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THE STRUCTURE AND ABSOLUTE CONFIGURATION OF PENTALENOLACTONE (PA 132)

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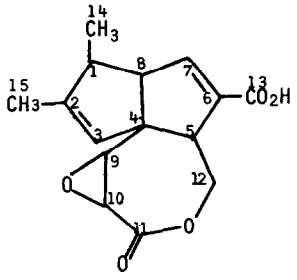
In the course of our screening program for antimetabolites having potential antitumor activity (1), we isolated an acidic lipophilic antibiotic from the fermentation broth of *Streptomyces* UC 5319 which was identical with PA 132 (2,3) by direct comparison (4).

Recently, Takeuchi *et al.* proposed structure 1 for the antibiotic and suggested the name pentalenolactone (5).



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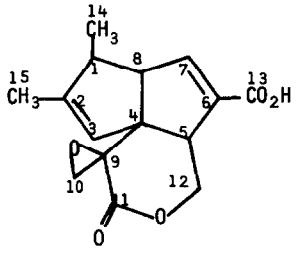

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Although spectral data gathered in our laboratories were in agreement with the published data, we found that structure 2 was also consistent with the data. In particular, the doublets (J = 5 Hz) observed at 2.75 and 3.25δ in the NMR spectrum of the antibiotic were assigned (5) as the protons H9 and H10 of structure 1, but could be assigned (6) as the geminal protons on the exocyclic epoxide of structure 2.

Reduction of the antibiotic with $LiAlH_4$ afforded a mixture of products only partially resolved on silica gel. NMR spectroscopy of the chromatographed mixture indicated the presence of a new unsplit CH_3 group consistent with the reduction product of an exocyclic epoxide.

This preliminary evidence favoring structure 2 led us to prepare the crystalline bromohydrin of tetrahydropentalenolactone (5) in order to establish its structure by x-ray diffraction.

Several recrystallizations from CH_2Cl_2 and a final recrystallization from aqueous acetone afforded an acetone solvate of the bromohydrin, mp 175-177° with scintering at 130° (7), consistent with $C_{15}H_{21}O_5Br$ (1/2 C_3H_6O) by analysis (C H Br).

Crystals are monoclinic with crystal data shown below:

$\underline{a}$ = 19.007 ± 0.001 Å

$\underline{b}$ = 7.886 ± 0.001

$\underline{c}$ = 12.223 ± 0.001

β = 102.47° ± 0.01°

V = 1788.8 Å^3

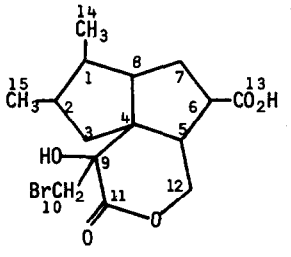
Space Group C2

Z = 4

ρ_{calc} = 1.44 g/cm^3

Three-dimensional intensity data (1818 reflections) were collected using CuK_α radiation. A trial structure was obtained using the heavy atom method. Anisotropic thermal parameters and hydrogen atoms were added during least squares refinement. Anomalous dispersion techniques (8) were used to establish the absolute configuration; all 15 reflection pairs used agreed with the assigned configuration. The final agreement index (R) is 0.077 (9).

The structure of the bromohydrin of tetrahydropentalenolactone is therefore 3. The NMR spectrum (d_7DMF) was consistent with 3 and confirmed the presence of 1/2 equivalent of acetone. The geminal protons on C10 appeared as on AB multiplet at 3.77, 4.10δ, J_{AB} = -11 Hz (6). A computer drawing of the bromohydrin in correct absolute configuration is shown in Figure 1.



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The structure of the bromohydrin coupled with the work of Takeuchi *et al.* (5) establishes that pentalenolactone (PA 132) has structure 2 with the absolute configuration as shown in Figure 1.

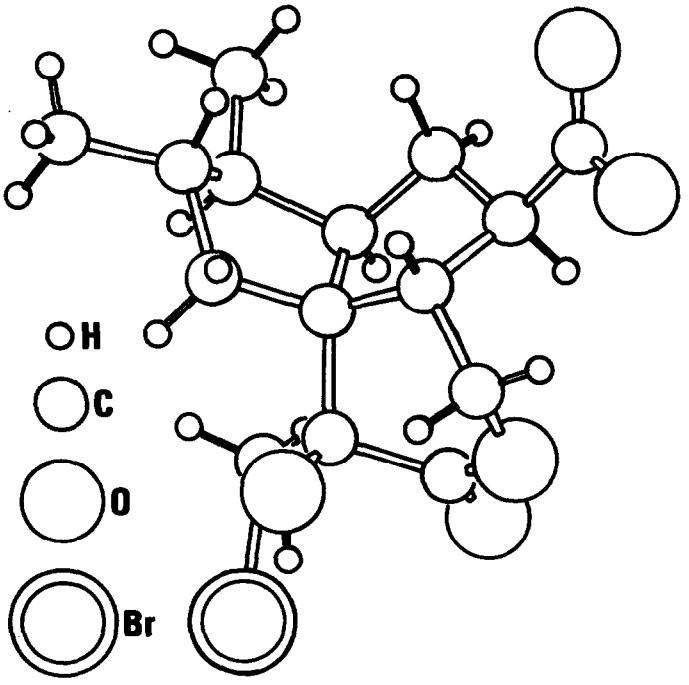

Figure 1

ACKNOWLEDGMENTS

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