# Crystal Structure of Higenamine [1,2,3,4-Tetrahydro-1-(4-hydroxybenzyl)isoquinoline-6,7-diol] Hydrobromide

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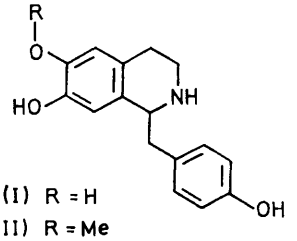
Higenamine, a heart-beat regulating compound, recently extracted from *Aconitum japonicum* Thunb. was examined by *X*-ray crystallographic analysis as its hydrobromide. Crystals are triclinic, space group $P\bar{1}$, with $Z = 2$ in a unit cell of dimensions $a = 10.071(7)$, $b = 9.111(7)$, $c = 9.643(7)$ Å, $\alpha = 105.56(8)$, $\beta = 103.73(7)$, $\gamma = 64.73(5)°$. The structure was refined by full-matrix least-squares methods to $R$ 12.7% for 2 878 independent reflections visually estimated from photographic data. The conformation of the molecules and the system of binding of the bromine atom are almost identical to those of coclaurine in coclaurine hydrobromide monohydrate. The molecular packing and the hydrogen-bonding network in higenamine crystals were determined. The enhanced β-adrenergic stimulating activity of higenamine compared to coclaurine is discussed.

RECENTLY the active component of a well known crude drug, *Aconitum japonicum* Thunb., which acts as a heart-beat regulator, was extracted, and given the name higenamine (I).[1] Higenamine [1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)isoquinoline-6,7-diol] which has also been extracted from *Nelumbo nucifera*[2] is an unmethylated coclaurine and is a much more effective β-adrenergic agonist than is coclaurine (II). Pharmacological




(I) R = H
(II) R = Me

investigation of the action of the benzyltetrahydroisoquinoline series of molecules[3] has confirmed that the replacement of the hydrogen in the isoquinoline hydroxy-group by a methyl group causes a drastic reduction of activity. The crystal structure of coclaurine hydrobromide monohydrate has already been determined by *X*-ray analysis.[4] An *X*-ray crystallographic analysis of higenamine hydrobromide was therefore undertaken in order to determine the effect of methyl-group replacement on the crystal structure.

## EXPERIMENTAL

Higenamine hydrobromide were recrystallized from methanol as yellow plates developed along the {100} plane. Oscillation and Weissenberg photographs calibrated by aluminium powder were taken about all three crystallographic axes to determine unit-cell dimensions.

*Crystal Data.*—$C_{16}H_{18}BrNO_3$, $M = 352.2$. Triclinic, $a = 10.071(7)$, $b = 9.111(7)$, $c = 9.643(7)$ Å, $\alpha = 106.56(8)$, $\beta = 103.73(7)$, $\gamma = 64.73(5)°$, $U = 760.1$ Å$^3$, $D_m = 1.542$ (by flotation), $Z = 2$, $D_c = 1.540$ g, cm$^{-3}$ $F(000) = 360$. Space group $P\bar{1}$. Cu-$K_\alpha$ radiation, $\lambda = 1.541\,8$ Å, $\mu$(Cu-$K_\alpha$) = 41.5 cm$^{-1}$. (Crystals of higenamine hydrochloride are isomorphous, cell dimensions: $a = 9.93$, $b = 8.96$, $c = 9.51$ Å, $\alpha = 108.6$, $\beta = 106.6$, $\gamma = 63.8°$.)

Intensity data were estimated visually from equi-inclination Weissenberg photographs taken along the $a$ and $b$ axes with nickel-filtered Cu-$K_\alpha$ radiation. These were corrected for spot shape and for Lorentz and polarization factors but not for absorption and then put on a single scale. 2 878 independent reflections were finally evaluated.

*Structure Determination.*—A Fourier synthesis following identification of a bromine atom on a Patterson map revealed all non-hydrogen atom positions. Initially three cycles of block-diagonal least-squares refinement were carried out with isotropic temperature factors the quantity minimized being $w(|F_o| - |F_c|)^2$ with unit weights. At this stage, the positional parameters of hydrogen atoms other than those in hydroxy-groups were calculated geometrically. These parameters were recalculated after every three cycles of refinement and used only for structure-factor calculations. Non-hydrogen atoms were then refined anisotropically by block-diagonal and full-matrix least-squares with unit weights. Refinement was terminated at the point when the shifts of parameters in each cycle became $<0.03\sigma$. The final $R$ factor was 12.7%. The final positions of the hydrogen atoms showed reasonable fitting to the difference map. All atom scattering factors were taken from ref. 5. Final observed and calculated structure factors, thermal parameters of non-hydrogen atoms, and hydrogen-atom positional parameters are listed in Supplementary Publication No. SUP 21932 (15 pp., 1 microfiche).†

† See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1976, Index issue.

[1] T. Kosuge and M. Yokota, *Chem. Pharm. Bull.* (*Japan*), 1976, **24**, 176.

[2] H. Koshiyama, H. Ohkuma, H. Kawaguchi, H. Hsü, and Y. Chen, *Chem. Pharm. Bull.* (*Japan*), 1970, **18**, 2564.

[3] Y. Iwasawa and A. Kiyomoto, *Japan J. Pharmacol.*, 1967, **17**, 143.

[4] J. Fridrichsons and A. McL. Mathieson, *Tetrahedron*, 1968, **24**, 5785.

[5] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

RESULTS AND DISCUSSION

Final positional parameters are given in Table 1, and bond lengths and angles calculated from them in Figure 1. The C(3)–C(4) (1.51) and C(5)–C(6) (1.36) bond lengths are shorter than the widely accepted values for a C–C single bond (1.54 Å) and aromatic ring (1.39 Å) but are not significant ($\leqslant 1.5\sigma$). Other bond lengths and angles are as expected. The molecular structure, drawn with the aid of the ORTEP [6] program, is shown in Figure 2. Two hydroxy-groups are located at one end, and the third one at the opposite end of the molecule. The molecule as a whole is fully extended and its length is *ca.* 16 Å. The protonated nitrogen atom is situated about half way along. Of its four tetrahedral bonds, two are hydrogen bonds connecting bromine atoms. The molecule is composed of three rings, A—C, rings B and C being planar. Deviations of atoms from least-squares planes are listed in Table 2. The deviation of C(1) out of the plane of ring B (0.11 Å) is significant, and seems to be due to the large side-chain attached to C(1).

TABLE 1

Final fractional atomic co-ordinates, with standard deviations in parentheses

| Atom | *x/a* | *y/b* | *z/c* |
|---|---|---|---|
| Br | 0.853 6(1) | 0.901 1(2) | 0.580 4(1) |
| C(1) | 0.936 7(13) | 0.775 7(16) | 1.123 6(13) |
| N(2) | 0.997 5(11) | 0.815 3(13) | 1.278 6(11) |
| C(3) | 1.123 4(13) | 0.671 2(17) | 1.331 7(12) |
| C(4) | 1.254 9(14) | 0.620 8(17) | 1.253 5(13) |
| C(5) | 1.318 1(12) | 0.503 3(15) | 0.995 9(14) |
| C(6) | 1.284 8(12) | 0.486 6(14) | 0.848 5(13) |
| C(7) | 1.139 7(12) | 0.567 5(14) | 0.786 1(12) |
| C(8) | 1.028 9(12) | 0.660 3(15) | 0.876 9(13) |
| C(9) | 1.062 4(12) | 0.680 1(15) | 1.028 0(12) |
| C(10) | 1.209 3(12) | 0.601 4(14) | 1.088 8(12) |
| O(6) | 1.397 9(9) | 0.395 3(12) | 0.763 4(9) |
| O(7) | 1.110 1(10) | 0.545 3(11) | 0.636 9(9) |
| C(1′) | 0.699 3(13) | 1.026 5(15) | 1.175 7(13) |
| C(2′) | 0.597 6(14) | 0.958 3(16) | 1.174 8(15) |
| C(3′) | 0.489 3(14) | 1.040 2(15) | 1.268 6(15) |
| C(4′) | 0.481 3(12) | 1.191 7(14) | 1.360 0(12) |
| C(5′) | 0.581 5(14) | 1.260 2(15) | 1.360 5(15) |
| C(6′) | 0.691 0(13) | 1.175 5(14) | 1.268 5(15) |
| C(7′) | 0.819 6(14) | 0.934 5(17) | 1.075 9(15) |
| O(4′) | 0.372 3(11) | 1.280 6(13) | 1.450 0(10) |

TABLE 2

Displacements (Å) of the atoms from least-squares planes through rings B and C

Plane of ring B: C(1) 0.11, N −0.24, C(3) 0.44, C(4) −0.06, C(5) 0.01, C(6) 0.01, C(7) −0.02, C(8) 0.02, C(9) 0.00, C(10) −0.01, O(6) −0.04, O(7) 0.00

Plane of ring C: C(1′) 0.00, C(2′) −0.01, C(3′) 0.01, C(4′) 0.00, C(5′) −0.01, C(6′) 0.01, C(7′) −0.02, O(4′) 0.05

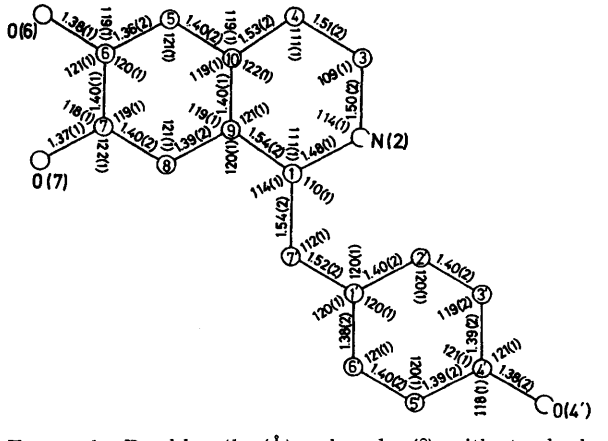



FIGURE 1 Bond lengths (Å) and angles (°), with standard deviations in parentheses

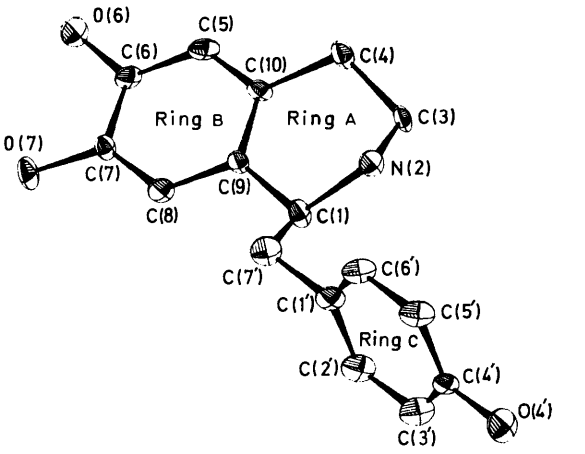



FIGURE 2 Molecular structure of higenamine, showing the numbering system used in the crystallographic analysis

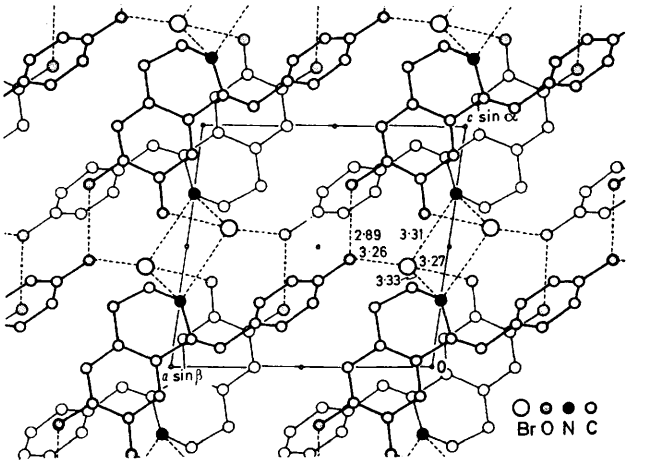



FIGURE 3 Higenamine hydrobromide: Projection of the structure along the *b* axis showing intermolecular hydrogen bonds (Å)

N and C(3) are shifted in opposite directions from the plane of ring B, to make ring A adopt a twisted half-chair form. Thus the benzyl group is attached to ring A *via* an equatorial bond through C(1). This conformation seems to be the most stable of the four possible for ring A: two twisted half-chair and two boat forms. Atom C(1′) is *trans* to C(9) about C(1)–C(7′), $\tau$ 179°, and ring C is rotated so as to be nearly orthogonal (109°) to ring B, so that the molecule has a less hindered structure. All parameters defining the molecular conformation have values in accord with the most stable form of the molecule. Moreover the molecule is in a form favourable for the linkage of bromine ions by N–H · · · Br hydrogen bonds.

The crystal structure is shown in Figure 3 where hydrogen bonds are indicated by broken lines. The

[6] C. K. Johnson, ORTEP, Report ORNL 3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1965.

molecules are joined head-to-tail by O(4′) · · · H–O(6) hydrogen bonds to form infinite chains parallel to the [1$\bar{1}\bar{1}$] axis. The chains are also nearly parallel to the

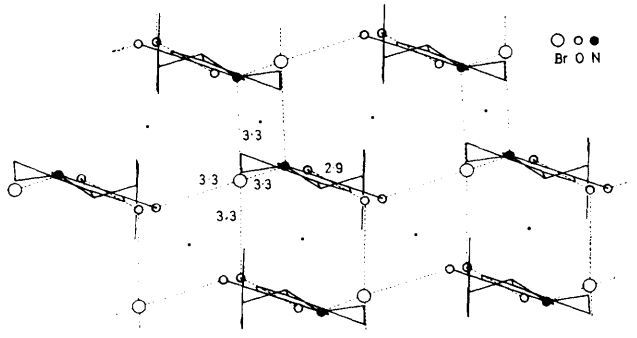



FIGURE 4 Arrangement of the molecules in the unit cell as seen along the [1$\bar{1}\bar{1}$] direction

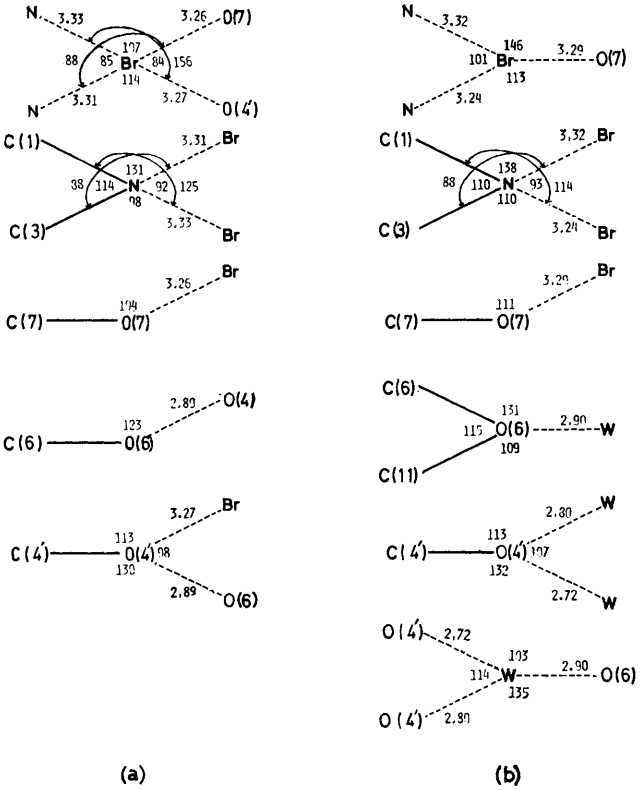



FIGURE 5 Hydrogen bond system in (a) higenamine hydrobromide (I), and (b) coclaurine hydrobromide monohydrate (II) (the numbering system is modified from that used in the original structure determination)

longest molecular axis of each molecule. Viewed along the [1$\bar{1}\bar{1}$] axis, each chain is surrounded by two parallel and four antiparallel chains making a hexagonal closed-packed structure (Figure 4). Pairs of molecules in adjacent antiparallel chains are linked *via* two Br · · · H–N hydrogen bonds. Together with the intramolecular Br · · · H–N hydrogen bonds in each molecule these bonds form a four-unit hydrogen-bond system in the form of a parallelogram. Each bromine ion is bonded *via* four hydrogen bonds in an almost tetrahedral structure to two nitrogen and two oxygen atoms [O(7) and O(4′)] of four separate molecules. Each bromine is also associated with the aromatic ring C of one of these molecules, and this proximity is responsible for the minor disruption of the tetrahedral hydrogen-bonding. The bromine ion is essentially located in the low-density region in the centre of the ring C. Although the arrangement is similar to those found in benzene–halogen adducts,[7,8] the distance between the plane and the bromine atom (3.9 Å) does not seem to be indicative of a charge-transfer complex.

There are three major differences in the crystal structures of coclaurine (II) and higenamine (I). (II) crystallizes as a monohydrate existing only in the D-form whereas (I) is anhydrous, and contains both D- and L-forms. The third difference, the absence of a methyl group in (I), is the most important in its effect on the crystal structure. In crystals of both (I) and (II), the conformations of the molecules and their manner of association with bromine are almost the same. Hydrogen bonds in both crystals are represented schematically in Figure 5. The arrangement of atoms around nitrogen are similar in (I) and (II). However, in (II) N–H · · · Br hydrogen bonds form a ladder-like structure stretching along a screw axis, while in (I) they form a closed system. This difference is a result of interaction between the D- and L-forms which exist in a 1 : 1 ratio throughout the crystal. In other respects the hydrogen bonding systems of the two molecules are almost identical, except where the methyl group of (I) is involved.

The water molecule in (II) is located between O(6) and O(4′), at the position occupied by O(4′) in higenamine and provides an additional hydrogen bond, minimizing the effect due to the presence of the methyl group in (I). Higenamine molecules are joined together in infinite long chains with individual molecules aligned parallel to the chains. The infinite chains in (II) are formed by individual molecules being linked through water molecules so that adjacent molecules are aligned to each other at 40°. As a result of this the C rings are some distance from the methyl groups of molecules in adjacent chains. The differences between the two crystal structures seem to be largely due to the effects of substitution by the methyl group.

Regarding the differences in β-adrenergic activity of higenamine and coclaurine, the results of the *X*-ray analyses are, in a sense negative, since the molecular conformations are nearly the same. The stronger activity of higenamine is therefore probably due to the better binding between the receptor and the O(6)H group of higenamine as compared with the O(6)Me group of coclaurine.

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