$$X + BH \overset{K_4}{\rightleftharpoons} X' \qquad X + B \overset{K_5}{\rightleftharpoons} X''$$

$$X' \xrightarrow{k_{13}} P_1 \qquad X'' \xrightarrow{k_{14}} P_1$$

Assuming that the ratio of the reactivity of species B to that of species BH is given by

$$e = \frac{k_{14}/K_5}{k_{13}/K_4}$$

it may be shown that

$$K_{\text{app}} = \frac{(K_4k_3/k_{13})([H] + K')([H] + K_2)}{[H]([H] + eK_2)} \qquad (11)$$

When $e = 0$ (*i.e.*, species B is unreactive), eq. 11 reduces to eq. 6. When $e = 1$ (*i.e.*, both buffer species equally reactive), eq. 11 reduces to eq. 10.

Acknowledgment. We are grateful to the National Institutes of Health for financial support (Grant No. AM-04288) and to Dr. Josef Rudinger for helpful discussion. During this investigation, B. A. C. was supported by a training grant (2G-53) of the U. S. Public Health Service (1963–1964) and was a Predoctoral Fellow of the National Institute of General Medical Sciences, U. S. Public Health Service (1964–1965).

Reaction of Acyclic α-Halo Sulfones with Base.[1a] Stereochemistry of the Intermediate Episulfones

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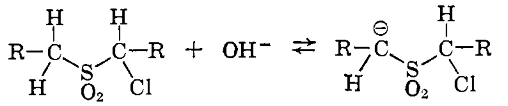
Contribution from the Esso Research and Engineering Company, Baytown Research and Development Division, Baytown, Texas. *Received July 19, 1965*

Abstract: The reaction of α-halo sulfones with base to give olefins has been investigated with a variety of acyclic sulfones and a variety of bases. The *cis/trans* ratios of the product olefins have permitted conclusions to be drawn about the reaction mechanism. The internal displacement of halide from the halo sulfone anion appears to favor formation of the *cis* episulfones which then give *cis* olefins. The magnitude and nature of this "*cis* effect" is briefly discussed. The postulated intermediates, *cis*- and *trans*-2-butene episulfones, have been synthesized by an independent route and their reactions have been examined.

The intriguing transformation of α-halo sulfones into olefins upon treatment with dilute alkali, first reported in 1940 by Ramberg and Bäcklund,[2] has been of both synthetic and mechanistic interest. Although the reaction has not found broad use in olefin synthesis, there appeared recently two reports of several practical synthetic schemes involving α-halo sulfones.[3,4] A salient feature of the reaction is its general applicability. With very few exceptions, notably in systems leading to small ring olefins,[5] the reaction is general for molecules containing the structural elements of a sulfonyl group, an α-halogen, and at least one α'-hydrogen atom. The double bond in the product cleanly and unequivocally supplants the sulfonyl group in the starting material.

A mechanistic study by Bordwell and Cooper[6] was interpreted to be consistent with the sequence shown in eq. 1 and 2. The reaction was first order in both hydroxide ion and in sulfone. The data pointed to rapid equilibrium between the sulfone and its anion, rate-controlling elimination of halide from the anion, and rapid loss of sulfur dioxide from the episulfone intermediate, either thermally or with participation of hydroxide ion.[7]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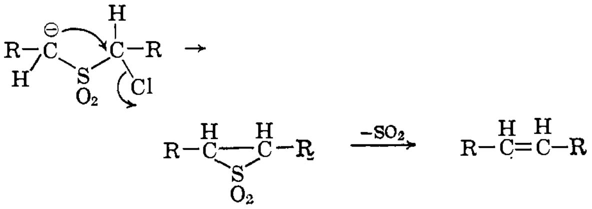
(2)

Ramberg and Bäcklund[2] had concluded from simple physical data that the products from α-bromoethyl ethyl sulfone and ethyl α-bromopropyl sulfone were mainly *cis*-2-butene and *cis*-2-pentene, respectively. Bordwell and Cooper, on the other hand, recovered a 94% yield of *trans*-stilbene from the reaction of α-chlorobenzyl benzyl sulfone.[6] The stereochemistry of the reaction required clarification. At this point the present work was begun.

Stereochemical Results. When α-chloroethyl ethyl sulfone was gently refluxed with 2 *N* potassium hydroxide solution, the sole olefinic product (76% yield)

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[1] (a) These results were communicated in preliminary form by N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **85**, 1209 (1963). (b) c/o American Embassy, Bonn/Bad Godesberg, Germany. Reprints available from Esso Research and Engineering Company.

[2] (a) L. Ramberg and B. Bäcklund, *Arkiv Kemi, Mineral. Geol.*, A13, No. 27 (1940); (b) see also B. Bäcklund, Thesis, Uppsala, 1945.

[3] N. P. Neureiter, *J. Org. Chem.*, **30**, 1313 (1965).

[4] L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4383 (1964).

[5] See, for example, the unsuccessful attempt of I. Mischon to prepare cyclobutene through this reaction, Ph.D. Thesis, Technische Hochschule zu Karlsruhe, Germany, 1955.

[6] F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **73**, 5187 (1951).

[7] There recently have appeared two papers on the mechanism of this reaction by L. A. Paquette. His evidence also supports the internal displacement reaction and formation of the episulfone intermediate: *ibid.*, **86**, 4085 (1964). He has also presented evidence against the possibility of a carbene mechanism in that instance: *ibid.*, **86**, 4089 (1964).

was shown to be about 78% *cis*- and 22% *trans*-2-butene. There was a clear preference for formation of the thermodynamically less stable olefinic isomer.[8]

The prodigious quantity of data assembled by Cram and co-workers on the stereochemistry of α-sulfonyl carbanions and the variations in their configurational stability as a function of solvent suggested that the medium might be an important factor in this reaction.[9] Accordingly, we expected to find a change in the stereochemistry with a change in solvent. The surprising results of experiments in which both the solvent and the basic reagents were varied are shown in Table I.

The stereochemistry of the reaction is remarkably insensitive to changes in the nature of the solvent and, over a wide range, in the nature of the base. However, with the strong, hindered base potassium *t*-butoxide, a profound change in stereochemistry occurs with predominance of *trans*-2-butene. The base must play an important role in determining the configuration of the product.

Table I. 2-Butene from α-Chloroethyl Ethyl Sulfone

Base	Solvent	Temp., °C.	Yield, %	% *cis*[a]	% *trans*[a]
2 *M* KOH	H_2O	100	76	78.1	21.9
2 *M* NaOH	H_2O	100	75	78.8	21.2
2 *M* KOH	H_2O	60	...	81.5	18.5
1 *M* $Ba(OH)_2$	H_2O	100	66	78.6	21.4
2 *M* LiOH	H_2O	100	...	76.1	23.9
1 *M* NaOBu	*n*-BuOH	117	74	74.6	25.4
0.75 *M* C_6H_5Li[b]	C_6H_6	80	...	73.3[f]	26.7
0.75 *M* C_6H_5Li[c]	C_6H_6	...	...	78.1[f]	21.9
1.0 *M* *t*-BuOK	*t*-BuOH	~93	82[d]	22.6[f]	77.4
1.3 *M* *t*-BuOK[e]	*t*-BuOH	82	...[d]	18.6[f]	81.4
1.0 *M* *t*-BuOK	Toluene	110	...[d]	24.5[f]	75.5

[a] The total of *cis*- and *trans*-2-butene is normalized to 100%. [b] Sulfone added all at once to refluxing phenyllithium solution. [c] Sulfone added to stirred phenyllithium solution at room temperature; mixture heated for gas evolution. [d] Product contaminated with 3–5% isobutylene. [e] Sulfone added at room temperature; mixture heated to reflux. [f] Small variations in product composition in different runs in the same solvent may be explained in a number of ways: partial fractionation of *cis*- and *trans*-2-butene by the solvent; decrease in base concentration as the reaction proceeds; small amounts of hydroxide in the *t*-butoxide; differences in reaction temperature; etc. It is not known to what extent these small reported differences may be real. However, a clear-cut difference between the *t*-butoxide and the other bases is incontrovertible.

Episulfone Studies. The successful synthesis of ethylene sulfone from diazomethane and sulfur dioxide[10] suggested the possibility of preparing the proposed intermediate episulfone[6] and studying its stereochemistry.

An ethereal solution of diazoethane was treated with sulfur dioxide at temperatures between −40 and −10°. Concentration of the solution *in vacuo* gave a liquid residue which on heating to 65° rapidly decomposed to sulfur dioxide and a mixture of nearly equal amounts of *cis*- and *trans*-2-butene. The ratio of the isomeric olefins corresponded to the ratio of *cis*- and *trans*-2-butene episulfone, respectively, in the product mixture. The over-all yield of episulfone based on the diazoethane precursor (N-nitroso-N-ethyl ethyl carbamate) was about 56%.

By chilling a methanol solution of the *cis*- and *trans*-episulfone mixture to −78°, white crystals were obtained to which the structure of *cis*-2-butene episulfone was assigned. The freshly recrystallized material was converted by heating, either neat or in a solvent, to an essentially quantitative yield of sulfur dioxide and *cis*-2-butene.

Repeated chilling and filtering of the methanol filtrate led to a noncrystallizable liquid residue which on heating to 60–100° gave sulfur dioxide and a mixture of 20% *cis*- and 80% *trans*-2-butene. This residue therefore was a mixture of 20% *cis*- and 80% *trans*-2-butene episulfone.

The episulfones were moderately unstable materials. They slowly decomposed at room temperature, although crystals could be retained for several days. At −10 to 15°, they could be kept for long periods of time, although some polysulfone was always present in stored samples. Thermal decomposition of pure *cis* episulfone which had been kept for several days always gave a small amount of *trans*-2-butene.

When the freshly recrystallized *cis* episulfone was heated alone, with 2 *N* potassium hydroxide, or in an organic solvent (*e.g.*, isopropyl alcohol), *cis*-2-butene (<0.5% *trans* by v.p.c.) was the only organic material obtained. Hence upon either thermal treatment or under normal Ramberg–Bäcklund reaction conditions (2 *N* potassium hydroxide) the elimination of sulfur dioxide is a stereospecific *cis* process. The ratio of *cis*- and *trans*-2-butenes in the reaction product from the α-halo sulfones must correspond to the ratio of *cis*- and *trans*-2-butene episulfones formed as intermediates in the reaction if, indeed, the episulfone is an intermediate.

The removal of sulfur dioxide from the *cis* episulfone was examined in the presence of several different bases (see Table II).

Table II. *cis*-2-Butene Episulfone Decompositions

			2-Butene	
Base	Solvent	Temp., °C.	% *cis*	% *trans*
2 *N* KOH	H_2O	100	>99[a]	<1
2 *N* NaOH	H_2O	100	>99.5	<0.5
2 *N* NaOH	H_2O	100	>99[a]	<1
None	*i*-C_3H_7OH	82	>99[a]	<1
None	Neat	65–85	>99[a]	<1
0.5 *M* *t*-BuOK[b]	*t*-BuOH	80	27	73
1 *M* *t*-BuOK[b]	*t*-BuOH	80	24	76
0.75 *M* *t*-BuOK[b]	*t*-BuOH	80	22	78
1 *M* *t*-BuOK[c]	*t*-BuOH	80	19.4	80.6

[a] If the *cis* episulfone was allowed to stand for several hours or days even at −10°, the decomposition gave a small fraction of the *trans* isomer. [b] It was observed that when slightly moist *t*-butyl alcohol was used, or when the *t*-butoxide became dilute or exhausted during the reaction, the percentage of *cis*-2-butene in the product increased. No careful study was made of the product composition *vs.* water (hydroxide) content. [c] The episulfone solution was evacuated just before addition to remove any butene formed by thermal decomposition prior to contact with the base which would increase the *cis*-2-butene content.

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(8) The reported difference in $\Delta F_f°$ of *cis*- and *trans*-2-butene at 100° is 0.63 kcal./mole (see "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," API Project 44, Dec. 31, 1952, API, Carnegie Press, Pittsburgh, Pa., 1953), which would correspond to an equilibrium value of about 30% *cis* and 70% *trans*.

(9) See D. J. Cram and A. S. Wingrove, *J. Am. Chem. Soc.*, **85**, 1100 (1963), for a summary of the pertinent arguments.

(10) See G. Hesse, E. Reichold, and S. Majmudar, *Ber.*, **90**, 2106 (1957).

The striking result is that with potassium *t*-butoxide in dry *t*-butyl alcohol, the olefin was a mixture of about 20% *cis*- and 80% *trans*-2-butene. The *t*-butoxide effected a complete change in the stereochemistry of the elimination, just as it had in the α-halo sulfone reaction.

Deuterium-Exchange Experiments. The episulfone decomposition and the α-chloro sulfone hydrolysis were carried out in deuterium oxide solvent with sodium deuteroxide as the base. The episulfone gave 2-butene with only about 5% of the two theoretical hydrogens replaced by deuterium, while the chloro sulfone gave 2-butene with 97% deuteration around the double bond. The episulfone in 2 *N* alkali decomposes to 2-butene more rapidly than it exchanges, while the chloro sulfone exchanges all of its α-hydrogens more rapidly than chloride ion is eliminated or olefin is formed. In fact, this equilibration is so facile that it can be used as a synthetic procedure for deuterated olefins.[3,7]

However, when the decomposition of 2-butene episulfone was carried out in deuterated *t*-butyl alcohol with potassium *t*-butoxide, the 2-butene product was essentially completely deuterated at the 2- and 3-positions. We conclude that in the presence of the strong, hindered base, potassium *t*-butoxide, the episulfone exchanges its α-hydrogens more rapidly than it loses sulfur dioxide. During the process of exchange, the episulfone is isomerized to an equilibrium mixture of *cis*- and *trans*-2-butene episulfones.[11] This mixture then loses sulfur dioxide, perhaps by a thermal process.[12] Protonation of the anion would take place from both sides of the three-membered ring in a ratio dependent upon the relative stabilities of the *cis*- and *trans*-episulfones. Control experiments showed that potassium *t*-butoxide did not isomerize *cis*- to *trans*-2-butene under the reaction conditions.

These exchange results are manifestly relevant to the halo sulfone rearrangement mechanism. They indicate that the change in stereochemistry in going from the hydroxide to the *t*-butoxide system is fully reconcilable with the episulfone as an intermediate.

Reactions of Other Sulfones. The reaction was extended to a number of other sulfones in which both the alkyl groups and the halogen atoms were varied. In addition to the new preparations, Table III includes reactions of particular stereochemical interest reported elsewhere.

Table III. Reaction of Various Sulfones with 2 *N* Potassium Hydroxide[a]

Sulfone	Product	Yield, %	% *cis*	% *trans*
α-Chloroethyl ethyl	2-Butene	76	78.1	21.9
α-Bromoethyl ethyl	2-Butene	~85	79.5	20.5
α-Iodoethyl ethyl	2-Butene	~87	78.2	21.8
α-Chloroethyl propyl	2-Pentene	~74	65.8	34.3
α-Bromoethyl propyl[b]	2-Pentene	85	60	40
α-Chloropropyl ethyl	2-Pentene	~57	71.3	28.7
α-Bromopropyl ethyl[b]	2-Pentene	71	70	30
α-Chloropropyl propyl[c]	3-Hexene	...	57	43
α-Iodopropyl propyl	3-Hexene	>57	55.5	44.5
α-Iodobutyl butyl	4-Octene	>50	52.5	47.5
α-Chlorobenzyl benzyl[d]	Stilbene	94	0	100

[a] Usually, the mixture was stirred and heated until gas evolution began. This was at 75° with the iodoethyl ethyl sulfone, at 85° with the bromoethyl, and close to 100° for the chloroethyl system. The total of *cis* and *trans* olefins in each case is normalized to 100%. [b] These values are from Bäcklund's thesis[2b] and were calculated by the author based on the reported refractive indices of the olefinic products. While the absolute values may be in error, the precision of the Swedish work seemed to justify their use on a relative basis. [c] This experiment was carried out by Mr. Thomas Whitney at Northwestern University, independent of the present work. The author is indebted to Mr. Whitney for this additional datum point. [d] Carried out in aqueous dioxane with NaOH.[6]

While the qualitative rates of the haloethyl ethyl sulfone eliminations increased markedly in the order chloro < bromo < iodo, the three sulfones gave essentially identical *cis*- and *trans*-2-butene mixtures. The forces controlling the stereochemistry of the reaction are either nearly independent of the nature, size, and the ease of elimination of the halogen atom, or they are affected by these variables in different, compensatory ways.[13]

Care was taken in comparing the reaction of α-chloroethyl propyl sulfone with α-chloropropyl ethyl sulfone. The 5.5 ± 0.3% difference in *cis*-2-pentene from the two systems is real and reproducible, showing quite convincingly, if not dramatically, that the two sulfones do not pass through the same mixture of intermediate sulfones in the course of the reaction. While this observation fails to positively exclude a zwitterion intermediate that would be formed by loss of the chloride by ionization, it does eliminate the possibility of an electrically symmetrical intermediate of the type which in the halo ketone system has sometimes been suggested for the Favorskii rearrangement.[14] Paquette has also argued against the zwitterion intermediate in concluding that his system reacts *via* a displacement.[7]

The present work clearly suggests that the elimination of the halide ion is a legitimate displacement process in which the α-sulfonyl carbanion's electron pair attacks the α′ carbon from the back side displacing the halogen and forming the three-membered ring. The slightly different steric requirements of the ethyl group when on the attacking carbon (A) rather than on the attacked carbon (B) could produce the slightly different stereochemical results. Since B gives a higher percentage of

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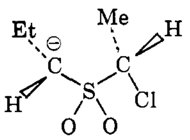
(11) This conclusion is consistent with the observations on α-sulfonyl carbanions in cyclic systems of E. J. Corey, H. Konig, and T. H. Lowry, *Tetrahedron Letters*, No. 12, 515 (1962).

(12) The interesting question of whether the base participates in the loss of sulfur dioxide from the episulfone has not been answered. The more complete exchange with *t*-butoxide as compared to hydroxide could be partially ascribed to a lower rate of attack on the sulfur of the episulfone ring by the hindered *t*-butoxide. While it is clear that a thermal process is sufficient for sulfur dioxide loss, it is not known whether a strong nucleophile can accelerate the cleavage. In the case of ethylene episulfone, Hesse, *et al.*,[10] have shown that treatment with barium hydroxide gives a β-hydroxyethanesulfinic acid salt which loses water and sulfur dioxide on heating to produce ethylene. While that is an example of attack on carbon, nucleophilic attack by hydroxide on sulfur, to give 2-butene, either directly or through intermediate carbanion formation cannot be excluded. Direct butene formation would be analogous to the desulfurization of episulfides with alkyl phosphites or phosphines: see N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **81**, 578 (1959) and D. B. Denney and M. J. Boskin, *ibid.*, **82**, 4736 (1960). Furthermore, the observed isolation of sulfonic acid salts from the reaction of dichloro sulfones is best interpreted on the basis of hydroxide participation in the cleavage step.[6,7] This question is now under investigation by J. M. Williams and F. G. Bordwell at Northwestern University (private communication).

(13) It is not easy to predict what stereochemical effect should be expected from a change in the halogen. A discussion of the possibilities and difficulties appears in W. H. Saunders, S. R. Fahrenholtz, E. A. Caress, J. P. Lowe, and M. Schreiber, *J. Am. Chem. Soc.*, **87**, 3401 (1965).

(14) (a) See R. C. Cookson and M. J. Nye, *Proc. Chem. Soc.*, 129 (1963); (b) A. W. Fort, *J. Am. Chem. Soc.*, **84**, 2620 (1962), and references mentioned therein. It is clear that the sulfone system is not as attractive for writing this intermediate as is the ketone.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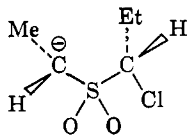
B

the *cis* isomer than A, one must conclude that stereochemically speaking it is easier to displace a halogen from a propyl group with an ethyl carbanion than it is to displace the halogen from an ethyl group with a propyl carbanion. It is easier for an ethyl group to "get out of the way" when it is on the attacked atom than when it is on the attacking atom.[15]

The same two sulfones were treated with 1 *M* potassium *t*-butoxide in *t*-butyl alcohol in matched experiments. Both α-chloropropyl ethyl sulfone and α-chloroethyl propyl sulfone gave identical mixtures of 15.8 ± 0.3% *cis*-2-pentene and 84.2% *trans*-2-pentene. In this instance the two starting sulfones do appear to pass through a common mixture of intermediates in the course of the reaction. This appears to be most convincing evidence for the intermediacy of the episulfone which is equilibrated by the strong, hindered potassium *t*-butoxide.

A final glance at Table III shows how the percentage of *cis* olefin drops as the size of the substituent groups increase. The α-chloropropyl propyl sulfone gave a mixture of 55.5% *cis*- and 44.5% *trans*-3-hexene. The chlorobutyl sulfone gave 52.5% *cis*- and 47.5% *trans*-4-octene. Even though there is increasing resistance to formation of the *cis* olefin as the size of the substituent groups increases, there is clearly a pronounced "*cis* effect" operating in this rearrangement.

Discussion. The "*cis* Effect." In the expression $\Delta\Delta F^* = -RT \ln k_2/k_1$, $\Delta\Delta F^*$ is the difference in free energies of activation of two reaction paths, one leading to the *cis* olefin and the other to the *trans* olefin. Since the yields of each olefin are proportional to the rates of their formation, k_2/k_1 is equal to the ratio of the yield of *trans* to *cis* olefin. In the case of the iodoethyl sulfone, the 22:78 ratio for k_2/k_1 at 75° corresponds to a $\Delta\Delta F^*$ of 0.87 kcal./mole favoring the *cis* isomer.

However, *cis*-2-butene is thermodynamically less stable than *trans*-2-butene to the extent of 0.65 kcal./mole at 75°.[8] If the forces of *cis* methyl repulsion in the transition state can be approximated by the thermodynamic forces favoring *trans*-2-butene over *cis*-2-butene, the total magnitude of the "*cis* effect" is 0.87 plus 0.65 or 1.52 kcal./mole at 75°.

If the episulfone is truly a reaction intermediate as concluded above, then the forces operating in the *cis*- and *trans*-2-butene episulfones would more closely approximate the transition state forces in the halo sulfone rearrangement. If one assumes that the experiments with potassium *t*-butoxide represent establishment of true thermodynamic equilibrium at the episulfone stage, one can estimate the magnitude of the forces favoring the *trans* episulfone from the *cis*/*trans* ratio (k_1/k_2). At 75°, k_1/k_2 is about 19:81 corresponding to 1.00 kcal./mole in favor of the *trans* episulfone. Hence, the magnitude of the "*cis* effect" becomes 1.00 plus 0.87 or 1.87 kcal./mole, if we base our estimate on the episulfones.

While the magnitude of the "*cis* effect" is not great, neither is it readily explanable. Several examples of preferential formation of *cis*-2-butene in elimination or isomerization reactions appear in the literature; however, the explanations offered do not appear to be readily applicable to the present sulfone system.[16]

The sulfone system apparently involves preferential formation of a *cis*-2,3-dialkyl ethylene sulfone by an internal S_N2 displacement reaction.[17] From a consideration of models there is no apparent steric reason why the *cis* isomer should be favored.[18]

An iconoclastic suggestion has been made that at the critical transition state distance during episulfone formation, there is a net force of attraction predominating over repulsion between the two alkyl groups, leading to formation of the *cis* episulfone.[1] As the size of the alkyl groups increases, the repulsion increases and the per cent of *cis* isomer drops.

While it remains to examine this suggestion with detailed calculations, a simple example is of interest. If the attractive forces (F_A) vary as the reciprocal sixth power of the distance[19] and the repulsive forces (F_R) vary as the reciprocal of the twelfth power,[20] it is reasonable that at some distance methyl–methyl attraction will be greater than repulsion. In the skew form of *n*-butane Pitzer and Catalano estimated for methyl–methyl interaction that the repulsive forces of 2.5 kcal./mole slightly exceeded the attractive forces of about 2.0 kcal./mole. Using these values for F_R and F_A, respectively, at an assumed distance between methyl group centers of 2.95 Å., and assuming a $1/r^{12}$ dependence for F_R and a $1/r^6$ dependence for F_A, it is easy to calculate that $F_A = F_R$ at a methyl–methyl distance of 3.06 Å. At greater distances the attractive forces F_A will predominate up to a certain maximum.

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[15] It should be pointed out that the yield of 2-pentene from the chloropropyl ethyl sulfone (56%) was considerably lower (by 18%) than that from the chloroethyl propyl sulfone (74%). The same effect was observed by Bäcklund with the bromoethyl and bromopropyl sulfones (85 *vs.* 71% yields). This fact is assumed to be unrelated to the stereochemical results although no conclusive evidence on this point is available. Possibly a larger portion of the sulfone in one case was consumed by side reactions such as metathesis with sulfite ion or direct hydrolysis to the aldehyde.

(16) (a) Pyrolysis of trimethyl-*sec*-butylammonium hydroxide gave mostly 1-butene, but the *cis*/*trans* ratio of the 2-butene was 1.41: A. C. Cope, N. A. LeBel, H. H. Lee, and W. R. Moore, *J. Am. Chem. Soc.*, **79**, 4720 (1957); (b) the isomerization of 1-butene over a silica–alumina catalyst gave preferentially *cis*-2-butene: P. J. Lucchesi, D. L. Baeder, and J. P. Longwell, *ibid.*, **81**, 3235 (1959); (c) the isomerization of 1-butene with sodium on alumina, and other strongly basic catalysts gave mainly *cis*-2-butene: W. O. Haag and H. Pines, *ibid.*, **82**, 389 (1960); the same authors, *ibid.*, **82**, 2488 (1960), found that alumina or liquid phosphoric acid, when used to isomerize 1-butene, also led to *cis*-2-butene production at a rate higher than that for the *trans;* similar results were observed in the alumina-catalyzed dehydration of 2-butanol: *ibid.*, **83**, 2847 (1961); their explanation of the stereochemical results has been questioned by W. B. Smith and W. H. Watson, *ibid.*, **84**, 3174 (1962); (d) A. Schriesheim, J. E. Hofmann, and C. A. Rowe, Jr., *ibid.*, **83**, 3731 (1961), and subsequent papers have studied the stereoselective conversion of 1-butene to *cis*-2-butene by treatment with potassium *t*-butoxide in dimethyl sulfoxide.

(17) Although the stereochemistry of the initially formed episulfone intermediate in the *t*-butoxide system is not known, one would expect it to be mainly the *cis* isomer as is observed in the hydroxide system where little or no episulfone isomerization occurs before elimination of sulfur dioxide.

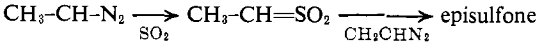
(18) L. L. McCoy, *J. Am. Chem. Soc.*, **84**, 6416, 2246 (1962), and other references cited therein, has reported a solvent dependent stereoselective ring closure to *cis*-substituted cyclopropanes when the substituents are polar moities such as COOR. His explanation was based on a dipolar interaction in the transition state which could be interrupted by the proper solvent. Again, there appears to be no lesson relevant to the sulfone system.

(19) K. S. Pitzer and E. Catalano, *ibid.*, **78**, 4844 (1956).

(20) J. O. Hirschfelder, C. F. Curtis, and R. B. Bird, "Molecular Theory of Gases and Liquids," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 1070–1075.

Using this very simple relationship, the two resulting simultaneous equations only can be solved for the distance r when $F_A - F_R \le 0.4$ kcal./mole. This condition at which F_A is maximally greater than F_R occurs at $r = 3.49$ Å. At greater distances the difference decreases again. Whether this is a realistic value for the methyl-methyl distance at the critical point during formation of the transition state leading to the episulfone is unknown.

Comment is required on the stereochemistry of the reaction of diazoethane with sulfur dioxide to give nearly equal mixtures of *cis*- and *trans*-2-butene sulfones (*trans* isomer slightly predominating) even at quite low temperatures. It appears that the reaction proceeds through methyl sulfene (C)[11,21] which then reacts with a new molecule of diazoethane.[21c] However, the various results which have been reported for different diazo compounds seem rather surprising.

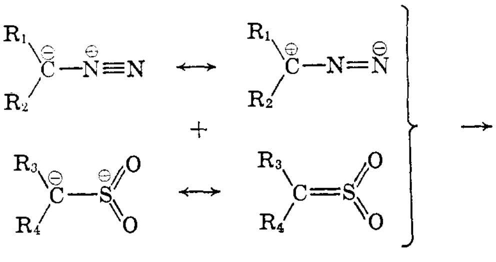


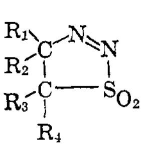
$$CH_3\text{-}CH\text{-}N_2 \xrightarrow[SO_2]{} CH_3\text{-}CH{=}SO_2 \xrightarrow[CH_2CHN_2]{} \text{episulfone}$$

C

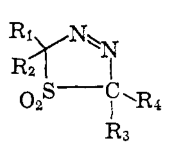
Diazomethane[10] and diazoethane gave moderately stable episulfones in reasonable yield. Ethylphenyldiazomethane, and the corresponding *p*-methoxy and *p*-bromo derivatives[22] all gave episulfones which on heating readily lost sulfur dioxide to give the olefins. Diphenyldiazomethane gave an episulfone which on heating in different solvents underwent a series of rearrangements.[23] However, ethylcyclohexyldiazomethane gave instead of an episulfone, a 1,3,4-thiadiazoline (E) which was thermally stable up to about 180° when it lost sulfur dioxide to give the azine.[24]

It may be useful to visualize the interaction of a sulfene with a diazo compound as a 1,3 addition[25] in which two directions of addition are possible.[26] To our knowledge there are no reported examples of Δ^2-thiadiazoline 1,1-dioxides such as D. Possibly, this fact is a reflection of their low stability. Loss of nitrogen could give either the episulfone or polysulfone which was observed in small amount as a by-product in the butene episulfone synthesis.[27]

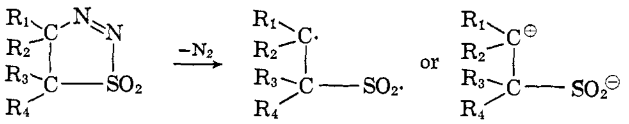




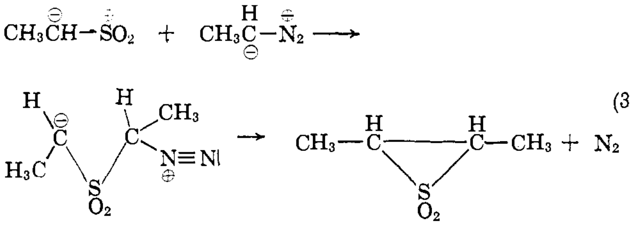
D



E



If the reaction of the sulfene were to take place according to eq. 3, the intermediate F would be nearly analogous to the carbanionic intermediate in the halo sulfone elimination, and therefore the stereochemical results (with the *cis* isomer predominating) should be similar. The fact that the *cis* and *trans* isomers are formed in nearly equal amounts suggests that a different sequence applies.[28]



F

(3)

Regrettably the recent, extensive work on the stereochemistry and configuration of α-sulfonyl carbanions has not provided a satisfactory explanation of the "*cis* effect." For that reason these highly interesting results will not be discussed further.[9,29]

Experimental Section[30]

α-Halo Sulfones and Reactions with Bases. All procedures for the syntheses and alkaline decompositions of α-halo sulfones have been reported previously.[3] When different reagents or solvents were used in the decompositions of the halo sulfones, the reaction mixture was gently refluxed under an efficient condenser while the volatile reaction product was carried over into a cold trap by a slow stream of nitrogen. In certain cases the product was contaminated with small amounts of solvent, which, however, did not complicate the v.p.c. analysis.

Preparation of 2-Butene Episulfones. A solution of diazoethane in anhydrous ethyl ether was prepared[31] and dried for several hours at 0° over potassium hydroxide pellets. The solution was transferred to a 1-l. round-bottomed flask equipped with gas inlet and outlet tubes, and treated with sulfur dioxide in a manner similar to that described by Hesse, *et al.*,[10] for diazomethane. Dry, gaseous sulfur dioxide was passed slowly over the diazoethane solution which was cooled to between −10 and −45° in different experiments. As sulfur dioxide was introduced, nitrogen was

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[21] (a) I. J. Borowitz, *J. Am. Chem. Soc.*, **86**, 1146 (1964), and other references cited therein; (b) H. Kloosterziel, M. H. Deinema, and H. J. Backer, *Rec. trav. chim.*, 71, 1228 (1952). (c) The recent report of G. Opitz and K. Fischer, *Angew. Chem.*, 77, 41 (1965), on the formation of episulfones from the reaction of diazoalkanes with sulfenes generated from sulfonyl halides provides very convincing evidence for this sequence.

[22] L. N. Vargha and E. Kovács, *Ber.*, **75**, 794 (1942).

[23] H. Kloosterziel and H. J. Backer, *Rec. trav. chim.*, 71, 1235 (1952).

[24] G. Hesse and E. Reichold, *Chem. Ber.*, **90**, 2101 (1957).

[25] R. Huisgen, *Angew. Chem.*, 75, 604, 742 (1963).

[26] Concomitant addition of diazomethane to substituted olefins with two orientations is known: *cf.* R. Huisgen, ref. 25, p. 615.

[27] The ease of the analogous loss of nitrogen from Δ^1-pyrazolines formed by diazoalkane addition to olefins is a function of the ring substituents. Some are stable, many undergo facile isomerization to Δ^2-pyrazolines, and others lose nitrogen to give cyclopropanes as rapidly as they are formed.[26]

[28] See R. Huisgen, ref. 25, p. 165.

[29] (a) H. E. Zimmerman and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **82**, 2505 (1960); (b) W. E. Truce and L. B. Lindy, *J. Org. Chem.*, **26**, 1463 (1961); (c) H. L. Goering, D. L. Towns, and B. Dittmar, *ibid.*, **27**, 736 (1962); (d) F. J. Corey, H. Konig, and T. H. Lowry, *Tetrahedron Letters*, No. 12, 515 (1962).

[30] Nuclear magnetic resonance spectra were recorded on a Varian A-60 instrument in carbon tetrachloride or deuterated chloroform solution with tetramethylsilane as an internal standard. Melting points are uncorrected unless indicated. Vapor phase chromatographic analyses were carried out by W. C. Jones, J. Dzilsky, H. C. Reeder, and V. H. Rushing according to procedures developed in the laboratories of Esso Research and Engineering Company over many years of work with petroleum hydrocarbons. Combustion analyses were by Mr. Earl Bowers of Humble Oil & Refining Co.

[31] A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, 13, 770 (1948).

evolved; the reaction could be accelerated by gentle agitation of the diazoethane solution. Most experiments were carried out between -20 and $-30°$ using a methanol bath into which pieces of Dry Ice were placed periodically to maintain the desired temperature. The reaction was complete when the orange solution became colorless.

The ether solution occasionally contained a small amount of suspended solid which was removed by filtration. The ether was removed on a Rinco evaporator *in vacuo* while the temperature was maintained below 0° to minimize product decomposition. Propanol (from the diazoethane preparation) was also removed by lowering the pressure to below 1 mm. In a typical run the total residue weighed 5.82 g. for a crude yield of 56% of episulfone based on the N-nitroso-N-ethyl ethyl carbamate starting material (25.0 g.). No careful study of yields or variables was made, but it appeared that higher temperatures, higher rates of sulfur dioxide introduction, and contaminants such as water in the diazoethane, all adversely affected the yield of episulfone. Hesse discusses some of these possibilities for the diazomethane reaction.[10] The isomeric composition of the product in different runs was determined by thermal decomposition of the crude product either neat or in solution (dilute base or isopropyl alcohol). The 2-butenes formed were analyzed by v.p.c. In a series of runs carried out between -38 and $-10°$ the compositions of the products varied from 45.7 to 48.8% *cis*- and 54.3 to 51.2% *trans*-2-butene.

There are a number of ways of recovering the product. The following technique was used though others might be found with further work. The crude residue was taken up in methanol, filtered to remove a little solid, and chilled at $-78°$. The white crystals were rapidly filtered in the cold and sucked dry. The 2.2 g. of solid consisted mainly of *cis*-2-butene episulfone. The 3.6 g. of faintly yellow filtrate, after methanol was removed, was mainly *trans*-2-butene episulfone with smaller amounts of the *cis* isomer. Several additional chillings and quick filtrations slightly increased the yield of solid *cis* episulfone, but no greater purification of the *trans* isomer above about an 80% mixture with the *cis* was achieved. Crystalline *trans* episulfone was never obtained.

The *cis*-2-butene episulfone could be recrystallized from cold ethanol or methanol although the best crystals were obtained by taking the product up in ether and adding hexane or petroleum ether along with a seed crystal and then letting the solution stand at 0° until formation of the long white needles was complete. When stored at room temperature the *cis* episulfone gradually decomposed into 2-butene and sulfur dioxide. It could, however, be stored for long periods of time (months or more) in the cold. Even at $-10°$, however, crystals which had been kept for some time should be dissolved in ether, the solution filtered and the episulfone recrystallized before use. Invariably a small amount of polymer had formed, and thermal decomposition of crystals stored for long periods always gave some of the *trans*-2-butene (a few per cent).

The episulfones were insoluble in hexane or petroleum ether, but otherwise quite soluble in the usual organic solvents and in water. The *cis*-2-butene episulfone had a melting point which varied somewhat with conditions. Several small crystals in an open capillary heated slowly had m.p. 57–57.5°. Heated rapidly in a capillary immersed at a bath temperature of 54°, it showed m.p. 59.0–59.5°. A single crystal on a Fisher-Johns melting point block endured up to 62° corr. when it melted all at once with some decomposition. It is possible that the product sometimes contained either small amounts of moisture or very small percentages of the *trans* isomer which caused the difference in melting points. One sample (recrystallized from ethanol and vacuum dried) had m.p. 61–62° (capillary tube), though the most commonly observed melting point was about 57°.

Thermal decomposition by heating to above the melting point of freshly recrystallized *cis*-episulfone gave a 98% yield of gas (by volume) consisting of a mixture of sulfur dioxide (odor) and *cis*-2-butene (>99.5% pure by v.p.c.). The n.m.r. spectrum of the *cis* compound had multiplets centered at τ 6.64 (CH groups) and 8.57 (J = 6 c.p.s.) (CH_3 groups), while the liquid residue which decomposed to predominantly *trans*-2-butene contained a second material (*trans*-2-butene episulfone) with multiplets centered at τ 7.22 (CH groups) and 8.43 (J = 6 c.p.s.) (CH_3 groups). This relative positioning of the two multiplets in the episulfones is analogous to those of *cis*- (τ 7.17 and 8.67; J = 6 c.p.s.) and *trans*- (τ 7.56 and 8.66; J = 6 c.p.s.) 2-butene episulfide; and *cis*- (τ 7.27 and 8.87; J = 6 c.p.s.) and *trans*- (τ 7.47 and 8.89; J = 6 c.p.s.) 2-butene epoxide.[32] It was also possible to use n.m.r. for analysis of crude episulfone mixtures. These values checked well with the v.p.c. analysis of 2-butenes from thermal decompositions of the same mixtures. *Anal.* Calcd for $C_4H_8SO_2$ (*cis*-2-butene episulfone): C, 39.98; H, 6.71. Found: C, 39.33; H, 7.17.

The liquid residue of ~80% *trans*- and 20% *cis*-2-butene episulfone (purified by dissolution in carbon tetrachloride, filtration, and solvent removal) gave the following analysis. *Anal.* Calcd. for $C_4H_8SO_2$: C, 39.98; H, 6.71. Found: C, 40.44; H, 6.78.

Reactions of Episulfones. The episulfone decompositions were carried out essentially in the same way as with the halo sulfones. The reagent solution was stirred and occasionally heated as the episulfone (dissolved in a few milliliters of the appropriate solvent) was added through a serum cap.

For the equilibration with potassium *t*-butoxide, the best results (*i.e.*, maximum isomerization) were obtained in the following way. The solid episulfone was placed in the reaction flask, the flask was evacuated or flushed with nitrogen for a few seconds to remove any butenes formed by thermal decomposition, and then the reagent solution was added all at once with stirring for rapid dissolution of the episulfone. The mixture was heated to boiling and the product was collected as usual. In experiments in which care was not taken to avoid some thermal decomposition of the episulfone prior to contact with the base, the percentage of *cis*-2-butene in the product was always a few per cent higher (see Table II).

Deuterium Exchanges in Deuterium Oxide. The deuterium exchange experiments were carried out with the α-chloroethyl sulfone and the deuterium content of the butene product was analyzed as described previously.[3] The gaseous product was 97% 2-butene-2,3-d_2 consisting of 79% *cis* and 21% *trans*.

A sample of the *cis*-2-butene episulfone (0.1062 g.) was dissolved in deuterium oxide (3.0 ml.) and added to a solution of sodium metal (0.2 g.) in 2.5 ml. of deuterium oxide. The solution was heated to gentle boiling and the gaseous product was collected. It was 99.5% *cis*-2-butene and mass spectral analysis showed 91.4% d_0, 8.3% d_1, and 0.4% d_2 to be present corresponding to about 4% exchange. In another experiment the estimated exchange was 6 ± 2%.

The experiment was repeated using a liquid mixture of 23% *cis*- and 77% *trans*-2-butene episulfone (0.2709 g.) dissolved in deuterium oxide (5 ml.). This solution was added to a hot solution of sodium metal (0.220 g.) in deuterium oxide (10 ml.). The yield of gas was 100% consisting of 23% *cis*- and 77% *trans*-2-butene with 89.1% d_0, 10.3% d_1, and 0.6% d_2 (all values ± 0.2%) corresponding to about 5% of the theoretical exchange, just as with the *cis*-episulfone above.

Deuterium Exchanges in *t*-Butyl Alcohol-d_1. A sample of deuterated *t*-butyl alcohol was prepared by repeated exchange of *t*-butyl alcohol with deuterium oxide followed by distillation from calcium hydride.[33] Analysis of the sample used in the exchange showed 92.4% *t*-BuOD, by mass spectrometry.[34]

To a sample of *cis*-2-butene episulfone (0.0874 g.) was added all at once at room temperature 8.5 ml. of a 1 M solution of potassium *t*-butoxide in deuterated *t*-butyl alcohol (92.4%). The solution was stirred for 1 min. and heated to gentle reflux. The gaseous product was about 80% *trans*- and 20% *cis*-2-butene (4% isobutylene also present). While the isobutylene complicated the mass spectral analysis, it was estimated that exchange was at least 94% of the theoretical with the principal product being 2-butene-d_2.

Matched Decomposition of α-Chloropropyl Ethyl Sulfone and α-Chloroethyl Propyl Sulfones. While the decompositions were carried out as described previously,[3] care was taken that conditions for collection and analysis were identical for both sulfones. In a series of runs, 6.1 to 6.6 mmoles of the sulfone was stirred and refluxed for 0.5 hr. with 25 ml. of 1.8 M potassium hydroxide solution. The 2-pentene products were carried over with a nitrogen stream into a cold trap and were then handled as liquids (yields were measured by volume) for charging to the vapor phase chromatograph. Two runs were made with the chloroethyl propyl sulfone giving 73 and 77% yields of 34.2 ± 0.3% *trans*- (65.8 ± 0.3% *cis*-) and 34.5% *trans*- (65.5% *cis*-) 2-pentenes, respectively. The chloropropyl ethyl sulfone in two runs gave 57 and 56% yields of 28.4 ± 0.3% *trans*- (71.6% *cis*-) and 29.0 ± 0.1% *trans*- (71.0% *cis*-) 2-pentenes, respectively. The pentene product had an aldehyde-like odor indicating a small amount of impurity which was

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[32] The author is indebted to N. F. Chamberlain of Esso Research and Engineering Co. for these data.

[33] Procedure of D. J. Cram and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 2178 (1961).

[34] Carried out by Dr. T. Aczel and associates of the Esso Research and Engineering Co.

not identified. At the end of the run with the chloropropyl ethyl sulfone, the reaction mixture was yellow, while the chloroethyl propyl sulfone reaction mixture was colorless.

Acknowledgment. The author is deeply grateful to Professor F. G. Bordwell for initially calling attention to this interesting system and for his thoughtful comments and valuable counsel in preparation of the manuscript. Special thanks are due to N. F. Chamberlain of the Esso Research and Engineering Co. for his help with the n.m.r. determinations, and to Esso Research and Engineering Co. directly for permission to publish these results.

New Method for Structural Assignments of Hydroxy Analogs of Coenzyme Q[1]

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Contribution from the Stanford Research Institute, Menlo Park, California.
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Abstract: A new method is now available which permits a direct structural assignment of quinones, chromenols, and chromanols of the coenzyme Q group which are unsymmetrically substituted in the benzenoid nucleus. The new method is based upon assignment of the nuclear magnetic resonance absorption of each of the two methoxy groups to a position on the chromenol and chromanol nucleus of a typical coenzyme Q; in turn, such assignments may be related to the quinone. Certain hydroxyquinones related to both coenzyme Q_7 and Q_{10} have been assigned structures in the past on the basis of the understanding that such hydroxyquinones were single compounds. This new method for structural assignments has revealed that the previously described hydroxy analogs of coenzyme Q_7 and Q_{10} are in reality approximately 50:50 mixtures of the two possible hydroxy derivatives.

Several compounds in the coenzyme Q group have been described in which one of the two methoxy groups has been replaced by another substituent.[2–7] Until now, no technique has been reported that could distinguish which of the two methoxy groups had been replaced or modified. A procedure utilizing nuclear magnetic resonance (nmr) spectroscopy has now been developed which allows unambiguous structural assignments of such compounds. This procedure involves the conversion of a substituent on the quinone nucleus into a deuterated methoxy group followed by ring closure to the chromenol (V) or chromanol (VI) derivative. The separate absorptions of the two methoxy groups in the nmr spectra of the chromenol and chromanol derivatives have now been structurally assigned, and comparison of the spectrum of the deuterated derivative with that of its undeuterated analog allows unequivocal structural assignments.

The chemical shifts of the methoxy protons in hexahydrocoenzyme Q_4 are almost identical, differing by only *ca.* 0.1 cps. In contrast, the nmr spectra of the chromenol (V)[8] and the chromanol (VI)[9,10] show clearly distinguishable methoxy absorptions at τ 6.13, 6.25, 6.14, and 6.25, respectively. There has been unequivocal assignment of the peak at τ 6.13 to the C_7-methoxy and the peak at τ 6.25 to the C_8-methoxy in the chromenol (V), and the peak at τ 6.14 for the C_7-methoxy group and the peak at τ 6.25 for the C_8-methoxy group in the chromanol (VI) have been established from the nmr spectra of the corresponding compounds in which the C_7-methoxy group was labeled with deuterium.

These deuterated derivatives were synthesized as depicted in I → V and VI. Fumigatin, 2-hydroxy-3-methoxy-6-methyl-1,4-benzoquinone (I), was reduced to the hydroquinone (II) by aqueous sodium dithionite. The hydroquinone II was alkylated with phytol and the hydroxyquinone (III) was obtained in 41% yield after ferric chloride oxidation followed by purification by column chromatography on Florisil. The procedure used to prepare III was a modification of the one used previously to make isoprenoid derivatives of fumigatin.[11]

The spectral data (ultraviolet, infrared, and nmr) of III are in agreement with the structure. The infrared spectrum shows O–H stretching absorption at 3400 cm^{-1} and typical quinone carbonyl absorptions at 1640 and 1615 cm^{-1}. The ultraviolet absorption spectrum shows $\lambda_{\max}$ 271 mμ ($\epsilon^{1\%}_{1\text{cm}}$ 237), 278 mμ ($\epsilon^{1\%}_{1\text{cm}}$ 238), and 440 mμ ($\epsilon^{1\%}_{1\text{cm}}$ 5.3). The nmr spectrum shows absorptions at τ 5.12 (1) t, CH=; 6.00 (3) s, $-OCH_3$; 6.85 (2) d, ring $-CH_2$; 7.98 (3) s, ring $-CH_3$; 8.07 (2) t, allylic $-CH_2$; 8.23 (3) s, allylic $-CH_3$; 8.91 (19) m, $-CH_2CH_2CH-$; 9.15 (12) m, $-CH_3$.

Methylation of III with deuterated methyl iodide in acetone in the presence of anhydrous potassium carbonate gave an 83% yield of deuterated hexahydrocoenzyme Q_4 (IV). The nmr spectrum of IV differed only from that of undeuterated hexahydrocoenzyme Q_4

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(1) Coenzyme Q. LXVI.

(2) I. Imada, *Chem. Pharm. Bull.* (Tokyo), 11, 815 (1963).

(3) I. Imada and H. Morimoto, *ibid.*, 13, 130 (1965).

(4) I. Imada, Y. Sanno, and H. Morimoto, *ibid.*, 12, 1056 (1964).

(5) B. O. Linn, N. R. Trenner, C. H. Shunk, and K. Folkers, *J. Am. Chem. Soc.*, **81**, 1263 (1959); C. H. Shunk, D. E. Wolf, J. F. McPherson, B. O. Linn, and K. Folkers, *ibid.*, **82**, 5914 (1960).

(6) C. H. Shunk, J. F. McPherson, and K. Folkers, *J. Org. Chem.*, **25**, 1053 (1960).

(7) H. W. Moore and K. Folkers, *J. Am. Chem. Soc.*, **87**, 1409 (1965).

(8) D. McHale and J. Green, *Chem. Ind.* (London), 1867 (1962).

(9) N. R. Trenner, E. L. Wong, B. O. Linn, and K. Folkers, *J. Am. Chem. Soc.*, **85**, 239 (1963).

(10) H. W. Moore and K. Folkers, *ibid.*, **86**, 3393 (1964).

(11) C. H. Shunk, J. F. McPherson, and K. Folkers, *J. Org. Chem.*, in press.