

10-Hydroxy-10-methyl-10,11-dihydroquinidine

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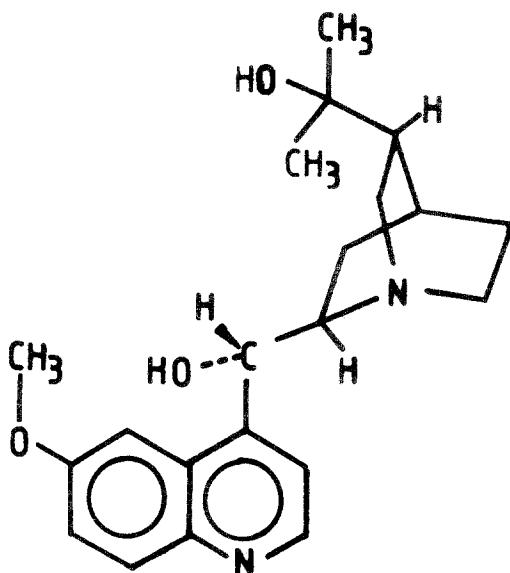
Abstract

10-Hydroxy-10-methyl-10,11-dihydroquinidine, $C_{21}H_{28}N_2O_3$, $M_r = 365.5$, crystallizes in the orthorhombic system: $P2_12_12_1$ (No. 19), $a = 9.539(1)$, $b = 9.682(2)$, $c = 21.073(4)$ Å, $Z = 4$, $V_c = 1946(4)$ Å³, $D_x = 1.216$ g cm⁻³, $\mu(\text{Cu } K_{\alpha}) = 5.72$ cm⁻¹. The final $R = 0.0346$ for 1381 observed reflections. The intermolecular contacts between the hydroxyl groups and the nitrogen atoms linked each molecule to four others, with distances $N \cdots O$ 2.795(5) Å and 2.996(5) Å. Three six-membered rings in the quinuclidine moiety adopt a conformation midway between a boat and a twist boat. The geometry of the *N*-quinuclidine atom is compared with that from previous data.

Introduction

The structural studies of Cinchona alkaloids and its derivatives were published in several works (Oleksyn *et al.*, 1978, 1979; Karle and Karle, 1981; Oleksyn, 1982; Kashino and Haisa, 1983; Dupont *et al.*, 1985; Suszko-Purzycka *et al.*, 1985).

In this paper the structure of a new derivative of quinidine is reported. The present compound, a potential antimalarial and antiarrhythmic agent, was prepared in a four-step procedure from natural quinidine by stereoretention synthesis involving transformation of vinyl group. The principal analytical data for 10-hydroxy-10-methyl-10,11-dihydroquinidine were also obtained. The second hydroxyl group may expand the biological activity of quinidine. The chemical structural formula is shown below.



Experimental

General procedure

10-Hydroxy-10-methyl-10,11-dihydroquinidine was prepared from natural quinidine according to the published procedure for the corresponding hydroxy derivative of quinine (Suszko-Purzycka *et al.*, 1985). A crude product was recrystallized several times from anhydrous diethylether. Colorless crystals were obtained with mp 167–167.5°C and $[\alpha]_D^{24} = 197.5^\circ$ (96% EtOH, $c = 1$, $l = 2$). The melting point was taken on a Bötius apparatus ($\Delta = \pm 1^\circ\text{C}$); the optical rotation was determined on a typical Lippich polarimeter (Carl Zeiss, Jena). The homogeneity of the product was determined by thin-layer chromatography using silufol precoated plates, silica gel 60 F₂₅₄ (Merck), and developing solvent system benzene–methanol 1:4 to give one band at R_f 0.18. Elemental analysis (Perkin-Elmer 240 analyzer) found (%): C 70.85, H 7.98, N 8.31; calculated for C₂₁H₂₈O₃N₂: C 70.78, H 7.88, N 7.86. Mass spectra (m/e , % relative intensity), $M + 1^+$ 357 (22.8), M^+ 356 (88.3), 168 (100), were obtained using LKB 2091 instrument at 70 eV. IR spectra (KBr, cm⁻¹), 3400–3100, 2960, 2940, 2870, 1620, 1590, 1470, 1435, 1370, 1245, 1230, 1200, 1170, 1140, 1100, 1030, 995, 955, 925, 910, 860, 830, 720, 645, were recorded on a Perkin-Elmer 577 spectrometer.

X-ray analysis

The crystals suitable for X-ray analysis were obtained by cooling a solution in anhydrous diethylether. The density was measured by flotation in aqueous KI solution. The space group and cell parameters were determined by Weissenberg methods: systematic absence of reflections $h00$ for h odd, $0k0$ for k odd, and $00l$ for l odd uniquely determined the space group as $P2_12_12_1$ (No. 19). A crystal $0.26 \times 0.26 \times 0.22$ mm was used for diffractometer measurements. Data were collected with a Syntex P2₁ diffractometer, using Cu K_α radiation and a graphite monochromator. Unit cell parameters were refined from the setting angles of 15 reflections having $15 \leq \theta \leq 30^\circ$; 1528 unique reflections, in the index ranges $0 \leq h \leq 10$, $0 \leq k \leq 9$, $0 \leq l \leq 23$, were measured up to $2\theta \leq 115^\circ$ using θ - 2θ scan and variable scan rate. The background and integrated intensity reflections were evaluated from a profile analysis according to Lehman and Larsen (1974) using the PRARA program (Jaskólski, 1981c). Two standard reflections 102, and 201 were measured every 100 measurements, with an intensity variation $\leq 6\%$; no absorption correction was made. A total of 1386 reflections with $|F| \geq 3.92\sigma(F)$ was used in refinement. The structure was solved by direct methods, with MULTAN 80 (Main, *et al.*, 1980) and refined with SHELX 76 (Sheldrick, 1976) programs. All H atoms were successively located from a ΔF synthesis and refined isotropically. Full-matrix least-squares refinement, in the final cycles with anisotropic thermal parameters for nonhydrogen atoms, gave a final $R = 0.0346$ and $\max \Delta/\sigma = 0.03$; the residual electron density was within $+0.1 \text{ e } \text{\AA}^{-3}$ and $-0.2 \text{ e } \text{\AA}^{-3}$. Five strong reflections affected by secondary extinction were suppressed during the last few cycles of refinement.

The enantiomorph was selected by comparison with that found in the molecular structure of quinidine (Kashino and Haisa, 1983).

Atomic scattering factors were as supplied by the program. The geometrical data were calculated using PLANE (Jaskólski, 1981a) and GEOME (Jaskólski, 1981b) programs. All calculations were performed on the BASF computer.

Discussion

The atomic parameters are given in Table 1 (those for hydrogen atoms in Table 5), anisotropic thermal parameters in Table 2, and selected torsion angles in Table 3.

The bond lengths and angles (Fig. 1), in the molecule are very similar to those found in other structures of Cinchona alkaloids.

The bond lengths and angles in the quinoline ring, with the exception of

Table 1. Fractional atomic coordinates ($\times 10^4$)

Atom	x	y	z
N(1)	3330(4)	-927(3)	2404(1)
C(2)	4004(5)	-2107(5)	2733(2)
C(3)	3022(4)	-2750(4)	3238(2)
C(4)	1523(4)	-2335(4)	3053(2)
C(5)	1391(6)	-779(5)	3203(2)
C(6)	2655(6)	-37(5)	2897(2)
C(7)	1267(4)	-2514(5)	2332(2)
C(8)	2168(4)	-1427(4)	1981(2)
C(9)	2763(4)	-1904(4)	1335(2)
C(10)	3323(4)	-4287(5)	3373(2)
C(11)	2939(5)	-5276(5)	2842(2)
C(12)	2589(7)	-4737(6)	3985(3)
N(2)	-147(4)	-1741(4)	-251(2)
C(22)	200(6)	-2912(5)	24(2)
C(23)	1110(5)	-3011(4)	546(2)
C(24)	1673(4)	-1839(4)	807(2)
C(25)	1742(4)	747(4)	786(2)
C(26)	1248(5)	1952(4)	529(2)
C(27)	352(5)	1946(5)	-2(2)
C(28)	-62(5)	720(5)	-256(2)
C(29)	367(4)	-550(4)	14(2)
C(30)	1275(4)	-548(4)	543(2)
C(31)	2294(6)	3288(5)	1354(2)
O(1)	4819(3)	-4378(4)	3498(2)
O(2)	3339(3)	-3260(3)	1387(1)
O(3)	1563(3)	3242(3)	758(1)

the methoxy group, agree well with those in the analogous hydroxy derivative of quinine (Suszko-Purzycka *et al.*, 1985). In the present structure the quinoline ring is more distorted from planarity ($\chi^2 = 472$), with maximum deviations of 0.047(5) and 0.046(5) Å by C(26) and C(22) atoms respectively. The O(3) and C(31) atoms of the methoxy group are twisted by 0.142(3) and 0.347(5) Å out of the quinoline plane, while in the hydroxy derivative of quinine these atoms lie almost in the ring plane.

The quinuclidine part of the molecule adopts a skew conformation (Table 3). The quinuclidine ring is more deformed than that in the structure of quinine (Kashino and Haisa, 1983) due to the values of the torsion angles around the nonbonded lines N(1) \cdots C(4): C(2)-N(1) \cdots C(4)-C(3) 13.0(3)° and 6.9(2)°, C(8)-N(1) \cdots C(4)-C(7) 12.0(3)° and 8.9(2)°, and C(6)-N(1) \cdots C(4)-C(5) 10.4(4)° and 7.4(2)° for this structure and the quinidine base, respectively.

The torsion angles (Fig. 2) and the asymmetry parameters (Duax and Norton, 1975) for each of the six-membered rings of the quinuclidine moiety in-

Table 2. Anisotropic thermal parameters ($\times 10^3$) for nonhydrogen atoms in the form
 $\exp [-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	46(2)	41(2)	32(2)	-4(2)	-2(2)	-2(1)
C(2)	35(2)	54(3)	37(2)	-4(2)	-6(2)	4(2)
C(3)	40(2)	42(2)	28(2)	2(2)	-1(2)	-1(2)
C(4)	39(2)	47(2)	36(2)	7(2)	9(2)	6(2)
C(5)	68(3)	54(3)	42(3)	22(3)	6(2)	-4(2)
C(6)	84(4)	39(2)	41(3)	7(3)	-5(3)	-6(2)
C(7)	30(2)	45(3)	41(2)	3(2)	-1(2)	6(2)
C(8)	35(2)	40(2)	30(2)	4(2)	0(2)	-1(2)
C(9)	39(2)	33(2)	33(2)	2(2)	-1(2)	2(2)
C(10)	41(2)	52(2)	42(2)	5(2)	-3(2)	2(2)
C(11)	50(3)	43(3)	60(3)	2(3)	-6(3)	-2(2)
C(12)	78(4)	59(4)	52(3)	5(3)	4(3)	18(3)
N(2)	63(3)	48(2)	48(2)	-1(2)	-21(2)	-6(2)
C(22)	66(3)	46(3)	55(3)	-10(3)	-23(3)	-10(3)
C(23)	67(3)	32(2)	48(3)	1(2)	-11(2)	-2(2)
C(24)	40(2)	37(2)	32(2)	-1(2)	1(2)	-1(2)
C(25)	39(2)	35(2)	31(2)	-4(2)	-5(2)	2(2)
C(26)	45(2)	39(2)	40(2)	-3(2)	-3(2)	3(2)
C(27)	63(3)	43(3)	54(3)	-2(3)	-17(3)	15(2)
C(28)	65(3)	54(3)	42(2)	1(3)	-22(2)	4(2)
C(29)	46(2)	42(2)	35(2)	-3(2)	-8(2)	1(2)
C(30)	39(2)	36(2)	29(2)	1(2)	-1(2)	2(2)
C(31)	60(3)	41(3)	45(3)	-7(3)	-4(2)	-2(2)
O(1)	45(2)	65(2)	56(2)	17(2)	-12(2)	-10(2)
O(2)	49(2)	37(1)	36(1)	12(1)	4(1)	1(1)
O(3)	64(2)	32(1)	54(2)	-4(2)	-12(2)	3(1)

Table 3. Selected torsion angles (deg), with esd's in parentheses

C(24)-C(9)-C(8)-N(1)	-155.8(4)
C(24)-C(9)-C(8)-C(7)	78.9(4)
O(2)-C(9)-C(8)-C(7)	-45.5(4)
O(2)-C(9)-C(8)-N(1)	79.9(3)
O(2)-C(9)-C(24)-C(30)	-161.0(4)
O(2)-C(9)-C(24)-C(23)	15.0(4)
C(8)-C(9)-C(24)-C(23)	-109.1(4)
C(8)-C(9)-C(24)-C(30)	74.9(4)
C(25)-C(26)-O(3)-C(31)	-8.9(5)
C(2)-N(1) ... C(4)-C(3)	13.0(3)
C(8)-N(1) ... C(4)-C(7)	12.0(3)
C(6)-N(1) ... C(4)-C(5)	10.4(4)

Table 4. Comparison of the bond lengths (Å) and angles (deg) of the *N*-quinuclidine atom, with esd's in parentheses

Configuration at C(8), C(9) atoms	C(2)–N(1)–C(8)	C(8)–N(1)–C(6)	C(2)–N(1)–C(6)	N(1)–C(8)	N(1)–C(6)	N(1)–C(2)
<i>R</i> , <i>S</i> ^a	110.4(3)	106.3(3)	107.8(3)	1.502(5)	1.496(5)	1.483(5)
<i>R</i> , <i>S</i> ^b	111.2(2)	107.6(2)	107.5(2)	1.486(4)	1.474(4)	1.480(4)
<i>R</i> , <i>S</i> ^c	110.6(3)	107.1(3)	107.5(3)	1.491(4)	1.485(5)	1.474(5)
<i>S</i> , <i>R</i> ^d	107.0(2)	112.2(2)	107.3(2)	1.484(4)	1.477(4)	1.479(4)
<i>S</i> , <i>R</i> ^e	106.3(2)	110.8(2)	108.2(2)	1.479(4)	1.479(4)	1.474(3)
<i>S</i> , <i>R</i> ^f	106.8(2)	111.0(2)	108.0(2)	1.486(3)	1.483(3)	1.483(3)

^a 10-Hydroxy-10-methyl-10,11-dihydroquinidine, this work.^b Quinidine (Kashino and Haisa, 1983).^c Cinchonine (Oleksyn *et al.*, 1979).^d Cinchonidine (Oleksyn, 1982).^e 9-Acetylquitenine ethyl ester (Dupont *et al.*, 1985).^f 10-Hydroxy-10-methyl-10,11-dihydroquinine (Suszko-Purzycka *et al.*, 1985).**Table 5.** Final fractional coordinates and isotropic temperature factors

Atom	<i>X</i>	<i>Y</i>	<i>Z</i>	<i>U</i> (Å ²)
H(21)	0.479(4)	−0.177(4)	0.290(2)	0.03(1)
H(22)	0.439(4)	−0.285(4)	0.241(2)	0.05(1)
H(3)	0.323(4)	−0.232(3)	0.364(2)	0.031(9)
H(4)	0.083(4)	−0.292(4)	0.330(2)	0.04(1)
H(51)	0.134(4)	−0.073(4)	0.367(2)	0.05(1)
H(52)	0.050(5)	−0.034(5)	0.304(2)	0.07(2)
H(61)	0.348(5)	0.022(5)	0.328(2)	0.08(2)
H(62)	0.234(5)	0.073(5)	0.271(2)	0.06(1)
H(71)	0.029(4)	−0.232(4)	0.225(2)	0.04(1)
H(72)	0.149(4)	−0.353(4)	0.219(1)	0.029(9)
H(8)	0.145(4)	−0.059(4)	0.188(2)	0.05(1)
H(9)	0.354(4)	−0.127(4)	0.119(2)	0.04(1)
H(111)	0.331(4)	−0.620(4)	0.297(2)	0.05(1)
H(112)	0.184(5)	−0.533(4)	0.281(2)	0.05(1)
H(113)	0.347(4)	−0.497(4)	0.245(2)	0.04(1)
H(121)	0.282(6)	−0.567(6)	0.405(2)	0.09(2)
H(122)	0.302(6)	−0.416(5)	0.433(2)	0.09(2)
H(123)	0.145(6)	−0.449(6)	0.395(2)	0.10(2)
H(221)	−0.015(5)	−0.382(4)	−0.011(2)	0.06(1)
H(23)	0.124(5)	−0.390(4)	0.070(2)	0.05(1)
H(25)	0.250(4)	0.072(4)	0.113(2)	0.04(1)
H(27)	0.011(5)	0.285(5)	−0.017(2)	0.07(1)
H(28)	−0.067(4)	0.067(4)	−0.066(2)	0.05(1)
H(311)	0.238(4)	0.435(4)	0.148(2)	0.06(1)
H(312)	0.339(6)	0.295(6)	0.127(3)	0.10(2)
H(O1)	0.525(4)	−0.466(5)	0.321(2)	0.05(2)
H(O2)	0.388(5)	−0.338(5)	0.108(2)	0.06(1)
H(313)	0.164(4)	0.282(4)	0.171(2)	0.06(1)

Fig. 1. Bond distances (Å) and angles (deg); with esd's in parentheses.

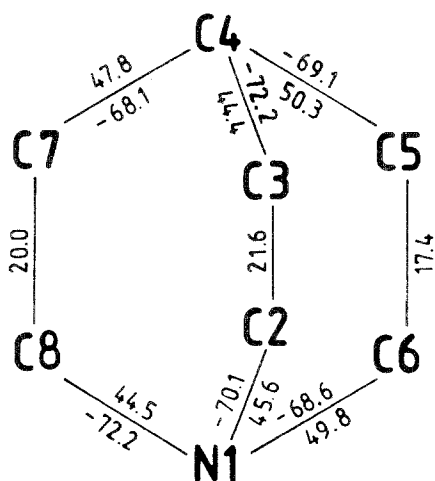


Fig. 2. Torsion angles (deg) in the quinuclidine ring, with esd's 0.4°.

dicate a conformation midway between the boat and the twist-boat. The asymmetry parameters with esd's <0.5° are:

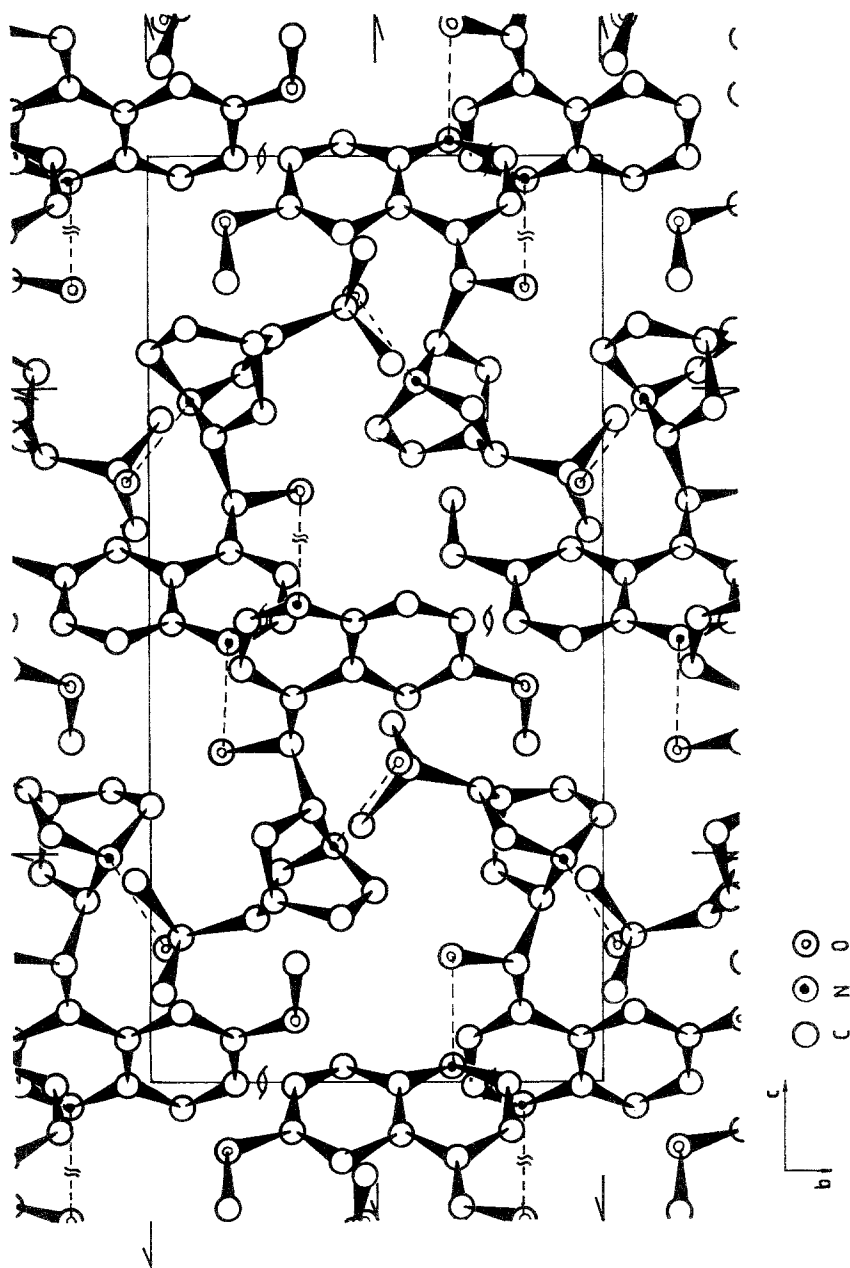
Ring: N(1)-C(2)-C(3)-C(4)-C(7)-C(8)
 $\Delta C_2^{3,8} = 19.4$, $\Delta C_2^{1,2} = 23.6$, $\Delta C_s^{2,3} = 24.7$

Ring: N(1)-C(2)-C(3)-C(4)-C(5)-C(6)
 $\Delta C_2^{2,5} = 23.5$, $\Delta C_2^{1,6} = 28.4$, $\Delta C_s^{5,6} = 22.8$

Ring: N(1)-C(6)-C(5)-C(4)-C(7)-C(8)
 $\Delta C_2^{6,7} = 24.7$, $\Delta C_2^{1,8} = 30.1$, $\Delta C_s^{7,8} = 22.0$

The average bond distance in the quinuclidine ring C-C 1.545(6) Å and the angles N-C-C 110.9(3)° and C-C-C 107.9(3)° are comparable within 3σ limits with 1.540(4) Å, 111.3(2)°, and 108.8(2)° respectively in the hydroxy derivative of quinine.

The most noteworthy feature is the geometry of pyramidal nitrogen atom in the quinuclidine ring. The C(2)-N(1)-C(8) angle of 110.4(3)° is larger than the C(8)-N(1)-C(6) and C(2)-N(1)-C(6) angles [106.3(3)° and 107.8(3)° respectively]. This trend is found in other molecules of Cinchona alkaloids. In the compounds with *R* and *S* configurations at C(8) and C(9) atoms (quinidine, cinchonine) respectively, the C(8)-N(1)-C(2) angle being larger than two others, replacement of the substituents to the configurations *S* and *R* at C(8), and C(9) atoms (quinine, cinchonidine) respectively generates an increase in the C(8)-N(1)-C(6) angle and a decrease in the C(8)-N(1)-C(2) angle. These changes of angles are not always connected with changes in the lengths of the bond at the N(1) atom (Table 4) and probably are caused by steric effects.



Two types of intermolecular H bonding link the molecules in a three-dimensional network; each molecule is H-bonded to four others by the hydroxyl groups and nitrogen atoms. For the first one, the O(2) atom is H-bonded with the N(2) atom of an adjacent molecule related by the screw axis parallel to *a*, with distances O(2) \cdots N(2) 2.795(5) Å, H(O2) \cdots N(2) 1.98(4) Å, and angle O(2)–H(O2) \cdots N(2) 165(3)°. For the other one, the O(1) atom is H-bonded to the N(1) atom of the molecule related by screw axis parallel to *b*, with distances O(1) \cdots N(1) 2.996(5) Å, H(O1) \cdots N(1) 2.25(4) Å, and angle O(1)–H(O1) \cdots N(1) 163.(3)°. It is interesting that the stronger basic nitrogen atom N(1) forms a longer hydrogen bond than does the N(2) atom. The packing of molecules and the hydrogen-bonding scheme is shown in Fig. 3.

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References

- Duax, W. L., and Norton, D. A. (1975) *Atlas of Steroid Structure* (Plenum Press, New York and London).
- Dupont, L., Konsur, A., Lewinski, K., and Oleksyn, B. (1985) *Acta Crystallogr. C* **41**, 616.
- Jaskólski, M. (1981a) PLANE, program to calculate the mean plane through a set of N atoms (University of Poznań, Poland).
- Jaskólski, M. (1981b) GEOME, program to calculate geometrical features of molecules (University of Poznań, Poland).
- Jaskólski, M. (1981c) PRARA, program for data reduction from syntax data tapes on IBM computers (University of Poznań, Poland).
- Karle, I. L., and Karle, J. (1981) *Proc. Natl Acad. Sci. USA* **78**, 5938.
- Kashino, A., and Haisa, M. (1983) *Acta Crystallogr. C* **39**, 310.
- Lehman, M. S., and Larsen, F. K. (1974) *Acta Crystallogr. A* **30**, 580.
- Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J. P., and Woolfson, M. M. (1980) MULTAN 80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data (Universities of York, England, and Louvain, Belgium).
- Oleksyn, B. J. (1982) *Acta Crystallogr. B* **38**, 1832.
- Oleksyn, B. J., Städtnicka, K. M., and Hodorowicz, S. A. (1978) *Acta Crystallogr. B* **34**, 811.
- Oleksyn, B., Lebiada, L., and Ciechanowicz-Rutkowska, M. (1979) *Acta Crystallogr. B* **35**, 440.
- Sheldrick, G. M. (1976) SHELX 76, program for crystal structure determination (University of Cambridge, England).
- Suszko-Purzycka, A., Lipińska, T., Piotrowska, E., and Oleksyn, B. J. (1985) *Acta Crystallogr. C* **41**, 977.