for 4-hydroxycyclophosphamide[14] and investigation with the ^{13}C nmr "off-resonance" technique, however, necessitated reconsideration of this conclusion. In the "off-resonance" spectrum the signals at 62.64, 49.08, 41.89, and 28.30 ppm (C_6, $C_{\alpha\alpha}$, $C_{\beta\beta}$, and C_5, respectively; *cf.* ref 13) are found as triplets, whereas the signal at 86.73 ppm appears as a doublet, giving conclusive evidence for the structure of 4-hydroxycyclophosphamide (IV).

The gradual appearance of IV in the extracts indicated the existence of a precursor of the compound. Chromatography on 0.2-mm layers of silica gel, solvent system CH_2Cl_2–*n*-BuOH (9:1), proved useful for the isolation of this precursor, which was in other procedures easily converted to IV: mp of the crystalline compound 102.5–103.5° (uncorrected): $\mathrm{ir}_{\max}^{\mathrm{KBr}}$ (cm^{-1}) 3320, 3110, 2960, 2800, 1465, 1435, 1330, 1245, 1215, 1165, 1090, 1045, 985, 960, 930, 840, and 750; on deuterium exchange the absorptions above 2000 cm^{-1} at 3320, 3110, and 2800 cm^{-1} disappeared, while absorptions at 2470, 2440, 2300, and 2060 cm^{-1} appeared; nmr (TMS, $CDCl_3$) (HA-100 spectrometer) δ 1.80–2.20 (2 H, m, C_5 H_2), 3.15–4.40 (9 H, m, C_6 H + exocyclic H), 4.45–4.85 (1 H, m, C_6 H), 4.90–5.40 (2 H, m, N-H + C_4 H), 11.61 (1 H, OOH). On deuterium exchange δ 11.61 disappeared and 2 H δ 4.90–5.40 became 1 H, indicating the exchangeability of two protons. Elemental analysis pointed to a structure containing four O atoms. The similarity of the ir spectrum in Nujol with that described by Takamizawa, *et al.*,[3] for synthetically prepared 4-hydroperoxycyclophosphamide (II) provided additional support for the assignment of this structure to the compound.

The *in vivo* occurrence of IV has been observed. One and one-half hours after ip administration to BC_3H_f mice of [^{14}C]cyclophosphamide (600 mg/kg; sp act. 1.0 μCi/mg) dissolved in 6% dextran solution in isotonic saline, the fluid withdrawn from the peritoneal cavity was found to contain a small amount of ^{14}C-labeled IV.

In an aqueous solution of neutral pH, IV is apparently readily converted to VI. This is among others clearly indicated by the recovery of the theoretical amount of acrolein from IV on incubation for 4–5 hr at pH 7.2 and 37°, as determined by gas chromatography. A lag phase of 30 min was noticed for the release of acrolein. Since the same findings hold true for a similarly treated solution of II, this hydroperoxy compound must also spontaneously be converted to VI, from which the elimination of acrolein apparently occurs. The latter is inferred from the finding that the hydrolysis of the alkylating groups was markedly retarded in comparison with the release of acrolein.

In vitro both II and IV are cytostatically active against BHK cells. When the drug-supplemented medium was left on the cells during the full period of growth, an ED_{50} of 2–3 μg/ml (7–10 μM) was found for both compounds. For the cytotoxic acrolein[15] an ED_{50} of 7–13 μM was measured under these conditions. However, when the compounds acted upon the cells during only the first 30 min of a 48-hr period of growth, the ED_{50} value for acrolein varied from 50 to over 120 μM in three separate experiments, while for II and IV ED_{50} values between 20 and 28 μM (6–8 μg/ml) were measured (two experiments).

More elaborate studies of the relative efficacies of the various *in vitro* active metabolites of I are expected to reveal more about the role that is played by their conversion to aldophosphamide and by their spontaneous breakdown, both intra- and extracellularly, to the two cytotoxic substances acrolein and *N*,*N*-bis(2-chloroethyl)phosphorodiamidic acid.[16]

Acknowledgment. The valuable technical assistance of Mr. E. J. Spanjersberg and Mr. H. J. Krol is gratefully acknowledged. The ^{13}C nmr spectra were obtained by Mr. C. Kruk, Laboratory of Organic Chemistry, University of Amsterdam. The authors wish to thank him for his collaboration and for helpful discussion throughout the work.

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[14] The authors are most grateful to Dr. R. F. Struck, *et al.*, Southern Research Institute, Birmingham, Ala., for their willingness to make their paper[13] available before publication for comparing the spectral data.

[15] R. A. Alarcon, *Arch. Biochem. Biophys.*, 106, 240 (1964).

[16] O. M. Friedman, E. Boger, V. Grubliauskas, and H. Sommer, *J. Med. Chem.*, 6, 50 (1963).

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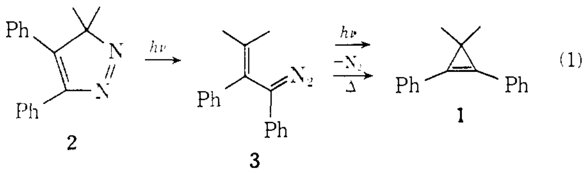
Received June 12, 1973

Electronic Excited States of Small Ring Compounds. Cyclopropene and the Vinylcarbene[1]

Sir:

As part of a continuing study of the thermal and photochemical interconversions of three-membered rings, 1,3 dipoles, and 1,3 biradicals,[2] we wish to report preliminary results for a cyclopropene system.

3,3-Dimethyl-1,2-diphenylcyclopropene (**1**)[3] was prepared from 5,5-dimethyl-3,4-diphenyl-5*H*-pyrazole (**2**)[4,5] in 92% yield by photolysis in 9:1 benzene–pyridine[6] above 350 nm;[7a] less than 1% of *cis*- and *trans*-1,2-diphenyl-3-methylbutadiene[8] (**4** and **5**, respectively) was formed. During the photolysis the solution turned deep red suggesting the diazo compound **3** was an intermediate (see eq 1). This was confirmed by generating **3**[9] in high yield by photolyzing **2** between 330 and 410



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[1] Contribution No. 86 from the Photochemistry Unit.

[2] D. R. Arnold, A. B. Evnin, and L. A. Karnischky, *Pure Appl. Chem.*, **24**, 523 (1970).

[3] New compounds gave satisfactory spectral and elemental analyses.

[4] Addition of 2-diazopropane to diphenylacetylene gave **2** in 3% yield.

[5] W. H. Williams and W. R. Dolbier, *J. Amer. Chem. Soc.*, **94**, 3955 (1972).

[6] This reaction is sensitive to acid catalysis.

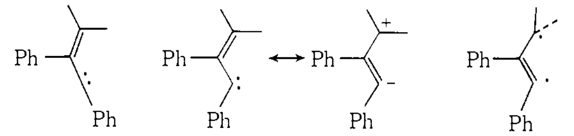
[7] Filter solutions: (a) 1 cm, 4 × 10^{-3} *M* $BiCl_3$ in 10% HCl; (b) 2 cm, 1.0 *M* $CoSO_4 \cdot 7H_2O$ and 0.1 *M* $NiSO_4 \cdot 6H_2O$ in 5% H_2SO_4, and 1 cm, 0.4 *M* $SnCl_2 \cdot 2H_2O$ in 10% HCl.

[8] The structure of these compounds has been established by independent synthesis.

[9] The instability of **3** precludes isolation but the assigned structure is consistent with the spectral properties: nmr (CCl_4) δ 1.87 (3 H, s, CH_3), 1.81 (3 H, s, CH_3); ir (CCl_4) 2070 cm^{-1} (diazo band); uv (benzene) 510 nm (ϵ *ca.* 50).

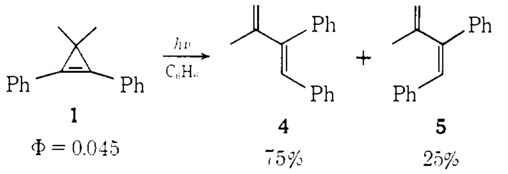
nm[7b] where, after complete conversion of **2**, only 10% of **1** had formed presumably by photodecomposition of **3**, which also absorbs in this region, rather than directly from **2**. Photolysis[7a] of **3** then leads to the cyclopropene (**1**). Similar generation of **3** followed by pyrolysis ($t_{1/2}$ ~ 12 hr at 60°) gave **1** in greater than 90% yield. Closs[10] has observed similar behavior on photolysis of alkyl-substituted 5*H*-pyrazoles but could not exclude direct pyrazole to cyclopropene conversions.

The accepted mechanism for the thermal and photochemical decompositions of diazo compounds is loss of nitrogen to form, in this case, a vinylcarbene. Little is known about the structure and reactivity of such species.[11] They are strongly implicated as intermediates in cyclopropene synthesis[10,12] and in the pyrolysis of cyclopropenes.[11,13] Several fundamentally different structures, either singlet or triplet,[14] can be envisioned (**6a–c**). Hoffmann[15] has presented EHMO calculations for unsubstituted vinylcarbene which suggest a ground-state triplet bent at the carbene carbon (**6b** only syn). We report here that this intermediate (**6**) can also be obtained by photolysis of the cyclopropene (**1**).



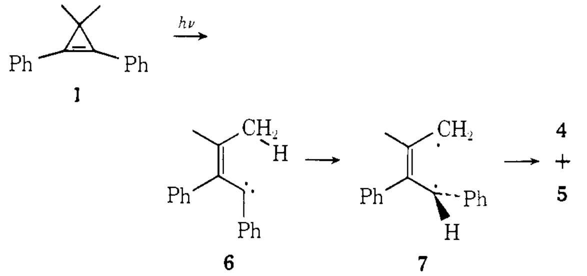
6a **6b** **6c**

Direct irradiation[7a] of **1** in 9:1 benzene–pyridine gave a mixture of **4** and **5** in a ratio of 75:25[16] (Φ = 0.045) (eq 2). The product ratio was constant from 3 to 15% conversion and is therefore not a result of direct photochemical equilibration (the photostationary state[7a] is **4–5**, 35:65). Photosensitized isomerization of **4** and **5**, with **1** as the sensitizer, seems unlikely since intersystem crossing efficiencies close to zero have been reported for similar diphenylcyclopropenes ($E_T \simeq 60$ kcal/mol).[17] This primary product ratio from **1** is similar to the thermodynamic ratio of **4–5**, 70:30. In contrast to direct irradiations, attempted sensitization with benzophenone led to a decrease in reaction efficiency and attempted quenching with dimethyl fumarate ($E_T \simeq 60$ kcal/mol)[18] gave no decrease in quantum yield.



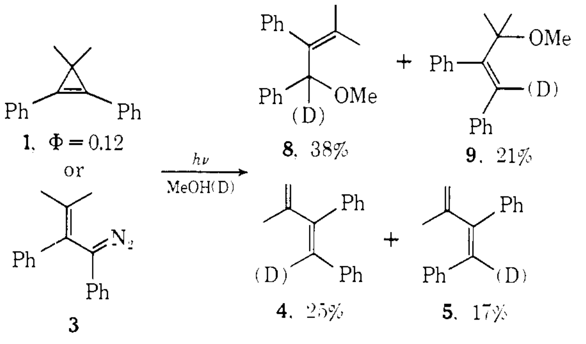
(2)

To account for these observations we propose that the excited singlet state of **1** opens to give **6**; intramolecular migration of hydrogen gives **7** which partitions to **4** and **5** (see eq 3). The low quantum yield for the disappearance of cyclopropene may indicate return of **6** to **1** as observed in the thermal decomposition of a cyclopropene.[11] Since generation of **6** from **3**, thermally or photochemically, leads to a cyclopropene:diene ratio >100:1 (*vide supra*), ring closure in this case is efficient.[19]

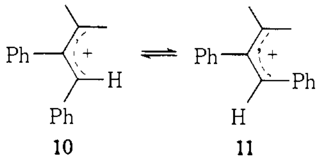


(3)

Photolysis of **1** in 9:1 methanol–pyridine[6] gave 38% 1,2-diphenyl-1-methoxy-3-methyl-2-butene (**8**),[8] 21% *cis*-1,2-diphenyl-3-methoxy-3-methyl-1-butene (**9**),[8] 25% **4**, and 17% **5**[20a] (Φ disappearance of cyclopropene = 0.122). The same product distribution, plus 45% of the cyclopropene (**1**), results from photolysis[21] of **3**. Photolysis of either **1** or **3** in MeOD gives the same products but now deuterated[20b] (eq 4). These results are again consistent with intervention of **6** which can be trapped by protonation in methanol to give the allyl cation **10,11**. Deprotonation or reaction with methanol then gives the observed products. Although we might expect rapid equilibration of **10** and **11**,[22] only cis products are observed under a variety of conditions. Thus, acid-catalyzed decomposition of **1** (toluenesulfonic acid in benzene) gives **4**. Acid-catalyzed decomposition of **3** also leads only to **4**. Finally, pho-



(4)



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(10) G. L. Closs, W. A. Böll, H. Heyn, and V. Dev, *J. Amer. Chem. Soc.*, **90**, 173 (1968).

(11) E. J. York, W. Dittmar, J. R. Stevenson, and R. G. Bergman, *ibid.*, **94**, 2882 (1972); **95**, 5680 (1973).

(12) For example: M. Franck-Neumann and C. Buchecker, *Tetrahedron Lett.*, 15 (1969); L. Schrader, *Chem. Ber.*, **104**, 941 (1971); I. S. Krull and D. R. Arnold, *Tetrahedron Lett.*, 1247 (1969).

(13) M. A. Battiste, B. Halton, and R. H. Grubbs, *Chem. Commun.*, 907 (1967); R. Srinivasan, *J. Amer. Chem. Soc.*, **91**, 6250 (1969); R. D. Streeper and P. D. Gardner, *Tetrahedron Lett.*, 767 (1973).

(14) Closs[10] has reported the esr detection of a triplet vinylcarbene for a phenyl-substituted case.

(15) R. Hoffmann, G. D. Zeiss, and G. W. Van Dine, *J. Amer. Chem. Soc.*, **90**, 1485 (1968).

(16) The yields were determined by nmr integration.

(17) C. D. DeBoer, D. H. Wadsworth, and W. C. Perkins, *J. Amer. Chem. Soc.*, **95**, 861 (1973).

(18) G. S. Hammond, J. Saltiel, A. A. Lamola, N. H. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Amer. Chem. Soc.*, **86**, 3197 (1964).

(19) This ratio suggests the quantum yield for cyclopropene disappearance should be <0.01. Possibly an intermediate different in either structure or multiplicity is generated by the two routes.

(20) (a) These irradiations were carried out to high conversion; some photoisomerization of **4** and **5** has undoubtedly occurred. (b) The dienes are 80–90% deuterated in these experiments suggesting 10–20% intervention of the intramolecular route for diene formation.

(21) In 9:1 methanol–pyridine **3** is stable, but decomposes rapidly in methanol alone.

(22) V. Buss, R. Gleiter, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 3927 (1971).

tolysis of either **1** or **3** in methanol–pyridine gives the *cis*-ether **9**.[23] These results suggest that the equilibrium between **10** and **11** lies heavily toward **10** and product formation reflects this equilibrium. That **4** and **5** also equilibrate in favor of **4** is support for this argument.

Further studies on the interconversion of these intriguing species are currently underway, particularly trapping of **6** with olefins.

Acknowledgment. We wish to thank the National Research Council of Canada for support of this research.

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[23] The thermodynamic ratio for **9** and its trans isomer has not been determined.

[24] Alfred P. Sloan Fellow, 1972–1974.

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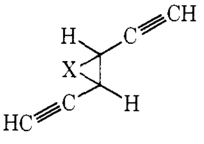
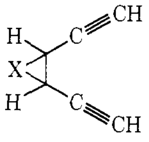
Competition between Sulfur Extrusion and Thermal Synthesis of Thienocyclobutadiene in the Pyrolysis of *cis*- and *trans*-1,2-Diethynylthiiranes. Dimerization of the Rearrangement Product to Bisthienocyclooctatetraene

Sir:

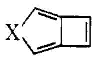
Thermal rearrangement of both cis and trans isomers of three-membered ring diacetylenes **1** and **2** affords[1,2] efficient syntheses of bicyclic triene **4** and furocyclobutadiene **5**. In principle, rearrangement of sulfur analog **3** should lead to thienocyclobutadiene **6**; this material is of interest because, despite recent syntheses[3,4] of substituted analogs **7–10**, preparation of the parent compound has not been recorded. We now wish to report the synthesis of **6** and its dimerization to the interesting 16π-electron bisthienocyclooctatetraene **12**. However, the pyrolysis of **3** is considerably more complicated than that of either **1** or **2**. Desulfurization overtakes C–C bond cleavage in the trans isomer, and this is the first instance in which the lower energy cis rearrangement[1,2] must be taken advantage of in order to successfully obtain the bicyclic triene. Besides the synthesis of **6** and **12**, our results provide some interesting insights into the mechanism of thermal desulfurization of thiiranes.



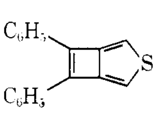
1T, X = CH_2
2T, X = O
3T, X = S



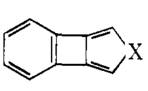
1C, X = CH_2
2C, X = O
3C, X = S



4, X = CH_2
5, X = O
6, X = S



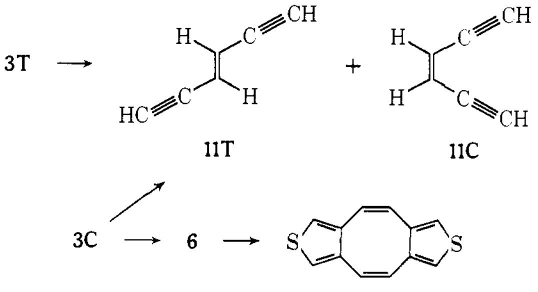
7



8, X = S
9, X = SO
10, X = SO_2

Only desulfurized olefins **11C** and **11T**[5] (Scheme I) can be isolated from solution pyrolysis of **3C** and **3T**[6] (toluene-d_8, 100°). Both reactions occur with greater than 90% retention of stereochemical configuration under these conditions, but the decomposition kinetics are complex. At nmr observable concentrations (~0.15 *M*) the reactions exhibit second-order kinetics initially; these change to first-order kinetics as the reactions proceed (*e.g.*, for **3T**, $k_2 = 3.9 \times 10^{-6}$ l./(mol sec), $k_1 = 1.18 \times 10^{-6}$ sec^{-1}; for **3C**, $k_2 = 1.03 \times 10^{-5}$ l./(mol sec), $k_1 = 1.03 \times 10^{-5}$ sec^{-1}). In a gas-phase nitrogen flow system, pyrolysis of **3T** is quantitative at 395° (15-sec contact time) and still gives only **11**, but under these conditions the reaction is considerably less stereoselective,[7] giving a 4:3 ratio of **11T** to **11C**. Flow pyrolysis of the cis isomer **3C** at 250° gave a 1:2 ratio of **11T** to **11C**, but admixed with them a new compound (**6**, ~5% yield, ~30% of the mixture of volatile products) which exhibited two resonances in the proton nmr (τ 3.25 and 3.99, acetone-d_6; τ 4.00 and 4.50, benzene-d_6). Compound **6** decomposes immediately on attempted chromatography or exposure to air. A mass spectrum could be obtained using break-seal techniques; this gave a parent peak at *m/e* 108; uv (cyclohexane) λ_{max} 286 and a higher wavelength band of considerable fine structure (12 peaks) extending to 442 mμ. Raney nickel desulfurization gave *cis*- and *trans*-1,2-dimethylcyclobutanes.

Scheme I



On standing at room temperature in benzene-d_6, the yellow solution decolorized and the nmr resonances due to **6** slowly disappeared at the expense of two new signals at τ 3.71 and 3.53. After 48 hr, the sealed nmr tube containing the sample was opened and a colorless oil isolated by preparative thin layer chromatography. On the basis of the nmr (*vide infra*), uv (diethyl ether,

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[1] (a) M. B. D'Amore and R. G. Bergman, *J. Amer. Chem. Soc.*, **91**, 5694 (1969); (b) M. B. D'Amore, R. G. Bergman, M. Kent, and E. Hedaya, *J. Chem. Soc., Chem. Commun.*, 49 (1972); (c) T. J. Henry and R. G. Bergman, *J. Amer. Chem. Soc.*, **94**, 5103 (1972).

[2] (a) K. P. C. Vollhardt and R. G. Bergman, *J. Amer. Chem. Soc.*, **94**, 8950 (1972); (b) R. G. Bergman and K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.*, 214 (1973).

[3] P. J. Garratt and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, **94**, 7087 (1972).

[4] P. J. Garratt and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, **94**, 1022 (1972).

[5] (a) W. H. Okamura and F. Sondheimer, *J. Amer. Chem. Soc.*, **89**, 5991 (1967); (b) R. R. Jones and R. G. Bergman, *ibid.*, **94**, 660 (1972).

[6] Prepared either by the reaction of 1,2-diethynyloxiranes **2T** and **2C** with thiourea or by the reaction of diazopropyne with sulfur. For some analogies, see (a) R. D. Schuetz and R. L. Jacobs, *J. Org. Chem.*, **26**, 3467 (1961); (b) N. Latif and J. Fathy, *ibid.*, **27**, 1633 (1962); (c) A. Schönberg and E. Frese, *Chem. Ber.*, **95**, 2810 (1962).

[7] In order to assure ourselves that **11C** and **11T** were stable to cis–trans isomerization under the exact desulfurization reaction conditions, the following experiment was carried out. A sample of 50 mg of *trans*-thiirane **3T** doped with ~2 mg of tritiated olefin **11T** was subjected to pyrolysis. The pyrolysate was diluted with cold **11C** and **11T** and each olefin isolated by preparative gas chromatography. Scintillation counting showed that >99% of the radioactivity remained in the trans isomer **11T** and <1% was present in **11C**.