Tetrahedron Letters,Vol.30,No.48,pp 6649-6652,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

STRUCTURE AND SYNTHESIS OF MURRAPANINE, A NOVEL SKELETAL INDOLE-NAPHTHOQUINONE ALKALOID AND CYTOTOXIC PRINCIPAL FROM *MURRAYA PANICULATA VAR. OMPHALOCARPA*

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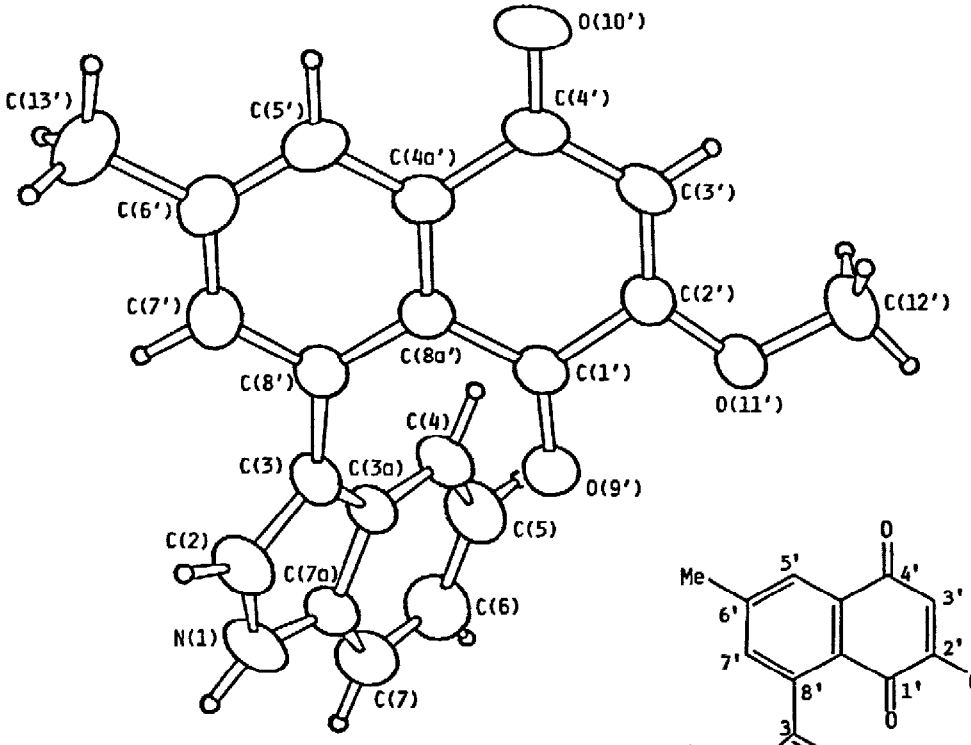
Summary: A novel skeletal cytotoxic indole-naphthoquinone alkaloid, murrapanine, has been isolated from the root bark of *Murraya paniculata var. omphalocarpa* and its structure has been established from spectral data and single-crystal X-ray analysis; the synthesis of murrapanine from indole-3-aldehyde is also described.

Certain *Murraya* species are known to be rich sources of new alkaloids.[1] In continuation of our studies on the constituents of *Murraya paniculata var. omphalocarpa* Hayata (Rutaceae) collected in Taiwan for novel bioactive compounds,[2] we report herein on the structural elucidation of murrapanine (**1**), a new alkaloid isolated from the root bark of this plant.

Murrapanine (**1**) [$C_{20}H_{15}NO_3$; calc. (M^+) *m/z* 317.1051, found 317.1031][3] was isolated as deep purplish prisms, m.p. 278-280 ^{0}C (Et_2O). That **1** contained an indole-naphtho-1,4-quinone moiety was suggested by its u.v. [$\lambda_{max.}$ (MeOH) nm (log ε): 220.7(4.56), 246.1(4.25), 280.9(4.32), and 323.3(3.73)] and i.r. [$\nu_{max.}$ (KBr) cm^{-1}; 3369 (NH), 1678, 1651, 1616, 1594, 1562, and 1538] spectra coupled with the appearance of two carbonyl carbon signals at δ 179.1 and 185.1 in the ^{13}C n.m.r. spectrum. The ^{1}H n.m.r. spectrum of **1** displayed signals which were assigned as follows: four mutually-coupled protons at δ 6.98 [dt, J=1.2 and 7.9 Hz, H(5)]; 7.12 [dt, H(6)], 7.24 [dd, J=1.2 and 7.9 Hz, H(7)], and 7.48 [dd, H(4)]; a pair of meta-coupled protons at δ 7.59 [d, J=1.5 Hz, H(7')] and 7.89 [d, H(5')]; a proton doublet at δ 7.50 [J=2.6

Hz, H(2)]; a sharp singlet at δ 6.21 [H(3')]; a broad NH signal at δ 10.47; and two three-proton singlets at δ 2.52 and 3.87 for Ar-Me and Ar-OMe, respectively.

A single-crystal X-ray analysis established the complete structure of **1**.[4] A view of the solid-state conformation is provided in Figure 1. Steric overcrowding of substituents at C(1') and C(8') of the naphthoquinone system is relieved by a combination of effects: exocyclic bond angle deformation at C(8') [C(3)-C(8')-C(7')=118.1(1)^{o} << C(3)-C(8')-C(8a')=124.2(1)^{o}]; twisting about the C(1')-C(8a') and C(8a')-C(8') bond, which results in buckling of the naphthoquinone rings, as well as the C(3)-C(8') bond;[5] out-of-plane bending of C(8') (Δ = 0.096 Å) from the least-squares plane through the atoms of the planar indole moiety (r.m.s.d. = 0.008 Å). In crystals of **1**, molecules related by the 2_1 screw axis along *b* are associated by an N-H···O hydrogen bond [N(1)···O(9') = 2.830(2) Å].

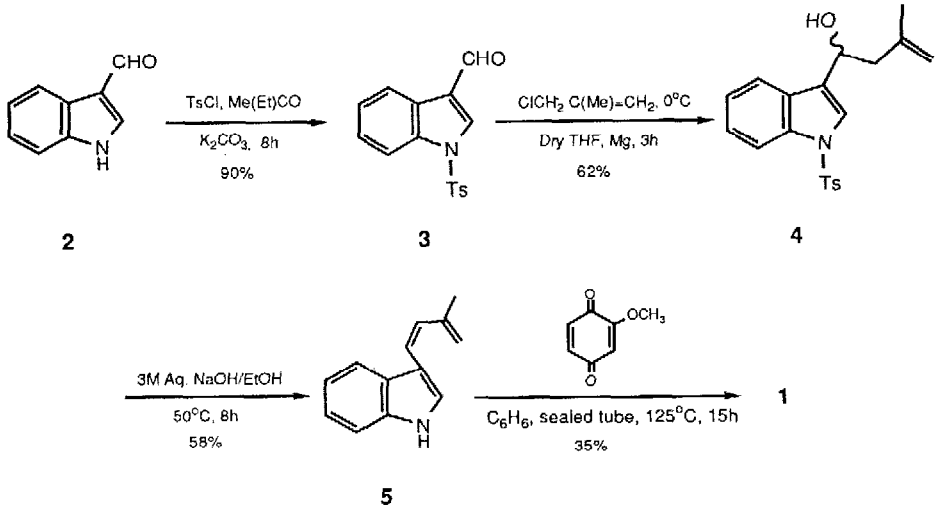


1

Figure 1

Structure and solid-state conformation of murrapanine (**1**); small circles represent hydrogen atoms.

The synthesis of **1** is summarized in Scheme 1. The indole-3-aldehyde (**2**) was tosylated to yield **3** (mp 148-150°C). The diene-substituted indole [**5**, *m/z* 183(M^+)] was obtained by treatment of **3** with isobutenyl magnesium chloride to give **4** [*m/z* 355 (M^+)], followed by dehydration. Cyclization of **5** with methoxyquinone via a Diels-Alder [4+2] thermal reaction afforded **1** as violet crystals.[6,7] The identity of this synthetic compound with the naturally occurring murrapanine reported above was established by a direct comparison (mixed mp and spectral data).[6]



Scheme 1

Murrapanine (**1**) represents the first instance of the occurrence of an indole-naphthoquinone alkaloid in a natural source.[8] In the KB tissue culture assay, murrapanine demonstrated significant cytotoxicity (ED_{50} = 3.3 μg/ml).

Acknowledgement. We thank the National Science Council of the Republic of China (T. S. Wu) and the U.S. National Cancer Institute (K. H. Lee) for financial support. We are grateful to Dr. M. Niwa (Meijo University, Japan) for mass spectral data.

References and Notes

1. C. Ito, T. S. Wu, and H. Furukawa, *Chem. Pharm. Bull.*, **36**, 2377 (1988), and earlier literature cited therein.
2. T. S. Wu, M. J. Liou, T. T. Jong, Y. J. Chen, and J. S. Lai, *Phytochemistry*, in press (1989), and literature cited therein.
3. EIMS *m/z* (%): 317(M^+, 100), 302(14), 286(7), 273(7), 259(5), 236(13), 219(11), 218(12), 217(11), 203(8), 189(8), 174(38), 158(10), 144(10). ^{13}C n.m.r. ($CDCl_3$ + DMSO-d_6): δ185.1(s), 179.1(s), 161.2(s), 143.9(s), 138.6(d), 137.0(s), 136.1(s), 133.6(s), 126.2(s), 125.6(d), 124.2(d), 121.3(d), 119.4(d), 119.2(d), 115.9(s), 115.4(s), 111.7(d), 107.9(d), 56.2(q), and 21.6(d).
4. *Crystal data.* $C_{20}H_{15}NO_3$ (**1**), M = 317.35, monoclinic, space group $P2_1/c$,*a* = 12.229(6), *b* = 8.711(3), *c* = 16.183(4) Å, β = 115.17(2)° (from 25 orientation reflections; 59°<θ<67°), *U* = 1560.2 Å^3, *Z* = 4, D_c = 1.351 g cm^{-3}, μ(Cu-*K*α radiation, λ = 1.5418 Å) = 7.0 cm^{-1}, crystal dimensions: 0.14 x 0.20 x 0.50 mm. Intensity data (+*h*,+*k*,±*l*, θ_{max} = 67°; 2784 nonequivalent reflections) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-*K*α radiation, incident-beam graphite monochromator, ω-2θ scans). The crystal structure was solved by direct methods (MULTAN11/82). Full-matrix least-squares refinement of atomic parameters (anisotropic C, N, O; isotropic H) converged at *R* = 0.041 (R_w = 0.062) over 2242 reflections with $I > 3.0\ \sigma(I)$. Crystallographic calculations were performed on PDP11/44 and MicroVAX II computers by use of the Enraf-Nonius Structure Determination Package. Atomic parameters, bond lengths and angles for **1** have been deposited at the Cambridge Crystallographic Data Centre.
5. Torsion angles (σ ± 0.2°) for the molecule shown in Fig. 1 follow: O(9')-C(1')-C(8a')-C(8')=-11.7°, C(1')-C(8a')-C(8')-C(3)=-15.3°, C(8a')-C(8')-C(3)-C(3a)=-49.9°; C(2')-C(1')-C(8a')-C(4a')=-14.5°, C(1')-C(8a')-C(4a')-C(4')=12.6°, C(5')-C(4a')-C(8a')-C(8')=6.3°, C(4a')-C(8a')-C(8')-C(7') = -6.8°.
6. Compounds **3**-**5** gave spectroscopic (UV, IR, NMR and mass) data in agreement with the assigned structures.
7. The significant dehydrogenation of the Diels-Alder reaction product was due to the use of an excess of methoxyquinone which serves as a dehydrogenation agent.
8. It is unlikely that murrapanine is an artifact, as none of the indole or quinone was isolated from this plant or used in the work-up procedure.

(Received in USA 15 August 1989)