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The Crystal Structure of Dihydro-β-Erythroidine Hydrobromide

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The crystal is orthorhombic, $P2_12_12_1$, with $a=10{\cdot}22$, $b=17{\cdot}97$, $c=8{\cdot}72$ Å, $Z=4$. The structure was determined by the heavy-atom method, and refined with the aid of three-dimensional differential syntheses. The relative configuration of methoxyl-bearing and nitrogen-bearing carbon atoms is the same as that found in erythraline. The absolute configuration was confirmed by measuring the effect on a set of related reflections of the dispersion of copper radiation by the bromine atom.

Introduction

The extraction (from the seeds of the genus *Erythrina*) and curare-like physiological action of the erythrina alkaloids have been described by Folkers & Major (1937). Boekelheide & Prelog (1955) and their associates have demonstrated chemical interrelationships within the group and more recently the crystal structure of erythraline hydrobromide has been determined by Nowacki & Bonsma (1958). However, attempts to relate erythraline and dihydro-β-erythroidine have not been successful (Boekelheide, 1961), and it is for this reason that the present structure determination was undertaken. A brief statement of the results of the analysis has already appeared (Hanson, 1963). The structural formula of dihydro-β-erythroidine is given in Fig. 1.

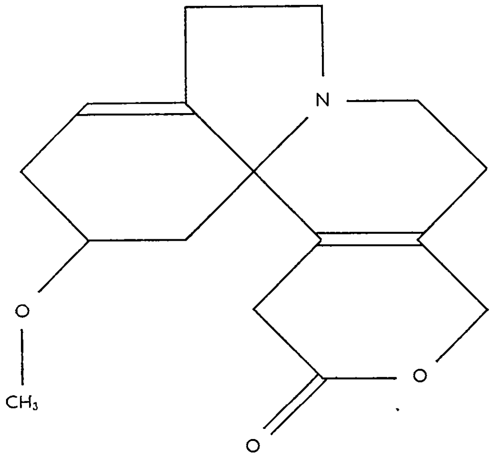

Fig. 1. Structural formula.

Experimental

Crystal data at −110 °C:
Orthorhombic

$a=10{\cdot}22\pm0{\cdot}02$, $b=17{\cdot}97\pm0{\cdot}04$, $c=8{\cdot}72\pm0{\cdot}02$ Å.

(From precession photographs, corrected for film shrinkage).
$V=1601{\cdot}5$ Å³.
Formula $C_{16}H_{21}NO_3.HBr$. Formula weight 356·26.
D_x (calculated density) = 1·48 g.cm⁻³.
D_m (measured density) = 1·46 g.cm⁻³ (room temperature).
$Z = 4$.
μ = 38 cm⁻¹ (Cu $K\alpha$).
Space group $P2_12_12_1$ (D_2^4) (from examination of zero- and upper-level precession and Weissenberg photographs.)
Molecular symmetry: none.
The material is colourless, crystallizing in elongated prisms {120}.

Preliminary X-ray photographs showed the high background scatter and rapid decrease of intensity with Bragg angle characteristic of strong thermal motion. To reduce this motion, and to prevent possible damage to the specimen, all photographs used in the analysis were taken with the specimen at a temperature of −110 °C.

The low-temperature technique used for precession photographs was essentially that described by Burbank & Bensey (1953) in which the crystal is maintained in a stream of cold nitrogen gas which is itself surrounded by an envelope of warm, scrupulously dry air. For Weissenberg photographs the warm-air envelope was not used; instead, the layer-line screen (the double-slit screen described by Hanson, 1958) was heated, and partially sealed. In order to prevent dislodgement by the nitrogen flow, the specimen was enclosed in a thin-walled Lindemann-glass tube. The working temperature was measured by substituting a thermocouple for the specimen.

The crystal used for data collection was a prism with cross section 0·3 × 0·3 mm, and length 0·5 mm. It was mounted with the long axis parallel to the rotation axis. Intensity data were recorded on z-axis Weissenberg photographs, using copper radiation, for values of l from zero to eight. The equi-inclination setting was used for upper levels, and correlation of the data was accomplished by means of the double-slit technique. The Nonius integrating Weissenberg goniometer was used; errors due to distortion of spots on upper levels were minimized by the use of some integration in the horizontal direction. A few reflections on and near the z^* axis were not accessible, but some of these were obtained from precession photographs.

Intensities were measured visually by comparison with a standard wedge. Absorption corrections were deemed to be unnecessary, and were not made. Of the 1831 reflections accessible on the photographs, 1580 were observed. The range of observed amplitudes is about 1 to 47.

On completion of the analysis it was desired to confirm the accepted absolute configuration of the molecule. The only set of reflections showing, on the photographs, an obvious violation of Friedel's law was $\{111\}$. Some of the members of this set, with other reflections for correlation purposes, were measured on the General Electric XRD5 spectrogoniometer and goniostat, with copper radiation and a scintillation counter. The 'moving-crystal moving-counter' technique of Furnas (1957) was used. The original specimen, and one other, were examined, and the cooling technique was that earlier described for precession photographs. The relative intensities of the few reflections measured are believed to be in error by no more than 5%.

Structure determination

The bromine atom was readily located with the aid of Patterson projections. Unfortunately the z coordinate of this atom was apparently $\frac{1}{4}$, and consequently a three-dimensional Fourier synthesis, for which the phases were assumed to be those of the bromine contribution, did not reveal the structure unambigously. There was a mirror plane at $z=\frac{1}{4}$, and each peak might represent an atom either in one position or in the mirror-related one. Thus stereochemical assumptions were necessary for interpretation. A trial structure was deduced, but although initial indications were promising, the agreement residual could not be reduced to less than about 0·25, and the structure had to be abandoned.

That a fair measure of agreement should have been obtained for a wrong structure is hardly surprising. Each true peak in the initial Fourier synthesis represents an atom, and even if a wrong choice between z and $\frac{1}{2}-z$ is made for any peak, either the A or the B part of each structure factor is unaffected. (The invariant part of each structure factor is of course the only part to which the bromine atom can contribute.) This consideration suggested a way of improving the original synthesis which, because of the omission of many terms for which the bromine contribution was small, included many ripples and other artifacts. The synthesis was repeated, assuming the phases to be those of the invariant parts of the calculated structure factors. The mirror plane at $z=\frac{1}{4}$ remained, of course, but the marked improvement in the synthesis made interpretation easier, and a second trial structure (which ultimately proved to be correct) was deduced. It appears that an incorrect choice between z and $\frac{1}{2}-z$ was made for five atoms of the first trial structure. It may well be true that the correct structure could have been deduced from the first synthesis, or an incorrect one from the second. Nevertheless, the procedure described was found to be helpful, and is recommended when the position of the heavy atom causes false symmetry.

The position of the bromine atom was refined somewhat with the aid of a difference-Fourier projection along **a**. Further refinement was effected by differential syntheses. The coordinate shifts applied to each atom were the differences between the shifts indicated by F_o and F_c syntheses, multiplied by 1·66 in accordance with the 'n-shift rule' of Shoemaker, Donohue, Schomaker & Corey (1950). Refinement was continued until the shifts were seen to be of the same order of magnitude as the expected standard deviations; the greatest shifts in the last cycle were 0·0026 Å for the bromine atom, and 0·022 Å for light atoms.

The scattering-factor curves used in all structure-factor calculations were those of Freeman (1959) for light atoms, and that of Thomas & Umeda (1957) for the bromine atom. The temperature factors applied to individual atoms were modified somewhat by comparison of peak heights in the F_o and F_c syntheses. Appreciable anisotropy of thermal motion was observed for many atoms, but as this was not considered to be prejudicial to the analysis, or interesting in

Table 1. *Atomic positions*

$(x, y, z;\ \frac{1}{2}-x, \bar{y}, \frac{1}{2}+z;\ \frac{1}{2}+x, \frac{1}{2}-y, \bar{z};\ \bar{x}, \frac{1}{2}+y, \frac{1}{2}-x)$

Atom	x	y	z	B (Å^2)	ϱ_o (e.Å^{-3})	ϱ_c (e.Å^{-3})
Br(1)	0·2677	0·1957	0·7366	2·70	84·3	86·2
O(2)	0·8132	0·0425	0·0530	2·17	14·5	14·7
O(3)	0·9591	0·0253	0·8720	2·38	14·0	14·6
O(4)	0·2422	0·3306	0·1792	2·14	14·8	15·0
N(5)	0·0834	0·1236	0·4890	1·91	12·4	12·2
C(6)	0·1124	0·0420	0·4940	2·04	10·1	10·2
C(7)	0·2182	0·0282	0·3801	2·69	9·0	9·6
C(8)	0·2297	0·1024	0·2971	1·79	10·8	10·5
C(9)	0·3347	0·1313	0·2234	2·17	10·0	10·2
C(10)	0·3412	0·2086	0·1553	2·22	9·8	10·0
C(11)	0·2088	0·2520	0·1763	2·21	10·3	10·5
C(12)	0·1337	0·2338	0·3225	1·78	10·8	10·5
C(13)	0·1052	0·1470	0·3283	1·71	10·9	10·6
C(14)	0·9919	0·1236	0·2295	1·78	10·9	10·7
C(15)	0·8757	0·1087	0·2833	1·77	11·5	11·1
C(16)	0·8407	0·1110	0·4578	2·12	10·3	10·4
C(17)	0·9498	0·1467	0·5489	2·13	9·6	9·8
C(18)	0·0103	0·1207	0·0576	2·02	10·5	10·3
C(19)	0·9261	0·0589	0·9855	2·32	10·0	10·4
C(20)	0·7648	0·0880	0·1745	2·52	9·4	10·0
C(21)	0·1292	0·3811	0·1877	2·42	9·5	10·0

ϱ_o and ϱ_c are taken from the differential syntheses corresponding to the penultimate structure-factor calculation.

itself, it was disregarded. As a final check on the structure, difference-Fourier projections along the three axes were computed. None of these showed any detail palpably inconsistent with the proposed model, given plausible hydrogen positions, and the anisotropic thermal motion referred to above. The final atomic positions, isotropic temperature factors, and observed and calculated peak heights are given in Table 1.

Assessment of results

Stereochemical plausibility, agreement between observed and calculated peak heights, and the appearance of the difference projections all suggest that the proposed structure is correct. The final proof, however, is to be found in the reasonable agreement between observed and calculated structure amplitudes. A summary of the agreement is given in Table 2; the observed structure amplitudes range from 3 to 143, $F_c(000) = 736$, and the agreement residual $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0{\cdot}13$, for observed reflections only. (A complete list of F_o and F_c is available from the author, on request.)

Table 2. *Agreement summary*

Category	Number of reflections Observed	Unobserved
1. $(\lvert\Delta F\rvert \le F_T$ or $\lvert\Delta F\rvert \le 0{\cdot}2F_o)$	1482	170
2. $(F_T < \lvert\Delta F\rvert \le 2F_T$ or $0{\cdot}2F_o < \lvert\Delta F\rvert \le 0{\cdot}4F_o)$	95	73
3. $(2F_T < \lvert\Delta F\rvert \le 3F_T$ or $0{\cdot}4F_o < \lvert\Delta F\rvert \le 0{\cdot}6F_o)$	3	8

$\Delta F = |F_o| - |F_c|$.
F_T = estimated minimum observable structure amplitude for reflection concerned.

The standard deviations of atomic coordinates have been estimated by Cruickshank's method (Lipson & Cochran, 1953). The mean values are: bromine, 0·0018; oxygen, 0·011; nitrogen, 0·014; carbon, 0·015 Å. Because of finite summation effects, and the anisotropy of thermal motion, individual estimates for the standard deviations of the light-atom coordinates differ from the quoted values by as much as 38%.

The absolute configuration

Chemical considerations have already indicated the absolute configuration of the methoxyl-bearing carbon (Boekelheide, 1961). Nevertheless it was felt that independent confirmation was desirable. Unfortunately only the {111} set of reflections was found to demonstrate a significant violation of Friedel's law. Moreover, a survey of non-zonal reflections, using the criteria of low angle, small intensity, and large bromine contribution, shows that there can be no other suitable sets, and the confirmation is therefore based on only one.

Table 3. *Effect of dispersion on* {111}

	Observed	Calculated
F_{111}	22·6	25·6
$F_{11\bar{1}}$	17·5	19·9
$I_{111}/I_{11\bar{1}}$	1·66	1·65

The structure factors for the set were recalculated, using, for the bromine atom, $f = f_0 + \Delta f' + i\Delta f''$, where f_0 is the conventional scattering factor, $\Delta f' = -0{\cdot}9e$, and $\Delta f'' = 1{\cdot}5e$ (Dauben & Templeton, 1955). The contributions of 19 of the 22 hydrogen atoms (assumed to be in their obvious positions) were included; the 3 hydrogen atoms of the methyl group were not considered, because the orientation of the group was not known. Observed and calculated structure amplitudes are compared in Table 3. The agreement seems satisfactory, and it is concluded that the coordinates in Table 1 correspond to a right-handed set of axes.

Description of the structure

A sketch of the molecule, viewed along a convenient direction, is shown in Fig. 2. C(11)–O(4) is *cis* to C(13)–N(5), which is the configuration found in erythraline. This is the information which was sought. Bond lengths and angles are given in Fig. 3; C(8)–C(9) is obviously a double bond, as implied in the structural formula of Fig. 1. This position for the double bond was considered probable, but not certain (Boekelheide,

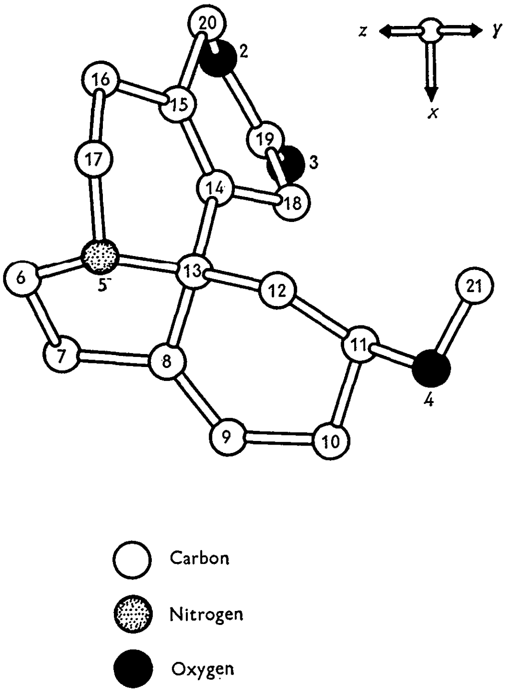

Fig. 2. A sketch of the molecule.

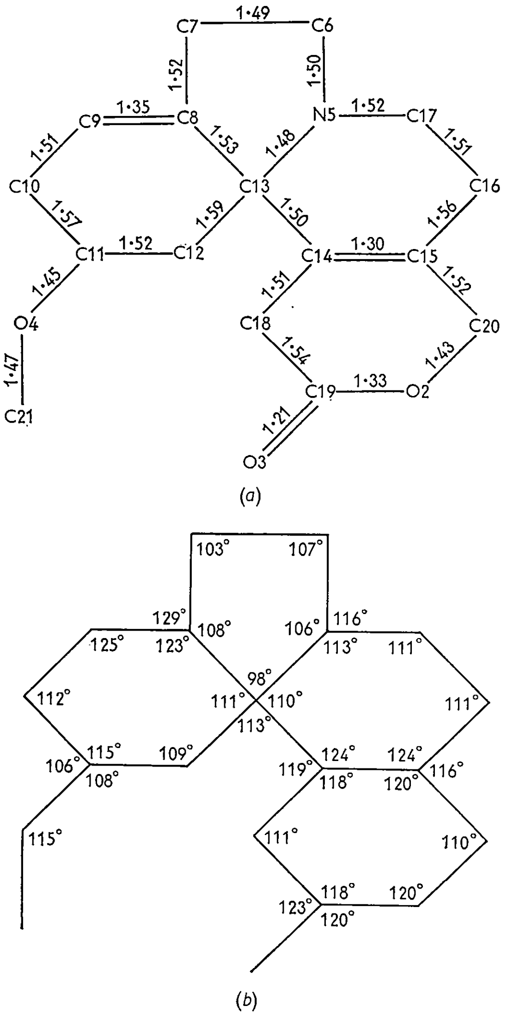

Fig. 3. (a) Bond lengths; the standard deviation is 0·02 Å. (b) Bond angles; the standard deviation is 1·0°. Two angles not shown are N(5)–C(13)–C(12), 110°; C(8)–C(13)–C(14), 113°.

1961). The bond lengths do not differ significantly from standard values; it may be noted that the single bond C(19)–O(2) is typically shortened by the action of the adjacent double bond C(19)–O(3). The absolute configuration of the molecule (as shown in Fig. 2) is consistent with optical-rotation studies of degradation products (Wenzinger & Boekelheide, 1963).

The shortest bromine–nitrogen distance is 3·14 Å, and this vector makes angles of 105, 116, and 101° with the bonds C(6)–N(5), C(13)–N(5) and C(17)–N(5). Thus the relative positions of the bromine and nitrogen atoms are such as one would expect for a Br · · · HN bond. There are no other bromine to light-atom distances less than 3·69 Å. Intermolecular distances involving oxygen are rather short. Some values are: O(2)–O(4′), 3·14; O(4)–C(19′), 3·09; O(2)–C(21′), 3·14; O(4)–C(17′), 3·21 Å. However, the shortest intermolecular distance not involving oxygen is C(20)–C(21′): 3·49 Å.

The crystalline material for the analysis was supplied by Prof. V. Boekelheide. All computations for the project were carried out by Dr F. R. Ahmed of this laboratory, using the IBM 650 Computer at No. 1 Army Pay Ledger Unit, and the IBM 1620 Computer of the National Research Council. Their assistance, and the continued encouragement of Dr W. H. Barnes, are gratefully acknowledged.

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