Reactions of cyclic β-keto esters and other enol derivatives with 3-acetoxyamino-2-isopropylquinazolin-4(3*H*)-one: further oxidation of the cyclic α-(3,4-dihydro-2-isopropyl-4-oxoquinazolin-3-yl)amino ketones with lead tetraacetate leading to ring-expansion (in dichloromethane) and ring-cleavage (in methanol)

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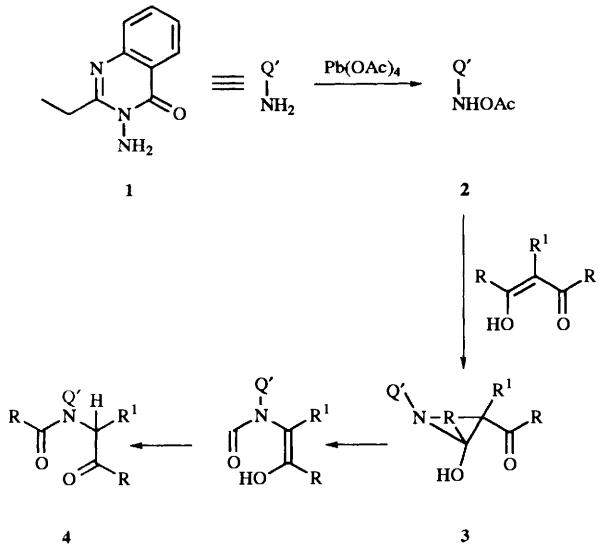
The cyclic β-keto esters **12**, **20**, **22**, **26**, the β-diketone **28** and the enol silyl ethers **24** and **30** have been converted in 60–77% yields into the corresponding α-(oxoquinazolinyl)amino cyclic ketone derivatives **16**, **21**, **23**, **29**, **27**, **25** and **31**, respectively, by reaction with 3-acetoxyamino-2-isopropylquinazolin-4(3*H*)-one **11**. Further oxidation of some of these products with lead tetraacetate gives products whose nature depends on the solvent used; in dichloromethane, **16**, **21** and **25**, which contain 5-membered ring ketones, give ring-expanded products **32**, **38** and **39**, respectively whereas, in methanol, ring-cleavage of **16**, **25** and **27** occurs to give imino-esters **41**, **44** and **42**/**43**, respectively. Ring-expansion of **23**, **27** and **31**, which contain 6-membered ring ketones, does not occur and the only isolated product in each case is the benzoxazinone **40**. A mechanism which accounts for this dependence on the solvent is presented: radical intermediates do not appear to be implicated.

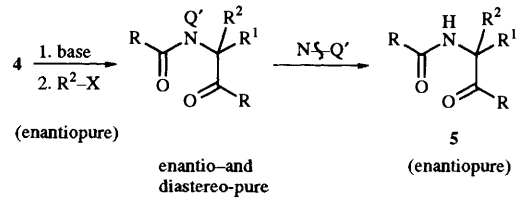
In a previous paper,[1] we examined the reaction of 3-acetoxyaminoquinazolinone **2** (Q'NHOAc) with acyclic β-diketones as a route to, for example, *N*-acyl-N(Q')-α-amino ketones **4** (Scheme 1).



Scheme 1

This conversion which is analogous to that first discovered by Foucaud *et al.*[2] using oxidative addition of *N*-aminophthalimide to β-diketones, involves the enolic form of the β-diketone and ring-opening of the intermediate aziridine **3** by C–C bond cleavage. Simple acyclic β-keto esters are unreactive in this reaction, presumably because of their low enol content.

Compounds of type **4** are of interest because there is no rotation around the N–N bond that they contain and this bond, therefore, constitutes a chiral axis.[3] In principle, **4** could be prepared in enantiopure form and the N–N chiral axis used to bring about complete diastereoselectivity in alkylation adjacent to the carbonyl group (Scheme 2). Reductive cleavage of the



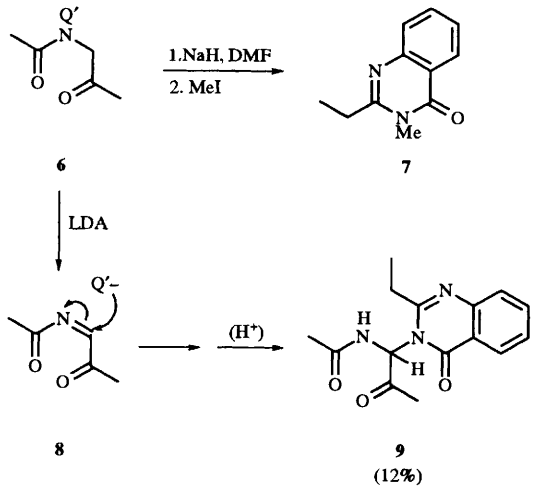
Scheme 2

N–N bond would give an enantiopure product **5** containing the newly-created (quaternary) chiral centre adjacent to the carbonyl group. We have shown previously that the presence of an acyl group on the exocyclic nitrogen in **4** assists in the reductive cleavage of the N–N bond.[4]

Attempts to bring about the conversion in Scheme 2 using initially the racemic substrate **6**, however, were thwarted by the unexpectedly easy elimination of the quinazolinone anion even at low temperature. Thus, treatment of **6** with sodium hydride in dimethylformamide followed by methyl iodide, gave 3-methylquinazolinone **7** (66%) as the only homogeneous product isolated (Scheme 3).

The keto amide **6** when treated first with lithium diisopropylamide (LDA) and then with methyl iodide in tetrahydrofuran gave a crystalline solid in 12% yield by chromatography which was identified as **9** from its spectroscopic data and confirmed by an X-ray structure determination (Fig. 1). The rearranged product **9**, in whose formation the methyl iodide plays no part, presumably arises by elimination of the quinazolinone anion from **6** and then its re-addition to the intermediate diacylimine **8** (Scheme 3); an analogous rearrangement product was isolated previously from reaction in base of a presumed *N*-acyl-N(Q')α-amino ester intermediate.[1]

One way in which this facile and unwanted elimination of the



Scheme 3

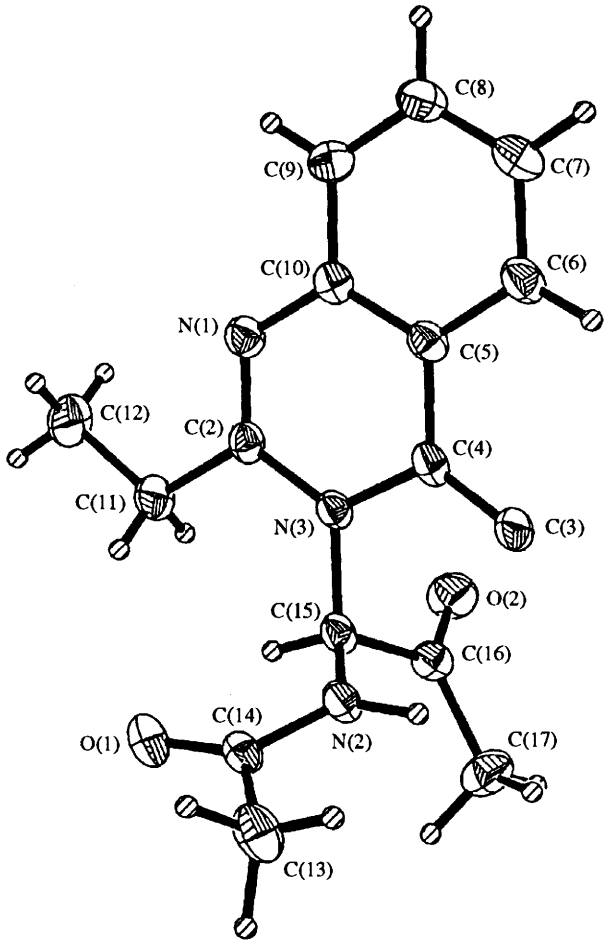
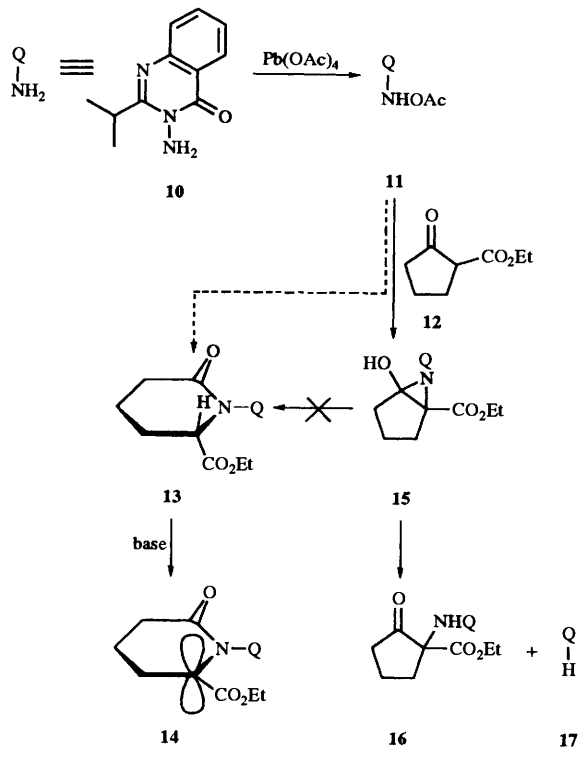
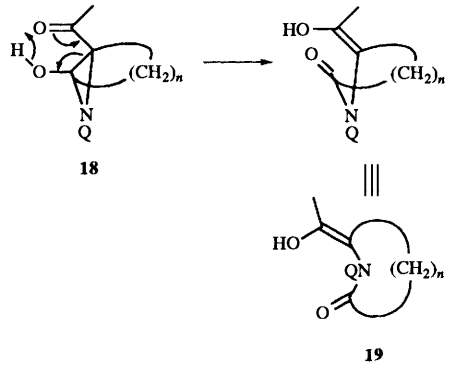


Fig. 1 X-ray crystal structure of compound **9**



Scheme 4

accessible in one step from the cyclic β-keto ester **12** (Scheme 4) since, unlike simple acyclic β-keto esters, cyclic β-keto esters such as **12** possess a considerable enol content. Reaction of the 3-acetoxyaminoquinazolinone **11** (QNHOAc) with ethyl 2-oxocyclopentanecarboxylate **12**, however, yielded none of the required ester amide **13**. Instead, a crystalline product was obtained in 77% yield and identified as the α-QNH-β-keto ester **16**; a minor product (12%) was the 3*H*-quinazolinone **17**. This product **16** presumably arises from the more usual C–N bond cleavage of the intermediate aziridine **15**, catalysed by acetic acid. The absence of C–C bond cleavage (the Foucaud reaction) in this reaction and in all other analogous reactions using 5- and 6-membered ring-contained β-keto esters and β-diketones examined in this work may be the result of the strain in the presumed first-formed conformation of the product **19** from the opening of the aziridine ring in **18** (Scheme 5) when *n* is 3 or 4.

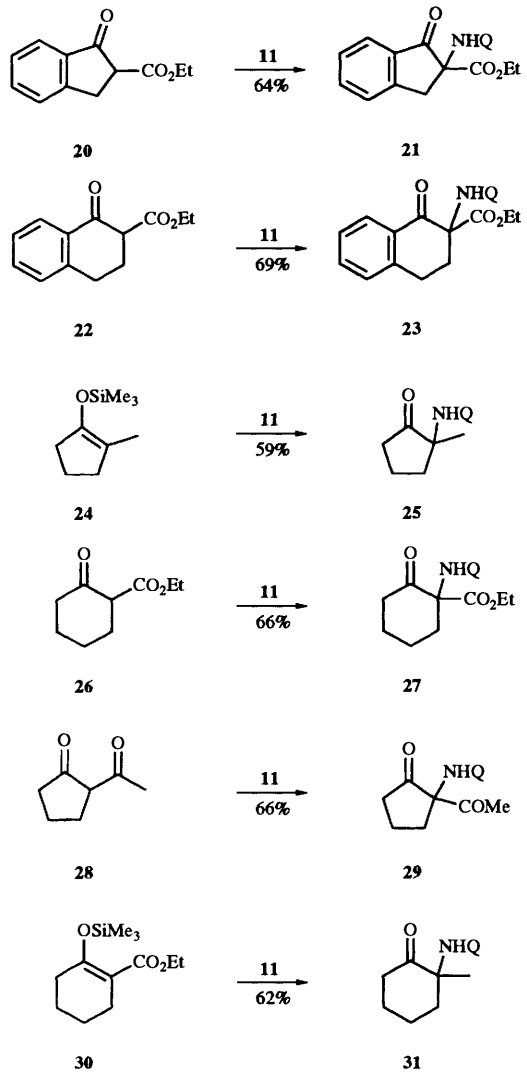


Scheme 5

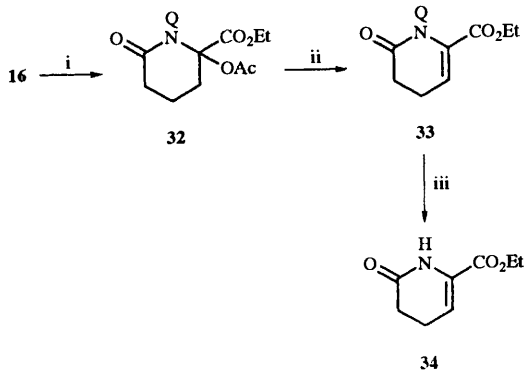
Oxidative substitution of the QNH group into the α-position of the β-keto esters **20**, **22** and **26** and of the β-diketone **28** also took place in good yields to give **21**, **23**, **27** and **29**, respectively (Scheme 6). The enol silyl ethers **24** and **30** also reacted with QNHOAc **11** and gave the analogous α-(QNH)-substituted ketones **25** and **31**, respectively, in good yields.

quinazolinone ring might be retarded would be to incorporate the elements of **4** into a ring. The carbanion formed by removal of the proton α to the ester in *e.g.* **13** (Scheme 4) is orthogonal to the N–Q bond (as in **14**) and this might result in slower loss of the quinazolinone anion and thus permit competitive alkylation of the carbanion. (The 2-isopropyl-substituted quinazolinone Q was used in all subsequent reactions in this paper.)

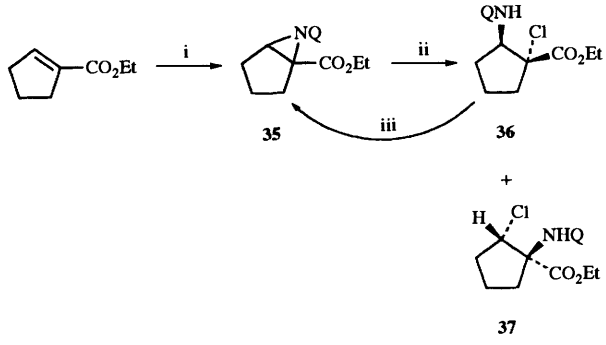
By analogy with the conversion of β-diketones into keto amides **4** (Scheme 1), the cyclic ester amide **13** should be



Scheme 6



Scheme 7 *Reagents and conditions:* i, LTA, CH_2Cl_2, 59%; ii, heat, 250 °C 98%; iii, SmI_2, THF, Bu^{t}OH, 51%



Scheme 8 *Reagents:* i, **11**, 65%; ii, HCl; iii, NaH, DMF

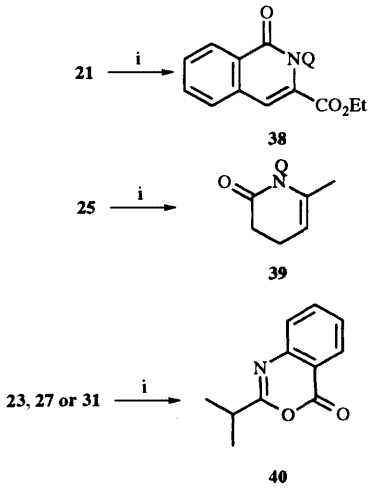
Oxidation of α-(QNH)-substituted ketones 16, 21, 23, 25, 27, 29 and 31 with LTA in dichloromethane

The α-QNH-β-keto ester **16** when dissolved in dichloromethane and stirred with LTA overnight gave, as the major product, isolated by chromatography, the α-acetoxy ester **32** (59%) (Scheme 7). Thermal elimination of acetic acid from **32** by heating at 250 °C (Kugelrohr distillation) gave the enamide **33** as the sole product.

Although the α-acetoxy ester **32** is expected to be capable of existing as diastereoisomers because of the presence of the chiral centre and a N–N chiral axis about which a high barrier to rotation is expected (see below), from its NMR spectrum it appears to be a single diastereoisomer.

We have investigated the dependence of this unprecedented ring-expansion in Scheme 7 on changes in ring size (5 ⟶ 6) and substitution using **20, 22, 24, 26, 28** and **30**. For comparison purposes we also prepared, and attempted the LTA oxidation of the α- and β-chloro esters **35** and **36**, respectively, prepared by ring-opening of the aziridine **35** (Scheme 8). Although the ^1H NMR spectra of these two ring-opened products were consistent with their assigned structures, with the NH proton appearing in **36** as a doublet but as a singlet in **37**, in the ^{13}C NMR spectrum of **36**, 3 carbon resonances for a CH_2, a CH and 2 CH_3 apparently overlapped and appeared as a single broad resonance at δ 21.05. We have shown elsewhere[4] that signals in the ^1H NMR spectrum of compounds similarly substituted to **36** give rise to broadened peaks which are associated with the onset of slow rotation around the N–N bond on the NMR timescale. (The barrier to rotation around this bond is considerably lower when the exocyclic nitrogen is sp^3-hybridised, as it is in **36**, than when it is sp^2-hybridised as it is in **4**.[5]) Presumably a similar effect is responsible for the coalescence, probably of the isopropyl carbons and the N–CH_2 on the 5-membered ring in the ^{13}C spectrum of **36**. To confirm the structure of the α-chloro ester **36**, it was reconverted back into the aziridine **35** by treatment with sodium hydride in dimethylformamide which occurred in good yield.

Oxidation of α-(QNH)-β-keto ester **21** with LTA in dichloromethane also gave a ring-expanded product **38** (Scheme 9) in 32% yield (60% based on recovered starting



Scheme 9 *Reagents:* i, LTA, CH_2Cl_2

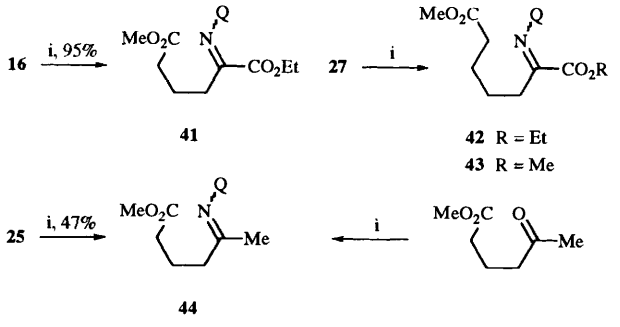
material). Likewise, oxidation of α-(QNH)-substituted ketone **25** also lead to the ring-expanded enamide **39** (60%). The diastereotopic methyl groups of the isopropyl in the NMR spectra of both **38** and **39** suggest that the N–N bonds in both compounds are chiral axes as would be expected.

No ring-expanded products, however, were isolated after treatment of the 6-membered ring containing α-(QNH)-substituted ketones **23, 27** and **31** with LTA in dichloromethane. In these cases, the oxidations were slower as judged by the rate of disappearance of starting material and the only homogeneous product isolated was identified as the 2-isopropylbenzoxazinone **40** (79% in the case of **31**, based on recovered starting material) by comparison with an authentic sample.

Neither the α-chloro ester **36** nor the β-chloro ester **37** reacted with LTA in dichloromethane under conditions which brought about complete reaction of **16**. Although oxidation of the diketone-derived **29** took place at a rate comparable with that of **16**, the only homogeneous product isolated was 2-isopropylquinazolinone **17** in low yield.

Oxidation of α-(QNH)-substituted ketones 16, 25 and 27 with LTA in methanol

Oxidation of **16** with LTA in methanol takes a different course to that in dichloromethane and no ring-expansion products are obtained. From **16**, the product was identified as the imino diester **41** (Scheme 10) which was isolated as a mixture of



Scheme 10 *Reagents and conditions:* i, LTA, MeOH; ii, **10**, 130 °C

double bond isomers (1.83:1) around the C=N bond. Kugelrohr distillation of this mixture (250 °C/0.1 mmHg, bath temp.) changed this ratio to 1:1.8. One indication in the NMR spectrum of **41** that loss of chirality had occurred was the equivalence of the two methyls of the isopropyl group and of the two protons in the methylene group of the ethyl ester; in the NMR spectrum of the starting mixture **16**, these methyl groups are non equivalent (diastereotopic) as are the two methylene protons. Another indication that ring-opening had occurred was the changed appearance of the signals in the NMR spectrum for the aliphatic protons $(CH_2)_3$ in **41** by comparison with **16**.

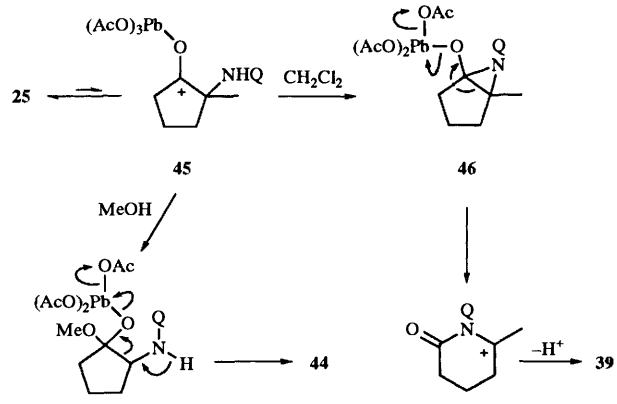
A similar ring-opening took place in the oxidation of α-(QNH)-substituted ketone **25** with LTA in methanol to give the imine ester **44** as a 2.4:1 ratio of C=N double bond isomers. The minor component of this mixture was shown to be identical with the major C=N double-bond isomer in a sample of **44** prepared by heating methyl 5-oxohexanoate and the 3-aminoquinazolinone **10** together at 130 °C (Scheme 10); in this case the ratio was *ca.* 1:7. A crystalline sample of the pure major C=N double bond isomer in this latter case was obtained from ethanol; when heated at 250 °C for 30 min it was converted into a 1:6 ratio of double bond isomers in which the major component (the crystalline material above) has the Q and methyl groups *cis*.[6]

Oxidation of the 6-membered ring analogue **27** with LTA in methanol gave a mixture of ring-opened imino diesters **42** and **43** as a result of some ester-exchange having occurred (Scheme 10). These two imino diesters were separated by flash chromatography: their C=N double bond isomer ratios were 2.4:1 and 4:1 respectively.

In the NMR spectrum of the major double bond isomer of imino ester **44**, the methyl groups of the isopropyl are non-equivalent whereas in the imino diester analogues **41, 42** and **43** these methyl groups appear to be equivalent in each case (see above). It appears that only in **44** is rotation around the N–N slow on the NMR time-scale so rendering the isopropyl methyl groups diastereotopic.

Mechanisms of oxidation of α-(QNH)-substituted ketones 16, 21, 23, 25, 27, 29 and 31 in dichloromethane and in methanol

A mechanism for oxidation of, for example, **25** which accounts for the different course taken in dichloromethane and in methanol is that shown in Scheme 11. Since neither chloro ester



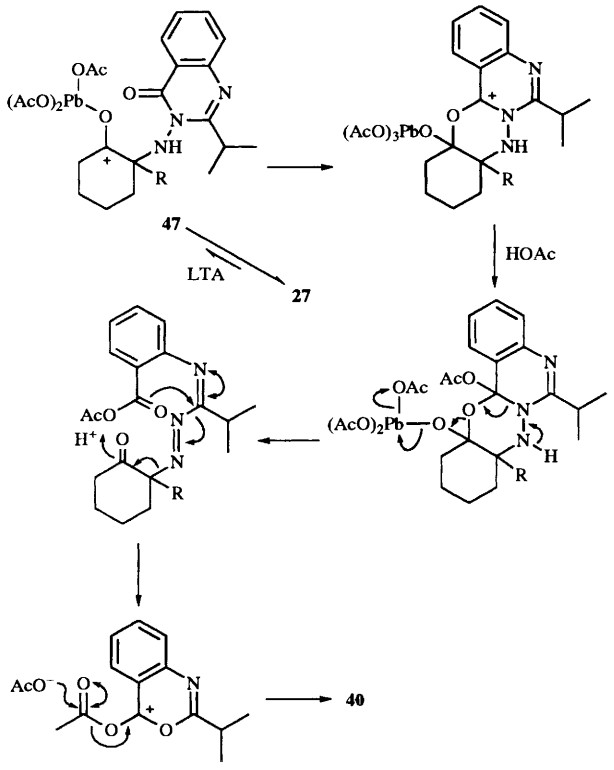
Scheme 11

36 nor **37** is reactive, the keto group is required for oxidation of the QNH group. Coordination of the LTA to the carbonyl oxygen is presumably the first step in the known oxidations of ketones with this reagent.[7] In methanol, the carbocation **45** is trapped by the solvent and fragmentation with elimination of lead diacetate occurs. Intermediates analogous to the fragmentation product **44** have previously been proposed in LTA oxidations of α-amino ketones[8] but initial attack of lead(IV) on nitrogen was proposed in this case.

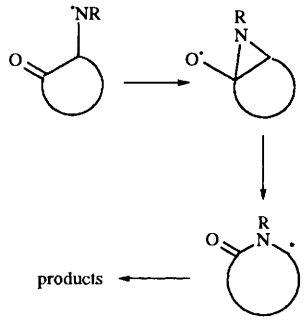
In dichloromethane as solvent (Scheme 11), nucleophilic attack on the same carbocation **45** by the exocyclic nitrogen occurs to give the aziridine **46** before fragmentation and proton loss to give **39**.

The formation of benzoxazinone **40** in oxidations of 6-membered ring-contained α-(QNH)-substituted ketones, *e.g.* **27**, in dichloromethane could arise by the route shown in Scheme 12. There appear to be factors which retard attack by the QNH nitrogen on the presumably reversibly formed carbocation **47** in the 6-membered ring case since the disappearance of starting material is much slower than with oxidations of the 5-membered ring analogue. It is possible that, whatever these factors are, they allow a slower attack of the quinazolinone carbonyl oxygen in **47** to supervene. We have previously isolated benzoxazinones from experiments involving attempted reaction of 3-acetoxyaminoquinazolinones, *e.g.* **2**, with other substrates.[4,9]

Ring-expansions of cyclic α-amino ketones are known, with incorporation of the nitrogen into the ring by way of nitrogen-centred radical intermediates[10] (Scheme 13). However, in the present work there was no evidence for the intermediacy of radicals even though the QNR radical might be expected to be



Scheme 12

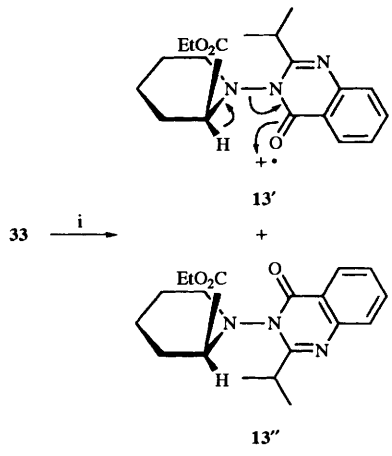


Scheme 13

a relatively stabilised species. The α-QNH-β-keto ester **16** when heated in benzene at 80 °C with tributyltin hydride and AIBN (1 mol equiv.), was recovered unchanged in 72% yield.

Attempted alkylation of N-(Q)-α-pyridone 13

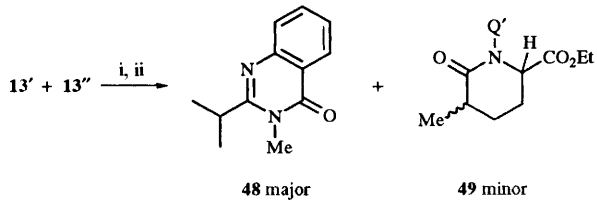
Reduction of the enamide **33** with Adams' catalyst and hydrogen gave rise to both diastereoisomers of **13** (**13′** and **13″**) (Scheme 14), the compound originally required to test its stability towards elimination of the quinazolinone anion (Scheme 4). Separation of these diastereoisomers was accomplished by chromatography over silica (faster:slower eluted diastereoisomers *ca.* 2:1). Although the spectroscopic data for these diastereoisomers are similar, there is a significant difference in their mass spectra in the intensities of their respective molecular ion peaks M^+ (357) relative to those for QH^+ (188). Thus, in the faster-eluted diastereoisomer this ratio 357:188 was 7:96 but for the slower-eluted diastereoisomer it was 41:96. [In both cases the base peak (100%) is at 173.] If it is assumed that formation of QH^+ is easier from that diastereoisomer **13′** (Scheme 14) in which the quinazolinone carbonyl oxygen and the $CHCO_2Et$ are *cis*, then it would appear that the major (faster-eluted) diastereoisomer is **13′**



Scheme 14 *Reagents:* i, PtO_2, H_2

which would correspond to delivery of hydrogen from the less-hindered side of the enamide **33** in the hydrogenation.†

An attempt to alkylate the mixture of diastereoisomers **13′** + **13″** α- to the ester group and the chiral axis was not successful; with base and methyl iodide the major product was the 3-methylquinazolinone **48** arising from the unwanted elimination of Q (*cf.* Scheme 3) followed by its methylation (Scheme 15). A



Scheme 15 *Reagents:* i, LDA; ii, MeI

minor product, isolated by chromatography, but not completely separated from **48**, was shown to retain the quinazolinone ring and to contain an additional methyl group from NMR and mass spectroscopy. However, from the NMR spectrum of this mixture, the $CHCO_2Et$ proton appeared to be retained in the methylated product and it is likely the methyl group is incorporated elsewhere in the molecule, conceivably α- to the amide carbonyl to give **49** (as a mixture of diastereoisomers).

In this paper both the ring-cleaved reactions in methanol and the ring-expansion reaction in dichloromethane could prove useful in synthesis. The sequence (cyclic) β-ketoester ⟶ α-(QNH)-β-keto ester ⟶ β-imino α,ω-diester is efficient (73% for **12** ⟶ **41**) and delivers a product having three differentiated electrophilic carbon atoms in the chain and which is a potential amino acid precursor. The ring-expansion products **33** and **39** are chiral molecules as a result of the N–N chiral axes they contain. If they could be prepared in enantiopure form they could prove useful for the synthesis of enantiopure substituted α-pyridones by diastereoselective addition to the enamide double bond followed by N–Q bond cleavage (*cf.* Scheme 2). We have shown (Scheme 7) that reductive cleavage of the N–Q bond in the enamide **33** can be accomplished by samarium diiodide and the dihydropyridine derivative **34** was isolated in 51% yield (70% based on recovered starting material).

† The poor diastereoselectivity in this reduction is surprising: it is possible that other mechanisms besides direct addition of hydrogen to the double bond are operative.

Experimental

For instrumentation used and general experimental details see ref. 4. Unless otherwise indicated, ^{1}H NMR spectra were measured at 300 MHz in $CDCl_3$ using tetramethylsilane as internal standard and ^{13}C spectra at 75 MHz in the same solvent and with the same internal standard. Assignments of ^{13}C resonances were made using DEPT (*J* values in Hz.) IR spectra were measured using Nujol mulls unless otherwise indicated. Mass spectra were obtained using a Kratos Concept mass spectrometer; high resolution accurate masses were obtained by peak-matching using perfluorokerosene.

The following commercially available materials were used as received: ethyl 2-oxocyclopentanecarboxylate, methyl 2-oxocyclohexanecarboxylate, 2-acetylcyclopentanone, ethyl cyclopent-1-enecarboxylate, samarium diiodide (0.1 mol dm^{-3} in THF), butyllithium (2.5 mol dm^{-3} in hexane).

In experiments using methanol as the solvent for lead tetraacetate, it was necessary to dry the methanol using magnesium and iodine. Light petroleum refers to the fraction bp 60–80 °C.

Attempts to alkylate 3-[acetyl(acetylmethyl)amino]-2-ethylquinazolin-4(3*H*)one 6

(*a*) Sodium hydride (50% dispersion in oil; 0.04 g) was added to dry dimethylformamide (2 cm^3) and the slurry stirred for 5 min at room temperature. The keto amide **6** (0.235 g) was then added over 15 min to the slurry and the resulting mixture stirred for a further 5 min; then methyl iodide (0.23 g) was added to it. After the mixture had been stirred for a further 30 min it was diluted with water and diethyl ether and then shaken thoroughly. The organic layer was separated, dried and evaporated under reduced pressure to give 2-ethyl 3-methylquinazolin-4(3*H*)one **7** (0.102 g, 66%), as colourless crystals, identical with an authentic sample[11] by IR spectra comparison. (*b*) A solution of lithium diisopropylamide was prepared by addition of butyllithium (46 mg as a 2 mol dm^{-3} solution in hexane) to dry tetrahydrofuran (THF) (3.3 cm^3) containing diisopropylamine (72.2 mg) at −5 °C. After the mixture had been cooled to −78 °C, the keto-amide **6** (0.15 g) in dry THF (7.2 cm^3) was added dropwise to it followed after 2 min by methyl iodide (0.44 g). The mixture was stirred at −78 °C for 2 h then quenched with saturated aqueous ammonium chloride (10 cm^3), and extracted with dichloromethane (40 cm^3). The combined organic extracts were dried and evaporated under reduced pressure. Chromatography of the residue over silica with ethyl acetate as eluent afforded the unchanged keto amide (15 mg) followed by the rearranged compound 3-[acetyl(acetylamino)methyl]-2-ethylquinazolin-4(3*H*)one **9** (16 mg, 12% based on recovered starting material) as colourless crystals, mp 192–195 °C (from ethanol) (Found: M^+, 287.1270. $C_{15}H_{17}N_3O_3$ requires M^+, 287.1266); δ_H 1.42 (t, *J* 7.3, CH_2CH_3), 2.08 (s, CH_3COC), 2.29 (s, CH_3CON), 3.36 (ABX_3, *J* 16.3, 7.3, CH_2CH_3), 6.56 (d, *J* 9.3, CHNH), 7.44 (dd, *J* 8.1, 1.2, Q′6-H), 7.48 (s, br, NH), 7.70 (d, *J* 7.6, Q′8-H), 7.76 (dd, *J* 8.5, 1.4, Q′7-H) and 8.12 (dd, *J* 8.1, 1.4, Q′5-H). On irradiation of the singlet at δ 7.48 (NH), the doublet at δ 6.56 collapsed to a singlet, δ_C 10.99 (CH_2CH_3), 22.86 ($COCH_3$), 25.61 ($NCOCH_3$), 28.05 (CH_2CH_3), 66.54 (CHNH), 120.06 (Q′CCO), 126.23, 126.72, 127.41, 134.97 (4 × OCH), 147.64 (Q′CN=C), 156.59 (Q′C=N), 163.01 (Q′C=O), 170.32 (CH_3CON) and 199.10 (CH_3COCH). An X-ray crystal structure determination was carried on a crystal of **8** grown from ethanol.

Preparation of a solution of 3-acetoxyamino-2-isopropylquinazolin-4(3*H*)one 11 in dichloromethane

Powdered dry lead tetraacetate (LTA) (9.15 g, 21 mmol) and 3-amino-2-isopropylquinazolin-4(3*H*)one **10**[1] (3.99 g, 19.7 mmol) were added alternately in very small portions and continuously over 15 min to vigorously stirred dichloromethane (40 cm^3) at −20 °C in a cooling bath. The mixture was stirred for a further 5 min at this temperature and then used in the following experiments.

Reaction of 11 with ethyl 2-oxocyclopentanecarboxylate 12. To a solution of **11**, prepared as described previously, the β-keto ester **12** (9.21 g, 59 mmol) was added and the solution allowed to rise to ambient temperature. Insoluble lead diacetate was separated and washed with dichloromethane (50 cm^3). The combined dichloromethane solutions were washed with aqueous sodium hydrogen carbonate and then water, dried and evaporated under reduced pressure. The solid/oil mixture obtained was triturated with cold diethyl ether and the insoluble 2-isopropylquinazolin-4(3*H*)one **17** (0.43 g, 12%) separated. After removal of the bulk of the excess of β-keto ester **12** [Kugelrohr, 0.02 mmHg, 60 °C (bath temp.)], the residue was chromatographed over silica using ethyl acetate–light petroleum (1:2) to give *α-QNH-β-keto ester* **16** (R_f 0.57) as colourless crystals (5.42 g, 77%), mp 87–88 °C (from ethanol) (Found: C, 63.75; H, 6.5; N, 11.75. $C_{19}H_{23}N_3O_4$ requires C, 63.85; H, 6.5; N, 11.75%); δ_H 1.29–1.35 (m, CH_3CHCH_3, CH_2CH_3), 1.67 (ddd, *J* 13.4, 9.6, 7.6, HCH), 1.85–2.06 (m, CH_2CH_2CO), 2.40 (ddd, *J* 13.4, 6.9, 4.0, HCH), 2.51 (m, CH_2CO), 3.72 [heptet, *J* 6.8, $(CH_3)_2CH$], 4.29 (ABX_3, CH_2CH_3), 6.06 (s, NH), 7.41 (ddd, *J* 8.2, 6.7, 1.5, Q 6-H), 7.67 (ddd, *J* 8.2, 1.5, 0.5, Q 8-H), 7.73 (ddd, *J* 8.2, 6.7, 1.5, Q 7-H) and 8.16 (ddd, *J* 8.2, 1.5, 0.5, Q 5-H); δ_C 14.00 (CH_2CH_3), 18.64 (CH_2), 20.73 (CH_3CHCH_3), 21.03 (CH_3CHCH_3), 29.56 (CH_2), 30.70 [$(CH_3)_2CH$], 35.90 (CH_2), 62.33 (CH_3CH_2), 71.99 (CNH), 120.23 (QCCO), 126.29, 126.54, 127.37, 134.48 (4 × QCH), 147.02 (QCN=C), 163.32, 163.98 (QC=N, QC=O), 169.22 ($CO_2CH_2CH_3$), 211.19 ($COCH_2$); ν_{max}/cm^{-1} 3275m, 1750s, 1730s and 1682m; *m/z* (%) 286 (13), 284 (17), 256 (28), 228 (12), 189 (52), 188 (78), 187 (31), 173 (100) and 160 (39).

Reaction of 11 with ethyl 1-oxoindane-2-carboxylate 20. To a solution of **11** prepared as described earlier from **10** (0.61 g) and LTA (1.39 g) in dichloromethane (6 cm^3) at −20 °C was added the β-keto ester **20**[12] (1.7 g) and the temperature of the solution allowed to rise to ambient with stirring. Work-up as described above gave an oil which was chromatographed with light petroleum–ethyl acetate (3:1) as eluent to afford the *α-QNH-β-keto ester* **21** (R_f 0.31) as a colourless solid (0.75 g, 64%), mp 142–145 °C (from ethanol) (Found: C, 67.15; H, 5.5; N, 10.6. $C_{22}H_{21}N_3O_4$ requires C, 67.5; H, 5.4; N, 10.75%); δ_H 1.05, 1.25 (2 × d, *J* 6.8, CH_3CHCH_3), 2.83 (d, *J* 17.4, HCH), 3.50 [h, *J* 6.8, $(CH_3)_2CH$], 3.68 (d, *J* 17.4, HCH), 3.85 (s, OCH_3), 6.49 (s, NH), 7.33–7.50 (m, 3 × ArCH), 7.57 (ddd, *J* 7.5, 7.4, 1.0, ArCH), 7.65 (d, *J* 7.4, ArCH), 7.74 (ddd, *J* 8.2, 6.8, 1.4, ArCH), 7.81 (d, *J* 7.6, ArCH) and 8.16 (dd, *J* 8.0, 1.0, ArCH); δ_C 20.28, 20.99 (CH_3CHCH_3), 30.61 [$(CH_3)_2CH$], 32.62 (CH_2), 53.46 (OCH_3), 72.57 (CNHQ), 120.10 (ArC), 125.09, 126.05, 126.20, 126.47, 127.22, 128.10 (6 × ArCH), 133.30 (ArC), 134.42, 135.80 (2 × ArCH), 146.67 (QCN=C), 151.16, 163.09, 163.86, 169.37 (QC=N, QC=O, CO_2CH_3, ArC) and 198.67 (C=O); ν_{max}/cm^{-1} 3320m, 1720s, 1680s and 1595m.

Reaction of 11 with ethyl 2-oxocyclohexanecarboxylate 26. To a solution of **11** prepared as earlier from **10** (3.17 g) and LTA (7.27 g) in dichloromethane (32 cm^3) at −20 °C, the β-keto ester **26** (7.9 g) was added and the solution allowed to warm to ambient temperature with stirring. Work-up as described above afforded the quinazolinone **17** (0.17 g, 6%) after trituration with cold diethyl ether and separation. After removal of the diethyl ether, the bulk of the unchanged β-keto ester was removed by distillation under reduced pressure (Kugelrohr) and the residue chromatographed over silica with light petroleum–ethyl acetate (4:1) as eluent. The *α-QNH-β-keto ester* **27** (R_f 0.21) was obtained as colourless crystals (3.82 g, 66%), mp 79–82 °C

(from ethanol) (Found: C, 64.5; H, 6.75; N, 11.25. $C_{20}H_{25}N_3O_4$ requires C, 64.65; H, 6.8; N, 11.3%); δ_H 1.26–1.35 (6 lines, CH_3CHCH_3, CH_2CH_3), 1.59–1.83 (m, 2 × CH_2), 2.01–2.07 (m, CH), 2.30–2.33 (m, CH), 2.46–2.57 (m, CH), 2.70–2.75 (m, CH), 3.70 [heptet, *J* 6.5, $(CH_3)_2CH$], 4.18–4.34 (m, 2 × CH), 6.94 (s, br, NH), 7.44 (ddd, *J* 8.0, 6.8, 1.5, Q 6-H), 7.68–7.78 (m, Q 7- and 8-H) and 8.17 (ddd, *J* 8.0, 1.5, 0.6, Q 5-H); δ_C 13.84, 20.80, 20.86 (3 × CH_3), 22.03 (CH_2), 25.97 (CH_2), 30.57 [$(CH_3)_2CH$], 31.92, 39.79 (2 × CH_2), 69.27 ($CO_2CH_2CH_3$), 71.90 (CNHQ), 120.34 (QCCO), 126.14, 126.52, 127.26, 134.31 (4 × QCH), 146.96 (QCN=C), 163.11, 164.13 (QC=N, QC=O), 168.83 ($CO_2CH_2CH_3$) and 203.03 (CH_2CO); ν_{max}/cm^{-1} 3260m, 1740m, 1680s and 1590s.

Reaction of 11 with ethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 22. To a solution of **11** prepared as described earlier from **10** (0.56 g) and LTA (1.29 g) in dichloromethane (6 cm^3) at −20 °C, the β-keto ester **22**[12] (1.7 g), was added and the solution allowed to warm to ambient temperature with stirring. Work-up described above gave an oil which was chromatographed over silica using light petroleum–ethyl acetate (3:1) as eluent to afford the *α-QNH-β-keto ester* **23** (R_f 0.41) as an off-white solid (0.78 g, 69%), mp 164–165 °C (from ethanol) (Found: M$^+$, 405.1686. $C_{23}H_{23}N_3O_4$ requires M^+, 415.1689); δ_H 1.32, 1.34 (2 × d, *J* 6.8, CH_3CHCH_3), 2.11–2.14 (m, CH), 2.34–2.41 (m, CH), 2.78–3.05 (m, 2 × CH), 3.67 (OCH_3), 3.89 [heptet, *J* 6.8, $(CH_3)_2CH$], 7.03 (NH), 7.17 (d, *J* 7.6, ArCH), 7.34–7.41 (m, 2 × ArCH), 7.49 (ddd, *J* 7.5, 7.4, 1.5, ArCH), 7.66–7.74 (m, 2 × ArCH), 8.11 (ddd, *J* 8.6, 1.9, 0.8, ArCH) and 8.20 (dd, *J* 8.0, 7.0, 1.1, ArCH); δ_c 20.37, 21.03 (CH_3CHCH_3), 25.63 (CH_2), 28.61 (CH_2), 30.36 [$(CH_3)_2CH$], 53.11 (OCH_3), 66.90 (CNHQ), 120.26 (QCCO), 124.16 (ArC), 126.07, 126.41, 126.74, 126.99, 127.15, 128.40 (6 × ArCH), 130.45 (ArC), 133.39, 134.24 (2 × ArC), 142.24 (ArCH), 146.66 (ArC), 163.13, 164.12 (QC=N, QC=O), 191.30 (ArC=O), (one CO not visible); ν_{max}/cm^{-1} 3280w, 1730s, 1680s and 1595s.

Reaction of 11 with 2-acetylcyclopentanone 28. To a solution of **11** prepared as described above from **10** (1 g) and LTA (2.29 g) in dichloromethane (10 cm^3) at −20 °C the β-diketone **28** (1.86 g) was added and the solution allowed to warm to ambient temperature with stirring. Work-up as before gave an oil which was chromatographed over silica with light petroleum–ethyl acetate (3:1) as eluent to afford the *α-QNH-β-diketone* **29** as a colourless solid (1.06 g, 66%), mp 130–132 °C (from ethanol) (Found: C, 65.95; H, 6.5; N, 12.8. $C_{18}H_{21}N_3O_3$ requires C, 66.05; H, 6.45; N, 12.85%); δ_H 1.30, 1.35 (2 × d, *J* 6.8, CH_3CHCH_3), 1.81–2.01 (m, CH_2), 2.33–2.65 (m, 2 × CH_2), 2.44 (s, $COCH_3$), 3.25 [heptet, *J* 6.8, $(CH_3)_2CH$], 6.21 (s, br, NH), 7.43 (ddd, *J* 8.1, 6.9, 1.5, Q 6-H), 7.70 (ddd, *J* 8.2, 1.3, 0.9, Q 8-H), 7.75 (ddd, *J* 8.3, 6.8, 1.5, Q 7-H) and 8.14 (ddd, *J* 8.0, 1.4, 0.5, Q 5-H); δ_C 18.71 (CH_2), 20.10, 20.97, 25.42 (3 × CH_3), 26.57 (CH_2), 31.22 [$(CH_3)_2CH$], 35.35 (CH_2), 78.40 (CNHQ), 119.85 (QCC=O), 126.37, 126.39, 127.37, 134.48 (4 × QCH), 146.80 (QCN=C), 162.70, 162.97 (QC=N, QC=O), 202.89, 213.07 (2 × CO); ν_{max}/cm^{-1} 3260m, 1750s, 1715s, 1670s and 1600s.

Reaction of 11 with 1-methyl-2-trimethylsilyloxycyclopentene 24. To a solution of **11** prepared as described above from **10** (1 g) and LTA (2.29 g) in dichloromethane (10 cm^3) at −20 °C was added the trimethylsilyl enol ether **24**[13] (2.51 g) and the solution allowed to rise to ambient temperature with stirring. Work-up as described above gave an orange oil which was chromatographed over silica with light petroleum–ethyl acetate (3:1) as eluent to afford the *α-QNH-α-methylcyclopentanone* **25** (870 mg, 59%) as a colourless solid, mp 128–130 °C (from ethanol) (Found: C, 68.0; H, 7.05; N, 14.0. $C_{17}H_{21}N_3O_2$ requires C, 68.2; H, 7.05, N, 14.05%); δ_H 1.21 (s, CH_3), 1.28, 1.33 (2 × d, *J* 6.7, CH_3CHCH_3), 1.83–2.20 (m, 4 × CH), 2.22–2.31 (m, CH), 2.53–2.62 (m, CH), 3.79 [heptet, *J* 6.7, $(CH_3)_2CH$], 7.40 (ddd, *J* 8.1, 6.6, 1.5, Q 6-H), 7.65–7.73 (m, Q 7- and 8-H) and 8.13 (dd, *J* 8.1, 1.1, Q 5-H); δ_C 18.17 (CH_2), 20.45, 20.86, 21.41 (3 × CH_3), 30.52 (CH_3CHCH_3), 35.82 (CH_2), 65.31 (CNHQ), 120.22 (QCCO), 126.00, 126.32, 127.13, 134.13 (4 × QCH), 146.64 (QCN=C), 163.18, 163.53 (QC=N, QC=O) (one CH_2 and one C=O not visible); ν_{max}/cm^{-1} 3320m, 1740s, 1670s and 1590s.

Reaction of 11 with 1-methyl-2-trimethylsilyloxycyclohexene 30. To a solution of **11** prepared as described previously from **10** (1 g) and LTA (2.3 g) in dichloromethane (10 cm^3) at −20 °C, the enol silyl ether **30**[13] (2.72 g) was added and the solution allowed to rise to ambient temperature. Work-up as described above gave an oil which was chromatographed over silica with light petroleum–ethyl acetate (4:1) as eluent to afford the *α-QNH-α-methylcyclohexanone* **31** (0.95 g, 62%) as a colourless solid, mp 102–104 °C (from ethanol) (Found: C, 68.85; H, 7.4; N, 13.4. $C_{18}H_{23}N_3O_2$ requires C, 69.0; H, 7.4; N, 13.4%); δ_H 1.15 (s, CCH_3), 1.29, 1.34 (2 × d, *J* 6.7, CH_3CHCH_3), 1.73–1.93 (m, 5 × CH), 2.04–2.15, 2.49–2.58, 2.98–3.03 (3 × m, 3 × CH), 3.69 (heptet, *J* 6.7, CH_3CHCH_3), 6.39 (s, NH), 7.41 (ddd, *J* 8.1, 6.8, 1.5, Q 6-H), 7.65–7.75 (m, Q 7- and 8-H), 8.17 (dd, *J* 8.0, 1.4, Q 5-H); δ_C 20.55 (br), 20.91 (br) (2 × CH_3), 21.34, 26.54 (2 × CH_2), 30.77 [$(CH_3)_2CH$], 38.14 (CH_2), 65.44 (CCH_3), 120.15 (QCC=O), 126.04, 126.52, 127.14, 134.16 (4 × QCH), 146.69 (QCN=C), 163.12, 163.86 (QC=N, QC=O) and 210.26 (NC=O); ν_{max}/cm^{-1} 3300m, 1700m, 1670s and 1610w.

Aziridination of ethyl cyclopentenecarboxylate with 11. To a solution of **11** prepared as described above using **10** (0.24 g) and LTA (0.54 g) in dichloromethane (3 cm^3) at −20 °C, the title ester (0.49 g) was added and the solution allowed to warm to ambient temperature with stirring. After work-up as described above, the product was chromatographed over silica using light petroleum–ethyl acetate (3:1) as eluent to afford the *aziridine* **35** (R_f 0.41) as a colourless solid (250 mg, 63%), mp 108–110 °C (from ethanol) (Found: C, 66.65; H, 6.8; N, 12.2. $C_{19}H_{23}N_3O_3$ requires C, 66.85; H, 6.8; N, 12.3%); δ_H 0.92 (t, *J* 7.1, CH_2CH_3), 1.35, 1.37 (2 × d, *J* 6.7, CH_3CHCH_3), 1.63–1.84, 1.91–2.02, 2.17–2.29, 2.37–2.51 (4 × m, 6 H), 3.34 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.95 (ABX_3, CH_2CH_3), 4.00–4.03 (m, NCH), 7.38 (dd, *J* 8.1, 6.3, 2.0, Q 6-H), 7.60–7.69 (m, Q 7- and 8-H) and 8.17 (ddd, *J* 8.0, 1.4, 0.6, Q 5-H); δ_C 13.41, 19.89, 20.79 (3 × CH_3), 20.90, 27.83, 28.55 (3 × CH_2), 31.16 [$(CH_3)_2CH$], 55.02 (NCH), 59.42 ($CCO_2CH_2CH_3$), 61.51 (CH_2CH_3), 120.96 (QCCO), 125.86, 126.63, 133.20 (3 × QCH), 145.82 (QCN=C), 159.79, 159.92 (QC=N, QC=O) and 166.86 ($CO_2CH_2CH_3$); ν_{max}/cm^{-1} 1720s, 1670s and 1590s.

Ring-opening of the aziridine 35 with hydrochloric acid

The aziridine **35** (170 mg) was dissolved in diethyl ether (10 cm^3) and the solution cooled to 0 °C. Conc. hydrochloric acid (0.1 cm^3) was added to the solution which was then stirred at 0 °C for 3 h, and then diluted with diethyl ether, washed with water, dried and evaporated. Chromatography of the residual oil (Chromatotron) with light petroleum–ethyl acetate (3:1) as eluent afforded the *α-chloro ester* **36** (R_f 0.25) as a colourless oil (90 mg, 48%) (Found: M$^+$, 377.1507. $C_{19}H_{24}ClN_3O_3$ requires M^+, 377.1506); δ_H 1.27–1.38 (m, CH_3CHCH_3, CH_2CH_3), 1.60–1.80 (m, br, CH), 1.87–2.10 (m, 3 × CH), 2.23–2.32 (m, CH), 2.64–2.75 (m, CH), 3.66 [heptet, *J* 6.7, $(CH_3)_2CH$], 4.22–4.39 (m, CH_2CH_3, CHNHQ), 5.95 (d, *J* 5.8, NH), 7.42 (ddd, *J* 8.2, 6.4, 1.9, Q 6-H), 7.67–7.75 (m, Q 7- and 8-H) and 8.20 (ddd, *J* 8.0, 1.5, 0.7, Q 5-H); δ_C 14.01 (CH_3), 21.05 br (2 × CH_3, CH_2, CH), 20.53 (CH_2), 30.36 (CH), 37.73, 62.41 (2 × CH_2), 74.60 (C), 120.53 (QCCO), 126.27, 126.50, 127.26, 134.30 (4 × QCH), 146.93 (QCN=C), 162.07 (QC=N), 163.27 (QCO) and 169.24 ($CO_2CH_2CH_3$); ν_{max}/cm^{-1} (CH_2Cl_2) 3290w, 1740s, br, 1680s and 1595s; *m/z* (%) 377 (M$^+$, 2), 341 (41), 189 (53), 188 (47), 187

(33) and 173 (100). Further elution gave the *β-chloro ester* **36** (R_f 0.18) as a colourless solid (30 mg, 16%), mp 119–121.5 °C (from ethanol) (Found: M^+, 377.1506. $C_{19}H_{24}ClN_3O_3$ requires M^+, 377.1506); δ_H 1.26 (d, *J* 6.8, CH_3CHCH_3), 1.32 (t, *J* 7.2, CH_2CH_3), 1.36 (d, *J* 6.8, CH_3CHCH_3), 2.05–2.19 (m, 3 × CH), 2.39–2.84 (m, 3 × CH), 3.62 [heptet, *J* 6.8, $(CH_3)_2CH$], 4.28–4.67 (m, CH_2CH_3, CHCl), 6.01 (s, NH), 7.41 (ddd, *J* 8.2, 6.8, 1.4, Q 6-H), 7.66–7.75 (m, Q 7- and 8-H) and 8.18 (dd, *J* 7.9, 0.8, Q 5-H); ν_{max}/cm^{-1} (CH_2Cl_2) 3300w, 1735s, 1680s and 1595s; *m/z* (%) 377 (M^+, 24), 306 (33), 304 (100), 268 (91), 203 (56) and 173 (49).

Reconversion of the α-chloro ester 36 into the aziridine 35

Sodium hydride (60% dispersion in oil; 11 mg) was added to anhydrous dimethylformamide (0.5 cm^3), followed by a solution of the α-chloro ester **36** (30 mg) dissolved in dry dimethylformamide (0.5 cm^3); the mixture was stirred at room temp. under nitrogen for 3 h. It was then diluted with water and the bulk of the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with water, dried and evaporated. Crystallisation of the residue gave aziridine **35** (21 mg, 78%) (from ethanol), identical with that used above.

Oxidation of α-QNH-amino ketones with LTA in dichloromethane

Oxidation of 16: ring expansion to the α-acetoxy ester 32. To a solution of **16** (4.28 g) dissolved in dry dichloromethane (43 cm^3), LTA (5.58 g) was added and the mixture stirred overnight. Insoluble lead diacetate was separated and washed with dichloromethane (40 cm^3). The combined dichloromethane solutions were washed with saturated aqueous sodium hydrogen carbonate and then with water, dried and evaporated under reduced pressure. Chromatography of the crude product over silica with light petroleum–ethyl acetate (2:1) as eluent afforded the *α-acetoxy ester* **32** (R_f 0.31) as a colourless oil (2.94 g, 59%) (Found: M^+, 415.1726. $C_{21}H_{25}N_3O_6$ requires M^+, 415.1743); δ_H 0.96 (t, *J* 7.2, CH_2CH_3), 1.24, 1.46 (2 × d, *J* 6.7, CH_3CHCH_3), 1.96–2.09 (m, 1 *H*), 2.11 (s, $OCOCH_3$), 2.23–2.36 (m, 1 *H*), 2.51–2.59 (m, 1 *H*), 2.72–2.88 (m, 2 *H*), 3.17 (ddd, *J* 13.8, 10.1 and 3.5, C*H*), 3.38 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.93 (ABX_3, CH_2CH_3), 7.38 (ddd, *J* 8.0, 6.9 and 1.4, Q 6-H), 7.66 (ddd, *J* 8.2, 1.4 and 0.5, Q 8-H), 7.72 (ddd, *J* 8.2, 6.9 and 1.5, Q 7-H) and 8.13 (ddd, *J* 8.0, 1.5 and 0.5, Q 5-H); δ_C 12.29 (CH_2CH_3), 15.22 ($CH_2CH_2CH_2$), 20.23 (CH_3CHCH_3), 20.48 (CH_3CHCH_3), 21.53 (CH_3CO), 29.46 (CH_2), 30.03 [$(CH_3)_2CH$], 31.48 (CH_2), 61.83 (CH_2CH_3), 92.17 (COAc), 119.97 (QCCO), 125.33, 125.95, 126.28, 133.73 (4 × QCH), 146.00 (QCH=C), 158.96, 162.67, 162.94 (CH_2CON, QC=N, QC=O) and 167.33, 168.06 (CO_2Et, OCOMe).

Oxidation of 21: ring expansion to 38. A solution of **21** (200 mg) and LTA (235 mg) in dry dichloromethane (2 cm^3) was stirred at room temp. for 24 h. Work-up as described above, followed by chromatography of the crude product on silica with light petroleum–ethyl acetate (3:1) as eluent gave unchanged **21** (80 mg) followed by the *isoquinolone* **38** (R_f 0.21) as a colourless solid (60 mg, 50% based on the recovered starting material), mp 262–263.5 °C (from ethanol) (Found: M^+, 389.1376. $C_{22}H_{19}N_3O_4$ requires M^+, 389.1376); δ_H 1.34, 1.35 (2 × d, *J* 6.7, CH_3CHCH_3), 2.87 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.76 (s, OCH_3), 7.41–7.46 (m, ArCH), 7.60 (s, C=CH), 7.65–7.85 (m, 5 × ArCH), 8.21 (dd, *J* 8.0, 1.4, ArCH) and 8.46 (dd, *J* 7.5, 0.4, ArCH); δ_C 21.15, 21.73 (CH_3CHCH_3), 31.51 [$(CH_3)_2CH$], 53.14 (CO_2CH_3), 115.28 (C=CH), 121.00 (QCC=O), 126.69, 127.23, 127.47 (3 × ArCH), 127.98 (C), 128.23 (ArCH), 128.80 (C), 129.10 (ArCH), 129.50 (C), 130.07 (ArCH), 130.50, 130.70 (2 × C), 134.10 (ArCH), 134.29 (C), 135.06 (ArCH), 160.44 (C=O) and 163.16 (C=O); ν_{max}/cm^{-1} 1740s, 1705m, 1685s and 1600s; *m/z* (%) 390 (M + 1, 3), 389 (M^+, 10), 331 (23) and 330 (100).

Oxidation of 25: ring expansion to 39. The ketone **25** (100 mg) and LTA (156 mg) in dichloromethane (2 cm^3) were stirred at room temp. for 12 h. Work-up as described above, followed by chromatography of the product over silica with light petroleum–ethyl acetate (2:1) as eluent gave the *enamido ester* **39** (60 mg, 60%) as a colourless oil (Found: M^+, 297.1475. $C_{17}H_{19}N_3O_2$ requires M^+, 297.1477); δ_H 1.33, 1.39 (2 × d, *J* 6.8, CH_3CHCH_3), 1.70 (d, *J* 1.5, CH_3C=), 2.43–2.50 (m, CH_2), 2.72–2.92 (m, CH_2), 3.03 [heptet, *J* 6.8, $(CH_3)_2CH$], 5.26–5.30 (m, C=CH), 7.47 (ddd, *J* 8.1, 6.9 and 1.5, Q 6-H), 7.74 (dd, *J* 7.3 and 1.5, Q 8-H), 7.79 (ddd, *J* 8.3, 6.9 and 1.5, Q 7-H) and 8.25 (ddd, *J* 8.0, 1.5 and 0.9, Q 5-H); ν_{max}/cm^{-1} (CH_2Cl_2) 1730s, 1715s, 1690s and 1600s.

Oxidation of 27. To a solution of **27** (4.54 g) in dry dichloromethane (33 cm^3) was added LTA (5.69 g) and the solution stirred at room temp. for 3 d. Work-up as described above, followed by chromatography of the crude product over silica with light petroleum–ethyl acetate (3:1) as eluent gave the *benzoxazinone* **40** (0.52 g) as a colourless solid, mp 102–106 °C (from ethanol) (Found: C, 69.45; H, 5.95; N, 7.4. $C_{11}H_{11}NO_2$ requires C, 69.85; H, 5.85; N, 7.4%); δ_H 1.38 [d, *J* 6.9, $(CH_3)_2CH$], 2.94 [heptet, *J* 6.9, $(CH_3)_2CH$], 7.48 (ddd, *J* 8.4, 7.9 and 1.1, Q 6-H), 7.56 (dd, *J* 8.1 and 0.5, Ar 8-H), 7.78 (ddd, *J* 8.1, 7.3 and 1.6, Q 7-H) and 8.17 (ddd, *J* 7.9, 1.5 and 0.4, Q 5-H); ν_{max}/cm^{-1} 1770s, br and 1640s. Futher elution gave unchanged **27** (2.36 g).

Oxidation of 23. A solution of **23** (200 mg) and LTA (230 mg) in dry dichloromethane (2 cm^3) was stirred for 3 d at room temp. Work-up as described above, followed by chromatography of the crude product with light petroleum–ethyl acetate (3:1) as eluent gave the benzoxazinone **40** (20 mg) identical with that isolated above. Further elution gave unchanged starting material **23** (0.1 g).

Oxidation of 31. The ketone **31** (200 mg) was dissolved in dry dichloromethane (2 cm^3) and LTA (297 mg) was added to the solution which was then stirred at room temp. for 12 h. Work-up as described above, followed by chromatography of the crude product gave the benzoxazinone **40** (68 mg) identical with that isolated above and unchanged starting ketone (60 mg).

Oxidation of α-(oxoquinazolinyl)amino ketones with LTA in methanol

Oxidation of 16: ring-cleavage to 41. To **16** (0.381 g) dissolved in dry methanol (3 cm^3) was added LTA (0.50 g) and the solution stirred overnight. The lead diacetate was separated and the bulk of the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (30 cm^3) and the solution washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated under reduced pressure. Chromatography of the residue over silica, using light petroleum–ethyl acetate (3:1) as eluent gave the imino diester **41** (R_f 0.65) as a colourless oil (0.391 g, 95%) as a mixture of imine double bond diastereoisomers (1.83:1); δ_H major diastereoisomer, 1.32 [d, *J* 6.7, $(CH_3)_2CH$], 1.44 (t, *J* 7.1, CH_2CH_3), 1.88–1.98 (m, $CH_2CH_2CH_2$), 2.28–2.33 (m, 2 *H*), 2.46–2.55 (m, 2 *H*), 3.21 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.55 (s, *OMe*), 4.46 (q, *J* 7.1, CH_2CH_3), 7.38–7.48 (m, Q 6-H), 7.67–7.78 (m, Q 7- and 8-H) and 8.25 (dd, *J* 7.5 and 0.6, Q H-5); minor diastereoisomer (observable peaks), 1.11 (t, *J* 7.1, CH_2CH_3), 1.36 [d, *J* 6.7, $(CH_3)_2CH$], 2.10–2.20 (m, $CH_2CH_2CH_2$), 2.93–2.98 (m, 2 *H*), 3.38 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.70 (s, OCH_3), 4.15 (q, *J* 7.1, CH_2CH_3) and 8.18 (dd, *J* 7.5 and 0.6, Q 5-H). Kugelrohr distillation of this product [0.01 mmHg/250 °C (bath temp.)] changed the diastereoisomer ratio to 1:1.8; additional signals from the previously minor component were now visible at δ 2.45–2.55 (m, 2 H), 7.38–7.48

(m, Q 6-H) and 7.69–7.78 (m, Q 7- and 8-H). Further elution gave 2-isopropylquinazolinone **17** (R_f 0.45) as colourless crystals (6 mg, 3%).

Oxidation of 27: ring cleavage to 42 and 43. A solution of **27** (0.33 g) and LTA (0.41 g) in dry methanol (3 cm^3) was stirred overnight. Work-up as described above, followed by chromatography of the crude product with light petroleum–ethyl acetate (4:1) as eluent gave unchanged **27** (0.11 g) and then the *imino diester* **42** (R_f 0.42) (mixture of imine double bond isomers) as an oil (0.08 g, 22%) (Found: M^+, 401.1953. $C_{21}H_{27}N_3O_5$ requires M^+, 401.1951); δ_H(mixture of imine double-bond isomers, 2.44:1) major diastereoisomer: δ_H 1.10 (t, *J* 7.2, CH_2CH_3), 1.36 [d, *J* 6.7, $(CH_3)_2CH$], 1.60–1.62, 1.81–1.83, 2.24–2.29, 2.39–2.43, 2.89–2.93 (5 × m, 8 × CH), 3.37 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.68 (s, OCH_3), 4.15 (q, *J* 7.2, CH_2CH_3), 7.37–7.48 (m, Q 6-H), 7.67–7.78 (m, Q 7- and 8-H) and 8.17 (ddd, *J* 8.0, 1.0 and 0.7, Q 5-H); δ_C 13.95, 20.05 [$(CH_3)_2CH$, CH_2CH_3], 24.22, 24.72, 30.80 (3 × CH_2), 31.57 (CH), 33.18 (CH_2), 51.33 (OCH_3), 62.54 (OCH_2), 120.45 (QCC=O), 126.28, 126.97, 127.25, 134.03 (4 × QCH), 146.67 (QCN=C) and 155.71, 158.99, 162.91, 172.72 and 173.10 (3 × C=O, 2 × C=N); ν_{max}/cm^{-1} (CH_2Cl_2) 1740s, 1680s and 1590s; minor diastereoisomer, δ_H(observable peaks) 1.31 [d, *J* 6.7, $(CH_3)_2CH$], 1.43 (t, *J* 7.2, CH_2CH_3), 3.21 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.61 (s, OCH_3), 4.44 (q, *J* 7.2, CH_2CH_3), 8.26 (ddd, *J* 8.5, 1.3 and 0.8, Q 5-H); δ_C(observable peaks) 13.56, 20.10 [$(CH_3)_2CH$, CH_2CH_3], 24.15, 25.03 (2 × CH_2), 31.78 [$(CH_3)_2CH$]. 33.47, 34.47 (2 × CH_2), 51.38 (OCH_3), 61.83 (OCH_2CH_3), 120.36 (QCCO), 126.00, 126.93, 127.16, 133.87 (4 × OCH), 146.51 (QCN=C), 158.83, 160.21, 168.65, 173.39 (2 × C=O, 2 × C=N). Further elution gave *imino diester* **43** (0.05 g, 15%) (mixture of imine double bond isomers) as an oil (R_f 0.32) (Found: M^+, 387.1795. $C_{20}H_{25}N_3O_5$ requires M^+, 387.1794); ratio of imine double-bond isomers 4:1, major diastereoisomer; δ_H 1.30 [d, *J* 6.7, $(CH_3)_2CH$], 1.56–1.65, 1.79–1.82, 2.24–2.29, 2.41–2.44, 2.87–2.92 (5 × m, 8 × CH), 3.20 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.61, 3.98 (2 × s, OCH_3), 7.38–7.49 (m, Q 6-H), 7.69–7.78 (m, Q-7 and 8-H), 8.26 (dd, *J* 7.9 and 0.8, Q 5-H); δ_C 20.30 (CH_3), 24.43, 24.90, 31.00 (3 × CH_2), 31.73 [$(CH_3)_2CH$], 33.37 (CH_2), 51.53, 53.33 (2 × OCH_3), 120.60 (QCC=O), 126.48, 127.19, 127.43, 134.24 (4 × QCH), 146.84 (QCN=C), 158.89, 159.13, 163.50, 172.61, 173.32 (3 × C=O, 2 × C=N); minor diastereoisomer (observable peaks) δ_H 1.35 [d, *J* 6.7, $(CH_3)_2CH$], 3.38 [heptet, *J* 6.7, $(CH_3)_2CH$], 3.69, 3.71 (2 × s, 2 × OCH_3) and 8.17 (m, Q 5-H); δ_C(observable peaks) 20.22 (CH_3), 24.31, 25.18, 31.09 (3 × CH_2), 32.04 [$(CH_3)_2CH$]. 33.65 (CH_2), 52.81, 53.83 (2 × OCH_3), 126.19, 134.10 (2 × QCH) and 173.59 (C=O).

Oxidation of 25: ring cleavage to 44. The ketone **25** (90 mg) and LTA (140 mg) were stirred in dry methanol (2 cm^3) for 12 h. Work-up described above followed by chromatography of the product over silica with light petroleum–ethyl acetate (2:1) as eluent gave the *imino ester* **44** (R_f 0.13)(mixture of imine double-bond isomers, 5.2:1) as a colourless oil (46 mg, 47%) (Found: M^+, 329.1738. $C_{18}H_{23}N_3O_3$ requires M^+, 329.1739); δ_H major diastereoisomer; 1.25 and 1.35 (2 × d, *J* 7.0, CH_3CHCH_3), 1.85 (s, CH_3C=N), 2.08–2.27, 2.21–2.35, 2.51–2.57, 2.63–2.69 (4 × m, 6 *H*), 3.20 [heptet, *J* 7.0, $(CH_3)_2CH$], 3.69 (s, OCH_3), 7.42 (ddd, *J* 8.2, 7.7 and 1.6, Q 6-H), 7.67–7.74 (m, Q 7- and 8-H) and 8.22 (dd, *J* 8.1 and 0.4, Q 5-H); δ_C 19.32, 19.58, 20.57 (3 × CH_3), 21.02 (CH_2), 31.18 [$(CH_3)_2CH$], 32.84, 37.82 (2 × CH_2), 51.48 (OCH_3), 120.80 (QCCO), 125.90, 126.65, 127.13, 133.57 (4 × QCH), 146.89 (QCN=C), 156.56, 159.27, 173.42, 180.53 (2 × C=N, 2 × C=O); minor diastereoisomer (observable peaks); δ_H 1.25, 1.38 (2 × d, *J* 6.6, CH_3CHCH_3), 2.15–2.20, 2.25–2.32, 2.55–2.60, 2.66–2.72 (4 × m, 8 × CH), 2.35 (s, CH_3C=N), 3.17 [heptet, *J* 6.6, $(CH_3)_2CH$] and 3.56 (s, OCH_3); ν_{max}/cm^{-1} 1730s, 1670s and 1590s.

An authentic sample of **44** was prepared by heating methyl 5-oxohexanoate (0.355 g) and **10** (0.5 g) at 130 °C for 4 h. Chromatography of the product on silica using light petroleum–ethyl acetate (3:1) gave the pure, minor double-bond isomer of **44** isolated above (from NMR comparison) as a colourless solid (486 mg, 59%), mp 49–51 °C (from ethanol).

Conversion of the α-acetoxy ester 32 into 33

The α-acetoxy ester **32** (0.095 g) was Kugelrohr distilled [bp 0.1 mmHg, 250 °C (bath temp.)] and the distillate (0.08 g) which solidified on cooling, was crystallised from ethanol to give *enamide* **33** as a colourless solid, mp 139–140 °C (Found: C, 64.25; H, 6.05; N, 11.75. $C_{19}H_{21}N_3O_4$ requires C, 64.2; H, 5.95; N, 11.85%); δ_H 1.09 (t, *J* 7.1, CH_2CH_3), 1.27, 1.43 (2 × d, *J* 6.7, CH_3CHCH_3), 2.50–2.65 (m, 1 H), 2.77–2.90 (m, 3 H), 3.19 [heptet, *J* 6.7, $(CH_3)_2CH$), 4.05 (ABX_3, CH_2CH_3), 6.75 (m, CH=CN), 7.39 (ddd, *J* 8.1, 6.1 and 2.0, Q 6-H), 7.67–7.75 (m, Q 7- and 8-H), 8.16 (ddd, *J* 8.1, 1.4 and 0.6, Q 5-H); δ_C 13.82 (CH_2CH_3), 20.37 (CH_2), 21.01 (CH_3CHCH_3), 22.19 (CH_3CH-CH_3), 31.10 (CH_2), 31.29 [$(CH_3)_2CH$], 61.55 ($CO_2CH_2CH_3$), 120.83 (QCC=O), 123.00 ($CCO_2CH_2CH_3$), 126.14. 126.76, 127.45 (3 × QCH), 133.05 (CH=CN), 134.55 (QCH), 147.19 (QCN=C), 159.35, 160.07 (QC=N, QC=O) and 163.62 and 168.43 (2 × C=O); ν_{max}/cm^{-1} 1723s, 1693s and 1595s.

Reduction of the enamido ester 33 with Adams' catalyst

The ester **33** (1.0 g) was dissolved in dry ethanol (17 cm^3) and reduced under hydrogen at atmospheric pressure in the presence of Adams' catalyst (platinum oxide) (1.29 g). After separation of the catalyst, the solvent was removed under reduced pressure and the residue chromatographed over silica with light petroleum–ethyl acetate (2:1) as eluent to give one diastereoisomer of the *tetrahydropyridone* **13′** (R_f 0.15) as a colourless oil (0.341 g, 34%) (Found: M^+, 357.1696. $C_{19}H_{23}N_3O_4$ requires M^+, 357.1688); δ_H 1.14 (t, *J* 7.1, CH_2CH_3), 1.26, 1.32 (2 × d, *J* 6.7, CH_3CHCH_3), 1.98–2.27 (m, 3 *H*), 2.45–2.55 (m, 1 *H*), 2.71–2.75 (m, 2 *H*), 3.53 [h, *J* 6.7, $(CH_3)_2CH$], 4.10 (ABX_3, CH_2CH_3), 4.67 (dd, *J* 7.0 and 5.4, $CHCO_2CH_2CH_3$), 7.42 (ddd, *J* 8.0, 4.5 and 1.5, Q 6-H), 7.68 (ddd, *J* 8.2, 4.5 and 1.5, Q 7-H), 7.74 (ddd, *J* 8.2, 1.5 and 0.6, Q 8-H) and 8.2 (ddd, *J* 8.0, 1.5 and 0.6, Q 5-H); δ_C 13.48 (CH_2CH_3), 17.42 (CH_2), 21.32 (CH_3CHCH_3), 21.59 (CH_3CHCH_3), 25.83 (CH_2), 30.60 [$(CH_3)_2CH$], 31.98 (CH_2), 61.80 ($CO_2CH_2CH_3$), 62.56 ($CHCO_2CH_2CH_3$), 121.00 (QCCO), 126.30, 126.86, 127.12, 134.40 (4 × QCH), 146.66 (QCN=C), 159.26, 161.31 (QC=N, QC=O), 167.95, 168.26 (2 × C=O); ν_{max}/cm^{-1} 1732s, 1680s and 1600; *m/z* (%) 357 (M^+, 7), 189 (23), 188 (96), 187 (31), 174 (11), 173 (100) and 160 (40). Further elution gave a second diastereoisomer of the *tetrahydropyridone* **13″** (R_f 0.03) as a colourless oil (0.161 g, 16%) (Found: M^+, 357.1693. $C_{19}H_{23}N_3O_4$ requires M^+, 357.1688); δ_H 1.04 (t, *J* 7.1, CH_2CH_3), 1.28, 1.42 (2 × d, *J* 6.7, CH_3CHCH_3), 1.90–1.97 (m, 1 *H*), 2.19–2.40 (m, 2 *H*), 2.51–2.68 (m, 2 *H*), 2.83–2.95 (m, 2 *H*), 4.07 (ABX_3, CH_2CH_3), 4.18 (dd, *J* 5.8 and 3.3, $CHCO_2CH_2CH_3$), 7.40 (ddd, *J* 8.1, 7.0 and 1.4, Q 6-H), 7.64–7.75 (m, Q 7- and 8-H) and 8.18 (ddd, *J* 8.1, 1.9 and 0.4, Q 8-H); δ_C 13.77 (CH_2CH_3), 18.67 ($CH_2CH_2CH_2$), 21.72, 22.31 (CH_3CHCH_3), 27.35 (CH_2), 30.24 [$(CH_3)_2CH$], 32.26 (CH_2), 61.58 (CH_2CH_3), 63.41 ($CHCO_2CH_2CH_3$), 120.90 (QCC=O), 126.07, 126.62, 127.18, 134.54 (4 × QCH), 147.07 (QCN=C), 159.22, 163.71 (QC=N, QC=O) and 169.81 and 170.20 (2 × C=O); ν_{max}/cm^{-1} 1745s, 1700s and 1600s; *m/z* (%) 357 (M^+, 41), 314 (13), 284 (75), 189 (51), 188 (96), 187 (31), 173 (100) and 160 (48).

Reduction of 33 with samarium diiodide

The enamide ester **33** (230 mg), was dissolved in dry THF (10 cm^3) containing dry *tert*-butyl alcohol (1 cm^3) in a two-necked

flask and the solution purged with argon using a 3-way tap connected to a vacuum pump and an argon supply. A solution of samarium diiodide (0.1 mol dm^{-3} in THF; 14.3 cm^3, 2.2 mol equiv.) was added *via* a syringe through a septum cap at room temp. to the solution which was then stirred for 20 min during which the colour changed from blue to green. The bulk of the solvent was then removed under reduced pressure and the residue dissolved in dichloromethane. This solution was washed with aqueous sodium hydrogen carbonate, dried, and then evaporated. Chromatography of the residue over silica with light petroleum–ethyl acetate (2:1) as eluent gave the *enamido ester* **34** (56 mg), mp 54–55 °C (from ethanol) (Found: M^+, 169.0739. $C_8H_{11}NO_3$ requires M^+, 169.0740); δ_H 1.34 (t, J 7.1, CH_2CH_3), 2.50–2.53 (m, CH_2CH_3), 4.30 (q, J 7.1, CH_2CH_3), 6.26–6.30 (m, C=CH) and 7.57 (s, br, NH); δ_C 14.01 (CH_2CH_3), 20.64, 29.04 (2 × CH_2), 61.68 (CH_2CH_3), 113.78 (C=CH), 128.74 ($CCO_2CH_2CH_3$) and 161.47, 169.43 (2 × C=O); ν_{max}/cm^{-1} (CH_2Cl_2) 3390m, 1685s and 1660; m/z (%) 169 (M^+, 100), 157 (63), 140 (70), 112 (52) and 96 (69). Further elution gave unchanged starting material **33** (60 mg).

X-Ray crystallography

Crystal data for $C_{15}H_{17}N_3O_3$ **9**, M = 287.32, Triclinic, space group $P\bar{1}$, a = 7.738(10), b = 10.462(13), c = 10.260(3) Å, α = 105.6(1), β = 97.56(3), γ = 107.01(1)°, V = 745(2), Z = 2, μ = 0.48 cm^{-1}, λ (Mo-Kα) = 0.7107 Å, $F(000)$ = 304, D_c = 1.28 g cm^{-3}, T = 293 K, crystal dimensions 0.40 × 0.28 × 0.18 mm.

The unit cell parameters were determined by least-squares refinement of omega measurements for different layers. The intensities of 2847 data were measured ($-9 < h < 9$, $-13 < k < 12$, $0 < l < 11$) on a Stoe STADI-2 Weissenberg diffractometer with an omega-scan technique. The data were corrected for Lorentz and polarisation effects to yield 1982 data with $I > 2\sigma(I)$. The structure was solved by direct methods using SHELXS 86.[14] All subsequent calculations were carried out using the computer program SHELX 76.[15] The hydrogen atoms bonded to N-2, C-13, C-15 and C-17 were located on difference Fourier maps and refined as isotropic atoms, all other hydrogen atoms were included in calculated positions (C–H = 0.96 Å). All non-hydrogen atoms were refined with anisotropic displacement parameters.

Final cycles of least-squares refinement used a weighting scheme $w = 1/[\sigma^2(F) + 0.018\ F^2]$ and gave the final residual indices of $R = [\Sigma(|F_o| - |F_c|)/\Sigma|F_o|] = 0.0696$ and $R_w = \{[\Sigma_w(|F_o| - |F_c|)/\Sigma_w|F_o|]\} = 0.0914$. The final residual Fourier map was featureless ($\pm$ 0.3 e $Å^{-3}$). Tables of atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.‡

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‡ For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1.

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