

Crystal and molecular structure of analgesics. II. Dezocine hydrobromide¹

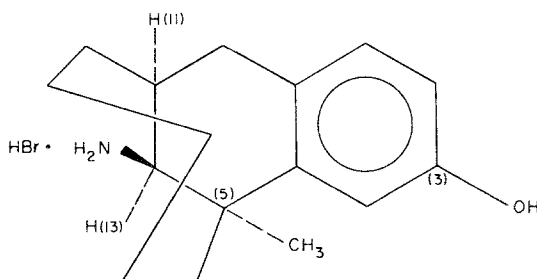
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Introduction

The conventional structural formula for the title compound is as shown, and its absolute stereochemistry has now been determined to be [*5R*-(*5* α , *11* α , *13S**)] -13-amino-5,6,7,8,9,10,11,12-octahydro-5-methyl-5,11-methanobenzocyclodecen-3-ol.



It is potent analgesic (Freed et al., 1973) of clinical interest (Oosterlink and Verbaeys, 1980). Although the relative stereochemistry is fairly certain on the basis of its preparation, the large five-membered bridge could theoretically be *trans* fused to the aminotetralin instead of the assumed *cis* fusion. Furthermore, even though the amino group was indicated to be *trans* to the methyl group by the chemical shift of the *N*-methyl derivative, this conclusion is not

¹IUPAC name: (-)-13 β -amino-5,6,7,8,9,10,11,12-octahydro-5 α -methyl-5-11-methanobenzocyclodecen-3-ol hydrobromide.

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entirely unequivocal, since the conformations of the carbocyclic rings are not known (Freed et al., 1973). Also, the coupling of the C(11) and C(13) protons suggests *cis*, but this is also not easily determined. In addition, the absolute stereochemistry is of intrinsic interest. Obviously, a complete X-ray crystallographic investigation could be used to settle these points, and as a special bonus would be expected to yield interesting information concerning the rather infrequently encountered $N^+-H \cdots Br^-$ hydrogen bond. Hydrogen bonding of this and other kinds have long been a subject of interest in these laboratories.

Experimental

Three-dimensional X-ray diffraction data were collected on a Picker FACS-I automatic diffractometer from crystals which had a rectangular parallelepipedal habit. The radiation was graphite-monochromatized $Mo K\alpha$; the θ - 2θ scan technique was used over a dispersion-corrected base width of 1.3° , with a scan speed of 2.0° per minute. There was no diminution of intensity as a function of time in periodically measured standard reflections. The intensity data was reduced to structure amplitudes in the usual way; no absorption correction was applied. Additional crystal data and details of the data collection are presented in Table 1. Note that there are three molecules in the asymmetric unit.

Structure Solution and Refinement

The structure was solved by Patterson and Fourier techniques. The positions of the bromide ions were obtained from a sharpened $P(uvw)$

Table 1. Crystal data and data collection

Formula	$C_{16}H_{24}NO^+Br^-$
M_r	326.28
Crystal system	Orthorhombic
Lattice constants	$a = 23.080(9) \text{ \AA}$ $b = 17.000(8)$ $c = 11.780(4)$
Space group	$P2_12_12_1$
Z	12
D_x	1.41 g cm^{-3}
Crystal size	$0.4 \times 0.1 \times 0.1 \text{ mm}$
$(\sin \theta / \lambda)_{\max}$	0.54 \AA^{-1}
Number of unique reflections	2998
Threshold	$I_o = 3.09 \sigma(I)$
Number of reflections < threshold	1078
$\sigma(I)$	Counting statistics
$\sigma(F)$	$\sigma(F) = [F^2 \times \sigma(I)]^{1/2} - F$

function: successive $\rho(xyz)$ maps, initially phased with the bromide positions, led quickly to the complete structure (excluding the hydrogen atoms). The heavy atom positions were refined by the full-matrix least-squares method of Gantzel et al. (1969). In the final stages the bromide ions were assigned anisotropic temperature factors, while the carbon, nitrogen, and oxygen atoms were retained as isotropic. The weights used were $w = \sigma^{-2}(F)$, but zero for reflections below threshold. The function minimized was $\sum w(|F_o| - |F_c|)^2$. All scattering factors were those in the *International Tables for X-ray Crystallography*, Volume 3 (1962). The final positional and thermal parameters, with their esd's, are presented in Table 2. The final R value for observed data is 6.3%.

Other computer programs used included the CRYSTNET series (Berstein et al., 1974) and the graphics programs VIEW (Carrell, 1976) and DOCK (Badler et al., 1979).

Discussion

Bond distances, bond angles, and torsion angles

The presence of three molecules in the asymmetric unit leads to a moderately unusual opportunity to assess the accuracy of this refinement. The bond distances, bond angles, and selected torsion angles are shown in Fig. 1, 2, and 3. These figures do not depict the true conformations of the molecules, but are distorted in order to provide room for the numbers.

There is a total of 20 C-C, C-N, and C-O bond distances in each molecule. The average rms difference in bond lengths among the three molecules is 0.033 Å, or a bit larger than the average esd on a bond distance of 0.031 Å as obtained from the least-squares refinement. With regard to bond distances, the three molecules are not significantly different. The same conclusion is reached with regard to the bond angles, of which there are 29 in each molecule, and the average rms difference is only 2.2°, compared with the least-squares average esd of 1.9°.

In the case of the torsion angles a different conclusion is reached. For the 11 internal torsion angles not in the plane of the benzene ring, the average difference between molecule *A* and molecule *B* is 5.6°, but the *A-C* and *B-C* differences are much larger, at 8.0° and 9.5°, respectively. The conclusion is that molecule *C* is conformationally significantly different from molecules *A* and *B*. It seems likely that this difference arises from the geometrical requirements of the hydrogen bonding by the NH_3^+ group, with a small influence, perhaps, of packing forces. Stereo views of molecules *A*, *B*, and *C*, perpendicular to their benzene rings, are shown in Fig. 4, where it is seen that molecule *C* is different from the other two.

Table 2. Refined positional and thermal parameters^a

Atom	Molecule A				Molecule B				Molecule C			
	x	y	z	B (Å ²)	x	y	z	B (Å ²)	x	y	z	B (Å ²)
Isotropic Atoms, $x, y, z \times 10^3, \sigma(x) = 0.001; \sigma(y) = 0.001; \sigma(z) = 0.002$												
C(1)	637	085	577	4.1(6)	492	488	277	3.4(5)	837	449	168	3.5(6)
C(2)	658	119	676	3.5(6)	495	417	215	3.5(5)	852	367	169	3.3(5)
C(3)	695	180	666	3.6(5)	552	400	182	2.8(5)	908	348	212	3.3(5)
C(4)	717	210	562	2.9(5)	603	441	203	2.8(5)	948	400	255	2.8(5)
C(4a)	695	176	456	3.1(5)	594	514	260	1.9(4)	931	480	255	2.7(5)
C(5)	719	207	340	3.2(5)	651	564	282	3.1(5)	974	544	304	3.1(5)
C(6)	788	194	342	4.2(6)	681	588	173	3.8(5)	1030	546	237	2.9(5)
C(7)	815	121	402	5.3(6)	647	604	068	5.6(7)	1024	541	106	3.5(5)
C(8)	812	044	340	6.3(7)	619	681	053	7.5(7)	1016	622	043	3.7(5)
C(9)	754	002	353	4.4(6)	559	689	122	6.9(8)	952	647	032	5.1(5)
C(10)	714	013	246	4.1(6)	564	724	236	4.3(6)	930	694	130	5.9(7)
C(11)	666	079	254	3.8(6)	574	676	343	5.1(6)	900	655	236	3.7(5)
C(12)	630	070	361	3.9(6)	529	611	364	5.1(6)	854	592	208	3.7(5)
C(12a)	656	111	462	2.9(5)	538	536	300	3.2(5)	875	506	211	3.8(6)
C(13)	685	168	245	3.7(5)	635	637	362	4.0(6)	937	621	332	3.6(6)
O	719	221	762	4.7(4)	560	330	117	5.1(4)	923	269	213	4.1(4)
N	716	179	134	2.9(4)	681	698	359	3.9(4)	978	687	374	3.6(4)
C(Me)	707	295	329	4.2(5)	694	513	356	3.5(5)	991	515	427	3.7(5)

Anisotropic atoms, $x, y, z \times 10^4, \sigma(B_{ij}) = (0, 1)$												
Atom	x	y	z	B ₁₁	B ₂₂	B ₃₃	B ₁₂	B ₁₃	B ₂₃			
Br(1)	3926(1)	6626(2)	5447(2)	5.2	5.1	4.0	0.3	-0.1	-0.1			
Br(2)	7945(1)	6487(1)	5147(2)	3.9	4.6	4.0	-0.3	-0.4	-0.4			
Br(3)	8582(1)	1567(1)	0332(2)	5.8	3.4	4.3	0.4	0.2	0.1			

^a Estimated standard deviations with respect to the last digit reported are in parentheses, unless otherwise noted. The isotropic temperature factor expression is $T = \exp(-B \sin^2 \theta / \lambda^2)$, and the anisotropic temperature factor expression is $T = \exp[-\frac{1}{4}(h^2 a^{*2} B_{11} + k^2 b^{*2} B_{22} + l^2 c^{*2} B_{33} + 2hka^*b^*B_{12} + 2hla^*c^*B_{13} + 2klb^*c^*B_{23})]$.

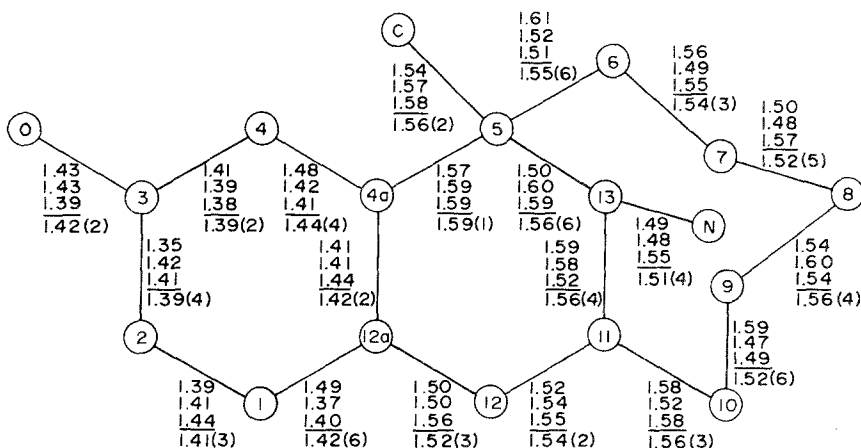


Fig. 1. Bond distances (Å) in the order molecule *A*, *B*, *C*. For each distance the average and its standard error are given. No stereochemistry should be inferred from the molecular skeleton, which is purely schematic for convenience.

Stereochemistry

The absolute configuration was determined by the use of $\Delta f'' = -0.3$ and $\Delta f''' = +2.5$ for the bromide ion for Mo $K\alpha$ radiation. Relevant data for which $I(hkl)$ was markedly different from $I(\bar{k}\bar{h}\bar{l})$ are presented in Table 3. In these calculations the positional parameters of Table 2 were used, and it is these that correspond to the correct absolute configuration.

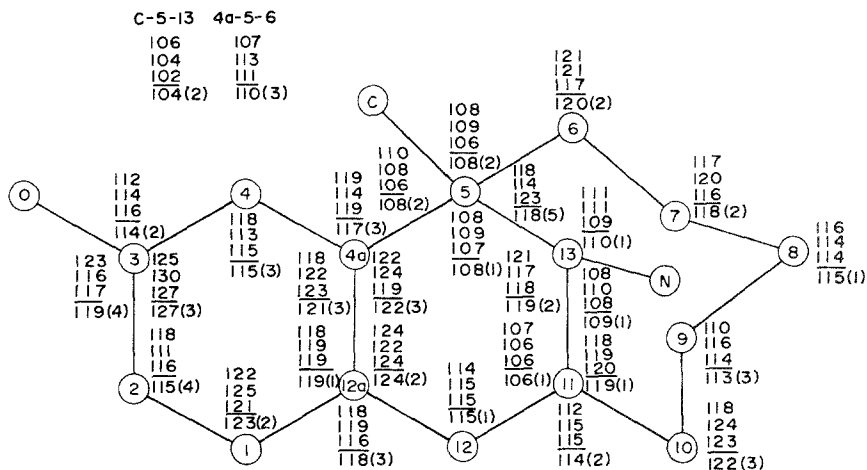


Fig. 2. Bond angles (deg). For each angle the average and its standard error are given. See legend to Fig. 1.

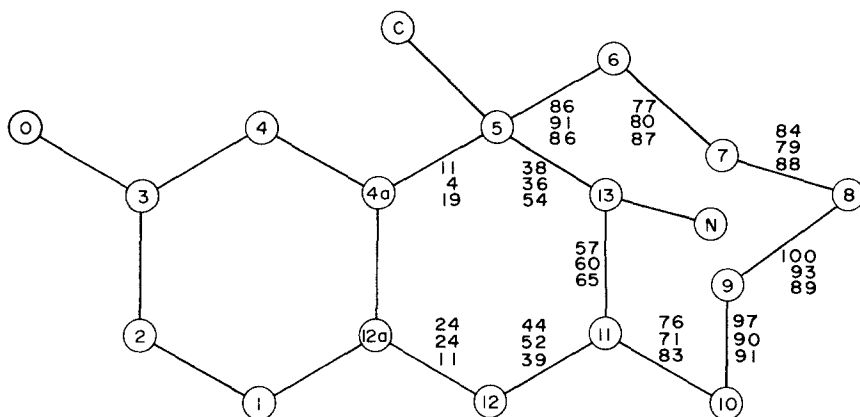


Fig. 3. Interior torsion angles. For each angle the average and its standard error are given. See legend to Fig. 1.

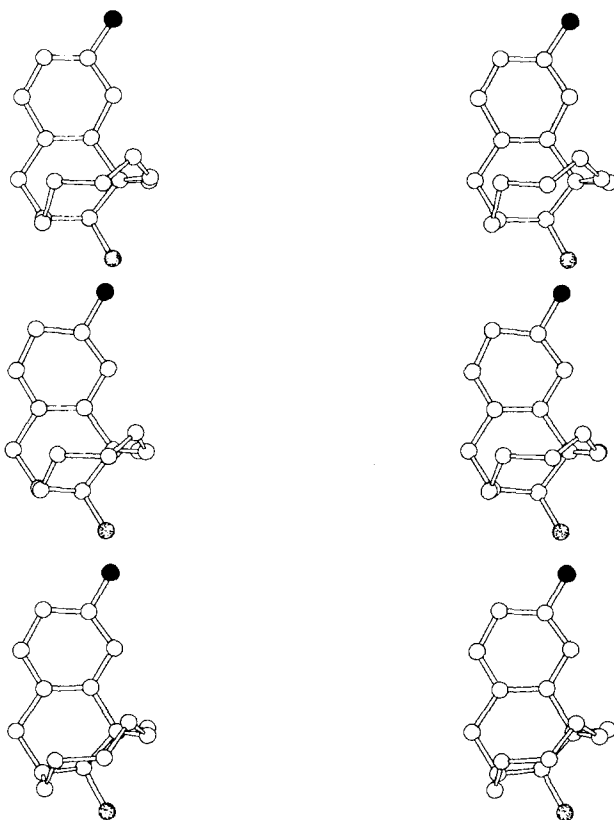


Fig. 4. Stereo views of the three molecules. Upper, molecule A; middle, molecule B; lower, molecule C.

Table 3. Anomalous dispersion data^a

<i>hkl</i>	RI_{obs}	RI_{calc}	<i>hkl</i>	RI_{obs}	RI_{calc}
921	-0.08	-0.09	344	+0.09	+0.09
814	+0.08	+0.07	342	-0.13	-0.13
714	+0.08	+0.09	325	+0.08	+0.08
643	+0.12	+0.12	314	+0.08	+0.07
652	+0.08	+0.08	112	+0.11	+0.11
371	+0.10	+0.08			

^a $RI = (I_+ + I_-)/(I_+ - I_-)$, where I_+ is the intensity of (*hkl*), and I_- of ($\bar{h}\bar{k}\bar{l}$). For Br^- and $Mo K\alpha$, $\Delta f' = -0.3$ and $\Delta f'' = +2.5$.

A stereo view of molecule *A* which includes the hydrogen atoms in their assumed positions is shown in Fig. 5. The carbon, nitrogen, and oxygen atoms of Table 2 were used in the preparation of this figure, which therefore not only shows the correct relative configurations at atoms C(5), C(11), and C(13), but also the correct absolute configuration.

The *cis* fusion of the five-membered bridge to the aminotetralin moiety is confirmed, and the methyl group is indeed *trans* to the amino group. The tentative conclusions of Freed et al. (1973) are thus verified.

Molecular packing and hydrogen bonding

The crystals are held together by a complex network of $O-H \cdots Br^-$ and $N-H \cdots Br^-$ hydrogen bonds, as may be seen in Fig. 6, which is a stereo view of one unit cell. There are no abnormally short intermolecular non-bonded distances.

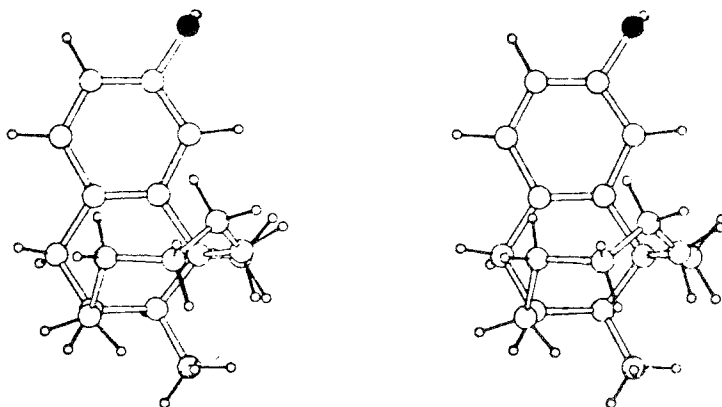


Fig. 5. Stereo view of molecule *A*, with the hydrogen atoms in their assumed positions. The oxygen atom is shown as a filled circle, the nitrogen atom is faintly stippled.

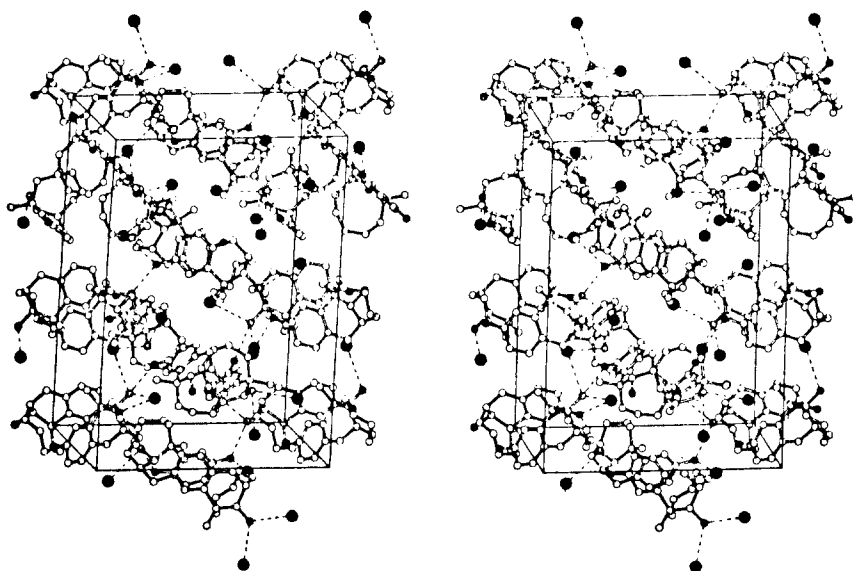


Fig. 6. Stereo view of one unit cell showing the molecular packing and hydrogen bonding.

The details of the proposed hydrogen bonding scheme by the $-\text{NH}_3^+$ groups are shown in Fig. 7. In these figures, the hydrogen atoms, the positions of which were not determined directly, were placed in idealized positions, with $\text{C}(13)\text{-N-H}$ and H-N-H bond angles as tetrahedral, and N-H bond lengths of 1.01 \AA .

The $\text{N}(A)\text{H}_3^+$ group forms three hydrogen bonds to bromide ions, and this group is staggered with respect to the two ligands of $\text{C}(13A)$, namely,

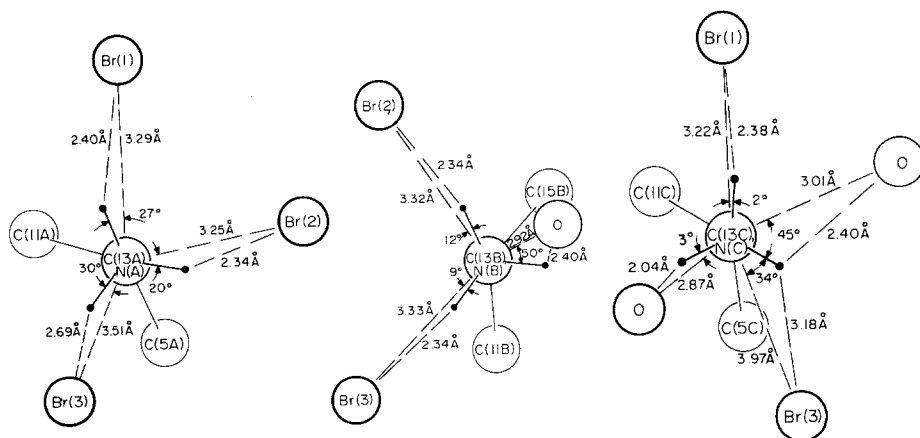


Fig. 7. Details of the hydrogen bonding by the three $-\text{NH}_3^+$ groups.

C(5A) and C(11A). The average deviation of the $N^+-H \cdots Br^-$ systems from linearity is 26° .

The $N(B)H_3^+$ group appears to form only two good nitrogen-hydrogen bonds to bromide ions. A third neighbor of N(B) is an O atom at 2.92 Å, a value close to those observed in $N-H \cdots O$ systems, but it is seen that the $N-H \cdots O$ atoms here deviate greatly from linearity and the $H \cdots O$ distance of 2.40 Å is only slightly shorter than the van der Waals radius sum, so that this interaction is at best very weak and should not properly be termed a hydrogen bond. The $N(B)H_3^+$ group is very nearly staggered with respect to the ligands of C(13B). The two $N^+(B)-H \cdots Br^-$ systems deviate from linearity by an average of only 11° .

The $N(C)H_3^+$ group forms one hydrogen bond to a bromide ion and one to an oxygen atom of a neighboring molecule. A third near neighbor of N(C), although only 3.01 Å distant, is a second oxygen atom, but it is not favorably situated nor is a fourth neighbor, a bromide ion at 3.97 Å; here the $H \cdots Br$ of 3.18 Å is the same as the van der Waals sum of 3.15 Å, so no interaction of the hydrogen bond type is indicated. An alternate, but much less satisfactory, explanation could be offered. The hydrogen atom in question on N(C) is involved in a bifurcated hydrogen bond [to Br(3) and O], both parts of which are quite weak. In the six $N-H \cdots Br$ systems in this crystal the $H \cdots Br$ distances range from 2.34 Å to 2.69 Å, or significantly smaller than the van der Waals radius sum. For hydrogen bond formation, the NH_3^+ is again seen to be in the staggered conformation with respect to the ligands of C(13C). The average deviation of the $N-H \cdots Br, O$ atoms from linearity is 3° .

The phenolic hydrogen atoms are each involved in hydrogen bonds to bromide ions. The details of these are shown in Fig. 8, where the O-H bond lengths were assumed to be 0.97 Å and the C-O-H bond angles set at 110° . The deviations from linearity are found to be 15, 8 and 7° , and the $H \cdots Br$ distances are 2.65, 2.62, and 2.24 Å, all of which are much shorter than the van der Waals radius sum of 3.15 Å.

To sum up, in the proposed hydrogen bonding scheme of the 12 hydrogen atoms per asymmetric unit which are available as hydrogen bond donors, 10

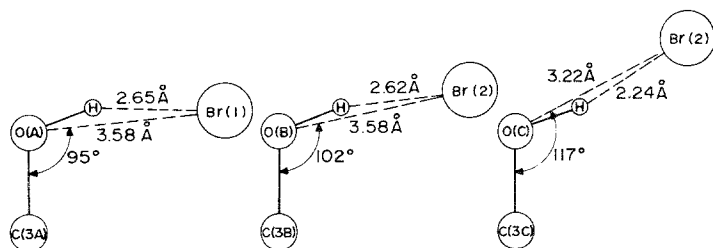


Fig. 8. Details of the hydrogen bonding by the three -OH groups.

of them are in fact involved in such interactions. Although it is uncommon to have such "unused" hydrogen atoms, this situation is not without precedent (Donohue, 1952). In a structure as complicated as this one it is remarkable that as many as 10 of the suitable hydrogen atoms find appropriate acceptors.

Acknowledgments

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References

- Badler, N., Stodola, R. K., and Wood, W. (1979) DOCK. Program from The Institute for Cancer Research and the University of Pennsylvania, Philadelphia, Pennsylvania.
- Bernstein, H. J., et al. (1974) Report BNL 18803, pp. 148-158, Brookhaven National Laboratory, Upton, New York.
- Carrell, H. L. (1976) VIEW. Program from The Institute for Cancer Research, Philadelphia, Pennsylvania.
- Donohue, J. (1952) *J. Phys. Chem.* **56**, 502.
- Freed, M. E., Potoski, J. R., Freed, E. H., and Conklin, G. L. (1973) *J. Med. Chem.* **16**, 595.
- Gantzel, P. K., Sparks, R. A., and Trueblood, K. N. (1969) UCLALS4. Program in Fortran IV. *International Tables for X-ray Crystallography* (1962) Vol. 3 (Kynoch Press, Birmingham).
- Oosterlinck, W., and Verbaeys, A. (1980) *Curr. Med. Res. Opin.* **6**, 472.

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