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(±)-DIONCOPHYLLACINE A, A NAPHTHYLISOQUINOLINE ALKALOID WITH A 4-METHOXY SUBSTITUENT FROM THE LEAVES OF *TRIPHYOPHYLLUM PELTATUM**

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Key Word Index—*Triphyophyllum peltatum*; Dioncophyllaceae; leaves; (±)-dioncophyllacine A; naphthylisoquinoline alkaloids; biaryls, naturally occurring; structure elucidation.

Abstract—The isolation and structure elucidation of *rac*-dioncophyllacine A from the leaves of *Triphyophyllum peltatum*, is described. Unlike all other naphthylisoquinoline alkaloids, this fully dehydrogenated representative has an additional methoxy group at C-4, the position of which is deduced from NOE results. Dioncophyllacine A has a 7,1′-site of the biaryl axis, as in dioncophylline A. Its constitution is confirmed by an X-ray structure analysis, which shows that the crystalline form of this new alkaloid is racemic.

INTRODUCTION

The genus *Triphyophyllum* with its only species *T. peltatum* Airy Shaw belongs to the family of the Dioncophyllaceae, a very small group of African medicinal plants [2], the taxonomical position of which in the plant kingdom is not yet completely established [3]. An eventual chemotaxonomical connection may be deduced from the occurrence of the acetogenic [4] naphthoquinone plumbagin [5], which also occurs i.a. in Droseraceae, Plumbaginaceae, Nepenthaceae, Ebenaceae [6], and finally in the Ancistrocladaceae [7, 8]. A distinctly more specific relationship can be recognized, especially to this latter family, by the joint occurrence of naphthylisoquinoline alkaloids; structurally intriguing natural biaryls of apparently acetogenic origin [9, 10]. After early work on the chemical constituents of *T. peltatum* [5, 11–13], we have been able to isolate and elucidate the structures of the alkaloids dioncophylline A (**1a**) [14–18], dioncopeltine A (**2a**) [19], dioncolactone A (**3**) [19], and dioncophylline B (**4**) [20] from the root bark of this plant. Despite their structural differences, some joint features are common to all of these four alkaloids, e.g. the identical tetrahydroisoquinoline part, with its *R*-configured stereocentre at C-3. In this paper, we describe the isolation and structure elucidation of dioncophyllacine A (**5**), which occurs as both atropenantiomers **5a** and **5b**. Some of the results described herein have recently been reported in a preliminary form [21].

RESULTS AND DISCUSSION

The leaves of *T. peltatum* were extracted with dichloromethane. The early fractions obtained on CC of the extract yielded a nitrogen-containing crystalline solid (130 mg). ^{1}H NMR spectroscopy reveals a strong structural relationship with dioncophylline A (**1a**) for the resonances and multiplicity patterns of the protons in the naphthalene part. By contrast, the isoquinoline moiety shows distinctly different signals: the lack of the resonances for protons at C-1, C-3 and C-4, as present in **1a**, as well as the chemical shifts of the signals of Me-1 and Me-3 (δ3.04 and 2.64, resp.), which moreover appear as singlets, clearly hint at a fully dehydrogenated isoquinoline moiety. And indeed, the ^{1}H NMR spectrum of the new alkaloid is largely superimposable to that of '*O*-methyltetradehydro-triphyophylline' (**6**), which was likewise reported to occur in *T. peltatum* [12]. The constitution of this naphthylisoquinoline was confirmed by our first total synthesis [22]. Yet, despite the synthetic availability of this compound as a reference substance, we could not detect it in our plant material of *T. peltatum*, so far. The only distinct difference in the ^{1}H NMR spectra of **6** and the new alkaloid is the presence of an additional methoxy group, obviously in an aromatic position, because one of the aromatic protons (a singlet) found in **6** is missing in the new alkaloid.

This is confirmed by the molecular formula, $C_{26}H_{27}NO_4$, as deduced from the mass spectrum (m/z = 417 $[M]^+$) and from combustion analysis. The exact position of this methoxy substituent can be determined by NOE spectroscopy (Fig. 1), revealing a close proximity of this additional functional group to Me-3 and H-5, which clearly shows the methoxy group to be located at C-4. From these NOE experiments, the coupling position

*Part 35 in the series 'Acetogenic Isoquinoline Alkaloids'. For Part 34 see ref. [1].

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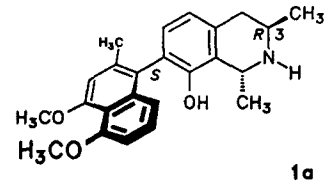
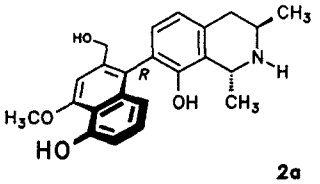
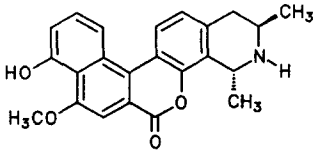


1a



2a



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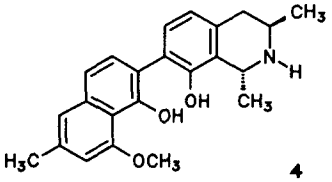

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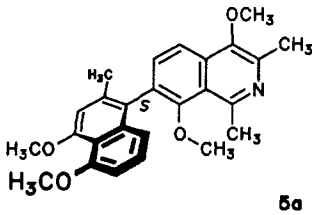
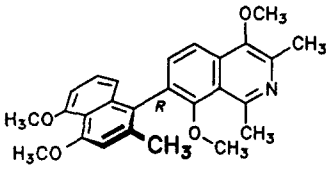


5a



5b

in the isoquinoline part becomes evident: from the continuous array of the NOE-interacting protons—Me-3, OMe-4, H-5, H-6—the naphthalene substituent must be located at C-7, as in dioncophylline A (**1a**). This is underlined by the signal of the 8-methoxy group, whose aryl-induced highfield shift (δ3.26 ppm) hints at a direct proximity to the naphthalene substituent. And the position of this methoxy group, for its part, is demonstrated by its nuclear Overhauser interaction with Me-3.

As to the naphthalene moiety, the presence of three neighbouring aromatic protons (H-6′ to H-8′) indicates that the isoquinoline moiety must be connected with the methyl-containing aromatic ring of the naphthalene. This is underlined again by the highfield shift (δ2.21) of this methyl group, which thus must be in *ortho*-position with respect to the biaryl axis. The normal chemical shift (δ4.02) for the methoxy group at C-4′ excludes the isoquinoline substituent from being located between OMe-4′ and Me-2′. Hence, the new alkaloid is based on the very same 7,1′-coupling type as dioncophylline A (**1a**) and can thus be identified as 4-methoxy-8-*O*-methyl-1,2,3,4-tetradehydro-dioncophylline A (**5**), subsequently named dioncophyllacine A, the first 4-oxygenated naphthylisoquinoline alkaloid ever isolated.

In contrast to **1**–**4**, this new alkaloid **5** possesses no stereocentre at either C-1 or C-3. Nonetheless, **5** is a chiral compound, due to restricted rotation at the biaryl axis, whereas **3** and **4** have no stable configuration at the axis. With respect to the fact that the related alkaloids **1a** and **2a** have been found to be stereochemically homogeneous, i.e. not or not noticeably accompanied by the corresponding atropisomers **1b** and **2b**, it was interesting to investigate whether the new alkaloid would have the same absolute configuration at the axis as **1a** and **2a*** and would thus be represented by structure **5a**, or whether it would have the opposite configuration or whether it would be a mixture of both isomers, e.g. the racemate.

Crystalline **5** is optically inactive ($[\alpha]_D$ 0°), i.e. a first, though not conclusive, hint at the latter possibility (cf. the stereochemically homogeneous alkaloid ancistrotectorine, which is optically inactive! [23]). Furthermore, the CD spectrum of **5** is nearly flat, showing only very weak, non-characteristic peaks, possibly arising from impurities or from a slight excess of one of the two enantiomers. Hence, at least in the crystals investigated, the new alkaloid seems to be a racemic mixture of both atropenantiomers **5a** and **5b**.

This was unambiguously confirmed by an X-ray structure analysis performed on crystals grown in MeOH, which clearly shows both atropisomers to occur in the crystal (Fig. 2). Simultaneously, this crystal structure analysis fully confirms the constitution of this new alkal-

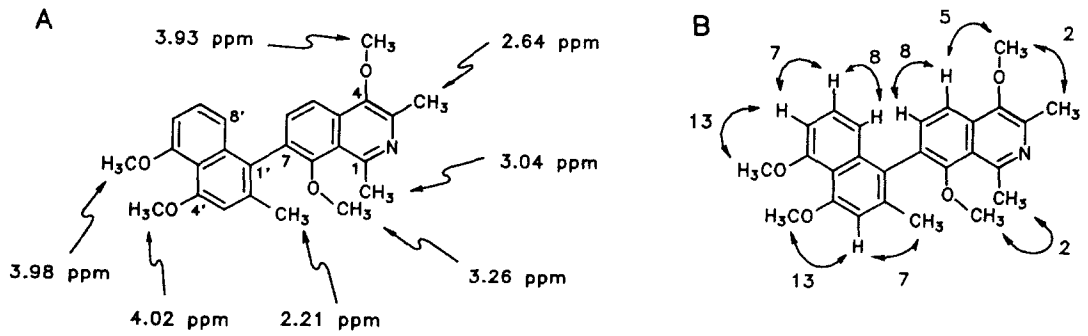


Fig. 1. Selected chemical shifts (A, δ values) and nuclear Overhauser effects (B, in %) of dioncophyllacine A (**5**): evidence for the constitution.

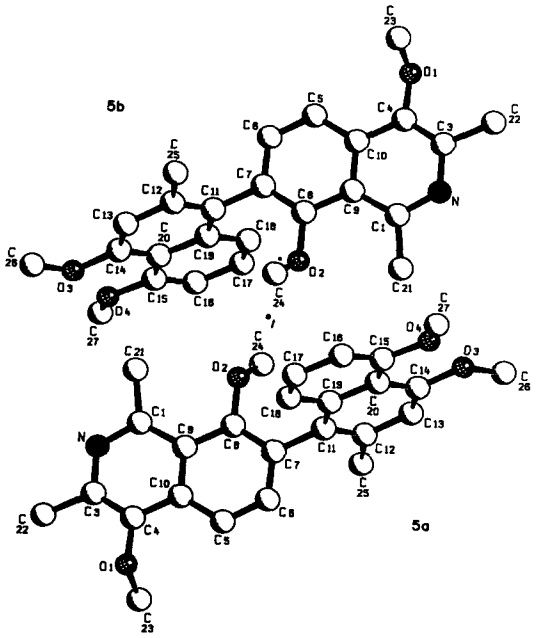
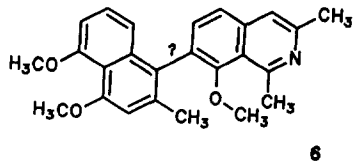


Fig. 2. Schakal plot [24] of the structure of **5a/b** in the crystal, as determined by X-ray diffraction (●$_i$ = inversion centre).

oid with its unprecedented additional methoxy group at C-4.

It has to be noted that the racemic nature of the new alkaloid in the crystals investigated does not necessarily mean that **5a** and **5b** also form a 1:1 mixture in the plant. It may well be that these two atropisomers occur in unequal amounts, i.e. one enantiomer dominating, in which case the X-ray results might be due to preferential crystallization of the racemate, leaving the excessive enantiomer in the mother liquors. This possibility cannot be excluded, since the crude alkaloid is still slightly optically active. Work to develop an enantiomer analysis, e.g. by chromatography on chiral phases, for the investigation of the mother liquors and the genuine alkaloid before its crystallization, is in progress. In any case, **5** is the first naphthylisoquinoline alkaloid that has clearly been demonstrated to be present as both atropisomers **5a** and **5b** in a Dioncophyllaceae species.

With respect to the probable biosynthetic origin of naphthylisoquinoline alkaloids from acetate units [9, 10], it is of interest that the new alkaloid dioncophyllacine A (**5**) bears an additional, apparently non-acetate-derived



6

oxygen on the isoquinoline nucleus; a hint at early stages of an oxidative biotransformation of the alkaloids in the plant, possibly the beginning of a catabolic sequence, complementary to the structures of **2** and **3**, where the methyl group of the naphthalene moiety has been oxidized.

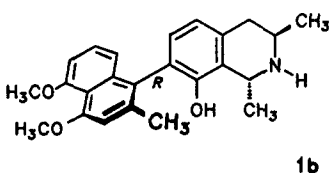
EXPERIMENTAL

General. Mps: uncorr. Optical rotation: 25°, 10 cm cell, $CHCl_3$ (filtered through basic Al_2O_3); IR: KBr; ^1H NMR (400 MHz): $CDCl_3$ with TMS as int. standard; EIMS: 70 eV. Analyses (C, H and N) were performed by the Institute of Inorganic Chemistry, University of Würzburg. CC: silica gel (60–200 mesh, Merck) by addition of 7.5% aq. NH_3. TLC: precoated silica gel 60 F_{254} plates (Merck), deactivated with gas NH_3. Spots were visualized under UV light and by Dragendorff's reagent. The X-ray measurement was carried out by a Nonius CAD-4 diffractometer.

Plant material. Leaves of *T. peltatum* were collected in West Ivory Coast in July 1990 and identified by one of us (L.A.A.). A voucher specimen is deposited at the Conservatoire et Jardin Botaniques de l'Université d'Abidjan, République de Côte d'Ivoire.

Extraction and isolation. Leaves (*ca* 1 kg) were extracted with CH_2Cl_2 and 7% NH_4OH in a Soxhlet apparatus. On TLC, the extract was found to contain a mixt. of at least 6 alkaloids. The soln was evapd and the residue (54 g) was subjected to CC on 850 g silica gel. The column was eluted with mixts of CH_2Cl_2–MeOH of increasing polarity.

Isolation of (±)-dioncophyllacine A (**5**). Early frs with 1% MeOH in CH_2Cl_2 contained dioncophyllacine A (**5**), which was obtained as needles (130 mg) by crystallization from MeOH. Mp 177–179°, $[\alpha]_D$ 0° ($CHCl_3$; *c* 0.54). IR ν_{max} cm^{-1}: 2990, 2960 (C–H), 1580 (C=C), 1260 (C–O); ^1H NMR (400 MHz): δ 2.21 (3H, *s*, Me-2'), 2.64 (3H, *s*, Me-3), 3.04 (3H, *s*, Me-1), 3.26 (3H, *s*, OMe-8), 3.93 (3H, *s*, OMe-4), 3.98 (3H, *s*, OMe-5'), 4.02 (3H, *s*, OMe-4'), 6.80 (1H, *d*, J = 7.8 Hz, H-6'), 6.82 (1H, *s*, H-3'), 6.99 (1H, *d*, J = 8.4 Hz, H-8'), 7.22 (1H, *t*, J = 8.1 Hz, H-7'), 7.39 (1H, *d*, J = 8.5 Hz, H-6), 7.86 (1H, *d*, J = 8.5 Hz, H-5); MS *m/z* (rel. int.): 417 $[M]^+$ (100), 402 $[M-Me]^+$ (6). Found: C, 74.53; H, 6.77; N, 3.45. $C_{26}H_{27}NO_4$ requires: C, 74.80; H, 6.52; N, 3.35%.



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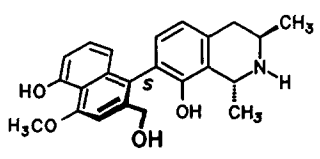

2b

X-Ray analysis of compound **5**. Compound **5** crystallizes from MeOH in the triclinic space group P-1(2) with a = 839.7(3), b = 1039.4(6), c = 1431.5(5) pm; α = 108.38(4), β = 101.18(4), γ = 103.84°, V = 1101(1) pm^3. Calcd density = 1.259 g cm^{-3} for Z = 2. Using graphite monochromated MoK_α radiation (λ = 0.70930 Å), 4142 unique reflections were measured in the

*Note that, despite the same stereo-orientation of the two molecular moieties in **1a** and **2a**, the configurations at the axis of these two related alkaloids are denoted by opposite Cahn-Ingold-Prelog descriptors, due to the extra oxygen function in **2a**.

Table 1. Atomic parameters ($\times 10^4$) and equivalent isotropic displacement parameters ($pm^2 \times 10^{-1}$) of non-hydrogen atoms for dioncophyllacine A (**5**)

Atom	x	y	z	U_{eq}
O (1)	−30 (3)	2911 (2)	−4473 (2)	53 (1)
O (2)	133 (3)	566 (2)	−1085 (2)	51 (1)
O (3)	6176 (3)	3732 (2)	2978 (2)	48 (1)
O (4)	4259 (3)	5084 (3)	3651 (2)	61 (1)
N	−2684 (4)	−66 (3)	−4082 (2)	53 (1)
C (1)	−1893 (5)	125 (3)	−3139 (2)	47 (1)
C (3)	−2016 (5)	789 (3)	−4553 (2)	49 (1)
C (4)	−553 (4)	1913 (3)	−4050 (2)	43 (1)
C (5)	2002 (5)	3242 (3)	−2539 (2)	48 (1)
C (6)	2907 (5)	3416 (3)	−1589 (2)	52 (1)
C (7)	2305 (4)	2515 (3)	−1091 (2)	45 (1)
C (8)	764 (4)	1423 (3)	−1585 (2)	42 (1)
C (9)	−257 (4)	1197 (3)	−2578 (2)	41 (1)
C (10)	415 (4)	2135 (3)	−3051 (2)	39 (1)
C (11)	3326 (4)	2790 (3)	−26 (2)	44 (1)
C (12)	4801 (5)	2441 (3)	150 (2)	50 (1)
C (13)	5736 (4)	2744 (3)	1166 (2)	48 (1)
C (14)	5261 (4)	3427 (3)	1989 (2)	40 (1)
C (15)	3271 (4)	4720 (3)	2674 (2)	47 (1)
C (16)	1847 (5)	5122 (4)	2464 (3)	59 (1)
C (17)	874 (5)	4732 (4)	1449 (3)	64 (1)
C (18)	1332 (4)	3964 (3)	653 (3)	52 (1)
C (19)	2802 (4)	3535 (3)	826 (2)	41 (1)
C (20)	3795 (4)	3893 (3)	1856 (2)	40 (1)
C (21)	−2866 (5)	−884 (4)	−2722 (3)	72 (1)
C (22)	−3031 (5)	398 (4)	−5654 (3)	68 (1)
C (23)	1142 (5)	2637 (4)	−5059 (3)	82 (1)
C (24)	858 (6)	−536 (4)	−1099 (3)	77 (1)
C (25)	5476 (5)	1717 (4)	−711 (3)	77 (1)
C (26)	7653 (5)	3302 (4)	3130 (3)	64 (1)
C (27)	3931 (5)	6097 (4)	4466 (3)	76 (1)

range $2 < 2\Theta < 50°$. The molecular structure of **5** was solved by direct methods (SHELXS [25]) and refined by full-matrix least-squares (SDP) to a final R value of 0.056 ($R_\omega = 0.051$) for 2489 reflections with $F_0 > 2\sigma(F_0)$. All non-hydrogen atoms were refined anisotropically (the positional parameters are tabulated in Table 1), hydrogen atoms were considered riding with fixed thermal parameters. Atomic coordinates, bond lengths and angles, and thermal parameters are deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

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REFERENCES

1. Bringmann, G., Zagst, R., Reuscher, H. and Aké Assi, L. (1992) *Phytochemistry* **31**, 4011.
2. Cooper, G. P. and Record, S. J. (1931) *Yale Univ. School For. Bull.* **147**, 27.
3. Marburger, J. E. (1979) *Am. J. Botany* **66**, 404.
4. Durand, R. and Zenk, M. H. (1971) *Tetrahedron Letters* 3009.
5. Bruneton, J., Bouquet, A., Fournet, A. and Cavé, A. (1976) *Phytochemistry* **15**, 817.
6. Thomson, R. H. (1987) *Naturally Occurring Quinones* III, p. 159. Cambridge University Press, Cambridge.
7. Bringmann, G., Schneider, Ch. and Aké Assi, L. (1991) *Planta Med.* **57/8A**, 96.
8. Bringmann, G., Pokorny, F. and Zinsmeister, H.-D. (1991) *Der Palmengarten* **55/3**, 13.
9. Bringmann, G. (1986) in *The Alkaloids*, Vol. 29 (Brossi, A., ed.), p. 141. Academic Press, New York.
10. Bringmann, G., Pokorny, F., Stäblein, M., Govindachari, T. R., Almeida, M. R. and Ketkar, S. M. (1991) *Planta Med.* **57/8A**, 98.
11. Lavault, M., Kouhon, M. T. and Bruneton, J. (1977) *C.R. Acad. Sci., Ser. C* **285**, 167.
12. Lavault, M. and Bruneton, J. (1978) *C.R. Acad. Sci., Ser. C.* **287**, 129.
13. Lavault, M. and Bruneton, J. (1980) *Planta Med. (J. Med. Plant Res.) Suppl.* 17.
14. Bringmann, G., Rübenacker, M., Jansen, J. R., Scheutzow, D. and Aké Assi L. (1990) *Tetrahedron Letters* **31**, 639.
15. Bringmann, G., Jansen, J. R., Reuscher, H., Rübenacker, M., Peters, K. and von Schnering, H. G. (1990) *Tetrahedron Letters* **31**, 643.
16. Bringmann, G., Zagst, R., Schöner, B., Busse, H., Hemmerling, M. and Burschka, Ch. (1991) *Acta Cryst.* **C47**, 1703.
17. Bringmann, G., Geuder, T., Rübenacker, M. and Zagst, R. (1991) *Phytochemistry* **30**, 2097.
18. Bringmann, G., Jansen, J. R. and Busse, H. (1991) *Liebigs Ann. Chem.* 803.
19. Bringmann, G., Rübenacker, M., Vogt, P., Busse, H., Aké Assi, L., Peters, K. and von Schnering, H. G. (1991) *Phytochemistry* **30**, 1691.
20. Bringmann, G., Rübenacker, M., Geuder, T. and Aké Assi, L. (1991) *Phytochemistry* **30**, 3845.
21. Bringmann, G., Ortmann, T., Rübenacker, M. and Aké Assi, L. (1991) *Planta Med.* **57/8A**, 96.
22. Bringmann, G. and Jansen, J. R. (1984) *Tetrahedron Letters* **25**, 2537.
23. Ruangrungsi, N., Wongpanich, V., Tantivatana, P., Cowe, H. J., Cox, P. J., Funayama, S. and Cordell, G. A. (1985) *J. Nat. Prod.* **48**, 529.
24. Keller, E. (1990) *SCHAKAL* 88. *A FORTRAN Program for the Graphic Representation of Molecules and Crystallographic Models.* Kristallographisches Institut der Universität Freiburg, Germany.
25. Sheldrick, G. M. (1986) *Program for Crystal Structure Determination.* Universität Göttingen, Germany.