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CADABICINE, AN ALKALOID FROM *CADABA FARINOSA*

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Key Word Index—*Cadaba farinosa*; Cappariaceae; alkaloid; cadabicine; X-ray crystallography.

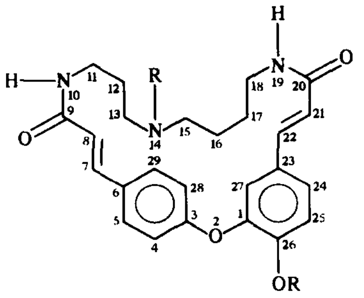
Abstract—A new spermidine alkaloid, cadabicine, has been isolated from *Cadaba farinosa*. Its structure was determined by X-ray crystallographic and spectral methods.

INTRODUCTION

Cadaba farinosa Forssk. (syn. *C. fruticosa* L. Druce, *C. indica* Lam) is a multi-branched shrub which grows widely in the Sind province of Pakistan. Its leaves and roots are reported to have purgative, antihelmintic, antispasmodic, amenagogue and aperient properties [1]. The isolation of stachydrine from the leaves [2] and of cadabalone, a dilactone from the pods [3] of the plant has been reported. In this paper we wish to report the isolation and structure determination of a new spermidine alkaloid cadabicine (**1**) from this plant.

RESULTS AND DISCUSSION

Cadabicine, mp 270° (decomp.), gave a positive test for phenols with $FeCl_3$. HR mass spectrometry gave an $[M]^+$ at m/z 435.2145 corresponding to the molecular formula $C_{25}H_{29}N_3O_4$ (calc. 435.2157). The UV spectrum diplayed maxima at 217 (log ε3.55), 284 (log ε3.76) and a shoulder at 310 nm. These values are very close to those of codonocarpine [4]. The IR spectrum had bands at 3400–3240 (br, OH and NH), 1655 (α,β-unsaturated amide) and 1600 cm^{-1} (aromatic ring). On acetylation a crystalline diacetate, mp 265–268°, was formed. The UV spectrum of the diacetate had maxima at 210 (log ε4.12), 273 (log ε4.08) and 305 nm (shoulder). The IR spectrum (KBr) showed absorptions at 1760 (phenolic acetate) and 1655 cm^{-1} (amides). The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of diacetyl cadabicine in DMSO-d_6 showed doubling of several signals which may be due to slowly interconverting conformers of the N-acetate. A similar phenomenon has been reported by other authors [5, 6] in amides. However, the observed doubling of the signals could also be due to the existence of conformers in solution as a result of the flexibility of the macrocyclic molecule of cadabicine. In the ^{1}H NMR spectrum there are two singlets which together integrate to 3H at δ1.95 and 1.97 for N–Ac. A singlet at δ2.34 (3H) is attributed to the phenolic acetate. A multiplet between δ1.25 and 1.75 (6H) is assigned to three methylene groups and another multiplet between δ3.05 and 3.40 (8H) is due to the four methylene groups adjacent to nitrogens. There are four doublets (J = 15 Hz) at δ6.03 (1H), 6.56 (1H), 7.23 (1H) and 7.50 (1H) from the olefenic protons of the *trans* cinnamic acid residues. A doublet at δ6.45 (J = 1.7 Hz) is assigned to H-27 with *meta* coupling. There are two doublets at δ7.15 (2H) and 7.74 (2H) each with *ortho* coupling (J = 7.4 Hz) typical of a *para* disubstituted benzene ring. Another doublet is present at δ7.23 (J = 8.1 Hz) showing only *ortho* but no *meta* coupling and is attributed to H-25. A double doublet at δ7.15 (J = 8.1, 1.7 Hz) is due to H-24.



1 R = H
1a R = Ac

The ^{13}N NMR spectrum (DMSO-d_6) of the diacetate has several doubled peaks (Table 1). The mass spectral fragmentation pattern of cadabicine is shown in Scheme 1. Since the spectral data cannot lead to a decision between the structure **1** and the alternate one in which the attachment of the spermidine moiety with the rest of the molecule is reversed, a single crystal X-ray diffraction experiment was undertaken. Preliminary X-ray diffraction photographs showed monoclinic symmetry. Accurate lattice parameters of $a = 13.216(3)$, $b = 9.495(1)$, $c = 21.361(2)$ Å and $\beta = 75.15(1)°$ were calculated from a least-squares fit of fifteen diffractometer measure 20-values. Systematic extinctions and the crystal density were uniquely accommodated by the achiral space group $P2_1/c$ with one molecule of composition $C_{25}H_{29}N_3O_4$ forming the asymmetric unit. All unique diffraction maxima with $20 \leqslant 114°$ were collected on a computer controlled four-circle diffractometer using variable speed 1°ω-scans and graphite monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å). Of the 2747 reflections measure in this way, 1472 (54%) were judged observed ($F_0 \geqslant 3\sigma$ (F_0)) after correction for

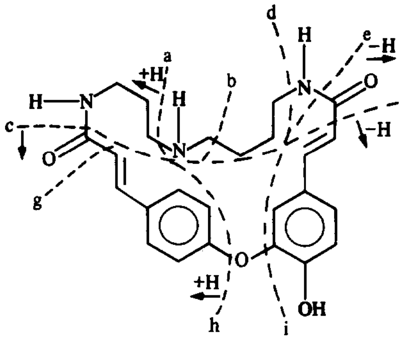
Table 1. ^{13}C NMR chemical shifts for cadabacine (100 MHz, DMSO-d_6)

Carbon No.*	ppm	Carbon No.	ppm
1	151.81	20	164.78/164.88^{e}†
3	155.16	21	124.66/124.70^{d}†
4	122.31^{a}	22	136.98/137.06^{c}†
5	129.54	23	133.52^{b}
6	133.54^{b}	24	124.01
7	137.62/137.72^{c}†	25	110.78/110.81†
8	124.44/124.54^{d}†	26	140.33
9	164.09^{e}	27	122.22^{a}
11	45.00/47.42†	28	122.31^{a}
12	27.04/27.73†	29	129.54
13	38.26/38.44†	$O\underline{C}OCH_3$	168.54
15	35.36/35.94†	$OCO\underline{C}H_3$	20.41
16	26.48/26.58†	$N\underline{C}OCH_3$	169.01/169.04†
17	25.89	$NCO\underline{C}H_3$	21.08/21.20†
18	42.43/43.72†		

^{a,b,c,d,e}These assignments are interchangeable.

*The numbering is according to that adopted by *Chemical Abstracts.*

†The doubling of peaks is due to the presence of *Z* and *E* conformers, see Discussion.



1

m/z		m/z	
(a–b) = 407	($C_{24}H_{27}N_2O_4$)	(b–c) = 349	($C_{21}H_{19}NO_4$)
(c–d) = 307	($C_{18}H_{13}NO_4$)	(c–e) = 291	($C_{18}H_{11}O_4$)
(c–f) = 264	($C_{17}H_{12}O_3$)	(g–f) = 235	($C_{16}H_{11}O_2$)
(a–h) = 189	($C_{12}H_{15}NO$)	(e–i) = 146	($C_9H_6O_2$)
(c–h) = 131	(C_9H_7O)		

Scheme 1. Mass spectral fragmentation of cadabicine.

Lorentz, polarization and background effects. A multisolution sign determining procedure gave a good phasing model and 30 of the 32 nonhydrogen atoms were located in the initial E-synthesis. The structure was extended by weighted Fourier techniques to give all of the nonhydrogen atoms. The hydrogens were located in ΔF-synthesis after partial refinement of the nonhydrogen atoms. Block diagonal least-squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.081 for the observed reflections. A computer generated perspective drawing of the final X-ray model is presented in Fig. 1. Hydrogens are omitted for clarity. The aromatic rings are roughly orthogonal with torsional angles of 21° about the C-1–O-2 bond, and 79° about the O-2–C-3 bond. In general the molecular parameters agree well with accepted values. The fractional coordinates and thermal parameters are given in Table 2.

EXPERIMENTAL

Mps are uncorr. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in DMSO-d_6 using TMS as int. standard. UV spectra were recorded in MeOH and IR spectra on KBr discs.

Extraction of plant material. Stem bark of *Cadaba farinosa* (31 kg) was collected from the Karachi University campus. It was chopped into small pieces and extracted exhaustively with EtOH. The residue obtained on evapn of the alcoholic extraction was partitioned between EtOAc and H_2O. The aq. layer was then extracted with $CHCl_3$, basified with ammonia (pH = 10) and extracted repeatedly with $CHCl_3$. The alkaloid containing $CHCl_3$ layers were combined, washed, dried and concd. This soln on storing at 0° deposited crystals of cadabicine (300 mg). After recrystallization from MeOH pure cadabicine was obtained.

Cadabicine (1). Mp 270–272° (decomp.); UV λ_{max}^{MeOH} nm (log ε): 217 (3.55), 284 (3.76), 310 (shoulder); IR ν_{max}^{KBr} cm^{-1}: 3400–3240 (OH), 1655 (α,β-unsatd amide), 1600 (aromatic ring); HRMS: *m/z* 435.2145 (calc. for $C_{25}H_{29}N_3O_4$, 435.2157), 407.2001 (calc. for $C_{24}H_{27}N_2O_4$ 407.1970), 349.1347 (calc. for $C_{21}H_{19}NO_4$, 349.1313), 291.0657 (calc. for $C_{18}H_{11}O_4$ 291.0657), 264.0771 (calc. for $C_{17}H_{12}O_3$ 264.0786), 235.0752 (calc. for $C_{16}H_{11}O_2$ 235.0758), 146.0346 (calc. for $C_9H_6O_2$ 146.0367), 131.0488 (calc. for C_9H_7O, 131.0496).

Acetylation. Compound 1 (20 mg) was treated with Ac_2O

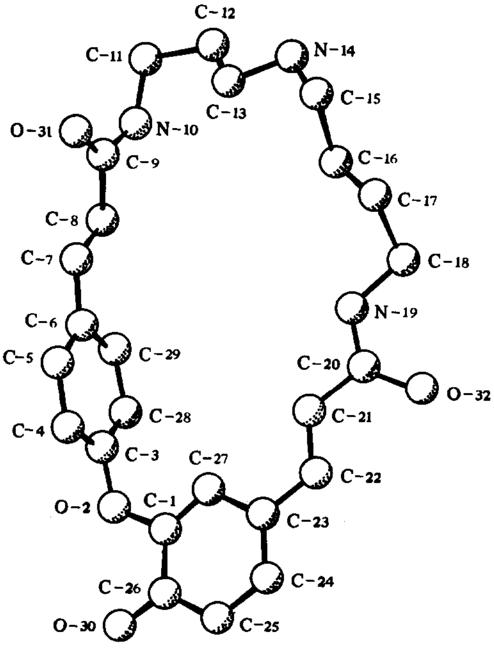


Fig. 1. Computer generated perspective drawing of the X-ray model of cadabicine.

Table 2. Fractional coordinates and thermal parameters for Cadabicine

Atom	*x*	*y*	*z*	B
C-1	0.7540 (10)	0.1674 (15)	0.4227 (6)	4.5 (7)*
C-2	0.6964 (7)	0.1775 (11)	0.3756 (4)	5.3 (5)*
C-3	0.5871 (10)	0.1936 (16)	0.3994 (6)	4.5 (8)*
C-4	0.5252 (10)	0.0824 (16)	0.4222 (6)	5.0 (8)*
C-5	0.4137 (10)	0.1060 (15)	0.4495 (6)	4.5 (8)*
C-6	0.3742 (10)	0.2346 (17)	0.4521 (7)	5.4 (8)*
C-7	0.2657 (10)	0.2580 (16)	0.4881 (6)	4.7 (8)*
C-8	0.2169 (10)	0.3795 (17)	0.5021 (6)	4.9 (8)*
C-9	0.1101 (11)	0.3835 (16)	0.5497 (7)	5.5 (8)*
N-10	0.0732 (9)	0.5152 (18)	0.5658 (5)	5.4 (7)*
C-11	−0.0234 (10)	0.5358 (16)	0.6175 (7)	5.1 (8)*
C-12	0.0008 (10)	0.5875 (15)	0.6818 (6)	4.7 (8)*
C-13	0.0751 (10)	0.4874 (16)	0.7034 (6)	4.6 (7)*
N-14	0.0785 (8)	0.5263 (12)	0.7715 (5)	4.5 (6)*
C-15	0.1560 (11)	0.4404 (16)	0.7958 (7)	5.4 (8)*
C-16	0.2693 (10)	0.4773 (15)	0.7616 (6)	4.7 (8)*
C-17	0.3401 (11)	0.4028 (21)	0.7973 (7)	6.0 (9)*
C-18	0.4567 (11)	0.4494 (20)	0.7712 (7)	6.2 (9)*
N-19	0.5012 (8)	0.3833 (13)	0.7088 (5)	4.8 (6)*
C-20	0.6038 (11)	0.3570 (16)	0.6883 (7)	5.6 (3)*
C-21	0.6382 (10)	0.2968 (15)	0.6236 (6)	4.7 (8)*
C-22	0.7373 (10)	0.2664 (14)	0.5957 (6)	4.5 (7)*
C-23	0.7770 (9)	0.2104 (14)	0.5291 (6)	4.0 (7)*
C-24	0.8763 (10)	0.1524 (16)	0.5078 (7)	5.0 (8)*
C-25	0.9121 (10)	0.0989 (17)	0.4456 (7)	5.0 (8)*
C-26	0.8526 (10)	0.1031 (15)	0.3989 (7)	4.5 (8)*
C-27	0.7149 (9)	0.2191 (14)	0.4840 (6)	4.1 (7)*
C-28	0.5488 (11)	0.3312 (17)	0.3977 (7)	5.9 (9)*
C-29	0.4418 (11)	0.3586 (17)	0.4231 (7)	5.6 (9)*
O-30	0.0647 (8)	0.2760 (11)	0.5728 (5)	7.0 (7)*
O-31	0.6662 (7)	0.3913 (13)	0.7206 (4)	6.3 (6)*
O-32	0.8867 (6)	0.0551 (10)	0.3403 (4)	4.8 (5)*
SOL1	0.8528 (7)	0.3019 (9)	0.7374 (4)	5.0 (5)*
SOL2	0.3790 (8)	0.2005 (12)	0.1148 (5)	7.6 (7)*
SOL3	0.2617 (10)	0.3835 (14)	0.2013 (6)	4.3 (8)*
H-4	0.570 (10)	−0.028 (15)	0.426 (6)	9.9 (41)
H-5	0.354 (9)	−0.001 (13)	0.473 (5)	7.1 (33)
H-7	0.231 (8)	0.156 (11)	0.517 (5)	5.7 (30)
H-8	0.267 (9)	0.471 (12)	0.486 (5)	6.9 (32)
H-10	0.121 (12)	0.602 (18)	0.549 (8)	13.8 (55)
H-11A	−0.075 (9)	0.605 (13)	0.608 (6)	8.0 (36)
H-11B	−0.079 (10)	0.433 (14)	0.640 (6)	8.9 (38)
H-12A	0.035 (7)	0.680 (10)	0.675 (4)	3.5 (24)
H-12B	−0.083 (8)	0.580 (12)	0.720 (6)	6.2 (30)
H-13A	0.051 (10)	0.370 (14)	0.707 (6)	9.3 (39)
H-13B	0.164 (8)	0.500 (12)	0.671 (5)	6.0 (29)
H-14A	0.108 (9)	0.628 (12)	0.765 (5)	6.9 (33)
H-14D	0.006 (10)	0.517 (14)	0.797 (6)	8.3 (36)
H-15A	0.143 (9)	0.460 (13)	0.836 (6)	8.2 (36)
H-15B	0.147 (12)	0.306 (17)	0.791 (7)	12.6 (51)
H-16A	0.285 (9)	0.582 (13)	0.760 (6)	7.8 (35)
H-16B	0.278 (7)	0.439 (10)	0.712 (5)	4.3 (25)
H-17A	0.313 (8)	0.423 (12)	0.845 (5)	6.9 (33)
H-17B	0.320 (10)	0.278 (16)	0.803 (7)	10.4 (44)
H-18	0.453 (12)	0.563 (18)	0.765 (8)	13.6 (55)
H-18B	0.502 (9)	0.416 (12)	0.802 (8)	6.9 (32)
H-19	0.453 (10)	0.380 (14)	0.678 (6)	9.6 (41)
H-21	0.588 (11)	0.286 (15)	0.594 (7)	10.7 (44)
H-22	0.780 (15)	0.248 (21)	0.579 (10)	18.7 (73)
H-24	0.917 (9)	0.132 (14)	0.540 (6)	8.6 (37)
H-25	0.979 (10)	0.069 (14)	0.435 (6)	8.7 (38)
H-27	0.645 (9)	0.271 (13)	0.509 (6)	7.5 (34)
H-28	0.607 (9)	0.427 (13)	0.373 (6)	7.5 (34)
H-29	0.404 (8)	0.286 (12)	0.446 (5)	5.8 (29)
OH-32	0.863 (13)	0.157 (18)	0.298 (8)	13.9 (55)

Standard deviations of the least significant figures are given in parentheses. The isotropic equivalent thermal parameter is given for anisotropic atoms (denoted by an asterisk).

(2 ml) and pyridine (0.5 ml), warmed slightly and kept overnight. Ice was added to the reaction mixture, the colourless ppt filtered, dried and crystallized from MeOH to yield shining rods of **1a**, mp 265–268°. UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm (log ε): 210 (4.12), 273 (4.02), 305 (shoulder). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1760 (phenol acetate), 1655 (amide carbonyls); ^{1}H NMR: see Discussion; ^{13}C NMR: see Table 1. MS *m/z*: 519 $[M]^+$, 447 $[M-CH_2CO]^+$, 434 $[477-Ac]$. Other peaks as in **1**.

X-ray analysis. All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University 1978; MULTAN 78 and MULTAN 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. De-clearcq and M. M. Wollfson, University of York England, 1978 and 1980; BLAS78A, and anisotropic block diagonal least squares refinement written by K. Hirotsu and E. Arnold, Cornell University 1980; PLUTO78, and anisotropic block diagonal least squares refinement written by K. Hirotsu and E. Arnold, Cornell University 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978. Crystallographic parameters have been deposited with the Cambridge Crystallographic Data File, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England and are available from them.

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