Enamine Chemistry. Part 36.[1] Alkylation of Imines of Medium–Large Ring Ketones with Electrophilic Alkenes

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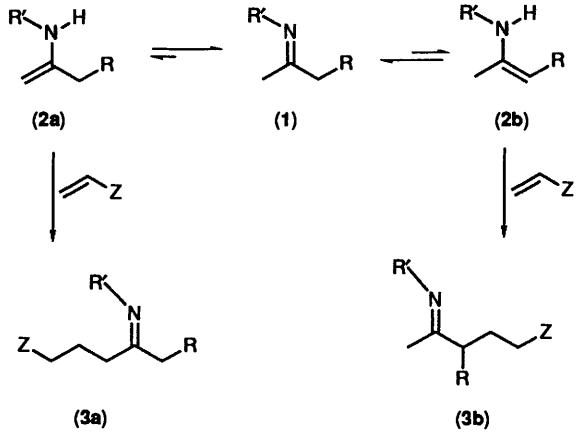
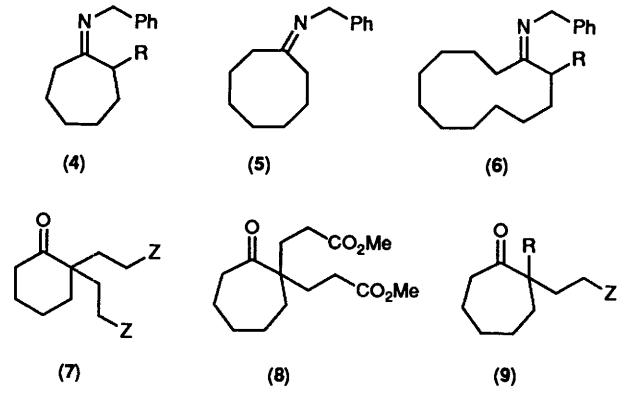
The alkylation of the benzylamine imines of cycloheptanone, cyclo-octanone, and cyclododecanone with acrylonitrile, methyl acrylate, methyl vinyl sulphone, phenyl vinyl ketone, and phenyl vinyl sulphone, has been studied. The course of the reaction is surprisingly sensitive to the size of the ring, the size of any substituent at C-2, and the relative reactivity of the electrophilic alkene. Only mono-2-substituted cycloalkanones were produced with all electrophilic alkenes except methyl acrylate, which reacted twice with cycloheptanone imine and, under forcing conditions, twice with cyclo-octanone imine, to give 2,2-bis-β-methoxycarbonylethylcycloheptanone and 2,8-bis-β-methoxycarbonylethylcyclo-octanone, the latter in very low yield. Methylcycloheptanone imine gave the 2-alkylated-2-methyl ketone with acrylonitrile and methyl acrylate whereas 2-methylcyclododecanone imine gave a mixture of 2-alkylated-2-methyl- and 12-alkylated-2-methyl ketones.

We,[2–4] and also Pfau *et al.*,[5] have recently demonstrated that in the Stork reaction[6] of electrophilic alkenes with imines of unsymmetrical ketones, alkylation occurs *via* the secondary enamine tautomer at the more substituted α-position of the ketone, as we had previously predicted from mechanistic considerations.[7] Furthermore, when dialkylation occurs, the reaction goes α,α- rather than α,α'- in contrast to the corresponding reaction of a tertiary enamine.[8,†] The reason for this is two-fold. Firstly, formation of the more substituted secondary enamine tautomer (**2b**) (Scheme) is thermo-



Scheme.

dynamically favoured by the hyperconjugative and inductive interactions between the substituent R and the double bond, and kinetically favoured by these developing interactions in the transition state. Thus in the equilibrium between an unsymmetrical imine and its secondary enamine tautomers [(**2a**) ⇌ (**1**) ⇌ (**2b**)], the equilibrium will be almost exclusively in favour of (**2b**). Secondly, the transition state for subsequent reaction at the more substituted β-position of a secondary enamine is not destabilised, as it is in the reaction at the corresponding position of a tertiary enamine,[6a] by the development of strong $A^{(1,3)}$-interactions[10] since the molecule can take up a conformation (**2b**) in which the *N*-substituent (R') is remote from the C_β-substituent (R). Although (**2a**) may be more reactive than (**2b**), provided subsequent reaction of (**2b**) is faster than tautomeric interconversion into (**2a**), then (**3b**) will be the main or exclusive product of the reaction.



Results and Discussion

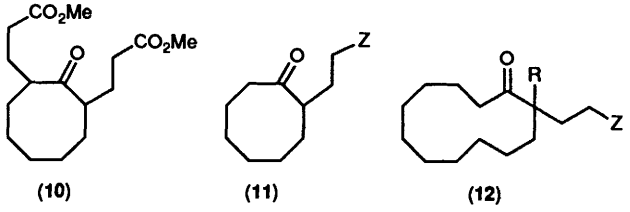
We have now applied this reaction to the imines (**4–6**; R = H) of medium-large ring ketones and an unexpected limitation to the reaction has emerged. Despite the fact that cyclohexanone imines can be bis-alkylated with methyl acrylate and phenyl vinyl sulphone to give (**7**; Z = CO_2Me or SO_2Ph),[4] the cycloheptanone imine reacted twice only with methyl acrylate, to give (**8**). The structure followed from the analytical and spectral data. In particular, the ^1H NMR spectrum showed the signal due to the presence of two methoxy groups (δ_H 3.7) and the ^{13}C NMR spectrum showed the signal due to C-2 as a singlet (δ_C 52.2). Acrylonitrile and phenyl vinyl sulphone reacted to give only the mono-alkylated ketone (**9**; R = H, Z =

† For solvent dependent exceptions to the α,α'-dialkylation of tertiary enamines, see references 6 and 9.

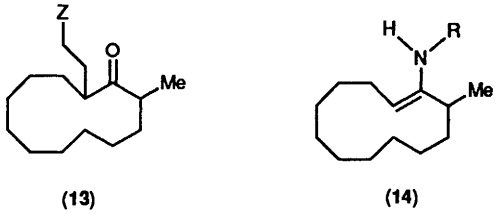
CN, SO_2Ph) on hydrolysis. In both cases, the ^{13}C NMR spectrum now showed the C-2 signal as a doublet (δ_C 49.5).

These results are interesting for two reasons. First, they imply that the reactivity of methyl acrylate is greater than that of either acrylonitrile or phenyl vinyl sulphone, despite the anion stabilising power of electron withdrawing groups being in the order $SO_2 > CO_2R > CN > CONH_2$.[11] This greater reactivity means that the transition state for alkylation will be more reactant-like in nature and bonding interactions will consequently begin at greater interatomic distances and the influence of steric effects will be decreased. Thus, despite the greater steric impediment of a β-methoxycarbonylethyl group relative to a β-cyanoethyl group, further reaction at C-2 occurs. In the case of phenyl vinyl sulphone, the electrophilicity of the β-carbon is reduced by electronic interactions between the sulphone and phenyl groups, and further reaction at C-2 will be impeded by the bulkiness of the phenyl group. To evaluate the significance of these factors we carried out the reaction with methyl vinyl sulphone. Unfortunately, evidence for the formation of the di-substitution product (**9**; R = CH_2CH_2Z, Z = SO_2CH_3) could not be obtained by GC–MS and if formed it is in very low yield. The main product, isolated in high yield (70%), was the mono-alkylated ketone (**9**; R = H; Z = SO_2CH_3).

Secondly, comparing these results with those from the corresponding cyclohexanone imine,[4] it would appear that despite the greater flexibility of the larger ring, or probably because of it, the larger ring imine is significantly more sterically hindered at C-2 and there is therefore a greater tendency for reaction to stop at the mono-alkylation stage. To test this conclusion, we investigated the reactivity of cyclo-octanone and cyclododecanone imines. Although the cyclo-octanone imine reacted twice with a large excess of methyl acrylate under forcing conditions, the product obtained (**10**) was that of α,α′-dialkylation, not α,α-dialkylation, and the yield was very low (7%); the main product was again the mono-alkylated ketone (**11**; Z = CO_2Me). The ^{13}C NMR spectrum of (**10**) clearly



(10) (11) (12)



(13) (14)

showed the signal due to C-2 and C-8 as a doublet (δ_C 49.3) whereas in (**11**) the C-2 signal was a doublet δ_C 48.8) and the C-8 signal a triplet (δ_C 41.7). Predictably, acrylonitrile and phenyl vinyl sulphone gave only the mono-alkylated ketones (**11**; Z = CN, SO_2Ph). Only mono-alkylated ketones (**12**; R = H, Z = CN, CO_2Me, SO_2Ph, SO_2CH_3, COPh) were obtained from the cyclododecanone imine (**6**; R = H). There was no evidence for the occurrence of any di-alkylation even with phenyl vinyl ketone and methyl vinyl sulphone. In each case GLC analysis of the crude reaction product showed only one peak in addition to that due to unchanged cyclododecanone, and ^{13}C NMR showed the signal attributed to C-2 as a doublet.

Finally we wished to ascertain whether the steric impediment to reaction at C-2 arising from the ring could be overcome if the bulkiness of the C-2 substituent itself was reduced. Accordingly, the reactivities of 2-methylcycloheptanone and 2-methylcyclododecanone imines were investigated. In the case of the 7-membered ring imine, both acrylonitrile and methyl acrylate reacted at C-2 to give the 2,2-disubstituted ketone (**9**; R = Me, Z = CN, CO_2Me) in high isolated yield (83–97%). The IR spectra showed the presence of a cyano or methoxycarbonyl group, respectively, and the ^{13}C NMR spectra showed the C-2 signal as a singlet (δ_C 49.85) in both cases. So clearly the relatively small change ($CH_2CH_2Z \longrightarrow$ Me) has reduced the overall steric interactions sufficiently to enable reaction to occur at the more substituted C-2 position even with the less reactive acrylonitrile. The regioselectivity changed radically when the reaction was applied to the larger 12-membered ring imine (**6**; R = Me). We were unable to isolate the pure 2,2-disubstituted ketones (**12**; R = Me, Z = CN, CO_2Me) from reaction with acrylonitrile and methyl acrylate in a pure state, although GC–MS analysis of the crude reaction products indicated that they were formed (see Experimental section). However, the main product in each case was the 2,12-disubstituted ketone (**13**; Z = CN, CO_2Me) arising from reaction at C-12. In the former case, the ketone (**13**; Z = CN) was isolated as a mixture of *cis* and *trans* isomers. The ^{13}C NMR spectrum showed four doublets attributed to the C-2 and C-12 carbon signals (δ_C 41.5, 42.0, 44.7, 47.65). In the latter case (**13**; Z = CO_2Me), only one geometric isomer was formed and the ^{13}C NMR spectrum showed two doublets due to the C-2 and C-12 carbons (δ_C 41.7, 47.25). So it would appear that, in the case of the 12-membered ring imine, the change ($CH_2CH_2Z \longrightarrow$ Me) has reduced the combined steric impediment sufficiently to allow reaction at C-2 to take place, but the rate of reaction is less than the rate of tautomeric interconversion into the less substituted secondary enamine tautomer (**14**) which then reacts more rapidly to give the 2,12-disubstituted ketone (**13**) as the main product.

Experimental

^{13}C NMR and ^1H NMR spectra were obtained with a Varian Associates FT-80A spectrometer operating at 20 MHz and a Varian Associates T-60 spectrometer operating at 60 MHz, respectively, in $CDCl_3$ solutions. IR spectra were recorded with a Pye Unicam SP 1000 spectrometer and were calibrated against the 1 601 cm^{-1} peak of polystyrene film. GLC analyses were carried out with a Varian 3400 gas chromatograph using ultra high purity nitrogen as carrier (gas flow 27 cm s^{-1}), a 20 m glass capillary column (Phase PS 25S; film thickness 0.53 μm; column temperature 150 °C) and a flame ionization detector. Mass spectra were recorded on a Varian Associates MAT-212 spectrometer operating at 70 eV. Microanalyses were determined by the Processing and Chemical Manufacturing Technology Division of the CSIR and, together with the GC–MS determinations, by the Chemistry Department of the University of Natal, Pietermaritzburg. Silica gel (0.2 mm) containing fluorescent indicator (F_{254}) on aluminium backed plates (Merck: Art 5554) was used for TLC and silica gel (Merck: Art 9385) was used for flash chromatography.[12]

Preparation of Imines: General Method.—A solution of the ketone (10–20 g), benzylamine (1.25 equiv.), and toluene-*p*-sulphonic acid (0.1 g) in benzene (150 ml) was heated under reflux under a Dean–Stark head for 20 h. The solvent was removed under vacuum and the residue distilled. In the case of the 2-methylcycloheptanone and 2-methylcyclododecanone imines, the reflux time was increased to 44 h and 48 h, respectively. In this way, the following imines were prepared.

N-*Cycloheptylidenebenzylamine* (**4**; R = H) (85%), b.p. 118–

120 °C at 0.3 mmHg; ν_{max}(film) 1 644 cm^{-1} (C=N); δ_H 1.54 (8 H, br s, 4 × CH_2), 1.96–2.76 (4 H, m, 2 × α-CH_2), 4.36 (2 H, s, CH_2N), and 7.23 (5 H, br s, Ph).

N-*Cyclo-octylidenebenzylamine* (**5**) (81%), b.p. 120–126 °C at 0.2 mmHg; ν_{max}(film) 1 647 cm^{-1} (C=N); δ_H 1.13–2.06 (10 H, m, 5 × CH_2), 2.06–2.7 (4 H, m, 2 × α-CH_2), 4.46 (2 H, s, CH_2N), and 7.2 (5 H, s, Ph).

N-*Cyclododecylidenebenzylamine* (**6**; R = H) (92%), b.p. 152–156 °C at 0.2 mmHg; ν_{max}(film) 1 661 cm^{-1} (C=N); δ_H 0.54–2.54 (22 H, complex methylene envelope, 11 × CH_2), 4.47 (2 H, br s, CH_2N), and 7.13 (5 H, m, Ph).

N-(2-*Methylcycloheptylidene)benzylamine* (**4**; R = Me) (64%), b.p. 112–114 °C at 0.15 mmHg; ν_{max}(film) 1 650 cm^{-1} (C=N); δ_H 1.09 (3 H, d, CH_3), 1.1–2.4 (11 H, methylene envelope), 4.07 (2 H, s, CH_2Ph), and 7.0 (5 H, br s, Ph).

N-(2-*Methylcyclododecylidene)benzylamine* (**6**; R = Me) (58%); b.p. 152–154 °C at 0.2 mmHg; ν_{max}(film) 1 660 cm^{-1} (C = N); δ_H 1.04 (3 H, d, CH_3), 1.1–2.6 (21 H, methylene envelope), 4.53 (2 H, s, CH_2Ph), and 7.2 (5 H, br s, Ph).

Alkylation of Imines: General Method.—The electrophilic alkene (6 equiv.) was added to the imine (3–15 mmol) in dry methanol (10–15 ml) and the solution heated under reflux for 17 h. Hydrolysis was carried out by the addition of 10% acetic acid (4–10 ml) and the mixture heated under reflux for 1 h. The methanol and the more volatile reagents were removed *in vacuo* and the residue extracted with ether (3 × 25 ml), and the combined ethereal extracts were washed with 2M hydrochloric acid (3 × 25 ml), saturated aqueous sodium hydrogen carbonate (2 × 25 ml), and saturated brine (2 × 25 ml) and dried ($MgSO_4$). Filtration and evaporation of the ether gave the crude product which was analysed by GLC and purified by flash chromatography (hexane–dichloromethane–ethyl acetate) (1:1:0.08). For the mono-alkylation of 2-methylcycloheptanone and 2-methylcyclododecanone imines, the proportion of electrophilic alkene was reduced (2 equiv.) and the reflux time increased to 24 h. In this way the following products were obtained.

3-(2-*Oxocycloheptyl)propanenitrile* (**9**; R = H, Z = CN) (57%); ν_{max}(film) 1 700 (C=O), 2 234 cm^{-1} (C≡N); δ_H 0.8–3.0 (methylene envelope); δ_C 14.6 (t, C-2), 23.3 (t), 27.1 (t), 28.3 (t), 28.6 (t, C-3, C-4′, C-5′, C-6′), 31.0 (t, C-7′), 42.8 (t, C-3′), 49.5 (d, C-1′), 119.1 (s, C-1), and 213.7 (s, C-2′) (Found: C, 72.3; H, 9.3; N, 8.1. Calc. for $C_{10}H_{15}NO$: C, 72.7; H, 9.1; N, 8.5%).

2,2-*Bis*-β-*methoxycarbonylethylcycloheptanone* (**8**) (49%); ν_{max}(hexane) 1 744 (CO_2Me), 1 701 cm^{-1} (C=O); δ_H 0.94–2.93 (18 H, methylene envelope), 3.7 (6 H, s, 2 × CH_3); δ_C 24.3 (t), 26.5 (t, C-4, C-5), 28.8 (t), 29.2 (t, C-α, C-β), 30.5 (t), 34.4 (t, C-3, C-6), 40.4 (t, C-7), 51.6 (q, MeO), 52.2 (s, C-2), 173.7 (s, CO_2), 215.9 (s, C-1) (Found: C, 62.8; H, 8.3. Calc. for $C_{15}H_{24}O_5$: C, 63.4; H, 8.45%).

2-β-*Phenylsulphonylethylcycloheptanone* (**9**; R = H, Z = SO_2Ph) (65%); ν_{max}(film) 1 700 (C=O), 1 319, and 1 150 cm^{-1} (SO_2); δ_H 0.7–2.83 (13 H, methylene envelope), 3.1 (2 H, t, CH_2SO_2), 7.67 (5 H, m, Ph); δ_C 23.5 (t), 24.8 (t, C-4, C-5), 28.6 (t), 28.8 (t, C-α, C-6), 31.5 (t, C-3), 43.0 (t, C-7), 49.5 (d, C-2), 53.8 (t, C-β), 127.8 (d), 129.1 (d), 133.6 (d), 139.0 (s, Ph), and 214.2 (s, C-1) (Found: C, 64.0; H, 7.3; S, 11.4. Calc. for $C_{15}H_{20}O_3S$: C, 64.3; H, 7.1; S, 11.4%).

3-(2-*Oxocyclo-octyl)propanenitrile* (**11**; Z = CN) (54%); ν_{max}(film) 1 699 (C=O), 2 236 cm^{-1} (C≡N); δ_H 0.88–3.16 (methylene envelope); δ_C 14.5 (t, C-2), 24.0, 24.3, 24.5 (C-5′, C-6′, C-7′), 26.6, 26.8 (t, C-3, C-4′), 31.9 (t, C-8′), 41.9 (t, C-3′), 47.8 (t, C-1′), 118.8 (s, C-1), and 217.4 (s, C-2′) (Found: C, 73.2; H, 9.7; N, 7.8. Calc. for $C_{11}H_{17}NO$: C, 73.7; H, 9.5; N, 7.8%).

Methyl 3-(2-*oxocyclo-octyl)propanoate* (**11**; Z = CO_2Me) (40%), b.p. 128 °C at 0.3 mmHg; ν_{max}(film) 1 742 (CO_2Me) and 1 704 cm^{-1} (C=O); δ_H 0.9–2.83 (17 H, methylene envelope), 3.66 (3 H, s, OMe); δ_C 24.2, 24.7, 24.9, 26.9 (C-4′, C-5′, C-6′, C-7′), 26.8 (t, C-3), 31.2 (t, C-2), 32.4 (t, C-8′), 41.7 (t, C-3′), 48.8 (d, C-1′), 50.8 (q, MeO), 172.9 (s, C-1), and 218.3 (s, C-2′) (Found: C, 67.8; H, 9.8. Calc. for $C_{12}H_{20}O_3$: C, 67.9; H, 9.4%).

2,8-*Bis*-β-*methoxycarbonylethylcyclo-octanone* (**10**) (7%) δ_C 24.6, 24.75, 26.2, 26.3, 28.0, 31.6, 32.0, 32.6 (t, CH_2s), 49.3 (d, C-2, C-8), 51.5, 51.6 (q, OCH_3), 170.3, 173.4 (s, CO_2Me), and 220.6 (s, C=O) (Found: C, 64.4; H, 9.0. Calc. for $C_{16}H_{26}O_5$: C, 64.4, H, 8.7%). This product was prepared by increasing the reflux time from 17 to 68 h, adding a further 2.5 equivalents of methyl acrylate and heating under reflux for a further 17 h.

2-β-*Phenylsulphonylethylcyclo-octanone* (**11**; Z = SO_2Ph) (73%); ν_{max}(Nujol) 1 700 (C=O), 1 310 and 1 150 cm^{-1} (SO_2); δ_H 0.9–3.3 (methylene envelope), 7.7 (m, Ph); δ_C 24.5 (t), 24.7 (t), 24.9 (t), 25.0 (t, C-4, 5, 6, 7), 27.3 (t, C-α), 32.9 (t, C-3), 42.4 (t, C-8), 48.1 (d, C-2), 54.0 (t, C-β), 127.9 (d), 129.3 (d), 133.7 (d), 138.2 (s, Ph), and 218.4 (s, C-1) (Found: C, 65.2; H, 7.5; S, 10.8. Calc. for $C_{16}H_{22}O_3S$: C, 65.3; H, 7.5; S, 10.9%).

3-(2-*Oxocyclododecyl)propanenitrile* (**12**; R = H, X = CN) (66%), m.p. 63–64 °C (hexane); ν_{max}(film) 1 700 (C=O) and 2 235 cm^{-1} (C≡N); δ_H 0.9–3.2 (methylene envelope); δ_C 14.8 (t, C-2), 20.8 (t), 21.2 (t), 21.7 (t), 22.2 (t), 22.7 (t), 23.4 (t), 24.7 (t), 25.5 (t), 25.6 (t), 28.2 (t, 10 × CH_2), 37.2 (t, C-3′), 49.4 (d, C-1′), 118.9 (s, C-1), and 211.6 (s, C-2′) (Found: C, 76.4; H, 10.4; N, 5.8. Calc. for $C_{15}H_{25}NO$: C, 76.6; H, 10.6; N, 5.95%).

Methyl 3-(2-*oxocyclododecyl)propanoate* (**12**; R = H, Z = CO_2Me) (41%), m.p. 36–37 °C; ν_{max}(film) 1 740 (CO_2Me), 1 700 cm^{-1} (C=O); δ_H 1.0–3.0 (methylene envelope) and 3.6 (3 H, s, OMe); δ_C 21.7, 22.0, 22.2, 23.2, 23.5, 24.0, 25.6, 25.7, 26.0 (9 × CH_2), 29.2 (t, C-2), 31.8 (t, C-12′), 37.4 (t, C-3′), 50.7 (d, C-1′), 51.5 (q, MeO), 173.5 (s, CO_2), and 213.6 (s, C-2′) (Found: C, 71.5; H, 10.6. Calc. for $C_{16}H_{28}O_3$: C, 71.6; H, 10.45%).

2-β-*Phenylsulphonylethylcyclododecanone* (**12**; R = H, Z = SO_2Ph) (60%); ν_{max}(CH_2Cl_2) 1 703 (C=O), 1 310 and 1 150 cm^{-1} (SO_2); δ_H 0.76–2.36 (23 H, methylene envelope), 3.0 (2 H, m, CH_2SO_2), 7.67 (5 H, m, Ph); δ_C 21.6, 21.8, 22.8, 23.5, 25.8 (ring CH_2s), 27.7 (t, C-α), 42.8 (d, C-2), 53.7 (t, C-β), 127.7 (d), 129.2 (d), 133.6 (d), 138.8 (s, Ph), and 214.0 (s, C-1) (Found: C, 68.1; H, 8.5; S, 9.1. Calc. for $C_{20}H_{30}O_3S$: C, 68.6; H, 8.6; S, 9.1%).

1-*Phenyl*-3-(2-*oxocyclododecyl)propan*-1-*one* (**12**; R = H, Z = COPh) (80%), m.p. 98–100 °C (from ethanol); ν_{max}(mull) 1 710 and 1 690 cm^{-1} (C=O); δ_H 1.1–3.1 (methylene envelope) and 7.2–8.1 (m, Ph); δ_C 21.8, 22.2 (two signals), 23.2, 23.6, 24.0, 25.1, 25.8, 26.1, 29.6, 32.3, 37.3 (all t, ring and side chain CH_2s), 51.1 (d, C-1′), 128.0, 128.5, 133.0 (all d, Ph), 136.8 (s, Ph), 199.5 (s, C-1), and 214.0 (s, C-2′) (Found: C, 80.4; H, 9.75. Calc. for $C_{21}H_{30}O_2$: C, 80.25; H, 9.55%).

2-β-*Methylsulphonylethylcycloheptanone* (**9**; R = H, Z = SO_2Me) (70%) was not obtained analytically pure; ν_{max}(film) 1 700 (C=O) and 1 360 and 1 150 cm^{-1} (SO_2); δ_H 1.1–3.3 (methylene envelope), 2.93 (overlaid s, SO_2CH_3), 3.06 (overlaid t, CH_2SO_2); δ_C 23.7, 24.8 (t, C-4, C-5), 28.8, 29.0 (t, C-α, C-6), 31.7 (t, C-3), 40.4 (q, CH_3), 43.2 (t, C-7), 49.1 (d, C-2), 52.4 (t, C-β), and 214.4 (s, C-1); *m/z* 218 (M^+) GC–MS analysis of the crude reaction product showed no evidence for the presence of even trace amounts of any 2,2- or 2,7-dialkylation products.

2-β-*Methylsulphonylethylcyclododecanone* (**12**; R = H, Z = SO_2Me) (70%), m.p. 135–137 °C (from ethanol); ν_{max}(mull) 1 700 (C=O) and 1 305 and 1 130 cm^{-1} (SO_2); δ_H 1.4–2.7 (methylene envelope), 3.2 (overlaid s and m, $CH_2SO_2CH_3$); δ_C 21.1, 21.6, 22.2, 22.5, 22.6, 23.2, 23.9, 25.9, 26.0, 29.0 (t, CH_2s), 37.5 (t, C-3), 40.45 (q, CH_3), 49.75 (d, C-2), 52.7 (t, C-β), 212.7 (C-1) (Found: C, 62.4; H, 9.75. Calc. for $C_{15}H_{28}SO_3$: C, 62.5; H, 9.7%; *m/z* 288 (M^+). There was no evidence for the occurrence of any dialkylation.

3-(1-*Methyl*-2-*oxocycloheptyl)propanenitrile* (**9**; R = Me, Z = CN) (97%); ν_{max}(film) 2 300 (CN), 1 700 cm^{-1} (C=O); δ_H 1.08 (3 H, s, CH_3), 1.33–2.66 (14 H, methylene envelope); δ_C 12.5

(t, C-2), 21.5 (q, CH_3), 24.4, 26.4, 30.3, 34.3, 37.2, 40.2 (t, 6 × CH_2), 49.85 (s, C-1'), 119.8 (s, C-1), 215.9 (s, C-2') (Found: C, 74.0; H, 9.95; N, 7.8. Calc. for $C_{11}H_{17}NO$: C, 73.7; H, 9.5; N, 7.8%).

Methyl 3-(1-*methyl*-2-*oxocycloheptyl*)*propanoate* (**9**; R = Me, Z = CO_2Me) (83%); $\nu_{max}(CCl_4)$ 1 742 (CO_2Me), 1 701 cm^{-1} (C=O); δ_H 1.06 (3 H, s, CH_3), 1.1–3.0 (14 H, methylene envelope), 3.66 (3 H, s, OMe); δ_C 20.9 (q, CH_3), 24.2, 26.3, 28.8, 30.3, 33.95, 37.55, 39.9 (t, 7 × CH_2), 49.85 (s, C-1'), 51.2 (q, OMe), 173.5 (s, C-1), 216.4 (s, C-2') (Found: C, 68.0; H, 9.5. Calc. for $C_{12}H_{20}O_3$: C, 67.9; H, 9.4%).

3-(3-*Methyl*-2-*oxocyclododecyl*)*propanenitrile* (**13**; Z = CN) (54%) isolated as a mixture of stereoisomers; ν_{max}(film) 2 298 (C≡N), 1 695 cm^{-1} (C=O); δ_H 1.06 (3 H, d, CH_3), 1.1–3.2 (24 H, methylene envelope); δ_C 15.4 (t, C-2), 15.8 and 18.6 (q, CH_3s of *cis* and *trans* isomers), 20.5, 21.9, 22.6, 22.9, 23.1, 23.5, 24.0, 24.1, 24.7, 24.9, 26.1, 26.15, 26.2, 28.4, 28.9, 31.05, 31.2 (all t, CH_2s of *cis* and *trans* isomers), 41.5, 42.0, 44.7, 47.65 (all d, C-1' and C-3' of *cis* and *trans* isomers), 119.4 (C-1), 215.5 and 216.1 (s, C-2' of *cis* and *trans* isomers) (Found: C, 77.3; H, 11.0; N, 5.3. Calc. for $C_{16}H_{27}NO$: C, 77.1; H, 10.8; N, 5.6%).

GLC analysis of the crude product showed three peaks (t_R 24.8, 25.7, 32.7 min at 200 °C; peak area ratio 7:1:2). The first two are the geometric isomers of (**13**; Z = CN) and the last is attributed to the regioisomer (**12**; R = Me, Z = CN) which was not isolated but showed the required molecular ion at *m/z* 249 (GC–MS) and the ^1H NMR spectrum of the crude mixture showed an overlaid singlet at δ 1.16, which could be due to the methyl group in (**12**), in addition to the doublet at δ 1.06 [CH_3 in (**13**)].

Methyl 3-(3-*methyl*-2-*oxocyclododecyl*)*propanoate* (**13**; Z = CO_2Me) (48%); $\nu_{max}(CCl_4)$ 1 740 (CO_2Me), 1 700 cm^{-1} (C=O); δ_H 1.0 (3 H, d, CH_3), 1.2–2.9 (24 H, methylene envelope), and 3.66 (3 H, s, OMe); δ_C 17.2 (q, Me), 23.4, 23.7, 24.3 (several signals superimposed), 24.6, 24.95, 26.5, 29.6, 31.8, 31.9 (all t, ring and side chain CH_2s), 41.7 (d, C-3'), 47.25 (d, C-1'), 51.5 (q, OMe), 173.6 (s, CO_2Me), and 217.3 (s, C-2') (Found: C, 72.2, H, 10.2. Calc. for $C_{17}H_{30}O_3$: C, 72.3; H, 10.6%).

GLC analysis of the crude product showed two peaks (t_R 30.2 and 36.9 min at 200 °C; peak area ratio 6.5:3.5) due to the two regioisomers (**13**; Z = CO_2Me) and (**12**, R = Me, Z = CO_2Me), respectively. A sample of methyl 3-(1'-methyl-2'-oxocyclodecyl)propanoate (**12**; R = Me, Z = CO_2Me) contaminated with its regioisomer (**13**; Z = CO_2Me) was isolated by flash chromatography and showed: $\nu_{max}(CCl_4)$ 1 742 (CO_2-Me) and 1 707 cm^{-1} (C=O); δ_H 1.0 (s, CH_3); δ_C 20.1 (q, Me), 20.5, 21.6, 22.3 (two signals superimposed), 22.9, 23.7, 26.45, 26.8, 29.6, 32.0, 32.9, 37.8 (all t, ring and side chain CH_2s), 51.2 (s, C-1'), 51.6 (q, OMe), 174.4 (s, CO_2Me), 214.25 (s, C-2'), in addition to smaller signals due to (**13**; Z = CO_2Me).

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