

C18	0.4513 (5)	0.4552 (5)	0.3522 (5)	0.072 (2)
C19	0.6364 (6)	0.4106 (5)	0.2859 (5)	0.091 (2)
O1	0.3601 (4)	-0.0575 (4)	0.6711 (4)	0.086 (2)
O2	0.2555 (3)	0.1988 (3)	0.2318 (3)	0.0597 (12)

Table 5. Selected geometric parameters ( $\text{\AA}$ ,  $^\circ$ ) for (II)

N1—C2	1.379 (6)	C7—C18	1.523 (7)
N1—C8a	1.379 (6)	C7—C19	1.529 (7)
C2—C3	1.369 (6)	C7—C8	1.531 (7)
C2—C9	1.522 (6)	C8—C8a	1.496 (6)
C3—C10	1.450 (7)	C10—O1	1.227 (6)
C3—C4	1.530 (6)	C10—C11	1.519 (7)
C4—C4a	1.504 (7)	C12—C17	1.382 (7)
C4—C12	1.526 (7)	C12—C13	1.394 (7)
C4a—C8a	1.355 (6)	C13—C14	1.357 (8)
C4a—C5	1.453 (7)	C14—C15	1.359 (10)
C5—O2	1.244 (5)	C15—C16	1.388 (9)
C5—C6	1.495 (7)	C16—C17	1.386 (8)
C6—C7	1.553 (7)		
C2—N1—C8a	122.7 (5)	C4a—C8a—N1	118.9 (5)
C3—C2—N1	120.2 (5)	C4a—C8a—C8	124.9 (5)
C2—C3—C4	119.3 (5)	O1—C10—C11	116.6 (6)
C4a—C4—C3	110.6 (4)	C17—C12—C13	118.0 (6)
C8a—C4a—C5	119.4 (5)	C14—C13—C12	121.1 (7)
C8a—C4a—C4	121.5 (5)	C13—C14—C15	121.1 (8)
C4a—C5—C6	117.2 (5)	C14—C15—C16	119.3 (8)
C5—C6—C7	114.6 (5)	C17—C16—C15	119.9 (8)
C8—C7—C6	106.5 (5)	C12—C17—C16	120.6 (7)
C8a—C8—C7	113.1 (5)		
C8a—N1—C2—C3	-14.5 (8)	C6—C7—C8—C8a	-47.2 (6)
C9—C2—C3—C10	0.6 (8)	C4—C4a—C8a—N1	10.1 (8)
N1—C2—C3—C4	-5.2 (8)	C5—C4a—C8a—C8	5.4 (8)
C2—C3—C4—C4a	23.8 (7)	C2—N1—C8a—C4a	12.2 (8)
C3—C4—C4a—C8a	-26.6 (7)	C7—C8—C8a—C4a	19.8 (8)
C8a—C4a—C5—C6	2.0 (8)	C2—C3—C10—O1	0.4 (9)
C4a—C5—C6—C7	-34.1 (7)	C4a—C4—C12—C17	-75.9 (7)
C5—C6—C7—C8	55.6 (6)	C4a—C4—C12—C13	103.6 (6)

Table 6. Hydrogen-bonding geometry ( $\text{\AA}$ ,  $^\circ$ ) for (II)

D—H...A	D—H	H...A	D...A	D—H...A
N1—H1...O2 <sup>i</sup>	0.83 (5)	2.07 (5)	2.864 (8)	160 (5)

Symmetry code: (i)  $\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$ .

The structures were solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and were refined riding with common isotropic displacement parameters, except for H(1) which was refined isotropically in both structures.

Data collection: *CAD-4 Software* (Enraf-Nonius, 1994). Cell refinement: *CRYSDA (DIRDIF)*; Beurskens *et al.*, 1992). Data reduction: *REFLEX* (local program). Program used to solve structure: *SHELXS86* (Sheldrick, 1990). Program used to refined structure: *SHELXL93* (Sheldrick, 1993). Geometrical calculations: *PARST* (Nardelli, 1983). Molecular graphics: *EUCLID* (Spek, 1982). Software used to prepare material for publication: *SHELXL93*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1225). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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## The Anhydrous Racemate of the Carcinostatic Agent Cyclophosphamide and the Bicyclic Degradation Product 1-(2-Chloroethyl)tetrahydro-1*H*,5*H*-1,3,2-diazaphospholo[2,1-*b*][1,3,2]oxazaphosphorine 9-Oxide

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### Abstract

Anhydrous racemic cyclophosphamide, [(±)-*N,N*-bis(2-chloroethyl)-tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-amine 2-oxide, C<sub>7</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>P, (1)], displays a chair conformation with an axial phosphoryl O atom and approximately planar geometry at the N atoms. The molecules are linked by N—H...O=P hydrogen bonds into chains. One chloroethyl side chain is extended, the other is *gauche*. The C—Cl bond lengths are C1—C5 1.789 (2) and C12—C7 1.791 (2) Å. The bicyclic degradation product, 1-(2-chloroethyl)tetrahydro-1*H*,5*H*-1,3,2-diazaphospholo[2,1-*b*][1,3,2]oxazaphosphorine 9-



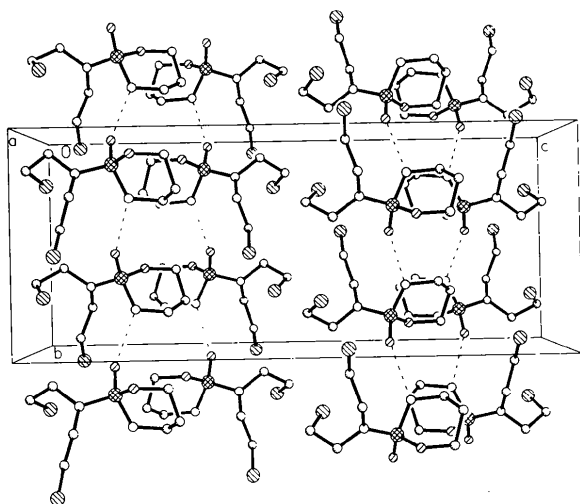


Fig. 2. Packing diagram of compound (1). Radii are arbitrary, H atoms are omitted for clarity. Hydrogen bonds are drawn as broken lines.

101.8(2) and  $-116.1(2)^\circ$ . The P—N bond lengths are P—N2 (ring) 1.633(2) and P—N1 (exocyclic) 1.641(2) Å. The C—Cl bond lengths are C11—C5 1.789(2) and C12—C7 1.791(2) Å, which may be regarded as normal, and the displacement parameters are in the normal range for low temperature structures.

In conclusion, we may state that cyclophosphamide in its various forms (racemate monohydrate, anhydrous racemate or anhydrous single enantiomers) can adopt differing side-chain conformations and hydrogen-bonding patterns; the conformational and hydrogen-bonding energies of different modifications must be very similar, and the presence or absence of water of hydration obviously plays an important role. Furthermore, the incorporation into a regular crystal lattice reduces the tendency to decomposition, which takes place more readily in oily samples by intramolecular alkylation, leading to the bicyclic derivative (2) (Niemeyer *et al.*, 1996; Zon *et al.*, 1977).

We also report here the structure of (2), 1-(2-chloroethyl)tetrahydro-1*H*,5*H*-1,3,2-diazaphospholo[2,1-*b*][1,3,2]oxazaphosphorine 9-oxide. The molecule of (2) is shown in Fig. 3 [the crystallographic numbering does not correspond to the IUPAC name, but is consistent with the numbering of (1)]. A preliminary report of this structure has appeared as a conference abstract (Niemeyer *et al.*, 1996). The X-ray structure determination confirms the connectivity established by chemical and spectroscopic means (Gilard *et al.*, 1994). The six-membered ring displays the expected chair conformation; the annelation causes no change in torsion angle greater than  $3^\circ$ . The newly formed five-membered ring is in envelope form, with an N2—P—N1—C6 torsion angle of  $2.75(12)^\circ$ . The chloroethyl side chain exhibits a *gauche* conformation, with N1—C4—C5—Cl  $60.2(2)^\circ$  *cf.* the more usual extended conformation (see above). The C—Cl bond length is normal at 1.790(2) Å.

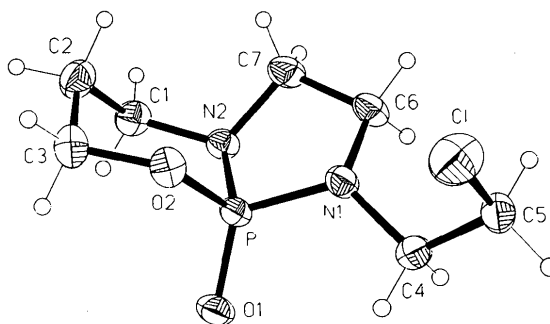


Fig. 3. The molecule of compound (2) in the crystal. Ellipsoids correspond to 50% probability levels, H-atom radii are arbitrary.

The major change of bond length upon annelation is for P—N2, which is 1.633(2) Å in (1) but 1.6593(14) Å in (2). Concomitantly, N2 is pyramidalized (angle sum  $339.1^\circ$ ). The angle N1—P—N2 necessarily becomes narrower upon its incorporation into the five-membered ring [from  $105.84(8)^\circ$  in (1) to  $97.36(7)^\circ$  in (2)], which is largely accommodated by an increase in O1—P—N1 from  $110.86(8)$  to  $117.89(7)^\circ$ .

The lengthening of the P—N2 bond is consistent with the observation that (2) is hydrolysed immediately and exclusively at this bond, forming successively the nine-membered heterocycle (3) and the phosphate monoester (4) (as shown in the reaction scheme). The alternative hydrolysis of P—N1 would lead to compound (5), which is not detected (Gilard *et al.*, 1994; Niemeyer *et al.*, 1996).

The molecular packing of (2) shows no unusually short contacts.

## Experimental

Compound (1) was recrystallized from dry diethyl ether. Compound (2) was synthesized according to Zon, Ludeman & Egan (1977) and recrystallized from diethyl ether.

### Compound (1)

#### Crystal data

$C_7H_{15}Cl_2N_2O_2P$   
 $M_r = 261.08$   
 Orthorhombic  
*Pbca*  
 $a = 9.9062(10)$  Å  
 $b = 9.8380(10)$  Å  
 $c = 24.061(3)$  Å  
 $V = 2344.9(4)$  Å<sup>3</sup>  
 $Z = 8$   
 $D_x = 1.479$  Mg m<sup>-3</sup>  
 $D_m$  not measured

#### Data collection

Siemens P4 diffractometer  
 $\omega$ -scans  
 Absorption correction:  
 none

Mo  $K\alpha$  radiation  
 $\lambda = 0.71073$  Å  
 Cell parameters from 64 reflections  
 $\theta = 5-12.5^\circ$   
 $\mu = 0.669$  mm<sup>-1</sup>  
 $T = 173(2)$  K  
 Tablet  
 $0.85 \times 0.80 \times 0.20$  mm  
 Colourless

$\theta_{\max} = 27.50^\circ$   
 $h = 0 \rightarrow 12$   
 $k = -12 \rightarrow 8$   
 $l = 0 \rightarrow 31$

4654 measured reflections  
2695 independent reflections  
2018 observed reflections  
[ $I > 2\sigma(I)$ ]  
 $R_{\text{int}} = 0.0331$

### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.0351$   
 $wR(F^2) = 0.0901$   
 $S = 0.971$   
2693 reflections  
131 parameters  
H(N) atom refined freely,  
others riding, C—H  
0.99 Å  
 $w = 1/[\sigma^2(F_o^2) + (0.0503P)^2]$   
where  $P = (F_o^2 + 2F_c^2)/3$

3 standard reflections  
monitored every 247  
reflections  
intensity decay: none

$(\Delta/\sigma)_{\text{max}} < 0.001$   
 $\Delta\rho_{\text{max}} = 0.488 \text{ e } \text{Å}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.423 \text{ e } \text{Å}^{-3}$   
Extinction correction: none  
Atomic scattering factors  
from *International Tables*  
for *Crystallography* (1992,  
Vol. C, Tables 4.2.6.8 and  
6.1.1.4)

### Compound (2)

#### Crystal data

C<sub>7</sub>H<sub>14</sub>ClN<sub>2</sub>O<sub>2</sub>P  
 $M_r = 224.62$   
Monoclinic  
 $P2_1/n$   
 $a = 10.580 (2) \text{ Å}$   
 $b = 10.021 (2) \text{ Å}$   
 $c = 10.779 (2) \text{ Å}$   
 $\beta = 118.95 (2)^\circ$   
 $V = 1000.0 (3) \text{ Å}^3$   
 $Z = 4$   
 $D_x = 1.492 \text{ Mg m}^{-3}$   
 $D_m$  not measured

Mo  $K\alpha$  radiation  
 $\lambda = 0.71073 \text{ Å}$   
Cell parameters from 58  
reflections  
 $\theta = 10\text{--}11.5^\circ$   
 $\mu = 0.513 \text{ mm}^{-1}$   
 $T = 143 (2) \text{ K}$   
Block  
 $0.90 \times 0.80 \times 0.75 \text{ mm}$   
Colourless

#### Data collection

Stoe Stadi-4 diffractometer  
 $\omega/\theta$ -scans  
Absorption correction:  
none

2012 measured reflections  
1764 independent reflections  
1681 observed reflections  
[ $I > 2\sigma(I)$ ]

$R_{\text{int}} = 0.0136$   
 $\theta_{\text{max}} = 25.04^\circ$   
 $h = 0 \rightarrow 12$   
 $k = -11 \rightarrow 1$   
 $l = -12 \rightarrow 11$   
3 standard reflections  
frequency: 60 min  
intensity decay: 1%

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters ( $\text{Å}^2$ ) for (1)

$$U_{\text{eq}} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	$U_{\text{eq}}$
P	0.38902 (5)	0.15394 (5)	0.32586 (2)	0.01627 (12)
Cl1	0.18907 (6)	0.23390 (7)	0.45703 (3)	0.0438 (2)
Cl2	0.64920 (7)	0.54731 (6)	0.41361 (3)	0.0433 (2)
N1	0.4538 (2)	0.1928 (2)	0.38658 (6)	0.0194 (3)
N2	0.3410 (2)	0.2977 (2)	0.29835 (7)	0.0197 (3)
O1	0.29079 (14)	0.04196 (13)	0.33110 (6)	0.0252 (3)
O2	0.51383 (13)	0.11429 (13)	0.28774 (5)	0.0213 (3)
C1	0.3290 (2)	0.3105 (2)	0.23736 (8)	0.0217 (4)
C2	0.4585 (2)	0.2638 (2)	0.20995 (8)	0.0241 (4)
C3	0.4946 (2)	0.1201 (2)	0.22756 (8)	0.0243 (4)
C4	0.4277 (2)	0.1061 (2)	0.43477 (8)	0.0255 (4)
C5	0.3490 (2)	0.1734 (2)	0.48115 (9)	0.0317 (5)
C6	0.5612 (2)	0.2944 (2)	0.39085 (8)	0.0225 (4)
C7	0.5095 (2)	0.4319 (2)	0.41097 (9)	0.0285 (5)

### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.0278$   
 $wR(F^2) = 0.0753$   
 $S = 1.077$   
1763 reflections  
119 parameters  
H atoms refined as riding,  
C—H 0.99 Å  
 $w = 1/[\sigma^2(F_o^2) + (0.0350P)^2 + 0.6358P]$   
where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\text{max}} < 0.001$

$\Delta\rho_{\text{max}} = 0.293 \text{ e } \text{Å}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.302 \text{ e } \text{Å}^{-3}$   
Extinction correction:  
*SHELXL93* (Sheldrick,  
1993)  
Extinction coefficient:  
0.0223 (17)  
Atomic scattering factors  
from *International Tables*  
for *Crystallography* (1992,  
Vol. C, Tables 4.2.6.8 and  
6.1.1.4)

Table 2. Selected geometric parameters ( $\text{Å}$ ,  $^\circ$ ) for (1)

P—O1	1.4753 (14)	N1—C6	1.463 (2)
P—O2	1.5881 (13)	N2—C1	1.478 (2)
P—N2	1.633 (2)	O2—C3	1.462 (2)
P—N1	1.641 (2)	C1—C2	1.514 (3)
C11—C5	1.789 (2)	C2—C3	1.518 (3)
Cl2—C7	1.791 (2)	C4—C5	1.514 (3)
N1—C4	1.463 (2)	C6—C7	1.526 (3)
O1—P—O2	112.29 (8)	C1—N2—P	119.98 (13)
O1—P—N2	119.31 (8)	C3—O2—P	117.45 (11)
O2—P—N2	101.85 (8)	N2—C1—C2	109.8 (2)
O1—P—N1	110.86 (8)	C1—C2—C3	111.1 (2)
O2—P—N1	105.48 (8)	O2—C3—C2	110.11 (15)
N2—P—N1	105.84 (8)	N1—C4—C5	114.9 (2)
C4—N1—C6	118.1 (2)	C4—C5—C11	111.26 (15)
C4—N1—P	120.04 (13)	N1—C6—C7	112.6 (2)
C6—N1—P	120.41 (13)	C6—C7—Cl2	108.33 (14)
O1—P—N1—C4	9.3 (2)	N1—P—O2—C3	-159.45 (13)
O2—P—N1—C4	-112.46 (15)	P—N2—C1—C2	-52.0 (2)
N2—P—N1—C4	140.07 (15)	N2—C1—C2—C3	55.5 (2)
O1—P—N1—C6	175.43 (13)	P—O2—C3—C2	60.6 (2)
O2—P—N1—C6	53.6 (2)	C1—C2—C3—O2	-60.4 (2)
N2—P—N1—C6	-53.8 (2)	C6—N1—C4—C5	77.4 (2)
O1—P—N2—C1	-78.6 (2)	P—N1—C4—C5	-116.1 (2)
O2—P—N2—C1	45.7 (2)	N1—C4—C5—C11	58.1 (2)
N1—P—N2—C1	155.72 (14)	C4—N1—C6—C7	-91.8 (2)
O1—P—O2—C3	79.69 (14)	P—N1—C6—C7	101.8 (2)
N2—P—O2—C3	-49.12 (14)	N1—C6—C7—Cl2	-179.29 (13)

Table 3. Fractional atomic coordinates and equivalent isotropic displacement parameters ( $\text{Å}^2$ ) for (2)

$$U_{\text{eq}} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	$U_{\text{eq}}$
P	0.26115 (4)	0.45935 (4)	0.59559 (4)	0.0215 (2)
Cl1	0.31770 (6)	0.07054 (5)	0.46014 (6)	0.0435 (2)
O1	0.27983 (14)	0.45715 (12)	0.73967 (12)	0.0309 (3)
O2	0.41448 (12)	0.46983 (11)	0.60014 (12)	0.0274 (3)
N1	0.17690 (14)	0.33446 (13)	0.49115 (13)	0.0245 (3)
N2	0.16172 (15)	0.58055 (13)	0.48746 (14)	0.0244 (3)
C1	0.2351 (2)	0.7103 (2)	0.5084 (2)	0.0306 (4)
C2	0.3825 (2)	0.6996 (2)	0.5160 (2)	0.0337 (4)
C3	0.4785 (2)	0.6026 (2)	0.6295 (2)	0.0323 (4)
C4	0.1535 (2)	0.2104 (2)	0.5469 (2)	0.0269 (4)
C5	0.1507 (2)	0.0898 (2)	0.4626 (2)	0.0287 (4)
C6	0.0617 (2)	0.3804 (2)	0.3527 (2)	0.0290 (4)
C7	0.0917 (2)	0.5273 (2)	0.3415 (2)	0.0305 (4)

Table 4. Selected geometric parameters ( $\text{Å}$ ,  $^\circ$ ) for (2)

P—O1	1.4678 (12)	N1—C6	1.471 (2)
P—O2	1.6026 (12)	N2—C1	1.475 (2)
P—N1	1.6299 (14)	N2—C7	1.477 (2)
P—N2	1.6593 (14)	C1—C2	1.525 (3)

Cl—C5	1.790 (2)	C2—C3	1.507 (3)
O2—C3	1.457 (2)	C4—C5	1.504 (2)
N1—C4	1.453 (2)	C6—C7	1.523 (3)
O1—P—O2	110.66 (7)	C1—N2—C7	115.90 (14)
O1—P—N1	117.89 (7)	C1—N2—P	115.47 (11)
O2—P—N1	106.17 (7)	C7—N2—P	107.74 (11)
O1—P—N2	117.98 (7)	N2—C1—C2	113.29 (14)
O2—P—N2	105.17 (7)	C3—C2—C1	111.01 (15)
N1—P—N2	97.36 (7)	O2—C3—C2	110.68 (14)
C3—O2—P	115.08 (10)	N1—C4—C5	113.29 (13)
C4—N1—C6	117.64 (13)	C4—C5—C1	111.38 (12)
C4—N1—P	121.13 (11)	N1—C6—C7	106.32 (13)
C6—N1—P	111.59 (11)	N2—C7—C6	106.29 (13)

The crystals of compound (1), although large, were mostly of poor quality and invariably shattered on attempts to cut them. We therefore used a crystal that may have been larger than the homogeneous beam area.

For compound (2), the crystal was also large. Furthermore, a referee has drawn our attention to the fact that absorption corrections might have been desirable (calculated systematic errors are *ca* 10%). In principle he is correct, although for compound (1) the wide and irregular reflection profiles would have militated against successful  $\psi$  scans. It is possible that the *U* values may be systematically affected to some extent by the factors mentioned here. However, we have campaigned for, rather than against, the use of large crystals (Jones, 1995).

Data collection: *XSCANS* (Siemens, 1994*a*) for (1); *DIF4* (Stoe & Cie, 1991*a*) for (2). Cell refinement: *XSCANS* for (1); *DIF4* for (2). Data reduction: *XSCANS* for (1); *REDU4* (Stoe & Cie, 1991*b*) for (2). For both compounds, program(s) used to solve structures: *SHELXS86* (Sheldrick, 1990); program(s) used to refine structures: *SHELXL93* (Sheldrick, 1993); molecular graphics: *XP* (Siemens, 1994*b*); software used to prepare material for publication: *SHELXL93*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: FG1178). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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## Coumarin 338

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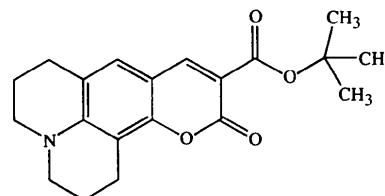
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## Abstract

In the title compound, 1,1-dimethylethyl 2,3,6,7-tetrahydro-11-oxo-1*H*,5*H*,11*H*-[1]benzopyrano[6,7,8-*ij*]-quinolizine-10-carboxylate, C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>, the coumarin moiety is approximately planar. The two piperidine rings have sofa conformations and one is disordered. The N atom adopts a planar configuration and the carboxyl group is out of the coumarin plane.

## Comment

The title compound, (I), (Eastman Kodak Co., Rochester, NY, USA) is used as an efficient laser dye. Derivatives with a structurally rigid amino group such as the title compound have been reported to show high quantum yields of fluorescence in polar solvents (Reynolds & Drexhage, 1975). The crystal structure



(I)