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# THE CRYSTAL AND MOLECULAR STRUCTURE OF ISOALFILERAMINE DIHYDROBROMIDE[1]

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**Abstract**—The crystal and molecular structure of isoalfileramine dihydrobromide has been determined from 3-dimensional single crystal X-ray diffraction data collected by counter techniques. Isoalfileramine is a cyclized derivative of the novel alkaloid, alfileramine, which has been isolated from leaves of *Zanthoxylum punctatum* Vahl. The crystals of isoalfileramine dihydrobromide were triclinic, space group $P\bar{1}$ (No. 2), with two formula units in a unit cell of dimensions $a = 16.380(12)$ Å, $b = 9.917(7)$ Å, $c = 10.648(7)$ Å, $\alpha = 116.39(2)°$, $\beta = 91.10(2)°$ and $\gamma = 101.40(2)°$. The structural model, which employed anisotropic thermal parameters only for the bromide ions, was refined using full matrix least squares methods to an $R$ value of 0.089 ($R_w = 0.090$) for 1053 independent reflections with $F^2 > 3\sigma(F^2)$. Isoalfileramine dihydrobromide is shown to be a unique pentacycle exhibiting a strained pyran ring. This work was critical in establishing structure for the parent alkaloid, alfileramine, and pointed out the clear structural relationship of alfileramine to tetrahydrocannabinols.

Extraction of the leaves of *Zanthoxylum punctatum* yielded a novel alkaloid assigned the name alfileramine.[2] A unique structure for alfileramine could not be assigned from the usual spectroscopic and analytical data. Therefore, it became desirable to determine the structure of this new alkaloid by means of single crystal X-ray diffraction. Alfileramine did not provide suitable crystals for this structural determination, and the dimethiodide and dihydrochloride derivatives, while crystalline, proved unsuitable also. Finally, very small single crystals of the dihydrobromide derivative were obtained which were suitable for the diffraction experiment.

Spectroscopic analysis of the product resulting from treatment of alfileramine with HBr suggested that some chemical change more substantial than protonation had occurred. The product was accordingly named isoalfileramine dihydrobromide. The structure found for isoalfileramine dihydrobromide is the subject of this report. From the structure reported here, that for alfileramine could be deduced.[2]

## EXPERIMENTAL

The preparation and spectroscopic characterization of the title compound have been previously described.[2] Crystals suitable for single crystal X-ray diffraction were obtained by slow evaporation of an EtOAc/MeOH solution.

*Crystal data.* For $C_{30}H_{44}N_2O_2Br_2$: Mol wt 624.5; triclinic, $a = 16.380(12)$ Å, $b = 9.917(7)$ Å, $c = 10.648(7)$ Å, $\alpha = 116.39(2)°$, $\beta = 91.10(2)°$, $\gamma = 101.40(2)°$, $V = 1508$ Å$^3$; $\rho_{obs} = 1.39$ g cm$^{-3}$, $\rho_{calcd} = 1.38$ g cm$^{-3}$, $Z = 2$; $F(000) = 648$; space group $P\bar{1}$; MoK$_\alpha$ radiation (Zr filter), $\lambda_1$ 0.70930 Å, $\lambda_2$ 0.71359 Å, $\mu$(MoK$_\alpha$) = 11.8 cm$^{-1}$.

*Data collection and reduction.* Weissenberg and precession photographs of the colorless crystals of the title compound revealed a diffraction pattern which was only consistent with the triclinic space groups $P1$ or $P\bar{1}$.[3] The crystal chosen for data collection was accurately centered on the Enraf–Nonius CAD-3 diffractometer with the $a^*$ axis approximately coincident with the diffractometer $\phi$ axis. The orientation matrix for data collection and the unit cell parameters reported above were obtained from least squares calculation on the automatically determined[4] setting angles of 22 reflections (20 ± 1°) with $2\theta$ values in the range of 16–20°. The observed density was determined by flotation in a mixture of heptane and 1,2-dibromoethane.

The intensities of all accessible reflections with $4.5° < \theta < 22.0°$ were measured by $\theta$–$2\theta$ scans. The scan range employed was 1.0°, at a constant scan rate of 10 deg min$^{-1}$. Weak reflections were scanned a maximum of four times, and background was counted at both ends of the scan for a total time equal to the scan time. The intensity of one of three reference reflections ($33\bar{3}$, 500 and $6\bar{2}3$) was measured every 25 reflections, and these intensities showed no significant changes during data collection. Lorentz and polarization corrections were applied to the data, and equivalent reflections were averaged. The uncertainty parameter, $g$, in the calculation of the standard deviation in the intensity[5,6] was taken to be 0.04. Of the approximately 3300 reflections measured, 1053 unique observed reflections for which $F^2 > 3\sigma(F^2)$ were employed in the solution and refinement of the structure. No absorption correction was applied to the data, due to the very small size (0.13 × 0.06 × 0.15 mm) of the data collection crystal. This small crystal was the largest high quality crystal which could be found, and its size is the reason for the relatively small number of observed reflections obtained.

The choice of $P\bar{1}$ as the space group was made at this point. Although the molecule was found to contain several chiral centers, the centric space group was likely to be correct on several grounds. First, both alfileramine and isoalfileramine were not optically active, indicating that a racemic mixture was present.[2] Statistical analysis of the intensities of the X-ray reflections indicated a centric distribution,[7] and the presence of two double intensity and two single intensity Br–Br peaks in the Patterson map was only consistent with a centric distribution of these ions.

The positions of the two bromide ions were assigned from a sharpened, origin-removed Patterson map, and all of the non-H atoms were located in two successive Fourier syntheses. For the light atoms found, the assignment of the N atoms was straightforward from their position in the molecule and from the known spectroscopic data. On attempted refinement of the model (bromide ions anisotropic, nitrogen and carbon atoms isotropic) two of the "carbon" atoms immediately assumed non-positive values for their thermal parameters. Normal refinement was only possible when O atoms were placed at these positions, thus leading to the assignment of the positions of the two pyran O atoms of the structure.

Scattering factors for the bromide ions and for O, N, and C atoms were taken from Ref. 8, as were correction terms $\Delta f'$ and $\Delta f''$ for anomalous dispersion due to bromide. Scattering factors for spherically bonded H atoms[9] were also taken from Ref. 8, and H atoms were placed in fixed, calculated positions 0.95 Å from carbon, with isotropic thermal parameters 1 Å$^2$ larger than those for the atoms to which they were attached. Methyl H-positions were determined by a least squares fit to observed positions in a difference Fourier map.

Refinement of the model (fixed isotropic H atoms, anisotropic

Table 1. Atomic coordinates (fractional) and isotropic thermal parameters[a]

| Atom | X | Y | Z | $B^b$ |
|---|---|---|---|---|
| Br1 | 0.0674(2) | 0.1584(4) | 0.3250(4) | |
| Br2 | 0.0950(2) | -0.2868(4) | -0.0051(4) | |
| C1 | 0.358(2) | 0.532(3) | 0.000(3) | 2.8(7) |
| C2 | 0.423(2) | 0.641(3) | -0.032(3) | 2.9(7) |
| C3 | 0.424(2) | 0.602(3) | -0.186(3) | 2.6(7) |
| C4 | 0.333(2) | 0.586(3) | -0.254(3) | 2.6(7) |
| C5 | 0.269(2) | 0.465(3) | -0.223(3) | 1.8(6) |
| C6 | 0.269(2) | 0.527(3) | -0.064(3) | 2.5(7) |
| C7 | 0.363(2) | 0.576(3) | 0.151(3) | 4.0(8) |
| C8 | 0.334(2) | 0.563(3) | -0.401(3) | 1.4(6) |
| C9 | 0.369(2) | 0.438(4) | -0.503(3) | 4.4(8) |
| C10 | 0.249(2) | 0.555(3) | -0.473(3) | 4.1(8) |
| C11 | 0.339(2) | 0.279(3) | -0.201(3) | 2.1(6) |
| C11' | 0.462(2) | 0.774(3) | -0.308(3) | 3.8(8) |
| C12 | 0.282(2) | 0.306(3) | -0.285(3) | 1.9(6) |
| C12' | 0.484(2) | 0.720(3) | -0.217(3) | 2.0(6) |
| C13 | 0.241(2) | 0.187(3) | -0.410(3) | 1.9(6) |
| C13' | 0.564(2) | 0.793(3) | -0.136(3) | 2.2(7) |
| C14 | 0.255(2) | 0.038(3) | -0.467(3) | 1.9(6) |
| C14' | 0.619(2) | 0.901(3) | -0.159(3) | 2.2(7) |
| C15 | 0.318(2) | 0.011(3) | -0.390(3) | 3.4(7) |
| C15' | 0.594(2) | 0.944(4) | -0.257(3) | 4.3(8) |
| C16 | 0.358(2) | 0.138(3) | -0.262(3) | 2.2(6) |
| C16' | 0.514(2) | 0.875(3) | -0.340(3) | 2.9(7) |
| C17 | 0.208(2) | -0.098(3) | -0.603(3) | 3.0(7) |
| C17' | 0.704(2) | 0.986(3) | -0.063(3) | 2.4(7) |
| C18 | 0.118(2) | -0.133(3) | -0.572(3) | 2.8(7) |
| C18' | 0.758(2) | 0.871(3) | -0.075(3) | 3.3(7) |
| C19 | -0.028(2) | -0.271(4) | -0.700(3) | 6.0(9) |
| C19' | 0.837(2) | 1.033(4) | 0.158(4) | 5.6(9) |
| C20 | 0.086(3) | -0.415(5) | -0.722(4) | 8.9(12) |
| C20' | 0.892(2) | 0.842(4) | 0.000(4) | 6.1(10) |
| O1 | 0.378(1) | 0.381(2) | -0.072(2) | 2.8(4) |
| O2 | 0.384(1) | 0.709(2) | -0.395(2) | 3.2(4) |
| N1 | 0.067(2) | -0.271(3) | -0.709(3) | 4.8(7) |
| N2 | 0.842(1) | 0.955(3) | 0.016(2) | 3.0(6) |

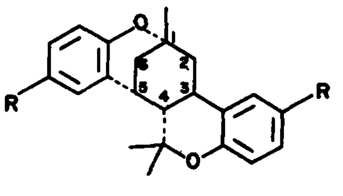
[a] The calculated hydrogen atom positions may be obtained from the authors on request. Estimated standard deviations in the least significant digit are given in parentheses.

[b] The form of the isotropic thermal motion function was $\exp\{-\underline{B}(\sin^2\theta)/\lambda^2\}$. The two bromide ions were refined anisotropically, with the form of the anisotropic thermal ellipsoid given by $\exp\{-(h^2\beta_{11}+\ldots+2hk\,\beta_{12}+\ldots)\}$. Values of the $\beta_{ij}$ x $10^4$ for these two ions were: Br1, 33(3), 324(11), 205(8), -22(4), -36(4), 152(8); Br2, 19(2), 129(7), 185(7), -12(3), -20(3), 58(6).

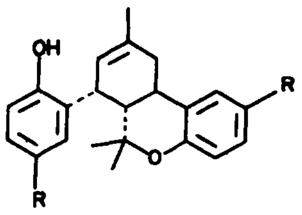
bromide ions, and isotropic C, N, and O) was carried to convergence, with the final value of $R(=\Sigma\|F_o|-|F_c\|/\Sigma|F_o|)$ being 0.089 and $R_w(=[\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2})$ being 0.090. While it would be possible to lower these $R$ values dramatically by allowing more atoms of the model to vibrate anisotropically, the authors do not feel that this step is justified, since it would further lower the data/parameter ratio (now standing at 6.8). In the final difference Fourier map, only three peaks above the level expected for an H atom were seen. Two of these peaks (3–4 times an H atom) were in the immediate vicinity of the two bromide ions, and the third peak (twice H intensity) was in the region of C17' and C18', where a large amount of thermal libration which was not well represented by the isotropic model was occurring. Therefore, it was concluded that no other atoms were present in the lattice. The final atomic positional and thermal parameters of the non-H atoms may be found in Table 1. The calculated H atom positions[a] and the final list of observed and calculated structure factors are available from the authors upon request.

## RESULTS AND DISCUSSION

The detailed structure of isoalfileramine dihydrobromide (1) is shown in Fig. 1, together with the numbering scheme used in the following discussion. The derivation of the structure of the parent compound, alfileramine (2), from that of 1 is described in Ref. 2, which also discusses the structural similarities between alfileramine and the tetrahydrocannabinols.



1 $R = CH_2CH_2\overset{+}{\underset{H}{N}}Me_2Br^-$



2 $R = CH_2CH_2NMe_2$

The contents of the unit cell are shown in Fig. 2. The lattice is held together by the ionic interactions present, and no other specific intermolecular forces could be discerned from the derived intermolecular distances.

Table 2 contains a listing of the bond lengths and angles observed for isoalfileramine dihydrobromide. A

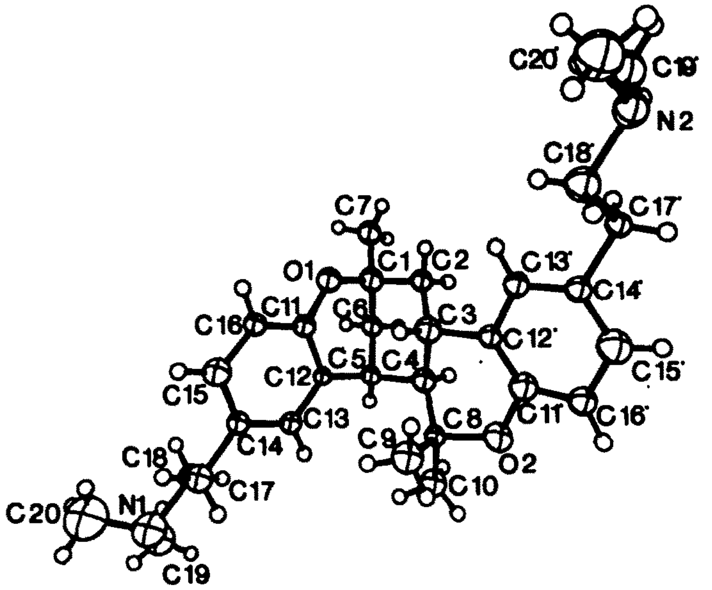


Fig. 1. A view, in perspective, of the cation of isoalfileramine dihydrobromide. Thermal ellipsoids for non-hydrogen atoms are drawn at the 50% probability level.

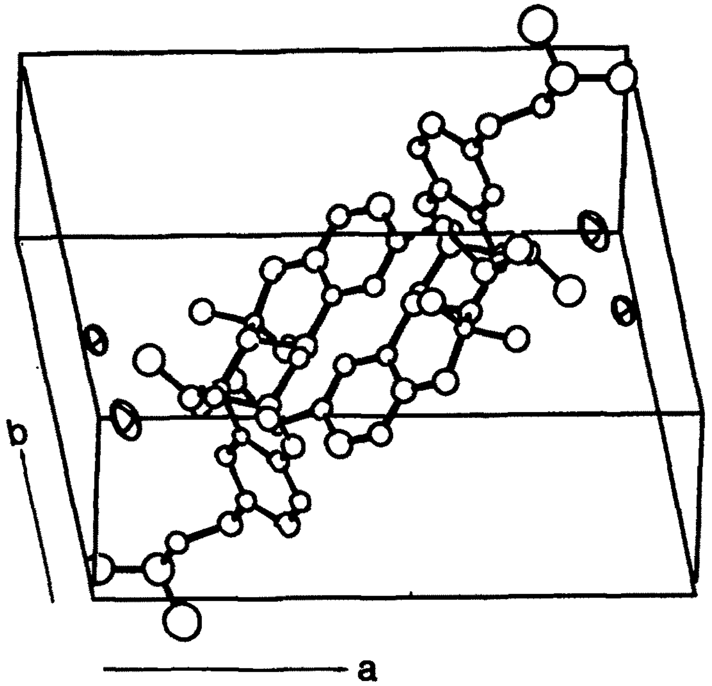


Fig. 2. A view of the unit cell contents of isoalfileramine dihydrobromide, showing the positions of the bromide ions relative to the protonated isoalfileramine cations.

wider range of bond lengths than normal is observed for the dimethylamino side chains, as a consequence of the rather large and anisotropic thermal libration of these atoms, which is poorly represented by the isotropic model imposed here. Comparison of the remainder of the structure of isoalfileramine with the structures of related compounds,[10–12] including $\Delta^9$-tetrahydrocannabinolic acid B,[13] shows that most of the bond parameters reported in Table 2 are as expected for this type of compound.

The aromatic rings (C11–C16 and C11′–C16′) exhibit bond lengths in the range of 1.36–1.43 Å and bond angles between 115° and 126°. These types of variations have been seen in similar systems[13] and attributed to the strain induced by formation of the pyran rings. The estimated standard deviations characteristic of the atomic positions of the present structure do not allow similar conclusions to be made with confidence. The phenyl rings are highly planar, as expected (Table 2), but O1, in particular, deviates markedly from the plane of the phenyl ring to which it is attached. The 0.2 Å out-of-plane displacement of O1 and the short C11–O1 bond length of 1.34(3) Å may be attributed to the strain induced by the formation of the pyran ring and the bicyclic ring system. Strain due to the fused ring system is also manifested in the long

Table 2. Bond lengths (Å) and angles (Deg)[a]

(a) Bond Lengths

| | | | |
|---|---|---|---|
| C1-C2 | 1.52(5) | C11'-C12' | 1.37(5) |
| C1-C6 | 1.58(4) | C12-C13 | 1.37(3) |
| C1-C7 | 1.47(5) | C12'-C13' | 1.42(4) |
| C1-O1 | 1.45(4) | C13-C14 | 1.39(4) |
| C2-C3 | 1.50(4) | C13'-C14' | 1.37(4) |
| C3-C12' | 1.54(4) | C14-C15 | 1.43(5) |
| C3-C4 | 1.60(4) | C14'-C15' | 1.37(5) |
| C4-C5 | 1.59(4) | C14-C17 | 1.53(3) |
| C4-C8 | 1.47(4) | C14'-C17' | 1.55(4) |
| C5-C6 | 1.53(4) | C15-C16 | 1.41(3) |
| C5-C12 | 1.48(4) | C15'-C16' | 1.42(4) |
| C8-C9 | 1.47(4) | C17-C18 | 1.52(4) |
| C8-C10 | 1.55(4) | C17'-C18' | 1.53(5) |
| C8-O2 | 1.49(4) | C18-N1 | 1.56(3) |
| C11-C16 | 1.36(4) | C18'-N2 | 1.52(3) |
| C11'-C16' | 1.35(4) | C19-N1 | 1.57(5) |
| C11-O1 | 1.34(3) | C19'-N2 | 1.37(4) |
| C11'-O2 | 1.42(3) | C20-N1 | 1.47(6) |
| C11-C12 | 1.43(5) | C20'-N2 | 1.46(5) |

(b) Bond Angles

| | | | |
|---|---|---|---|
| C2-C1-C6 | 108(3) | C13-C12-C5 | 125(3) |
| C2-C3-C12' | 116(2) | C13'-C12'-C3 | 119(3) |
| C2-C3-C4 | 110(2) | C14-C15-C16 | 116(3) |
| C3-C2-C1 | 116(2) | C14'-C15'-C16' | 122(3) |
| C4-C5-C12 | 116(2) | C14-C17-C18 | 106(2) |
| C5-C4-C3 | 107(3) | C14'-C17'-C18' | 111(2) |
| C6-C5-C4 | 109(2) | C15-C14-C17 | 118(3) |
| C6-C5-C12 | 109(3) | C15'-C14'-C17' | 121(3) |
| C7-C1-C2 | 112(2) | C16-C11-C12 | 116(2) |
| C7-C1-C6 | 113(2) | C16'-C11'-C12' | 126(3) |
| C8-C4-C3 | 111(2) | C18-N1-C19 | 108(2) |
| C8-C4-C5 | 119(2) | C18-N1-C20 | 109(3) |
| C9-C8-C4 | 120(3) | C18'-N2-C19' | 115(2) |
| C9-C8-C10 | 108(2) | C18'-N2-C20' | 109(2) |
| C4-C8-C10 | 114(2) | C19-N1-C20 | 113(3) |
| C11-C12-C5 | 115(2) | C19'-N2-C20' | 106(3) |
| C11'-C12'-C3 | 124(3) | N1-C18-C17 | 107(2) |
| C11-C16-C15 | 126(3) | N2-C18'-C17' | 111(2) |
| C11'-C16'-C15' | 115(3) | O1-C1-C2 | 106(2) |
| C11-O1-C1 | 120(2) | O1-C1-C6 | 110(2) |
| C11'-O2-C8 | 116(3) | O1-C1-C7 | 107(3) |
| C11-C12-C13 | 120(3) | C1-C6-C5 | 108(2) |
| C11'-C12'-C13' | 116(3) | O1-C11-C16 | 118(3) |
| C12-C13-C14 | 123(3) | O1-C11-C12 | 126(3) |
| C12'-C13'-C14' | 121(3) | O2-C8-C4 | 107(2) |
| C12'-C3-C4 | 106(3) | O2-C8-C9 | 106(2) |
| C13-C14-C15 | 118(2) | O2-C8-C10 | 100(3) |
| C13'-C14'-C15' | 119(3) | O2-C11'-C12' | 121(3) |
| C13-C14-C17 | 124(3) | O2-C11'-C16' | 112(3) |
| C13'-C14'-C17' | 120(3) | | |

[a] Estimated standard deviations in parentheses.

Table 3. Deviations from least squares planes (Å)[a]

Plane A: C11 (-0.09), C12 (0.00), C13 (0.00), C14 (0.00), C15 (0.03), C16 (0.02), C5 (0.01), C17 (-0.05), O1 (-0.21)

Plane E: C11' (-0.02), C12' (0.04), C13' (-0.02), C14' (0.01), C15' (0.00), C16' (0.05), C3 (-0.01), C17' (-0.14), O2 (0.04)

[a] The equations of the planes (in the form $Ax + By + Cz = D$) involved coefficients A, B, C and D as follows:

Plane A: 11.22, 3.89, -7.40, 6.47
Plane E: 8.46, -5.49, -4.67, -1.43

In each case, the first six atoms listed establish the plane.

C11′–O2 bond length of 1.42(3) Å, since earlier work[10,11,13] would lead one to expect a value of ~1.39 Å for these C–O bonds. The C–C bond lengths of the cyclohexane ring cluster about the expected distance of 1.54 Å.

One unique feature in the $^1$H NMR of alfileramine (2) was the appearance of a C–$CH_3$ resonance at the abnormally low shift of 0.53 ppm. This was attributed[2] to shielding of one of the *gem*-dimethyl groups by the $\pi$-cloud of the aromatic ring at C-5 in the most favorable conformation of 2. In isoalfileramine, the most shielded C–$CH_3$ gives rise to a signal at 0.87 ppm. It is clear from Fig. 1 that in isoalfileramine the aromatic $\pi$-cloud is not in as favored a position for shielding as it is in the conformation suggested for 2. These considerations are of value in establishing the double bond position of 2.

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