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# The Structure and Conformation of Alkaloid A Hydroiodide

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## Abstract

Crystals of alkaloid A hydroiodide, $C_{25}H_{40}NO_6^+.I^-$, are monoclinic, $P2_1$, with $a = 10{\cdot}425$ (3), $b = 12{\cdot}443$ (4), $c = 9{\cdot}595$ (3) Å, $\beta = 95{\cdot}80$ (2)°, $V = 1238{\cdot}3$ Å$^3$, $D_c = 1{\cdot}549$ Mg m$^{-3}$, $M_r = 577{\cdot}48$, $Z = 2$, $\mu$(Mo $K\alpha$) = $1{\cdot}354$ mm$^{-1}$, and $F(000) = 596$; $R = 0{\cdot}039$ for 2579 reflections. The substitution pattern is: 1$\alpha$-OH, 6$\beta$-$OCOCH_3$, 8$\beta$-$OCH_3$, 14$\alpha$-OH, 16$\beta$-$OCH_3$, N-ethyl. Absence of an oxygenated functional group at C(7) establishes alkaloid A as an aconitine-type alkaloid.

## Introduction

Alkaloid A was isolated from *Delphinium bicolour* Nutt., a short-stemmed, spring-blooming larkspur found on south-facing slopes of the Rocky Mountains. The structure has been assigned and reassigned on the basis of $^{13}C$ NMR (Jones & Benn, 1972, 1973; Pelletier, Mody, Jones & Benn, 1976). In a preliminary publication of this structural work (Codding, Kerr, Benn, Jones, Pelletier & Mody, 1980) the formula of the compound was drawn incorrectly with a methoxy group at C(1).

Colourless, tabular crystals were grown by diffusion of diethyl ether vapour into an ethanol solution of the hydroiodide of the alkaloid. The crystal chosen for analysis had dimensions *ca* 0·25 × 0·30 × 0·10 mm and was mounted about the *b* axis. After preliminary examination by Weissenberg and precession photography, which established the space group ($P2_1$; $0k0$: $k = 2n + 1$ absent), the crystal was transferred to a Picker FACS-I diffractometer for data collection. Cell dimensions were established by least-squares refinement of the parameters of 12 high-angle reflections. Data were collected in the $\theta/2\theta$ scan mode with a scan width of $\Delta 2\theta = (1{\cdot}4 + 0{\cdot}692 \tan\theta)°$, with background measured for 20 s at either end of the scan. Of the 2704 unique reflections measured in the range $3° < 2\theta \leq 55{\cdot}0°$, 317 had intensities $I \leq 3\sigma(I)$ where $\sigma(I) = [T + S^2B + (0{\cdot}02I)^2]^{1/2}$, $T$ is the total peak count, $B$ is the background count, and $S$ is the scale factor required to normalize the background count to time interval of the scan. There was no evidence for deterioration of the crystal during the experiment. Data were corrected for Lorentz, polarization and absorption effects; maximum and minimum values of the analytic absorption correction were 1·573 and 1·129.

To solve the structure by heavy-atom techniques, it was necessary to discriminate between the molecule and its mirror image in pseudosymmetric Fourier maps. Simple inclusion of a known fragment (a five-membered ring) in the phase-angle calculations did not help; however, inclusion of the same fragment with scattering factors appropriate to S rather than C provided the necessary enhancement. A similar technique has been used by Kartha & Haas (1964).

The structure was refined by full-matrix least squares to a final $R$ value of 0·039. The function minimized was $\sum w|F_o - F_c|^2$ with $w = 1{\cdot}00$ for the 2579 reflections included in the refinement. Reflections with $I \leq 3\sigma(I)$ were given a weight of zero if $F_o \geq F_c$. The value of $[\sum w\Delta^2/(m - n)]^{1/2}$ is 2·50. Scattering factors and anomalous-dispersion terms were taken from *International Tables for X-ray Crystallography* (1974). Programs used for data reduction were from the *LASLS* system (A. C. Larson); that for absorption correction was written by D. H. Templeton. These were run on a CDC Cyber 172 computer. The remaining programs are from the XRAY 76 system (Stewart, 1976) implemented on a Honeywell computer with a MULTICS operating system.

Final atomic coordinates are given in Table 1.† 36 of the 40 H atoms in the structure were located in a series of difference Fourier syntheses. They were included in the model with the isotropic temperature factor of the atom to which they are attached. Parameters of the H atoms were not refined.

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† Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35682 (23 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. *Fractional coordinates* ($\times 10^4$) *and* $U_{eq}$ ($Å^2 \times 10^3$) *for nonhydrogen atoms in alkaloid A hydroiodide*

The $y$ coordinate of the iodide ion was used to fix the origin of the cell, and so was not refined. $U_{eq} = \frac{1}{3}$ trace $\tilde{U}$ where $\tilde{U}$ is the diagonalized $U_{ij}$ matrix.

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| $I^-$ | 335·4 (6) | 3·0 (–) | 3342·4 (5) | 51 |
| C(1) | 9988 (6) | 192 (7) | 7820 (7) | 31 |
| C(2) | 10648 (7) | 608 (7) | 9183 (8) | 38 |
| C(3) | 10133 (8) | 1700 (8) | 9543 (8) | 41 |
| C(4) | 8620 (7) | 1757 (7) | 9424 (7) | 33 |
| C(5) | 8019 (7) | 629 (6) | 9226 (7) | 30 |
| C(6) | 6549 (7) | 751 (6) | 8903 (7) | 30 |
| C(7) | 6285 (6) | 572 (6) | 7285 (7) | 27 |
| C(8) | 5801 (7) | −581 (6) | 6849 (7) | 28 |
| C(9) | 6676 (7) | −1415 (6) | 7629 (8) | 30 |
| C(10) | 8131 (7) | −1117 (6) | 7738 (7) | 28 |
| C(11) | 8500 (6) | 100 (8) | 7898 (6) | 25 |
| C(12) | 8634 (7) | −1664 (6) | 6449 (9) | 31 |
| C(13) | 7460 (7) | −2194 (6) | 5623 (8) | 31 |
| C(14) | 6678 (8) | −2487 (7) | 6811 (9) | 37 |
| C(15) | 5687 (7) | −733 (7) | 5228 (8) | 34 |
| C(16) | 6752 (7) | −1357 (6) | 4600 (8) | 33 |
| C(17) | 7634 (6) | 727 (6) | 6794 (6) | 23 |
| C(18) | 8233 (9) | 2290 (8) | 10762 (9) | 47 |
| C(19) | 8086 (8) | 2450 (6) | 8163 (8) | 34 |
| C(20) | 7339 (7) | 2559 (6) | 5648 (8) | 32 |
| C(21) | 7689 (10) | 2233 (9) | 4215 (9) | 54 |
| C(22) | 4943 (10) | 448 (8) | 10443 (10) | 51 |
| C(23) | 4189 (9) | −394 (9) | 11121 (11) | 61 |
| C(24) | 3540 (7) | −38 (12) | 6776 (9) | 51 |
| C(25) | 6969 (12) | −2091 (9) | 2359 (10) | 59 |
| N | 8080 (6) | 1887 (5) | 6771 (6) | 27 |
| O(1) | 10336 (5) | 924 (5) | 6730 (5) | 37 |
| O(2) | 5858 (5) | 40 (8) | 9731 (5) | 40 |
| O(3) | 4762 (12) | 1370 (8) | 10523 (13) | 141 |
| O(4) | 4545 (5) | −750 (5) | 7301 (6) | 37 |
| O(5) | 6121 (6) | −1884 (5) | 3373 (6) | 44 |
| O(6) | 5439 (6) | −2912 (5) | 6372 (7) | 46 |

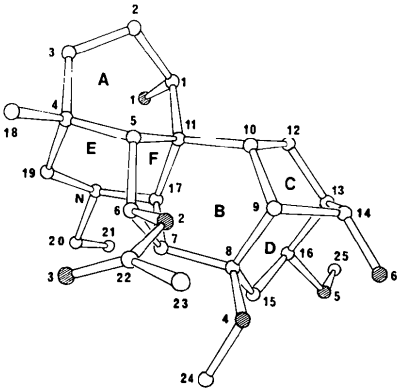



Fig. 1. A perspective drawing of alkaloid A showing the numbering scheme used in the text.

Table 2. *Bond lengths* (Å) *in alkaloid A hydroiodide*

| | | | |
|---|---|---|---|
| C(1)–C(11) | 1·565 (9) | | |
| C(1)–C(2) | 1·507 (10) | C(1)–O(1) | 1·460 (10) |
| C(2)–C(3) | 1·513 (13) | | |
| C(3)–C(4) | 1·571 (12) | C(4)–C(18) | 1·536 (12) |
| C(4)–C(5) | 1·540 (11) | C(11)–C(5) | 1·561 (10) |
| C(5)–C(6) | 1·541 (10) | C(6)–O(2) | 1·431 (11) |
| C(6)–C(7) | 1·565 (9) | O(2)–C(22) | 1·329 (12) |
| C(7)–C(17) | 1·540 (9) | C(22)–O(3) | 1·167 (15) |
| C(17)–C(11) | 1·534 (9) | C(22)–C(23) | 1·498 (15) |
| C(17)–N | 1·517 (9) | N–C(20) | 1·513 (9) |
| N–C(19) | 1·508 (9) | C(20)–C(21) | 1·512 (12) |
| C(19)–C(4) | 1·543 (10) | | |
| C(7)–C(8) | 1·564 (10) | C(8)–O(4) | 1·436 (9) |
| C(8)–C(9) | 1·526 (10) | O(4)–C(24) | 1·425 (12) |
| C(9)–C(10) | 1·554 (10) | | |
| C(10)–C(11) | 1·566 (12) | | |
| C(10)–C(12) | 1·550 (11) | | |
| C(12)–C(13) | 1·538 (10) | | |
| C(13)–C(14) | 1·512 (12) | C(14)–O(6) | 1·420 (10) |
| C(13)–C(16) | 1·564 (11) | C(16)–O(5) | 1·446 (9) |
| C(16)–C(15) | 1·528 (11) | O(5)–C(25) | 1·403 (13) |
| C(15)–C(8) | 1·559 (11) | | |
| C(14)–C(9) | 1·548 (11) | | |

## Results and discussion

The structure of alkaloid A and the numbering scheme used in the text are shown in Fig. 1. For atoms C(1) to C(19) the numbering convention corresponds to the scheme proposed by Pelletier & Keith (1970) for $C_{19}$ diterpenoid alkaloids. Although the absolute stereochemistry has not been established in this study, the coordinates and diagrams correspond to the enantiomer reported for chasmanine (DeCamp & Pelletier, 1977), delphisine (Pelletier, Djarmati, Lajšić & DeCamp, 1976), condelphine (Pelletier, DeCamp, Herald, Page & Newton, 1977), and related alkaloids. The points at issue in the previous reports on this compound have been the configuration at C(6) and the nature of the substituents at C(6) and C(8). The X-ray analysis has established unequivocally that the substitution pattern is 1α-OH, N-ethyl, 6β-$OCOCH_3$, 8β-$OCH_3$, 14α-OH, 16β-$OCH_3$ where an α substituent is on the same side of the molecule as the nitrogen bridge and a β substituent is on the opposite side. The bond lengths and bond angles for the non-hydrogen atoms are given in Tables 2 and 3 respectively.

Data for least-squares planes for the various rings are given in Table 4. Torsional angles are given in Table 5. Ring *A* is a boat with C(2) and C(5) displaced by about −0·64 Å from the plane of the other four atoms. This conformation is commonly observed in alkaloids of this class with oxygenated substituents at O(1) and a protonated N atom. In this case, the conformation is stabilized by an N–H···O hydrogen bond with the 1α-hydroxy group as acceptor. The hydroxy group is also hydrogen bonded to the iodide ion. Relevant dimensions are: N···O(1) 2·643 (8), N–H 1·09, H···O 1·79 Å, ∠N–H···O 131·5°; O(1)···I 3·431 (5), O–H 0·98, H···I 2·57 Å, ∠O–H···I 146·70°.

Table 3. *Bond angles* (°) *in alkaloid A hydroiodide*

| | | | |
|---|---|---|---|
| C(11)–C(1)–C(2) | 110·6 (6) | C(1)–C(11)–C(5) | 114·2 (6) |
| C(11)–C(1)–O(1) | 113·5 (6) | C(1)–C(11)–C(10) | 107·5 (7) |
| C(2)–C(1)–O(1) | 106·4 (6) | C(1)–C(11)–C(17) | 116·6 (6) |
| C(1)–C(2)–C(3) | 111·5 (7) | C(5)–C(11)–C(10) | 113·0 (6) |
| C(2)–C(3)–C(4) | 113·6 (7) | C(10)–C(11)–C(17) | 107·6 (6) |
| C(3)–C(4)–C(5) | 111·1 (7) | C(5)–C(11)–C(17) | 97·7 (6) |
| C(3)–C(4)–C(18) | 107·8 (6) | C(10)–C(12)–C(13) | 106·5 (6) |
| C(3)–C(4)–C(19) | 111·3 (7) | C(12)–C(13)–C(14) | 100·2 (6) |
| C(5)–C(4)–C(18) | 111·0 (7) | C(12)–C(13)–C(16) | 109·8 (6) |
| C(5)–C(4)–C(19) | 107·6 (6) | C(14)–C(13)–C(16) | 112·2 (6) |
| C(18)–C(4)–C(19) | 108·0 (7) | C(9)–C(14)–C(13) | 101·7 (6) |
| C(11)–C(5)–C(6) | 105·8 (5) | C(9)–C(14)–O(6) | 115·0 (7) |
| C(11)–C(5)–C(4) | 108·9 (6) | O(6)–C(14)–C(13) | 114·2 (7) |
| C(6)–C(5)–C(4) | 108·6 (6) | C(8)–C(15)–C(16) | 118·0 (6) |
| C(7)–C(6)–O(2) | 114·6 (6) | C(13)–C(16)–C(15) | 114·0 (6) |
| C(7)–C(6)–C(5) | 104·9 (6) | C(13)–C(16)–O(5) | 110·9 (6) |
| O(2)–C(6)–C(5) | 112·0 (6) | C(15)–C(16)–O(5) | 105·2 (6) |
| C(6)–C(7)–C(8) | 114·5 (6) | C(7)–C(17)–N | 114·5 (6) |
| C(6)–C(7)–C(17) | 102·2 (5) | C(7)–C(17)–C(11) | 102·5 (5) |
| C(8)–C(7)–C(17) | 108·2 (6) | C(11)–C(17)–N | 109·5 (6) |
| C(7)–C(8)–C(9) | 109·3 (5) | C(4)–C(19)–N | 113·8 (6) |
| C(9)–C(8)–O(4) | 105·7 (6) | C(17)–N–C(19) | 113·8 (5) |
| C(7)–C(8)–O(4) | 109·4 (6) | C(17)–N–C(20) | 113·6 (5) |
| O(4)–C(8)–C(15) | 107·7 (5) | C(19)–N–C(20) | 109·3 (6) |
| C(7)–C(8)–C(15) | 111·6 (6) | N–C(20)–C(21) | 110·3 (7) |
| C(9)–C(8)–C(15) | 112·9 (6) | O(2)–C(22)–C(23) | 113·1 (9) |
| C(8)–C(9)–C(10) | 113·7 (6) | O(2)–C(22)–O(3) | 122·6 (11) |
| C(8)–C(9)–C(14) | 111·6 (6) | O(3)–C(22)–C(23) | 124·3 (11) |
| C(10)–C(9)–C(14) | 100·8 (6) | C(6)–O(2)–C(22) | 118·5 (9) |
| C(9)–C(10)–C(11) | 117·7 (6) | C(8)–O(4)–C(24) | 117·6 (7) |
| C(9)–C(10)–C(12) | 104·4 (6) | C(16)–O(5)–C(25) | 112·4 (7) |
| C(11)–C(10)–C(12) | 113·7 (6) | | |

Table 4. *Least-squares planes for alkaloid A*

Atoms not included in the plane are marked with asterisks.

(*a*) Deviations from the mean plane (Å)

| Ring *A* | | Ring *B* | | Ring *C* | |
|---|---|---|---|---|---|
| C(1) | 0·0662 (6) | C(7) | 0·0590 (7) | C(9) | −0·0110 (6) |
| C(3) | −0·0660 (8) | C(8) | −0·0548 (7) | C(10) | 0·0170 (6) |
| C(4) | 0·0652 (7) | C(10) | 0·0544 (7) | C(12) | −0·0172 (7) |
| C(11) | −0·0655 (6) | C(11) | −0·0585 (6) | C(13) | 0·0113 (7) |
| *C(5) | −0·6346 (7) | *C(9) | 0·4730 (8) | *C(14) | −0·7413 (8) |
| *C(2) | −0·6553 (8) | *C(17) | −0·8671 (6) | | |

| Ring *D* | | Ring *E* | | Ring *F* | |
|---|---|---|---|---|---|
| C(13) | −0·0328 (6) | C(4) | 0·0285 (7) | C(5) | 0 |
| C(16) | 0·0294 (7) | C(5) | −0·0313 (7) | C(6) | 0 |
| C(8) | −0·0302 (6) | N | −0·0288 (6) | C(7) | 0 |
| C(9) | 0·0337 (7) | C(17) | 0·0316 (6) | *C(17) | 0·4484 (6) |
| *C(14) | −0·8435 (8) | *C(11) | 0·9248 (6) | *C(11) | −0·3721 (8) |
| *C(15) | −0·2996 (7) | *C(19) | −0·5399 (8) | | |

Acetoxy

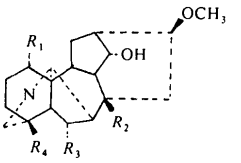
| | | | | | |
|---|---|---|---|---|---|
| O(2) | 0·0054 (5) | C(22) | −0·0139 (10) | *C(6) | −0·1099 (7) |
| O(3) | 0·0028 (13) | C(23) | 0·0057 (11) | | |

(*b*) Coefficients in the expression $Px + Qy + Rz = S$ where $x,y,z$ are fractional coordinates

| | *P* | *Q* | *R* | *S* | σ |
|---|---|---|---|---|---|
| Ring *A* | 0·0168 | 7·6996 | −7·5003 | −5·7664 | 0·076 |
| Ring *B* | −3·3459 | −1·1289 | 9·3106 | 4·5563 | 0·066 |
| Ring *C* | −1·5907 | 10·4715 | −4·7984 | −6·1929 | 0·017 |
| Ring *D* | 7·9490 | 7·9212 | 0·3630 | 4·4297 | 0·036 |
| Ring *E* | 9·7131 | −4·2994 | −1·9719 | 5·7308 | 0·035 |
| Ring *F* | 1·3504 | 12·1945 | −1·5659 | 0·4055 | 0 |
| Acetoxy | 6·1097 | 0·7602 | 7·1444 | 10·5290 | 0·009 |

Table 5. *Torsional angles* (°) *for alkaloid A and related alkaloids*

The sign of the angles is positive if a clockwise rotation will cause the first-named atom to eclipse the last.




| | | | | |
|---|---|---|---|---|
| (I) Alkaloid A | $R_1$ = OH | $R_2$ = $OCH_3$ | $R_3$ = OAc | $R_4$ = $CH_3$ |
| (II) Condelphine | $R_1$ = OH | $R_2$ = OH | $R_3$ = H | $R_4$ = $CH_2OCH_3$ |
| (III) Chasmanine | $R_1$ = $OCH_3$ | $R_2$ = OH | $R_3$ = $OCH_3$ | $R_4$ = $CH_2OCH_3$ |
| (IV) Delphisine | $R_1$ = OH | $R_2$ = OAc | $R_3$ = $OCH_3$ | $R_4$ = $CH_2OCH_3$ |

| | (I) | (II*a*) | (II*b*) | (III) | (IV) |
|---|---|---|---|---|---|
| Ring *A* | | | | | |
| C(1)–C(2)–C(3)–C(4) | 48·9 (9) | 46·8 | 53·0 | 51·1 | 51·2 |
| C(2)–C(3)–C(4)–C(5) | 10·4 (9) | 10·9 | 2·6 | 4·9 | 9·0 |
| C(3)–C(4)–C(5)–C(11) | −57·1 (7) | −59·7 | −52·7 | −54·5 | −56·9 |
| C(4)–C(5)–C(11)–C(1) | 47·2 (9) | 52·9 | 49·8 | 51·0 | 47·2 |
| C(5)–C(11)–C(1)–C(2) | 9·8 (10) | 4·4 | 4·9 | 2·7 | 10·8 |
| C(11)–C(1)–C(2)–C(3) | −58·9 (9) | −55·9 | −56·7 | −55·1 | −60·9 |
| Ring *B* | | | | | |
| C(7)–C(8)–C(9)–C(10) | −40·6 (8) | −36·8 | −42·4 | −37·5 | −41·2 |
| C(8)–C(9)–C(10)–C(11) | 34·6 (8) | 36·5 | 39·6 | 32·0 | 35·8 |
| C(9)–C(10)–C(11)–C(17) | −47·6 (7) | −51·8 | −52·4 | −48·0 | −48·9 |
| C(10)–C(11)–C(17)–C(7) | 65·9 (6) | 68·1 | 69·5 | 67·4 | 66·3 |
| C(11)–C(17)–C(7)–C(8) | −77·6 (6) | −78·3 | −79·8 | −81·3 | −78·1 |
| C(17)–C(7)–C(8)–C(9) | 64·4 (7) | 62·3 | 65·7 | 65·5 | 65·0 |
| Ring *C* | | | | | |
| C(9)–C(10)–C(12)–C(13) | 2·9 (7) | −0·3 | −1·2 | 2·1 | 2·3 |
| C(10)–C(12)–C(13)–C(14) | −32·2 (7) | −28·2 | −30·3 | −31·6 | −31·6 |
| C(12)–C(13)–C(14)–C(9) | 49·6 (7) | 48·4 | 51·3 | 50·1 | 50·1 |
| C(13)–C(14)–C(9)–C(10) | −48·1 (7) | −49·9 | −50·0 | −49·8 | −49·6 |
| C(14)–C(9)–C(10)–C(12) | 26·9 (7) | 30·5 | 30·3 | 28·3 | 28·2 |
| Ring *D* | | | | | |
| C(9)–C(14)–C(13)–C(16) | −66·8 (7) | −70·3 | −69·0 | −68·6 | −67·2 |
| C(14)–C(13)–C(16)–C(15) | 19·6 (9) | 23·2 | 23·6 | 22·8 | 18·7 |
| C(13)–C(16)–C(15)–C(8) | 26·7 (9) | 21·7 | 22·9 | 25·4 | 28·7 |
| C(16)–C(15)–C(8)–C(9) | −21·5 (9) | −20·8 | −21·6 | −23·9 | −24·9 |
| C(15)–C(8)–C(9)–C(14) | −29·0 (9) | −27·1 | −24·8 | −25·1 | −26·1 |
| C(8)–C(9)–C(14)–C(13) | 72·9 (7) | 71·5 | 68·3 | 70·5 | 70·8 |
| Ring *E* | | | | | |
| N–C(17)–C(11)–C(5) | 70·6 (6) | 67·2 | 69·2 | 67·1 | 69·2 |
| C(17)–C(11)–C(5)–C(4) | −76·6 (6) | −73·7 | −77·1 | −72·9 | −76·6 |
| C(11)–C(5)–C(4)–C(19) | 64·9 (7) | 62·3 | 66·9 | 67·3 | 65·6 |
| C(5)–C(4)–C(19)–N | −44·7 (8) | −42·8 | −50·1 | −50·3 | −45·4 |
| C(4)–C(19)–N–C(17) | 42·4 (8) | 36·5 | 45·8 | 46·2 | 42·5 |
| C(19)–N–C(17)–C(11) | −57·8 (7) | −49·2 | −56·0 | −57·4 | −56·7 |
| Ring *F* | | | | | |
| C(5)–C(6)–C(7)–C(17) | −17·3 (7) | −10·0 | −10·7 | −7·0 | −10·3 |
| C(6)–C(7)–C(17)–C(11) | 43·6 (7) | 36·6 | 37·4 | 37·3 | 39·1 |
| C(7)–C(17)–C(11)–C(5) | −51·3 (7) | −49·7 | −49·9 | −52·9 | −51·6 |
| C(17)–C(11)–C(5)–C(6) | 40·1 (7) | 43·5 | 43·4 | 48·7 | 44·7 |
| C(11)–C(5)–C(6)–C(7) | −14·3 (8) | −21·3 | −20·3 | −25·7 | −21·5 |
| Side chains | | | | | |
| C(16)–C(15)–C(8)–O(4) | −137·8 (7) | | C(12)–C(13)–C(14)–O(6) | | 174·1 (6) |
| C(15)–C(8)–O(4)–C(24) | −61·9 (9) | | C(6)–O(2)–C(22)–O(3) | | −7·2 (13) |
| C(8)–C(15)–C(16)–O(5) | 148·4 (6) | | C(6)–O(2)–C(22)–C(23) | | 173·0 (7) |
| C(15)–C(16)–O(5)–C(25) | 153·8 (7) | | C(5)–C(6)–O(2)–C(22) | | 128·5 (7) |
| C(17)–C(7)–C(6)–O(2) | −140·5 (6) | | C(7)–C(6)–O(2)–C(22) | | −112·2 (8) |
| C(5)–C(11)–C(1)–O(1) | −109·7 (7) | | | | |

A similar hydrogen-bonding scheme has been observed in delphisine hydrochloride (Pelletier, Djarmati, Lajšić & DeCamp, 1976). Conformations of the *A* rings in the two compounds are virtually identical. Examination of molecular models suggests that ring *A* has considerable conformational mobility with a low energy barrier between boat and chair forms. In crystal

structures of related alkaloids where the N is not protonated, the *A* ring exists as a chair (Birnbaum, Wiesner, Jay & Jay, 1971; Przybylska, 1961, 1976).

Ring *D* is also in a boat form, puckered at C(14) and flattened at C(15). This ring does not have the mobility of ring *A*. The ring junction at C(8) tends to produce a sofa conformation in ring *D*. Displacement of C(15) towards C(14) increases the separation between the substituents on C(8) and C(16). The puckering at C(14) arises from the fact that ring *D* is *cis*-fused to the five-membered ring *C* which has an envelope conformation with C(14) at the flap. The other five-membered ring, *F*, is a half-chair with an approximate twofold axis through C(6).

Rings *B* and *E* are both chairs; hence each can be described relative to three different four-membered planes. The figures in Table 4 correspond to the plane with the lowest e.s.d. Ring *E* is somewhat flattened at C(19) and puckered at C(11) but retains a reasonably good mirror through C(19) and C(11). In ring *B*, each atom is at a ring junction; thus it is hardly surprising that the chair form is highly distorted. The best four-membered plane is through atoms C(7)–C(8)–C(10) and C(11) but the best twofold axis bisects the C(9)–C(10) bond [$\Delta C_2(9–10) = 5{\cdot}1°$].

The methoxy groups at C(8) and C(16) are in synclinal and anticlinal configurations, respectively, relative to C(15). The torsional angles have opposite signs, indicating that the groups rotate away from one another to minimize steric interactions between them.

The acetoxy group at C(6) is in an anticlinal configuration with C(6) displaced about −0·11 Å from the plane of the group. This distortion can be described in terms of a 7° rotation about the O(2)–C(22) bond and may be caused by steric interactions involving O(3). These include two intramolecular contacts: O(3)···C(6) 2·658 (15) and O(3)···H(6) 2·14 Å; and intermolecular contacts, O(3)···H(25*c*) [$-1-x, \frac{1}{2}+y, -z$] 2·59 and O(3)···O(6) [$1-x, \frac{1}{2}+y, 1-z$] 3·14 (1) Å. However, the thermal parameters of O(3) are higher than those of any other atom in the structure and may indicate some disorder in this portion of the molecule.

The H attached to O(6) was not located. Although O(6) has two contacts within hydrogen-bonding distance [the intermolecular contact mentioned above, and an intramolecular contact O(6)···O(4) of 3·011 (9) Å], examination of Fig. 2 shows that the two possible acceptor oxygens would be accessible by rotation about the O(6)–C(14) bond. There is a peak in the difference Fourier map of 0·22 e Å$^{-3}$ at the position appropriate for a hydrogen bond with O(3) (which would be expected to be the better acceptor), but the peak height is at the noise level of the map. If the C(14) hydroxyl group were disordered, it would explain both the high thermal parameters of O(3) and the low electron density for the H on O(6).

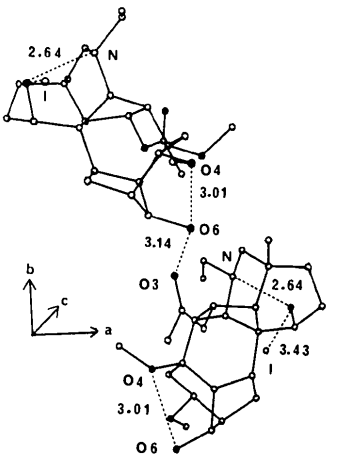



Fig. 2. A drawing of two molecules related by the screw axis. Hydrogen bonds are indicated with broken lines. Distances are in Å (e.s.d.'s range from 0·008 to 0·010 Å).

## Conclusions

A comparison of the conformational angles of alkaloid A and related alkaloids shows that the $C_{19}$ diterpenoid skeleton is remarkably rigid. The observed conformation is not sensitive to packing considerations nor to the identity of the counter ion. If the conformation in solution is close to that observed in the solid state, it should be possible to correlate structural parameters with physiological activity *in vivo*.

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# Structure of the Asthma Drug Beclomethasone Dipropionate

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## Abstract

Beclomethasone dipropionate, 9$\alpha$-chloro-16$\beta$-methyl-3,20-dioxo-1,4-pregnadiene-11$\beta$,17,21-triol 17,21-dipropionate, $C_{28}H_{37}ClO_7$, crystallizes as the monohydrate in the orthorhombic space group $P2_12_12_1$ [$a$ = 14·152 (2), $b$ = 16·268 (1), $c$ = 12·0849 (7) Å, $\lambda$ = 1·5418 Å, $T$ = 271 K, $V$ = 2782·2 Å$^3$, $Z$ = 4, $\rho_x$ = 1·29 Mg m$^{-3}$]. Final $R$ = 0·056 for 1842 observed reflections. The overall conformation of the molecule is similar to that of other anti-inflammatory steroids. The progesterone side chain takes up one of two conformations common to 16$\beta$-substituted steroids. There is a tightly bound water molecule linking the C(11) hydroxyl and the carbonyl O of the 21-propionate group. The 5000-fold enhancement in anti-asthmatic properties appears to be due primarily to the fact that the drug can be administered in aerosol form. The presence of the propionate groups and to some extent the bound water account for the efficacy of this means of administration.

## Introduction

Asthma can be combated with drugs that antagonize the chemical mediators causing it and by $\beta$-adrenergic stimulants, anti-cholinergics, phosphodiesterase inhibitors, steroids, and prostaglandins. Steroids have been used to block the inflammation of the bronchial tubes, which is the end result of many pulmonary allergic responses. Although the mechanism of the anti-inflammatory effect of cortisol is not fully understood, its effect appears to be related to its ability to stabilize membranes of cellular lysosomes so that they rupture only with difficulty and to decrease the formation of bradykinin, a powerful vasodilating substance (Guyton, 1976). Whether these effects are achieved by direct interaction or are mediated by specific receptor interaction remains uncertain.

Beclomethasone dipropionate, the title compound, is an asthma drug found to be 5000 times more potent than most other steroids. Because the drug is administered in aerosol form (Smith, Clegg, Cook & Butler, 1975) many side effects that have accompanied the use of systemic steroids are avoided.

The structure determination was undertaken in order to examine the effects of the dipropionate substitution on the conformation of the already crowded $D$ ring and side chains, and to compare its conformation with those of other steroidal anti-inflammatory agents.

Crystallographic diffraction data were measured on a specimen crystal of dimensions 0·10 × 0·12 × 0·40 mm on an Enraf–Nonius CAD-4 automated diffractometer using Ni-filtered Cu $K\alpha$ radiation. The lattice parameters were refined by a least-squares fit to measured $2\theta$ values for 22 reflections in the interval $50° < 2\theta < 78°$. Integrated relative intensities for 3212 independent reflections with $2\theta < 150°$ were measured as $\omega$–$2\theta$ scans; 1842 of these reflections were measured to be observed above background ($I > 2\sigma_I$).

The intensities were reduced to structure factor amplitudes, and phase angles sufficient for location of the nonhydrogen atoms were derived using the direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971) in conjunction with the negative-quartet figure of merit (DeTitta, Edmonds, Langs & Hauptman, 1975). 31 of 37 H atoms on the steroid and

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