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The Crystal and Molecular Structure of Codeine Hydrobromide Dihydrate

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Codeine hydrobromide dihydrate is orthorhombic with space group $P2_12_12_1$, and cell edges, $a = 13{\cdot}10$, $b = 20{\cdot}83$, $c = 6{\cdot}83$ Å. There are four molecules in the unit cell. The structure has been determined from electron-density projections on (100), (010), and (001). Phases of reflexions in all three zones were obtained by direct comparison with corresponding reflexions from the isomorphous codeine hydriodide dihydrate. Refinement was carried out using F_o and F_o-F_c syntheses. Bond lengths and angles have been measured with standard deviations of 0·06 Å and 6°, respectively. The stereochemical configuration of the codeine molecule is found to agree with that deduced solely from chemical data.

Introduction

In 1931 Small stated that after 125 years of chemical research, 'the constitutional problem of morphine must still be regarded as not completely solved' (Small, 1932), although he concluded that the structural formula of Gulland & Robinson (1925) accounted best for all the facts of morphine chemistry available at that time. This formula has recently been confirmed by the total synthesis of codeine, the methyl ether of morphine, by Gates & Tschudi (1952), and of morphine by Ginsburg (Bentley, 1954).

Following various attempts by others to establish an acceptable stereochemical configuration for morphine and related compounds, including codeine, Stork (1952), by an analysis of the very large number of known reactions of the morphine alkaloids, deduced a complete three-dimensional model which is shown (for codeine) in conventional form in Fig. 1. On the basis of a systematic series of degradation studies, Rapoport and coworkers (Rapoport & Lavigne, 1953), although questioning the validity of at least one of Stork's arguments, are in agreement with his conclusions, while Bose (1954) and Ginsburg (1954) have shown that the proposed spatial arrangement is in harmony with the results of applying the methods of conformational analysis (Becket, Pitzer & Spitzer, 1947; Barton, 1953) to the problem. The most important features of the configuration represented in Fig. 1 are (1) the mutual *cis* relationship of the H atoms at C_5, C_6, and C_{14}, and the C_{13}–C_9 ethanamine chain, and (2) the *trans* position of these relative to the O atom of the five-membered ring.

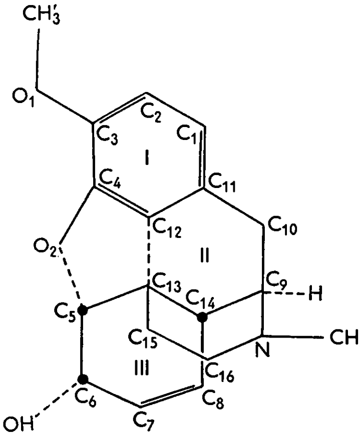

Fig. 1. The stereochemical configuration of codeine.

Interest in the opium alkaloids was stimulated initially in this laboratory by the collection of powder data for the identification of a number of narcotics (Barnes & Sheppard, 1954). In several cases this led to the determination of unit-cell constants and space groups (Barnes & Forsyth, 1954; Barnes & Lindsey, 1955). Morphine, codeine, and thebaine were selected as the first to be considered for structural investigation as a means of attacking the stereochemical problem of the morphine alkaloids by a direct method which would be independent of interpretations of the course of chemical reactions. Because the molecules of each of these three closely-related alkaloids are asymmetric, and each contains more than twenty atoms, it was considered advisable to work with the hydrohalides, rather than with the free bases, in order to simplify the analysis. Of the salts examined (Barnes & Lindsey, 1955), the isomorphous codeine hydrobromide dihydrate and codeine hydriodide dihydrate gave the best crystals on recrystallization from water, and, therefore, were adopted for detailed study. This proved to be a fortunate choice because, at an early stage in the present study, it was learned that the structure of morphine hydriodide dihydrate was under investigation elsewhere (Hodgkin, 1954).

The structure analysis of codeine hydrobromide dihydrate unambiguously confirms the stereochemical configuration depicted in Fig. 1, and it should be

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mentioned that no attempt to correlate the electron-density maps with molecular models was made until refinement had proceeded to a stage at which all atoms had been located on the most important (001) projection.

Crystal data

The crystals of both the hydrobromide and the hydriodide were colourless needles, elongated parallel to c, and showing faces of the forms $\{001\}$, $\{110\}$, $\{1\bar{1}0\}$. They were almost square in cross-section and were cut to approximately cubic shape. The unit-cell dimensions and space groups were obtained from precession photographs (Cu$K\alpha$, $\lambda = 1{\cdot}5418$ Å); the densities (at ~22° C.) were measured by flotation in benzene–carbon tetrachloride solutions. Results are summarized in Table 1. (The orientation of the unit cells has been changed from that adopted originally (Lindsey, 1954) in order to conform with the convention $c < a < b$.)

Table 1. *Single-crystal data*

	$C_{18}H_{21}O_3N.HBr.2H_2O$	$C_{18}H_{21}O_3N.HI.2H_2O$
a (Å)	$13{\cdot}10 \pm 0{\cdot}04$	$13{\cdot}44 \pm 0{\cdot}04$
b (Å)	$20{\cdot}86 \pm 0{\cdot}06$	$21{\cdot}38 \pm 0{\cdot}06$
c (Å)	$6{\cdot}82 \pm 0{\cdot}02$	$6{\cdot}83 \pm 0{\cdot}02$
S.G.	$P2_12_12_1$	$P2_12_12_1$
Z	4	4
ϱ_c (g.ml.$^{-1}$)	1·483	1·568
ϱ_o (g.ml.$^{-1}$)	1·489	1·565

Intensities were estimated visually from a-, b-, and c-axis zero-level Weissenberg films (Cu $K\alpha$ radiation). They were corrected for the Lorentz and polarization factors, and were placed on an absolute scale by Wilson's method (1942). When the structure had been determined this scale was verified for each principal zone by direct comparison of observed and calculated F's. No absorption corrections were applied.

Determination of the structure

The c-axis projection

Because crystals of codeine hydrobromide dihydrate and codeine hydriodide dihydrate are isomorphous, it was possible to determine the signs of the structure amplitudes directly, once the heavy atoms had been located. The x and y coordinates of Br and of I were found from Patterson projections on (001), and, since corresponding values were similar but not identical for the two atoms, the equations

$$F_{\rm I}(hk0) - F_{\rm Br}(hk0)$$
$$= 4f_{\rm I}\cos 2\pi hx_{\rm I}\cos 2\pi ky_{\rm I} - 4f_{\rm Br}\cos 2\pi hx_{\rm Br}\cos 2\pi ky_{\rm Br}\,,$$
$$\text{when}\quad (h+k) = 2n, \quad\text{and}$$
$$F_{\rm I}(hk0) - F_{\rm Br}(hk0)$$
$$= 4f_{\rm I}\sin 2\pi hx_{\rm I}\sin 2\pi ky_{\rm I} - 4f_{\rm Br}\sin 2\pi hx_{\rm Br}\sin 2\pi ky_{\rm Br}\,,$$
$$\text{when}\quad (h+k) = 2n+1\,,$$

were used in the sign determinations. Uncertainties arose in the signs of some terms when the contributions of the heavy atoms were small, and, consequently, these F's (about 20% of those observed) were not included in the first Fourier summations.

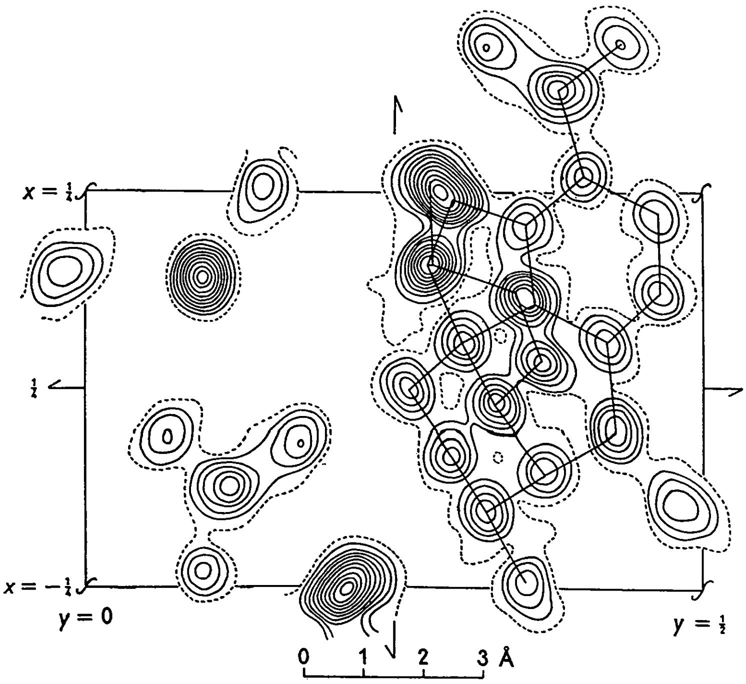

Fig. 2. Final electron-density projection on (001); contours at intervals of 2 e.Å^{-2} (8 e.Å^{-2} for the bromine atom), with that at 2 e.Å^{-2} broken.

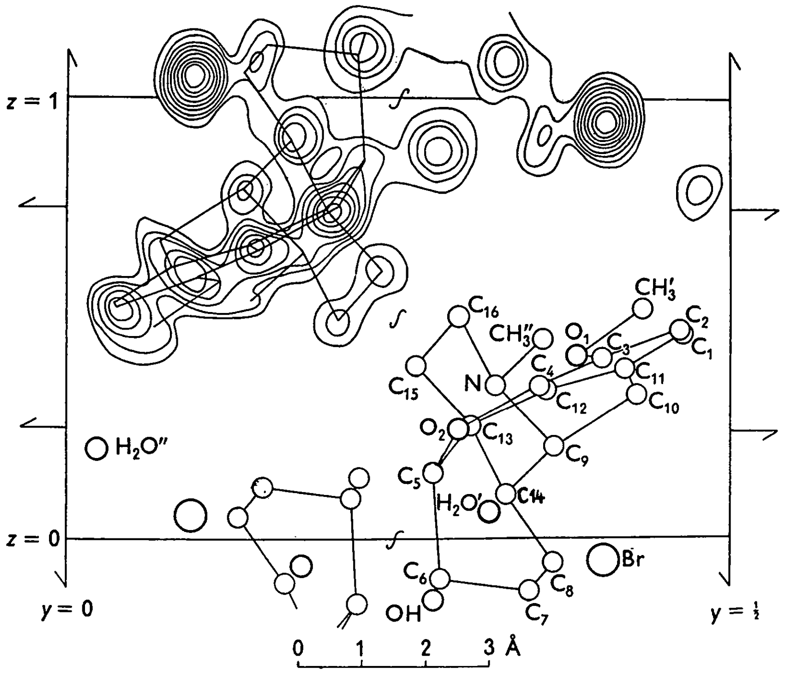

Fig. 3. Final electron-density projection on (100); contours at intervals of 4 e.Å^{-2} (10 e.Å^{-2} for the bromine atom), with the first at 6 e.Å^{-2}.

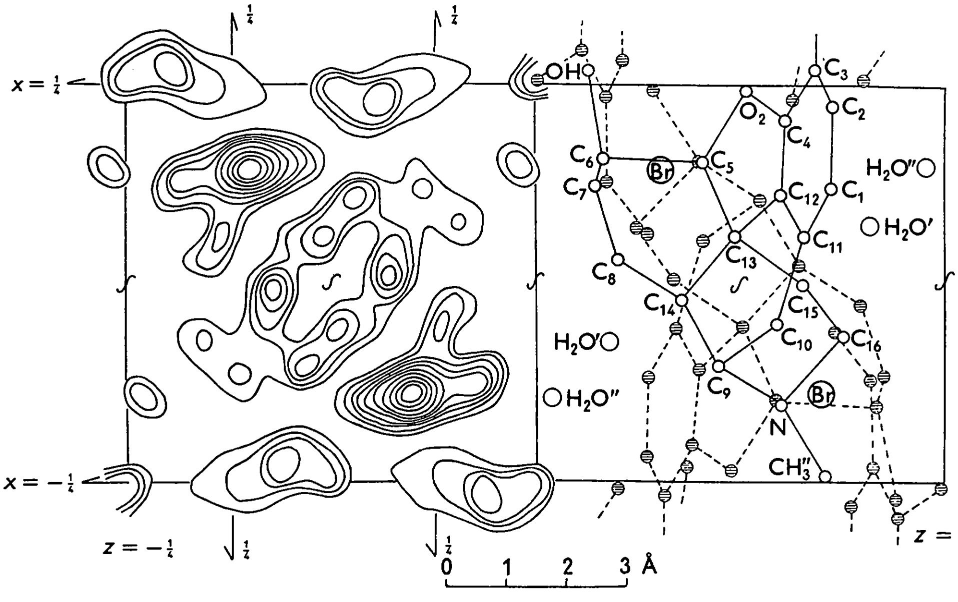

Fig. 4. Final electron-density projection on (010); contours initially at intervals of 4 e.Å^{-2}, 12 e.Å^{-2} above 24 e.Å^{-2}, with the first at 4 e.Å^{-2}.

The resulting electron-density maps of the two salts were sufficiently alike to enable the positions of about thirteen of the twenty-five atoms in the asymmetric unit to be deduced with some confidence. Structure factors were calculated with these atomic coordinates and refinement of the structure of the hydrobromide was carried out without recourse to any molecular model. The hydrobromide was selected rather than the hydriodide to avoid the more pronounced diffraction ripples associated with the latter. The degree of resolution of atomic peaks in the first Fourier map was very good, and the positions of all twenty-five atoms could be fixed with reasonable certainty after the fourth cycle of refinement. Attempts to fit various molecular models to this projection showed immediately that only one based on the stereochemical formula of Fig. 1 could be successful. At this stage, the discrepancy index (R) was 0·28. Refinement was continued by means of successive difference syntheses (Cochran, 1951) with a reduction in R to 0·19. The final electron-density map is shown in Fig. 2, where it is evident (as it was in the difference maps) that the bromine atom is subject to anisotropic thermal motion; no allowance for this factor, however, was made in the structure-amplitude calculations.

The a- and b-axis projections

The z coordinates of the heavy atoms were obtained from Patterson projections on (100), and the signs of the structure amplitudes were determined by the use of equations similar to those given for the $\{hk0\}$ zone. Only five atoms were clearly resolved on the (100) electron-density map. For this reason, and in spite of the length of the b axis, it was decided to compute the electron-density projection on (010) and to refine the two maps simultaneously. That on (010) showed three peaks clearly resolved, two of which (corresponding to C_1 and H_2O') were not resolved in the a-axis projection.

The final (100) and (010) Fourier maps are reproduced in Figs. 3 & 4; the values of R for these zones are 0·24 and 0·28, respectively. It was not considered worthwhile to refine these projections further because of the serious overlapping of peaks which precluded the attainment of high accuracy in bond lengths without the use of three-dimensional methods of analysis, and because the primary objective of the structure investigation, the solution of the stereochemical problem, had been achieved.

Results

The x and y coordinates deduced from the (001) difference syntheses, and the best z coordinates obtained from the (100) and (010) Fourier maps (Figs. 3 and 4) are given in Table 2. A list of observed and calculated structure factors is available on application to the authors.

Table 2. *Fractional atomic coordinates*

Atom	x	y	z
C_1	0·120	0·465	0·460
C_2	0·222	0·463	0·477
C_3	0·268	0·403	0·417
C_4	0·207	0·355	0·347
C_5	0·155	0·277	0·150
C_6	0·157	0·281	−0·083
C_7	0·120	0·348	−0·112
C_8	0·031	0·368	−0·050
C_9	−0·107	0·371	0·212
C_{10}	−0·053	0·429	0·333
C_{11}	0·058	0·422	0·392
C_{12}	0·107	0·364	0·347
C_{13}	0·055	0·304	0·263
C_{14}	−0·022	0·330	0·103
C_{15}	−0·003	0·261	0·392
C_{16}	−0·082	0·295	0·503
CH_3'	0·446	0·435	0·525
CH_3''	−0·245	0·356	0·455
N	−0·153	0·323	0·350
O_1	0·377	0·383	0·422
O_2	0·241	0·296	0·256
OH	0·265	0·280	−0·133
H_2O'	0·433	0·327	0·067
H_2O''	0·857	0·478	0·796
Br	0·1406	0·0953	0·0497

The structure of codeine hydrobromide dihydrate, projected on (001), is illustrated in Fig. 5, and the intramolecular bond lengths and angles are shown in Fig. 6.

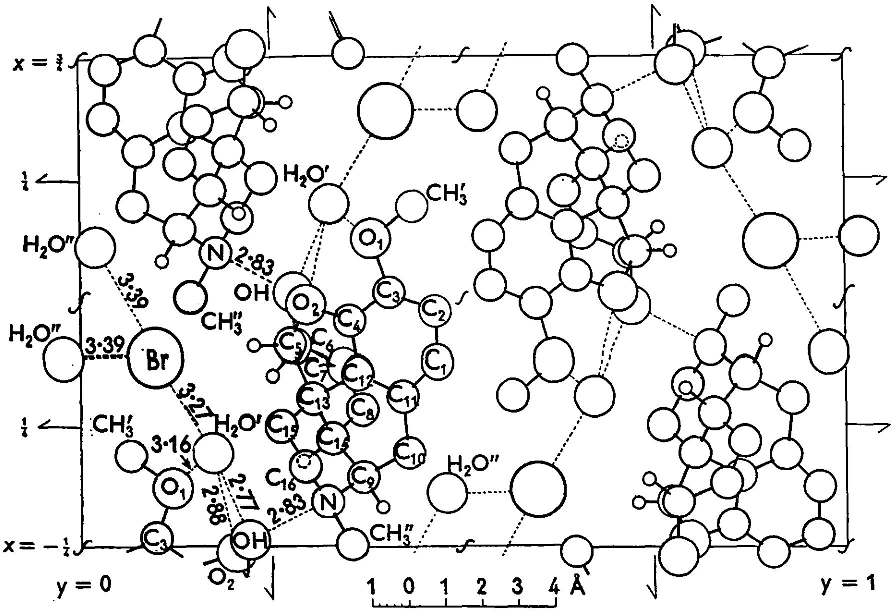

Fig. 5. Structure of codeine hydrobromide dihydrate projected on (001); probable hydrogen bonds, and short van der Waals contacts, indicated by broken lines.

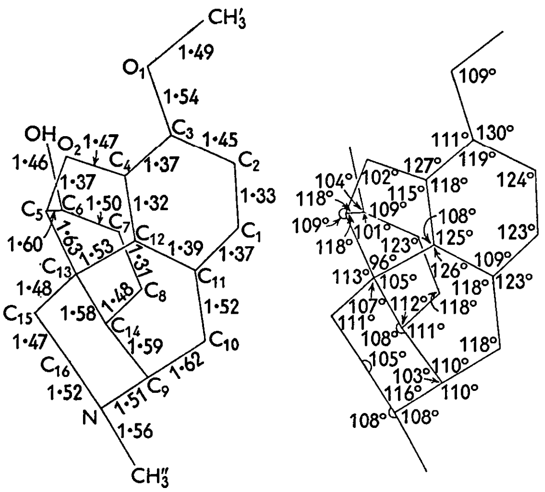

Fig. 6. Intramolecular bond lengths and angles.

Discussion

The standard deviations of the values given in Fig. 6 from those generally accepted are 0·06 Å for the bond lengths and 6° for the angles. Thus, differences of 0·18 Å among the former and 18° among the latter cannot be regarded as significant (Cruickshank, 1949); all apparent discrepancies are within these tolerances. It is of interest to note that for different types of bonds, values for C–C (aromatic) are in the range 1·32–1·45 Å with an average of 1·37 Å, those for the C–C single bonds vary from 1·47 to 1·63 Å with an average of 1·55 Å, while the only C=C bond present has a length of 1·31 Å. The bond angles C–C–C lie between 96° and 118° with an average value of 108° 47′ and the two C=C–C angles are 123° and 118°.

Intermolecular distances

The distance separating the hydroxyl group attached to C_6 from the nitrogen atom of a neighbouring molecule is 2·83 Å (see Fig. 5). This length is typical of hydrogen bonding between O and N (Donohue, 1952) and, if so identified, gives the nitrogen atom a total of four bonds which are distributed tetrahedrally. Although close contact between the nitrogen atom and the bromine ion might be expected, the distance between them is found to be 4·2 Å.

As in strychnine hydrobromide dihydrate (Robertson & Beevers, 1951), the bromine ion is closely associated with three water molecules at distances of 3·27, 3·39, and 3·39 Å, respectively. The last two involve the water molecule, H_2O'', which is more than 3·5 Å from any other atom.

The hydroxyl group is only 2·77 Å from H_2O', which, within the accuracy attained, suggests that the two may be joined by a bond of the type $O\text{–}H \cdots O_{H_2O}$. This water molecule makes van der Waals contacts with O_1 and O_2 at distances of 3·16 and 2·88 Å, respectively.

The structure of the codeine molecule

The benzene ring (I) which is tilted at ~ 20° to (001) (see Fig. 5) is planar to within the limits of experimental error, and the five-membered ring continues in this plane, with the exception of C_5 which is displaced below it by 0·4 Å. The oxygen atom, O_1, linked to C_3 is in the plane of the benzene ring, and the methyl group, CH_3', is about 0·2 Å above it.

The carbocyclic ring (II) is approximately planar apart from C_{14}, which is displaced downwards by 0·7 Å. The plane of this ring is inclined at ~ 30° to (001) with C_{10} below the plane of ring I by 0·35 Å (i.e. in the same direction as C_5). The piperidine ring is in the Sachse *trans* form with C_9, C_{13}, C_{15}, and N in the same plane. It is joined to ring II through the polar bonds C_{13}–C_{15} and C_9–N, and the hydrogen atom attached to C_9, therefore, must be equatorial. The piperidine ring makes an angle of ~ 60° with (001) in the opposite sense to rings I and II.

The other carbocyclic ring (III) is tilted in the same direction as the piperidine ring so that the two form the arms of an approximately T-shaped molecule with the other three rings as the upright. In ring III, the atoms C_5, C_7, C_8, and C_{14} are approximately coplanar with C_6 above, and C_{13} below, the plane. Assuming a tetrahedral distribution of bonds about C_5, C_6, and C_{14}, it is apparent from Fig. 5 that the attached hydrogen atoms must all be *cis* to the ethanamine chain, and *trans* to the oxygen atom, O_2, of the five-membered ring. The stereochemical configuration illustrated in Fig. 1, therefore, is fully confirmed.

Grateful acknowledgment is made to Dr C. G. Farmilo, Department of National Health and Welfare, for specimens of the various narcotics examined in connection with the present investigation. Although most of the calculations were carried out in the laboratory, in part by Mrs M. E. Pippy, some of the structure factors were calculated with I. B. M. equipment by Mr C. N. Hellyer, Communications Branch, and two Fourier syntheses were evaluated by Dr J. Kates on the electronic digital computer, 'Ferut', at the Computation Centre, University of Toronto.

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On the Crystal Structure of the ζ Phase in the Silver–Zinc System and the Mechanism of the β–ζ Transformation*

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The space group and approximate structure of the ζ phase in the silver–zinc system have been determined by the use of single-crystal and powder methods. The results are in agreement with those obtained by Edmunds & Qurashi through a rather lengthy procedure using powder data only.

The mechanism of the transformation from the cubic β phase to the structurally closely related hexagonal ζ phase has been clarified. The mechanism, which has 'oriented' character, consists of a displacement of the atoms in the β phase mainly in the [111] direction.

Introduction

A structure investigation of the ζ phase in the Ag–Zn system was first reported by Straumanis & Weerts (1931). By X-ray powder methods they found that the phase has a structure of hexagonal symmetry with $c_0/a_0 = 0{\cdot}367$ and with a unit cell containing nine atoms. A report on a complete structure determination was published by Edmunds & Qurashi (1951). They reported the lattice parameters

$$a_0 = 7{\cdot}6360,\ c_0 = 2{\cdot}8197\ \text{Å}\,,$$

and an atomic arrangement closely related to that of the body-centered β phase. Their structure determination was based entirely on powder diffraction data.

Although the agreement between the observed and calculated intensities as given by Edmunds & Qurashi was relatively good and the structure therefore most likely correct, it was decided that an attempt be made to check the reported structure by single-crystal methods. This decision was made as crystal-structure determinations based on powder data only, in general, are less reliable than those based on single-crystal data. In this particular case the confirmation by single-crystal techniques of the space group proposed by Edmunds & Qurashi was of primary interest. It was also hoped that single-crystal work would give some information with respect to the mechanism of the transformation from the β phase to the structurally closely related ζ phase.

Experimental: space group and approximate structure

Since the ζ phase is formed through a solid-state transformation and, furthermore, since it is quite soft and malleable, considerable difficulties were anticipated in isolating single crystals. The procedure adopted was the following. An alloy containing 50 atomic % Ag and 50 atomic % Zn was prepared by melting the pure elements in an evacuated silica tube. Single crystals of the β phase were then made by lowering glass capillaries containing the molten alloy through a temperature gradient. Attempts to grow single crystals of the ζ phase were made by slow cooling and subsequent annealing of the thin rods obtained in this way. Ultimately a region of one of the rods was found to give Laue photographs which indicated the presence of a single-crystal domain of fairly large size (at least 4 mm. long). The Laue symmetry was found to be O_h; however, the diffraction maxima were

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* Contribution No. 1921 from the Gates and Crellin Laboratories.