The ^{31}P resonance of the *trans* form of **2** appears to show line broadening effects even when the *cis* isomer is in the slow-exchange limit (Figure 2). It is probable that the energy minimum for the *trans* molecule corresponds to the distorted structure indicated in Figure 3a and that the inequivalent phosphorus ligands are undergoing rapid intramolecular exchange.

The passage of the *cis* and *trans* ^1H resonances in **2** to a simple quintet with increasing temperature shows that *cis–trans* isomerization *via* a polytopal[1,4] rearrangement is operative here. The analysis of the hydride spectrum for compound **1** is the same as for **2** except that only the *cis* isomer was detected.

The distortions in the *cis* and *trans* isomers indicated in Figure 3 suggest a polytopal rearrangement alternative to the trigonal or "Bailar" twist.[5] The distortion modes could, in highly excited vibrational states, approach a tetrahedral disposition of phosphorus nuclei about the iron nucleus; hydrogen traverse (tunneling or classical) of trigonal faces would then complete the nuclear permutation process. This alternative is more attractive on steric grounds because of the obvious steric relief in the transition state. We cannot now rigorously distinguish between these two possible rearrangements, but detailed analysis of nmr transitional line shapes using the density matrix approach and analogous studies of other L_4MH_2 complexes now in progress may provide a definitive answer. Full details of spectral assignments and mechanistic studies will be published shortly.

(4) E. L. Muetterties, *J. Amer. Chem. Soc.*, **91**, 1636 (1969).
(5) J. C. Bailar, Jr., *J. Inorg. Nucl. Chem.*, **8**, 165 (1958).

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The Isolation and Structure of Daphnetoxin, the Poisonous Principle of *Daphne* Species[1]

Sir:

Daphne mezereum L. and other species of the thymelaeaceous genus *Daphne* have been recognized since at least the 11th century[2] as virulent poisons, and more recent cases have confirmed the toxicity, doses of a few berries or a few grams of bark being reported fatal to man, dog, or horse.[3–6] Despite the striking toxicity[7] and the widespread occurrence of the genus both wild and cultivated in Europe and North America, no modern chemical studies of the principle have been made and the activity has been variously ascribed to the coumarin glycosides,[3,4] which are well known constituents of the bark,[8] or to an ill-defined mezerinic acid or mezerinic anhydride.[5,6,9]

Fractionation of CH_2Cl_2 extracts of *D. mezereum* bark or commercial "mezeron" bark (*D. mezereum*, *D. laureola*, and *D. gnidium*) by partitioning between hexane–CH_2Cl_2 and aqueous methanol, removal of phenolic materials by careful base washings, countercurrent fractionation, and finally crystallization from cold ethanol led in approximately 0.02% yield to a crystalline product, daphnetoxin.[10] The isolation procedure was devised on the basis of toxicity tests using goldfish[11] and appears to yield the major toxic component.[12]

Daphnetoxin, mp 194–196°, $[\alpha]D$ +63°, λ_{max}^{EtOH} (ϵ) 243 (8950), 337 (84) nm, $C_{27}H_{30}O_8$, suffers degradation to complex mixtures of products in either acid or base but yields with acetic anhydride–pyridine a diacetate, mp 122–124°, $C_{31}H_{34}O_{10}$. Basic hydrolysis affords benzoic acid and suggested the molecule to be the benzoate ester of a diterpene alcohol, a result supported by nmr signals corresponding to five aromatic protons and by an intense peak for $C_6H_5CO^+$ in the mass spectrum of the acetate. The formation of another intense ion corresponding to $C_6H_5C_2O_3^+$, and the ready reduction of daphnetoxin by $NaBH_4$ to products showing typical alkyl benzene fine structure in the uv, however, indicated additional complications.

The parent molecule and a number of derivatives were examined for possible crystallographic study but all proved unsuitable until the bisbromoacetate was found to crystallize in part in hexagonal plates, mp 228–229°, space group $P3_121$ (or $P3_221$) with one molecule in the asymmetric unit, $a = 12.458$, $c = 34.441$ Å.

Intensity data collected on a Picker automatic diffractometer using Cu Kα radiation yielded 2660 reflections of $2\theta \leq 120°$. After correction for absorption ($\mu = 41.5$ cm^{-1}) these yielded a Patterson synthesis showing the location of one bromine. A series of structure factor and Fourier calculations revealed in stages the remaining atoms and culminated in the structure **1a**.[13] Because extensive crystal degradation occurred during data collection (average intensity loss *ca.* 25%), the data were remeasured using three separate crystals and discarding these when the intensity losses reached 10%. Refinement on the new data has yielded an R of 8.4% and is continuing, but the presence of

(1) A portion of the work described here was reported at an intermediate stage as paper D1 at the meeting of the American Crystallographic Association, Seattle, Wash., March 25, 1969. The abstract shows the molecule in what is now known to be the incorrect absolute configuration, and, owing to an error in drawing, with the wrong relative configuration at C-5.

(2) Avicenna (A.D. 980–1037), as cited by Rufinus (*ca.* 1287); *cf.* "The Herbal of Rufinus," L. Thorndyke, Ed., University of Chicago Press, Chicago, Ill., 1946, pp 189–190. The toxicity is also mentioned, although in less vigorous terms, by Dioscorides (1st century A.D.).

(3) J. M. Kingsbury, "Poisonous Plants of the United States and Canada," Prentice-Hall, Englewood Cliffs, N. J., 1964, pp 386–388.

(4) W. C. Muenscher, "Poisonous Plants of the United States," Macmillan, New York, N. Y., 1951, pp 168–171.

(5) O. Gessner, "Die Gift - und Arzneipflanzen von Mitteleuropa," Carl Winter, Universitatsverlag, Heidelberg, 1953, pp 548–551.

(6) A. A. Forsyth, "British Poisonous Plants," Bulletin 161, HMSO, London, 1954, pp 64–66.

(7) These properties are apparently widespread in the family, many genera of which have been popularly recognized as having strong irritant properites (*e.g.*, "burn nose bark" for *Daphnopsis* sp. of Jamaica), and at least one of which (*Schoenobiblus*) has been used as the basis of a Peruvian arrow poison (Dr. H. V. Pinkley, personal communication).

(8) *Cf.* W. Karrer, "Konstitution und Vorkommen der Organischen Pflanzenstoffe," Birkhauser Verlag, Basel, 1958, compounds 1320, 1334, 1449.

(9) Buchheim, *Arch. Path.*, 1 (1872), cited in C. Wehmer, "Die Pflanzenstoffe," Vol. II, Gustav Fischer, Verlag, Jena, 1929, p 814.

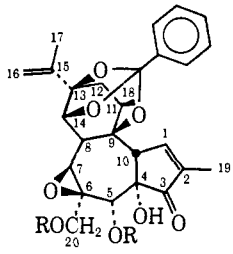
(10) W. J. Balkenhol, Ph.D. Thesis, University of Washington, Seattle, Wash., 1967.

(11) W. A. Gersdorff, *J. Amer. Chem. Soc.*, **52**, 3440 (1930).

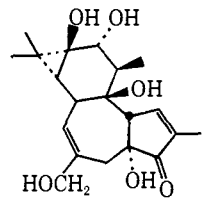
(12) Daphnetoxin in mice shows LD_{50} *ca.* 275 μg/kg, *i.e.*, approximately half that of strychnine. Goldfish tests indicate that about one-third the total toxicity of the crude extracts is isolated as crystalline product.

(13) The numbering system indicated follows that of Hecker, *et al.*, for phorbol,[14] since this accommodates more reasonably than that of Crombie[15b] the cyclopropyl opening which constitutes the formal distinction between the two skeletons.

residual degradation effects even after correction for average dI/dt and clear evidence of some packing disorder indicate that high precision is not to be expected.



1a, R = $BrCH_2C(=O)-$
b, R = H



2

The structure **1b** implied for daphnetoxin itself shows striking similarities, both in the skeleton and in the sites of functional groups to phorbol (**2**), the diterpene parent of the toxic esters of croton oil.[14-16] Comparisons of the physical properties of the two compounds show the expected correspondences, especially in the nmr spectra. Furthermore, the absolute configuration of daphnetoxin bisbromoacetate, as shown both by parallel structure-factor calculations[17] including Br anomalous dispersion in $P3_121$ and $P3_221$ to R's of 10.9 and 11.1%, respectively, and by the comparison of 40 pairs of observed and calculated $F_{hkl}/F_{\bar{h}\bar{k}\bar{l}}$, all of which were in accord with $P3_121$, is as shown in **1** and is the same as found crystallographically for phorbol.[16a] Figure 1 shows a stereoscopic view of the molecule in the proper hand. Strikingly, the CD curve of daphnetoxin, $[\theta]_{342} + 3050$, $[\theta]_{243} - 8300$, is nearly enantiomeric with that reported for phorbol.[18] Comparison of the atomic parameters for the one phorbol derivative for which these have been reported[16b] with those for **1a**, however, suggests that the α,β-unsaturated keto systems have opposite chirality in the two molecules despite the configurational identity. Both systems then agree with the CD correlation proposed for cyclopentenones by Snatzke.[19]

The structure of daphnetoxin, although unique in detail, is similar in its high degree of oxygen bridging to a number of other highly toxic nitrogenous and non-nitrogenous compounds.[20] The orthobenzoate structure in particular, although without exact analogy, is strongly reminiscent of the hemilactal structure of tetrodotoxin.[20a] The similarity to phorbol is clearly of chemotaxonomic interest in view of the much disputed phylogenetic placing of the Thymeleaceae,[21] especially since one of the numerous proposals posits on the grounds of pollen morphology a close connection to the crotonoid members of the Euphorbiaceae.[21d,22]

(14) E. Hecker, H. Bartsch, H. Bresch, M. Gschwendt, E. Härle, G. Kreibich, H. Kubinyi, H. U. Schairer, Ch. v. Szczepanski, and W. H. Thielmann, *Tetrahedron Lett.*, 3165 (1967), and references cited therein.

(15) (a) R. C. Pettersen, G. Ferguson, L. Crombie, M. L. Games, and D. J. Pointer, *Chem. Commun.*, 716 (1967); (b) L. Crombie, M. L. Games, and D. J. Pointer, *J. Chem. Soc., C*, 1347 (1968).

(16) (a) W. Hoppe, F. Brandl, I. Strell, M. Röhrl, I. Gassmann, E. Hecker, H. Bartsch, G. Kreibich, and Ch. V. Szczepanski, *Angew. Chem. Intern. Ed. Engl.*, **6**, 809 (1967); (b) R. C. Pettersen, G. I. Birnbaum, G. Ferguson, K. M. S. Isham, and J. G. Sime, *J. Chem. Soc., B*, 980 (1968); (c) W. Hoppe, K. Zechmeister, M. Röhrl, F. Brandl, E. Hecker, G. Kreibich, and H. Bartsch, *Tetrahedron Lett.*, 667 (1969).

(17) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(18) E. Hecker, C. v. Szczepanski, H. Kubinyi, H. Bresch, E. Härle, H. V. Schairer, and H. Bartsch, *Z. Naturforsch.*, **21b**, 1204 (1966). These are the $n-\pi^*$ and $\pi-\pi^*$ bands of the cyclopentenone chromophore. The additional CD band at 270 nm in phorbol does not appear in daphnetoxin.

(19) G. Snatzke in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden and Son, London, 1967, pp 217–8.

(20) *Inter alia* (a) tetrodotoxin, R. B. Woodward, *Pure Appl. Chem.*, **9**, 49 (1964); (b) batrachotoxin, T. Tokuyama, J. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, **91**, 3931 (1969); (c) picrotoxinin, H. Conroy, *ibid.*, **79**, 5550 (1957).

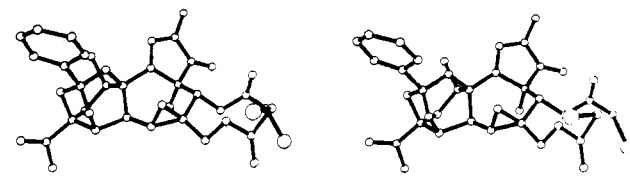


Figure 1. A stereoview of daphnetoxin bisbromoacetate.

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(21) (a) A. Engler, "Syllabus der Pflanzenfamilien," Vol. II, 12th ed, Gebruder Borntraeger, Berlin, 1964, pp 316–321; (b) J. Hutchinson, "The Genera of Flowering Plants," Vol. II, Oxford, 1967, pp 239–271; (c) A. Cronquist, "The Evolution and Classification of Flowering Plants," Houghton Mifflin, Cambridge, Mass., 1968, pp 238–241; (d) A. Takhtajan, "Die Evolution der Angiospermen," Gustav Fischer Verlag, Jena, 1959, pp 216–217.

(22) G. Erdtman, "Pollen Morphology and Plant Taxonomy," Vol. I, Hafner, New York, N. Y., 1966, pp 175, 431–433.

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Intermolecular Methyl Transfers in the Methylation of Anisole

Sir:

We wish to report a study of the methylation of anisole which reveals that the major reaction pathway involves initial alkylation on oxygen followed by intermolecular transfer of a methyl group to oxygen or carbon.

Reaction of 0.1 M methyl chloroformate with silver hexafluoroantimonate[1] and a fivefold excess of anisole in chlorobenzene for 10 hr at room temperature gives a 24 ± 3% yield[2] of methylanisoles with an *ortho*:*meta*:*para* isomer distribution of 35:5:60.[3] Reaction of methyl-d_3 chloroformate with anisole under the same conditions gives a 26 ± 3% yield of methylanisoles with an isotope distribution of 72 ± 6% **1**, 25 ± 3% **2**, 3 ± 1% **3**, and <1% **4**. Recovered excess anisole con-

(1) P. Beak, R. J. Trancik, and D. A. Simpson, *J. Amer. Chem. Soc.*, **91**, 5073 (1969).

(2) Yields are based on initial methyl chloroformate unless otherwise specified.

(3) Thermodynamic and kinetic evidence shows that the relative yield of *ortho* methylanisole is not deceptively low because of equilibration to *meta* and *para* isomers or selective reaction of the *ortho* isomer. Equilibration would lead to considerably more *meta* compound than the 5% observed.[4] Separate reactions of each of the methylanisoles with a solution made by reaction of *n*-propyl chloroformate with silver hexafluoroantimonate in chlorobenzene, at room temperature for 10 hr, gave recovery of the *ortho*, *meta*, and *para* isomers of 89, 71, and 31%, respectively.

(4) D. A. McCaulay, "Friedel-Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience Publishers, New York, N. Y., 1965, Chapter XXIV.