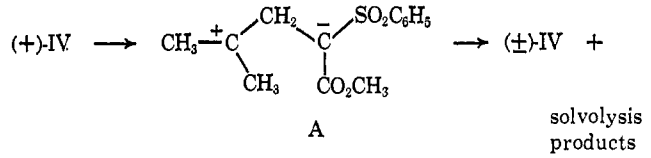

served characteristic of carbanions stabilized by ester groups[8a] but not by sulfone groups.[8b]

A large number of novel reactions can be envisioned which are based on the carbonium ion–carbanion ion pair concept and generalized systems such as I, II, and III. Molecular rearrangements of the allylic variety, ring enlargements, epimerizations, racemizations, additions to polarized double bonds, solvolyses, and eliminations are all anticipated. A survey of these possibilities is actively being pursued.

(8) (a) D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 3678 (1961); (b) D. J. Cram, W. D. Nielsen, and B. Rickborn, *ibid.*, **82**, 6415 (1960).

(9) Fulbright Visiting Scholar at University of California at Los Angeles from The Institute of Technology (Politechnika), Lodz, Poland.

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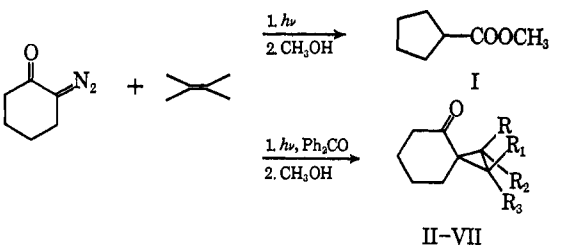
Formation of Cyclopropanes *via* the Photosensitized Decomposition of Aliphatic α-Diazo Ketones[1]

Sir:

Intramolecular reactions of carbenes very often dominate intermolecular ones. Typical of this general problem is the inability to avoid the photochemical Wolff rearrangement[2,3] on irradiation of aliphatic α-diazo ketones.[4] It seemed to us that triplet intermediates should find intramolecular pathways more difficult than do their singlet counterparts, and might well be trapped by intermolecular agents.

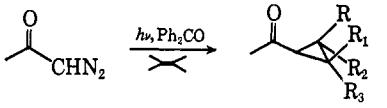
This communication reports some examples in which the photochemical Wolff rearrangement can be avoided or diminished by employing benzophenone as a sensitizing agent. Irradiation of an olefinic solution of diazocyclohexanone with two GE Sunlamps followed by addition of methanol led to moderate yields of the Wolff product, I. When benzophenone was added to the solutions I was replaced in 17–40% yield with the spiro ketones produced, at least formally, by addition of the ketocarbene to the host olefin. Of the few examples known of cyclopropane formation on irradiation of α-diazo ketones, the best studied involves benzoylcarbene. Cyclopropanes are formed in both the sensitized and unsensitized decompositions, indicating rapid intersystem crossing in this aromatic system.[5] Increased hydrogen abstraction in polar media has also been found in the sensitized reaction.[6]



II–VII

II, R = R1 = R2 = CH3; R3 = H
III, R = R1 = CH3; R2 = R3 = H
IV, R = R3 = CH3; R1 = R2 = H
V, R = R2 = CH3; R1 = R3 = H
VI, R = CH3; R1 = R2 = R3 = H
VII, R2 = CH3; R = R1 = R3 = H

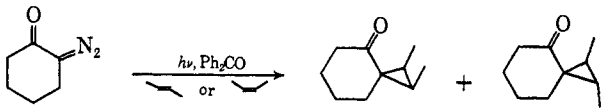
The sensitized decomposition of diazoacetone in olefins yields similar adducts in comparable yields. No adducts could be found in the unsensitized reactions.



VIII–XII

VIII, R = R2 = R3 = CH3; R1 = H
IX, R = R3 = CH3; R1 = R2 = H
X, R = R1 = CH3; R2 = R3 = H
XI, R2 = R3 = CH3; R = R1 = H
XII, R = R2 = CH3; R1 = R3 = H

The gross structures of the adducts are determined by independent synthesis (X–XII), comparison of spectra with those of authentic samples (VI, VII, XII),[7–9] and spectral analysis of all. Details of the stereochemistry of the adducts are also settled. The sensitized decomposition of diazocyclohexanone in either *cis*- or *trans*-2-butene leads to the same mixture of cyclopropanes.[10] The *trans* relation of the methyl groups in IV can be determined from the nmr spectrum which shows two different methyl signals. The structure of III is determined in the following manner: a chemical shift of *ca.* 0.2 ppm is observed between methyl groups *syn* and *anti* to the carbonyl [nmr (ppm): II, 8.95 (1), 9.12 (2); III, 9.07; IV, 8.95 (1), 9.10 (1); V, 8.78 (1), 9.06 (1); VI, 9.07; VII, 8.88]. It remains only to determine which set belongs to *syn* methyls and which to *anti*. Of the two products of addition to propylene, VI and



III: IV ≅ 1:6

VII, only VI is rearranged to allylcyclohexanone on heating to 250° and therefore must have the *syn* structure.[9] As VI has its methyl signal at high field, it is the high-field group of signals which belongs to the *syn* methyl groups and the low-field group which belongs to the *anti* methyl groups. On this basis III must have the *syn* structure. Similarly, II has two methyl groups *syn* and one *anti*. The absence of the *anti,cis* isomer is

(1) This work was supported by the National Science Foundation (Grants GP-5257 and GP-7819). Additional thanks are due for generous help in purchasing a Varian Associates HA-100 nmr spectrometer through Grant GP-5200.

(2) W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, p 115 ff.

(3) F. Weygand and H. J. Bestmann, *Angew. Chem.*, 72, 535 (1960).

(4) An exception seems to be the carbene derived from ethyl trifluoroacetyldiazoacetate: F. Weygand, W. Schwenke, and H. J. Bestmann, *ibid.*, 73, 409 (1961).

(5) D. O. Cowan, M. M. Couch, K. R. Kopecky, and G. S. Hammond, *J. Org. Chem.*, 29, 1922 (1964).

(6) A. Padwa and R. Layton, *Tetrahedron Letters*, 2167 (1965).

(7) We thank Professor William G. Dauben[8] for providing infrared spectra of VI and VII and Professor Royston Roberts[9] for the infrared spectrum of XII.

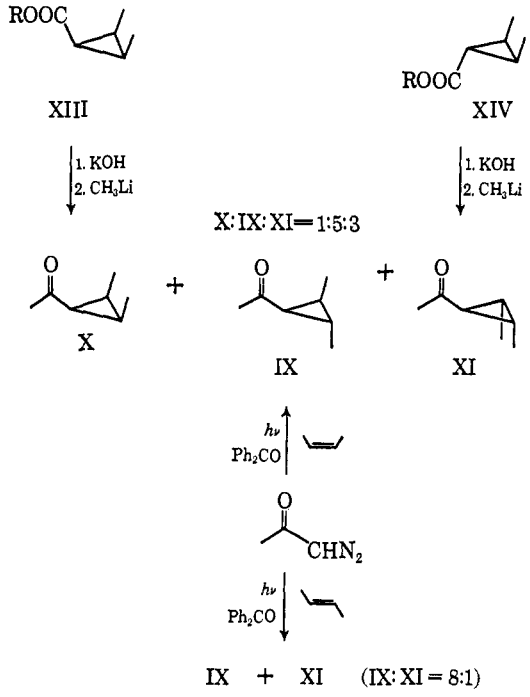
(8) W. G. Dauben and G. H. Berezin, *J. Am. Chem. Soc.*, **89**, 3449 (1967).

(9) R. M. Roberts and R. G. Landolt, *ibid.*, **87**, 2281 (1965).

(10) Control experiments show that these ketones are only very slowly isomerized under the reaction conditions.

attributed to unfavorable interactions between the methyl groups and the proximate ring hydrogens.

The sensitized decomposition of diazoacetone in *cis*-2-butene leads to all three possible 1,2-dimethyl-3-acetylcyclopropanes. We have synthesized the two *cis* isomers X and XI from esters XIII and XIV of known[11] stereochemistry and have confirmed our and previous[11] assignments by noting that only XI and XIV are not rearranged on heating to 250°. The methyl–hydrogen interaction noted above is missing in these compounds, and it is the *anti,cis* isomer XI that predominates. We were unable to detect any of the least favored *syn,cis* isomer X in the products of reaction with *trans*-2-butene.



IX + XI (IX:XI = 8:1)

It is tempting to describe these changes in the most simple terms: that is, singlet carbenes are involved in the unsensitized and triplet in the sensitized decompositions. The singlet finds an accessible pair of electrons in the adjacent carbon–carbon single bond and reacts with these at a faster rate than with the more distant π electrons of the external olefin. Were the triplet to follow the same reaction path it would have to rearrange to a triplet ketene, many kilocalories/mole in energy above the ground-state singlet. The difficulty of this reaction allows the intermediate to add to the external π system of the solvent. The loss of stereochemical integrity is consistent with what has been observed for postulated triplet carbenes in solution.[12–14] Such an explanation, however comforting, is not necessarily correct. There is no evidence that in these reactions (or in many others) nitrogen has left the molecule at the time of reaction. The question of even the gross mechanism is therefore still open.

It is hoped that the control over product formation demonstrated in the preceding examples will prove useful in synthesis and be capable of extension to other intramolecular reactions of carbenes.

(11) W. von E. Doering and T. Mole, *Tetrahedron*, **10**, 65 (1960).
(12) K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *J. Am. Chem. Soc.*, **84**, 1015 (1962).
(13) M. Jones, Jr., W. Ando, and A. Kulczycki, Jr., *Tetrahedron Letters*, 1391 (1967).
(14) M. Jones, Jr., and K. R. Rettig, *J. Am. Chem. Soc.*, **87**, 4013, 4015 (1965), and references therein.

(15) Alfred P. Sloan Research Fellow, 1967–1968.

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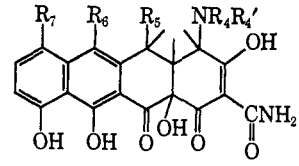
Biosynthesis of the Tetracyclines. IX. 4-Aminodedimethylaminoanhydrodemethylchlortetracycline from a Mutant of *Streptomyces aureofaciens*[1]

Sir:

At an early point in our work on the biosynthesis of the tetracycline antibiotics, we observed that the anhydrotetracyclines, **1**, were biologically reconverted to



1 (anhydrotetracyclines), $R_4 = R_4' = CH_3$; R_5 = H or OH; R_6 = H or CH_3; R_7 = H or Cl
2 (4-aminodedimethylaminoanhydrodemethylchlortetracycline), $R_4 = R_4' = R_5 = R_6 = H$; R_7 = Cl

the tetracyclines from which they were derived. The conversions were accomplished by the action of the tetracycline-producing species of the genus *Streptomyces*.[2] This observation was interpreted to mean that the anhydrotetracyclines were normal biosynthetic intermediates to the tetracyclines, and this concept successfully pointed the way to the identification of yet earlier stages in the biosynthetic pathway.[3]

Nonetheless, our failure to find any anhydrotetracycline-accumulating mutants of *S. aureofaciens* left some question that the original interpretation—fruitful though it was—might not be correct. The failure to find a mutant producing an anhydrotetracycline was finally rationalized by the thought that, since the anhydrotetracyclines are toxic to *Streptomyces*,[4] a mutant blocked at the 6-hydroxylation step might be self-lethal by virtue of accumulating the toxic anhydrotetracycline derivative and thus would not be expressed as a viable clone.

In 1964, Miller and coworkers[5] reported that inhibitors of biological methylation, such as ethionine, when added to tetracycline-producing fermentations resulted in the accumulation of N-demethyl analogs of the anhydrotetracyclines. This was felt to be good confirmation of the role of anhydrotetracyclines as biosynthetic intermediates. Meanwhile, we continued to search for a mutant of *S. aureofaciens* that would accumulate an anhydrotetracycline, and we now wish to report that mutant 1E1407[6] accumulates, as a major

(1) Paper VIII: J. R. D. McCormick and E. R. Jensen, *J. Am. Chem. Soc.*, **87**, 1794 (1965).
(2) J. R. D. McCormick, P. A. Miller, S. Johnson, N. Arnold, and N. O. Sjolander, *ibid.*, **84**, 3023 (1962).
(3) J. R. D. McCormick, U. H. Joachim, E. R. Jensen, S. Johnson, and N. O. Sjolander, *ibid.*, **87**, 1793 (1965).
(4) J. J. Goodman, M. Matrishin, and E. J. Backus, *J. Bacteriol.*, **69**, 70 (1955).
(5) P. A. Miller, A. Saturnelli, J. H. Martin, L. A. Mitscher, and N. Bohonos, *Biochem. Biophys. Res. Commun.*, **16**, 285 (1964).
(6) Mutant 1E1407 was isolated by Mr. N. Deduck and Dr. J. Growich of these laboratories as a nonproducing mutant of a demethylchlortetracycline-producing parent.