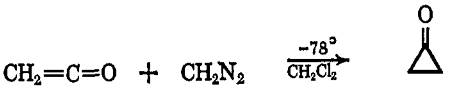
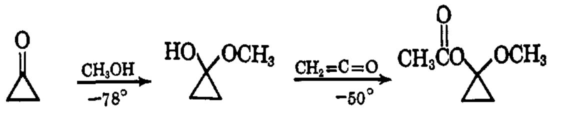
ene chloride (5 ml) solution of ketene[3b] (45 mmoles) yields **1** in 90% yield. Removal of the excess ketene by vacuum distillation (−78°) affords pure solutions of **1** (50–60% over-all yields based on diazomethane[4]). Compound **1** shows infrared absorption[5,6] at 3045 (cyclopropane C–H) and 1813 cm^{-1} (strained carbonyl); nmr singlet[7] at τ 8.35; ultraviolet spectrum $\lambda_{max}^{CH_2Cl_2}$ 3100 (ϵ ~23) and 3300 A (infl).



1, 90%

(1)

Addition of CH_3OH to a pure CH_2Cl_2 solution of **1** at −78° affords **4** in 98% yield.[6] If an equivalent amount of CH_3OH is added to **1** *in the presence of a 3–4-fold excess of ketene*, **4** is formed exclusively[8] and



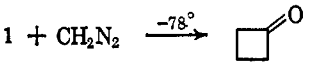
1 4, 98% 5, 99%

(2)

then is acylated quantitatively by ketene to yield **5**, infrared $\lambda_{max}^{CCl_4}$ 2832 (OCH_3) and 1745 cm^{-1} (CH_3COO); nmr two sharp singlets at τ 6.44 (three protons) and 7.92 (three protons) and a broadened multiplet centered at τ 9.0 (four protons); mass spectrum *inter alia: m/e* 130 (M^+, very weak), 115 ($M - CH_3$, 3%), 88 ($M - CH_2{=}C{=}O$, 12%), 71 ($M - CH_3COO$, 7%), and 43 (CH_3CO^+, 100%).

Thus *there is a remarkable difference in reactivity of* **1** *and ketene toward nucleophiles* since **1** is attacked by CH_3OH at least 10–100 times faster than ketene, but ketene is much more reactive toward diazomethane.[9]

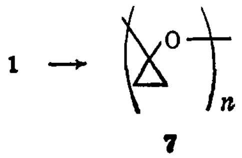
Cyclopropanone nonetheless reacts smoothly with diazomethane[6,9] even at −78° to yield cyclobutanone (**6**).



6, 90%

(3)

At room temperature **1** rapidly polymerizes[6] to yield a compound assigned structure **7**: nmr broad singlet at τ 9.1, infrared 1130 cm^{-1} (C–O) and 1050, 980, and 950 cm^{-1} (Δ-C–C stretch).



7

(4)

This polymerization reaction completes favorably with addition of **3** to dienes such as furan and cyclopentadiene.[10]

Acknowledgment. The authors gratefully acknowledge the generous support of the Air Force Office of Scientific Research (Grant AFOSR-1000-66) and the National Science Foundation (Grant NSF-GP-4280).

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(4) Analysis by nmr of flash distilled solutions of **1**.

(5) A. Kende, Ph.D. Dissertation, Harvard University, Cambridge, Mass., 1957.

(6) P. Lipp and R. Doster, *Ber.*, **64**, 2823 (1931).

(7) Methylene chloride solution, TMS external standard.

(8) No methyl acetate; the product of reaction of ketene and methanol is detectable in the reaction mixture by nmr analysis.

(9) D. A. Semenow, E. F. Cox, and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 3221 (1956).

(10) Reaction does occur with more nucleophilic unsaturated compounds such as enamines: W. B. Hammond, unpublished results.

(11) Alfred P. Sloan Fellow.

(12) National Science Foundation Predoctoral Fellow, 1964–present.

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A Generalized Theoretical Basis for the Octant Rule[1]

Sir:

The octant rule for optically active ketones[2] is a generalization giving absolute molecular configuration. The purpose of this note is to report a general theoretical relationship which predicts the correct octant behavior and gives the correct absolute sign of rotatory strength. While this development is part of a larger program for obtaining sector or regional rules for the optical activity of intrinsically inactive chromophores,[3] it seems sufficiently straightforward and important to warrant early notice.

A quantal development for the $^1A_2 \leftarrow {}^1A_1$ (n–π^*) transition rotatory strength of a carbonyl group interacting with a negligibly overlapped nonpolar perturber gives

$$R_{0,\mathrm{n}\pi} = +i \sum_{1} 2(E_1{}^2 - E_{\mathrm{n}\pi}{}^2)^{-1} E_1 (\mathrm{A}_{\mathrm{n}\pi}\mathrm{B}_1|V|\mathrm{A}_0\mathrm{B}_0)\mu^z{}_{0,1} m^z{}_{\mathrm{n}\pi,0} \quad (1)$$

Both ground and excited spectroscopic state carbonyl wave functions are perturbed to the first order.

Here $m^z{}_{\mathrm{n}\pi,0}$ is the z component of magnetic dipole transition moment of the isolated carbonyl group, $\mu^z{}_{0,1}$ is a "borrowed" electric transition dipole moment of the perturber. $(\mathrm{A}_{\mathrm{n}\pi}\mathrm{B}_1|$ represents a product wave function with the carbonyl group A in the upper state of its n–π^* transition and perturber group B in its 1 state. V is the electrostatic potential between the charge distributions of A and B.

Expansion of the perturbation matrix element shows it depends in part on the product of $\theta^{xy}{}_{0,\mathrm{n}\pi}$, the xy component of electric quadrupole transition moment of the isolated carbonyl group, and $\mu^z{}_{0,1}$. The sum over excited states 1 of the perturber then defines its mean polarizability measured at the n–π^* transition frequency, $\bar{\alpha}(\nu_{\mathrm{n}\pi})$, to give[4]

$$R_{0,\mathrm{n}\pi} = -15i\bar{\alpha}(\nu_{\mathrm{n}\pi})R^{-7}XYZ\theta^{xy}{}_{0,\mathrm{n}\pi}m^z{}_{\mathrm{n}\pi,0} \quad (2)$$

R is the distance from carbonyl to perturber centers of gravity; X, Y, and Z are the signed components of that distance on a right-handed coordinate system centered on the carbonyl oriented so that Z is in the C–O direc-

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(1) This work supported in part by Public Health Service Grant GM-11644 and in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(2) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(3) O. E. Weigang, Jr., and E. G. Höhn, to be published.

(4) See D. J. Caldwell and G. Eyring, *Rev. Mod. Phys.*, **35**, 577 (1963), where limited sets of one-center hydrogenic wavefunctions describing average electronic properties are used to predict similar behavior.

tion and X and Y are in the symmetry planes. If the wave functions are taken to be real, $m^z{}_{n\pi,0}$ is pure imaginary, so that the indicated factor $i = \sqrt{-1}$ yields a real rotatory strength.

Since $i\theta^{xy}{}_{0,n\pi}m^z{}_{n\pi,0}$ is itself an observable,[5] the expression gives the absolute configuration of the composite system in terms of parameters measurable in the independent subsystems. Approximating the n–π* transition as $p_y \leftarrow p_x$ on the oxygen (and thus further specifying the orientation of the coordinate system), the factor is calculated to be negative and large in atomic units. It will not be sensitive in sign to refinement of the transition description. With this result, eq 2 gives the empirically verified sign of rotatory strength.

Equation 2 as given applies only to nonpolar isotropic perturbers, or a tetrahedral arrangement of equivalent bonds approximating the methyl group, or any nonpolar groups which attain virtual isotropy through free rotation about bonds. With a persistent anisotropy of the perturber, the simple XYZ octant behavior is modified by terms with more complicated coordinate dependence. If the perturber is dipolar or charged, terms which must be added to eq 2 obtain within the same theoretical framework.

In the case of a charged perturber, the added contribution that arises is identical in coordinate dependence with that which Schellman obtained by general symmetry arguments.[7] A previously proposed perturbation,[8,9] the incompletely screened nucleus which acts like a static charge, also should give XY dependence for its leading terms. However, limitation of the wave function basis set and neglect of multicenter integrals can circumvent such terms, causing the first nonvanishing ones to have XYZ dependence.

It has been suggested that the magnitude of incomplete screening and hence the concomitant differential overlap of subsystems has been considerably overestimated.[10] Equation 2, on the other hand, with parameters appropriate to 3-methylcyclopentanone,[8] gives a magnitude completely satisfactory in its agreement with experiment. Using polarizabilities measured at zero frequency and taking the transition as $p_y \leftarrow p_x$, the partial molecular rotation at the D line is calculated to be about 120°. The observed total molecular rotation is 130°.[8]

As presented here, vicinal action arises from additive van der Waals interactions. The development is essentially an extension of the Kirkwood polarizability theory of optical activity[11] considering a transition ignored in that work. Electric transition moment "borrowing" that is implicit in this approach readily accounts for the modification of ordinary absorption intensity laid to charge-transfer processes, the basis of yet another interpretation of the octant rule.[12] Nevertheless the fundamental question remains, which only extensive calculation can answer, as to how large and important overlap may be in α- or β-substituted halo ketones and the like.

Acknowledgment. A number of helpful discussions with Dr. L. C. Cusachs are gratefully acknowledged.

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[5] The term is the *difference* of components of a second-order absorption mechanism.[6]

[6] See, for example, G. Araki, *Phys. Rev.*, 74, 472 (1948); H. F. Hameka, "Advanced Quantum Chemistry," Addison-Wesley Publishing Co., Inc., Reading, Mass., 1965, p 123.

[7] J. A. Schellman, *J. Chem. Phys.*, **44**, 55 (1966).

[8] W. J. Kauzmann, J. E. Walter, and H. Eyring, *Chem. Rev.*, **26**, 339 (1940).

[9] A. Moscowitz, *Advan. Chem. Phys.*, **4**, 67 (1962).

[10] M. V. Vol'kenshtein and M. P. Kruchek, *Opt. Spectry*, **9**, 243 (1960).

[11] J. G. Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937).

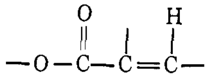
[12] S. F. Mason, *Quart. Rev.* (London), 17, 20 (1963), and references cited therein.

The Isolation and Structural Elucidation of Two Novel Sesquiterpenoid Tumor Inhibitors from *Elephantopus elatus*[1,2]

Sir:

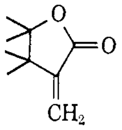
In a search for tumor inhibitors from plant sources, alcoholic extracts of dried *Elephantopus elatus* Bertol. (Compositae)[3] showed significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[4] We report herein the isolation and structural elucidation of two novel tumor-inhibitory sesquiterpene dilactones of the germacrane type from *E. elatus*.

Fractionation involving successive partitions and chromatography yielded elephantin[5] (IVa), $C_{20}H_{22}O_7$, mp 242–244°, $[\alpha]^{27}D$ −380°, $\lambda_{\max}^{\text{MeOH}}$ 215 mμ (ε 25,200), $\lambda_{\max}^{\text{KBr}}$ 5.64, 5.68, 5.84, and 6.07 μ, and nmr[6] signals at τ 1.95 (2.42 in $DCCl_3$, 1 H, s, I),[7,8] 3.85 and 4.22 (2 H, doublets, J = 3 cps, II), 4.24 (1 H, s, vinyl H), 4.50 (m, >CH–O or vinyl H), 5.80 (2 H, m, >CH–O), 7.97 and 8.12 (6 H, doublets, J = 1 cps, vinyl methyls), and 8.83 (3 H, s, tertiary CH_3). Alkaline hydrolysis of elephantin (IVa) gave elephantol (IIIc, $C_{15}H_{16}O_6$, mp 282–284°, $[\alpha]^{27}D$ +274°, $\lambda_{\max}^{\text{MeOH}}$ 209 mμ (ε 18,300), $\lambda_{\max}^{\text{KBr}}$ 2.94, 5.68, 5.73, and 6.06 μ) and dimethylacrylic acid.



$-O-\overset{\overset{O}{\|}}{C}-\overset{|}{C}=\overset{\overset{H}{|}}{C}-$

I



II

Further chromatography yielded a dilactone, elephantopin[5] (IVb), $C_{19}H_{20}O_7$, mp 262–264°, $[\alpha]^{25}D$

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[1] Tumor Inhibitors. XVI. Part XV: S. M. Kupchan, S. Kubota, E. Fujita, S. Kobayashi, J. H. Block, and S. A. Telang, *J. Am. Chem. Soc.*, in press.

[2] Supported by grants from the National Cancer Institute (CA-04500), the American Cancer Society (T-275), the National Science Foundation (G-B2878), and a contract with the C.C.N.S.C. (PH 43-64-551).

[3] Specimens were gathered in Florida, Sept. 1963. The authors acknowledge with thanks receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with the U. S. Department of Agriculture, by the C.C.N.S.C.

[4] Cytotoxicity and *in vivo* inhibitory activity were assayed under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, by the procedures described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

[5] Elephantin and elephantopin showed significant inhibitory activity against Walker carcinosarcoma 256 in rats at 50–100 mg/kg and cytotoxicity (ED_{50}) against KB (human carcinoma of the nasopharynx) cell culture at 0.28–2.0 μg/ml.[4]

[6] Determined in hexadeuteriodimethyl sulfoxide.

[7] H. Immer, J. Polonsky, R. Toubiana, and H. D. An, *Tetrahedron*, 21, 2117 (1965).

[8] W. Herz, H. Watanabe, M. Miyazuki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).