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2-(2,4:3,5-Di-*O*-benzylidene-D-*glycero*-D-*allo*-pentitol-1-yl)pyridine, $C_{24}H_{23}NO_5$

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Abstract

$C_{24}H_{23}NO_5$, $M_r = 405.4$, orthorhombic, $P2_12_12_1$, $a = 8.762$ (1), $b = 13.984$ (1), $c = 16.569$ (1) Å, $V = 2030$ (1) Å^3, $Z = 4$, $D_x = 1.327$ Mg m^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.087$ mm^{-1}, $F(000) = 856$, room temperature, $wR = 0.034$, $R = 0.035$ for 2049 observed reflections [$I \geq 3\sigma(I)$] out of 2536 measured reflections and 341 variables. The sugar moiety has the D-*allo* configuration, which provides further proof that the ring closure of the title compound to an α-nucleoside follows an S_N2-like mechanism. The title compound consists of two 1,3-dioxane rings in the chair form, *trans* fused to each other, with two phenyl rings and a (2-pyridyl)hydroxymethyl substituent in equatorial positions. The variation of the C—O lengths in the dioxane rings follows the rules of the anomeric effect. The 1,3-dioxane rings are more puckered than their carbon analogues in *trans*-decalin. The pyridine ring is nearer to C(3) than to O(2), with a synclinal conformation around C(1)—C(2). An intermolecular hydrogen bond is observed, but no intramolecular hydrogen bonds were found. Molecular-mechanics calculations (*MM*3 force field) reproduce the bond lengths with an e.s.d. of 0.011 Å and the valence angles with an e.s.d. of 1.0°. *MM*3 supports conclusions drawn from the X-ray determination concerning the conformational behaviour of the free molecule. In the force field the absence of parameters dedicated to aromatic N atoms makes calculations more difficult.

Introduction

The title compound, shown in Fig. 1, is a useful intermediate in the synthesis of C2-pyridine nucleosides. Modified nucleosides have been shown to be valuable candidates for treatment of viral infections and cancer. In a synthetic study of a novel series of pyridine C-nucleosides with potential antiviral and/or cytostatic properties 2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridines are synthetic precursors of such C-nucleosides (Belmans, Esmans, Lepoivre & Alderweireldt, 1986; Belmans, Vrijens, Esmans, Dommisse, Lepoivre, Alderweireldt, Townsend, Wotring, Balzarini & De Clercq, 1989; Joos, Esmans, Dommisse, Van Dongen, Lepoivre, Alderweireldt, Balzarini & De Clercq, 1991). As shown in Fig. 2 they are obtained as D-*allo*/D-*altro* mixtures by coupling of the appropriate lithiopyridine with 2,4:3,5-di-*O*-benzylidene-*aldehydo*-D-ribose. The D-*allo*/D-*altro* epimers of 2-(2,4:3,5-di-*O*-benzylidenepentitol-1-yl)pyridine were separated and for one of the epimers (m.p. = 426 K) single crystals

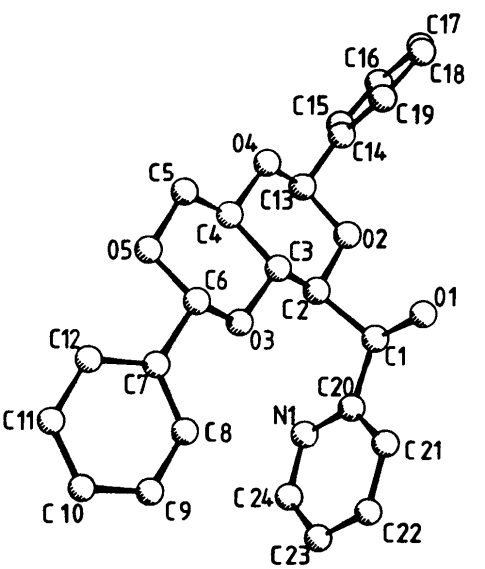

Fig. 1. Structural formula showing atomic numbering scheme, configuration and conformation of the molecule.

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could be obtained by slow evaporation of a $CHCl_3$ solution.

The determination of the structure, and particularly of the D-*allo*/D-*altro* configuration, of the title compound is important, because it will help to assign the ^1H and ^{13}C NMR data to the different epimers and will also constitute final proof of the reaction mechanism by which these adducts are transformed into the corresponding D-ribofuranosyl C-nucleosides.

Experimental

Unit-cell dimensions were deduced from 25 reflections in the range $13 < \theta < 18°$. Enraf–Nonius CAD-4 diffractometer. $\omega/2\theta$-scan mode. Mo radiation monochromatized by pyrolytic graphite. Three intensity-control reflections monitored every 2 h showed no drift; three orientation-control reflections monitored every 150 reflections showed no angular deviations. Maximum Bragg angle 40°, 2536 independent measurements, of which 2049 with $I > 3\sigma(I)$ were considered observed. *hkl* range: $0 \le h \le 11$, $0 \le k \le 17$, $0 \le l \le 21$. Space group from systematic extinctions. No absorption correction ($\mu = 0.087$ mm^{-1}, crystal size 0.10 × 0.10 × 0.15 mm). Structure solved using *MULTAN* (Germain, Main & Woolfson, 1971). All H atoms located in difference electron-density maps. Full-matrix least-squares refinements (on *F*'s) on all positional parameters. Non-H atoms refined anisotropically, H atoms given a fixed value of *B* equal to 4.0 Å^2. Reflections given individual weights according to counting statistics. No extinction correction applied. Convergence reached at $R = 0.035$ and $wR = 0.034$, $S = 3.3$, $(\Delta/\sigma)_{max} = 0.16$, 341 variables. The noise level in the final difference Fourier map was between −0.15 and 0.20 e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV). Enraf–Nonius *SDP* (Frenz, 1978) employed. Refined parameters* are given in Table 1 and the atomic numbering scheme in Fig. 1.

Results and discussion

The molecule consists of two 1,3-dioxane rings, *trans* fused to one another, onto which two phenyl rings and one (2-pyridyl)hydroxymethyl substituent are attached *via* equatorial bonds. One also recognizes the D-*allo* configuration in the positioning of the C—O bonds along the C(1)–C(5) chain. This result agrees with assignment of the configuration at C(1) in the title compound and in related compounds by ^1H NMR as reported by De Vos (1991), and confirms the results of optical rotation dispersion experiments by Snatzke (cited in De Vos, 1991) on 2-(2,4:3,5-di-*O*-benzyldenepentitol-1-yl)-3-methylpyridine. In addition, mesylation and ring closure of the title compound results exclusively in the corresponding α-nucleoside (see Fig. 2). The same sequence of reactions starting from the other C(1) epimer (D-*altro* configuration) results exclusively in the β-nucleoside. Under the reaction conditions no anomerization takes place between α- and β-nucleoside. Hence, these results are unambiguous proof of the S_N2 like mechanism of ring closure as proposed by Belmans, Vrijens, Esmans, Dommisse, Lepoivre, Alderweireldt, Townsend, Wotring, Balzarini & De Clercq (1986) and by Kabat, Pankiewicz, Sochacka & Watanabe (1988).

* Lists of structure factors, anisotropic thermal parameters and molecular-mechanics input parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55878 (32 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: MU0306]

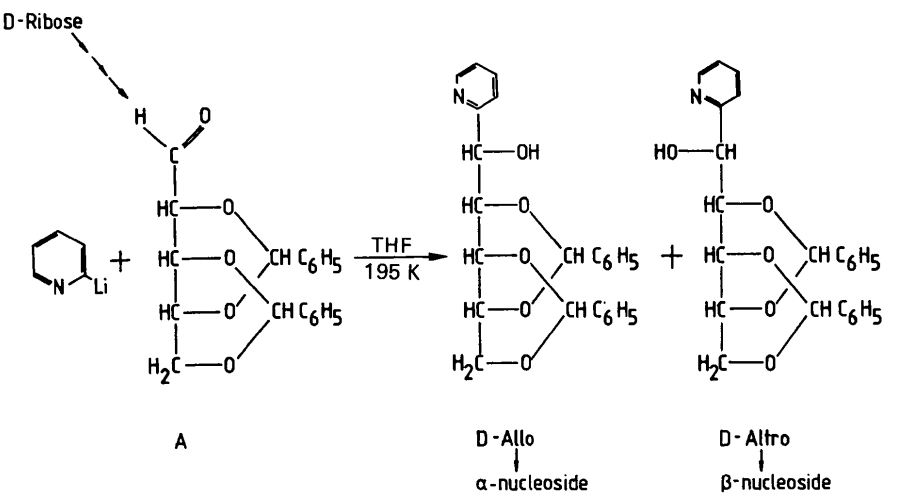

Fig. 2. Synthesis of the title compound within the framework of a synthetic route to pyridine C-nucleosides.

Table 1. *Positional parameters in fractions of the cell edges and isotropic temperature parameters* (Å^2)

The e.s.d.'s given in parentheses refer to the last significant digit. Isotropic temperature parameters were calculated from anisotropic temperature parameters using $B_{iso} = 4/3[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$. All anisotropic temperature parameters were physically acceptable. Starred B values were fixed.

	x	y	z	B_{iso}
N(1)	0.6069 (2)	0.1462 (1)	0.0201 (1)	3.54 (4)
O(1)	0.8673 (2)	0.3262 (1)	0.0985 (1)	3.09 (3)
O(2)	0.7074 (1)	0.4424 (1)	−0.0086 (1)	3.34 (3)
O(3)	0.4573 (1)	0.3132 (1)	0.1281 (1)	3.29 (3)
O(4)	0.5195 (1)	0.5468 (1)	0.0385 (1)	3.70 (3)
O(5)	0.2611 (2)	0.4152 (1)	0.1708 (1)	4.00 (3)
C(1)	0.7661 (2)	0.2879 (1)	0.0401 (1)	3.11 (4)
C(2)	0.6353 (2)	0.3579 (1)	0.0237 (1)	2.94 (4)
C(3)	0.5449 (2)	0.3907 (1)	0.0961 (1)	3.03 (4)
C(4)	0.4340 (2)	0.4682 (1)	0.0694 (1)	3.59 (4)
C(5)	0.3373 (2)	0.4989 (1)	0.1400 (2)	4.31 (5)
C(6)	0.3668 (2)	0.3438 (1)	0.1941 (1)	3.47 (4)
C(7)	0.2822 (2)	0.2580 (1)	0.2262 (1)	3.38 (4)
C(8)	0.3436 (3)	0.1678 (2)	0.2168 (1)	4.37 (5)
C(9)	0.2712 (3)	0.0891 (2)	0.2492 (2)	5.04 (6)
C(10)	0.1356 (3)	0.0992 (2)	0.2905 (2)	5.05 (6)
C(11)	0.0745 (3)	0.1886 (2)	0.2999 (2)	5.60 (6)
C(12)	0.1466 (3)	0.2678 (2)	0.2673 (2)	4.86 (6)
C(13)	0.6042 (2)	0.5164 (1)	−0.0296 (1)	3.38 (4)
C(14)	0.6971 (2)	0.5981 (1)	−0.0610 (1)	3.59 (4)
C(15)	0.6991 (3)	0.6207 (2)	−0.1415 (2)	4.76 (5)
C(16)	0.7956 (3)	0.6936 (2)	−0.1695 (2)	6.16 (6)
C(17)	0.8850 (4)	0.7432 (2)	−0.1169 (2)	6.82 (7)
C(18)	0.8796 (3)	0.7227 (2)	−0.0363 (2)	6.73 (7)
C(19)	0.7882 (3)	0.6505 (2)	−0.0086 (2)	5.41 (6)
C(20)	0.7119 (2)	0.1892 (1)	0.0668 (1)	3.12 (4)
C(21)	0.7789 (2)	0.1442 (1)	0.1323 (1)	3.89 (4)
C(22)	0.7381 (3)	0.0502 (2)	0.1494 (1)	4.67 (5)
C(23)	0.6318 (3)	0.0058 (2)	0.1012 (2)	4.96 (5)
C(24)	0.5686 (2)	0.0557 (1)	0.0391 (2)	4.36 (5)
H(C1)	0.822 (3)	0.282 (2)	−0.015 (1)	4.0*
H(C2)	0.566 (3)	0.327 (1)	−0.021 (1)	4.0*
H(C3)	0.616 (3)	0.414 (1)	0.136 (1)	4.0*
H(C4)	0.365 (3)	0.442 (1)	0.027 (1)	4.0*
H(1,C5)	0.400 (3)	0.530 (1)	0.187 (1)	4.0*
H(2,C5)	0.263 (3)	0.543 (1)	0.129 (1)	4.0*
H(C6)	0.436 (2)	0.373 (2)	0.238 (1)	4.0*
H(C8)	0.437 (3)	0.163 (1)	0.183 (1)	4.0*
H(C9)	0.316 (3)	0.025 (2)	0.238 (1)	4.0*
H(C10)	0.087 (3)	0.042 (1)	0.313 (1)	4.0*
H(C11)	−0.017 (3)	0.200 (1)	0.332 (1)	4.0*
H(C12)	0.108 (3)	0.332 (1)	0.274 (1)	4.0*
H(C13)	0.530 (2)	0.487 (2)	−0.072 (1)	4.0*
H(C15)	0.631 (3)	0.582 (1)	−0.175 (1)	4.0*
H(C16)	0.779 (3)	0.702 (2)	−0.221 (1)	4.0*
H(C17)	0.963 (2)	0.798 (2)	−0.133 (1)	4.0*
H(C18)	0.948 (3)	0.765 (2)	−0.001 (2)	4.0*
H(C19)	0.779 (2)	0.636 (2)	0.047 (1)	4.0*
H(C21)	0.852 (3)	0.177 (1)	0.162 (1)	4.0*
H(C22)	0.791 (3)	0.016 (2)	0.193 (1)	4.0*
H(C23)	0.603 (3)	−0.056 (1)	0.114 (1)	4.0*
H(C24)	0.492 (2)	0.029 (2)	0.002 (1)	4.0*
H(O1)	0.951 (3)	0.335 (1)	0.070 (1)	4.0*

Table 2. *Bond lengths* (Å), *valence and endocyclic torsion angles* (°) *of the title compound*

	Experimental	*MM3*		Experimental	*MM3*
C(1)—O(1)	1.417 (2)	1.430	C(10)—C(11)	1.369 (2)	1.396
C(1)—C(2)	1.532 (2)	1.535	C(11)—C(12)	1.385 (2)	1.397
C(1)—C(20)	1.526 (2)	1.512	C(13)—O(2)	1.418 (1)	1.416
C(2)—O(2)	1.442 (1)	1.425	C(13)—O(4)	1.416 (2)	1.417
C(2)—C(3)	1.509 (2)	1.530	C(13)—C(14)	1.496 (2)	1.510
C(3)—O(3)	1.430 (1)	1.418	C(14)—C(15)	1.372 (3)	1.403
C(3)—C(4)	1.521 (2)	1.526	C(14)—C(19)	1.388 (3)	1.402
C(4)—O(4)	1.426 (1)	1.418	C(15)—C(16)	1.403 (2)	1.397
C(4)—C(5)	1.507 (2)	1.524	C(16)—C(17)	1.362 (3)	1.395
C(5)—O(5)	1.441 (2)	1.422	C(17)—C(18)	1.366 (3)	1.396
C(6)—O(3)	1.417 (1)	1.416	C(18)—C(19)	1.368 (2)	1.397
C(6)—O(5)	1.415 (1)	1.417	C(20)—C(21)	1.384 (2)	1.400
C(6)—C(7)	1.507 (2)	1.510	C(20)—N(1)	1.344 (2)	1.354
C(7)—C(8)	1.380 (2)	1.402	C(21)—C(22)	1.393 (2)	1.395
C(7)—C(12)	1.376 (2)	1.402	C(22)—C(23)	1.374 (2)	1.394
C(8)—C(9)	1.380 (2)	1.396	C(23)—C(24)	1.361 (2)	1.394
C(9)—C(10)	1.379 (2)	1.395	C(24)—N(1)	1.347 (2)	1.350
O(1)—C(1)—C(2)	110.4 (2)	107.3	C(8)—C(9)—C(10)	120.6 (2)	120.1
O(1)—C(1)—C(20)	109.8 (2)	109.7	C(9)—C(10)—C(11)	119.2 (2)	119.8
C(2)—C(1)—C(20)	113.4 (1)	112.7	C(10)—C(11)—C(12)	120.6 (2)	120.1
C(1)—C(2)—O(2)	105.2 (1)	105.5	C(7)—C(12)—C(11)	120.4 (2)	120.7
C(1)—C(2)—C(3)	116.5 (1)	114.8	O(2)—C(13)—O(4)	111.0 (2)	110.8
O(2)—C(2)—C(3)	106.0 (1)	106.0	O(2)—C(13)—C(14)	107.2 (1)	106.6
C(2)—O(2)—C(13)	114.2 (1)	111.7	O(4)—C(13)—C(14)	109.5 (2)	107.2
C(2)—C(3)—O(3)	110.3 (1)	110.9	C(13)—C(14)—C(15)	121.4 (1)	120.6
C(2)—C(3)—C(4)	108.7 (1)	109.6	C(13)—C(14)—C(19)	120.0 (1)	120.7
O(3)—C(3)—C(4)	107.8 (1)	105.5	C(15)—C(14)—C(19)	118.7 (1)	118.7
C(3)—O(3)—C(6)	111.0 (1)	109.5	C(14)—C(15)—C(16)	119.8 (2)	120.7
C(3)—C(4)—O(4)	108.6 (2)	106.4	C(15)—C(16)—C(17)	120.3 (2)	120.1
C(3)—C(4)—C(5)	109.6 (1)	109.1	C(16)—C(17)—C(18)	119.9 (2)	119.8
O(4)—C(4)—C(5)	110.7 (1)	110.8	C(17)—C(18)—C(19)	120.1 (2)	120.1
C(4)—O(4)—C(13)	109.2 (1)	109.0	C(14)—C(19)—C(18)	121.1 (2)	120.6
C(4)—C(5)—O(5)	107.7 (2)	107.2	C(1)—C(20)—N(1)	116.8 (1)	117.7
C(5)—O(5)—C(6)	111.4 (1)	111.0	N(1)—C(20)—C(21)	122.7 (1)	119.2
O(3)—C(6)—O(5)	111.7 (2)	110.5	C(1)—C(20)—C(21)	120.4 (1)	123.1
O(3)—C(6)—C(7)	108.0 (2)	106.6	C(20)—C(21)—C(22)	118.6 (1)	120.0
O(5)—C(6)—C(7)	109.6 (2)	107.7	C(21)—C(22)—C(23)	118.9 (1)	119.2
C(6)—C(7)—C(8)	119.7 (1)	120.6	C(22)—C(23)—C(24)	118.9 (1)	119.1
C(6)—C(7)—C(12)	121.3 (1)	120.8	C(23)—C(24)—N(1)	123.9 (1)	120.5
C(8)—C(7)—C(12)	118.9 (1)	118.7	C(20)—N(1)—C(24)	117.1 (1)	122.0
C(7)—C(8)—C(9)	120.4 (1)	120.7			
C(2)—C(3)—C(4)—O(4)	−61.5 (2)	−60.4	O(3)—C(3)—C(4)—C(5)	57.9 (2)	60.6
C(3)—C(4)—O(4)—C(13)	61.9 (2)	62.7	C(3)—C(4)—C(5)—O(5)	−57.1 (2)	−57.7
C(4)—O(4)—C(13)—O(2)	−60.5 (2)	−65.3	C(4)—C(5)—O(5)—C(6)	58.1 (2)	58.0
O(4)—C(13)—O(2)—C(2)	60.0 (2)	63.9	C(5)—O(5)—C(6)—O(3)	−60.8 (2)	−62.9
C(13)—O(2)—C(2)—C(3)	−57.2 (2)	−58.5	O(5)—C(6)—O(3)—C(3)	61.3 (2)	66.2
O(2)—C(2)—C(3)—C(4)	56.7 (2)	57.4	C(6)—O(3)—C(3)—C(4)	−59.0 (2)	−63.8

Bond distances, valence and endocyclic torsion angles are given in Table 2. Some additional torsion angles are presented in the Newman projections shown in Fig. 3. From these data the following structural details emerge. Firstly, the *trans* fusion (Fig. 3*a*) of the two 1,3-dioxane rings, involving the tertiary C atoms C(3) and C(4), leads to torsion angles around C(3)—C(4) and valence angles at C(3) and C(4) which are typical for a *trans*-fused decalin system involving quaternary C atoms as bridgeheads (Geise, Altona & Romers, 1967). This is one indication that the fused 1,3-dioxane system is more puckered than the corresponding decalin system. Another indication comes from the comparison of averaged endocyclic valence (θ) and torsion angles (φ) in the two systems:

$\langle\theta\rangle = 109.9\ (0.4)°$, $\langle\varphi\rangle = 59.0\ (1)°$ for C(3)—C(4)—C(5)—O(5)—C(6)—O(3)

$\langle\theta\rangle = 109.6\ (0.4)°$, $\langle\varphi\rangle = 59.6\ (1)°$ for C(3)—C(4)—O(4)—C(13)—O(2)—C(2)

$\langle\theta\rangle = 115.5\ (1)°$, $\langle\varphi\rangle = 55.0\ (3)°$ for *trans*-decalin systems (Geise *et al.*, 1967).

Secondly, using the conformational energies of substituents on a 1,3-dioxane ring (Eliel, 1972), it might be argued that substituents on C(1) of the title compound would suffer more from steric interactions with the disubstituted C(3) than from those with O(2). Hence, the sterically demanding pyridine ring might be expected to be near O(2) rather than near C(3). In other words one might expect an anticlinal conformation around C(1)—C(2) [see IUPAC (1974), for definitions] with a torsion angle

H—C(1)—C(2)—H of about 180°. Nevertheless, the conformation around C(1)—C(2) is found to be synclinal, with the H—C(1)—C(2)—H torsion being about 60° (Fig. 3*b*). This conformation would have a small vicinal NMR ^3J(H,H) coupling constant and would explain the value ^3J(H,H) = 2.9 Hz observed in solution (De Vos, 1991). The steric hindrance, probably present in synclinal form, is relieved by opening the valence angles C(1)—C(2)—C(3) and C(2)—C(1)—C(20). The conformation may be stabilized by an intramolecular hydrogen bond [O(1)—H···O(2)], or an intermolecular hydrogen bond. The latter is found in the solid between O(1)—H and N(1) of a molecule at $x+\frac{1}{2}, -y+\frac{1}{2}, -z$. The details are: H—O(1) = 0.88 (2), H···N(1) = 2.04 (2), O(1)···N(1) = 2.901 (2) Å, O(1)—H···N(1) = 166 (1)°.

Thirdly, the variation in the conformations around C(6)—C(7), C(13)—C(14) and C(1)—C(20) (Figs. 3*c*–3*e*) suggests a relatively low barrier opposing the rotation of the phenyl and pyridine rings. This is consistent with the relatively high B_{iso} values (Table 1) observed particularly for the phenyl-ring atoms. A large amplitude motion of the phenyl rings would account for the observed shrinkage of the corresponding C—C bonds. Average C—C bond lengths of 1.378 and 1.377 Å are found for the rings attached to C(6) and C(13), respectively, to be compared with the normal value of 1.395 Å. The rings themselves are approximately planar with endocyclic torsion angles (not tabulated) up to 2.0 (4)°, and distances of individual atoms to the least-squres plane of the corresponding ring up to 0.011 (2) Å.

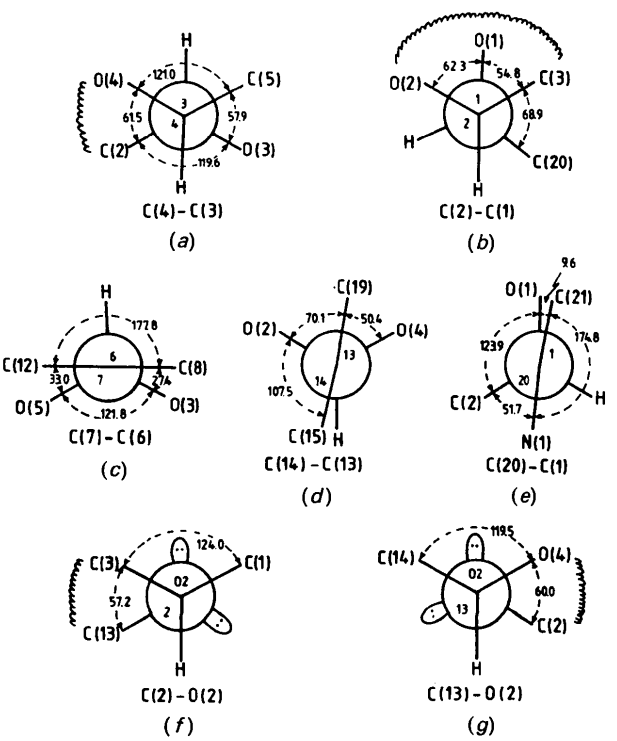

Fig. 3. Newman projections (*a*) along C(4)—C(3) showing *trans* fusion of 1,3-dioxane rings; (*b*) along C(2)—C(1) showing D-*allo* configuration; (*c*) along C(7)—C(6); (*d*) along C(14)—C(13); (*e*) along C(20)—C(1), showing the conformation of the phenyl and pyridine rings, respectively; (*f*) along C(2)—O(2); and (*g*) along C(13)—O(2) showing the anomeric effect near O(2). Angles are given in °.

Fourthly, one notes that the bonds O(3)—C(6), O(5)—C(6), O(2)—C(13) and O(4)—C(13) are considerably shorter than O(3)—C(3), O(5)—C(5), O(2)—C(2) and O(4)—C(4). Inspection of Figs. 3(*f*) and 3(*g*) reveals that the variation is caused by the anomeric effect. A description of this effect and its consequences on the geometry of dimethoxymethane (which mimics the relevant C—O—C—O—C sequence in the 1,3-dioxane rings) is given by Williams, Scarsdale, Schäfer & Geise (1981) and Van Alsenoy, Schäfer, Scarsdale, Williams & Geise (1981).

Molecular-mechanics calculations

To check upon the conclusions stated above, molecular-mechanics calculations were performed using the *MM*3(89) program and force field (Allinger, Yuh & Lii, 1989). The force field contains parameters for standard sp^2-type N atoms and for N atoms specific for pyrrole, but lacks those for an aromatic N atom required here. Therefore, two series of computations were performed in which the pyridine rings were described by: (i) pyrrole-type N atoms combined with standard sp^2-type C atoms; (ii) standard sp^2-type N atoms, combined with benzene-type C atoms. The latter approach, which seems more realistic physically requires the input of many more parameters and thus introduces larger uncertainties. Nevertheless, we report here the results of the slightly (but not statistically significantly) better approach.

Conformational energies and relaxed geometries were calculated while driving the torsion angles φ[O(1)—C(1)—C(2)—O(2)] and φ[N(1)—C(20)—C(1)—C(2)] over 360° and φ[O(2)—C(13)—C(14)—C(15)] and φ[O(3)—C(6)—C(7)—C(8)] over 180°, all in steps of 20°. The molecular conformation of lowest energy calculated by *MM*3(89) only differs from that in the solid by the position of the phenyl group at C(6); *MM*3(89): C(6)—H eclipsing the phenyl ring; X-ray experiment: C(6)—H perpendicular to the ring, Fig. 3(*c*). This difference can easily be caused by the crystal packing. Around C(1)—C(2) the local conformation of lowest energy is calculated to be synclinal (Fig. 3*b*), as observed in the solid, but now with an intramolecular hydrogen bridge O(1)—H···O(2). In altering φ[N(1)—C(20)—C(1)—C(2)], *i.e.* during rotation of the pyridine ring, six eclipsed

forms are met, for which *MM*3(89) finds energy minima only if O(1) is eclipsed by either C(21) or N(1). The former conformation, observed in the solid (Fig. 3*e*), is calculated to be 2.5 kcal mol^{-1} more stable than the latter. These two forms are separated by a strongly asymmetric rotational energy path (Fig. 4) with barrier heights of 4.6 kcal mol^{-1} [N(1) passes over C(2)] and of 8.3 kcal mol^{-1} [C(21) passes over C(2)]. The barrier height calculated for the rotation of the phenyl ring at C(6) is 1.2 kcal mol^{-1} and that for the rotation at C(13) is 0.9 kcal mol^{-1}. Thus, the *MM*3(89) calculations support the second and third lines of argument in the discussion of the experimental details. Conversely, the other well established facts may help to estimate the accuracy of *MM*3(89) results.

Table 2 also compares the calculated with the experimental geometry. The *MM*3(89) calculated puckering of the 1,3-dioxane rings ($\langle\theta\rangle = 108.9°$ and $\langle\varphi\rangle = 61.5°$ for both rings) is in good agreement with experiment. Even more gratifying is the fact that the correct sequence is calculated for the C—O distances affected by the anomeric effect: O(2)—C(13) ≃ O(4)—C(13) ≃ O(3)—C(6) ≃ O(5)—C(6) < O(3)—C(3) ≃ O(4)—C(4) < O(2)—C(2) ≃ O(5)—C(5).

Further comparison of bond lengths reveals large discrepancies between the aromatic rings. For the phenyl rings the discrepancies are as a result of the shrinkage effect (large amplitude motion) present in the experimental values. We believe, however, that the disagreement in the pyridine ring arises because the force field lacks parameters dedicated to aromatic N atoms. Omitting the distances of the three aromatic rings we find for the 16 remaining bond lengths that the e.s.d. = 0.011 Å and Δ_{max} = −0.022 Å (obs. − calc.).

Regarding the valence angles one notes that *MM*3(89) reproduces the opening of the C(1)—C(2)—C(3) and C(2)—C(1)—C(20) angles as the result of steric strain. Serious discrepancies are seen again in the pyridine ring, particularly near the N atom. This again shows that a correct description of the pyridine ring requires parameters dedicated to aromatic N atoms. Omitting the pyridine angles we find for the 39 remaining angles that the e.s.d. = 1.0 Å and Δ_{max} = 3.1°. The two largest deviations are for O(1)—C(1)—C(2) (Δ = 3.1°) and C(2)—O(2)—C(13) (Δ = 2.6°); they are probably caused by the fact that the *MM*3(89) geometry relates to a molecule with an intramolecular hydrogen bond, whereas the experimental geometry concerns a molecule with an intermolecular hydrogen bond.

We conclude that, apart from the pyridine ring, *MM*3(89) reproduces the experimental geometry as well as can be expected given the experimental accuracy and the omission of packing effects from the calculations.

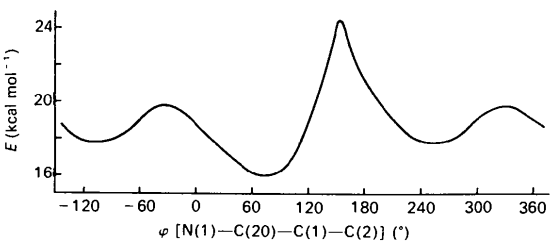

Fig. 4. Rotational energy (kcal mol^{-1}) as a function of N(1)—C(20)—C(1)—C(2) as calculated by *MM*3(89).

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