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An *ABC*-ring Analogue of Paclitaxel (Taxol™)

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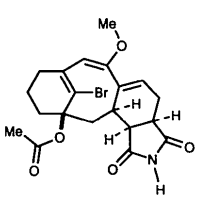
Abstract

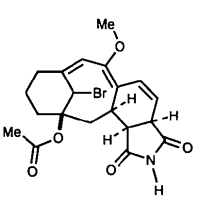
The X-ray crystal structure determination of the title compound ($C_{20}H_{22}BrNO_5$, systematic name methyl 14-bromo-6-methoxy-1,3-dioxo-2,3,3a,9,10,11,12,13,13a,13b-decahydro-1*H*-8,12-methanocyclodeca[*e*]isoindol-12-yl acetate), an *ABC*-ring analogue of the diterpene paclitaxel, reveals that the stereochemical relationships between C(3), C(4) and C(5) (C13a, C13b and C3a, respectively, by systematic numbering) are the same as observed in the natural product.

Comment

Cyclohexannulated [5.3.1]propellanes are readily available molecules which can be converted into *ABC*-ring analogues of the potent *anti*-mitotic agent paclitaxel (taxol™) (Nicolaou, Dai & Guy, 1994). During our investigations of such conversions (Banwell, Gable, Phyland & Peters, 1995), we observed that the primary products of reaction can engage in various isomerization processes, including skeletal rearrangements and/or double-bond migrations. In an attempt to capitalize on such processes we had occasion to subject compound (1) to thermolytic conditions and observed its smooth and efficient rearrangement to an isomeric species which, by spectroscopic analysis, seemed to possess structure (2).



(1)



(2)

However, given the rather vigorous reaction conditions employed in this conversion, there was some concern that the stereochemistries at C(3) and C(5) in the product may have changed relative to those associated with the analogous stereogenic centres in the starting material (1). In order to address this issue, compound (2) was subjected to single-crystal X-ray analysis. The results reveal two chemically equivalent molecules per asymmetric unit, and clearly show that the hoped-for stereochemistries have been retained at C(3), C(4) and C(5).

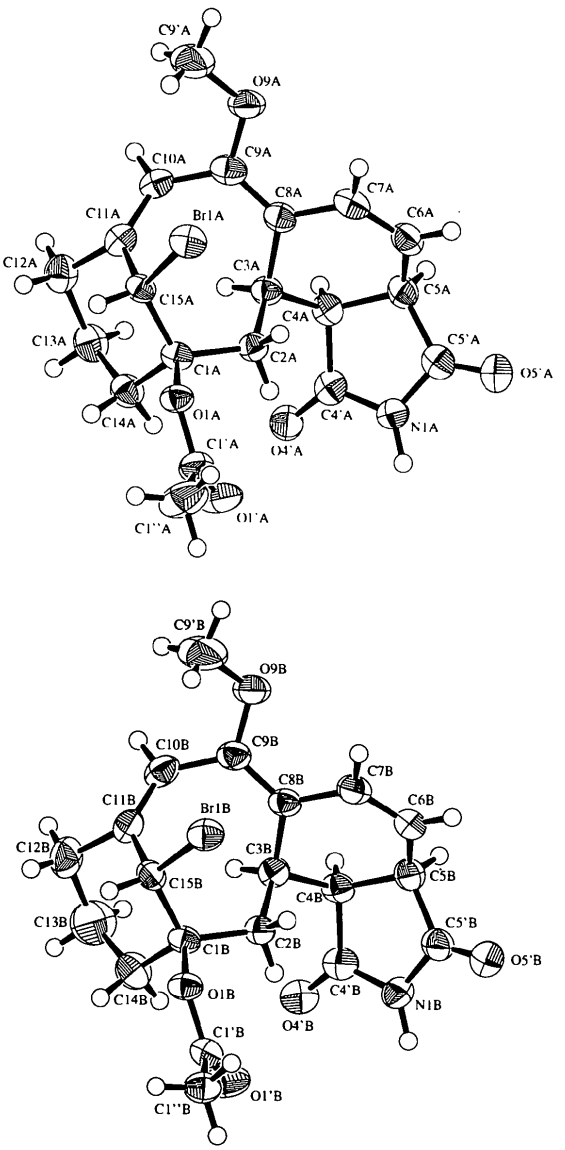


Fig. 1. View of the title compound, (2), showing the labelling of all non-H atoms. Displacement ellipsoids are shown at the 50% probability level. H atoms are drawn as circles of arbitrary radii.

Experimental

Compound (2) was obtained by heating a benzene solution of isomer (1) (Banwell, Gable, Phyland & Peters, 1995) at 403 K (sealed tube) for 15 h. The cooled reaction mixture was concentrated under reduced pressure and the residue subjected to preparative TLC (silica, 2:2:1 CH_2Cl_2/hexane/ethyl acetate elution, two sweeps). Extraction of the appropriate

chromophoric band (R_f 0.3) afforded compound (2), which was recrystallized from CH_2Cl_2/Et_2O/hexane then ethanol (m.p. 517–526 K).

Crystal data

$C_{20}H_{22}BrNO_5$
M_r = 436.30
Monoclinic
$P2_1/n$
a = 7.906 (4) Å
b = 14.687 (3) Å
c = 32.908 (2) Å
β = 92.05 (2)°
V = 3818 (1) Å^3
Z = 8
D_x = 1.518 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 24 reflections
θ = 40.2–47.7°
μ = 3.210 mm^{-1}
T = 213 (1) K
Prism
0.180 × 0.160 × 0.080 mm
Colourless

Data collection

Rigaku AFC-6*R* diffractometer
$\omega/2\theta$ scans
Absorption correction: empirical using azimuthal (ψ) scans (North, Phillips & Mathews, 1968)
T_{min} = 0.838, T_{max} = 1.000
6412 measured reflections
5926 independent reflections
4412 observed reflections [$I > 3\sigma(I)$]
R_{int} = 2.16
θ_{max} = 60.27°
$h = 0 \rightarrow 8$
$k = 0 \rightarrow 16$
$l = -36 \rightarrow 36$
3 standard reflections monitored every 150 reflections
intensity decay: 5.44%

Refinement

Refinement on F
R = 0.041
wR = 0.041
S = 2.230
4412 reflections
488 parameters
H-atom parameters not refined
$w = 4F_o^2/[\sigma^2(F_o^2) + (0.010F_o^2)^2]$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.70 e Å^{-3}
$\Delta\rho_{min}$ = −0.56 e Å^{-3}
Extinction correction: Zachariasen (1968) type 2 Gaussian isotropic
Extinction coefficient: 4 (5) × 10^{-7}
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

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

	x	y	z	U_{eq}
Br(1*A*)	0.85693 (7)	0.84349 (3)	0.50241 (1)	0.0424 (1)
O(1*A*)	0.7682 (4)	1.0116 (2)	0.45052 (9)	0.0354 (9)
O(1′*A*)	0.6305 (5)	1.0794 (2)	0.3970 (1)	0.058 (1)
O(4′*A*)	0.7242 (4)	0.9022 (2)	0.30455 (9)	0.048 (1)
O(5′*A*)	0.2501 (4)	0.7463 (2)	0.33927 (10)	0.050 (1)
O(9*A*)	0.9622 (4)	0.6236 (2)	0.46211 (10)	0.049 (1)
N(1*A*)	0.4655 (5)	0.8421 (2)	0.3208 (1)	0.037 (1)
C(1*A*)	0.8631 (6)	0.9460 (3)	0.4259 (1)	0.031 (1)
C(1′*A*)	0.6651 (6)	1.0745 (3)	0.4327 (2)	0.047 (1)
C(1″*A*)	0.6011 (8)	1.1376 (4)	0.4647 (2)	0.071 (3)
C(2*A*)	0.7330 (6)	0.8820 (3)	0.4050 (1)	0.033 (1)
C(3*A*)	0.8067 (6)	0.7953 (3)	0.3849 (1)	0.034 (1)
C(4*A*)	0.7069 (6)	0.7636 (3)	0.3457 (1)	0.035 (1)
C(4′*A*)	0.6404 (6)	0.8440 (3)	0.3210 (1)	0.039 (1)
C(5*A*)	0.5478 (6)	0.7047 (3)	0.3516 (1)	0.039 (1)
C(5′*A*)	0.3996 (7)	0.7634 (3)	0.3377 (1)	0.040 (1)
C(6*A*)	0.5358 (6)	0.6619 (3)	0.3927 (1)	0.041 (1)
C(7*A*)	0.6623 (6)	0.6648 (3)	0.4200 (1)	0.042 (1)
C(8*A*)	0.8180 (6)	0.7172 (3)	0.4153 (1)	0.036 (1)
C(9*A*)	0.9593 (6)	0.7007 (3)	0.4378 (1)	0.040 (1)
C(9′*A*)	1.0914 (9)	0.6176 (4)	0.4924 (2)	0.082 (2)
C(10*A*)	1.1129 (6)	0.7549 (3)	0.4343 (1)	0.038 (1)
C(11*A*)	1.1159 (6)	0.8452 (3)	0.4399 (1)	0.036 (1)
C(12*A*)	1.2412 (6)	0.9074 (3)	0.4210 (1)	0.047 (1)
C(13*A*)	1.1439 (6)	0.9551 (3)	0.3850 (1)	0.048 (1)
C(14*A*)	0.9789 (6)	1.0008 (3)	0.3979 (1)	0.041 (1)
C(15*A*)	0.9787 (6)	0.9016 (3)	0.4586 (1)	0.031 (1)
Br(1*B*)	0.73020 (7)	1.26315 (4)	0.90099 (1)	0.0436 (1)
O(1*B*)	0.6625 (4)	1.3218 (2)	0.81220 (8)	0.037 (3)
O(1′*B*)	0.5508 (5)	1.2901 (2)	0.74958 (10)	0.058 (1)
O(4′*B*)	0.6975 (4)	1.0244 (2)	0.73291 (10)	0.047 (1)
O(5′*B*)	0.2209 (5)	0.9801 (2)	0.8048 (1)	0.055 (1)
O(9*B*)	0.9179 (4)	1.0445 (2)	0.93391 (9)	0.052 (1)
N(1*B*)	0.4386 (5)	1.0038 (3)	0.7610 (1)	0.042 (1)
C(1*B*)	0.7804 (6)	1.2433 (3)	0.8143 (1)	0.033 (1)
C(1′*B*)	0.5593 (6)	1.3368 (3)	0.7796 (1)	0.039 (1)
C(1″*B*)	0.4548 (6)	1.4208 (3)	0.7860 (1)	0.044 (1)
C(2*B*)	0.6716 (6)	1.1564 (3)	0.8140 (1)	0.034 (1)
C(3*B*)	0.7638 (6)	1.0658 (3)	0.8251 (1)	0.035 (1)
C(4*B*)	0.6768 (6)	0.9810 (3)	0.8043 (1)	0.038 (1)
C(4′*B*)	0.6139 (7)	1.0042 (3)	0.7619 (1)	0.041 (1)
C(5*B*)	0.5157 (6)	0.9471 (3)	0.8250 (1)	0.043 (1)
C(5′*B*)	0.3705 (7)	0.9784 (3)	0.7977 (1)	0.044 (1)
C(6*B*)	0.5007 (6)	0.9720 (3)	0.8686 (1)	0.045 (1)
C(7*B*)	0.6234 (6)	1.0139 (3)	0.8894 (1)	0.045 (1)
C(8*B*)	0.7751 (6)	1.0503 (3)	0.8708 (1)	0.037 (1)
C(9*B*)	0.9112 (6)	1.0737 (3)	0.8941 (1)	0.041 (1)
C(9′*B*)	1.005 (1)	1.0995 (5)	0.9626 (2)	0.108 (3)
C(10*B*)	1.0540 (6)	1.1239 (3)	0.8779 (1)	0.046 (1)
C(11*B*)	1.0354 (6)	1.2018 (3)	0.8581 (1)	0.041 (1)
C(12*B*)	1.1624 (6)	1.2361 (4)	0.8286 (2)	0.056 (1)
C(13*B*)	1.0833 (8)	1.2181 (5)	0.7861 (2)	0.084 (1)
C(14*B*)	0.9062 (7)	1.2530 (3)	0.7797 (1)	0.048 (1)
C(15*B*)	0.8777 (6)	1.2609 (3)	0.8543 (1)	0.036 (1)

Table 2. *Selected geometric parameters (Å, °)*

O(1*A*)—C(1*A*)	1.481 (5)	O(1*B*)—C(1*B*)	1.483 (5)
C(1*A*)—C(2*A*)	1.537 (6)	C(1*B*)—C(2*B*)	1.539 (6)
C(1*A*)—C(14*A*)	1.547 (6)	C(1*B*)—C(14*B*)	1.545 (6)
C(1*A*)—C(15*A*)	1.533 (6)	C(1*B*)—C(15*B*)	1.522 (6)
C(2*A*)—C(3*A*)	1.557 (6)	C(2*B*)—C(3*B*)	1.555 (6)
C(3*A*)—C(4*A*)	1.558 (6)	C(3*B*)—C(4*B*)	1.568 (6)
C(4*A*)—C(4′*A*)	1.516 (6)	C(4*B*)—C(4′*B*)	1.506 (6)
C(4*A*)—C(5*A*)	1.545 (6)	C(4*B*)—C(5*B*)	1.547 (6)
C(5*A*)—C(6*A*)	1.497 (6)	C(5*B*)—C(6*B*)	1.491 (6)
C(6*A*)—C(7*A*)	1.320 (6)	C(6*B*)—C(7*B*)	1.319 (6)
C(7*A*)—C(8*A*)	1.464 (6)	C(7*B*)—C(8*B*)	1.466 (6)
C(8*A*)—C(9*A*)	1.339 (6)	C(8*B*)—C(9*B*)	1.344 (6)
C(9*A*)—C(10*A*)	1.460 (6)	C(9*B*)—C(10*B*)	1.465 (7)
C(10*A*)—C(11*A*)	1.340 (6)	C(10*B*)—C(11*B*)	1.321 (6)
C(11*A*)—C(12*A*)	1.500 (6)	C(11*B*)—C(12*B*)	1.508 (7)
C(11*A*)—C(15*A*)	1.512 (6)	C(11*B*)—C(15*B*)	1.521 (6)
O(1*A*)—C(1*A*)—C(15*A*)	101.1 (3)	O(1*B*)—C(1*B*)—C(15*B*)	101.9 (3)
C(2*A*)—C(1*A*)—C(14*A*)	117.0 (3)	C(2*B*)—C(1*B*)—C(14*B*)	116.5 (4)
C(2*A*)—C(1*A*)—C(15*A*)	115.2 (3)	C(2*B*)—C(1*B*)—C(15*B*)	114.4 (3)
C(1*A*)—C(2*A*)—C(3*A*)	115.8 (4)	C(1*B*)—C(2*B*)—C(3*B*)	116.8 (4)
C(3*A*)—C(4*A*)—C(5*A*)	117.0 (4)	C(3*B*)—C(4*B*)—C(5*B*)	114.8 (4)
C(4′*A*)—C(4*A*)—C(5*A*)	103.6 (4)	C(4′*B*)—C(4*B*)—C(5*B*)	103.3 (4)
C(4*A*)—C(5*A*)—C(6*A*)	115.2 (4)	C(4*B*)—C(5*B*)—C(6*B*)	116.0 (4)
C(10*A*)—C(11*A*)—C(15*A*)	126.1 (4)	C(10*B*)—C(11*B*)—C(15*B*)	127.7 (5)
C(12*A*)—C(11*A*)—C(15*A*)	109.2 (4)	C(12*B*)—C(11*B*)—C(15*B*)	108.6 (4)
C(1*A*)—C(14*A*)—C(13*A*)	117.4 (4)	C(1*B*)—C(14*B*)—C(13*B*)	119.2 (4)
Br(1*A*)—C(15*A*)—C(11*A*)	116.1 (3)	Br(1*B*)—C(15*B*)—C(11*B*)	116.9 (3)

The θ scan width used was (0.84 + 0.3tanθ)° at a speed of 16.0° min^{-1} (in ω). The weak reflections were rescanned a maximum of four times and the counts accumulated to ensure good counting statistics. Stationary background counts were made on each side of the reflection with a 2:1 ratio of peak to background counting time. *MSC/AFC Diffractometer Control*

Software (Molecular Structure Corporation, 1988) was used for data collection and cell refinement. *TEXSAN* (Molecular Structure Corporation, 1992) was used for data reduction. The structure was solved by Patterson methods (*PATTY* in *DIRDIF*; Beurskens *et al.*, 1992) and expanded using Fourier techniques (Beurskens *et al.* 1992). H atoms were located from a difference map and fixed at ideal positions with $U_{iso} = 1.2U_{eq}$(C). All calculations were performed using *TEXSAN*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: TA1039). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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5-Amino-8-methyl-1,2-dihydrothieno-(and furo)[2,3-*h*][1,6]naphthyridines

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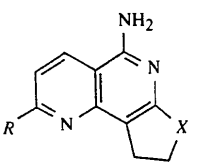
Abstract

X-ray structure analyses of Smiles rearrangement and further cyclization products of 2-[3-cyanopropylthio-(and oxy)]pyridine-3-carbonitriles revealed the structures of 5-amino-8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]-naphthyridine, $C_{11}H_{11}N_3S$, and 5-amino-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine, $C_{11}H_{11}N_3O$. The crystals of both compounds are isomorphous; monoclinic, space group $P2_1/n$. The molecules, related by a centre of symmetry, are linked through N—H···N hydrogen bonds. Common features of bond lengths and angles that characterize the thieno and furo[2,3-*h*][1,6]-naphthyridine skeletons are described.

Comment

We have found a novel method of synthesis of the thieno[2,3-*h*]naphthyridine skeleton from 2-(3-cyanopropylthio)pyridine-3-carbonitrile and its 5-methyl derivative (Sasaki, Rouf, Kashino & Hirota, 1994, 1995). Further application of the method to 2-(3-cyanopropyloxy)-6-methylpyridine-3-carbonitrile gave rise to the furo[2,3-*h*][1,6]naphthyridine skeleton (Rouf, 1995). This unique synthetic method, including Smiles rearrangement followed by cyclization, has proved useful for the syntheses of heterocyclic systems containing N, O and S atoms. 5-Amino-1,2-dihydrothieno[2,3-*h*][1,6]-naphthyridine, (I), 5-amino-8-methyl-1,2-dihydrothieno-[2,3-*h*][1,6]naphthyridine, (II) and 5-amino-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine, (III) showed relaxation activity against carbamylcholine chloride-induced tracheal muscular contraction (Rouf, 1995). In the present paper, the structures of (II) and (III) are reported and compared with that of (I) (Sasaki, Rouf, Kashino & Hirota, 1994).



(I) R = H, X = S
(II) R = Me, X = S
(III) R = Me, X = O

The overall ring systems of (I), (II) and (III) are planar with maximum deviation of 0.299 (4), 0.132 (4) and 0.094 (3) Å, respectively, at C(2). Among (I), (II) and (III), some differences are observed in the deviation of the amino and methyl substituents from the ring plane: the amino N(14) atom of (I) shows a significant deviation of 0.167 (4) Å from the ring plane, in contrast with those of (II) and (III) where the deviations are 0.003 (2) and 0.031 (2) Å, respectively. The methyl group in (III) is distorted by 0.106 (2) Å from the ring plane, which is larger than the deviation of 0.012 (3) Å in (II). However, shortening of the N(9)—C(8), C(6)—C(7), N(4)—C(5) and C(10)—C(11) bonds is commonly observed for the molecules of (I), (II) and (III). These molecules are also characterized by widening of the N(4)—C(11)—C(10) angle.

In the crystals of (I), (II) and (III), pairs of molecules, related by a centre of symmetry, are linked through