X-Ray Crystal and Molecular Structure of Nirurine, a Novel Alkaloid related to the Securinega Alkaloid Skeleton, from *Phyllanthus niruri* (Euphorbiaceae)

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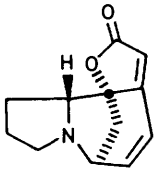
Nirurine, an alkaloid from the aerial parts of *Phyllanthus niruri* L. (Euphorbiaceae), was shown by single-crystal *X*-ray crystallography to possess the structure (**2**). Through extensive decoupling experiments a complete n.m.r. assignment of all of the protons and carbons in nirurine has been achieved.

The genus *Phyllanthus* in the family Euphorbiaceae has previously yielded a number of alkaloids in the (nor)securinine (**1**) series,[1–6] in addition to various terpenoid derivatives,[7–13] some of biological significance.[14]



(1)

Phyllanthus niruri L., a liana native to many subtropical areas of the world, is reputedly used against fever,[15] against jaundice,[16] and as a diuretic.[17] We therefore became interested in examining this plant and report here the isolation of a new alkaloid closely related biogenetically to, but quite distinctly different from, the *Securinega* alkaloids.

P. niruri has been investigated phytochemically on a number of previous occasions, and has been shown to afford lignans,[18–22] flavanoids,[23–25] triterpenes,[26,27] and steroids.[28,29] The enantiomer of norsecurinine[30] and 4-methoxynorsecurinine[31] are the only alkaloids to have been previously characterized from this plant, although three securinine-type alkaloids have been isolated.[27]

Chromatography of the alkaloid fraction (1.87%) on silica gel afforded nirurine (0.003 7% yield) as colourless crystals from chloroform–propane-2-ol (1:1). A molecular ion at *m/z* 219 in the mass spectrum analysed for $C_{12}H_{13}NO_3$, and the i.r. spectrum demonstrated the presence of an α,β-unsaturated γ-lactone ($\nu_{max.}$ 1 755 cm^{-1}) similar to that found in the dihydrosecurinine series. This conclusion was substantiated by the u.v. spectrum ($\lambda_{max.}$ 243 nm). No additional conjugation, or carbonyl or hydroxy groups, were observed in the u.v. or i.r. spectra and this led to the possibility that nirurine contained an additional ring in the form of an ether linkage. From the number of carbon atoms, nirurine was identified as a member of the norsecurinine series of alkaloids in which the γ,δ-double bond has been reduced. When the possible ether linkages to be formed within this skeleton were examined, none of them could account for the observed multiplicity of the downfield protons in the ^1H n.m.r. spectrum. It was therefore apparent that a new skeleton was present, and the molecule was examined by single-crystal *X*-ray crystallography.

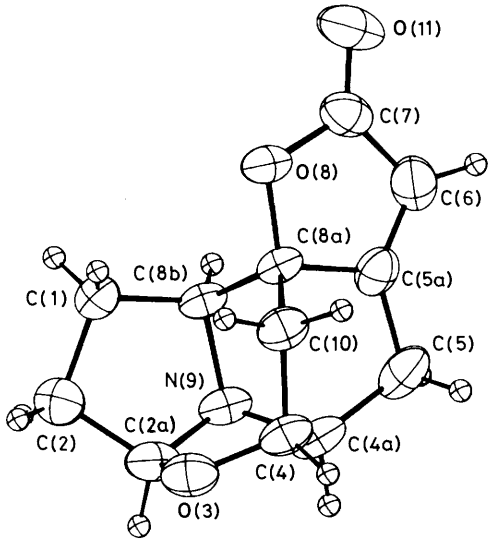


Figure 1. ORTEP display of the structure and conformation of nirurine (**2**) with crystallographic numbering scheme. Thermal ellipsoids are drawn at the 50% probability level, and hydrogen atoms are shown as spheres of arbitrary radius

Nirurine crystallized in the orthorhombic space group $P2_12_12_1$, and structure refinement with 1 051 reflexions converged at an *R*-value of 4.3%. The atomic arrangement deduced for nirurine is shown in Figure 1 and a stereoscopic view of the crystal packing is shown in Figure 2. There are three five-membered rings in the molecule; the γ-lactone is planar to within 0.01 Å, the pyrrolidine ring adopts an envelope conformation with C-2a at the flap, and the oxazolidine ring also has an envelope conformation with C-4a as the out-of-plane atom. The three six-membered rings all adopt boat conformations. The bridged perhydro-oxazepine ring adopts a chair conformation with the symmetry axis intersecting C-8a

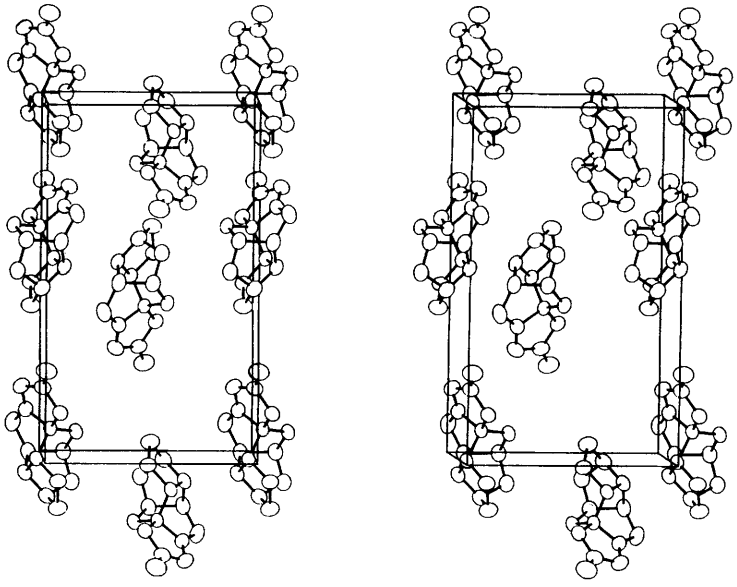


Figure 2. Stereoscopic view of the crystal packing of nirurine (**2**)

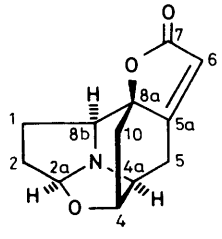
and the mid-point of the O-3–C-2a bond, and the bridged perhydro-oxacine ring adopts a somewhat distorted twist-boat-chair conformation. A number of the angles in the molecule were found to be highly strained. For example the three valency angles around the sp^2 carbon C-5a are 109.6(2), 112.7(2), and 132.7(3)°.

With the crystal structure in hand, our attention was refocussed on assigning the 360 MHz ^{1}H n.m.r. spectral signals. Inspection of the molecule reveals that nirurine should contain two quite discrete groups of coupled protons, namely 6-H—10-H and 2a-H—8b-H. Delineation of the assignments was achieved by systematic homonuclear decoupling experiments, beginning with 6-H.

The chemical shift of 6-H (δ 5.740) is comparable to that observed previously for the corresponding proton (3-H) in the *Securinega* alkaloids. The triplet nature (*J* 2.0 Hz) of the 6-H signal suggested that the proton bisected the angle between the two protons on C-5, and this was confirmed when irradiation reduced the complexity of signals at δ 3.338 and 2.956 to two doublets of doublets. Irradiation at δ 2.956 confirmed that δ 3.338 was the chemical shift of the other C-5 methylene proton, and also markedly simplified the broadened doublet of doublets at δ 3.542 which must therefore be due to 4a-H. The respective assignment of the two 5-H protons was made on the basis of established data.[32]

When the signal at δ 3.542 was irradiated, the two 5-H protons were again simplified to doublets of doublets, but more dramatically the doublet of doublets (*J* 4.26, 6.03 Hz) at δ 4.220 was reduced to a doublet (*J* 6.0 Hz). This proton is therefore 4-H which is coupled to 4a-H and to only one of the methylene protons 10-H. Inspection of a Dreiding model indicates that this proton is 10α-H since 10β-H subtends an angle of *ca.* 100° with 4-H. The β-proton at C-10 should therefore couple only with the geminal 10-H and appear as a simple doublet. One candidate for such a proton is that resonating as a doublet (*J* 14.1 Hz) at δ 2.287 and this was verified as follows.

Irradiation at δ 4.220 (4-H) simplified the resonance of 4a-H (δ 3.542) but more importantly also affected the doublet of doublet of doublets at δ 1.625, reducing it to a doublet of doublets (*J* 1.84 and 14.11 Hz). On decoupling at δ 1.625 the doublet at δ 2.287 collapsed to a singlet, and the resonance for 4-H (δ 4.220) changed to a narrow doublet. Additionally, the signal at δ 3.265 was simplified to a doublet of doublets; a small (*J* 1.84 Hz) coupling constant being eliminated in this process. Since all vicinal and geminal couplings have been accounted for, this must be a long-range coupling. The Dreiding model of nirurine (**2**) indicates that 10α-H and 8b-H have a classic W relationship, thereby permitting long-range coupling. This is the only coupling which exists between what are otherwise two isolated systems. At this point signals for 1-H_2, 2-H_2, and 2a-H remain to be assigned.

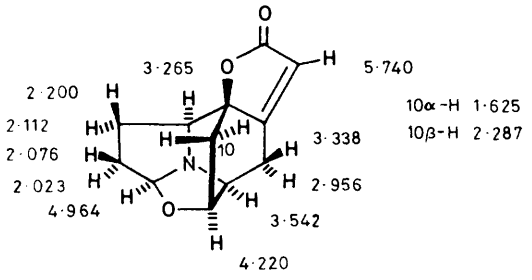


(**2**)

The only unattributable signal downfield is a doublet at δ 4.964, which must be 2a-H, on a carbon attached to both oxygen and nitrogen. Only one of the C-3 protons is coupled to 2a-H, and molecular models indicate that this is 2α-H, since 2β-H subtends an angle of 90° with 2a-H. This same proton (2β-H) also, from molecular models, should couple only to 1β-H and *not* 1α-H.

The four methylene protons of C-1 and C-2 appear in the region δ 1.995—2.295, and irradiation of 8b-H and 2a-H permitted unequivocal assignment of these protons. Thus irradiation at 8b-H substantially reduced in complexity the signal at δ 2.200 (1β-H) without affecting any other signals in this region. Similarly, irradiation at 4.964 (2a-H) reduced in complexity the multiplet at δ 2.023 which, based on Dreiding models could be assigned to 2α-H. The two remaining protons at δ 2.076 and 2.112 were assigned to 2β-H and 1α-H, respectively, thereby completing the assignment of the ^{1}H n.m.r. spectrum of nirurine as shown in diagram (**3**).

The ^{13}C n.m.r. spectrum of nirurine (**2**) provided some interesting problems in assignment. Spectra were recorded at 75.4 MHz and each of the carbon resonances was independently



	Hz		Hz		Hz
$J_{1\alpha,1\beta}$	n.d.	$J_{2\alpha,2\beta}$	n.d.	$J_{4a,5\beta}$	3·0
$J_{1\alpha,2\alpha}$	n.d.	$J_{2\alpha,2a}$	2·8	$J_{5\alpha,5\beta}$	19·6
$J_{1\alpha,2\beta}$	0	$J_{2\beta,2a}$	0	$J_{5\alpha,6}$	2·0
$J_{1\alpha,8b}$	7·1	$J_{4,4a}$	4·3	$J_{5\beta,6}$	2·0
$J_{1\beta,2\alpha}$	n.d.	$J_{4,10\alpha}$	6·0	$J_{8b,10\alpha}$	1·8
$J_{1\beta,2\beta}$	n.d.	$J_{4,10\beta}$	0	$J_{8b,10\beta}$	0
$J_{1\beta,8b}$	7·1	$J_{4a,5\alpha}$	2·2	$J_{10\alpha,10\beta}$	14·1

(3)

^{1}H N.m.r. data for nirurine (2). n.d. = not determined.

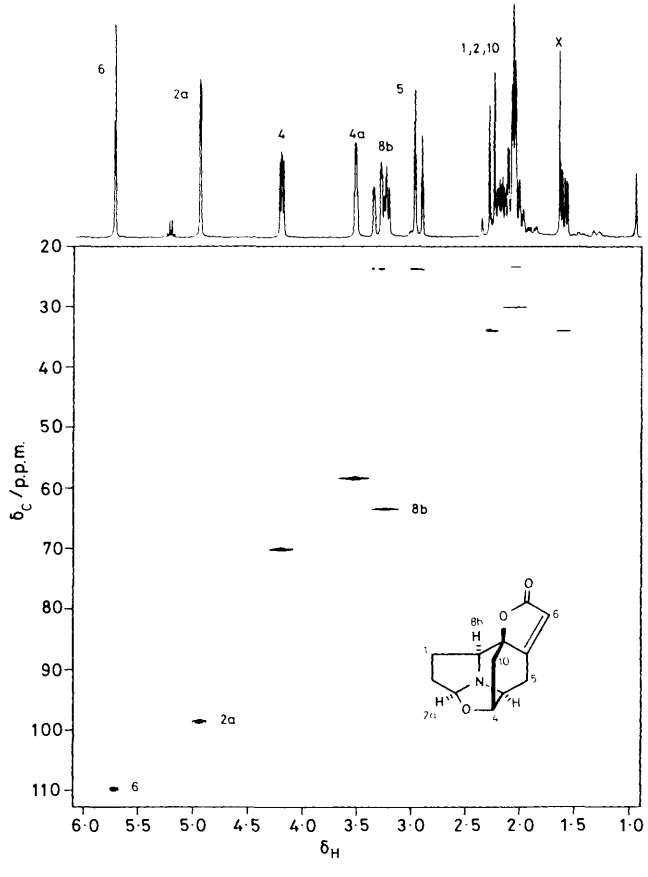


Figure 3. Heteronuclear 2D-n.m.r. correlation spectrum of nirurine (2)

observed. An attached proton test (APT) indicated that the four methylene carbons resonated at δ_C 23.30, 23.79, 30.13, and 34.05 p.p.m., and the five methine carbons at δ_C 58.37, 63.48, 70.16, 98.50, and 109.85 p.p.m. Quaternary carbons were observed at δ_C 82.50, 172.68, and 173.34 p.p.m.

Assignment of the resonance at δ_C 82.50 to C-8a was straightforward, as was the assignment of the protonated vinylic carbon C-6 to δ_C 109.85 and the methine carbon (C-2a) with two attached heteroatoms to δ_C 98.50. Initial assignment of the three remaining methine carbons, all of which are attached to heteroatoms, was through selective irradiation. Thus irradiation at δ 4.20(4-H) collapsed the resonance at δ_C 70.16, and irradiation at δ 3.55 (4a-H) specifically enhanced the resonance at δ_C 58.37, leaving the δ_C 63.48 signal to be assigned to C-8b.

The downfield quaternary carbons were distinguished by means of their respective multiplicities in the coupled carbon spectrum. Thus, while the signal at δ_C 173.34 was unchanged between the coupled and fully decoupled spectra, the resonance at δ_C 172.68 was markedly sharpened, indicating this to be the signal for C-5a, coupled to 4a-H and 5-H_2. The former carbon was therefore assigned to C-7.

The chemical shifts of the various methylene protons precluded selective irradiation experiments in order to make unambiguous assignments. A heteronuclear correlation spectrum permitted these attributions. The resulting heteronuclear 2D plot (Figure 3) categorically confirmed the assignments of the five methine carbons and established that C-5 resonated at δ_C 23.79 and that C-10 resonated at δ_C 34.05. There remained the assignment of C-1 and C-2 to the resonances at δ_C 23.30 and 30.13. Expansion and enhancement of the 20—36 p.p.m. region (Figure 4) demonstrated that the rather diffuse methylene protons attached to C-1 were associated with the resonance at δ_C 23.30, and the higher-field protons of C-2 with the resonance of δ_C 30.13. The complete ^{13}C assignments of nirurine are shown in diagram (4).

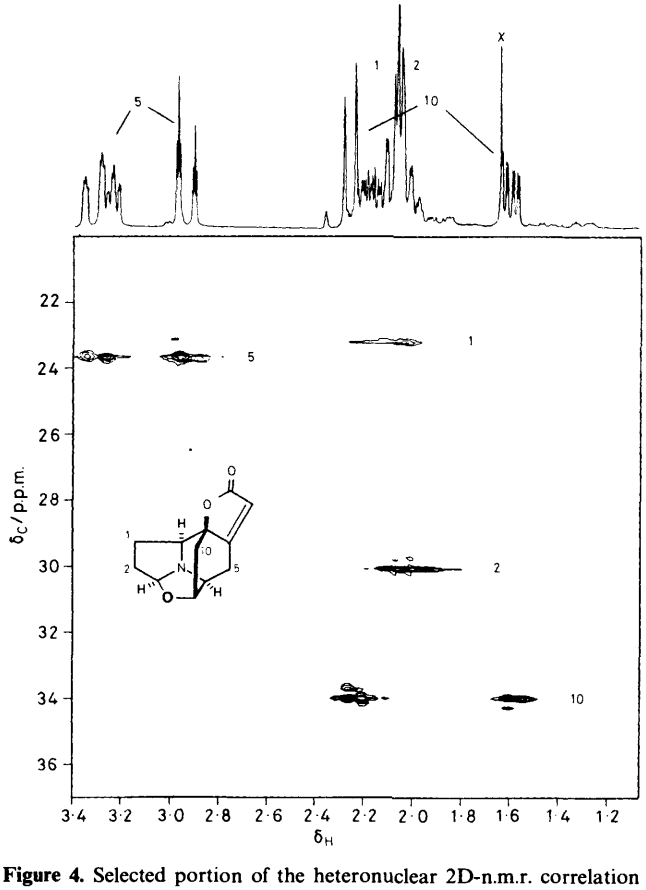
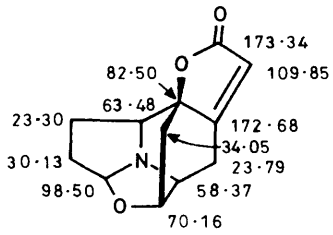


Figure 4. Selected portion of the heteronuclear 2D-n.m.r. correlation spectrum of nirurine (2)

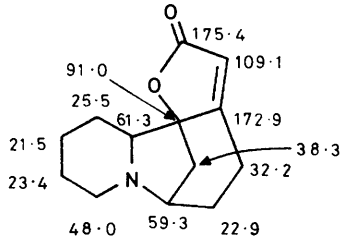
During the course of this work Beutler and Livant [33] reported on the 13C n.m.r. assignments of securinine and some of its analogues. For comparison with nirurine, diagram (4), the data



(4)

^{13}C N.m.r. data for nirurine (2)

for dihydrosecurinine are shown in diagram (5). No ^{13}C data have been reported for the norsecurinine (1) series of alkaloids. Because of the difference in carbon framework it is difficult to generalize about such a comparison, but certainly the similarities of signals for C-11, C-12, and C-13 in (5) with C-7, C-6, and C-5a, respectively, in (4) is noteworthy. The chemical shift of C-9 (securinine series) may be important in helping to distinguish the carbon skeletons.

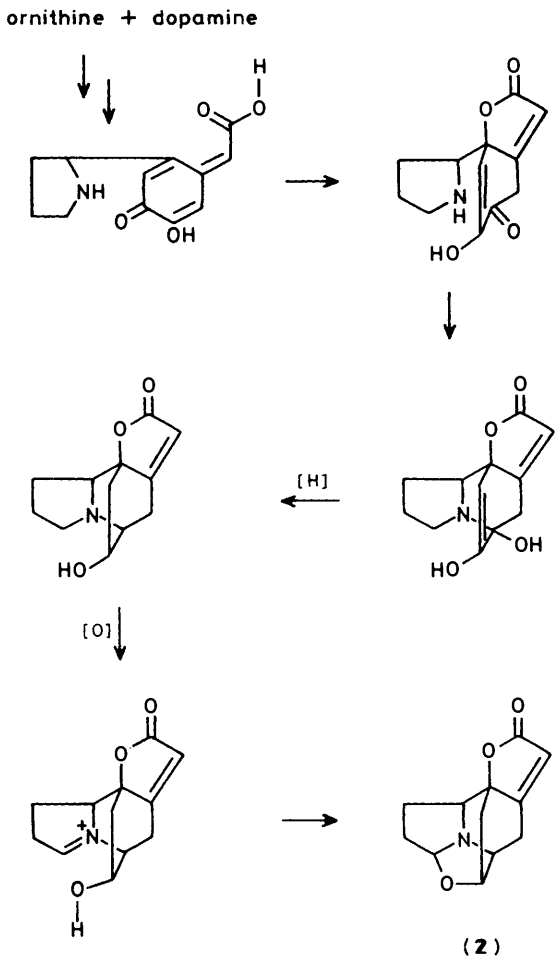


(5)

^{13}C N.m.r. data for dihydrosecurinine (5). Data are from ref. 33

The most important fragment ion in the mass spectrum of nirurine (2) appeared at *m/z* 191, analysing for $C_{11}H_{13}NO_2$, and representing a loss of CO from the molecular ion. Since dihydrosecurinine[1,34] and dihydronorsecurinine did not exhibit this loss, the carbinolamine ether unit is probably involved. The data thus provide an indication of the relative configuration; the absolute configuration of nirurine is currently under investigation.

It is well established that securinine is derived from lysine and tyrosine, the latter amino acid providing the six-membered carbocyclic ring and the γ-lactone.[35] In the case of nirurinê (2) it is clear that a strong structural similarity exists between this and the securinine skeleton. The principal difference is that in the case of securinine, the lysine-derived nitrogen is joined to C-4′ of tyrosine, whereas in nirurine the (presumably) ornithine-derived nitrogen is attached to C-3′ of the aromatic amino acid. A number of mechanisms can be written for this process, depending on whether the carbinolamine ether oxygen is regarded as being introduced after the skeleton has been formed or whether the oxygen is introduced from the aromatic amino acid. In the Scheme a biogenetic pathway is proposed which outlines the latter case where dopamine has replaced tyrosine. The initial steps are analogous to those in securinine biosynthesis; however, a critical step is attack of the ornithine-derived nitrogen on C-3′ of the dopamine-derived nucleus followed by reduction of the carbinolamine. Formation of the iminium species and nucleophilic attack by oxygen then affords nirurine (2).



Scheme. Biogenesis of nirurine (2)

Experimental

M.p.s were determined using a Kofler hot-stage microscope and are uncorrected. I.r. spectra were recorded with a Beckman model IR 18-A spectrophotometer with polystyrene calibration at 1 601 cm^{-1} or with a Nicolet MX-1 FT-IR interferometer; absorption bands are recorded in wavenumbers (cm^{-1}). U.v. spectral data were measured with a Beckman model DB-G spectrophotometer. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ at 360 MHz on a Nicolet NT-360 instrument at the Midwest Regional NMR Facility, University of Illinois at Urbana. ^{13}C N.m.r. spectra were recorded in $CDCl_3$ at 75.43 MHz on a Varian Associates XL-300 instrument. Mass spectra were obtained at 70 eV on a Varian MAT 112S double-focussing spectrometer.

Plant Material.—The aerial parts of *Phyllanthus niruri* (Euphorbiaceae) were collected in Chon Buri, Thailand and identified by Dr. P. Trisonthi through comparison with specimen numbers 21449 and 30692 deposited at the Forest Herbarium, Royal Forest Department, Bangkok, Thailand. A herbarium sample is deposited in the herbarium of the Faculty of Pharmacy, Mahidol University.

Isolation of Nirurine (2).—The dried aerial part of *Phyllanthus niruri* (1.5 kg) was defatted with light petroleum (b.p. 60—80 °C), and the marc was basified with calcium hydroxide (225 g) and successively extracted with chloroform (12 l) and methanol (12 l) in a Soxhlet apparatus. Evaporation of the chloroform fraction afforded a crude residue (187.3 g), and similar treatment of the methanol extract afforded another residue (200 g). Using

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for nirurine (**2**) with e.s.d.s in parentheses[a]

Atom	*x*	*y*	*z*
C(1)	9 906(4)	0 450(3)	5 319(2)
C(2)	11 445(5)	0 405(4)	6 022(2)
C(2a)	13 306(4)	−0 167(3)	5 604(2)
O(3)	14 357(3)	0 954(2)	5 165(1)
C(4)	14 463(4)	0 558(3)	4 313(2)
C(4a)	14 230(4)	−1 065(3)	4 345(2)
C(5)	13 635(4)	−1 776(3)	3 536(2)
C(5a)	11 710(4)	−1 126(3)	3 261(2)
C(6)	10 386(5)	−1 312(3)	2 660(2)
C(7)	8 795(4)	−0 270(3)	2 761(2)
O(8)	9 210(2)	0 552(2)	3 446(1)
C(8a)	11 046(3)	0 049(2)	3 809(1)
C(8b)	10 665(3)	−0 595(3)	4 667(2)
N(9)	12 644(3)	−1 174(2)	4 985(1)
C(10)	12 684(4)	1 191(3)	3 827(2)
O(11)	7 304(4)	−0 042(3)	2 359(1)

[a] Crystallographic numbering scheme, as in Figure 1.

Table 2. Bond lengths (Å) for niruvine (**2**) with e.s.d.s in parentheses

C(1)–C(2)	1.538(4)	C(5)–C(5a)	1.497(4)
C(1)–C(8b)	1.531(4)	C(5a)–C(6)	1.329(4)
C(2)–C(2a)	1.519(4)	C(5a)–C(8a)	1.488(3)
C(2a)–O(3)	1.456(3)	C(6)–C(7)	1.460(4)
C(2a)–N(9)	1.450(4)	C(7)–O(8)	1.382(3)
O(3)–C(4)	1.431(4)	C(7)–O(11)	1.213(4)
C(4)–C(4a)	1.539(4)	O(8)–C(8a)	1.445(3)
C(4)–C(10)	1.549(4)	C(8a)–C(8b)	1.538(3)
C(4a)–C(5)	1.525(5)	C(8a)–C(10)	1.539(3)
C(4a)–N(9)	1.489(4)	C(8b)–N(9)	1.525(3)

a typical acid–base shakeout with chloroform as the solvent, the chloroform fraction afforded 1.3 g of crude alkalides and the methanol fraction 1.5 g of crude alkaloids.

A portion of the crude alkaloid fraction (2 g) was subjected to flash chromatography on silica gel G (100 g), with chloroform (340 ml; 20 fractions) and chloroform (340 ml, 20 fractions) and chloroform–ethanol (95:5; 200 ml; 10 fractions) as eluant. The last 6 fractions eluted with chloroform and the first nine eluted with chloroform–ethanol were combined and rechromatographed on silica gel (70 g), with benzene (100 ml; 5 fractions) and then benzene–methanol (9:1; 400 ml; 20 fractions) as eluant. Fractions 16—19 from this column were further chromatographed on silica gel (70 g) with chloroform (60 ml; 6 fractions), ethyl acetate (120 ml; 12 fractions), and finally methanol (80 ml; 4 fractions) as eluant. Nirurine was observed (by t.l.c.) in fractions 7—12 and was recrystallized from chloroform–propan-2-ol (1:1) to afford the pure alkaloid (**2**) (39.8 mg, 0.0037%) as white, orthorhombic crystals, m.p. 205—209 °C; $\nu_{max.}$(KBr) 2 906, 1 755, 1 746, 1 658, 1 650, 1 235, 1 200, 1 112, 991, 943, 925, 892, 855, and 775 cm^{-1}; $\lambda_{max.}$(MeOH) 243 nm (log ε 4.17); $\alpha_D(\lambda_{max.})$ +196° (589), +56° (578), −35° (546), −53° (436), and −13° (365); *m/z* (% rel. int.) 219 (M^+, 100%), 192 (11), 191 (90), 190 (15), 175 (41), 163 (26), 162 (26), 148 (16), 147 (15), 146 (10), 135 (50), 134 (37), 121 (17), 120 (52), 119 (21), 118 (18), 109 (12), 107 (12), 106 (15), 96 (14), 95 (18), 94 (19), 93 (17), 92 (10), 91 (12), 82 (10), 81 (19), 80 (49), 79 (17), 78 (21), 77 (24), 68 (47), and 54 (51) (Found: M^+, 219.0892. $C_{12}H_{13}NO_3$ requires *M*, 219.0895); δ_{Hg} see Diagram (**3**) and Figure 3; δ_C see Diagram (**4**) and Figure 3.

Crystal Data.—$C_{12}H_{13}NO_3$, *M* = 219.2, Orthorhombic, *a* = 6.710(5), *b* = 9.431(8), *c* = 16.192(22) Å, *V* = 1024.7 Å^3, D_c = 1.41 g cm^{-3}, *Z* = 4, *F*(000) = 464, space group $P2_12_12_1$, Mo-K_α radiation, λ = 0.7107 Å, μ = 0.62 cm^{-1}.

Crystallographic Measurements.—Unit-cell dimensions and data were obtained for a crystal, size 1.5 × 0.7 × 2.75 mm, on a Nicolet P3 automatic diffractometer. Reflexions, surveyed by the θ–2θ scan method, in the range θ < 25° were treated as observed, and the intensities of 1 051 independent reflexions were obtained.

X-*Ray Structure Analysis.*—The structure was elucidated by direct methods utilizing the MULTAN program.[36] All H atoms were located in difference electron density maps calculated at intermediate stages of structure refinement using the SHELX program.[37] The co-ordinates for all atoms, anisotropic thermal parameters for the non-H atoms, and the isotropic thermal parameters for the H atoms were varied in least-squares calculations. The C–H bond lengths were constrained to 1.00 Å at the beginning of each cycle of least-squares refinement. Convergence was reached at *R* 4.3% and the weighting scheme used in the final cycles of least-squares refinement was $w = 1.8144/(\sigma^2F_o + 0.001\ 51F_o^2)$. Final positional parameters for non-H atoms are listed in Table 1 and bond lengths are given in Table 2. There are no short intermolecular contacts. Valency angles, torsion angles, H-atom co-ordinates, and thermal parameters are listed in Supplementary Publication No. SUP 56595 (5 pp).

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