Crystal Structures of the Teonanácatl Hallucinogens. Part I. Psilocybin $C_{12}H_{17}N_2O_4P$

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The crystal structure of psilocybin. the major hallucinogenic component of Teonanácatl, the sacred mushroom of Mexico. has been determined in crystals of the monomethanolate. Crystals are monoclinic. space group $P2_1/c$. a = 1264(1). b = 2911(2). c = 884·7(6) pm, β = 107·37(2)°. and contain two molecules of psilocybin and two molecules of methanol of solvation per asymmetric unit. Data were collected on a four-circle diffractometer: the structure was solved by direct methods and refined by block-diagonal least squares to R 0·049 over 4217 significant reflections. The two independent molecules are both zwitterions, have different conformations. and are involved in a complex hydrogen-bonding scheme in which there are very short phosphate–phosphate hydrogen bonds. and in which the methanol of solution also takes part. Significant deviations of the substituents from the indole plane are apparent. Bond lengths have been determined to a precision of 0·5 pm.

TEONANÁCATL is one of the three magic drugs of Mexico, the others being Peyotl and Ololiuqui. The name means 'sacred mushroom' and its worship and use by the Indians of Central America is very ancient. In 1956 the sacred mushrooms were identified and grown from cultures, and a full review of the historical, ethnological, botanical, and chemical aspects of these hallucinogenic plants has appeared.[1] The active principle of the plant was isolated from the species *Psilocybe Mexicana* Heim in these laboratories,[2] characterised, and finally synthesised. There are actually two compounds responsible for the hallucinogenic effect, psilocybin, of which the crystal structure is described here, and in lesser amounts, psilocin, of which the crystal structure is described in the following paper. Psilocin, formed by metabolic dephosphorylation of psilocybin, is the active species in the central nervous system.[3,4] We have solved the crystal structures as part of an investigation of the structure–activity relationship of hallucinogenic substances.

EXPERIMENTAL

Crystal Data.—Psilocybin monomethanolate, $C_{12}H_{17}N_2O_4P,CH_3OH$, $M = 316$. Monoclinic, $a = 1264(1)$, $b = 2911(2)$, $c = 884{\cdot}7(6)$ pm, $\beta = 107{\cdot}37(2)^\circ$, $U = 3107(6) \times 10^6$ pm^3, $D_m = 1{\cdot}34$, $D_c = 1{\cdot}35$, $Z = 8$. Space group $P2_1/c$ (C^5_{2h}, No. 14). Mo-K_α radiation, $\lambda = 71{\cdot}07$ pm; μ(Mo-K_α) = 1·31 cm^{-1}.

Structure Analysis.—Data were collected on a four-circle computer controlled diffractometer using graphite monochromatised Mo-K_α radiation for $2\theta \leqslant 50^\circ$. A total of 5467 measurements yielded 4217 significant reflections with $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects and placed on an absolute scale by means of a Wilson plot:

	Theoretical values
$B_{\text{overall}} = 4{\cdot}0$	
$\langle\lvert E\rvert\rangle = 0{\cdot}844$	0·798
$\langle\lvert E^2 - 1\rvert\rangle = 0{\cdot}952$	0·968
$\langle\lvert E^2\rvert\rangle = 1{\cdot}003$	1·000

The structure was solved by direct methods using the symbolic addition procedure; all non-hydrogen atoms were located in the first E map, and hydrogen atoms were placed from a difference Fourier synthesis. The structure was refined by block-diagonal least-squares, using anisotropic thermal parameters for C, N, O, and P, and isotropic vibrations for hydrogen, to R 0·049 over the 4217 significant reflections and 0·071 over all 5333 data. An isotropic extinction correction [5] was applied and refined to a value of 7(1), assuming an overall isotropic $\bar{T}$ of 0·02 cm. Structure factors and B_{ij} parameters are deposited as Supplementary Publication No. SUP 20979 (33 pp., 1 microfiche).*

DISCUSSION

Molecular Conformation.—The different conformations of the two independent psilocybin molecules are shown in Figures 1 and 2. These molecules differ in conformation of both the *NN*-dimethylamino-side chain, and of the phosphate group. Both are zwitterions formed by donation of a phosphate proton to the amine nitrogen, and each has both the phosphate group and ethylamino chain displaced out of the mean plane of the indole ring. The conformational differences between the two independent molecules are detailed in Table 1.

TABLE 1

Torsion angles (deg.) [a] illustrating the conformational differences between the two independent molecules

	Molecule A	Molecule B [b]
C(5)–O(1)–P–O(2)	−78·2	−63·8
C(5)–O(1)–P–O(3)	+50·2	+170·8
C(5)–O(1)–P–O(4)	+166·4	+54·8
C(4)–C(5)–O(1)–P	−148·7	−139·9
C(6)–C(5)–O(1)–P	+34·1	+43·8
C(2)–C(3)–C(10)–C(11)	−72·4	−107·6
C(4)–C(3)–C(10)–C(11)	+97·7	+65·5
C(3)–C(10)–C(11)–N(12)	−166·0	+174·7
C(10)–C(11)–N(12)–C(13)	+83·9	+143·7
C(10)–C(11)–N(12)–C(14)	−154·1	−91·5

[a] Standard deviation $\leqslant 0{\cdot}4^\circ$. [b] These torsion angles are for molecule B at $\bar{x}, \bar{y}, \bar{z}$ in order to facilitate the comparison. The torsion angles of molecule B at x, y, z are simply reversed in sign.

The mean molecular geometry of the two molecules is shown in Figure 3, which also gives the numbering scheme we have used. Final positions and standard

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* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1972, Index Issue.

[1] R. Heim and R. G. Wasson, 'Les Champignons Hallocinogènes du Mexique,' 'Muséum national d'Histoire Naturelle,' Paris, 1958.

[2] A. Hofmann, R. Heim, A. Brack, and H. Kobel, *Experientia*, 1958, **14**, 107.

[3] A. Horita and L. J. Weber, *Toxicol. Appl. Pharmacol.*, 1962, **4**, 730.

[4] A. Horita, *J. Neuropsychiatry*, 1963, **4**, 270.

[5] P. Coppens and W. C. Hamilton, *Acta Cryst.*, 1971, **A26**, 71.

deviations are presented in Table 2, where asterisked atoms belong to molecule B. The distances and angles of the indole ring and ethylamino side chain correspond rather closely with the mean values found by Falkenberg[6] in a survey of 16 derivatives of indole. The bond lengths in the six-membered ring C(4)–C(9) in particular are non-equivalent, differing from each other by between 4 and 10 standard deviations. As a check, we have computed 'figures of merit' (1) and (2) for the two independent molecules which are measures of the internal consistency of the analysis. We find $F = 1{\cdot}22$ and $F' = 2{\cdot}94$ over 20 bond lengths and 29 bond angles, respectively. The individual values of F and F' are tabulated in Tables 3 and 4. If all angles involving P are removed from the average, then F' drops to 1·66, in other words the biggest differences in bond angles are found in the phosphate groups, especially in the four angles involving O(1) and P. These differences are brought about by the different conformations of the phosphate groups relative to the indole rings, and reflect the different non-bonded contacts between the phosphate group and C(6) which give rise to two different types of strain in the phosphate groups. In molecule A, C(6) is 313, 327, and 332 pm from P, O(2), and O(3) respectively, and H–C(6) is 263 and 304 pm from O(2) and O(3). In molecule B, C(6*) is 324, 321, and 353 pm from P*, O(2*), and O(4*), with H–C(6*) 260 and 351 pm from O(2*) and O(4*). The situation is shown in Figure 4.

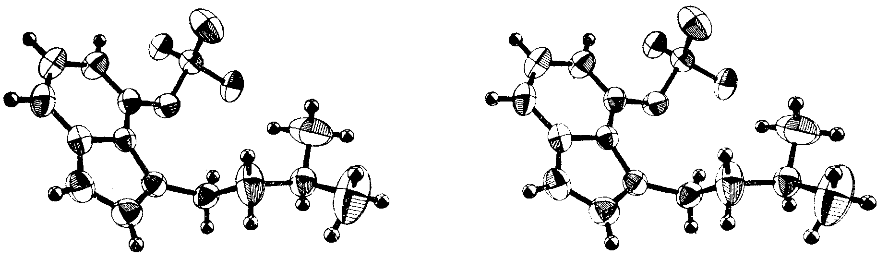

FIGURE 1 Stereo-pair of molecule A, showing 50% probability thermal ellipsoids

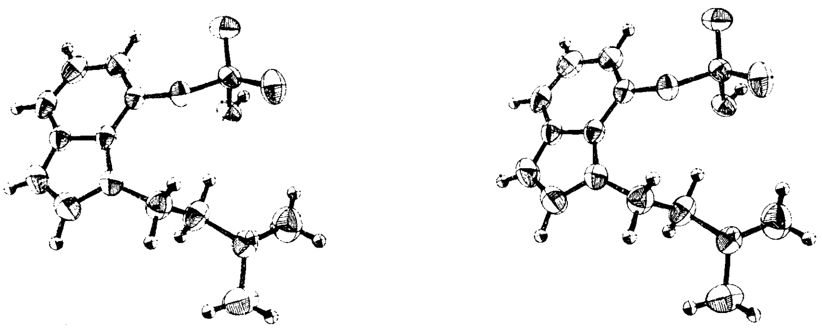

FIGURE 2 Stereo-pair of molecule B

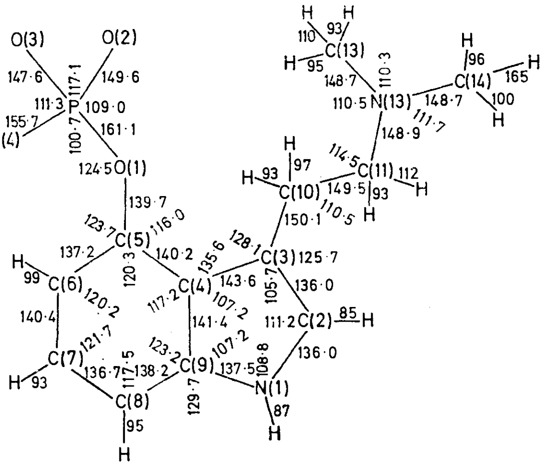

FIGURE 3 Mean molecular geometry of the two psilocybin molecules, showing the numbering scheme

$$F = \left\langle \frac{|d_{\mathrm{AB}} - d_{\mathrm{A^*B^*}}|}{\sqrt{\sigma^2_{\mathrm{AB}} + \sigma^2_{\mathrm{A^*B^*}}}} \right\rangle = \left\langle \frac{\Delta_{\mathrm{length}}}{\sigma(\Delta_{\mathrm{length}})} \right\rangle \qquad (1)$$

$$F' = \left\langle \frac{|\theta_{\mathrm{ABC}} - \theta_{\mathrm{A^*B^*C^*}}|}{\sqrt{\sigma^2_{\mathrm{ABC}} + \sigma_{\mathrm{A^*B^*C^*}}^2}} \right\rangle = \left\langle \frac{\Delta_{\mathrm{angle}}}{\sigma(\Delta_{\mathrm{angle}})} \right\rangle \qquad (2)$$

The P–O bond lengths are not like those found in free H_2PO_4[7,8] or HPO_4[9] groups, but most closely resemble those found in DL-*O*-serine phosphate monohydrate[10] and L-*O*-serine phosphate[11] where short hydrogen bonds similar to those found in this study were present. The indole rings are planar to within 3 pm (Figure 5) but the O(1) and C(10) substituents deviate

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[6] G. Falkenberg, Ph.D. Thesis, Karolinska Institutet, Stockholm, 1972.

[7] E. C. Kostansik and W. R. Busing, *Acta Cryst.*, 1972, **B28**, 2454.

[8] W. Saenger and K. G. Wagner, *Acta Cryst.*, 1972, **B28**, 2237.

[9] A. A. Kahn, J. P. Roux, and W. J. James, *Acta Cryst.*, 1972, **B28**, 2065.

[10] E. F. Putkey and M. Sundaralingam, *Acta Cryst.*, 1970, **B26**, 782.

[11] M. Sundaralingam and E. F. Putkey, *Acta Cryst.*, 1970, **B26**, 790.

significantly from the plane, one on each side of the plane. These distortions reflect the strain imposed by close contacts between the phosphate group and the C(11) hydrogen atoms and between O(1) and one of the C(10) hydrogen atoms. Although the two molecules have rather different conformations, the displacements of O(1) and C(10) are rather similar.

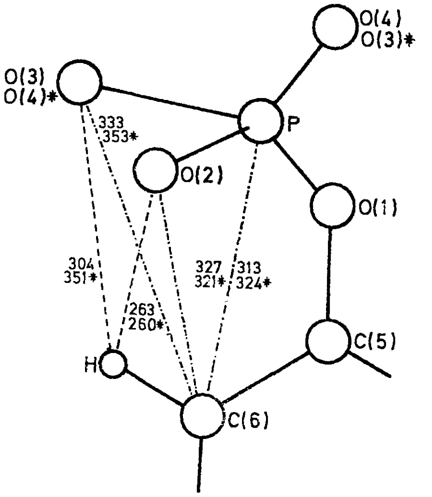

FIGURE 4 Important non-bonded contacts in the phosphate groups (pm). Values for molecule B are marked with an asterisk

TABLE 2

Final positions ($\times 10^4$, $\times 10^3$ for H) [a] and standard deviations

	x	*y*	*z*	*B*
N(1)	7203(2)	2189(0)	2154(3)	
C(2)	7812(2)	2507(1)	3177(4)	
C(3)	8893(2)	2373(0)	3766(3)	
C(4)	8957(2)	1932(0)	3066(3)	
C(5)	9788(2)	1603(0)	3194(3)	
C(6)	9564(2)	1208(1)	2315(3)	
C(7)	8499(3)	1132(1)	1273(4)	
C(8)	7656(2)	1437(1)	1127(3)	
C(9)	7889(2)	1831(1)	2040(3)	
C(10)	9838(2)	2661(1)	4738(3)	
C(11)	10139(3)	3016(1)	3736(4)	
N(12)	11210(2)	3253(0)	4420(2)	
C(13)	12149(3)	2982(1)	4173(5)	
C(14)	11194(4)	3719(1)	3710(5)	
O(1)	10813(1)	1698(0)	4305(2)	
O(2)	12122(1)	1034(0)	4505(2)	
O(3)	12009(2)	1666(1)	2498(2)	
O(4)	12779(1)	1832(0)	5387(2)	
P	11974(0)	1532(0)	4083(0)	
N(1 *)	8750(2)	4538(1)	1537(3)	
C(2 *)	8441(2)	4899(1)	2283(4)	
C(3 *)	7531(2)	4796(1)	2726(3)	
C(4 *)	7239(2)	4334(0)	2205(3)	
C(5 *)	6422(2)	4018(0)	2304(3)	
C(6 *)	6363(2)	3594(1)	1608(3)	
C(7 *)	7135(2)	3467(1)	0822(3)	
C(8 *)	7974(2)	3757(1)	0751(3)	
C(9 *)	8018(2)	4184(1)	1450(3)	
C(10 *)	6919(2)	5129(1)	3459(3)	
C(11 *)	5822(2)	5257(1)	2290(3)	
N(12 *)	5221(1)	5624(0)	2917(2)	
C(13 *)	4012(2)	5535(1)	2360(4)	
C(14 *)	5486(3)	6094(1)	2496(4)	
O(1 *)	5744(1)	4154(0)	3209(2)	
O(4 *)	3984(1)	4283(0)	1105(2)	
O(3 *)	4102(1)	4346(0)	3983(2)	
O(2 *)	4175(1)	3567(0)	2734(2)	
P *	4429(0)	4069(0)	2789(0)	
C(Me1)	1486(3)	4812(1)	1867(5)	
O(Me1)	0779(1)	4518(0)	0781(3)	
C(Me2)	4687(3)	2457(1)	3777(5)	
O(Me2)	5088(2)	2843(0)	4691(3)	
H(1)	653(2)	221(1)	150(3)	4·37(85)
H(2)	754(2)	276(0)	338(3)	2·54(68)
H(6)	1016(2)	098(0)	237(3)	2·36(66)
H(7)	837(2)	086(1)	074(3)	3·65(79)
H(8)	697(2)	138(0)	045(3)	2·53(68)
H(101)	1050(2)	249(1)	516(3)	2·77(71)
H(102)	968(2)	277(1)	558(4)	4·29(85)
H(111)	947(3)	328(1)	369(4)	7·56(107)
H(112)	1008(2)	296(1)	272(3)	3·27(75)
H(12)	1138(2)	327(1)	553(3)	3·44(76)
H(131)	1198(2)	297(1)	303(4)	5·53(92)
H(132)	1208(3)	261(1)	476(5)	9·86(124)
H(133)	1273(3)	321(1)	452(4)	6·27(100)
H(141)	1090(3)	375(1)	249(4)	6·40(100)
H(142)	1050(2)	379(1)	417(3)	3·10(72)
H(143)	1178(3)	387(1)	433(4)	8·79(122)
H(O4)	1320(2)	170(1)	617(3)	3·68(82)
H(1*)	931(2)	454(1)	118(3)	4·30(85)
H(2 *)	889(2)	520(1)	242(3)	4·11(86)
H(6 *)	582(2)	335(1)	168(3)	3·15(75)
H(7 *)	704(2)	317(1)	033(3)	3·23(74)
H(8 *)	852(2)	368(1)	020(3)	3·00(73)
H(101 *)	680(2)	502(1)	436(4)	4·69(89)
H(102 *)	738(2)	543(1)	379(4)	5·06(91)
H(111 *)	596(2)	538(0)	136(3)	2·51(67)
H(112 *)	526(2)	495(1)	209(4)	5·05(92)
H(12 *)	543(2)	560(0)	393(3)	2·39(67)
H(131 *)	388(2)	529(1)	285(4)	5·25(95)
H(132 *)	376(3)	551(1)	117(4)	6·97(113)
H(133 *)	359(2)	575(1)	269(4)	4·51(85)
H(141 *)	515(2)	628(1)	296(3)	3·62(79)
H(142 *)	632(3)	611(1)	287(4)	5·44(97)
H(143 *)	515(2)	613(0)	133(3)	2·64(69)
H(O4 *)	331(2)	412(1)	057(4)	4·93(94)
H1(Me1)	120(2)	507(1)	197(4)	5·83(96)
H2(Me1)	225(3)	474(1)	205(5)	9·71(127)
H3(Me1)	175(3)	466(1)	298(4)	8·17(112)
H–O(Me1)	119(2)	434(1)	040(3)	3·75(79)
H1(Me2)	501(3)	222(1)	412(4)	8·25(113)
H2(Me2)	462(3)	250(1)	267(5)	10·10(126)
H3(Me2)	390(3)	243(1)	336(4)	6·96(102)
H–O(Me2)	485(2)	307(1)	416(3)	4·22(84)

[a] Atoms labelled with an asterisk, *e.g.* C(9*), belong to molecule B.

TABLE 3

Bond lengths (pm) in the two independent molecules

	Molecule A	Molecule B	*F*[= Δ/δ(Δ)]
N(1)–C(2)	136·2(4)	135·9(5)	0·4
N(1)–C(9)	137·8(4)	137·1(4)	1·2
C(2)–C(3)	136·6(5)	135·5(5)	1·5
C(3)–C(4)	143·7(4)	143·5(4)	0·3
C(3)–C(10)	150·1(4)	150·1(4)	0·0
C(4)–C(5)	140·0(4)	140·5(4)	0·8
C(4)–C(9)	141·4(4)	141·3(4)	0·1
C(5)–C(6)	137·1(4)	137·2(4)	0·1
C(5)–O(1)	140·0(4)	139·4(3)	1·2
C(6)–C(7)	140·2(4)	140·6(5)	0·5
C(7)–C(8)	136·4(5)	137·1(5)	0·9
C(8)–C(9)	138·2(4)	138·1(5)	0·1
C(10)–C(11)	148·3(5)	150·8(5)	3·5
C(11)–N(12)	147·9(5)	150·8(4)	4·5
N(12)–C(13)	149·3(6)	148·2(5)	1·4
N(12)–C(14)	149·2(6)	148·2(5)	1·2
O(1)–P	161·1(2)	161·0(2)	0·3
P–O(2)	149·6(2)	149·5(2)	0·3
P–O(3)	146·9(3)	148·3(2)	3·8
P–O(4)	155·7(2)	155·7(2)	0·0

Hydrogen Bonding.—There is a complex system of hydrogen bonds in the crystal, involving the phosphate groups, the indole and ethylamino nitrogens, and the methanol of solvation (Figure 6 and Table 5). Each phosphate group of a molecule A is strongly hydrogen-bonded to the phosphate group of a molecule B. Then N(12) of molecule A is hydrogen-bonded to the formally double-bonded O(3) of the phosphate group in a symmetry-related molecule A, and similarly N(12*) to

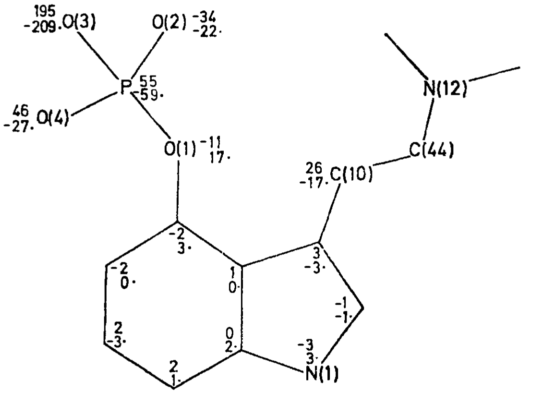

Figure 5 Deviations (pm) from the least-squares plane of the indole ring

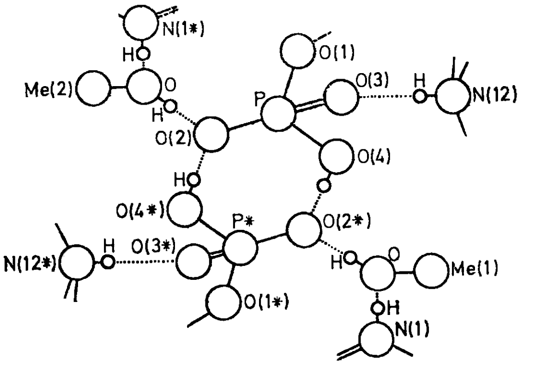

Figure 6 Schematic diagram of the hydrogen bonding about two phosphate groups

TABLE 4

Bond angles (deg.) in the two independent molecules

	Molecule A	Molecule B	$F'[=\Delta/\delta(\Delta)]$
N(1)–C(2)–C(3)	111·2(3)	111·2(3)	0·0
N(1)–C(9)–C(4)	107·2(3)	107·1(3)	0·2
N(1)–C(9)–C(8)	129·8(3)	129·6(3)	0·5
C(2)–N(1)–C(9)	108·7(3)	108·8(3)	0·2
C(2)–C(3)–C(4)	105·6(3)	105·8(3)	0·4
C(2)–C(3)–C(10)	126·3(3)	125·1(3)	2·8
C(3)–C(4)–C(5)	135·4(3)	135·8(3)	0·9
C(3)–C(4)–C(9)	107·3(3)	107·1(3)	0·4
C(3)–C(10)–C(11)	110·4(3)	110·5(3)	0·2
C(4)–C(3)–C(10)	127·4(3)	128·9(3)	3·5
C(4)–C(5)–C(6)	120·4(3)	120·2(3)	0·4
C(4)–C(5)–O(1)	115·9(3)	116·1(3)	0·4
C(4)–C(9)–C(8)	123·0(3)	123·3(3)	0·7
C(5)–C(4)–C(9)	117·3(3)	117·1(3)	0·4
C(5)–C(6)–C(7)	120·0(3)	120·3(3)	0·7
C(5)–O(1)–P	122·8(3)	126·3(2)	9·7
C(6)–C(5)–O(1)	123·7(3)	123·6(3)	0·2
C(6)–C(7)–C(8)	121·9(4)	121·4(3)	1·0
C(7)–C(8)–C(9)	117·4(3)	117·5(3)	0·2
C(10)–C(11)–N(12)	116·6(3)	112·5(3)	9·6
C(11)–N(12)–C(13)	111·3(3)	109·7(3)	3·7
C(11)–N(12)–C(14)	110·8(3)	112·7(3)	4·4
C(13)–N(12)–C(14)	109·3(3)	111·4(3)	4·9
O(1)–P–O(2)	108·1(1)	110·8(1)	19·0
O(1)–P–O(3)	109·0(1)	103·8(1)	36·7
O(1)–P–O(4)	99·2(1)	102·3(1)	21·9
O(2)–P–O(3)	117·2(1)	116·9(1)	2·1
O(2)–P–O(4)	110·7(1)	110·3(1)	2·8
O(3)–P–O(4)	111·1(1)	111·5(1)	2·8

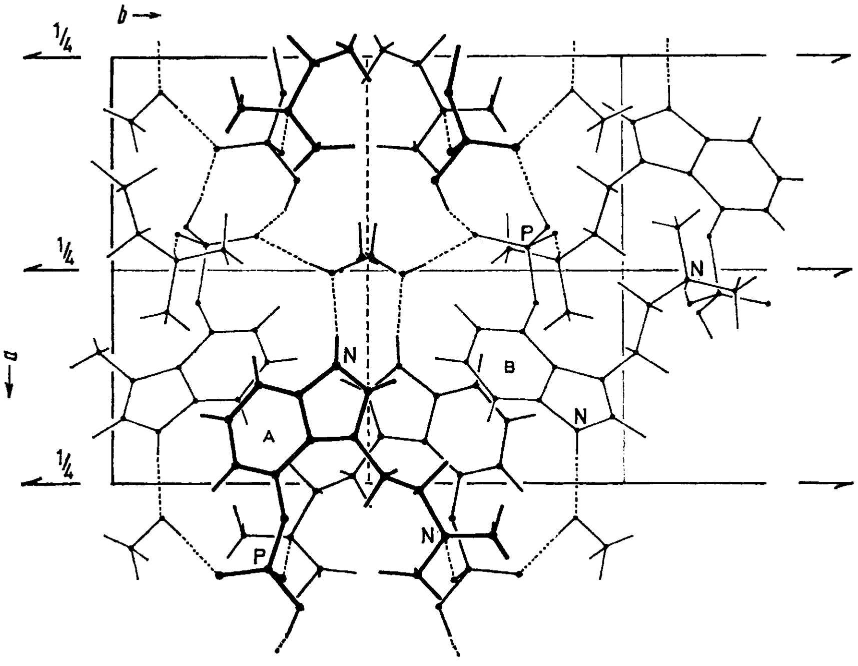

Figure 7 Packing of the structure, viewed down the *c* axis. The glide symbol, shown dashed, should be dotted

TABLE 5

Hydrogen bond donor–acceptor relationships, distances (pm) and angles (deg.)

Donor	Acceptor	d_{DH}	d_{HA}	d_{DA}	D–H · · · A
O(4 *)–H^{II}	O(2^{I})	96	159	253	166
O(Mel)–H^{II}	O(2^{I})	87	194	281	178
N(12)–H^{III}	O(3^{I})	94	170	262	165
O(4)–H^{IV}	O(2 $*^{I}$)	82	175	257	175
O(Me2)–H^{I}	O(2 $*^{I}$)	80	195	275	174
N(12 *)–H^{V}	O(3 $*^{I}$)	86	177	262	172
N(1)–H^{I}	O(Me2^{III})	88	204	290	167
N(1 *)–H^{I}	O(Mel^{VI})	85	200	284	169

I x, y, z
II $x + 1, \frac{1}{2} - y, \frac{1}{2} + z$
III $x, \frac{1}{2} - y, z - \frac{1}{2}$
IV $x - 1, \frac{1}{2} - y, z - \frac{1}{2}$
V $1 - x, 1 - y, 1 - z$
VI $x + 1, y, z$

O(3*). The methanols of solvation are then hydrogen-bonded to O(2) and O(2*), the phosphate oxygens which are already acceptors of one hydrogen bond, and finally N(1) the indole nitrogen, is hydrogen-bonded to that methanol which donates to O(2*) in molecule B and *vice versa*. The result is endless alternate sheets of A and of B molecules, normal to the *b* axis, which are cross-linked through the methanol of solvation. A view of the molecular packing is shown in Figure 7. Examination of the other intermolecular distances reveals no unusual contacts.

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