193. *Fungal Metabolites. Part I. The Stereochemistry of Griseofulvin: X-Ray Analysis of 5-Bromogriseofulvin.*

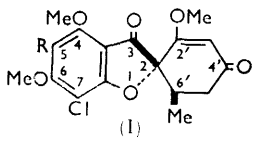
By W. A. C. Brown and G. A. Sim.

Crystals of 5-bromogriseofulvin belong to the monoclinic system, space group $P2_1$ (C_2^2), with two molecules of $C_{17}H_{16}BrClO_6$ in a unit cell of dimensions $a = 10{\cdot}96$, $b = 8{\cdot}61$, $c = 10{\cdot}27$ Å, $\beta = 108°30'$. An X-ray crystal-structure determination has been carried out and our final results concerning the stereochemistry of griseofulvin are summarized in formula (I). Initial phase determination was based on the bromine and the chlorine atom and several three-dimensional Fourier syntheses were evaluated, followed by least-squares refinement of the atomic parameters. The final discrepancy R over the 1129 observed reflexions is 14%.

Extensive degradative studies by Raistrick and his collaborators [1] and later by the group at Imperial Chemical Industries Limited [2] established the constitution (I; R = H)

[1] Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240.
[2] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.

for griseofulvin, the important antibiotic [3] metabolite of *Penicillium patulum*. Several total syntheses have subsequently been reported.[4]



(I)

Treatment of griseofulvin with alkali produces a mixture of griseofulvin and the diastereoisomer in which the configuration of the spiran centre has been inverted.[5] Since optical-rotation measurements indicated that the mixture contains 40% of griseofulvin and 60% of the diastereoisomer, MacMillan attributed [5] to griseofulvin the sterically less favoured configuration in which the 3-carbonyl and the 6′-methyl groups are *cis*. The absolute stereochemistry at position 6′ shown in (I) has been defined by the degradation of griseofulvin to (+)-methylsuccinic acid.[6]

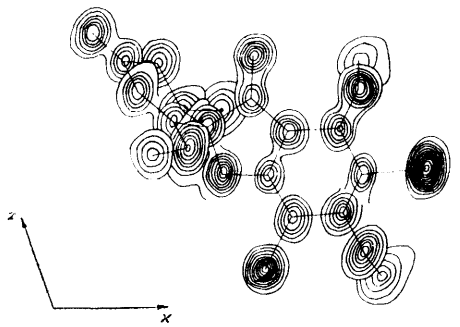


FIG. 1.

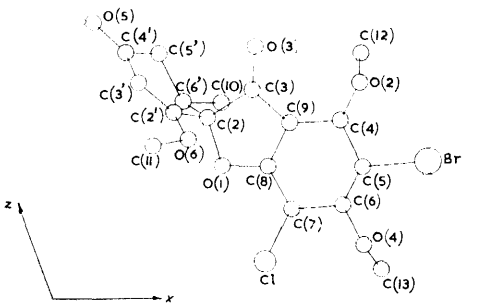


FIG. 2.

FIG. 1. Final three-dimensional electron-density distribution for 5-bromogriseofulvin shown by means of superimposed contour sections drawn parallel to (010). Contour interval 1 e/Å^3, except around the chlorine and bromine atoms where it is 2 e/Å^3 and 3 e/Å^3, respectively.

FIG. 2. Atomic arrangement corresponding to Fig. 1.

We have carried out a quantitative *X*-ray study of 5-bromogriseofulvin in order to define unambiguously the stereochemical relationship of the 2- and the 6′-centre. Our results, summarized in formula (I; R = Br), confirm MacMillan's assignment of stereochemistry. Several three-dimensional Fourier syntheses and several cycles of least-squares refinement of positional and thermal atomic parameters were computed and the final value of *R*, the average discrepancy between measured and calculated structure amplitudes, is 14·0%.

The final electron-density distribution is shown in Fig. 1 as superimposed contour sections drawn parallel to (010) and covering the region of one molecule; the corresponding atomic arrangement and numbering system (the latter conforming as far as possible with established convention in the griseofulvin series) are explained in Fig. 2. The final atomic co-ordinates are listed in Table 1, and the various interatomic distances and valency angles derived from these are in Table 2. The standard deviations of the final atomic co-ordinates were estimated in the usual manner from the least-squares residuals (see Experimental section) and are shown in Table 3; from the results the average e.s.d. (estimated standard deviation) of a distance between two light atoms (carbon or oxygen) is about 0·05 Å, and the average e.s.d. of a valency angle about 3°.

The average sp^3-carbon–oxygen single bond length of 1·46 Å is in good agreement with

[3] Sulzberger and Baer, *Excerpta Medica*, 1959, **13**, XIII, 145; Gentles, Barnes, and Fantes, *Nature*, 1959, **183**, 256.

[4] Day, Nabney, and Scott, *Proc. Chem. Soc.*, 1960, 284; Brossi, Baumann, Gerecke, and Kyburz, *Helv. Chim. Acta*, 1960, **43**, 2071; Kuo, Hoffsommer, Slates, Taub, and Wendler, *Chem. and Ind.*, 1960, 1627.

[5] MacMillan, *J.*, 1959, 1823.

[6] Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3967.

TABLE 1.

Atomic co-ordinates.

(Origin of co-ordinates on two-fold screw axis.)

Atom	*x/a*	*y/b*	*z/c*	Atom	*x/a*	*y/b*	*z/c*
C(2)	−0·2798	0·1978	0·2451	C(10)	−0·2257	−0·0758	0·2991
C(3)	−0·1367	0·2235	0·3291	C(11)	−0·4552	0·5720	0·161
C(4)	0·0597	0·2181	0·2251	C(12)	0·1780	0·0877	0·4221
C(5)	0·0778	0·2504	0·0924	C(13)	0·0287	0·1170	−0·2148
C(6)	−0·0114	0·2441	−0·0213	O(1)	−0·2883	0·1890	0·1028
C(7)	−0·1414	0·2140	−0·0412	O(2)	0·1525	0·2232	0·3458
C(2′)	−0·3703	0·3140	0·2523	O(3)	−0·0934	0·2416	0·4505
C(3′)	−0·4283	0·3346	0·3571	O(4)	0·0069	0·2596	−0·1540
C(4′)	−0·4312	0·2026	0·4402	O(5)	−0·4921	0·1951	0·5249
C(5′)	−0·3450	0·0672	0·4380	O(6)	−0·3491	0·4381	0·1852
C(6′)	−0·3296	0·0577	0·2932	Cl	−0·2665	0·2277	−0·1888
C(8)	−0·1657	0·2063	0·0926	Br	0·2545	0·2648	0·1018
C(9)	−0·0731	0·2132	0·2194				

TABLE 2.

Interatomic distances (Å) and angles.

Intramolecular bonded distances

C(2)–C(3)	1·55	C(8)–C(9)	1·38	O(4)–C(13)	1·43	C(5′)–C(6′)	1·55
C(3)–C(9)	1·50	C(8)–O(1)	1·39	C(7)–Cl	1·69	C(6′)–C(2)	1·47
C(4)–C(9)	1·44	C(2)–O(1)	1·44	C(3)–O(3)	1·19	C(2′)–O(6)	1·33
C(4)–C(5)	1·46	C(4)–O(2)	1·33	C(2)–C(2′)	1·43	O(6)–C(11)	1·60
C(5)–C(6)	1·26	O(2)–C(12)	1·38	C(2′)–C(3′)	1·42	C(4′)–O(5)	1·26
C(6)–C(7)	1·40	C(5)–Br	1·91	C(3′)–C(4′)	1·43	C(6′)–C(10)	1·61
C(7)–C(8)	1·48	C(6)–O(4)	1·45	C(4′)–C(5′)	1·51		

Intramolecular non-bonded distances

C(2) · · · C(4′)	2·98	C(3) · · · O(6)	2·97	C(13) · · · Br	3·63	C(11) · · · C(3′)	2·82
C(2) · · · C(11)	3·71	C(12) · · · Br	3·95	C(13) · · · Cl	3·46	C(11) · · · O(1)	3·91
C(3) · · · C(4′)	3·75	C(12) · · · O(3)	3·35	C(10) · · · O(3)	3·25	O(3) · · · O(6)	3·65
C(3) · · · C(10)	2·74	C(12) · · · C(3)	3·48	C(10) · · · O(1)	2·98		

Intermolecular distances (<4 Å)

O(5) · · · Cl_I	3·20	O(5) · · · $C(12)_{VI}$	3·55	C(5) · · · $C(13)_{IV}$	3·72	O(2) · · · $C(5')_{III}$	3·90
C(11) · · · $O(1)_{II}$	3·38	C(4) · · · $C(13)_{IV}$	3·56	O(5) · · · $C(5')_V$	3·75	C(5′) · · · Cl_I	3·91
C(11) · · · Cl_{II}	3·43	C(11) · · · $O(5)_V$	3·61	O(5) · · · $O(2)_{VI}$	3·75	C(2′) · · · Br_{IV}	3·93
O(3) · · · $C(13)_I$	3·44	C(4′) · · · Cl_I	3·67	O(6) · · · $C(13)_{IV}$	3·76	O(2) · · · $C(13)_{IV}$	3·94
O(3) · · · $C(12)_{III}$	3·50	C(3′) · · · $C(12)_{III}$	3·67	O(3) · · · $O(4)_I$	3·86	O(3) · · · $C(10)_{III}$	3·95
O(4) · · · $C(10)_{IV}$	3·50	C(3′) · · · Br_{VI}	3·68	O(2) · · · $C(10)_{III}$	3·88	C(12) · · · $C(10)_{III}$	3·99
C(9) · · · $C(13)_{IV}$	3·51	C(13) · · · $C(10)_{IV}$	3·69	C(8) · · · $C(13)_{IV}$	3·89		
C(3′) · · · $O(5)_V$	3·54			C(3) · · · $C(13)_{IV}$	3·89		

The subscripts refer to the following positions:

I	$x, \quad y, 1+z$	III	$-x, \frac{1}{2}+y, 1-z$	V	$-1-x, \frac{1}{2}+y, 1-z$
II	$-1-x, \frac{1}{2}+y, \quad -z$	IV	$-x, \frac{1}{2}+y, \quad -z$	VI	$-1+x, \quad y, \quad z$

Valency angles

O(1)C(2)C(3)	108°	C(4)C(5)C(6)	124°	C(7)C(8)O(1)	123°	C(3′)C(2′)O(6)	119°
C(2)C(3)C(9)	102	C(4)C(5)Br	114	O(1)C(8)C(9)	112	C(2′)C(3′)C(4′)	117
C(2)C(3)O(3)	127	C(6)C(5)Br	122	C(8)O(1)C(2)	109	C(3′)C(4′)O(5)	125
C(9)C(3)O(3)	132	C(6)O(4)C(13)	115	O(1)C(2)C(6′)	113	C(3′)C(4′)C(5′)	118
C(3)C(9)C(4)	132	C(5)C(6)C(7)	127	O(1)C(2)C(2′)	106	C(5′)C(4′)O(5)	116
C(3)C(9)C(8)	110	C(5)C(6)O(4)	125	C(3)C(2)C(6′)	110	C(4′)C(5′)C(6′)	108
C(8)C(9)C(4)	118	C(7)C(6)O(4)	109	C(3)C(2)C(2′)	118	C(5′)C(6′)C(2)	116
C(9)C(4)C(5)	114	C(6)C(7)C(8)	110	C(2′)C(2)C(6′)	103	C(5′)C(6′)C(10)	107
C(9)C(4)O(2)	120	C(6)C(7)Cl	128	C(2)C(2′)C(3′)	128	C(2)C(6′)C(10)	105
C(5)C(4)O(2)	125	C(8)C(7)Cl	120	C(2)C(2′)O(6)	107	C(2′)O(6)C(11)	115
C(4)O(2)C(12)	117	C(7)C(8)C(9)	126				

TABLE 3.

Standard deviations of the final atomic co-ordinates (Å).

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$	Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$	Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
C(2) ...	0·022	0·035	0·025	C(5′) ...	0·027	0·046	0·030	O(1).....	0·015	0·027	0·019
C(3) ...	0·023	0·042	0·026	C(6′) ...	0·028	0·042	0·025	O(2).....	0·015	0·023	0·017
C(4) ...	0·021	0·033	0·027	C(8)	0·022	0·047	0·024	O(3).....	0·018	0·030	0·017
C(5) ...	0·020	0·042	0·022	C(9)	0·021	0·037	0·023	O(4).....	0·016	0·034	0·015
C(6) ...	0·021	0·048	0·021	C(10) ...	0·033	0·042	0·033	O(5).....	0·022	0·028	0·022
C(7) ...	0·024	0·035	0·027	C(11) ...	0·041	0·057	0·041	O(6).....	0·018	0·029	0·022
C(2′) ...	0·025	0·036	0·036	C(12) ...	0·043	0·056	0·048	Cl.....	0·006	0·012	0·007
C(3′) ...	0·025	0·037	0·031	C(13) ...	0·033	0·041	0·035	Br	0·006	0·009	0·005
C(4′) ...	0·023	0·036	0·026								

values of 1·460 Å in hydroxy-L-proline,[7] 1·466 Å in L-serine phosphate,[8] and 1·464, 1·465 Å in dibenzyl phosphate; [9] slightly lower values have been reported for methanol, 1·427 Å,[10] DL-serine, 1·425 Å,[11] and L-threonine, 1·424 Å.[12] The average sp^2-carbon–oxygen single bond length, 1·37 Å, agrees well with values of 1·36 Å in salicylic acid,[13] 1·37 Å in furan,[14] and 1·36 Å in phloroglucinol.[15] The average carbon–oxygen double bond length of 1·23 Å compares favourably with the values of 1·222 Å in *p*-benzoquinone,[16] 1·212 Å in parabanic acid,[17] and 1·23 Å in formaldehyde.[18]

The average carbon–carbon bond length in the benzene ring, 1·40 Å, agrees well with the value of 1·397 Å in benzene,[19] and the average sp^3-carbon–sp^3-carbon single-bond length, 1·54 Å, with the value of 1·545 Å in diamond. The average sp^2-carbon–sp^2-carbon single-bond length, 1·47 Å, is close to the standard value of 1·479 Å proposed by Dewar and Schmeising [20] and to the values of 1·483 Å in butadiene,[21] 1·477 Å in *p*-benzoquinone,[16] and 1·48 Å in benzoic acid.[22] The average sp^2-carbon–sp^3-carbon single-bond length of 1·49 Å does not differ significantly from the expected value of 1·51 Å.

In the five-membered ring O(1),C(2),C(3),C(9),C(8) the average valency angle is 108°. Average valency angles consistently smaller than tetrahedral have been reported for the five-membered rings in hydroxy-L-proline (106°),[7] clerodin bromolactone (106°),[23] bromodihydroisophotosantonic lactone acetate (105°),[24] isoclovene hydrochloride (105°),[25] and himbacine hydrobromide (105°); [26] these values are consistent with the non-planarity and consequent angle deformations in cyclopentane.[27] When the five-membered ring is fused to an aromatic ring (as in 5-bromogriseofulvin) or incorporates a double bond the average valency angle is slightly larger than in the above examples. Thus in bromogeigerin acetate [28] the average valency angle in the lactone ring is 105° and in the cyclopentenone ring 107°, while in echitamine bromide [29] the average valency angle in the

[7] Donohue and Trueblood, *Acta Cryst.*, 1952, **5**, 419.
[8] McCallum, Robertson, and Sim, *Nature*, 1959, **184**, 1863.
[9] Dunitz and Rollett, *Acta Cryst.*, 1956, **9**, 327.
[10] Venkateswarlu and Gordy, *J. Chem. Phys.*, 1955, **23**, 1200; Swalen, *J. Chem. Phys.*, 1955, **23**, 1739.
[11] Shoemaker, Barieau, Donohue, and Chia-Si Lu, *Acta Cryst.*, 1953, **6**, 241.
[12] Shoemaker, Donohue, Schomaker, and Corey, *J. Amer. Chem. Soc.*, 1950, **72**, 2328.
[13] Cochran, *Acta Cryst.*, 1953, **6**, 260.
[14] Bak, Hausen, and Rastrup-Andersen, *Discuss. Faraday Soc.*, 1955, **19**, 30.
[15] Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149.
[16] Trotter, *Acta Cryst.*, 1960, **13**, 86.
[17] Davies and Blum, *Acta Cryst.*, 1955, **8**, 129.
[18] Davidson, Stoicheff, and Bernstein, *J. Chem. Phys.*, 1954, **22**, 289.
[19] Stoicheff, *Canad. J. Phys.*, 1954, **32**, 339.
[20] Dewar and Schmeising, *Tetrahedron*, 1959, **5**, 166.
[21] Almenningen, Bastiansen, and Traetteberg, *Acta Chem. Scand.*, 1958, **12**, 1221.
[22] Sim, Robertson, and Goodwin, *Acta Cryst.*, 1955, **8**, 157.
[23] Paul, Sim, Hamor, and Robertson, *J.*, 1962, 4133.
[24] Asher and Sim, *Proc. Chem. Soc.*, 1962, 111; and unpublished work.
[25] Clunie and Robertson, *J.*, 1961, 4382.
[26] Fridrichsons and Mathieson, *Acta Cryst.*, 1962, **15**, 119.
[27] Pitzer and Donath, *J. Amer. Chem. Soc.*, 1959, **81**, 3213; Brutcher, Roberts, Barr, and Pearson, *ibid.*, p. 4915.
[28] Hamilton, McPhail, and Sim, *J.*, 1962, 708.
[29] Hamilton, Hamor, Robertson, and Sim, *J.*, 1962, 5061.

five-membered ring not fused to the benzene ring is 106° and in that fused to the benzene ring 107°. The value of 108° in 5-bromogriseofulvin is consistent with this pattern.

The mean plane through the twelve atoms C(4), C(5), C(6), C(7), C(8), C(9), C(3), O(2), Br, O(4), Cl, and O(1) of the hexasubstituted benzene ring was calculated by the method of Schomaker *et al.*,[30] and the atomic deviations from this plane are listed in Table 4. When

TABLE 4.

Displacements (Å) of atoms from the mean plane through the aromatic system C(4), C(5), C(6), C(7), C(8), C(9), C(3), O(2), Br, O(4), Cl, and O(1).

C(4)	0·10	C(8)	0·06	Br	−0·02	O(3)	−0·40
C(5)	−0·07	C(9)	0·01	O(4)	−0·06	C(2)	−0·09
C(6)	−0·03	C(3)	−0·21	Cl	−0·04	C(4′)	−0·41
C(7)	0·11	O(2)	0·08	O(1)	0·08	O(5)	−0·46

compared with the estimated standard deviations of atomic co-ordinates shown in Table 3 few of the displacements from the aromatic plane are established as significant; nevertheless, the results suggest that the atoms directly attached to the benzene ring are possibly

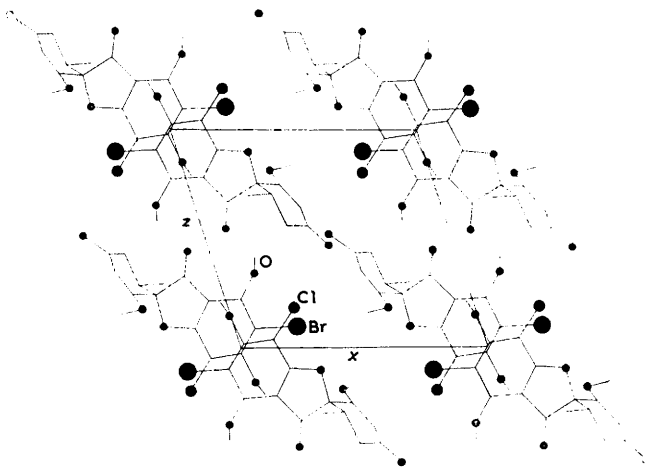


FIG. 3. The arrangement of molecules in the crystal as viewed in projection along the *b*-axis.

displaced by small amounts alternately above and below the aromatic plane: Br −0·02, O(2) +0·08, C(3) −0·21, O(1) +0·08, Cl −0·04, O(4) −0·06 Å. Though this conclusion must be only tentative it is in accord with the established deviations from planarity in *ortho*-disubstituted benzenes.[31] The displacement of O(3), 0·40 Å, from the aromatic plane is highly significant and is probably due to steric interaction with O(2). The involvement of C(2) in the five-membered ring prevents this displacement of O(3) from the aromatic plane occurring through a simple rotation of the group C(9),C(3), O(3),C(2) around the C(9),C(3)-bond; there is therefore an out-of-plane bending of the exocyclic C(9),C(3)-bond, and the deviation of C(3) from the aromatic plane, 0·21 Å, is appreciably greater than that of any of the other atoms directly bonded to the benzene ring.

The arrangement of the molecules in the crystal as viewed in projection along the *b*-axis is shown in Fig. 3. The intermolecular contacts (see Table 2) are all greater than 3 Å and correspond to normal van der Waals interactions.

[30] Schomaker, Waser, Marsh, and Bergman, *Acta Cryst.*, 1959, **12**, 600.
[31] Ferguson and Sim, *Proc. Chem. Soc.*, 1961, 162; *Acta Cryst.*, 1961, **14**, 1262; 1962, **15**, 346; *J.*, 1962, 1767.

TABLE 5.

Measured and calculated values of the structure factors.

h	k	l	$\|F_o\|$	$\|F_c\|$	α°
0	0	1	46	59	0
		2	28	23	180
		3	64	60	180
		4	28	30	180
		5	22	23	180
		6	14	14	180
		7	10	11	180
		8	11	9	180
		9	17	18	0
		10	7	10	0
		11	10	10	0
0	1	1	75	83	183
		2	43	39	261
		3	64	66	173
		4	49	46	162
		5	19	18	139
		6	31	33	338
		7	44	41	355
		8	35	34	1
		9	4	5	329
		10	6	8	163
0	2	1	80	60	189
		2	23	20	136
		3	37	38	331
		4	28	30	20
		5	24	23	18
		6	15	14	350
		7	20	19	353
		8	5	5	264
		9	19	18	173
0	3	1	42	35	1
		2	31	16	10
		3	29	28	3
		4	38	38	4
		5	7	6	15
		6	19	22	180
		7	27	30	172
		8	25	27	170
		9	4	2	232
		10	3	6	319
0	4	1	36	35	1
		2	10	8	30
		3	26	20	164
		4	24	23	224
		5	10	15	214
		6	7	9	226
		7	13	11	119
		8	8	5	110
0	5	1	17	14	158
		2	6	9	240
		3	25	25	208
		4	11	9	206
		5	6	7	169
		6	12	15	12
		7	15	14	338
		8	15	16	340
1	0	0	35	31	0
		1	37	40	0
		2	62	66	180
		3	27	31	180
1	0	4	2	7	180
		5	23	21	0
		6	16	11	180
		8	9	9	0
		9	14	14	0
		10	2	2	0
		11	11	7	180
	-1	0	38	43	0
	-2	0	58	64	0
	-3	0	62	67	0
	-4	0	6	10	0
	-5	0	9	10	180
	-6	0	14	7	0
	-7	0	8	14	180
	-8	0	9	11	180
	-9	0	2	2	180
	-10	0	2	4	180
	-11	0	13	4	0
1	1	1	29	32	158
		2	17	17	160
		3	13	15	206
		4	42	44	351
		5	33	34	11
		6	20	21	19
		7	3	1	274
		8	4	2	148
		9	4	4	177
	-1	1	29	31	219
	-2	1	45	45	188
	-3	1	22	15	221
	-4	1	32	40	6
	-5	1	55	57	29
	-6	1	5	15	16
	-7	1	8	6	274
	-8	1	35	32	174
1	2	0	56	53	162
		1	20	25	24
		2	54	63	356
		3	26	34	44
		4	12	17	32
		5	21	22	142
		6	9	12	250
		7	16	17	266
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		4	28	33	196
		5	20	23	187
		6	11	15	195
		7	11	4	240
		8	10	4	126
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	-8	0	25	27	344
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		1	26	31	211
		2	27	32	191
		3	22	31	245
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		5	8	8	328
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		7	9	15	75
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	-8	1	11	12	216
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		7	9	8	0
		8	3	2	180
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		10	15	12	180
		11	8	6	180
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		-8	14	10	0
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		4	34	39	358
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		6	24	25	184
		7	20	21	171
		8	10	10	189
		9	6	5	7
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		5	15	19	202
		6	6	7	129
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		10	3	9	355
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	-5	1	25	25	177
	-6	1	31	30	193
	-7	1	7	9	181
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	-9	1	5	3	57
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		9	5	6	151
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		1	27	24	174
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		3	9	14	15
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		6	9	11	84
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		2	16	25	24
		3	19	25	3
		4	14	18	328
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		3	4	8	0
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		6	11	10	180
		7	8	6	0
		8	8	9	180
		9	12	9	180
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		11	8	4	0
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	-4	1	24	26	208
	-5	1	21	17	208
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		7	6	10	104
		8	6	6	25
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	-6	2	15	14	210
	-7	2	16	14	230
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		1	33	35	194
		2	17	24	170
		3	5	4	22
		4	17	18	34
		5	30	31	0
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		7	11	12	162
		8	6	7	204
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	-5	3	13	11	47
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	-7	3	14	15	22
	-8	3	8	7	250
	-9	3	14	16	178
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		1	34	36	354
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		3	14	18	69
		4	13	17	104
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		6	5	9	206
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		2	10	12	7
		3	6	5	270
		4	10	10	249
		5	13	18	168
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		7	8	3	180
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		3	37	36	194
		4	27	26	165
		5	3	2	33
		6	15	16	5
		7	24	25	353
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	-9	1	4	4	187
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	-7	3	37	38	343
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		3	18	19	170
		4	11	17	235
		5	5	6	189
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		1	12	12	257
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		4	10	10	179
		5	23	18	151
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		-7	20	21	147
		-8	15	17	215
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	-8	0	13	14	180
	-9	0	24	27	180
	-10	0	14	11	180
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		3	14	11	41
		4	22	22	356
		5	26	31	358
		6	10	9	3
		7	6	6	152
		8	6	8	174
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		5	9	8	141
		6	7	9	182
		7	9	11	190
		8	7	10	187
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	-8	1	13	14	8
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		-10	10	8	333
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		1	22	25	28
		2	14	13	1
		3	12	12	238
		4	17	17	180
		5	22	24	183
		6	11	11	189
		7	5	3	306
		8	3	9	341
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	-6	3	32	35	197
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	-9	3	12	17	9
	-10	3	11	10	352
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		1	23	22	185
		2	18	21	175
		3	9	15	252
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	-6	4	14	15	284
	-7	4	16	17	256
	-8	4	11	11	165
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		2	10	6	146
		3	14	16	59
		4	13	14	1
		5	11	15	357
		6	7	10	19
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	-3	5	14	11	105
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		4	7	8	0
		5	5	4	0
		6	12	16	0
		7	10	10	0
		8	4	2	0
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		-5	26	24	0
		-6	24	24	0
		-7	6	7	0
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		-9	9	9	180
		-10	9	9	180
		-11	8	14	180
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		3	31	32	7
		4	6	7	42
		5	7	7	353
		6	15	10	204
		7	8	9	192
	-1	1	18	19	171
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		2	14	13	158
		3	20	23	162
		4	9	9	220
		5	8	8	268
		6	12	15	173
		7	7	7	155
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	-3	2	36	34	164
	-4	2	24	24	197
	-5	2	25	21	213
	-6	2	31	27	205
	-7	2	7	6	219
	-8	2	6	6	146
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	-10	2	8	11	19
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		1	19	20	202
		2	23	23	193
		3	31	31	187
		4	7	7	244
		5	9	9	118
		6	11	13	13
		7	6	6	7
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	-3	3	27	27	38
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	-5	3	32	31	324
	-6	3	23	21	155
	-7	3	12	12	198
6	3	-8	15	14	184
		-9	8	7	236
		-10	3	3	310
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		1	10	10	218
		2	12	9	286
		3	20	22	346
		4	10	10	64
		5	9	11	80
		6	10	11	345
	-1	4	25	20	201
	-2	4	17	12	227
	-3	4	15	17	359
	-4	4	18	17	46
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	-7	4	18	23	66
	-8	4	8	6	322
	-9	4	9	11	206
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		1	10	10	63
		2	18	23	11
		3	13	15	10
		4	8	10	77
		5	9	8	274
		6	22	21	220
		7	22	24	200
	-1	5	18	18	199
	-2	5	16	15	126
	-3	5	7	10	346
	-4	5	13	12	27
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		2	41	39	0
		3	22	20	0
		4	7	7	180
		5	7	6	180
		6	4	1	180
		7	16	16	0
		8	18	20	0
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	-3	7	9	19	22
	-4	7	10	4	3
	-5	7	11	15	4
7	1	0	21	17	29
		1	29	27	11
		2	32	28	3
		3	6	10	196
		4	24	27	183
		5	13	15	173
		6	3	2	177
		7	4	7	337
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TABLE 5. (*Continued.*)

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		−6	41	43	178
		−7	16	14	187
		−8	4	3	119
		−9	13	15	4
		−10	12	14	7
	2	0	34	32	158
		1	28	26	155
		2	29	26	188
		3	19	19	192
		4	6	5	297
		5	4	4	336
		6	3	1	199
		7	6	6	23
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		−2	46	45	353
		−3	28	28	12
		−4	31	29	1
		−5	14	11	198
		−6	24	22	193
		−7	21	25	193
		−8	8	11	220
		−9	13	15	166
		−10	3	4	136
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		1	20	23	198
		2	19	20	163
		3	7	8	335
		4	18	17	350
		5	7	9	353
		6	7	6	69
		7	4	5	114
		−1	28	26	188
		−2	12	7	160
		−3	14	9	123
		−4	20	18	35
		−5	31	31	17
		−6	39	35	338
		−7	12	12	341
		−8	4	7	209
		−9	8	10	186
		−10	7	9	203
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		1	18	17	4
		2	15	18	356
		3	11	11	356
		4	5	6	65
		−1	13	12	237
		−2	25	26	193
		−3	17	19	215
		−4	16	15	204
		−5	8	8	27
		−6	23	27	43
		−7	13	19	9
		−8	5	8	48
		−9	9	10	334
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		1	18	20	21
7	5	2	13	11	339
		−3	10	12	270
		−4	10	13	269
		−5	20	20	187
		−6	24	23	149
		−7	11	8	160
8	0	0	29	29	0
		1	8	8	0
		2	5	4	0
		3	6	5	180
		4	3	1	180
		5	5	5	180
		6	3	2	180
		−1	38	39	0
		−2	5	5	0
		−3	16	16	180
		−4	25	29	180
		−5	20	21	180
		−6	6	6	0
		−7	15	15	0
		−8	8	9	0
		−9	4	2	180
		−10	7	9	0
8	1	0	3	5	348
		1	17	16	316
		2	15	11	189
		3	16	13	167
		4	16	12	170
		5	6	6	337
		6	8	8	2
		−1	15	13	341
		−2	17	13	30
		−3	22	21	27
		−4	23	28	3
		−5	3	4	145
		−6	19	19	197
		−7	27	29	175
		−8	13	15	187
		−9	10	9	186
		−10	6	6	359
8	2	0	29	29	194
		1	16	15	185
		2	6	5	102
		3	4	5	33
		4	5	5	36
		5	7	6	32
		6	4	4	32
		−1	26	23	198
		−2	8	8	220
		−3	12	13	45
		−4	20	19	4
		−5	21	18	5
		−6	13	13	135
		−7	8	6	192
		−8	4	4	87
		−9	4	5	225
		−10	9	12	197
8	3	0	9	10	150
		1	12	14	110
		2	11	10	60
8	3	3	12	13	11
		4	9	9	336
		5	6	7	162
		6	8	8	201
		−1	9	7	214
		−2	11	12	275
		−3	13	16	211
		−4	30	30	165
		−5	19	18	233
		−6	15	16	346
		−7	22	22	17
		−8	15	19	18
		−9	8	8	15
		−10	5	6	185
8	4	0	14	19	8
		1	5	5	71
		−1	23	22	7
		−2	13	12	5
		−3	5	4	219
		−4	20	22	180
		−5	5	7	161
		−6	23	26	287
		−7	9	8	306
		−8	11	7	253
		−9	13	15	286
		−10	11	8	51
8	5	0	11	7	253
		1	13	15	286
		−1	11	8	51
		−2	8	13	79
		−3	15	16	27
		−4	18	16	345
		−5	15	10	81
		−6	17	17	180
9	0	0	17	17	180
		1	24	24	180
		2	12	10	180
		3	9	7	180
		4	3	1	180
		−1	6	4	0
		−2	27	27	0
		−3	34	39	0
		−4	13	15	0
		−5	9	8	0
		−6	5	3	0
		−7	6	8	0
		−8	19	23	180
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		−10	10	8	180
9	1	0	20	16	191
		1	4	1	252
		2	7	7	291
		3	8	7	341
		4	19	17	4
		5	9	11	6
		−1	21	19	171
		−2	24	21	180
		−3	4	2	343
		−4	9	9	13
		−5	24	25	1
		−6	24	24	20
		−7	21	22	349
		−8	6	7	220
		−9	15	20	181
9	1	−10	10	11	176
9	2	0	25	24	340
		1	29	26	351
		2	7	7	21
		3	8	8	33
		4	3	3	127
		5	4	1	313
		−1	10	12	192
		−2	30	33	174
		−3	32	34	183
		−4	4	3	217
		−5	12	9	160
		−6	4	2	112
		−7	11	15	111
		−8	11	13	5
		−9	8	9	354
		−10	8	9	330
9	3	0	15	15	23
		1	10	10	101
		2	4	3	59
		3	8	6	181
		4	6	12	175
		5	11	8	177
		−1	15	15	8
		−2	14	13	356
		−3	7	5	197
		−4	17	19	240
		−5	15	18	199
		−6	19	18	175
		−7	12	12	142
		−8	5	5	78
		−9	9	14	352
		−10	6	7	8
9	4	0	14	17	142
		1	15	16	166
		−1	8	11	5
		−2	16	19	5
		−3	16	14	2
		−4	10	9	37
		−5	15	14	303
		−6	8	5	279
		−7	7	11	288
		−8	5	7	186
		−9	13	13	82
		−10	16	18	13
9	5	−4	13	13	82
		−5	16	18	13
		−6	12	14	355
10	0	0	26	26	180
		1	4	5	180
		2	5	3	0
		3	4	4	0
		4	3	4	0
		−1	24	25	180
		−2	3	5	0
		−4	19	23	0
		−5	17	20	0
		−6	12	14	0
		−8	7	7	0
		−9	2	2	180
		−10	6	8	180
10	1	0	4	3	182
10	1	1	9	9	29
		2	12	14	16
		3	15	15	354
		−1	13	15	169
		−2	7	8	275
		−3	6	6	212
		−4	24	22	180
		−5	8	9	124
		−9	9	9	340
		−10	17	19	341
10	2	0	15	15	6
		1	5	7	23
		2	7	5	187
		3	3	3	213
		−1	19	19	7
		−2	6	5	34
		−3	8	8	355
		−4	18	20	172
		−5	28	26	197
		−6	11	12	178
		−7	9	9	211
		−8	6	4	143
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		−10	3	8	23
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		1	4	9	204
		2	10	11	190
		3	8	10	183
		−1	4	4	22
		−2	14	13	356
		−3	7	5	197
		−4	16	20	12
		−5	4	4	349
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		−7	10	13	185
		−8	10	14	188
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		−1	14	15	187
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		−3	5	1	209
		−4	9	10	355
		−5	17	17	32
		−6	10	12	30
		−7	7	10	5
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		2	11	11	5
		−7	18	19	0
		−8	11	13	0
12	1	−5	8	11	345
		−6	6	4	150
		−7	13	14	191
		−8	13	19	189
		−9	5	10	189
12	2	0	12	13	188
		1	5	5	219
		2	2	2	306
		−1	12	13	195
		−2	14	14	177
		−3	6	5	0
		−4	13	17	17
		−5	14	15	356
		−6	7	5	37
		−7	5	5	45
		−8	2	2	265
		−9	2	5	237
12	3	0	3	1	97
		2	3	8	356
		−2	7	9	227
		−3	13	15	208
		−4	12	14	188
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		−6	6	6	45
		−7	13	15	21
		−8	10	15	11
12	4	0	9	2	6
		1	5	7	34
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		−2	12	12	0
		−3	15	19	0
		−4	7	9	0
		−5	3	3	180
		−6	6	8	180
		−7	7	10	180
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13	2	−1	4	6	189
		−2	6	9	188
		−3	9	12	175
		−4	12	11	201
11	0	−9	7	9	0
11	1	0	15	12	5
		1	8	10	353
		2	3	1	88
		3	4	6	173
		4	8	9	178
		−1	15	13	9
		−2	13	12	7
		−3	13	9	330
		−4	7	6	170
		−5	14	13	204
		−6	23	24	191
		−7	16	18	163
		−8	3	4	25
		−9	10	11	2
11	2	0	12	10	172
		1	16	18	174
		2	8	9	192
		3	2	4	267
		4	2	2	207
		−1	6	6	5
		−2	20	21	4
		−3	20	22	8
		−4	11	10	351
		−5	4	5	101
		−6	8	10	255
		−7	12	13	183
		−8	9	12	181
		−9	8	9	181
11	3	0	12	15	191
		1	8	9	199
		2	3	3	301
		3	4	6	15
		−1	8	7	216
		−2	8	7	162
		−3	11	11	129
		−4	3	4	61
		−5	9	8	20
		−6	17	20	9
		−7	13	15	348
		−8	5	2	74
		−9	8	11	186
11	4	−2	8	9	207
		−3	16	19	180
		−4	12	11	166
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		1	6	5	0
		−1	8	9	0
		−2	13	13	0
		−3	6	7	180
		−4	8	11	180
		−5	17	16	180
		−6	9	7	180
		−7	5	5	180
12	1	1	6	7	176
		2	6	10	188
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		−2	5	4	12
		−3	16	15	8
		−4	14	13	2
		−5	11	2	170
		−6	6	6	18
		−7	6	9	354
		−8	2	8	13
13	3	−3	3	4	343
		−4	3	3	229
		−5	8	12	201
		−6	6	12	176
		−7	2	6	167

EXPERIMENTAL

Crystal Data.—5-Bromogriseofulvin, $C_{17}H_{16}BrClO_6$; $M = 431{\cdot}7$. Monoclinic, $a = 10{\cdot}96$, $b = 8{\cdot}61$, $c = 10{\cdot}27$ Å, $\beta = 108°30'$, $U = 919$ Å^3, $D_m = 1{\cdot}54$ g. cm.$^{-3}$ (by flotation), $Z = 2$, $D_c = 1{\cdot}56$ g. cm.$^{-3}$, $F(000) = 436$, space group $P2_1$ (C_2^2). Absorption coefficient for X-rays ($\lambda = 1{\cdot}542$ Å) $\mu = 47{\cdot}7$ cm.$^{-1}$.

Experimental Measurements.—Rotation, oscillation, Weissenberg, and precession photographs were taken with copper-K_α ($\lambda = 1{\cdot}542$ Å) and molybdenum-K_α ($\lambda = 0{\cdot}7107$ Å) radiation. Cell dimensions were obtained from rotation and precession photographs. For the intensity measurements small crystals were employed, completely bathed in a uniform X-ray beam, and no corrections for absorption were applied. The intensities were estimated visually from multiple-film equatorial and equi-inclination upper-layer Weissenberg photographs obtained from a crystal rotated about the *b*-axis, and from precession photographs of the *hk*0 and 0*kl* zones. Values of $|F_o|$ were derived from the intensities by the usual mosaic-crystal formulæ. The various sets of structure amplitudes were put on the same relative scale by comparison of common reflexions; the absolute scale was obtained at a later stage by correlation with the final calculated structure amplitudes, $|F_c|$. In all 1129 independent structure amplitudes were measured (see Table 5). The crystal density was determined by flotation in aqueous potassium iodide.

Structure Analysis.—The positions of the bromine and the chlorine atom were determined initially from two-dimensional Patterson syntheses along the *a*-, *b*-, and *c*-crystal axes (see Fig. 4) and were confirmed and refined by a study of the three-dimensional Patterson function.

It had been hoped that by having two halogen atoms in the molecule the usual phase ambiguity associated with space group $P2_1$ would be avoided. However, both halogen atoms have very similar y co-ordinates (see Table 1), and the first three-dimensional electron-density distribution based on the halogen phases therefore showed a false mirror plane of symmetry at $y = \frac{1}{4}$.

From this electron-density distribution we learned that the benzene carbon atoms and the atoms directly bonded to them lay near to the plane $y = \frac{1}{4}$. The co-ordinates of the better defined atoms, Br, Cl, O(4), O(2), O(3), O(5), C(2), C(4), and C(6), were estimated carefully from the electron-density values, and the equation of the mean plane through these atoms was calculated. The x- and z-co-ordinates of C(3), C(5), C(7), C(8), C(9), and O(1) were then

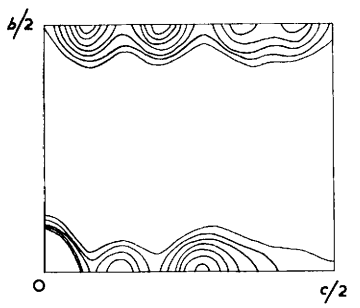

FIG. 4*a*.

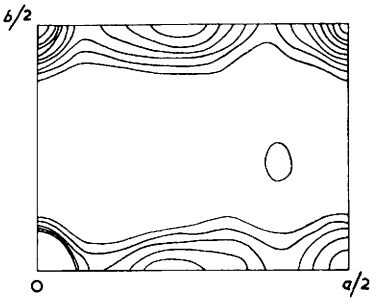

FIG. 4*c*.

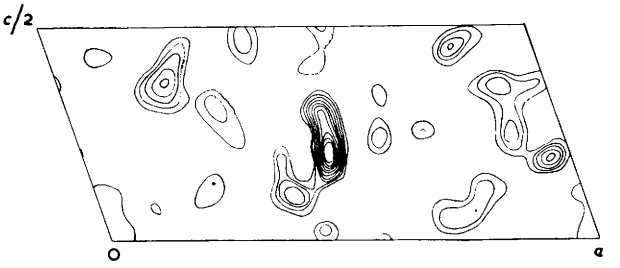

FIG. 4*b*.

FIG. 4. Patterson projections along the *a*, *b*, and *c* crystal axes. Contour scale arbitrary.

obtained by fitting to the electron-density distribution a model of this part of the molecule based on standard bond lengths and valency angles, and the y-co-ordinates were determined by substituting the x- and z-co-ordinates in the equation of the plane. When structure factors based on these fifteen atoms were calculated the average discrepancy between calculated and observed structure amplitudes (R) fell from the previous value of 42·2% to 35·7%.

The y-co-ordinates of the fifteen atoms included in the structure-factor calculation were all rather similar ($y \approx \frac{1}{4}$), and the electron-density distribution which we derived from the improved phases still showed a marked degree of spurious symmetry. Nevertheless, careful consideration of the various peaks in this distribution allowed us to place C(2′), C(3′), C(4′), C(5′), C(6′), C(11), and O(6). With the inclusion of these atoms in the structure-factor calculation the value of R fell to 30·2%.

In the next three-dimensional Fourier synthesis all the carbon and oxygen atoms apart from C(10) were located and on the subsequent calculation of structure factors R fell to 26·3%. A further Fourier synthesis then led to the unambiguous placing of C(10) and the value of R was reduced to 24·3%.

Two further rounds of structure-factor and Fourier calculations were carried out and back-shift corrections for errors due to termination of series were applied to the atomic co-ordinates. The value of R fell to 22·4%.

The next stage of the analysis consisted of adjustment of the atomic co-ordinates and isotropic temperature factors by means of a differential synthesis programme written by Dr. J. G. Sime. The value of R was reduced to 20·0%.

An examination of the agreement between $\sum|F_o|$ and $\sum|F_c|$ for each of the sets of reflections $h0l$, $h1l$, ..., $h5l$ revealed a systematic trend in the scaling factors. This suggested that anisotropic temperature factors should be employed and we therefore undertook some further refinement by means of Dr. J. S. Rollett's least-squares programme [32] which adjusts the positional and anisotropic thermal parameters of the atoms. After several cycles of calculations the value of R fell to 14·0%. The final values of $|F_o|$, $|F_c|$, and α are shown in Table 5.

With the phase constants of Table 5 a final three-dimensional electron-density distribution was evaluated and this is shown in Fig. 1 by means of superimposed contour sections drawn parallel to (010). The corresponding atomic arrangement is illustrated in Fig. 2.

The theoretical atomic scattering factors used in the structure-factor calculations were those of Berghuis *et al.*[33] for carbon and oxygen, those of Tomiie and Stam [34] for chlorine, and the Thomas–Fermi values for bromine.[35] The final atomic co-ordinates, molecular dimensions, and some non-bonded distances are listed in Tables 1 and 2. The parameters defining the anisotropic thermal vibrations are in Table 6; they are values of b_{ij} in the equation

$$\exp(-B\sin^2\theta/\lambda^2) = 2^{-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{23}kl + b_{13}hl)}.$$

TABLE 6.

Anisotropic temperature-factor parameters ($10^5 b_{ij}$).

	b_{11}	b_{22}	b_{33}	b_{12}	b_{23}	b_{13}
C(2)	818	919	1142	−1851	521	450
C(3)	873	2290	1531	−1346	−431	724
C(4)	705	399	1796	−254	−244	547
C(5)	1134	652	1490	−508	−1166	1216
C(6)	1436	548	1520	324	631	2204
C(7)	1005	745	1549	−1777	823	368
C(2′)	1179	722	4097	820	2904	2866
C(3′)	1133	1643	2373	−1088	282	1909
C(4′)	1205	1598	1728	1361	322	1788
C(5′)	1467	1739	2261	3588	1019	1925
C(6′)	1507	2937	1102	− 791	1917	1365
C(8)	684	5057	1062	−1773	382	669
C(9)	674	2143	1206	372	1324	804
C(10)	2242	997	2230	1736	−990	2102
C(11)	1916	4230	2371	2172	−486	447
C(12)	2413	3793	3383	2302	−724	1957
C(13)	2039	1367	2722	−2200	1097	2283
O(1)	483	3980	1706	−599	211	746
O(2)	986	411	1905	209	−288	1015
O(3)	1537	1820	1321	−928	−720	974
O(4)	2036	1238	1986	618	748	3044
O(5)	1854	2839	2406	−222	460	2493
O(6)	1148	2568	3094	795	−880	2572
Cl	1076	2866	1270	−221	−515	807
Br	967	3148	2052	−636	267	1489

The standard deviations of the final atomic co-ordinates were derived from the least-squares residuals by application of the equation

$$\sigma^2(x_i) = \sum_j w_j(\Delta F_j)^2/[(n - s)\sum_j w_j(\partial F_j/\partial x_i)^2].$$

The results are listed in Table 3.

In the application of the heavy-atom method to a non-centrosymmetrical crystal structure the final electron-density distribution is dependent to a considerable extent on the choice of

[32] Rollett, in " Computing Methods and the Phase Problem in X-ray Crystal Analysis," ed. Pepinsky, Robertson, and Speakman, Pergamon Press, Oxford, 1961, p. 87.

[33] Berghuis, Haanappel, Potters, Loopstra, MacGillavry, and Veenendaal, *Acta Cryst.*, 1955, **8**, 478.

[34] Tomiie and Stam, *Acta Cryst.*, 1958, **11**, 126.

[35] " Internationale Tabellen zur Bestimmung von Kristallstrukten," Borntraeger, Berlin, 1935, Vol. II, p. 572.

the correct set of atomic sites for the lighter atoms. This is shown clearly in the description by Hodgkin *et al.* of their analysis of the structure of vitamin B_{12} hexacarboxylic acid.[36] In the projection along the *b*-axis in $P2_1$, however, a centrosymmetrical electron-density distribution is involved and this is much less dependent on the assumed light-atom positions, the signs of the structure factors employed in the Fourier synthesis being largely determined

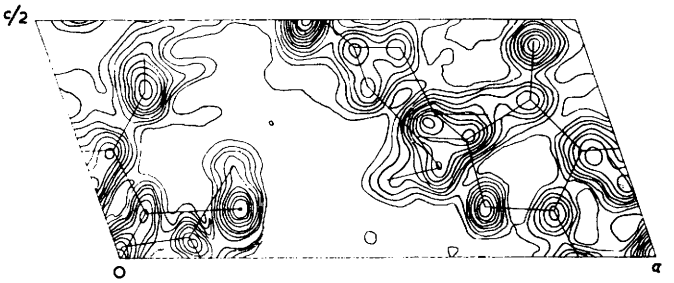

FIG. 5. Electron-density projection on (010). Contour interval 1 e/Å^2, except around the bromine and chlorine atoms where the interval is 5 e/Å^2. The positions deduced for the atoms by the three-dimensional refinement are indicated.

by the heavy atoms, *i.e.*, by the bromine and the chlorine atom in the present case. The x and z atomic co-ordinates resulting from the three-dimensional refinement (Table 1) are shown superimposed on the *b*-axis electron-density projection in Fig. 5. There is a satisfactory measure of agreement.

The extensive calculations were performed on the Glasgow University DEUCE computer with programmes devised by Dr. J. S. Rollett and Dr. J. G. Sime. We are grateful to Professor J. Monteath Robertson, F.R.S., for his encouragement, to Dr. T. Walker (Glaxo Laboratories Ltd.) for supplies of 5-bromogriseofulvin, to Dr. A. I. Scott for helpful discussions, and to the Department of Scientific and Industrial Research for a maintenance grant (to W. A. C. B.).

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[36] Hodgkin, Pickworth, Robertson, Prosen, Sparks, and Trueblood, *Proc. Roy. Soc.*, 1959, *A*, **251**, 306.