulfur to give the

(1) J. L. Kice, *Accounts Chem. Res.*, **1**, 58 (1968); J. L. Kice and J. P. Cleveland, *J. Amer. Chem. Soc.*, **95**, 104 (1973).

(2) B. Miller and C. H. Han, *Chem. Commun.*, 623 (1970); *J. Org. Chem.* **36**, 1513 (1971).

(3) (a) G. K. Helmkamp, H. N. Cassey, B. A. Olsen, and D. J. Pettitt, *J. Org. Chem.*, **30**, 933 (1965); (b) H. Meerwein, K. F. Zenner, and R. Gipp, *Justus Liebigs Ann. Chem.*, **688**, 67 (1965).

(4) J. L. Kice and N. A. Favstritsky, *J. Amer. Chem. Soc.*, **91**, 1751 (1969).

(5) S. H. Smallcombe and M. C. Caserio, *J. Amer. Chem. Soc.*, **93**, 5826 (1971).

(6) The specific rate *k* for the reaction of eq 1 in nitromethane at 40° has been determined by nmr methods as $4.5 \times 10^5\ M^{-1}\ \text{sec}^{-1}$ (ref 4 and 5).

(7) $RSCD_3$ was prepared from the sodium salt of 1-phenylethanethiol[8] and CD_3I.

(8) S. Siegel and A. F. Graefe, *J. Amer. Chem. Soc.*, **75**, 4521 (1953).

(9) The salt IIIb isolated from reaction 2 was identical with that prepared from the methylation of IIb with trimethyloxonium fluoroborate; nmr in CH_3NO_2 δ 2.65 and 2.91 (s, 3, CH_3S), 1.92 (d, 3, J = 7 Hz, CH_3-CH), 4.82 (quart, 1, J = 7 Hz, CH_3CH), and 7.56 (m, 5, C_6H_5).

(10) Using a slight excess of $RSCD_3$ over I, the relative intensity of the $M\cdot^+$ peaks 94, 97, and 100 of methyl disulfide was 10:28:20.

(11) (−)-IIb, prepared from sodium methylthiolate and 1-phenylethyl chloride $[\alpha]^{23}D$ +76.5° in ethanol, had $[\alpha]^{23}D$ −112.9°; the chloride was obtained from 1-phenylethanol $[\alpha]^{24}D$ −42.6° and phosphorus oxychloride and pyridine in carbon disulfide (R. L. Burwell, A. D. Shields, and H. Hart, *J. Amer. Chem. Soc.*, **76**, 908 (1954); W. J. Chambers, W. R. Brasen, and C. R. Hauser, *ibid.*, **79**, 879 (1957)); 1-phenylethanol was resolved by way of the brucine salt of the acid phthalate as described in A. J. H. Houssa and J. Kenyon, *J. Chem. Soc.*, 2260 (1930); J. Kenyon, "Organic Syntheses," Coll. Vol. I, Wiley, New York, N. Y., 1941, p 418; E. D. Hughes, C. K. Ingold, and A. D. Scott, *J. Chem. Soc.*, 1202 (1937).

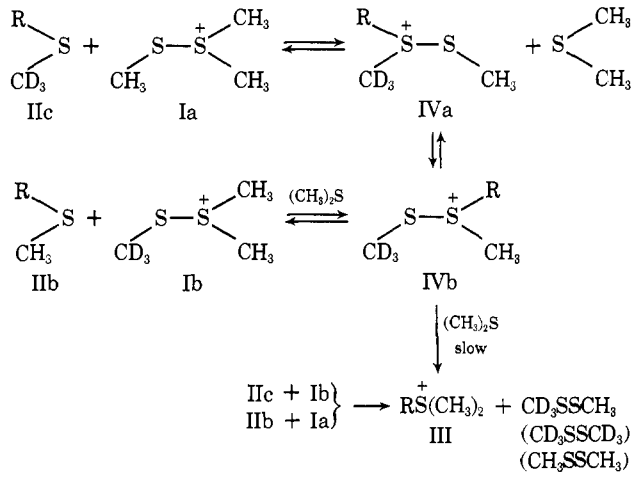
(12) (−)-IIIb $[\alpha]^{20}D$ −20.9° (CH_3NO_2) was prepared as the fluoroborate salt by the methylation of IIb $[\alpha]^{20}D$ −29.95° (CH_3NO_2).

Table I. Reactions of Dimethylmethylthiosulfonium Fluoroborate with Nucleophiles in Nitromethane at 25°

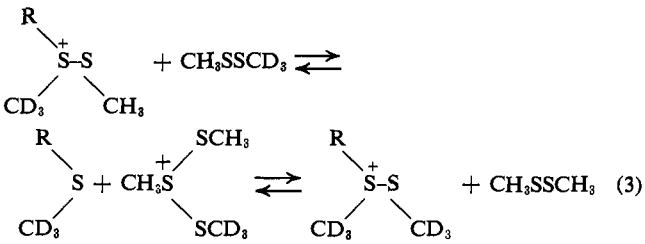
Nucleophile RX[b]	Product distribution[a]							
	$RS^+(CH_3)_2$	$R_2SCH_3^+$	$(CH_3)_3S^+$	$(CH_3)_2S$	$(CH_3)_2S_2$	$(CH_3)_2S_3$	$(CH_3)_2S_x$[c]	$CH_3S(=O)_2SCH_3$
$RSCH_3$	100		7	8	115			
$RSSCH_3$	100	20	6	18	48	37	37	
RSR	100	41	4	25	12	13	13	
RSSR	100	20	5		8	16	16	
RSH	100		4	50	18	20	12	
ROH	100		3		22			32
$ROCH_3$[d]	100		30	*d*	*d*			36

[a] Determined by nmr analysis and expressed relative to $RS^+(CH_3)_2$ as 100; the nucleophile RX was added gradually to solutions of the salt until present in slight excess. [b] R is 1-phenylethyl. [c] Dimethyl polysulfides, $x > 3$. [d] Four days at room temperature; product distribution uncertain because of slow reaction.

Scheme I



alkylated disulfide salt IV and methyl sulfide. In a second slower step nucleophilic attack of methyl sulfide at the phenylethyl group of IV gives III and methyl disulfide as the thermodynamic products. To explain the observed methyl exchange in the disulfide product derived from $RSCD_3$, IIc, a variety of rapid exchange reactions between IV (or I) and disulfide have strong precedent[5] and can be invoked here (eq 3); but, to account for the apparent methyl exchange in the sulfide, it is proposed that IV undergoes a degenerate rearrangement, which, in the case of IVa to IVb, results in the equilibration of $RSCD_3$ and $RSCH_3$ by way of the exchange reactions of IV with dialkyl sulfides (Scheme I). The proposed rearrangement is supported by the optical rotation data, particularly the observed racemization of the sulfide (Figure 1), which indicates that the configuration of the 1-phenylethyl group is lost in the prequilibrium steps. This could occur by the reversible dissociation of IV by way of the 1-phenylethyl cation and methyl disulfide or by an internal nucleophilic displacement by neighboring sulfur at the chiral center with inversion of configuration. Other achiral formulations of IV are conceivable.



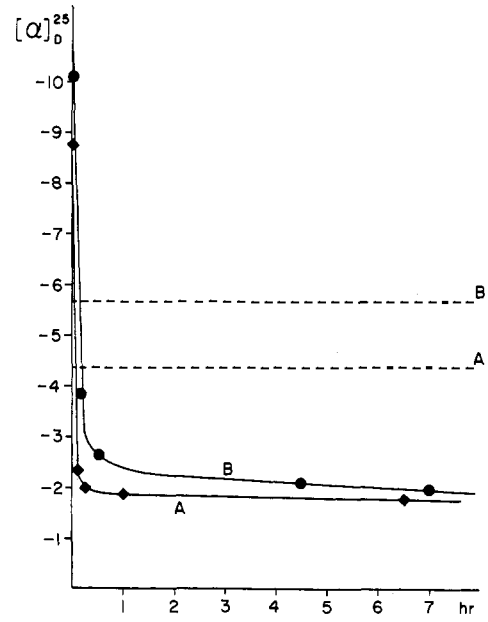
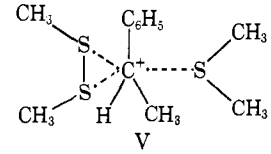


Figure 1. Time dependence of optical rotation of solutions of (−)-1-phenylethyl methyl sulfide (II) and dimethylmethylthiosulfonium fluoroborate (I) in nitromethane at 25°. Curve A is for I (1.05×10^{-3} mol) and II (2.0×10^{-3} mol) in 1 ml; curve B is for I (1.4×10^{-3} mol) and II (3.2×10^{-3} mol) in 1 ml. Dashed lines represent the estimated optical rotation due to excess II if no racemization of II occurred.

Two other observations are possibly important. No styrene or styrene adducts with I were observed, and no salt of structure $R_2S^+CH_3$ was formed. If, therefore, a 1-phenylethyl cation is formed by the dissociation of IV, it reacts *selectively* with methyl sulfide to give III which suggests that the ion remains intimately associated with both the sulfide and disulfide moieties—possibly in an ion-dipole complex, V, of the type proposed by Sneen, *et al.*[13]



V

An alternate route to IV is by the reaction of I with methanesulfenyl chloride (eq 4). We have investigated

(13) R. A. Sneen, G. R. Felt, and W. C. Dickason, *J. Amer. Chem. Soc.*, **95**, 638 (1973).

$$(-)\text{-RSCH}_3 + \text{CH}_3\text{SCl} \longrightarrow \underset{\text{CH}_3}{\overset{+}{\text{R}}\text{SSCH}_3} + \text{Cl}^- \longrightarrow (\pm)\text{-RCl} + \text{CH}_3\text{SSCH}_3 \quad (4)$$

this reaction using (−)-IIb and find it to be very rapid at room temperature—giving *racemic* 1-phenylethyl chloride and methyl disulfide consistent with rapid formation and racemization of IV as the reactive intermediate.[14]

Reactions of I with other nucleophiles of the type RX where R is 1-phenylethyl and X is SH, SR, $SSCH_3$, OH, and OCH_3 were studied with very similar results. The products are listed in Table I and, while they may appear more complex than for IIb X = SCH_3, they can be rationalized by formation of alkylthio- and dialkylthiosulfonium salts related to IV that suffer migration of the 1-phenylethyl group along the sulfur chain prior to capture of this group by dialkyl sulfides.

These results signify that a polysulfide is an exceptionally labile leaving group in SN reactions and that sulfides can behave as alkylating agents when the sulfur is methylthiolated. It is also possible that the rearrangement reported here is related to the allylic rearrangement described recently in the reaction of allylic thioethers with elemental sulfur[15] in which case it seems unlikely that a free carbonium ion is involved.

(14) Related reactions of methanesulfenyl chloride with optically active alcohols are reported to result in alkyl chlorides with a high degree of inversion: I. B. Douglass, R. V. Norton, P. M. Cocanour, D. A. Koop, and M-L. Kee, *J. Org. Chem.*, **35**, 2131 (1970).

(15) R. D. Baechler, J. P. Hummel, and K. Mislow, *J. Amer. Chem. Soc.*, **95**, 4442 (1973).

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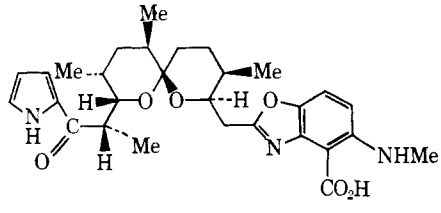
The Structure of A23187, a Divalent Cation Ionophore

Sir:

The carboxylic acid antibiotic A23187 is a divalent cation ionophore which has been shown to uncouple oxidative phosphorylation and inhibit ATPase in rat liver mitochondria.[1] The compound crystallizes from cultures of *Streptomyces chartreusensis* as the mixed magnesium–calcium salt, which can be converted to the crystalline free acid.[2] The structure of this unusual antibiotic has now been shown to be I using chemical



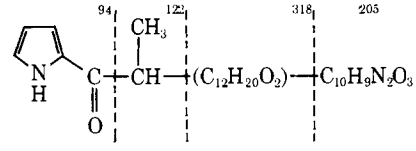
I

and physical methods. The free acid, $C_{29}H_{37}N_3O_6$, melts at 181–182°, the optical rotation is $[\alpha]^{25}D$ +362° (*c* 1, $CHCl_3$), and the pK_a' is 6.9 (90% DMSO). The infrared spectrum in chloroform shows peaks in the carbonyl region at 1640 and 1690 cm^{-1}.

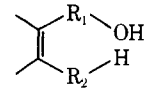
The ^1H nmr spectrum of A23187 contains five resonances in the aromatic region. Two of these occur as an isolated AB spectrum (δ_A 7.58, δ_B 6.65, J_{AB} = 9 Hz) characteristic of a 1,2,3,4-tetrasubstituted benzene derivative. The remaining three aromatic protons (δ 7.06, 6.92, 6.25) appear as multiplets with somewhat smaller coupling constants, reminiscent of five-membered heteroaromatics. From both ^1H and ^{13}C nmr spectra, using 2-formylpyrrole as a model, the presence of a pyrrole ketone moiety was inferred. The ^{13}C spectrum also suggested the presence of 13 sp^2-hybridized carbons in the molecule.

Also evident in the ^1H nmr spectrum were the resonances of five secondary methyl groups, one of which was assigned on the basis of its chemical shift (doublet at δ 2.98, J_{CH_3NH} = 4 Hz) to be an *N*-methyl group. A large nuclear Overhauser effect between this doublet and that at δ 6.65 suggested that the *N*-methyl was attached to the benzene ring. Proton resonances at δ 3.69 and 4.26 were inferred to be the carbinyl protons of secondary ether functions. Resonances at 96.0, 72.7, and 68.3 ppm (downfield from internal TMS) in the ^{13}C nmr spectrum suggested that these ethers occurred as part of a ketal structure.

The mass spectrum of A23187 had its molecular ion at *m/e* 523, with the composition $C_{29}H_{37}N_3O_6$ (found 523.2669, calcd 523.2682). Methylation yields a monomethyl derivative, $C_{30}H_{39}N_3O_6$ (found 537.2838, calcd 537.2839). Acetylation of A23187 and its methyl derivative yields acetyl and methylacetyl derivatives with molecular ions at *m/e* 565 and 579, respectively. Prominent fragments occur in the mass spectrum of A23187 at *m/e* 94 (C_5H_4NO), 123 (C_7H_9NO), 206 ($C_{10}H_{10}N_2O_3$), and 318 ($C_{19}H_{28}NO_3$ and $C_{16}H_{18}N_2O_5$). The peak at *m/e* 206 and the more oxygenated one at *m/e* 318 shift 14 mu on methylation and 56 mu on methylation, followed by acetylation. These results, in conjunction with nmr data, yielded the partial structure



where the $C_{12}H_{20}O_2$ moiety likely has an H substituent γ to the carbonyl group to account for the intense peak at *m/e* 123. Elimination of water from the peak at *m/e* 206 in the spectrum of A23187 and methanol from the peaks at *me* 220 and 262 in the spectra of the methyl and methylacetyl derivatives, respectively, indicated the presence of



in A23187, where R_2 is not oxygen.

The free acid of A23187 crystallizes from acetone as colorless needles, with the crystal parameters given in Table I. A total of 1553 independent reflections to θ = 70° were measured on a four-circle automated diffractometer using monochromated copper radiation.

(1) P. W. Reed and H. A. Lardy, *J. Biol. Chem.*, **247**, 6970 (1972); D. T. Wong, J. R. Wilkinson, R. L. Hamill, and J.-S. Horng, *Arch. Biochem. Biophys.*, **156**, 578 (1973).

(2) R. L. Hamill, M. Gorman, R. M. Gale, C. E. Higgens, and M. M. Hoehn, Abstracts, 12th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N. J., Sept 26–29, 1972, p 65.