Structure of Methyl β-Carboline-3-carboxylate (βCCM),* C₁₃H₁₀N₂O₂†

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Abstract. $M_r = 226 \cdot 24$, monoclinic, $P2_1/c$, $a = 11 \cdot 467$ (2), $b = 5 \cdot 803$ (2), $c = 32 \cdot 382$ (11) Å, $\beta = 97 \cdot 11$ (2)°, $V = 2138$ (1) Å³, $Z = 8$, $D_x = 1 \cdot 40$ Mg m⁻³, $\lambda(\text{Mo } K\alpha) = 0 \cdot 71069$ Å, $\mu = 0 \cdot 09$ mm⁻¹, $F(000) = 944$, $T = 298$ K, $R = 0 \cdot 058$ for 1593 unique observed reflections. The asymmetric unit contains two hydrogen-linked molecules [NA—H(NA)···OB $2 \cdot 825$ (5) Å] and the packing consists of ribbons of planar molecules linked by NB—H(NB)···OA hydrogen bonds [$2 \cdot 912$ (5) Å] along **a**. C—H···O hydrogen bonds stabilize the crystal packing. The pharmacological effects of β-carbolines as ligands of the benzodiazepine receptor are briefly discussed.

Introduction. Benzodiazepines (BDZ's) are a class of compounds widely employed as anxiolytic, sedative and anticonvulsant agents. Specific high-affinity BDZ receptor sites have been discovered in the central nervous system (Squires & Braestrup, 1977; Möhler & Okada, 1977). More recently several compounds, chemically unrelated to BDZ's, have been found to bind to BDZ receptors with high or very high affinity. Rather surprisingly they display a spectrum of biological activities ranging from compounds having full BDZ-like properties (agonists) to those having completely opposite effects (inverse agonists) through a third class of compounds (antagonists) able to bind to BDZ receptors without producing any *per se* biological effect (Braestrup, Nielsen, Honoré, Jensen & Petersen, 1983). From a stereochemical point of view the problem appears to be of great interest as agonists, antagonists and inverse agonists must have a *common chemical moiety* responsible for binding at the same receptor site, while agonists and inverse agonists should possess additional and different stereochemical features able to trigger opposite biological effects.

Accordingly we have undertaken a systematic program of structure determination on these compounds. We report here the crystal and molecular

structure of βCCM, a BDZ-receptor ligand of the inverse-agonist type (Braestrup & Nielsen, 1981).

Experimental. Crystals kindly provided by Dr C. Braestrup, A/S Ferrosan, Soeborg (Denmark) and recrystallized from ethyl acetate. Largest crystal ($0 \cdot 08 \times 0 \cdot 13 \times 0 \cdot 40$ mm) submitted for analysis. Automatic Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$ radiation, cell parameters from 22 reflections in range $10 < \theta < 14°$, $\omega/2\theta$ scan, $2 \leq \theta \leq 27°$, 4666 independent reflections ($0 \leq h \leq 14$, $0 \leq k \leq 6$, $-38 \leq l \leq 38$), 1593 having $I > 2\sigma(I)$ considered observed, crystal stable through data collection (two reflections monitored every 2 h), absorption ignored; direct methods: *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); full-matrix least squares on F, anisotropic non-H atoms, isotropic H atoms (from ΔF synthesis) not refined in last two cycles, $1/w^2 = \sigma^2(I) + 0 \cdot 070 |F_o|^2$, max. Δ/σ $0 \cdot 1$, $R = 0 \cdot 058$, $R_w = 0 \cdot 068$, $S = 1 \cdot 83$, scattering factors from *International Tables for X-ray Crystallography* (1974), final $\Delta \rho$ excursion $-0 \cdot 2$–$0 \cdot 2$ e Å⁻³; all calculations performed by CAD-4 *SDP* system of programs (Frenz, 1978) and *PARST* (Nardelli, 1983).

Discussion. Atomic parameters are given in Table 1‡ and bond distances and angles in Table 2. The asymmetric unit (Fig. 1) contains two hydrogen-linked N(A1)—H(NA1)···O(B1) [N(A1)···O(B1) = $2 \cdot 825$ (5), H(NA1)···O(B1) = $2 \cdot 06$ (4) Å, N(A1)—H(NA1)··· O(B1) = 140 (4)°] molecules. In the crystal molecular couples are linked together in infinite ribbons, lying approximately in the *ab* plane and running along **a**, by the hydrogen bonds N(B1)— H(NB1)···O(A1) (x−1, y−1, z) [N(B1)···O(A1) = $2 \cdot 912$ (5), H(NB1)···O(A1) = $2 \cdot 21$ (6) Å, N(B1)— H(NB1)···O(A1) = 138 (4)°].

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* Methyl 9*H*-pyrido[3,4-*b*]indole-3-carboxylate.
† Stereochemistry of Benzodiazepine-Receptor Ligands. I.

‡ Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39603 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
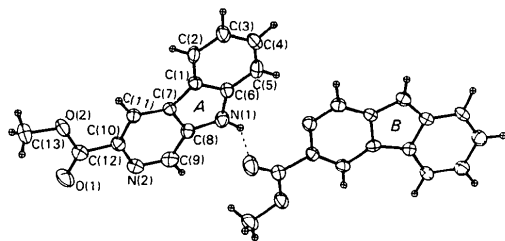
Fig. 1. An *ORTEP* (Johnson, 1971) view of the molecule showing the thermal ellipsoids at 40% probability.

Assuming $O \cdots H$ and $N \cdots H$ contact distances of 2·70 and 2·75 Å respectively (Bondi, 1964), there are three other distances shorter than or very close to the sum of the van der Waals radii. They are $C(A9)$–$H(A9) \cdots O(B1)(x,y,z)$ [C–H = 0·91 (4), $H \cdots O$ = 2·74 (4), $C \cdots O$ = 3·388 (6) Å, C–H$\cdots$O = 129 (3)°], $C(B9)$–$H(B9) \cdots O(A1)(x-1, \quad y-1, \quad z)$ [C–H = 0·93 (4), $H \cdots O$ = 2·40 (4), $C \cdots O$ = 3·095 (7) Å, C–H$\cdots$O = 131 (3)°] and $N(B1)$–$H(NB1) \cdots N(A2)$-$(x-1, \quad y-1, \quad z)$ [N–H = 0·86 (6), $H \cdots N$ = 2·55 (6), $N \cdots N$ = 3·307 (6) Å, N–H$\cdots$N = 147 (4)°]. The two

Table 1. *Positional* $(\times 10^4 \, for \, non\text{-H} \, atoms, \; \times 10^3 \, for \, H \, atoms)$ *and isotropic thermal* $(\text{Å}^2 \times 10^3)$ *parameters with e.s.d.'s in parentheses*

U_{eq} according to Hamilton (1959).

	Molecule A				Molecule B			
	x	y	z	U_{eq}/U	x	y	z	U_{eq}/U
O(1)	11854 (3)	3920 (7)	4090 (1)	77 (2)	5586 (3)	2177 (7)	3400 (1)	88 (3)
O(2)	12193 (3)	718 (7)	4471 (1)	63 (2)	4343 (3)	4268 (6)	2991 (1)	63 (2)
N(1)	6869 (3)	−632 (8)	4008 (1)	58 (2)	756 (3)	−2924 (7)	3459 (1)	51 (2)
N(2)	9530 (4)	2807 (7)	3927 (1)	53 (2)	3812 (3)	−822 (7)	3545 (1)	53 (2)
C(1)	8010 (4)	−2825 (9)	4475 (1)	45 (3)	288 (4)	272 (8)	3065 (1)	43 (3)
C(2)	8223 (4)	−4640 (10)	4753 (2)	59 (3)	−457 (4)	1749 (8)	2826 (1)	47 (3)
C(3)	7345 (5)	−6110 (10)	4820 (2)	66 (4)	−1632 (4)	1231 (9)	2756 (2)	56 (3)
C(4)	6220 (5)	−5810 (10)	4607 (2)	70 (3)	−2066 (4)	−800 (10)	2920 (2)	59 (3)
C(5)	5980 (4)	−4050 (10)	4331 (2)	64 (3)	−1349 (4)	−2284 (9)	3164 (2)	55 (3)
C(6)	6872 (4)	−2527 (9)	4263 (1)	48 (3)	−151 (4)	−1749 (8)	3233 (1)	43 (3)
C(7)	8716 (4)	−1031 (8)	4327 (1)	42 (2)	1526 (4)	268 (8)	3193 (1)	41 (3)
C(8)	7968 (4)	278 (9)	4047 (1)	48 (3)	1782 (4)	−1728 (8)	3436 (1)	44 (3)
C(9)	8406 (5)	2198 (9)	3859 (2)	59 (3)	2935 (4)	−2175 (9)	3609 (2)	52 (3)
C(10)	10257 (4)	1478 (9)	4193 (1)	48 (3)	3558 (4)	1103 (9)	3304 (1)	45 (3)
C(11)	9894 (4)	−424 (9)	4400 (1)	46 (3)	2453 (4)	1704 (8)	3124 (1)	44 (3)
C(12)	11491 (5)	2222 (9)	4237 (1)	55 (3)	4596 (4)	2490 (9)	3247 (2)	52 (3)
C(13)	13427 (5)	1290 (10)	4540 (2)	74 (4)	5288 (5)	5810 (10)	2924 (2)	73 (4)
H(N1)	619 (4)	−19 (8)	385 (1)	83 (16)	75 (4)	−422 (9)	359 (2)	108 (19)
H(2)	897 (2)	−488 (5)	487 (1)	16 (9)	−15 (3)	313 (7)	270 (1)	50 (11)
H(3)	747 (4)	−753 (8)	502 (1)	73 (14)	−215 (3)	214 (6)	260 (1)	28 (10)
H(4)	563 (4)	−698 (9)	463 (1)	95 (17)	−287 (3)	−107 (7)	283 (1)	52 (10)
H(5)	526 (4)	−378 (8)	421 (1)	76 (15)	−160 (3)	−384 (7)	325 (1)	51 (11)
H(9)	792 (4)	295 (8)	366 (1)	67 (13)	311 (3)	−349 (8)	377 (1)	66 (14)
H(11)	1050 (3)	−129 (7)	460 (1)	53 (12)	232 (3)	295 (6)	297 (1)	26 (9)
H(131)	1352 (4)	264 (9)	466 (1)	98 (17)	593 (6)	497 (12)	289 (2)	177 (29)
H(132)	1377 (6)	−4 (12)	474 (2)	172 (29)	500 (4)	674 (9)	269 (1)	114 (19)
H(133)	1375 (5)	126 (11)	427 (2)	147 (24)	551 (5)	640 (10)	318 (2)	111 (18)

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

	Molecule A	Molecule B		Molecule A	Molecule B		Molecule A	Molecule B
O(1)–C(12)	1·192 (6)	1·195 (6)	C(1)–C(2)	1·388 (8)	1·378 (6)	C(7)–C(8)	1·394 (6)	1·411 (6)
O(2)–C(12)	1·354 (6)	1·333 (7)	C(1)–C(6)	1·408 (6)	1·412 (6)	C(7)–C(11)	1·388 (6)	1·390 (6)
O(2)–C(13)	1·444 (7)	1·442 (7)	C(1)–C(7)	1·437 (7)	1·429 (6)	C(8)–C(9)	1·393 (8)	1·395 (6)
N(1)–C(6)	1·375 (6)	1·376 (5)	C(2)–C(3)	1·357 (8)	1·372 (6)	C(10)–C(11)	1·382 (7)	1·373 (6)
N(1)–C(8)	1·358 (6)	1·376 (6)	C(3)–C(4)	1·396 (8)	1·409 (8)	C(10)–C(12)	1·469 (7)	1·467 (7)
N(2)–C(9)	1·328 (6)	1·312 (6)	C(4)–C(5)	1·363 (8)	1·372 (8)	N(1)–H(N1)	0·91 (4)	0·86 (6)
N(2)–C(10)	1·362 (6)	1·373 (6)	C(5)–C(6)	1·390 (7)	1·399 (6)	C–H (average)	0·94 [2]	0·92 [2]
C(12)–O(2)–C(13)	116·2 (4)	117·6 (4)	C(4)–C(5)–C(6)	119·2 (5)	117·4 (5)	C(7)–C(8)–C(9)	119·6 (4)	119·9 (4)
C(6)–N(1)–C(8)	108·8 (4)	108·4 (4)	N(1)–C(6)–C(1)	108·9 (4)	109·5 (4)	N(2)–C(9)–C(8)	122·4 (5)	122·1 (5)
C(9)–N(2)–C(10)	117·4 (4)	117·6 (4)	N(1)–C(6)–C(5)	131·0 (4)	129·6 (4)	N(2)–C(10)–C(11)	124·2 (4)	124·6 (4)
C(2)–C(1)–C(6)	119·2 (4)	120·5 (4)	C(1)–C(6)–C(5)	120·0 (4)	120·8 (4)	N(2)–C(10)–C(12)	113·7 (4)	113·5 (4)
C(2)–C(1)–C(7)	134·8 (4)	133·5 (4)	C(1)–C(7)–C(8)	106·6 (4)	107·1 (4)	C(11)–C(10)–C(12)	122·1 (4)	121·8 (4)
C(6)–C(1)–C(7)	105·9 (4)	106·0 (4)	C(1)–C(7)–C(11)	134·7 (4)	134·8 (4)	C(7)–C(11)–C(10)	117·7 (4)	117·6 (4)
C(1)–C(2)–C(3)	120·4 (5)	119·0 (4)	C(8)–C(7)–C(11)	118·7 (4)	118·1 (4)	O(1)–C(12)–O(2)	122·9 (5)	119·9 (4)
C(2)–C(3)–C(4)	120·1 (6)	120·4 (5)	N(1)–C(8)–C(7)	109·8 (4)	108·9 (4)	O(1)–C(12)–C(10)	125·7 (4)	127·5 (5)
C(3)–C(4)–C(5)	121·1 (5)	121·9 (5)	N(1)–C(8)–C(9)	130·6 (4)	131·2 (4)	O(2)–C(12)–C(10)	111·3 (4)	112·7 (4)

Table 3. *Pharmacological effects of some β-carboline derivatives binding with high affinity to BDZ receptor sites*

AG = agonist, ANT = antagonist, IAG = inverse agonist.
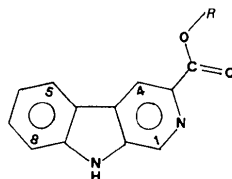
Compound	Substituents	Effect
DMCM	$R = CH_3$	Strong IAG
	4-(CH_2-CH_3); 6,7-di$(O-CH_3)$	
βCCM	$R = CH_3$	Medium IAG
PrCC	$R = CH_2-CH_2-CH_3$	ANT
ZK91296	$R = CH_2-CH_3$	
	4-(CH_2-O-CH_3); 5-$(O-CH_2-Ph)$	Medium AG

$C-H\cdots O$ interactions can be classified as '$C-H\cdots O$ hydrogen bonds' according to Taylor & Kennard (1982) and their rôle in crystal packing has been recently discussed by Berkovitch-Yellin & Leiserowitz (1984).

All the molecule is remarkably planar. The dihedral angles between the central five-membered ring and the terminal six-membered rings are 0·9 (2) and 2·4 (2)° for molecule *A* and 0·5 (1) and 1·4 (1)° for molecule *B*. The methoxycarbonyl group lies approximately in the plane of the molecule, the torsion angles N(2)—C(10)—C(12)—O(1) being 6·2 (7) and −3·8 (8)° in molecules *A* and *B* respectively. This can be ascribed to a relevant contribution of the canonical form

$$-H\overset{\oplus}{N}(1)=\overset{|}{C}(8)-\overset{|}{C}(9)=N(2)-\overset{|}{C}(10)=\overset{|}{C}(12)-\overset{\ominus}{O}(1)$$

to the ground state of the molecule. This is supported by the bond-distances pattern. The C(10)—C(12) distances [1·469 (6) and 1·467 (6) Å in *A* and *B* respectively] are on the short-length side of the distribution of the Ar—COO*R* values [1·484 (12) Å] given by Schweizer & Dunitz (1981); the N(2)—C(9) distance [1·328 (7) in *A* and 1·312 (6) Å in *B*] is significantly shorter than N(2)—C(10) [1·362 (6) in *A* and 1·373 (6) Å in *B*] while the N(1)—C(8) distance is on average statistically indistinguishable from N(1)—C(16) (1·366 [9] against 1·376 [4] Å).

From the point of view of structure–properties relationships, it is presently impossible to discover how β-carbolines can mimic such different molecules as BDZ's, whose molecular features can be illustrated by

the structures of two of their most potent members, *i.e.* diazepam (Camerman & Camerman, 1972) and nitrazepam (Gilli, Bertolasi, Sacerdoti & Borea, 1977). Nevertheless, a correlation *inside* the β-carboline series can be obtained from the data of Table 3, all referring to compounds with high BDZ-receptor binding abilities and derived from Braestrup *et al.* (1983). Increasing dimensions of the *R* substituent apparently shift the properties from inverse agonists to antagonists and further addition of a bulky substituent in position 5 (see ZK91296) can even produce agonist effects. Conversely, the addition of substituents in positions 6 and 7 strengthens the inverse-agonist properties (compare DMCM with βCCM), while substitution in position 4 does not produce any clear effect. This seems to suggest the existence of a well defined stereochemical pattern responsible for the continuous variations of molecular properties.

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