Reactions Between Enaminones and Enones. Part 2.[1] Alkylation of Enaminones with Acrylic Esters

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The anion of 3-amino-5,5-dimethylcyclohex-3-enone (1) reacts with ethyl acrylate to give the product of C- or N-alkylation, depending on the conditions. With methyl methacrylate or methyl crotonate, the major product results from *N*-alkylation, but this reacts further to give a 1,3-bis(3-oxocyclohex-1-enylamino)-propan-1-one. Evidence for the mechanism of this reaction is presented. The structure of an unidentified by-product from Part 1 is given.

In Part 1 it was shown that 3-aminocyclohex-2-enones react by both C- and N-alkylation under acidic conditions. Under basic conditions iodoalkanes normally favour N-alkylation.[2] Base-catalysed alkylations with unsaturated esters are reported here.

Reaction of the primary enaminone (1) with ethyl acrylate in the presence of sodium hydride gave the β-alanine ester (2). The reaction gave good yields in tetrahydrofuran (THF) and dioxane, but in diglyme C-alkylation followed by ring closure gave the quinolinedione (3). 90% Recoveries were made after the ester (2) was heated in diglyme for prolonged periods with or without sodium hydride. Thus there was no rearrangement of the initially formed compound (2) during formation of the quinolinedione (3). If 15-crown-5 was added to the THF the reaction again gave the quinolinedione (3). It appears that diglyme as well as crown ethers can complex with the sodium cation. Presumably, the bulky complex stays close to the deprotonated nitrogen and deflects the incoming alkyl group to C-2. Recent [3] work has confirmed the ability of open-chain polyethers to react with cations; in some cases crystalline complexes were isolated. Subsequent reactions were conducted in THF or dioxane (see Experimental section).

Repeating these reactions with methyl methacrylate and methyl crotonate gave new, sparingly soluble products (4) and (5). The compounds showed typical enaminone u.v. absorptions (EtOH, H_2O, HCl), but extinction coefficients were about twice those expected. High resolution mass spectrometry gave the molecular formula $C_{20}H_{30}N_2O_3$ which confirmed the reaction of two enaminone molecules with one of the ester. In dilute NaOH, the u.v. spectrum showed a new band at 342 nm which disappeared over a few minutes. This was due to deprotonation of the enamidone nitrogen. Not surprisingly, this vinylogous imide group hydrolysed rapidly at high pH. That the other enaminone group had been N-alkylated was shown by the presence of two vinyl CH singlets in the ^1H n.m.r. spectra and confirmed when the ^{13}C n.m.r. spectra showed C-2 for each ring as a ^{13}C–^1H doublet. The important ^{13}C assignments, shown on the formulae, were made by comparison with the chemical shifts of the simple enaminones, shown in the Table, with compound (3), and with published data.[4] After the separation of compound (4), two by-products were isolated in low yield from the mother-liquors.

Spectral comparison (i.r., u.v., n.m.r.) showed that one was the 2-methyl-β-alanine (6), closely similar to compound (2), and the other was the 3-methyl derivative of the quinolinedione (3). The former of these would appear to be the intermediate which is attacked by a second enaminone anion to give the enamidone (4). Indeed the ester did react with the enaminone anion in THF to give compound (4). However, an alternative route could involve preliminary formation of the enamidone (7) followed by conjugate addition to give the observed product. The enamidones (7) and (8) were prepared

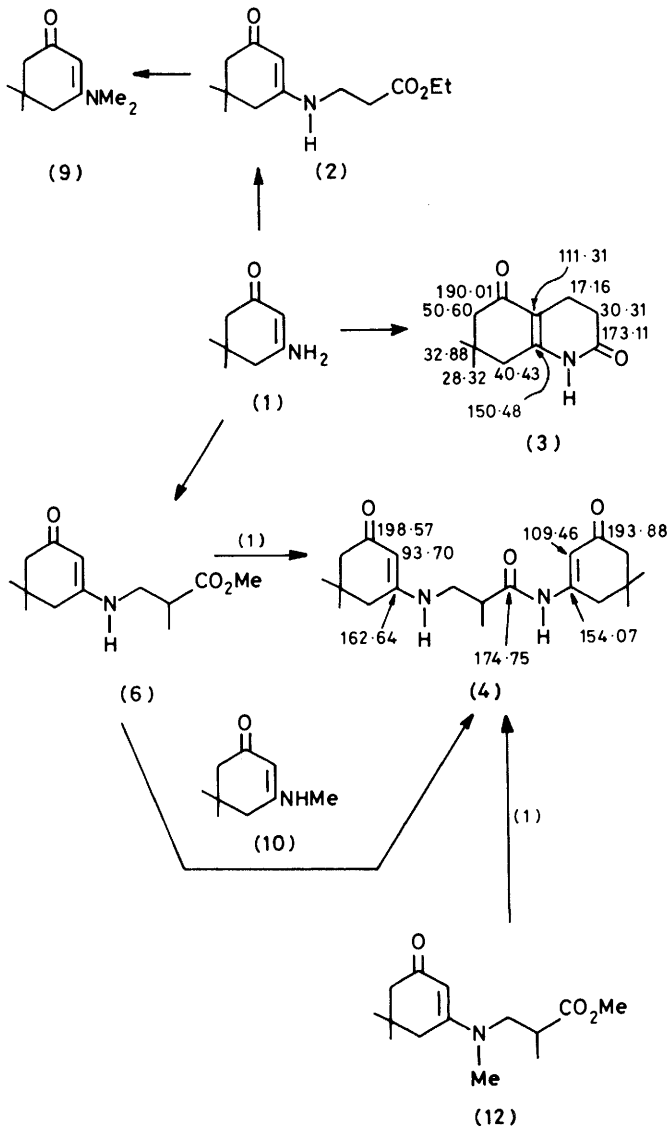
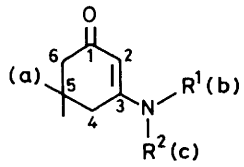
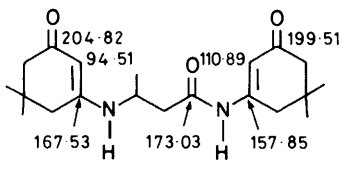


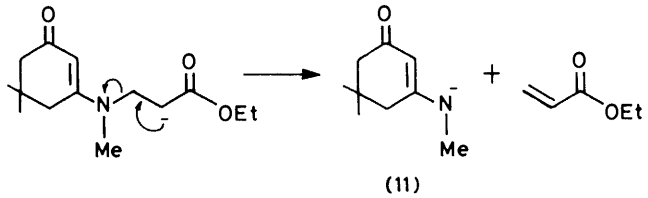
Table. ^{13}C N.m.r. assignments for simple enaminones in $(CD_3)_2SO$



		δ(^{13}C)/p.p.m.								
R^1	R^2	C-1	C-2	C-3	C-4	C-5	C-6	a	b	c
H	H	192.7	94.7	164.2	40.3	30.9	48.5	26.7		
Me	H	193.7	93.1	163.6	41.9	32.2	50.3	27.9	28.7	
Me	Me	193.5	96.1	163.5	39.8	32.1	49.4	28.3	39.3	39.3

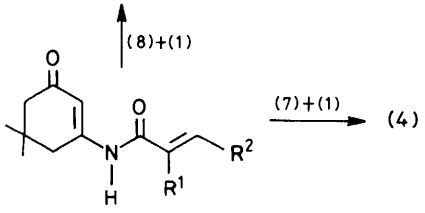


(5)

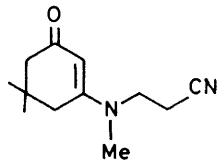


(11)

Scheme 1.



(7) R^1 = Me, R^2 = H
(8) R^1 = H, R^2 = Me



(13)

by addition of the appropriate acid chloride to the enaminone anion. When treated with further quantities of the anion in dioxane, each gave a small yield of the corresponding trione (4) or (5). Clearly, conjugate addition to the double bonds of compounds (7) and (8) is possible. However, after prolonged reflux in THF (6 h) no trace of the trione (4) or (5) could be detected. We would expect an anion to react more rapidly with methyl methacrylate than with an unsaturated enamidone (7) or (8) and this evidence is consistent with the suggestion that the β-alanine enaminones are the intermediates in the formation of the triones (4) and (5).

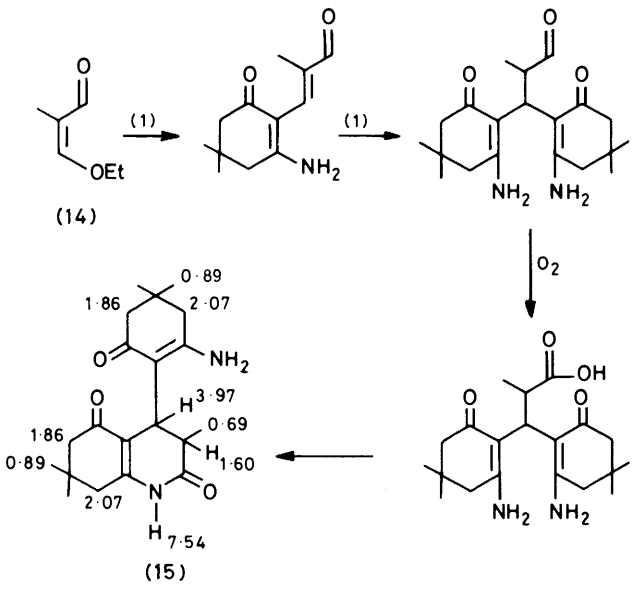
Several methods were investigated for the preparation of derivatives of compound (4) with one or both nitrogens methylated. Treatment of the enaminone (2) with sodium hydride in THF followed by iodomethane [2] gave none of the expected *N*-methyl derivative, but it did give the *N*,*N*-dimethyl enaminone (9). As the ester was unchanged by sodium hydride alone, it must have been N-methylated and then deprotonated, followed by decomposition (Scheme 1) to the anion (11), which reacted again with the iodomethane. The *N*-methyl derivative (12) was prepared from the *N*-methyl-β-alanine and dimedone and treated with the primary enaminone (1). None of the expected product was obtained, but the reaction gave a 35% yield of compound (4). T.l.c. showed the presence of the secondary enaminone (10) in the mother-liquors, as well as starting materials and compound (4), but no other spot. Deprotonation of the CH(Me)CO group must have released a methacrylate unit which reacted with the primary enaminone. Treatment of the ester (2) with the enaminone (1) in THF, dioxane, or diglyme failed to give any trace of a trione derivative, and starting materials were recovered. However, compounds (6) and (10) did react to give only the trione (4).

It appears that some decomposition of the secondary enamino ester (6) could occur, to provide the primary enaminone (1) to react with the unchanged (6). Finally, the nitrile (13) was prepared and treated with the primary enaminone (1). Again, no trace of a trione could be detected, but a good yield of the secondary enaminone (10) was obtained. Presumably, the difference in reactivity between the acrylate and methacrylate derivatives reflects the different rates of CH deprotonation, governed by the extent of steric hindrance to the approach of the base.

In Part 1 we were unable to assign a structure to one of the by-products ($C_{20}H_{28}N_2O_3$) of the acid-catalysed reaction between the enaminone (1) and the vinylogous ester (14). In spite of the compound's very low solubility, we have now obtained a satisfactory 90 MHz ^1H n.m.r. spectrum in $(CD_3)_2SO$ by the multiscan Fourier Transform technique. The structure is assigned as (15) which has the chemical shifts (δ) shown on the formula. The mechanism suggested in Scheme 2 requires an oxidation step by atmospheric oxygen. Re-running the reactions under nitrogen produced none of this by-product.

Experimental

General Method for Reactions between Enaminones and Esters.—A solution of the enaminone (10 mmol) and sodium hydride (20 mmol) in the named solvent (100 ml) was refluxed



Scheme 2.

for 1 h and cooled. The ester (20 mmol) was added and the solution again refluxed for 1 h. The solvent was evaporated, the residue taken up in ethyl acetate or dichloromethane (100 ml), washed (H_2O), dried ($MgSO_4$), and the solvent evaporated to give the product. The following were thus obtained.

(i) From 3-amino-5,5-dimethylcyclohex-2-enone (1)[5] and ethyl acrylate in THF: N-(5,5-*dimethyl*-3-*oxocyclohex*-1-*enyl*)-β-*alanine ethyl ester* (2) (72%), m.p. 138—140 °C (from toluene) (Found: C, 65.4; H, 8.9; N, 5.9. $C_{13}H_{21}NO_3$ requires C, 65.3; H 8.8; N, 5.9%); $\nu_{max.}$ (KBr) 1 730, 1 600, and 1 550 cm^{-1}; δ($CDCl_3$) 6.20 (1 H, br, NH), 5.19 (1 H, s, =CH), 4.20 (2 H, q, OCH_2), 3.98 (2 H, t, NCH_2), 2.65 (2 H, t, CH_2CO_2), 2.20 (4 H, s, 2 × CH_2), 1.75 (3 H, t, CH_2CH_3), and 1.00 (6 H, s, 2 × Me).

(ii) Similarly, from methyl acrylate: N-(5,5-*dimethyl*-3-*oxocyclohex*-1-*enyl*)-β-*alanine methyl ester* (62%), m.p. 134—136 °C (from ethyl acetate) (Found: C, 63.7; H, 8.5; N, 5.9. $C_{12}H_{19}NO_3$ requires C, 64.0; H, 8.4; N, 6.2%).

(iii) From the enaminone (1) and ethyl acrylate in diglyme: 7,7-*dimethyl*-3,4,7,8-*tetrahydroquinoline*-2(1H),5(6H)-*dione* (3) (49%), m.p. 158—160 °C (from toluene–light petroleum) (Found: C, 68.4; H, 7.9; N, 7.3. $C_{11}H_{15}NO_2$ requires C, 68.4; H, 7.8; N, 7.3%); $\nu_{max.}$ (KBr) 1 690, 1 640, and 1 490 cm^{-1}; $\lambda_{max.}$ (H_2O) 295 nm (ε 13 600); $\lambda_{max.}$ (0.1M-HCl) 295 nm (ε 13 600); $\lambda_{max.}$ (0.01M-NaOH), 296 (ε 19 000) and 347 nm (2 800 2 min after mixing, but zero after 5 min). The same product was obtained (62%) from the enaminone, ethyl acrylate, and 15-crown-5 (4.4 g, 20 mmol) in THF.

(iv) From the enaminone (1) and methyl methacrylate in dioxane: 1,3-*bis*(5,5-*dimethyl*-3-*oxocyclohex*-1-*enylamino*)-2-*methylpropan*-1-*one* (4) (58%), m.p. 232—234 °C (from ethanol) (Found: C, 69.8; H, 8.7; N, 8.1. $C_{20}H_{30}N_2O_3$ requires C, 69.4; H, 8.7; N, 8.1%); $\nu_{max.}$ (KBr) 1 720, 1 640, and 1 540 cm^{-1}; $\lambda_{max.}$ (H_2O) 296 nm (ε 38 500); $\lambda_{max.}$ (0.1M-HCl) 287 nm (ε 37 311); $\lambda_{max.}$ (0.1M-NaOH) 300 (ε 41 400), and 342 nm (11 100), run within two min (the 342 nm peak had disappeared after 10 min). δ [$(CD_3)_2SO$] 0.92 (12 H, s, 4 × Me), 1.00 (3 H, d, Me), 1.84 (2 H, s, CH_2), 2.00 (2 H, s, CH_2), 2.06 (2 H, s, CH_2), 2.24 (2 H, s, CH_2), 2.80 (1 H, m, side chain CH) 3.17 (2 H, s, NCH_2), 4.65 (1 H, s, =CH), 6.38 (1 H, s, CONC=CH), 6.70 (1 H, br, enaminone NH), and 9.30 (1 H, br, enamidone NH); δ_C [$(CD_3)_2SO$] peaks not shown on the formula: 15.50 (q), 27.80 (q), 32.04 (s), 32.14 (s), 41.04 (t), 41.91 (t), 44.57 (t), 49.94 (t), 50.23 p.p.m. (t); other signals obscured by solvent.

(v) From the enaminone (1) and the enamidone (7) in dioxane was obtained the same trione (4) (29%), identical (m.p., mixed m.p., and i.r.) with the sample prepared under (iv).

(vi) From the enaminone (1) and the enamino ester (6) in THF was obtained the same trione (4) (35%), identical (m.p., mixed m.p., and i.r.) with the sample prepared under (iv).

(vii) From 3-methylamino-5,5-dimethylcyclohex-2-enone (10) and the enamino ester (6) in dioxane was obtained the same trione (4) (12%), identical (m.p., mixed m.p., and i.r.) with the sample prepared under (iv).

(viii) From the enaminone (1) and *N*,2-dimethyl-*N*-(5,5-dimethyl-3-oxocyclohex-1-enyl)-β-alanine methyl ester (12) in THF was obtained the same trione (4) (35%), identical (m.p., mixed m.p., and i.r.) with the sample prepared under (iv).

(ix) From the enaminone (1) and methyl crotonate in dioxane: 1,3-*bis*(5,5-*dimethyl*-3-*oxocyclohex*-1-*enylamino*)-3-*methylpropan*-1-*one* (5) (58%), m.p. 246—248 °C (from ethanol) (Found: C, 69.4; H, 9.1; N, 8.1. $C_{20}H_{30}N_2O_3$ requires C, 69.4; H, 8.7; N, 8.1%); $\nu_{max.}$ (KBr) 1 715, 1 640, and 1 540 cm^{-1}; $\lambda_{max.}$ (H_2O) 291 nm (ε 38 100); $\lambda_{max.}$ (0.1M-HCl) 285 nm (ε 38 500); $\lambda_{max.}$ (0.1M-NaOH) 299 (ε 44 900) and 342 nm (9 500 within 2 min of mixing, zero after 10 min); δ [$(CD_3)_2SO$] 0.93 (12 H, s, 4 × Me), 1.12 (3 H, d, side-chain Me), 1.88 (2 H, s, CH_2), 2.02 (2 H, s, CH_2), 2.08 (2 H, s, CH_2), 2.26 (2 H, s, CH_2), 2.62 (2 H, s, side-chain CH_2 + 1 H, m, $CHCH_3$), 4.72 (1 H, s, =CH), 6.38 (1 H, s, CON–C=CH), 6.46 (1 H, m, NH), and 9.30 (1 H, s, CONH); δ_C [$(CD_3)_2SO$] peaks not shown on the formula: 20.22(q), 28.09(q), 28.22(q), 33.40 p.p.m. (s); others obscured by the solvent.

(x) From the enaminone (1) and the enamidone (8) in dioxane was obtained the trione (5) (29%), identical (m.p., mixed m.p., and i.r.) with the sample prepared under (ix).

N-(5,5-*Dimethyl*-3-*oxocyclohex*-1-*enyl*)-2-*methyl*-β-*alanine Methyl Ester* (6) *and* 3,4,7,8-*Tetrahydro*-3,7,7-*trimethylquinoline*-2(1H),5(6H)-*dione*.—*Method* 1. After separation of the trione described under (iv), the mother-liquors were concentrated and the residue dissolved in toluene and chromatographed on an alumina column. Elution with toluene gave the β-*alanine* (6) (14%), m.p. 93—94 °C (from benzene–light petroleum) (Found: C, 65.4; H, 8.9; N, 5.9. $C_{13}H_{21}NO_3$ requires C, 65.3; H, 8.8; N, 5.9%); $\nu_{max.}$ (KBr) 3 260, 1 735, and 1 570br cm^{-1}; $\lambda_{max.}$ (H_2O) 293 nm (ε 29 700); $\lambda_{max.}$ (0.1M-HCl) 284 nm (ε 25 000); $\lambda_{max.}$ (0.1M-NaOH) 294 nm (ε 29 900); δ($CDCl_3$) 1.06 (6 H, s, 2 × Me), 1.20 (3 H, d, $CHCH_3$), 2.17 (4 H, s, 2 × CH_2), 2.30—3.50 (3 H, m, CH_2CH), 3.70 (3 H, s, OMe), 5.12 (1 H, s, =CH), and 5.40 (1 H, br, NH). Further elution with 5% ethyl acetate in toluene gave 3,4,7,8-tetrahydro-3,7,7-trimethylquinoline-2(1*H*),5(6*H*)-dione (2%), m.p. 197—198 °C (from benzene); *m/z* 207; $\nu_{max.}$ (KBr) 3 260, 3 200, 1 710, 1 640, and 1 615 cm^{-1}; $\lambda_{max.}$ (H_2O) 299 nm (ε 14 600); $\lambda_{max.}$ (0.1M-HCl) 299 nm (ε 14 400); $\lambda_{max.}$ (0.1M-NaOH) 297 (ε 20 000) and 348 nm (2 400), run within 2 min of mixing; δ($CDCl_3$) 1.08 (6 H, s, 2 × Me), 1.20 (3 H, d, $CHCH_3$), 2.26 (4 H, s, 2 × CH_2), 2.50 (3 H, m, $CHCH_2$), and 8.74 (1 H, br, NH).

Method 2. 2-Methyl-β-alanine methyl ester hydrochloride[6] (2 g) was treated with a minimum of ammonium hydroxide and the base extracted with dichloromethane (3 × 20 ml). The solvent was evaporated, the residue was taken up in toluene (50 ml), dimedone (0.7 g) was added, and the solution refluxed for 2½ h under a Dean–Stark water separator. Evaporation of the solvent gave the β-alanine enaminone (6) (0.8 g, 26%), m.p. and mixed m.p. identical with the sample obtained above, 93—94 °C.

3-(2-*Methylpropenoylamino*)-5,5-*dimethylcyclohex*-2-*enone* (7).—Sodium hydride (3 g, 0.125 mol) was added to a solution of 3-amino-5,5-dimethylcyclohex-2-enone (1) (14 g, 0.1 mol) in THF (400 ml) and refluxed (20 min). The mixture was stirred on an ice-bath for 15 min before a solution of 2-methylpropionyl chloride in THF (100 ml) was added dropwise during 1 h. Stirring on the ice-bath was continued for a further 2 h and the product was allowed to stand at room temperature overnight. The supernatant solution was decanted off and the solvent evaporated to give the *enamidone* (7) (5 g, 24%), m.p. 142—143 °C (from acetone) (Found: C, 69.8; H, 8.1; N, 6.7. $C_{12}H_{17}NO_2$ requires C, 69.6; H, 8.2; N, 6.8%); $\nu_{max.}$ (KBr) 3 340, 1 690, 1 635, 1 615, and 1 530 cm^{-1}; $\lambda_{max.}$ (H_2O) 293 nm (ε 14 100); $\lambda_{max.}$ (0.1M-HCl) 293 nm (14 300); $\lambda_{max.}$ (0.1M-NaOH) 290 (ε 9 800) and 341 nm (8 800) run within 2 min of mixing [after 20 min the spectrum had changed to 288 nm (ε 22 700)]; δ($CDCl_3$) 1.06 (6 H, s, 2 × Me), 1.96 (3 H, s, Me), 2.18 (2 H, s, CH_2), 2.45 (2 H, s, CH_2), 5.50 and 5.78 (both 1 H, s, $=CH_2$), 6.74 (1 H, s, ring =CH), and 8.18 (1 H, br, NH).

3-*Crotonoylamino*-5,5-*dimethylcyclohex*-2-*enone* (8).—Sodium hydride (1.5 g, 0.06 mol) was added to a solution of 3-amino-5,5-dimethylcyclohex-2-enone (7 g, 0.05 mol) in THF (250 ml) and refluxed (½ h). The mixture was stirred on an ice-bath and crotonoyl chloride (6.55 g, 0.06 mol) in THF (50 ml) was added dropwise (20 min). Stirring and cooling were continued for a further 2 h. Acetic acid (3 ml) was added and the solvent evaporated. The residue was dissolved in ethyl acetate, washed (H_2O), dried ($MgSO_4$) and the solvent evaporated to give the *enamidone* (8) (2.4 g, 23%), m.p. 168—169 °C (from toluene) (Found: C, 69.5; H, 8.3; N, 6.7. $C_{12}H_{17}NO_2$ requires C, 69.6; H, 8.2; N, 6.8%); $\nu_{max.}$ (KBr) 3 340, 1 700, 1 650, 1 620, and 1 530 cm^{-1}; $\lambda_{max.}$ (H_2O) 299 nm (ε 20 400); $\lambda_{max.}$ (0.1M-HCl) 299 nm (ε 20 000); $\lambda_{max.}$ (0.1M-NaOH) 297 (ε 14 200) and 348 nm (14 600), run within 2 min of mixing [after 90 min, 288 nm (ε 26 900)]; δ($CDCl_3$) 1.06 (6 H, s, 2 × Me), 1.85 (2 H, d, *J* 6 Hz, Me), 2.20 (2 H, s, CH_2), 2.42 (2 H, s, CH_2), 6.90 (1 H, s, ring =CH), 7.00 (1 H, m, β =CH), and 8.95 (1 H, br, NH).

3-*Dimethylamino*-5,5-*dimethylcyclohex*-2-*enone* (9).—Sodium hydride (0.48 g, 20 mmol) was added to a solution of the enaminone (2) (2.4 g, 10 mmol) in THF (200 ml) and refluxed for 1 h. Iodomethane (2.8 g, 20 mmol) was added and refluxing continued for a further 2 h. Water (200 ml) was added and the solvent reduced in volume. The residue was extracted with dichloromethane (2 × 100 ml) and the organic phase dried ($MgSO_4$) and evaporated to give the 3-dimethylamino-5,5-dimethylcyclohex-2-enone (9) (0.6 g, 36%), m.p. 98—99 °C, undepressed with an authentic sample.[5]

3-[2-*Cyanoethyl*(*methyl*)*amino*]-5,5-*dimethylcyclohex*-2-*enone* (13).—A solution of dimedone (7 g, 50 mmol) and *N*-methyl-β-alaninenitrile (4.2 g, 50 mmol) in xylene (120 ml) was refluxed under a Dean–Stark water separator for 3 h. The theoretical volume of water was collected. The solvent was evaporated to give the *enaminone* (13) (9 g, 87%), m.p. 85—86 °C (from toluene; m.p. varies with rate of heating) (Found: C, 69.5; H, 9.0; N, 13.4. $C_{12}H_{18}N_2O$ requires C, 69.9; H, 8.7; N, 13.6%); $\nu_{max.}$ ($CHCl_3$) 1 615 and 1 570 cm^{-1}; δ($CDCl_3$) 1.06 (6 H, s, 2 × Me), 2.10 (2 H, s, 6-H_2), 2.31 (2 H, s, 4-H_2), 2.63 (2 H, t, CH_2CN), 3.01 (3 H, s, Me), 3.62 (2 H, t, NCH_2), and 5.10 (1 H, s, =CH).

Reaction of the Enamino-nitrile (13) *with the Primary Enaminone* (1).—This was carried out in dioxane by the general method described for esters to give 5,5-dimethyl-3-methylaminocyclohex-2-enone (0.45 g, 59%), m.p. 150—151 °C, undepressed on admixture with an authentic sample.[5]

N-(5,5-*Dimethyl*-3-*oxocyclohex*-1-*enyl*)-N,2-*dimethyl*-β-*alanine Methyl Ester* (12).—A solution of *N*,2-dimethyl-β-alanine methyl ester [7] (8.5 g) and dimedone (9 g) in benzene (300 ml) was refluxed under a Dean–Stark water separator for 4½ h. The solvent was evaporated and the residue distilled to give the enaminone (12) (9.3 g, 57%), b.p. 164—166 °C at 0.4 mmHg; δ($CDCl_3$) 1.06 (6 H, s, 2 × Me), 1.16 (3 H, d, $CHCH_3$), 2.05 (2 H, s, CH_2), 2.30 (2 H, s, CH_2), 2.94 (3 H, s, NMe), 3.00—3.50 (3 H, m, $CHCH_2$), 3.68 (3 H, s, OMe), and 5.10 (1 H, s, =CH).

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