Intramolecular Michael-type Additions. A 5-*Endo-Trig* Ring Closure?†

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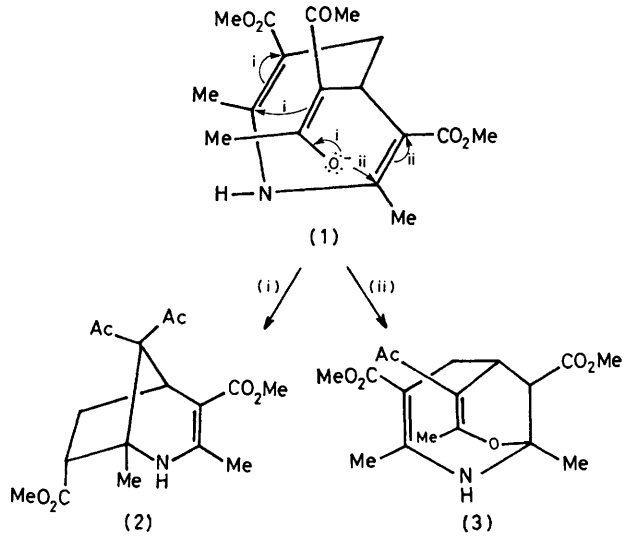
Summary Enolates of 1,3-diketones react with 4-chloroalkyl-1,4-dihydropyridines, giving 4-substituted-4,5-dihydroazepines, then, under more vigorous conditions, 2-azabicyclo[3.2.1]oct-3-enes, a cyclisation which may be an exception to Baldwin's 5-*endo-trig* rule.

Two alternative modes‡ of intramolecular Michael addition would appear possible for enolate (**1**) (Scheme 1). Using Baldwin's rules,[2] the *C*-alkylation (**1**) → (**2**) is at once a 6-*exo-trig* cyclisation from the viewpoint of the so formed six-membered ring and a 5-*endo-trig* cyclisation when the five-membered ring is considered. In such circumstances, considerations regarding the 5-*endo-trig* process must take precedence and so the formation of the 2-azabicyclo-[3.2.1]oct-3-ene (**2**) by this route should be disfavoured.[2,3] In contrast, the simultaneous 6-*endo-trig*/9-*exo-trig* formation of (**3**) by *O*-alkylation should be favoured. We now report that reaction gives the apparently disfavoured product (**2**) and appears to necessitate either a modification of the 5-*endo-trig* rule or of a previously accepted mechanism.

† For previous paper in the series Intramolecular Michael-type Additions see ref. 1.

‡ *O*-Alkylation by C-7 or *C*-alkylation by C-2 in (**1**) would generate 7- or 4-membered rings and are considered less likely.



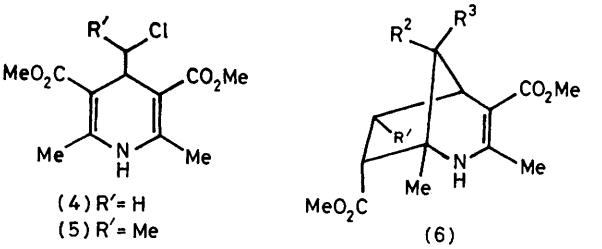
SCHEME 1.

4-Chloroalkyl-1,4-dihydropyridines (**4**) and (**5**) are well-known to undergo ring-expansion reactions in the presence of basic nucleophiles.[4,5] Reaction of (**4**) with sodium acetylacetonate in dimethylformamide at 0—5 °C yielded the dihydroazepine (**7**), while reaction of (**4**) or (**7**) with the same reagents at 60—65 °C afforded the 2-azabicyclo-[3.2.1]oct-3-ene (**2**).§ Similarly, from (**4**) or (**5**) we have prepared other 2-azabicyclo[3.2.1]octenes (**6**) (see Table) including spiro compounds from cyclic diketones and cyclopentadiene. The stereochemistry at C-6 and C-7 of the bicyclic compounds follows by analogy with earlier work,[5,6] and from the coupling constants of protons at C-5, C-6, and C-7 when these can be seen clearly in the n.m.r. spectra.

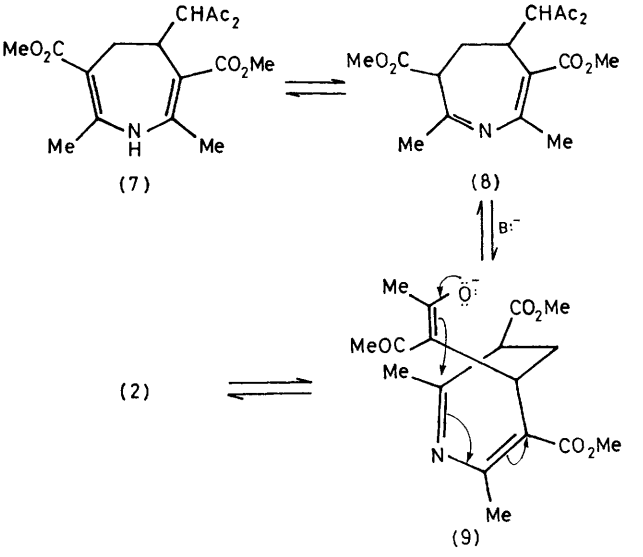
TABLE. Preparation of the 2-azabicyclo[3.2.1]oct-3-enes (**6**)[a]

R^1	R^2	R^3	M.p./°C	Yield[b]/%
H	Ac	Ac	192·5—193·5	85
Me	Ac	Ac	180—181	74
H	–C(:O)[CH_2]$_3$C(:O)–		219·5—220·5	90
Me	–C(:O)[CH_2]$_3$C(:O)–		137—138·5	60
H	–C(:O)$CH_2CMe_2CH_2$C(:O)–		221·5—222·5	82
Me	–C(:O)$CH_2CMe_2CH_2$C(:O)–		218·5—219·5	68
H	–CH=CHCH=CH–		195—196·5	68
Me	–CH=CHCH=CH–		158—159·5	38

[a] Satisfactory elemental analysis and spectral data were obtained. [b] Yields shown are from (**4**) or (**5**) by the direct route.



Although we are unaware of any previous application of Baldwin's rules to the formation of bridged ring systems, intuitively such an extrapolation seems valid. It might be concluded from the above results that this reaction is an exception to the *5-endo-trig* rule or that the rule may require modification when applied to bridged systems. Alternatively, mechanism (i) (Scheme 1) may be incorrect, although such a mechanism has been postulated in the formation of related bridged species.[5,6] A reasonable alternative pathway is shown in Scheme 2 and involves initial tautomerism of the dihydroazepine (**7**) to give (**8**), followed by intramolecular Michael addition of the enolate to the iminocrotonate system, a reaction which is *5-exo-trig*/*6-endo-trig* and is favoured.



SCHEME 2.

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§ We have been unable to prepare (**3**) and therefore cannot determine whether formation of (**2**) results from a kinetically or thermodynamically controlled process.

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