X-Ray Determination of the Molecular Structure of the Novel Antibiotic DC-52-d, 6-Hydroxymethyl-3,12-imino-7-methoxy-13-methyl-1,2,3,4-tetrahydroazepino[1,2-*b*]isoquinoline-1-carboxylic Acid

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The molecular geometry of the title compound has been determined by *X*-ray diffraction. The molecule has a novel tetracyclic skeleton. Crystallographic data are $a = 11.185(2)$, $b = 15.878(2)$, $c = 11.1184(9)$ Å, $Z = 4$, space group $P2_12_12_1$. Diffractometer intensity measurements were made with Mo-K_α radiation and least-squares adjustment of the atomic parameters converged at R_w 0.069 for 1 793 $|F_0|$ values.

The antitumour antibiotic DC-52 produced by a novel strain of *Streptomyces* showed strong activity against P388 lymphocytic leukemia in mice.[1,2] The antibiotic DC-52-d was also isolated from the same fermentation broth. Although it showed activity against gram-positive bacteria, it had only marginal activity against P388. The molecular weights of DC-52 and DC-52-d were determined as 330 and 332, respectively, by the mass spectra. ^1H and ^{13}C n.m.r. spectra showed that DC-52 has a carbon skeleton closely related to that of DC-52-d, but could not determine the structures unequivocally.[3] DC-52-d is more stable than DC-52 and affords good single crystals. Although the structure of DC-52 is more interesting from the standpoint of biological activity, DC-52 itself has not yet been crystallised. Therefore *X*-ray analysis of DC-52-d has been carried out to disclose the molecular structure of this novel type of antitumour antibiotic.

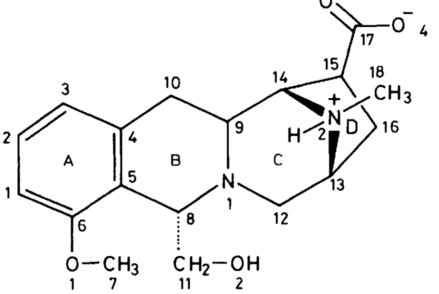

Figure 1. Numbering system and chemical structure of DC-52-d

Experimental

Crystal Data.—$C_{18}H_{22}N_2O_4{\cdot}C_2H_6O$, $M = 376.5$. Orthorhombic, space group $P2_12_12_1$, $a = 11.185(2)$, $b = 15.878(2)$, $c = 11.1184(9)$ Å, $U = 1\,974.4(7)$ Å^3, $D_c = 1.267$ g cm^{-3}, $Z = 4$, $F(000) = 984$, $\mu(\text{Mo-}K_\alpha) = 0.853$ cm^{-1}.

Crystallographic Measurements.—DC-52-d was recrystallised from water–ethanol–acetone solution. After initial measurements from oscillation and Weissenberg photographs, the final cell dimensions and intensity data were measured with an Enraf–Nonius CAD4 diffractometer. A crystal of dimensions 0.4 × 0.1 × 0.1 mm^3 was sealed in a glass capillary. Reflections were scanned within the range $1° \leqslant \theta \leqslant 27.5°$ by use of Mo-K_α radiation. Of these 1 793 having intensities $I > 2.0\sigma(I)$ were considered observed and were used in the structure analysis. The ω–2θ scan technique was used, the scan range being calculated by the expression $\omega = A + B \tan\theta$, with $A = 0.44$ and $B = 0.35$. Intensities were converted into structure amplitudes in the usual way, but absorption corrections were not applied.

Structure Analysis.—The structure was solved by direct methods using the MULTAN program.[4] The phases of 338 reflections with $|E_0| \geqslant 1.45$ were assigned. The best set of phases was used to calculate an *E* map, which gave 22 chemically significant peaks. Successive Fourier and difference Fourier syntheses showed the location of the two other non-hydrogen atoms in the molecule and a solvent molecule, *i.e.*, ethanol. The solvent molecule is disordered and it is statistically distributed to three different locations with the occupancies of 0.3, 0.2, and 0.2. Hydrogen atoms except those of the solvent molecule were found in the difference maps. One hydrogen atom bonded to the terminal hydroxy-group was not located because of the large thermal vibration of the O(2) atom. The structural parameters were refined by full-matrix least-squares with the CAD4 structure determination package.[5] The weighting system used in the final stage was $w = 4F_0/\sigma(F_0^2)$, with $\sigma(F_0^2) = [\sigma(I_0)^2 + (0.05I_0)^2]/\text{LP}^2$. The final *R* and R_w values are 0.057 and 0.069, respectively. Atomic scattering factors were taken from ref. 6. Atomic parameters are listed in Table 1. Observed and calculated structure amplitudes, thermal parameters, and the atomic parameters of the solvent molecule are listed in Supplementary Publication No. SUP 23709 (16 pp.).*

Results and Discussion

The numbering system and the chemical structure of the title compound are shown in Figure 1. A stereoscopic drawing of the molecule is depicted in Figure 2. The geometrical parameters of the molecule are shown in Table 2.

The benzene ring is almost planar, but C(4) and C(5) deviate from the mean plane by 0.016(4) and 0.019(4) Å, respectively. Although O(1) is in the plane, C(7) deviates from the plane by 0.365 Å. Ring B has a half-chair conformation. C(9) and N(1) deviate from the mean plane (±0.031 Å) consisting of C(4), C(5), C(8), and C(10) by 0.929 and 0.301 Å, respectively. Both atoms are on the same side of the plane. C(11) is axial to ring B. The piperidine ring (ring C) has a chair conformation. The *d* values [the deviation (Å) of the two atoms from the least-squares plane of the other four atoms forming the seat of a chair][7] of the atoms in the ring are as follows:

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* For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc.*, *Perkin Trans. 2*, 1983, Issue 1.

Table 1. Fractional atomic co-ordinates with their estimated standard deviations (e.s.d.s in parentheses)

Atom	*x*/*a*	*y*/*b*	*z*/*c*
O(1)	0.747 1(3)	−0.003 0(2)	0.806 4(3)
O(2)	0.419 9(4)	−0.028 1(3)	0.668 1(4)
O(3)	0.020 4(2)	0.159 1(2)	0.992 7(3)
O(4)	−0.022 6(3)	0.227 6(2)	0.824 9(3)
N(1)	0.422 4(3)	0.130 0(2)	0.810 0(3)
N(2)	0.313 5(2)	0.276 5(2)	0.915 6(3)
C(1)	0.690 9(4)	−0.088 2(3)	0.979 5(4)
C(2)	0.601 4(5)	−0.110 1(3)	1.061 3(4)
C(3)	0.487 9(4)	−0.070 6(3)	1.057 9(4)
C(4)	0.465 8(3)	−0.009 8(2)	0.970 2(4)
C(5)	0.552 2(3)	0.010 6(2)	0.884 3(3)
C(6)	0.665 1(4)	−0.027 7(2)	0.891 7(4)
C(7)	0.870 3(4)	−0.024 0(3)	0.827 4(5)
C(8)	0.527 7(3)	0.073 9(2)	0.784 7(3)
C(9)	0.380 3(3)	0.130 7(2)	0.935 0(3)
C(10)	0.350 4(3)	0.040 2(2)	0.971 3(4)
C(11)	0.510 9(4)	0.030 8(3)	0.664 1(4)
C(12)	0.443 7(3)	0.215 7(2)	0.763 9(3)
C(13)	0.332 7(3)	0.269 0(2)	0.782 1(4)
C(14)	0.271 7(3)	0.188 5(2)	0.944 5(3)
C(15)	0.176 1(3)	0.171 7(2)	0.846 9(3)
C(16)	0.218 7(3)	0.225 4(3)	0.739 3(4)
C(17)	0.046 9(3)	0.187 6(2)	0.891 2(4)
C(18)	0.228 6(4)	0.343 6(2)	0.952 0(3)
H(1)	0.763(3)	−0.118(2)	0.984(3)
H(2)	0.622(4)	−0.180(3)	1.104(4)
H(3)	0.418(4)	−0.082(2)	1.121(3)
H(7a)	0.899(3)	−0.016(2)	0.769(3)
H(7b)	0.864(4)	−0.093(3)	0.802(5)
H(7c)	0.891(4)	−0.012(3)	0.903(4)
H(8)	0.609(4)	0.106(3)	0.773(4)
H(9)	0.446(3)	0.154(2)	0.988(3)
H(10a)	0.309(3)	0.037(2)	1.057(4)
H(10b)	0.282(3)	0.017(2)	0.900(4)
H(11a)	0.488(4)	0.078(3)	0.603(4)
H(11b)	0.535(3)	−0.043(2)	0.635(3)
H(12a)	0.456(3)	0.214(3)	0.669(4)
H(12b)	0.502(3)	0.241(2)	0.809(3)
H(13)	0.345(3)	0.317(2)	0.757(3)
H(14)	0.238(3)	0.184(2)	1.022(3)
H(15)	0.174(3)	0.105(2)	0.817(3)
H(16a)	0.242(4)	0.192(3)	0.669(4)
H(16b)	0.172(3)	0.250(2)	0.721(4)
H(18a)	0.154(3)	0.337(2)	0.912(4)
H(18b)	0.214(4)	0.350(3)	1.037(4)
H(18c)	0.228(4)	0.393(3)	0.933(4)
H(N2)	0.371(3)	0.285(2)	0.945(3)

Table 2. Molecular dimensions

(a) Bond distances (Å) with estimated standard deviations in parentheses

C(1)–C(2)	1.397(5)	C(9)–N(1)	1.467(3)
C(1)–C(6)	1.399(4)	C(11)–O(2)	1.384(5)
C(2)–C(3)	1.416(5)	C(12)–C(13)	1.516(4)
C(3)–C(4)	1.394(4)	C(12)–N(1)	1.473(3)
C(4)–C(5)	1.397(4)	C(13)–C(16)	1.528(4)
C(4)–C(10)	1.515(4)	C(13)–N(2)	1.504(4)
C(5)–C(6)	1.404(4)	C(14)–C(15)	1.547(4)
C(5)–C(8)	1.521(4)	C(14)–N(2)	1.507(4)
C(6)–O(1)	1.376(4)	C(15)–C(16)	1.544(4)
C(7)–O(1)	1.438(4)	C(15)–C(17)	1.548(4)
C(8)–C(11)	1.517(5)	C(17)–O(4)	1.246(4)
C(8)–N(1)	1.504(3)	C(17)–O(3)	1.251(4)
C(9)–C(10)	1.530(4)	C(18)–N(2)	1.484(4)
C(9)–C(14)	1.526(3)		

Table 2 (*continued*)

(b) Bond angles (°) with estimated standard deviations in parentheses

C(2)–C(1)–C(6)	118.5(3)	C(13)–C(12)–N(1)	109.7(2)
C(1)–C(2)–C(3)	121.0(3)	C(12)–C(13)–C(16)	112.9(3)
C(2)–C(3)–C(4)	119.0(3)	C(12)–C(13)–N(2)	107.0(2)
C(3)–C(4)–C(5)	121.0(3)	C(16)–C(13)–N(2)	102.9(2)
C(3)–C(4)–C(10)	120.6(3)	C(9)–C(14)–C(15)	113.4(2)
C(5)–C(4)–C(10)	118.3(2)	C(9)–C(14)–N(2)	107.2(2)
C(4)–C(5)–C(6)	118.8(3)	C(15)–C(14)–N(2)	103.0(2)
C(4)–C(5)–C(8)	121.8(2)	C(14)–C(15)–C(16)	103.6(2)
C(6)–C(5)–C(8)	119.4(3)	C(14)–C(15)–C(17)	113.2(2)
C(1)–C(6)–C(5)	121.6(3)	C(16)–C(15)–C(17)	116.4(3)
C(1)–C(6)–O(1)	122.6(3)	C(13)–C(16)–C(15)	105.5(3)
C(5)–C(6)–O(1)	115.8(3)	C(15)–C(17)–O(3)	116.7(3)
C(5)–C(8)–C(11)	111.6(2)	C(15)–C(17)–O(4)	118.5(3)
C(5)–C(8)–N(1)	113.4(2)	O(3)–C(17)–O(4)	124.7(3)
C(11)–C(8)–N(1)	109.6(3)	C(8)–N(1)–C(9)	115.7(2)
C(10)–C(9)–C(14)	111.9(2)	C(8)–N(1)–C(12)	110.8(2)
C(10)–C(9)–N(1)	108.2(2)	C(9)–N(1)–C(12)	112.0(2)
C(14)–C(9)–N(1)	109.0(2)	C(13)–N(2)–C(14)	100.5(2)
C(4)–C(10)–C(9)	107.7(2)	C(13)–N(2)–C(18)	114.6(3)
C(8)–C(11)–O(2)	111.5(3)	C(14)–N(2)–C(18)	114.2(2)
C(6)–O(1)–C(7)	117.4(3)		

(c) Torsion angles (°)

C(6)–C(1)–C(2)–C(3)	−1.6
C(2)–C(1)–C(6)–C(5)	−0.2
C(1)–C(2)–C(3)–C(4)	0.8
C(2)–C(3)–C(4)–C(5)	1.9
C(3)–C(4)–C(5)–C(6)	−3.7
C(10)–C(4)–C(5)–C(8)	−7.0
C(10)–C(4)–C(5)–C(6)	172.0
C(3)–C(4)–C(5)–C(8)	177.3
C(4)–C(5)–C(6)–C(1)	2.8
C(5)–C(4)–C(10)–C(9)	−34.3
C(3)–C(4)–C(10)–C(9)	141.4
C(4)–C(5)–C(8)–N(1)	18.1
C(6)–C(5)–C(8)–N(1)	−160.9
C(5)–C(8)–N(1)–C(9)	15.2
C(11)–C(8)–N(1)–C(9)	140.6
C(5)–C(8)–N(1)–C(12)	144.0
C(11)–C(8)–N(1)–C(12)	−90.6
C(10)–C(9)–N(1)–C(8)	−56.6
C(10)–C(9)–N(1)–C(12)	175.2
C(14)–C(9)–N(1)–C(12)	53.3
C(14)–C(9)–N(1)–C(8)	−178.5
N(1)–C(9)–C(10)–C(4)	65.2
C(14)–C(9)–C(10)–C(4)	−174.7
N(1)–C(9)–C(14)–N(2)	−64.4
N(1)–C(9)–C(14)–C(15)	48.6
C(10)–C(9)–C(14)–N(2)	176.0
C(10)–C(9)–C(14)–C(15)	−71.0
C(9)–N(1)–C(12)–C(13)	−53.6
C(8)–N(1)–C(12)–C(13)	175.7
N(1)–C(12)–C(13)–N(2)	64.2
N(1)–C(12)–C(13)–C(16)	−48.3
C(12)–C(13)–N(2)–C(14)	−72.2
C(16)–C(13)–N(2)–C(14)	47.0
C(12)–C(13)–N(2)–C(18)	165.0
C(16)–C(13)–N(2)–C(18)	−75.9
N(2)–C(13)–C(16)–C(15)	−28.6
C(12)–C(13)–C(16)–C(15)	86.3
C(9)–C(14)–N(2)–C(13)	72.5
C(9)–C(14)–N(2)–C(18)	−164.3
C(15)–C(14)–N(2)–C(13)	−47.4
C(15)–C(14)–N(2)–C(18)	75.8
N(2)–C(14)–C(15)–C(16)	29.4
C(9)–C(14)–C(15)–C(16)	−86.1
N(2)–C(14)–C(15)–C(17)	−97.6
C(9)–C(14)–C(15)–C(17)	146.9
C(14)–C(15)–C(16)–C(13)	−0.5
C(17)–C(15)–C(16)–C(13)	124.4

Table 2 (*continued*)

C(1)–C(6)–O(1)–C(7)	−15.9
C(5)–C(6)–O(1)–C(7)	165.1
N(1)–C(8)–C(11)–O(2)	−69.7
C(5)–C(8)–C(11)–O(2)	56.8
C(14)–C(15)–C(17)–O(3)	−44.6
C(16)–C(15)–C(17)–O(3)	−164.5
C(14)–C(15)–C(17)–O(4)	134.9
C(16)–C(15)–C(17)–O(4)	15.0

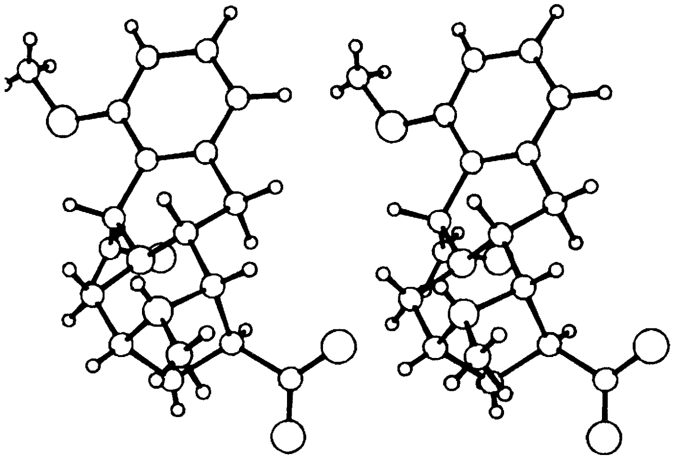

Figure 2. Stereoscopic view of the molecule

C(9) 0.703(3), C(13) 0.806(4), C(12) 0.697(4), C(14) 0.810(3), N(1) 0.624(3), and N(2) 0.878(3). The average *d* value is 0.753 Å, which indicates that ring C is a rather puckered chair. The five-membered ring (ring D) has an envelope conformation. The N(2) atom deviates 0.712 Å from the mean plane (±0.003 Å) which consists of C(13), C(14), C(15), and C(16). Rings C and D constitute a partial structure which resembles the tropane skeleton.[8]

The molecule takes a zwitterion structure. The average bond lengths and angles around N(1) and N(2) are 1.481 Å and 112.8°, and 1.498 Å and 109.8°, respectively. These values and the electron density around the atoms in the final difference Fourier map revealed that only N(2) is protonated. The hydrogen atom is axial and the C(18) methyl group is equatorial to ring C as in the tropane skeleton.[8] Therefore the lone-pair electron of N(1) is *trans*-axial to HN(2). Although the C(18)–N(2) distance is remarkably short among the C–N bond lengths around N(2), around the N(1) atom C(8)–N(1) is remarkably long. The intramolecular non-bonded distances N(1) · · · N(2) and N(1) · · · O(2) are 2.875(3) and 2.966(4) Å, respectively. In naphthyridinomycin,[9] which possesses a similar skeleton to DC-52-d, there is an intramolecular hydrogen bond between a hydroxy-group and a tertiary amine, but there is no such intramolecular hydrogen bond in DC-52-d. The bond angles in rings C and D are similar to the corresponding values in the tropane skeleton.[8]

Figure 3 shows the crystal structure viewed along the *c* axis. The dotted lines indicate hydrogen bonds. The molecules are connected through a hydrogen bond between O(3) and O(2) [O · · · O 2.928(4) Å]. They are further hydrogen bonded to the disordered solvent molecules [O · · · O 2.688(6)—2.871(10) Å].

A partial structure of DC-52-d is similar to that of benztropine,[10] which is known as a strong anticholinergic agent. It has been deduced that the distance between the nitrogen atom and the centre of gravity of the benzene ring in such compounds is related to their biological activity.[10] The distance in DC-52-d is 5.993(4) Å. Table 3 shows the benzene-ring centre to nitrogen atom distances for some tricyclic antidepressants and benztropine.[10] From the distance–activity criterion DC-52-d should show certain anticholinergic activity, but it did not, in fact, show any.

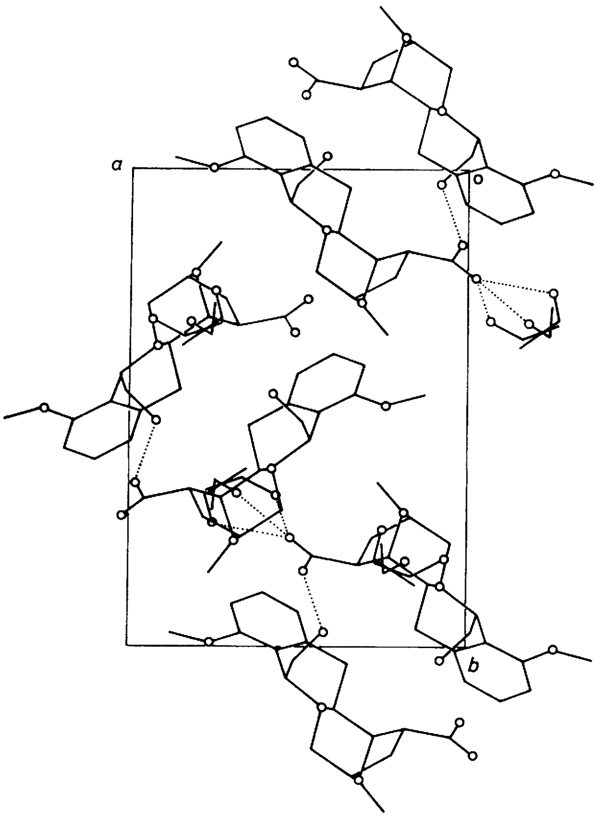

Figure 3. Crystal structure viewed along the *c* axis

Table 3. Distance between the nitrogen atom and the benzene-ring centre(s) (Å) in various antibiotics

DC-52-d	5.99	
Benztropine methanesulphonate	6.91	7.07
Dopamine HCl	5.14	
Imipramine HCl *	7.22	6.25
	6.08	6.54
Chlorimipramine HCl	6.10	6.55
NN-Dimethylspiro[5*H*-dibenzo[*a*,*d*]cyclohex]-4′-ylamine	5.53	7.23

* Two independent molecules

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