tive. To 4.92 g (7.0 ml, 60 mmol) of 1-hexyne dissolved in 50 ml of *n*-hexane were added 25 ml (60 mmol) of 2.40 *M* *n*-butyllithium (0°, 30 min) and 2.70 g (20 mmol) of aluminum chloride (0°, 30 min). *n*-Hexane was removed under reduced pressure (~1 mm). To the residue thus obtained were added 100 ml of 1,2-dichloroethane and 2.13 g (20 mmol) of 2-chloro-2-methylbutane at 0°. After stirring for 1 hr at this temperature, the reaction mixture was poured into ice-cold aqueous hydrochloric acid (3 *N*). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried ($MgSO_4$), and distilled to yield 2.58 g (85%) of 3,3-dimethyl-4-nonyne: bp 82–83° (40 mm) [lit.[8] bp 82° (40 mm)]; $n^{20}D$ 1.4314 [lit.[8] $n^{20}D$ 1.4312]; ^1H NMR (CCl_4, Me_4Si) δ 0.9–0.93 (t, J = 6 Hz, 6 H), 1.1 (s, 6 H), 1.23–1.66 (m, 6 H), and 2.1 (t, 6 Hz, 2 H) ppm.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

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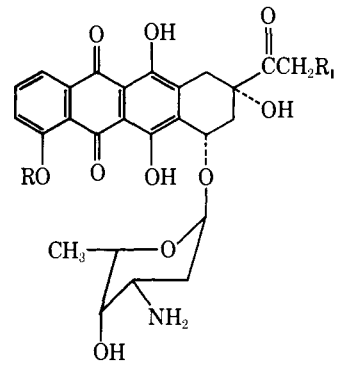
Received June 2, 1975

The Structure of Carminomycin I[1]

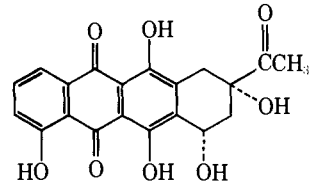
Sir:

The useful antineoplastic properties of certain anthracycline antibiotics are now widely recognized. Both daunomycin[2] (**1a**) and adriamycin[3] (**1b**), produced respectively by *Streptomyces peucetius* (Streptomycetaceae family) and a mutant strain, have displayed pronounced anticancer activity in various experimental tumor systems and in certain types of human cancer.[4] However, the utility of anthracyclines **1a** and **1b** in human treatment is restricted by a dose-limiting cardiotoxicity (congestive heart failure).[4a,5] The need for related substances with superior antineoplastic activity but devoid (or with less) such toxic properties is presently of great concern.

In 1973 the very promising anthracycline, carminomycin I (**1c**), was isolated from *Actinomadura carminata* sp. nov. (Actinomycetaceae family)[6] and assigned a desmethyl daunomycin structure.[7] The stereochemistry in ring D appeared to differ somewhat from that of daunomycin but was



1a, R = CH_3; R_1 = H
b, R = CH_3; R_1 = OH
c, R = R_1 = H



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not definitely established. Subsequently carminomycin was found to be more effective than the related antibiotics **1a** and **1b** in inhibiting DNA synthesis[8] and growth of murine lymphoid leukemia L1210 (some cures).[7] Also anthracycline **1c** was found to suppress the growth (by 95%) of a murine bronchogenic lung carcinoma,[7] to give evidence of less severe cardiotoxicity (rabbit evaluation) and to be better absorbed from the gastrointestinal tract then daunomycin.[9] In view of the promising antineoplastic activity of carminomycin I this anthracycline is now in clinical trial in the Soviet Union, and we have undertaken an x-ray crystal structure determination to confirm the overall structure and to define the stereochemistry of ring D substituents.

Carminomycin I hydrochloride was purified by chromatography on a Merck prepacked silica gel column (elution with 32:9.5:1.6 chloroform:methanol:water) and recrystallization from ethanol–benzene to afford brick red crystals decomposing at 210–212°; ORD in methanol $[\alpha]^{25}_{589}$ +290°, $[\alpha]^{25}_{370}$ +465°, and $[\alpha]^{25}_{305}$ −4180°. The corresponding free base (**1c**) was prepared (5.3 mg → 4.8 mg) by ion exchange chromatography (DEAE Sephadex A-50, treated with 0.5 *N* sodium hydroxide, elution with 10% acetic acid) and isolated as a red powder; ORD in methanol $[\alpha]^{25}_{589}$ +330°, $[\alpha]^{25}_{366}$ +666°, and $[\alpha]^{25}_{302}$ −3830°; CD in methanol $[\theta]$ nm +5370 (345), +3530 (318), and −7370 (286). The specimen of carminomycin I (**1c**) was found to be identical[10] with a specimen of carminomycin I isolated by Wall and colleagues from a different microorganism.[11] In addition the specimens of carminomycin I from both sources were individually hydrolyzed (5 mg of **1c** in 6.1 ml of 0.1 *N* HCl, 60–80° for 25 min, chromatographed on a silica gel column and eluted with 9:1 chloroform–methanol) to yield 1.2 mg of the aglycone (**2**) decomposing at 205–212°; ORD in chloroform $[\alpha]^{25}_{589}$ +330°, $[\alpha]^{25}_{366}$ +1700°, $[\alpha]^{25}_{334}$ +400°, and $[\alpha]^{25}_{316}$ +1030°; mass spectrum *m/e* 384 (M^+), 366 (M − H_2O), 348 (M − $2H_2O$), 341 (M − CH_3CO), 333 (348 − CH_3), 323 (341 − H_2O), 305 (348 − CH_3, and from 333 − CO), 295 (323 − CO), 277 (305 − CO), 249 (277 − CO), and 221 (249 − CO) with metastable ions observed for 348 → 333, 333 → 305, 323 → 295, 305 → 277, and 277 → 249. The specimens of carminomycin aglycone obtained in this manner were found to be identical.[10]

Single crystals of carminomycin I HCl·H_2O of sufficient

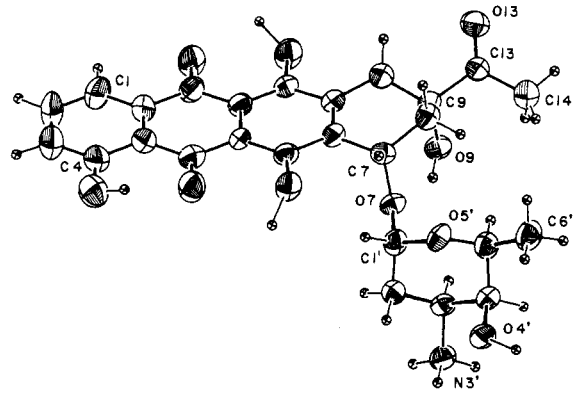

Figure 1. A perspective representation of the structure of carminomycin I. A hydrogen atom on C10 is hidden from view.

size for data collection were obtained from ethanol–toluene. The observed Laué symmetry and extinctions correspond to the monoclinic space group $P2_1$ with a = 20.027 (4) Å, b = 5.487 (1) Å, c = 11.900 (2) Å, β = 93.710 (3)°; Z = 2; ρ_{calcd} = 1.445 g/cm^3 for $C_{26}H_{30}O_{11}NCl$, ρ_{obsd} = 1.42 g/cm^3. Diffraction intensities were measured in the θ–2θ scan mode using Ni-filtered Cu K$\bar{\alpha}$ radiation on a Syntex P$\bar{1}$ diffractometer; of the 2779 reflections examined within the limits of the diffractometer (sin $\theta/\lambda \leq 0.609$), a total of 2631 unique reflections were retained as objectively observed. No corrections were applied for either absorption or extinction.

The structure was readily solved by direct methods using the MULTAN-74 system of programs.[12] Large block least-squares refinement[13] of the structure with anisotropic thermal parameters and fixed hydrogen positions (351 independent variables in four blocks) yielded a standard residual R = 0.0710 for all observed data; a weighted residual $R_w = (\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{1/2}$ of 0.0752 was obtained with $w = 1/\sigma_{F^2}$. All hydrogen positions had been observed in a difference synthesis based on a refined anisotropic model and the C–H atoms were placed at idealized positions. All others were placed as found in the map.

The perspective view shown in Figure 1 displays the essential configurational and conformational features of the molecule. The six chiral centers are C7 (S), C9 (S), C1′ (R), C3′ (S), C4′ (S), and C5′ (S). Since the configuration of the daunosamine unit of carminomycin I has been shown to be the same as that obtained from daunomycin[7] whose absolute configuration is known,[2,3] carminomycin I is herein shown (Figure 1) in the correct enantiomorphic form.

The structure of carminomycin I originally proposed[7] is in complete accord with the results of this crystal structure analysis, and with the stereochemistry at C7 now established is shown to be the desmethyl derivative of daunomycin with identical configurations at all chiral centers.

Investigation of the structural details of carminomycin reveals some interesting bonding patterns which affect the conformation of the molecule; these will be discussed in a detailed presentation of the structure.

Acknowledgments. We are pleased to acknowledge support of this investigation by the National Cancer Institute, National Institutes of Health (performed pursuant to Contract No. N01-CM-12308 with the Division of Cancer Treatment, NCI, Department of Health, Education and Welfare), and by Public Health Research Grant No. CA-16049-02 from the National Cancer Institute, the J. W. Kieckhefer Foundation and the Fannie E. Rippel Foundation. The calculations for the structure analysis were performed with computer time kindly provided by Arizona State University.

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Received July 7, 1975

Electronic Structure and Electric Field Gradients in Oxyhemoglobin and -cytochrome P-450 Model Compounds

Sir:

The large quadrupole splittings observed in the Mössbauer resonance spectra of oxyhemoglobin (oxy Hb)[1] and oxycytochrome P-450[2] are thought to be anomalous for low spin ferrous heme complexes. These results have been used[1,2] to support the proposal[3,4] that these complexes, while formally Fe(II)–O_2, are best described by a Fe(III)–O_2^- configuration in which two unpaired electrons couple