

X-Ray Analysis of Synthetic (4*S*)-2-(Prop-2-enyl)rethron-4-yl (1*R*,3*R*)-Chrysanthemate 6-Bromo-2,4-dinitrophenylhydrazone, and Chiroptical Correlation with the Six Natural Pyrethrin Esters

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The X-ray structure and absolute configuration of (4*S*)-2-(prop-2-enyl)rethron-4-yl (1*R*,3*R*)-chrysanthemate (10) have been determined for the 6-bromo-2,4-dinitrophenylhydrazone derivative, $a = 9.840 \pm 0.008$, $b = 7.724 \pm 0.01$, $c = 19.783 \pm 0.015$ Å, $\beta = 105.00 \pm 0.05^\circ$, $Z = 2$, space group $P2_1$ for 614 observed reflections. Chiroptical data (o.r.d. and c.d.) for (10), and for the six natural pyrethrin esters (1)–(6), show that the latter all have the same *S*-configuration at C(4).

THE insecticidal activity of the six natural pyrethrin esters (1)–(6),¹ which occur in *Chrysanthemum cinerariaefolium* is combined with low mammalian toxicity, short persistence, and rapid insect paralysis ('knock-down') effects. These desirable characteristics have inspired synthesis of many analogues in the search for new commercial insecticides. Hypothetical structure-activity relationships have been discussed in some detail.² Satisfactory development of such relationships requires reliable information on absolute stereochemistry, molecular dimensions, and conformation. Knowledge of the absolute configuration of the cyclopropane acid section of the pyrethrins is soundly based on chemical³ and crystallographic † work. However, stereochemical assignments⁴ for the ketols are much less certain. The chirality at C(4) of (+)-pyrethrolone (7) was deduced from oxidation of the (+)-methyl ether (8) to (–)-2-

methoxysuccinic acid of known configuration. The ketol methyl ether (8) was prepared by treatment of the semicarbazone ‡ (9) of (+)-pyrethrolone with methanolic acid; the allylic C(4)-O bond must have been cleaved in this sequence (despite a contrary statement⁴), and partial inversion, retention, or racemisation may have ensued. Indeed, the (±)-ketol ether (8) was obtained from (+)-pyrethrolone using methanolic acid.⁴ The reported specific rotations support this contention Pyrethrolone methyl ether $[\alpha]_D^{26} +10.5^\circ$ (EtOH) was oxidised to 2-methoxysuccinic acid $[\alpha]_D^{27} -25^\circ$ (Me₂CO) {optical purity ca. 43%, the pure (–)-(S)-acid⁵ having $[\alpha]_D^{13} -58.2^\circ$ (Me₂CO)}. However, pure (+)-pyrethrolone methyl ether has since been shown⁶ to have $[\alpha]_D^{20}$

¹ L. Crombie and M. Elliot, *Fortschr. Chem. Org. Naturstoffe*, 1961, **19**, 120.

² M. Elliot, *Chem. and Ind.*, 1969, 778; *Bull. World Health Organisation*, 1971, **44**, 315.

³ L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1954, 470.

⁴ Y. Katsuda, T. Chikamoto, and Y. Inouye, *Bull. Agric. Chem. Soc. Japan*, 1958, **22**, 427; 1959, **23**, 174.

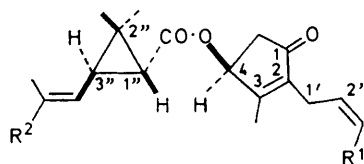
⁵ T. Purdie and W. Marshall, *J. Chem. Soc.*, 1895, **67**, 944.

⁶ M. Elliot, *J. Chem. Soc.*, 1964, 888; T. F. West, *ibid.*, 1944, 240.

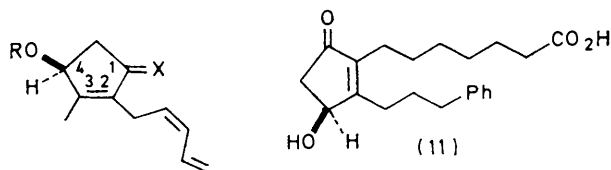
† X-Ray analysis of the *p*-bromophenacyl ester of natural (1*R*,3*R*)-*trans*-chrysanthemate acid confirms the chemical results (G. Ferguson, personal communication).

‡ Elemental analysis of this semicarbazone supports the molecular formula given by these authors;⁴ this formula is, however, incorrect.

+99° (MeOH); the ether used in the oxidation was thus *ca.* 11% optically pure. Isolation of methoxy-succinic acid of 43% optical purity remains unexplained.



- (1) $R^1 = \text{CH}=\text{CH}_2, R^2 = \text{Me}$ (Pyrethrin I)
- (2) $R^1 = \text{CH}=\text{CH}_2, R^2 = \text{CO}_2\text{Me}$ (Pyrethrin II)
- (3) $R^1 = R^2 = \text{Me}$ (Cinerin I)
- (4) $R^1 = \text{Me}, R^2 = \text{CO}_2\text{Me}$ (Cinerin II)
- (5) $R^1 = \text{Et}, R^2 = \text{Me}$ (Jasmolin I)
- (6) $R^1 = \text{Et}, R^2 = \text{CO}_2\text{Me}$ (Jasmolin II)
- (10) $R^1 = \text{H}, R^2 = \text{Me}$



- (7) $R = \text{H}, X = \text{O}$
- (8) $R = \text{Me}, X = \text{O}$
- (9) $R = \text{H}, X = \text{NNHCONH}_2$

We have therefore reinvestigated the problem by crystallographic methods.*

synthetic (+)-allethronyl (+)-*trans*-chrysanthemate (10) [*(S)*-bioallethrin]. Intensity data were collected with a four-circle diffractometer, and 614 reflections were considered observed. The structure was solved using the standard heavy-atom procedure, and refined by least-squares and difference Fourier methods. The *R* index converged to 0.0885 using anisotropic temperature factors for bromine, and individual isotropic factors for other atoms. General views of the final structure are shown in Figures 1 and 2.

The determination of the absolute configuration was attempted in three ways. First, the structure determination itself demonstrates the relation between the asymmetric centres in the rethronolone and chrysanthemic acid parts of the molecule. Since (+)-*trans*-chrysanthemic acid has the 1*R*,3*R*-stereochemistry,³ it follows by inspection that the ketol has the 4*S*-configuration. This deduction was confirmed by independent measurement of Bijvoet pairs of reflections. Criteria for the choice of these reflections are discussed in the Experimental section. Of the twenty-two pairs compared (Table 2), twenty-one indicated the absolute configuration displayed in Figures 1 and 2 and compound (10). In agreement, the *R* factor for this configuration was significantly lower (at the 0.025 level) than that of its enantiomer.

For crystallographic purposes, the numbering scheme of Figure 1 was employed. Bond lengths and angles are

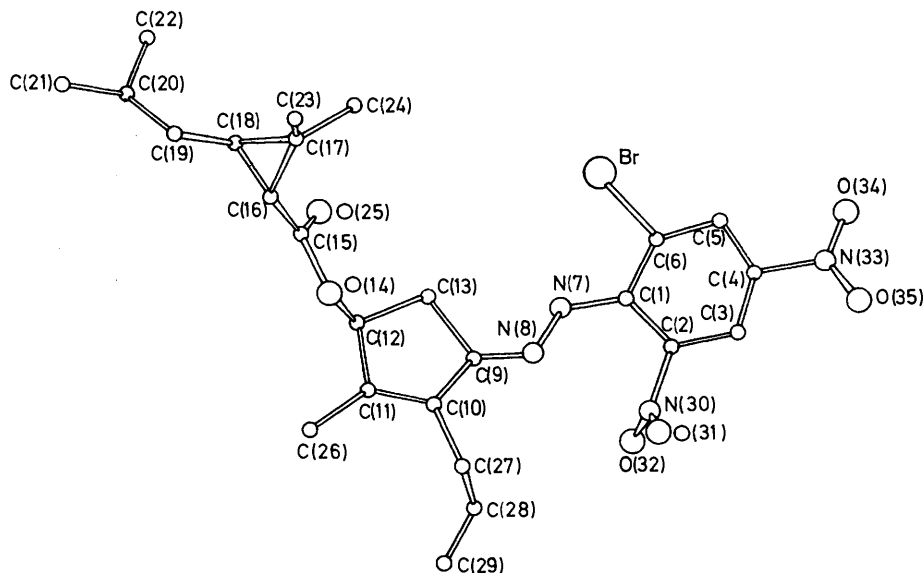


FIGURE 1 (+)-Allethronyl (+)-*trans*-chrysanthemate 6-bromo-2,4-dinitrophenylhydrazone. A general view of the final 1*R*,3*R*,4*S*-structure, and the crystallographic numbering scheme

For structural work, the heavy-atom derivative of a suitable chiral rethrin was sought, in order to provide adequate anomalous dispersion. After a series of trials, a satisfactory subject for *X*-ray examination was found in the 6-bromo-2,4-dinitrophenylhydrazone of

* See ref. 7 for a preliminary account.

⁷ M. J. Begley, L. Crombie, D. J. Simmonds, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1972, 1276.

displayed, with their standard deviations, in Figures 3 and 4, and the arrangement of molecules in the unit cell in Figure 5. The cyclopentenone arylhydrazone section [atoms (1)—(13)] of the molecule is essentially flat and approximately in the plane $y = 0$. The corresponding section of the second molecule, related to the first by the two-fold screw axis near the N(7)–N(8) bond, forms a parallel plane near $y = 1/2$. These 'planar' sections

form a close-packed stack parallel to the y axis. The attached chrysanthemyl unit [atoms (15)—(25)] is relatively unconstrained by neighbouring molecules. In particular, the 2-methylpropenyl side chain is not very

plane, and the mean bond length and bond angle are 1.40 Å and 120°. Both nitro-functions are essentially flat, but the 2-nitro-group makes an angle of 65° with the aryl ring, presumably in order to avoid contact with

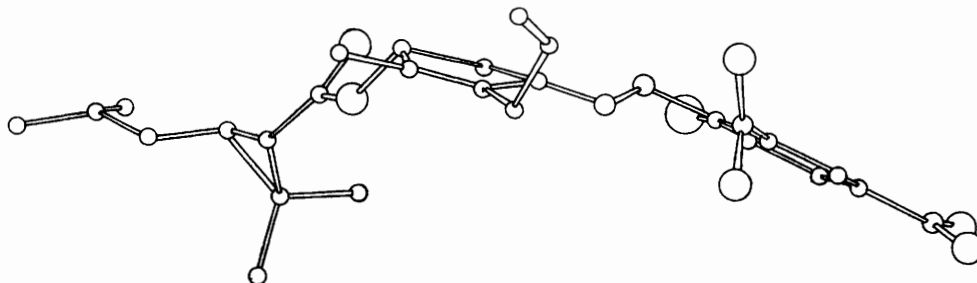


FIGURE 2 View of the out-of-plane and nitro-groups of the hydrazone

restricted, and vibration about the C(18)—C(19) bond is indicated by the high temperature factors (Table 3) of C(20)—(22).

The aromatic ring is planar ($\chi^2 = 0.41$) with all directly attached atoms [Br, N(7), N(30), N(33)] in the

N(8), whilst the 4-nitro-function is twisted only 10° from the benzene plane. The five-membered ring adopts

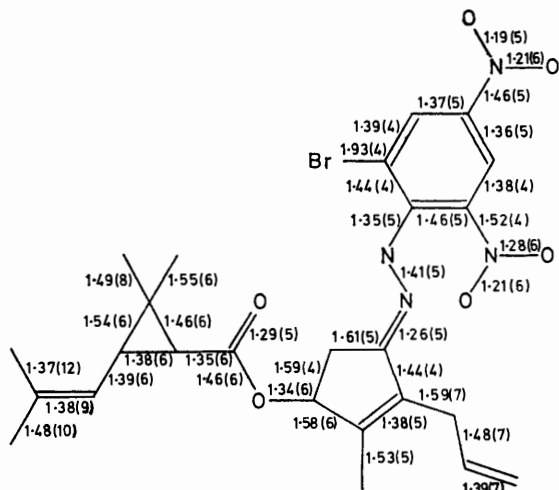


FIGURE 3 Bond lengths (Å) and standard deviations of the hydrazone

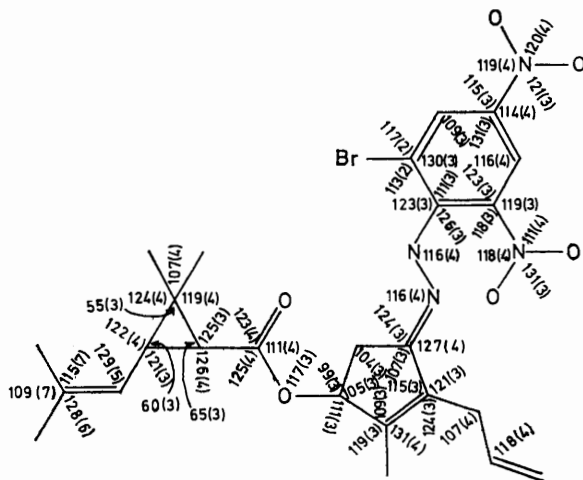


FIGURE 4 Bond angles (deg.) and standard deviations of the hydrazone

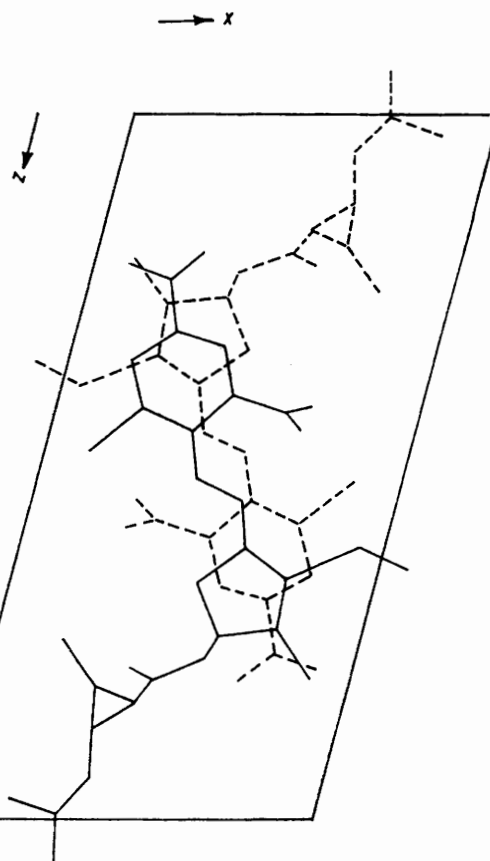


FIGURE 5 Arrangement of molecules in the unit cell of the hydrazone, viewed down the b axis

an envelope shape, with C(9)—(12) in plane, and C(13) 0.18 Å out of plane. Interestingly, both N(8) and C(26) are also out of this plane, by 0.17 and 0.22 Å respectively, with N(8) on the same side of the ring as C(13), and C(26) on the opposite side. The N(7)—N(8) link between the five- and six-membered rings is characterised by the torsion angles C(1)—N(7), 32°; N(7)—N(8), 10°; and N(8)—C(9), 15°. Torsion angles for the allyl attachment

at C(10) are C(10)–C(27), 79°, and C(27)–C(28), 61°. In the crystal C(27) does not lie near a line through C(23) and C(24), as has been contemplated in structure–activity relations.² Atoms O(14), C(15), O(25), and C(16) of the ester unit form a plane, which also includes C(12), and this plane has dihedral angles of 55 and 75° with the five-, and three-membered rings, respectively. The disposition of C(12) and C(16) is *s-trans* rather than *s-cis*. Finally, the 2-methylpropenyl unit C(19)–(22) is approximately flat (high temperature factors), and *ca.* 65° from the cyclopropane plane.

With the absolute configuration of (*S*)-bioallethrin [(4*S*)-2-(prop-2-enyl)rethron-4-yl (1*R*,3*R*)-chrysanthemate (10)] completely defined, the determination of the absolute configuration of the six natural pyrethrin esters became possible as a result of the elegant chromatographic separation work of Dr. F. E. Rickett.⁸ Comparative o.r.d. and c.d. data for the compounds (1)–(6) and for (10), are shown in Figures 6 and 7. The chiroptical behaviour in the region of the spectra illustrated is determined by the configuration at C(4) and convincingly demonstrates that all the esters have the same absolute stereochemistry at this centre: c.d. maxima

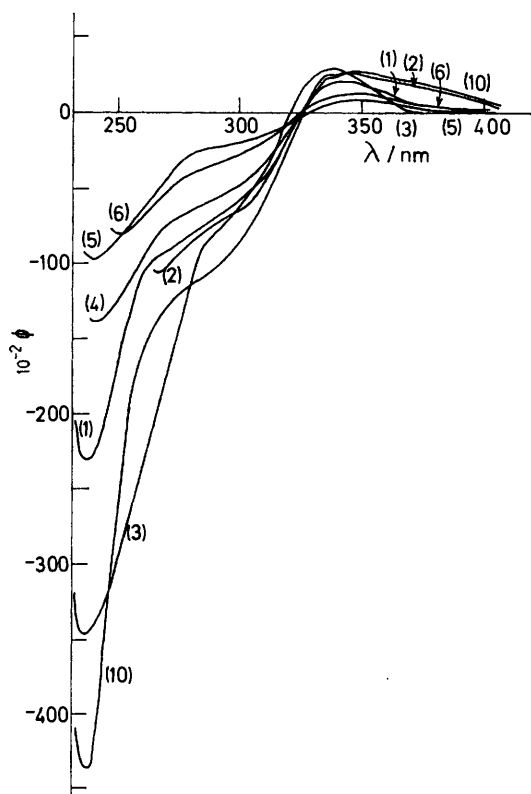


FIGURE 6 O.r.d. data for natural pyrethrin esters (1)–(6) and (*S*)-bioallethrin (10)

are listed in Table I. In view of the lability of the natural rethrins, however, absolute values for the curve amplitudes must be accepted as subject to error. O.r.d.

⁸ F. E. Rickett, *J. Chromatography*, 1972, **66**, 356.

⁹ M. Miyano and C. R. Dorn, *J. Amer. Chem. Soc.*, 1973, **95**, 2664.

data for the crystalline 6-bromo-2,4-dinitrophenylhydrazone of (10), used in the X-ray study, are given in the Experimental section.

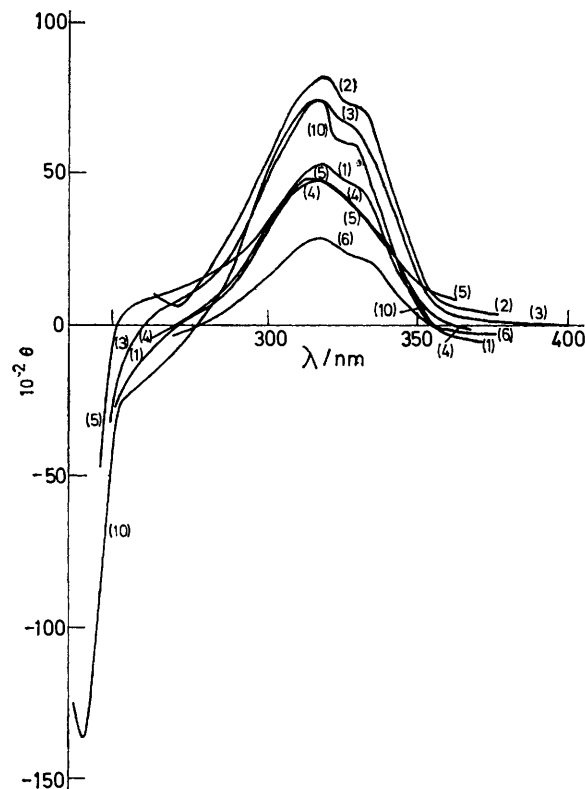


FIGURE 7 C.d. spectra for natural pyrethrin esters (1)–(6) and (*S*)-bioallethrin (10)

Since this work was reported in preliminary form, Miyano and Dorn⁹ have shown that the prostaglandin relative (11) (enantiomeric, unnatural prostaglandin

TABLE I

C.d. of natural pyrethrin esters and (<i>S</i>)-bioallethrin				
Compound	$\lambda_{\text{max}}/\text{nm}$	$10^{-2}\theta$	$\lambda_{\text{min}}/\text{nm}$	$10^{-2}\theta$
(1)	317	54	330	47
(2)	317	80	329	73
(3)	318	76	329	67
(4)	316	48	328	42
(5)	316	49	328	41
(6)	317	29	330	26
(10)	317	71	328	61

series) can be correlated with natural (+)-pyrethrolone by o.r.d. and c.d. data. This result further supports the absolute configuration at C(4) shown in (7).

EXPERIMENTAL

(+)-*Allethronyl* (+)-*trans-Chrysanthemate* 6-Bromo-2,4-dinitrophenylhydrazone.—(*S*)-Bioallethrin (100 mg) in dry, redistilled dimethyl sulphoxide (0.3 cm³)¹⁰ was added to 6-bromo-2,4-dinitrophenylhydrazine (80 mg). The mixture was acidified with aqueous hydrochloric acid (0.05 cm³, 0.1M), and set aside at ambient temperature for 50 h. The whole mixture was separated by p.l.c. on silica gel G, using benzene–ethyl acetate (95 : 5). The major product

¹⁰ J. Carrick and J. W. Rasburn, *Canad. J. Chem.*, 1965, **43**, 3453.

band was isolated, and yielded the desired *hydrazone* as thin yellow plates (93 mg, 54%), m.p. 80–83° (decomp.) from methanol (Found: C, 53.7; H, 5.2; Br, 12.5; N, 9.6. $C_{25}H_{29}BrN_4O_6$ requires C, 53.5; H, 5.2; Br, 14.3; N, 10.0%), m/e 562 (M) and 560 (M), λ_{max} (dioxan) 261 (ϵ 12,700) and 390 nm (21,790), $[\alpha]_D^{25} -92.2^\circ$ (c 0.11, dioxan), o.r.d. λ_{min} 292 (λ_{inf} 330), λ_{max} 360 nm, $a = +128$.

Crystallography.—Oscillation and Weissenberg photographs were taken about the b axis to establish the space group and approximate unit cell dimensions. Only small specimens of the thin plates could be obtained, and for intensity measurement one was mounted about the b axis on a Hilger and Watts four-circle diffractometer. The unit cell dimensions were refined by a least squares fit on the positions of 12 peaks found on the diffractometer. Intensity data (both the hkl and $h\bar{k}l$ sets) were collected with Mo- K_α radiation for $2\theta \leq 40^\circ$, using $\omega/2\theta$ scan. 614 Independent observed reflections, with net count $> 3\sigma$, were used in structure solution and refinement. No absorption corrections were made. Data reduction and subsequent crystallographic calculations were performed using the National Research Council (Ottawa) programs of Ahmed, Hall, Pippy, and Saunders. Atomic scattering factors were taken from ref. 11.

Crystal Data.— $C_{25}H_{29}BrN_4O_6$, $M = 561.43$. Monoclinic, $a = 9.840 \pm 0.008$, $b = 7.724 \pm 0.01$, $c = 19.783 \pm 0.015$ Å, $\beta = 105.00 \pm 0.05^\circ$, $U = 1452$ Å³, $Z = 2$, $D_c = 1.28$, $F(000) = 580$. Space group $P2_1$ from systematic absences $0k0$ when $k = 2n + 1$. Mo- K_α radiation $\lambda = 0.7107$ Å, $\mu = 15.46$ cm⁻¹.

The bromine, x, z co-ordinates were found from a Patterson synthesis using the observed intensity data sharpened by $1/L\phi$ corrections. A three-dimensional Fourier summation enabled a further 27 non-hydrogen atoms to be located despite additional mirror planes perpendicular to y at 0 and 1/2. After a structure factor calculation with the new model, a second Fourier synthesis appeared to reveal the remaining non-hydrogen atoms. However many of the atoms are close to the false mirror plane and in some cases a wrong choice had been made. After three more structure factor calculations, omitting certain dubious atoms, and three corresponding difference syntheses, the correct positions of all non-hydrogen atoms were found.

Four cycles of block-diagonal least squares refinement of atomic positions and isotropic temperature factors were performed with all the data, and unit weights. After analyses of the $F_c - F_o$ agreement, a weighting scheme $w = (|F_o|/30)^2$ for $|F_o| \leq 30$, and $w = (30/|F_o|)^2$ for $|F_o| > 30$ was adopted. Four more cycles of least-squares refinement now reduced R to 0.108. The temperature factors of the bromine atom were then allowed to vary anisotropically, and four more cycles lowered R to 0.0887.

At this stage absolute stereochemistry was investigated by introducing anomalous scattering factors for bromine into the structure factor calculations. The agreement factor R had values 0.0885 and 0.0890 for the two configurations. This difference in R is significant at the 0.025 level,¹² and indicates a 97.5% probability that the configuration shown in Figure 1 is correct. This assignment is supported by examination of Bijvoet pairs of reflections. A list was prepared of hkl and $h\bar{k}l$ pairs of reflections for which F_c differed between the sets by $> 10\%$

¹¹ 'International Tables for Crystallography,' Kynoch Press, Birmingham, vol. III, 1962.

¹² W. C. Hamilton, *Acta Cryst.*, 1965, **8**, 502.

and for which the observed intensities differed by more than 3σ . Twenty-two such pairs were found. Table 2 shows

TABLE 2

Comparison of F_c and I for the Bijvoet pairs of reflections

hkl	$F_c(hkl)$	$F_c(h\bar{k}l)$	$I(hkl)$	$I(h\bar{k}l)$	Indication
0,1,9	14.57	21.38	95	207	+
0,2,3	24.41	20.01	217	124	+
0,2,5	44.73	50.62	883	1115	+
0,2,9	20.76	23.42	127	216	+
0,3,5	22.79	25.50	136	201	+
0,4,0	49.85	43.77	453	544	—
1,1,0	39.59	32.39	1571	1144	+
1,1,2	34.40	31.23	888	650	+
1,2,0	5.67	12.15	187	359	+
1,4,—1	33.35	37.48	205	529	+
2,1,—1	5.72	15.06	94	302	+
2,1,6	28.99	34.74	268	390	+
2,2,—3	22.41	26.35	269	459	+
2,3,1	34.51	31.23	294	217	+
2,4,—8	32.95	29.62	216	103	+
3,1,1	29.31	32.79	416	487	+
3,1,4	35.22	38.80	382	446	+
3,2,3	20.37	23.90	154	202	+
4,2,—2	33.15	37.62	313	498	+
4,2,—5	30.54	34.09	221	338	+
4,2,—7	31.19	27.73	249	164	+
5,1,—3	25.04	29.75	195	255	+

TABLE 3

Atomic co-ordinates ($\times 10^3$) and thermal parameters with standard deviations in parentheses

Atom	x/a	y/b	z/c	B
Br	129(0)	0(0)	479(0)	*
C(1)	396(3)	—3(9)	449(2)	4.3(8)
C(2)	480(3)	11(8)	399(2)	3.4(8)
C(3)	421(3)	40(6)	328(2)	3.5(9)
C(4)	279(4)	58(6)	308(2)	4.6(11)
C(5)	181(3)	51(4)	346(2)	1.8(7)
C(6)	248(3)	16(9)	416(2)	4.5(9)
N(7)	446(3)	—34(6)	518(2)	5.1(8)
N(8)	581(4)	34(7)	550(2)	8.1(11)
C(9)	619(3)	27(7)	616(2)	3.2(8)
C(10)	755(3)	73(5)	660(2)	2.6(9)
C(11)	763(4)	78(6)	731(2)	4.4(10)
C(12)	612(4)	39(6)	742(2)	3.9(10)
C(13)	511(3)	26(6)	665(2)	2.6(8)
O(14)	592(3)	187(4)	773(1)	4.6(7)
C(15)	472(4)	195(6)	803(2)	4.4(10)
C(16)	436(4)	333(6)	836(2)	2.7(8)
C(17)	318(5)	450(7)	808(2)	7.1(14)
C(18)	336(4)	335(6)	874(2)	3.0(9)
C(19)	366(5)	406(7)	940(3)	6.7(14)
C(20)	297(7)	381(10)	992(3)	11.6(21)
C(21)	327(6)	464(12)	1062(3)	11.6(19)
C(22)	156(10)	351(18)	968(5)	22.4(40)
C(23)	315(5)	643(7)	810(3)	6.4(13)
C(24)	200(5)	392(7)	744(3)	6.9(14)
O(25)	390(2)	64(3)	783(1)	4.2(7)
C(26)	888(4)	91(6)	795(2)	4.5(11)
C(27)	885(5)	106(7)	628(3)	6.9(13)
C(28)	938(5)	—66(6)	614(2)	6.5(13)
C(29)	1076(6)	—109(8)	649(3)	9.3(17)
N(30)	638(3)	—11(7)	424(1)	4.0(7)
O(31)	702(3)	128(5)	414(2)	6.3(8)
O(32)	682(3)	—153(5)	443(1)	5.5(7)
N(33)	221(4)	85(6)	233(2)	7.8(12)
O(34)	97(3)	78(4)	210(2)	7.7(9)
O(35)	297(3)	117(5)	195(2)	6.6(8)

* Anisotropic temperature factors † for bromine

B_{11}	0.0115(4)
B_{22}	0.0211(8)
B_{33}	0.0035(1)
B_{12}	0.0037(31)
B_{13}	0.0075(4)
B_{23}	0.0007(15)

† In the form $\exp[-(h^2B_{11} + k^2B_{22} + l^2B_{33} + hkB_{12} + \dots + hlB_{13} + klB_{23})]$.

that twenty-one pairs supported the assigned absolute configuration.

As there were insufficient observed data (limits of crystal size) to allow for anisotropic vibration of the remaining non-hydrogen atoms, refinement was terminated. The final R factor was 0.0885 after a total of 12 cycles, the largest parameter shifts being of the order 0.4σ . A final difference map showed no peaks or depressions greater than $0.4 \text{ e } \text{\AA}^{-3}$. Final atomic co-ordinates and thermal parameters are listed in Table 3. Observed and calculated

structure factors are listed in Supplementary Publication No. 20984 (3 pp.).*

We thank the S.R.C. for a Postdoctoral award to M. J. B. Mr. N. C. Brown (Cooper Technical Bureau) and Roussel Uclaf kindly provided samples of the pyrethrin esters and (S)-bioallethrin.

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