Scheme I

$$1^+ \xrightleftharpoons{e} 1\cdot \xrightleftharpoons{e} 1^-$$

$$\text{H}^+ \Updownarrow \qquad \Updownarrow \text{H}^+$$
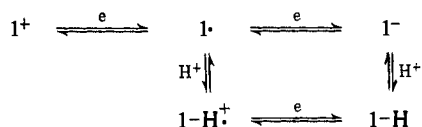
$$1\text{-H}^{\dot{+}} \xrightleftharpoons{e} 1\text{-H}$$

nects the hydrazyl radical 1· and the hydrazine 1-H by proton and electron transfers. Breslow and Chu[2] have pointed out the power of such cycles in measuring acidities and, by using the formal step RH $\rightleftharpoons$ ROH, have applied them to the measurement of the relative acidities of hydrocarbons. For the cycle of Scheme I

$$\text{p}K_a(1\text{-H}) = \text{p}K_a(1\text{-H}^+) +$$
$$(1/0.059)\{E^0(1\text{-H}, 1\text{-H}\cdot^+) - E^0(1^-, 1\cdot)\}$$

where $\text{p}K_a(1\text{-H})$ refers to the equilibrium 1-H $\rightleftharpoons$ 1⁻ + H⁺. Direct measurement of $E^0(1\text{-H}, 1\text{-H}\cdot^+)$ is complicated by the fact that 1-H·⁺ deprotonates to 1· before diffusion away from the electrode surface, forming 1· at an electrode which is far anodic of its E^0 value for oxidation to 1⁺, resulting in rapid removal of 1-H·⁺, and leading to an irreversible-appearing oxidation wave and no observable rereduction wave on the back scan. The peak potential observed for the oxidation wave in cyclic voltametry experiments was $E_p = -0.08$ V vs. sce in acetonitrile which must be cathodic (more negative) of the true E^0 values.[3] We contend that 2, which lacks an NH proton and therefore gives the stable 2·⁺ cation in an electrochemically reversible oxidation, serves as a reasonable model. We observe $E_{1/2}(2, 2\cdot^+) = +0.17$ V and suggest that, if anything, 2 ought to be somewhat more easily oxidized than 1-H, because of the inductive effect of the methyl group, and so E^0 (1-H, 1-H⁺) ought to be $\geq +0.17$ V, but in any event is certainly greater than 0.1 V.

Significantly, 1· is very difficult to reduce. Scanning a 1⁺ solution to −2.5 V and back showed no reduction wave beyond the 1⁺ + e → 1· wave, although the oxidation wave for 1· → 1⁺ + e was still observed, demonstrating that the standard potential $E^0(1^-, 1\cdot) \leq -2.5$ V. Thus, the radical 1· is as difficult to reduce as naphthalene.

A cycle such as that of Scheme I will normally be useful for measuring $\text{p}K_a$ values for radical ions, which have been obtained by flash photolysis[4] or pulse radiolysis[5] techniques and esr spectroscopy.[6] Electrochemistry is a poor tool for such measurements, since four rate constants must be measured accurately to obtain $\text{p}K_a$ values of radical ions;[7] such has rarely, if ever, been done. In our case, however, nothing is known

(2) R. Breslow and W. Chu, *J. Amer. Chem. Soc.*, 91, 5182 (1969); 92, 2165 (1970); 95, 411 (1973).

(3) R. S. Nicholson and I. Shain, *Anal. Chem.*, 36, 722 (1964).

(4) For an example of $\text{p}K_a$ measurements in the hydrouroquinone system, see E. J. Land, G. Porter, and E. Strachand, *Trans. Faraday Soc.*, 57, 1885 (1971); and for analine radical cation, see E. J. Land and G. Porter, *J. Chem. Soc.*, 2027 (1963).

(5) E. Hayon and M. Simic, *J. Amer. Chem. Soc.*, 94, 42 (1972).

(6) R. W. Fessenden and P. Neta, *J. Phys. Chem.*, 76, 2857 (1972), were able to estimate $\text{p}K_a$ for Me₂NH·⁺ by esr experiments using continuous radiolysis, since the esr spectrum of the protonated form was observed in acid and of the unprotonated form in base. Similar experiments using electrolysis of 1⁺ have failed, possibly because the equilibrium constant for 1H·⁺ + 1· $\rightleftharpoons$ 1H + 1⁺ is so large.

(7) For a discussion of the experimental problems, cast as a measurement of the rate of dissociation of acetic acid (a simpler case), see R. R. Schroeder and I. Shain, *J. Phys. Chem.*, 73, 197 (1969).

about $\text{p}K_a$ values for hydrazines, but $\text{p}K_a$ of $\text{N}_2\text{H}_4\cdot^+$ has been determined to be 7.1 ± 0.1 by Hayon and Simic[5] using pulse radiolysis, and we argue that $\text{p}K_a$ of 1H·⁺ cannot be many pK units different from this figure, although there are both steric and inductive differences in the two compounds. We assert that $\text{p}K_a(1\text{H}\cdot^+) > 0$ is a conservative estimate.

The cycle in Scheme I shows, then, that $\text{p}K_a(1\text{-H}) > 0 + (1/0.059)(0.1 - (-2.4)) > 42$. This is an astonishingly high value for $\text{p}K_a$,[8] considering that the conventional experimental value for ammonia is 33 and that for methane 40.[9] Deprotonation of 1-H increases lone pair–lone pair interactions seriously, and we suggest that this effect is important in destabilizing 1⁻. The amide 1-Li is formed when *tert*-butyllithium is added to a THF solution of 2,3-diazanorbornene at −78° and is present in the solution, since quenching with methyl iodide gives 2. This extremely basic hindered amide could prove useful as an unusually strong base.

Acknowledgment. We thank the National Science Foundation for financial support, and Professor D. H. Evans of this department for frequent discussions.

(8) Following Breslow and Chu,[2] we have used electrochemical measurements in a nonaqueous solvent. The solvent effect on E^0 (1·, 1⁺) is small. We observe $E_{1/2}$ for 1⁺ reduction in water to be −0.75 ± 0.01 in water buffered at pH 10–13. Increasingly rapid scan rates must be used to observe the reoxidation wave at lower pH values, because of protonation and reduction to 1-H rapidly removing 1·. Since $E_{1/2}(1\cdot, 1^+)$ is −0.72 in acetonitrile,[1] the solvent effect on this step is certainly negligible.

(9) The value of 40 for methane is probably too low, and 55–60 might be a more reasonable estimate.

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Structure of Cytochalasin E, a Toxic Metabolite of *Aspergillus clavatus*

Sir:

Aspergillus clavatus collected from mold-damaged rice in a Thai household, where a young boy died of an unidentified toxicosis, produced a highly toxic mixture of metabolites. We previously described the two major, but nontoxic, metabolites kotanin and desmethylkotanin,[1] and now report isolation and characterization of the toxin which has absolute stereostructure 1.

A. clavatus was grown on rice and the toxin isolated by extractive and chromatographic techniques: mp 206–208° dec; $[\alpha]^{25}\text{D}$ −25.6° (methanol) after recrystallization from acetone–hexane; m/e (found) 495.2258, calcd for $\text{C}_{28}\text{H}_{33}\text{NO}_7$ 495.2257.[2] The substance is neutral and has ir absorptions typical of γ-lactams. One tertiary hydroxyl group was revealed by ir absorption at 3475 cm⁻¹ and one exchangeable proton at δ 5.0 (singlet in DMSO-d_6). Intense ir bands at 1765, 1660, and 1720 cm⁻¹ are consistent with a vinyl

(1) G. Büchi, D. H. Klaubert, R. C. Shank, S. M. Weinreb, and G. N. Wogan, *J. Org. Chem.*, 36, 1143 (1971). The organism was incorrectly identified as *A. glaucus*.

(2) The high-resolution mass spectrum was measured in the National Institutes of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.
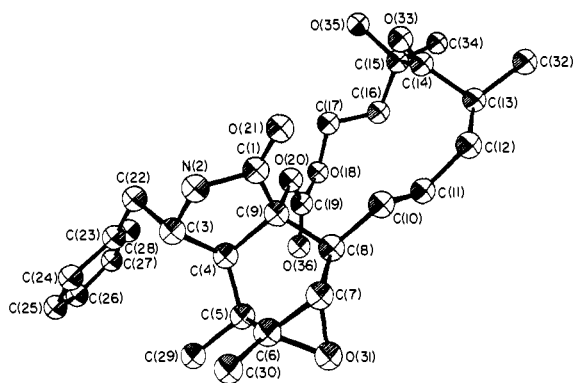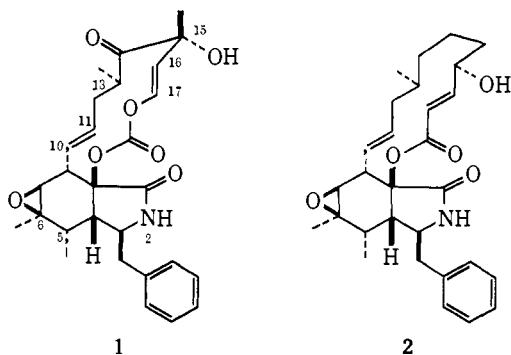
Figure 1. A computer generated drawing of the final X-ray model. The absolute configuration is as shown.

1   2

carbonate[3] and a saturated ketone, respectively, while a positive thiosulfate test revealed an epoxide.[4] Other functionalities follow from the proton spectrum (Table I).

Table I. Proton Chemical Shifts of Cytochalasin E in CDCl₃

| Proton	Chemical shift (δ)	Multiplicity
2-NH	6.93	m, exchangeable
3-H	3.7	m
5-CH₃	1.0	d, J = 6 Hz
6-CH₃	1.2	s
10-H 11-H	4.8–5.9	m
13-CH₃	1.13	d, J = 6 Hz
15-CH₃	1.4	s
15-OH	4.1	s, exchangeable
16-H	5.45	d, J = 11 Hz
17-H	6.25	d, J = 11 Hz
Aromatic H	7.1	m

Methanolysis of the toxin in the presence of sodium bicarbonate gave a neutral substance, in which the quartet owing to H_{16} and H_{17} was replaced by an aldehyde signal at 9.5. Disappearance of bands at 1765 and 1660 cm⁻¹ and appearance of a new carbonyl band at 1750 cm⁻¹ accompanied the transformation of A to B.

The foregoing evidence and the presence of an intense mass peak at 190.0880 ($C_{11}H_{12}NO_2$) (C)[5] strongly suggested that the toxin is a cytochalasin.[6–8]

(3) S. Murahashi, S. Nozakura, S. Fuji, and K. Kikukawa, *Bul.l Chem. Soc. Jap.*, 38, 1905 (1965).
(4) G. G. Freeman, J. E. Gill, and W. S. Waring, *J. Chem. Soc.*, 1128 (1959).
(5) D. C. Aldridge, J. J. Armstrong, R. N. Speake, and W. B. Turner, *J. Chem. Soc. C*, 1667 (1967).

A   B   C
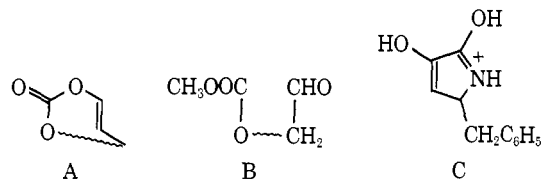
A silver complex was prepared by dissolving *ca.* 10 mg of toxin in methanol and adding a large excess of 30% aqueous AgNO₃. The complex crystallized from the reaction mixture and was recrystallized from isopropyl alcohol.

Initial X-ray photographs displayed 2/m Laue symmetry and the systematic absence on *hkl* (absent if $h + k = 2n + 1$). Diffractometer measured cell constants are a = 27.63 (1), b = 7.312 (5), c = 17.893 (8) Å, and β = 49.63 (5)°. A measured density of 1.65 g/cm³ indicated one formula unit of $C_{28}H_{33}NO_7 \cdot AgNO_3 \cdot H_2O$ per asymmetric unit of the monoclinic space group $C_2(C_2{}^3)$. All unique reflections with $\theta \leq 63°$ were collected on a fully automated Hilger-Watts diffractometer. A total of 2395 reflections were measured and 2065 of these had $F_o{}^2 \geq 3\sigma(F_o{}^2)$ after correction for Lorentz, polarization, and background effects.

A three-dimensional Patterson synthesis was computed and no Ag–Ag peaks could be discerned.[9] The Ag atom was consequently placed at the origin. Successive three-dimensional electron density syntheses, which were strongly influenced by the pseudomirror plane generated by the Ag, finally revealed all 40 nonhydrogen atoms of the toxin AgNO₃·H₂O structure. All atoms were initially identified as C and careful inspection of the temperature factors and molecular geometry allowed unambiguous assignment of O and N atoms. Full-matrix least-squares refinements with anisotropic temperature factors for all atoms and excluding hydrogens converged to R = 0.093.[10] The mirror image was refined to a discrepancy index of 0.102, indicating that the correct mirror image had been fortuitously chosen at the start.[11] A computer generated drawing of the final X-ray model indicating the absolute stereochemistry is shown in Figure 1.[12] All bond distances and angles agree well with generally accepted values.[13] The Ag atom, which is located on the exterior of the toxin molecule on a twofold axis, makes close contacts with two NO₃ anions, two toxin molecules, and two waters of crystallization. The NO₃ anion is also located on the twofold axis generating an array of Ag's interspersed with NO₃'s.

(6) D. C. Aldridge, B. F. Burrows, and W. B. Turner, *J. Chem. Soc., Chem. Commun.*, 148 (1972).
(7) Y. Tsukuda and H. Kayama, *J. Chem. Soc., Perkin Trans. 2*, 739 (1972).
(8) M. Binder and Ch. Tamm, *Helv. Chim. Acta*, 55, 2486 (1972); G. M. McLaughlin, G. A. Sim, J. R. Kiechel, and Ch. Tamm, *Chem. Commun.*, 1398 (1970).
(9) C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and Programs ALFF, ALFFDP, ALFFPROJ, ALFFT, and FRIEDEL," U. S. Atomic Energy Commission Report IS-2625, Iowa State University, Ames Institute for Atomic Research, 1971.
(10) W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program," U. S. Atomic Energy Commission Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(11) W. C. Hamilton, *Acta Crystallogr.*, 18, 502 (1965).
(12) C. R. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations," U. S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(13) O. Kennard and D. G. Watson, Molecular Structures and Dimensions, Crystallographic Data Centre, Cambridge, 1970.

The Ag to O distances are 2.72 (O(40)) and 2.98 Å (O(39)). The closest approach between the toxin and the Ag is the 2.42 Å distance to O(21). The distance from the water of crystallization (O(41)) to the Ag is 2.61 Å and between O(41) and O(33) of the toxin the distance is 3.01 Å. The coordination about Ag is approximately octahedral. There are no other abnormally short intermolecular contacts in the crystal structure.[14]

After these studies had been completed identity of the toxin with cytochalasin E[6] was established by comparison of melting point and mixture melting point, ir and mass spectra, and optical rotations.[15] The previously proposed structure of cytochalasin E therefore

D   E
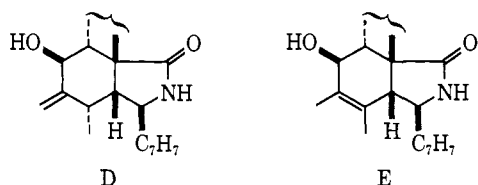
is incorrect and has to be replaced by 1. Acid-catalyzed isomerization to compounds with part structures D and E is now unexceptional. By analogy cytochalasin F[6] has structure 2.

Cytochalasin E killed rats within a few hours after dosing, the LD_{50} value being 2.6 or 9.1 mg/kg body weight after intraperitoneal or oral administration of a single dose. Death was due to circulatory collapse caused by massive extravascular effusion of plasma.

Supplementary Material Available. A listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-73-5423.

(14) See paragraph at end of paper regarding supplementary material.
(15) We are indebted to Dr. W. B. Turner for a sample of cytochalasin E.
(16) Camille and Henry Dreyfus Foundation Teacher–Scholar Grant Awardee, 1972–1977, and Fellow of the Alfred P. Sloan Foundation, 1973–1975.

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Received April 6, 1973

Chromic Acid Oxidation of Cyclopropanols

Sir:

In all previously investigated chromic acid oxidations of secondary alcohols, the chromium(VI) oxidation step yields the corresponding ketone.[1] The rate-limiting step in these oxidations is the breaking of the α-carbon–hydrogen bond. Strained alcohols, like cyclobutanol or 7-norbornanol, form no exception to this rule,[2,3] although they are very prone to undergo a ring-opening reaction under carbon–carbon bond cleavage with one-electron oxidants like chromium-(IV),[2] cerium(IV),[4] vanadium(V),[5] or manganese-(III).[5]

In this communication we wish to report the strikingly different behavior of cyclopropanols.[6] We have found that cyclopropanol reacts with chromic acid about 2000 times faster than typical secondary alcohols (Table I) to yield β-hydroxypropionaldehyde.[7,8]

The oxidation product of 1-phenylcyclopropanol, β-hydroxyethyl phenyl ketone, isolated directly by extraction and column chromotography accounted for 73% of the isolated product (43% yield): ir (CCl$_4$) 3480 (broad), 1680 cm^{-1}; nmr (CCl$_4$) δ 7.90 (m, 2), 7.44 (m, 3), 3.90 (t, $J = 5$ Hz, 2), 3.10 (t, $J = 5$ Hz, 2), and 2.54 (s, 1); mass spectrum (70 eV) m/e 132 (P − H$_2$O), 105, 77.

The cyclopropane ring itself is rather unreactive toward chromic acid, as is clearly indicated by the low reactivity of cyclopropylcarbinol, methyl cyclopropyl ether, and 1,2,2-trimethylcyclopropyl acetate.

Tertiary cyclopropanols are more reactive than the corresponding secondary cyclopropanols. This enhanced reactivity is in sharp contrast with the very low reactivity of other[9,10] tertiary alcohols.[11-13]

The reactivity of both secondary and tertiary cyclopropanols is greatly increased by substitution in the ring; 1,2,2,3,3-pentamethylcyclopropanol is about 6 × 10^6 times more reactive than isopropyl alcohol and is, with respect to chromic acid oxidation, the most reactive organic compound known.

The mechanism of the reaction can best be understood in terms of a rate-limiting oxidative decomposition of a chromic acid ester of the alcohol (Scheme I). The driving force for the reaction is the relief of the

(1) For a review of this subject, see K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1965.
(2) J. Roček and A. E. Radkowsky, *J. Amer. Chem. Soc.*, 90, 2987 (1968).
(3) H. Kwart, *Chem. Ind. (London)*, 40, 610 (1962).
(4) K. Meyer and J. Roček, *J. Amer. Chem. Soc.*, 94, 1209 (1972).
(5) J. Roček and A. E. Radkowsky, *J. Org. Chem.*, 38, 89 (1973).
(6) For a review of the chemistry of cyclopropanols, *cf.* C. H. De Puy, *Accounts Chem. Res.*, 1, 33 (1968).
(7) After treatment with 2,4-dinitrophenylhydrazine, a mixture of the derivatives of β-hydroxypropionaldehyde and acrolein is obtained. By following the ultraviolet absorption at 210 nm during the oxidation reaction, it can be demonstrated that no acrolein is formed during the oxidation; it therefore must be formed by dehydration of the β-hydroxypropionaldehyde during the treatment with dinitrophenylhydrazine. The same mixture of dinitrophenylhydrazones is obtained from a solution of β-hydroxypropionaldehyde and acrolein (9:1) obtained by acid catalyzed hydration of acrolein.[8]
(8) R. H. Hall and E. S. Stern, *J. Chem. Soc.*, 490 (1950).
(9) The observation[10] that chromium(VI) oxidizes triphenylcarbinol faster than diphenylcarbinol in highly acidic media (but not at lower acid concentrations) represents the only previously recorded exception to this rule.
(10) R. Stewart and F. Banoo, *Can. J. Chem.*, 47, 3207 (1969).
(11) J. Roček and A. Radkowsky, *Tetrahedron Lett.*, 2835 (1968).
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Communications to the Editor