1,7-Addition of Enamines to 1,1-Bisethoxycarbonyl-2-vinylcyclopropane: a Useful Method of Introducing a Six Carbon Fragment α to a Ketone

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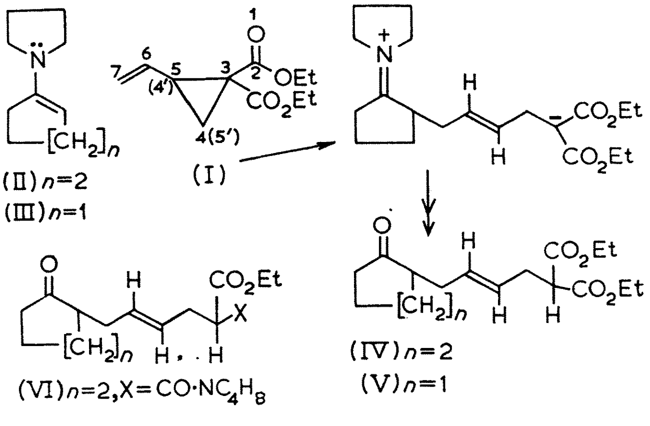
Summary The pyrrolidine enamines of cyclopentanone and cyclohexanone, in contrast to other nucleophiles, undergo exclusive 1,7-addition with 1,1-bisethoxycarbonyl-2-vinylcyclopropane.

As part of a study concerned with the reaction of electrophiles with enamines,[1] we have examined the behaviour of compound (I), which could, in principle, undergo nucleophilic attack in a 1,5, 1,5′, or 1,7† sense with respect to the ester oxygen. A previous study,[2] employing sodiomalonic ester in ethanol as the nucleophile, suggested that 1,7-addition occurs to a minute extent (*ca.* 1%), though the nature of the major product did not permit differentiation between the 1,5 or 1,5′ modes.‡



(II) $n=2$
(III) $n=1$
(I)
(IV) $n=2$
(V) $n=1$
(VI) $n=2$, $X=CO{\cdot}NC_4H_8$

We now report the interesting and synthetically useful finding that pyrrolidine enamines undergo exclusive 1,7-addition with compound (I). The reaction of (I) with (II; $n = 2$) in *p*-cymene under reflux, followed by mild acidic hydrolysis, gives a 52% yield of a ketone (semicarbazone m.p. 130—131°) corresponding to the formula $C_{17}H_{26}O_5$. This compound is assigned structure (IV; $n = 2$) on the basis of its n.m.r. spectrum which contains a low-field 2H multiplet (τ 4·4—4·7) arising from the vinylic hydrogens and a 1H triplet (τ 6·75, J 7Hz.) assigned to the malonyl hydrogen coupled to a methylene group. Its i.r. spectrum contains a maximum at 10·25 μm. ascribable to a *trans*-double bond.

Careful examination of the reaction mixture did not reveal the presence of any isomeric compounds. The remainder of the material is largely recovered starting compound (I), resinified enamine,§ and a higher-boiling product, which though incompletely separated and characterized, could be assigned structure (VI) through combined g.l.c.-mass spectrometry.

An essentially identical result was obtained in the reaction of the enamine of cyclopentanone (III; $n = 1$) with compound (I). The ketodiester (VI), (54% yield) was characterized as its semicarbazone (m.p. 106—109°).

While the essential result, *i.e.*, terminal addition to a multiply conjugated system, is not, in itself, surprising, the contrast between the reaction of (I) with enamines and sodiomalonic ester is noteworthy. We tentatively suggest that when the opening involves a purely nucleophilic attack, which precedes protonation at position 3 (or 1), terminal attack will prevail.[3] Such a process will also have a considerably higher activation energy than a related possibility where the transfer of a proton (or other elecrophilic species) to position 3 (or 1) is concerted with nucleophilic attack. In the latter case cationic character is developed at position 5. For reasons of stereochemistry or diminution of cationic character with vinylogous extension, the nucleophile attacks at a ring carbon.

By this line of reasoning, one would expect preponderant attack in a 1,5 rather than 1,5′ sense since the double bond would stabilize cationic character. Indeed, we and others[5] have found that the reaction of pyrrolidine with (I) does give exclusive 1,5 addition. These reports will be reported shortly. For a recent postulation of cationic character in the opening of related cyclopropanes, see ref. 4.

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† We suggest the designation 1,5 and 1,5′ (which arises from alternative numbering) to indicate the electronic equivalence of the process and to differentiate these and 1,7 addition from the usual Michael reactions which are designated by the terms 1,4 and 1,6.

‡ We have repeated this experiment using combined g.l.c.–mass spectrometric analysis. The result of Kierstead is essentially correct. We were able to find additional products which were not previously[2] noted but they were all derivable from initial 1,5- or 1,5′-attack.

§ In a blank run, we determined that compound (II) suffers extensive decomposition at these high temperatures. This, rather than alternate modes of attack, is responsible for the relatively low yield.

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