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BIOGENETIC-TYPE SYNTHESIS OF VEPRIDIMERINES A-D

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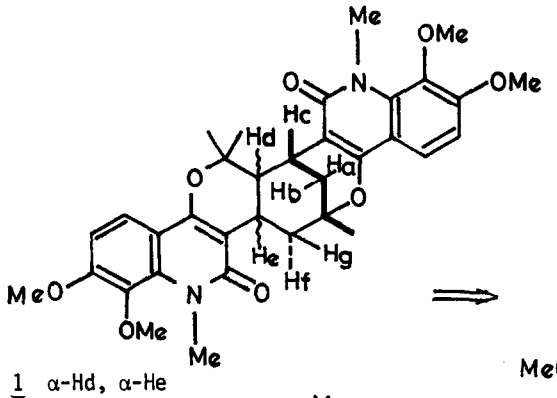
Summary : A simple synthesis of vepridimerines A-D based on thermolysis of veprisine is presented. In addition, the structure of a novel synthetic veprisine dimer is reported. Since veprisine has been previously synthesized, this report constitutes the first total synthesis of the vepridimerines.

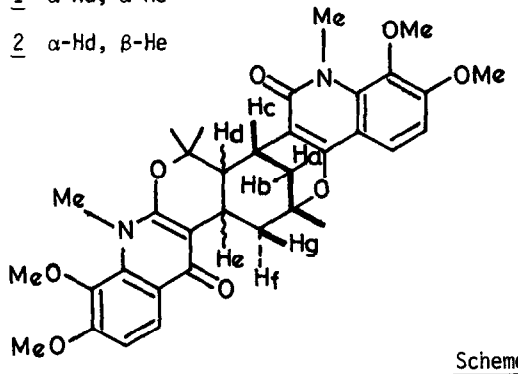
Recently we described the structure elucidation of vepridimerines A-D, four heptacyclic dimeric 2-quinoline alkaloids from the bark of Vepris louisii and Oricia renieri[1]. We were interested in the synthesis of these alkaloids since preliminary investigations had shown that the major dimer, vepridimerine B 2, was cytotoxic, but the limited amounts of 2 and its isomers, vepridimerines -A 1, -C 3, and -D 4, had precluded adequate biological testing. The vepridimerines together with their lower analogues, paraensidimerins A, C and F, isolated from Euxylophora paraensis[2,3], are also interesting because of their novel skeleton and lack of optical activity. One possible explanation for their racemic nature involves a nonenzymatic synthesis from other Vepris, Oricia or Euxylophora secondary metabolites. Thus in the particular case of V. louisii and O. renieri, 1, 2, 3, and 4 may arise by Diels-Alder dimerization of the diene 5 derived from veprisine (6), the major constituent of these two plants[4], as illustrated retrosynthetically in Scheme 1. We now wish to report a synthesis of these alkaloids based on the idea mentioned above.

Our synthetic approach to the vepridimerines 1-4 was based on the thermolysis of veprisine 6. We reasoned that 6 would undergo a thermal heteroelectrocyclic ring opening reaction of the "cyclohexadiene $\rightleftharpoons$ hexatriene" type to give the quinoline quinone methide 7 which was expected to yield the requisite diene 5 following a {1, 7} sigmatropic shift. Diels-Alder dimerization of the diene 5 thus generated in situ followed by addition of the free hydroxyl groups to the residual double bonds of the resulting adducts would then give the dimeric



1 α-Hd, α-He

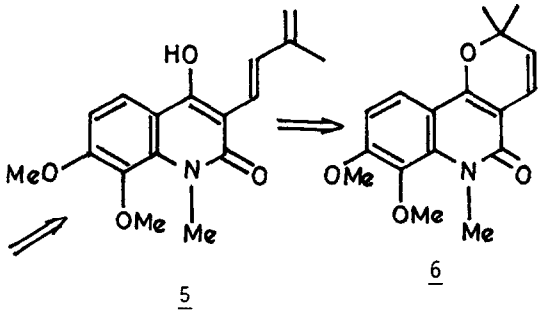
2 α-Hd, β-He



3 α-Hd, α-He

4 α-Hd, β-He

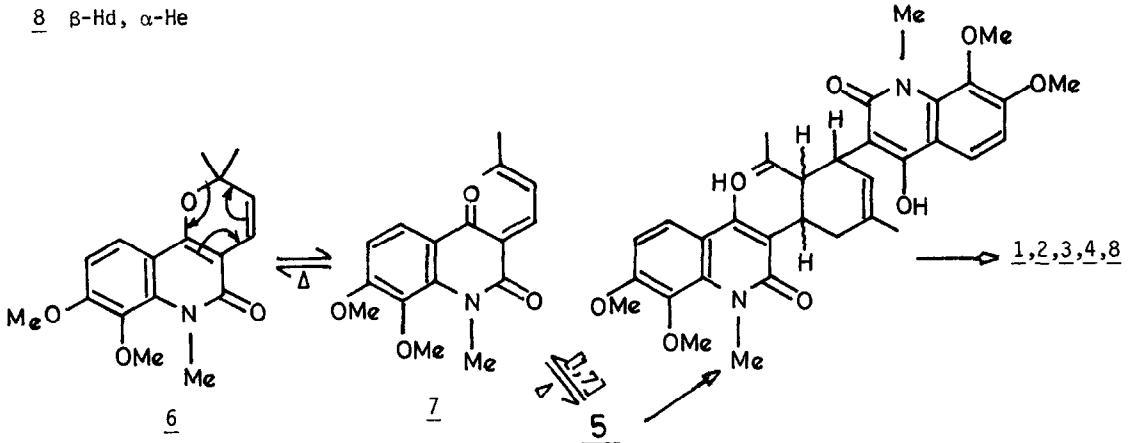
8 β-Hd, α-He



5

6

Scheme 1



6

7

5

1,2,3,4,8

Scheme 2

alkaloids (Scheme 2). Considering the various modes of dimerization of 5 and the possibility of the existence of many tautomeric forms of the adducts, the formation of several stereoisomeric vepridimerines appeared reasonable. Interestingly, the transformations envisaged in Scheme 2 are all thermal pericyclic reactions permissible by the Woodward-Hoffmann rules[6].

To test our hypothesis, 3.01 g (10 mmol) of veprisine 6 were placed in a pyrex tube and the tube sealed under reduced pressure. After heating in an oil-bath at 200-220° for 15 h, the tube was cooled, broken, and its contents dissolved in chloroform. The resulting solution showed seven TLC spots (SiO_2 gel, EtOAc/n-hexane 3:1). Extensive column chromatographic separation of the mixture afforded five pure compounds in 42% overall recovery yield. Four of the compounds were positively identified as vepridimerine A 1 (34%), vepridimerine B 2 (38%), vepridimerine C 3 (8%), and vepridimerine D 4 (12%) by direct comparison (CO-TLC and mixed melting point determination and IR, UV, ^{1}H- and ^{13}C-NMR spectral data) with authentic samples[1].

It was apparent from the spectroscopic data of the fifth dimer, provisionally named vepridimerine E 8, m.p. 287-288° (from methanol), that it was isomeric with the vepridimerines and contains a 4-quinolone unit as well as a 2-quinolone. Thus one of the H-5 resonances (δ_H 8.02) and one of the carbonyl carbon resonances (δ_C 176.20) exhibit the large downfield shifts expected of a 4-quinolone. Consonant with the presence of a 4-quinolone moiety the U.V spectrum of 8 underwent a small bathochromic shift upon addition of acid. Decoupling experiments at 360 MHz established the coupling constants between the protons shown in expression 9 (Chemical shifts in parenthesis) and led to the structure 8 for vepridimerine E. The relative stereochemistry shown is consistent with the coupling information in expression 9 which reveals in particular, the trans relationship of Hd and He (^{3}J 12.0 Hz). Inspection of models shows that, with the cyclohexane ring in the chair conformation, Hg and Ha have an ideal W relationship for the observed ^{4}J coupling (3.0 Hz). These ^{1}H-NMR spectral data are also virtually identical with those reported by Jurd et al[8] for paraensidimerin F which has an equivalent stereochemistry. No unequivocal spectral evidence justifying the placement of the 4-quinolone unit on the left side, however, could be found, but the simultaneous isolation from the reaction mixture of vepridimerine-C, -D and -E, and their proposed mode of formation was strongly in favour of structure 8 for vepridimerine E.

This simple laboratory preparation of the vepridimerines from veprisine 6 constitutes the first total synthesis of these heptacyclic alkaloids since 6 itself has been previously synthesized[4,9]. Furthermore, from the ease of the thermolytic reaction, one may be tempted to consider the vepridimerines as artifacts of the hot Soxhlet extraction procedure. We maintain that this is not the case since veprisine was recovered unchanged after prolonged heating under similar conditions.

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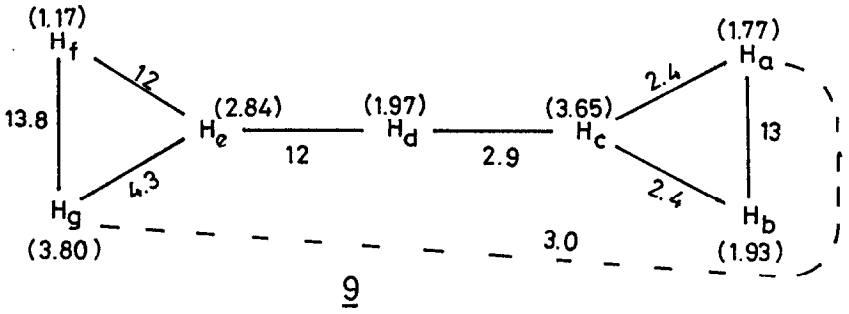

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7. Additional spectral data for 8 : I.R. ν_{max}^{KBr} 1625, 1590, 950, 900, 880, 860, 825, 810, and 780 cm^{-1} ; U.V λ_{max}^{EtOH} (ε) 326 (10,700), 314 (12,100), 250 (40,300), and 237 nm (43,700) ; $\lambda_{max}^{EtOH + HCl}$ (ε) 326 (10,500), 314 (12,000), 254 (41,000) and 237 nm (41,100) ; MS m/z 602.2620 (M^+, 100% ; $C_{34}H_{38}N_2O_8$ requires 602.2628), 587 (M^+, 15,28), 368(30), 355(42), 354(32), 316(40), 302(40) and 301(71) : ^{1}H-NMR δ_H (360 MHz, TMS) 1.01, 1.48, and 1.91 (3H each, C-Me), 3.72, 3.88, 3.92, and 3.95 (3H each, OMe), 3.75 (6H, 2 x N-Me), 6.88, 6.93, 7.82, and 8.02 (all 1H doublets, J 9 Hz, aromatic protons) ; ^{13}C-NMR δ_C (100 MHz) 176.20(s), 164.75(s), 159.18(s), 157.21(s), 155.31(s), 155.15(s), 137.61(s), 136.51(s), 134.90(s), 133.98(s), 121.91(d), 121.44(s), 119.67(d), 111.90(s), 108.22(d), 107.11(d), 56.25(q), 104.26(s), 100.40(s), 83.66(s), 78.05(s), 61.59(q), 61.25(q), 56.19(q), 53.26(d), 42.66(t), 39.26(t), 35.56(q), 33.87(q), 28.05(q), 27.91(d), 27.66(d), 26.92(q) and 19.5(q). Complete assignement will be given in the full paper along with those of the other compounds.

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