to the free olefinic protons (H_2, H_3, H_7, H_8). The fact that the high-field resonance is not a single peak but apparently two overlapping peaks of somewhat different widths can be explained on the assumption that the molecule has only C_s symmetry so that two (say H_1 and H_6) protons of the bound olefin groups are in a slightly different environment from the other two (H_2 and H_5).[15,16]

(15) No prior example of this form of nonequivalence can be cited since all other known 1,5-diene or tub-bonded C_8H_8 complexes either have molecular symmetry making all four protons on the bonded olefins equivalent (*e.g.*, $C_8H_8Mo(CO)_4$, $[C_8H_8RhCl]_2$), or time-average equivalence would be expected owing to rotation of a π-C_5H_5 ring (*e.g.*, in $C_8H_8Co(\pi\text{-}C_5H_5)$ or $C_8H_8Rh(\pi\text{-}C_5H_5)$).

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(17) National Science Foundation Predoctoral Fellow, 1963–1966.

F. A. Cotton, A. Davison, J. W. Faller[17]

Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

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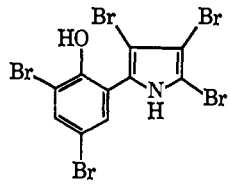
Synthesis of a Bromine-Rich Marine Antibiotic

Sir:

We wish to report the synthesis of an unusual antibiotic (**1**) isolated from a marine bacterium[1] and having



1

the empirical formula $C_{10}H_4NOBr_5$. The antibiotic is unique in that over 70% of its weight consists of covalently bound bromine (*Anal.* Calcd for $C_{10}H_4NOBr_5$ (mol wt, 553.72): C, 21.69; H, 0.73; N, 2.53; Br, 72.16). Found: C, 21.45; H, 0.73; N, 2.73; Br, 71.23. It exhibits an indefinite melting point with decomposition between 130 and 170° and is soluble in common organic solvents but is insoluble in hydrocarbons and water.

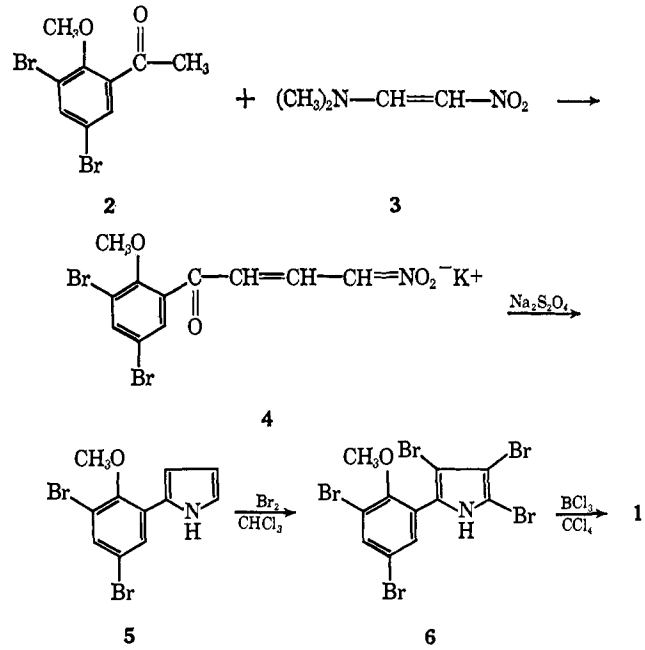
The mass spectrum[2] suggested a molecular weight of 553.5 and the presence of five bromine atoms from the isotope peaks. A preferential and sequential loss of one, two, and three bromine atoms from the molecular ion together with loss of hydrogen cyanide was observed; metastable ion peaks corresponding to these losses were also evident. No fragments corresponding to a simple cleavage of the phenol and pyrrole portions could be seen.

While our studies were in progress, the structure of the antibiotic was established independently by X-ray crystallographic analysis[3] and was kindly communicated to us. The synthesis of this substance was therefore undertaken.

(1) The antibiotic was originally isolated by Dr. P. R. Burkholder and co-workers of the Lamont Geological Observatory of Columbia University, Palisades, N. Y., and was kindly provided to us for structure elucidation studies; see P. R. Burkholder, R. M. Pfister, and F. M. Leitz, *Appl. Microbiol.*, **14**, 649 (1966).

(2) We thank Dr. D. C. DeJongh, Chemistry Department, Wayne State University, for recording the mass spectrum and assisting in its interpretation. The spectrum was obtained with an Atlas CH4 mass spectrometer at an ionizing potential of 70 ev and an ionizing current of 18 ma, using a direct inlet introduction system.

(3) F. M. Lovell, preceding paper.



2 **3** **4**

5 **6**

Condensation of 3,5-dibromo-2-methoxyacetophenone[4,5] (**2**) with 1-nitro-2-dimethylaminoethylene[6] (**3**) in the presence of potassium ethoxide and ethanol afforded the intermediate *aci*-nitro salt **4** which was reduced with sodium dithionite essentially according to Severin and Brück[6] to give crystalline 2-(3,5-dibromo-2-methoxyphenyl)pyrrole (**5**), mp 103.5–105°; doublets centered at τ 2.26 and 2.42 (J = 2 cps, aromatic hydrogens) and multiplets centered at τ 3.02, 3.33, 3.62 (pyrrole ring hydrogens), and 6.23 (OCH_3). Bromination of **5** in chloroform at room temperature afforded crystalline 2-(3,5-dibromo-2-methoxyphenyl)-3,4,5-tribromopyrrole (**6**) in good yield, mp 124–125°; doublets centered at τ 2.33 and 2.00 (J = 2.5 cps, aromatic hydrogens), 6.35 (OCH_3). Demethylation of the precursor **6** in benzene or carbon tetrachloride containing a slight excess of aluminum chloride was remarkably fast, some product being formed even within 2 min at 40°. The reaction however was difficult to control as evidenced by the disappearance of both **5** and the product **1** after 5 min and the appearance of by-products of higher mobility on thin layer chromatograms.[7] A satisfactory procedure was found using excess boron trichloride[8] in carbon tetrachloride at room temperature. On standing overnight in the dark the tan solution deposited colorless needles which were presumably a boron chloride complex, since its infrared spectrum showed the lack of a resolved doublet expected of the OH and NH groups in **1**. The complex was decomposed by washing its ethereal solution with dilute hydrochloric acid. Processing the organic phase in the

(4) C. M. Christian and G. C. Amin, *J. Indian Chem. Soc.* **36**, 111 (1959).

(5) All compounds reported herein gave correct analyses. Melting points are uncorrected.

(6) T. Severin and B. Brück, *Angew. Chem.*, **76**, 993 (1964); *Chem. Ber.*, **98**, 3847 (1965).

(7) Thin layer chromatography was carried out on silica gel HF plates using the solvent system benzene–2,2,4-trimethylpentane (5:1), and the components were detected under ultraviolet light and by iodine vapor. The antibiotic had an intermediate mobility and produced a rapid and characteristic olive-green color with iodine vapor.

(8) This reagent has been used effectively in demethylation of carbohydrate derivatives: T. G. Bonner, E. J. Bourne, and S. McNally, *J. Chem. Soc.*, 2929 (1960). Aromaic ethers have been demethylated with boron tribromide: J. F. W. McOmie and M. L. Watts, *Chem. Ind.* (London), 1658 (1963).

usual way afforded a solid which was recrystallized from benzene–hexane to give **1** as colorless crystals. The synthetic material had spectral and chromatographic properties identical with the crystalline bacterial product.

The antibiotic showed pronounced *in vitro* activity against Gram-positive bacteria and *Mycobacterium tuberculosis* H37R but was inactive against Gram-negative organisms. In mice, a single intravenous dose of 25 mg/kg was tolerated but one of 50 mg/kg was instantly lethal; a single subcutaneous dose of 250 mg/kg was tolerated but one of 200 mg/kg failed to protect mice against an experimental acute infection with *Staphylococcus aureus* UC-76.

Acknowledgment. We thank Dr. J. M. Vandenbelt and his staff of these laboratories for the physical measurements, Dr. Carl L. Heifetz of our Detroit laboratories for the biological data, and Dr. H. M. Crooks, Jr., for helpful discussions.

Stephen Hanessian, James S. Kaltenbronn
Research Laboratories, Parke, Davis and Company
Ann Arbor, Michigan 48106
Received July 21, 1966

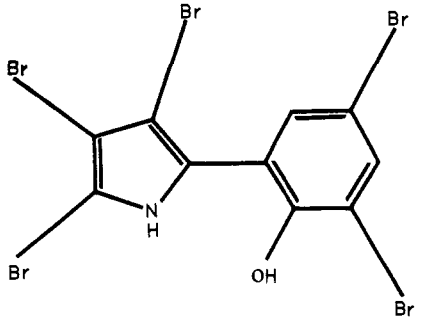


Figure 1. The structure of the antibiotic.

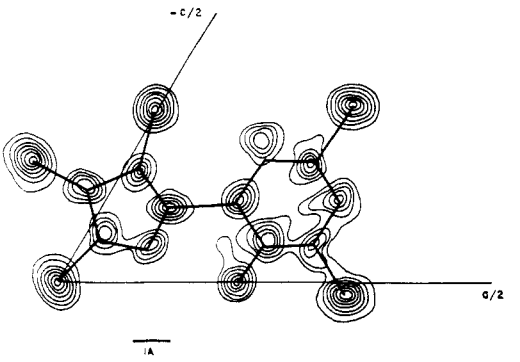


Figure 2. The final electron-density synthesis projected along the *b* axis. Contours are drawn at arbitrary intervals; not all contours are shown in the bromine atoms.

The Structure of a Bromine-Rich Marine Antibiotic

Sir:

The structure of a new antibiotic, $C_{10}H_4NOBr_5$, containing more than 70% by weight of bromine, isolated in the course of studies on marine bacteria,[1] has been determined. Preliminary ultraviolet analysis of the antibiotic had earlier suggested that the molecule might contain a pyrrole ring. This was the only chemical information available during the interpretation of the X-ray results which first established the correct molecular weight.

Table I. Data for the Two Crystal Forms of the Antibiotic

Crystal form	*a*, A	*b*, A	*c*, A	β	D_mD_c	g/ml	Space group	*Z*	Mol wt	*V*, A³
Monoclinic laths, elongated along b	22.15	7.47	16.96	108°	2.74	2.76	$P2_1/c$	8	550	2665
Monoclinic tables,[a] elongated along b, lying on (001)	23.04 ± 0.02	3.96 ± 0.05	16.71 ± 0.02	119°20 ± 5	2.76	2.76	Cc	4	552	1328

[a] Crystals used in the X-ray analysis.

Crystals of the antibiotic originally supplied for the X-ray study were very small, thin, monoclinic laths crystallized from chloroform which were unsuitable for the structure analysis. Recrystallization of the material by slow cooling from warm chloroform yielded large monoclinic crystals of a new form which were used for the remaining X-ray work. The unit cell dimensions and space groups of both crystal forms were determined and these results are shown in Table I. The noncentrosymmetric space group Cc was chosen rather than the formally possible C2/c, and this was confirmed when the structure had been determined.

The molecular weights found for the two crystal forms are in good agreement, so it may be concluded that they probably differ only in the packing arrangement of the molecules. The value of 552 ± 5 was confirmed by mass-spectrographic measurements which gave a molecular weight of 553 ± 1.[2] Preliminary chemical analysis had indicated a much higher molecular weight, but a new series of analyses led to the empirical formula $C_{10}H_4NOBr_5$ with mol wt 553.7.

The *b* axis of the unit cell is extremely short, so it appeared probable that the structure would be resolved, without any overlap of atoms, in the projection of the cell along this axis. Consequently, since the purpose of the investigation was to establish the structure of the molecule and accurate bond lengths and angles were not required, the data collection was limited to the *h0l* reflections which were recorded photographically using the Weissenberg multiple film technique with copper radiation. The intensities of 192 reflections

(1) P. R. Burkholder, R. M. Pfister, and F. H. Leitz, *Appl. Microbiol.*, 14, 649 (1966).

(2) Dr. D. C. DeJongh, Chemistry Department, Wayne State University, kindly made available the molecular weight decuced from mass-spectrographic studies of the antibiotic.