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

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(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$_2$Cl$_2$ was added, the mixture washed with water several times, and the organic layer dried (Na$_2$SO$_4$). 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).
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(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.

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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°, [α]D +65° (EtOH), on electron impact gave M$^+$ at 348.1582 (calcd for C$_{19}$H$_{24}$O$_6$,

1   **1a**

OR
(relative configurations)
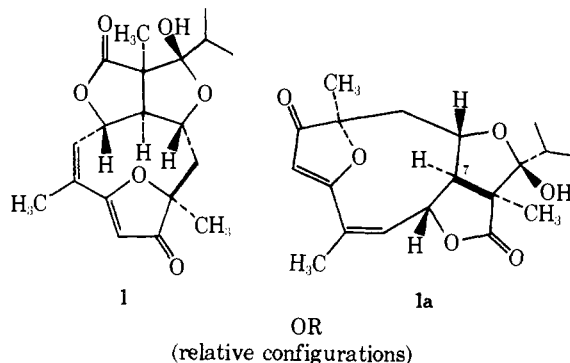
348.1514). The uv spectrum showed λ_{max}^{EtOH} 266 nm (ϵ 9900), and the ir (KBr) ν_{max} 3400 (O–H), 1770 ($\alpha\beta$-saturated γ-lactone C=O), 1695 (enone C=O), 1653 (C=C) and 1582 cm.$^{-1}$ as characteristic absorptions. Eremantholide A is neutral, and was unaffected by acetic anhydride-pyridine, 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$_2$O exchange) at δ 2.75, over-lying a 1 H doublet of doublets centered at δ 2.8.

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$_3$)$_2$CH–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
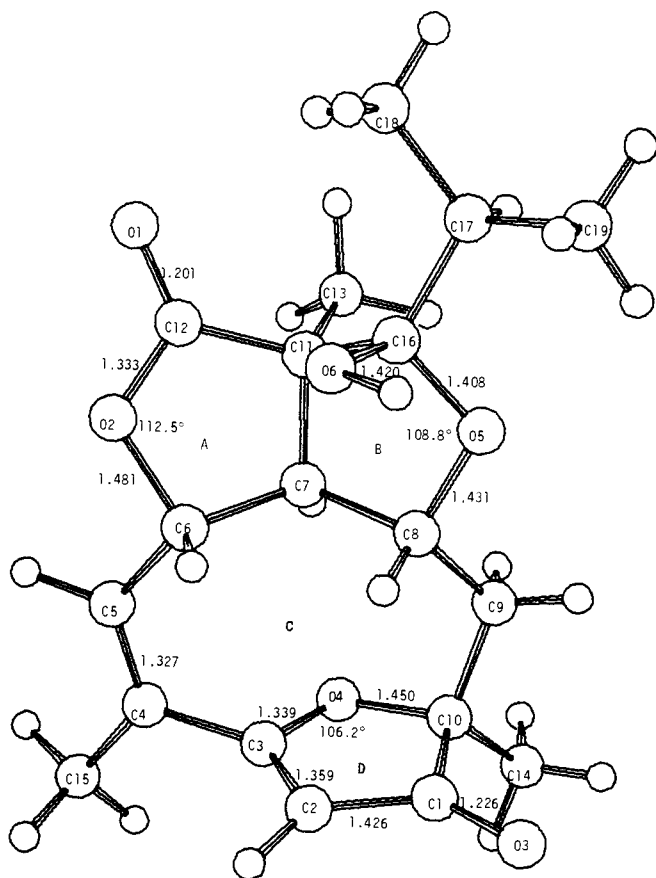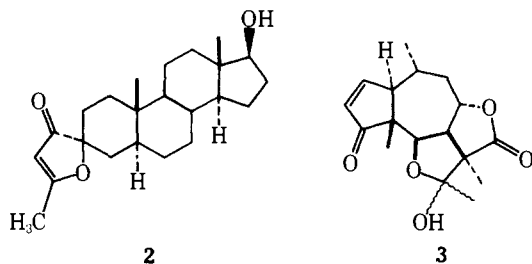
singlet at δ 5.60 to C2-H; the analogous proton in **2** resonates at δ 5.21,[1] but in eremantholide A this proton may be further deshielded by the 4,5-double bond. The multiplets at δ 4.9 and 4.0 are assigned to C6-H and C8-H, respectively, while C7-H gives rise to the doublet of doublets signal (J = 8 Hz, 4 Hz) at δ 2.8. The C15 allylic methyl gives rise to the broadened 3 H signal at δ 2.0, while the upfield 3 H singlets at δ 1.45 and 1.35 are assigned to the C14 and C13 methyl groups, respectively.

Preliminary experiments indicate that eremantholide A is very sensitive to dilute base catalyzed hydrolysis or to borohydride reduction even under very mild conditions and that the bridgehead enol ether dienone system is readily attacked in these circumstances giving complex mixtures of products. Kupchan[4] has shown that for many antitumor active sesquiterpenoids having an α-methylene-γ-lactone function, activity is associated with the ability of this group to undergo nucleophilic attack, e.g., by sulfhydryl groups, in Michael-type addition reactions. Eremantholide A has an $\alpha\beta$-saturated lactone function, and clearly must owe its activity to an entirely different array of functional groups—perhaps, analogously, to specific nucleophilic attacks on the dienone system. Experiments bearing on this question are underway in our laboratories.

Eremanthus elaeagnus is one of 20 species of the genus native to Brazil and a member of the same subfamily and tribe of the Compositae to which belong *Vernonia* and *Elephantopus*. It is also closely related to *Eupatorium*. Antitumor active compounds have been isolated from all of these genera. Eremantholide A can be regarded as comprised of three clear isoprenoid fragments (C1-C15), linked to a C_4(C16-C19) fragment by carbon-carbon and carbon-oxygen bonds. It is not certain whether it should be regarded as a nor-diterpenoid or as a tetrahomosesquiterpenoid, although the latter possibility is strongly favored on phytochemical grounds; notably, sesquiterpenoids have previously been obtained from nonpolar extracts of the wood of *E. elaeagnus*.[5] Further, resemblances may be seen to germacrane sesquiterpenoids such as liatrin **4**[6] and, in particular, ciliarin **5**.[7] Indeed, an eremantholide A analogue may be

Figure 1. Computer-generated representation of the crystal structure of eremantholide A.

bond angles about ring oxygen atoms. Other bond distances and angles are not quoted here and, except as noted below, are within the range of normally expected values. The numbering system we have employed is shown in Figure 1.

The structure of eremantholide A has a number of highly interesting features. In particular, the cyclodecadienone ring incorporating a bridgehead enol ether system (C3-O4-C10) is remarkable. A Dreiding model of the molecule can be constructed if the 2,3 and 4,5 double bonds are twisted considerably out of plane, and in the crystal they are twisted 88° from coplanarity. In accord with consequent expectations, the absorption maximum at 266 nm for eremantholide A is almost coincident with that for furenones such as **2**,[1] and shows no effects of extended conjugation. The dioxabicyclo[3.3.0]octane system of rings A and B incorporates γ-lactone and hemiacetal functions (cf. tenulin **3**[2]).
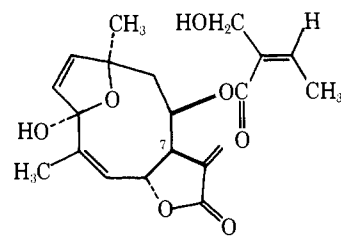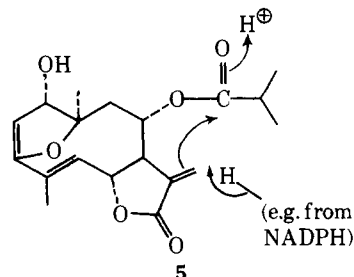

2   3

The x-ray determination shows that the A and B rings are each puckered, and at an angle of 127° to each other, indicating that the molecule is markedly strained here also. From the NMR spectrum, however, there is no evidence of ring-opened ketol tautomer in chloroform solution. The hemiacetal function clearly facilitates the mass spectral α-cleavage of the isopropyl group.[3] In the NMR spectrum, the multiplet at δ 6.0 is assigned to C5-H, and the sharp

conceived as arising from a ciliarin-type precursor by reductive intramolecular addition involving the α-methylene-γ-lactone function and the carbonyl group of the adjacent isobutyryl side chain, as outlined in **5**. In this event, eremantholide A may be regarded as a novel transformed germacranolide of structure and likely absolute configuration **1a**, in view of the stereochemical uniformity at C7 among

4

(e.g. from NADPH)

5

these compounds.[8,9] Further work on the eremantholides is in progress.

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Photoreactions of Ketones with Amines. CIDNP Criteria for the Intermediacy of Aminoalkyl Radicals and Aminium Radical Ions

Sir:

Many intermolecular reactions of photoexcited species involve hydrogen abstraction (a) whereas others proceed via electron transfer (b). Since many substrates are potential electron donors as well as hydrogen atom sources, it is not always trivial to distinguish between these mechanisms. We have applied the CIDNP technique[1,2] to this problem and have suggested two methods[3,4] to distinguish between CIDNP effects originating in pairs of neutral radicals, which would result from reaction (a), and in pairs of radical ions produced via route (b). In photoreactions of aromatic ketones with anilines we favored reaction (a), because *N,N*-dialkylanilines, which may form anilinium radical ions but not neutral anilinyl radicals, did not show CIDNP effects similar to those found for anilines.[3] In other ketone-amine systems an assignment was based on the relatively large difference in the electron g factors of aminoalkyl radicals (1; $g \sim 2.0032$) and aminium radical ions (2; $g \sim 2.0040$).[4] In this paper, we introduce a third criterion which is based on the difference in the hyperfine coupling patterns of the neutral radicals (1)[5] and the radical cations (2).[6]
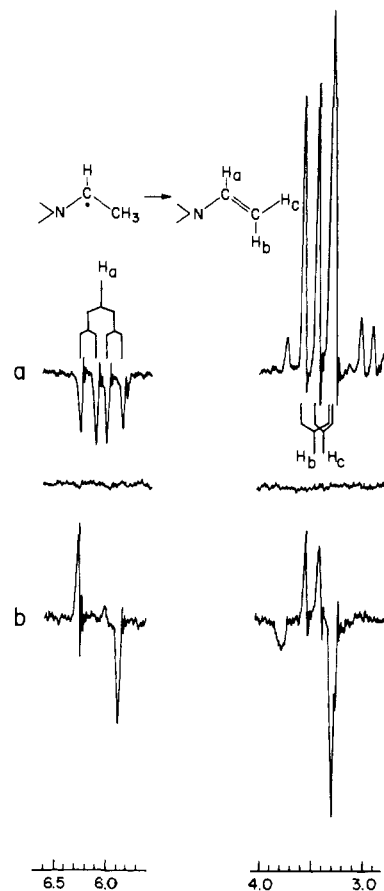
We illustrate the CIDNP patterns induced in these

Figure 1. ^{1}H NMR spectra (60 MHz) of the internal (left) and terminal olefinic protons (right) of polarized diethylvinylamine observed during uv irradiation of solutions of 0.05 M triethylamine and 0.01 M p,p'-dichlorobenzophenone (a) or p,p'-dimethylbenzophenone (b), respectively, in acetonitrile-d_3. The center trace shows the spectrum of the same region in the absence of uv irradiation.

species with spectra observed during the photoreactions of benzophenones (3) with tertiary amines (4). In these systems, the effect of solvent polarity on the quantum yields suggests that charge transfer is involved in the initial stages of the reaction.[7] If this interaction results in hydrogen abstraction and thus in the formation of **1**, nuclear spin polarization of comparable magnitude is expected for the protons in α- and β-position. In contrast, only the α-protons are expected to show polarization, if the charge transfer interaction leads to electron transfer and thus to the formation of **2** as an intermediate.

1	**2**
$g = 2.0030$	$g = 2.0040$
$a_{CH} = -13.6\,G$	$a_{CH_2} = +37\,G$
$a_{CH_3} = +19.6\,G$	$a_{CH_3} < 1\,G$
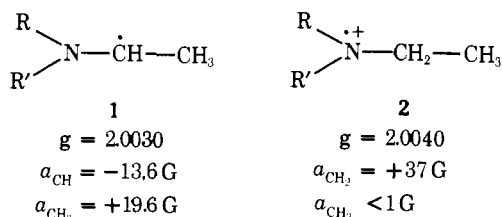
The irradiation of p,p'-dichlorobenzophenone (**3a**) in the presence of triethylamine (**4a**) in acetonitrile-d_3 produced an enhanced spectrum (Figure 1) which we ascribe to the olefinic protons of diethylvinylamine (**5a**). The signals of the terminal (β-) protons, two overlapping doublets near 3.5 ppm (A), were of comparable magnitude but of opposite sign to the doublet of doublets at 6.1 ppm representing the internal (α-) proton. This result reflects the hyperfine coupling pattern of the neutral radical, **1a**, and thus established this species as an intermediate in the formation of **5a**. When