

Crystal and molecular structure of a *N*(2)-benzyl-1,3-disubstituted-1,2,3,4-tetrahydro- β -carboline

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(1*R*,3*S*)-2-Benzyl-3-methoxycarbonyl-1-methylcarboxymethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, C₂₃H₂₄N₂O₄, was synthesized by a modified Pictet-Spengler reaction, and its crystal and molecular structure determined by single crystal X-ray diffraction methods. The crystals are monoclinic: P2₁ (No. 4), *a* = 11.336(1), *b* = 8.919(1), *c* = 10.314(1) Å, β = 100.81(1)°, *Z* = 2. The structure has been solved by direct methods, and refined to *R* = 0.041 for 2203 observed reflections. The six-membered heterocyclic ring is in a half-chair conformation, and the substituents at C(3) and C(5) occupy axial and equatorial positions respectively. The CH₂Ph group attached to N(4) is in the generally less favoured axial position. The nitrogen atom of the indole system forms an intermolecular hydrogen bond with the carbonyl oxygen of the CH₂CO₂ Me group, the N · · · O distance being 2.995(3) Å.

Introduction

The tetrahydro- β -carboline unit is central to an enormous range of indole alkaloids, and stereospecific syntheses of derivatives are widely sought. By using a recently developed modification of the Pictet-Spengler reaction (Vercauteren *et al.*, 1984), a new series of 1,3- and 1,1,3-trisubstituted 1,2,3,4-tetrahydro- β -carbolines were prepared (Bailey *et al.*, 1985; Bailey and Hollinshead, 1988); in an attempt to determine the stereochemistry of their products, they studied the ¹³C spectra in detail. Cook and coworkers (Sorens *et al.*, 1979) successfully used carbon-13 NMR spectroscopy for the assignment of stereochemistry to 1,3-disubstituted-1,2,3,4-tetrahydro- β -carbolines. The ¹³C NMR spectra of *trans* compounds (Fig. 1a) gave chemical shifts for

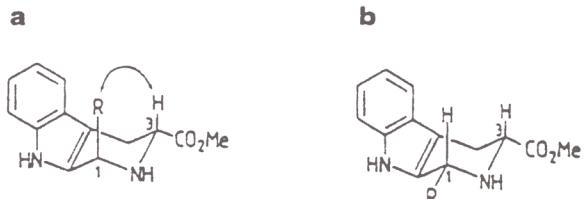


Fig. 1. Structural formulae showing (a) a *trans*- and (b) a *cis*-1,3-disubstituted-1,2,3,4-tetrahydro- β -carboline.

C-1 and C-3 that were consistently upfield from those of the corresponding *cis* isomers (Fig. 1b), due to 1,3-diaxial spatial crowding. Bailey *et al.*, (1985, 1988) found that, although ¹³C NMR spectroscopy could be used to confirm the presence of two diastereoisomers in all their purified products, the C-1 and C-3 chemical shifts failed to give unambiguous stereochemical assignments for some of their compounds. Crystal structure determinations were undertaken on two key derivatives, chemical modifications of which could be used to infer the stereochemistries of a set of 16 inter-related com-

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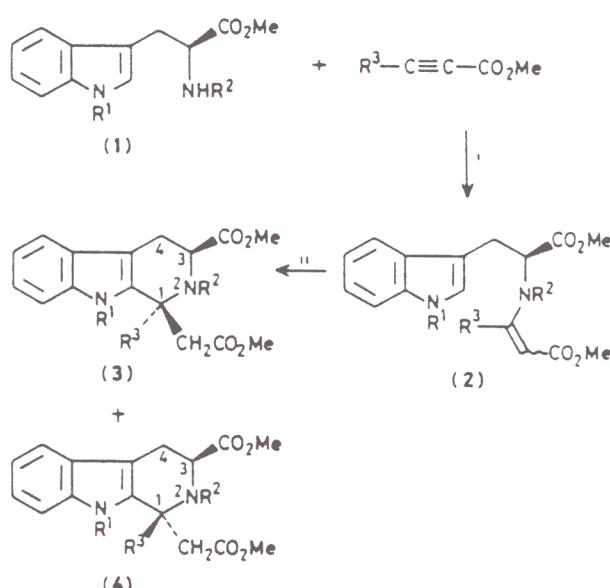
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pounds. We report here the structure of (*1R,3S*)-2-benzyl - 3 - methoxycarbonyl - 1 - methoxycarbonylmethyl - 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*] indole. A preliminary account of this structure has already been published (Bailey *et al.*, 1985).

Experimental

The compound was prepared (Fig. 2) as described previously (Bailey and Hollinshead, 1988). Crystals suitable for X-ray analysis were obtained by recrystallization from ethanol. Preliminary precession photographic studies gave approximate unit-cell data. The systematic absences ($0k0$, $k = 2n$) deduced from the photographs and the chirality of the molecule excluded all space groups other than $P2_1$. A specimen of 0.55, 0.60, 0.10 mm was selected for diffraction studies, and mounted approximately along b . Accurate unit-cell dimensions were determined by centring twenty-five reflections measured on a four-circle diffractometer and refining the orientation matrix.

Integrated intensities were measured on an Enraf-



R¹ = H or Me, R² = H or CH₂Ph, R³ = H or CO₂Me

Fig. 2. (*S*)-tryptophan methyl esters (1) react with conjugated alkynoates yielding 1,3-disubstituted or 1,1,3-trisubstituted tetrahydro-β-carbolines. Reagents: i, CHCl₃, room temp., 1-10 days (R³ = H) or 5-10 min. (R³ = CO₂Me); ii, TFA (2-4 mol equiv.), CHCl₃, room temp. 5-10 min.

Nonius CAD-4 computer controlled four-circle diffractometer, using the $\theta/2\theta$ scanning technique. Table 1 gives a summary of the crystal data, data collection and refinement conditions used.

The structure was solved by direct methods using the program MULTAN (1978), and refined by the full-matrix least-squares technique. All nonhydrogen atoms were located from an *E*-map. The positions of all hydrogen atoms, except some methyl hydrogens, were determined from successive Fourier differences syntheses. The hydrogen atoms were included in the structure-factor calculations with isotropic thermal parameters

Table 1. Crystal data, data collection, and refinement conditions

Formula	C ₂₃ H ₂₄ N ₂ O ₄
<i>M</i> , g	392.5
<i>a</i> /Å	11.336(1)
<i>b</i> /Å	8.919(1)
<i>c</i> /Å	10.314(1)
β /deg	100.81(1)
<i>V</i> /Å ³	1024.3(3)
Space group	<i>P</i> ₁ ² (No. 4)
Number of reflections to determine cell constants	25
<i>Z</i>	2
<i>D</i> , mg m ⁻³	1.273
$\bar{\lambda}$ /Å (Cu $K\alpha$)	1.54184
Filter	Ni
Linear absorption coefficient/mm ⁻¹	0.047
Crystal size/mm	0.55, 0.60, 0.10
Diffractometer	Enraf-Nonius CAD-4
Data collection method	$\theta/2\theta$
2θ limit/deg	3.0 – 154.0
Scan rate/deg min ⁻¹	3.0 to 30.0
Number of standard reflections	6
Variation in standard intensities	±2%
Number of unique reflections collected	2267
Number of unique reflections used in refinement	2203
Data: parameter ratio	8.44
Final $R \Sigma F_o - F_c /\Sigma F_o $	0.041
Final $R_w [\sum \omega (F_o - F_c)^2 / \sum \omega (F_o)]^{1/2}$	0.045
Final $S [\sum \omega (F_o - F_c)^2 / (n - p)]^{1/2}$	2.75
Final $(\Delta \rho)/e \text{ Å}^{-3}$	±0.15
Final $(\Delta \rho)_{\max}$	0.10
Function minimized	$\Sigma \omega (F_o - F_c)^2$
<i>T</i> /K	290
<i>F</i> (000)/e	416
<i>h</i> range	0 to 14
<i>k</i> range	0 to 11
<i>l</i> range	-12 to 12

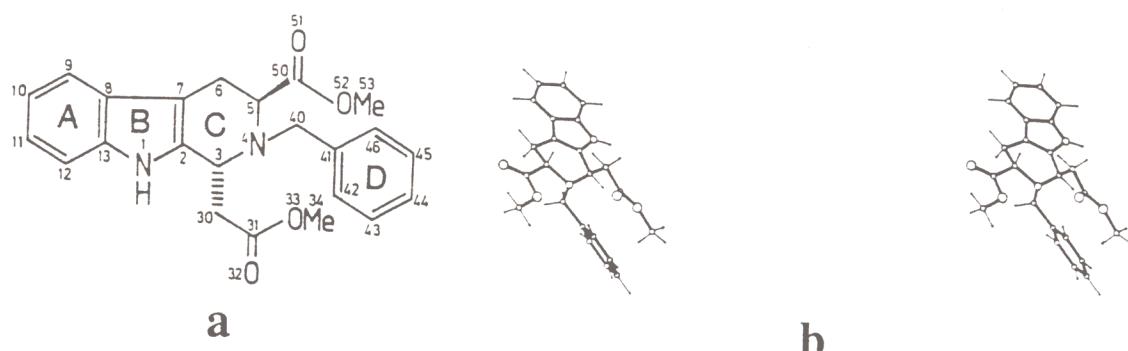


Fig. 3. (a) Structural formula and atom-labelling scheme and (b) stereoview of the molecular structure of (1*R*,3*S*)-2-benzyl-3-methoxycarbonyl-1-methylcarboxy-methyl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*] indole.

derived from those of the parent atoms, but were not refined. Several cycles of refinement of co-ordinates and anisotropic thermal parameters for non-hydrogen atoms gave a final *R* value of 0.041.

Atomic scattering factors for all atoms were taken from the *International Tables for X-ray Crystallography* (1974). All calculations were performed on a VAX computer.

Discussion

The structural formula, atom numbering scheme and molecule structure are shown in Figs. 3a and b. The final atomic parameters are listed in Tables 2 and 3. The bond lengths and valency angles are given in Table 4, while selected torsional angles are presented in Table 5. The bond lengths agree well with those found in other 1,2,3,4-tetrahydro- β -carbolines derivatives (Coding, 1983; Everett *et al.*, 1989; Ungemach *et al.*, 1980). The average C-C bond lengths in phenyl rings *A* and *D* are 1.395(5) and 1.389(5) Å, respectively. The values of the other types of carbon-carbon bonds are: C(phenyl)-C(*sp*³) 1.511(3); C(phenyl)-C(*sp*²) 1.437(4); C(*sp*³)-C(*sp*³) 1.537(3)(mean); C(*sp*³)-C(*sp*²) 1.502(3) and C(*sp*²) = C(*sp*²) 1.366(4) Å. The average C(methyl)-O bond length is 1.447(5) Å, compares well with the value of 1.454(12) tabulated by Allen *et al.*, (1987). The C(carbonyl)-O and C(carbonyl) = O bond lengths have mean values of 1.327(4) and 1.196(4) Å, respectively. The C-N bonds fall into three categories: C(phenyl)-N 1.376(3) Å; C(*sp*²)-N 1.371(3) Å; C(*sp*³)-N 1.475(3) Å (mean).

The short intramolecular contact of 2.712(3) Å between N(4) and O(52) causes the angles N(4)-C(5)-C(6) and N(4)-C(5)-C(50) to widen to 114.1(2) and 112.9(2)°, respectively.

The most important structural feature is the heterocyclic ring *C*, which exists in a half-chair conformation [with C(5) 0.45 Å above and N(4) 0.28 Å below the least-squares plane defined by the other 4 atoms]. The most striking observation, however, is that both the CH₂CO₂Me attached to C(3) and the Ph group attached to N(4) are in axial positions, with only the CO₂Me on C(5) being equatorial; the intermolecular interactions between these bulky substituents are partly responsible for the distortions found in ring *C*. [The same axial/axial/equatorial relationship was found in a closely related compound, in which the C(1) substituent was CH₂CH₂CO₂Me, and the indole nitrogen was methylated (Shimizu *et al.* 1984).] This largely explains why stereochemical assignment using ¹³C NMR is unreliable for *N*(2)-benzyl-1,3-disubstituted 1,2,3,4-tetrahydro- β -carbolines, for which the diagnostic 1,3-diaxial interactions (Figure 1) are further complicated by the influence of the N(2)-benzyl substituent. In the light of further structural studies on *N*(2)-benzyl-1,3-disubstituted tetrahydro- β -carbolines, we hope to be able to explain the observation that the benzyl CH₂ in the 1,3-*cis* isomers appear downfield of those from the corresponding *trans* isomers (Bailey and Hollinshead, 1987).

The nitrogen atom N(1) forms an intermolecular hydrogen bond with O(32) at (2 - *x*, - $\frac{1}{2}$ + *y*, 1 - *z*): N(1) · · · O(32) 2.995(3) Å, N(1)-H(1) 0.904(30) Å, O(32) · · · H(1) 2.176(30) Å, N(1)-H(1) · · · O(32) 150.3(20)°. There is also a weak intermolecular contact of 3.228(4) Å between N(1) and O(51) (*x*, -1 + *y*, *z*).

Table 2. Atomic coordinates, with esd's in parentheses

Atom	<i>x</i>	<i>y</i>	<i>z</i>
N(1)	0.6875(2)	0.1411(-)	0.3441(2)
C(2)	0.7000(2)	0.2787(3)	0.4044(2)
C(3)	0.7983(2)	0.3189(3)	0.5186(2)
N(4)	0.7705(1)	0.4618(3)	0.5788(2)
C(5)	0.7241(2)	0.5736(3)	0.4771(2)
C(6)	0.6018(2)	0.5322(4)	0.3913(3)
C(7)	0.6112(2)	0.3738(4)	0.3463(2)
C(8)	0.5383(2)	0.2901(4)	0.2420(2)
C(9)	0.4365(2)	0.3244(4)	0.1468(2)
C(10)	0.3892(3)	0.2147(5)	0.0572(3)
C(11)	0.4405(3)	0.0721(5)	0.0602(3)
C(12)	0.5401(2)	0.0342(4)	0.1535(3)
C(13)	0.5885(2)	0.1454(4)	0.2440(2)
C(30)	0.9216(2)	0.3256(4)	0.4766(2)
C(31)	1.0223(2)	0.3473(4)	0.5923(3)
O(32)	1.0901(2)	0.4524(4)	0.6080(3)
O(33)	1.0312(2)	0.2324(4)	0.6754(2)
C(34)	1.1263(3)	0.2429(7)	0.7906(3)
C(40)	0.6896(2)	0.4383(4)	0.6735(2)
C(41)	0.7573(2)	0.3752(4)	0.8021(2)
C(42)	0.8604(3)	0.4469(5)	0.8669(3)
C(43)	0.9197(3)	0.3952(6)	0.9890(3)
C(44)	0.8753(4)	0.2711(6)	1.0470(3)
C(45)	0.7730(4)	0.1999(5)	0.9825(4)
C(46)	0.7146(3)	0.2507(4)	0.8597(3)
C(50)	0.7206(2)	0.7320(4)	0.5328(3)
O(51)	0.6511(3)	0.8248(4)	0.4834(3)
O(52)	0.8074(2)	0.7568(3)	0.6361(2)
C(53)	0.8132(4)	0.9068(4)	0.6893(4)

Hydrogen atom atomic coordinates and isotropic thermal parameters

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{iso}
H(N1)	0.7352	0.0607	0.3681	4.78
H(C3)	0.8027	0.2321	0.5920	4.13
H(C5)	0.7870	0.5780	0.4104	4.47
H(C6A)	0.5816	0.6068	0.3072	5.02
H(C6B)	0.5314	0.5420	0.4485	5.02
H(C9)	0.3961	0.4347	0.1431	5.56
H(C10)	0.3108	0.2405	-0.0167	6.16
H(C11)	0.4014	-0.0098	-0.0121	5.97
H(C12)	0.5794	-0.0760	0.1564	5.43
H(C30A)	0.9218	0.4182	0.4086	4.61
H(C30B)	0.9360	0.2227	0.4273	4.61
H(C34A)	1.1121	0.3421	0.8460	8.14
H(C34B)	1.1250	0.1445	0.8501	8.14
H(C34C)	1.2116	0.2517	0.7580	8.14
H(C40A)	0.6197	0.3613	0.6316	4.71
H(C40B)	0.6496	0.5443	0.6922	4.71
H(C42)	0.8947	0.5435	0.8224	6.10
H(C43)	0.9994	0.4519	1.0394	7.63
H(C44)	0.9220	0.2306	1.1416	8.22
H(C45)	0.7374	0.1058	1.0281	7.70
H(C46)	0.6357	0.1934	0.8087	6.18
H(C53A)	0.7292	0.9322	0.7203	7.09
H(C53B)	0.8864	0.9143	0.7721	7.09
H(C53C)	0.8268	0.9855	0.6133	7.09

Table 3. Anisotropic thermal parameters ($\times 10^{**4}$) with esd's in parentheses^a

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	452(9)	394(9)	554(10)	40(8)	-29(8)	-53(9)
C(2)	388(9)	385(10)	473(10)	17(8)	-6(8)	-16(9)
C(3)	348(9)	371(9)	434(9)	11(8)	-8(7)	15(8)
N(4)	401(8)	364(9)	432(8)	3(7)	27(6)	23(7)
C(5)	460(10)	339(9)	492(11)	2(8)	27(8)	42(9)
C(6)	479(11)	400(11)	585(13)	77(10)	-55(10)	15(10)
C(7)	400(9)	407(11)	483(11)	28(9)	-29(8)	18(9)
C(8)	408(9)	485(12)	431(10)	-26(9)	20(8)	28(9)
C(9)	482(11)	647(15)	533(12)	-1(12)	-58(10)	90(12)
C(10)	547(13)	851(21)	483(12)	-112(14)	-104(10)	65(14)
C(11)	622(14)	756(19)	473(12)	-211(14)	38(10)	-73(13)
C(12)	584(13)	569(14)	516(12)	-130(12)	84(10)	-119(12)
C(13)	418(10)	491(12)	429(10)	-36(9)	41(8)	4(10)
C(30)	372(9)	504(11)	469(10)	26(9)	25(7)	7(10)
C(31)	361(9)	524(14)	586(12)	-12(9)	33(8)	-63(11)
O(32)	593(11)	725(15)	1067(17)	-257(12)	-13(11)	-53(14)
O(33)	582(10)	690(13)	609(10)	-16(10)	-135(8)	93(11)
C(34)	684(18)	1314(39)	598(15)	136(23)	-156(14)	-9(23)
C(40)	429(10)	470(12)	508(11)	1(9)	91(8)	31(10)
C(41)	530(11)	463(11)	476(11)	24(10)	136(9)	-1(10)
C(42)	687(15)	659(17)	564(13)	-99(15)	45(11)	9(13)
C(43)	896(22)	993(30)	551(15)	-2(22)	-58(15)	-33(18)
C(44)	1222(31)	1032(31)	488(14)	326(28)	142(17)	191(18)
C(45)	1083(27)	741(23)	740(19)	59(21)	290(19)	238(18)
C(46)	775(17)	541(16)	680(16)	-27(14)	227(13)	77(13)
C(50)	587(13)	355(11)	649(14)	-15(10)	97(11)	14(11)
O(51)	1041(18)	414(10)	1282(22)	181(12)	-298(16)	-66(14)
O(52)	748(12)	403(9)	669(11)	-42(9)	33(9)	-77(8)
C(53)	994(24)	477(15)	836(20)	-116(15)	183(18)	-205(15)

^aThe temperature factor employed was: $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^{*}c^{*} + 2U_{13}hla^{*}c^{*} + 2U_{12}hka^{*}b^{*})]$

Table 4. Bond lengths/Å and bond angles/deg

N1	C2		1.371(3)		C11	C12		1.381(4)
N1	C13		1.376(3)		C12	C13		1.401(4)
C2	C3		1.506(3)		C30	C31		1.502(3)
C2	C7		1.366(4)		C31	O32		1.203(4)
C3	N4		1.478(4)		C31	O33		1.327(4)
C3	C30		1.539(3)		O33	C34		1.451(4)
N4	C5		1.471(3)		C40	C41		1.511(3)
N4	C40		1.475(3)		C41	C42		1.389(4)
C5	C6		1.544(3)		C41	C46		1.388(5)
C5	C50		1.528(4)		C42	C43		1.390(4)
C6	C7		1.497(4)		C43	C44		1.396(7)
C7	C8		1.437(3)		C44	C45		1.379(6)
C8	C9		1.401(3)		C45	C46		1.391(5)
C8	C13		1.409(5)		C50	O51		1.189(4)
C9	C10		1.383(5)		C50	O52		1.326(3)
C10	C11		1.397(6)		O52	C53		1.443(5)
C2	N1	C13	108.4(2)		C11	C12	C13	117.2(2)
N1	C2	C3	124.5(2)		N1	C13	C8	107.9(2)
N1	C2	C7	110.6(2)		N1	C13	C12	129.9(2)
C3	C2	C7	124.8(2)		C8	C13	C12	122.2(2)
C2	C3	N4	110.4(2)		C3	C30	C31	112.1(2)
C2	C3	C30	111.5(2)		C30	C31	O32	125.3(2)
N4	C3	C30	111.2(2)		C30	C31	O33	111.5(2)
C3	N4	C5	111.2(2)		O32	C31	O33	123.1(2)
C3	N4	C40	111.4(2)		C31	O33	C34	115.7(2)
C5	N4	C40	112.7(2)		N4	C40	C41	111.0(2)
N4	C5	C6	114.1(2)		C40	C41	C42	119.6(2)
N4	C5	C50	112.9(2)		C40	C41	C46	120.9(2)
C6	C5	C50	110.7(2)		C42	C4	C46	119.5(2)
C5	C6	C7	107.1(2)		C41	C42	C43	120.2(3)
C2	C7	C6	122.7(2)		C42	C43	C44	119.9(3)
C2	C7	C8	106.2(2)		C43	C44	C45	119.8(3)
C6	C7	C8	131.1(2)		C44	C45	C46	120.1(3)
C7	C8	C9	134.0(2)		C41	C46	C45	120.4(3)
C7	C8	C13	106.9(2)		C5	C50	O51	123.0(2)
C9	C8	C13	119.1(2)		C5	C50	O52	112.8(2)
C8	C9	C10	118.7(2)		O51	C50	O52	124.1(2)
C9	C10	C11	121.4(2)		C50	O52	C53	115.8(2)
C10	C11	C12	121.4(2)					

Table 5. Torsion angles/deg, with esd's in parentheses

N1	C2	C3	N4	-167.2(2)	C40	N4	C5	C50	67.1(3)
N1	C2	C3	C30	68.6(3)	N4	C5	C6	C7	-48.7(3)
C7	C2	C3	N4	13.0(3)	C50	C5	C6	C7	-177.4(2)
C7	C2	C3	C30	-111.2(3)	C5	C6	C7	C2	16.6(3)
N1	C2	C7	C6	-180.0(2)	C3	C30	C31	O32	-118.9(3)
C2	C3	N4	C5	-43.4(3)	C3	C30	C31	O33	63.3(3)
C2	C3	N4	C40	83.2(2)	C30	C31	O33	C34	179.9(3)
C30	C3	N4	C5	81.0(2)	O32	C31	O33	C34	2.1(5)
C30	C3	N4	C40	-152.5(2)	N4	C40	C41	C42	52.4(3)
C3	N4	C5	C6	65.3(3)	N4	C40	C41	C46	-130.8(3)
C3	N4	C5	C50	-167.1(2)	C5	C50	O52	C53	176.9(3)
C40	N4	C5	C6	-60.5(3)	O51	C50	O52	C53	0.7(5)

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 60648 (16 pages).