rate constants were obtained by dividing the pseudo-first-order rate constants by the base concentrations.

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# The Ramberg–Backlund Reaction of Benzyl α-Halobenzyl and Halomethyl Sulfones

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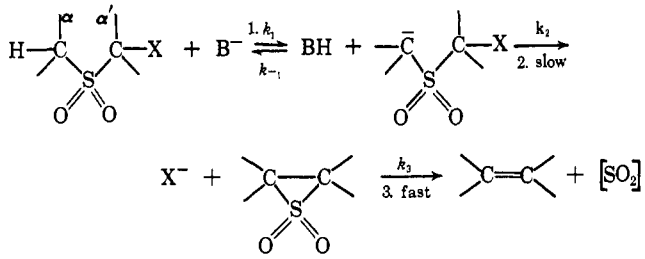
**Abstract:** Kinetic and deuterium exchange studies of the reactions of $PhCH_2SO_2CHXPh$ (X = Cl, Br, I) with methoxide ion in methanol have supported the stepwise mechanism suggested previously and have demonstrated that reversible carbanion formation occurs in the first step. The observation of an unusually large leaving group effect (Br/Cl rate ratio = 620 at 0°) forms part of the basis for the conclusion regarding reversible carbanion formation. Arguments are presented to show that halide loss occurs by an intramolecular displacement initiated by the α′-carbanion. The rate of formation of *trans*-stilbene from these α-halo sulfones is slow compared to its rate of formation from the episulfone intermediate, 2,3-diphenylthiirane 1,1-dioxide. The mechanism thus requires that the rate of halide ion release and product formation be equal. This prediction was verified. Rate constants (estimated or observed) have been assigned to each of the steps in the Ramberg–Bäcklund reaction. Evidence against a concerted 1,3 elimination is presented.

In an earlier paper[2] we suggested that the reaction of α-halo sulfones with strong bases to give alkenes (Ramberg–Bäcklund reaction[3]) occurred in the following steps.[4]



Since that time the following additional evidence has been accumulated in support of this mechanism. (1) Deuterium exchange experiments have shown that step 1 is reversible for alkyl α-halo sulfones.[5] (2) A dipolar ion intermediate has been ruled out for step 2.[5] (3) A conformational requirement has been indicated for step 2.[6] (4) 2,3-Diphenylthiirene 1,1-dioxide ("2,3-diphenylvinylene sulfone") has been isolated from a reaction of α-bromobenzyl sulfone under conditions somewhat similar to those used in the Ramberg–Bäcklund reaction.[7] (5) The formation of alkynes, alkenes, and vinyl halides as products from the reaction of dihaloalkyl sulfones has been observed and explained in terms of thiirene 1,1-dioxide intermediates.[8,9] The purpose of the present investigation was to learn further mechanistic details concerning the reaction. In particular, we were interested: (1) in obtaining estimates of the rate constants $k_1$, $k_{-1}$, $k_2$, and $k_3$, and (2) in discovering which of these steps is rate determining. The studies of the rates of deuterium exchange in α-methylbenzyl sulfones,[10] and of the rates of decomposition of equisulfones[11] evolved as part of this investigation.

**Evidence for Reversible Carbanion Formation.** Reaction of benzyl α-bromobenzyl sulfone with sodium methoxide in methanol-O-*d* was found to give *trans*-stilbene-1,2-$d_2$ (>95% deuterated) in agreement with the results obtained in similar experiments with alkyl α-haloalkyl sulfones,[5] and with the results of Paquette with benzyl α-chlorobenzyl sulfones.[6] However, this experiment alone does not establish the reversibility of step 1, since exchange could have occurred with the episulfone intermediate. Indeed, this turned out to be the case.[11] An experiment was performed, therefore, in which the starting material was recovered from this reaction after one half-life. The recovered benzyl

(1) National Institutes of Health Predoctoral Fellow, 1964–1966.
(2) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **73**, 5187 (1951).
(3) (a) L. Ramberg and B. Bäcklund, *Arkiv Kemi, Mineral. Geol.*, **13A**, No. 27 (1940); (b) B. Bäcklund, Doctoral Dissertation, University of Uppsala, Uppsala, Sweden, 1945.
(4) The mechanism of the reaction was not discussed in the original publication,[3a] but Bäcklund in his dissertation,[3b] which was kindly sent to us by Professor Arne Fredga after the appearance of our paper, suggested the formation of a thiirane 1,1-dioxide (episulfone) intermediate.
(5) N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **85**, 1209 (1963); N. P. Neureiter, *ibid.*, **88**, 558 (1966).
(6) L. A. Paquette, *ibid.*, **86**, 4085 (1964).
(7) L. A. Carpino and L. V. McAdams, III, *ibid.*, **87**, 5804 (1965).
(8) F. Scholnick, Ph.D. Dissertation, University of Pennsylvania, 1955; *Dissertation Abstr.*, **15**, 708 (1955).
(9) L. A. Paquette and L. S. Wittenbrook, *Chem. Commun.*, 471 (1966).
(10) F. G. Bordwell, D. D. Phillips, and J. M. Williams, Jr., *J. Am. Chem. Soc.*, **90**, 426 (1968).
(11) F. G. Bordwell, J. M. Williams, Jr., E. B. Hoyt, Jr., and B. B. Jarvis, *ibid.*, **90**, 429 (1968).

α-bromobenzyl sulfone showed complete deuterium exchange at the α′, as well as the α, position, thus conclusively establishing the presence of a preequilibrium.

The evidence for a preequilibrium requires, with reference to the mechanism written above, that $k_{-1} \gg k_2$. Since sulfones are known to be very weak acids,[12] the α′-sulfonylcarbanion would be expected to be formed in no more than a steady-state concentration. Application of the steady-state approximation and the knowledge that $k_{-1} \gg k_2$ lead to the following expression for $k_{obsd}$.

$$k_{obsd} = \frac{k_1 k_2}{k_{-1}[BH] + k_2} = \frac{k_1 k_2}{k_{-1}[BH]} = K_{eq} k_2$$

The observed rate will depend, therefore, on the position of the equilibrium ($K_{eq}$) and on the rate of halide loss ($k_2$). The mechanism thus predicts a change in rate for a change in the nature of the halogen (leaving group). Qualitative evidence for a leaving group effect was given by Neureiter,[5] and the quantitative data (Table I) confirm this, and provide further evidence for the mechanism given.

**Table I.** Kinetic Data for the Reaction of Benzyl α-Halobenzyl and Halomethyl Sulfones, $PhCH_2SO_2CHXR$, with Sodium Methoxide in Methanol

| R | X | Temp, °C | [MeO⁻][a] | $k_{obsd}$,[b] $M^{-1}$ sec⁻¹ | $E_a$,[c] kcal/mole | $\Delta S^{\neq}$,[d] eu |
|---|---|---|---|---|---|---|
| H | Cl | 50.0 | 0.08628 | $3.25 \times 10^{-4}$ | | |
| Ph | Cl | 0.0 | 0.0155 | $2.65 \times 10^{-6}$ | | |
| | | 25.0 | 0.0155 | $2.67 \times 10^{-4}$ | 29 | +23 |
| | | 50.0 | 0.0155 | $1.32 \times 10^{-2}$ | | |
| H | Br | 0.0 | 0.0175 | $1.26 \times 10^{-5}$ | | |
| | | 25.0 | 0.0175 | $1.00 \times 10^{-3}$ | 28 | +21 |
| | | 50.0 | 0.0175 | $4.15 \times 10^{-2}$ | | |
| Ph | Br | 0.0 | 0.0155 | $1.65 \times 10^{-3}$ | | |
| | | 25.0 | 0.0155 | $7.50 \times 10^{-2}$ | 25 | +17 |
| | | 50.0 | 0.0155 | 1.89 | | |
| Ph | I | 0.0 | 0.00197 | $4.25 \times 10^{-3}$ | | |
| | | 25.0 | 0.00197 | $1.80 \times 10^{-1}$ | 24 | +17 |
| | | 50.0 | 0.00197 | 4.31 | | |

[a] There is about a 10% increase in the rate constant for a fivefold increase in base concentration (bulk salt effect). [b] The rate constants were determined spectrophotometrically from at least triplicate runs; they were calculated by dividing the pseudo-first-order rate constants by the base concentration. The rates at 0, 25, and 50° were calculated using the equation $\log (k_2/k_1) = E_a(T_2 - T_1)/4.5761 T_1 T_2$. [c] Determined graphically from plots of log $k$ *vs.* $1/T$ at three temperatures. [d] Standard state of the solvent taken as unity; values based on $k_1 k_2/k_{-1} = k_{obsd}$[solvent] are +30, +26, +24, and +24 eu (reading downward).

Examination of Table I reveals that the leaving group effect is unusually large (Br/Cl rate ratio = 620 at 0°).[13] The Br/Cl rate ratio for $PhCH_2SO_2CHXPh$ decreases with increasing temperature, since the activation energy of the chloride is 4 kcal/mole higher than that of the bromide (Br/Cl is 143 at 50°; 280 at 25°). For $PhCH_2SO_2CH_2X$ the Br/Cl rate ratio is 128 at 50°.

**Mode and Rate of Halide Loss.** Although the evidence for a preequilibrium provides strong circumstantial evidence for the mechanism given, alternative possibilities do exist. One such involves loss of halide ion from the $PhCH_2SO_2\bar{C}XPh$ carbanion to form a carbene, which then forms the episulfone by an insertion reaction. This mechanism can be ruled out on at least three counts. In the first place it fails to explain the effect of phenyl substitution on the rate of reaction. Substitution of a phenyl group at the α′ position should retard the rate of an α elimination by virtue of its inductive effect, but instead, this substitution causes a greater than $10^3$-fold rate acceleration.[2] This is explicable in terms of the mechanism given since substitution of a phenyl group at the α′ position will increase the equilibrium concentration of α′-carbanion by about $10^6$.[12] The rate is not enhanced to this extent because increased stability of the carbanion is of necessity accompanied by decreased basicity and nucleophilicity.

A second argument against the carbene mechanism stems from the success of the Ramberg–Bäcklund reaction in instances where no α-hydrogen atom is available for elimination, such as with certain α,α-dihalo sulfones.[14]

Finally, in the present work we have found that the sulfones $t$-$BuSO_2CH_2Cl$ and $PhCHClSO_2Ph$, which are capable of α elimination, but not of the Ramberg–Bäcklund reaction *via* a carbene mechanism, lose chloride ion at a rate many orders of magnitude less than does the chloride $PhCH_2SO_2CH_2Cl$.

Loss of halide ion from the α′-carbanion to form a zwitterion has been ruled out by Neureiter.[5] This leaves displacement of halide ion by intramolecular attack of the α′-carbanion as the most reasonable representation.

The recent measurement of the $pK_a$ of benzyl sulfone ($pK_a = 22$)[12] allows an estimate of $K_{eq}$. By assuming that the α-halogen atom decreases the $pK_a$ to the same extent as does halogen substitution in acetic acid (the same number of atoms intervene between the halogen and the acidic hydrogen atom), the $pK_a$ of the α′-C–H of the sulfone can be assigned a value of 20. Using this value it is possible to calculate $k_2$.

$$K_{eq} = \frac{k_1}{k_{-1}} = \frac{K_{(sulfone)}}{K_{(methanol)}}$$

$$k_2 = \frac{k_{obsd}}{K_{eq}} = \frac{k_{obsd} K_{(methanol)}}{K_{(sulfone)}}$$

For $PhCH_2SO_2CHClPh$ at 25°, $k_{obsd} = 2.7 \times 10^{-4}$ $M^{-1}$ sec⁻¹ (Table I)

$$k_2 = \frac{2.7 \times 10^{-4} \times 10^{-16.7}}{10^{-20}} = 5.3 \times 10^{-1} \text{ sec}^{-1}$$

For $PhCH_2SO_2CHBrPh$ the $k_2$ value at 25° would be $1.5 \times 10^2$.

It is of interest to compare the $k_2$ value for the Ramberg–Bäcklund reaction with that for the formation of ethylene oxide from $ClCH_2CH_2OH$. For this reaction $k_{obsd}$ in methanolic sodium methoxide is $3.75 \times 10^{-4}$ $M^{-1}$ sec⁻¹ at 30°.[15] Using this value and $pK_a$

(12) F. G. Bordwell, R.H. Imes, and E. C. Steiner, *J. Am. Chem. Soc.*, **89**, 3905 (1967).

(13) For intermolecular displacements (SN2 and SN1) the average Br/Cl rate ratio is about 50; see A. Streitwieser Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 30 [*Chem. Rev.*, **56**, 571 (1956)].

(14) L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4089 (1964).

(15) J. E. Stevens, C. L. McCabe, and J. C. Warner, *ibid.*, 70, 2449 (1948).

= 14.3 for $ClCH_2CH_2OH$[16] gives $k_2 = 9.5 \times 10^{-7}$ $sec^{-1}$.

For $CH_3SO_2CH_2Cl$ the rate at 75° in water is $1.6 \times 10^{-6}$ $M^{-1}$ $sec^{-1}$.[2] Assuming $E_a \cong 30$ kcal/mole, the rate at 25° would be $10^{-9}$ $M^{-1}$ $sec^{-1}$. By assuming that the $pK_a$ of $CH_3SO_2CH_2Cl$ ($\alpha'$-C–H) is about 2 units less than the value of 29 reported for methyl sulfone,[12] $k_2$ in this reaction can be estimated at $2 \times 10^1$. According to this calculation the rate of intramolecular displacement initiated by the carbanion in $^-CH_2SO_2CH_2Cl$ is over $10^7$ that initiated by the oxide ion in $^-OCH_2CH_2Cl$. This probably reflects for the most part the difference in anion nucleophilicities, but other factors including the electronic effect of $SO_2$ *vs.* $CH_2$ and differences in angle strain must also be contributory. (The value $10^7$ is a maximum since the $pK_a$ of methyl sulfone determined in DMSO[12] may be several units higher than its $pK_a$ in methanol.)

The data in Table I show that phenyl substitution at the $\alpha$-carbon atom increases the rate by 40–130-fold, depending on the temperature. Discussion of the nature of this effect had best await the completion of studies now in progress concerning electronic effects in the Ramberg–Bäcklund reaction.

It has been pointed out with respect to 1,2-elimination reactions that even though it may be possible to demonstrate the presence of carbanions (by deuterium exchange experiments or the like), this does not necessarily mean that such carbanions are intermediates.[17] This applies, of course, also to 1,3-elimination reactions of which the Ramberg–Bäcklund reaction is an example. In fact, the Ramberg–Bäcklund reaction provides a good illustration of this point, since $\alpha$-carbanions are no doubt formed in considerably higher concentration than are $\alpha'$-carbanions,[18] yet they do not enter into the elimination reaction path. For this reason the data presented above do not rule out the possibility of a concerted 1,3-elimination mechanism. If a concerted mechanism is to obtain, however, it must possess some feature that makes it more favorable energetically than the carbanion mechanism. Presumably one could argue that part of the energy gained in forming the new C–C bond is made available for breaking the H–C and C–X bonds. This would be expected to result in a lower enthalpy of activation; the entropy term would be expected, however, to favor the stepwise process.[17]

The best approach to this question with the data presently available appears to be through comparison of the Ramberg–Bäcklund reaction with the reaction of 2-haloethanols plus hydroxide ion to form ethylene oxide. There seems to be general agreement that the latter reaction, at least in the case of the 2-chloroethanol, proceeds through a stepwise mechanism involving an oxide ion intermediate.[15,19] (On the other hand, the comparable ring closure of 4-chlorobutanol to tetrahydrofuran, which occurs at a tenfold slower rate at 50°, apparently utilizes a concerted mechanism.[19]) Ethylene oxide formation from 2-fluoroethanol is 910-fold slower than from 2-chloroethanol (at 50°), yet the activation energy for the 2-fluoroethanol reaction is 2 kcal/mole *lower*.[20] This decrease in activation energy accompanied by a drop of about 19 units in activation entropy is the result anticipated for a change from a stepwise to a concerted mechanism.[17]

The Ramberg–Bäcklund reaction resembles ethylene oxide formation in that the large increase in rate for the bromide *vs.* the chloride is due principally to a drop in activation energy. The entropies of activation of the bromide and chloride are somewhat more positive in the Ramberg–Bäcklund reaction than in ethylene oxide formation (+17 and +23 eu *vs.* +11 and +9 eu[20]).

It would be of interest to compare the activation parameters for the step $HO^- + HOCH_2CH_2Cl \rightarrow HOH + {}^-OCH_2CH_2Cl$ with those for the over-all reaction (epoxide formation), but the data are not available. It is known, however, that the rate of oxide ion formation is very fast (of the order of $10^7$ $M^{-1}$ $sec^{-1}$). The activation energy for this step is, then, presumably much lower than the 23 kcal/mole observed for the over-all reaction. The rate of carbanion formation (as determined by deuterium exchange) for $PhCD_2SO_2CD_2Ph$ was measured in the present study to serve as a model for the first step in the nonconcerted Ramberg–Bäcklund mechanism. The activation energy for this reaction is 9 kcal/mole lower than that of episulfone formation in the Ramberg–Bäcklund reaction of $PhCH_2SO_2CHClPh$. This appears to be more in line with a stepwise mechanism than a concerted mechanism.

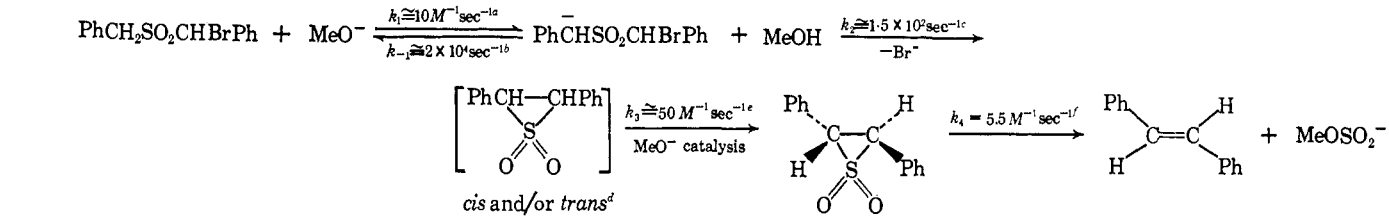
The large leaving group effect for the Ramberg–Bäcklund reaction also seems to be better rationalized in terms of a carbanion mechanism. For concerted 1,2 eliminations the Br/Cl rate ratio is 40:1 at 80° for isopropyl halides in 80% ethanol with sodium ethoxide[21a] and 80:1 for $\beta$-phenylethyl halides in ethanol with sodium ethoxide at 30°.[21b] The Br/Cl rate ratio for the 1,3 elimination of $PhCH_2SO_2CHXPh$ is over three times as large. This is more in accord with the value of 103:1 for ethylene oxide formation in aqueous methanol at 0°.[20,22]

**Episulfone Formation and Decomposition.** It was shown in the previous paper[11] that in methanolic sodium methoxide *cis*-2,3-diphenylthiirane 1,1-dioxide epimerizes completely to the *trans* isomer prior to decomposition. Therefore, the formation of *trans*-stilbene in the reaction of $PhCH_2SO_2CHXPh$ with base provides no information with respect to the stereochemistry of episulfone formation, which, in turn, governs the stereochemistry of the Ramberg–Bäcklund reaction.

Inasmuch as the rate of methoxide-promoted decomposition of the *trans*-episulfones is fast ($k$ = 5.5 $sec^{-1}$ at 25°) compared to the observed rates for

(16) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, 82, 795 (1960).
(17) R. Breslow, *Tetrahedron Letters*, 399 (1964).
(18) Deuterium exchange for $ClCH_2SO_2Ph$ or $BrCH_2SO_2Ph$ in MeOD catalyzed by sodium methoxide is over 1000 times faster than that of $CH_3SO_2Ph$ at 25°: D. A. Schexnayder, unpublished results.
(19) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, 87, 1553 (1965).
(20) C. L. McCabe and J. C. Warner, *ibid.*, 70, 4031 (1948).
(21) (a) E. D. Hughes and V. G. Shapiro, *J. Chem. Soc.*, 1177 (1937); (b) C. H. DePuy and C. A. Bishop, *J. Am. Chem. Soc.*, 82, 2535 (1960).
(22) The Br/Cl rate ratio is, of course, sensitive to temperature and solvent. Unpublished results on solvent effects in the Ramberg–Bäcklund reaction lend further support to the postulate of comparable mechanisms for the reactions of bases with $HOCH_2CH_2Cl$ and of $PhCH_2SO_2CHClPh$. The changes in rates for the reactions of $PhCH_2SO_2CHClPh$ plus base with changes in solvent were found to mimic in a striking manner the unusual solvent effects observed by Stevens, McCabe, and Warner for the reaction of $HOCH_2CH_2Cl$ with base.[15] These effects will be discussed in a later paper in this series.

Scheme I




[a] The rate of exchange for $PhCD_2SO_2CD_2Ph$ (*vide supra*) was multiplied by five to correct for the isotope effect and by ten to correct for the inductive effect of bromine. [b] Obtained from $k_{-1} = k_1K_{(MeOH)}/K_{(sulfone\ in\ DMSO)}$. [c] Calculated from $k_2 = k_{obsd}/K_{eq}$ (*vide supra*). [d] The stereochemistry here is unknown. [e] The estimated rate of epimerization of *cis* to *trans*.[11] [f] Measured directly.[11]

the formation of *trans*-stilbene from the chloride, bromide, or iodide (Table I), this step is not rate controlling. Because the half-life for the methoxide ion promoted decomposition of this episulfone is equal to that of its solvolytic decomposition at a rather low concentration of methoxide ion (0.0066 *M*),[11] episulfone decomposition will be base promoted under the usual reaction conditions.

Since the rate of halide release is rate controlling (highest hump on the energy profile) this rate must be equal to the rate of product formation. In agreement with this prediction it was found that the rate of chloride ion release from $PhCH_2SO_2CHClPh$ at 25° in 40% aqueous dioxane was equal, within experimental error, to the spectrophotometric rate.

Sufficient data are now available to be confident that the individual steps originally suggested for the Ramberg–Bäcklund reaction are correct.[2] In addition, considerable information concerning the detailed mechanism of the steps wherein the halide ion is lost (*vide supra*) and wherein the episulfone is decomposed[11] have been obtained. Rate constants for each step in the reaction can now be estimated for a number of systems. Such estimates are given over the arrows for the reaction of $PhCH_2SO_2CHBrPh$ with sodium methoxide in methanol at 25°, which is diagramed in Scheme I.

## Experimental Section[23]

**Deuterium Exchange with Benzyl α-Bromobenzyl Sulfone.** A solution of benzyl α-bromobenzyl sulfone (0.0655 g, 0.201 mmole) in 10 ml of methanol-O-*d* (99% deuterated) and a solution of sodium methoxide (0.137 g, 2.54 mmoles) in 10 ml of the same solvent were thermostated in a 0.20° bath for 3 hr, combined, and kept at 0.20° for 3400 sec (about one half-life). The reaction mixture was quenched with 50 ml of 3 *N* hydrochloric acid and extracted twice with 50-ml portions of methylene chloride. The organic layer was washed and dried; concentration gave 0.0353 g of an oily solid, which had infrared bands characteristic of the starting sulfone. The nmr spectrum showed no protons other than aromatic ones.

From a similar experiment carried out at 25° for 5 hr there was isolated 89% of *trans*-stilbene-$d_2$, mp 112–115°. Its nmr was identical in the aromatic region with that of authentic *trans*-stilbene, except for the absence of the vinyl proton peak at δ 7.10.

**Benzyl α-Bromobenzyl Sulfone.** Bromine (4.84 g, 0.0303 mole) was added dropwise to a solution of 6.42 g (0.030 mole) of benzyl sulfide in 50 ml of refluxing dry carbon tetrachloride. After heating for an additional hour the reaction mixture was cooled in an ice bath, and a solution of 13.1 g (0.0645 mole) of *m*-chloroperbenzoic acid in 150 ml of dry methylene chloride was added dropwise. After standing overnight at 20° the mixture was washed with aqueous sodium bisulfite, aqueous sodium bicarbonate, and water. After drying, concentration of the organic layer gave 9.6 g of solid, mp 78–98°. Crystallization from methylene chloride–hexane gave 7.59 g (78%) of material mp 106–108°.

*Anal.* Calcd for $C_{14}H_{13}BrO_2S$: C, 51.70; H, 4.03. Found: C, 51.77; H, 3.90.

Benzyl α-chlorobenzyl sulfone, mp 116.5–117° (lit.[2] mp 116.2–117°), was prepared from benzyl sulfide in 85% yield in a similar manner using sulfuryl chloride.

**Benzyl α-Iodobenzyl Sulfone.** Two 500-ml three-necked flasks were connected through the side necks by an 8-mm piece of glass tubing bent so that it touched the bottom of the right-hand flask and just entered the left-hand flask. The two flasks were also connected by a rubber tube. The right-hand flask was fitted with a serum cap and the left with a condenser protected with a calcium chloride drying tube. Into the right flask was placed a solution of 2.46 g (0.01 mole) of benzyl sulfone in 100 ml of dry methylene chloride. Into the left flask was placed a mixture of 3.8 g (0.015 mole) of iodine in 250 ml of dry methylene chloride. Both flasks were cooled to −78° and 6.45 ml (0.01 mole) of commercial *n*-butyllithium in hexane was added to the right flask, while stirring and sweeping with nitrogen (through a needle in the syringe cap). After several minutes, the lithium salt mixture was slowly forced into the iodine solution by slightly constricting the rubber tubing. The red-brown solution was allowed to warm to room temperature, and water (100 ml) was added. Sodium bisulfite was added to remove excess iodine, and the methylene chloride layer was removed, washed, and dried. Partial removal of the solvent gave 2.26 g of light yellow material. Crystallization from methylene chloride–hexane gave the following crops: 0.174 g (mp 164–165°), 0.201 g (161.5–162.5°), 0.049 g (158.5–161.5°), 0.258 g (156–159°), 0.068 g (140–143°), and 1.28 g of residue. The second, third, and fourth crops were combined and recrystallized to give 0.302 g of colorless platelets, mp 165–166°.

*Anal.* Calcd for $C_{14}H_{13}IO_2S$: C, 45.17; H, 3.52. Found: C, 44.93; H, 3.62.

**Reaction of *t*-Butyl Chloromethyl Sulfone and α-Chlorobenzyl Phenyl Sulfone with Base.** A mixture of 1.7 g (0.01 mole) of *t*-butyl chloromethyl sulfone and 18 ml (0.04 mole) of 2 *N* aqueous sodium hydroxide was stirred and heated at 100°. No chloride was observable after 3 hr and very little was obtained after 96 hr. The starting material was recovered (88%) by acidifying and extracting with ether. Similar results were obtained with α-chlorobenzyl phenyl sulfone.[24]

**Benzyl Halomethyl Sulfones.** The sample of benzyl chloromethyl sulfone was that used earlier;[2] benzyl bromomethyl sulfone was prepared by the same method.

***trans*-Stilbene-1,2-$d_2$ from α-Bromobenzyl Sulfone.** Solutions of sodium methoxide (0.1857 g, 3.438 mmoles) in 5.00 ml of deuteriomethanol ($CH_3OD$), and α-bromobenzyl benzyl sulfone (57.00 mg, 0.753 mmole) in 5.00 ml of deuteriomethanol ($CH_3OD$), which had been thermostated at 25.0°, were combined. After 5 hr the solution was quenched by adding it to 30 ml of 3 *N* hydrochloric acid. This solution was extracted with 50 ml of ether, washed twice with 10-ml portions of water, and dried over anhydrous magnesium sulfate. Removal of the solvent gave white platelets (0.02837 g, 0.1557 mmole, 89%, mp 112–115°). The nmr spectrum in carbon tetrachloride was identical with that of *trans*-stilbene, except that the peak for the vinyl protons (7.10 ppm) was absent.

**Kinetic Procedures.**[25] **A. Spectrophotometric Measurements.** Rates were determined spectrophotometrically by the method described previously.[11]

**B. Titrimetric Measurements.** Sample solutions of α-halo sulfone were prepared by dissolving enough sulfone in the appro-

(23) Microanalyses were by Micro-Tech, Skokie, Ill.

(24) Unpublished results of R. Rak (National Science Foundation Undergraduate Research Participant, 1965–1966).

(25) We wish to thank Dr. Earle B. Hoyt, Jr., for carrying out most of the kinetic runs with the benzyl halomethyl sulfones.

priate solvent to give 250–500 μmoles of halide when a 5-ml aliquot was taken from the reaction mixture. After thermostating for several hours, the base and sample solutions were combined. Aliquots taken at appropriate intervals were quenched in a solution of 2 ml of acetone and 4 ml of nitric acid (0.25 *M*) and titrated potentiometrically.[26] The recorder chart units were tabulated and corrected for a blank.

Pseudo-first-order rate constants were obtained by plotting log $(N_\infty - N_t)$ *vs.* *t*, where $N_\infty$ is the number of chart units at infinity and $N_t$ is the number at time *t*. These plots were linear for more than four half-lives.

Titrimetric rate constants were determined in duplicate for $PhCH_2SO_2CHClPh$: $k = 2.58 \times 10^{-2}\ M^{-1}\ sec^{-1}$ at 25° in 40% (volume) dioxane–water. The spectrophotometric rate constant under the same conditions was $2.51 \times 10^{-2}\ M^{-1}\ sec^{-1}$.

**Bis(α,α-dideuteriobenzyl) Sulfone.** Benzyl sulfone (2.46 g, 9.97 mmoles), sodium hydroxide (0.20 g, 5.0 mmoles), deuterium oxide (9 ml, 500 mmoles, 99.77% deuterated), and dioxane (40 ml) were kept at 60° for 12 hr. The resulting solution was acidified with 1 ml of 12 *N* hydrochloric acid and concentrated. The yellow platelets obtained were washed with water and crystallized from absolute ethanol to give 2.35 g (9.39 mmoles, 94%) of colorless needles, mp 146.0–146.5°. The nmr spectrum showed 97% deuteration.

The rate of exchange was determined by dissolving sufficient sulfone in methanol to give 0.03 g/10-ml aliquot. This solution was thermostated and mixed at $t_0$ with a thermostated sample of methanolic sodium methoxide; the base concentration in the resulting solution was $1.60 \times 10^{-2}\ M$. Aliquots (10 ml) were removed at appropriate time intervals and quenched with 10 ml of 0.25 *N* nitric acid. The sulfone was collected on a sintered-glass filter and, after drying, transferred quantitatively to an nmr tube. Acetonitrile was used as a solvent; the same volume was used for each aliquot.

The instrument (Varian A-60) was tuned, and the aliquot samples were run, one after the other, without instrument readjustments. Each spectrum was integrated (relative to the phenyl hydrogens) eight to ten times. The reactions were allowed to continue for three to four half-lives. Rates were determined by plotting log $(A_\infty - A_t)$ *vs.* *t*, where *A* is the percentage of α,α′-hydrogens. The slope multiplied by 2.303 and divided by the base concentration gave the second-order rate constant. The values obtained (uncorrected for statistical or isotope effects) were: $8.9 \times 10^{-3}$ and $9.5 \times 10^{-3}\ M^{-1}\ sec^{-1}$ at 0.2° and $2.0 \times 10^{-1}$ and $2.2 \times 10^{-1}$ at 25.1° ($E_a$ = 20 kcal/mole; $\Delta S^{\pm} = +1$ eu).

**Activation Parameters.** The activation energy was calculated in each instance from the slope of the linear plot of log *k* *vs.* $1/T$ (three temperatures); $E_a = 4.576 \times$ slope. Activation entropies were obtained from the equation

$$\Delta S^{\pm} = 4.576[-10.7531 - \log T + \log k + (E_a/4.576\ T)]$$

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# The Total Synthesis of *dl*-6-Demethyl-6-deoxytetracycline[1]

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**Abstract:** The first total synthesis of the prototypic tetracycline antibiotic, *dl*-6-demethyl-6-deoxytetracycline (**7**), from methyl *m*-methoxybenzoate (**10**), is described.

Interest in the tetracyclines, a class of uniquely constituted hydronaphthacene derivatives characterized by the intricacy of their chemistry and notable for their utility in medical practice, had its origin in the announcement by Duggar in 1948 of the discovery of Aureomycin [(chlortetracycline (**1**)].[2] The molecular structures of Aureomycin and Terramycin[3] [oxytetracycline (**2**)] were elucidated in these laboratories in 1952,[4] two years after Finlay and his colleagues announced the preparation of the latter antibiotic[5] by fermentation of the actinomycete, *Streptomyces rimosus*. Production of tetracycline itself (**3**) by catalytic hydrogenolysis of Aureomycin was reported in 1953;[6a,b] subsequently, the preparation by this compound by cultivation of certain strains of *Streptomyces aureofaciens* was reported.[6c]

Since 1953 a prodigious number of investigations has been recorded, directed toward a definition and rationalization of the biogenetic origin and of the chemical, microbiological, pharmacological, and clinical properties of these polyoxygenated hydronaphthacenes,[7] while simultaneously a search for new mem-

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(3) Terramycin is a registered trademark of Chas. Pfizer & Co., Inc. Aureomycin is a registered trademark of Lederle Laboratories Division, American Cyanamid Co.

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