Asymmetric Resolution and Molecular Recognition. Part 2.† The *X*-Ray Crystal Structures of Ephedrine–*N*-Benzyloxycarbonyl-L-leucine and Ephedrine–*N*-Acetyl-L-valine‡

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The crystal structures of ephedrine–*N*-benzyloxycarbonyl-L-leucine (**1**) ($P2_12_12_1$, a = 14.067, b = 29.982, c = 5.737 Å) and ephedrine–*N*-acetyl-L-valine monohydrate (**2**) ($P2_12_12_1$, a = 13.501, b = 19.173, c = 7.694 Å) are reported and the conformations of the ephedrine moieties are compared with those in other structures. Charge–charge interactions, hydrogen bonding, and specific phenyl–phenyl interactions play a part in these stereospecific crystallisations.

(−)-Ephedrine is an alkaloid produced by plants of the *Ephedra* family which have been used for over 5 000 years as a treatment for bronchial asthma, hay fever, and other allergies.[1] The naturally occurring compound has the *S*-configuration at the α-carbon [C(2)] and the *R*-configuration at the β-carbon [C(1)], and is about 40 times more biologically active than the other isomers. As an optically active organic base, it has been widely used as a chemical resolving agent,[2,3] and is frequently able preferentially to co-crystallise with one component of a racemic acid solution. In one study,[4] D(−)-ephedrine was used to complex with and resolve a series of *N*-benzyloxycarbonyl (*N*-Cbz) derivatives of β-methyl-D-aspartate, D-leucine, D-methionine, L-phenylaline, L-valine, and L-isoleucine. Our previous crystallographic studies[5,6] of Pasteur's method to resolve amino acids using strychnine and brucine suggested that the distinctive sheet-like packing arrangement of the cation to form inclusion compounds may be the driving force for the resolution. Such a mechanism seemed less likely for the smaller ephedrine molcule. This study of ephedrine–peptide complexes was undertaken to examine the similarities in co-crystal complex formation in an effort to provide some information about the recognition of chiral molecules.

Ephedrine is structurally related to adrenaline and noradrenaline,[1] the principal neurotransmitters in the adrenergic nervous system. It acts as an indirect adrenergic agent and stimulates the nervous system by enhancing release of noradrenaline. There may also be some direct stimulation of the adrenergic receptors by direct binding with ephedrine. The molecular nature of these protein receptors is not known; the crystal structures presented here, however, provide good models for some of the specific interactions to be expected between the drug and a protein surface.

Experimental

Data sets for compounds (**1**) and (**2**) were collected with a Stoe Stadi-2 diffractomer using graphite-monochromated radiation. Experimental data are summarised in Table 1.

Ephedrine–N-*Benzyloxycarbonyl*-L-*leucine* (**1**).—Lamellar plates were grown from a saturated solution of an equimolar mixture of ephedrine and *N*-benzyloxycarbonyl-L-leucine in 1 : 4 water–ethanol. The very thin (0.02 mm) crystals gave poor diffraction at higher angles. An initial data set collected to θ = 20° did not solve the structure. Data were re-collected; there were sufficient measured to θ = 25° to enable a straightforward solution by direct methods (SHELX 84[6]). All non-hydrogen atoms were refined anisotropically. Most hydrogen atoms were included in calculated positions and allowed to 'ride' on their carbon atoms with a fixed C–H bond length of 1.08 Å. Twelve hydrogen atoms which were easily distinguished from difference Fourier maps were included in the refinement with variable positional parameters. All hydrogen atoms were given a fixed temperature factor (U = 0.09 Å^2).

Crystal data: $C_{10}H_{16}NO^+ \cdot C_{14}H_{18}NO_4^-$, M = 430.5, space group $P2_12_12_1$, a = 14.067(5), b = 29.982(16), c = 5.737(3) Å, U = 2 419.7 Å^3, Z = 4, D_c = 1.182 g cm^{-3}, Mo-K_α radiation, λ = 0.710 69 Å, μ = 0.8 cm^{-1}, F(000) = 928, T = 20 °C.

Table 1. Experimental data

	(1)	(2)
Crystal dimensions (mm)	0.5 × 0.13 × 0.02	0.6 × 0.3 × 0.1
Maximum θ	25	20
hkl range *h*:	0 to 16	0 to 12
k:	0 to 34	0 to 18
l:	0 to 5	0 to 7
Total data measured	2 321	1 078
Data used in refinement, $I > 2\sigma(I)$	955	923
Parameters	322	241
R	0.070	0.046
R'	0.035	0.053
S	3.05	1.08
Weighting scheme parameter	0.0005	0.0005
Max. Δ/σ, last cycle	0.30	0.5
Final difference map (e Å^{-3})		
max.	0.28	0.14
min.	−0.27	−0.19

Ephedrine–N-*Acetyl*-L-*valine* (**2**).—Crystals were formed as lamallar plates from a 4:1 water–ethanol solution of an equimolar mixture of ephedrine and *N*-acetylvaline. A crystal was selected and mounted in a sealed glass Lindemann tube to prevent loss of water of crystallisation. The structure was solved using direct methods.[8] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in their calculated positions with a fixed temperature factor (U = 0.07

† Part 1, ref. 5.

‡ *Supplementary data available* (SUP 56424, 3 pp.): anisotropic thermal parameters. For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, Issue 1, 1986. Structure factor tables are available from the editorial office on request.

Å^2). The hydroxy and water hydrogen atoms were located in difference Fourier maps and refined with a constrained O–H distance of 1.08 Å (SHELX 76 [8]).

Crystal data: $C_{10}H_{16}NO^+ \cdot C_7H_{12}NO_3^- - H_2O$, M = 342.4, space group $P2_12_12_1$, a = 13.501(5), b = 19.173(20), c = 7.694(6) Å, U = 1 991.7 Å^3, Z = 4, D_c = 1.142 g cm^{-3}, Mo-K_α radiation, λ = 0.710 69 Å. μ = 0.78 cm^{-1}, $F(000)$ = 744, T = 20 °C.

Results.—Fractional co-ordinates for structures (**1**) and (**2**) are given in Tables 2(a) and (b), respectively. Bond lengths and angles for ephedrine in both structures are given together in Table 3(a). Bond lengths and angles for *N*-Cbz-leucine and *N*-Ac-valine are given in Tables 3(b) and 3(c), respectively. Labelled drawings of ephedrine in structures (**1**) and (**2**) are given in Figures 1(a) and 2(a), respectively. Labelled drawings of *N*-Cbz-leucine and *N*-Ac-L-valine are given in Figures 1(b) and 2(b) respectively.

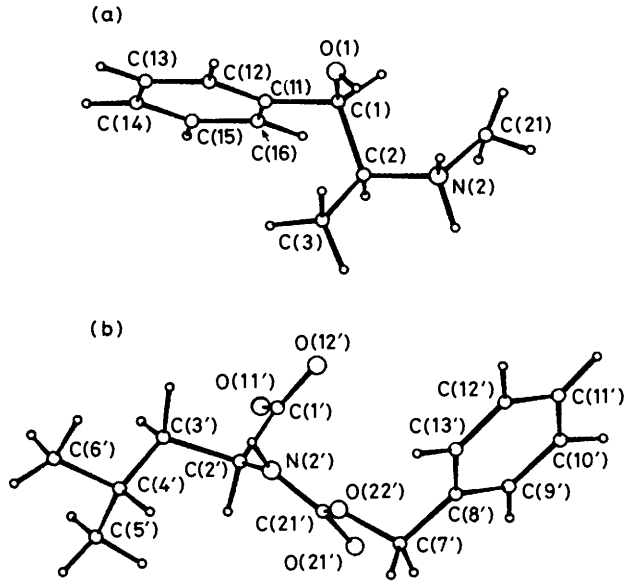

Figure 1. Labelled drawings of (a) the ephedrine ion in structure (**1**), (b) the *N*-Cbz-L-leucine ion in (**1**)

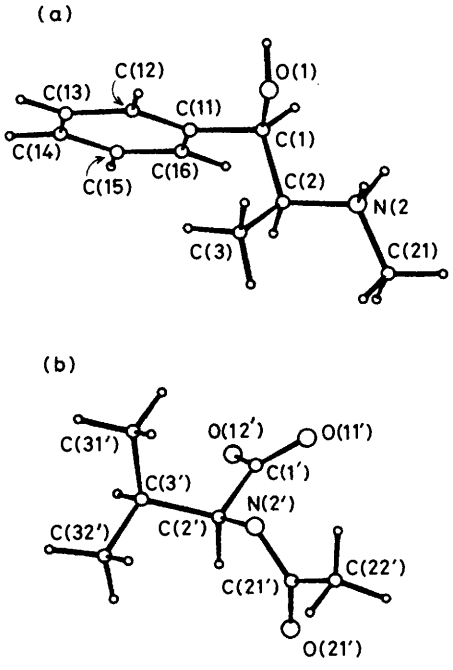

Figure 2. Labelled drawings of (a) the ephedrine ion in structure (**2**), (b) the *N*-acetyl-L-valine ion in (**2**)

Discussion

Weak diffraction from very thin crystals resulted in rather large C–C bond length e.s.d.s of 0.02 Å in (**1**) and 0.01 Å in (**2**);

Table 2. Fractional co-ordinates of atoms with standard deviations

(a) Compound (**1**)

	x	y	z	U_{eq}
C(9')	0.682 7(12)	0.303 5(5)	0.233(3)	0.0926
C(10')	0.596 1(14)	0.324 0(5)	0.269(3)	0.1105
C(11')	0.542 1(12)	0.315 9(5)	0.462(4)	0.0960
C(12')	0.578 5(12)	0.288 4(5)	0.625(3)	0.0909
C(13')	0.666 2(12)	0.269 4(4)	0.608(3)	0.0735
C(8')	0.721 2(10)	0.276 1(4)	0.409(3)	0.0659
C(7')	0.814 0(10)	0.253 8(6)	0.381(3)	0.0691
O(22')	0.799 0(5)	0.207 0(3)	0.315 9(14)	0.0652
C(21')	0.806 1(9)	0.193 9(5)	0.088 5(22)	0.0501
O(21')	0.834 6(6)	0.219 2(3)	−0.057 6(14)	0.0757
N(2')	0.777 1(6)	0.153 0(3)	0.073 6(14)	0.0459
C(2')	0.777 9(8)	0.127 9(4)	−0.142 8(18)	0.0502
C(3')	0.784 3(9)	0.076 3(5)	−0.079 0(23)	0.0639
C(4')	0.874 3(10)	0.063 8(4)	0.013(3)	0.0810
C(5')	0.948 4(9)	0.057 0(4)	−0.169(3)	0.1277
C(6')	0.870 4(9)	0.017 8(4)	0.129(3)	0.1275
C(1')	0.687 3(9)	0.134 2(4)	−0.291 4(20)	0.0497
O(11')	0.691 8(5)	0.119 78(24)	−0.494 8(11)	0.0583
O(12')	0.614 1(5)	0.149 05(25)	−0.195 0(11)	0.0590
N(2)	0.540 2(6)	0.147 9(3)	0.234 6(13)	0.0404
C(21)	0.519 7(11)	0.195 1(5)	0.267(3)	0.0713
C(2)	0.457 3(9)	0.117 0(5)	0.237 9(19)	0.0506
C(3)	0.492 7(7)	0.069 8(3)	0.203 1(23)	0.0636
C(1)	0.397 9(8)	0.124 4(4)	0.461 7(21)	0.0531
O(1)	0.448 2(6)	0.112 3(4)	0.658 8(16)	0.1093
C(12)	0.290 5(11)	0.061 6(5)	0.598 1(24)	0.0859
C(13)	0.207 7(12)	0.037 7(5)	0.581(3)	0.0924
C(14)	0.141 5(11)	0.047 0(6)	0.412(3)	0.0985
C(15)	0.158 4(10)	0.081 7(5)	0.271(3)	0.0884
C(16)	0.242 5(10)	0.106 8(4)	0.287(3)	0.0804
C(11)	0.308 4(9)	0.096 2(5)	0.451 0(24)	0.0572
H(9')	0.721 3(12)	0.308 4(5)	0.073(3)	0.0900
H(10')	0.570 2(14)	0.437 0(5)	0.139(3)	0.0900
H(11')	0.472 8(12)	0.330 9(5)	0.483(4)	0.0900
H(12')	0.535 7(12)	0.281 1(5)	0.776(3)	0.0900
H(13')	0.692 8(12)	0.249 0(4)	0.749(3)	0.0900
H(29')	0.751 2(6)	0.136 7(3)	0.229 1(14)	0.0900
H(4')	0.891 8(10)	0.090 1(4)	0.134(3)	0.0900
H(51')	0.959 8(9)	0.089 7(4)	−0.244(3)	0.0900
H(52')	0.924 7(9)	0.034 4(4)	−0.304(3)	0.0900
H(53')	1.014 1(9)	0.044 9(4)	−0.095(3)	0.0900
H(61')	0.812 2(9)	0.024 8(4)	0.246(3)	0.0900
H(62')	0.927 3(9)	0.001 9(4)	0.224(3)	0.0900
H(63')	0.846 2(9)	−0.004 1(4)	−0.009(3)	0.0900
H(2')	0.845(6)	0.130(3)	−0.230(16)	0.0900
H(31')	0.768(7)	0.057(3)	−0.249(17)	0.0900
H(32')	0.717(6)	0.069(3)	0.057(17)	0.0900
H(71')	0.861(7)	0.257(3)	0.523(19)	0.0900
H(72')	0.848(9)	0.264(4)	0.281(20)	0.0900
H(21)	0.575 7(6)	0.143 7(3)	0.069 1(13)	0.0900
H(22)	0.587 4(6)	0.137 9(3)	0.373 7(13)	0.0900
H(31)	0.527 3(7)	0.063 0(3)	0.367 3(23)	0.0900

Table 2 (*continued*)

(a) Compound (1)

	x	*y*	*z*	U_{eq}
H(32)	0.542 5(7)	0.064 8(3)	0.062 4(23)	0.0900
H(33)	0.433 0(7)	0.047 5(3)	0.181 4(23)	0.0900
H(12)	0.340 2(11)	0.053 2(5)	0.734 8(24)	0.0900
H(13)	0.194 3(12)	0.009 7(5)	0.695(3)	0.0900
H(14)	0.076 8(11)	0.028 0(6)	0.394(3)	0.0900
H(15)	0.106 5(10)	0.090 7(5)	0.141(3)	0.0900
H(16)	0.255 9(10)	0.134 4(4)	0.171(3)	0.0900
H(1)	0.382(6)	0.165(3)	0.457(18)	0.0900
H(2)	0.421(7)	0.126(4)	0.101(16)	0.0900
H(19)	0.503(7)	0.109(4)	0.648(23)	0.0900
H(211)	0.570(6)	0.213(3)	0.213(21)	0.0900
H(212)	0.471(6)	0.200(3)	0.112(18)	0.0900
H(213)	0.528(8)	0.211(4)	0.405(20)	0.0900

(b) Compound (2)

C(1)	0.425 5(5)	0.504 1(4)	0.782 5(8)	0.0542
C(11)	0.512 2(5)	0.587 3(4)	0.663 1(8)	0.0509
C(16)	0.533 0(6)	0.586 8(4)	0.616 5(10)	0.0660
C(15)	0.611 2(7)	0.601 8(5)	0.507 4(11)	0.0816
C(14)	0.671 2(6)	0.548 8(6)	0.447 7(11)	0.0811
C(13)	0.653 7(7)	0.480 0(5)	0.491 5(11)	0.0772
C(12)	0.572 0(6)	0.463 8(4)	0.599 7(10)	0.0643
O(1)	0.391 6(4)	0.433 59(25)	0.781 3(6)	0.0625
C(2)	0.454 4(5)	0.522 4(4)	0.090 7(8)	0.0557
N(2)	0.364 7(4)	0.522 17(25)	1.083 5(6)	0.0498
C(21)	0.377 5(6)	0.562 8(4)	1.251 0(10)	0.0739
C(3)	0.533 4(6)	0.473 7(5)	1.045 5(11)	0.0831
C(1′)	0.294 0(5)	0.373 9(3)	0.033 05(11)	0.0504
O(11′)	0.304 2(5)	0.395 38(22)	0.178 4(7)	0.0849
O(12′)	0.300 5(3)	0.410 81(21)	0.464 6(6)	0.0621
C(2′)	0.270 4(5)	0.296 4(3)	0.352 6(8)	0.0442
N(2′)	0.258 5(4)	0.263 29(24)	0.185 3(7)	0.0455
C(21′)	0.169 9(6)	0.245 6(4)	0.123 6(9)	0.0557
O(21′)	0.093 3(4)	0.248 0(3)	0.211 5(7)	0.0929
C(22′)	0.164 6(6)	0.222 7(4)	−0.063 2(9)	0.0664
C(3′)	0.346 3(6)	0.260 1(4)	0.468 5(9)	0.0657
C(31′)	0.450 9(6)	0.264 3(5)	0.391 4(11)	0.0926
C(32)′	0.313 8(8)	0.184 7(4)	0.502 6(12)	0.1142
O(1w)	0.090 4(4)	0.710 6(3)	0.415 8(7)	0.0671
H(1)	0.366 (5)	0.536 5(4)	0.734 5(8)	0.0700
H(16)	0.487 4(6)	0.628 5(4)	0.666 7(10)	0.0700
H(15)	0.625 2(7)	0.655 1(5)	0.468 8(11)	0.0700
H(14)	0.733 4(6)	0.561 4(6)	0.365 0(11)	0.0700
H(13)	0.701 6(7)	0.439 1(5)	0.444 0(11)	0.0700
H(12)	0.555 8(6)	0.410 3(4)	0.632 8(10)	0.0700
H(19)	0.360(5)	0.418(4)	0.682(9)	0.0700
H(2)	0.486 2(5)	0.574 1(4)	0.968 6(8)	0.0700
H(21)	0.304 1(4)	0.544 84(25)	1.011 4(6)	0.0700
H(22)	0.347 2(4)	0.468 75(25)	1.115 7(6)	0.0700
H(211)	0.310 1(6)	0.566 2(4)	1.326 0(10)	0.0700
H(212)	0.408 0(6)	0.614 4(4)	1.233 4(10)	0.0700
H(213)	0.430 5(6)	0.530 6(4)	1.318 9(10)	0.0700
H(31)	0.592 6(6)	0.480 2(5)	0.952 6(11)	0.0700
H(32)	0.509 0(6)	0.420 0(5)	1.045 0(11)	0.0700
H(33)	0.559 7(6)	0.487 3(5)	1.173 7(11)	0.0700
H(2′)	0.200 2(5)	0.291 7(3)	0.418 9(8)	0.0700
H(21′)	0.233 7(6)	0.233 2(4)	−0.128 9(9)	0.0700
H(22′)	0.104 6(6)	0.246 8(4)	−0.133 8(9)	0.0700
H(23′)	0.152 7(6)	0.167 0(4)	−0.057 2(9)	0.0700
H(3′)	0.349 9(6)	0.286 7(4)	0.592 0(9)	0.0700
H(31′)	0.501 5(6)	0.243 1(5)	0.486 6(11)	0.0700
H(33′)	0.471 1(6)	0.317 6(5)	0.363 0(11)	0.0700
H(35′)	0.454 8(6)	0.233 6(5)	0.273 8(11)	0.0700
H(32′)	0.240 0(8)	0.189 3(4)	0.555 4(12)	0.0700
H(34′)	0.359 6(8)	0.155 4(4)	0.591 5(12)	0.0700
H(36′)	0.310 6(8)	0.158 1(4)	0.379 1(12)	0.0700
H(1w)	0.126(6)	0.720(4)	0.447(11)	0.0700
H(2w)	0.026(5)	0.718(3)	0.394(9)	0.0700

Table 3. Bond lengths (Å), angles (°), and selected torsion angles (*a*) for ephedrine in structures (1) and (2)

	(1)	(2)	Database
N(2)–C(21)	1.458(17)	1.516(9)	1.490(15)
N(2)–C(2)	1.490(15)	1.490(8)	1.508(12)
C(2)–C(3)	1.513(17)	1.530(11)	1.521(8)
C(2)–C(1)	1.549(17)	1.540(10)	1.536(9)
C(1)–O(1)	1.381(16)	1.427(18)	1.423(12)
C(1)–C(11)	1.516(18)	1.509(10)	1.519(9)
C(12)–C(13)	1.373(21)	1.417(12)	1.394(8)
C(12)–C(11)	1.360(20)	1.394(11)	1.382(6)
C(13)–C(14)	1.373(23)	1.380(14)	1.373(10)
C(14)–C(15)	1.338(23)	1.381(13)	1.380(15)
C(15)–C(16)	1.405(21)	1.380(12)	1.393(7)
C(16)–C(11)	1.358(19)	1.407(11)	1.389(6)

	(1)	(2)	Database
C(21)–N(2)–C(2)	116.6(9)	113.6(5)	114.7(13)
N(2)–C(2)–C(3)	108.9(9)	110.2(6)	109.9(5)
N(2)–C(2)–C(1)	110.1(9)	110.0(5)	107.5(9)
C(3)–C(2)–C(1)	114.9(10)	113.0(6)	113.5(10)
C(2)–C(1)–O(1)	111.4(10)	107.7(5)	108.0(20)
C(2)–C(1)–C(11)	109.5(10)	109.7(5)	110.9(4)
O(1)–C(1)–C(11)	108.2(10)	113.9(5)	112.1(19)
C(13)–C(12)–C(11)	120.8(14)	119.7(7)	120.6(7)
C(12)–C(13)–C(14)	121.2(15)	119.1(8)	119.9(7)
C(13)–C(14)–C(15)	117.7(16)	121.5(9)	120.4(7)
C(14)–C(15)–C(16)	121.8(14)	119.9(8)	119.6(8)
C(15)–C(16)–C(11)	119.7(13)	120.4(7)	120.6(5)
C(1)–C(11)–C(12)	123.6(12)	122.5(6)	121.9(9)
C(1)–C(11)–C(16)	117.7(12)	118.0(6)	119.1(9)
C(12)–C(11)–C(16)	118.7(13)	119.5(7)	118.9(4)

	(1)	(2)
C(21)–N(2)–C(2)–C(3)	−179.7(10)	74.9(7)
C(21)–N(2)–C(2)–C(1)	−53.0(13)	−159.9(5)
N(2)–C(2)–C(1)–O(1)	−66.2(12)	−66.0(6)
N(2)–C(2)–C(1)–C(11)	174.1(9)	169.5(5)
C(3)–C(2)–C(1)–O(1)	57.1(14)	57.5(7)
C(3)–C(2)–C(1)–C(11)	−62.6(13)	−66.9(7)
C(2)–C(1)–C(11)–C(16)	−66.9(15)	−77.1(8)
O(1)–C(1)–C(11)–C(12)	−7.5(18)	−18.4(9)
O(1)–C(1)–C(11)–C(16)	171.4(12)	162.1(6)

(*b*) For *N*-Cbz-leucine in (1)

C(9′)–C(10′)	1.379(25)	C(21′)–N(2′)	1.297(16)
C(9′)–C(8′)	1.410(22)	N(2′)–C(2′)	1.451(15)
C(10′)–C(11′)	1.36(3)	C(2′)–C(3′)	1.593(18)
C(11′)–C(12′)	1.35(3)	C(2′)–C(1′)	1.545(17)
C(12′)–C(13′)	1.362(23)	C(3′)–C(4′)	1.422(19)
C(13′)–C(8′)	1.392(22)	C(4′)–C(5′)	1.490(20)
C(8′)–C(7′)	1.475(21)	C(4′)–C(6′)	1.531(21)
C(7′)–O(22′)	1.467(17)	C(1′)–O(11′)	1.246(14)
O(22′)–C(21′)	1.366(15)	C(1′)–O(12′)	1.251(14)
C(21′)–O(21′)	1.198(16)		

C(10′)–C(9′)–C(8′)	119.5(15)	O(21′)–C(21′)–N(2′)	131.1(12)
C(9′)–C(10′)–C(11′)	122.2(17)	C(21′)–N(2′)–C(2′)	123.0(10)
C(10′)–C(11′)–C(12′)	117.4(17)	N(2′)–C(2′)–C(3′)	107.9(9)
C(11′)–C(12′)–C(13′)	123.4(16)	N(2′)–C(2′)–C(1′)	113.7(9)
C(12′)–C(13′)–C(8′)	120.1(15)	C(3′)–C(2′)–C(1′)	106.9(10)
C(9′)–C(8′)–C(13′)	117.2(14)	C(2′)–C(3′)–C(4′)	113.0(11)
C(9′)–C(8′)–C(7′)	121.7(14)	C(3′)–C(4′)–C(5′)	113.5(12)
C(13′)–C(8′)–C(7′)	121.0(14)	C(3′)–C(4′)–C(6′)	111.5(12)
C(8′)–C(7′)–O(22′)	109.5(12)	C(5′)–C(4′)–C(6′)	102.0(11)
C(7′)–O(22′)–C(21′)	120.6(10)	C(2′)–C(1′)–O(11′)	115.6(10)
O(22′)–C(21′)–O(21′)	120.7(12)	C(2′)–C(1′)–O(12′)	118.6(10)
O(22′)–C(21′)–N(2′)	108.2(10)	O(11′)–C(1′)–O(12′)	125.4(10)

Table 3 (*continued*)

(*b*) For *N*-Cbz-leucine in (**1**)

C(9′)–C(8′)–C(7′)–O(22′)	−100.3(16)
C(13′)–C(8′)–C(7′)–O(22′)	77.2(17)
C(8′)–C(7′)–O(22′)–C(21′)	99.1(14)
C(7′)–O(22′)–C(21′)–O(21′)	8.2(18)
C(7′)–O(22′)–C(21′)–N(2′)	−171.4(10)
O(22′)–C(21′)–N(2′)–C(2′)	−178.0(9)
O(21′)–C(21′)–N(2′)–C(2′)	2.5(21)
C(21′)–N(2′)–C(2′)–C(3′)	154.5(11)
C(21′)–N(2′)–C(2′)–C(1′)	−87.0(13)
N(2′)–C(2′)–C(3′)–C(4′)	−70.4(13)
C(1′)–C(2′)–C(3′)–C(4′)	166.9(11)
N(2′)–C(2′)–C(1′)–O(11′)	167.9(9)
N(2′)–C(2′)–C(1′)–O(12′)	−18.7(15)
C(3′)–C(2′)–C(1′)–O(11′)	−73.1(12)
C(3′)–C(2′)–C(1′)–O(12′)	100.3(12)
C(2′)–C(3′)–C(4′)–C(5′)	−80.0(14)
C(2′)–C(3′)–C(4′)–C(6′)	165.5(11)

(*c*) For *N*-acetylvaline in (**2**)

C(1′)–O(11′)	1.249(9)	N(2′)–C(21′)	1.331(9)
C(1′)–O(12′)	1.254(8)	C(21′)–O(21′)	1.237(10)
C(1′)–C(2′)	1.528(10)	C(21′)–C(22′)	1.505(10)
C(2′)–N(2′)	1.444(8)	C(3′)–C(31′)	1.534(11)
C(2′)–C(3′)	1.527(10)	C(3′)–C(32′)	1.533(12)

O(11′)–C(1′)–O(12′)	125.3(7)	N(2′)–C(21′)–O(21′)	123.2(7)
O(11′)–C(1′)–C(2′)	116.6(6)	N(2′)–C(21′)–C(22′)	117.2(6)
O(12′)–C(1′)–C(2′)	118.1(6)	O(21′)–C(21′)–C(22′)	119.6(7)
C(1′)–C(2′)–N(2′)	110.6(5)	C(2′)–C(3′)–C(31′)	111.6(6)
C(1′)–C(2′)–C(3′)	111.7(5)	C(2′)–C(3′)–C(32′)	109.8(6)
N(2′)–C(2′)–C(3′)	113.2(5)	C(31′)–C(3′)–C(32′)	112.3(7)
C(2′)–N(2′)–C(21′)	122.0(5)		

O(11′)–C(1′)–C(2′)–N(2′)	−3.5(8)
O(11′)–C(1′)–C(2′)–C(3′)	123.5(7)
O(12′)–C(1′)–C(2′)–N(2′)	175.8(6)
O(12′)–C(1′)–C(2′)–C(3′)	−57.2(8)
C(1′)–C(2′)–N(2′)–C(21′)	−105.2(7)
C(3′)–C(2′)–N(2′)–C(21′)	128.6(7)
C(1′)–C(2′)–C(3′)–C(31′)	−60.8(8)
C(1′)–C(2′)–C(3′)–C(32′)	174.0(6)
N(2′)–C(2′)–C(3′)–C(31′)	64.8(7)
N(2′)–C(2′)–C(3′)–C(32′)	−60.4(8)
C(2′)–N(2′)–C(21′)–O(21′)	−9.3(11)
C(2′)–N(2′)–C(21′)–C(22′)	169.9(6)

however, the importance of the structures rests on molecular shape and packing interactions.

Geometry of Ephedrine.—A search of the Cambridge Crystallographic Database [9] revealed 18 related structures. Of the 11 structures with the *R*-configuration at C(1) and *S*-configuration at C(2), only 5 had an *R* factor less than 0.09 and had sufficiently accurate parameters for comparison purposes. These were (−)-ephedrine dihydrogen phosphate,[10] (−)-ephedrine hydrochloride,[11] ephedrine monohydrogen phosphate (two independent molecules),[12] and *p*-hydroxyephedrine hydrochloride.[13] Average values of bond lengths and angles for the five structures are given in Table 3(a). All bond lengths are in the expected ranges with the C–N^+ bonds close to the expected value of 1.50 Å. Bond angles at sp^3 carbon atoms C(1) and C(2) are close to tetrahedral. There is a small but consistent widening of the C(1)–C(11)–C(12) angle by about 2° (to 122°) caused by steric repulsion of the hydroxy group at O(1) lying approximately *cis* to C(12). The C(21)–N(2)–C(2) angle is rather wide (115°). Molecular shape can be quite well

Table 4. Torsion angles for related ephedrine structures

	Reference	τ	ω	χ
Structure (**1**)	This work	−7.5	−66.2	−53.0
Structure (**2**)	This work	−18.5	−66.0	−159.9
Ephedrine dihydrogen phosphate	9	−21.4	−73.6	177.3
Ephedrine hydrochloride	10	−21.4	−70.6	−170
Ephedrine monohydrogen phosphate (**1**)	11	−35.8	−57.3	−168.5
(**2**)	11	−11.5	−68.9	−169.0
p-Hydroxyephedrine hydrochloride	12	−18.9	−59.7	−157.7

defined by three torsion angles:[12] τ [C(12)–C(11)–C(1)–O(1)], ω [O(1)–C(1)–C(2)–N(2)], and χ [C(1)–C(2)–N(2)–C(21)], which are tabulated for all related structures in Table 4. The range in τ is −8 to −36° and the angle shows an average twist of −19° to relieve steric strain between the hydroxy and phenyl groups. The torsion angle ω lies in the range −60 to −74° which places the amino group *gauche* with respect to the hydroxy group. This has important consequences concerning the possible formation of intermolecular hydrogen bonds. Structure (**1**) is unique in having the terminal methyl C(21) *gauche* to C(11) rather than *trans* as found in all other structures.

Geometry of N-*Cbz*-L-*Leucine and* N-*Ac*-L-*Valine.*—Comparison of data for the two amino acids with average values obtained from a comprehensive literature survey[14] shows that most bond lengths and angles lie within the expected ranges. The narrow C(5′)–C(4′)–C(6′) angle of 102° and the long C(2′)–C(3′) bond length of 1.59 Å in *N*-Cbz-leucine is a likely result of refinement using very weak data. Conformation about the amide bond is described by the torsion angle ω which in structure (**1**) is O(22′)–C(21′)–N(2′)–C(2′) = −178° and in (**2**) is C(22′)–C(21′)–N(2′)–C(2′) = 169.9°. This second value shows significant twisting out of the expected antiperiplanar (ω = 180°) conformation. The peptide side-chain conformation in (**1**) can be described by three torsion angles: χ^1 [N(2′)–C(2′)–C(3′)–C(4′) = −70.4°], χ^{21} [C(2′)–C(3′)–C(4)–C(5′) = −80.0°], and χ^{22} [C(2′)–C(3′)–C(4′)–C(6′) = 165.5°]. From a survey of 40 crystal structures containing a leucine side chain,[15] it was found that the most favoured idealised staggered conformation showed $\chi^1 = -60°$, $\chi^{21} = -60$, $\chi^{22} = 180$.

Corresponding χ^{11} and χ^{12} values for the valine side chain in structure (**2**) are [N(2′)–C(2′)–C(3′)–C(31′)] 64.5° and [N(2′)–C(2′)–C(3)–C(32′)] −60.4°. A survey of the crystallographic database shows that 8 out of a total of 26 valine structures adopt this conformation. A slightly more favoured conformation, adopted by 11 structures, has $\chi^{11} = -60°$ and $\chi^{12} = 180°$.

*Molecular Interactions in Ephedrine–*N-*Cbz-Leucine* (**1**).—(i) *Hydrogen bonding.* Hydrogen bond lengths are given in Table 5(a) and are shown as dotted lines in Figures 3 and 4(a). The peptide molecules stack up the short 5.7 Å *c*-axis and form a hydrogen-bonded column with the amide nitrogen N(2′) acting as a donor to the carboxy oxygen O(11′) of the molecule at $Z + 1$. The remaining three hydrogen bonds are between ephedrine and the carboxy group of Cbz-leucine. The hydroxy group at O(1) and the protonated nitrogen N(2) form hydrogen bonds with O(12′) and O(11′) of the same carboxy group. N(2) also acts as a hydrogen bond donor to O(12′) in an adjacent unit cell along the *c*-axis. The columns of ephedrine–peptide dimers [Figure 4(a)] do not form any inter-column hydrogen bonds.

(ii) *Van der Waals interactions.* It is interesting that most of

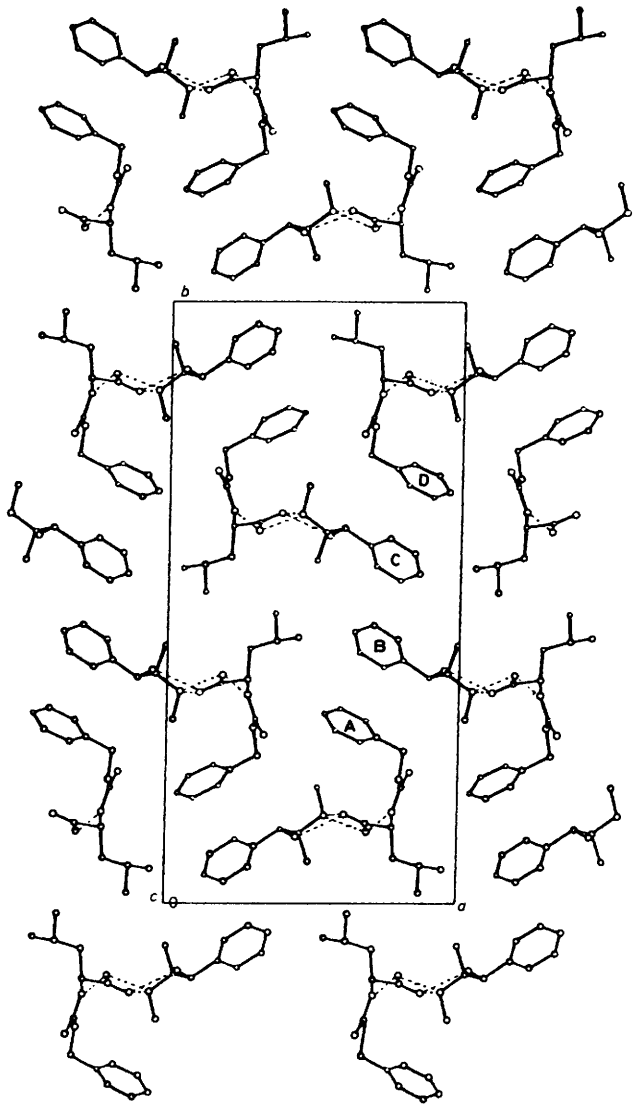

Figure 3. Packing diagram of structure (**1**) viewed down the *c*-axis; hydrogen bonds are shown as dashed lines

the shorter non-bonded contacts [Table 5(a)] are between ephedrine and Cbz-leucine, and are not ephedrine–ephedrine or peptide–peptide contacts. All short ephedrine–peptide contacts are shown in Figure 4(b). The three shortest C - - C interactions are methyl - - - benzene ring contacts with C - - - C distances as low as 3.57 Å and corresponding C(benzene) - - - H(methyl) distances as short as 2.73 Å. A similar benzene–methyl interaction, where the methyl group lies directly over the face of an aromatic group, has also been observed in the crystal structure of a complex of brucine and *N*-benzoyl-D-alanine.[5] In that case a methoxy methyl group was involved and it may be that a methyl group attached to a more electronegative N or O atom gives the methyl hydrogen atom a small positive charge, sufficient to interact with the π-cloud of the benzene group.

On striking feature of the packing diagram (Figure 3) is the pattern of benzene groups (labelled A, B, C, D). In a survey of 28 phenylalanine crystal structures, it has been observed that interacting benzene groups tend to lie steeply inclined to each other with a mean interplanar angle of 74°.[15] The interplanar angles and shortest contacts for the benzene groups in this

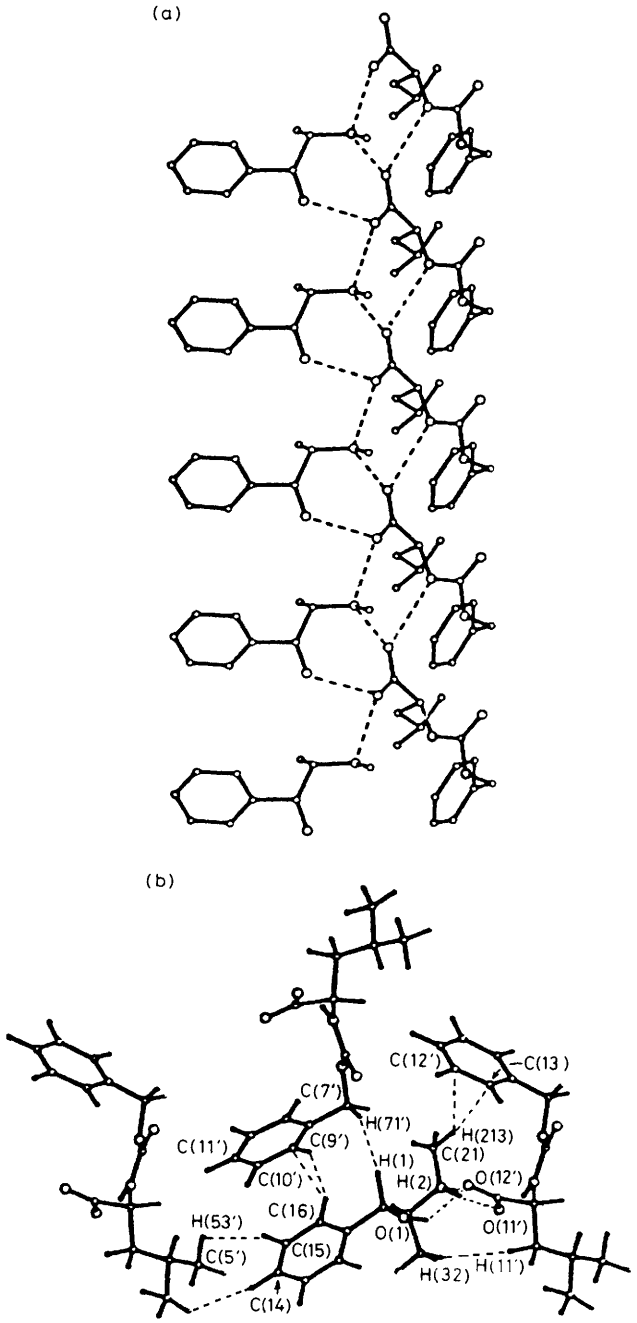

Figure 4. (a) The hydrogen bonding scheme in structure (**1**) with the ion pairs viewed perpendicular to the *c* axis. (b) A portion of the unit cell contents of structure (**1**) showing hydrogen atoms and viewed along the *c*-axis; significant intermolecular ephedrine - - - peptide contacts are shown as dashed lines

structure are: A–B interplanar angle 15° and shortest ring–ring contacts [C(9′) - - H(16)] 3.15 Å and [H(9′) - - H(16)] 2.26; B–C interplanar angle between the screw-related benzene groups of ephedrine 79.8° with shortest contacts [C(13) - - - H(13)] 2.97Å, [H(12) - - - H(14)] 2.85 Å; the interaction between the B and C planes is close to the expected minimum-energy configuration.[15] The C–D interaction is identical with the A–B interaction which, with nearly parallel benzene rings and a short H - - H contact, does not fit the expected arrangement.

Table 5. Non-bonded and hydrogen-bonded contacts[a]

(a) Ephedrine–*N*-Cbz-leucine

(i) Hydrogen bonds

*N(2) – – – O(12′)	2.675	x,y,z
*N(2) – – – O(11′)	2.769	$x,y,1+z$
N(2′) – – – O(11′)	2.926	$x,y,1+z$
*O(1) – – – O(12′)	2.714	$x,y,1+z$
H(21) – – – O(12′)	1.617	x,y,z
H(22) – – – O(11′)	1.739	$x,y,1+z$
H(29) – – – O(11′)	1.861	$x,y,1+z$
H(19) – – – O(12′)	2.157	$x,y,1+z$

(ii) Van der Waals contacts

C – – – C ≤3.8 Å

C(12) – – – C(21)	3.568	x,y,z
C(13′) – – – C(21)	3.611	x,y,z
C(5′) – – – C(14)	3.639	$1+x,y,-1+z$
C(9′) – – – C(13′)	3.736	$x,y,-1+z$
C(11′) – – – C(15)	3.800	$\frac{1}{2}+x,\frac{1}{2}-y,1-z$

C – – – H ≤2.8 Å

[C(1′) – – – H(22)	2.383	$x,y,1-z$]
[C(1′) – – – H(21)	2.612	x,y,z]
[C(1′) – – – H(19)	2.714	$x,y,1-z$]
*C(12′) – – – H(213)	2.726	x,y,z
*C(7′) – – – H(1)	2.773	$\frac{1}{2}+x,\frac{1}{2}-y,1-z$

C – – – O ≤3.4 Å

C(21) – – – O(12′)	3.270	x,y,z
C(2) – – – O(1)	3.328	$x,y,-1+z$
C(7′) – – – O(21′)	3.394	$x,y,1+z$
C(13′) – – – O(21′)	3.400	$x,y,1+z$

H – – – H ≤2.5 Å

*H(9′) – – – H(16)	2.264	$\frac{1}{2}+x,\frac{1}{2}-y,-z$
*H(53′) – – – H(15)	2.326	$1+x,y,z$
*H(71′) – – – H(1)	2.345	$\frac{1}{2}+x,\frac{1}{2}-y,1+z$
*H(62′) – – – H(14)	2.448	$\frac{1}{2}+x,\frac{1}{2}-y,1-z$
[H(29′) – – – H(22)	2.450	x,y,z]
*H(32′) – – – H(32)	2.459	x,y,z
H(33) – – – H(13)	2.482	$\frac{1}{2}-x,-y,-\frac{1}{2}+z$

H – – – O ≤2.8 Å (excluding those involved in hydrogen bonding)

H(13′) – – – O(21′)	2.452	$x,y,1+z$
H(22) – – – O(12′)	2.525	$x,y,1+z$
H(2) – – – O(1)	2.599	$x,y,-1+z$
H(71′) – – – O(21′)	2.692	$x,y,1+z$
H(19) – – – O(11′)	2.791	$x,y,1+z$

(b) Ephedrine–*N*-Ac-valine

(i) Hydrogen bonds

N(2) – – – O(11′)	2.667	$x,y,1+z$
N(2) – – – O(12′)	2.732	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
N(2′) – – – O(1w)	2.951	$\frac{1}{2}-x,1-y,-\frac{1}{2}+z$
O(21′) – – – O(1w)	2.761	$-x,-\frac{1}{2}+y,\frac{1}{2}-z$
O(1) – – – O(12′)	2.764	x,y,z
O(1) – – – O(1w)	2.962	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
H(22) – – – O(11′)	1.597	$x,y,1+z$
H(21) – – – O(12′)	1.687	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
H(29) – – – O(11′)	1.815	$\frac{1}{2}-x,1-y,-\frac{1}{2}+z$
O(21′) – – – H(2w)	1.890	$\frac{1}{2}-x,-\frac{1}{2}+y,\frac{1}{2}-z$
H(19) – – – O(12′)	1.862	x,y,z
O(1) – – – H(1w)	1.805	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$

Table 5 (*continued*)

(b) Ephedrine–*N*-Ac-valine

(ii) Van der Walls contacts

C – – – C ≤3.8 Å

C(16) – – – C(21)	3.539	$x,y,1+z$
C(11) – – – C(12)	3.758	$x,y,-1+z$
C(1) – – – C(1′)	3.793	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
C(15) – – – C(21)	3.795	$x,y,-1+z$
C(13) – – – C(3)	3.799	$x,y,-1+z$

C – – – C ≤2.8 Å

[C(1′) – – – H(21)	2.473	$\frac{1}{2}-x,1-y,-\frac{1}{2}+z$]
[C(1′) – – – H(22)	2.560	$x,y,-1+z$]
C(21′) – – – H(2w)	2.697	$-x,-\frac{1}{2}+y,\frac{1}{2}-z$
C(13) – – – H(33)	2.759	$x,y,-1+z$

C – – – O ≤3.4 Å

C(21) – – – O(12′)	3.299	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
C(21) – – – O(11′)	3.406	$x,y,1+z$
C(7′) – – – O(21′)	3.394	$x,y,1+z$

H – – – H ≤2.5 Å

H(19) – – – H(1w)	2.130	$\frac{1}{2}+z,1-y,\frac{1}{2}+z$
H(32) – – – H(1w)	2.313	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
H(22) – – – H(35′)	2.322	$-\frac{1}{2}+x,\frac{1}{2}-y,-z$
[H(29′) – – – H(1w)	2.385	$\frac{1}{2}-x,-y,-\frac{1}{2}+z$]
[H(15) – – – H(29′)	2.426	$1-x,\frac{1}{2}+y,\frac{1}{2}-z$]

H – – – N 3.0 Å

H(15)–N(2′)	2.859	$1-x,\frac{1}{2}+y,\frac{1}{2}-z$

H – – – O 2.8 Å (excluding those involved in hydrogen bonding)

H(3′) – – – O(1w)	2.619	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
H(16) – – – O(21)	2.629	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
H(21) – – – O(1w)	2.630	$\frac{1}{2}+x,1-y,-\frac{1}{2}+z$
O(31′) – – – O(21′)	2.639	$\frac{1}{2}+x,\frac{1}{2}-y,1-z$
H(1) – – – O(11′)	2.679	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
[H(1w) – – – O(11′)	2.727	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$]
H(211) – – – O(1)	2.744	$\frac{1}{2}-x,1-y,\frac{1}{2}+z$
H(15) – – – O(1w)	2.764	$\frac{1}{2}+x,1\frac{1}{2}-y,1-z$

[a] Hydrogen bonds and non-bonded contacts are given in Å. The symmetry operator is applied to atom 2. Those contacts shown as dashed lines in Figure 4(b) are marked with an asterisk. Contacts in brackets indicate that atoms are in close proximity because they are bonded neighbours in a hydrogen-bonded interaction.

Molecular Interactions in Ephedrine–N-Acetylvaline (**2**).—(i) *Hydrogen bonding.* Hydrogen bond lengths are given in Table 5(b) and the bonds are shown in Figure 5. Six distinct hydrogen bonds are formed in this complex out of a total of six potential donor and nine hydrogen-bond acceptors. The three sites which are not utilised are second acceptor sites for the water of crystallisation, one of the carbonyl oxygen atoms, and the acetyl carbonyl group. As in (**1**), the strongest hydrogen-bond donor for N(2) forms salt bridges with the carboxy oxygen, but instead of dimer pairs, infinite hydrogen-bonded helices involving two ephedrine and two peptide molecules are formed round a screw axis parallel to *c*. The water of crystallisation acts as a bridge between O(2′) and N(2′) on different molecules and forms hydrogen-bonded sheets of peptide.

(ii) *Van der Waals interaction.* In contrast with structure (**1**), ephedrine–ephedrine contacts are generally shorter than ephedrine–peptide contacts. The shortest C – – – C and C – – – H contacts (3.54 and 2.57 Å, respectively) are

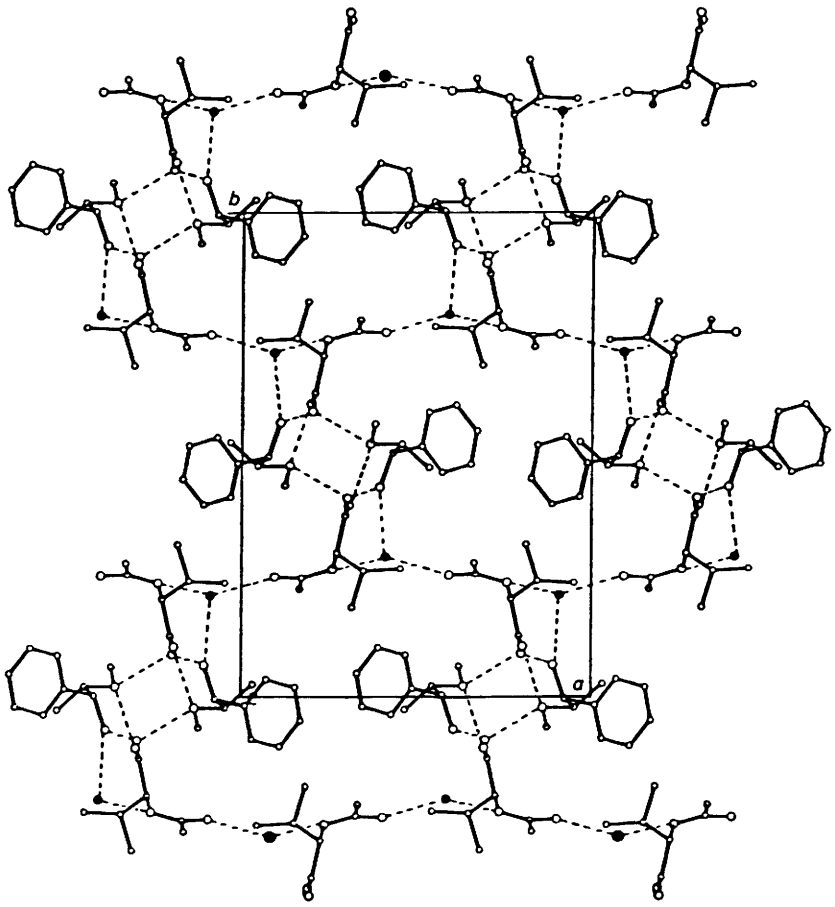

Figure 5. Packing diagram of structure (**2**) viewed down the *c*-axis; hydrogen bonds are shown as dashed lines

methyl - - - phenyl group interactions which result from ephedrine stacking up the short 7.7 Å axis. The shortest benzene contacts are H(14) - - - C(13) (3.34 Å) and H(14) - - - C(12) (3.36 Å), with an interplanar angle between the screw-related rings of 73°. Both contacts H(16) - - - O(21) (2.63 Å) and H(15) - - - O(1w) (2.76 Å) fit the observation that an aromatic group in a crystal tends to pack with oxygen atoms round the electron-deficient edge of the ring.[15]

Conclusions

The purpose of this study was to investigate the way in which ephedrine recognises and binds to peptides, either in its capacity as a resolving agent or as a drug. In the former case the recognition site is a peptide sheet on the face of a growing crystal; in the latter, ephedrine binds to a cleft in a receptor protein.

Our previous work on the resolution of D- and L-benzoylalanine with brucine and strychnine suggested a number of features which were important in selective co-crystallisation, namely (i) the formation of a salt bridge between protonated amine and carboxy group, (ii) specific hydrogen bonds normally involving water of crystallisation, (iii) specific interaction of aromatic and amide groups in which the π-clouds tend to interact with protons of phenyl or methyl groups, and (iv) packing effects to form laminar structures of alternating sheets of alkaloid and peptide.

This very different system, in which ephedrine has replaced the large and rigid brucine molecule as the organic base, still conserves a number of these features. Crystal structures of both (**1**) and (**2**) form the expected salt bridge between the protonated amine and the carboxy group. Ephedrine–peptide hydrogen bonds in structures (**1**) and (**2**) lead to different packing arrangements. With the smaller *N*-acetylvaline, a water molecule of crystallisation is incorporated to produce a network in which the six hydrogen bonds completely dominate the packing. In (**1**), the larger *N*-Cbz-leucine molecule is involved in more hydrophobic (van der Waals) interactions, though again all four hydrogen bond donors are involved in hydrogen bonds. The conserved ephedrine torsion angle N–C–C–O [$= -65°$ ($\pm 7°$)] allows the molecule to act as a bidentate hydrogen bond donor with O(H) and N(H) able to 'clip' onto a single carboxy group [as in (**1**)] or act as a hydrogen-bonding bridge between two separate molecules [as in (**2**)].

As in the brucine and strychnine complexes, interactions involving phenyl groups appear to be specific. Methyl groups sit with hydrogen atoms less than 2.8 Å above the electron-rich aromatic face. Interacting phenyl groups [with the exception of A and B in (**1**)] are steeply inclined at about 75°, again with a phenyl proton pointing into the neighbouring face.

It is reasonable to assume that the ephedrine–peptide interactions found in crystal structures of (**1**) and (**2**) play a part in the recognition and binding process of the drug–receptor interactions in biological systems.

Acknowledgements

We thank the S.E.R.C. for financial support.

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Received 1*st July* 1985; *Paper* 5/1104