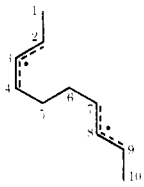

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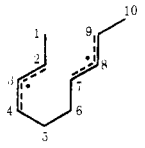

16

certed mechanism offers a simpler interpretation.

The previous finding[16] that the rearrangement of *trans*-1,2-*trans,trans*-dipropenylcyclobutane to **5a** and **6a** occurs with a slight predominance of *inversion* of configuration at the migrating group, when combined with the present observation of *complete retention* at the same site (the dienophile) in the Diels-Alder dimerization, excludes a common intermediate for the two reactions.

References and Notes

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(19) By Mr. Josef Nemeth, Urbana, Ill.
(20) Preparative GC on a 3 m × 10 mm 20% Carbowax 20M on Chromosorb W 60–80 at 190°; analytical GC on a 35 m XE 60 capillary column at 100°.
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(27) We are indebted to Professor C. H. DePuy and Mr. Ashley of the University of Colorado for the Fourier transform spectra, which were taken with the Varian XL-100 system.
(28) Supported by a postdoctoral fellowship from the Stiftung für Stipendien auf dem Gebiete der Chemie, Basel, Switzerland.

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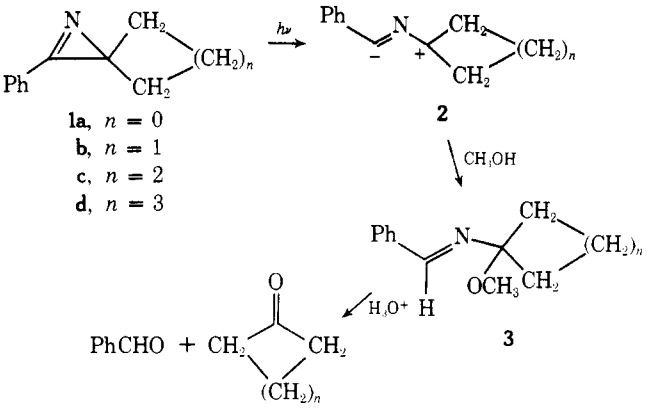
Generation of 2-Phenylazirinylidene from the Photolysis of 2-Phenyl-1-azaspiro[2.2]pent-1-ene[1]

Sir:

In order to rationalize the intriguing photochemical cycloadditions that arylazirines undergo with electron-deficient olefins, we proposed the intervention of a nitrile ylide intermediate.[2,3] As a 1,3-dipole, this species can be intercepted with a variety of dipolarophiles to form five-membered rings.[4-9] In addition, it has been possible to trap the intermediate nitrile ylide with methanol and with other active hydrogen compounds.[10,11] This suggested to us the possibility of devising a new synthesis of cycloalkanones based upon the photolysis of spiroazirines **1a–d**[12] in the presence of alcohol followed by a hydrolysis step (Scheme I). In exploring this synthetic route, we discovered an unusual photochemical cycloelimination of 2-phenyl-1-azaspiro[2.2]pent-1-ene (**1a**) giving the extremely novel carbene, 2-phenylazirinylidene. We wish to report herein evidence concerning the formation and reactions of this species.

Scheme I



1a, $n = 0$
b, $n = 1$
c, $n = 2$
d, $n = 3$

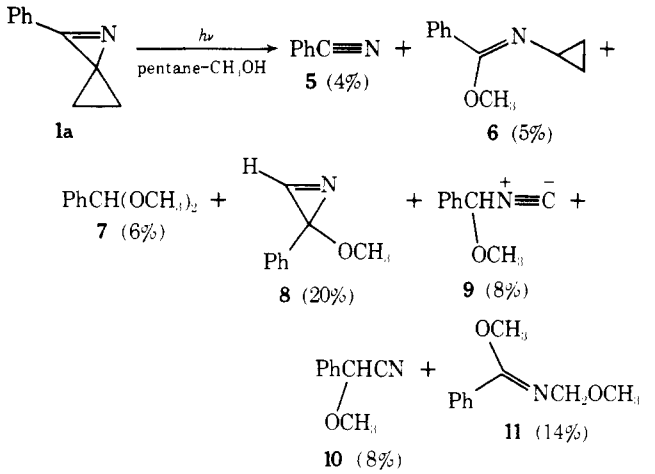
2

3

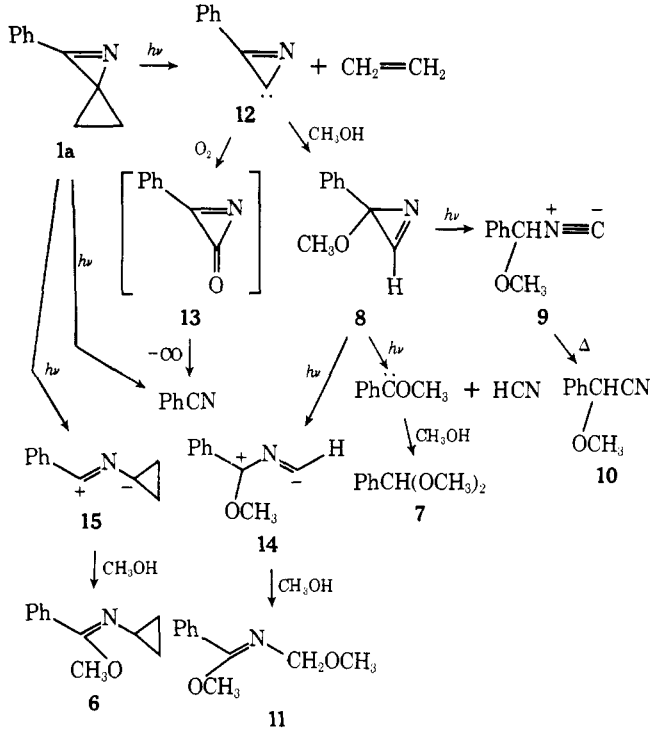
4

Irradiation of spiroazirines **1b–d** in methanol, or in pentane containing excess methanol, resulted in the quantitative formation of imines **3b–d.**[13] Clean conversion to benzaldehyde and the corresponding cycloalkanone **4** was accomplished by treating the photoproduct with a 10% aqueous hydrochloric acid solution.

In contrast to the above results, photolysis of spirocyclopropylazirine **1a** under a nitrogen atmosphere in pentane containing excess methanol produced a complex mixture of products. Analysis of the mixture by GLPC and NMR indicated the presence of eight major components, seven of which have been identified on the basis of their spectral properties or by comparison with known compounds.[13] Hy-



Scheme II



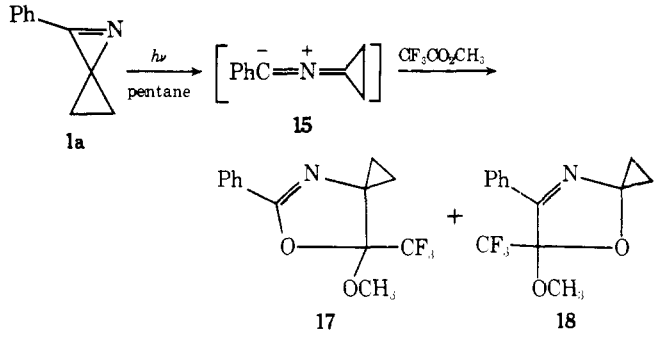
drolysis of the crude reaction mixture with 10% aqueous hydrochloric acid produced a mixture of benzaldehyde and methyl benzoate, along with unchanged **5** and **10.** Examination of the crude photolysis mixture of a short term irradiation experiment showed the presence of azirine **8** (NMR ($CDCl_3$) τ 6.72 (s, 3 H), 2.97 (m, 5 H), −0.27 (s, 1 H)) which isomerized to isocyanide **9** (ir (CCl_4) 2110 cm^{-1}) on further irradiation. The latter compound was converted to nitrile **10** on standing in the dark for 12 hr.

The formation of the major photoproducts (see Scheme II) is readily explicable in terms of a Griffin fragmentation[14] of spiroazirine **1a** to 2-phenylazirinylidene (**12**) which is subsequently trapped by methanol to give azirine **8**. Supporting evidence for this fragmentation was obtained by bubbling the nitrogen purge through a solution of bromine in carbon tetrachloride and trapping ethylene as 1,2-dibromoethane. Benzaldehyde dimethylacetal, **7**, can be seen as arising by cycloelimination of hydrogen cyanide from azirine **8** followed by reaction of the transient phenylmethoxycarbene with methanol. Hafner and Bauer had previously reported that the related spiro[2*H*-azirine-2,9′-fluorene] (**16**) undergoes loss of HCN and generates 9-fluorenylidene,[15] thereby providing good precedent for this suggestion. These workers also reported that the photolysis of **16** leads to a mixture of 9-cyano- and 9-isocyanofluorene. This reaction is quite similar to the conversion of azirine **8** into isocyanide **9**. On further irradiation, azirine **8** was found to undergo ring opening to generate nitrile ylide **14** which reacts with methanol in the normal fashion to give methoxyimine **11.**[13]

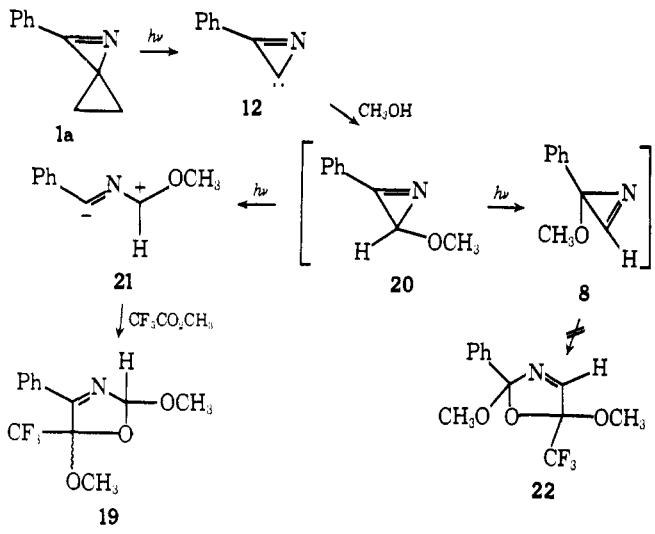
2-Phenylazirinylidene (**12**), by analogy with diphenylcyclopropenylidene,[16] should be a carbene whose normal electrophilicity has been suppressed by conjugation of the double bond electrons of the azirine ring with the vacant p orbital of the carbene. In an attempt to verify the nucleophilicity of this carbene, we tried to trap **12** with several electron-deficient olefins. Unfortunately, attempts to intercept **12** utilizing a large excess of dimethyl fumarate or methyl acrylate failed and no spirocycloadduct could be detected. However, the irradiation of **1a** in the presence of oxygen met with reasonable success. Trapping of 2-phenylazirinylidene with oxygen would be expected[17] to lead initially to 2-phenylazirinone (**13**) which could readily fragment[18] to benzonitrile and carbon monoxide. In fact, this reaction occurs and produces benzonitrile in 20% yield. In the absence of oxygen, an extremely small quantity of benzonitrile was formed (<4%) and is presumably derived by competitive cycloelimination from **1a.**[19]

The formation of methoxyimine **6** from the previous irradiation experiments may be formulated as proceeding via a nitrile ylide intermediate, **15,** which undergoes subsequent addition of methanol. It is particularly interesting to note that only a small quantity (ca. 5%) of **6** was obtained upon irradiation of **1a** in methanol.[20] This stands in marked contrast to the smooth photochemical ring-opening reactions encountered with spiroazirines **1b–d.** From this observation it would appear as though cycloelimination of ethylene from **1a** is much more efficient than C–C bond scission of the azirine ring. Undoubtedly, the stability of the "aromatic" carbene **12** contributes to this mode of cleavage.

We were able to trap nitrile ylide **15** by carrying out the irradiation of **1a** in pentane in the presence of the very reactive dipolarophile, methyl trifluoroacetate.[21] Two regio isomers **17** (2%) and **18** (7%) were isolated in low yield and were identified by their spectral characteristics.[13] The remainder of the reaction mixture consisted of a brownish polymer, which may stem from the products of a Griffin fragmentation of **1a.**



A most unusual result was encountered when the irradiation of **1a** was carried out in pentane in the presence of both methanol (1.2 equiv) and methyl trifluoroacetate (excess). Under these conditions, a mixture of the two stereoisomers of 3-oxazoline (**19**) (ratio 2.8:1) were the only cycloadducts obtained.[13] If one makes the reasonable assumption that methyl trifluoroacetate, even though it is a reactive dipolarophile, does not participate in bimolecular cycloadditions with unopened azirines, then the chemistry revealed by its presence should be the same as in its absence. Consequently, one might have expected to trap the nitrile ylide **14** derived from azirine **8** (i.e., cycloadduct **22**) in the above experiment.[22] The fact that only cycloadduct **19** was obtained suggests that 2-phenylazirinylidene (**12**) reacts with methanol to give mainly **20** which is subsequently converted to nitrile ylide **21** (and thus cycloadduct **19**) on further irradiation. The formation of azirine **8** could then be explained by a photoinduced methoxy migration of **20** which competes with C–C bond cleavage of the azirine ring.[23] Ciabattoni and Cabell[24] have previously reported that 3-chloro-1-azirines undergo ready isomerization at room temperature via a 2π-electron azacyclopropenyl cation. A similar mechanism would rationalize the apparent interconversion of azirines **20** and **8** in the above system. Further work on the quantitative aspects of these systems and on additional photoreactions of related azaspiro[2.2]pentenes is in progress and will be reported at a later date.



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(20) Control experiments established that **8** was stable toward irradiation. This observation eliminates a Griffin fragmentation of **8** to an iminocarbene followed by reaction with methanol as the path responsible for the formation of methoxyimine **11**.
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(22) It is conceivable that cycloadduct **22** is formed initially but rearranges to **19** under the reaction conditions. However, all attempts to detect **22** in the crude photolysate have failed thus ruling out this possibility.
(23) It should be pointed out that **8** was the only azirine detected in the crude photolysate. An alternate explanation to account for its formation is that 2-phenylazirinylidene (**12**) reacts with methanol to give both **8** and **20**. Under the photolytic conditions (Corex filter), the more strongly absorbing azirine (i.e., **20**) undergoes subsequent secondary photochemistry (e.g., formation of **11**) and leaves behind the weaker absorbing isomer (i.e., **8**). Attempts to synthesize **20** in order to verify this point are in progress.
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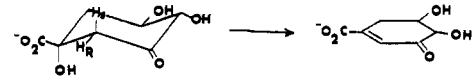
Dehydroquinase Catalyzed Dehydration. II. Identification of the Reactive Conformation of the Substrate Responsible for Syn Elimination[1]

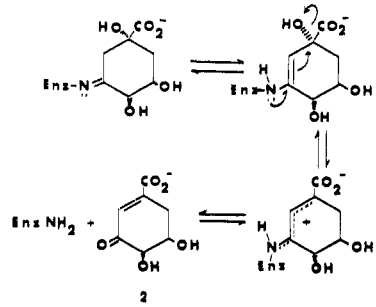
Sir:

Beginning with the demonstration of the syn dehydration catalyzed by the enzyme dehydroquinase,[2] this catalytic mechanism, as an example of rarely observed biological syn dehydration, has attracted much speculation.[3,4] Although overshadowed by the stereospecific pro-*R* proton abstraction of the enzymic reaction, the stereoselective pro-*S* proton abstraction of the base-catalyzed enolization of dehydroquinate (**1**)[5] is an important key in understanding the stereochemistry of the enzymic reaction. The enzymic conversion of **1** to dehydroshikimate (**2**) involves a Schiff base



1 **2**

intermediate.[1] Thus, the mechanistic sources of the anti stereochemistry, which are observed in eliminations involving both enolates and Schiff base intermediates,[6] must be circumvented in the parallel mechanistic conversion of the enzyme Schiff base to the enzyme enamine. It is this step which determines the syn stereochemistry of the biological elimination. Chemical modification of both the carboxyl function at C-1 and the hydroxyl functions at C-4 and C-5 in the substrate **1** have allowed the identification of the mechanistic source of this unusual syn dehydration.



2

We have synthesized the methyl ester of **1** by treatment of the silver salt derived from **1** with methyl iodide. The compound is obtained as an oil; after ion exchange chromatography, its NMR spectrum is superposable with that of **1** except for the methyl resonance at 4.31 ppm.[7] This ester is neither a substrate nor an inhibitor for dehydroquinase; thus the carboxyl group of **1** is an important site for binding the substrate to the enzyme. Haslam and coworkers have suggested that the carboxylate, acting as an internal base, is responsible for the pro-*S* stereoselectivity of the nonenzymatic enolization of **1**.[5] To the extent that such a mechanism is important, binding the carboxylate to the enzyme could negate this pro-*S* stereoselectivity of the enolization process and thus accentuate other factors which could control the stereochemistry of the biological elimination.[6] We have tested this hypothesis by comparing the pseudo-first-order