Tetrahedron Letters,Vol.24,No.13,pp 1333-1336,1983 0040-4039/83/131333-04$03.00/0
Printed in Great Britain

ARISTOLINDIQUINONE - A NEW NAPHTHOQUINONE FROM ARISTOLOCHIA INDICA L. (ARISTOLOCHIACEAE) [1,2]

Chun-tao Che, Geoffrey A. Cordell* and H.H.S. Fong

Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL. 60612 U.S.A.

and

C. Anderson Evans
JEOL (USA) Inc. Analytical Instruments Division
235 Birchwood Avenue, Cranford, NJ 07016 U.S.A.

Abstract: The roots of Aristolochia indica have afforded a new naphthoquinone, aristolindiquinone (2), whose structure was deduced through nmr spectroscopy.

As part of our continuing program on the isolation of fertility-regulating agents from plants, we have examined extracts of the roots of Aristolochia indica L. (Aristolochiaceae)[3], in order to perform confirmatory bioassays on constituents previously reported to be active.[4-8] In the course of these studies a new naphthoquinone, aristolindiquinone, was isolated and characterized.

Aristolindiquinone (0.00025% yield) crystallized from methanol as orange needles, mp 176-178° and displayed a molecular ion at m/z 218 regarded as $C_{12}H_{10}O_4$. The uv spectrum (λ_{max} 208 (log ε 4.62), 236 (4.59), 284 (4.52) and 433 nm (3.91) attested to the presence of a naphthoquinone moiety[9] and was further supported by the strong carbonyl absorptions (ν_{max} 1645 and 1615 cm^{-1}) observed in the ir spectrum. The bathochromic shift (λ_{max} 220 (log ε 4.60), 238 (4.58), 270 (4.59), 394 (3.91) and 495 nm (3.89)) in the uv spectrum on the addition of base, and the broad absorption at 3340 cm^{-1} indicated the presence of at least one phenolic group. The ^1H nmr spectrum (100 MHz, $CDCl_3$, 50° C) was quite simple, displaying two three-proton singlets at δ 2.06 and 2.64, two aromatic doublets (J = 8.8 Hz) at 7.17 and 7.32 and two D_2O- exchangeable absorptions at δ 7.65 and 13.03 ascribed to hydroxy groups, the latter being strongly H-bonded.

The ^{1}H nmr data suggested a 2-hydroxy-3-methyl naphthoquinone nucleus since no quinonoid proton was observed. One phenolic group must be peri to the carbonyl function and from examination of the data for model compounds,[10-14] it was found that peri- hydroxyl protons resonate at ca. 11 ppm in 2,8-dihydroxy naphthoquinones, but above 12 ppm in 2,5-dihydroxy naphthaquinones Thus, the chemical shift of the hydrogen bonded hydroxy group and the shift to λ_{max} 495 nm in alkali[9] indicated a 2,5-dihydroxynaphthoquinone in which it remained to locate the aromatic methyl (δ 2.64) at either C-6 or C-8 (1 or 2).

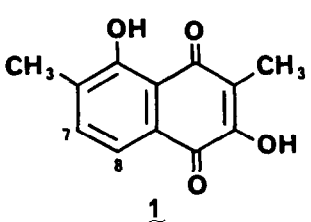
The relationship of the Ar-CH_3 and one of the aromatic protons was established when irradiation at δ 2.54 gave an nOe of 24% in the adjacent Ar-H at δ 7.32, and also sharpened the doublet substantially[15].

Examination of the reported ^{1}H chemical shift data of selected reference compounds [10,11] and of the effects of substituents[16], permitted calculation of the chemical shifts of the aromatic protons for 1 (δ 7.45 and 7.68) and 2 (δ 7.16 and 7.43), which could be compared with the observed values of δ 7.10 and 7.46.

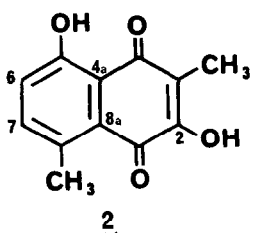
On this basis, and the observed shift for the peri-hydroxy-proton[17] the structure 2 was preferred. Definitive evidence in support of this structure was obtained from examination of the ^{13}C nmr spectrum (25.05 MHz) in both $CDCl_3$ and DMSO-d_6. Crucial in the assignment of the spectrum was the availability of data for the compounds 3-6 [18-21]. This led to calculated values for 1 and 2 which could be compared with the observed values (Table 1).

Table 1. Calculated and Observed Carbon-13 Shifts for 1 and 2

Compound	Carbon									
	1	2	3	4	4a	5	6	7	8	8a
1 (Calcd.)	177.2	156.9	126.1	190.4	100.5	164.8	139.6	136.2	121.6	125.6
2 (Calcd.)	179.4	158.3	121.4	190.0	108.8	162.0	126.3	140.3	136.0	128.8
Obsd. ($CDCl_3$)	181.5	154.0	118.5	191.2	114.8	160.8	126.3	139.3	135.2	125.9
Obsd. (DMSO-d_6)	181.0	156.3	117.5	190.9	114.0	159.2	124.5	139.2	133.2	126.3



1

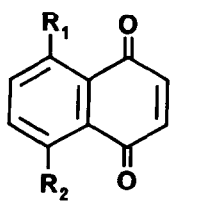


2

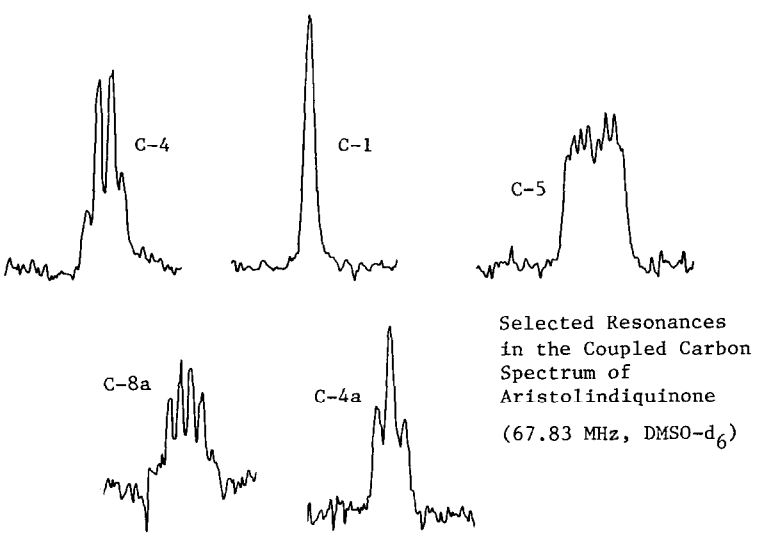
A preliminary distinction between the two structures was made through examination of the coupled carbon spectrum (DMSO-d_6) followed by single-frequency selective decoupling of the two methyl groups. Irradiation at δ 1.89 sharpened the signals at δ 190.9 (C-4), 156.3 (C-2) and 117.5 (C-3). No effect was observed on the C-1 carbonyl carbon. On the other hand, irradiation at δ 2.54 collapsed the signal at δ 133.2 (C-8) to a doublet ($^3J_{CH}$ = 6.5 Hz) and the multiplet at δ 126.3 (C-8a) to a doublet ($^3J_{CH}$ = 6.8 Hz)[22]. In addition, the broadened doublet at δ 139.2 (C-7) was substantially sharpened. The C-3 and C-8 methyl carbons were observed at δ 7.9 and δ 22.3 ($CDCl_3$), and δ 7.4 and 21.4 (DMSO -d_6), respectively.

When the high-field (67.83 MHz) coupled carbon spectrum was examined, the enhanced resolution indicated the C-1 carbonyl carbon at δ 181.0 to be a singlet, and not a doublet whereas C-4 appeared as a distinct quartet ($^3J_{CH}$ = 3.45 Hz). Also, C-5 was observed as a ddd (J = 1.9, 4.4 and 9.7 Hz) indicating that it was coupled to H-6, H-7 and the hydroxyl proton, and C-4a appeared as a triplet ($^3J_{CH}$ = 4.75 Hz) coupled to both H-6 and the hydroxyl proton. Finally, C-8a appeared as a pair of quartets ($^3J_{CH}$ = 3.7 and 6.8 Hz) indicating coupling to a methyl group and an aromatic proton. These multiplicities can only be explained if the aromatic methyl group is at C-8 rather than C-6. We have therefore assigned aristolindiquinone the structure **2**.[23] Confirmation of this is being sought through X-ray crystallographic analysis.

Acknowledgements: This work was supported, in part, by funds from the Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization (HRP project 77918C). One of us (C.-t.C.) would like to thank the Graduate College, University of Illinois at the Medical Center for the award of a fellowship. Special thanks are due Dr. D.C. Lankin, Borg Warner Corporation for his extensive efforts on the carbon-13 nmr spectra of aristolindiquinone.



	R_1	R_2
3	H	H
4	OH	H
5	H	CH_3
6	OH	CH_3



Selected Resonances in the Coupled Carbon Spectrum of Aristolindiquinone (67.83 MHz, DMSO-d_6)

REFERENCES

1. Paper 2 in the series "Studies on Aristolochia"; for paper 1, see S. Mukopadhyay, S. Funayama, G.A. Cordell and H.H.S. Fong, J. Nat. Prod., in press.

2. This work was submitted (by C.-t.C.) in partial fulfillment of the Ph.D. requirements of the Graduate College, University of Illinois at the Medical Center, Chicago and was presented at the 23rd Annual Meeting of the American Society of Pharmacognosy, Pittsburgh, PA, August 2-5, 1982, Abstract 72.

3. Details of the extraction, isolation, structure determination and biological evaluation procedures will be published subsequently.

4. A. Pakrashi and B. Chakrabarty, Experientia, 34, 1377 (1978).

5. A. Pakrashi and B. Chakrabarty, Indian J. Exptl. Biol., 16, 1283 (1978).

6. A. Pakrashi and C. Shaha, Experientia, 34, 1192 (1978).

7. A. Pakrashi and C. Shaha, IRCS Med. Sci., 7, 78 (1979).

8. A. Pakrashi and C. Shaha, Indian J. Exptl. Biol., 17, 437 (1979).

9. R.H. Thompson, "Naturally Occurring Quinones," 2nd ed., Academic Press, London, England, 1971

10. R.E. Moore, and P.J. Scheuer, J. Org. Chem., 31, 3272 (1966).

11. R.E. Moore, H. Singh, C.W.J. Chang and P.J. Scheuer, Tetrahedron, 23, 3217 (1967).

12. H. Singh, T.L. Folk and P.J. Scheuer, Tetrahedron, 25, 5301 (1969).

13. M. Tezuka, M. Kuroyanagi, K. Yoshihira and S. Natori, Chem. Pharm. Bull., 20, 2029 (1972).

14. R.G.F. Giles and G.H.P. Roos, J. Chem. Soc. Perkin Trans. I, 2057 (1976).

15. These experiments were conducted in DMSO-d_6. Chemical shifts in this solvent were δ 1.89 (3H, s), 2.54 (3H, bs), 7.14 (1H, d, J = 8.6 Hz), 7.42 (1H, bd d, J = 8.6 Hz) and 13.02 (1H, s).

16. L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry." 2nd ed., Pergamon Press, Oxford, England, 1969.

17. T.J. Lillie and O.C. Musgrave, J. Chem. Soc. Perkin Trans. I, 355 (1977).

18. M. Kobayashi, Y. Terui, K. Tori and N. Tsuji, Tetrahedron Letts., 619 (1976).

19. G. Hofle, Tetrahedron, 33, 1963 (1977).

20. G. Castillo, G.H. Ellames, A.G. Oxborne and P.G. Sammes, J. Chem. Res. (M), 833 (1978).

21. B.F. Bowden, D.W. Cameron, M.J. Crossley, G.I. Feutrill, P.G. Griffiths and D.P. Kelly, Aust. J. Chem., 32, 769 (1979).

22. Irradiation at δ 2.54 also caused enhancement in the signal at δ 133.2 due to the nOe of the methyl group on C-8. The signal at δ 126.3 was not enhanced and thus the assignment of these two carbons can be made unequivocally.

23. The systematic name of aristolindiquinone is 2,5-dihydroxy-3,8-dimethyl-1,4-naphthoquinone.

(Received in USA 13 December 1982)