SYNTHESIS OF CORYNANTHEINE ALKALOIDS WITH (19E)-ETHYLIDENE GROUP: ON THE STRUCTURES OF RHAZIMANINE AND BHIMBERINE

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Abstract——Syntheses of four indoloquinolizidine alkaloids having a (19E)-ethylidene group at the 20-position, (±)-isositsirikine (1), (±)-16-epi-isositsirikine (2), and the proposed structures of (±)-rhazimanine (3) and (±)-bhimberine (4), were accomplished and have suggested that the structures of rhazimanine (3) and bhimberine (4) require revision.

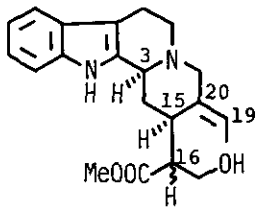
There have been known six stereoisomeric alkaloids of the indoloquinolizidine structure with an ethylidene group (E or Z) at the 20-position and three chiral centers at the 3-, 15-, and 16-positions.[1] Their structure determinations[1-3] by spectral analysis have encountered serious difficulty due to their flexible structures, particularly to cis or trans quinolizidine structure, two adjacent side chains at the 15- and 20-positions, and a mobile substituent at the 16-position.
We have now succeeded in the synthesis of all four alkaloids having a (19E)-ethylidene group at the 20-position, i.e., (±)-isositsirikine (1)[1] and (±)-16-epiisositsirikine (2),[1] both with 3α-configuration, and its 3β-isomers rhazimanine (3)[4] and bhimberine (4),[5] of which the structures of the latter two alkaloids are based on the proposal by Atta-ur-Rahman's group.

The starting compound, (±)-15,20-trans-3,15-anti olefin **7a**, for the synthesis of these alkaloids was prepared from the indoloquinolizidine **6** with a tetrahydrofuran moiety according to the modified procedure[6] involving the elimination-addition reaction that improved the yield of this conversion to 67%. Treatment of the trans-anti olefin **7a** with sodium hydride at room temperature afforded the thermodynamically stable (19E)-lactam **8a**[7] in 87% yield, which would be formed as a result of the steric

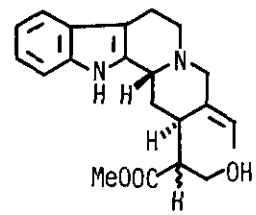
repulsion between the 19-methyl and lactam carbonyl groups. Similarly, the cis-anti olefin **7b**[6] was converted into the identical lactam **8a** in 93% yield. Chemoselective reduction of the lactam carbonyl group in the lactam **8a** with aluminum hydride followed by treatment of the resulting amino ester **9a**[7] with methanol in the presence of conc. sulfuric acid gave the methyl ester **9b**[7] in 56% yield. Finally, formylation of the methyl ester **9b** with ethyl formate in the presence of lithium diisopropylamide at -40°C gave the formyl ester **10**, which was then reduced with sodium borohydride to afford the epimeric hydroxy esters **3**[7] (mp 191-192°C) and **4**[7] (mp 202-203°C) in a ratio of 2 : 3 upon separation by silica gel chromatography. The structures of these two hydroxy esters **3** and **4** were confirmed by the respective ^{1}H nmr spectra and further unambiguously by the single-crystal X-ray analysis[8] (Figure) on the former isomer **3**. However, comparisons of the ^{1}H nmr spectra of natural and synthetic rhazimanines and bhimberines clearly showed non-identity, thereby suggesting that the structures proposed for rhazimanine[4] and bhimberine[5] by Atta-ur-Rahman's group have to be revised.

Further, the (19E)-olefin **8a** was converted into the known key intermediate **12**[9-11] for the synthesis of the 3α-alkaloids, (±)-isositsirikine (**1**) and its 16-epimer **2**. Inversion of the configuration at the 3-position was achieved in a manner similar to that reported by Winterfeldt et al.[9] Autooxidation of **8a** in trifluoroacetic acid in the presence of copper acetate followed by methylation of the resulting acid **11a** with diazomethane afforded the enamino ester **11b**[7] in 63% yield. Reduction of **11b** with sodium borohydride in acetic acid at 5-10°C gave a 1 : 1 mixture of the desired 3,15-syn lactam **12**[7] and the 3,15-anti lactam **8b**[7] in 90% yield, the former **12** of which has been known as the key intermediate for the synthesis of (±)-geissoschizine (**5**),[9,10] (±)-isositsirikine (**1**),[11] and (±)-16-epiisositsirikine (**2**).[11]

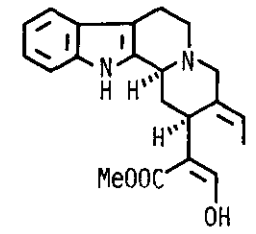
In conclusion, we have succeeded in the total synthesis of (±)-isositsirikine (**1**) and its other stereoisomers **2**, **3**, and **4**, all of which possess a (19E)-ethylidene group on the corynantheine skeleton and found that rhazimanine and bhimberine have been incorrectly formulated.



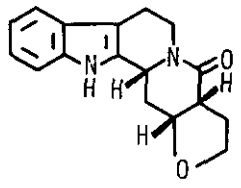
(1) 16R: isositsirikine
(2) 16S: 16-epiisositsirikine



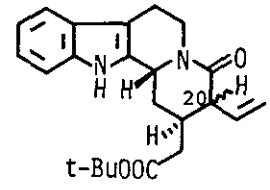
(3) 16R: rhazimanine
(4) 16S: bhimberine



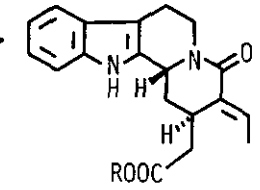
(5) geissoschizine



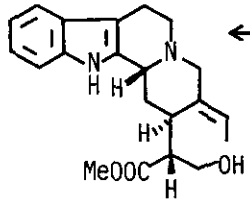
(6)



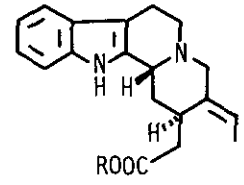
(7a) 20β-H
(7b) 20α-H



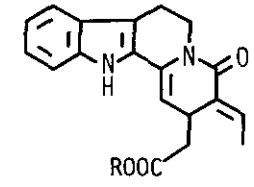
(8a) R=t-Bu
(8b) R=Me



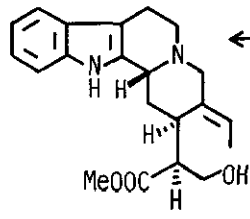
(3)



(9a) R=t-Bu
(9b) R=Me



(11a) R=H
(11b) R=Me



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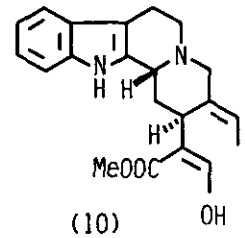
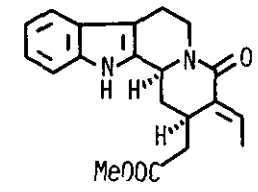


(10)



(12)

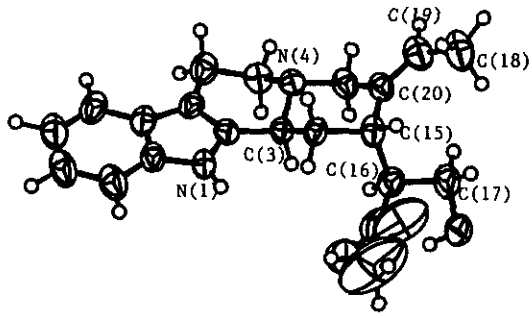


Figure. X-Ray crystal structure of compound **3**

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7. All compounds reported herein gave ir, nmr, and mass spectral data consistent with the assigned structures.
8. Crystal data: $C_{25}H_{36}N_2O_4$, M=428.573, monoclinic, space group $P2_1/n$, a = 11.099(5), b = 14.098(3), c = 16.145(3)Å, β= 98.54(2)°, V = 2498(1)Å^3, Dx = 1.1395 gcm^{-3}, Z = 4. The structure was solved by direct methods (MULTAN 78) and refined by least squares to R = 0.15 using 4263 independent reflections (Cu $K\alpha$, $2\theta_{max} \leq 130°$).
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