IUPHAR Satellite Symposium on "Active Intermediates: Formation, Toxicity and Inactivation," Turku, Finland, July 1975, p 15. See also W. Levin, A. W. Wood, H. Yagi, P. M. Dansette, D. M. Jerina, and A. H. Conney, *Proc. Nat. Acad. Sci.*, in press.

(23) The biological testing is being done in collaboration with Drs. A. H. Conney, A. Wood, and W. Levin, Department of Biochemistry and Drug Metabolism, Hoffmann-La Roche.

(24) Since submission of the present manuscript, P. B. Hulbert, *Nature (London)*, **256**, 146 (1975), has come to similar conclusions regarding the importance of diol epoxide **6a** for which anchimeric assistance to attack by nucleophiles is possible. In addition, D. J. McCaustland and J. F. Engel, *Tetrahedron Lett.*, 2549 (1975), described a modification of the original synthesis[5] of **3**. Although this procedure also results in impure material based on NMR and mass spectra after silylation, Dr. McCaustland kindly suggested the use of THF as solvent for the oxidation. Pure **4a** results and has the following NMR spectrum (HA 100, DMSO-d_6): C_7–OH δ 5.98, C_8–OH 5.75, H_7 4.83, H_8 4.00, H_9 3.91, H_{10} 5.24, H_6 8.56, H_{11} 8.70, and six aromatic hydrogens at δ 7.96–8.35 with $J_{7,OH}$ = 7.5, $J_{7,8}$ = 9.0, $J_{8,OH}$ = 5.0, $J_{8,9}$ = 1.0, and $J_{9,10}$ = 4.5 Hz. The hydroxyl groups in **4a** occupy mainly pseudo-equatorial positions, and the stereochemistry of **6a** is thus unequivocally established

(25) Once both **4a** and **6a** were available, *tert*-butyl alcohol was found to be sufficiently nonnucleophilic to allow measurement of reaction rates with sodium *p*-nitrothiophenolate (loss of absorbance at 450 nm). Rates were measured at 30° in 3.0 ml of dry *tert*-butyl alcohol plus 0.05 ml of DMSO containing the diol epoxides: **4a** (0.43 M^{-1} sec^{-1}), **6a** (70 M^{-1} sec^{-1}), **4b** (0.01 M^{-1} sec^{-1}), and **6b** (3.3 M^{-1} sec^{-1}). In this solvent, the isomers **6a,b** with stereochemistry similar to triptolide are more than 100-fold more reactive than **4a,b**, presumably due to anchimeric assistance by the benzylic hydroxyl group. Evidence to support this was found by examination of 7,8,9,10-tetrahydrobenzo[*a*]pyrene 9,10-oxide which has a comparatively low rate constant (0.15 M^{-1} sec^{-1}). The hydroxyl groups in **6a** cause a >400-fold increase in rate on reaction with the thiolate.

H. Yagi, O. Hernandez, D. M. Jerina*

National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health
Bethesda, Maryland 20014

Received July 22, 1975

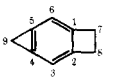
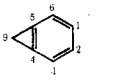
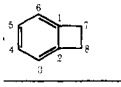
Cyclopropa[4,5]benzocyclobutene[1]

Sir:

Benzene has been bent,[2,3] twisted,[3] and strained.[2-4] As a system it has shown that its properties are remarkably resilient to such treatment. One of the more acute sources of strain has been provided by annelating benzene with small rings. Initial interest was in the fusion of four-membered rings as exemplified by the synthesis of benzo[1,2:4,5]dicyclobutene,[5] but more recently the dramatic success achieved in annelating benzene with a three-membered ring[6,7] has led to a considerable effort in the synthesis of benzocyclopropenes.[4] We would now like to report a further intensification of the strain on benzene by the synthesis of cyclopropa[4,5]benzocyclobutene (**8**),[1] the first compound known in which benzene is annelated by both a three- and a four-membered ring.

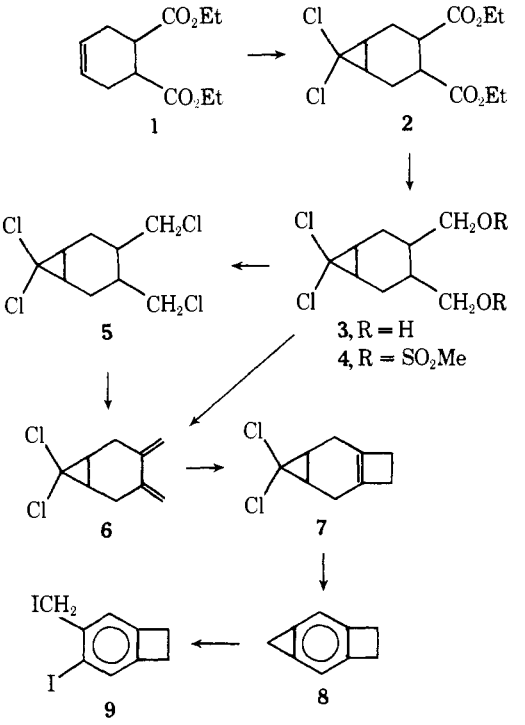
Dichlorocarbene addition to the diester **1** was effected by the phase transfer method[8] using triethylbenzylammonium chloride and gave **2** in 85% yield.[9-11] Reduction of **2** with $LiAlH_4$ in Et_2O for 8 hr gave the diol **3**, mp 75–79°, 66%.[9,10] Treatment of **3** with methanesulfonyl chloride, NEt_3 at 0°[12] for 30 min, gave the dimesylate **4**, mp 99–100°, 80–85%.[9,10] Reaction of the diol **3** with thionyl chloride in boiling pyridine for 20 min gave the tetrachloride **5**, mp 74–75°, 20%.[9,10] When either the dimesylate **4** or the tetrachloride **5** was treated with 3 equiv of KO*t*-Bu in THF at room temperature the diene **6**, bp 50–60°, 0.02 mm, was obtained in 65% yield.[9] The ^{1}H NMR spectrum showed two bands at τ 4.80 and 5.20 due to the exocyclic methylene protons, and the electronic spectrum showed an absorption at 243 nm (ϵ 7000).[13] Photoirradiation of **6** in pentane with an Hanovia 250-W medium pressure lamp through quartz under argon for 8 hr gave the cyclobutene **7**, bp 40–46°, 0.01 mm, in 50% yield.[9,14] The ^{1}H NMR spectrum showed a singlet (τ 7.62) superimposed on a multiplet τ 7.4–8.0, and a multiplet at τ 8.25 in the ratio 4:1, and the ^{13}C NMR spectrum showed bands at 19.4, 25.1, 30.3, 66.3, and 137.4 ppm.[15] Treatment of **7** (100 mg, 0.5 mmol) with KO*t*-Bu (225 mg, 2.0 mmol) in DMSO (1 ml)[16] gave cyclopropa[4,5]benzocyclobutene (**8**) in 30–40% yield.[17] The mass spectrum (20 eV) had *m/e* 116 (M^+, 100%), 115 (M − 1, 95%); high resolution (70 eV) 116.0609 (C_9H_8 requires 116.0625). The ^{1}H NMR spectrum showed only two singlets at τ 3.15 (2 H) and 6.92 (6 H),[18] and the ^{13}C spectrum had five absorptions (see Table I).

Table I. ^{13}C NMR Shifts in **8**, Benzocyclobutene, and Benzocyclopropene[a]

	C-1,2	C-3,6	C-4,5	C-7,8	C-9	Ref
	145.5	110.0	122.8	29.0	19.2	
	128.8	114.7	125.4		18.4	21
	145.2	122.1	125.8	29.5		21

[a] The numbering of benzocyclopropene has been chosen for ease of comparison with 8.

The electronic spectrum (cyclohexane) showed a broad band with maxima at 284 nm (ϵ ca. log 3.0) 287.5 (ϵ ca. log 3.0) and 294 (ϵ ca. log 2.8).[19,20]



The above data are clearly in accord with the assigned structure. A comparison of the ^{13}C spectrum with those of benzocyclopropene[21] and benzocyclobutene[21] is made in Table I. The chemical shifts observed for **8** are very close to those observed in these compounds, except that carbons-3,6 in **8** are at higher field than the corresponding carbon atoms in benzocyclopropene and benzocyclobutene.[22] This upfield shift is presumably due to the increase of strain in **8**.

Treatment of **8** with iodine at room temperature caused cleavage of the cyclopropene ring to give **9**, mp 138–139°.[7,9,10]

We are now studying the chemistry of **8**, and are attempting to prepare the other isomer, cyclopropa[3,4]benzocyclobutene, by a related route.

Acknowledgment. One of us (D.D.) thanks the Pahlavi Foundation for a grant. We thank Dr. A. G. Loudon for the high resolution mass spectral determinations.

References and Notes

(1) Tricyclo[6.1.0.0^{3,6}]nona-1,3(6),7-triene.
(2) See V. V. Kane, A. D. Wolf, and M. Jones, *J. Am. Chem. Soc.*, **96**, 2644 (1974).
(3) See D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, **4**, 204 (1971); "Aromatic and Heteroaromatic Compounds", *Chem. Soc., Spec. Publ.*, **1–3**, Chapter 1 (1973–1975).
(4) See B. Halton, *Chem. Rev.*, **73**, 113 (1973).
(5) M. P. Cava, A. A. Deana, and K. Muth, *J. Am. Chem. Soc.*, **82**, 2524 (1960).
(6) R. Anet and F. A. L. Anet, *J. Am. Chem. Soc.*, **86**, 525 (1964).
(7) E. Vogel, W. Grimme, and S. Korte, *Tetrahedron Lett.*, 3625 (1965).
(8) M. Makosza and M. Wawrzyniewicz, *Tetrahedron Lett.*, 4659 (1969).
(9) Satisfactory microanalytical and/or high resolution mass spectral data have been obtained for this compound.
(10) ^{1}H NMR ($CDCl_3$, τ): **2**, 5.86 (q, 4 H), 7.1–8.4 (m, 8 H), 8.78 (t, 6 H); **3**, 5.80 (s, 2 H), 6.40 (d, 4 H), 7.6–8.5 (m, 8 H); **4**, 5.80 (d, 4 H), 6.93 (s, 6 H), 7.6–8.2 (m, 8 H); **5**, 6.54 (d, 4 H), 7.6–8.3 (m, 8 H); **9** (CCl_4), 2.64 (s, 1 H), 2.83 (s, 1 H), 5.50 (s, 2 H), 6.87 (s, 4 H).
(11) Compounds **2–5** each appear to be one stereoisomer, presumably with the cyclopropane ring anti to the cis diester derived group.
(12) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).
(13) The diene **6** reacts readily with a variety of dienophiles (SO_2, maleic anhydride, dimethylacetylene dicarboxylate) to give the expected adducts. Compound **6** is a potential precursor to a variety of cyclopropa-aromatics.
(14) See J. M. Garrett and G. J. Fonken, *Tetrahedron Lett.* 191 (1969).
(15) Peaks measured from $CHCl_3$ which was taken as 77.2 ppm downfield from TMS.
(16) W. E. Billups, A. J. Blakeney, and W. Y. Chow, *J. Chem. Soc. D*, 1461 (1971).
(17) The method of isolation was similar to that described by Billups et al. (ref 16). The solvents and **8** were removed by distillation, CH_2Cl_2 was added, the mixture washed with water several times, and the organic layer dried (Na_2SO_4). The solvent was removed by evaporation. Compound **8** has a pungent smell, similar to benzocyclopropene.
(18) In the ^{1}H NMR spectrum of benzocyclobutene, the four-membered ring protons appear at τ 6.88 (see P. Radlick and L. R. Brown, *J. Org. Chem.*, **38**, 3412 (1973)), while the methylene protons of benzocyclopropene appear at τ 6.89 (see ref 16).
(19) The electronic spectrum of benzo[1.2:4,5]dicyclobutene has maxima (EtOH) at 276 nm (log ϵ 3.66), 280 (3.71), and 286 (3.59) (see ref 5).
(20) These are minimal values for the extinction coefficients.
(21) H. Günther, G. Jikeli, H. Schmickler, and J. Prestien, *Angew. Chem., Int. Ed. Eng.*, **12**, 762 (1973).
(22) The assignment to the ^{13}C absorptions in **8** was made on the basis of the comparison of the shifts with those in benzocyclopropene and benzocyclobutene and from relative peak heights.

Dariush Davalian, Peter J. Garratt*
Department of Chemistry, University College London
London WC1H OAJ, England
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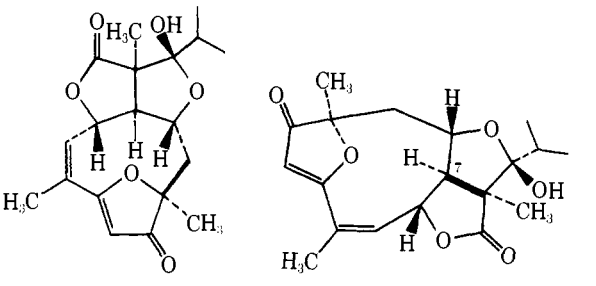
Eremantholide A, a Novel Tumor-Inhibiting Compound from *Eremanthus elaeagnus* Schultz-Bip. (Compositae)

Sir:

Recent work in our laboratories has established that a 50% aqueous ethanolic extract of the Brazilian plant *Eremanthus elaeagnus* (Fam: Compositae) shows significant inhibitory activity against cells derived from human carcinoma of the nasopharynx (KB) carried in vitro. We have now isolated, by countercurrent distribution and extensive chromatography, guided at all stages by the KB assay, a crystalline substance having constant KB activity of 2 μg/ml. This has further been resolved by high pressure liquid chromatography into two compounds of equal activity (2 μg/ml): eremantholide A, $C_{19}H_{24}O_6$, and eremantholide B, $C_{20}H_{26}O_6$. We now report the highly novel structure **1** for eremantholide A.

Eremantholide A, mp 181–183°, $[\alpha]_D$ +65° (EtOH), on electron impact gave M^+ at 348.1582 (calcd for $C_{19}H_{24}O_6$, 348.1514). The uv spectrum showed λ_{max}^{EtOH} 266 nm (ϵ 9900), and the ir (KBr) ν_{max} 3400 (O–H), 1770 ($\alpha\beta$-saturated γ-lactone C=O), 1695 (enone C=O), 1653 (C=C) and 1582 cm.$^{-1}$ as characteristic absorptions. Eremantholide A is neutral, and was unaffected by acetic anhydride–pyridine, although trimethylsilyl chloride–pyridine converted it into a mono-TMS derivative. The base peak in the mass spectrum of eremantholide A arises from monodehydration (*m/e* 330.1463; calcd for $C_{19}H_{22}O_5$, 330.1467). These data suggest a tertiary alcohol, an $\alpha\beta$-saturated γ-lactone, and an enone function. The remaining two oxygen atoms were assigned to ether functions when microhydrolysis experiments, by giving no small fragments, ruled out an ester side chain. The NMR spectrum of eremantholide A shows four protons resonating below δ 4.0, i.e., a 1 H multiplet at δ 6.0, a sharp 1 H singlet at δ 5.60, a 1 H multiplet at δ 4.9, and a six-line 1 H singlet at δ 4.0. The O–H signal occurs as a sharp singlet (confirmed by D_2O exchange) at δ 2.75, over-lying a 1 H doublet of doublets centered at δ 2.8.



1 OR 1a
(relative configurations)

An allylic methyl signal, somewhat split by long range coupling, falls at δ 2.0, as well as two methyl singlets at δ 1.45 and 1.35. Centered at δ 1.0 are two superimposed 3 H doublets from an isolated isopropyl group. The mass spectrum shows that this isopropyl group is readily lost, giving rise to a large peak at *m/e* 305.1039 (calcd for $C_{16}H_{17}O_6$, 305.0966). These data suggest the presence of a $(CH_3)_2CH$–C–O– function undergoing facile α-cleavage on electron impact.

The structural features suggested by these data are substantiated by x-ray determination of the structure and relative configuration **1** for eremantholide A. The x-ray structure further reveals a novel carbon skeleton and an apparently unique array of contiguous functional groups. Monoclinic crystals of eremantholide A, obtained from ethanol, belong to the space group $P2_1$ with unit cell dimensions a = 10.242 (2) Å, b = 10.397 (3) Å, c = 8.965 (2) Å, and β = 98.08 (2)° (2 molecules/unit cell). Three-dimensional intensity data were collected on a Syntex $P2_1$ automated diffractometer using monochromatized Mo radiation to a maximum 2θ value of 48°. The structure was solved using the MULTAN program package, which employs a multiple solution-tangent refinement technique. The 25 non-hydrogen atom parameters were refined by conventional least-squares techniques using 1098 reflections having intensities greater than $1.5\sigma(I)$. The six oxygen atoms were initially assigned on the basis of chemical data, and the assignments were subsequently supported by the behavior of the isotropic temperature factors during the refinement procedure. Eventual confirmation of the oxygen locations was obtained by location of all 24 hydrogen atoms in difference electron density maps. The current residual (R) factor is 0.069.

Figure 1 is a computer drawing of the structure and relative configuration of eremantholide A, including all hydrogen atoms, at R factor 0.069. Included are distances for oxygen–carbon and nonsingle carbon–carbon bonds and