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A Possible Synthetic Precursor to the Tropoloisoquinoline Alkaloid Pareirubrine A

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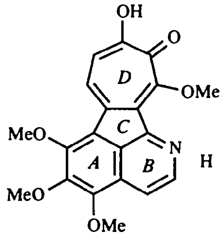
Abstract

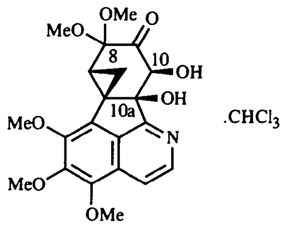
X-ray analysis established that in the title compound, (6bα,7α,10α,10aα)-7,7a,8,9,10,10a-hexahydro-10,10a-dihydroxy-4,5,6,8,8-pentamethoxycyclopropa[1,2-*d*]-indeno[1,2,3-*ij*]isoquinolin-9-one trichloromethane solvate, $C_{21}H_{23}NO_8.CHCl_3$, a potential precursor to the natural product pareirubrine A, the cyclopropane ring and the two hydroxy groups reside on the same face of the cyclohexane ring to which they are attached.

Comment

We have recently reported (Banwell, Hamel, Ireland & MacKay, 1994) the first total synthesis of the tropoloisoquinoline alkaloid imerubrine which was achieved using a biomimetic approach to create the troponoid *D* ring (for related and very recent work see Boger & Takahashi, 1995, and references therein). In seeking to extend such chemistry to the more highly oxygenated congener pareirubrine A, (1), an alkaloid with demonstrated antileukaemic properties (Morita, Matsumoto, Takeya, Itokawa & Iitaka, 1993), we required quantities of the title compound, (2), and/or the diastereoisomeric C-10β,C-10aβ-diol. In the event, compound (2) was readily prepared, in a diastereoselective fashion, by osmium tetroxide-mediated *cis*-dihydroxylation (Büchi, Demole & Thomas, 1973) of the corresponding olefin. In the absence of samples of the other possible diastereoisomer, however, NMR spectroscopic analysis of the product did not allow unequivocal determination of the stereochemical relationship between the newly introduced hydroxy groups and the nearby cyclopropane ring. Furthermore, the chemical behaviour of the product diol suggested that there might be a close contact between one of the newly introduced hydroxy groups and a transannularly located C-8 methoxy methyl group. Such an observation could be accommodated by either of the two possible (diastereoisomeric) reaction products. In order to establish the C-10 and C-10a stereochemistries within compound (2), as well as detect any significant through-space interactions within the molecule, a single-crystal X-ray analysis of (2) was undertaken and the results are reported herein.



(1)



(2)

The present results clearly confirm that in compound (2), the cyclopropane ring and the two hydroxy groups reside on the same face of the cyclohexane ring to which they are attached. In the solid state, there does not appear to be any significant close contact between either hydroxy group and the *syn*-related C-8 methoxy methyl C atom. Inspection of molecular models suggests there is sufficient flexibility within the non-aromatic six-membered ring such that this type of contact could occur in solution. Intermolecular interactions are present, however, involving the hydroxy groups at the C(10) and C(10a) atoms. The H atom on O(10) interacts with the N(1) atom [O(10)···N(1) 2.837 (7) and H(O10)···N(1) 2.06 Å] and the H atom on O(10a) interacts with the O(10) atom [O(10a)···O(10) 2.782 (6) and H(O10a)···O(10) 1.86 Å] of a centrosymmetrically related molecule resulting in weakly bonded dimers.

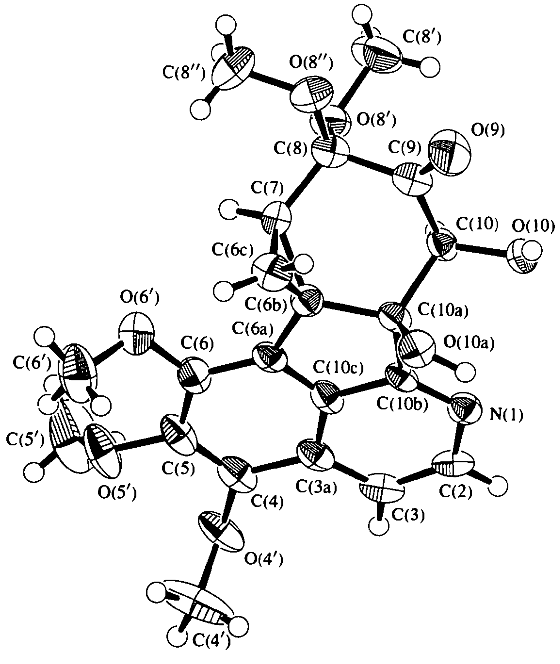


Fig. 1. View of the title compound showing the labelling of all non-H atoms. Displacement ellipsoids are shown at the 50% probability level. H atoms are drawn as circles of arbitrary radii.

Experimental

A 1:1 *tert*-butanol/water solution of the precursor enone (Banwell *et al.*, 1994) was treated with potassium chlorate and then osmium tetroxide according to the method of Büchi *et al.* (1973). The resulting mixture was stirred at room temperature for 7 d. The solid obtained on aqueous work-up was recrystallized from chloroform/hexane to give compound (2) [m.p. 448–458 K (decomp.)] as pale yellow plates in 73% yield.

Crystal data

$C_{21}H_{23}NO_8.CHCl_3$
$M_r = 536.78$
Monoclinic
$P2_1/c$
$a = 14.453\,(2)$ Å
$b = 10.149\,(3)$ Å
$c = 17.136\,(1)$ Å
$\beta = 91.315\,(7)°$
$V = 2512.8\,(7)$ Å^3
$Z = 4$
$D_x = 1.419$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 24 reflections
$\theta = 30.9–44.4°$
$\mu = 3.714$ mm^{-1}
$T = 213\,(1)$ K
Plate
0.28 × 0.20 × 0.04 mm
Pale yellow

Data collection

Rigaku AFC-6*R* diffractometer
$\omega/2\theta$ scans
Absorption correction: semi-empirical using azimuthal (ψ) scan data (North, Phillips & Mathews, 1968)
$T_{\min} = 0.701$, $T_{\max} = 0.862$
4164 measured reflections
3986 independent reflections

1700 observed reflections [$I > 3\sigma(I)$]
$R_{\rm int} = 2.81$
$\theta_{\max} = 60.08°$
$h = 0 \rightarrow 16$
$k = -11 \rightarrow 0$
$l = -19 \rightarrow 19$
3 standard reflections monitored every 150 reflections
intensity decay: none

Refinement

Refinement on *F*
$R = 0.0615$
$wR = 0.0641$
$S = 2.175$
1700 reflections
331 parameters
H-atom parameters not refined
$w = 4F_o^2/[\sigma^2(F_o^2) + (0.013F_o^2)^2]$
$(\Delta/\sigma)_{\max} = 0.0860$

$\Delta\rho_{\max} = 0.32$ e Å^{-3}
$\Delta\rho_{\min} = -0.36$ e Å^{-3}
Extinction correction: Zachariasen (1967) type 2, Gaussian isotropic
Extinction coefficient: $2\,(2) \times 10^{-7}$
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)

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

	x	y	z	$U_{\rm eq}$
Cl(1)	0.4937 (2)	0.8584 (3)	0.8365 (1)	0.150 (1)
Cl(2)†	0.3901 (6)	0.7770 (9)	0.9685 (2)	0.262 (4)
Cl(2′)‡	0.4672 (10)	0.936 (2)	0.9760 (6)	0.211 (5)
Cl(3)†	0.3586 (2)	0.6623 (4)	0.8193 (2)	0.177 (2)
Cl(3′)‡	0.382 (1)	0.702 (2)	0.941 (1)	0.159 (5)
O(4′)	0.9711 (2)	1.1790 (3)	0.3220 (2)	0.052 (1)
O(5′)	0.7777 (3)	1.1946 (3)	0.3346 (2)	0.060 (1)
O(6′)	0.6809 (2)	1.0045 (4)	0.4139 (2)	0.053 (1)
O(8′)	0.7682 (2)	0.7986 (4)	0.6721 (2)	0.049 (1)
O(8″)	0.6512 (2)	0.6455 (4)	0.6453 (2)	0.057 (1)
O(9)	0.7860 (2)	0.4776 (4)	0.6244 (2)	0.063 (1)
O(10)	0.9595 (2)	0.5326 (3)	0.5826 (2)	0.0368 (10)
O(10a)	0.8636 (2)	0.5647 (3)	0.4419 (2)	0.0386 (10)
N(1)	1.0440 (3)	0.7377 (4)	0.4596 (2)	0.035 (1)
C(01)†	0.3833 (8)	0.796 (2)	0.8663 (6)	0.148 (3)
C(01′)‡	0.411 (2)	0.855 (2)	0.894 (1)	0.038 (7)
C(2)	1.0986 (3)	0.8334 (5)	0.4271 (3)	0.039 (2)
C(3)	1.0665 (3)	0.9487 (5)	0.3943 (3)	0.040 (1)
C(3a)	0.9710 (3)	0.9747 (5)	0.3939 (2)	0.035 (1)
C(4)	0.9219 (3)	1.0832 (5)	0.3598 (3)	0.040 (1)
C(4′)	0.9619 (5)	1.1747 (8)	0.2388 (3)	0.105 (3)
C(5)	0.8271 (4)	1.0923 (5)	0.3662 (3)	0.043 (1)
C(5′)	0.7962 (5)	1.3213 (6)	0.3671 (4)	0.099 (3)
C(6)	0.7745 (3)	0.9932 (5)	0.4045 (3)	0.039 (1)
C(6′)	0.6222 (4)	1.0217 (7)	0.3470 (4)	0.076 (2)
C(6a)	0.8207 (3)	0.8864 (5)	0.4364 (2)	0.034 (1)
C(6b)	0.7905 (3)	0.7673 (5)	0.4794 (2)	0.035 (1)
C(6c)	0.6968 (3)	0.7051 (5)	0.4691 (3)	0.046 (2)
C(7)	0.7195 (3)	0.7794 (5)	0.5435 (3)	0.039 (1)
C(8)	0.7312 (3)	0.7042 (6)	0.6189 (3)	0.045 (1)
C(8′)	0.7839 (4)	0.7520 (7)	0.7505 (3)	0.074 (2)
C(8″)	0.5731 (4)	0.7327 (7)	0.6478 (4)	0.076 (2)
C(9)	0.8023 (3)	0.5920 (6)	0.6086 (3)	0.042 (1)
C(10)	0.8933 (3)	0.6343 (5)	0.5756 (3)	0.033 (1)
C(10a)	0.8772 (3)	0.6780 (5)	0.4898 (2)	0.033 (1)
C(10b)	0.9553 (3)	0.7640 (5)	0.4604 (2)	0.030 (1)
C(10c)	0.9166 (3)	0.8815 (5)	0.4303 (2)	0.033 (1)

† Site occupancy = 0.777 (4). ‡ Site occupancy = 0.223 (4).

The θ-scan width used was $(1.30 + 0.3\tan\theta)°$ 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. All non-H atoms were refined anisotropically. H atoms were located from a difference map and fixed at ideal positions, with C—H = 0.95 Å and $U_{\rm iso} = 1.2U_{\rm eq}$(C). The structure contains a disordered trichloromethane solvent molecule which was refined anisotropically over two positions, except for the central C atom of the minor component. The H atom on this molecule was omitted from the calculations. The structure was solved by direct methods using *SIR*92 (Altomare *et al.*, 1994) and expanded using the Fourier programs of *DIRDIF*94 (Beurskens *et al.*, 1994). All calculations were performed using the *TEXSAN* software (Molecular Structure Corporation, 1995).

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1993). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN*. Program(s) used to refine structure: *TEXSAN*. Software used to prepare material for publication: *TEXSAN*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: TA1095). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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(Z)-3-Phenyl-2-(trifluoromethyl)prop-2-enoic Acid: a Hydrogen-Bonded Dimer

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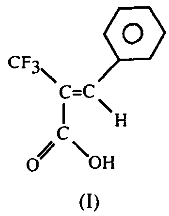
Abstract

The crystal structure of the title compound confirms the *cis* assignment for (Z)-3-phenyl-2-(trifluoromethyl)prop-2-enoic acid, $C_{10}H_7F_3O_2$. The two molecules in the asymmetric unit form a hydrogen-bonded dimer but have different conformations. One molecule has the carbonyl O atom *cis* with respect to the trifluoromethyl group, while the other molecule has the hydroxyl O atom *cis* to the trifluoromethyl group.

Comment

The fluorinated allylic alcohol $F_2C{=}C(CF_3)CH(OH)$-C_6H_5 rearranges with DAST $[(C_2H_5)_2NSF_3]$ to give $C_6H_5CH{=}C(CF_3)C(O)F$, which on hydrolysis gives the title compound, (I).



(I)

The crystal structure confirms the double-bond configuration to be *cis* for both molecules in the asymmetric unit. The two molecules form a hydrogen-bonded dimer (Fig. 1). The conformations of the molecules differ in the relative orientation of the carboxyl group to the double bond. Molecule *A* (C1–C10, O1, O2, F1–F3) has the carbonyl O atom *cis* with respect to the trifluoromethyl group and molecule *B* (C11–C20, O3, O4, F5–F6) has the hydroxyl O atom *cis* to the trifluoromethyl group. Due to steric interactions, the carboxyl and phenyl groups are not coplanar with the double bonds. Additionally, the double bonds have a slight twist, 8 (3) for C2═C3 and 10 (1)° for C12═C13. The dihedral angles between the planes of the carboxyl group (C1, C2, O1, O2 for molecule *A* and C11, C12, O3, O4 for molecule *B*) and the double-bond planes (C1, C2, C3, C4, C5, H3 for molecule *A* and C11, C12, C13, C14, C15, H13 for molecule *B*) are 20 (1) for *A* and 14.1 (3)° for *B*. The dihedral angles between the planes

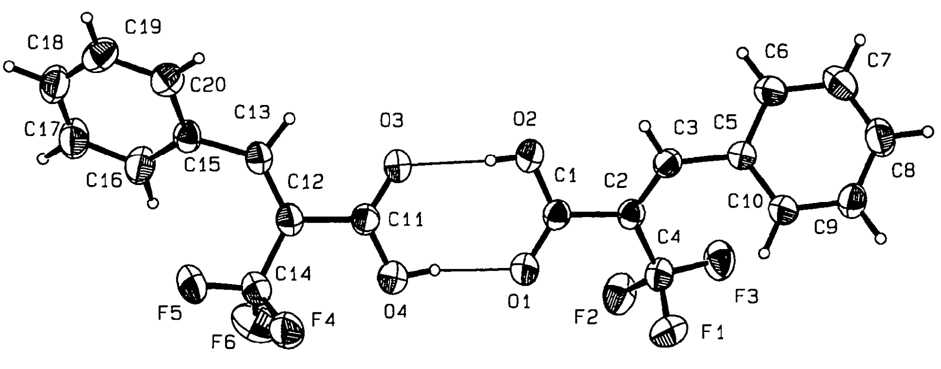


Fig. 1. *ORTEPII* (Johnson, 1976) view of the subject molecules shown as the hydrogen-bonded dimer. Displacement ellipsoids are shown at the 35% probability level.