# The Crystal and Molecular Structure of 7α-(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine Hydrobromide (19-Propylthevinol Hydrobromide)

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**Abstract:** The crystal structure of the hydrobromide salt of a Diels–Alder adduct derivative of thebaine (19-propylthevinol) has been determined *via* the phase-determining heavy-atom method. The crystals, which are orthorhombic with the space group $P2_12_12_1$, have the unit cell dimensions $a = 10.60$, $b = 22.34$, and $c = 10.14$ A. Calculation of a three-dimensional Patterson function, followed by several cycles of electron density and finally least-squares refinement, yielded the complete structure. Both the relative configuration at $C_{19}$ and the absolute configuration of the molecule as a whole were established, the latter *via* anomalous scattering techniques, and the assignments made previously by Kalvoda, *et al.*, for the morphine series were confirmed. The molecular shape, which is partly defined by a complex cage structure, is severely distorted when compared with an idealized Dreiding model. An observed intramolecular hydrogen bond suggests a favored $sp^2$ rather than $sp^3$ hydridization for an ether oxygen atom. Accurate bond lengths and valency angles have been obtained and all the protons associated with the rigid molecular framework have been located, including the quaternizing proton, which is in close proximity to a bromide anion.

It has been reported by Bentley and Hardy[1] that the preparation of compounds more rigid and complex than morphine could lead to physiologically active substances at least as effective as analgesics as morphine, but not exhibiting its unwanted side effects. A series of such compounds, ready access to which was provided by the Diels–Alder addition of dienophiles to thebaine, has been studied in these laboratories and their interesting chemistry reported.[2]

In view of the fact that prior knowledge of the detailed molecular structure of the morphine alkaloids as obtained *via* X-ray crystallographic analysis had been limited, it was considered to be imperative to initiate a comprehensive study of at least one of these adducts. Thus, certain aspects of the molecular geometry would be established and a relationship might be obtained between the more subtle structure details and the observed physical characteristics.

## Experimental Section

The preparation of the compound which was chosen for this work has been reported by Bentley, *et al.*[2] 19-Propylthevinol (I) is the 7α-(1-(*R*)-hydroxy-1-methylbutyl)-*t*-carbinol obtained from 7α-acetyl-6,7,8,14-tetrahydro-6,14-*endo*-ethenothebaine by treatment with propylmagnesium iodide.

Single crystals[3] of 19-propylthevinol·HBr were obtained in various sizes by slow crystallization from an aqueous ethanolic solution of I to which an equivalent of HBr was added. Oscillation, Weissenberg, and precession photographic work established the crystals to be orthorhombic, with the unit cell lattice constants $a = 10.60$ A, $b = 22.34$ A, and $c = 10.14$ A. The space group is $P2_12_12_1$, which assignment was made due to the absence of all reflections of the types ($h00$), ($0k0$), and ($00l$) for which $h$, $k$, or $l$ are odd. The cell constants as obtained with film techniques were confirmed using a GE XRD-6 diffractometer equipped with a Eulerian cradle. The measured density, 1.383 g/cc, is in good agreement with the calculated value of 1.397 g/cc for a cell content of four molecules of $C_{26}H_{35}NO_4\cdot HBr$.

A specimen of approximate dimensions of 200 × 100 × 60 μ was chosen for the intensity data collection after inspection under polarized light and additional photographic fingerprinting had shown it to be a single crystal. Its mosaic spread was found to vary from 0.4 to 0.6° and three-dimensional intensity data were taken for those reflections present in the octant with the least variation. Cu Kα radiation was used, with a divergent incident beam, with the stationary counter–stationary crystal technique. Balanced Co and Ni filters were used throughout, and the take-off angle of the X-ray tube was 2.2°. A preliminary investigation had shown the peak widths to vary only slightly, from 0.5° at low scattering angles to about 1.0° at $2\theta$ values of 100°. The photographic work had shown that all diffraction was limited to the reflections accessible within a sphere determined by this range. During the course of the data gathering several reflections were monitored as a means for observation of possible decay and/or misalignment of the crystal. No decomposition could be detected.

In all, 1772 independent reflections were monitored, of which 516 were deemed to be too weak to be measurable with sufficient accuracy, since they exhibited a count rate smaller than twice that of the background.

Even though the linear absorption coefficient ($\mu_r = 28.0$) indicated that absorption corrections were unnecessary, a systematic variation of the count rate of the polar reflections ($00l$) upon rotation of $\varphi$ was observed and was attributed to the noncylindrical shape of the crystal and the corresponding difference in the X-ray path lengths. A $\varphi$-dependent correction was therefore applied in the subsequent data reduction, which also included the conventional Lorentz and polarization corrections.

The crystal structure was elucidated by the phase-determining heavy-atom method.[4]

A three-dimensional Patterson function $P(u, v, w)$ was computed with the input data, $|F|^2$, sharpened with a coefficient ($Z^2_{Br}/f^2_{Br}$ $\exp[2B(\sin\theta/\lambda)^2]$), where $Z_{Br}$ is the atomic number of bromine, $f_{Br}$ the scattering amplitude of a bromide ion at rest at a Bragg angle $\theta$, and $B$ is an over-all temperature factor, which was taken to be 2.5 A². Perusal of the Harker sections at $u$, $v$, and $w = {}^1/_2$ led at once to the deduction of coordinates for the bromide ions. Assignment of phases based on the calculated contributions of these ions and a subsequent Fourier synthesis ($\rho(1)$) led to the location of 11 additional atomic sites, six of which seemed to form a ring system. Refinement of the phases by the inclusion of the additional atoms followed by a second density map calculation ($\rho(2)$) yielded 11 more atoms, of which one was latter found to be incorrectly placed. A third cycle of Fourier refinement revealed

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(1) K. W. Bentley and D. G. Hardy, *Proc. Chem. Soc.*, 220 (1963).

(2) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, in press.

(3) We wish to thank Dr. C. F. Howell of Lederle Laboratories for kindly supplying the samples.

(4) J. M. Robertson and I. Woodward, *J. Chem. Soc.*, 219 (1937); 36 (1940).

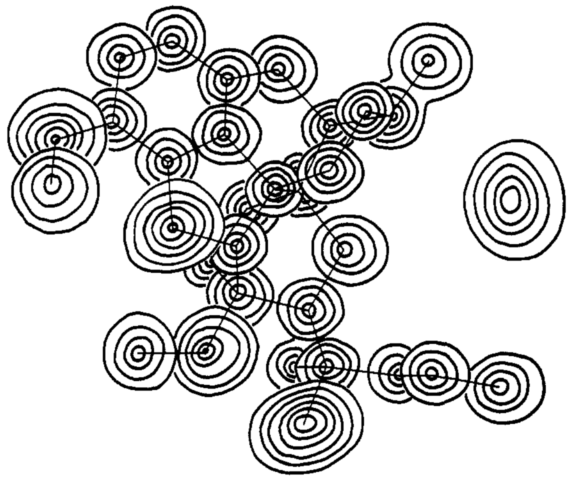

Figure 1. Final three-dimensional electron-density distribution shown by means of superimposed contour sections drawn parallel to (001) through the calculated atomic centers. Contour intervals 1.5 eA$^{-3}$, except around the bromide ion, where it is 7 eA$^{-3}$.

the complete structure. The average difference between the observed and calculated form factors at this stage was 28%. Two cycles of isotropic block-diagonal least-squares refinement afforded a drop in $R$ to 0.18 but it was observed that several of the atoms showed large temperature factors, thus placing doubt as to their actual location. A fourth density map ($\rho(4)$) was calculated, omitting these atoms from the phase calculations. This led to the repositioning of two of the atoms (the methyl group on $C_{19}$, and $C_1$ of the phenyl ring), but the three other peaks returned in the previously assigned positions. Refinement of the light atoms, which were given individual isotropic temperature factors, while the bromide ions were allowed to vibrate in an anisotropic fashion, led in three more cycles of block-diagonal refinement to an $R$ value of 0.086. Two cycles of anisotropic refinement of the lighter atoms then yielded an $R$ of 0.078.[5] At this stage it was found that the parameter shifts were insignificant compared to the calculated standard deviations, and therefore the refinement was terminated.[6] The value of $R$ including all unobserved reflections as $0.5F_{\min}$ was 0.12.[7]

A composite final electron density map was evaluated and an area covering one molecule is shown in Figure 1 which contains superimposed sections taken through the centers of the atoms, and is drawn in a direction parallel to (001). The corresponding atomic arrangement is explained in Figure 2. The coordinates and thermal parameters obtained are given in Tables I and II and their standard deviations in Table III. The latter were determined from the least-squares residuals by application of the equation[8]

$$\sigma^2(x_i) = \sum_j w_j(\Delta F_j)^2/[(n - s)\sum_j w_j(\delta F_j/\delta x_i)^2]$$

**Table I.** Atomic Coordinates and Isotropic Temperature Factors

| Atom | $x/A$ | $y/B$ | $z/C$ | $B$ |
|---|---|---|---|---|
| $C_1$ | 0.4277 | 0.2578 | 0.2288 | 6.88 |
| $C_2$ | 0.4700 | 0.2080 | 0.2980 | 6.94 |
| $C_3$ | 0.5901 | 0.2006 | 0.3523 | 6.39 |
| $O_3$ | 0.6268 | 0.1449 | 0.3996 | 8.35 |
| $Me_3$ | 0.7170 | 0.1439 | 0.4930 | 9.44 |
| $C_4$ | 0.6707 | 0.2490 | 0.3489 | 5.54 |
| $O_4$ | 0.7970 | 0.2526 | 0.3814 | 5.25 |
| $C_5$ | 0.8410 | 0.3129 | 0.3445 | 4.29 |
| $C_6$ | 0.9337 | 0.3121 | 0.2271 | 4.95 |
| $O_6$ | 1.0473 | 0.2820 | 0.2481 | 5.39 |
| $Me_6$ | 1.0467 | 0.2188 | 0.2818 | 7.06 |
| $C_7$ | 0.9674 | 0.3809 | 0.2111 | 3.55 |
| $C_8$ | 0.8533 | 0.4144 | 0.1528 | 3.59 |
| $C_9$ | 0.6084 | 0.4032 | 0.1304 | 4.36 |
| $C_{10}$ | 0.4921 | 0.3598 | 0.1347 | 4.61 |
| $C_{11}$ | 0.5100 | 0.3073 | 0.2316 | 5.11 |
| $C_{12}$ | 0.6222 | 0.3027 | 0.2997 | 5.43 |
| $C_{13}$ | 0.7269 | 0.3500 | 0.3042 | 4.29 |
| $C_{14}$ | 0.7331 | 0.3729 | 0.1616 | 3.01 |
| $C_{15}$ | 0.6964 | 0.4001 | 0.4039 | 4.82 |
| $C_{16}$ | 0.5755 | 0.4342 | 0.3659 | 4.12 |
| N | 0.5890 | 0.4544 | 0.2269 | 4.30 |
| NMe | 0.4770 | 0.4941 | 0.1834 | 7.30 |
| $C_{17}$ | 0.7651 | 0.3211 | 0.0701 | 3.88 |
| $C_{18}$ | 0.8680 | 0.2903 | 0.1043 | 4.27 |
| $C_{19}$ | 1.0880 | 0.3949 | 0.1346 | 4.12 |
| $O_{19}$ | 1.1965 | 0.3741 | 0.2050 | 5.45 |
| $Me_{19}$ | 1.0867 | 0.3702 | −0.0084 | 7.63 |
| $Pr_1$ | 1.1044 | 0.4678 | 0.1387 | 5.95 |
| $Pr_2$ | 1.1043 | 0.4932 | 0.2717 | 6.65 |
| $Pr_3$ | 1.1291 | 0.5622 | 0.2700 | 7.47 |
| Br | 0.7626 | 0.5681 | 0.2214 | 5.03 |

**Table II.** Anisotropic Temperature Factors as Obtained for the Different Atoms of the Form[a]

$$T = e^{-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)}$$

| Atom | $B_{11}$ | $B_{22}$ | $B_{33}$ | $B_{12}$ | $B_{13}$ | $B_{23}$ |
|---|---|---|---|---|---|---|
| $C_1$ | 1135 | 317 | 1936 | 91 | −196 | −52 |
| $C_2$ | 452 | 265 | 1139 | 444 | 352 | 321 |
| $C_3$ | 2600 | 85 | 1535 | 172 | −1043 | 626 |
| $O_3$ | 1927 | 260 | 2036 | −93 | −95 | 417 |
| $Me_3$ | 3335 | 283 | 2371 | 116 | −665 | 83 |
| $C_4$ | 593 | 434 | 642 | −186 | 748 | 46 |
| $O_4$ | 1460 | 250 | 1498 | −185 | 292 | −37 |
| $C_5$ | 996 | 260 | 1061 | −67 | −213 | 112 |
| $C_6$ | 1165 | 123 | 1221 | 180 | −892 | 488 |
| $O_6$ | 975 | 255 | 1315 | −97 | 117 | 95 |
| $Me_6$ | 1207 | 260 | 1275 | −26 | 776 | 135 |
| $C_7$ | 261 | 140 | 1430 | 226 | 327 | −432 |
| $C_8$ | 628 | 207 | 636 | −104 | 266 | 102 |
| $C_9$ | 474 | 147 | 856 | 112 | 227 | 222 |
| $C_{10}$ | 850 | 356 | 1673 | −156 | 756 | −368 |
| $C_{11}$ | 552 | 121 | 1080 | 185 | 276 | 96 |
| $C_{12}$ | 1223 | 373 | 1172 | −301 | −6 | 8 |
| $C_{13}$ | 860 | 207 | 1364 | 27 | 282 | −124 |
| $C_{14}$ | 1163 | 271 | 892 | −369 | 176 | −94 |
| $C_{15}$ | 1631 | 293 | 279 | −372 | 279 | 303 |
| $C_{16}$ | 1363 | 265 | 1549 | 371 | −117 | −117 |
| N | 497 | 166 | 1042 | 143 | 404 | −67 |
| NMe | 832 | 225 | 1994 | −94 | −42 | 728 |
| $C_{17}$ | 802 | 155 | 754 | 52 | 142 | 16 |
| $C_{18}$ | 1089 | 247 | 642 | 24 | 26 | 76 |
| $C_{19}$ | 827 | 183 | 1156 | 97 | −383 | −11 |
| $O_{19}$ | 632 | 345 | 1701 | −67 | 155 | −48 |
| $Me_{19}$ | 948 | 608 | 1567 | 45 | 338 | −396 |
| $Pr_1$ | 1792 | 332 | 1530 | −58 | −196 | −29 |
| $Pr_2$ | 1878 | 204 | 1404 | 66 | −431 | 235 |
| $Pr_3$ | 1237 | 264 | 1140 | 84 | 544 | 398 |
| $Br^-$ | 1208 | 178 | 1532 | 77 | −6 | −34 |

[a] Values given are multiplied by $10^5$.

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(5) The theoretical atomic scattering factors for carbon, nitrogen, oxygen, and bromide used in all the structure factor calculations were taken from the "International Tables for X-Ray Crystallography," Vol. III, The Kynoch Press, Birmingham, 1962, where bromide was corrected for anomalous dispersion. All calculations were carried out on an IBM 7094 digital computer at the ITT Data Processing Center, Paramus, N. J. The Fourier program used was that of Sly–Shoemaker–van den Hende; the least-squares, distance, and other peripheral calculations were carried out using our own programs.

(6) The weighting of the contributions of the individual reflections to the residuals was based on the following scheme: for reflections with $|F| > 10F_{\min}$ the weight $w$ was given by $w = 10F_{\min}/|F|$, for $4F_{\min} < |F| < 10F_{\min}$, $w = 10$, and for $|F| < 4F_{\min}$, $w = |F|/4F_{\min}$.

(7) A table with the final values of $F_o$ and $F_c$ and the phase angles $\alpha$ has been deposited as Document No. 9371 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington, D. C. 20540 A copy may be secured by citing the document number and by remitting $2.50 for photoprints, or $1.75 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

(8) D. W. J. Cruickshank, *Acta Cryst.*, 2, 65 (1949); 3, 72 (1950).

**Table III.** Standard Deviations of the Final Atomic Coordinates (A)

| Atom | $\sigma(x)$ | $\sigma(y)$ | $\sigma(z)$ | Atom | $\sigma(x)$ | $\sigma(y)$ | $\sigma(z)$ |
|---|---|---|---|---|---|---|---|
| $C_1$ | 0.010 | 0.012 | 0.012 | $C_{12}$ | 0.009 | 0.011 | 0.009 |
| $C_2$ | 0.012 | 0.016 | 0.013 | $C_{13}$ | 0.009 | 0.009 | 0.009 |
| $C_3$ | 0.014 | 0.013 | 0.013 | $C_{14}$ | 0.007 | 0.008 | 0.008 |
| $C_3$ | 0.010 | 0.011 | 0.011 | $C_{15}$ | 0.009 | 0.011 | 0.009 |
| $Me_3$ | 0.019 | 0.017 | 0.016 | $C_{16}$ | 0.011 | 0.014 | 0.012 |
| $C_4$ | 0.009 | 0.012 | 0.010 | N | 0.007 | 0.008 | 0.008 |
| $O_4$ | 0.007 | 0.007 | 0.007 | NMe | 0.009 | 0.013 | 0.015 |
| $C_5$ | 0.007 | 0.009 | 0.008 | $C_{17}$ | 0.008 | 0.009 | 0.008 |
| $C_6$ | 0.009 | 0.011 | 0.010 | $C_{18}$ | 0.009 | 0.010 | 0.009 |
| $O_6$ | 0.006 | 0.007 | 0.007 | $C_{19}$ | 0.008 | 0.010 | 0.008 |
| $Me_6$ | 0.014 | 0.011 | 0.013 | $O_{19}$ | 0.006 | 0.007 | 0.007 |
| $C_7$ | 0.006 | 0.007 | 0.007 | $Me_{19}$ | 0.012 | 0.015 | 0.012 |
| $C_8$ | 0.007 | 0.009 | 0.008 | $Pr_1$ | 0.012 | 0.012 | 0.012 |
| $C_9$ | 0.008 | 0.010 | 0.009 | $Pr_2$ | 0.013 | 0.013 | 0.013 |
| $C_{10}$ | 0.008 | 0.010 | 0.010 | $Pr_3$ | 0.012 | 0.014 | 0.015 |
| $C_{11}$ | 0.009 | 0.011 | 0.011 | Br | 0.001 | 0.001 | 0.001 |

## Discussion of the Structure

The spatial configuration of the molecule of 19-propylthevinol, as shown in projection in Figure 2, in many ways resembles that of codeine and morphine, as described by Lindsey and Barnes[9] and by Mackay and Hodgkin.[10]

Since both of these previous analyses were performed with two-dimensional intensity data, we feel compelled to describe the molecular geometry of I with some detail.

Moreover, the absolute configuration of the morphinoids had not been confirmed previously by X-ray analysis even though the elegant chemical work of Kalvoda, *et al.*,[11] leaves little doubt as to its being well established.

The average sp$^3$-carbon–sp$^3$-carbon single bond length, of 1.543 A (Table IV), and the average bond length in the aromatic A ring, 1.392 A, as well as the sp$^2$-carbon–sp$^2$-carbon length of 1.335 A, do not differ significantly from expected values.[12]

**Table IV.** Table of Interatomic Distances

| Atoms | Distance, A | Atoms | Distance, A |
|---|---|---|---|
| $C_1$–$C_2$ | 1.389 | $C_9$–$C_{14}$ | 1.518 |
| $C_1$–$C_{11}$ | 1.409 | $C_9$–$C_{10}$ | 1.570 |
| $C_2$–$C_3$ | 1.397 | $C_9$–N | 1.519 |
| $C_3$–$C_4$ | 1.378 | $C_{10}$–$C_{11}$ | 1.541 |
| $C_3$–$O_3$ | 1.391 | $C_{11}$–$C_{12}$ | 1.379 |
| $O_3$–$Me_3$ | 1.346 | $C_{12}$–$C_{13}$ | 1.534 |
| $C_4$–$O_4$ | 1.380 | $C_{13}$–$C_{14}$ | 1.535 |
| $C_4$–$C_{12}$ | 1.398 | $C_{13}$–$C_{15}$ | 1.541 |
| $O_4$–$C_5$ | 1.473 | $C_{14}$–$C_{17}$ | 1.521 |
| $C_5$–$C_6$ | 1.543 | $C_{15}$–$C_{16}$ | 1.540 |
| $C_5$–$C_{13}$ | 1.523 | $C_{16}$–N | 1.486 |
| $C_6$–$C_7$ | 1.586 | N–NMe | 1.545 |
| $C_6$–$O_6$ | 1.396 | $C_{17}$–$C_{18}$ | 1.335 |
| $O_6$–$Me_6$ | 1.451 | $C_{19}$–$Me_{19}$ | 1.551 |
| $O_6$–$C_{18}$ | 1.507 | $C_{19}$–$O_{19}$ | 1.431 |
| $C_7$–$C_8$ | 1.541 | $C_{19}$–$Pr_1$ | 1.638 |
| $C_7$–$C_{19}$ | 1.529 | $Pr_1$–$Pr_2$ | 1.463 |
| $C_8$–$C_{14}$ | 1.578 | $Pr_2$–$Pr_3$ | 1.565 |

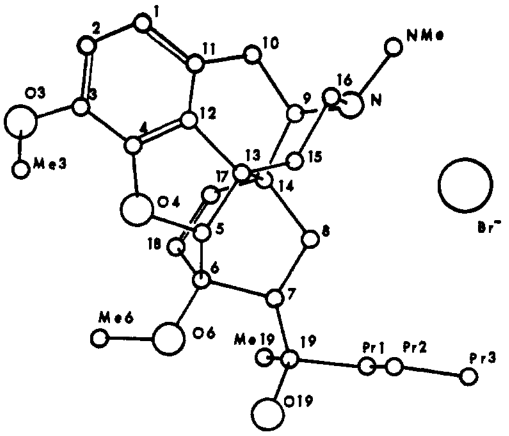

Figure 2. The atomic arrangement corresponding to Figure 1.

The carbon–nitrogen single bonds, which average 1.516 A, are longer than expected, however, while the carbon–oxygen bond lengths are in the normal range.

The lengths of the bonds around the atom labeled $Pr_1$ are quite anomalous, and there is no satisfactory chemical explanation for this effect. We therefore consider it possible that the $Pr_1$ carbon atom has been misplaced by about 0.1 A by the least-squares refinement procedure.

A comparison of the results with an idealized Dreiding model shows that the molecule is subject to considerable distortion. The phenyl ring itself is flat, but it can readily be understood that the spacial requirements of the complex cage structure connected to it explain why the connecting bonds ($C_4$–$O_4$, $C_{12}$–$C_{13}$, and $C_{11}$–$C_{10}$) are not coplanar with the six phenyl carbons.

As is usually observed in methyl phenyl ethers, the 3-methoxyl carbon atom does not lie in the phenyl carbon plane. The five-membered oxygen-containing ring is planar and the piperidyl system is in the chair conformation with the N-methyl equatorial.

In the bicyclo[2.2.2]octene cage, the carbon atoms 17 and 18 are the ones originally present and labeled as $C_8$ and $C_7$ in the morphinoids. The ring $C_5$–$C_6$–$C_{18}$–$C_{17}$–$C_{14}$–$C_{13}$ has, because of the added $C_7$–$C_8$ bridge, a different conformation than in morphine, where it is found as a pseudo chair.

As a result of this analysis the conformation at $C_{19}$ has been established. The hydroxyl oxygen, $O_{19}$, is coplanar with $O_6$, $C_6$, and $C_{19}$, and the methyl group, $Me_{19}$, is oriented toward the morphine ethenyl bridge. This result is in agreement with stereochemical considerations of the Grignard coupling which was carried out at $C_{19}$ in the preparation of I, since it is reasonable to assume that the MgI ion would preferably interact with both the $C_{19}$ and $C_6$ oxygen atoms in the Grignard complex.

The 19-hydroxyl group forms an intramolecular hydrogen bond with the ether oxygen $O_6$. The 6-methyl group is located in such a manner as to facilitate this bonding with the free pairs of O electrons. The O–O distance is 2.63$^4$ A, and the position of the proton, which was located from a difference density map calculation (Figure 3), indicates a O–H··O hydrogen bond angle of 111.2°, with H–$O_{19}$ and H–$O_6$ distances of 1.05$^4$ and 1.79$^2$ A, respectively. The location of the hydroxyl proton, which is virtually coplanar with the $C_6$–$O_6$–Me atoms, seems to indicate that the ether

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(9) J. M. Lindsey and W. H. Barnes, *Acta Cryst.*, **8**, 227 (1955).

(10) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955).

(11) J. Kalvoda, P. Buchschacher, and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955).

(12) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configuration in Molecules and Ions," Special Publication No. 11, The Chemical Society, London, 1958, p S12.

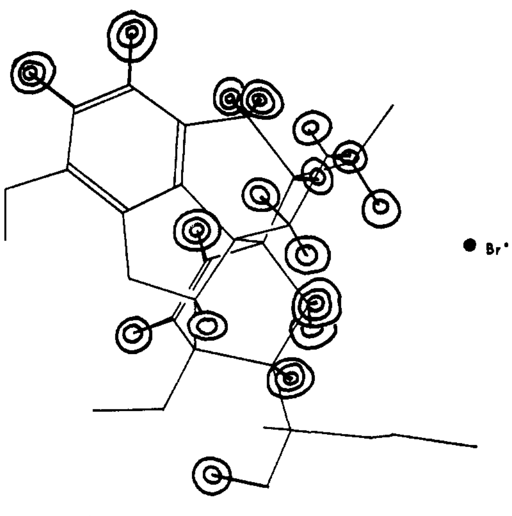

Figure 3. Hydrogen atom positions as obtained from $F_o - F_c$ synthesis. Contours drawn represent 0.1 electron/A$^3$.

oxygen has an unshared pair of electrons emanating from the atomic center in the same plane as the bonded electrons. This implies that the oxygen atom is not an sp$^3$ hybrid, but rather that it is sp$^2$, trigonal. This is supported by the $C_6$–$O_6$–$Me_6$ valence angle of 120°. In view of this it should also be observed that the angle $C_3$–$O_3$–$Me_3$, 117°, is close to the ideal trigonal value of 120°.

The closest nonbonded intramolecular distances are given in Table V, and Table VI is a list of valency bond angles. A survey of these angles reveals that most ring bond angles are slightly larger than the expected sp$^3$ valence angles, which must be caused by the constraints placed upon them by the fusion of such a large number of rings into a single molecular skeleton in order to allow it some "breathing space." The results are consistent with the nmr and infrared spectral data.[13]

Table V. Nonbonded Intramolecular Distances below 3.00 A

| Atoms | Distance, A | Atoms | Distance, A | Atoms | Distance, A |
|---|---|---|---|---|---|
| $C_1-C_3$ | 2.48 | $C_5-C_{18}$ | 2.50 | $C_{12}-C_{15}$ | 2.54 |
| $C_1-C_4$ | 2.86 | $C_6-C_8$ | 2.55 | $C_{12}-C_{17}$ | 2.81 |
| $C_1-C_{10}$ | 2.56 | $C_6-C_{13}$ | 2.48 | $C_{13}-N$ | 2.86 |
| $C_1-C_{12}$ | 2.40 | $C_6-C_{14}$ | 2.61 | $C_{13}-C_{16}$ | 2.55 |
| $C_2-O_3$ | 2.41 | $C_6-C_{17}$ | 2.40 | $C_{13}-C_{17}$ | 2.49 |
| $C_2-C_4$ | 2.37 | $O_6-C_{19}$ | 2.81 | $C_{13}-C_{18}$ | 2.85 |
| $C_2-C_{11}$ | 2.36 | $O_6-O_{19}$ | 2.63 | $C_{14}-C_{15}$ | 2.56 |
| $C_2-C_{12}$ | 2.66 | $C_7-C_{13}$ | 2.80 | $C_{14}-N$ | 2.47 |
| $C_3-Me_3$ | 2.33 | $C_7-C_{14}$ | 2.54 | $C_{14}-C_{16}$ | 2.99 |
| $C_3-O_4$ | 2.50 | $C_7-C_{17}$ | 2.90 | $C_{14}-C_{18}$ | 2.41 |
| $C_3-C_{11}$ | 2.81 | $C_7-C_{18}$ | 2.52 | $C_{15}-N$ | 2.45 |
| $C_3-C_{12}$ | 2.37 | $C_8-C_9$ | 2.62 | $NMe-C_{16}$ | 2.51 |
| $O_3-C_4$ | 2.43 | $C_8-C_{13}$ | 2.49 | $C_{19}-Pr_2$ | 2.60 |
| $Me_3-C_4$ | 2.81 | $C_8-C_{17}$ | 2.43 | $O_{19}-Pr_1$ | 2.41 |
| $Me_3-O_4$ | 2.81 | $C_8-C_{18}$ | 2.82 | $O_{19}-Pr_2$ | 2.91 |
| $C_4-C_5$ | 2.30 | $C_9-C_{12}$ | 2.83 | $Pr_1-Pr_3$ | 2.51 |
| $C_4-C_{11}$ | 2.45 | $C_9-C_{13}$ | 2.47 | $Me_{19}-Pr_1$ | 2.65 |
| $C_4-C_{13}$ | 2.38 | $C_9-C_{15}$ | 2.93 | $C_7-Me_{19}$ | 2.57 |
| $O_4-C_6$ | 2.51 | $C_9-NMe$ | 2.52 | $O_4-Me_6$ | 2.93 |
| $O_4-C_{12}$ | 2.32 | $C_9-C_{16}$ | 2.51 | $C_5-O_6$ | 2.49 |
| $O_4-C_{13}$ | 2.43 | $C_9-C_{17}$ | 2.55 | $C_6-Me_6$ | 2.47 |
| $C_5-C_7$ | 2.43 | $C_{10}-C_{12}$ | 2.51 | $C_6-C_{19}$ | 2.64 |
| $C_5-C_8$ | 2.99 | $C_{10}-C_{14}$ | 2.58 | $C_7-O_{19}$ | 2.43 |
| $C_5-C_{12}$ | 2.37 | $C_{10}-N$ | 2.53 | $C_7-Pr_1$ | 2.53 |
| $C_5-C_{14}$ | 2.56 | $C_{11}-C_{13}$ | 2.60 | $C_7-Pr_2$ | 2.96 |
| $C_5-C_{15}$ | 2.55 | $C_{11}-C_{14}$ | 2.87 | $C_8-C_{19}$ | 2.53 |
| $C_5-C_{17}$ | 2.90 | $C_{12}-C_{14}$ | 2.41 | $C_8-Pr_1$ | 2.92 |

Table VI. Valency Angles for 19-Propylthevinol

| Atoms | Angle, deg | Atoms | Angle, deg |
|---|---|---|---|
| $C_{11}-C_1-C_2$ | 115 | $C_{11}-C_{12}-C_{13}$ | 126 |
| $C_1-C_2-C_3$ | 126 | $C_4-C_{12}-C_{13}$ | 108 |
| $C_2-C_3-C_4$ | 118 | $C_{12}-C_{13}-C_5$ | 102 |
| $C_2-C_3-O_3$ | 120 | $C_{12}-C_{13}-C_{14}$ | 103 |
| $C_4-C_3-O_3$ | 122 | $C_{12}-C_{13}-C_{15}$ | 112 |
| $Me_3-O_3-C_3$ | 117 | $C_5-C_{13}-C_{14}$ | 114 |
| $C_3-C_4-C_{12}$ | 117 | $C_5-C_{13}-C_{15}$ | 113 |
| $C_3-C_4-O_4$ | 130 | $C_{14}-C_{13}-C_{15}$ | 113 |
| $C_{12}-C_4-O_4$ | 113 | $C_{13}-C_{14}-C_8$ | 107 |
| $O_4-C_5-C_6$ | 113 | $C_{13}-C_{14}-C_9$ | 108 |
| $O_4-C_5-C_{13}$ | 108 | $C_{13}-C_{14}-C_{17}$ | 109 |
| $C_6-C_5-C_{13}$ | 108 | $C_8-C_{14}-C_9$ | 115 |
| $C_5-C_6-C_7$ | 102 | $C_8-C_{14}-C_{17}$ | 103 |
| $C_5-C_6-C_{18}$ | 110 | $C_9-C_{14}-C_{17}$ | 114 |
| $C_5-C_6-O_6$ | 116 | $C_{13}-C_{15}-C_{16}$ | 112 |
| $C_7-C_6-O_6$ | 107 | $C_{15}-C_{16}-N$ | 108 |
| $C_7-C_6-C_{18}$ | 109 | $C_9-N-C_{16}$ | 113 |
| $O_6-C_6-C_{18}$ | 112 | $C_9-N-NMe$ | 111 |
| $C_6-C_7-C_8$ | 109 | $C_{16}-N-NMe$ | 112 |
| $C_6-C_7-C_{19}$ | 116 | $C_{14}-C_{17}-C_{18}$ | 115 |
| $C_6-O_7-Me_6$ | 120 | $C_6-C_{18}-C_{17}$ | 115 |
| $C_8-C_7-C_{19}$ | 111 | $C_7-C_{19}-O_{19}$ | 111 |
| $C_7-C_8-C_{14}$ | 109 | $C_7-C_{19}-M_{19}$ | 113 |
| $C_{14}-C_9-C_{10}$ | 114 | $C_7-C_{19}-Pr_1$ | 106 |
| $C_{14}-C_9-N$ | 109 | $O_{19}-C_{19}-M_{19}$ | 111 |
| $C_{10}-C_9-N$ | 110 | $O_{19}-C_{19}-Pr_1$ | 103 |
| $C_9-C_{10}-C_{11}$ | 113 | $M_{19}-C_{19}-Pr_1$ | 112 |
| $C_{10}C_{11}-C_1$ | 121 | $C_{19}-Pr_1-Pr_2$ | 114 |
| $C_{10}-C_{11}-C_{12}$ | 119 | $Pr_1-Pr_2-Pr_3$ | 112 |
| $C_1-C_{11}-C_{12}$ | 119 | | |
| $C_{11}-C_{12}-C_4$ | 124 | | |

Table VII. Short Intermolecular Nonbonded Approaches

| | |
|---|---|
| $Br-Pr_2$ | 3.99[a] |
| $Br-Pr_3$ | 3.89[a] |
| $Br-C_8$ | 4.01[b] |
| $Br-C_9$ | 3.87[b] |
| $Br-C_{17}$ | 3.86[b] |
| $Br-C_2$ | 4.06[c] |
| $Br-Me_6$ | 3.98[c] |
| $Br-C_8$ | 3.79[a] |
| $Br-C_{15}$ | 4.02[a] |
| $Br-N$ | 3.18[a] |
| $Br-NMe$ | 3.58[a] |
| $Br-C_{16}$ | 3.70[a] |
| $Br-C_{15}$ | 3.89[b] |
| $C_1-C_{17}$ | 3.91[d] |
| $C_1-C_{18}$ | 3.60[d] |
| $C_1-O_{19}$ | 3.58[e] |
| $C_1-Me_{19}$ | 4.00[f] |
| $C_2-O_4$ | 3.83[g] |
| $C_2-O_5$ | 3.90[g] |
| $C_2-Me_{19}$ | 3.64[h] |
| $C_3-Me_{19}$ | 3.83[h] |
| $O_3-NMe$ | 3.64[c] |
| $O_3-Pr_3$ | 3.62[i] |
| $Me_3-Pr_3$ | 3.62[i] |
| $Me_3-O_6$ | 3.89[g] |
| $Me_3-O_{19}$ | 3.10[g] |
| $Me_6-Pr_3$ | 4.00[i] |
| $C_{10}-O_{19}$ | 3.23[e] |

The superscripts refer to the following positions of the atom mentioned last: [a] $x, y, z$; [b] $1.5 - x, 1 - y, 0.5 + z$; [c] $1 - x, -0.5 + y, 0.5 - z$; [d] $0.5 + x, 0.5 - y, 1 - z$; [e] $-1 + x, y, z$; [f] $0.5 + x, 0.5 - y, -z$; [g] $-0.5 + x, 0.5 - y, 1 - z$; [h] $-0.5 + x, 0.5 - y, -z$; [i] $2 - x, -0.5 + y, 0.5 - z$.

The bromide ions are located in such a manner that a very strong interaction exists with the basic nitrogen of the piperidyl ring. The quaternizing N-proton is directed from the nitrogen in the general direction of a single bromide anion, with the short N···Br approach distance of 3.17[10] A. The N–H···Br ionic bond angle is 107° with N–H and H···Br distances of 1.08 and 2.13 A, respectively. The errors in the bond distances are estimated at ±0.02 A, and those in the valency angles as ±3°.

All other short intermolecular distances seem to give rise to only the expected van der Waals contacts (see Table VII). Apart from the above described van der Waals bonding and the ionic N–H···Br interactions no strong intermolecular forces seem to hold the lattice together. This may explain the relatively high thermal motion which is ascribed to the terminal atoms of the functional groups.

## Absolute Configuration Determination

The absolute configuration was established using the anomalous dispersion of the bromide ions, which causes the reflections $(h, k, l)$ and $(\bar{h}, \bar{k}, \bar{l})$ to be different in both phase and scattering amplitude, in violation of Friedel's law. Two methods were used: first, the more obvious one in which the structure was refined first with the observed crystal planes assigned as $(hkl)$ and then as $(-h, -k, -l)$. Even though no dramatic difference in over-all $R$ was observed (0.078 and 0.084, respectively) a simple review of the data showed that for most of the reflections no large changes were calculated, but that *some* showed dramatic differences between $F_c(hkl)$ and $F_c(-h, -k, -l)$. For all reflections where this difference was more than 10% in $|F_o|$ it was obvious that the hand originally chosen was the correct one; for *these* planes $R(+++)$ and $R(---)$ were 0.107 and 0.152, respectively. In order to confirm this result the intensities of the $(-h, -k, -l)$ reflections were measured.[14] The data are shown in Table VIII, and they confirm the other work.

In all figures the absolute configuration has been depicted.

**Table VIII.** Anomalous Scattering Data for 19-Propylthevinol

| $h$ | $k$ | $l$ | $F_o(+++)/$ $F_o(---)$ | $F_c(+++)/$ $F_c(---)$ |
|---|---|---|---|---|
| 8 | 1 | 1 | 1.061 | 1.112 |
| 8 | 2 | 4 | 1.053 | 1.101 |
| 7 | 2 | 1 | 1.115 | 1.110 |
| 2 | 1 | 3 | 1.100 | 1.101 |
| 7 | 5 | 5 | 0.948 | 0.877 |
| 9 | 7 | 2 | 1.055 | 1.103 |
| 1 | 2 | 2 | 1.080 | 1.102 |
| 1 | 2 | 5 | 1.096 | 1.108 |
| 5 | 12 | 2 | 1.027 | 1.110 |
| 5 | 12 | 3 | 0.887 | 0.880 |
| 6 | 15 | 1 | 0.903 | 0.896 |
| 4 | 10 | 4 | 0.909 | 0.885 |
| 4 | 10 | 5 | 0.858 | 0.853 |
| 4 | 15 | 2 | 0.889 | 0.859 |
| 2 | 11 | 3 | 1.121 | 1.108 |
| 2 | 12 | 5 | 1.084 | 1.105 |
| 1 | 12 | 4 | 1.047 | 1.115 |

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# The Crystal and Molecular Structure of N-Brosylmitomycin A

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*Contribution from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut, and Lederle Laboratories, a Division of American Cyanamid Company, Pearl River, New York.* *Received January 19, 1967*

**Abstract:** The structure of N-brosylmitomycin A, a crystalline derivative of an anticancer antibiotic extracted from soil isolates of *Streptomyces verticillatus* strains, has been determined using X-ray crystallographic techniques. The crystals are monoclinic with $a = 19.70$, $b = 8.24$, $c = 16.05$ A, $\beta = 95.80°$, space group C2, and there are four molecules per unit cell. The structure was solved using the heavy atom method and refined using Fourier and least-squares techniques. The mitomycin molecule contains four fused ring systems, one of which is an aziridine. Evidence was found indicating an interaction between the lone electron pairs of the two ring nitrogen atoms. The molecules are held in the crystal by continuous chains of N–H···O hydrogen bonds and a strong affinity between bromine atoms and the components of quinoid rings of adjacent molecules. The crystals are solvated with 0.5 mole of benzene/mole of antibiotic located in voids of the structure. The absolute configuration of the molecule has been determined from the comparision of observed and calculated structure factors utilizing the anomalous scattering contribution of bromine and sulfur for Cu K$\alpha$ radiation with respect to alternative atomic positions.

Three soil isolates of *Streptomyces verticillatus*, Lederle strains AA-849, AB-286, and AB-929, were found to produce mixtures of ethyl acetate extractable antibiotics which were active in bacterial mouse protection tests.[2] When purified preparations made

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