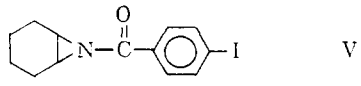
and by microbiological assay.[8] It was now clear that IV must have been formed by a pinacolic deamination of a 1,2-aminoalcohol function in II-A; indeed reaction of II-A with phosgene[9] yielded a new compound with a carbonyl, λ_{max}^{KBr} 5.68 μ, characteristic of an oxazolidinone.[4]

The formation by acid hydrolysis of a 1,2-amino alcohol in II-A from a group in the precursor I-A containing only $\rangle$NH suggested that I-A must contain a fused ring aziridine structure. The presence of this unusual group was supported by the following spectral properties: (1) in antibiotics I-A, -B, -C and -D: weak bands in the 3.3 μ region assignable to aziridine C-H stretching,[10] (2) in N-acetyl I-A (prepared *via* 1-acetylimidazole),[11] a carbonyl band at 5.84 μ,[12] (3) in N-(4-iodobenzoyl) 1-A (also prepared *via* 1-acylimidazole)[11] a new λ_{max} at 262 mμ (in addition to the λ_{max} found in I-A) not in the usual location for *p*-iodobenzamide (approx. 252 mμ) but in good agreement with the λ_{max} of 1-(4′-iodobenzoyl)-1-azabicyclo[4.1.0]heptane (V), m.p. 124–5°, prepared similarly.[11]



V

Finally, the acid-labile methoxyl group (6.8 τ, $CDCl_3$) could be assigned to either position C-9 or C-9a in structure I-A. A detailed analysis of the n.m.r. spectrum[13] of I-A clearly indicated 9a; a typical 12 peak ABX pattern was present as expected for the coupling of a single proton on the asymmetric C-9 with the two dissimilar protons at C-10. The spectrum of I-A did not have the doublet and non-equivalence quartet that would be expected if there were a methoxyl at 9 and a proton at 9a. In fact all details[14] of the n.m.r. spectra of I-A, -B, -C and -D are in complete accord with the proposed structures.

After the completion of this work a complete 3-dimensional X-ray structure analysis, carried out by Dr. A. Tulinsky on the N-4′-bromobenzenesulfonyl derivative, m.p. 130–145°, of I-A (prepared[15] by us specifically for this purpose) confirmed our proposed structure in every respect and in addition revealed the relative stereochemistry at the four asymmetric centers, 1, 2, 9, 9a. His work is reported in an accompanying Communication.[16]

(8) H. P. Sarett and V. H. Cheldelin, *J. Bacteriology*, **49**, 31 (1945).

(9) G. M. Tener and H. G. Khorana, *J. Am. Chem. Soc.*, **79**, 437 (1957). The yield of this cyclic derivative was nearly 50% indicating at least this proportion of *cis*-isomer in the mixture; see (13) in previous communication.

(10) H. T. Hoffman, Jr., *et al.*, *ibid.*, **73**, 3028 (1951); there were no aromatic or ethylenic protons in the n.m.r. spectra of the antibiotics.

(11) G. W. Anderson and R. Paul, *ibid.*, **80**, 4423 (1958).

(12) H. C. Brown and A. Tsukamoto, *ibid.*, **83**, 2016 (1961).

(13) We are indebted to Dr. J. H. Shoolery of Varian Associates for assistance in interpreting this part of the spectrum.

(14) A particularly interesting feature of these spectra is the apparent low order (0 and 0.2 c.p.s.), of coupling between the proton on C-2 and those on C-3.

(15) By the reaction of I-A with brosyl chloride in $CHCl_3$ in the presence of ethyldiisopropylamine.

(16) A. Tulinsky, *J. Am. Chem. Soc.*, **84**, 3188 (1962).

JOHN S. WEBB
DONNA B. COSULICH
JOHN H. MOWAT
JAMES B. PATRICK
ROBERT W. BROSCHARD
WALTER E. MEYER
RICHARD P. WILLIAMS
CARL F. WOLF
WILLIAM FULMOR
CHARLES PIDACKS

ORGANIC CHEMISTRY SECTION
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

JOHN E. LANCASTER

RESEARCH SERVICE DEPARTMENT
CENTRAL RESEARCH DIVISION
AMERICAN CYANAMID COMPANY
STAMFORD, CONNECTICUT

RECEIVED JUNE 27, 1962

THE STRUCTURE OF MITOMYCIN A[1]

Sir:

The preceding communication reports the elucidation of the gross structure of the mitomycins by chemical means. This one represents a preliminary account of the X-ray structure determination of the N-brosyl derivative of mitomycin A, $C_{22}H_{22}N_3O_8SBr$. When the determination was initiated (Oct. 13, 1961), the author knew only that the molecule was some complex fused ring system with the brosyl group linked to nitrogen.[2]

Slow evaporation from a solution in methylene chloride and benzene (1:4) yielded monoclinic crystals. The space group eventually was fixed to be C2, a = 19.70 Å., b = 8.24 Å., c = 16.05 A., β = 95.80°, with 4 molecules/unit cell; empirical formula, $C_{25}H_{25}N_3O_8SBr$. The carbon content (high by three) and density measurements (X-ray molecular weight, 605.6) indicated solvation with half a mole of benzene.[2] Intensity data were collected using the stationary crystal-stationary counter technique employing balanced filters; of the 1,481 reflections accessible to 1 A. resolution, 1,352 (91.3%) were taken to be observable.

The structure was solved by the heavy atom method. To enhance the heavy atom vectors, the Patterson coefficients were sharpened with $(z_{Br}/f_{Br})^2$, where z_{Br} and f_{Br} are, respectively, the atomic number and scattering form of bromine. The coördinates of the bromine and sulfur atoms were determined readily and the positions of the two carbons linked to them inferred. Phases based on these four atoms were employed to compute a 3-dimensional electron density (ρ_1). Two days afterward, (Nov. 17, 1961), this density was analyzed to contain 45 peaks greater than 1.7 e.A.$^{-3}$ (included carbons are in this count). Of these peaks, 30 belonged to the molecule, 7 were eliminated because of close approaches to either the brosyl system or the bromine atom; 2 others approached too close to a 2-fold rotation

(1) This research has been supported by the National Institutes of Health, U. S. Public Health Service and Lederle Laboratories Division of the American Cyanamid Company.

(2) The author wishes to thank the personnel of the Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, for supplying samples and information, and especially Dr. J. H. Mowat, who furnished 8 mg. of this derivative and the crystallization method; and Mr. A. Mistretta, who demonstrated benzene of solvation by gas chromatography.

axis (*i.e.*, their symmetry related peaks, necessarily from another molecule, would produce extremely short van der Waals contacts). The remaining 6 peaks turned out to be spurious. At this stage, the recognizable features of the molecule are shown in Fig. 1 as solid lines, asterisks representing

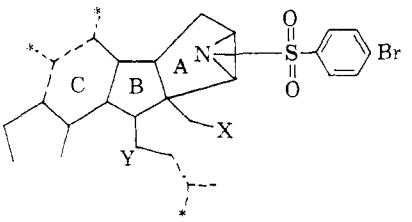


Fig. 1.

other significant peaks; the N-brosylaziridine is fused to a 5-membered ring (A) and ring (A) fused to another 5-membered ring (B). From ring B, the density was ambiguous; either ring B was fused to a 6-membered ring bearing short side chains (shown dotted) or a longer side chain emanated from B. Also, there was a 2-atom chain at a bridgehead position between rings A and B (X) and a seemingly longer chain at Y. Consultation with the Lederle group then revealed agreement between their structure and the one described above. Using their information and the location of three additional weaker peaks (1.3 to 1.6 e. Å.$^{-3}$) the remainder of the structure shown in Fig. 1 was recognized; the density about ring C indicated a quinone system bearing methyl and methoxyl groups. Side chains (X and Y, Fig. 1) were another methoxyl group (X) and a carbamoyloxymethyl group (partially dotted); the fused 5-membered rings appeared as a pyrrolizine system.

Two structure factor computations then were carried out, the first (ρ_2) based on the complete structure including atoms of correct chemical identity; the second (ρ_3) included bromine and sulfur and 25 carbon atoms (the crystallographically unambiguous structure) shown in Fig. 2.

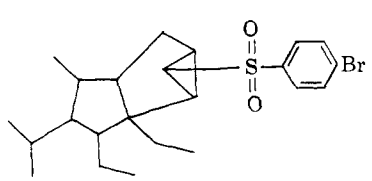


Fig. 2.

The R factors for these computations were 0.22 and 0.28, respectively. A comparison of these electron densities verified 32 atoms included in ρ_2. Peaks in ρ_2 increased by 2.5 or more except two, which had other reasonable peaks (1.6 e. Å.$^{-3}$) within bonding distance of the bridgehead methoxyl and the carbamate nitrogen. Unfortunately, an incorrect choice was made in both instances.

The peaks included in ρ_3 increased in a similar fashion; those not included remained essentially unchanged or increased in height. Also, in ρ_3, nitrogen and oxygen atoms, included as carbon, appeared 1–3 e.Å.$^{-3}$ greater than included carbon

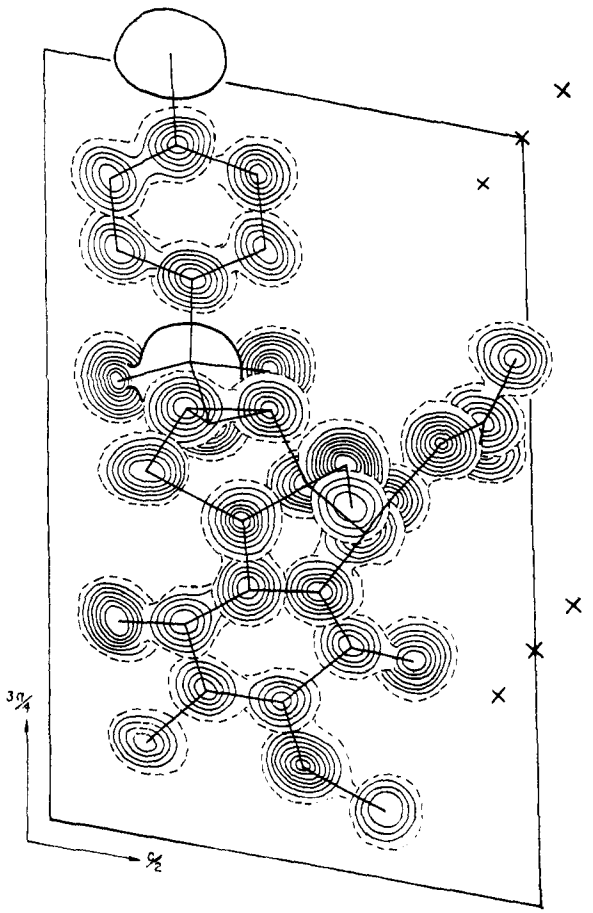


Fig. 3a.—Composite electron density viewed along *b*; crosses indicate benzene orientation.

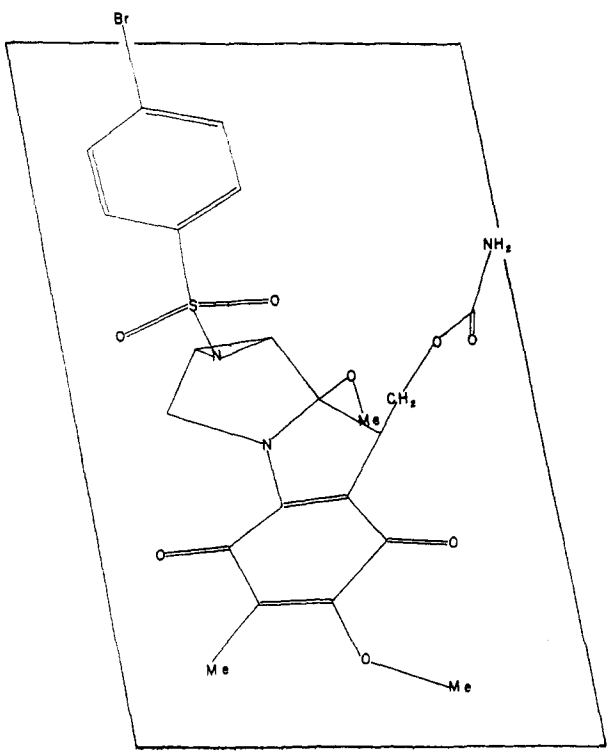


Fig. 3b.—Chemical identity of peaks shown in Fig. 3a.

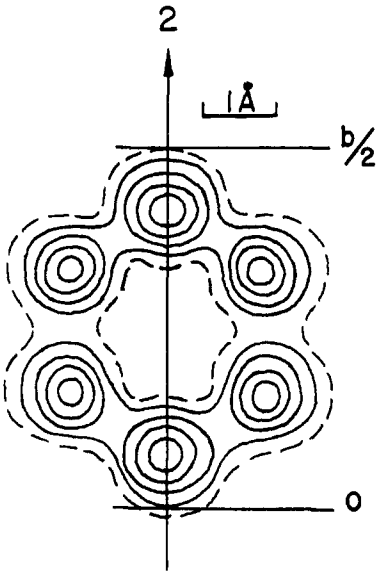


Fig. 4.—Electron density in the plane of the benzene ring.

atoms. All spurious peaks decreased and practically disappeared in both ρ_2 and ρ_3.

The two peaks ignored in ρ_1 as being too close to a 2-fold axis ($\sim$ 1.2 Å.) persisted and increased in height in ρ_2 and ρ_3. It now became apparent that the benzene molecules were on 2-fold axes (multiplicity two in C2) thus accounting for a half of a mole of solvent.

Refinement continued through conventional electron and difference density considerations employing individual isotropic thermal parameters. The sixth and final structure factor computation gave R = 0.146. The density based on these phases is shown in Fig. 3; that of the benzene is shown in Fig. 4.

In addition to confirming the structure deduced by chemical means, this determination revealed the stereochemistry of the molecule; the bridgehead methoxy is *trans* to the carbamoyloxymethyl group and the aziridine. Moreover, the methyl and methoxy functions on the quinone are established with certainty. The pyrrolizine nitrogen in this molecule was known to be non-basic[3]; in the solid, this nitrogen is planar within the accuracy of its determination (± 0.03 Å.). And finally, the nitrogen and oxygen atoms of neighboring carbamate groups are intermolecularly hydrogen bonded along the *b* axis.

A more detailed account of this determination will appear elsewhere.

(3) Lederle Laboratories, private communication.

STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY A. TULINSKY
NEW HAVEN, CONNECTICUT

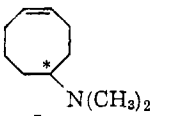
RECEIVED JUNE 28, 1962

OPTICALLY ACTIVE *cis-trans*-1,5-CYCLOÖCTADIENE FROM AN ASYMMETRIC HOFMANN ELIMINATION[1]

Sir:

The labile 1,5-cycloöctadiene obtained from N-methylgranatanine by two successive Hofmann exhaustive methylation reactions[2] must differ from the stable *cis-cis*-1,5-cycloöctadiene by the geometric configuration of one or both of the double bonds.[3,4] The *trans-trans*-configuration was considered most probable for the labile diene because of the smaller amount of steric strain indicated by molecular models.[4]

We have obtained unequivocal evidence that the compound is *cis-trans*-1,5-cycloöctadiene. The product of the first Hofmann exhaustive methylation of N-methylgranatanine proved to be *cis*-4-cycloöcten-1-yl dimethylamine, identical with a sample prepared from *cis*-4-cycloöcten-1-yl brosylate[5] and dimethylamine. This amine (I) has an asymmetric carbon atom, and has been resolved



I

by fractional crystallization of the *d*-10-camphorsulfonic acid salts from diisobutyl ketone. The less soluble form had m.p. 144.0–145.5°, $[\alpha]^{27}D$ −1.88° (*c* 13.0, water), and the more soluble form had m.p. 142.5–143.5°, $[\alpha]^{26}D$ +30.71° (*c* 13.0, water). (*Anal.* Calcd. for $C_{20}H_{35}NO_4S$: C, 62.29; H, 9.15; N, 3.63. Found for the (−) isomer: C, 62.42; H, 9.17; N, 3.83. Found for the (+) isomer: C, 62.43; H, 9.20; N, 3.61.) The salts were converted to the tertiary amines I, $[\alpha]^{25}D$ −59.5° (*c* 7.0, acetone) (obtained from levorotatory salt) and $[\alpha]^{25}D$ +61.5° (*c* 2.4, acetone) (obtained from the dextrorotatory salt). The amines were characterized by conversion to picrates and methiodides. The methiodide obtained from the (−) amine had m.p. 258° (dec.), $[\alpha]^{25}D$ −14.92° (*c* 6.0, water), while that obtained from the (+) amine had m.p. 262° (dec.), $[\alpha]^{25}D$ +14.30 (*c* 2.7, water). (*Anal.* Calcd. for $C_{11}H_{22}NI$: C, 44.75; H, 7.51; N, 4.75. Found for the (−) isomer: C, 43.58; H, 7.19; N, 4.86. Found for the (+) isomer: C, 44.44; H, 7.64; N, 4.80.)

The optically active methiodides were converted separately to the corresponding methohydroxides with suspensions of silver hydroxide in water. The solutions were concentrated, and then distilled under reduced pressure under the usual conditions of the Hofmann elimination. The (−) methiodide yielded (+)-*cis-trans*-1,5-cycloöctadiene, $n^{25}D$ 1.4893, $[\alpha]^{25}D$ +121.3° (*c* 2.0, pentane), while the (+) methiodide formed the enantiomer, $n^{25}D$ 1.4885, $[\alpha]^{25}D$ −120.5° (*c* 2.0, pentane).

This demonstration of optical activity confirmed the fact that the labile diene must be different from the symmetrical *cis-cis*-1,5-cycloöctadiene. The *trans-trans* structure for the labile diene is ruled out by the *cis* geometry of the double bond in amine I. This double bond would not change to *trans* geometry during the second Hofmann elimination since the *cis* double bond is highly favored

(1) Presented at the Carl S. Marvel Honorary Symposium, Tucson, Arizona, December 28, 1961.

(2) R. Willstätter and H. Veraguth, *Ber.*, **38**, 1975 (1905).

(3) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950).

(4) K. Ziegler, H. Sauer, L. Burns, H. Froitzheim-Kühlhorn and J. Schneider, *ibid.*, **589**, 122 (1954).

(5) A. C. Cope and P. E. Peterson, *J. Am. Chem. Soc.*, **81**, 1643 (1959).