That biphenylene (**5**) is a result of benzyne dimerization was assured since **5** obtained by decomposing **1′** in excess benzene-d_6 was found to be deuterium free, m/e 152, C–D stretch absent in the infrared.

None of the other metal ions (Tl^+, Cu^+, Cu^{2+}, Hg_2^{2+}, Hg^{2+})[11] screened thus far altered the course of the benzyne–benzene reaction. The study is being extended however, to transition metals and their complexes in anticipation that an isolable benzyne complex may result.[12]

amounts of biphenyl-d_{10} were formed *via* benzene-d_6 thermal dimerization;[10b] biphenyl-d_6:biphenyl-d_{10} ~0.1. Biphenylene was not detected. Acenaphthylene and acenaphthene are formed *only* by thermal rearrangement of **3**. Based on *isolated* and *characterized* hydrocarbon products, it can be concluded that at 690° the major reaction of benzyne with benzene is 1,4 addition (~75%) to give **2**, followed by loss of acetylene to give thermally stable naphthalene. The balance is electrophilic attack (*vide supra*) to give **4** (~10%) and **3** (~15%) (which rearranges (60%) to form acenaphthene, which in turn is partially dehydrogenated to acenaphthylene) and pyrolysis (40%) to naphthalene. These results are somewhat different from earlier reports[2a] (D. F. Lindow, unpublished data). (b) *Cf.* G. M. Badger, *Progr. Phys. Org. Chem.*, **3**, 1 (1966).

[11] The absence of any effect is a strong argument against benzyne attacking a benzene–metal complex.

[12] The assistance of L. R. Rice and D. F. Lindow in carrying out some of the initial experiments is gratefully acknowledged.

Lester Friedman
Department of Chemistry, Case Western Reserve University
Cleveland, Ohio 44106

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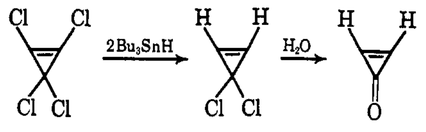
Cyclopropenone

Sir:

Studies of various cyclopropenones, including diphenylcyclopropenone,[1] the earliest example, and the more recent monoalkylcyclopropenones,[2] have fully established the unusual stability of this strained system. Most chemical properties of importance have also been investigated on these derivatives.[1–3] However, although the parent ketone III is clearly of interest, it has resisted our synthetic attempts to prepare it by the methods used to make substituted derivatives. We have now succeeded in synthesizing unsubstituted cyclopropenone.



I II III

Reaction of tetrachlorocyclopropene[4] (I) with 2 equiv of tri-*n*-butyltin hydride at room temperature in paraffin oil produced a volatile mixture[5] of chlorocyclopropenes containing 3,3-dichlorocyclopropene (II) (nmr: δ 8.0), 1,3-dichlorocyclopropene (δ 7.2, 4.5, $J_{AB} = 2$ cps), and mono- and trichlorocyclopropene isomers. The distilled mixture was taken up in CCl_4 and cautiously hydrolyzed with cold water (or D_2O). The aqueous phase contained as the only detectable signal (the solvent peak could be moved by adding potassium phosphate or removed by using D_2O) a sharp singlet at δ 9.0 which we assign to the protons of cyclopropenone (III).

The nmr spectrum unambiguously establishes this structure. Thus the singlet shows ^{13}C satellites with the very large coupling ($J_{^{13}C-H} = 230$ cps) characteristic of a cyclopropene[6] or acetylene. The latter is, of course, excluded by the chemical shift of δ 9.0; this also excludes nonketonic cyclopropene structures since 1,3,3-trimethylcyclopropene has its vinyl proton at δ 6.7 and the 3,3-dichlorocyclopropene signal is at δ 8.0, while methylcyclopropenone is at δ 8.7. The ^{13}C satellites of III appear, as expected, as a doublet ($J_{H-H} = 3$ cps).

The aqueous solution of III shows broad infrared absorption centered at 1850 cm^{-1}. On standing it slowly ($t_{1/2}$ at 25° >1 week) is hydrolyzed to acrylic acid.[8] Treatment with alkali produces a dark polymer, but the compound is stable to a variety of strong mineral acids. Although III is very polar, it can be extracted from the water solution with methylene chloride or ethylene chloride by salting out. The protons in III are still at δ 8.9–9.0, there are no other signals in the nmr, and the infrared spectrum shows a strong cyclopropenone doublet[9] at 1835 and 1870 cm^{-1} and no absorption in the O–H region. Thus III is apparently present as the free ketone, rather than a *gem*-diol, even in aqueous solution.

Attempts to isolate III by removal of solvent, distillation, or vapor phase chromatography under a variety of conditions have so far failed, leading to at least partial polymerization of the compound; the parent ketone is apparently more sensitive than its derivatives. However, the low reactivity of III compared with cyclopropanone,[10] and in particular its retention of the unhydrated carbonyl group in water solution, confirm our previous conclusion that the cyclopropenone system has considerable conjugative stabilization.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health, and thank Mr. John Groves for several experimental contributions.

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[1] R. Breslow, R. Haynie, and J. Mirra, *J. Am. Chem. Soc.*, **81**, 247 (1959); M. E. Vol'pin, Y. D. Koreshkov, and D. N. Kursanov, *Dokl. Akad. Nauk SSSR*, 506 (1959); R. Breslow, T. Eicher, A. Krebs, R. Peterson, and J. Posner, *J. Am. Chem. Soc.*, **87**, 1320 (1965).

[2] R. Breslow and L. J. Altman, *ibid.*, **88**, 504 (1966).

[3] A. Krebs, *Angew. Chem. Intern. Ed. Engl.*, **4**, 10 (1965).

[4] S. Tobey and R. West, *J. Am. Chem. Soc.*, **88**, 2481 (1966).

[5] Although the allylic chlorines must be most reactive, the resulting conjugated cyclopropenyl radical may pick up hydrogen on any ring position and the cyclopropenyl chlorides undergo rapid allylic isomerizations. Under appropriate conditions the essentially pure mixture of dichlorides can be prepared. On treatment with $AgBF_4$ in a variety of solvents Mr. John Groves has found that this affords chlorocyclopropenium ion, with an nmr singlet at δ 9.6 ($J_{^{13}C-H} = 242$ cps, $J_{H-H} = 2$ cps).

[6] Methylcyclopropenone[2] has $J_{^{13}C-H} = 213$ cps and 1,3,3-trimethylcyclopropene[7] has $J_{^{13}C-H} = 218$ cps.

[7] G. L. Closs, *Proc. Chem. Soc.*, 152 (1962).

[8] Identified by comparison of vpc, nmr, and mass spectra with those of an authentic sample.

[9] The spectra in aqueous and nonaqueous solution mirror those for alkylcyclopropenones[2] and indicate that the carbonyl group is still present in water, albeit hydrogen bonded.

[10] N. J. Turro and W. B. Hammond, *J. Am. Chem. Soc.*, **88**, 3672 (1966).

Ronald Breslow, Gordon Ryan
Department of Chemistry, Columbia University
New York, New York 10027

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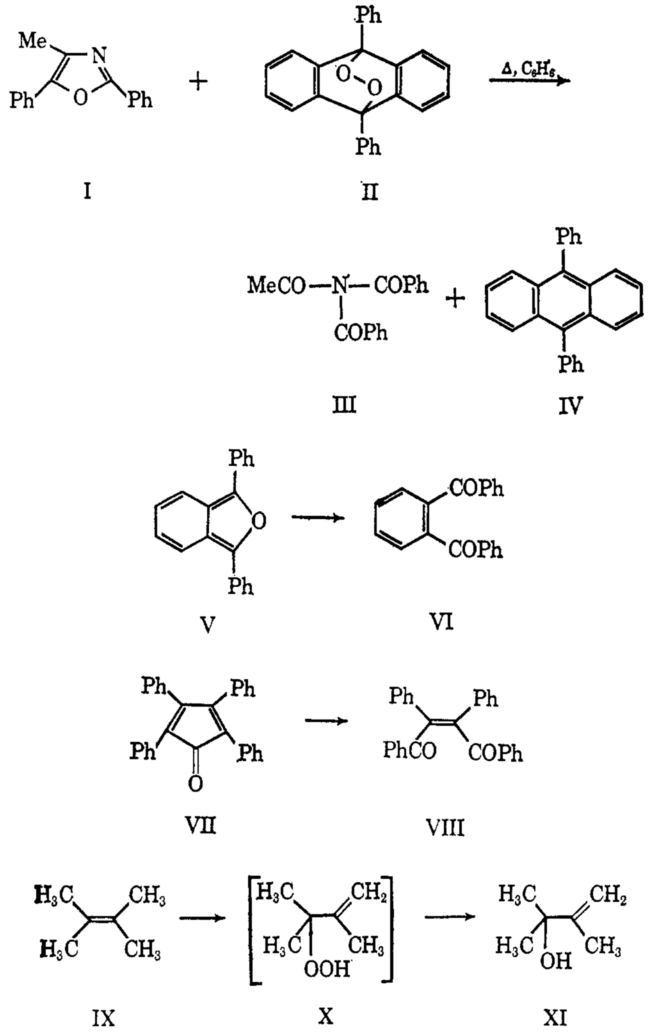
Singlet Oxygen Reactions from Photoperoxides

Sir:

It has been known for some time that aromatic hydrocarbons such as anthracene, rubrene, and tetra-

Chart I. Oxidation of Singlet Oxygen Acceptors by 9,10-Diphenylanthracene Peroxide



cene undergo photosensitized autoxidation to form transannular peroxides,[1] and a number of recent reports have provided strong evidence indicating that singlet oxygen is involved in the formation of these "photoperoxides."[2] It is also well known that many of these peroxides undergo dissociation on heating to regenerate oxygen and the parent hydrocarbon. The ease of oxygen release from these systems depends on the polycyclic aromatic system and the nature of the substituents in the *meso* positions.[3]

We now report that 9,10-diphenylanthracene peroxide (II) may be used to bring about typical singlet oxygen reactions when it is allowed to decompose[4,5] in the presence of a variety of known singlet oxygen acceptors.

Examples of the oxidations studied are given in Chart I. In each case the reaction was carried out by heating a mixture of peroxide and acceptor (ratio 2:1) in benzene or chloroform for 2–4 days. The products isolated were identical with those formed in parallel dye-photosensitized autoxidation reactions and were characterized by comparison (mixture melting point or vpc retention time, infrared and nmr spectra) with authentic samples. Thus, 2,5-diphenyl-4-methyloxazole (I) was converted to N-acetyldibenzamide (III)[6] (82%) along with 10% of dibenzamide. 1,3-Diphenylisobenzofuran (V) was oxidized to *o*-dibenzoylbenzene (VI)[7] in 95% yield, while treatment of tetracyclone VII with II afforded *cis*-dibenzoylstilbene (VIII) in 50% yield.[8] The intermediate hydroperoxide X from the tetramethylethylene oxidation was not isolated, but was reduced with triphenylphosphine to form the unsaturated alcohol XI. No attempt was made to optimize yields in these initial runs. Control reactions using 9,10-diphenylanthracene (IV) in place of the photoperoxide II resulted in essentially quantitative recovery of starting materials either in air or under nitrogen.

The oxidation of 2,5-diphenyl-4-methyloxazole (I)[9] by the peroxide II is outlined as a typical procedure. A solution of 0.724 g (0.002 mole) of 9,10-diphenylanthracene peroxide[10] and 0.235 g (0.001 mole) of 2,5-diphenyl-4-methyloxazole[11] in 50 ml of anhydrous benzene was stirred at reflux temperature in the dark for 94 hr under a positive pressure of nitrogen. Benzene was removed *in vacuo*, yieding a solid residue, 0.960 g, which, after chromatography on deactivated silica gel using ether–hexane as eluent, could be separated into a mixture of N-acetyldibenzamide[12] (0.17 g), mp 64–65°, dibenzamide (0.062 g), mp 147–149°,[13] as well as 9,10-diphenylanthracene (0.538 g) and unreacted 9,10-

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[1] The first example of an aromatic transannular peroxide, rubrene peroxide, was reported by C. Moreau, C. Dufraisse, and P. M. Dean, *Compt. Rend.*, **182**, 1440, 1584 (1926). For a recent review, see Y. A. Arbuzov, *Russ. Chem. Rev.*, **34**, 558 (1965).

[2] C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3879, 3880 (1964); C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Letters*, **46**, 4111 (1965); E. J. Corey and W. C. Taylor, *J. Am. Chem. Soc.*, **86**, 3881 (1964); T. Wilson, *ibid.*, **88**, 2898 (1966); E. McKeown and W. A. Waters, *J. Chem. Soc., Sect. B*, 1040 (1966).

[3] For a review, see W. Bergmann and M. J. McLean, *Chem. Rev.*, **28**, 367 (1941).

[4] C. Dufraisse and L. Enderlin, *Compt. Rend.*, **191**, 1321 (1930); C. Dufraisse and J. LeBras, *Bull. Soc. Chim. France*, **4**, 349 (1937).

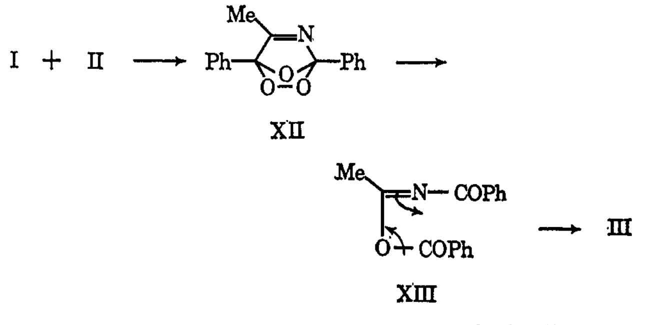
[5] Preliminary kinetic studies on the thermal decomposition of 9,10-diphenylanthracene peroxide in methylene chloride at 90° indicate a first-order rate constant for oxygen release of 2.5×10^{-5} sec^{-1} ($t_{1/2}$ 8 hr). This value is considerably faster than the rate of decomposition of tertiary peroxides such as *t*-butyl or trityl (which, furthermore, decomposes by peroxide bond cleavage) and suggests that 9,10-diphenylanthracene peroxide undergoes a concerted oxygen release (E. Hedaya, private communication).

[6] H. H. Wasserman and M. B. Floyd, *Tetrahedron Suppl.*, **7**, 441 (1966).

[7] A. Guyot and J. Catel, *Bull. Soc. Chim. France*, **35**, 1124 (1906); C. Dufraisse and S. Ecary, *Compt. Rend.*, **223**, 735 (1946).

[8] C. F. Wilcox, Jr., and M. P. Stevens, *J. Am. Chem. Soc.*, **84**, 1258 (1962); G. O. Schenck, *Z. Elektrochem.*, **56**, 855 (1952).

[9] Earlier studies[6] on dye-photosensitized autoxidations have shown that oxazoles are remarkably sensitive to the action of singlet oxygen. Formation of the triamide in this process appears to involve rearrangement of the intermediates XII and XIII.



[10] C. Dufraisse and A. Etienne, *Compt. Rend.*, **201**, 280 (1935).

[11] G. H. Cleland and C. Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).

[12] Identical (mixture melting point, infrared and nmr spectra) with the product formed in the dye-photosensitized autoxidation of I.

[13] Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5841 (1951). Dibenzamide apparently results from hydrolysis of the triamide during chromatography since this diamide could not be detected (infrared spectrum) in the crude reaction mixture before work-up.

diphenylanthracene peroxide (0.08 g). The over-all yield of di- and triamide was 92%.

We are investigating mechanistic aspects of the process by which oxygen is transferred from photoperoxide to acceptor, as well as the possibility that other types of cyclic peroxides may provide sources of singlet oxygen.

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(14) National Institutes of Health Postdoctoral Fellow, 1966–1967.

Harry H. Wasserman, John R. Scheffer[14]
Department of Chemistry, Yale University
New Haven, Connecticut 06520

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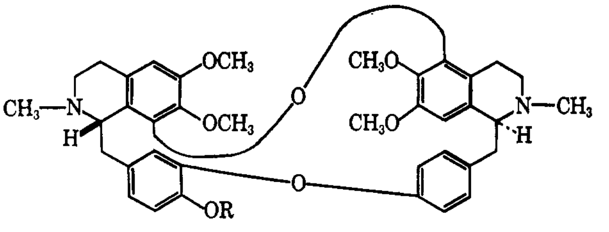
The Isolation and Structural Elucidation of Thalidasine, a Novel Bisbenzylisoquinoline Alkaloid Tumor Inhibitor from *Thalictrum dasycarpum*[1,2]

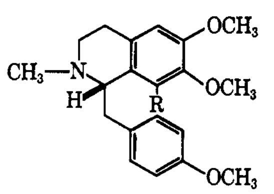
Sir:

The genus *Thalictrum* has served as a uniquely profuse source of new and novel benzylisoquinoline and aporphine alkaloids.[3–6] We report herewith the isolation and elucidation of the structure (Ia) of thalidasine, a new alkaloid tumor inhibitor[7] from *T. dasycarpum*. Thalidasine appears to be the first bisbenzylisoquinoline recognized to contain a diphenyl ether terminus at C-5 and the first unsymmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring.[8] Furthermore, the alkaloid thalfoetidine, from *T. foetida*,[9] is shown to possess structure Ib on the basis of evidence which includes interrelation with thalidasine.

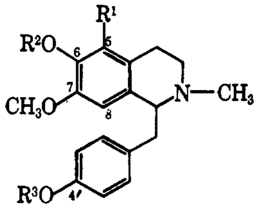
Thalidasine (Ia), $C_{39}H_{44}N_2O_7$, mol wt (mass spectroscopy)[10] 652, is an amorphous solid, mp 105–107°, $[\alpha]^{27}\mathrm{D}$ −70° (*c* 0.89, MeOH), $\lambda_{\max}^{\mathrm{EtOH}}$ 275 mμ (ϵ 4560), 282 mμ (ϵ 4530), and nmr signals (in $CDCl_3$) at τ 7.38, 7.75 (6 H, two NCH_3), 6.09, 6.13, 6.25, 6.50, 6.73 (15 H, five OCH_3), and 2.46–3.70 (9 H, aromatic H). The alkaloid was characterized as the oxalate, mp 160–162°, picrate, mp 175–177°, and methiodide, mp 182–183°. Permanganate oxidation of Ia yielded 2-methoxydiphenyl ether 4′,5-dicarboxylic acid (V), characterized by mixture melting point and infrared comparison with an authentic sample.[11] Sodium in liquid ammonia reduction of Ia afforded, as principal products, L-O-methylarmepavine (IIa), mp 61–62°, $[\alpha]^{26}\mathrm{D}$ +99° (*c* 1.10, $CHCl_3$), and a dihydroxydimethoxybenzylisoquinoline (A), $C_{19}H_{33}NO_4$, mp 194–196°, $[\alpha]^{27}\mathrm{D}$ +51° (*c* 0.50, MeOH), $\lambda_{\max}^{\mathrm{EtOH}}$ 279 mμ (ϵ 2750), nmr signals at τ 7.48 (3 H, NCH_3), 6.13, 6.45 (6 H, two OCH_3), 4.33 (1 H, C-8 H), 3.92 (2 H, two OH), 3.08, 3.35 (4 H, two doublets, *J* = 8.5 cps). Methylation of phenol A with diazomethane gave 1-(4-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (IIIa), characterized by infrared and nmr comparison with the *dl* compound.[4b] Nmr spectral characteristics and reactivity toward Gibbs reagent[12] led to consideration of 4′,6-diphenol (IIIb) and 4′,5-diphenol (IIIc) structures as most likely for phenol A. However, the infrared spectrum of synthetic [*via* the dibenzyl ether IIId, mp 83–86°, nmr signals at τ 7.49 (3 H, NCH_3), 6.19, 6.55 (6 H, two OCH_3), 4.97, 5.02 (4 H, two OCH_2Ph), 3.02, 3.13 (4 H, two doublets, *J* = 8.5 cps, disubstituted aromatic



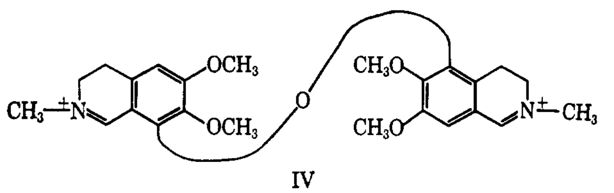
Ia, R = CH_3
b, R = H



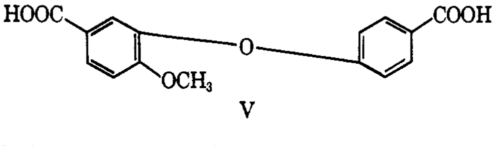
IIa, R = H
b, R = OH



IIIa, $R^1 = OCH_3$; $R^2 = R^3 = CH_3$
b, $R^1 = OCH_3$; $R^2 = R^3 = H$
c, $R^1 = OH$; $R^2 = CH_3$; $R^3 = H$
d, $R^1 = OCH_3$; $R^2 = R^3 = CH_2Ph$
e, $R^1 = H$; $R^2 = CH_3$; $R^3 = H$



IV



V

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(2) Supported by grants from the National Heart Institute (HE-02952) and the National Cancer Institute (CA-04500).

(3) (a) S. M. Kupchan, K. K. Chakravarti, and N. Yokoyama, *J. Pharm. Sci.*, **52**, 985 (1963); (b) M. Tomita, H. Furukawa, S.-T. Lu, and S. M. Kupchan, *Tetrahedron Letters*, 4309 (1965).

(4) (a) E. Fujita and T. Tomimatsu, *J. Pharm. Soc. Japan*, **79**, 1082 (1959); (b) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).

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(6) (a) S. M. Kupchan, Symposium on Selected Recent Advances in Natural Products Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, Abstracts, p 31P; (b) H. B. Dutschewska and N. M. Mollov, *Chem. Ind.* (London), 770 (1966).

(7) Thalidasine showed significant inhibitory activity against Walker intramuscular carcinosarcoma 256 in rats at 200 mg/kg. Tumor inhibitory activity was assayed, under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National stitutes of Health, by the procedures described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

(8) Cissampareine was the first symmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring (S. M. Kupchan, S. Kubota, E. Fujita, S. Kobayashi, J. H. Block, and S. A. Telang, *J. Am. Chem. Soc.*, **88**, 4212 (1966)).

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(10) The authors thank Professor A. L. Burlingame and Dr. H. K. Schnoes, University of California, Berkeley, for the mass spectral data and helpful discussions.

(11) The authors thank Professor M. Tomita cordially for the authentic sample of 2-methoxydiphenyl ether 4′,5-dicarboxylic acid.

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