Phytochemistry, Vol 28, No 4, pp 1245–1249, 1989
Printed in Great Britain

0031–9422/89 $3 00+0 00

ALKALOIDS OF *CORYDALIS PALLIDA* VAR. *SPARSIMAMMA* AND THE STRUCTURE AND STEREOCHEMISTRY OF PALLIMAMINE*

SHENG-TEH LU,† JENG-FEN HWANG,† TIAN-SHUNG WU,‡ DONALD R MCPHAIL,§ ANDREW T MCPHAIL§ and KUO-HSIUNG LEE‖

†School of Pharmacy, Kaohsiung Medical College, Kaohsiung 80731, Taiwan, R O.C, ‡Department of Applied Chemistry, Providence College of Arts and Sciences, Shalu 43309, Taichung Hsien, Taiwan, R.O.C, §Department of Chemistry, P M Gross Chemical Laboratory, Duke University, Durham, NC 27706, U.S A., ‖Natural Products Laboratory, Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, U S.A

(*Received* 20 *September* 1988)

Key Word Index—*Corydalis pallida* var *sparsimamma*, Fumariaceae; alkaloids; (±)-pallimamine; α-allocryptopine, protopine, (±)-tetrahydropalmatine; (−)-capaurimine; X-ray crystal structure

Abstract—A novel berbine alkaloid, (±)-pallimamine, as well as four known alkaloids, protopine, α-allocryptopine, (±)-tetrahydropalmatine, and (−)-capaurimine, have been isolated from the whole herb of *Corydalis pallida* var. *sparsimamma* The structure of (±)-pallimamine was established from spectral data in conjunction with a single-crystal X-ray analysis.

INTRODUCTION

As part of our continuing investigation on the constituents of Formosan *Corydalis* genus [1], we have isolated a novel berbine alkaloid, (±)-pallimamine (**1**) together with four known alkaloids, protopine (**2**), α-allocryptopine (**3**), (±)-tetrahydropalmatine (**4**) and (−)-capaurimine (**5**) from the whole plant of *corydalis pallida* var. *sparsimamma* (Ohwi) Ohwi. We herein describe the isolation and elucidation of the structure of these alkaloids.

RESULTS AND DISCUSSION

(±)-Pallimamine (**1**) was isolated in the form of pale yellow prisms, mp 203–207°; $[\alpha]_D^{23}$ 0°($CHCl_3$; *c* 0.05) HRMS established the molecular formula as $C_{23}H_{27}NO_5$(M^+ *m/z* 397.1848). Peaks at 214 and 277 nm in the UV spectrum, which showed no shift upon addition of KOH, suggested the presence of a non-phenolic berbine nucleus in this alkaloid

The ^{1}H NMR spectrum of **1** contained signals for four methoxy groups [δ 3 85 (6H, *s*) and 3.86 (6H, *s*)] and a sharp three-proton singlet at δ 1.15 due to a tertiary methyl group at C-13 Three aromatic proton resonances at δ 6.28 (1H, *s*), 6.81 (1H, *d*, J = 9 Hz), and 6 92 (1H, *d*, J = 9 Hz), were ascribed to H-4, H-11, and H-12, respectively. Signals for the C-8 methylene protons appeared at δ 3 38 and 4.34 (each 1H, *d*, J = 16.3 Hz) while those for the C-14 methylene group were at δ 4.19 and 4.69 (each 1H, *d*, J = 10.5 Hz). A sharp one-proton singlet for H-13a occurred at δ 3.34. Signals at δ 2.57 (1H, *dt*, J = 3.0 and 11.2 Hz), 2 74 (1H, *dd*, J = 3.0 and 16 4 Hz), 3.08 (1H, m), and 3.27 (1H, *dd*, J = 5.4 and 11.2 Hz) for four mutually-coupled protons were assigned to H-5eq, H-6ax, H-6eq, and H-5ax, respectively Lack of a hydroxy group absorption in the IR spectrum, absence of any NMR signal for a proton at C-13, and the upfield shift, by *ca* δ 0.5, for the C-4 proton signal pointed to the presence of an oxymethylene bridge between C-1 and C-13, and this was supported by the appearance of fragment ions at *m/z* 206 and 191 in the mass spectrum (Scheme 1). The IR spectrum of **1** contained a Bohlmann band at 2840 cm^{-1} characteristic of a *trans*-quinolizidine skeleton The above data were in excellent accord with structure **1** for pallimamine but left undefined the relative stereochemistry at C-13 and C-13a.

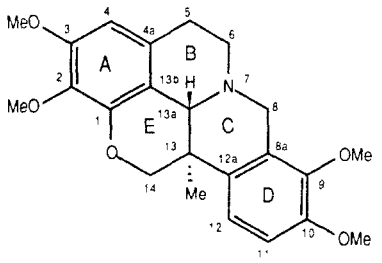
Single-crystal X-ray analysis defined the complete structure and relative stereochemistry of **1**. The crystal structure was solved by direct methods.* Full-matrix least-squares refinement of atomic positional and thermal parameters converged at R = 0 044 (R_w = 0.064)† over 2867 reflections Non-hydrogen atom positional parameters are listed in Table 1 The solid-state conformation of one enantiomer is illustrated in Fig 1 and it clearly shows that the methyl group at C-13 and the hydrogen atom at C-13a are mutually *trans* The shortest intermolecular distance between non-hydrogen atoms in crystals of **1**, C-14 . 0-16 = 3.248(2) Å, corresponds to a normal van der Waals type separation

Bond lengths and angles in **1** (Fig 2) are generally close to accepted values [2]. Aromatic rings A and D, with mean dihedral angles of 1 6° and 1 0°, respectively, about ring bonds are both approximately planar. The conformations adopted by their methoxy substituents and the associated geometries agree with expectations [3–6]. Thus, whereas C-20 lies only 0.114 Å from the least-squares plane through ring A carbon atoms and C-24 is

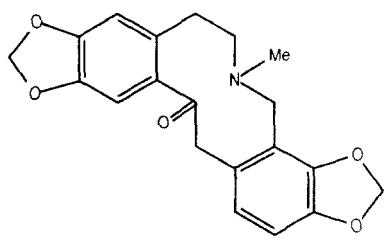
*Part 9 in the series 'Studies on the Alkaloids of Formosan *Corydalis* Species' For part 8, see ref [1].

* Crystallographic calculations were performed on a PDP11/44 computer by use of the Enraf–Nonius Structure Determination Package incorporating the direct methods program MULTAN11/82

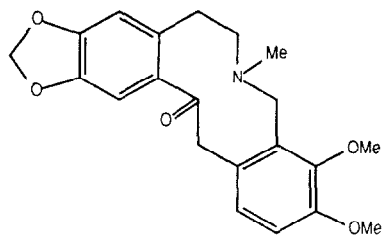
† $R = \Sigma||F_o|-|F_o||/\Sigma|F_o|$, $R_w = [\Sigma w(|F_o|-|F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.



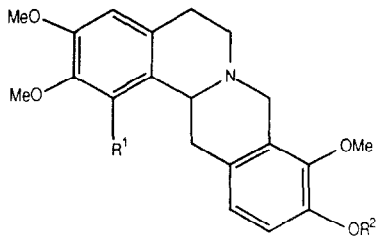
1



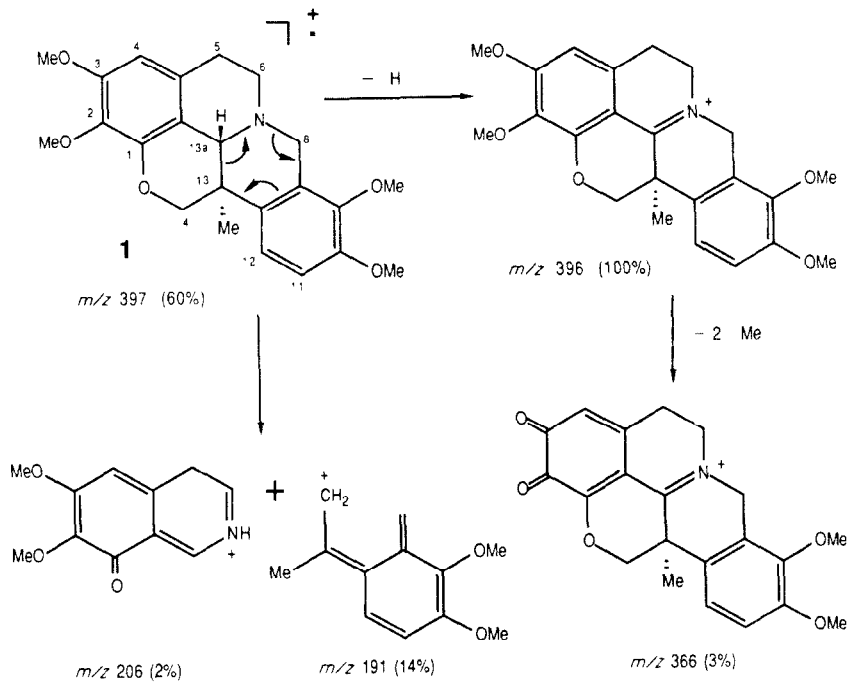
2



3



4 R^1 = H, R^2 = Me
5 R^1 = OH, R^2 = H



Scheme I. Mass fragments of pallimamine **(1)**

only 0 113 Å from the corresponding ring D plane, steric overcrowding of substituents forces C-18 and C-22 to lie 1 266 and 1 255 Å, respectively, from these planes These conformational differences are reflected in the values of the C(ar)—O bonded distances, variations in the exocyclic bond angles subtended at the phenyl ring carbon atoms bearing the methoxy substituents, and the C(ar)—O —C(Me) angles When the methoxy carbon atoms lie

Table 1 Non-hydrogen atom fractional coordinates and equivalent isotropic thermal parameters for pallimamine (1), with estimated standard deviations in parentheses

Atom	x	y	z	B(Å^2)
C(1)	0 2953(2)	0 02060(5)	0.3268(2)	2 54(3)
C(2)	0 2987(2)	0.06727(5)	0.2905(2)	2 70(3)
C(3)	0 4328(2)	0 08551(5)	0.2217(2)	2 81(3)
C(4)	0 5594(2)	0 05604(6)	0.1871(2)	2 90(3)
C(4a)	0 5537(2)	0 00905(5)	0 2224(2)	2 55(3)
C(5)	0 6840(2)	−0 02387(6)	0 1731(2)	2 99(3)
C(6)	0 6840(2)	−0 07005(6)	0 2559(2)	2 99(3)
N(7)	0 5181(2)	−0 08947(4)	0 2580(2)	2 56(2)
C(8)	0 5330(2)	−0 13471(6)	0 3345(2)	3 06(3)
C(8a)	0 3723(2)	−0 15305(6)	0 3844(2)	2 74(3)
C(9)	0 3677(2)	−0 19879(6)	0.4336(2)	3 19(3)
C(10)	0 2244(2)	−0 21830(6)	0.4820(2)	3 70(4)
C(11)	0 0850(2)	−0 19025(7)	0.4842(2)	3 92(4)
C(12)	0 0901(2)	−0 14447(6)	0.4372(2)	3 42(3)
C(12a)	0 2315(2)	−0 12503(6)	0.3310(2)	2 41(3)
C(13)	0.2367(2)	−0.07518(5)	0.3871(2)	2 69(3)
C(13a)	0 4171(2)	−0 05887(5)	0.3453(2)	2 40(3)
C(13b)	0 4246(2)	−0 00905(5)	0.2956(2)	2.41(3)
C(14)	0 1507(2)	−0 04274(6)	0.4357(2)	2 71(3)
C(15)	0 1565(2)	−0 07199(6)	0.1652(2)	2 96(3)
O(16)	0 1569(1)	0 00526(4)	0.3890(1)	3 18(2)
O(17)	0.1729(1)	0 09618(4)	0 3272(1)	3 21(2)
C(18)	0 0494(3)	0 10265(9)	0 2043(3)	5 81(5)
O(19)	0.4268(2)	0 13199(4)	0.1939(2)	3 91(3)
C(20)	0 5655(3)	0 15261(7)	0.1326(3)	5 01(5)
O(21)	0 5061(2)	−0 22605(4)	0.4269(2)	3 84(3)
C(22)	0 5969(3)	−0 23410(8)	0.5726(3)	5 47(5)
O(23)	0.2338(2)	−0 26389(5)	0.5234(2)	5 19(3)
C(24)	0.0889(3)	−0 28548(8)	0 5654(3)	5 88(5)

close to the aromatic ring plane and π-electron delocalization is maximized, the C(ar)–O bond lengths [C-3–O-19 = 1.359(2) Å, C-10–O-23 = 1.361(2) Å] are significantly shorter than those involving the other two methoxy substituents [C-2–O-17 = 1 382(2) Å, C-9–O-21 = 1 382(2) Å]. In contrast to the situation at C-2 and C-9 where exocyclic C–C–O angles are approximately equal, the C-4–C-3–O-19 and C-11–C-10–O-2 angles are respectively greater than the C-2–C-3–O-19 (Δ 9.7°) and C-9–C-10–C-23 (Δ 6.8°) angles in order to reduce intramolecular non-bonded H(Me)... H(aryl) interactions. Enlargement of the C(ar)–O–C(Me) bone angles at O-19 [117.3(2)°] and O-23 [117 7(2)°] from the values found at the out-of-plane methyl groups [113 3(1)° at O-17, 114,3(2)° at O-21] also aids in relieving these same interactions.

Endocyclic torsion angles in the *trans*-fused B and C rings are related by approximate C_2 symmetry axes passing through the mid-points of the C-4a–C-13a and C-6–N-7 bonds in the former and through the mid-points of the C-8a–C-12a and N-7–C-13a bonds in the latter, and thus these rings are best described as half-chair forms. The bonding geometry at N-7 (mean bond angle = 108.9°) is pyramidal An approximate mirror plane of symmetry passing through C-1 and C-13 relates endocyclic torsion angles in ring E, and, with small torsion angles about adjacent C-1–C-13b and C-1–O-16 bonds, this ring has an envelope conformation in which C-13 is the out-of-plane atom. Although C-14 lies in the aromatic ring A plane (Δ = 0 008 Å), the slightly longer C-1–O-16 distance of 1 373(2) Å compared with the mean of 1.360(2) Å for corresponding bonds at C-3 and C-10 is indicative of some degree of bond strain in ring E.

Other alkaloids isolated from the same source were characterized as protopine (**2**) [7], α-allocryptopine (**3**) [7], (±)-tetrahydropalmatine (**4**) [8], and (−)-capauri-

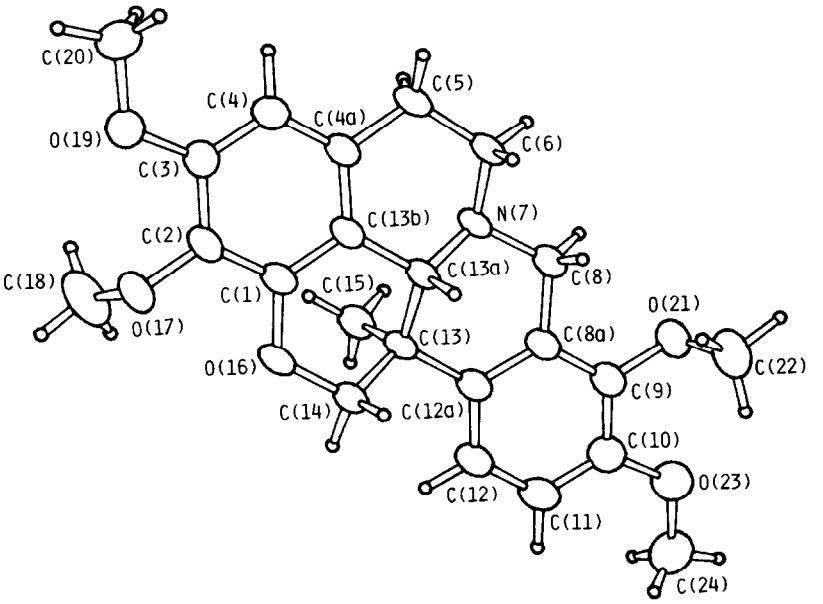


Fig 1 Structure and solid-state conformation of one enantiomer of pallimamine (**1**); small circles denote hydrogen atoms. Endocyclic torsion angles ($\omega_{i,j}$, $\sigma \pm 0\,2 - 0\,3°$) for the enantiomer shown follow $\omega_{1,2} - 0\,1$, $\omega_{2,3}$ 1 6, $\omega_{3,4} - 0\,8$, $\omega_{4,4a} - 1\,6$, $\omega_{4a,13b}$ 3 1, $\omega_{13b,1} - 2.3$ in ring A, $\omega_{4a,5} - 18\,5$, $\omega_{5,6}$ 46 8, $\omega_{6,7} - 63\,8$, $\omega_{7,13a}$ 49 7, $\omega_{13a,13b} - 23.0$, $\omega_{13b,4a}$ 7.4 in ring B, $\omega_{7,8}$ 44 7, $\omega_{8,8a} - 13\,0$, $\omega_{8a,12a}$ 3 0, $\omega_{12a,13} - 23.9$, $\omega_{13,13a}$ 57 4, $\omega_{13a,7} - 69.4$ in ring C, $\omega_{8a,9}$ 1 9, $\omega_{9,10} - 1.8$, $\omega_{10,11}$ 0 9, $\omega_{11,12} - 0\,1$ $\omega_{12,12a}$ 0 1, $\omega_{12a,8a} - 1\,0$ in ring D, $\omega_{1,13b} - 5\,5$, $\omega_{13b,13a}$ 34 2, $\omega_{13a,13} - 59\,5$, $\omega_{13,14}$ 61.4, $\omega_{14,16} - 35\,0$, $\omega_{16,1}$ 5 2 in ring E

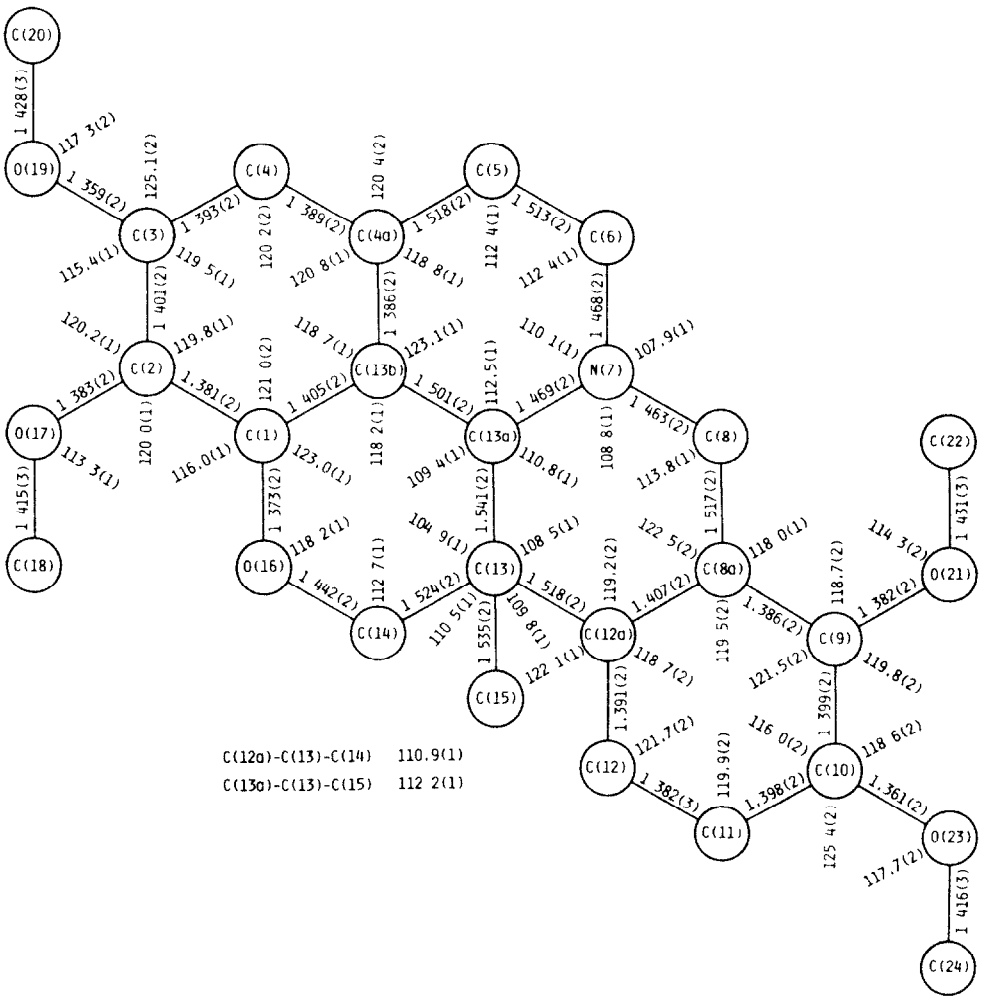


Fig 2 Bond lengths (Å) and bond angles (deg) in pallimamine (**1**), with estimated standard deviations in parentheses

mine (**5**) [9] by comparison with authentic samples and/or from spectral data (UV, IR, ^{1}H NMR, and MS)

EXPERIMENTAL

Mps uncorr, ^{1}H NMR 400 MHz, chemical shifts are reported in ppm (δ) from TMS as internal standard, MS 70 eV, TLC, Pre-coated silica gel plates were used for analytical (Merck, 60F-254, 0 25 mm) and prep (Merck, silica gel GF, 20 × 20 cm, 2000 μ) TLC

Plant material Corydalis pallida var *sparsimamma* was collected in Nan-Shan village, Yilan-Hsien, Taiwan, in July, 1973, and verified by Prof C -S Kuoh A voucher specimen is deposited in the Herbarium of Kaohsiung Medical College, Kaohsiung, Taiwan, R O C

Extraction and separation The fresh whole herb (27 5 kg) was exhaustively extracted with warm EtOH Following removal of EtOH, the solid residue was dissolved in 3% AcOH The resulting acidic soln was basified with NH_4OH and extracted with $CHCl_3$ The $CHCl_3$ layer was shaken with 2% NaOH and then with 2% H_2SO_4 Neutralization of the combined aq extracts with conc NH_4OH was followed by extraction with $CHCl_3$ Drying and evapn of this $CHCl_3$ extract afforded the crude non-phenolic alkaloids (Part A, 40.7 g) CC on silica gel with elution by $CHCl_3$–MeOH mixtures of increasing polarity afforded 10 fractions Colourless crystalline protopine (**2**) (2 03 g) was obtained from fraction 2 which, following removal of **2**, was further purified by silica gel prep TLC by use of $CHCl_3$–MeOH (10 1) as eluant to give pale yellow prisms of α-allocryptine (**3**) (R_f 0 37, 72 mg)

The mother liquor remaining after removal of **3** was repeatedly purified by prep TLC (silica gel, $CHCl_3$–Me_2CO 14 1) to furnish pale yellow prisms of (±)-pallimamine (**1**) (R_f 0 73, 5 mg) Compound **1** mp 203–207°, Calcd for $C_{23}H_{27}NO_5$ (M^+) *m/z* 397 1887, Found 397 1848, $[\alpha]_D^{24}$ 0° ($CHCl_3$, *c* 0 05), IR ν_{max}^{KBr} cm^{-1} 2840, 1610, 1590, 1500, UV λ_{max}^{EtOH} nm (log ε) 214 (4 56) and 279 (3 18), MS *m/z*(rel int) 397 (M^+, 60), 396 (100), 366 (3), 206 (2), 191 (14), and 160 (4) Fraction 4 was further sepd by prep TLC (silica gel, $CHCl_3$–Me_2CO 3 1) to afford colourless crystals of (±)-tetrahydropalmatine (**4**) (R_f 0 87, 28 mg)

Tertiary phenolic alkaloids (Part B, 4 3 g) were obtained by work-up of the aq. NaOH extract of the tertiary base. Part B was chromatographed on a silica gel column with $CHCl_3$–Me_2CO (10 1) as eluant to give a red-brown residue which was purified by prep TLC (silica gel, $CHCl_3$–Me_2CO 2 1) to afford a yellow amorphous substance, (−)-capaurimine (**5**) (R_f 0 48, 65 mg)

X-Ray analysis of (±)-*Pallimamine* (1) Crystal data $C_{23}H_{27}NO_5$, $M_r = 397.48$, monoclinic, $a = 7.274(2)$ Å, $b = 28.975(7)$ Å, $c = 6.089(2)$ Å, $\beta = 95.39(2)°$ (from 25 orientation reflections $51° < \theta < 67°$), $V = 1283.3$ Å^3, $Z = 4$, $D_{calc} = 1.291$ g/cm^3, μ(CuKα radiation, $\lambda = 1.5418$ Å) = 7.0 cm^{-1}. Space group $P2_1/c(C_{2h}^5)$ uniquely from the systematic absences $0k0$ when $k \neq 2n$, $h0l$ when $l \neq 2n$. Sample dimensions $0.12 \times 0.18 \times 0.80$ mm

Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs Intensity data ($+h$, $+k$, $\pm l$, $\theta_{max} = 67°$, 3646 unique reflections) were recorded on an Enraf-Nonius CAD-4 diffractometer [CuKα radiation, incident-beam graphite monochromator, ω-2θ scans, scanwidth $(1.15 + 0.14 \tan\theta)°$] A total of 2867 reflections with $I > 3.0\sigma(I)$ were retained for the analysis, and the usual Lorentz and polarization corrections were applied.

The crystal structure was solved by direct methods Approximate positions for 26 out of the total of 29 non-hydrogen atoms were derived from an *E*-map, and the remaining 3 atoms were then located in a weighted F_0 Fourier systhesis. Several rounds of full-matrix least-squares adjustment of positional and anisotropic temperature factor parameters for these atoms were followed by a series of difference Fourier syntheses which revealed hydrogen atom locations Inclusion of hydrogen atom positional and isotropic thermal parameters as variables in the subsequent least-squares iterations led to convergence (max shift/esd < 0.03) at $R = 0.044$ ($R_w = 0.064$). Final non-hydrogen atom positional parameters are listed in Table 1. A view of the solid-state conformation, with the atom numbering scheme, is provided in Fig. 1 Anisotropic temperature factor parameters, hydrogen atom positional and thermal parameters, bond lengths, bond angles, torsion angles, and a list of observed and calculated structure amplitudes have been deposited with the Cambridge Crystallographic Data Centre

Neutral atom scattering factors used in all structure-factor calculations were taken from lit. [10] In the least-squares iterations, $\Sigma w\Delta^2$ [$w = 1/\sigma^2(|F_0|)$, $\Delta = (|F_0| - |F_c|)$] was minimized

Acknowledgement— The authors are indebted to Prof H Furukawa (Meijo University, Japan) for high-resolution mass spectral data

REFERENCES

1 Wu, T. S., Huang, S -C, Lu, S -T, Wu, Y. -C, McPhail, D. R., McPhail, A T and Lee, K H (1988) *Heterocycles* **27**, 1565
2 Allen, F H, Kennard, O, Wastson, D G, Brammer, L, Orpen, A G and Taylor, R (1987) *J Chem Soc Perkin Trans II* S1
3 Coggon, P, McPhail, A T and Wallwork, S C (1970) *J Chem Soc B* 84.
4. Coggon, P, Farrier, D. S, Jeffs, P W and McPhail, A T (1970) *J Chem Soc B* 1267
5 Luhan, P A and McPhail, A T (1972) *J Chem Soc Perkin Trans II* 2006.
6 Luhan, P A and McPhail, A. T (1973) *J Chem. Soc. Perkin Trans II* 51
7 Lu, S -T, Wang, S - I and Su, T - L (1971) *Yakugaku Zasshi* **91**, 778
8 Lu, S - T, Lin, C.- N and Wu, T. S. (1972) *J Chinese Chem. Soc* **19**, 41.
9 Kaneko, H and Naru, S (1971) *Yakugaku Zasshi* **91**, 101.
10. *International Tables for X-Ray Crystallography* (1974) Vol VI Kynoch Press, Birmingham