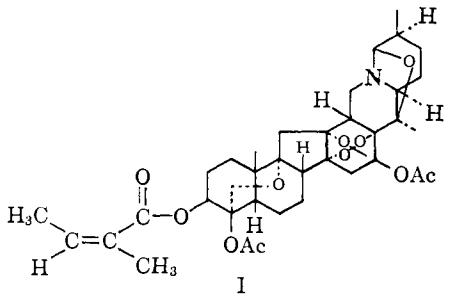
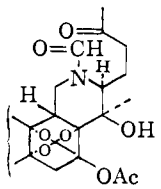
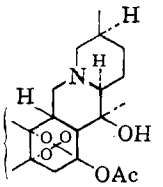


I



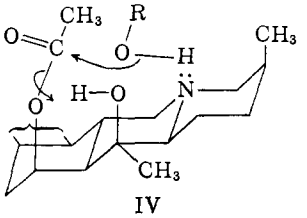
II



III

From the data in the table, it is evident that the conversion of the 16-β-axial acetate ester I into the 1,3-diazial 20-hydroxy-16-acetate II resulted in a 40-fold increase in the rate of solvolysis. Participation of the alkaloid nitrogen in the facilitation of the solvolysis of III is supported by the 25-fold increase in the rate of solvolysis relative to amide II.[12]

Intramolecular base-catalysis of the solvolysis of cevadine D-orthoacetate diacetate (III) (possibly to be regarded as in IV) was confirmed by the experimentally determined buffer ratio-rate profile (Fig. 1). In the central horizontal portion of the curve,



IV

the ring nitrogen is essentially non-protonated and serves as an intramolecular base for the normally general base-catalyzed solvolysis of 1,3-diaxial hydroxyacetates.[9] As the buffer is made more acidic, the rate drops off, decreasing approximately in proportion to the protonation of the ring nitrogen. With higher base concentrations, *intermolecular* general base catalysis plays an increasingly competitive role, adding its effect to that of the *intramolecular* general base. The effect of the external general base in the "high base" region is better indicated by the standard experiments for studying general base catalysis, shown in Fig. 2. Varying the buffer concentration produces no effect if the buffer ratio chosen is in the "intramolecular general base-catalyzed" region (*i.e.*, the flat portion of Fig. 1, TEA/TEAA = 0.5), whereas in the region of external competition (TEA/TEAA = 5.0), a definite intermolecular general base-effect is observed.[13]

Considerable evidence has been accumulated during the past few years to indicate that esters are catalytically hydrolyzed by esteratic enzymes through a double displacement reaction involving an acylated

(11) Control experiments with cevadine D-orthoacetate 4-monoacetate indicated that the 4-acetate group is stable under the reaction conditions, and that the rate of production of methyl acetate from III therefore corresponds to the pseudo-first-order rate constant for the solvolysis of the 16-acetate group.

(12) The very weak basicities of I (*cf.* reference 3b) and of II preclude intramolecular base-catalysis as an important factor in the solvolysis of the latter compounds.

(13) The extrapolated zero buffer values for these two buffer ratios indicate, as expected, that another base (perhaps methoxide from the solvent) is also playing a role.

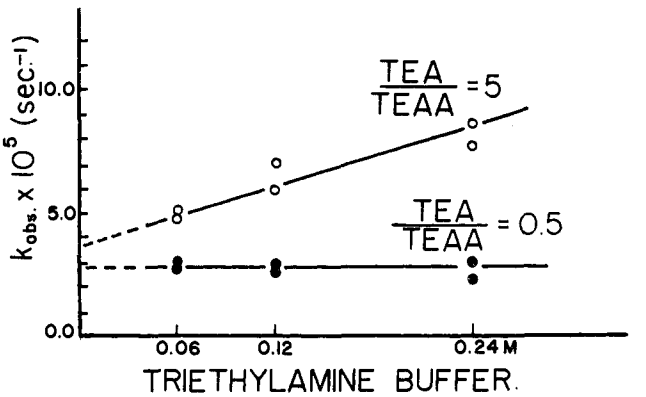


Fig. 2.—Triethylamine catalysis of the methanolysis of cevadine D-orthoacetate diacetate (III) at 25°, ionic strength 0.09, and two buffer ratios, triethylamine/triethylammonium acetate 1:2, ●, and 5:1, O.

enzyme intermediate. The formation of acyl-enzyme takes place after formation of an enzyme-substrate complex, and undoubtedly involves intracomplex participation of specific catalytic groups.[14,15] The deacylation step apparently utilizes the same enzymatic components and one widely accepted mechanism of hydrolytic enzyme action involves intramolecular general base–general acid-catalysis.[16,17] In view of the foregoing, much effort has been expended recently in a search for hydrolytic reactions which proceed *via* first order processes with assistance of an intramolecular nature. One instance of an intramolecular bifunctional general acid-nucleophilic catalysis of ester hydrolysis has been noted.[18] The solvolysis of cevadine orthoacetate diacetate appears to be the first recognized nonenzymatic example of intramolecular bifunctional general base–general acid-catalysis of ester solvolysis and may have considerable significance as an appropriate model for esteratic enzyme action.[19]

We take pleasure in thanking Professors M. L. Bender and T. Higuchi for stimulating discussions.

(14) H. Gutfreund and J. M. Sturtevant, *Biochem. J.*, **63**, 656 (1956).

(15) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(16) M. L. Bender, G. R. Schonbaum, G. A. Hamilton and B. Zerner, *J. Am. Chem. Soc.*, **83**, 1255 (1961).

(17) R. M. Krupka and K. J. Laidler, *ibid.*, **83**, 1458 (1961). *Cf.* especially Fig. 3 with IV of this paper.

(18) H. Morawetz and I. Oreskes, *ibid.*, **80**, 2591 (1958).

(19) This investigation was supported by grants from the National Institutes of Health (H-2275) and the Wisconsin Alumni Research Foundation.

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PRIMARY PRODUCTS OF DECALIN AUTOXIDATION[1]

Sir:

Although the autoxidation of decalin is a well known reaction,[2] detailed studies of the primary autoxidation products have not been reported. We have

(1) Autoxidation of Decalin. I.

(2) (a) A. Castiglioni, *Gazz. chim. ital.*, **64**, 465 (1934); (*C.A.*, **29**, 30 (1935)); (b) A. C. Cope and G. Holzman, *J. Am. Chem. Soc.*, **72**, 3062 (1950); (c) R. Criegee, *Ber.*, **77B**, 22 (1944); (d) M. S. Eventova and I. A. Yavich, *Vestnik Moskov. Univ., Ser. Mat., Mekhan., Astron., Fiz. i. Khim.*, **14**, No. 2, 149 (1959); (*C.A.*, **54**, 9797*i* (1960)); (e) H. L. Goering and A. C. Olsen, *J. Am. Chem. Soc.*, **75**, 5853 (1953); (f) H. E. Holmquist, H. S. Rothrock, C. W. Theobald and B. E. Englund, *ibid.*, **78**, 5339 (1956); (g) K. I. Ivanov and U. K. Savinova, *Doklady Akad. Nauk S.S.S.R.*, **48**, 32 (1945); (*C.A.*, **40**, 4706^7 (1946)); (h) A. I. Kamneva and A. I. Efimenkova, *Trudy Moskov. Khim.-Teknol. Inst. im. D. I. Mendeleeva*, 1957, No. 25, 38 (1957); (i) H. Kleinfeller, *Angew. Chem.*, **62**, 342 (1950); (j) C. Kroger and K. Struber, *Naturwissenschaften*, **32**, 229 (1944); (k) C. Kroger, K. Struber and C. Umland, *Erdöl u. Kohle*, **1**, 241 (1948); (C.A., **44**, 1683*f* (1950)).

TABLE I
GAS CHROMATOGRAPHY DATA FOR VARIOUS DECALOL MIXTURES

Peak no.	Ret. time min.	LAH red. decalin oxidates: 50% *cis* 50% *trans* area-%	LAH red. decalin oxidates: 100% *cis* area-%	LAH red. decalin oxidates: 99% *trans*[a] area-%	Cat. hydrog. α-naphthol area-%	Decahydro[b] β-naphthol area-%	Probable peak[c,d] composition
1	17.2	49.0	44.8	31.0	...	...	*trans*-9-Decalol
2	22.2	18.7	24.2	10.9	...	...	*cis*-9-Decalol
3	25.6	0.9	...	6.0	7.7	...	*trans-cis*-1
4	27.7	8.5	...	30.2	3.0	20.9	*trans-trans*-1 and -2
5	30.9	6.9	...	21.9	...	58.7	*trans-cis*-2
6	34.0	4.1	7.8		4.4	...	*cis-trans*-1
7	37.8	11.5	18.9		84.9	20.3	*cis-cis*-1 and -2
8	45.4	0.4	4.3				*cis-trans*-2

[a] This oxidation was run at 135°. The other two were run at 140°. [b] L. Light and Company's "Decahydro-β-naphthol (mainly *trans*)." [c] Peaks 1, 2, 5 and 7 were checked with authentic samples and peak 4 was shown to correspond to authentic *trans-trans*-1 decalol and a second component by infrared analysis. [d] The conformational designations are those proposed by W. G. Dauben (ref. 9).

determined the points of attack in decalin autoxidation by reducing oxidates high in hydroperoxide with lithium aluminum hydride[3] (LAH) and analyzing the reduced oxidates by gas chromatography.

Since LAH is expected to reduce stereospecifically[4] the hydroperoxides present to the corresponding decalols, the decalol composition of the reduced oxidates reflects the hydroperoxide composition of the oxidates. For verification we have reduced a sample of *trans*-9-decalylhydroperoxide with LAH and have obtained almost entirely *trans*-9-decalol (96.5%). This procedure avoided the difficulties of isolating and analyzing the relatively unstable hydroperoxides directly. Reduced oxidates were concentrated and analyzed in a Perkin–Elmer Model 154-D Vapor Fractometer (Rx column, Ucon LB-550X on diatomaceous earth, 160°, helium at 30 p.s.i., flow rate 124 ml./min.). Peaks were identified by considering the combined data from several samples, by infrared analysis of the trapped peaks, and by comparison with some authentic samples.[5] Table I summarizes the gas chromatographic data and shows the composition deduced for each peak. The composite nature of peaks 4 and 7 was verified by resolution of peak 4 into two peaks and partial resolution of peak 7 into a peak with a shoulder (300 ft. Perkin Elmer High Capacity Golay column coated with polypropylene glycol).

The initial hydroperoxide composition is accurately represented by the observed decalol composition of reduced oxidates only if no hydroperoxides decomposed. Since these oxidations were run at 140°, decomposition did occur, the least occurring with *cis*-decalin which oxidized most rapidly.[6] Thus, *cis*-decalin autoxidized for 55 minutes gave 9.1 wt.-% hydroperoxide which corresponded to 80% of the oxygen absorbed whereas *trans*-decalin autoxidized for 160 minutes gave 5.1 wt.-% hydroperoxide which accounted for only 60% of the oxygen absorbed. No catalysts were used in these oxidations.

Since tertiary hydroperoxides decompose to give mainly the corresponding alcohols [2f,2h,7] and secondary hydroperoxides decompose mainly to the corresponding alcohols and ketones,[7] the position of attack by oxygen in the decalin isomers is identifiable and corresponds very closely to the decalol composition of the reduced oxidates, especially when the extent of hydroperoxide decomposition is small. Greater uncertainty, however, exists in the correlation of hydroperoxide stereochemistry with the stereochemistry of the decalols in reduced oxidates.

The data of Table I show that all ten possible decalols were present in the reduced oxidates from the mixed decalins. This explains why high yields of *trans*-9-decalylhydroperoxide are not obtained from decalin oxidates.[2b,2c,2e] Oxidative attack in both decalin isomers occurs at all positions with the major portion occurring at the tertiary position as expected. Furthermore, the greater reactivity of *cis*-decalin correlates with a more selective attack at the tertiary position.

The presence of *cis*-9-decalol in all reduced oxidates suggests that *cis*-9-decalylhydroperoxide is a primary product present in decalin oxidates. We believe this to be the case even though we have found that *trans*-9-decalylhydroperoxide decomposes at 160° in a polypropylene glycol column when vapor phase chromatography is attempted, giving 54 area-% *trans*-9-decalol, 31 area-% *n*-butylcyclohexanone, and, surprisingly, 15 area-% *cis*-9-decalol. Using these data an estimate of maximum *cis*-9-decalol arising from decomposition can be made if it is assumed that the non-hydroperoxidic oxygen absorbed corresponded to *trans*-9-decalylhydroperoxide that decomposed. This indicates that only 3 wt.-% (0.20 × 0.15 × 100) of the *cis*-9-decalol could be formed by decomposition whereas 23.0 wt.-% of *cis*-9-decalol was observed in a *cis*-decalin oxidation run in which the oxygen uptake was measured. Unless non-identical 9-decalyl radical intermediates are considered,[8] it follows that *cis*-9-decalylhydroperoxide was a primary autoxidation product present in both *cis*- and *trans*-decalin oxidates.

Contrary to previous reports[2c,2i] *trans*-9-decalylhydroperoxide does form when *trans*-decalin is autoxidized. This is in accord with the work of Ivanov and Savinova,[2g] who obtained *trans*-9-decalylhydroperoxide when *trans*-decalin was photoöxidized at 75°. The *trans*-9-decalylhydroperoxide constitutes a smaller portion of the total hydroperoxide content of *trans*-decalin oxidates and is difficult to isolate by crystallization methods.

(3) J. Hoffman and C. E. Boord, *J. Am. Chem. Soc.*, **78**, 4973 (1956). These authors used a similar approach to determine the points of oxidative attack in ethylcyclohexane.

(4) (a) A. G. Davies, "Organic Peroxides," Butterworth, London, 1961, pp. 7, 140; (b) A. G. Davies, *J. Chem. Soc.*, 3474 (1958); (c) G. A. Russell, *J. Am. Chem. Soc.*, **75**, 5011 (1953); (d) H. R. Williams and H. S. Mosher, *ibid.*, **76**, 3495 (1954).

(5) We wish to thank Professor W. G. Dauben for providing authentic samples of *cis-cis*-1-, *cis-cis*-2-, *trans-trans*-1- and *trans-cis*-2-decalol and Professor N. C. Yang for an authentic sample of *cis*-9-decalol.

(6) G. A. Russell and D. G. Hendry, private communication: Russell and Hendry have measured the autoxidation rate of *cis*- and *trans*-decalin (containing 4.5% *cis*-isomer) in the presence of initiator and found that *cis*-decalin oxidized four times as fast as the *trans*-isomer. They calculated a relative oxidation rate, $K_p/(K_t)^{1/2}$, of 0.52 for *cis*-decalin and 0.16 for *trans*-decalin (based on a value of 1.00 for cumene). For comparison with numerous other hydrocarbons see G. A. Russell, *J. Am. Chem. Soc.*, **78**, 1047 (1956).

(7) E. G. E. Hawkins, "Organic Peroxides," D. Van Nostrand Co., Princeton, N. J., 1961, pp. 13, 51–55.

(8) No inferences can be drawn from the different tertiary alcohol ratios in *cis*- and *trans*-decalin oxidates because of differences in the extent of decomposition.

(9) W. G. Dauben, R. C. Tweit and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954).

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INTERPRETATION OF THE PATTERSON FUNCTION OF CRYSTALS CONTAINING A KNOWN MOLECULAR FRAGMENT. THE STRUCTURE OF AN *ALSTONIA* ALKALOID[1]

Sir:

The interpretation of the Patterson function can be greatly facilitated if the molecules composing the crystal contain a rigid group of atoms with a known internal geometry. We wish to outline a computer procedure by which the known presence of such a group can be exploited to yield a refinable approximation to the crystal structure.

The unit cell coördinates (x_0,y_0,z_0), $(x_1,y_1,z_1),\cdots,(x_{n-1},y_{n-1},z_{n-1})$ of the n atoms in the rigid group are expressible in terms of six parameters: the coördinates (x_0,y_0,z_0) of a point in the group, and the Euler angles ϕ,θ,ψ, defining the orientation of the group with respect to a Cartesian coördinate system, fixed in relation to the crystal axes. A practical computer procedure for determining the probable values of these parameters is a two-stage search of the Patterson function. The first stage computes a modified minimum function[2]

$$M_p(\phi,\theta,\psi) = \text{Min}\{P_1,P_2,\cdots,P_p\}$$

with $p = n(n-1)/2$, where the P's are the values of the Patterson function at the vertices of the p vectors between the n atoms of the group. The "most probable" values of ϕ, θ and ψ are the coördinates of the highest peak in this three-dimensional function. The second stage executes a similar search of the Patterson function with all vectors between the group in orientation (ϕ,θ,ψ) and its symmetry-related groups in the unit cell. The number, q, of such vectors depends on the number of symmetry-related groups, *i.e.*, on the multiplicity of the positions of the space group. The function $M_q(x_0,y_0,z_0)$ is less than three-dimensional whenever the space-group symmetry allows the origin to be arbitrarily specified in one or more dimensions. The coördinates of the maximum in $M_q(x_0,y_0,z_0)$ are the tentative values of the translational parameters x_0,y_0,z_0. If the peak value of $M_q(x_0,y_0,z_0)$ is less than that of $M_p(\phi\theta\psi)$, an improved fit, by the minimum criterion, may be accomplished by trial and error adjustment of ϕ, θ, and ψ so as to maximize $M_{p+q}(\phi,\theta,\psi,x_0,y_0,z_0) = \text{Min}\{M_p(\phi\theta\psi), M_q(x_0,y_0,z_0)\}$.

Having thus deduced a set of approximate coördinates for the rigid-group atoms the rest of the structure can be explored by means of multiple Patterson superposition techniques.

We have used this approach to determine the structure of Alkaloid C (m.p. 168–169°. $[\alpha]^{25}D$ +200° for $c = 1.0$ in ethanol) from *Alstonia Muelleriana*, first isolated by Gilman,[3] and characterized by him as having the approximate composition $C_{19-20}H_{20}O_3N_2$, and giving an ultraviolet spectrum indicating the presence of an oxindole group. Crystals of this compound are monoclinic, space group $P2_1$, containing two molecules per unit cell of dimensions $a = 9.09$ Å., $b = 13.11$ Å., $c = 7.14$ Å. and $\beta = 95°8'$. The crystal structure was determined using 1437 photographically recorded and integrated reflections.

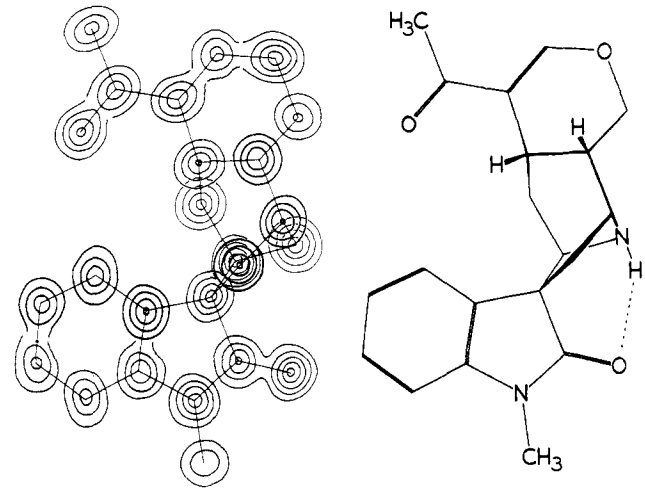

Fig. 1.—Electron density distribution and structure of the molecule.

A rotational and translational search of Patterson space was carried out using the vectors, respectively, within and between the ten atom ($n = 10$) oxindole groups of known internal geometry.[4] The rotational minimum function $M_{45}(\phi\theta\psi)$ showed two dominant peaks, whose relative positions corresponded, very nearly, to a 180 degree rotation about an axis along the carbon–oxygen bond, reflecting the near twofold symmetry of the oxindole group about this axis. The higher one of the two peaks was subsequently found to represent the correct orientation. The two-dimensional function $M_{55}(x_0,z_0)$ for the $q = n(n+1)/2 = 55$ independent vectors from the oxindole group in orientation $(\phi\theta\psi)$ to its screw-axis related group unambiguously gave the location of the two groups relative to the 2_1 screw axis. Finally a 20-fold Patterson superposition $M_{20}(xyz)$ was computed using the atom coördinates of the two oxindole groups. This yielded the positions of all remaining carbon, nitrogen and oxygen atoms; their respective chemical identity was brought out by the subsequent least-squares refinement. Difference Fourier syntheses calculated following several cycles of refinement revealed all hydrogen atoms. Using anisotropic thermal parameters for the nonhydrogen atoms the refinement continued to $R = 0.062$. The empirical formula is $C_{20}H_{22}O_3N_2$. Figure 1 shows the electron density distribution and the relative configuration of the molecule. The absolute configuration chosen for the figure is the one whose C(15) configuration is the same as that deduced for ajmalicine.[5] A fuller account of the results will be presented elsewhere.

The calculations were performed on an IBM 7090 computer. The Patterson function with origin peak removed, sharpened by $\exp(4.5\sin^2\theta/\lambda^2)$, and computed on a 15 × 15 × 60 grid, was stored in the magnetic core storage using a packed word format. A total of about 150 minutes of computer time was used for the three searches of Patterson space, that is, for deducing the complete, refinable trial structure from the Patterson function. In retrospect it is clear that the computing time could have been reduced by at least a factor

(1) Support of this investigation by Grant G-21408 from the National Science Foundation, and by Grant H-4179 from the National Heart Institute, U. S. Public Health Service, is gratefully acknowledged.

(2) M. J. Buerger, "Vector Space," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 242.

(3) R. E. Gilman, Ph.D. Thesis, University of Michigan, 1959.

(4) H. Pandraud, *Acta Cryst.*, **14**, 901 (1961).

(5) E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474 (1959); E. Wenkert, B. Wickberg and C. L. Leicht, *ibid.*, **83**, 5037 (1961); M. Shamma and J. B. Moss, *ibid.*, **83**, 5038 (1961).