Enamine Chemistry. Part 24.[1] 2,2- *versus* 2,6-Disubstitution in 2-Alkylcyclohexanone Enamines. Factors affecting the Regioselectivity and Stereoselectivity of Enamine Alkylation and Protonation

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The factors affecting the reversibility and energetics of competing reaction pathways are discussed and shown to provide a rational explanation for the regioselectivity of reaction of 2-substituted cyclohexanone enamines.

In 1969 we provided [2] confirmation and an explanation for an observation [3] that alkylation of the pyrrolidine enamine (1) of 2-methylcyclohexanone with methyl acrylate (2a), in dilute aprotic media of low dielectric constant, gave appreciable amounts of the 2,2-disubstituted product. A recent report [4] on the annelation of 2-substituted cyclohexanone and cyclopentanone enamines has prompted us to provide full details of our original investigation and to clarify and extend aspects of the explanation which we provided in view of the apparent doubt which Könst [4] has expressed concerning its specific and general applicability.

Alkylation with Electrophilic Olefins.—(i) *Energetics and reversibility of competing reaction pathways.* Our basic premise (Scheme 1) was that axial (path b) or equatorial (path b') C-1 attack † by the electrophile (2) on the enamine conformer having the 3-methyl substituent † axially oriented [*i.e.* (1*ax*)] were the preferred modes of reaction, having the lowest activation energy,‡ but were reversible under the above-mentioned conditions and did not lead to product. This conclusion was based on the following reasoning. The carbon–carbon bond formed in the resulting zwitterionic intermediates (4) and (5) is weakened by the push–pull influences of the negative and positive charges and is lined up with the *p* orbital of the iminium group so that elimination of the electrophilic olefin and re-formation of the enamine system would be a synchronous stereo-

† Positions 2 and 6 in the ketone are numbered 3 and 1, respectively, in the derived enamine.

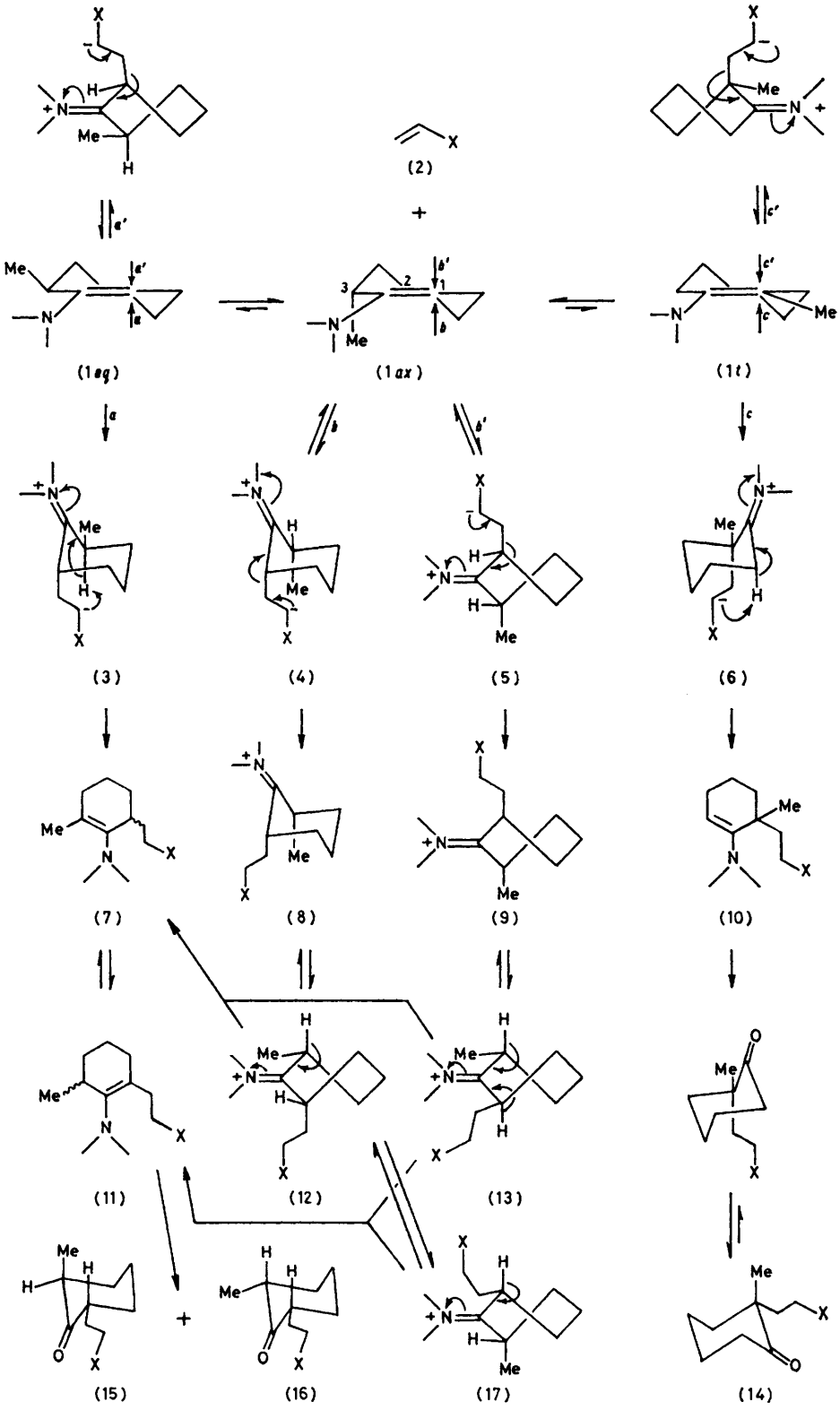
‡ The various steric interactions which contribute to the energies of the transition states are summarised in our preliminary communication.[2]

[1] Part 23, M. G. Ahmed, P. W. Hickmott, and M. Cais, *J.C.S. Dalton*, 1977, 1557.

[2] N. F. Firrell and P. W. Hickmott, *Chem. Comm.*, 1969, 544.

[3] H. O. House and M. Schellenbaum, *J. Org. Chem.*, 1963, **28**, 34.

[4] W. M. B. Könst, J. G. Witteveen, and H. Boelens, *Tetrahedron*, 1976, **32**, 1415.



SCHEME 1 a; X = CO_2Me, b; X = CN

electronically favoured process. Although this could be prevented by protonation of the anionic centre, under conditions of high dilution this would have to involve intramolecular transfer of the equatorially orientated C-1 hydrogen. This would be expected to be a higher energy process owing to the unfavourable stereoelectronic factors [5] involving a four-membered transition state and negligible overlap with the *p* orbital of the iminium group until appreciable rehybridisation of the developing C-1 anionic centre had taken place. Charge neutralisation by collapse to the cyclobutane introduces strain into the system and has been shown to be reversible even at room temperature.[6] Similar considerations apply to path a′ which, together with path c′, [(12), (13), and (17)] which can undergo deprotonation to regenerate the enamine system [(7) and (11)] under conditions of stereoelectronic control. Further protonation of the zwitterionic intermediates formed in greatest abundance, namely (4) and (5), can then occur. This process is therefore self-propagating, as reflected in the increase in the amount of 2,6-disubstitution (48 ⟶ 65 ⟶ 82%) as the enamine concentration is increased (0.11 ⟶ 2.3 ⟶ 36.5 mol l^{-1}) (Table 1, nos. 1—3), rising to a maximum of 85% in the absence of solvent (Table 1, no 12). The fact that 2,2-disubstitution still occurs at high enamine concentration or in the absence of solvent can be attributed to the short lifetime of the zwitterionic intermediates (4) and (5) in media of

TABLE 1

Effect of reaction conditions on the ratio of 2,2- to 2,6-disubstitution [a]

					Disubstituted cyclohexanone (% composition)		
No.	Electrophilic olefin	Solvent	Reaction time (h) (under reflux)	Yield (%)	*trans*-2,6 (15)	*cis*-2,6 (16)	2,2- (14)
1	Methyl acrylate	Dioxan	66 [b]	10	28	20	52
2	Methyl acrylate	Dioxan	66	65	45	20	35
3	Methyl acrylate	Dioxan	66 [c]	70	46	36	18
4	Methyl acrylate	Acetonitrile	66	65	65	30	5
5	Methyl acrylate	Methanol	3	70	70	30	0
6	Methyl acrylate	Methanol	66	50	56	44	0
7	Methyl acrylate	Benzene	66 [d]	60	55	25	20
8	Methyl acrylate	Mesitylene	66 [e]	65	43	24	33
9	Methyl acrylate	Mesitylene	66 [f]	40	30	20	50
10	Acrylonitrile	Dioxan	66	70	32	20	48
11	Acrylonitrile	Methanol	66	70	69	31	0
12	Methyl acrylate	None	66 [g]	80	52	33	15

[a] Enamine concentration 2.3 mol l^{-1} unless stated otherwise. [b] Enamine concentration 0.11 mol l^{-1}. [c] Enamine concentration 36.5 mol l^{-1}. [d] Temp. 80 °C. [e] Temp. 100 °C. [f] Temp. 160 °C, under pressure. [g] Temp. 80 °C.

must be regarded as a reversible pathway not leading to product under these conditions. Reaction must therefore proceed *via* the higher energy routes ‡ (paths a and c) involving axial attack on (1*eq*) and (1*t*), since these can be rendered irreversible by stereoelectronically controlled intramolecular proton transfer *via* a six-membered cyclic transition state [(3) ⟶ (7) and (6) ⟶ (10)]. Since the two zwitterionic intermediates thus formed [(3) and (6)] are destabilised by the same $A^{1,3}$ interactions,[7] the activation energy for their formation should be similar. Reaction should therefore lead to roughly equal amounts of 2,2- and 2,6-disubstituted products, as is in fact observed under conditions of high dilution in which intermolecular processes are reduced to a minimum (Table 1, no. 1). The probability of interaction between the starting reagents is of course reduced under these conditions, with consequent reduction in yield.

(ii) *Effect of concentration and solvent.* As the concentration of enamine is increased so the possibility of intermolecular proton exchange is increased. Once the anionic centres of (4) or (5) have been protonated, stable iminium salts (8) and (9) are produced which can undergo ring inversion or pseudorotation to give conformations low dielectric constant. This will cause a reduction in the rate of product formation *via* routes b and b′ so that routes a and c are still able to compete. Conversely in polar solvents of high dielectric constant (acetonitrile) the life-time of the initially formed zwitterionic intermediates (4) and (5) are presumably increased sufficiently to enable intervention by intermolecular protonation processes at lower dilution. Alternatively the increased lifetime could allow the zwitterions to undergo pseudorotation to give a twist conformation with the C-1 hydrogen axially oriented [2,8] followed by intramolecular proton transfer *via* a four-membered transition state. In either case increased product formation *via* routes b and b′ (Table 1, no. 4) would result. In protic solvents the formation of (4) and (5) will be rendered virtually irreversible by the combined effects of the increased dielectric constant and solvating power of the solvent together with the fact that the anionic centre can now be protonated directly by the solvent. Under these conditions only 2,6-disubstitution occurs, *via* the low energy paths b and b′ (Table 1, nos. 5, 6, and 11).

(iii) *Evidence for the intermediacy and reversible formation of zwitterionic intermediates.* We first ruled out the

‡ Same footnote as on page 340.

[5] E. J. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, Conformational Analysis,' Interscience, New York, 1965.

[6] I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 1964, 2165.

[7] F. Johnson, *Chem. Rev.*, 1968, **68**, 375.

[8] P. W. Hickmott, P. J. Cox, and G. A. Sim, *J.C.S. Perkin I*, 1974, 2544.

possibility that the 2,2-disubstituted ketone was being formed in the hydrolysis step, by a base-catalysed Michael reaction of methyl acrylate with the enolate anion of 2-methylcyclohexanone.[9] This was demonstrated by removal of the solvent and all unchanged methyl acrylate *in vacuo* before the reaction mixture was hydrolysed under non-epimerising conditions at pH 6.0—6.5. The resulting mixture of ketones was analysed by g.l.c. and n.m.r., showing that the yield of 2,2-disubstituted product was unchanged and that it could not therefore be formed during the aqueous work-up. Furthermore, the presence of the enamine precursor (10) of the 2,2-disubstituted ketone (14) was detected in the crude enamine residue prior to hydrolysis (see Experimental section). Further confirmation was obtained by heating a mixture of (1) and methyl acrylate (or 2-methylcyclohexanone, pyrrolidine, and methyl acrylate) under reflux in the presence of water. In no case was any 2,2- or 2,6-disubstituted ketone obtained. Treatment of (1) with methyl acrylate in methanol for 3 h under reflux and, after removal of the methanol, further treatment of the alkylated enamine with methyl acrylate in dioxan, under reflux for 66 h, gave none of the 2,2-disubstituted cyclohexanone on hydrolysis. This clearly demonstrates that the 1,3-disubstituted enamines (7) and (11), once formed, do not undergo reversion to the starting materials. When the reaction between (1) and methyl acrylate was carried out in monodeuteriomethanol the ^1H n.m.r. spectrum of the 2,6-disubstituted cyclohexanone obtained on hydrolysis showed the axial and equatorial methyl signals as doublets, indicating that no deuterium incorporation at C-3 of the enamine had occurred. Mass spectroscopy indicated however that *ca.* 70% deuteriation of the α-position of the methoxycarbonylethyl side-chain had occurred, thus demonstrating the intermediacy of the zwitterionic intermediates (4) and (5). Risaliti *et al.* have demonstrated that the formation of such zwitterionic intermediates is reversible, by showing that the isomerisation of maleate to fumarate esters is catalysed by enamines but not by tertiary amines.[10] We have also used this principle to develop conditions for changing the regioselectivity of reaction of certain dienamines. Thus although methylation of the pyrrolidine dienamine of 3-methyl-$\Delta^{1(8a)}$-2-octalone gives only the 1,3-disubstituted octalone in protic and aprotic solvents, the position of attack by acrylonitrile and methyl acrylate is solvent-dependent.[11]

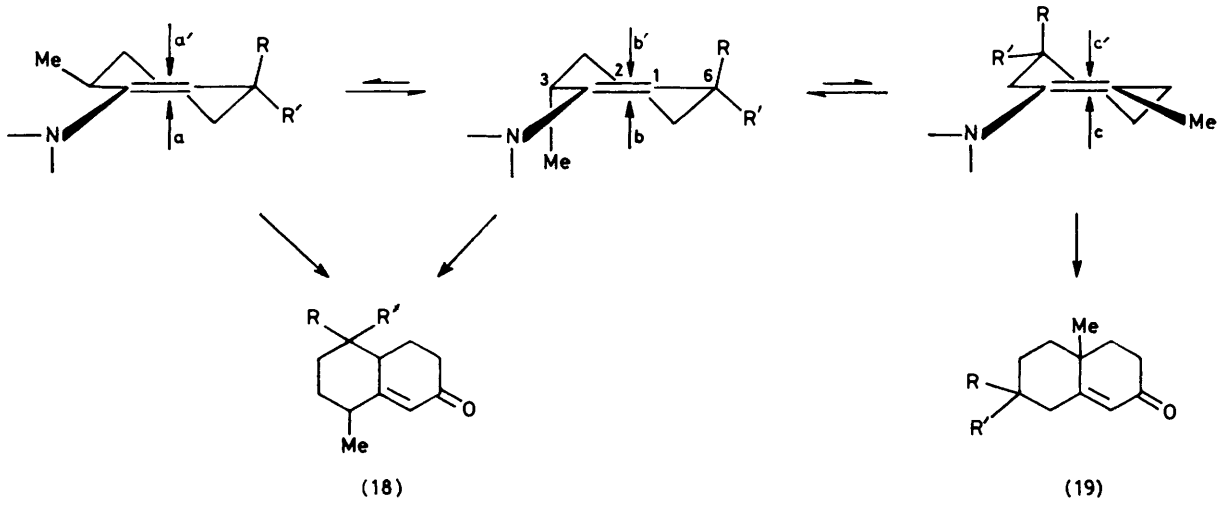
(iv) *Other factors affecting the lifetime of the zwitterionic intermediates* (4) *and* (5). In addition to the effect of the dielectric constant and solvating or protonating ability of the solvent, the lifetime of the initially formed zwitterionic intermediate will also be affected by (i) the temperature, (ii) the stabilisation of the anionic centre, and (iii) the ease of charge neutralisation by cyclisation. The change in the ratio of 2,6- to 2,2-disubstitution (*ca.* 2 : 1 in dioxan to 4 : 1 in benzene) which Könst has queried [4] is undoubtedly a temperature effect (Table 1, nos. 2 and 7). At the lower temperature (benzene) both the lifetime of the zwitterionic intermediate and therefore the probability of intermolecular protonation of the anionic centre will be increased. Product formation *via* the low-energy routes b and b' consequently becomes more feasible, thus leading to increased amounts of 2,6-disubstitution. This is confirmed by the fact that, at the same concentration in mesitylene (2.3 mol of enamine per l of solvent), the ratio (2,6- to 2.2-) changes from *ca.* 2 : 1 at 100 °C to 1 : 1 at 160 °C (Table 1, nos. 8 and 9). This can be attributed to the lifetime of the zwitterionic intermediates (4) and (5) being still further reduced at this higher temperature. Further confirmation is provided by the fact that at ambient temperature and in the absence of solvent, only the product derived by 2,6-disubstitution has been isolated, albeit in low yield.[6] This must be due to the now much longer lifetime of the zwitterionic intermediates (4) and (5), in equilibrium with their cyclobutane adducts, and to the inability of the molecules to surmount the higher energy barriers leading to the zwitterionic intermediates (3) and (6) at these low temperatures.

In addition to the effect of temperature, the lifetime of the zwitterionic intermediates produced by reaction with an enamine can be expected to be increased by factors which increase the stability of the anionic centre, such as increased electronegativity of the atom bearing the negative charge (O > N > C) and by substituent groups, the stabilising effect of which appears to increase in the order: $NO_2 > C{=}O > SO_2 > CO_2H > CO_2R > CN > CONH_2$.[12] This is supported by the observation that acrylonitrile (2b) gives a greater amount of 2,2-disubstituted ketone than does methyl acrylate (2a), at the same medium enamine concentration (2.3 mol l^{-1}) (Table 1, nos. 2 and 10). It follows that this can be attributed to reduced stabilisation of an anionic centre by a cyano than by an alkoxycarbonyl substituent, with consequent reduced lifetime of the corresponding zwitterionic intermediates (4b) and (5b). This factor is also reflected in the reactions of 2-substituted cyclohexanone enamines with isocyanates,[13] acid chlorides,[14] diethyl azodicarboxylate,[15] and nitro-olefins: [16] in every

[9] S. K. Malhotra and F. Johnson, *Tetrahedron Letters*, 1965, 4027.
[10] A. Risaliti, E. Valentin, and M. Forchiassin, *Chem. Comm.*, 1969, 233.
[11] C. T. Yoxall, Ph.D. Dissertation, Salford, 1971.
[12] R. G. Pearson and D. L. Dillon, *J. Amer. Chem. Soc.*, 1963, **75**, 2439.
[13] (*a*) F. P. Colonna, M. Forchiassin, G. Pitacco, A. Risaliti, and E. Valentin, *Tetrahedron*, 1970, **26**, 5289; (*b*) F. P. Colonna, G. Pitacco, and E. Valentin, *ibid.*, 1971, **27**, 5481.
[14] S. Hünig and H. Hoch, *Fortschr. Chem. Forsch.*, 1970, **14**, 235.
[15] (*a*) A. Risaliti and L. Marchetti, *Ann. Chim. (Italy)*, 1963, **53**, 718; A. Risaliti, M. Forchiassin, and S. Fatutta, *Tetrahedron*, 1967, **23**, 1451; A. Risaliti, M. Forchiassin, and E. Valentin, *ibid.*, 1968, **24**, 1889; F. P. Colonna, M. Forchiassin, G. Pitacco, A. Risaliti, and E. Valentin, *ibid.*, 1970, **26**, 5289; F. P. Colonna, M. Forchiassin, A. Risaliti, and E. Valentin, *Tetrahedron Letters*, 1970, 571; F. P. Colonna, S. Fatutta, A. Risaliti, and C. Russo, *J. Chem. Soc.* (*C*), 1970, 2377; (*b*) A. Risaliti, C. Russo, and E. Valentin, *Gazzetta*, 1972, **102**, 1008; (*c*) G. Pitacco, F. P. Colonna, C. Russo, and E. Valentin, *ibid.*, 1975, **105**, 1137.
[16] M. E. Kuehne and L. Foley, *J. Org. Chem.*, 1965, **30**, 4280.

case only the product of 2,6-disubstitution has been isolated, thus demonstrating the increased stability of the initially formed zwitterionic intermediates derived by path b or b'. Furthermore Pitacco *et al.* have recently demonstrated [15c] that the formation of the 2,6-disubstituted product does not occur by axial attack of diethyl azodicarboxylate on the equatorially orientated 3-substituted enamine [*i.e.* (1*eq*)], thus providing evidence for our conclusion that path a is a higher energy route than paths b or b'. When a zwitterionic intermediate is not produced, as in the reaction with acryloyl chloride, the problem of 2,2-disubstitution does not arise.[8,17]

(v) *Annelation with alkyl vinyl ketones.* Finally, as regards the reaction of enamines with methyl vinyl ketone, ever since the pioneering work of Stork *et al.* in the enamine field it has been well known that the annelation of (1) in aprotic solvents gives only 8-methyl-$\Delta^{1(8a)}$-2-octalone [18] [Scheme 2; (18; R = R' = H)]. Since none of the product (19) derived by initial reaction at the more substituted enamine position in (1) has been isolated, then application of our reasoning tells us that one of the preferred low energy routes (path b'; see later) is now not reversible and that therefore intramolecular proton transfer is not a prerequisite for product formation. This can be attributed to internal charge neutralisation * by dihydropyran formation, for which there is ample precedent with both enamines [20,21] and the less reactive enol ethers.[22] An understanding of Könst's results can then be obtained by making the assumptions that (i) an axial substituent at C-6 of the enamine (*i.e.* R ≠ H) prevents equatorial attack at C-1 (Scheme 2, path b'); (ii) an axial substituent at C-3 of the enamine (C-2 of the ketone) prevents ring closure to the dihydropyran from the same side (Scheme 2, path b); (iii) an equatorial substituent at C-6 inhibits, but does not prevent, equatorial and axial attack at C-1, presumably as a result of developing 1,4-bowsprit–flagpole interactions (path b') in a boat conformation and *gauche* butane interactions (Scheme 2, path b) in a chair conformation.† Thus in Scheme 2 (R = R' = Me), the one low energy route (path b) is reversible (*i.e.* gives a zwitterion but not a dihydropyran intermediate) and does not lead to products, and the other (path b') is sterically prevented. This leaves paths a and c available for product formation and since the former is additionally destabilised by developing *gauche* butane interactions with the C-6 equatorial substituent, path c is the most favoured energetically and thus leads to a majority of the cyclised product derived from initial attack at the more substituted enamine position. In ethanol path b can contribute to product formation owing to intervention by intermolecular protonation. The fact that similar amounts of the two products (18) and (19) are obtained suggests that the competing pathways (Scheme 2, b and c) may well have similar activation energies, possibly owing to the latter being a concerted cycloaddition whereas the former must be a stepwise process. When R = H and R' = Me or Pr^i), path b' is feasible,



SCHEME 2

* Charge neutralisation can also occur with nitro-olefins owing to the formation of nitronic esters.[19]

† There is ample evidence to sustain this assumption. Both alkylation [23] and acylation [24] of 3-substituted cyclohexanone enamines give the 3,6-disubstituted derivative as the major product.

[17] P. W. Hickmott and J. R. Hargreaves, *Tetrahedron*, 1967, **23**, 3151.

[18] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207.

[19] A. Risaliti, M. Forchiassin, and E. Valentin, *Tetrahedron*, 1968, **24**, 1889; A. T. Nielsen and T. G. Archibald, *ibid.*, 1970, **26**, 3475.

[20] R. C. Schulz and H. Hartmann, *Chem. Ber.*, 1962, **95**, 2375; G. Opitz and H. Holtmann, *Annalen*, 1965, **684**, 79; R. N. Schut and T. M. H. Liu, *J. Org. Chem.*, 1965, **30**, 2845; F. P. Colonna, S. Fattuta, A. Risaliti, and C. Russo, *J. Chem. Soc.* (*C*), 1970, 2377; M. Forchiassin, A. Risaliti, C. Russo, M. Calligaris, and G. Pitacco, *J.C.S. Perkin I*, 1974, 660.

[21] I. Fleming and M. H. Karger, *J. Chem. Soc.* (*C*), 1967, 226.

[22] C. W. Smith, D. G. Norton, and S. A. Ballard, *J. Amer. Chem. Soc.*, 1951, **73**, 5267.

[23] E. Valentin, G. Pitacco, and F. P. Colonna, *Tetrahedron Letters*, 1972, 2837; F. P. Colonna, E. Valentin, G. Pitacco, and A. Risaliti, *Tetrahedron*, 1973, **29**, 3011; 1974, **30**, 2741.

[24] G. Descotes and Y. Querou, *Compt. rend.*, 1966, **263C**, 1231.

but the activation energy may be increased by the aforementioned developing 1,4-interactions so that path c can still compete to a limited extent. With a larger substituent at C-2 of the ketone (*i.e.*, Pr^i instead of Me) paths a and c are ruled out by large $A^{1,3}$ interactions [7] and the reaction must occur solvely by route b′ leading only to the product derived from initial 2,6-disubstitution.

Protonation of Enamines.—One further point concerning the reaction of (1) with methyl acrylate (and acrylonitrile) deserves comment, and that is the stereochemistry of the 2,6-disubstituted cyclohexanones obtained on hydrolysis of the reaction mixture under non-epimerisable conditions. In every case a mixture of *cis*- and *trans*-isomers was obtained, with the thermodynamically less stable *trans*-isomer predominating. The stereochemical assignments are based on the solvent shifts [25]

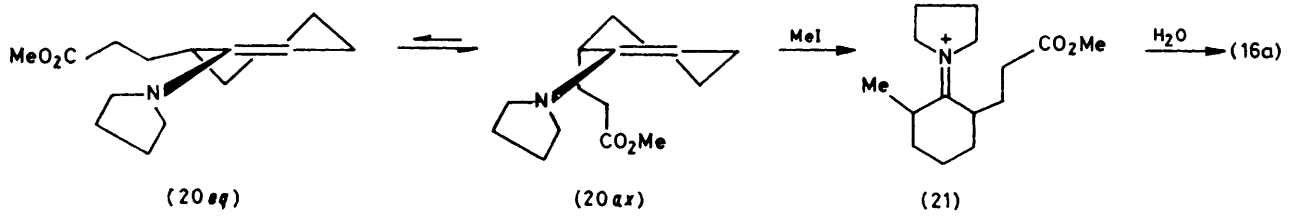
TABLE 2

Chemical (τ) and solvent shifts (p.p.m.) of methyl signals of 2,2- and 2,6-disubstituted cyclohexanones

Solvent	(15a) (*J* 7 Hz)	(16a) (*J* 6 Hz)	(14a) (s)
$CDCl_3$	8.92	9.00	8.92
C_6D_6	9.06	9.04	9.14
CCl_4	8.93	9.02	
C_5D_5N	8.98	9.01	
$\Delta(C_6D_6 - CDCl_3)$	+0.14	+0.04	+0.22
$\Delta(C_5D_5N - CCl_4)$	+0.05	−0.01	

of the methyl signals reported in Table 2. These assignments are not unequivocal owing to perturbation of the solute–solvent collision complex by the ester carbonyl group. Nevertheless if, as seems likely, the ketone carbonyl group exerts the major influence on the geometry of the complex, then the fact that the methyl group of (16a) is only weakly shielded in benzene relative to chloroform (Δ +0.04), and is deshielded slightly in pyridine relative to carbon tetrachloride (Δ −0.01), suggests that this is the equatorial methyl group of the *cis*-isomer. As would be expected for an axially oriented substituent, the methyl groups of (15a), the *trans*-isomer, and (14a) are more strongly shielded in benzene than in chloroform (Δ +0.14 and +0.22, respectively). These assignments were confirmed by equilibration of a sample of predominantly *trans* ketone [(16a), 35%; (15a), 65%] to give a mixture of predominantly *cis* ketone [(16a), 85%; (15a), 15%].

The fact that a mixture of stereoisomers is obtained is not surprising. We have previously shown that protonation of an enamine occurs *via* a reactant-like transition state [26] so that both equatorial and axial protonation, leading to a mixture of ketones, would be expected. Although there appears to be quite a wide fluctuation in the *cis* : *trans* ratio obtained, this may be partly due to experimental error arising from partial overlap of the methyl ^1H n.m.r. signals. However it seems significant that the average value (64% *trans*, 36% *cis*) is midway between the values we have obtained previously for the axial stereoselectivity of protonation of morpholine enamines (57%) and the corresponding less reactive enol ethers (70%). This suggests that the transition state for protonation has been displaced along the reaction co-ordinate and is less reactant-like in character. Such a displacement would be expected in view of the reduced electron density [27] at C-1 of the enamine arising from the electronic opposition to the polarisation of the double bond exerted by the C-1 substituent, and the steric interactions between the C-1 substituent and the amine ring which result in the nitrogen lone pair electrons being twisted out of alignment with the *p* orbitals of the double bond. Then, as a consequence of the different thermodynamic factors pertaining to the development of a twist or boat or chair transition state, an orbital bias [26] develops which favours bond formation from one side rather than the other. Unfortunately, owing to the conformational mobility of the disubstituted enamines (7) and (11), it is not possible to correlate the *cis* : *trans* ratios obtained with the ratio of equatorial to axial protonation. In view of this and the fact that Johnson *et al.*[28] have found total lack of stereoselectivity, whereas Risaliti *et al.*[13a,15b,29,30] have found very high stereoselectivity, in the hydrolysis of the respective enamine systems containing a tetrasubstituted double bond which they have studied, further work on this aspect of enamine chemistry is indicated.



(20eq) (20ax) (21)

SCHEME 3

Alkylation with Alkyl Halides.—Although methoxycarbonylethylation of (1) gives 2,2- and 2,6-disubstitution, methylation of the pyrrolidine enamine (20) of

[25] J. D. Connolly and R. McCrindle, *Chem. and Ind.*, 1965, 379; D. H. Williams and N. S. Bhacca, *Tetrahedron*, 1965, **21**, 2021; D. H. Williams, *Tetrahedron Letters*, 1965, 2305; D. H. Williams and D. A. Wilson, *J. Chem. Soc.* (*B*), 1966, 144.

[26] P. W. Hickmott and K. N. Woodward, *J.C.S. Chem. Comm.*, 1974, 275.

[27] M. G. Ahmed and P. W. Hickmott, *J.C.S. Perkin II*, 1977, 838.

[28] F. Johnson, L. G. Duquette, A. Whitehead, and L. C. Dorman, *Tetrahedron*, 1974, **30**, 3241.

[29] M. Forchiassin, C. Russo, and A. Risaliti, *Gazzetta*, 1972, **102**, 607.

[30] G. Pitacco, R. Toso, E. Valentin, and A. Risaliti, *Tetrahedron*, 1976, **32**, 1757.

methyl 3-(2-oxocyclohexyl)propionate with methyl iodide gives only the 2,6-disubstituted product in protic and aprotic solvents. Furthermore this product was obtained almost entirely as the *cis*-isomer (16a). In this case a zwitterionic intermediate is not formed, so the initial *C*-alkylation step is virtually irreversible. The high stereoselectivity which we have found can be attributed to the fact that in this case it is not an enamine system which is being hydrolysed but an iminium salt (21) (Scheme 3). The fact that predominantly the *cis*-isomer is obtained indicates high preference for axial attack on the axially orientated enamine conformer (20*ax*), as one would expect for a reaction involving what must be a product-like transition state. The alternative possibility, that the *cis*-isomer (16a) is formed by equatorial attack on the equatorially oriented enamine conformer (20*eq*), is less likely. This follows from our previous observation that, in the reaction between acryloyl chloride and the morpholine enamine of 2-methyl-4-t-butylcyclohexanone, initial carbon–carbon bond formation occurs predominantly from the axial side of the enamine double bond.[8]

EXPERIMENTAL

G.l.c. determinations were carried out with a Pye 104 chromatograph (polyethylene glycol adipate on Chromosorb A at 190 °C) unless otherwise stated. ^{1}H N.m.r. spectra were determined with a Varian HA-100 or A-60 instrument, and i.r. spectra with a Perkin-Elmer Infracord 521 or 257 grating spectrophotometer. Solvents were purified and dried, and reagents freshly distilled prior to use.

Verification of the Enamine Intermediate in 2,2-Disubstitution.—The procedure of House and Schellenbaum [3] was repeated. After 66 h reaction in boiling dioxan, under nitrogen, the solution was divided into two parts.

(*a*) One portion was worked up as described by House and Schellenbaum; [3] distillation gave a mixture (5.4 g, 60%) consisting of (14a), (15a), and (16a) in the ratios 37 : 45 : 18, respectively [by n.m.r. integration of the methyl signals (see Table 2 for assignments) relative to the methoxycarbonyl signal, assuming that each isomer exists predominantly in one conformation with the methyl groups axially oriented in (14a) and (15a) and equatorially oriented in (16a); this assumption appears to be valid to a first approximation since there were only two doublets and one singlet apparent in the high-field region which could be assigned to the three isomeric ketones]. G.l.c. confirmed the ratio of 2,2- to 2,6-disubstitution for both the distilled and the crude undistilled mixture of ketones.

(*b*) The other half of the unhydrolysed reaction mixture was heated *in vacuo* at 70 °C for 4 h in a Büchi evaporator to remove methyl acrylate. The ^{1}H n.m.r. spectrum ($CDCl_3$) of the crude enamine mixture clearly showed a singlet at τ 8.80, attributed to the methyl group of (10) and a triplet at τ 5.25 for the olefinic signal, at lower field than that of the unchanged enamine (1a) (τ 5.7). Integration indicated the presence of 33% (10). Hydrolysis of the crude enamine gave a mixture of ketones (5.66 g, 63%) in the ratios [(14) : (15) : (16)] 33 : 43 : 24. This slight difference from that obtained in (*a*) is attributed to experimental error. G.l.c. confirmed the ratio of (14) to (15) + (16) to be 35 : 65. This experiment was repeated several times and similar results were obtained.

(*c*) Further proof that the 2,2-disubstituted ketone could not be formed during the aqueous work-up, *via* the enolate anion of 2-methylcyclohexanone, was obtained as follows. A mixture of (1) (10 g), methyl acrylate (10.3 g), water (6 ml), and dioxan (26 ml) was heated under reflux for 1 h. Removal of the solvent, water, and methyl acrylate left crude methylcyclohexanone which was shown by g.l.c. to contain no 2,2- or 2,6-disubstituted cyclohexanone. Similar results were obtained when a mixture of 2-methylcyclohexanone (15 g), pyrrolidine (9.5 g), methyl acrylate (23 g), water (4 ml), and dioxan (60 ml) was heated under reflux for 1 h.

Effect of Reaction Conditions on the Ratio of 2,2- to 2,6-Disubstitution. General Method.—The results summarised in Table 1 were obtained by the following method unless otherwise indicated. A solution of the freshly distilled pyrrolidine enamine (1) of 2-methylcyclohexanone (15 g, 0.091 mol) and dry methyl acrylate (15.7 g, 0.182 mol) or acrylonitrile (9.65 g, 0.182 mol) in the solvent stated (40 ml) was heated under reflux for 66 h in nitrogen. The solvent and the excess of methyl acrylate (or acrylonitrile) were evaporated off *in vacuo* at 60 °C and a portion of the crude residue was distilled to give a mixture of the pyrrolidine enamines [(7)), (10), and (11)] of the disubstituted cyclohexanones. I.r. and ^{1}H n.m.r. spectra were then determined. The remainder of the crude enamine residue was hydrolysed under non-epimerising conditions by dropwise addition to a stirred buffer solution [0.1N-sodium hydroxide (5.6 ml) and 0.1N potassium dihydrogen phosphate (50 ml)]. The mixture was maintained at pH 6.0—6.5 by dropwise addition of 10% acetic acid and stirring was continued for 30 min after the pH had become constant. The mixture was then extracted with ether and the extract dried ($MgSO_4$) and evaporated to an oil which was distilled under reduced pressure to give a mixture of disubstituted ketones (Table 1). An estimate of the proportions of isomers present was obtained from integration of the methyl n.m.r. signals [$CDCl_3$ as solvent since this gave the best resolution of the signals, the methyl singlet of (14a) appearing in the middle of the (15a) methyl doublet (Table 2)]. These estimates were checked by g.l.c. and the 2,2- to 2,6- ratio was confirmed from integration of the methyl n.m.r. signals of the enamines since the methyl singlet of the enamine from the 2,2-disubstituted cyclohexanone (10) was to lower field and clearly separated from the methyl doublets of isomers (11) (Table 3). The b.p.s and i.r. spectra of the products thus obtained were as follows: (14a), (15a), (16a), b.p. 88—90° at 53 N m^{-2}, $\nu_{max.}$(film) 1 705 and 1 735 cm^{-1} (C=O); pyrrolidine enamines (7a), (10a), (11a), b.p. 106—113° at 33 N m^{-2}, $\nu_{max.}$(film) 1 735 (C=O) and 1 635 cm^{-1} (C=C); (14b), (15b), (16b), b.p. 95—98° at 33 N m^{-2}, $\nu_{max.}$(CCl_4) 2 240 (C≡N) and 1 698 cm^{-1} (C=O); pyrrolidine enamines (7b), (10b), (11b), b.p. 111—113° at 40 N m^{-2}, $\nu_{max.}$(CCl_4) 2 245 (C≡N) and 1 640 cm^{-1} (C=C).

Separation of the 2,2- and 2,6-Disubstituted Isomers (14a), (15a), *and* (16a) *by G.l.c.*—The use of Silicone Elastomer 30 on Chromosorb A at 150 °C resulted in no separation of the 2,2- and 2,6-disubstituted isomers. Both Apiezon L on Celite and polyethylene glycol adipate on Chromosorb A resulted in separation of the 2,2-disubstituted isomer (14a) from the 2,6-disubstituted isomers, but failed to separate the *cis*- and *trans*-forms of the latter. However separation of all three isomers was achieved using 10% diglycerol on

Celite at 120 °C. The *cis*-isomer had a shorter retention time than the *trans*-, although there was some overlap of the peaks. The 2,2-disubstituted isomer (14a) had an appreciably longer retention time. The 2,6-isomers were collected in three fractions, the middle mixed fraction being discarded, to give the pure *cis*-(16a) and almost pure *trans*-isomer (15a). Pertinent n.m.r. data are given in Table 2.

Equilibration of Methyl 3-(3-*Methyl*-2-*oxocyclohexyl*)*propionate*.—The *cis*-2,6-disubstituted isomer (16a) (0.37 g) was heated under reflux for 30 min with pyrrolidine (0.14 g) in aqueous methanol (5 ml). Removal of the volatile components and distillation of the resultant oil gave a mixture of the *cis*- and *trans*-isomers (16a) and (15a) which were shown by ^{1}H n.m.r. ($CDCl_3$) to be in the ratio 85 : 15, respectively. Similar treatment of the *trans*-2,6-disubstituted isomer (15a) gave the same proportions of *cis*- and *trans*-isomers and thus confirmed that (16a) was the thermodynamically more stable *cis*-isomer.

Reaction of the Pyrrolidine Enamine of Methyl 3-(2-*Oxocyclohexyl*)*propionate with Methyl Iodide*.—(a) *In dioxan*. Methyl iodide (9.0 g, 0.063 mol) in dry dioxan (10 ml) was added slowly to a solution of the pyrrolidine enamine of methyl 3-(2-oxocyclohexyl)propionate [31] (15 g, 0.063 mol) in dry dioxan (30 ml). The solution was heated to the boil over 20 min and heated under reflux (using an efficient double surface condenser) for 3 h. More methyl iodide (4.5 g) was added and the mixture heated under reflux for a further 63 h. The volatile components were then removed *in vacuo* and the residue was hydrolysed by stirring with cold water for 17 h. The mixture was extracted with ether and the extract dried ($MgSO_4$) and concentrated to give the crude disubstituted cyclohexanone (1.4 g, 9%), which was shown by t.l.c. to contain none of the 2,2-disubstituted isomer (14a). A portion of the crude product was purified by preparative t.l.c. on silica [benzene–ethanol (9 : 1)] to give the pure methyl 3-(3-methyl-2-oxocyclohexyl)propionate, shown by ^{1}H n.m.r. ($CDCl_3$) to be *ca.* 100% in the *cis* configuration (16a).

(b) *In methanol*. A solution of the pyrrolidine enamine of methyl 3-(2-oxocyclohexyl)propionate [31] (10 g, 0.042 mol) and methyl iodide (6 g, 0.042 mol) in methanol (50 ml) was heated under reflux for 24 h and the volatile components were removed *in vacuo* to give an oil (12.2 g). A portion of this (1.2 g) was hydrolysed and worked-up as in the method of House and Schellenbaum.[3] Distillation gave a mixture of the 2,6-disubstituted cyclohexanones (0.4 g, 45%) shown by ^{1}H n.m.r. ($CDCl_3$) to consist mainly of the *cis*-isomer (16a) (90%) and a little of the *trans*-isomer (15a) (10%). The remainder of the crude product was hydrolysed under non-epimerising conditions (see general method) to give a mixture of 2,6-disubstituted cyclohexanones (3.5 g, 47%) consisting of (16a) (95%) and (15a) (5%).

TABLE 3

Chemical shifts (τ) and proton assignments for the disubstituted cyclohexanone enamines (7), (10), and (11)

	Methyl signals of					
	(11a) * (d)					Olefinic H
Solvent	(*J* 7 Hz)	(*J* 6 Hz)	(7a) * (s)	(10a) (s)	OCH_3 (s)	(10a) (t)
CCl_4	9.06	9.05	8.46	8.83	6.42	5.24
C_6D_6	9.06	9.04	8.32		6.41	
C_5D_5N	9.07	9.04	8.34	8.83	6.38	5.24
	(11b) * (d)					
	(*J* 7 Hz)	(*J* 6 Hz)	(7b) * (s)	(10b) (s)		(10b) (t)
$CDCl_3$	9.02	8.98	8.39	8.79		5.15
C_6D_6	9.12	9.12	8.37	9.02		5.28
C_5D_5N	9.08	9.05	8.38	8.88		5.23

* Mixture of two conformers in which the C-3 substituent is either quasiaxial or quasiequatorial.

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