On the Annulation of Δ^2-Tetrahydropyridines. An Expeditious Total Synthesis of the Protoberberine Alkaloid Karachine

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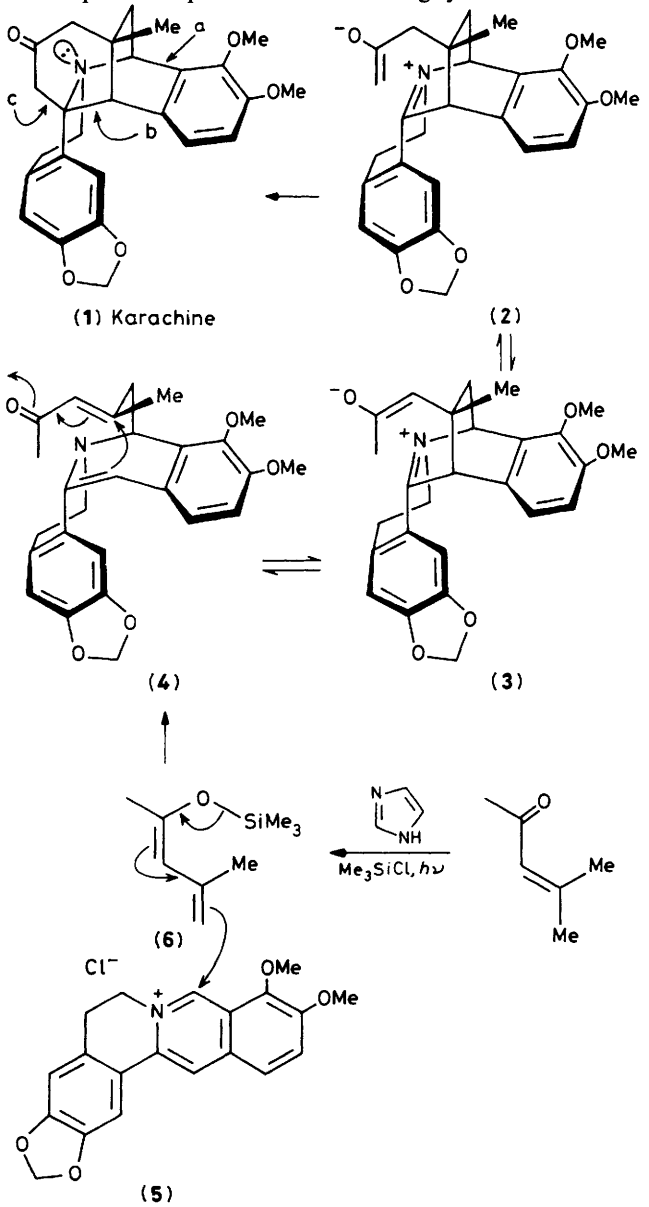
The various steric, stereoelectronic, and electrostatic factors which influence the bicycloannulation of Δ^2-tetrahydropyridines are discussed in connection with a concise two-step synthesis of the protoberberine alkaloid karachine (**1**).

Extracts known as 'rasaut' made from the root bark of *Berberis aristata* DC (Berberidaceae) are used in the Unani system of medicine for the treatment of jaundice and various diseases of the skin.[1] In addition to the common alkaloid berberine (**5**)[2] several minor alkaloids have been reported to be present in this shrub which is indigenous to the northern mountainous regions of India and Pakistan as well as in the Nilgiri hills of southern India. Recently, Shamma *et al.*,[3] isolated 8 mg of a novel, colourless, and optically inactive protoberberine alkaloid named karachine from 3 kg of 'rasaut' to which structure (**1**) was convincingly assigned. We now report an expeditious corroborating synthesis of this new alkaloid from commercially available berberine (**5**) and the readily prepared siloxydiene (**6**)[4] in which the stereoelectronic considerations advanced in the preceding communication[5] play a crucial role.



To begin with, we noted that the only bonds which are *anti* to the lone-electron pair on nitrogen in this conformationally rigid substance are those labelled a and b in formula (**1**). Unfortunately, the formation of either of these bonds by an *anti*-addition to the corresponding iminium salt is ruled out because both imines constitute violations of Bredt's rule. However, bond c is precisely *syn* to the lone-electron pair. Although all of our previous studies[5] have shown that *anti*-additions are strongly favoured, *syn*-additions, at least in the case of alkenes, are well documented especially when the *anti* mode is not possible. Therefore, the (**2**) to (**1**) transformation appeared to be feasible stereoelectronically. Of course, as noted previously,[5] such an addition would also require a boat-like transition state, but, in this case the heterocyclic ring is already in a boat conformation. Thus, in terms of energy requirements, the energy necessary for this otherwise unfavourable transformation has already been provided in the formation of the bicyclic system. We then realized that a Mannich condensation between siloxydiene (**6**) and berberine (**5**) should lead initially to the endocyclic enamine (**4**). An intramolecular Michael addition to provide (**3**) and equilibration of this enolate to its isomer (**2**) would complete the bicycloannulation sequence. One other question which arose concerned the stereochemistry of the (**4**) to (**3**) transformation. In principle, this process could lead to the stereoisomer where the methyl group and enolate anion are reversed. However, this mode of attack would certainly require much greater charge separation and accordingly should be strongly disfavoured. Furthermore, even if such an addition occurred it would not be deleterious since this step is undoubtedly reversible. With these considerations in mind we carried out this simple two step scheme with good results. Thus, heating a partial suspension of berberine with 20 equiv. of the silyloxydiene in dimethyl sulphoxide at 100 °C for 18 h followed by the usual extraction procedures provided a 66% yield of karachine (based on recovery of the sparingly soluble berberine). This result, coupled with those advanced in the preceding communication,[5] set the stage for further studies which will more fully define the scope of reactions of this type.

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