The cross tensor **S** has only four elements S_{12}, S_{21}, S_{23} and S_{32} not equal to zero because the molecule is lying on a mirror plane vertical to **b**. Only the element S_{21} is considerably larger than the standard deviations. The intramolecular distances and angles corrected for the librational motion are given in Table 5.

In the harmonic approximation one would expect **U**, **T**, **L**, and **S** to be proportional to the temperature. In our case this would mean: **U** (294 K) $\simeq$ 2 **U** (140 K). From Tables 3–5, however, one arrives rather at a factor of 3 between the 140 K and the 294 K values. The inclusion of zero-point oscillations cannot explain this discrepancy because this works in the opposite direction: the low-temperature amplitude would be above a line $\sim T$. This observation seems to indicate a fairly strong anharmonic contribution. The numerical relation between **U** (294 K) and **U** (140 K) might be an artefact due to the extinction correction. The refinements without an extinction parameter show, however, essentially the same relation among them.

Conclusion

The structure refinements did not give evidence of disordered molecules. The origin of the diffuse scattering mentioned in the *Introduction* is therefore probably due to the thermal motion of the atoms, which could be analyzed well in terms of the rigid-body parameters **T**, **L** and **S**.

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The Crystal Structure and Absolute Configuration of (–)-Dihydroergotamine Methanesulfonate Monohydrate

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Abstract

(–)-Dihydroergotamine methanesulfonate monohydrate, $C_{33}H_{38}N_5O_5^+.CH_3O_3S^-.H_2O$, crystallizes in the orthorhombic space group $P2_12_12_1$ with $Z = 4$. The unit-cell dimensions are a = 38·732 (4), b = 12·518 (2), c = 7·103 (1) Å. The structure was determined by direct methods and refined by a full-matrix least-squares procedure to an R value of 0·058 for 2667 statistically significant observed reflexions. The absolute configuration was found to be 5(R), 9(R), 11(S), 21(R), 26(S), 40(S), 41(S). The rotation about the peptide link is partly restricted due to steric hindrance and an intramolecular hydrogen bond O(42)–H(42)···O(19). The center of the benzene ring attached to the peptide moiety is at a maximum distance from the ring system of this part of the molecule. Intermolecular hydrogen bonds hold the structure together in the b direction.

Introduction

Hydrogenation in positions 10 and 11 (Fig. 1) of the double bond C(10)=C(11) in the lysergic acid moiety

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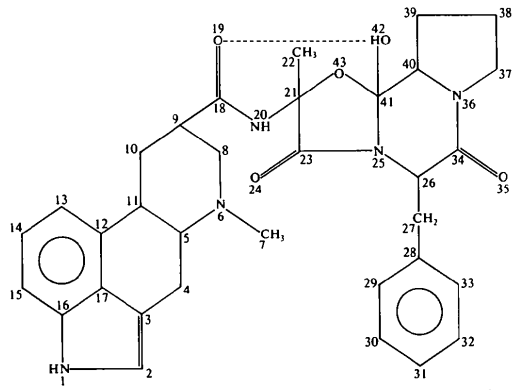

Fig. 1. The dihydroergotamine molecule, showing the non-hydrogen atom-numbering scheme. The non-H atoms of the methanesulfonate group are numbered S(44)–C(48) and O(49) refers to the O atom of the water molecule.

of ergotamine attenuates its uteronic effects and central nervous stimulation, while vasodilation and hypotension are enhanced (Stoll & Hofmann, 1965). Dihydroergotamine is used clinically to treat orthostatic hypotension and migraine. Its venoconstrictor effect has been shown to be mediated partially by α-adrenergic receptors (Müller-Schweinitzer, 1974).

Recently, [^{3}H]dihydroergokryptine and [^{3}H]-dihydroergotamine have been widely used as receptor ligands for binding studies. The binding sites for [^{3}H]-dihydroergokryptine have been identified as α-adrenergic receptors (Williams & Lefkowitz, 1976; Williams, Mullikin & Lefkowitz, 1976; Davis, Strittmatter, Hoyler & Lefkowitz, 1977; Greenberg & Snyder, 1977, 1978) and a two-site model of the α-receptor has been proposed (Peroutka, Greenberg, U'Prichard & Snyder, 1978). There is also evidence that [^{3}H]dihydroergokryptine labels dopamine receptors (Tittler, Weinreich & Seeman, 1977). Dihydroergotamine has been shown to inhibit the binding of both the α-agonist [^{3}H]clonidine and the antagonist [^{3}H]WB-4101 (U'Prichard, Greenberg & Snyder, 1977). However, if [^{3}H]dihydroergotamine itself is used as a ligand, serotonin is the only neurotransmitter tested capable of inhibition (Closse & Hauser, 1976). Furthermore, there is evidence for the existence of an endogenous dihydroergotamine-like factor in calf and rat brain (Closse & Hauser, 1978).

Knowledge of the molecular structures of these compounds is an important part in a project aiming at the elucidation of structural specificities for adrenergic effects. The crystal structure and the absolute configuration of dihydroergotamine are presented here, while dihydroergokryptine will be the subject of a subsequent crystal structure determination.

Experimental

(–)-Dihydroergotamine methanesulfonate was kindly supplied by Sandoz Pharmaceuticals. The sample was recrystallized from a methanol solution enclosed in a surrounding of ethanol. One optically perfect, colorless crystal, 0·3 × 0·3 × 0·1 mm, was used for the data collection. Preliminary unit-cell dimensions and systematic absences were derived from Weissenberg photographs, while accurate cell dimensions were obtained from diffractometer measurements by least-squares refinement of the setting angles of 25 accurately centered reflexions. The density was measured by flotation in a xylene–chloroform mixture. The (–)-dihydroergotamine cation will in the following text be referred to as DHEA.

Crystal data

(–)-Dihydroergotamine [9,10-dihydro-12′-hydroxy-2′-methyl-5′-α-(phenylmethyl)ergotaman-3′,6′,18-trione] methanesulfonate monohydrate, $C_{33}H_{38}N_5O_5^+ . CH_3O_3S^- . H_2O$, M_r = 697·82, a = 38·732 (4), b = 12·518 (2), c = 7·103 (1) Å, V = 3443·87 Å^3, D_m = 1·351, D_x (Z = 4) = 1·346 Mg m^{-3}, μ(Cu $K\alpha$) = 1·3348 mm^{-1}. Systematic absences: $h00$ when h is odd, $0k0$ when k is odd and $00l$ when l is odd establish the space group $P2_12_12_1$.

The intensities were measured on a Philips PW 1100 diffractometer with the ω–2θ scan technique. Using graphite-monochromatized Cu $K\alpha$ radiation (λ = 1·5418 Å), 3417 reflexions up to θ = 65° were collected at a scan speed of 0·03° s^{-1} and with a scan width of 1·5°. Reference reflexions recorded at regular intervals during the data collection showed no significant change in intensity. The measured intensities were corrected for Lorentz and polarization factors but not for absorption owing to the low μ value. 740 reflexions with $F < 5\sigma(F)$ were excluded from further calculations.

Structure determination and refinement

Multisolution tangent refinement with the *SHELX* program (Sheldrick, 1975) located 33 non-hydrogen atoms. One partially phased Fourier synthesis revealed the missing non-hydrogen atoms of the DHEA and the methanesulfonate group. The refinement was carried out by a full-matrix least-squares procedure. The water molecule and all H atoms except those of the methanesulfonate group were located from difference syntheses calculated during the anisotropic refinement of the non-hydrogen atoms. The positional parameters of the H atoms were refined, while their isotropic temperature factors were allotted an overall value of U = 0·05 Å^2. Nine strong reflexions affected by secondary extinction and one reflexion clearly in error were excluded from the calculations. The weighting scheme employed was $w = 1/|\sigma^2(F) + 0{\cdot}001F^2|$, where $\sigma(F)$ is the standard deviation in the observed amplitudes based on counting

statistics. The final $R' = \sum w^{1/2}||F_o| - |F_c||/\sum w^{1/2}|F_o|$ was 0·062 with a conventional R of 0·058. A conclusive difference map showed one peak (0·57 e Å^{-3}) close to the S atom, all others were <0·32 e Å^{-3}. The atomic fractional coordinates are given in Tables 1 and 2.* The atomic scattering factors were those of the *SHELX* system, also given in *International Tables for X-ray Crystallography* (1974). The drawings were produced by the plotting program *ORTEP* (Johnson, 1965) and all computations were performed on an IBM 370/165 computer.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34451 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final fractional coordinates* (×10^4) *for non-hydrogen atoms*

E.s.d.'s in parentheses are in units of the least significant digit.

	x	*y*	*z*
N(1)	1424 (1)	−1409 (3)	−5226 (8)
C(2)	1688 (2)	−1456 (5)	−3907 (10)
C(3)	1702 (1)	−542 (4)	−2907 (8)
C(4)	1916 (1)	−134 (5)	−1314 (9)
C(5)	1695 (1)	647 (4)	−172 (8)
N(6)	1916 (1)	1122 (3)	1409 (7)
C(7)	2086 (2)	312 (5)	2624 (9)
C(8)	1709 (1)	1877 (4)	2620 (8)
C(9)	1567 (1)	2794 (4)	1457 (8)
C(10)	1340 (1)	2356 (4)	−105 (8)
C(11)	1539 (1)	1571 (4)	−1329 (8)
C(12)	1320 (1)	1105 (4)	−2923 (8)
C(13)	1029 (1)	1534 (4)	−3774 (8)
C(14)	865 (1)	1007 (4)	−5246 (9)
C(15)	963 (2)	12 (5)	−5876 (8)
C(16)	1254 (1)	−435 (4)	−5037 (9)
C(17)	1428 (1)	110 (4)	−3582 (8)
C(18)	1375 (1)	3599 (4)	2698 (8)
O(19)	1080 (1)	3892 (3)	2286 (6)
N(20)	1545 (1)	3977 (3)	4200 (7)
C(21)	1391 (1)	4689 (4)	5559 (8)
C(22)	1661 (2)	5010 (5)	7009 (9)
C(23)	1229 (1)	5695 (4)	4680 (8)
O(24)	1385 (1)	6352 (3)	3742 (6)
N(25)	901 (1)	5718 (3)	5264 (6)
C(26)	644 (1)	6515 (4)	4724 (8)
C(27)	531 (2)	6398 (4)	2647 (9)
C(28)	579 (2)	7384 (4)	1451 (9)
C(29)	885 (2)	7530 (5)	449 (10)
C(30)	924 (2)	8436 (6)	−692 (10)
C(31)	670 (2)	9200 (6)	−782 (10)
C(32)	366 (2)	9043 (5)	201 (10)
C(33)	325 (1)	8142 (5)	1319 (10)
C(34)	327 (1)	6452 (4)	6003 (9)
O(35)	85 (1)	7030 (4)	5649 (8)
N(36)	326 (1)	5770 (4)	7439 (7)
C(37)	20 (2)	5632 (5)	8619 (10)
C(38)	65 (2)	4587 (6)	9600 (10)
C(39)	382 (2)	4051 (5)	8711 (10)
C(40)	593 (1)	4966 (5)	7886 (8)
C(41)	789 (1)	4714 (4)	6079 (8)
O(42)	582 (1)	4131 (3)	4896 (6)
O(43)	1102 (1)	4185 (3)	6498 (6)
S(44)	2572 (1)	3096 (2)	−4826 (4)
O(45)	2754 (2)	2892 (8)	−6667 (11)
O(46)	2598 (3)	2144 (6)	−3687 (14)
O(47)	2250 (1)	3478 (7)	−5044 (15)
C(48)	2816 (3)	4143 (9)	−3748 (17)
O(49)	2420 (2)	2370 (8)	−37 (12)

The absolute configuration

The absolute configuration was first determined by using Hamilton's (1965) statistical test. The R_G [$= (\sum w||F_o| - |F_c||^2/\sum w|F_o|^2)^{1/2}$] values for the two enantiomers were $R_G(1) = 0{\cdot}0788$ and $R_G(2) = 0{\cdot}0802$. Thus the configuration with the lower R_G value [5(*R*), 9(*R*), 11(*S*), 21(*R*), 26(*S*), 40(*S*), 41(*S*)] has a

Table 2. *Final fractional coordinates* (×10^3) *for hydrogen atoms having a temperature factor U of* 0·05 Å^2

E.s.d.'s in parentheses are in units of the last digit.

	x	*y*	*z*
H(1)	139 (1)	−192 (4)	−593 (8)
H(2)	182 (1)	−205 (4)	−384 (8)
H(4*A*)	200 (1)	−70 (4)	−54 (8)
H(4*B*)	211 (1)	28 (4)	−196 (8)
H(5)	149 (1)	26 (4)	33 (8)
H(6)	210 (1)	162 (4)	89 (8)
H(7*A*)	195 (1)	−17 (4)	303 (8)
H(7*B*)	223 (1)	−14 (4)	198 (8)
H(7*C*)	222 (1)	63 (4)	362 (8)
H(8*A*)	151 (1)	139 (4)	298 (7)
H(8*B*)	187 (1)	203 (4)	364 (8)
H(9)	178 (1)	313 (4)	91 (8)
H(10*A*)	122 (1)	276 (4)	−73 (8)
H(10*B*)	110 (1)	191 (4)	51 (8)
H(11)	171 (1)	185 (4)	−188 (7)
H(13)	94 (1)	224 (4)	−348 (8)
H(14)	69 (1)	129 (4)	−581 (7)
H(15)	87 (1)	−32 (4)	−686 (7)
H(20)	172 (1)	375 (4)	435 (7)
H(22*A*)	156 (1)	557 (4)	791 (8)
H(22*B*)	186 (1)	547 (4)	636 (8)
H(22*C*)	168 (1)	449 (4)	750 (8)
H(26)	75 (1)	724 (4)	493 (8)
H(27*A*)	64 (1)	587 (4)	215 (8)
H(27*B*)	28 (1)	621 (4)	262 (8)
H(29)	102 (1)	693 (4)	47 (8)
H(30)	110 (1)	848 (4)	−160 (8)
H(31)	72 (1)	988 (4)	−158 (8)
H(32)	19 (1)	958 (4)	−4 (8)
H(33)	14 (1)	796 (4)	195 (8)
H(37*A*)	1 (1)	627 (4)	946 (8)
H(37*B*)	−20 (1)	579 (4)	783 (8)
H(38*A*)	−15 (1)	417 (4)	962 (8)
H(38*B*)	11 (1)	471 (4)	1093 (8)
H(39*A*)	32 (1)	357 (4)	755 (8)
H(39*B*)	50 (1)	368 (4)	952 (8)
H(40)	79 (1)	535 (4)	873 (8)
H(42)	70 (1)	394 (4)	412 (8)
H(49*A*)	239 (1)	179 (4)	42 (8)
H(49*B*)	253 (1)	256 (4)	129 (8)

probability of being correct at a significance level lower than 0·5%. This result was further confirmed when the method of Bijvoet, Peerdeman & van Bommel (1951) was applied. Bijvoet pairs (hkl–$\bar{h}\bar{k}\bar{l}$) of reflexions showing a pronounced anomalous-dispersion effect were measured on the diffractometer under the same conditions as the data collection. A comparison of the observed and calculated structure factor ratios (Table 3) indicates that the wrong enantiomer was chosen initially. The configuration at the asymmetric centers 5(R), 9(R), 21(R), 26(S), 40(S), 41(S) is in perfect agreement with the absolute configuration of (−)-ergotamine determined chemically by Hofmann, Ott, Griot, Stadler & Frey (1963). The C(11) atom becomes asymmetric (S configuration) upon hydrogenation of ergotamine. For comparable asymmetric centers the configuration found is also the same as that of LSD, lysergic acid diethylamide (Baker, Chothia, Pauling & Weber, 1972).

Table 3. *Ratios of calculated and observed structure factors of reflexions showing the accentuated effect of anomalous dispersion*

$h\ k\ l$	$\lvert F_o(hkl)\rvert / \lvert F_o(\bar{h}kl)\rvert$	$\lvert F_c(hkl)\rvert / \lvert F_c(\bar{h}kl)\rvert$	$h\ k\ l$	$\lvert F_o(hkl)\rvert / \lvert F_o(\bar{h}kl)\rvert$	$\lvert F_c(hkl)\rvert / \lvert F_c(\bar{h}kl)\rvert$
12 1 1	0·96	1·04	4 7 2	1·01	0·97
8 2 1	0·98	1·01	18 9 2	1·02	0·96
2 3 1	0·96	1·02	9 11 2	1·03	0·96
2 4 1	0·98	1·01	4 1 3	0·97	1·04
7 6 1	1·02	0·98	12 1 3	0·98	1·02
2 7 1	0·98	1·02	15 4 3	1·02	0·96
10 7 1	0·98	1·05	7 4 3	1·01	0·98
10 9 1	1·02	0·98	26 6 3	1·06	0·96
15 1 2	1·04	0·98	18 1 4	1·04	0·97
6 1 2	1·01	0·99	17 4 4	0·99	1·02
11 2 2	0·98	1·01	7 3 5	0·96	1·03
15 3 2	0·97	1·01			

Description of the structure

The geometry of the (−)-dihydroergotamine molecule

The numbering of the atoms in DHEA is shown in Fig. 1 and intramolecular bond distances and angles, uncorrected for thermal vibration, are given in Tables 4 and 5. Fig. 2 is a stereoscopic drawing of the molecule.

Table 4. *Intramolecular bond distances* (Å) *with estimated standard deviations in parentheses*

N(1)–C(2)	1·390 (8)	C(23)–N(25)	1·335 (7)
N(1)–C(16)	1·391 (7)	N(25)–C(26)	1·461 (7)
C(2)–C(3)	1·348 (8)	N(25)–C(41)	1·451 (6)
C(3)–C(4)	1·493 (8)	C(26)–C(27)	1·545 (8)
C(3)–C(17)	1·423 (7)	C(26)–C(34)	1·527 (8)
C(4)–C(5)	1·532 (7)	C(27)–C(28)	1·510 (8)
C(5)–N(6)	1·532 (6)	C(28)–C(29)	1·395 (8)
C(5)–C(11)	1·542 (7)	C(28)–C(33)	1·370 (8)
N(6)–C(7)	1·486 (7)	C(29)–C(30)	1·402 (9)
N(6)–C(8)	1·508 (6)	C(30)–C(31)	1·372 (10)
C(8)–C(9)	1·518 (7)	C(31)–C(32)	1·385 (10)
C(9)–C(10)	1·518 (7)	C(32)–C(33)	1·388 (9)
C(9)–C(18)	1·532 (7)	C(34)–O(35)	1·212 (7)
C(10)–C(11)	1·522 (7)	C(34)–N(36)	1·330 (7)
C(11)–C(12)	1·531 (7)	N(36)–C(37)	1·462 (7)
C(12)–C(13)	1·385 (7)	N(36)–C(40)	1·476 (7)
C(12)–C(17)	1·395 (7)	C(37)–C(38)	1·493 (10)
C(13)–C(14)	1·391 (8)	C(38)–C(39)	1·535 (9)
C(14)–C(15)	1·378 (8)	C(39)–C(40)	1·523 (8)
C(15)–C(16)	1·392 (8)	C(40)–C(41)	1·525 (8)
C(16)–C(17)	1·409 (7)	C(41)–O(42)	1·371 (6)
C(18)–O(19)	1·232 (6)	C(41)–O(43)	1·414 (6)
C(18)–N(20)	1·341 (7)		
N(20)–C(21)	1·443 (6)		
C(21)–C(22)	1·523 (7)	S(44)–O(45)	1·506 (7)
C(21)–C(23)	1·539 (7)	S(44)–O(46)	1·444 (8)
C(21)–O(43)	1·446 (7)	S(44)–O(47)	1·344 (6)
C(23)–O(24)	1·220 (6)	S(44)–C(48)	1·788 (10)

Table 5. *Intramolecular bond angles* (°) *with estimated standard deviations in parentheses*

C(16)–N(1)–C(2)	108·7 (5)	C(13)–C(12)–C(17)	116·3 (5)	C(21)–C(23)–N(25)	106·2 (5)
N(1)–C(2)–C(3)	110·3 (5)	C(12)–C(13)–C(14)	121·1 (5)	O(24)–C(23)–N(25)	128·8 (5)
C(2)–C(3)–C(4)	135·3 (5)	C(13)–C(14)–C(15)	123·1 (5)	C(23)–N(25)–C(26)	125·6 (5)
C(2)–C(3)–C(17)	106·3 (5)	C(14)–C(15)–C(16)	116·6 (5)	C(23)–N(25)–C(41)	113·0 (5)
C(4)–C(3)–C(17)	118·3 (4)	N(1)–C(16)–C(15)	133·8 (5)	C(26)–N(25)–C(41)	119·4 (4)
C(3)–C(4)–C(5)	108·0 (4)	N(1)–C(16)–C(17)	105·6 (5)	N(25)–C(26)–C(27)	112·2 (5)
C(4)–C(5)–N(6)	108·9 (4)	C(15)–C(16)–C(17)	120·4 (5)	N(25)–C(26)–C(34)	110·9 (5)
C(4)–C(5)–C(11)	114·5 (4)	C(3)–C(17)–C(12)	128·5 (5)	C(27)–C(26)–C(34)	109·7 (5)
N(6)–C(5)–C(11)	108·6 (4)	C(3)–C(17)–C(16)	109·0 (4)	C(26)–C(27)–C(28)	115·2 (5)
C(5)–N(6)–C(7)	114·1 (4)	C(12)–C(17)–C(16)	122·4 (5)	C(27)–C(28)–C(29)	119·8 (5)
C(5)–N(6)–C(8)	111·4 (3)	C(9)–C(18)–O(19)	120·6 (5)	C(27)–C(28)–C(33)	121·1 (5)
C(7)–N(6)–C(8)	109·4 (4)	C(9)–C(18)–N(20)	116·8 (4)	C(29)–C(23)–C(33)	119·1 (6)
N(6)–C(8)–C(9)	110·9 (4)	O(19)–C(18)–N(20)	122·6 (5)	C(28)–C(29)–C(30)	119·4 (6)
C(8)–C(9)–C(10)	109·6 (4)	C(18)–N(20)–C(21)	123·1 (4)	C(29)–C(30)–C(31)	120·9 (6)
C(8)–C(9)–C(18)	111·2 (4)	N(20)–C(21)–C(22)	109·3 (4)	C(30)–C(31)–C(32)	119·2 (6)
C(10)–C(9)–C(18)	112·1 (4)	N(20)–C(21)–C(23)	113·7 (4)	C(31)–C(32)–C(33)	120·0 (6)
C(9)–C(10)–C(11)	110·9 (4)	N(20)–C(21)–O(43)	111·1 (4)	C(28)–C(33)–C(32)	121·3 (6)
C(5)–C(11)–C(10)	112·2 (4)	C(22)–C(21)–C(23)	109·8 (4)	C(26)–C(34)–O(35)	117·9 (5)
C(5)–C(11)–C(12)	109·0 (4)	C(22)–C(21)–O(43)	109·6 (4)	C(26)–C(34)–N(36)	119·5 (5)
C(10)–C(11)–C(12)	112·8 (4)	C(23)–C(21)–O(43)	103·2 (4)	O(35)–C(34)–N(36)	122·7 (5)
C(11)–C(12)–C(13)	128·7 (5)	C(21)–C(23)–O(24)	124·8 (5)	C(34)–N(36)–C(37)	121·2 (5)
C(11)–C(12)–C(17)	115·0 (4)				

C(34)–N(36)–C(40)	126·9 (5)		
C(37)–N(36)–C(40)	111·2 (5)		
N(36)–C(37)–C(38)	106·1 (5)		
C(37)–C(38)–C(39)	106·5 (5)		
C(38)–C(39)–C(40)	104·9 (5)		
N(36)–C(40)–C(39)	102·8 (5)		
N(36)–C(40)–C(41)	107·9 (4)		
C(39)–C(40)–C(41)	115·8 (5)		
N(25)–C(41)–C(40)	107·9 (4)		
N(25)–C(41)–O(42)	113·1 (5)		
N(25)–C(41)–O(43)	103·4 (4)		
C(40)–C(41)–O(42)	109·6 (4)		
C(40)–C(41)–O(43)	110·3 (5)		
O(42)–C(41)–O(43)	112·3 (4)		
C(21)–O(43)–C(41)	111·4 (4)		
O(46)–S(44)–O(45)	108·3 (5)		
O(47)–S(44)–O(45)	113·2 (6)		
O(47)–S(44)–O(46)	115·0 (6)		
C(48)–S(44)–O(45)	104·5 (6)		
C(48)–S(44)–O(46)	109·2 (6)		
C(48)–S(44)–O(47)	106·2 (5)		

Table 6. *Least-squares planes and deviations* (Å) *of individual atoms*

The equations of the planes are in the form $AX + BY + CZ = D$, where X, Y, Z are coordinates in orthogonal ångström space along a, b, c respectively. Asterisks indicate atoms not included in the calculations of the planes. E.s.d.'s in parentheses are in units of the last digit.

Plane of indole nucleus (rings *A* and *B*)

$0{\cdot}6032X + 0{\cdot}4297Y - 0{\cdot}6720Z = 5{\cdot}0661$

N(1)	−0·004 (4)	C(15)	−0·004 (7)
C(2)	−0·040 (6)	C(16)	0·034 (5)
C(3)	0·006 (5)	C(17)	0·038 (5)
C(12)	0·006 (5)	C(4)*	−0·034 (6)
C(13)	−0·035 (5)	C(5)*	−0·676 (5)
C(14)	0·000 (5)	C(11)*	0·009 (5)

Plane of ring *D*

$0{\cdot}6093X + 0{\cdot}4059Y - 0{\cdot}6811Z = 4{\cdot}4115$

C(5)	0·001 (5)	C(10)	−0·001 (5)
N(6)	−0·001 (4)	C(8)*	−0·692 (5)
C(9)	0·001 (5)	C(11)*	0·662 (5)

Plane of peptide bond

$0{\cdot}3738X + 0{\cdot}7589Y - 0{\cdot}5333Z = 4{\cdot}3880$

C(9)	−0·017 (5)	N(20)	0·036 (4)
C(18)	−0·001 (5)	C(21)	−0·026 (5)
O(19)	0·008 (4)		

Plane of ring *E*

$0{\cdot}1782X + 0{\cdot}4806Y + 0{\cdot}8586Z = 7{\cdot}1806$

C(21)	0·009 (5)	C(41)	0·092 (5)
C(23)	0·052 (5)	O(43)	−0·062 (4)
N(25)	−0·092 (4)	O(24)*	0·120 (4)
		C(26)*	−0·064 (5)

Plane of ring *F*

$0{\cdot}4301X + 0{\cdot}6689Y + 0{\cdot}6063Z = 8{\cdot}5542$

N(25)	0·002 (4)	C(40)	−0·013 (5)
C(26)	0·007 (5)	O(35)*	−0·094 (5)
C(34)	−0·022 (5)	C(37)*	−0·092 (7)
N(36)	0·025 (4)	C(41)*	−0·675 (5)

Plane of ring *G*

$0{\cdot}4204X + 0{\cdot}4089Y + 0{\cdot}8100Z = 7{\cdot}8740$

N(36)	0·109 (4)	C(39)	0·163 (7)
C(37)	−0·001 (7)	C(40)	−0·170 (5)
C(38)	−0·104 (7)		

Plane of ring *H*

$0{\cdot}3964X + 0{\cdot}4871Y + 0{\cdot}7782Z = 6{\cdot}1927$

C(28)	−0·001 (6)	C(32)	0·006 (7)
C(29)	−0·006 (7)	C(33)	0·001 (7)
C(30)	0·013 (7)	C(27)*	0·013 (6)
C(31)	−0·013 (7)		

The two ring systems of DHEA are connected by a peptide link with torsion angles 52·4 (6)° [C(8)–C(9)–C(18)–N(20)] and −53·6 (4)° [C(18)–N(20)–C(21)–C(23)]. Thus, the bonds C(8)–C(9) and C(21)–C(23) are nearly parallel. The comparatively large van der Waals radii of the carboxyl O(19) and O(24) atoms and the O(43) atom give rise to steric hindrance preventing free rotation about N(20)–C(21).

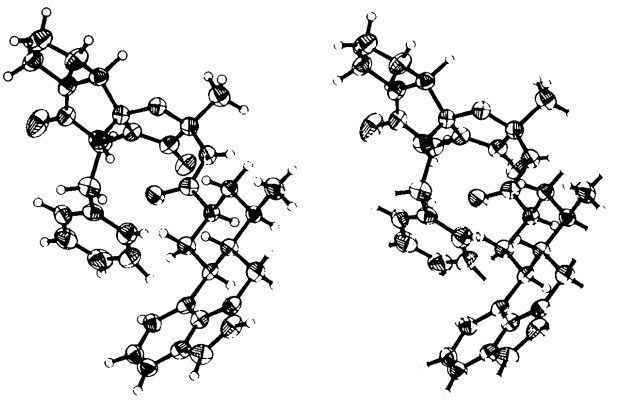

Fig. 2. Stereoview of the dihydroergotamine cation. Heavy atoms are represented by thermal ellipsoids of 50% probability. Hydrogen atoms are depicted as small circles.

No such impediment exists for rotation about C(9)–C(18). Additional preference for the conformation found is given by the intramolecular hydrogen bond O(42)–H(42)···O(19). The bond lengths and angles of the peptide link are very close to those generally accepted (Blundell & Johnson, 1976).

The hydrogenated LSD moiety of DHEA consists of four fused rings (*A*–*D*). The indole nucleus (rings *A* and *B*) is planar while the six-membered rings *C* and *D* have envelope and chair conformations respectively. Table 6 gives deviations of individual atoms from best planes calculated through the planar parts of the molecule. The torsion angles C(2)–C(3)–C(4)–C(5) and C(3)–C(4)–C(5)–N(6), which give the position of the N(6) atom in relation to the indole nucleus, are −150·1 (6) and −177·0 (6)°. These values are close to those calculated by Falkenberg (1972) for LSD (the opposite enantiomer). Comparable bond lengths and angles of the LSD moiety in DHEA do not deviate significantly from the values found in LSD *o*-iodobenzoate monohydrate (Baker, Chothia, Pauling & Weber, 1972) and lyserdol (Foresti Serantoni, Sabatino, Riva di Sanseverino & Sheldrick, 1977).

The ring system (*E*,*F*,*G*) at the amino end of the peptide link constitutes a rigid structure. Atoms C(21) and C(37) are almost in the least-squares planes calculated through *E* and *G* respectively (Table 6) with every second atom of each ring above and every second atom below the planes. The six-membered ring (*F*) has an envelope conformation with C(41) 0·675 (5) Å below the plane calculated through N(25), C(26), C(34), N(36) and C(40). The torsion angles N(25)–C(26)–C(27)–C(28) and C(26)–C(27)–C(28)–C(29) are −123·4 (7) and 91·7 (7)° respectively. Thus, the benzene ring (*H*) is situated at a maximum distance from the ring system (*E*,*F*,*G*) and the distances from the carboxyl O(24) and O(35) atoms to the center of *H* are nearly equal, 4·520 (4) and 4·601 (5) Å respec-

Table 7. *Hydrogen-bonded interactions*

The columns labelled x',y',z' give the symmetry of the acceptor atom Y'. The reference molecule is in x,y,z. E.s.d.'s in parentheses are in units of the last digit.

X	H	Y'	x'	y'	z'	$X\cdots Y'$	$H\cdots Y'$	X–H$\cdots Y'$
N(6)	H(6)	O(49)	x	y	z	2·684 (9) Å	1·64 (4) Å	177 (2)°
O(49)	H(49*B*)	O(45)	x	y	$z+1$	2·752 (11)	1·66 (4)	164 (2)
N(20)	H(20)	O(47)	x	y	$z+1$	2·854 (9)	2·07 (4)	162 (2)
N(1)	H(1)	O(24)	x	$y-1$	$z-1$	2·901 (6)	2·08 (4)	132 (2)
O(42)	H(42)	O(19)	x	y	z	2·692 (5)	1·97 (4)	148 (2)

tively. The normal to the phenyl ring is approximately in the plane C(26)–C(27)–C(28). The extended conformation is different from that found in a crystal structure determination of *p*-iodobenzoylaminocyclol (McPhail, Sim, Frey & Ott, 1966) where the phenyl ring approaches the hydroxyl group as closely as possible. This conformation was attributed to an OH$\cdots$benzene hydrogen bond. In DHEA such an interaction is excluded as H(42) is already occupied in an O(42)–H(42)$\cdots$O(19) hydrogen bond.

Hydrogen bonds and molecular packing

The hydrogen bonds observed are listed in Table 7. The N(6) atom, which is protonated as would be expected in a methanesulfonate salt, is the donor for a hydrogen bond to the water O(49) atom. The water molecule lacks one of the expected hydrogen-bonded interactions. The short contact O(46)$\cdots$O(49) is 2·75 (1) Å (both atoms in x,y,z), but the angle O(46)$\cdots$H(49*A*)–O(49) is 60·2 (2)° excluding the possibility of a hydrogen bond. In a difference synthesis calculated at the end of the refinement no peak of significant height that could be interpreted as an alternative position for H(49*A*) was observed. All other protons available participate in the hydrogen-bonding system holding the structure together in the *b* direction. In the *a* and *c* directions the structure is held together by van der Waals forces. The packing is shown in Fig. 3.

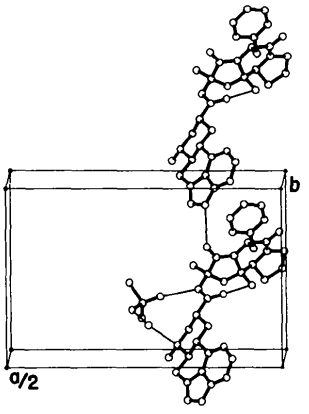

Fig. 3. The molecular packing as seen along *c*. Thin lines represent hydrogen bonds. H atoms are omitted.

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The Crystal Structure and the Absolute Configuration of a Chiral Vitamin B_6 Analogue, (–)-14-Hydroxy-2,8-dithia[9](2,5)-pyridinophane-15-methanol

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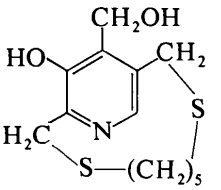
Abstract

The absolute configuration of the title compound, $C_{13}H_{19}NO_2S_2$, was determined through the anomalous-dispersion effect of the sulfur atoms. The crystals are orthorhombic, space group $P2_12_12_1$, with a = 15·642 (4), b = 16·360 (3) and c = 10·953 (2) Å, Z = 8. There are two independent molecules in the asymmetric unit. Both of them have the planar chirality of the S configuration. The two molecules are connected by an O···N hydrogen bond to make a linear molecular chain.

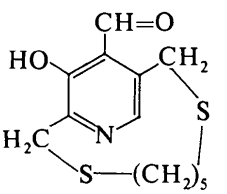
Introduction

In the course of the study directed towards enzyme models, a series of chiral vitamin B_6 analogues has been prepared and used as a catalyst for the non-enzymatic duplication of the stereospecific reactions catalyzed with vitamin B_6-dependent enzymes (Kuzuhara, Iwata & Emoto, 1977; Kuzuhara, Komatsu & Emoto, 1978). All of these B_6 analogues are '*ansa* compounds' with restricted rotations and hence have planar chirality. Correlation of the stereochemistry among enantiomers of each analogue has been established by mutual chemical conversion.

This paper deals with the results of the X-ray analysis of one such analogue, (–)-14-hydroxy-2,8-dithia[9](2,5)-pyridinophane-15-methanol (1), which clarifies the absolute configuration of all of these B_6 analogues.



(–)
(1)



(–)
(2)

Experimental and structure determination

Compound (1) was first obtained as a by-product in the reductive amination of (2) (Kuzuhara, Komatsu & Emoto, 1978). For the experiment in this paper, however, (1) was prepared by reduction of (2) with sodium borohydride in methanol and purified by ion-exchange chromatography, using Dowex 50 (H form) and aqueous ammonia as eluant. The sample for X-ray analysis was recrystallized from methanol. Colorless needle-shaped crystals were obtained. The crystal data are shown in Table 1. X-ray diffraction data were collected on a Rigaku four-circle automatic diffractometer. The intensity data for the structure determination were taken with graphite-monochromatized Mo $K\alpha$ radiation. The size of the crystal was 0·2 × 0·3 × 0·8 mm. At this stage the anomalous-dispersion effect was ignored, and the intensities were measured within the first octant up to 2θ = 45°. The usual Lorentz and polarization corrections were applied and 1813 independent reflections with $|F| > 3\sigma(F)$ were obtained.

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