HETEROCYCLES, Vol 20, No 5, 1983

A PHENANTHROID LACTONE, STEROID AND LIGNANS FROM ARISTOLOCHIA INDICA[1]

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Abstract - Aristololide, a new phenanthroid lactone characterised as 1b, has been isolated from the roots of Aristolochia indica Linn., along with 5α-stigmastane-3,6-dione, (-)-cubebin and (-)-hinokinin.

Aristolochia indica Linn. (Aristolochiaceae), an Indian medicinal plant with potent antifertility activity[2], is a good source of natural phenanthroids[3-5], sesquiterpenes[6] and 4,5-dioxoaporphines[7]. Further investigation of the roots of this plant has now led to the isolation of aristololide, another new phenanthrene derivative.

Aristololide was isolated from the alcohol extract of the dried roots as yellow solid ($CHCl_3$-MeOH), m.p. 259-260°C. The molecular composition $C_{17}H_{10}O_5$ was deduced from the molecular ion at m/z 294 (100%) in the mass spectrum which also showed fragment ions at m/z 279 (86%) and 251 (29%). Its ir spectrum displayed a carbonyl band (ν_{max}^{nujol} 1770 cm^{-1}) commensurate with a γ-lactone, while the phenanthroid nature was revealed by the uv spectrum[8].

The ^1H nmr spectrum (100 MHz, in $CDCl_3$) exhibited signals for an aromatic methoxy (δ 4.00, 3H,s) and a methylenedioxy (δ 6.40, 2H,s) groups. A set of two doublets (δ 8.18 and 7.08, J=8 Hz) and a triplet (δ 7.52, J=8 Hz) indicated a 1,2,3-tri-substituted aromatic nucleus. In addition, two one-proton singlets were observed at δ 7.64 and δ 7.57. The spectrum as a whole closely resembled that of aristololactam (1a).

The above data were compatible with the phenanthroid lactone structure 1b which was corroborated by the following chemical evidence.

When reduced with $NaBH_4$ in dioxane (100°C, 3h), the compound afforded aristolic acid (2a) as a minor product, while the major one (crystallised from benzene as colourless needles, m.p. 146°C) could be identified as aristyl alcohol (2b) from spectroscopic evidences[9] and its preparation from 2a by the mixed anhydride reduction procedure[10].

The mechanism of formation of aristyl alcohol from 1b is not yet very clear. However, the involvement of a keto intermediate (Scheme 1) appears to have a distinct possibility. Though there is no direct evidence, the existence of the keto form of 9-phenanthrol has been demonstrated[11] by the isolation of its 2,4-DNP derivative in high yield, while proton abstraction by benzylic carbanions from solvents like dioxane and tetrahydrofuran is well-known[12].

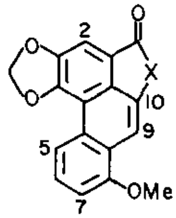
On the other hand, the formation of aristolic acid (2a) as a minor product suggests the concomitant involvement of a 9,10-dihydro derivative produced via initial hydride attack at the 9,10 double bond, analoguous to the $NaBH_4$ reduction[4,13] of aristolochic acid (2c) to its denitro derivative 2a. The cleavage of the C_{10}-O bond is otherwise difficult to conceive.

However, attempts to isolate any intermediate by carrying out the reaction at lower temperatures were unfruitful since the same mixture of products was obtained at room temperature, while no reaction took place at 10-15°C.

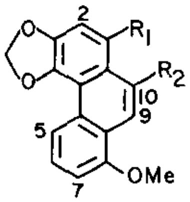
To our knowledge, aristololide (1b) is the first 10-oxygenated aristolic acid derivative encountered in nature. It can be viewed as a by-product of the biosynthesis of aristololactam (1a) from aristolochic acid (2c). Thus, the intermediate amino acid might tautomerise to the corresponding imine which could then be hydrolysed to the lactone (1b) via the hydroxy acid (Scheme 2). Alternatively, an intramolecular nucleophilic displacement of the nitro group of 2c by the carboxylate anion might generate 1b, though attempts to bring about a similar in vitro transformation were infructuous even after employing relatively drastic conditions (e.g. refluxing with dimethyl sulphoxide and KOH).

The petroleum ether extract of the plant material also yielded 5α-stigmastane-3,6-dione, (-)-cubebin (3a) and (-)-hinokinin (3b) which were characterised from their spectral data and the identity of the two lignans confirmed by direct comparison. Incidentally, besides their occurrence in other plants, these three compounds have recently been encountered in Aristolochia triangularis[14].

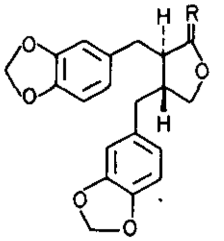
ACKNOWLEDGEMENT : We thank Prof. L. Crombie of the University of Nottingham, U.K., for an authentic specimen of (-)-cubebin.



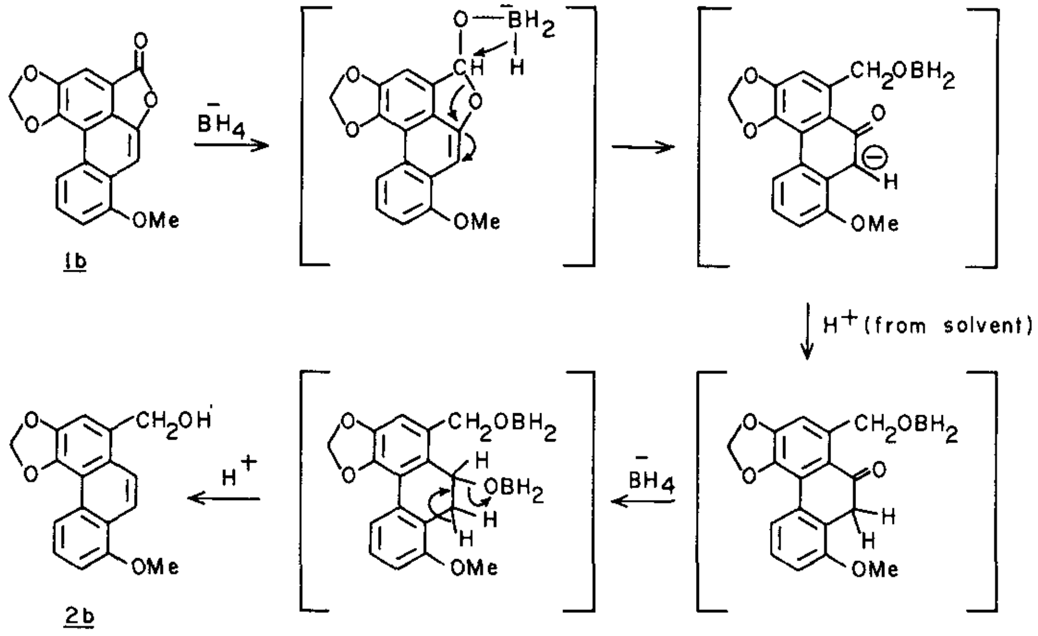
1a X = NH
b X = O



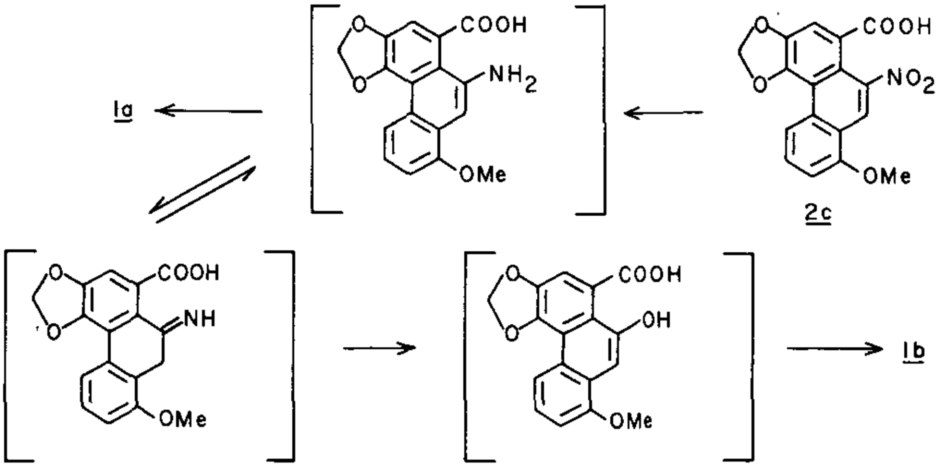
2a R_1 = COOH, R_2 = H
b R_1 = CH_2OH, R_2 = H
c R_1 = COOH, R_2 = NO_2



3a R = H,OH
b R = O



Scheme 1



Scheme 2

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8. λ_{max}^{EtOH} (log ε) 233 (4.46), 254 (4.26), 279 (4.18), 289sh (4.13), 322 (3.87), 340sh (3.70) and 396 (3.78); $\lambda_{max}^{0.01\underline{N}\ alc.\ KOH}$ (log ε) 234 (4.39), 253 (4.35), 278 (4.12), 289sh (4.03), 329 (3.84), 340sh (3.77) and 397 (3.67)nm.
9. ^{1}H nmr spectrum (100 MHz, in CDCl$_3$) :δ1.64 (1H,br *s*, exchangeable, -CH$_2$O*H*), 4.03 (3H, *s*, Ar-OMe), 5.11 (2H, *s*, -C*H*$_2$OH), 6.24 (2H, *s*, -OCH$_2$O-), 7.04 (1H, *d*, *J*=8 Hz, *H*-7), 7.34 (1H, *s*, *H*-2), 7.55 (1H, *t*, *J*=8 Hz, *H*-6), 7.92 (1H, *d*, *J*=9 Hz, *H*-9), 8.14 (1H, *d*, *J*=9 Hz, *H*-10), 8.71 (1H, *d*, *J*=8 Hz, *H*-5); ms: *m/z* 282 (100%, M$^+$), 267 (20%), 266 (22%), 265 (29%), 251 (12%), 223 (20%).
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Received, 11th January, 1983