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Structure of Quinidine, $C_{20}H_{24}N_2O_2$

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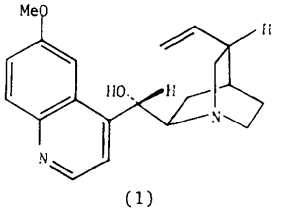
Abstract. $M_r = 324{\cdot}43$, monoclinic, $P2_1$, $a = 11{\cdot}883$ (2), $b = 7{\cdot}037$ (4), $c = 11{\cdot}256$ (2) Å, $\beta = 111{\cdot}95$ (1)°, $V = 873{\cdot}1$ (5) Å^3, $Z = 2$, $D_m = 1{\cdot}23$, $D_x = 1{\cdot}234$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 0{\cdot}60$ mm^{-1}, $T = 300$ K. Final $R = 0{\cdot}033$ for 1384 observed reflexions. Molecules related by a 2_1 axis are held together by a hydrogen bond between the hydroxyl group and N in the quinuclidine ring [O···N 2·763 (3), H···N 1·80 (4) Å, O—H···N 180 (4)°]. The molecular conformation is substantially the same as that in quinidine ethanolate irrespective of the difference in the crystallographic environments.

Introduction. Antimalarial agents such as quinidine (1) act by binding to the nucleic acids of the malaria parasite (Kier, 1971). As part of a study to understand the nature of the binding, the molecular conformation of (1) in the crystals has been determined, and compared with the structure of quinidine ethanolate (2) (Doherty, Benson, Maienthal & Stewart, 1978). An independent study of (2) by us (Kashino & Haisa, unpublished) has corrected the reported cell dimension.



(1)

Experimental. Commercially available crystals of (1) recrystallized from an ether solution by slow evaporation, colorless prisms elongated along **b** and bounded by {100}, {001} and {011}, density measured in aqueous KI solution by flotation, systematic absence $0k0$ for k odd, indicating space group $P2_1$, crystal 0·05 × 0·33 × 0·08 mm, Rigaku AFC-5 four-circle diffractometer, lattice parameters determined from 20 reflexions by least squares, intensities measured up to $2\theta = 120°$, ω–2θ scan method, scan speed 4° min^{-1} in 2θ, scan range 1·0° + 0·15° tanθ, Ni-filtered Cu $K\alpha$ at 40 kV and 200 mA, background measured for 4 s on either side of peak, three reference reflexions showed no intensity deterioration, intensities corrected for Lorentz and polarization factors, but not for absorption, 1420 independent reflexions, 1384 (ranging over $h = -8$ to 13, $k = 0$ to 7, $l = 0$ to 12) with $|F_o| > \sigma(F)$ used in refinement; structure solved by *MULTAN*, and refined by block-diagonal least squares, quantity minimized was $\sum w(|F_o| - |F_c|)^2$, with $w = 1{\cdot}0$ for $0 < |F_o| \leq 7{\cdot}0$ and $(7{\cdot}0/|F_o|)^2$ for $|F_o| > 7{\cdot}0$; locations of H atoms determined from a difference Fourier synthesis, refined by least squares, $wR = 0{\cdot}043$, $S = 0{\cdot}059$, maximum shifts in final refinement cycle for non-H and H atoms were $0{\cdot}3\sigma$ and $1{\cdot}0\sigma$ respectively, maximum and minimum heights in final difference Fourier synthesis $\pm 0{\cdot}12$ e Å^{-3}, $F(000) = 348$; atomic scattering factors taken from *International Tables for X-ray Crystallography* (1974), computations carried out at the Crystallographic Research Center, Institute for Protein Research, Osaka University, and at the Okayama University Computer Center; programs used were *MULTAN* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), *HBLS*-V (Ashida, 1973), *MOLCON* (Fujii, 1979) and *ORTEP* (Johnson, 1965).

Crystal data of (2) are: orthorhombic, $P2_12_12_1$, $a = 13{\cdot}190$ (2), $b = 16{\cdot}482$ (2), $c = 9{\cdot}700$ (4) Å, $V = 2109$ (1) Å^3, $Z = 4$ (Kashino & Haisa, unpublished). The relationships with the data of Doherty *et al.* (1978) (a', b', c') are: $a = a'$, $b = -c'$, $c = -b'$. The final R for (2) was 0·055 for 1680 reflexions above σ. After completion of the structure analysis we concluded that the structure was exactly the same as that reported by Doherty *et al.* (1978), and the reported value of b', 9·893 Å, should be replaced by 9·693 Å, which gave the calculated density and molecular geometry as reported.

Discussion. The final atomic parameters of (1) are listed in Table 1.* A stereoview of the molecule with atomic numbering is shown in Fig. 1. Bond lengths and angles are given in Table 2. A projection of the crystal structure viewed along **b** is shown in Fig. 2.

* Lists of structure factors, anisotropic thermal parameters, coordinates of the H atoms, and bond lengths and angles involving the H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38144 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final atomic parameters (positional* $\times 10^4$) *with e.s.d.'s in parentheses*

$B_{eq} = \frac{4}{3} \sum_i \beta_{ii} / a_i^{*2}$.

	x	y	z	B_{eq}(Å^2)
N(1)	3396 (2)	6629 (4)	−741 (2)	5·5 (1)
C(2)	4142 (2)	7796 (5)	99 (3)	5·5 (1)
C(3)	4631 (2)	7490 (4)	1430 (2)	4·7 (1)
C(4)	4346 (2)	5881 (4)	1932 (2)	3·9 (1)
C(5)	3102 (2)	2908 (4)	1454 (2)	4·0 (1)
C(6)	2288 (2)	1715 (4)	581 (2)	4·3 (1)
C(7)	1881 (2)	2139 (5)	−737 (2)	4·8 (1)
C(8)	2265 (2)	3752 (5)	−1134 (2)	5·0 (1)
C(9)	3077 (2)	5010 (4)	−257 (2)	4·3 (1)
C(10)	3512 (2)	4583 (4)	1072 (2)	3·8 (1)
O(11)	1937 (2)	161 (3)	1067 (2)	5·8 (1)
C(12)	1093 (3)	−1120 (5)	245 (3)	6·2 (2)
C(13)	4928 (2)	5462 (4)	3363 (2)	3·7 (1)
O(14)	5349 (1)	7163 (3)	4074 (2)	4·6 (1)
C(15)	5974 (2)	4051 (4)	3602 (2)	3·6 (1)
N(16)	6334 (2)	3099 (3)	4868 (2)	3·7 (1)
C(17)	7050 (2)	1404 (4)	4835 (2)	4·4 (1)
C(18)	8106 (3)	1931 (5)	4416 (3)	5·5 (1)
C(19)	8234 (2)	4092 (4)	4453 (2)	4·6 (1)
C(20)	7098 (2)	4928 (4)	3436 (2)	4·3 (1)
C(21)	7117 (2)	4345 (5)	5908 (2)	4·4 (1)
C(22)	8341 (2)	4778 (4)	5785 (2)	4·3 (1)
C(23)	8651 (3)	6852 (5)	6020 (3)	5·8 (2)
C(24)	9475 (3)	7582 (6)	6972 (3)	7·3 (2)

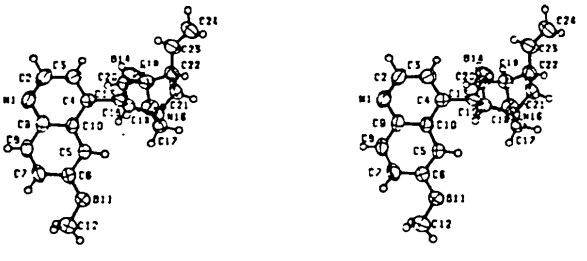

Fig. 1. Stereoview of the molecule and numbering of non-H atoms. Ellipsoids of 50% probability are used for non-H atoms; the H atoms are represented as spheres equivalent to $B = 1{\cdot}0$ Å^2.

Molecules related by a 2_1 axis are linked together by a hydrogen bond between O(14) of the hydroxyl group and N(16) in the quinuclidine ring to form a column along **b**. The coordination of O(14) to N(16) is tetrahedral: O(14)···N(16^{ii})–C(15^{ii}) 121·7 (2), O(14)···N(16^{ii})–C(17^{ii}) 109·6 (2), O(14)···N(16^{ii})–C(21^{ii}) 98·2 (2)°; H(14)···C(15^{ii}) 2·87 (4), H(14)···C(17^{ii}) 2·68 (4), H(14)···C(21^{ii}) 2·49 (4) Å. The columns are hexagonally packed by van der Waals interactions to complete the structure. The quinoline rings related by a 2_1 axis overlap with a dihedral angle of 59·28 (5)°, which is comparable to 52° in naphthalene (Cruickshank, 1957). Similar overlapping also exists in the crystals of the quinidine salt of (−)-1,1′-dimethylferrocene-3-carboxylic acid (3) (Carter, McPhail & Sim, 1967), the angle being 58·6 (3)°, but does not exist in the crystals of (2), in which the N atom in the quinuclidine ring accepts a hydrogen bond from the ethanol and the quinoline rings are separated from each other.

The quinoline ring of (1) is planar within 0·03 Å. The bonds N(1)–C(2), C(3)–C(4), C(5)–C(6) and C(7)–C(8) are shortened as found in some quinoline derivatives (Castellano & Prout, 1971; Kashino & Haisa, 1973) and as expected from the SCF–MO calculation.

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

N(1)–C(2)	1·314 (4)	C(13)–O(14)	1·423 (4)
N(1)–C(9)	1·376 (4)	C(13)–C(15)	1·534 (4)
C(2)–C(3)	1·406 (4)	C(15)–N(16)	1·486 (4)
C(3)–C(4)	1·363 (4)	C(15)–C(20)	1·545 (4)
C(4)–C(10)	1·427 (4)	N(16)–C(17)	1·474 (4)
C(4)–C(13)	1·525 (4)	N(16)–C(21)	1·480 (4)
C(5)–C(6)	1·377 (4)	C(17)–C(18)	1·542 (4)
C(5)–C(10)	1·403 (4)	C(18)–C(19)	1·527 (4)
C(6)–C(7)	1·410 (4)	C(19)–C(20)	1·524 (4)
C(6)–O(11)	1·356 (4)	C(19)–C(22)	1·534 (4)
C(7)–C(8)	1·360 (5)	C(21)–C(22)	1·542 (4)
C(8)–C(9)	1·406 (5)	C(22)–C(23)	1·504 (5)
C(9)–C(10)	1·420 (4)	C(23)–C(24)	1·260 (6)
O(11)–C(12)	1·407 (4)		

C(2)–N(1)–C(9)	116·4 (3)	C(4)–C(13)–C(15)	109·2 (2)
N(1)–C(2)–C(3)	124·7 (3)	O(14)–C(13)–C(15)	110·8 (2)
C(2)–C(3)–C(4)	120·1 (3)	C(13)–C(15)–N(16)	112·6 (2)
C(3)–C(4)–C(10)	117·9 (3)	C(13)–C(15)–C(20)	113·6 (2)
C(3)–C(4)–C(13)	120·9 (3)	N(16)–C(15)–C(20)	110·1 (2)
C(10)–C(4)–C(13)	121·2 (3)	C(15)–N(16)–C(17)	107·6 (2)
C(6)–C(5)–C(10)	121·7 (3)	C(15)–N(16)–C(21)	111·2 (2)
C(5)–C(6)–C(7)	119·7 (3)	C(17)–N(16)–C(21)	107·5 (2)
C(5)–C(6)–O(11)	116·3 (3)	N(16)–C(17)–C(18)	110·9 (2)
C(7)–C(6)–O(11)	124·0 (3)	C(17)–C(18)–C(19)	108·4 (2)
C(6)–C(7)–C(8)	119·8 (3)	C(18)–C(19)–C(20)	108·2 (2)
C(7)–C(8)–C(9)	121·4 (3)	C(18)–C(19)–C(22)	108·1 (2)
N(1)–C(9)–C(8)	117·5 (3)	C(20)–C(19)–C(22)	109·8 (2)
N(1)–C(9)–C(10)	123·1 (3)	C(15)–C(20)–C(19)	108·5 (2)
C(8)–C(9)–C(10)	119·4 (3)	N(16)–C(21)–C(22)	112·4 (2)
C(4)–C(10)–C(5)	124·2 (3)	C(19)–C(22)–C(21)	106·8 (2)
C(4)–C(10)–C(9)	117·8 (3)	C(19)–C(22)–C(23)	113·7 (3)
C(5)–C(10)–C(9)	118·0 (3)	C(21)–C(22)–C(23)	110·7 (3)
C(6)–O(11)–C(12)	120·2 (3)	C(22)–C(23)–C(24)	127·4 (4)
C(4)–C(13)–O(14)	110·9 (2)		

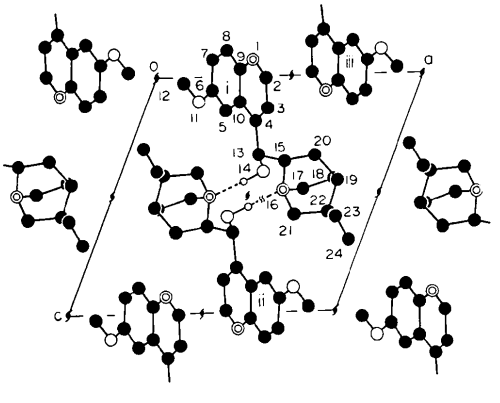

Fig. 2. Projection of the crystal along **b** (O:O, ◎:N, ●:C, o:H). The H atoms attached to the C atoms are omitted. Numbering of non-H atoms is shown for the molecule (i). Broken lines indicate hydrogen bonds. Symmetry code: (i) x, y, z; (ii) $1-x, \frac{1}{2}+y, 1-z$; (iii) $1-x, \frac{1}{2}+y, -z$.

The quinuclidine ring takes a skewed conformation as found in (2) and (3); when viewed down the N(16)–C(19) direction the bonds C(19)–C(18), C(19)–C(20) and C(19)–C(22) are rotated by 7·4 (2), 8·9 (2) and 6·9 (2)° from the eclipsed position of bonds N(16)–C(17), N(16)–C(15) and N(16)–C22), respectively. The bond lengths and angles in the ring are normal for an sp^3–sp^3 single bond: on average C–C = 1·535 (4), C–N = 1·480 (4) Å; C–C–C = 108·3 (2), C–N–C = 108·8 (2)°.

Conformations around the C(4)–C(13) and C(13)–C(15) bonds are mainly determined by the intramolecular requirements rather than the crystallographic environments:
τ_1[C(3)–C(4)–C(13)–C(15)] = −99·3 (3) for (1), −100·3 (4) for (2) and −109 (2)° for (3); τ_2[O(14)–C(13)–C(15)–N(16)] = 75·9 (3) for (1), 74·8 (4) for (2) and 48 (2)° for (3). The τ_2 results in the O(14)···N(16) distances of 3·093 (3) for (1), 3·110 (4) for (2) and 2·84 (2) Å for (3). A similar conformation of O with respect to N is found in procaine and related compounds (Kashino, Ikeda & Haisa, 1982).

On the other hand, the conformation in the side chains is varied by the crystal packing:
τ_3[C(5)–C(6)–O(11)–C(12)] = 179·0 (3) for (1), −5·8 (6) for (2) and 8(3)° for (3): τ_4[C(21)–C(22)–C(23)–C(24)] = 109·6 (4) for (1), 123 (1) for (2) and 180 (4)° for (3).

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α-(*p*-Bromobenzoyloxy)-β-phenylazostilbene, $C_{27}H_{19}BrN_2O_2$*

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Abstract. M_r = 483·36, monoclinic, $P2_1/c$, Z = 4, a = 10·210 (2), b = 16·594 (3), c = 14·546 (3) Å, β = 104·64 (2)°, V = 2384·4 Å^3, D_x = 1·346 Mg m^{-3}, Cu $K\alpha$ radiation (λ = 1·5418 Å, μ = 2·80 mm^{-1}), T = 298 K, $F(000)$ = 984. The structure was solved by the heavy-atom method and refined by block-diagonal least-squares methods using 3589 observed independent diffractometer-measured intensity data to R = 0·072, R_w = 0·044. Crystals were prepared by the reaction of benzil monophenylhydrazone with *p*-bromobenzoyl chloride. The configuration at the C=C bond is *trans*. This supports the proposed mechanism for the thermal rearrangement to the aroylhydrazone in which isomerization to the *cis* form is the rate-determining step and migration of the aroyl group a fast second step.

Introduction. α-Benzoyloxy-β-phenylazostilbene (I*a*) rearranges in quantitative yield to benzil monobenzoylphenylhydrazone (II*a*) in solution and in the solid state (Russell & Weisleder, 1967).

* α-Phenyl-β-phenylazostyryl *p*-bromobenzoate.

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