2,2-versus 2,6-Dialkylation of the Pyrrolidine Enamine of 2-Methylcyclohexanone with Electrophilic Olefins

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ALTHOUGH isolated reports of 2,2-disubstitution of cyclopentanone[1] and cyclohexanone[2] enamines have appeared, it is generally accepted that alkylation of the pyrrolidine enamine of 2-methylcyclohexanone normally leads to the 2,6-disubstituted derivative.[3] This has been rationalised in terms of steric interactions in the monosubstituted enamine favouring the least substituted form (II). However, House and Schellenbaum[4] reported that prolonged reaction of the pyrrolidine enamine with methyl acrylate in dioxan under reflux gave a 1 : 1 mixture of 2,2- and 2,6-disubstituted products and concluded that the preference for attack at the least substituted position was not as great as had previously been supposed. Subsequently Malhotra and Johnson[5] suggested that the formation of the 2,2-disubstituted product occurred in the hydrolysis step, by pyrrolidine-catalysed Michael reaction of methyl acrylate with 2-methylcyclohexanone. Since these conditions are unusually mild for formation of the required enolate anion, we have re-investigated this reaction and our preliminary results are summarised in the Table.

Removal of the solvent and all unchanged electrophilic olefin was effected by evaporation *in vacuo* before the enamine residue was hydrolysed under non-epimerising conditions at pH 6·0—6·5 and the resulting mixture of ketones analysed by g.l.c. and n.m.r. Under these conditions the 2,2-disubstituted product could not be formed during the aqueous work-up. Furthermore, the presence of the 2,2-disubstituted enamine (XIII) could be detected in the crude enamine residue [τ8·83(s), Me; τ† 5·25(t), ·CH:] prior to hydrolysis.

These results indicate that the 2,2-disubstituted derivative is formed by alkylation of the enamine, and that its formations is favoured by low enamine concentration and low dielectric constant of the solvent. Under these conditions the zwitterionic intermediates (Scheme) have short lifetimes, and intermolecular protonation or deprotonation processes (by iminium salts or unchanged enamine, respectively) are less probable. Unless the initial conformation of the zwitterionic intermediates are favourable for stereoelectronically controlled intramolecular proton transfer their formation can be regarded as reversible and little product formation takes place.‡ Consideration of the possible competing pathways shows that only paths *a* (V)→(X) and *c* (IX)→(XIII) meet these requirements and

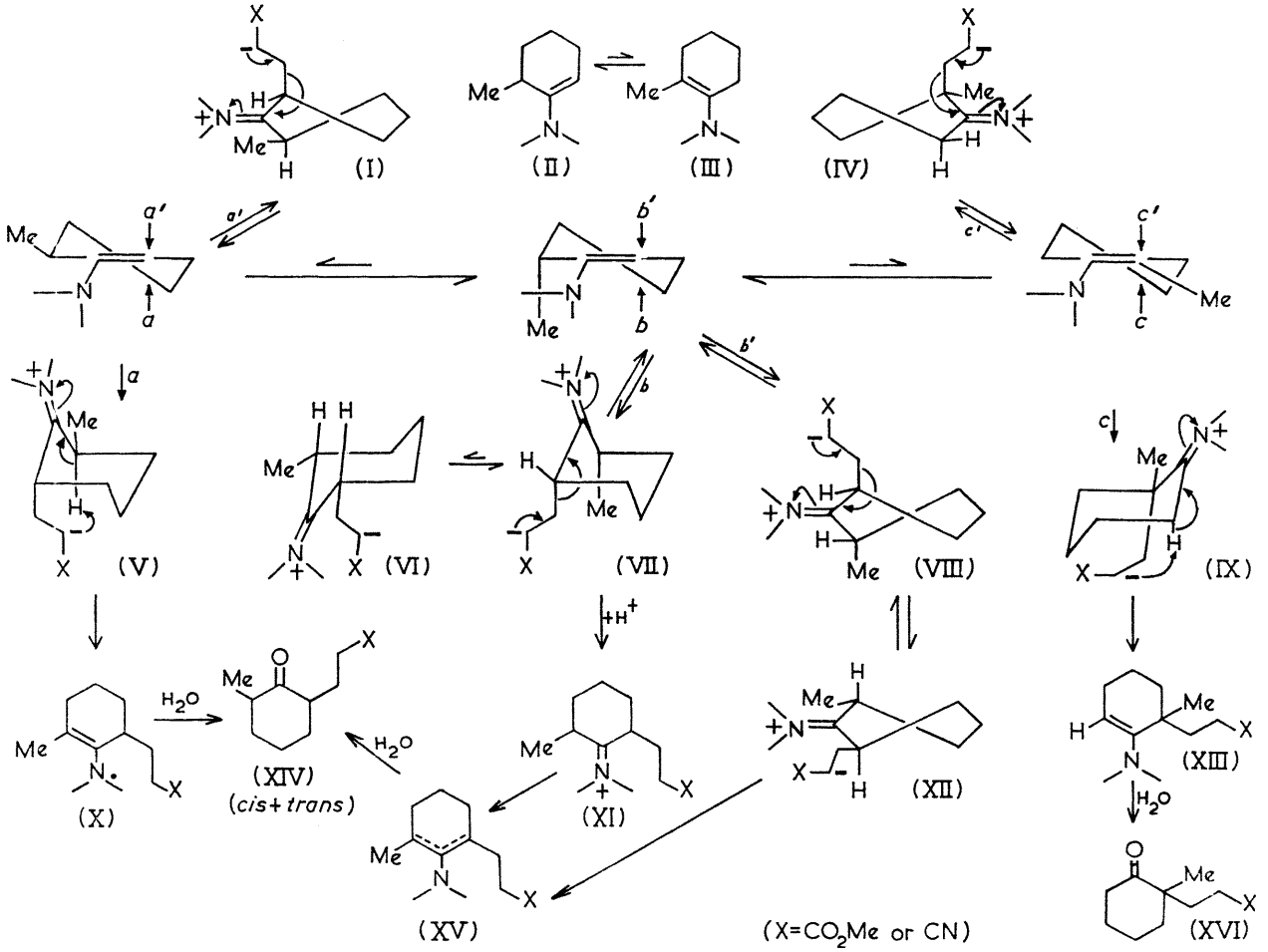
† At lower field than unchanged enamine [(II) τ 5·7(t), ·CH:].
‡ Cyclobutane formation can be ruled out since this is reversible even at room temperature.[6]

TABLE

Electrophilic olefin	Solvent	Reaction times (hr.) (under reflux)	Yield %	Disubstituted cyclohexanone. % Composition 2,6-	2,2-
Methyl acrylate	Methanol	3[b]	75	100	0
Methyl acrylate	Acetonitrile	66[b]	65	95	5
Methyl acrylate	Dioxan	66[a]	7	50	50
Methyl acrylate	Dioxan	66[b]	60	65	35
Methyl acrylate	Dioxan	66[c]	60	85	15
Methyl acrylate	Benzene	66[b]	60	80	20
Methyl acrylate	Mesitylene	66[b]	65	70	30
Acrylonitrile	Methanol	4[b]	65	100	0
Acrylonitrile	Dioxan	66[b]	70	55	45

The concentrations used were [a] 0·11; [b] 2·3; [c] 36·5 mole. of enamine per litre of solvent, and a 2:1 ratio of electrophilic olefin to enamine.

thus result in approximately equal amounts of 2,2- and 2,6-disubstituted products (XVI) and (XIV). Paths *a'*, *b*, and *b'* result in conformations (I), (VII), and (VIII), respectively which require the removal of an equatorial proton (by intramolecular processes) involving a substantial increase for their formation are (VII) and (VIII), since the steric interactions (1,3-diaxial and nonbonded twist interactions mainly) are less than those present in (V) and (IX) (one $A^{(1,3)}$-interaction[8]) or (I) and (IV) (one reduced§ $A^{(1,3)}$-interaction + nonbonded twist interactions) or (VI) (two



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in activation energy owing to unfavourable stereoelectronic factors,[7] and, together with path *c'*, can be regarded as reversible.

The intermediates requiring the least activation energy $A^{(1,3)}$-interactions) or (XII) (two reduced§ $A^{(1,3)}$-interactions + nonbonded twist interactions). In polar solvents of high dielectric constant (acetonitrile) the lifetimes of (VII) and (VIII) are presumably increased sufficiently

§ The two dihedral angles between the substituents at C-2 and C-6, and the imino-group are increased in the twist form.

to enable intermolecular protonation, or pseudorotation (VIII) → (XII) followed by intra- or inter-molecular proton transfer (XII) → (XV). Increase in reagent concentration will also favour these intermolecular processes, partially preventing reversion of (VII) or (VIII) to starting materials and favouring 2,6-disubstitution.

In protic solvents (VII) and (VIII) will be protonated immediately so that paths *b* and *b'* become irreversible and only 2,6-disubstitution occurs.

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