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# The Alkaloid Cinchonidine

BY BARBARA J. OLEKSYN

*Institute of Chemistry, Jagiellonian University, ul. Karasia* 3, 30-060 *Kraków, Poland*

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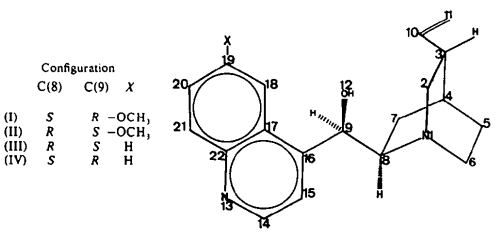
**Abstract.** $C_{19}H_{22}N_2O$, $M_r$ = 294·38, orthorhombic, $P2_12_12_1$, $a$ = 10·941 (3), $b$ = 20·883 (4), $c$ = 7·130 (2) Å, $Z$ = 4, $D_c$ = 1·22, $D_m$ = 1·22 Mg m$^{-3}$, $R$ = 0·0497 for 1626 observed reflexions. The molecular dimensions and conformation of cinchonidine are in good agreement with those of its optical isomer, cinchonine.

**Introduction.** The title compound is one of four *Cinchona* alkaloids: quinine (I), quinidine (II), cinchonine (III), and cinchonidine (IV), which differ from each other in the absolute configuration of C(9) and C(8) and in substituents at C(19).




The structural investigation of these compounds and their derivatives has been undertaken as part of a systematic study of the structure–activity relationship in antimalarial drugs.

A plate-shaped crystal of cinchonidine (0·10 × 0·25 × 0·50 mm) was mounted on an Enraf–Nonius CAD-4 automatic diffractometer equipped with a Mo source and a graphite monochromator. The lattice parameters, determined first by Griffiths (1959), were confirmed and refined by the autoindexing procedure from the settings of 15 reflexions.

Measurement of the intensities of 1921 independent reflexions in the range 0·5° ≤ $\theta$ ≤ 27° was performed in the $\omega/2\theta$ scanning mode with scan width: 0·70° + 0·50° tan $\theta$.

Of the collected data, 295 were treated as unobservable according to the condition $|F_o| < 3\sigma(F_o)$. The intensities of two control reflexions, recorded during data collection after every 50 reflexions, remained constant to within 3%.

The structure was solved by direct methods with the *SHELX*76 program system (Sheldrick, 1976) by the use of 344 normalized structure factors with $E > 1·2$. The $E$ map with the best consistency revealed 17 out of 22 non-hydrogen atoms. Four further atoms were found on an $E$ map after tangent refinement of the partial structure ($R$ = 0·22). The remaining non-hydrogen atom and all H atoms were found on the difference Fourier maps at various stages of isotropic (2 cycles) and anisotropic (16 cycles) full-matrix least-squares refinement. The positions and isotropic thermal parameters of the H atoms were refined in the last few cycles. The refinement was terminated at $R$ = 0·0497 ($R_w$ = 0·0503), when the shifts of most atomic parameters were less than 0·1 of their standard deviations. A final difference Fourier map showed no peaks higher than 0·2 e Å$^{-3}$. The weighting scheme was $w = k[\sigma^2(F_o) + gF_o^2]^{-1}$, where $k$ and $g$ refined to 1·8819 and 0·0009 respectively. Atomic scattering

Table 1. *Final fractional coordinates* (×10$^4$) *and equivalent isotropic thermal parameters* (×10$^4$) *for non-hydrogen atoms with estimated standard deviations in parentheses*

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

| | $x$ | $y$ | $z$ | $U_{eq}$ (Å$^2$) |
|---|---|---|---|---|
| N(1) | 8075 (2) | 5765 (1) | 7000 (4) | 455 (15) |
| C(2) | 8397 (4) | 6245 (2) | 5558 (4) | 559 (21) |
| C(3) | 8837 (3) | 6880 (1) | 6427 (6) | 581 (24) |
| C(4) | 8978 (3) | 6768 (1) | 8543 (5) | 552 (22) |
| C(5) | 7712 (4) | 6632 (2) | 9342 (6) | 644 (27) |
| C(6) | 7171 (3) | 6064 (2) | 8265 (6) | 544 (22) |
| C(7) | 9794 (3) | 6194 (2) | 8920 (6) | 574 (26) |
| C(8) | 9223 (3) | 5593 (1) | 7990 (4) | 436 (17) |
| C(9) | 9036 (3) | 5030 (1) | 9356 (4) | 438 (17) |
| C(10) | 9963 (4) | 7123 (2) | 5494 (7) | 817 (33) |
| C(11) | 10011 (6) | 7642 (3) | 4459 (11) | 1405 (69) |
| O(12) | 8465 (2) | 5230 (1) | 11027 (3) | 559 (15) |
| N(13) | 12599 (2) | 4169 (1) | 10424 (5) | 643 (21) |
| C(14) | 12041 (3) | 4543 (2) | 11638 (6) | 637 (23) |
| C(15) | 10889 (3) | 4824 (1) | 11361 (5) | 560 (21) |
| C(16) | 10260 (3) | 4708 (1) | 9740 (4) | 493 (17) |
| C(17) | 10802 (3) | 4290 (1) | 8401 (4) | 448 (17) |
| C(18) | 10246 (3) | 4108 (2) | 6687 (5) | 577 (20) |
| C(19) | 10813 (3) | 3710 (2) | 5466 (6) | 647 (23) |
| C(20) | 11982 (4) | 3475 (2) | 5824 (6) | 624 (24) |
| C(21) | 12544 (3) | 3629 (2) | 7456 (6) | 610 (26) |
| C(22) | 11981 (3) | 4033 (1) | 8800 (5) | 517 (20) |

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Table 2. *Final fractional coordinates* ($\times 10^3$) *for* H *atoms with estimated standard deviations in parentheses*

| | *x* | *y* | *z* |
|---|---|---|---|
| H(1C2) | 908 (3) | 606 (2) | 476 (5) |
| H(2C2) | 762 (3) | 633 (2) | 478 (5) |
| H(C3) | 822 (3) | 722 (1) | 628 (4) |
| H(C4) | 930 (3) | 711 (2) | 914 (5) |
| H(1C5) | 722 (3) | 697 (2) | 937 (5) |
| H(2C5) | 784 (5) | 655 (3) | 1092 (9) |
| H(1C6) | 685 (3) | 569 (2) | 911 (5) |
| H(2C6) | 648 (3) | 624 (2) | 745 (5) |
| H(1C7) | 982 (3) | 616 (2) | 1026 (6) |
| H(2C7) | 1066 (3) | 627 (1) | 835 (5) |
| H(C8) | 975 (3) | 539 (1) | 699 (5) |
| H(C9) | 852 (2) | 475 (1) | 872 (4) |
| H(C10) | 1076 (4) | 678 (2) | 573 (8) |
| H(1C11) | 1069 (6) | 789 (3) | 400 (11) |
| H(2C11) | 922 (5) | 805 (3) | 439 (11) |
| H(O12) | 792 (3) | 493 (2) | 1129 (5) |
| H(C14) | 1254 (3) | 467 (1) | 1278 (5) |
| H(C15) | 1059 (3) | 511 (1) | 1234 (5) |
| H(C18) | 943 (3) | 432 (2) | 639 (6) |
| H(C19) | 1043 (3) | 357 (2) | 435 (6) |
| H(C20) | 1236 (3) | 322 (1) | 493 (5) |
| H(C21) | 1334 (3) | 348 (1) | 768 (5) |

factors were those of *SHELX* 76. All calculations were carried out on a Cyber72 computer.

Final coordinates for the C, N and O atoms are given in Table 1 and for H atoms in Table 2.*

**Discussion.** The bond lengths and angles in the molecule of cinchonidine (Tables 3, 4) are very close to those determined for its *RS* optical isomer cinchonine (Oleksyn, Lebioda & Ciechanowicz-Rutkowska, 1979).

* Lists of structure factors and thermal parameters, and bond lengths, bond angles and some torsion angles involving H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36641 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Bond lengths* (Å) *with estimated standard deviations in parentheses*

The C–H bond lengths range from 0·89 (3) to 1·21 (6) Å, with a mean of 1·00 Å.

| | | | |
|---|---|---|---|
| N(1)–C(2) | 1·479 (4) | C(10)–C(11) | 1·313 (8) |
| C(2)–C(3) | 1·542 (5) | N(13)–C(14) | 1·317 (5) |
| C(3)–C(4) | 1·535 (5) | C(14)–C(15) | 1·404 (5) |
| C(4)–C(5) | 1·525 (5) | C(15)–C(16) | 1·367 (5) |
| C(5)–C(6) | 1·531 (5) | C(16)–C(17) | 1·424 (4) |
| C(6)–N(1) | 1·477 (4) | C(17)–C(18) | 1·417 (5) |
| C(7)–C(4) | 1·520 (5) | C(18)–C(19) | 1·354 (5) |
| C(7)–C(8) | 1·550 (5) | C(19)–C(20) | 1·393 (5) |
| C(8)–N(1) | 1·484 (4) | C(20)–C(21) | 1·355 (6) |
| C(9)–C(8) | 1·541 (4) | C(21)–C(22) | 1·417 (5) |
| C(9)–O(12) | 1·409 (4) | C(22)–C(17) | 1·427 (4) |
| C(9)–C(16) | 1·523 (4) | C(22)–N(13) | 1·370 (5) |
| C(10)–C(3) | 1·489 (6) | | |

Table 4. *Bond angles* (°) *involving non-hydrogen atoms, with estimated standard deviations in parentheses*

| | | | |
|---|---|---|---|
| C(2) N(1)–C(6) | 107·3 (2) | C(9)–C(16)–C(15) | 121·3 (3) |
| C(2)–N(1)–C(8) | 107·0 (2) | C(9)–C(16)–C(17) | 121·1 (3) |
| C(6) N(1)–C(8) | 112·2 (2) | C(11)–C(10)–C(3) | 124·4 (4) |
| N(1) C(2)–C(3) | 112·3 (3) | O(12)–C(9)–C(16) | 111·7 (3) |
| C(2) C(3) C(4) | 107·2 (3) | N(13)–C(14) C(15) | 124·9 (4) |
| C(2) C(3)–C(10) | 111·8 (3) | N(13) C(22) C(17) | 122·5 (3) |
| C(4) C(3)–C(10) | 114·1 (3) | N(13)–C(22) C(21) | 118·7 (3) |
| C(3)–C(4) C(5) | 107·8 (3) | C(14)–N(13)–C(22) | 116·7 (3) |
| C(3)–C(4) C(7) | 110·7 (3) | C(14)–C(15)–C(16) | 119·8 (3) |
| C(5)–C(4) C(7) | 108·6 (3) | C(15)–C(16)–C(17) | 117·7 (3) |
| C(4)–C(5)–C(6) | 108·0 (3) | C(16)–C(17) C(18) | 124·3 (3) |
| C(5)–C(6) N(1) | 112·0 (3) | C(16) C(17) C(22) | 118·3 (3) |
| C(4)–C(7)–C(8) | 109·0 (3) | C(18)–C(17) C(22) | 117·4 (3) |
| N(1) C(8)–C(7) | 110·5 (2) | C(17) C(18) C(19) | 121·5 (3) |
| N(1)–C(8)–C(9) | 111·9 (2) | C(17)–C(22) C(21) | 118·8 (3) |
| C(7) C(8)–C(9) | 113·6 (3) | C(18)–C(19)–C(20) | 121·3 (4) |
| C(8) C(9)–O(12) | 111·5 (2) | C(19)–C(20) C(21) | 119·4 (4) |
| C(8) C(9)–C(16) | 109·5 (2) | C(20) C(21)–C(22) | 121·7 (3) |

Table 5. *Torsion angles* (°) *selected to characterize the mutual orientation of the quinoline and quinuclidine moieties and of the carbinol group*

| | |
|---|---|
| C(16)–C(9)–C(8)–N(1) | 158·0 (6) |
| C(16)–C(9)–C(8)–C(7) | −76·1 (4) |
| O(12)–C(9)–C(8)–N(1) | −77·9 (4) |
| O(12)–C(9)–C(8)–C(7) | 48·0 (7) |
| O(12)–C(9)–C(16)–C(17) | 159·1 (7) |
| O(12)–C(9)–C(16)–C(15) | −22·6 (9) |
| C(8)–C(9)–C(16)–C(15) | 101·5 (7) |
| C(8)–C(9)–C(16)–C(17) | −76·8 (7) |

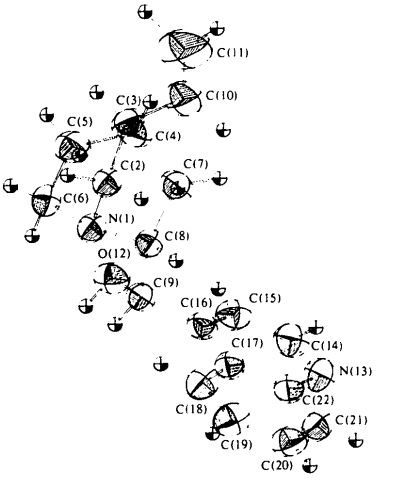


Fig. 1. A view of the molecule with the atom numbering.

The most important conformational features of the molecule (Table 5, Fig. 1) give further evidence of the stability of conformation in the *Cinchona* alkaloids (Oleksyn, 1978, 1979).

The lack of the intramolecular hydrogen bond N(1)···H(O12)–O(12) agrees with our hypothesis that the accessibility of N(1) and H(O12) for a receptor

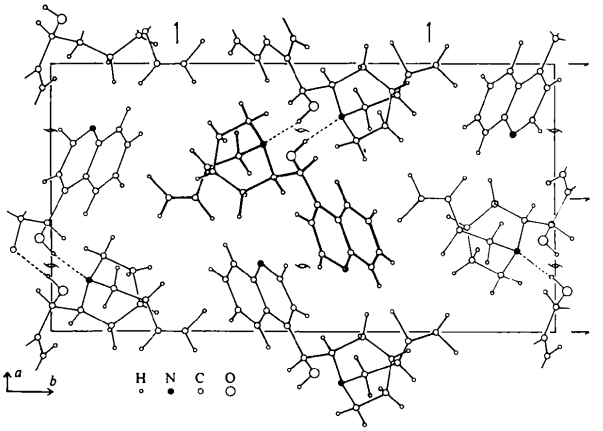


Fig. 2. A view down **c** showing the packing of the molecules.

is the necessary condition for antimalarial activity in *Cinchona* alkaloids (Oleksyn & Lebioda, 1980).

The packing of the molecules (Fig. 2) is very similar to that in cinchonine (Oleksyn, Lebioda & Ciechanowicz-Rutkowska, 1979). The intermolecular hydrogen bonds give rise to chains of molecules along alternate screw axes parallel to **c**. Within a chain each molecule interacts with two others through hydrogen bonds: O(12)–H(O12)···N(1$^{i}$), N(1)···H(O12$^{ii}$)–O(12$^{ii}$), where (i) = $\frac{3}{2} - x$, $1 - y$, $z + \frac{1}{2}$; (ii) = $\frac{3}{2} - x$, $1 - y$, $z - \frac{1}{2}$. The bond length is 2·76 (5) Å, and the angle N(1)···H(O12)–O(12) is 170(3)°.

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# Structure of 2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine–1,2-Benzisothiazol-3(2*H*)-one 1,1-Dioxide (1 : 1) Monohydrate

BY NOBUYUKI SHIMIZU AND SADAO NISHIGAKI

*Pharmaceutical Institute, School of Medicine, Keio University, Shinjuku-ku, Tokyo* 160, *Japan*

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**Abstract.** $C_{14}H_{18}N_4O_3.C_7H_5NO_3S.H_2O$, $M_r = 491{\cdot}5$, triclinic, $P\bar{1}$, $a = 9{\cdot}152\ (9)$, $b = 11{\cdot}487\ (6)$, $c = 12{\cdot}674\ (9)$ Å, $\alpha = 89{\cdot}81\ (5)$, $\beta = 103{\cdot}97\ (7)$, $\gamma = 113{\cdot}95\ (6)°$, $U = 1174{\cdot}9$ Å$^3$, $D_x = 1{\cdot}390$, $D_m$ ($n$-heptane/$CCl_4$) = 1·397 Mg m$^{-3}$, $Z = 2$, $\mu = 0{\cdot}210$ mm$^{-1}$, $F(000) = 516$, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å. The final $R$ value was 0·082 for 4486 observed reflections. It is highly probable that N(1) of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (DTMBP) is protonated by an H atom released from N(5) of 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (*o*-sulfobenzoimide, OSBI).

**Introduction.** DTMBP is used as an antifolate drug and OSBI as an artificial sweetener. The crystallographic investigation of the title compound was undertaken as part of our structural study of molecular complexes between different drugs. A single crystal for X-ray studies was obtained by slow evaporation of an aqueous solution containing equimolar amounts of DTMBP and OSBI. The crystal system was determined by oscillation and Weissenberg photographs. Intensity data of 5400 unique reflections were collected on a Syntex $R3$ computer-controlled diffractometer using an $\omega$-scan technique with monochromated Mo $K\alpha$ radiation in the range of $2\theta \leq 55°$ from a crystal 1·0 × 1·1 × 1·0 mm, 4486 of which were retained as observed [$I_o \geq 1{\cdot}96\sigma(I_o)$], and were corrected for Lorentz and polarization factors but not for absorption. The structure was solved by the direct method using *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). The first $E$ synthesis revealed all the molecular positions, except C(14) of the DTMBP part. The structure was refined by full-matrix

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