The Annelation of Δ^2-Tetrahydropyridines with Methyl Vinyl Ketone and its Derivatives

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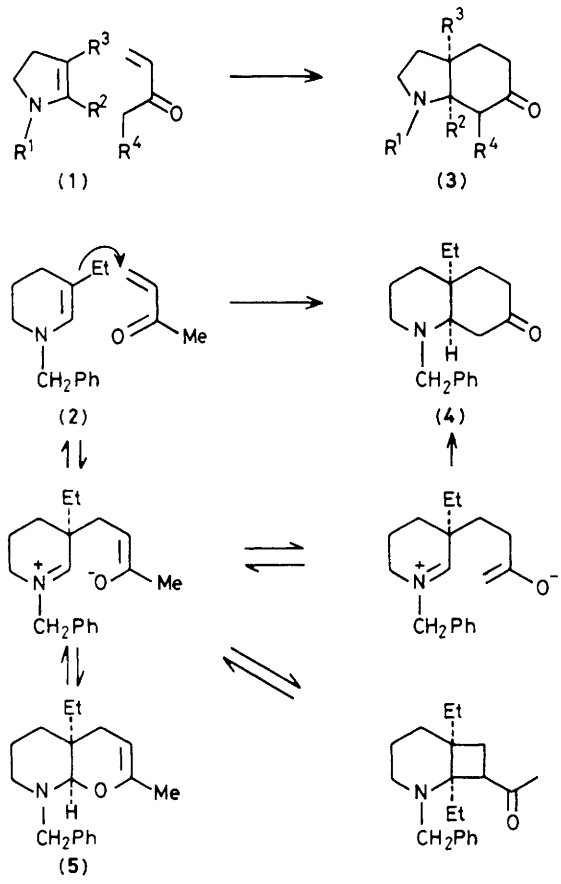
The various steric, stereoelectronic, and electrostatic factors which influence the annelation of Δ^2-tetrahydropyridines are discussed.

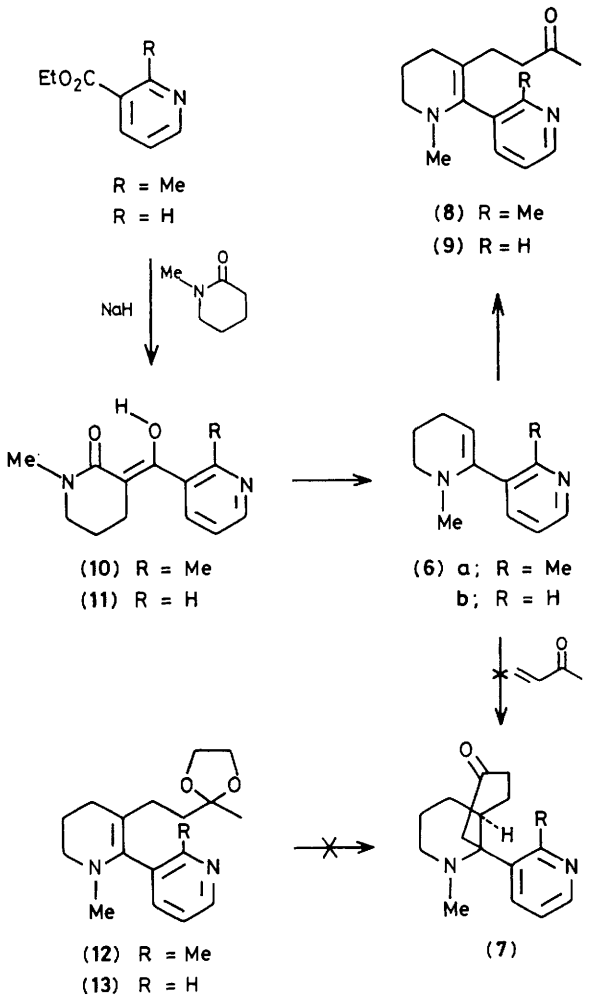
The annelation of Δ^2-pyrrolines (**1**) or Δ^2-tetrahydropyridines, *e.g.* (**2**), with methyl vinyl ketone or its derivatives has found wide application in the total synthesis of alkaloids.[1] Invariably, annelation of these endocyclic enamines affords exclusively *cis*-fused hydroindolones (**3**) or hydroquinolones, *e.g.* (**4**). We expected that this methodology could be employed in a total synthesis of *N*-methyl lycodine.[2] Thus, by analogy with successful annelations such as the (**2**) to (**4**) transformation[3] we expected that the Δ^2-tetrahydropyridine (**6a**) would react with methyl vinyl ketone to afford the *cis*-fused hydroquinolone (**7**).

The requisite endocyclic enamine (**6a**) was prepared by a modification of a procedure developed for the synthesis of imines.[4] Thus, condensation of ethyl 2-methylnicotinate with *N*-methylpiperidin-2-one provided (**10**) in 56% yield. The i.r. and ^{1}H n.m.r. spectra of (**10**) showed that it exists exclusively in the enol form shown. Refluxing (**10**) in conc. HCl, followed by basic work-up gave the desired endocyclic enamine (**6a**) in 85% yield. We were surprised to observe that reaction of (**6a**) with methyl vinyl ketone failed to provide the expected annelated product (**7**). Reaction occurred but afforded only the alkylated but uncyclized enamine (**8**) in 90% yield. In an effort to force the ring closure, (**8**) was converted into the corresponding acetal (**12**). When exposed to an anhydrous acid, substances of this type are known[5] to be in equilibrium with the corresponding enol ether which can undergo ring-closure on the protonated enamine. However, in this case only the starting material was recovered. At first we suspected the 2-methyl group might be responsible, sterically, for these failures. However, this possibility was ruled out when we prepared the corresponding demethyl derivative (**6b**) from (**11**) and observed identical behaviour. Thus (**6b**), when treated with methyl vinyl ketone, gave (**9**) in 95% yield, and as before, conversion into the corresponding acetal (**13**) failed to induce ring-closure.

At first we were puzzled by these results since we had exploited successfully similar transformations in the past; *e.g.*, (**2**) to (**4**). However, as several attempts to bring about this annelation failed, we realized that some unknown and serious limitation must be involved.

When examined closely, *three-dimensionally*, a number of subtle yet decisive features emerge. Consider first the initial Michael addition step. The fact that dihydropyrans [*e.g.*, (**5**)] are frequently observed at lower temperatures strongly implies that the enone is attacked in a conformation in which the two π-bonds are *cisoid*. In principle, this step can occur

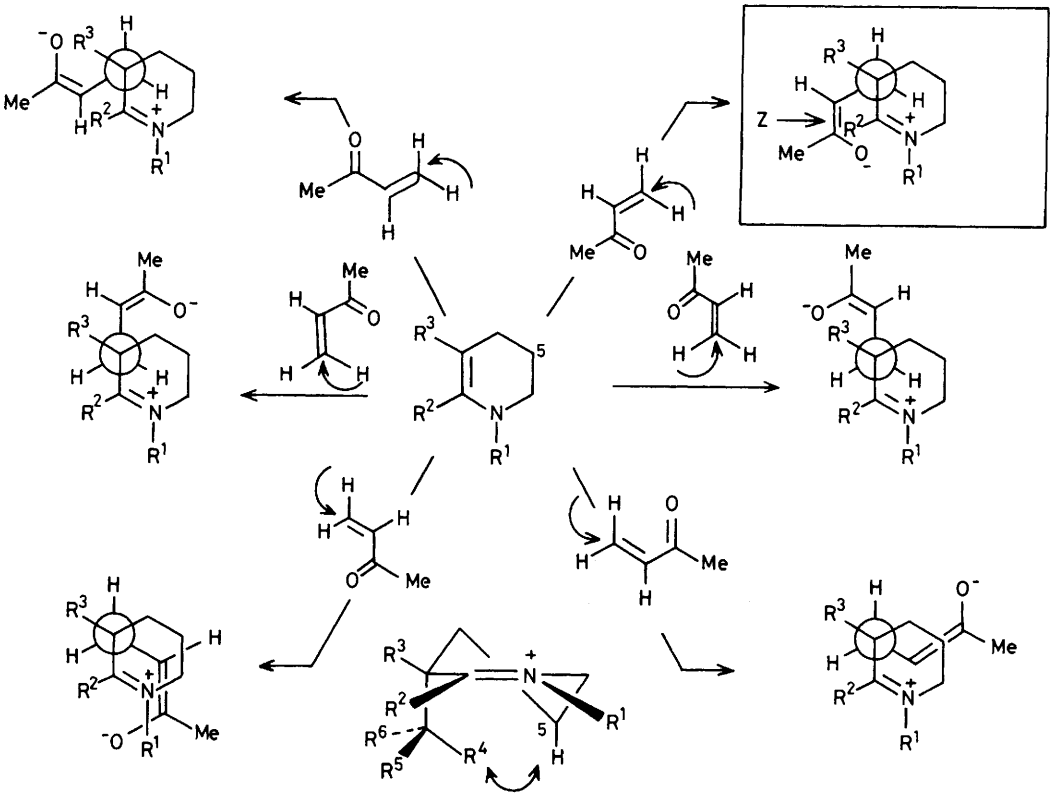




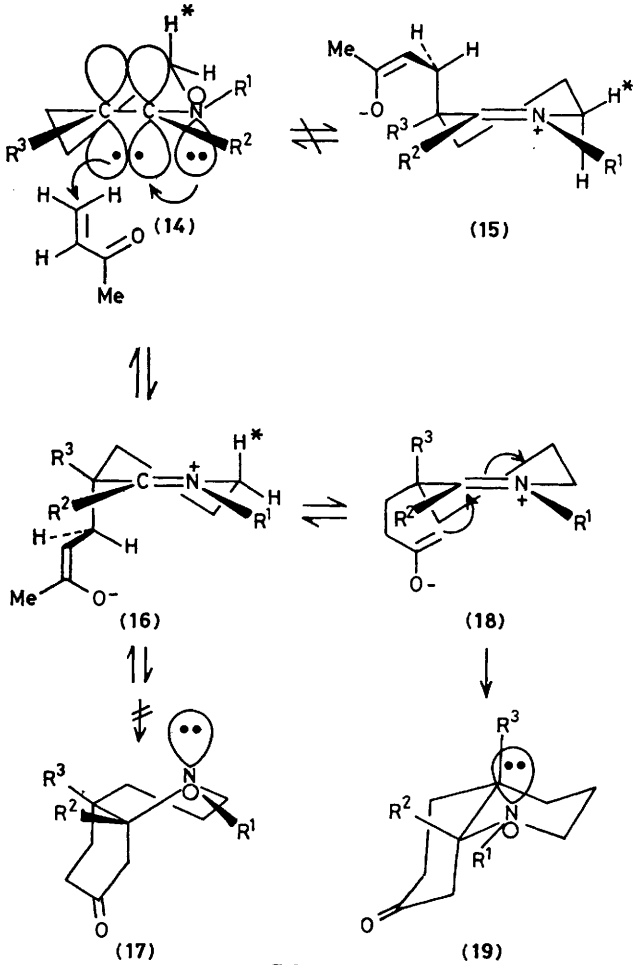
via a number of stereoisomeric transition states. However, if we make the reasonable assumption that there will be a steric bias favouring staggered transition states in the developing carbon–carbon bond then the number reduces to the six possibilities shown in Scheme 1. We suggest that the transition state leading to the zwitterion shown in the box (Scheme 1) (or the corresponding dihydropyran) will be strongly favoured for a combination of steric and electronic reasons. To begin with, the bottom two cases can be ruled out sterically. As inspection of the perspective drawing in Scheme 1 reveals, a severe 1,3-diaxial interaction between the enolate (R^4) and the C-5 axial proton would disfavour this mode of attack. The remaining four possibilities are similar sterically but only the one enclosed in the box brings the developing positively and negatively charged regions of the zwitterion into close proximity. The remaining three possibilities, though sterically feasible, require much greater separation of charge and accordingly are disfavoured.

Scheme 2 shows an alternative view of the initial Michael addition and illustrates a second important consideration. From *X*-ray and other data on other enamines[6] it is known that the nitrogen is not planar but pyramidal. The important point here is that if the lone-electron pair is pyramidal it can only overlap with the adjacent π-cloud if it adopts a quasi-axial conformation. As such, in principle, electrophilic addition can occur on either the same face of the molecule as the lone-pair to afford (**16**) or on the opposite face to provide (**15**). We assert that the latter mode of attack is highly unlikely. The problem involved can be seen most readily by following the fate of the axial proton marked with the asterisk. Note that in the product (**15**) this proton must be equatorial. Therefore, in order to maximize orbital overlap between the participating centres, a boat-like transition state is required. By contrast, attack on the α-face to produce (**16**) can proceed smoothly through a half-chair-like transition state; note the labelled proton remains axial.

We now turn our attention to the subsequent ring-closure. After isomerization of the enolate to the terminal position this closure can occur from either the conformation in which the enolate is axial (**16**) or, by conformational inversion, to one in which it is equatorial (**18**). As pointed out by Ziegler[7] the latter pathway is much more attractive because in this transition-state maximum orbital overlap can be achieved between the internal nucleophile and the developing lone-electron pair on nitrogen *via* a chair-like transition state with respect to *both* rings [*cf.*, (**18**) to (**19**)].[8] Maximum orbital overlap in the alternative conformation [(**16**) to (**17**)] can be achieved only at the expense of a boat-like transition state with respect to *both* rings and accordingly is disfavoured. In summary, we conclude that (a) *electrophilic additions to* Δ^2-*tetrahydropyridines occur in an axial fashion on the same face of the molecule as the lone-electron pair on nitrogen* and (b) in the case of an annelation reaction, *that the initially formed axial adduct* (**16**) *must undergo conformational inversion* [*to* (**18**)] *before ring closure can occur.* These considerations provide a rationale for the experimental observations cited above. Thus, when the Δ^2-tetrahydropyridine is substituted on the β-carbon (**14**, $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = CH_2Me$) there are no obvious steric or electronic impediments for



Scheme 1



Scheme 2

achieving annelation. However, when the α-carbon bears a substituent of substantial size (**14**, R^1 = Me, R^3 = aryl, R^3 = H) the initially formed adduct (**16**) cannot undergo the required conformational inversion to (**18**) because of allylic strain[9] between the enolate moiety and the aryl group. Therefor the reaction proceeds to afford the alkylated but uncyclized products observed. The following communication provides an illustration of how these considerations can be applied effectively in synthesis.[10]

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References

1 R. V. Stevens, *Acc. Chem. Res.*, 1977, **10**, 193, and references cited therein.
2 W. A. Ayer, J. A. Berezowsky, and G. G. Iverach, *Tetrahedron*, 1962, **18**, 567.
3 R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *J. Chem. Soc., Chem. Commun.*, 1969, 877.
4 E. Spath and H. Bretschneider, *Chem. Ber.*, 1928, **61**, 327; S. Brandange and L. Lindblom, *Acta Chem. Scand., Ser. B*, 1976, **30**, 93; E. Lecte and S. A. S. Leete, *J. Org. Chem.*, 1978, **43**, 2122.
5 E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Am. Chem. Soc.*, 1968, **90**, 6177.
6 *Cf.*, P. W. Hickmott, *Tetrahedron*, 1982, **38**, 1975, and references cited therein.
7 F. E. Ziegler and E. B. Spitzner, *J. Am. Chem. Soc.*, 1973, **95**, 7146.
8 For further examples involving *intermolecular* additions to Δ^1-tetrahydropyridinium salts *cf.*, R. V. Stevens and A. W. M. Lee, *J. Am. Chem. Soc.*, 1979, **101**, 7032; *J. Chem. Soc., Chem. Commun.*, 1982, **102**, 103.
9 F. Johnson, *Chem. Rev.*, 1968, **68**, 375.
10 R. V. Stevens and J. R. Pruitt, *J. Chem. Soc., Chem. Commun.*, 1983, following communication.