

X-ray Studies of C<sub>25</sub> Terpenoids. IV. The Crystal Structure of Retigeranic Acid *p*-Bromoanilide

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The structure of retigeranic acid, C<sub>25</sub>H<sub>38</sub>O<sub>2</sub>, a C<sub>25</sub> terpenoid isolated from a lichen, has been determined by X-ray analysis of its *p*-bromoanilide. The crystal is monoclinic, space group *P*2<sub>1</sub> with  $a=13.14_2$ ,  $b=9.37_7$ ,  $c=11.49_8$  Å,  $\beta=102.4_2^\circ$ ,  $Z=2$ . The absolute crystal structure was determined from the phases calculated by the anomalous dispersion method for 409 Friedel pairs measured on a four-circle diffractometer with Mo *K* $\alpha$  radiation. Refinement of the structure was carried out by the least-squares method for 1638 independent reflexions measured with Cu *K* $\alpha$  radiation. The final *R* value is 0.09 without hydrogen atoms. The molecule has a unique pentacyclic structure consisting of four five-membered rings and one six-membered ring. The structure has no close correlation with the sesterterpenes known to date.

## Introduction

Retigeranic acid, C<sub>25</sub>H<sub>38</sub>O<sub>2</sub>, was isolated from the lichens of *Lobaria isidiosa* Vain. var. *subsidiosa* Asah. collected in the eastern Himalayas, Bhutan (Kaneda, Takahashi, Iitaka & Shibata, 1972). The same compound was also found in the lichens of *L. retigera* group collected in the western Himalayas (Rao, Sarma & Seshadri, 1965, 1966). We investigated the structure of retigeranic acid by chemical methods based on the spectroscopic data and suggested that it may be a sesterterpene having an  $\alpha,\beta$ -unsaturated carboxyl group. To date several sesterterpenes have been reported including: ophiobolins A (Nozoe *et al.*, 1965; Morisaki, Nozoe & Iitaka, 1968), B and C (Nozoe, Hirai & Tsuda, 1966), D (Itai, Nozoe, Okuda & Iitaka, 1969), ceroplastol I (Iitaka, Watanabe, Harrison & Harrison, 1969), cheilanthatriol (Khan, Zaman, Chetty, Gupta & Dev, 1971) and fusicocin (Ballio *et al.*, 1968; Hough, Hursthouse, Neidle & Rogers, 1968; Barrow, Barton, Chain, Ohnsorge & Thomas, 1971; it has not yet been confirmed that fusicocin really is a sesterterpene). However, in view of the novelty of the present structure having no close correlation with the sesterterpenes known to date, we undertook the X-ray analysis. A preliminary report of the present work has already been published (Kaneda, Takahashi, Iitaka & Shibata, 1972).

## Experimental

Treatment of retigeranic acid with thionyl chloride at room temperature afforded the acid chloride, which readily reacted with *p*-bromoaniline to yield retigeranic acid *p*-bromoanilide. The crystals grown from acetone solution were colourless prisms elongated along the *b* axis. The density was measured by the flotation method using a mixture of hexane and carbon tetrachloride.

## Crystal data

Retigeranic acid *p*-bromoanilide, C<sub>31</sub>H<sub>42</sub>NOBr,  
M.W. 524, m.p. 276 ~ 278 °C,  $[\alpha]_D^{25} = 56.2^\circ$ .

Monoclinic, space group *P*2<sub>1</sub>.

$a=13.142 \pm 0.007$ ,  $b=9.377 \pm 0.005$ ,

$c=11.498 \pm 0.006$  Å,  $\beta=102.42 \pm 0.05^\circ$ .

$U=1383.8$  Å<sup>3</sup>,  $D_m=1.25_4$  g cm<sup>-3</sup>,  $D_x=1.262$  g cm<sup>-3</sup>,

$Z=2$ .  $F(000)=554$ ,  $\mu$  for Cu *K* $\alpha=23.3$  cm<sup>-1</sup>,

$\mu$  for Mo *K* $\alpha=16.4$  cm<sup>-1</sup>.

The lattice constants and intensity data were derived from measurements made on a Rigaku automatic four-circle X-ray diffractometer with Ni-filtered Cu *K* $\alpha$  radiation. For measuring the anomalous dispersion effect, Zr-filtered Mo *K* $\alpha$  radiation was used. Integrated intensities were measured by the  $\omega$ - $2\theta$  scan method (scan speed 4°  $2\theta$  min<sup>-1</sup>) for a crystal of dimensions 0.26 × 0.13 × 0.45 mm. The background was counted at both sides of the diffraction peak for 10 s. Weak reflexions having net intensities less than 3 $\sigma$  were omitted from the data. A total of 1638 independent data were obtained out of 1900 theoretically possible within 110°  $2\theta$ . Anomalous dispersion data were measured for 818 strong reflexions, consisting of *hkl* and *h $\bar{k}$ l* Friedel pairs within  $2\theta < 45^\circ$  with a scan speed of 2°  $2\theta$  min<sup>-1</sup>. These intensities were corrected for Lorentz and polarization factors but no correction was applied for absorption.

## Determination of the structure

The *x* and *z* coordinates of the bromine atom were determined on the Harker section and the *y* coordinate was arbitrarily chosen to be 0.5. The phases of about 400 reflexions were then evaluated by the anomalous dispersion method (Hall & Maslen, 1965) based on the Mo data. The resulting Fourier map, which had no apparent mirror plane, revealed 29 light atoms constituting the skeleton of the molecule. This structure when represented by the left-handed coordinate system gives the correct absolute configuration, since the anomalous data were collected for the reflexions indexed according to the left-handed set of axes.

A difference Fourier synthesis based on the Cu data enabled us to find the locations of the 4 remaining

Table 1. *Final atomic parameters and their estimated standard deviations*

Temperature factors are of the form  $T = \exp \{ -(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl) \}$ .

To represent the correct absolute configuration, the parameters should be referred to a left-handed set of axes.

	x	y	z	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
Br	0-8920 (2)	0-5018 (0)	0-9933 (2)	0-0106 (2)	0-0387 (6)	0-0104 (2)	-0-0022 (3)	-0-0040 (1)	0-0020 (4)
C(1)	0-1912 (10)	0-5169 (23)	0-2256 (13)	0-0043 (10)	0-0157 (27)	0-0097 (15)	0-0001 (16)	0-0005 (9)	0-0022 (22)
C(2)	0-2891 (11)	0-4287 (17)	0-2227 (12)	0-0056 (10)	0-0106 (23)	0-0056 (13)	0-0004 (13)	0-0004 (9)	-0-0004 (14)
C(3)	0-3720 (10)	0-5020 (20)	0-1619 (11)	0-0062 (10)	0-0108 (22)	0-0052 (11)	0-0027 (15)	0-0006 (8)	0-0034 (17)
C(4)	0-3813 (14)	0-6617 (19)	0-1830 (16)	0-0083 (14)	0-0073 (23)	0-0126 (20)	0-0010 (15)	0-0012 (13)	0-0012 (18)
C(5)	0-4935 (12)	0-6988 (18)	0-1688 (15)	0-0054 (11)	0-0091 (23)	0-0122 (19)	-0-0014 (14)	0-0041 (12)	-0-0006 (18)
C(6)	0-5581 (12)	0-5829 (18)	0-2435 (13)	0-0065 (11)	0-0106 (23)	0-0073 (14)	0-0014 (14)	0-0017 (10)	-0-0004 (16)
C(7)	0-6550 (12)	0-5337 (21)	0-1970 (13)	0-0073 (12)	0-0156 (29)	0-0086 (15)	-0-0031 (17)	0-0039 (11)	0-0012 (20)
C(8)	0-6151 (14)	0-4079 (22)	0-1137 (15)	0-0089 (14)	0-0163 (30)	0-0095 (17)	-0-0012 (18)	0-0045 (13)	0-0037 (20)
C(9)	0-5379 (12)	0-3262 (21)	0-1803 (15)	0-0044 (10)	0-0162 (29)	0-0113 (18)	-0-0028 (15)	0-0041 (11)	-0-0040 (20)
C(10)	0-4810 (10)	0-4495 (16)	0-2347 (11)	0-0053 (9)	0-0101 (22)	0-0032 (10)	0-0012 (12)	0-0018 (8)	0-0023 (12)
C(11)	0-4539 (10)	0-4013 (15)	0-3503 (12)	0-0035 (9)	0-0047 (17)	0-0082 (14)	0-0019 (11)	0-0009 (9)	-0-0005 (14)
C(12)	0-3561 (10)	0-3923 (16)	0-3478 (12)	0-0035 (9)	0-0069 (19)	0-0069 (13)	-0-0013 (11)	0-0010 (8)	-0-0026 (14)
C(13)	0-3002 (11)	0-3538 (21)	0-4467 (13)	0-0046 (10)	0-0186 (30)	0-0056 (13)	0-0022 (15)	0-0020 (9)	-0-0006 (17)
C(14)	0-2119 (11)	0-4570 (22)	0-4403 (13)	0-0053 (10)	0-0203 (35)	0-0061 (13)	0-0007 (16)	0-0003 (9)	-0-0024 (18)
C(15)	0-1321 (10)	0-4565 (19)	0-3157 (13)	0-0038 (9)	0-0140 (28)	0-0088 (14)	0-0028 (14)	0-0004 (9)	-0-0014 (17)
C(16)	0-0461 (11)	0-5545 (23)	0-3425 (16)	0-0031 (10)	0-0200 (36)	0-0136 (19)	0-0014 (16)	0-0005 (11)	-0-0005 (22)
C(17)	0-0321 (11)	0-5031 (34)	0-4695 (16)	0-0029 (10)	0-0376 (51)	0-0144 (20)	0-0067 (23)	0-0019 (11)	-0-0034 (36)
C(18)	0-1368 (13)	0-4236 (30)	0-5330 (17)	0-0056 (12)	0-0409 (61)	0-0110 (19)	0-0011 (23)	0-0045 (12)	-0-0025 (28)
C(19)	0-1815 (13)	0-4521 (33)	0-6545 (16)	0-0081 (14)	0-0443 (64)	0-0103 (18)	-0-0084 (26)	0-0074 (13)	-0-0012 (29)
C(20)	0-3471 (12)	0-4621 (22)	0-0275 (13)	0-0082 (12)	0-0192 (34)	0-0058 (13)	-0-0010 (18)	0-0004 (10)	0-0010 (19)
C(21)	0-7437 (12)	0-4857 (26)	0-3016 (15)	0-0056 (11)	0-0181 (32)	0-0120 (18)	-0-0009 (19)	0-0002 (11)	-0-0005 (25)
C(22)	0-0998 (10)	0-3694 (16)	0-4590 (12)	0-0045 (9)	0-0085 (20)	0-0062 (13)	0-0002 (12)	0-0032 (9)	0-0015 (14)
C(23)	0-0892 (13)	0-3038 (21)	0-2794 (16)	0-0075 (14)	0-0137 (28)	0-0118 (19)	-0-0042 (17)	0-0007 (13)	0-0017 (21)
C(24)	0-0998 (20)	0-4296 (43)	0-7343 (21)	0-0163 (25)	0-0604 (106)	0-0136 (25)	-0-0138 (44)	0-0082 (21)	-0-0136 (42)
C(25)	0-2438 (27)	0-5723 (50)	0-6962 (24)	0-0271 (41)	0-0805 (149)	0-0150 (30)	-0-0340 (69)	0-0076 (28)	-0-0130 (54)
C(26)	0-6393 (9)	0-4766 (19)	0-6440 (12)	0-0036 (9)	0-0120 (23)	0-0073 (13)	-0-0000 (13)	0-0013 (8)	0-0025 (17)
C(27)	0-7346 (10)	0-4193 (18)	0-6454 (13)	0-0045 (10)	0-0104 (22)	0-0074 (14)	0-0000 (13)	0-0012 (9)	0-0015 (15)
C(28)	0-8141 (12)	0-4256 (19)	0-7522 (15)	0-0065 (12)	0-0111 (25)	0-0101 (17)	-0-0015 (15)	-0-0011 (11)	0-0028 (18)
C(29)	0-7880 (13)	0-4903 (24)	0-8489 (12)	0-0101 (14)	0-0154 (29)	0-0060 (14)	-0-0020 (20)	0-0012 (11)	-0-0014 (21)
C(30)	0-6905 (12)	0-5499 (18)	0-8485 (12)	0-0075 (12)	0-0102 (24)	0-0055 (12)	-0-0001 (14)	0-0001 (10)	-0-0002 (15)
C(31)	0-6173 (11)	0-5450 (18)	0-7454 (12)	0-0061 (11)	0-0098 (24)	0-0070 (13)	-0-0015 (13)	0-0010 (10)	-0-0001 (15)
O	0-5813 (8)	0-2536 (11)	0-4725 (9)	0-0064 (7)	0-0064 (12)	0-0090 (10)	0-0015 (9)	0-0008 (7)	-0-0005 (10)
N	0-5599 (7)	0-4791 (13)	0-5362 (9)	0-0043 (7)	0-0063 (15)	0-0055 (9)	0-0007 (10)	0-0004 (6)	0-0003 (11)



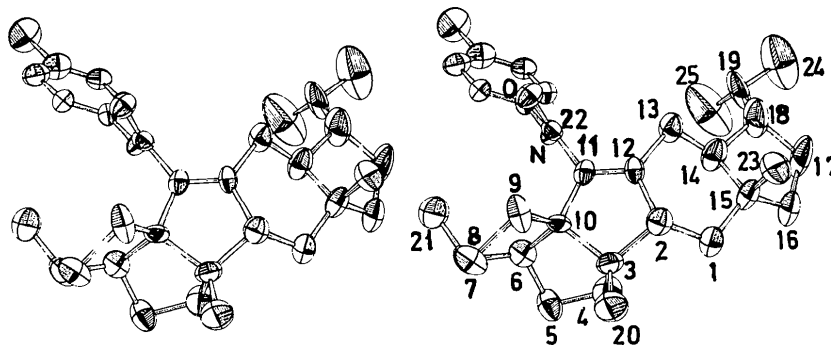


Fig. 1. A stereoscopic drawing of the molecule by the *ORTEP* program. The ellipsoid encloses the region in which the centre of the atom is found with a probability of 50%.

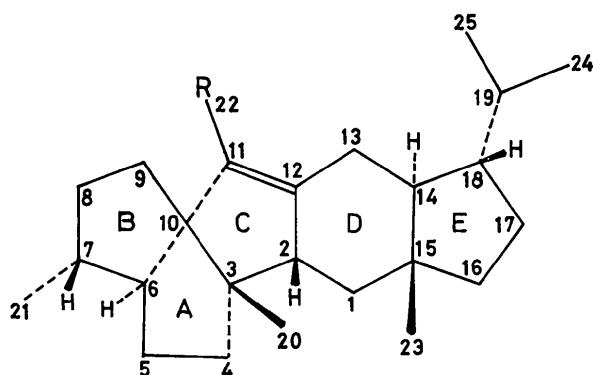


Fig. 2. Chemical structures of (I)  $R = \text{COOH}$ , retigeranic acid and (II)  $R = \text{CONH}-\text{C}_6\text{H}_4-\text{Br}$ , retigeranic acid *p*-bromoanilide.

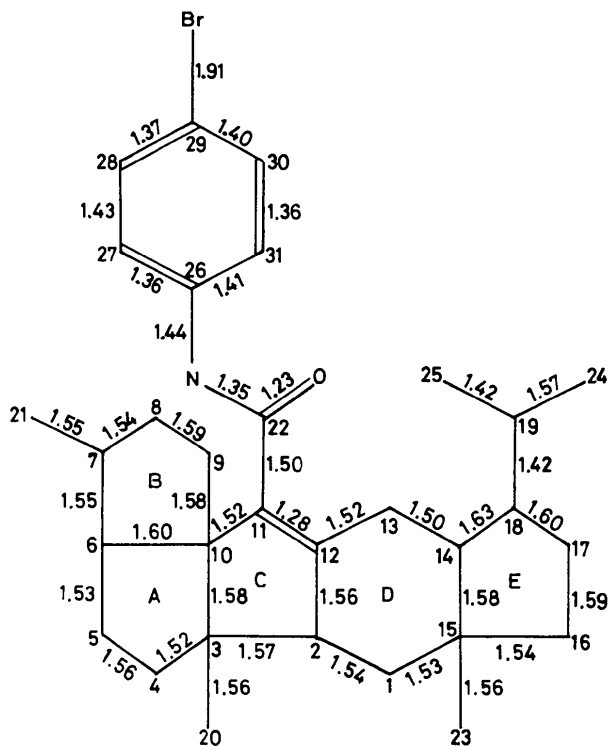


Fig. 3. Bond lengths (Å).

atoms and also to assign the atomic species. Refinement of the structure was carried out by the block-matrix least-squares method with the *HBL*S program (Okaya & Ashida, 1967). Seven cycles of calculation with isotropic temperature factors followed by four cycles with anisotropic reduced the  $R$  value to 0.09. These calculations were carried out on the Cu data and unit weight was assigned to each reflexion.

Table 1 lists the final atomic parameters along with their estimated standard deviations. A comparison of the observed and calculated structure factors is given in Table 2. All the figures presented in this paper are drawn with the correct absolute configuration.

### Discussion of the structure

Fig. 1 shows the molecular structure of retigeranic acid *p*-bromoanilide drawn by the *ORTEP* program (Johnson, 1965). The structure of retigeranic acid is now deduced as Fig. 2 (I). This structure is an  $\alpha,\beta$ -unsaturated carboxylic acid having a unique pentacyclic ring system consisting of four five-membered rings, *A*, *B*, *C* and *E*, and a six-membered ring, *D*. The structure of this type has never been found in natural products even in sesterterpenes. It can be shown however that retigeranic acid consists of five isoprene units linearly linked head to tail. Biogenetically it is therefore presumed to be derived from geranylarnesyl pyrophosphate through a particular type of cyclization scheme (Kaneda, Takahashi, Iitaka & Shibata, 1972) which is different from that of the ophiobolins (Nozoe *et al.*, 1965).

Bond lengths and angles of the retigeranic acid *p*-bromoanilide molecule are shown in Figs. 3 and 4. The mean standard deviations of the bond lengths are estimated to be  $\sigma(\text{Br}-\text{C}) = 0.014 \text{ \AA}$ ,  $\sigma(\text{C}-\text{C}) = 0.025 \text{ \AA}$ , and those of the angles are  $\sigma(\text{Br}-\text{C}-\text{C}) = 1.3^\circ$ ,  $\sigma(\text{C}-\text{C}-\text{C}) = 1.4^\circ$ . The terminal atoms C(17), C(18), C(19), C(24) and C(25), especially the last two, have large  $\beta_{22}$  temperature factors, and the bonds involving C(24) and C(25) may have larger e.s.d.'s of about  $0.05 \text{ \AA}$  and  $2.4^\circ$ . All the bond lengths and angles are normal except for those involving the terminal atoms mentioned above. As seen in Fig. 1, the marked anisotropy

of these atoms may be interpreted as a violent torsional vibration of the isopropyl side chain around the C(18)–C(19) bond coupled with the out-of-plane vibrations of C(17) and C(18).

The planarity and conformation of each ring will be seen in Table 3. In this Table, dihedral angles are also shown. Fig. 5 illustrates the internal rotation angles which may facilitate the interpretation of the molecular conformation. Each of the four five-membered rings essentially adopts the envelope form. The six-membered ring *D* takes a regular chair conformation but a slight distortion is observed due to the existence of the double bond at C(12).

As is clearly shown by the *B/C* dihedral angle, the *B* and *C* rings are linked together at C(10) in a spiro form. In ring *C*, C(9) and C(20) extend from the ring in axial direction resulting in the bonds C(3)–C(20) and C(9)–C(10) to be arranged in an eclipsed conformation, the internal rotation angle C(20)–C(3)–C(10)–C(9) being only 19°. The large bond angles observed for C(20)–C(3)–C(10) of 115° and C(3)–C(10)–C(9) of 118° may be the consequence of the repulsions between C(9) and C(20).

The amide group is planar with C(11) and C(26), but this plane is twisted at an angle of 82° from the plane formed by the double bond in the *C* ring. The benzene ring is also twisted at an angle of 42° from the plane of the amide group.

Fig. 6 shows the projection of the crystal structure along the *b* axis. It is clear that most of the close approaches of the atoms are seen between the molecules related by the screw diad axis at  $x=0.5$ ,  $z=0.5$ , the closest being 3.16 Å found between N and O of the amide groups which may probably form a hydrogen bond of the N–H···O type.

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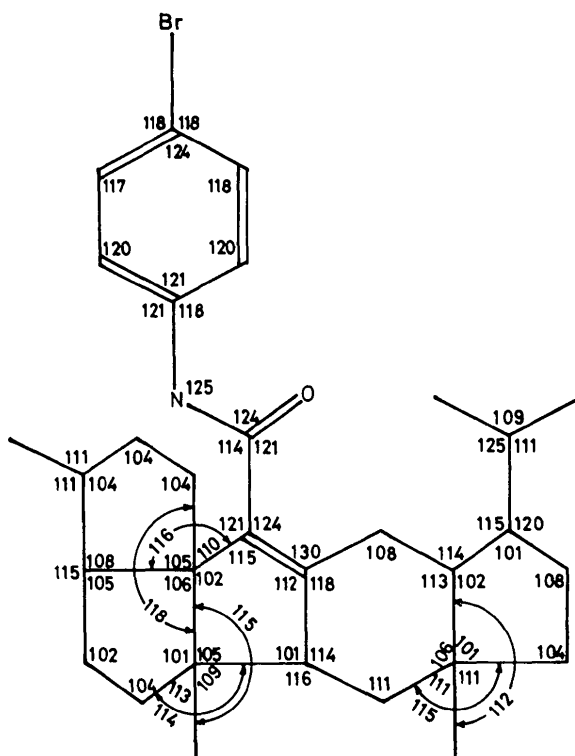


Fig. 4. Bond angles (°).

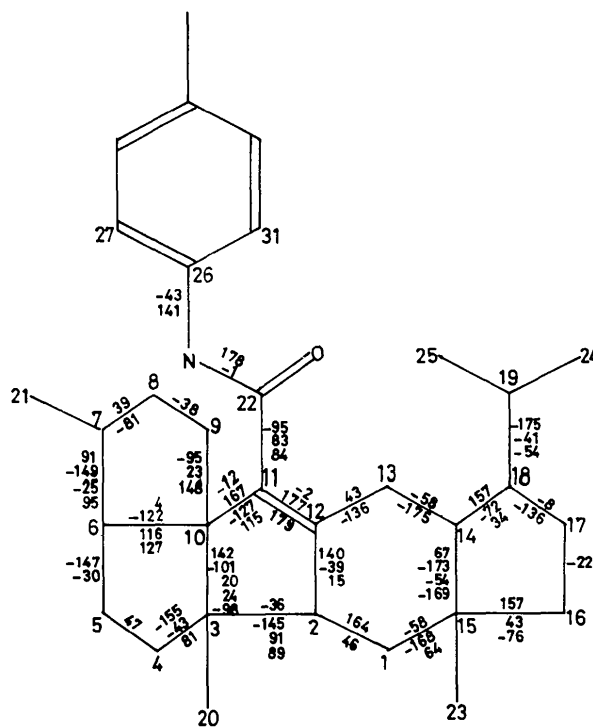


Fig. 5. Internal rotation angles (°). The definition and illustration of the internal rotation angles are given by Morisaki, Nozoe & Iitaka (1968).

Table 3. Planarity and conformation of various groups

	Deviation		Coefficient†		Internal rotation angle‡	
1. A Ring	C(3)	0.017 Å	A	-0.2576	C(3)—C(4)	-43°
	C(5)	-0.017	B	0.3291	C(4)—C(5)	47
	C(6)	0.026	C	0.9085	C(5)—C(6)	-30
	C(10)	-0.026	D	1.0388	C(6)—C(10)	4
	C(4)*	0.675			C(10)—C(3)	24
2. B Ring	C(6)	-0.004	A	0.4505	C(6)—C(7)	-25
	C(7)	0.003	B	-0.2846	C(7)—C(8)	39
	C(9)	-0.003	C	0.8462	C(8)—C(9)	-38
	C(10)	0.004	D	2.7110	C(9)—C(10)	23
	C(8)*	-0.607			C(10)—C(6)	1
3. C Ring	C(2)	-0.005	A	-0.0237	C(2)—C(3)	-21
	C(10)	0.005	B	0.9567	C(3)—C(10)	20
	C(11)	-0.011	C	0.2902	C(10)—C(11)	-12
	C(12)	0.010	D	4.2690	C(11)—C(12)	-2
	C(3)*	0.356			C(12)—C(2)	15
4. D Ring	C(1)	-0.042	A	0.6125	C(1)—C(2)	46
	C(2)	0.039	B	0.7764	C(2)—C(12)	-39
	C(13)	-0.040	C	0.1487	C(12)—C(13)	43
	C(14)	0.043	D	5.6132	C(13)—C(14)	-58
	C(12)*	0.487			C(14)—C(15)	67
	C(15)*	-0.768			C(15)—C(1)	-58
5. E Ring	C(14)	0.032	A	0.2935	C(14)—C(15)	-49
	C(16)	-0.034	B	0.8797	C(15)—C(16)	43
	C(17)	0.050	C	0.3741	C(16)—C(17)	-22
	C(18)	-0.048	D	6.2060	C(17)—C(18)	-8
	C(15)*	-0.725			C(18)—C(14)	34
6. Benzene ring	C(26)	-0.010	A	0.3159		
	C(27)	0.000	B	0.8753		
	C(28)	0.006	C	-0.3661		
	C(29)	-0.003	D	4.4640		
	C(30)	-0.008				
	C(31)	0.014				
	Br*	0.013				
	N*	0.061				
7. Amide group	C(22)	-0.012	A	0.6851		
	O	0.001	B	0.3256		
	N	-0.015	C	-0.6516		
	C(26)	0.014	D	3.4144		
	C(11)	0.013				
8. Double bond in C ring	C(2)	-0.022	A	-0.0097		
	C(12)	-0.005	B	0.9592		
	C(13)	0.022	C	0.2825		
	C(11)	-0.006	D	4.3345		
	C(10)	0.027				
	C(22)	-0.017				

Dihedral angles between

2 and 3	92° 8'
6 and 7	42° 16'
7 and 8	82° 15'

\* Atoms designated by an asterisk are not included in the least-squares calculation.

† Least-squares plane is expressed by  $AX + BY + CZ = D$ , where  $X$ ,  $Y$  and  $Z$  are the coordinates measured in Å referred to the orthogonal axes,  $X \parallel a^*$ ,  $Y \parallel b$  and  $Z \parallel c$  respectively, and  $D$  is the origin-to-plane distance.

‡ Endocyclic internal rotation angle about the bond specified, e.g. C(3)—C(4) means C(10)—C(3)—C(4)—C(5). For the definition of the internal rotation angles see Fig. 5.

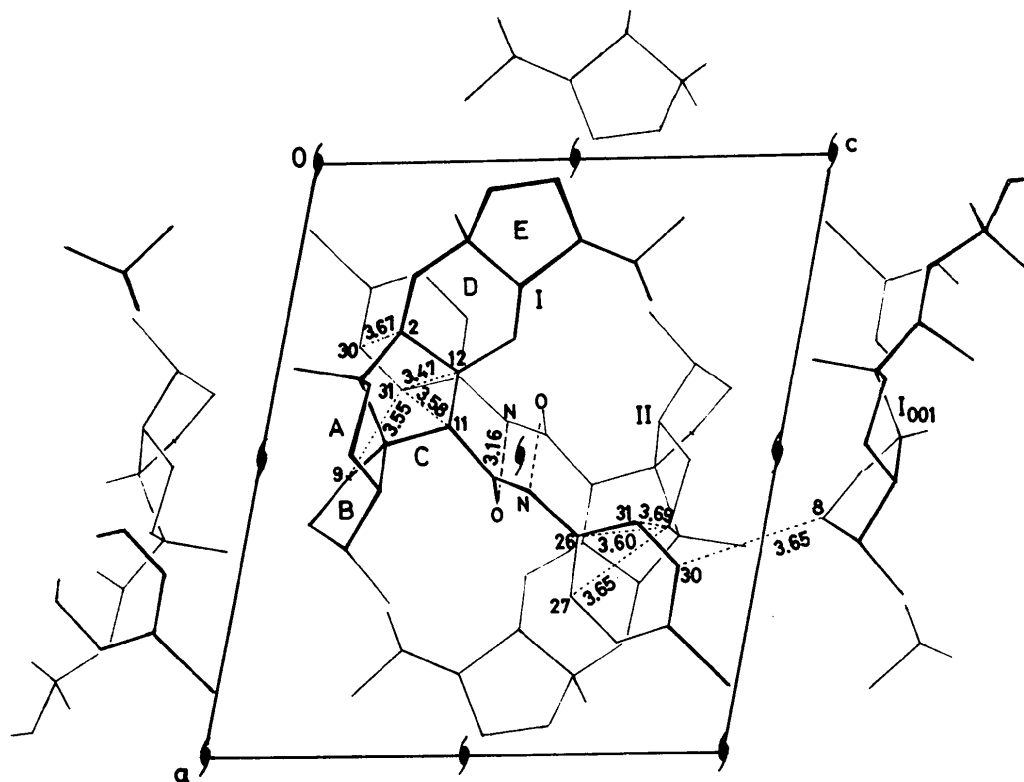


Fig. 6. Projection of the crystal structure along the  $b$  axis. Intermolecular short contacts of less than  $3.7 \text{ \AA}$  are shown. I and II indicate the molecules at  $(x, y, z)$  and  $(1-x, -\frac{1}{2}+y, 1-z)$  respectively;  $b$  axis upwards.

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