Synthesis of Quinolizidines and Indolizidines *via* an Intramolecular Mannich Reaction[1]

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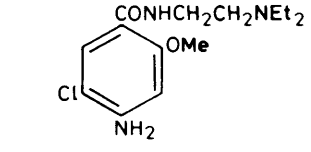
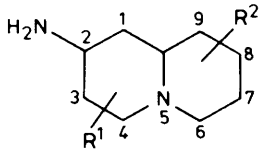
Acid treatment of the addition products (**13**) of an aminopentanal or aminobutanal diethyl acetal and an α,β-unsaturated ketone gave the quinolizidin-2-ones (**11**), (**12**), (**20**), (**36**), and (**37**) and the indolizidin-7-ones (**9**), (**10**), (**16**)—(**19**), (**34**), and (**35**) respectively. The ratios of stereoisomers obtained were rationalised by a consideration of the relative stabilities of the transition states and the effect of steric hindrance in the Mannich cyclisation.

As a part of a chemical programme on benzamides related to the dopamine receptor antagonist and gastric prokinetic agent, metoclopramide (**1**),[2] an efficient and versatile synthesis of alkyl and aryl substituted 2-aminoquinolizidines (**2**) and 7-aminoindolizidines (**3**) was required.

Although the widespread occurrence of both these aza bicycles in nature has stimulated much research into their synthesis,[3] none of the existing methods were readily applicable to compounds possessing all the substitution patterns required for a full structure–activity relationship study. In particular, a synthesis of 4-alkylquinolizidin-2-ones and 5-alkylindolizidin-7-ones was required to investigate the effects of a substituent α-to the bridgehead nitrogen. Of the standard methods tried, neither synthesis of the diester (**4**; R = Me) and subsequent Dieckman cyclisation,[4] nor the borohydride reduction of the imide (**5**; R = Me) and subsequent formic acid cyclisation,[5] gave acceptable yields of the required quinolizidines.



(**1**) Metoclopramide



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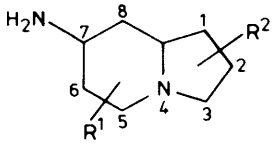

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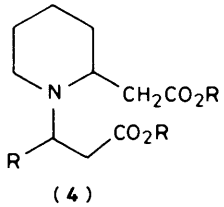
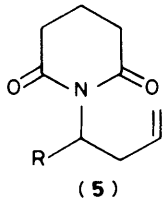


(**4**)

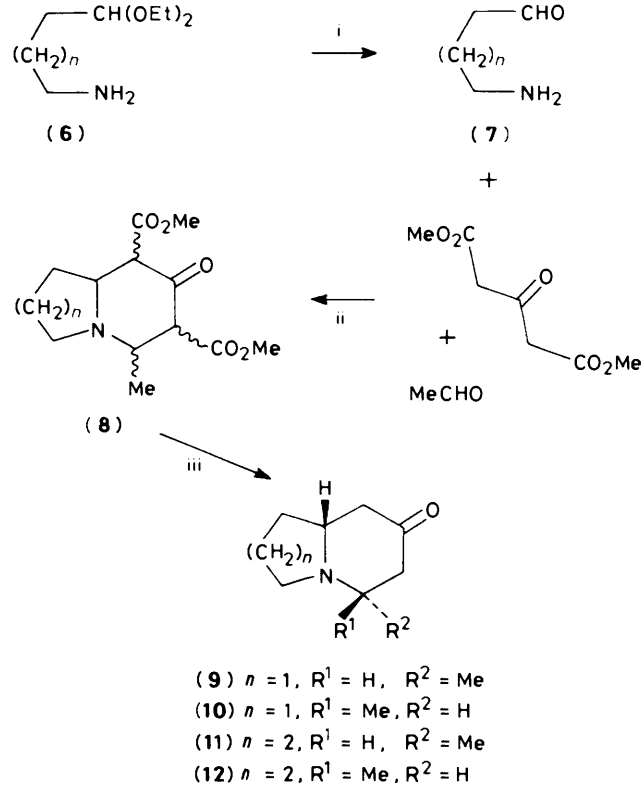


(**5**)

As an alternative, a little used method related to the Robinson–Schöpff tropane synthesis was investigated. By a consideration of the possible mechanism of this, a simpler method was developed which was applied to the synthesis of indolizidines and quinolizidines substituted in either ring.

Results and Discussion

The condensations of 4-aminobutanal and 5-aminopentanal diethyl acetals with dimethyl acetonedicarboxylate and acetaldehyde have been reported to give (**9**) and (**10**),[6] and either (**11**) or (**12**)[7] respectively (Scheme 1). Although the formation of both (**9**) and (**10**) was reported, only one isomer was isolated in a pure form and only one of (**11**) or (**12**) was isolated. In neither case were stereochemical assignments made.



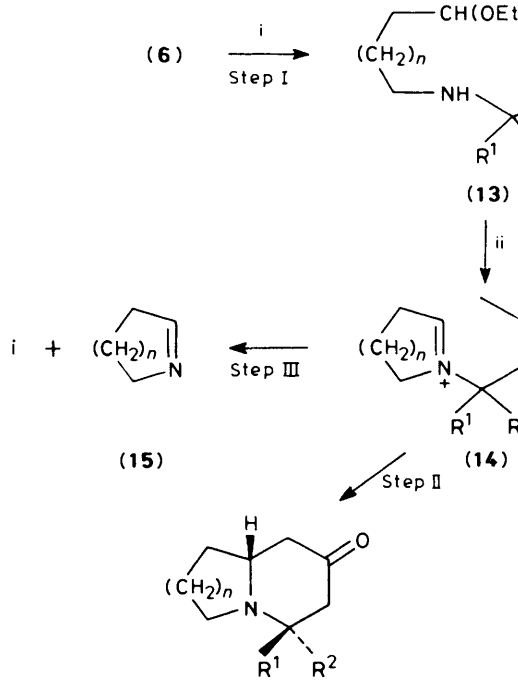
(**9**) *n* = 1, R^1 = H, R^2 = Me
(**10**) *n* = 1, R^1 = Me, R^2 = H
(**11**) *n* = 2, R^1 = H, R^2 = Me
(**12**) *n* = 2, R^1 = Me, R^2 = H

Scheme 1. *Reagents:* i, 2M-HCl; ii, pH 3—4 buffered with NaOAc; iii, 5M-HCl

On repeating the synthesis of (**9**) and (**10**), the two isomers were readily separated by column chromatography to give, in a 3:1 ratio, the less polar (**9**) and the more polar (**10**). Their stereochemistries were assigned by i.r. and n.m.r. spectroscopy. In the i.r. spectrum of (**9**), a prominent band at 2 790 cm^{-1} was indicative of a *trans*-ring fusion.[8] This band was much reduced in intensity in the spectrum of (**10**) which was indicative of an

axial orientation of the methyl substituent.[9] This assignment was confirmed from the chemical shift of the methyl doublets in the ^{1}H n.m.r. spectra. The relative field positions of δ 1.17 for (**9**) and δ 1.04 for (**10**) are consistent with equatorial and axial assignments respectively.[10] Furthermore, an isolated multiplet at δ 3.32 for the 3α-H of (**9**) when compared with overlapping multiplets at δ 3.7—3.0 for (**10**) is again consistent with this assignment.[11] From a comparison of the melting points of the picrate derivatives, it would appear that the pure isomer isolated by Lions and Willison[6] was (**10**).

Whilst repeating this work, great difficulty was encountered in reproducing the reported yields and only poor yields were initially obtained with higher homologues. In addition, the long reaction time, which could not be shortened by raising the reaction temperature, and the necessity for the second hydrolysis/decarboxylation step made it desirable to seek an alternative simpler method. A consideration of the possible mechanisms of this reaction led to an investigation of the method outlined in Scheme 2, which is reminiscent of the proposed biosynthesis of pyrrolizidines.[12]

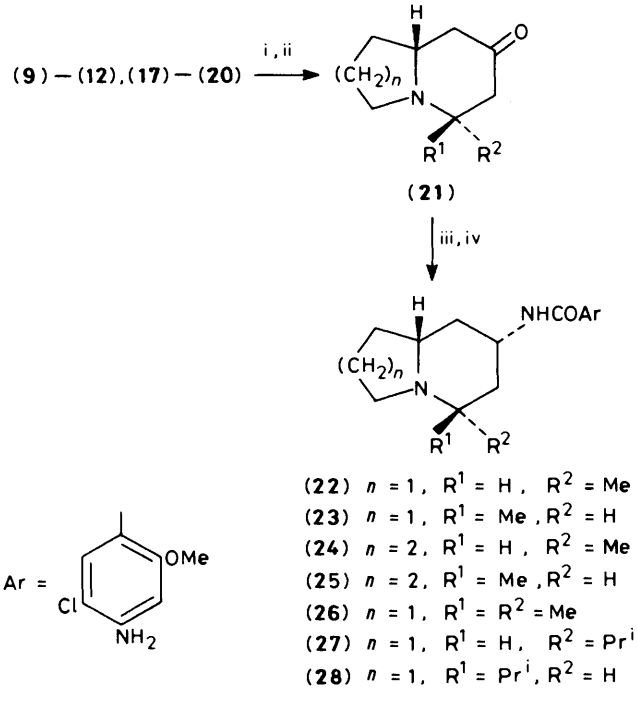


(**9**)	n = 1,	R^1 = H,	R^2 = Me	50%
(**10**)	n = 1,	R^1 = Me,	R^2 = H	15%
(**11**)	n = 2,	R^1 = H,	R^2 = Me	55%
(**12**)	n = 2,	R^1 = Me,	R^2 = H	20%
(**16**)	n = 1,	R^1 = R^2 = H		55%
(**17**)	n = 1,	R^1 = R^2 = Me		60%
(**18**)	n = 1,	R^1 = H,	R^2 = Pr^i	45%
(**19**)	n = 1,	R^1 = Pr^i,	R^2 = H	20%
(**20**)	n = 2,	R^1 = R^2 = H		50%

Scheme 2. *Reagents:* i, R^1R^2C=CHCOMe; ii, 2M-HCl

Although there were an encouraging number of literature precedents for the cyclisation, Step II,[1] in all of these examples the iminium ion and the nucleophile were connected in such a way that a reverse Michael reaction, Step III, was either disfavoured or impossible. Also, the addition of a primary amine to a simple α,β-unsaturated ketone, Step I, had been little explored and it was expected that it might be difficult to control the required selectivity. However, this was achieved by carefully varying the conditions appropriate to the substitution on the olefin. The intermediate amino ketones (**13**) were extracted directly into 2M-HCl, which both hydrolysed the acetal and induced the cyclisation. Scheme 2 summarises the results obtained.

Although t.l.c. indicated that both *trans*-4-phenylbut-3-en-2-one and cyclohex-2-enone gave the initial addition products (**13**), both failed to cyclise on acid treatment. For both the former, where conjugation with the phenyl ring facilitates elimination, and the latter, where the cyclisation is disfavoured for steric reasons, the retro-Michael reaction, Step III, probably predominates. The stereochemistry of (**11**) and (**12**) was assigned by spectroscopic and derivative comparison with the literature.[9] The stereochemistry of (**18**) and (**19**) was determined by spectral comparison with (**9**) and (**10**). In particular, both (**18**) and (**9**) exhibited an isolated one-proton multiplet at δ 3.32 in their n.m.r. spectra for the single equatorial proton at C-5. The ketones (**9**)—(**12**) and (**17**)—(**20**) were subsequently converted separately into the benzamides (**22**)—(**28**).

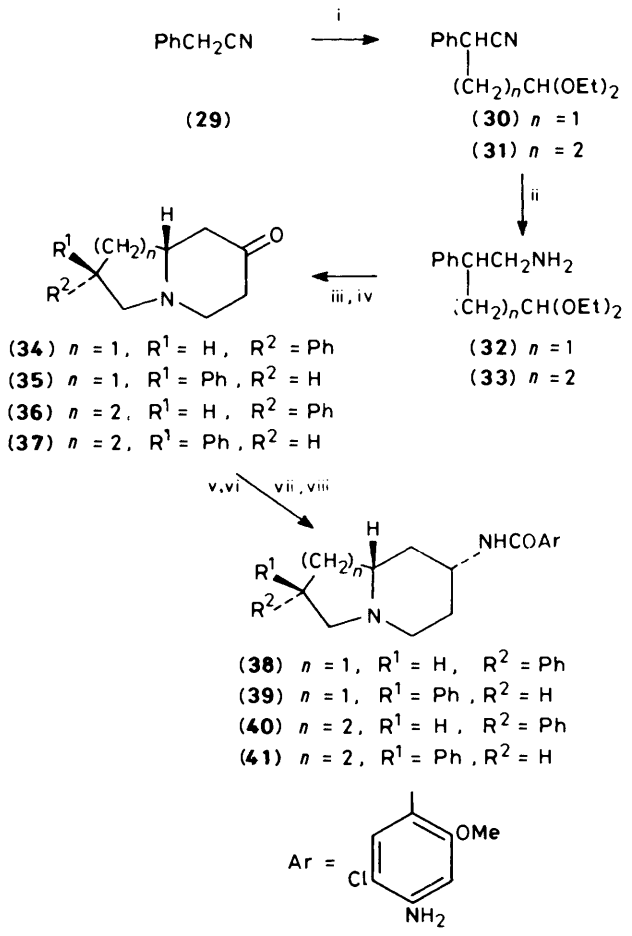


(**22**) n = 1, R^1 = H, R^2 = Me
(**23**) n = 1, R^1 = Me, R^2 = H
(**24**) n = 2, R^1 = H, R^2 = Me
(**25**) n = 2, R^1 = Me, R^2 = H
(**26**) n = 1, R^1 = R^2 = Me
(**27**) n = 1, R^1 = H, R^2 = Pr^i
(**28**) n = 1, R^1 = Pr^i, R^2 = H

Scheme 3. *Reagents:* i, H_2NOH·HCl–pyridine; ii, Na–$C_5H_{11}OH$; iii, Acetylaminoaroyl chloride–Et_3N; iv, OH^-

The 270 MHz n.m.r. spectra of (**22**)—(**28**) unambiguously defined the stereochemistry of the ring substituents. The equatorial assignment of the benzamide was confirmed by the appearance of a broad doublet at δ 7.48—7.71 (J 8 Hz) for the NH coupled to the axial proton at the amide-substituted carbon which appeared as a double triplet of triplets at δ 4.04—4.08 for (**22**), (**24**), and (**27**) and at δ 4.15—4.27 for (**23**), (**25**), (**26**), and (**28**). In addition, (**22**), (**24**), and (**27**) exhibited a one-proton isolated multiplet at δ 3.22, 3.26, and 3.11 respectively for the equatorial proton α- to the bridgehead nitrogen in the amide-substituted ring. In contrast (**23**), (**25**), and (**28**) each exhibited overlapping multiplets corresponding to four protons in the δ 2.5—3.5 region.

Although unsuitable for 5-arylindolizidines and 4-aryl-quinolizidines, it was possible to adapt this method to the



Scheme 4. *Reagents*: i, $BrCH_2CH(OEt)_2$–KBu^tO–Et_2O or $ClCH_2CH_2CH(OEt)_2$–NaH–DMF–Benzene; ii, AlH_3–THF; iii, $H_2C{=}CHCOMe$; iv, 2M-HCl; v, $HONH_2$·HCl–pyridine; vi, Na–$C_5H_{11}OH$; vii, Acetylaminoaroyl chloride–Et_3N; viii, OH^-

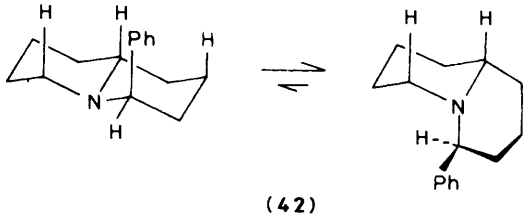
synthesis of the isomers with the aryl substituent in the second ring (Scheme 4). In addition, a patent,[13] and a subsequent paper[14] on the pharmacological activities of some β-phenylquinolizidine derivatives indicated a potential interest in this area.

The cyano acetals (**30**) and (**31**) were prepared by an adaptation of the method of Poulain[16,17] but using potassium t-butoxide for (**30**) and sodium hydride at elevated temperature for (**31**). Reduction of the nitriles with aluminium hydride gave the amines (**32**) and (**33**) respectively. The use of lithium trihydroaluminium chloride in ether gave lower yields of less pure amines. The addition of (**32**) and (**33**) to but-3-en-2-one and cyclisation as before gave, from (**32**), the ketones (**34**) (14%) and (**35**) (46) and from (**33**), the ketones (**36**) (53) and (**37**) (14). Again the isomers were readily separated by column chromatography. However, difficulty was encountered in obtaining analytically pure crystalline derivatives, and from spectral data available at the time, no definitive stereochemical assignment could be made. The ketones were therefore transformed separately into the crystalline benzamides (**38**)—(**41**) by the procedures described for (**22**)—(**28**). It proved necessary to perform the sodium reduction of the oximes as rapidly as possible to prevent a base-catalysed isomerisation at the benzylic position.

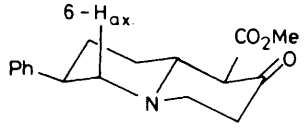
Unfortunately, it was not possible to assign unambiguously the stereochemistry of (**38**) and (**39**) by i.r. and n.m.r. spectroscopy alone. Both compounds had strong bands in their i.r. spectra at 2 800 cm^{-1} and the simple nature of the ^{13}C n.m.r. spectra indicated that they both adopt a *trans*-ring fusion.[10] Owing to the overlapping nature of the ^1H n.m.r. spectra, however, and the low-energy conformational changes in the 5-membered ring, the only definitive assignment was the confirmation of the equatorial orientation of the benzamide group. The orientation of the phenyl group in (**39**) was finally determined by *X*-ray analysis* as 2β. By implication the orientation of the phenyl group in (**38**) must, therefore, be 2α.

However, it was possible to assign the stereochemistry of (**40**) and (**41**) spectroscopically. In the n.m.r. spectrum of (**40**), the multiplicities and chemical shifts of the readily identifiable multiplets were consistent with a *trans* chair-chair conformation. The *trans* fusion was further confirmed by the appearance of bands in the Bohlmann region (2 800—2 700 cm^{-1}) of the i.r. spectrum. From spin-decoupling experiments, the signals at δ 3.12, 3.00, and 2.46 in the n.m.r. spectrum were all mutually coupled. Both the δ 3.12 and 2.46 signals appeared as double doublets with a large (12 Hz) and a small (3.5 Hz) coupling. These signals were assignable to 6-H_{eq} and 6-H_{ax} respectively. The small 3.5 Hz coupling with the signal at δ 3.00 indicates that this 7-H proton must be equatorially orientated, bisecting the 6-H_{eq},6-H_{ax} bond angle. By implication, the phenyl group must, therefore, be axial.

By comparison, the α-phenylquinolizidine (**42**) has been reported to exist predominantly in a *cis*-fused conformation.[17] This is presumably because in the *trans*-fused conformations there is severe steric interaction between the axial phenyl group and the three axial protons (Scheme 5).



(**42**)



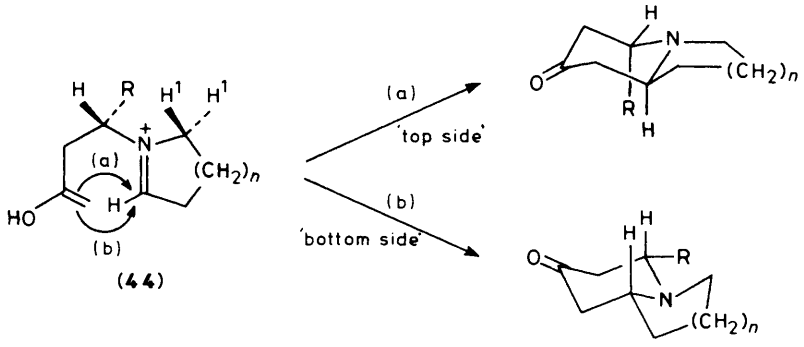
(**43**)

Scheme 5.

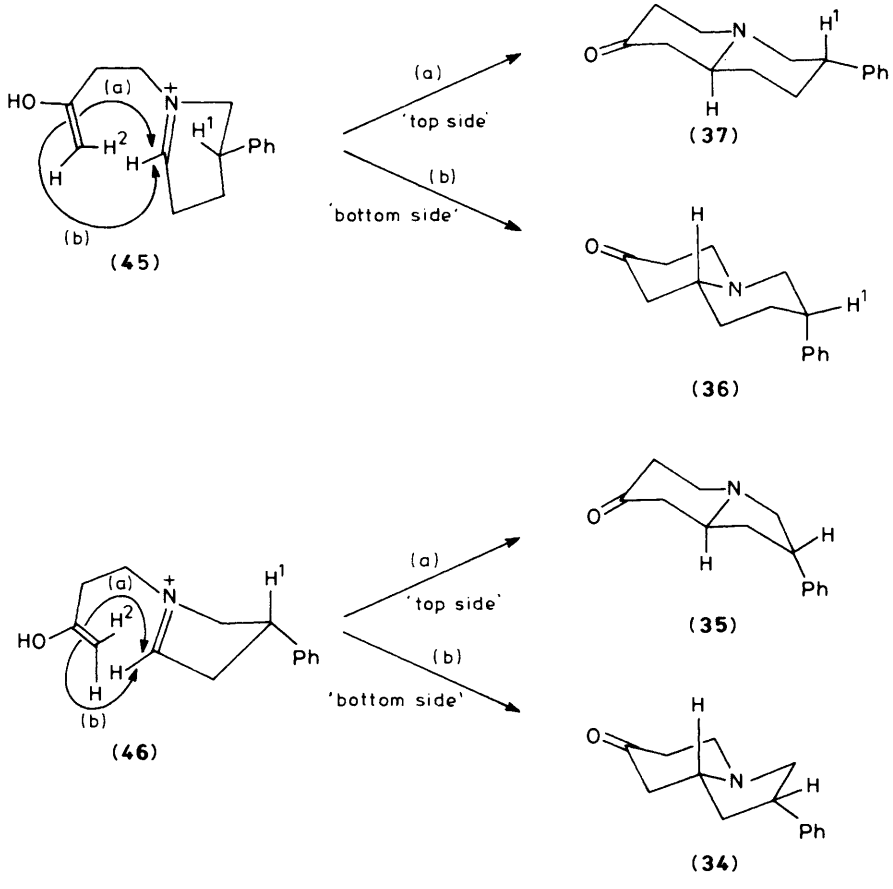
Unfortunately, the n.m.r. spectrum of (**41**) was less well resolved and therefore no conclusive assignment could be made from this alone. However, the appearance of a double triplet of triplets at δ 4.05 confirmed the equatorial orientation of the benzamide at C-2, and by implication the phenyl group at C-7 must be equatorial. Further evidence for this assignment was found from a comparison with the n.m.r. spectrum of methyl 2-oxo-7β-phenylquinolizidine-1β-carboxylate (**43**),[14] in which the 6-H_{ax} proton appeared as a triplet (*J* 11.5 Hz) at δ 2.22. A similar triplet at δ 2.14 (*J* 11.5 Hz) could be identified in the spectrum of (**41**).

From the foregoing results it appears that the preferred mode of cyclisation of the ketone, presumably as its enolate, onto the iminium ion is dependent upon both the ring size and the

* Determined by the late Prof. T. J. King (Nottingham).



Scheme 6.



Scheme 7.

position of substitution. Although it has been shown that (**12**) slowly isomerises on acid treatment at elevated temperatures,[9] neither (**12**), (**34**), nor (**36**) showed any significant isomerisation under the cyclisation conditions used. The product ratios obtained were not, therefore, subject to a thermodynamic equilibration. For substituents α- to the iminium ion nitrogen, the isomer ratio must be determined by whether 'top side' (a) or 'bottom side' (b) (Scheme 6) attack is preferred. In the transition state the substituent R adopts a pseudo-equatorial orientation in (b), and a pseudo-axial orientation in (a) leading to an equatorial and an axial substituted product respectively. The isomer ratio subsequently obtained probably reflects the lower energy of the pseudo-equatorial orientation. Minor differences between the ratios obtained for the 5- and 6-membered ring products could be accounted for by a small increase in steric interaction for the 6-membered ring between the H^1 protons and the substituent R.

Considering the β-phenyl substituted iminium ions (**45**) and (**46**) (Scheme 7), the preferred mode of cyclisation appears to be very different for the different ring sizes. From a study of molecular models, it appears that for (**45**), mode (a) is sterically hindered by the axial proton H^1 interacting with the olefinic proton H^2 and hence the major reaction pathway would appear to be from the same side of the ring as the phenyl group, mode (b). For (**46**) however, this interaction is now much reduced and the phenyl group is much closer to the approaching olefinic proton H^2 in the transition state of mode (b). This reversal of the steric hindrance now results in a preferred approach of the enolate on the opposite side of the ring from the phenyl substituent, mode (a).

Experimental

I.r. spectra were recorded on a Perkin-Elmer 197 spectrophotometer. ^{1}H N.m.r. were recorded in solution in $CDCl_3$ either on a Varian EM 360A (60 MHz) or CFT 20A (79.5 MHz), or a JEOL GX 270 (270 MHz) instrument using $SiMe_4$ as an internal standard. ^{13}C N.m.r. spectra were recorded on a Varian CFT 20A (20.0 MHz) instrument. Accurate mass measurements were recorded on a VG ZAB spectrometer. All evaporations of solvent were carried out under reduced pressure and organic solvents were dried over K_2CO_3 unless specified otherwise. For column chromatography, the silica gel used was Merck Kieselgel 60. Light petroleum refers to the fraction boiling in the range 60—80 °C.

(8aβH)-5α-*Methyloctahydroindolizin-7-one* (**9**) *and* (8aβH)-5β-*Methyloctahydroindolizin-7-one* (**10**).—(a) A solution of 4,4-diethoxybutan-1-amine (8.0 g, 0.05 mol) in EtOH (30 ml) and 2.5M-HCl (20 ml) was allowed to stand at room temperature for 0.5 h. The pH of the solution was then adjusted to *ca.* 3—4 with sodium acetate and dimethyl acetonedicarboxylate (8.7 g, 0.061 mol) and acetaldehyde (3.41 g, 0.077 mol) were added. After 2 days at room temperature, the reaction mixture was concentrated and the residue heated to reflux with 5M-HCl (100 ml) for 4 h. After evaporation, the residue was treated with an excess of saturated aqueous K_2CO_3 and extracted into $CHCl_3$ (3 × 100 ml). After being dried and concentrated, the residue from the $CHCl_3$ extracts was purified by column chromatography. Elution with EtOAc gave initially (**9**) (4.4 g, 57%); $\nu_{max.}$ 2 790 and 1 725 cm^{-1}; δ_H (60 MHz; 20 °C) 1.17 (3 H, d, *J* 6 Hz, 5α-Me and 3.32 (1 H, m, 3α-H); picrate, m.p. 179 °C (from EtOH) (Found: C, 47.2; H, 4.5; N, 14.6. $C_{15}H_{18}N_4O_8$ requires C, 47.1; H, 4.7; N, 14.7%). Further elution gave (**10**) (1.4 g, 18%); $\nu_{max.}$ 2 810 and 1 720 cm^{-1}; δ_H (60 MHz, 20 °C) 1.04 (3 H, d, *J* 7 Hz, 5β-Me); picrate, m.p. 191 °C (from EtOH) (Found: C, 47.2; H, 4.5; N, 14.7. $C_{15}H_{18}N_4O_8$ requires C, 47.1; H, 4.7; N, 14.7%).

(b) A solution of 4,4-diethoxybutan-1-amine (3.2 g, 0.02 mol) and pent-3-en-2-one (3.3 g, 0.04 mol) in Et_2O (10 ml) was stirred at room temperature until the addition reaction was complete by t.l.c. (*ca.* 1 h). The amine was extracted into 2.5M-HCl (50 ml). The acidic extract was then heated on a steam-bath for 2 h. Isolation as described in (a) gave (**9**) (1.8 g, 60%) and (**10**) (0.45 g, 15%).

(9aβH)-4α-*Methyloctahydro*-2H-*quinolizin*-2-*one* (**11**) *and* (9aβH)-4β-*Methyloctahydro*-2H-*quinolizin*-2-*one* (**12**).—Following the procedure (b) outlined for (**9**) and (**10**), 5,5-diethoxypentan-1-amine (3.5 g, 0.02 mol) was converted into a mixture of ketones. Separation of the isomers by column chromatography gave, on elution with Et_2O, (**11**) (1.9 g, 55%); $\nu_{max.}$ 2 790, 2 750, and 1 720 cm^{-1}; δ_H (60 MHz) 1.18 (3 H, d, *J* 6 Hz, 4α-Me) and 3.32 (1 H, m, 6-αH). Further elution gave (**12**) (0.7 g, 20%); $\nu_{max.}$ 2 810 and 1 715 cm^{-1}; δ_H (60 MHz) 0.97 (3 H, d, *J* 7 Hz, 4β-Me); picrate, m.p. 190 °C (from EtOH) (lit.,[7] 190—192 °C).

Octahydroindolizin-7-one (**16**).—To a stirred solution of 4,4-diethoxybutan-1-amine (3.2 g, 0.02 mol) in Et_2O (10 ml) at 0 °C was added freshly distilled but-3-en-2-one (1.8 g, 0.025 mol) dropwise and the reaction mixture was maintained at 0 °C for 1 h. Cyclisation as described before and purification by distillation afforded (**16**) (1.5 g, 55%), b.p. 60—63 °C/1 mmHg (lit.,[15] 104—105 °C/18 mmHg).

4,4-*Dimethyloctahydroindolizin-7-one* (**17**).—A mixture of 4,4-diethoxybutan-1-amine (3.2 g, 0.02 mol) and 4-methylpent-3-en-2-one (10 ml) was stirred at room temperature for 1 h. The amine was extracted into 2.5M-HCl (50 ml), and the solution washed with Et_2O (2 × 50 ml) and heated on a steam-bath for 2 h. Isolation by the standard procedure and distillation gave (**17**) (2.0 g, 60%), b.p. 65 °C/1 mmHg; $\nu_{max.}$ 2 820 and 1 720 cm^{-1}; δ_H (79.5 MHz, 35 °C) 0.95 (3 H, s, 4-Me) and 1.25 (3 H, s, 4-Me): picrate, m.p. 179 °C (from EtOH) (Found: C, 48.6; H, 5.0; N, 14.2%. $C_{16}H_{20}N_4O_8$ requires C, 48.5; H, 5.1; N, 14.1%).

(8aβH)-5α-*Isopropyloctahydroindolizin-7-one* (**18**) *and* (8aβH)-5β-*Isopropyloctahydroindolizin-7-one* (**19**).—Following the standard procedure, 4,4-diethoxybutan-1-amine (4.8 g, 0.04 mol) was treated with 5-methylhex-3-en-2-one (10 ml) in Et_2O (10 ml) for 1 h and cyclised in 2.5M-HCl (100 ml). Separation of the isomers by column chromatography gave, on elution with Et_2O–light petroleum (1:1), (**18**) (3.3 g, 45%); δ_H (60 MHz) 0.87 (3 H, d, *J* 7 Hz, 5-CHCH_3), 0.94 (3 H, d, *J* 7 Hz, 5-CHCH_3), and 3.32 (1 H, m, 3α-H); picrate, m.p. 169 °C (from EtOH) (Found: C, 49.8; H, 5.2; N, 13.6. $C_{17}H_{22}N_4O_8$ requires C, 49.8; H, 5.4; N, 13.7%). Further elution with Et_2O gave (**19**) (1.4 g, 20%); δ_H (60 MHz) 0.90 (3 H, d, *J* 7 Hz, 5-CHCH_3) and 0.93 (3 H, d, *J* 7 Hz, 5-CHCH_3); picrate, m.p. 171 °C (from EtOH) (Found: C, 49.8; H, 5.3; N, 13.5. $C_{17}H_{22}N_4O_8$ requires C, 49.8; H, 5.4; N, 13.7%).

Octahydro-2H-*quinolizin*-2-*one* (**20**).—Following the procedure described for (**16**); 5,5-diethoxypentan-1-amine (3.5 g, 0.02 mol) was converted into (**20**) (1.5 g, 50%), b.p. 75 °C/1 mmHg (lit.,[6] 74—76 °C/1 mmHg).

General Procedure for the Benzamides (**22**)—(**28**).—A solution of the appropriate ketone (**9**)—(**12**), (**17**)—(**19**) (0.02 mol), hydroxylamine hydrochloride (2.8 g, 0.04 mol), and pyridine (3 ml) in EtOH (50 ml) was heated under reflux for 1 h. The solution was concentrated and the residue treated with EtOAc (100 ml) and 2.5M-NaOH (15 ml). The organic layer was separated, dried, and evaporated to give the crude oximes (*ca.* 0.02 mol). An efficiently stirred solution of the crude oxime (0.02 mol) in pentyl alcohol (100 ml) was heated to reflux and the heat source removed. Sodium (5.5 g, 0.24 mol) was then added at such a rate as to maintain vigorous reflux, after which heating was maintained until all the sodium had dissolved. On being cooled, the reaction mixture was treated with 5M-HCl (140 ml) and washed with EtOAc (3 × 100 ml). The aqueous phase was then saturated with an excess of solid K_2CO_3 and the amine extracted into CH_2Cl_2 (3 × 100 ml). The organic extracts were dried and concentrated to give the crude diamines (*ca.* 0.015 mol). To a solution of the crude diamine (0.01 mol) in CH_2Cl_2 (100 ml) and Et_3N (4 ml) was added a solution of 4-acetylamino-5-chloro-2-methoxybenzoyl chloride [prepared *in situ* from the acid (2.43 g, 0.01 mol), oxalyl chloride (1.27 g, 0.01 mol) in CH_2Cl_2 (100 ml), and 5 drops of DMF at room temperature for 1 h], and the mixture stirred at room temperature for 2 h. The reaction mixture was then washed with 2.5M-NaOH (10 ml) and dried. After evaporation of the solvent, the residue was heated to reflux with 2.5M-NaOH (8 ml) in EtOH (50 ml) for 2 h. After concentration of the reaction mixture, the residue was extracted into $CHCl_3$ (3 × 50 ml) and dried. Evaporation gave the crude benzamides which were purified by column chromatography and/or recrystallisation as appropriate.

(5α,7α,8aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-5-*methylindolizin*-7-*yl*)*benzamide* (**22**). From (**9**) (3.0 g, 0.02 mol) purification by column chromatography on alumina (Basic, Brockman Grade II) and elution with $CHCl_3$ gave (**22**) (2.2 g, 32%), m.p. 175—176 °C (EtOAc–light petroleum) (Found: C, 60.3; H, 7.1; Cl, 10.5; N, 12.2. $C_{17}H_{24}ClN_3O_2$ requires C, 60.4; H, 7.2; Cl, 10.5; N, 12.4%); δ_H (270 MHz) 8.07 (1 H, s, 6′-H), 7.56 (1 H, d, *J* 8 Hz, CONH), 6.28 (1 H, s, 3′-H), 4.38 (2 H, br s, NH_2), 4.08 (1 H, dtt, *J* 8, 4.5, 12 Hz, 7β-H), 3.85 (3 H, s, OCH_3), 3.22 (1 H, dt, *J* 2, 9 Hz, 3α-H), 2.28—2.16 (2 H, m), 2.15—1.60 (7 H, m),

1.43 (1 H, dq, *J* 7, 11 Hz), 1.22 (1 H, q, *J* 12 Hz), and 1.14 (3 H, d, *J* 6 Hz, 5α-CH_3).

(5β,7α,8aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-5-*methylindolizin*-7-*yl*)*benzamide* (**23**). From (**10**) (1.5 g, 0.01 mol) purification by column chromatography on alumina (Basic, Brockman Grade II), elution with $CHCl_3$, gave (**23**) (1.5 g, 45%), m.p. 164—166 °C (EtOAc–light petroleum) (Found: C, 60.6; H, 7.5; N, 12.4%. $C_{17}H_{24}ClN_3O_2$ requires C, 60.4; H, 7.2; N, 12.4%); δ_H (270 MHz) 8.08 (1 H, s, 6′-H), 7.53 (1 H, d, *J* 8 Hz, CONH), 6.27 (1 H, s, 3′-H), 4.40 (2 H, br s, NH_2), 4.27 (1 H, dtt, *J* 8, 4, 12 Hz, 7β-H), 3.84 (3 H, s, OCH_3), 3.41 (1 H. ddq, *J* 2, 5, 7 Hz, 5α-H), 2.81 (1 H, dt, *J* 3, 8 Hz, 3α-H), 2.68—2.50 (2 H, m), 2.22 (1 H, dtt, *J* 4, 2, 12 Hz), 1.96—1.62 (5 H, m), 1.44—1.26 (1 H, m), 1.18 (3 H, d, *J* 7 Hz, 5β-CH_3), and 1.16 (1 H, q, *J* 12 Hz).

(2α,4α,9aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-4-*methyl*-2H-*quinolizin*-2-*yl*)*benzamide* (**24**). From (**11**) (1.7 g, 0.01 mol) was obtained (**24**) (1.5 g, 42%), m.p. 184—188 °C (EtOAc–light petroleum) (Found: C, 61.6; H, 7.6; Cl, 10.1; N, 11.9. $C_{18}H_{26}ClN_3O_2$ requires C, 61.4; H, 7.4; Cl, 10.1; N, 11.9%); δ_H (270 MHz) 8.07 (1 H, s, 6′-H), 7.52 (1 H, d, *J* 8 Hz, CONH), 6.28 (1 H, s, 3′-H), 4.43 (2 H, br s, NH_2), 4.04 (1 H, dtt, *J* 8, 4, 13 Hz, 2β-H), 3.84 (3 H, s, OCH_3), 3.26 (1 H, dm, *J* 12 Hz, 6α-H), 2.16 (1 H, ddq, *J* 2, 6, 10 Hz), 2.08—1.88 (3 H, m), 1.80—1.46 (5 H, m), 1.42—1.20 (4 H, m), and 1.13 (3 H, d, *J* 6 Hz, 4α-CH_3).

(2α,4β,9aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-4-*methyl*-2H-*quinolizin*-2-*yl*)*benzamide* (**25**). From (**12**) (1.7 g, 0.01 mol) was obtained (**25**) (2.0 g, 57%), m.p. 180—182 °C (EtOAc–light petroleum) (Found: C, 61.1; H, 7.4; Cl, 10.2; N, 11.4%; M^+, 351.1720. $C_{18}H_{26}ClN_3O_2$ requires C, 61.4; H, 7.4; Cl, 10.1; N, 11.9%; M^+, 351.1713); δ_H (270 MHz) 8.10 (1 H, s, 6′-H), 7.71 (1 H, d, *J* 8 Hz, CONH), 6.29 (1 H, s, 3′-H), 4.41 (2 H, br s, NH_2), 4.26 (1 H, dtt, *J* 8, 4, 13 Hz, 2β-H), 3.86 (3 H, s, OCH_3), 3.16 (1 H, ddq, *J* 4, 6, 7 Hz, 4α-H), 3.08 (1 H, dm, *J* 14 Hz, 6α-H), 2.88—2.82 (1 H, m), 2.62 (1 H, dt, *J* 2, 12 Hz), 2.11 (1 H, dt, *J* 13, 4 Hz), 1.90—1.22 (9 H, m), and 1.12 (3 H, d, *J* 6 Hz, 4β-CH_3).

(7α,8aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-5,5-*dimethylindolizin*-7-*yl*)*benzamide* (**26**). From (**17**) (1.7 g, 0.01 mol) was obtained (**26**) (1.6 g, 46%), m.p. 112—115 °C (EtOAc–light petroleum) (Found: C, 61.0; H, 7.4; Cl, 9.9; N, 11.7%; M^+, 351.1702. $C_{18}H_{26}ClN_3O_2$ requires C, 61.4; H, 7.4; Cl, 10.1; N, 11.9%; M^+, 351.1714); δ_H (79.5 MHz) 8.08 (1 H, s, 6′-H), 7.50 (1 H, d, *J* 8 Hz, CONH), 6.28 (1 H, s, 3′-H), 4.40 (2 H, br s, NH_2), 4.27 (1 H, dtt, *J* 8, 4, 12 Hz, 7β-H), 3.84 (3 H, s, OCH_3), 3.1—2.8 (1 H, m, 3α-H), and 2.7—1.8 (16 H, m, including 1.18, 3 H, s, and 1.04, 3 H, s, both 5-CH_3).

(5α,7α,8aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-5-*isopropylindolizin*-7-*yl*)*benzamide* (**27**). From (**18**) (1.8 g, 0.01 mol) purification by column chromatography and elution with EtOAc gave (**27**) (1.6 g, 44%), m.p. 174—176 °C (EtOAc–light petroleum) (Found: C, 62.3; H, 7.9; Cl, 9.8; N, 11.6. $C_{19}H_{28}ClN_3O_2$ requires C, 62.4; H, 7.7; Cl, 9.7; N, 11.5%); δ_H (270 MHz) 8.10 (1 H, s, 6′-H), 7.55 (1 H, d, *J* 8 Hz, CONH), 6.28 (1 H, s, 3′-H), 4.40 (2 H, br s, NH_2), 4.08 (1 H, dtt, *J* 8, 4, 12 Hz, 7β-H), 3.86 (3 H, s, OCH_3), 3.11 (1 H, dt, *J* 2.5, 8.5 Hz, 3α-H), 2.18 (1 H, dm, *J* 12 Hz), 2.12—1.36 (10 H, m), 1.13 (1 H, q, *J* 11 Hz), and 0.90 [6 H, d, *J* 6 Hz, 5α-$CH(CH_3)_2$].

(5β,7α,8aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-5-*isopropylindolizin*-7-*yl*)*benzamide* (**28**). From (**19**) (1.8 g, 0.01 mol) purification by column chromatography and elution with EtOAc–5% MeOH gave (**28**) (1.0 g, 28%), m.p. 153—155 °C (EtOAc–light petroleum) (Found: C, 62.3; H, 7.7; Cl, 9.7; N, 11.3. $C_{19}H_{28}ClN_3O_2$ requires C, 62.4; H, 7.7; Cl, 9.7; N, 11.5%); δ_H (270 MHz) 8.11 (1 H, s, 6′-H), 7.48 (H, d, *J* 8 Hz, CONH), 6.28 (1 H, s, 3′-H), 4.37 (2 H, br s, NH_2), 4.15 (1 H, dtt, *J* 8.5, 12 Hz, 7β-H), 3.88 (3 H, s, OCH_3), 3.24—3.12 (1 H, m, 5α-H), 2.94—2.80 (2 H, m), 2.58—2.48 (1 H, m), 2.08—1.88 (3 H, m), and 0.97—0.95 [6 H, 2 d, *J* 7 Hz, 5β-$CH(CH_3)_2$].

α-(2,2-*Diethoxyethyl*)*benzyl Cyanide* (**30**).—Potassium t-butoxide (12.3 g, 0.11 mol) was added to a stirred solution of benzyl cyanide (11.7 g, 0.1 mol) and bromoacetaldehyde diethyl acetal (20.7 g, 0.1 mol) in dry Et_2O (200 ml). After the reaction mixture had been stirred at room temperature for 2 days, water (10 ml) was carefully added with cooling and the Et_2O layer was separated, dried ($MgSO_4$), and concentrated. Distillation of the residue gave (**30**) (17.8 g, 75%), b.p. 125—129 °C/1 mmHg (lit.,[15] 134—137 °C/2 mmHg); δ_H (60 MHz) 7.23 (5 H, s), 4.46 (1 H, t, *J* 6 Hz), 3.9—3.2 (5 H, m), 2.09 (2 H, dd, *J* 6, 8 Hz), and 1.2 (6 H, br t, *J* 7 Hz).

α-(3,3-*Diethoxypropyl*)*benzyl Cyanide* (**31**).—Benzyl cyanide (18 g, 0.15 mol) was added to a stirred suspension of sodium hydride (4.8 g, 0.2 mol) in DMF (200 ml) at 70 °C under nitrogen. The mixture was stirred at 70 °C for 1 h, after which 3-chloropropionaldehyde diethyl acetal (26 g, 0.15 mol) was added and the reaction mixture was stirred at 70 °C for a further 1 h. On cooling, the reaction mixture was poured into 1 l of ice–water and the product was extracted into Et_2O (3 × 200 ml). The Et_2O extracts were dried ($MgSO_4$) and concentrated. Distillation of the residue gave (**31**) (30 g, 80%), b.p. 145 °C/1 mmHg (lit.,[16] 140 °C/2 mmHg); δ_H (60 MHz) 7.23 (5 H, s), 4.39 (1 H, t, *J* 5 Hz), 4.0—3.2 (5 H, m), 2.0—1.5 (4 H, m), and 1.15 (6 H, t, *J* 7 Hz).

4,4-*Diethoxy*-2-*phenylbutan*-1-*amine* (**32**).—Concentrated sulphuric acid (4 ml, 0.075 mol) was added, dropwise, to a stirred suspension of $LiAlH_4$ (6 g, 0.16 mol) in dry THF (300 ml) at 0 °C under nitrogen. After the mixture had been stirred at 0 °C for 1 h, a solution of (**30**) (44 g, 0.19 mol) in THF (50 ml) was added over a period of 30 min and the reaction mixture stirred at room temperature for 5 h. On being cooled to 0 °C, the reaction mixture was treated with 1M-NaOH (30 ml). After removal of the precipitate by filtration, the filtrate was concentrated and distilled to give (**32**) (38 g, 85%), b.p. 110—115 °C/0.1 mmHg; δ_H (60 MHz) 7.10 (5 H, s), 4.17 (1 H, dd, *J* 4, 6 Hz), 3.7—3.1 (4 H, m), 3.0—2.6 (3 H, m), 2.1—1.7 (2 H, m), 1.13 (3 H, t, *J* 7 Hz), 1.06 (3 H, t, *J* 7 Hz), and 0.93 (2 H, s).

5,5-*Diethoxy*-2-*phenylpentan*-1-*amine* (**33**).—Following the procedure described for compound (**32**), (**31**) (50 g, 0.2 mol) was reduced to (**33**) (42 g, 83%), b.p. 125—130 °C/0.1 mmHg; δ_H (60 MHz) 7.13 (5 H, br s), 4.30 (1 H, t, *J* 5 Hz), 3.7—3.1 (4 H, m), 2.9—2.3 (3 H, m), 1.8—1.3 (4 H, m), 1.11 (6 H, t, *J* 7 Hz), and 0.95 (2 H, s).

(2α,7α,8aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-2-*phenylindolizin*-7-*yl*)*benzamide* (**38**) *and* (2β,7α,8aβ)-4-*amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-2-*phenylindolizin*-7-*yl*)*benzamide* (**39**).—Following the procedure described for compound (**10**), (**32**) (2.4 g, 0.01 mol) was treated with but-3-en-2-one (0.84 g, 0.012 mol) and cyclised to give a mixture of ketones. Separation by column chromatography, and elution with Et_2O gave: (i) (**34**) (0.3 g, 14%); $\nu_{max.}$ 2 800 and 1 720 cm^{-1}; δ_H (79.5 MHz) 7.5—7.1 (5 H, m), 3.6—3.0 (3 H, m), 2.9—2.1 (8 H, m), and 1.9—1.4 (1 H, m); δ_C (20 MHz) 208.8, 147.1, 128.5, 127.1, 126.1, 64.6, 61.1, 50.2, 47.3, 42.8, 42.7, and 40.7; *m/z* 215 (M^+).

Conversion into the oxime, amine, aroylation, and de-acetylation as described in the general procedure gave, after column chromatography and elution with EtOAc, (**38**) (0.2 g, 35%), m.p. 167—170 °C (EtOAc–light petroleum) (Found: C, 65.8; H, 6.5; Cl, 8.9; N, 10.4. $C_{22}H_{26}ClN_3O_2$ requires C, 66.1; H, 6.6; Cl, 8.9; N, 10.5%); δ_H (79.5 MHz), 8.09 (1 H, s, 6′-H), 7.61 (1 H, d, *J* 8 Hz, CONH), 7.45—7.10 (5 H, m), 6.29 (1 H, s, 3′-H), 4.47 (2 H, br s, NH_2), 3.98 (1 H, dtt, *J* 8, 4, 12 Hz, 7β-H), 3.85 (3 H, s, OCH_3), 3.5—2.9 (3 H, m), 2.62 (1 H, t, *J* 10 Hz), 2.45—1.9 (5 H, m), and 1.9—1.0 (3 H, m).

(ii) Further elution with Et_2O–EtOAc (4:1) gave (**35**) (1.0 g, 46%), $\nu_{max.}$ 2 800 and 1 720 cm^{-1}; δ_H (79.5 MHz), 7.5—7.1 (5 H, m), 3.75—3.2 (3 H, m), and 2.8—1.9 (9 H, m); δ_C (20 MHz), 208.1, 144.6, 128.5, 127.3, 126.3, 64.4, 62.4, 50.0, 47.3, 42.7, 40.5, and 40.3; *m/z* 215 (M^+). Conversion into the benzamide as described in the general procedure gave, after column chromatography and elution with EtOAc–5% MeOH, (**39**) (0.85 g, 45%), m.p. 186—187 °C (EtOAc–light petroleum) (Found: C, 65.6; H, 6.7; Cl, 8.8; N, 10.3; M^+, 399.1709. $C_{22}H_{26}ClN_3O_2$ requires C, 66.1; H, 6.6; Cl, 8.9; N, 10.5; M^+, 399.1713); δ_H [270 MHz, $(CD_3)_2SO$)] 7.70 (1 H, d, *J* 8 Hz, CONH), 7.67 (1 H, s, 6′-H), 7.33—7.21 (4 H, m), 7.21—7.12 (1 H, m), 6.48 (1 H, s, 3′-H), 5.93 (2 H, br s, NH_2), 3.84—3.76 (4 H, m, 7β-H including 3.84, 3 H, s, OCH_3), 3.4—3.2 (2 H, m), 3.03 (1 H, dm, *J* 10 Hz), 2.32 (1 H, q, *J* 9 Hz), 2.18—2.0 (2 H, m), 1.98—1.80 (2 H, m), 1.52 (1 H, dq, *J* 4, 12 Hz), and 1.26 (1 H, q, *J* 12 Hz).

(2α,7α,9aβ)-4-*Amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-7-*phenyl*-2H-*quinolizin*-2-*yl*)*benzamide* (**40**) *and* (2α,7β,9aβ)-4-*amino*-5-*chloro*-2-*methoxy*-N-(*octahydro*-7-*phenyl*-2H-*quinolizin*-2-*yl*)*benzamide* (**41**).—Following the procedure described for (**38**) and (**39**), (**33**) (2.5 g, 0.01 mol) was treated with but-3-en-2-one (0.84 g, 0.012 mol) and cyclised to give a mixture of ketones. Column chromatography and elution with Et_2O gave the following. (i) (**36**) (1.2 g, 53%), $\nu_{max.}$ 2 810, 2 760, and 1 720 cm^{-1}; *m/z* 229 (M^+). Conversion into the benzamide as described in the general procedure gave, after column chromatography and elution with EtOAc (**40**) (0.98 g, 45%), m.p. 204—205 °C (EtOAc–light petroleum) (Found: C, 66.9; H, 6.8; Cl, 8.6; N, 10.2. $C_{23}H_{28}ClN_3O_2$ requires C, 66.7; H, 6.8; Cl, 8.6; N, 10.2%); δ_H (270 MHz) 8.10 (1 H, s, 6′-H), 7.60 (2 H, d, *J* 7 Hz), 7.55 (H, dm, *J* 8 Hz, CONH), 7.28 (2 H, tm, *J* 7 Hz), 7.17 (1 H, tm, *J* 7 Hz), 6.28 (1 H, s, 3′-H), 4.40 (2 H, br s, NH_2), 4.04 (1 H, dtt, *J* 8, 4, and 12 Hz, 2β-H), 3.87 (3 H, s, OCH_3), 3.12 (1 H, dd, *J* 2, 12 Hz, 6α-H), 3.01 (1 H, quin, *J* 3 Hz, 7β-H), 2.86 (1 H, ddd, *J* 3, 3.5, 12 Hz, 4α-H), 2.46 (1 H, dd, *J* 4, 12 Hz, 6β-H), 2.20 (1 H, dt, *J* 2, 12 Hz, 4β-H), 2.10—1.96 (2 H, m), 1.96—1.86 (1 H, dm, *J* 12 Hz, 1β-H), 1.56 (1 H, dq, *J* 4, 12 Hz, 3β-H), 1.44—1.36 (2 H, m), and 1.26 (1 H, q, *J* 12 Hz, 1α-H).

(ii) Further elution gave (**37**) (0.32 g, 14%); $\nu_{max.}$ 2 810, 2 770, and 1 720 cm^{-1}; *m/z* 229 (M^+). Conversion into the benzamide as described in the general procedure gave, after column chromatography and elution with EtOAc, (**41**) (0.29 g, 50%), m.p. 221—222 °C (EtOAc–light petroleum) (Found: C, 66.6; H, 6.9; Cl, 8.5; N, 10.4. $C_{23}H_{26}ClN_3O_2$ requires C, 66.7; H, 6.8; Cl, 8.6; N, 10.2%); δ_H (270 MHz) 8.10 (1 H, s, 6′-H), 7.58 (1 H, d, *J* 8 Hz, CONH), 7.35—7.15 (5 H, m), 6.30 (1 H, s, 3′-H), 4.41 (2 H, br s, NH_2), 4.05 (1 H, dtt, *J* 8, 4, 12 Hz, 2β-H), 3.02—2.80 (3 H, m), 2.23 (1 H, dt, *J* 2.5, 12 Hz), 2.14 (1 H, t, *J* 11 Hz, 6β-H), 2.14—1.88 (4 H, m), 1.82—1.72 (1 H, m), 1.65—1.36 (3 H, m), and 1.23 (1 H, q, *J* 12 Hz).

Acknowledgements

The author thanks the late Professor T. J. King (Nottingham) for the *X*-ray structure determination, Mr. D. Smith of P.A.S.U. at Harlow for the 270 MHz n.m.r. spectra and assistance with interpretation, and Dr. M. S. Hadley for initiating the chemical programme.

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Received 25*th June* 1985; *Paper* 5/1074