Tetrahedron, 1959, Vol. 6, pp. 103–108. Pergamon Press Ltd. Printed in Northern Ireland

THE STRUCTURE OF ψ-CONHYDRINE

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(*Received* 17 *October* 1958)

Abstract—The three-dimensional structure, except for the absolute configuration, of ψ-conhydrine has been determined in an X-ray diffraction study of ψ-conhydrine hydrobromide. In agreement with recent chemical evidence, the OH and propyl groups are found to be *trans* to each other, and in the equatorial position relative to the saturated six-membered ring. The unit cell is orthorhombic in the space group D_2^4-$P2_12_12_1$, contains four $C_8H_{18}NOBr$, and has dimensions $a = 15{\cdot}15$, $b = 9{\cdot}28$, $c = 7{\cdot}72$ A. Refinement, including anisotropic thermal motion, has yielded values of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0{\cdot}109$ and $r = \Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4 = 0{\cdot}056$ for the 920 observed reflections.

INTRODUCTION

CONHYDRINE and ψ-conhydrine were two of the members of the hemlock alkaloids whose configurations remained unknown at the time this study was originated. In the meantime, the stereochemistry of ψ-conhydrine has been established independently by Balenovic and Stimac,[1] and by Hill,[2] who disagree on the absolute configuration. Nevertheless, this study was completed in order to confirm the configuration of ψ-conhydrine by an independent method. A complete three-dimensional structure, except for absolute configuration, has now been obtained. In particular, the OH and propyl groups are found to be *trans* to each other. The very reasonable, but hitherto unproved, conclusion that OH and propyl groups are in the equatorial positions has also been reached in the present study. In addition, the exact three-dimensional geometry, molecular packing, and particularly the directions of hydrogen bonding, have been established; and it is hoped that these additional details may aid in the elucidation of the mechanisms of interactions of this type of molecule with other molecules in biosynthetic routes and in physiological activity.

EXPERIMENTAL

The synthesis of *dl*ψ-conhydrine,[3] the preparation of its HBr salt, and the establishment of its identity with the natural product were carried out by Leete. The crystals of ψ-conhydrine hydrobromide were needle-shaped and beautifully formed. A crystal 0·15 mm in diameter and 2 mm in length was chosen for the investigation.

The unit cell is orthorhombic, with parameters $a = 15{\cdot}15$, $b = 9{\cdot}28$ and $c = 7{\cdot}72$ A, where the c axis is parallel to the needle axis of the crystal. Systematic extinctions of $h00$ when h is odd, $0k0$ when k is odd and $00l$ when l is odd lead uniquely to the space group D_2^4-$P2_12_12_1$, which requires four or a multiple of four molecules in the unit cell. The assumption of four molecules leads to a reasonable calculated density of 1·37 g cm^{-3}. The space group also requires that in a single crystal all molecules have either the *d* form or the *l* form; therefore the separation of *d* and *l* form of the compound was completed in the process of crystallization.

Equi-inclination Weissenberg photographs were taken of levels 0, 1, 2, 3 and 4 about the c axis with Cu$K\alpha$ radiation, and precession photographs were taken, using Mo$K\alpha$ radiation, at $\mu = 30°$ of

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[1] K. Balenovic and N. Stimac, *Crotica Chem. Acta* **29**, 153 (1957).

[2] R. K. Hill, *J. Amer. Chem. Soc.* **80**, 1611 (1958).

[3] L. Marion and W. F. Cockburn, *J. Amer. Chem. Soc.* **71**, 3402 (1949).

the $0kl$, $1kl$, $2kl$, $h0l$, $h1l$, hhl, $2kkl$ and $3kkl$ levels, at $\mu = 28^\circ$ of the $3kl$ and $h2l$ levels and at $\mu = 25^\circ$ of the $4kl$, $5kl$ and $h3l$ levels. A total of 920 independent diffraction maxima were estimated visually with the aid of two intensity scales, one for the Weissenberg photographs and another for the precession photographs, prepared from timed exposures of a "typical" reflection from the same crystal. Absorption and extinction errors were neglected. The usual Lorentz-polarization corrections were made and the reflections were correlated to a single scale with the use of reflections common to the several films. The absolute scale was later established by the use of statistical methods and refined by correlation with trial structures.

Structure determination

The three-dimensional Patterson function was computed with sharpened coefficients $[F_o^2/(\hat{f})^2] \exp [2(B - B')(\sin^2\theta/\lambda^2)]$, where $B - B'$ was chosen as $2A^2$ and $\hat{f} = \Sigma f_i/\Sigma Z_i$ in the usual notation. Due to the fact that the bromide ions occur in pairs nearly at $y = 0$ and $y = \frac{1}{2}$, the Patterson function possessed planes of symmetry at $y = 0$ and $y = \frac{1}{2}$. Therefore, there was a twofold ambiguity in the interpretation of the Patterson function.

Careful analysis of the shapes and the heights of the single and the pseudo double Br $\cdots$ Br peaks indicated that the Br's were displaced from $y = 0$ by $\pm 0{\cdot}28$ A and $y = \frac{1}{2}$ by $\mp 0{\cdot}28$ A. The choice of signs is arbitrary in the sense that the $- +$ combination and $+ -$ combination correspond to different choices of origin in the space group when only Br are present. Another unusual feature of the Br $\cdots$ Br peaks was the elongation of the peaks along y, interpreted as pronounced anisotropic thermal motion of the Br ions, later verified as anisotropic motion of all atoms. Hence, the first three-dimensional electron density map was computed with the phases determined by the positions of Br ions only. The displacement of Br positions from $y = 0$ and $y = \frac{1}{2}$ was exaggerated a little to 0·3 A, in the hope that some improvement might be obtained in the separation of the true structure from its mirror image. All of the light atoms except hydrogen showed up in this map, along with some false peaks. The trial structure was selected on the basis of the known empirical formula of the compound, and the reasonableness of interatomic distances and the bond angles.

The first cycle of least-squares refinement with use of isotropic temperature factors yielded the very reassuring value of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ of 0·26, thus indicating the correct molecular geometry and Br positions. At this stage the O and C atoms had been introduced with their appropriate scattering factors. The identification of which peak of the six-membered ring was the N atom was left open at this stage by the use of the C scattering factors for all atoms in the six-membered ring. During the second cycle of least-squares refinement, the value of R fell only to 0·24, thus suggesting that anisotropic motions may be present. Four cycles of three-dimensional least-squares refinement were then made with anisotropic temperature factors of form $\exp -(\beta_1 h^2 + \beta_2 k^2 + \beta_3 l^2 + \beta_4 hk + \beta_5 kl + \beta_6 hl)$ for Br only, during which R fell to 0·18.

In the present study, we found a new use of the least-squares refinement. If one uses the C scattering factors for both N and C atoms in the least-squares refinement, the temperature factor of N decreases while that of C behaves normally. Thus, the temperature factor tends to adjust the total scattering factor of each atom. In this study, the temperature factor of C, which replaced N, had decreased from 3·0 A^2 to 2·8 A^2, while the temperature factors of other C atoms had increased to an average value of 4·5 A^2, thus indicating that use of a common scattering factor allows assignment of the correct identities of C, N, O atoms in a molecule by careful analysis of the behavior of temperature factors in the least-squares refinement.

At this stage, a three-dimensional difference electron density map was computed, in which the calculated map had a C atom in place of N. This map showed clearly the position of N, where the excess electron density was 1·3 eA^{-3}, and also showed strong anisotropic thermal motion of Br, as indicated by regions up to 3·1 eA^{-3} around Br. In addition, pronounced anisotropic thermal motion of the remainder of the molecule in the y direction was clearly indicated by peaks up to 0·8 eA^{-3} around nearly all atoms of the molecule. The remainder of the map showed no variation greater than 0·3 eA^{-3}. Thus, at this stage, expected peaks due to H atoms were overshadowed by the peaks due to anisotropic thermal motion of the molecule.

For subsequent cycles of least-squares refinement, the N scattering factor was introduced for N, all of the hydrogen atoms except those of the methyl group were placed at the positions calculated from the skeleton of the molecule, and all of the atoms except hydrogen were given anisotropic thermal parameters. The values of $\Sigma w(|F_o|^2 - |F_c|^2)^2$ for the next three cycles were 4188, 2749 and

2152, which indicated that further refinement of structure is still possible. Analysis of the shifts and the standard deviations of parameters indicated, however, that the further refinement would improve the thermal parameters but it would not improve the co-ordinates appreciably. Since the main purpose of the present study is to obtain the molecular geometry of this compound, the refinement of the structure was terminated at this point.

Final values of $R = 0{\cdot}109$ and $r = \Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w|F_o|^4 = 0{\cdot}056$ were obtained. The final three-dimensional electron density map was computed, composite sections of which are shown in Fig. 1; the background is below 0·6 eA^{-3}. The agreement for different classes of reflection is shown in Table 1. A list of co-ordinates, anisotropic thermal parameters and corresponding isotropic equivalents for atoms in one molecule is given in Table 2. The observed amplitudes of scattering are listed in Table 3. The shape of the molecule, its packing and intermolecular distances in the crystal are shown in Fig. 2.

DISCUSSION

The standard deviations in co-ordinates, calculated from the residuals in the final least-squares refinement,[4] were essentially isotropic. The standard deviations in bond lengths estimated from the above result were 0·028, 0·023, 0·025, 0·012 A in the C · · · C, C · · · N, C · · · O, N · · · Br bond lengths, respectively. As an independent estimate, the mean distance of 1·518 A for the seven C · · · C bonds in the molecule gave a standard deviation of 0·028 A. Standard deviations in bond angles are about 3°. The final bond lengths and bond angles are given in Figs. 3 and 4, respectively.

The OH and propyl groups are trans to each other and in the equatorial position relative to the saturated six-membered ring (Fig. 2). The propyl groups are stretched out in the general directions of equatorial bonds (Figs. 1 and 2). The shortest N · · · Br contact, 3·27 A (Fig. 2), is shorter than the $1{\cdot}95(Br^-) + 1{\cdot}2(H) + 1{\cdot}0(H - N) = 4{\cdot}15$ A non-interaction distance, and even shorter than the ordinary sum of Van der Waals radii, $1{\cdot}95(Br^-) + 1{\cdot}5(N^+) = 3{\cdot}45$ A, of N and Br. Thus there is very likely a fairly strong N^+—H · · · Br^- bond. Even the OH · · · Br^- seems to be hydrogen-bonded (Fig. 2). The sum of radii for O^- and Br^- is $1{\cdot}35 + 1{\cdot}95 = 3{\cdot}50$ A, but if H intervenes, then the non-interaction distance should be $0{\cdot}95(OH) + 1{\cdot}2(H) + 1{\cdot}95(Br^-) = 4{\cdot}10$ A. Therefore, the observed distance of 3·31 A suggests an OH · · · Br^- hydrogen bond.

The method described by Rossmann and Lipscomb[5] to calculate directions and magnitudes of principal axes of the ellipsoid of vibration from thermal parameters was applied to those of Br ion. The three solutions of the cubic equation gave one real and two conjugate imaginary roots, when $\beta_1 \cdots \beta_6$ listed for Br in Table 2 were employed. But when the full shifts, which were less than 5 per cent for $\beta_1 \cdots \beta_3$ and as high as 30 per cent for $\beta_4 \cdots \beta_6$, of corresponding parameters indicated by the final least-squares refinement were applied to $\beta_1 \cdots \beta_6$, the three solutions became real. This result suggests that the anisotropy and interactions of the thermal parameters are as yet incompletely refined. Since the difference electron density map showed strong anisotropic thermal motion in the y direction, we decided to ignore the cross terms β_4, β_5 and β_6. Magnitudes of vibration in the x, y and z directions were then recalculated for Br. The corresponding B's were then 3·35, 5·88, 2·65 A^2 in x, y and z directions, respectively, which seem very reasonable and suggest that this abbreviated interpretative procedure is satisfactory even when refinement of the thermal parameters is not complete.

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[4] E. W. Hughes and W. N. Lipscomb, *J. Amer. Chem. Soc.* **68**, 1970 (1946).

[5] M. G. Rossmann and W. N. Lipscomb, *Tetrahedron* **4**, 263 (1958).

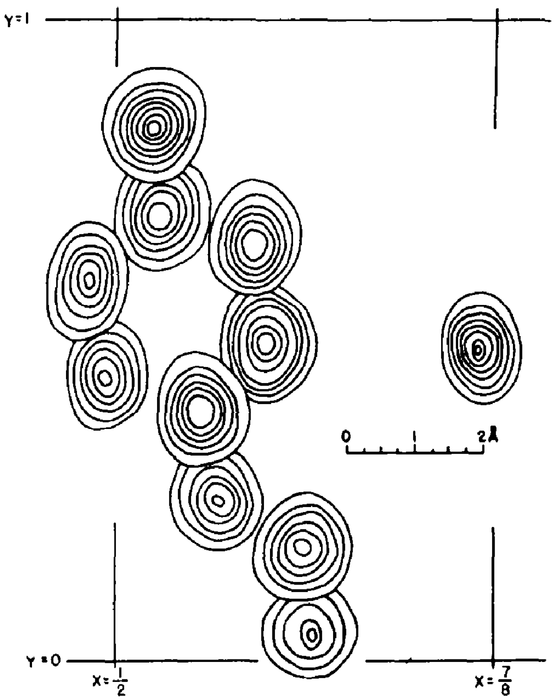

FIG. 1. Final electron density map. Contours are at intervals of 1 e/A^3, except around bromine The lowest contour is at a height of 1 e/A^3. Contours around bromine are at intervals of 4 e/A^3 and the lowest contour is 4 e/A^3.

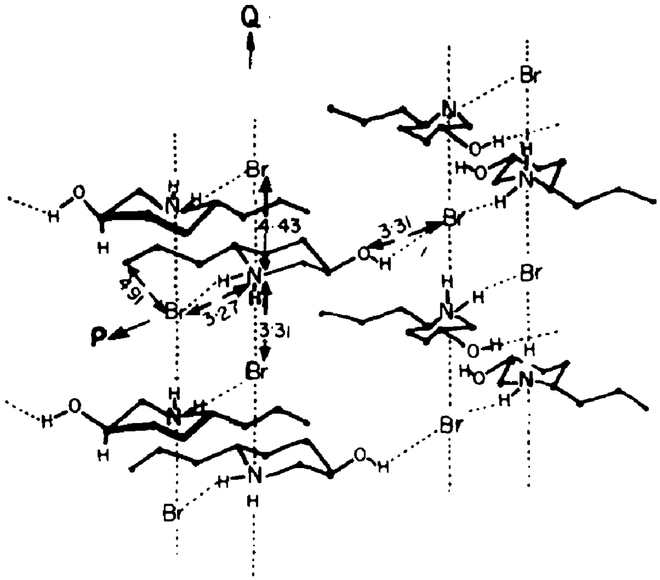

FIG. 2. Diagram showing the shape of the molecule, its packing and intermolecular distances.

TABLE 1. *R* FOR DIFFERENT CLASSES OF REFLECTIONS

Class	*R*	*n*	*a*	*b*
all	0·109	920	34	8
0*kl*	0·089	54	3	1
*h*0*l*	0·140	105	1	3
*hk*0	0·134	149	5	3
h odd	0·111	445	16	5
k odd	0·105	437	18	1
l odd	0·106	406	22	1
$h + k$ odd	0·107	472	12	6
$k + l$ odd	0·108	453	18	2
$h + l$ odd	0·110	455	20	6
$h + k + l$ odd	0·113	448	18	7

The number of reflections in each class is *n*. The number of planes showing $|F_o| > 2|F_c|$ is in column *a*, and those of $|F_o| < (\frac{1}{2})|F_c|$ are in column *b*.

TABLE 2. CO-ORDINATES AND THERMAL PARAMETERS OF ATOMS IN ONE MOLECULE

Atom	x/a	y/b	z/c	β_1	β_2	β_3	β_4	β_5	β_6	B in A^2
C_1	0·584	0·389	0·518	0·0028	0·0164	0·0211	−0·0002	0·0009	0·0018	5·10
C_2	0·491	0·440	0·495	0·0041	0·0175	0·0280	0·0014	0·0010	0·0097	6·33
C_3	0·475	0·596	0·556	0·0037	0·0191	0·0210	0·0035	0·0028	0·0074	5·41
C_4	0·544	0·697	0·500	0·0041	0·0176	0·0173	0·0035	0·0022	−0·0036	4·69
C_5	0·637	0·643	0·543	0·0045	0·0159	0·0147	0·0037	−0·0044	0·0011	4·14
C_6	0·603	0·242	0·435	0·0050	0·0140	0·0241	0·0027	−0·0027	0·0011	5·39
C_7	0·686	0·170	0·488	0·0051	0·0191	0·0266	0·0032	−0·0019	−0·0077	6·33
C_8	0·710	0·038	0·372	0·0089	0·0209	0·0315	0·0078	−0·0021	−0·0044	7·43
N	0·651	0·494	0·463	0·0033	0·0144	0·0068	−0·0020	0·0039	0·0004	2·71
O	0·540	0·832	0·588	0·0090	0·0251	0·0442	0·0039	−0·0106	−0·0062	9·83
Br	0·864	0·484	0·536	0·0037	0·0170	0·0111	−0·0011	−0·0032	−0·0005	3·69

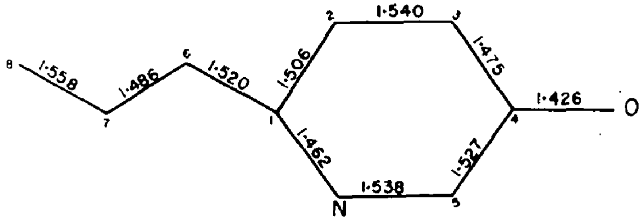

FIG. 3. Diagram showing bond length and atomic names.

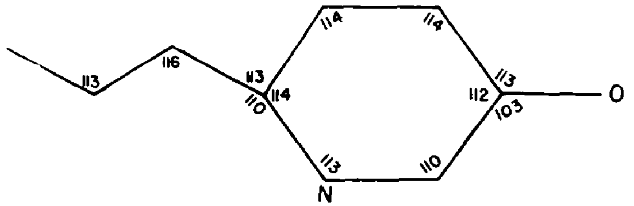

FIG. 4. Diagram showing bond angles.

The temperature factor of the oxygen atom behaved abnormally in the final anisotropic least-squares refinement (Table 2). However, since the isotropic temperature factor for this oxygen atom behaved normally in the earlier least-squares refinements, we feel that this later misbehavior is associated with compensation for unrefined anisotropic thermal parameters of the Br atom which is nearby. Since each cycle of three-dimensional least-squares refinement required one hour of computing time, we felt unwilling to carry out the necessary several refinements to test this surmise.

In Fig. 2, the directions P and Q are parallel to hydrogen bonding directions, which are also approximately parallel to x and z. Fairly "normal" amplitudes of vibration exist in the P, Q directions, while the amplitude of motion along y, perpendicular to PQ plane, is larger than these normal amplitudes. Even though the thermal parameters were not completely refined, the isotropic equivalents[6] of the thermal parameters for each atom were calculated. The resultant B's are listed in Table 2.

Had we been sure which molecular optical isomer was present in our particular small crystal, and had we been careful to photograph only one quandrant of reciprocal space, we no doubt could have established the absolute configuration from the type of data[7,8] which were obtained. However, modifications of our computing programs to include the effects of complex atomic scattering factors are still in progress, and hence the establishment of the absolute configuration from the X-ray evidence belongs to a later stage of this study.

Acknowledgments—We wish to thank Professor E. Leete who suggested this problem to us and who also supplied the sample of ψ-conhydrine hydrobromide. It is a pleasure to acknowledge the support of this research by the Air Force Office of Scientific Research as well as a fellowship to H. S. Yanai by the Visking Co. For assistance in the use of the Remington Rand 1103 computer, we wish to thank Dr. M. G. Rossmann, Dr. R. A. Jacobson and Mr. F. S. Mathews. We also wish to thank the University of Minnesota for contribution of a portion of the 18 hr of computing time used in this study.

[6] M. G. Rossmann, R. A. Jacobson, F. L. Hirshfeld and W. N. Lipscomb, *Acta Cryst.* To be published.

[7] A. F. Peerdeman, *Acta Cryst.* **9**, 824 (1956).

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