the presence of either 0, 1, or 3 μM concentrations of **2b**. The results, analyzed as Lineweaver-Burk plots, indicate that **2b** is a strongly bound ($K_I = 0.5$ μM), strictly competitive inhibitor of squalene synthesis.[23] This result is compatible with binding of **2b** at the first site, although it is not unequivocal proof, since competitive inhibition can also be explained by exclusive binding of **2b** at the second site when it is much poorer as a cosubstrate than **2a**.

The enzymatic formation of **1c**, with **2b** replacing the second farnesyl residue, requires that presqualene analogue **3b** also be a substrate.[3] This is somewhat surprising, because the extra methyl introduces a strong perturbation, both steric and electronic, into the postulated rearrangements which normally convert **3a** into **1a**.[24] The stability of cation **4a**, for example, a possible transient species in squalene formation,[24] is enhanced by methyl substitution (**4b**). It may be that the still unidentified radioactive product with the retention time of squalene results from abnormal drainage of some such intermediate into a chemical pathway made competitive by methyl substitution. Investigation of this point, as well as related studies with other substrate analogues, are continuing in our laboratory.

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(13) GLC on a Varian 2100 with flame ionization detectors, 6 ft × 2 mm i.d. glass columns, N_2 carrier gas (18 ml/min): system A, 3% OV-225 on 100–200 mesh Varoport 30; system B, 2.5% Dexyl 300 on 80–100 Chromosorb GHP.
(14) **1b** was obtained by $Ni(CO)_4$ coupling of 2-methylfarnesyl bromide.[15] The desired all-*E* isomer, present in 18% yield in the mixture of geometric and position isomeric products, was cleanly isolated by crystallization as a thiourea clathrate.[8,16]
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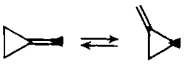
Maintenance of Chirality in a Photochemical Methylenecyclopropane Rearrangement

Sir:

Although there exists extensive literature related to the thermally induced automerization of methylenecyclopropanes (eq 1),[1] there is a notable paucity of data regarding the corresponding photochemically promoted process.



(1)

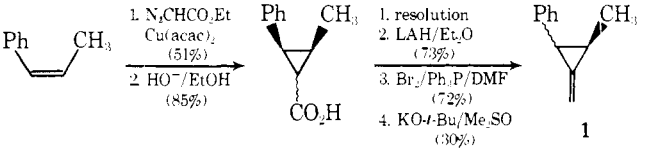
Kende et al.[2] as well as ourselves[3] have observed that in addition to suffering photofragmentation, aryl- or alkylmethylenecyclopropanes rearrange photochemically. Furthermore, the former investigators concluded that a singlet excited state is responsible for the reaction because the process could be neither triplet sensitized nor quenched by triplet acceptors.

Even though further mechanistic details for the photochemical rearrangement are lacking, it is already clear that the automerization of methylenecyclopropanes affords the rare opportunity to study a hydrocarbon reaction that can be initiated both thermally and photochemically. As one part of a program designed to exploit this potential, we have investigated the stereochemical fate upon rearrangement of an optically active methylenecyclopropane activated in these two significantly different ways.

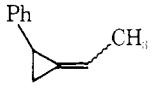
Synthesis of a suitable methylenecyclopropane,[4] 2-phenyl-3-methylmethylenecyclopropane (**1**), is outlined in Scheme I; all transformations, save for the final one, proceeded in an unexceptional fashion.[6] The strictly cis stereochemistry of the phenyl and methyl groups, which had been maintained up to this point,[6,7] was lost owing to the lability of the benzylic hydrogen of the methylenecyclopropane in the basic medium in which the elimination was performed.[8,9] Although it was not possible to effect the separation of the two isomers by GLC techniques, the mixture exhibited a rotation, $[\alpha]^{20}D$ +2.0°,[10] of sufficient magnitude for our purposes. It is to be noted that the base-catalyzed geometric isomerization has the effect of racemizing one of the two chiral centers in **1** and, because the asymmetry of the second center is lost during the expected methylenecyclopropane rearrangement (vide infra), a cis to trans ratio in **1** of 1:1 would have proven disastrous to our goals; fortunately, the trans isomer predominates by a factor of about three over the cis in the isolated mixture.

Thermolysis of the optically active mixture of *cis*- and

Scheme I. Synthesis of a Chiral Methylenecyclopropane



trans-**1** (35 min, 87°, trichloroethylene) partially equilibrated these isomers with *E*- and *Z*-2-phenylethylidenecyclopropane (**2**).[11] The two isomers were present in the ratio



2

18:1, as revealed by capillary GLC analysis, but it has not yet been possible to determine whether the *E* or *Z* isomer is the major component of the mixture.[12] As expected, the mixture of the isomers of **2** was optically active, having $[\alpha]^{20}D$ +9.4°. It can be presumed, by analogy to the studies with Feist's ester,[1c] that this rotation results from the formation of products (**2**) via migration of C-2 of **1** in a highly stereoselective fashion with inversion of configuration. The positional selectivity that results in the failure of 2-methylbenzylidenecyclopropane to be formed from **1** by migration of C-3 is amply precedented.[1]

Photolysis[13] of the mixture of isomers of **1**, $[\alpha]^{20}D$ +2.0°, for 6 h afforded a 1:1 mixture of **1** and the geometric isomers **2**; the latter were present in the ratio 1.4:1, the major component being the same as that observed in the thermolysis. The ethylidenecyclopropanes (**2**), upon GLC purification, had a rotation of $[\alpha]^{20}D$ +7.0°, and recovered **1** showed $[\alpha]^{20}D$ +1.0°.[14] In a second experiment, optically active **2**, $[\alpha]^{20}D$ +9.4°, obtained by thermolysis of **1**, was irradiated for 6.5 h.[13] The mixture of isomers of **1** that was isolated was found to have a rotation of +1.5°.

These results clearly demonstrate that chirality is maintained during the course of both the photochemical and the thermal methylenecyclopropane rearrangements. Furthermore, if it is accepted that the latter process occurs with inversion of configuration, our preliminary results suggest that the overall stereochemistry of the photochemical reaction also involves net inversion of configuration at the pivot atom, C-2. This second conclusion is open to some question since the *E*-**2**.*Z*-**2** is significantly different in the thermal and photochemical experiments. However, the ratio of the rates of isomerization of *cis*- and *trans*-**1** is essentially independent of the mode of molecular excitation, an observation that lends support to our interpretation of the results. In addition, the report that the *E* and *Z* isomers of a chiral 2-methylethylidenecyclopropane, a pair of molecules closely analogous to *E*- and *Z*-**2**, both produce rotations in the same direction[1b] is an additional basis for our belief that the direction of rotation for the two different mixtures of *E*- and *Z*-2-phenylethylidenecyclopropane (**2**) formed in our experiments is consonant with identical net stereochemistry for both the thermal and the photochemical rearrangements.[15]

Whether the photochemical results represent the stereochemical consequence of the transformation of a electronically excited molecule of **1** to an electronically excited molecule of **2** (or vice versa) followed by relaxation to ground state or whether photoexcited **1** (or **2**) relaxes to a ground vibrational state sufficiently "hot" to permit passage through the "thermal" transition state cannot be determined from our present observations. Our results, however, do definitively exclude the development of the planar geometry calculated to be favored for triplet trimethylenemethane.[16] Moreover these results add another dimension to Kende's conclusion[2] that the photochemical methylenecyclopropane rearrangement is a phenomenon of a singlet rather than a triplet manifold.

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(8) That the isolation of the mixture of geometric isomers is not the result of the prior base-catalyzed isomerization of the precursor bromide is shown by the observation that the bromide having the phenyl and methyl groups trans to one another fails to eliminate to give **1**.
(9) Treatment of 2-phenylmethylenecyclopropane with potassium *tert*-butoxide in Me_2SO-d_6 under the reaction conditions used to produce **1** afforded 2-phenylmethylenecyclopropane that was at least 90% monodeuterated at the 2-position.
(10) Optical rotations were taken of hexane solutions using a Perkin–Elmer Model 141 polarimeter.
(11) A mixture of *E*- and *Z*-2-phenylethylidenecyclopropane (**2**) was available by reaction of methyllithium with 1-carboxy-1-bromo-2-phenylcyclopropane followed by reduction of the resulting ketone to the alcohol, tosylation, and treatment of the tosylate with methyllithium.
(12) Consideration of steric factors in the reaction and analogy to the literature report that rearrangement of either *cis*- or *trans*-2,3-dimethylmethylenecyclopropane affords mainly *E*-2-methylethylidenecyclopropane[1b] prompt the conclusion that *E*-**2** is the major component.
(13) A 450-W medium pressure Hanovia lamp equipped with a Vycor filter was used. The substrate was contained in hexane, and the solution was held below 27° to prevent thermal isomerization of **1**.
(14) This value, at least in part, is a consequence of the unequal rates of photochemical rearrangement of *cis*- and *trans*-**1**.
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Nonadditive Carbon-13 Substituent and Solvent Effects in Substituted Benzenes

Sir:

There is much current interest in carbon-13 chemical shift measurements, particularly since they seem *to mirror total carbon atom electron densities* in restricted series of compounds such as substituted benzenes.[1] However, no comprehensive study has yet been reported either on the additivity of effects in di- and polysubstituted benzenes or on the importance of general solvent effects. We report here important initial results of such studies.

Recent theoretical results, at the ab initio level, have indicated that substituent polarity leads to significant polarization of the π system (π-inductive effect) in monosubstituted benzenes.[1] Experimental carbon-13 shifts have been similarly interpreted.[1,2]

The π-inductive effect appears[3] to be manifest to a marked degree in the nonadditive behavior of ^{13}C substitu-