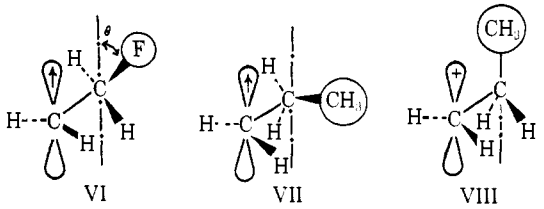
The shift in the g factor of the β-fluoroethyl radical is less than that of the β-chloroethyl radical (Table I). Thus, the magnitude of the p–p homoconjugation in this radical, previously proposed by Lossing[18] and by Iwasaki[19] on the basis of single-crystal studies, is smaller than the interaction in the β-chloroethyl radical. Interestingly, the conformation VI ($\theta = 50°$) adopted by the β-fluoroethyl radical is also intermediate between that of the n-propyl radical, VII, and the β-chloroethyl radical (see ref 1). Recent calculations[20] show that the stable conformation of the n-propyl cation VIII (in contrast to the n-propyl radical) is one in which



VI VII VIII

the methyl group eclipses the p orbital. The rotational barriers are also substantially higher (2.5 *vs.* 0.4 kcal/mol),[2b] which can be ascribed to stabilization of the cation by hyperconjugative effects. Since equilibrium conformations in an alkyl chain result from a delicate balance between steric repulsions and electron delocalization, the trend toward greater eclipsing of the halogen in proceeding from fluorine to chlorine is attributed to an increasing interaction between the odd electron orbital and the halogen,[16] and is consistent with the higher rotational barrier in the β-chloroethyl radical.

(18) R. J. Lossing, *J. Chem. Phys.*, **47**, 3634 (1967).
(19) M. Iwasaki, *Mol Phys.*, 20, 503 (1970); *J. Amer. Chem. Soc.*, **92**, 6348 (1970).
(20) L. Radom, J. A. Pople, V. Buss, and P. v. R. Schleyer, *ibid.*, **92**, 6380, 6987 (1970).

T. Kawamura, D. J. Edge, J. K. Kochi*
Department of Chemistry, Indiana University
Bloomington, Indiana 47401
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The Structure of Staphisine, a Novel Diterpene Alkaloid Dimer

Sir:

Staphisine, $C_{43}H_{60}N_2O_2$, mp 200–208°, $[\alpha]^{25}D$ −159° (benzene), was isolated by Jacobs and Craig in 1941 from the mother liquors accumulated during the isolation of delphinine from the seeds of *Delphinium staphisagria*.[1] Selenium dehydrogenation furnished a complex mixture from which products identified as pimanthrene and 1,3-dimethyl-7-isopropylphenanthrene were isolated.[2,3] Analytical and uv determinations showed the presence of an NCH_3 group and a conjugated double bond system in the molecule. Staphisine was reported to form several crystalline salts, including a mono- and a dimethiodide.[1] On the basis of these data, Craig and Jacobs postulated that staphisine is a diterpene alkaloid dimer with the molecular formula $C_{42}H_{60}N_2O$.[3]

(1) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **141**, 67 (1941).
(2) L. C. Craig and W. A. Jacobs, *ibid.*, **152**, 645 (1944).
(3) C. F. Huebner and W. A. Jacobs, *ibid.*, **169**, 211 (1947).

Although staphisine forms various salts, chemical degradation of the substance usually results in complex changes which give rise to numerous products. The alkaloid is also sensitive to heat and light. Staphisine does not react with hydroxylamine or acetic anhydride. Hydrogenation studies have shown absorption of approximately 2 mol of hydrogen/mol of staphisine, but the product is a mixture of isomers.[1] The mass spectrum of one of these isomers shows a molecular ion at m/e 640, indicating saturation of two double bonds. Microanalysis of staphisine shows 1.61% OCH_3, which, while low, is positive for the presence of a methoxyl group. The N-methyl analysis of 5.14% corresponds to between one and two N-methyl groups. The active hydrogen determination is negative.

The molecular ion at m/e 636.4648 in the mass spectrum of staphisine is in agreement with the molecular formula $C_{43}H_{60}N_2O_2$. The infrared spectrum of staphisine shows no absorption in the regions 4000–3100 and 2500–1750 cm^{-1}, and only very weak absorption at 1710 and 1630 in the region 1750–1500 cm^{-1}. This information, in view of the chemical data, suggests that the oxygen atoms are located in ether linkages [$\nu_{(CHCl_3)}$ 1101 (s), 1063 (s) cm^{-1} (COC)]. The ultraviolet spectrum shows absorption at λ_{max} (95% EtOH) 268 nm (ϵ 17,300), in agreement with a transoid heteroannular conjugated diene system adjacent to a cyclopropyl ring, as subsequently determined by the X-ray analysis (see below).

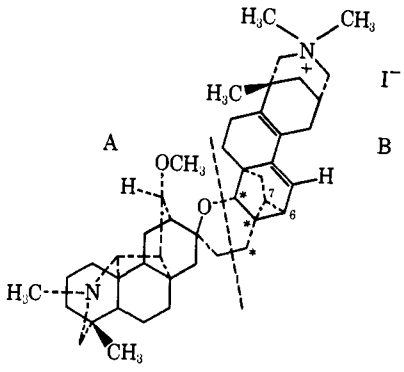
The nmr spectrum of staphisine is subject to a marked solvent dependence: (benzene-d_6) δ 0.18 (1 H, s, cyclopropyl), 0.72 (1 H, m, cyclopropyl), 0.85 (3 H, s, angular methyl), 0.95 (3 H, s, angular methyl), 2.03 (6 H, s, N-methyls), 2.22 (3 H, s, O-methyl), 3.18 (2 H, m, hydrogens adjacent to oxygen), 6.18 (1 H, d, vinyl proton) ppm. The nmr spectrum of a 2:1 molar mixture of $Eu(thd)_3$ to staphisine in CS_2 shows the 6 H singlet originally at δ 2.00 ppm shifted downfield and separated into two 3 H singlets at δ 2.99 and 3.28 ppm. The 3 H singlet at δ 2.20 ppm is not shifted and is assigned as the absorption of the methoxyl group.

Because of the small amount of staphisine available and the inconclusive nature of the chemical and spectral data we undertook a single-crystal X-ray structure determination of the monomethiodide of staphisine. This derivative [mp 285–290° dec] was prepared by treatment of an ethereal solution of staphisine with methyl iodide. Staphisine methiodide crystallized from 95% ethanol as thin plates in space group $P2_12_12_1$ with $a = 47.95$, $b = 10.54$, and $c = 8.60$ Å, $\alpha = \beta = \gamma = 90°$, $U = 4346$ Å^3. The density calculated for $C_{43}H_{60}N_2O_2 \cdot CH_3I$ and $Z = 4$ is 1.19 g/cm^3, a value significantly lower than the observed density of 1.35 g/cm^3 (by flotation in pentane–carbon tetrachloride). Assuming one molecule of ethanol of crystallization per formula gives a calculated density of 1.26 g/cm^3. The elemental analysis of the salt is in agreement with one molecule of ethanol of crystallization per formula. *Anal.* Calcd for $C_{43}H_{60}N_2O_2 \cdot CH_3I \cdot C_2H_6O$: C, 66.97; H, 8.43; I, 15.38. Found: C, 67.16; H, 8.67; I, 17.07

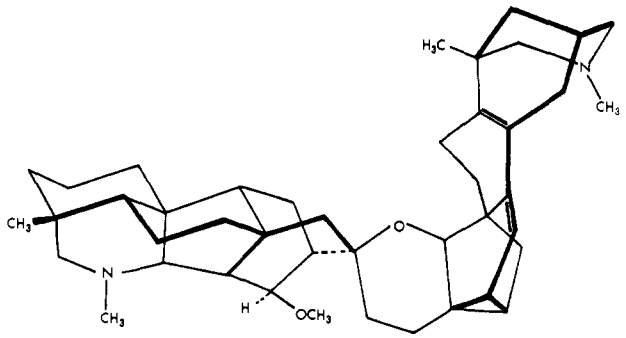
Initially, data were collected by the Weissenberg equiinclination technique using multiple films and Cu Kα radiation. Data were estimated visually using a standard intensity strip prepared from the same crystal. The 1838 unique nonzero reflections were corrected for

Lorentz and polarization effects, but not for absorption or spot shape. A partial structure was derived through the use of the heavy-atom method from this data set, but least-squares refinement of the data gave no R lower than 0.20, and many details of the structure were not clear.

The data were recollected on an Enraf-Nonius CAD-3 automated diffractometer using Cu Kα radiation. Lorentz, polarization, and absorption corrections[4] were made on the 1558 unique reflections measured and considered to be above background [$>1.5\sigma$ (counting statistics)]. These data were then used to complete and refine the coordinates obtained from the film data analysis. During this stage of the analysis, a molecule of ethanol was located and introduced in the refinement. The R value is 0.113 at this stage of refinement. The difference map generated using these refined coordinates shows no significant peaks. A perspective drawing[5] of one molecular unit (less solvent and iodide ion) is shown in Figure 1 and a planar representation for staphisine monomethiodide is shown in **1**. A conformational drawing of staphisine itself appears as **2**.



1



2

The average estimated standard deviation of bond lengths is 0.04 Å, and of bond angles is 2°. The C–C single bond lengths average 1.54 Å, C–O bond lengths average 1.46 Å, C–N^+ bond lengths average 1.53 Å, and the C–N bond lengths average 1.48 Å. The interbond and dihedral angles are consistent with the indicated ring system.

(4) C. K. Johnson, ORABS 2, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965 (revised), modified for the Enraf-Nonius CAD-3 geometry by L. H. Wright.

(5) C. K. Johnson, ORTEP II, ORNL-3794 (2nd revision), Oak Ridge National Laboratory, Oak Ridge, Tenn.

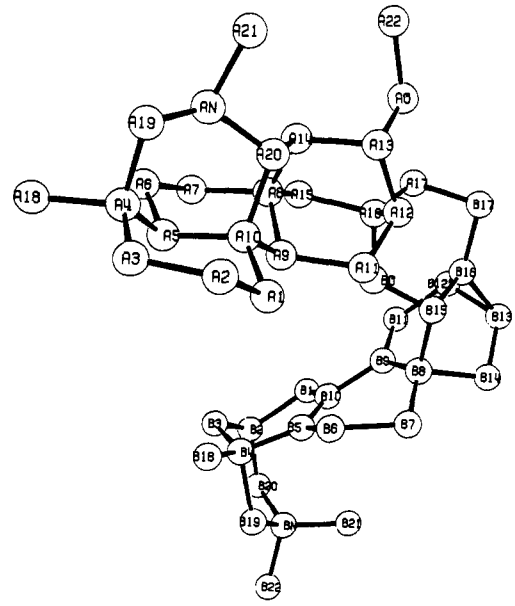


Figure 1. A perspective view of one molecular unit of staphisine methiodide (less solvent and iodide ion).

1 is thus in agreement with the chemical and physical data obtained for staphisine. The isolated dehydrogenation products are consistent with this structure, pimanthrene resulting from the A part of the dimer, and 1,3-dimethyl-7-isopropylphenanthrene from the B part (the asterisks identify carbon atoms which may be the source of the isopropyl group). The anomalous chemical shift for the methoxyl in the nmr spectrum and low microanalyses for the methoxyl groups remain unexplained.

Staphisine is thus established as a dimer of two diterpene alkaloid molecules of the atisine type[6] (labeled A and B in **1**). A rearrangement in the B unit has apparently given rise to the conjugated diene system. A rearrangement product of the diterpene alkaloid hetisine containing a cyclopropyl group similarly situated has been previously reported from this laboratory.[7,8] It is interesting to note that the location of the cyclopropyl group in the B unit of staphisine corresponds to that in the naturally occuring trachylobanic acid (*ent*-13,16-cycloatisan-18-oic acid).

Acknowledgment. This work was supported in part by a grant from the National Institutes of Health, U. S. Public Health Service.

(6) S. W. Pelletier and L. H. Keith in "Chemistry of the Alkaloids," S. W. Pelletier, Ed., Van Nostrand-Reinhold, 1970, p 503; *Alkaloids*, **12**, 15 (1970).

(7) H. E. Wright, M. G. Newton, and S. W. Pelletier, *Chem. Commun.*, 507 (1969).

(8) A comparison of the observed and calculated structure factors for staphisine methiodide will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche.

S. W. Pelletier,* A. H. Kapadi, L. H Wright
S. W. Page, M. Gary Newton
Department of Chemistry, University of Georgia
Athens, Georgia 30601
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