

substituents in a nonpolar solvent, however, a substantial repulsive interaction with the π electrons of the exocyclic double bond destabilizes the axial conformer, with the result that the equatorial position is favored even more for methylenecyclohexanes than for the parent cyclohexane. Lower electron densities on the substituent atom attached to the ring, as a result either of resonance delocalization to more distant atoms as in acetoxyl or of hydrogen bonding to polar solvents, result in increased amounts of the axial conformer. The "steric" interaction of π electrons observed in the nonpolar solvent may be present in other systems and should be readily identified by its solvent dependence. Our ongoing work is involved with defining more precisely the nature of the repulsive interaction between the various substituents and the π electrons.

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Structure and Synthesis of Moniliformin, a Novel Cyclobutane Microbial Toxin

Sir:

A new microbial toxin, moniliformin, was discovered by Cole, *et al.*,¹ while screening for toxigenic products of *Fusarium moniliforme* from naturally infected southern leaf blight damaged corn seed. The original moniliformin-producing isolate of *F. moniliforme* stopped producing the toxin during the course of our study. A new source, *Gibberella fujikuroi* (perfect stage of *F. moniliforme*), was located at the American Type Culture Collection and had been assigned the ATCC #12763. The only detectable difference between strains was that the moniliformin produced by the original organism was a sodium salt, while the ATCC strain produced moniliformin containing potassium instead of sodium.

The initial chemical and spectroscopic investigations on the structure of moniliformin were inconclusive but indicated that the toxin was a small ionic molecule, possibly a carboxylate salt.¹ On treatment with trimethylsilyl chloride, no silyl derivative was formed but instead a crystalline acid, mp 158° dec, was isolated, apparently by neutralization of the salt by the HCl formed. The acid gave a positive ferric chloride test and reacted with diazomethane to form a neutral methyl derivative. Confirming the original deduction of Cole, *et al.*, the nmr spectrum of this derivative showed, in addition to a three-proton methyl singlet at δ 4.3, a one-proton singlet at δ 8.65. Consequently, moniliformin apparently possesses a single hydrogen bound to carbon.

Because the limited analytical and spectroscopic data available could not be accommodated with a reasonable

(1) R. J. Cole, J. W. Kirksey, H. G. Cutler, B. L. Douppnik, and J. C. Peckham, *Science*, 179, 1324 (1973).

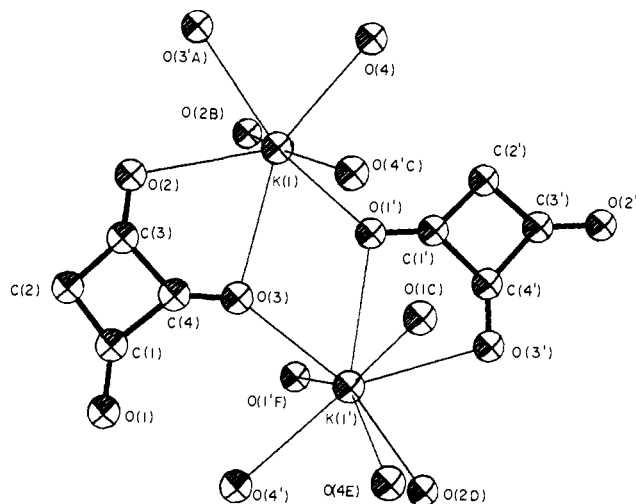


Figure 1. A perspective drawing of a portion of the moniliformin structure showing the environment of the 1-hydroxycyclobut-1-ene-3,4-dione anion and the potassium cations. The thin lines show all close contacts to potassium of less than 3.20 Å. Hydrogen atoms are not shown.

structure, a single-crystal X-ray diffraction structure was carried out to provide a definitive solution.

Crystals of moniliformin suitable for diffraction work could be grown from aqueous methanol solution. The crystals formed in the monoclinic space group $P2_1/c$, with $a = 8.46$ (1), $b = 10.918$ (9), $c = 13.28$ (1) Å, and $\beta = 100.75$ (8)°. An experimental density measurement (1.80 g/cm³) suggested a fragment of molecular weight of approximately 300 as the asymmetric unit. A complete set of diffraction maxima within a θ sphere of 60° was measured with a fully automated four-circle diffractometer using Ni-filtered Cu radiation (1.5418 Å). Of the 1899 reflections measured a total of 1547 were judged observed after correction for Lorentz, polarization, and background effects. A three-dimensional Patterson synthesis was computed, and two heavy atoms, which subsequently proved to be potassium, were clearly indicated. The potassium phased electron density synthesis revealed all the remaining nonhydrogen atoms. The potassium atoms were identified by elemental analysis and the carbons and oxygens distinguished by their heights in the electron density synthesis and isotropic temperature factor refinement. Full-matrix least-squares refinements with anisotropic temperature factors for all nonhydrogen atoms lowered the conventional discrepancy index to 0.074 for the observed reflections.² Figure 1 is a computer-generated perspective drawing of the X-ray model.

The X-ray structural work clearly showed that crystalline moniliformin was composed of the anion of 1-hydroxycyclobut-1-ene-3,4-dione, the potassium cation, and one water of crystallization. Two crystallographically independent fragments of this composition

(2) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT and FRIEDEL," USAEC Report IS-2625, Iowa State University-Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program," USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program," U. S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

form the asymmetric unit. This structure is consistent with all of the previously reported analytical data.

Structure 1, while without precedent for a natural product, is perfectly reasonable chemically and its dimensions are reminiscent of the closely related dipotassium salt of squaric acid, **3**.³ The two crystallographically independent anions in the asymmetric unit have the same geometry and C_{2v} symmetry within experimental error. The averaged geometry is given in Table I. The anion is planar with a maximum devia-

Table I

Averaged Bond Distances			
Bond	Distance (Å)	Bond	Distance (Å)
C(1)-C(2)	1.411 (8)	C(1)-O(1)	1.243 (7)
C(1)-C(4)	1.508 (8)	C(4)-O(3)	1.209 (7)
Averaged Bond Angles			
Bond	Angle (deg)	Bond	Angle (deg)
C(1)-C(2)-C(3)	94.4 (5)	O(1)-C(1)-C(2)	137.6 (6)
C(2)-C(3)-C(4)	89.4 (5)	O(1)-C(1)-C(4)	133.0 (6)
C(3)-C(4)-C(1)	86.8 (4)	O(3)-C(4)-C(1)	136.6 (5)

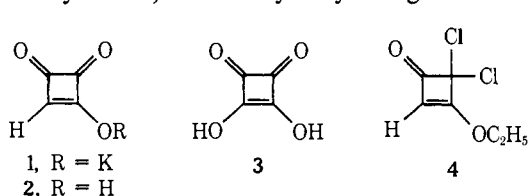
tion of 0.01 Å from the best least-squares plane. Oxygen atoms O(1) and O(2) formally share a negative charge, and their bond length to carbon (1.243 Å) is significantly longer than the O(3)-C(4) bond length (1.209 Å).

The coordination about the potassium cations is rather complex. K(1) is surrounded by seven oxygens at an average distance of 2.836 Å (the range is 2.721–2.990 Å) while K(1') is surrounded by eight oxygens at an average distance of 2.913 Å with a range of 2.757–3.167 Å.

The crystal structure is layered with a closest distance between layers of 3.27 Å. A similar short layer spacing was also observed in dipotassium squarate and attributed to a charge-transfer self-complex.³

The parent acid **2**, 1-hydroxycyclobut-1-ene-3,4-dione, was reported several years ago;⁴ infrared, ultraviolet, and nmr spectra kindly furnished by Professor Hoffmann confirmed its identity with the acid obtained by treatment of moniliformin with trimethylsilyl chloride.

An independent synthesis was devised to provide material for biological testing. Thermal addition⁵ of dichloroketene (generated from dichloroacetyl chloride and triethylamine) to ethoxyacetylene gave adduct **4**,



which could be hydrolyzed by aqueous hydrochloric acid to **2**. The synthetic material was identical by ir, uv, and nmr comparison with the parent acid of moniliformin and further elicited the same physiological behavior in cockerels as moniliformin.

The biosynthetic origin of moniliformin is unknown

(3) W. M. Macintyre and M. S. Werkeman, *J. Chem. Phys.*, **40**, 3563 (1964).

(4) R. W. Hoffmann, U. Bressel, J. Gehlhaus, and H. Häuser, *Chem. Ber.*, **104**, 873 (1971).

(5) N. Morita, T. Asao, and Y. Kitahara, *Chem. Lett.*, **1**, 927 (1972).

and the structure represents a novel structural type. The closest known natural compounds rhodizonic ($C_6H_2O_6$) and croconic ($C_5H_2O_5$) acids seemingly arise from microbial oxidation of myoinositol.⁶

(6) A. J. Fatiadi, H. S. Ishell, and W. F. Soger, *J. Res. Nat. Bur. Stand.*, **67A**, 153 (1963); A. J. Klugver, T. Hof, and A. J. Boczaardt, *Enzymologia*, **7**, 257 (1939); *Chem. Abstr.*, **34**, 6322 (1948); L. F. Heller, *Justus Liebigs Ann. Chem.*, **24**, 1 (1937).

(7) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1972–1977, and Fellow of the Alfred P. Sloan Foundation, 1973–1975.

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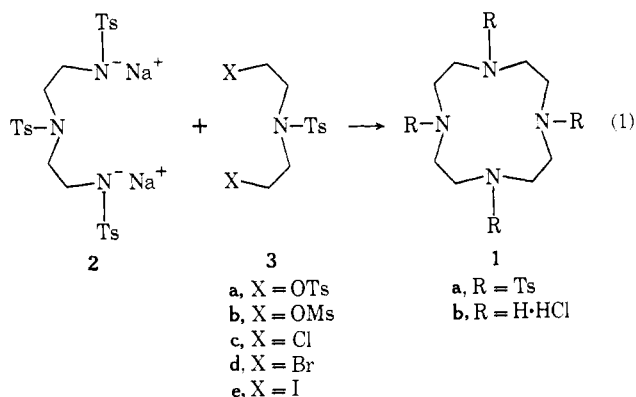
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Nitrogen Analogs of Crown Ethers

Sir:

A simple preparation of cyclic amines of medium-large ring size has long been sought. We report a simple and general synthesis of nine- to 21-membered rings containing three to seven heteroatoms. The method gives 40–90% yields and utilizes neither high dilution techniques nor template effects in the cyclization step.

Stetter and Roos¹ reported moderate cyclization yields in the condensation of terminal dihalides with bisulfonamide sodium salts under high dilution. We have found that using preformed bisulfonamide sodium salts (e.g., **2**) and sulfonate ester leaving groups in a dipolar aprotic solvent obviates the high dilution technique. Thus, large-scale preparations are now practical. For example, we have applied this method to the synthesis of "cyclen" (1,4,7,10-tetraazacyclododecane) tetrahydrochloride (**1b**).^{2,3}



(1) H. Stetter and E.-E. Roos, *Chem. Ber.*, **87**, 566 (1954).

(2) H. Stetter and K.-H. Mayer, *Chem. Ber.*, **94**, 1410 (1961).

(3) J. P. Collman and P. W. Schneider, *Inorg. Chem.*, **5**, 1380 (1966).