

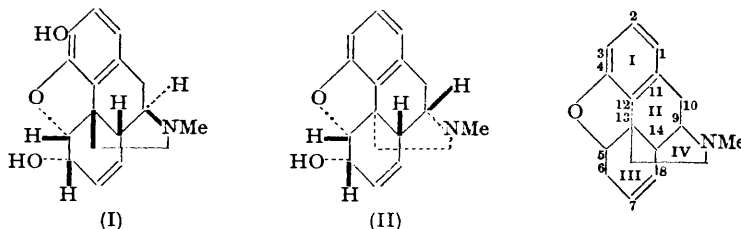
A Crystallographic Examination of the Structure of Morphine.

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Crystals of morphine hydriodide dihydrate have been examined by quantitative *X*-ray analysis. They are orthorhombic, space group $P2_12_12_1$ with four molecules, $C_{17}H_{19}O_3N, HI, 2H_2O$ per unit cell. Parameters for all the atoms in the crystal unit have been derived from calculation of the electron-density distribution projected down the *b* and *c* axes. The molecule is found to be approximately T shaped; the atoms of rings I and II and the oxide ring lie near one plane, while atoms of ring III and the ethanamine ring lie close to a second plane at right angles to the first; this is a consequence of the *cis*-fusion of rings II and III. Details of the stereochemical form of the different rings present are established.

THE exact stereochemical structure of morphine presents a chemical problem of considerable complexity. As the preceding paper by Bentley and Cardwell illustrates, the arguments used so far to derive the relations between the five different asymmetric centres in the molecule are often far from conclusive. At Dr. Cardwell's suggestion, we have therefore examined the morphine structure by *X*-ray analysis. We accepted at the outset of our examination the accumulated chemical evidence in favour of the Gulland-Robinson formula for morphine, and a major part of the stereochemical evidence reviewed by Bentley and Cardwell. The problem presented to us accordingly took the form of deciding whether formula (I) or (II) correctly represented the structure of morphine, and of these (I) (or its mirror image) had been supported by Rapoport and Lavigne (*J. Amer. Chem. Soc.*, 1953, **75**, 5329). Our conclusions are, however, independent of our initial structural postulates.



Crystals of the hydriodide, hydrobromide, and hydrochloride hydrates of morphine were kindly supplied to us by Dr. Cardwell. As no crystals of the hydrochloride of adequate size were obtained, no measurements were carried out on them. Several oscillation photographs were taken of the hydrobromide, but it was decided to carry out the main *X*-ray analysis on the hydriodide alone; data from this salt could give directly unambiguous results, owing to the high contribution of iodine to the structure factors. Preliminary crystallographic data on both morphine hydriodide and hydrobromide are summarised below.

Crystal Data.— $C_{17}H_{19}O_3N, HI, 2H_2O$; *M*, calc. 449; *d*, calc. 1.65, found 1.66. Slightly discoloured yellow orthorhombic needles. Unit-cell dimensions, $a = 20.32$, $b = 13.02$, $c = 6.84$ Å. Space group, $P2_12_12_1$. Four molecules per unit cell. (000) = 616.

$C_{17}H_{19}O_3N, HBr, 2H_2O$; *M*, calc. 402; *d*, calc. 1.47, found 1.46. Colourless orthorhombic needles. Unit-cell dimensions, $a = 20.07$, $b = 12.75$, $c = 6.94$ Å. Space group $P2_12_12_1$. Four molecules per unit cell. $F(000) = 544$.

Structure Analysis.—It was decided that sufficient accuracy would be obtained by working with two-dimensional data only, and intensities were therefore measured for the (*h*0*l*) and (*h**k*0) reflections. From the *b*- and the *c*-axis projections of the Patterson function calculated from the derived F^2 values, the *x*, *y*, and *z* co-ordinates of the iodine atoms were found directly; these are: *x*, 0.069; *y*, 0.058; *z*, 0.442.

FIG. 1. Electron density of morphine hydriodide dihydrate projected on (001). Contour lines are drawn at intervals of $2e \text{ \AA}^{-2}$, except for the iodine ion, where the intervals are arbitrary. The 1-electron contour is dotted.

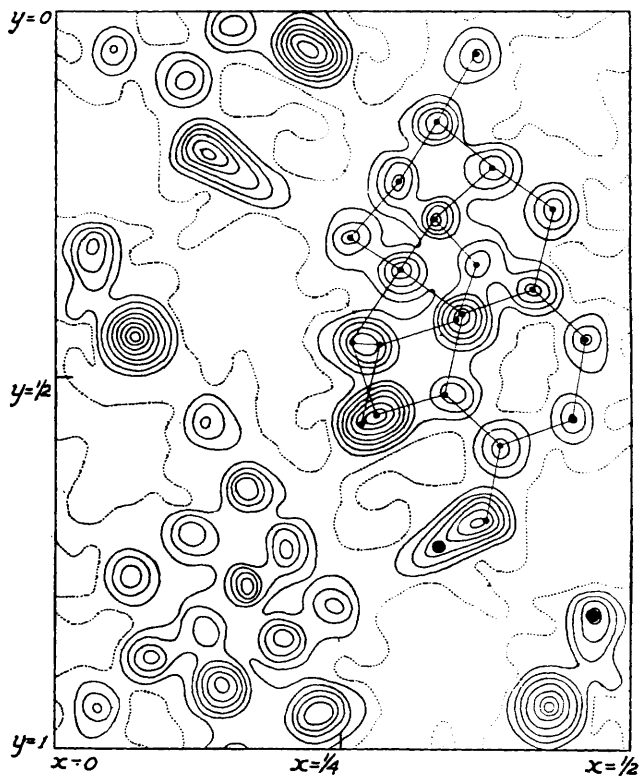
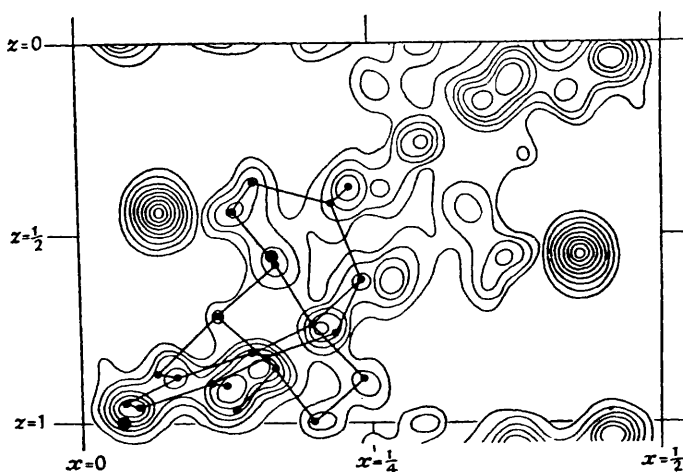
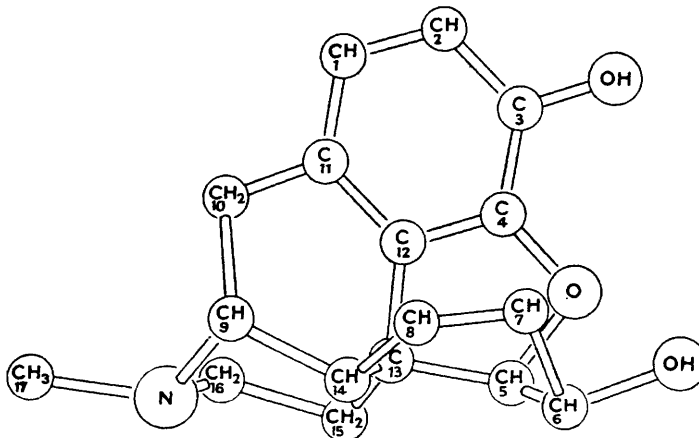


FIG. 2. Electron density of morphine hydriodide dihydrate projected on (010). Contour lines are drawn at intervals of $2e \text{ \AA}^{-2}$, except for the iodine ion, where the intervals are arbitrary. The first contour is drawn at the 4-electron level.



By using signs based on the contribution of the iodine atoms alone, and the observed structure amplitudes, electron-density projections along the *c* and *b* axes were calculated. Models of the possible structures of morphine were made, and projected on to the electron-density projections, by means of a mirror suitably placed, and a source of parallel light. It was found that the less planar model, *i.e.*, that corresponding to (I) above, exactly fitted the projections. Structure factors were then calculated based on possible positions for all the atoms in the unit cell and, with the corrected signs found, further electron-density projections were derived. In all, three refinements were carried out on each projection, and the latest electron-density distributions calculated are shown in Figs. 1 and 2. By the further use of models projected on these projections, and by calculation of the exact centres of resolved peaks, the atomic

FIG. 3. Molecule of morphine accurately drawn from final co-ordinates.



co-ordinates listed in Table 1 were derived. The reliability indices calculated on these co-ordinates were: $R = 13\%$ for (*hk*0) structure factors, and $R = 17\%$ for (*h*0*l*) structure factors, where

$$R = \frac{\sum |F_o| - |F_c|}{\sum |F_o|} \times 100$$

The F_c and the F_o values, for (*hk*0) and (*h*0*l*) structure factors, are compared in Table 2.

TABLE 1. Final co-ordinates.

C at position	<i>x</i>	<i>y</i>	<i>z</i>	C at position	<i>x</i>	<i>y</i>	<i>z</i>
1	0.038	0.553	0.943	14	0.170	0.717	0.582
2	0.050	0.445	0.953	15	0.242	0.690	0.880
3	0.113	0.410	0.892	16	0.200	0.768	1.000
4	0.160	0.480	0.828	17	0.133	0.942	0.967
5	0.242	0.548	0.623	O 3	0.125	0.308	0.900
6	0.217	0.547	0.418	6	0.233	0.440	0.375
7	0.150	0.567	0.358	(oxide)	0.227	0.467	0.758
8	0.133	0.657	0.437	(H ₂ O)	0.167	0.275	0.533
9	0.118	0.787	0.725	(H ₂ O)	0.035	0.158	1.000
10	0.065	0.728	0.863	N	0.167	0.848	0.858
11	0.083	0.620	0.875	I	0.069	0.058	0.442
12	0.145	0.580	0.825				
13	0.200	0.647	0.748				

Discussion.—The chemical structure of morphine is confirmed, and the detailed stereochemical form of the molecule in the crystal is established by the two calculated projections of the electron-density distribution shown in Figs. 1 and 2. The relations between the different stereochemical centres are shown in Fig. 3, which corresponds with formula (I) above; from our *X*-ray measurements we have no evidence on the absolute stereochemistry of the molecule.

We have not attempted from our present two-dimensional data to derive accurate

values for bond lengths and bond angles within the molecule. Bond lengths conformed on calculation to the expected values but our limits of error are quite wide. Between the molecules the contact distances are of the order 3.5–4 Å, except in the regions shown in Fig. 4 by the dotted lines. Here the shorter distances suggest a hydrogen-bond system running between the two water molecules and two hydroxyl groups in one molecule, and the nitrogen atom of an adjacent molecule. Around the iodine ions the nearest contacts are with water molecules: $I^- - OH_2$, 3.54, 3.94 Å; $I^- - I^-$, 4.12 Å; $I^- - N$, 4.38, 5.26 Å; $I^- - Me$, 4.15, 4.14 Å.

The detailed arrangement of the atoms in the molecule appears to be determined by normal stereochemical considerations. Roughly the molecule is T-shaped, with atoms lying close to two planes nearly at right-angles to one another. One plane includes the benzene ring I, the oxide ring, and ring II, while in the second plane lie ring III and the ethanamine ring IV. The benzene ring is flat; the small distortions from the regular hexagonal form which appear in the atomic positions in Fig. 1 are probably largely due to imperfections

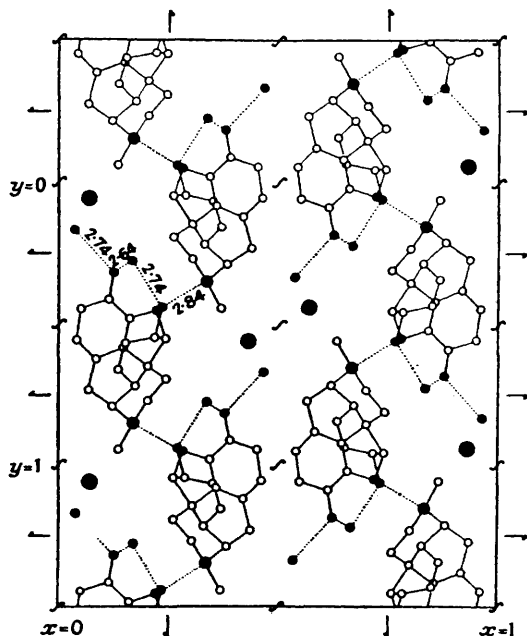


FIG. 4. Projections of the atomic positions in morphine hydriodide dihydrate on (001). The suggested hydrogen-bond system is dotted.

in our data. On the other hand, the bending of the bonds $C_{(4)}-O$ and $C_{(12)}-C_{(13)}$ inwards from the regular positions is likely to be real, and required for the formation of the five-membered oxide ring. This ring is, as usual, not planar, $C_{(5)}$ being out of the plane of the other four atoms. The ethanamine ring is of nearly regular chair form; the methyl group is attached to the nitrogen *cis* to the bond $C_{(9)}-C_{(10)}$. In ring III the atoms $C_{(6)}$, $C_{(7)}$, $C_{(8)}$, and $C_{(14)}$ lie nearly in one plane, as required by the presence of the 7:8-double bond. The nearly boat-shaped form of this ring appears to be required by the packing of the atoms attached to $C_{(6)}$ relative to the atoms of the oxide ring. The arrangement of atoms attached to $C_{(5)}$ and $C_{(6)}$ is not exactly staggered but approximately so, with the hydroxyl group *cis* to the oxygen atom in the oxide ring and in contact with it. Probably the most interesting feature of the structure is the *cis*-junction between rings II and III. The arrangement of these, approximately at right angles to one another, conforms in outline with the configuration found by Bastiansen and Hassel (*Nature*, 1946, 157, 765) for *cis*-decalin, though naturally it differs in detail owing to the presence of the double bond in ring III and the benzene ring attached to ring II.

After this investigation had begun, we learnt of similar studies undertaken by Dr. H. Scoloudi and Dr. J. Lindsay, with both of whom we compared conclusions. Dr. Lindsay's

TABLE 2. Measured and calculated values of the structure factor (hydrogen contributions and unobserved reflections are not included).

<i>hkl</i>	F (meas.)	F (calc.)	<i>hkl</i>	F (meas.)	F (calc.)	<i>hkl</i>	F (meas.)	F (calc.)	<i>hkl</i>	F (meas.)	F (calc.)
020	120	148	730	37	-40	15,6,0	14	10	6,10,0	60	47
040	42	51	830	100	-83	16,6,0	25	-26	7,10,0	21	-19
060	98	-99	930	34	-28	17,6,0	31	32	8,10,0	74	58
080	142	-148	10,3,0	101	-84	19,6,0	34	30	11,10,0	15	21
0,10,0	81	-93	11,3,0	28	24	22,6,0	12	12	12,10,0	14	-7
0,12,0	29	-28	12,3,0	74	-75	23,6,0	10	-10	13,10,0	15	13
0,14,0	22	22	13,3,0	30	25	24,6,0	10	10	14,10,0	35	-35
0,16,0	17	17	14,3,0	20	-23	170	54	-45	16,10,0	14	-14
200	15	-11	15,3,0	59	68	270	72	60	17,10,0	12	-10
400	85	-80	16,3,0	24	23	370	38	-34	21,10,0	9	-7
600	120	-125	17,3,0	15	15	470	69	60	1,11,0	27	-35
800	96	-97	18,3,0	52	59	570	68	68	2,11,0	27	-27
10,0,0	84	-113	19,3,0	25	-20	670	34	41	4,11,0	57	-65
12,0,0	24	40	20,3,0	41	30	770	91	85	5,11,0	47	42
14,0,0	97	79	21,3,0	14	-13	870	13	-13	6,11,0	42	-36
16,0,0	41	44	22,3,0	13	3	970	31	20	8,11,0	42	16
20,0,0	40	-41	23,3,0	12	-10	10,7,0	45	-45	10,11,0	35	35
22,0,0	39	-40	24,3,0	20	-20	11,7,0	24	-18	12,11,0	24	26
26,0,0	11	12	140	62	55	12,7,0	40	-45	13,11,0	14	-11
110	74	70	240	26	-37	13,7,0	26	-27	15,11,0	22	-28
210	30	-28	340	162	164	14,7,0	15	-7	18,11,0	16	-16
310	140	135	440	15	17	15,7,0	77	-75	19,11,0	14	7
410	110	104	540	57	59	16,7,0	34	25	1,12,0	21	-21
510	130	-128	740	11	23	18,7,0	14	19	3,12,0	62	-55
610	24	27	840	26	-24	19,7,0	14	14	5,12,0	25	-35
710	104	-90	940	83	-87	20,7,0	13	8	6,12,0	25	26
910	120	-115	10,4,1	16	-16	21,7,0	19	19	8,12,0	15	14
10,1,0	15	-20	11,4,0	108	-98	22,7,0	<5	-2	9,12,0	25	22
11,1,0	70	56	13,4,0	50	-50	23,7,0	12	14	11,12,0	32	30
12,1,0	17	-30	14,4,0	14	9	24,7,0	6	-6	13,12,0	24	27
13,1,0	53	34	15,4,0	24	25	180	12	11	14,12,0	12	-10
14,1,0	13	-3	17,4,0	53	48	280	46	-46	17,12,0	13	16
15,1,0	78	85	18,4,0	15	15	380	21	28	2,13,0	15	-17
16,1,0	13	5	19,4,0	36	39	480	<8	5	4,13,0	42	-42
17,1,0	25	24	22,4,0	17	-9	580	22	22	6,13,0	21	-21
18,1,0	15	16	24,4,0	<5	-3	680	85	84	7,13,0	19	-12
19,1,0	25	-18	25,4,0	18	-20	780	22	-17	8,13,0	20	15
21,1,0	40	-40	150	21	-28	880	32	34	10,13,0	32	32
23,1,0	17	-18	250	115	108	10,8,0	54	54	12,13,0	25	27
26,1,0	10	-10	350	9	17	11,8,0	25	22	16,13,0	10	-13
120	53	54	450	91	92	12,8,0	14	-13	1,14,0	14	-17
220	62	62	550	23	-9	14,8,0	52	-51	3,14,0	23	-20
320	124	121	650	74	65	15,8,0	15	-11	4,14,0	13	-10
420	33	40	750	11	18	16,8,0	35	-38	5,14,0	24	-24
520	142	148	850	74	-60	17,8,0	14	11	8,14,0	12	-13
620	135	-140	950	46	38	20,8,0	20	20	9,14,0	20	28
720	30	38	10,5,0	123	-111	21,8,0	16	5	11,14,0	21	27
820	78	-84	12,5,0	67	-75	190	77	-85	14,14,0	9	9
920	56	-58	13,5,0	34	-27	290	22	-17	1,15,0	16	16
10,2,0	43	-62	15,5,0	15	-10	390	23	-23	2,15,0	24	-20
11,2,0	89	-73	16,5,0	35	20	490	23	-17	4,15,0	11	-14
12,2,0	30	23	17,5,0	15	-18	590	62	60	5,15,0	14	-15
13,2,0	31	-42	18,5,0	51	53	690	14	-7	6,15,0	11	-8
14,2,0	76	81	20,5,0	24	26	790	54	54	7,15,0	11	-13
15,2,0	33	32	21,5,0	16	16	890	14	15	10,15,0	9	13
16,2,0	14	17	24,5,0	15	-16	990	83	82	2,16,0	16	15
17,2,0	59	48	160	10	7	11,9,0	36	-29	3,16,0	15	-14
19,2,0	15	-7	260	38	-38	13,9,0	53	-46	6,16,0	23	-23
20,2,0	20	-20	360	72	66	14,9,0	15	15	002	170	177
22,2,0	13	-13	460	15	21	15,9,0	34	-35	004	13	-20
23,2,0	12	-15	560	112	100	17,9,0	14	-14	006	20	-29
24,2,0	11	-17	660	74	66	18,9,0	13	-6	008	7	7
25,2,0	15	-13	760	12	24	19,9,0	12	12	101	53	-56
130	54	62	860	68	59	21,9,0	22	27	201	78	-90
230	95	95	960	50	-53	1,10,0	14	-29	301	50	-35
330	14	-14	10,6,0	23	23	2,10,0	24	43	401	67	-79
430	174	171	11,6,0	94	-87	3,10,0	34	-19	501	64	77
530	114	-110	12,6,0	25	-24	4,10,0	20	-19	601	12	-24
630	127	118	14,6,0	52	-44	5,10,0	14	-14	701	13	-13

TABLE 2 (Continued.)

<i>hkl</i>	F (meas.)	F (calc.)	<i>hkl</i>	F (meas.)	F (calc.)	<i>hkl</i>	F (meas.)	F (calc.)	<i>hkl</i>	F (meas.)	F (calc.)
801	23	-21	16,0,2	43	42	104	109	-96	15,0,5	7	12
901	111	102	17,0,2	11	-25	208	28	24	16,0,5	21	24
10,0,1	48	-41	19,0,2	26	12	304	30	-48	18,0,5	33	31
11,0,1	136	-142	20,0,2	36	-35	404	13	14	20,0,5	10	-16
12,0,1	40	31	21,0,2	34	32	504	60	68	106	27	27
13,0,1	53	-42	22,0,2	22	-27	704	80	94	206	11	-9
15,0,1	44	-36	23,0,2	19	27	804	34	-34	306	16	-17
16,0,1	15	27	24,0,2	9	-8	904	15	19	506	16	17
17,0,1	62	-60	103	15	-33	10,0,4	25	23	606	20	30
18,0,1	23	20	203	53	52	11,0,4	11	11	706	22	27
19,0,1	70	63	303	75	-77	12,0,4	39	-25	806	14	10
21,0,1	8	14	403	59	-60	13,0,4	21	-17	906	16	16
22,0,1	6	2	503	11	-12	14,0,4	8	3	10,0,6	11	-4
23,0,1	16	-16	603	59	-62	15,0,4	51	-53	11,0,6	7	7
25,0,1	25	34	703	9	5	17,0,4	21	-26	15,0,6	15	-15
102	190	-203	803	59	-70	19,0,4	27	17	16,0,6	11	-12
202	106	114	903	42	46	20,0,4	9	3	107	15	14
302	30	34	10,0,3	57	-41	21,0,4	28	30	207	13	7
402	32	-21	11,0,3	59	-69	22,0,4	13	-1	307	17	19
502	76	86	12,0,3	55	71	105	10	19	507	10	-6
602	74	-63	13,0,3	11	-11	205	44	44	807	15	-16
702	64	92	14,0,3	20	17	405	50	-61	907	14	-14
802	74	-102	15,0,3	22	-15	505	15	-20	10,0,7	9	-4
902	42	33	16,0,3	59	47	705	21	-17	11,0,7	6	7
10,0,2	44	-50	17,0,3	40	-22	805	11	-13	108	12	-8
11,0,2	28	37	18,0,3	43	43	10,0,5	48	-53	208	11	14
12,0,2	34	8	19,0,3	26	34	11,0,5	14	13	408	8	8
13,0,2	72	-60	20,0,3	32	-28	12,0,5	40	39	608	7	-3
14,0,2	50	48	23,0,3	14	11	13,0,5	14	12			
15,0,2	60	-49	24,0,3	34	-24	14,0,5	11	11			

work on codeine hydrobromide gives detailed results in agreement with ours and is being published in *Acta Crystallographica*. Dr. Scoloudi's work on morphine hydriodide has not been completed. She did, however, reach similar conclusions to ours on the stereochemistry of morphine from her first calculated electron-density projections.

EXPERIMENTAL

Preparation and Chemical Analysis of Crystals.—The hydriodide was crystallised from water on evaporation, forming slightly discoloured yellow needles (Found: C, 45.3; H, 5.4; N, 3.4; loss at 100° *in vacuo*, 7.4. Calc. for $C_{17}H_{19}O_3N, HI, 2H_2O$: C, 45.4; H, 5.3; N, 3.1; loss, 8.0%).

The hydrobromide crystallised in clusters of fine, colourless needles, by slow evaporation from water, under reduced pressure (Found: C, 50.8; H, 5.8; loss at 100° *in vacuo*, 7.4. Calc. for $C_{17}H_{19}O_3N, HBr, 2H_2O$: C, 50.7; H, 6.0; loss 9.0%).

X-Ray Measurements.—Copper- $K\alpha$ radiation was used throughout. The intensities of the ($hk0$) and ($h0l$) reflections were estimated visually from Weissenberg photographs, using the multiple-film technique. These intensities were subsequently put on to an approximately absolute scale by Wilson's method (*Nature*, 1942, 150, 151), which gave values lower than the final values taken. The latter were obtained by plotting the calculated structure factors divided by the unscaled observed structure factors against $\sin^2 \theta$; this method was used also for determining the temperature factor for the final structure-factor calculations. Of a possible 348 ($hk0$) reflections, 272 were measured, and of a possible 180 F($h0l$) reflections 145 were measured. The unit-cell dimensions were determined accurately by calibration against the diffraction pattern of a fine copper wire, recorded on the edges of Weissenberg films.

Calculations.—All Fourier series summations were performed on a Hollerith Tabulator, and at intervals of 1/60 along all three axes. When F^2 values were used for the summation, these values were sharpened by multiplication by the reciprocal of the scattering factor for nitrogen. The structure-factor calculations were carried out by a modification of the process used for Fourier series summation (see, *e.g.*, Booth, "Fourier technique in X-ray organic structure analysis," Cambridge University Press, 1948, p. 59), x co-ordinates were approximated first to the nearest 1/1000, and values for $\begin{Bmatrix} \cos \\ \sin \end{Bmatrix} 2\pi hx$ were written out from Buerger's tables.

y and z co-ordinates were approximated to the nearest $1/120$ of b and c , and the summations of $\begin{Bmatrix} \cos \\ \sin \end{Bmatrix} 2\pi hx$, $\begin{Bmatrix} \cos \\ \sin \end{Bmatrix} 2\pi \begin{Bmatrix} hy \\ lz \end{Bmatrix}$ necessary carried out on the Hollerith Tabulator over all the atoms except iodine, the individual atomic contributions in this sum being weighted oxygen 9, nitrogen 7, and carbon 6. The sums for each hkl reflection were multiplied by figures obtained from a normalised McWeeney scattering curve for nitrogen and added to the separately completed contributions for the iodide ion, for which the James and Brindley f curve for iodine was employed. For the $(hk0)$ structure factors a temperature factor $B = 3.4 \times 10^{-16}$ was applied to all atoms. For the $(h0l)$ structure factors a temperature factor $B = 3.1 \times 10^{-16}$ was applied to all atoms other than iodine, to which an anisotropic one was applied (see, *e.g.*, Cochran, *Acta Cryst.*, 1954, 7, 503), *viz.*, $B = 2.2 \times 10^{-16}$ along the a axis, and $B = 4.0 \times 10^{-16}$ along the c axis.

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UNIVERSITY MUSEUM, OXFORD.

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