

Electro-organic Reactions. Part 22. An Entry into the Quinolizidine and Benzoquinolizidine Ring Systems via Anodic Methoxylation *

PETER D. PALASZ, JAMES H. P. UTLEY ^a and J. DAVID HARDSTONE ^b

^a Queen Mary College, London E1 4NS and ^b Pfizer Central Research, Sandwich, Kent CT13 9NJ, England

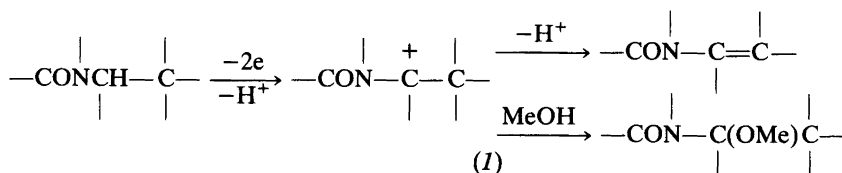
Examples of the quinolizidine and benzoquinolizidine ring systems (1,1-bisethoxycarbonyl-4-oxo-quinolizidine, 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizidine, and 1,2-*t*-butyl-3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizidine) have been synthesized by routes which involve initial anodic methoxylation of piperidine precursors with subsequent intramolecular Lewis acid-catalyzed cyclisation reactions. Reaction conditions for such cyclisations have been explored; success depends on a correct choice of catalyst (usually aluminium chloride) and, critically, on steric factors. The stereochemistry of the cyclic products has been established and the stereochemical course of the reactions is commented upon.

The preparation of α -methoxyamides by the Ross-Eberson-Nyberg method (anodic alkoxylation) is well documented.¹ These intermediates, and also enamides which are readily formed from them, typically undergo reaction with nucleophiles in the presence of acidic catalysts.

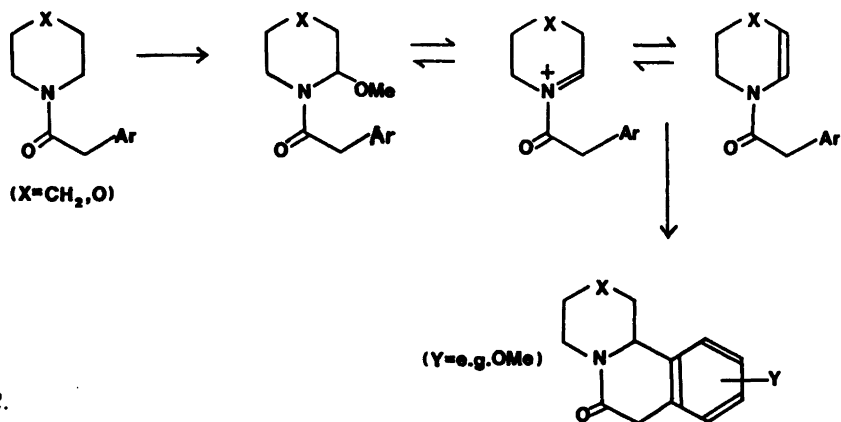
* Presented at the 10th Scandinavian Meeting on Organic Electrochemistry, Sandbjerg, June 10th–13th, 1982.

Nucleophiles such as aromatic hydrocarbons and dialkylmalonates are commonly used and, overall, the method constitutes a valuable route to α -functionalized amides. Furthermore the α -methoxylated intermediates may be produced, at graphite anodes, in simple undivided capillary gap cells, on a several molar scale.²

The key synthons produced in acidic conditions from either α -methoxyamides or enamides are *N*-acyliminium ions (I, Scheme 1). The intermediacy of iminium ions in synthetically interesting intramolecular cyclisations has been demonstrated by Rapoport and his co-workers;³ cyclic α -amino acids are converted into iminium ions by treatment with phosphorus oxychloride but preparation of the carboxylic acid precursor is often a multi-step process. By contrast anodic methoxylation provides direct entry from simpler starting materials. Intramolecular cyclisations which have been achieved⁴ either by initial anodic oxidation of suitably substituted amides or in some cases from anodically prepared enamides and α -methoxyamides which have been isolated and subsequently cyclised in the presence of a catalyst.



Scheme 1.



Scheme 2.

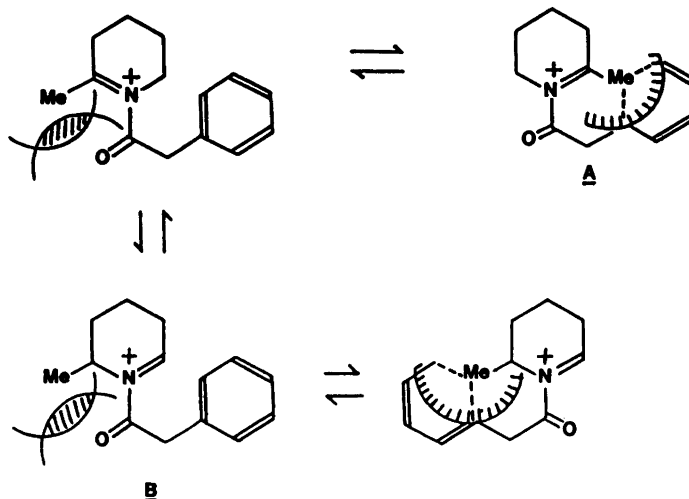
A preliminary account of the application of these reactions to the synthesis of quinolizidine and hexahydrobenzo[*a*]quinolizidines has been given⁵ and we report herein, in detail, on the scope and limitations of this approach. Related successful syntheses have been recently achieved by others^{6,7} and one of these is described in an accompanying publication.

RESULTS AND DISCUSSION

Hexahydrobenzo[*a*]quinolizidines. *The methoxylation of N-arylacetyl secondary amines.* The strategy employed for the preparation of the hexahydrobenzo[*a*]quinolizidines is outlined in Scheme 3. The first step involves anodic methoxylation of *N*-arylacetyl derivatives of

secondary amines; a variety of conditions were explored and the results are summarised in Table 1. A capillary gap flow cell was employed with a graphite anode and stainless steel cathode. Reactions were run on a 5–150 g scale, at *ca.* 45 °C, and at current densities in the range 0.06 to 0.24 A cm⁻². Purification by distillation can sometimes lead to decomposition of the methoxylated products (to enamides); the preferred method of purification was therefore column chromatography.

The presence of readily oxidized functions, *e.g.* methoxylated aromatic rings, led to polymerisation. A comparison of oxidation peak potentials (Table 2) confirms that successful methoxylation α to the amide function requires tolerance of other functions of *ca.* +2.3 V (*vs.* Ag/AgI).



Scheme 3.

Table 1. The anodic methoxylation of *N*-arylacetyl derivatives.^a

| Substrate | Isolated yield (%) | Product number ^b |
|---|---|-----------------------------|
| <i>N</i> -Phenylacetyl piperidine (2) | 59 | 9 |
| <i>N</i> -Phenylacetyl-2-methylpiperidine (3) | 84 ^c 65 ^d 73 ^e | 10 |
| <i>N</i> -Phenylacetyl-4- <i>t</i> -butylpiperidine (4) | 53 | 11 |
| <i>N</i> -Phenylacetylmorpholine (5) | 50 | 12 |
| <i>N</i> -Phenylacetyl-1,2,3,4-tetrahydroisoquinoline (6) | 83 ^c | 13 ^f |
| <i>N</i> -3,4-Dimethoxyphenyloxalylpiperidine (7) | polymer | — |
| <i>N</i> -3,4-Dimethoxyphenylacetylmorpholine (8) | polymer | — |

^a Methanol-dried LiNO₃ (0.1 M); electrolysis details in Experimental. ^b Unless stated otherwise this is the corresponding α -methoxyl derivative. ^c Higher yields, of this order, were associated with a change to a flow cell incorporating a larger anode – see experimental section and Table 6. ^d LiNO₃ (0.1 M)/5 °C. ^e LiNO₃ (0.1 M)/Li₂CO₃. ^f *N*-Phenylacetyl-1-methoxy-tetrahydroisoquinoline.

Table 2. Oxidation peak potentials.^a

| Substrate | E_p^{ox} /Volts |
|---|-------------------|
| <i>N</i> -Phenylacetylmorpholine (5) | 2.33 ^b |
| <i>N</i> -Phenylacetyl-2-methylpiperidine (3) | 2.38 ^b |
| <i>N</i> -4-Methoxyphenylacetyl piperidine (14) | 1.55 |
| <i>N</i> -3-Methoxyphenylacetyl piperidine (15) | 1.64 |
| <i>N</i> -3,4-Dimethoxyphenylacetyl piperidine (16) | 1.32 |
| <i>N</i> -3,4-Dimethoxyphenyloxalylpiperidine (7) | 1.61 |
| <i>N</i> -(<i>m</i> -Diethylphosphatebenzoyl)piperidine (17) | no oxidation peak |
| Phenyl-1-phenyltetrazol-5-yl ether (18) | no oxidation peak |

^a Pt bead anode. MeCN-Bu₄NBF₄ (0.1 M), 0.3 V s⁻¹, s.c.e. reference electrode; irreversible oxidation. ^b vs. Ag/AgI.

N-3,4-Dimethoxyphenyloxalylpiperidine (7) was examined in the hope that the aromatic ring would be sufficiently deactivated to allow methoxylation to the amide nitrogen; the oxidation potential of the aromatic ring is, however, increased by only 0.3 V. It is possible that hydroxyls at least might be protected and deactivated to oxidation. Conversion into tetrazolyl ethers or phosphonates achieve this; such derivatives are not oxidized at 2.5 V (vs. s.c.e.) in acetonitrile-Bu₄NBF₄ whereas the *N*-phenylacetyl derivatives have $E_p/2$ values in the region

of +2.2 V.

Attempted cyclisation of N-Phenylacetyl-2-methoxyamides. The variety of conditions used in attempts to catalyze intramolecular cyclisation are summarised in Table 3. The most generally successful catalyst is aluminium chloride, a finding in line with other reports.⁸ Unpredictable solvent effects are observed; for instance cyclisation of (9) is successful in dichloromethane but in nitrobenzene conversion into the enamide is preferred. It is noteworthy that concentrated mineral acid has been advocated⁹ as catalysts for

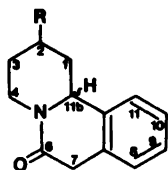
Table 3. Acid catalyzed cyclisation of α -methoxyamides.

| Starting material | Conditions ^a | Result |
|--|---|--|
| <i>N</i> -Phenylacetyl-2-methoxy piperidine (9) | AlCl ₃ -CH ₂ Cl ₂ AlCl ₃ -PhNO ₂ NafionH-CH ₂ Cl ₂ HCl-MeOH; HCO ₂ H; H ₂ SO ₄ ; polyphosphoric acid; BF ₃ -Et ₂ O; PBr ₃ ; CH ₂ Cl ₂ | Cyclisation to (19) (51 %) Enamide (20) (41 %) Enamide Polymerisation |
| <i>N</i> -Phenylacetyl-6-methoxy-2-methylpiperidine (10) | AlCl ₃ -CH ₂ Cl ₂ ; BF ₃ -Et ₂ O; AlCl ₃ -PhNO ₂ ; <i>p</i> -Me.C ₆ H ₄ .SO ₃ H-PhCH ₃ | Enamide (21) |
| <i>N</i> -Phenylacetyl-2-methoxy morpholine (12) | AlCl ₃ -CH ₂ Cl ₂ | Enamide (22) (58 %) |
| <i>N</i> -Phenylacetyl-4- <i>t</i> -butyl-2-methoxypiperidine (11) | AlCl ₃ -CH ₂ Cl ₂ | Cyclisation to (23) (18 %) |
| <i>N</i> -Phenylacetyl-1-methoxy tetrahydroisoquinoline (13) | AlCl ₃ -CH ₂ Cl ₂ ; AlCl ₃ -PhNO ₂ | Polymerisation |

^a See Experimental for details.

these cyclisation reactions but in our hands repeated attempts to cyclise (9) in this manner failed.

In the presence of acidic catalysts the acyliminium ion is formed; it may subsequently attack the aromatic ring (cyclisation) or lose a proton (enamide formation). These possibilities are included in Scheme 3. There is good evidence¹⁰ that some of the reactions in Scheme 3 are reversible although the rates of attainment of equilibrium are uncertain. In this context cyclisation may be envisaged as the product of kinetic control. It has been demonstrated¹¹ that intermolecular nucleophilic attack upon the intermediate *N*-acyliminium ions in the piperidine and morpholine series leads to axially substituted products. The dominant influence upon such substitution is the planarity and restricted rotation of the *N*-acyl substituent which greatly destabilises the equatorially substituted derivative.



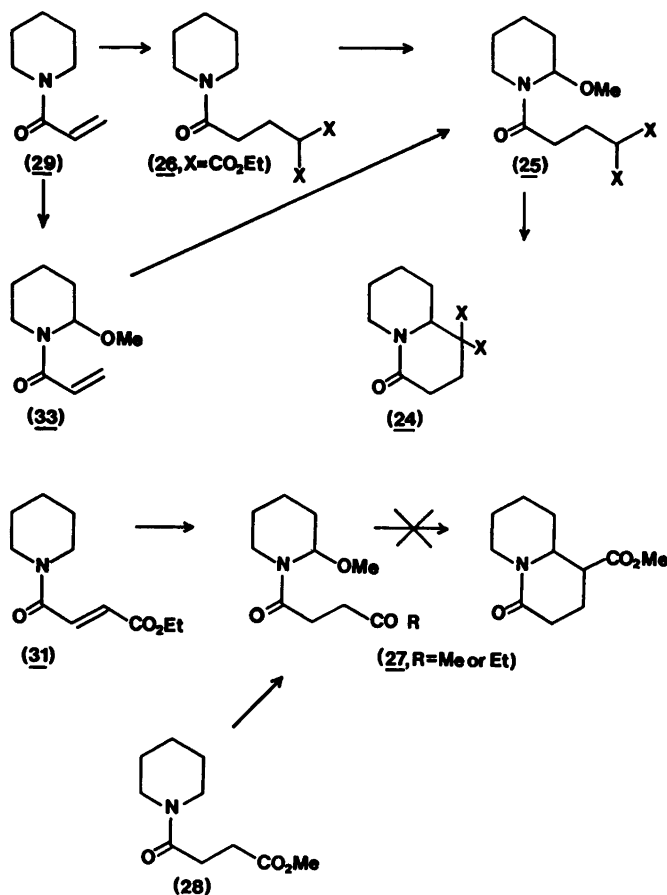
(19) R=H

(23) R=Bu^t

The failure of *N*-phenylacetyl-6-methoxy-2-methylpiperidine (10) to cyclise may therefore be understood in terms of the conformational equilibria depicted in Scheme 4; the conformations required for cyclisation to proceed (*A* and *B*) are highly strained whereas deprotonation is not conformation dependent. The failure of (13) to cyclise is not so readily understood as the necessary conformation is seemingly accessible.

The morpholine derivative (12) is converted under the conditions most favourable for cyclisation (AlCl₃/CH₂Cl₂) into the enamide. This is consistent with the observation¹² that *N*-formyl-2-methoxymorpholine reacts *via* the enamide (22, Table 3), with benzene in the presence of aluminium chloride to give the 3-phenyl and 2-phenyl isomers in a 2.6:1 ratio. In contrast the corresponding piperidine compound reacts cleanly at the 2-position.

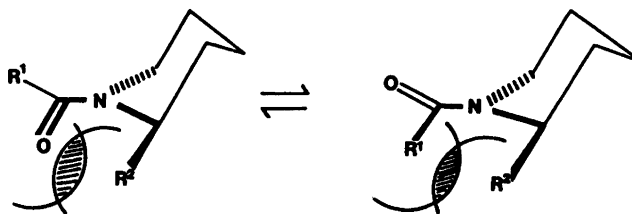
Stereochemistry of the Hexahydro-6-oxo-benzo[a]quinolizidines. The considerable preference for axial attack upon *N*-acyliminium ions raises the question of the stereochemistry of the ring junction in 19 and 20. The conformational biasing properties of the tertiary butyl group may be assumed to impart rigidity to the piperidine ring of (23); consequently the ¹H NMR spectrum of this compound may be analyzed in detail. The complete data are tabulated in the experimental section but key features are a 1.2:1



Scheme 4.

triplet signal at δ 2.62 (1H, $J=14$ Hz), a 1:1 doublet at δ 4.95 (1H, $J=14$ Hz), and a 1:1 doublet at δ 4.39 (1H, $J=11$ Hz). Each of the above signals is broadened by further, small, coupling. The δ 4.95 signal was assigned to the equatorial H-4 proton; irradiation at δ 2.62 caused it to collapse to a singlet, i.e. the H-4 axial proton absorbs at δ 2.62 and is involved in 14Hz

geminal and vicinal, diaxial coupling. In turn this leads to assignment of the doublet at δ 4.39 as arising from the H-11b proton. The large coupling for the H-11b proton signal (11 Hz) is compelling evidence for that proton being axial. The ring junction is therefore formed equatorially in contrast to substitution by independent nucleophiles. Consideration of the possible struc-

Fig. 1. Equatorial group hindrance to rotation of *N*-acyl substituent.

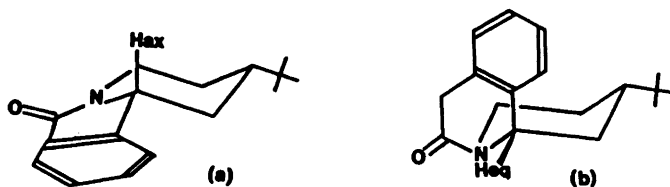


Fig. 2. Ring junction stereochemistry of hexahydro-6-oxobenzo[*a*]quinolizidine.

tures (Fig. 2a) and (Fig. 2b), using Dreiding models, reveals that an axial ring junction is not compatible with planarity of the amide function; this latter, stabilizing feature, is possible for the equatorially linked rings.

Synthesis of the quinolizidine ring system; 1,1-bisethoxycarbonyl-4-oxoquinolizidine (24). The strategy employed is outlined in Scheme 4. The key intermediate (25) may be obtained in two ways but the more successful route involved formation of (26) prior to anodic methoxylation. For the alternative, which involved Michael addition under basic conditions, the compound (25) was obtained admixed with the corresponding enamide (27) in the ratio 1:2. The preferred route compares well with the similar pathways explored by others.^{6,7,9}

The formation of 27 demonstrates a limitation of the undivided cell used. The cathodic discharge potential of the methanolic electrolyte, at stainless steel, was found by the construction of a steady state current-potential plot to be *ca.* -1.2 V (*vs.* Ag/AgI). Comparison with the reduction peak potentials of a number of N-acylated piperidine derivatives (Table 4) confirms that formation of 27 is a consequence of reaction at

both electrodes, i.e. anodic methoxylation and cathodic hydrogenation. (And also ester exchange!). The identity of (27, R=Me) was put beyond doubt following its preparation by the anodic methoxylation of 28.

The stereochemistry of 24 has been the subject of a separately reported¹³ investigation which involved detailed analysis of its 400 MHz proton NMR spectrum and nuclear Overhauser enhancement (NOE) difference spectroscopy. The preferred conformation is that shown in Fig. 3.

EXPERIMENTAL

Electrochemical cells and equipment. The flow cells of identical design but different sizes were used. They consisted of water jacketed glass cylinders (i.d. 40 mm) into which fitted stainless

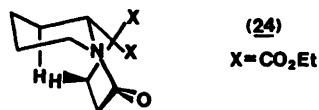


Fig. 3. Preferred conformation of 1,1-bisethoxycarbonyl-4-oxoquinolizidine.

Table 4. Reduction peak potentials.^a

| Substrate | $-E_p^{\text{red}}$ /Volts |
|--|----------------------------|
| <i>N</i> -Acryloylpiperidine (29) | 2.05 |
| <i>N</i> -(3,3-Dimethylacryloyl)piperidine (30) | 2.39 |
| <i>N</i> -(<i>trans</i> -3-Ethoxycarbonylacryloyl)piperidine (31) | 1.37 ^b ; 1.80 |
| <i>N</i> -(<i>trans</i> -3-Ethoxycarbonylacryloyl)morpholine (32) | 1.31 ^b ; 1.85 |
| Diethyl fumarate | 1.09 ^b ; 1.75 |
| Methyl acrylate | 1.67 |

^a Hg coated Pt bead, DMF-Bu₄NBF₄ (0.1 M), 0.3 Vs⁻¹, *vs.* Ag/AgI; irreversible reduction unless otherwise noted.

^b Reversible reduction.

steel cathodes of length 80 mm and 230 mm respectively. The cathodes were concentric with and equal in length to graphite rod anodes (diameter 28 mm). The electrode separation was in each case *ca.* 3 mm, maintained either by silicone rubber washers or by Teflon studs set in the anodes. The graphite was Link LY9 fine grained general purpose ungraphitised carbon supplied by Morganite Ltd. The electrolyte was flowed through the cells using an Eheim 1018 centrifugal pump with an isotactic polypropylene impeller. The flow system included a reservoir and cooling coil for larger scale runs at high currents.

A Farnell H60/50 stabilized power supply was used; other electrochemical equipment was as described in earlier papers in this series.

Instrumentation. ^1H NMR spectra were measured using the following spectrometers; Varian EM360, Bruker WP-80-DS, Bruker WH-400. ^{13}C NMR spectra were measured on the Bruker instruments. Gas-liquid chromatographic analysis was carried out using Hewlett-Packard 5830A or Pye 304 machines. An OV17 (3%) column was found to be suitable for most analyses. Mass spectra were recorded using an AEI MS902 machine in conjunction with an MSS Data Requisition System.

Starting materials. The N-arylacetyl derivatives. The appropriate acid chloride was prepared by treatment of the arylacetic acid with thionyl chloride. The acid chloride was dissolved in dry dichloromethane and added dropwise to a dichloromethane solution (ice-cold) of the secondary amine (1.2 equiv.), triethylamine (1.5 equiv.), and, importantly, one drop of the corresponding formylated amine. The solution was heated under reflux for 4 h, subjected to aqueous work-up, and the product purified as appropriate by distillation under reduced pressure, crystallization (ethyl acetate), or by column chromatography. Relevant physical and analytical data for new compounds so prepared are displayed in Table 5; good agreement with literature values for physical and spectroscopic data was found for the remaining *N*-arylacetyl derivatives.

N-3,4-Dimethoxyphenyloxalylpiperidine (7). To a solution of veratrole (27 g, 0.20 mol), ethyl oxalyl chloride (27 g, 0.21 mol) and 1,2-dichloroethane (200 cm³), anhydrous aluminium chloride (24.7 g, 0.19 mol) was added portionwise. The solution was heated under reflux for 8 h and then poured into ice-cold dilute hydrochloric acid (100 cm³). The solution was shaken with chloroform (200 cm³) and the organic layer was washed with sodium carbonate solution (10%, 40 cm³). The aqueous layer was separated, filtered and made

acidic with concentrated hydrochloric acid (100 cm³), and the product isolated after extraction into chloroform (100 cm³). It was crystallized from hexane/ethyl acetate to yield 3,4-dimethoxyphenylglyoxylic acid. M.p.: 136–138 °C (lit.¹⁴ 137 °C); yield 48%.

The glyoxylic acid (8 g, 0.04 mol) was treated in dichloromethane solution with one drop of dimethylformamide and oxalyl chloride (10.2 g, 0.08 mol). After 2 h, the solvents were removed under reduced pressure. The solid obtained was dissolved in dichloromethane (20 cm³, dried), and cooled in an ice bath. Piperidine (10 g, 0.12 mol) was added dropwise, after 2 h the solution was filtered and product was isolated after extraction into dichloromethane (50 cm³). M.p.: 140–143 °C; yield 63%. δ (60 MHz): 7.51, 6.85 (m, ArH, 3H); 3.92 (s, OCH₃, 6H); 3.7 (m, NCH₂, 4H); 1.68 (m, (CH₂)₃, 6H). ν (KBr): 2940; 1670; 1630; 1580 cm⁻¹. *m/z*: 277 (M⁺, 22%); 165 (100). Found (%) C 64.83; H 6.98; N 5.09. C₁₅H₁₉NO₄ requires (%) C 64.97; H 6.91; N 5.05.

N-Acryloylpiperidine (29): Acrylic acid was converted into its acid chloride which was used to acylate piperidine as described. Yield, 13%; b.p. 60–70 °C/0.3 mmHg (lit.¹⁵ 86–9 °C/5.6 mmHg). δ , 7.63 (d, d, *J* 10/16 Hz, =CH, 1H); 6.62 (d, d, *J* 10/3 Hz, 1H); 3.64 (m, NCH₂, 4H); 1.70 (m, (CH₂)₃, 6H); ν (liquid film): 3050, 2940, 2860, 1660 cm⁻¹.

N-(4,4-Bisethoxycarbonylbutyryl)piperidine (26). Sodium (2.7 g, 0.12 mol) was dissolved in ethanol (30 cm³). To this solution diethylmalonate (11 cm³, 0.07) was added rapidly, which was then followed by a slow addition of *N*-acryloylpiperidine (10 g, 0.07 mol) in ethanol (20 cm³). This solution was then heated under reflux for 3 h and, after cooling, acetic acid (*ca.* 10 cm³) was added. After evaporation under reduced pressure, the crude product was dissolved in dichloromethane (50 cm³), washed (H₂O) and dried (MgSO₄). The product was distilled under reduced pressure. B.p.: 170–180 °C/0.05 mmHg; yield 43%. δ : 4.02 (q, *J* 7 Hz, OCH₂, 4H); 3.31 (m, 5H); 2.20 (m, 4H); 1.45 (m, 6H); 1.20 (t, *J* 7 Hz, CH₃, 6H). ν (liquid film): 2980; 2940; 1740; 1640 cm⁻¹. *m/z*: 299.173 (M⁺ (20%), C₁₅H₂₅NO₅ requires 299.173).

N-(trans-3-ethoxycarbonylacyloyl)piperidine (31). Ethyl hydrogen fumarate was prepared from maleic anhydride by treatment with ethanol and thionyl chloride. This was converted into its acid chloride by further treatment with thionyl chloride and the crude acid chloride was allowed to react with piperidine in dichloromethane solution. Compound 31 was isolated after aqueous work-up. Yield 54%; b.p. 139–140 °C/

Table 5. *N*-arylacetyl derivatives.

| Compound | Yield, % | M.p. or b.p. °C | Physical Data |
|---|----------|-----------------|--|
| <i>N</i> -Phenylacetyl-1,2,3,4-tetrahydroisoquinoline (6) | 58 | 89–91 | Found (%): C, 81.19; H, 6.80; N, 5.49. C ₁₇ H ₁₇ NO requires: C, 81.24; H, 6.82; N, 5.57 δ: 7.30, 7.15 (s, ArH, 9H); 4.59, 4.82 (s, H-1, 2H); 3.85 (s, PhCH ₂ , 2H); 3.75 (m, 2H); 2.81 (m, 2H). ν: 3020; 2890; 1640; 1450 cm ⁻¹ |
| <i>N</i> -Phenylacetyl-4- <i>t</i> -butylpiperidine (4) | 56 | 80–83 | Found (%): C, 78.79; H, 9.71; N, 5.32. C ₁₇ H ₂₅ NO requires: C, 78.72; H, 9.72; N, 5.40. δ: 7.31 (s, ArH, 5H); 4.37 (d, J=12Hz, H-2, 1H); 3.90 (d, J=12Hz, H-6, 1H); 3.73 (s, ArCH ₂ , 2H); 2.85 (t, J=12Hz, H-6, 1H); 2.42 (t, J=12Hz, H-2, 1H); 1.3 (m, 5H); 0.80 (s, <i>t</i> -butyl, 9H) ν: 3020; 2940; 1635; 1600; 720 cm ⁻¹ |
| <i>N</i> -4-Methoxyphenylacetyl-piperidine (14) | 34 | 59–61 | Found (%): C, 71.91; H, 8.17; N, 5.87. C ₁₄ H ₁₉ NO ₂ requires: C, 72.06; H, 8.21; N, 6.01. δ: 7.25, 7.13, 6.93, 6.80 (m, ArH, 4H); 3.81 (s, OCH ₃ , 3H); 3.68 (s, ArCH ₂ , 2H); 3.50 (m, NCH ₂ , 4H); 1.51 (m, (CH ₂) ₃ , 6H) ν: 3020; 2950; 2860; 1655; 1620; 1520 cm ⁻¹ |
| <i>N</i> -3-Methoxyphenylacetyl-piperidine (15) | 36 | 166–8/0.2 mmHg | <i>m/z</i> : 233.142 (M ⁺ , (42 %), C ₁₄ H ₁₉ NO ₂ requires 233.142) δ: 7.21 (m, ArH, 1H); 6.82 (m, ArH, 3H); 3.81 (s, OCH ₃ , 3H); 3.74 (s, ArCH ₂ , 2H); 3.7–3.2 (m, NCH ₂ , 4H); 1.55 (m, (CH ₂) ₃ , 6H) ν: 3010; 2970; 2860; 1650; 1610 cm ⁻¹ |

0.3 mmHg. δ : 7.45, 6.70 (d, J 16 Hz, =CH, 2H); 4.26 (q, J 6 Hz, OCH₂, 2H); 3.6 (m, NCH₂, 4H); 1.7 (m, (CH₂)₃, 6H); 1.37 (t, J 6 Hz, CH₃, 3H). δ (20 MHz, ¹³C): 165.91, 163.24 (s, C-1'/4'); 130.12, 126.45 (d, t, C-2'/3'); 58.67 (t, C-6'): 45.87, 41.60 (t, C-2/6); 25.60, 24.53, 23.57 (m, C-3/4/5); 13.33 (q, C-7'). ν (liquid film): 3020; 1725; 1650; 1620 cm⁻¹. m/z : 211.121 (M⁺ (10 %), C₁₁H₁₇NO₃ requires 211.121).

N-(*trans*-3-ethoxycarbonylacryloyl)morpholine (32) was also prepared in the above manner: in this case the product was crystallized from ethyl acetate. Yield 28 %; m.p. 68–70 °C.

δ : 7.37, 6.77 (d, J 16 Hz, =CH, 2H); 4.25 (q, J 7 Hz, OCH₂, 2H); 3.71 (m, NCH₂CH₂O, 8H); 1.30 (t, J 7 Hz, CH₃, 3H).

ν (KBr): 2990; 2920; 2870; 1720; 1660; 1610; 1020; 960 cm⁻¹.

Found (%) C, 56.15; H, 6.96; N, 6.50. C₁₀H₁₅NO₄ requires (%) C, 56.30; H, 7.09; N, 6.57.

N-(3,3-dimethylacryloyl)piperidine (30) was prepared from 3,3-dimethylacrylic acid as described for *N*-acryloylpiperidine. Yield 51%; b.p. 80–85 °C/0.2 mmHg.

δ (60 MHz): 5.66 (s, =CH, 1H); 3.52 (m, NCH₂, 4H); 1.81 (s, CH₃, 6H); 1.55 (m, (CH₂)₃, 6H).

ν (liquid film): 2920; 2850; 1650; 1615; 1420; 1250 cm⁻¹.

m/z : 167.132 (M⁺ (36 %), C₁₀H₁₇NO requires 167.131).

Anodic methoxylation. The flow cells used are described above. The carbon anodes could be re-used many times provided that they were soaked in methanol and dried after each electrolysis.

Two procedures are described below which relate to particular small scale (5–15 g) and larger scale operations (40–150 g) but which are typical of the electrolyses carried out.

Typical small scale electrolysis (5–15 g): *N*-(4,4-bisethoxycarbonylbutyryl)piperidine (28) (8 g) was dissolved in methanol (290 cm³) with Bu₄NBF₄ (2 g) as the supporting electrolyte. This solution was put into the cell with no reservoir but provision for degassing. The flow rate was ca. 21 min⁻¹. The current was 10 A (at 22 V) and the solution temperature was maintained at 40–50 °C. After 3.7 F mol⁻¹ had been passed the electrolysis was stopped, electrolyte run off, the cell washed with methanol (300 cm³), which was added to the electrolyte and the solvent removed under reduced pressure. The methoxylated product was removed by ether extraction from the supporting electrolyte. The crude product was purified by column chromatography using silica and eluting with petroleum ether b.p. 60–80 °C

(100–80 %) and dichloromethane (0–20 %). Yield 7.0 g (80 %).

Typical large scale electrolysis (40–150 g): *N*-carbomethoxypiperidine (100 g) was dissolved in methanol (600 cm³) with Bu₄NBF₄ (17 g) as the supporting electrolyte. The current was controlled at 20A at a cell voltage of 20 V. Within one minute the temperature had increased from 20 to 45 °C. After 2.5 F mol⁻¹ was passed (ca. 143 min) the electrolysis was stopped, the solution was removed and the cell was washed with methanol (400 cm³). The solvent was removed under reduced pressure. The methoxylated product was distilled under reduced pressure (b.p. 56–59 °C/0.3 mmHg). The yield was 82 g (68 %) with a significant amount of polymeric material left as a residue.

New compounds prepared in the above manner, together with relevant physical and analytical data are described in Table 6. The data for previously reported compounds agreed well with that recorded in the literature.

Acid catalyzed cyclisation of the methoxylated amides. Attempts at Cyclisation in the Presence of Lowry-Bronsted Acids. The methoxy compound was added to an excess of the ice-cold acid. The solution was stirred for 3–10 h after which it was neutralized (NaOH) and attempts made to extract the product with dichloromethane. This approach was largely unsuccessful giving rise to tarry products; acids used were concentrated sulfuric acid, saturated methanolic HCl, formic acid, and orthophosphoric acid.

Cyclisation in the presence of Lewis acids. This approach was more successful (see Table 3). In a typical preparation a solution of the methoxylated intermediate (43 mmol) in dichloromethane (10 cm³) was added dropwise to good quality anhydrous aluminium chloride (150 mmol) previously dissolved in dichloromethane (30 cm³). The solution was stirred for 24 hours and then poured into ice-cold dilute hydrochloric acid (50 cm³). The product was extracted into dichloromethane and, after washing and drying, it was purified by column chromatography. Compounds prepared by this procedure, relevant physical and analytical data, and details of yields and modifications to the method are listed below.

1,3,4,6,7,11b-Hexahydro-6-oxo-2H-benzo[a]quinolizidine (19): Yield 51 %; m.p. 49–52 °C (lit.¹⁶ 75 °C). δ : 7.21 (s, ArH, 4H); 4.91 (d, d, J 12/3 Hz, H-4eq, 1H); 4.31 (d, J 10 Hz, H-11b ax, 1H); 3.65 (s, ArCH₂, 2H); 2.62 (t, d, J 12/3 Hz, H-4ax, 1H); 2.0–1.3 (m, H-1/2/3, 6H). ν (KBr): 2920; 2850; 1640; 1440; 750 cm⁻¹. m/z : 201 (M⁺, 63 %); 142 (100).

N-Phenylacetyl-2,3-dehydropiperidine (20): The only isolated product from attempted cyc-

Table 6. α -Methoxylated derivatives.

| Compound | Yield, % | M.p. or b.p. °C | Physical Data |
|--|----------|-------------------|---|
| <i>N</i> -Phenylacetyl-2-methoxy morpholine (12) | 50 | 143–149/0.08 mmHg | <i>m/z</i> : 235.121 (M^+ , (1.4 %), $C_{13}H_{17}NO_2$ requires 235.121) δ : 7.29 (s, ArH, 5H); 5.58, 4.85 (m, H-2, 0.57/0.43H); 4.0–3.3 (m, 9H); 3.26, 3.15 (s, OCH ₃ , 3H); <i>v</i> : 3015; 2990; 2910; 2870; 1640; 1610; 1415 cm^{-1} |
| <i>N</i> -Phenylacetyl-6-methoxy-2-methylpiperidine (10) | 84 | 56–57 | <i>m/z</i> : 247.158 (M^+ , (13 %), $C_{15}H_{21}NO_2$ requires 247.157) δ (400 MHz): 7.321, 7.265 (m, ArH, 5H); 5.901, 5.025 (t, <i>J</i> 3 Hz, H-6, 0.64/0.36H); 4.787, 4.083 (m, H-2, 1H); 3.874, 3.833, 3.818, 3.784, 3.797, 3.744 (two AB quartets, <i>J</i> 15 Hz, ArCH ₂ , 2H); 3.265, 3.220 (s, OCH ₃ , 3H); 2.00–1.77 (m, 2H); 1.63–1.30 (m, 4H); 1.275, 1.235 (d, <i>J</i> 7 Hz, CH ₃ , 3H) <i>v</i> : 3020; 2940; 2700; 1645; 1410 cm^{-1} |
| <i>N</i> -Phenylacetyl-4- <i>t</i> -butyl-2-methoxypiperidine (11) | 53 | 161–165/0.1 mmHg | <i>m/z</i> : 289.204 (M^+ , (8 %), $C_{18}H_{27}NO_2$ requires 289.204) δ : 7.28 (s, ArH, 5H); 5.87, 5.10 (s, H-2eq, 0.57/0.43H); 4.70 (d, <i>J</i> 12 Hz, H-5eq, 0.5H); 3.9–3.2 (m, 3H); 3.20, 3.13 (s, OCH ₃ , 3H); 3.0–1.0 (m, 5.5H); 0.82 (s, <i>t</i> -butyl, 9H) <i>v</i> : 3015; 2945; 2875; 1640 cm^{-1} |
| <i>N</i> -Phenylacetyl-1-methoxy-tetrahydroisoquinoline (13) | 83 | 110–120/0.1 mmHg | <i>m/z</i> : 281.145 (M^+ , (0.5 %), $C_{18}H_{19}NO_2$ requires 281.142) δ : 7.32 (m, ArH, 9H); 6.55, 5.82 (s, H-1, 0.71/0.29H); 4.0–2.5 (m, 4H); 3.29, 3.20 (s, OCH ₃ , 3H) <i>v</i> : 3030; 2950; 2850; 1650; 1450; 1070 cm^{-1} |
| <i>N</i> -Acryloyl-2-methoxy-piperidine (33) | 88 | 75–80/0.2 mmHg | <i>m/z</i> : 169.111 (M^+ , (21 %), $C_9H_{15}NO_2$ requires 169.110) δ : 7.75 (2×d, d, <i>J</i> 10/16 Hz, =CH, 1H); 7.32 (2×d, d, <i>J</i> 16/3 Hz, =CH, 1H); 6.75 (2×d, d, <i>J</i> 10/3 Hz, =CH, 1H); 5.40 (m, H-2, 0.7H); 3.35, 3.26 (s, OCH ₃ , 2/1H); 4.0–2.5 (m, 2.3H) <i>v</i> : 3000; 2940; 1650; 1615 cm^{-1} |
| <i>N</i> -(4,4-Bisethoxycarbonyl-butyl)-2-methoxypiperidine (25) | 80 | 220–30/0.05 mmHg | <i>m/z</i> : 329.184 (M^+ , (2.4 %), $C_{16}H_{27}NO_6$ requires 329.184) δ : 5.73, 5.01 (m, H-2, 0.51/0.49H); 4.21 (q, <i>J</i> 8 Hz, OCH ₂ , 5H); 3.52 (m, CH, 1H); 3.31, 3.23 (s, OCH ₃ , 3H); 2.7–1.0 (m, 11H); 1.27 (t, <i>J</i> 8 Hz, CH ₃ , 6H) <i>v</i> : 2940; 1740; 1660; 1450; 840 cm^{-1} |

| | | | |
|---|----|----------------|--|
| N-(3-Ethoxycarbonylpropionyl)-2-methoxypiperidine (27, R=Et) | 82 | 130/0.1 mmHg | <p><i>m/z</i>: 243.148 (M^+, 1.6 %), $C_{12}H_{21}NO_4$ requires 243.147 δ: 5.76, 5.09 (m, H-2, 0.59/0.41H); 4.13 (q, <i>J</i> 6 Hz, OCH_2, 2H); 4.2–2.9 (m, H-6, 2H); 3.32, 3.25 (s, OCH_3, 3H); 2.75 (m, CH_2CH_2, 4H); (m, H-3/4/5, 6H); 1.07 (t, <i>J</i> 6 Hz, CH_3, 3H) (100 MHz, ^{13}C): 172.91, 172.82 (s, C-1'/4'); 83.29; 79.16 (d, C-2); 60.50, 60.42 (t, C-6'); 56.19, 55.11 (q, OCH_3); 40.27, 36.48 (t, C-6); 30.61, 27.70 (m, C-2'/3'); 25.59, 24.85, 18.53, 13.14, 10.80 (t, C-3/4/5); 14.00 (q, C-7') ν: 2950; 2880; 1735; 1660; 1440 cm^{-1}</p> |
| N-(3-Methoxycarbonylpropionyl)-2-methoxypiperidine (27, R=Me) | 83 | 120–6/0.3 mmHg | <p><i>m/z</i>: 229.132 (M^+, 9 %), $C_{11}H_{19}NO_4$ requires 229.131 δ: 5.73, 5.12 (m, H-2, 0.56/0.44H); 3.69 (s, OCH_3, 3H); 4.2–3.0 (m, H-6, 2H); 3.32, 3.24 (s, OCH_3, 3H); 2.75 (m, CH_2CH_2, 4H); 1.51 (m, H-3/4/5, 6H) ν: 2960; 1740; 1660 cm^{-1}</p> |

lisation of (9) using aluminium chloride in nitrobenzene. Yield 41 %; b.p. 135–140 °C/0.5 mmHg. δ : 7.30 (m, ArH, 5.5H); 6.69 (d, t, *J* 8/5 Hz, =CH, 0.5H); 4.95 (m, =CH, 1H); 3.77 (m, ArCH₂, 2H); 3.5–2.2 (m, 2H); 1.82 (m, 4H). ν (liquid film): 3060; 3020; 2950; 1650 cm^{-1} . *m/z*: 201.115 (M^+ , 34 %), $C_{12}H_{15}NO$ requires 201.116).

1,2-t-Butyl-3,4,6,7,11b-hexahydro-6-oxo-2H-benzo[a]quinolizidine (23): Yield 18 %; m.p. 107–109 °C. δ : 7.23 (s, ArH, 4H); 4.95 (d, m, *J* 14 Hz, H-4eq, 1H, this signal collapsed to a singlet when δ 2.62 was irradiated); 4.39 (d, J11Hz, H-11b ax, 1H); 3.71 (s, ArCH₂, 2H); 2.62 (t, *J* 14 Hz, H-4ax, 1H); 2.12 (d, J11Hz, 1H); 1.71 (t, *J* 12 Hz, 1H); 1.5–1.0 (m, 3H); 0.87 (s, *t*-butyl, 9H). ν (KBr): 2950; 2860; 1640; 1460; 755 cm^{-1} . *m/z*: 257.178 (M^+ (100 %), $C_{17}H_{23}NO$ requires 257.178).

N-Phenylacetyl-2,3-dehydromorpholine (22). Yield 58 %; b.p. 130–140 °C/0.15 mmHg. δ : 7.28 (m, ArH, 5H); 5.90 (d, d, *J* 14/3 Hz, 1H); 4.0–3.0 (m, 9H); ν (liquid film): 3020; 2920; 1640; 1410; 1070 cm^{-1} . *m/z*: 203.095 (M^+ (38 %), $C_{12}H_{13}NO_2$ requires 203.095).

N-Phenylacetyl-5,6-dehydro-2-methylpiperidine (21). Yield 50 %; b.p. 146–148 °C/0.3 mmHg. δ : 7.27 (m, ArH, 5.5H); 6.55 (d, t, *J* 12/1 Hz, =CH, 0.5H); 4.87 (m, =CH, CHMe, 2H); 3.77 (s, ArCH₂, 2H); 2.0–1.5 (m, 5H); 1.11 (d, *J* 7 Hz, CH₃, 3H). ν (liquid film): 3300; 2960; 1640; 1600 cm^{-1} . *m/z*: 215.131 (M^+ (47 %), $C_{15}H_{21}NO$ requires 215.131).

1,1-Bisethylcarboxylate-4-oxo-quinolizidine (24): Yield 68 %; b.p. 160–164 °C/0.05 mmHg. δ (400 MHz): 4.69 (d, d, d, d, *J* 13.0/2.2/2.3/1.8 Hz, H-6eq); 4.20, 4.18, 4.17, 4.11, 4.09 (q, J7.5Hz, OCH_2 , 4H); 4.01 (m, ABX, H-10ax, 1H); 2.47 (t, d, *J* 13.4/2.4 Hz, H-6ax, 1H); 2.39 (d, d, d, *J* 16.8/4.8/1.6 Hz, H-3'', 1H); 2.27 (d, d, t, *J* 12.8/6.4/1.8 Hz, H-2'', 1H); 2.20 (t, d, *J* 12.8/6.5 Hz, H-2'', 1H); 2.05 (d, d, d, *J* 16.8, 13.6/6.6 Hz, H-3', 1H); 1.91 (m, H-8eq, 1H); 1.59 (m, H-8ax/7eq, 2H); 1.35 (m, H-9ax/9eq/7ax, 3H); 1.95, 1.90 (t, J7.5Hz, CH₃, 6H). ν (liquid film): 2950; 2860; 1740; 1650 cm^{-1} . *m/z*: 297.156 (M^+ (30 %), $C_{15}H_{23}NO_5$ requires 297.158).

Reduction of the amides. Typically a solution of the amide (36 mmol) in dry ether (30 cm^3) was added under a nitrogen atmosphere to lithium aluminium hydride (80 mmol) in ether (20 cm^3). The solution was heated under reflux for 5 h after which a few drops of a saturated solution of sodium sulfate were added. The suspension was filtered, and the filtrate treated with isopropanol (3 cm^3). Removal of the solvent gave an oily product which was immediately converted into

the hydrochloride salt. Products obtained in this way are listed below.

1,3,4,6,7,11b-Hexahydro-2H-benzo[a]quinolizidinium chloride (34). Yield 69%; m.p. 234–237 °C (lit.¹⁷ 260–261 °C). δ : 7.27 (s, ArH, 4H); 4.38 (d, *J* 10 Hz, 1H); 3.40 (m, 6H); 2.0 (m, 6H). δ (100 MHz, ¹³C): 131.19 (s, C-11a); 130.97 (s, C-7a); 128.89 (d, C-8); 127.89 (d, C-9); 127.23, 126.85 (d, C-10); 124.29 (d, C-11); 64.09, 57.76 (d, C-11b); 56.17, 49.83 (t, C-4); 51.98, 46.06 (t, C-6); 28.29, 27.46 (t, C-1); 25.90, 24.31 (t, C-7); 22.91, 19.81 (m, C-3); 22.27, 20.05 (m, C-2). ν (KBr): 2700, 2490; 1490; 1440; 775; 760; 750 cm⁻¹. Found (%) C, 69.47; H, 8.03; N 6.31. C₁₃H₁₈NCl requires (%) C, 69.79; H, 8.11; N, 6.26.

1,2-t-Butyl-3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizidinium chloride (35). Yield 74%; m.p. 228–229 °C. δ (400 MHz): 12.250, 11.590 (m, NH, 1H); 7.200, 7.102 (m, ArH, 4H); 4.395 (d, *J* 11 Hz, 0.4H); 4.268 (t, *J* 11 Hz, 0.4H); 3.862, 3.717 (t, d, *J* 11/7 Hz, 0.8H); 3.515, 3.308, 3.155 (m, 4H); 2.948, 2.767 (d, d, *J* 16/3 Hz, 1H); 2.525 (d, *J* 14 Hz, 0.6H); 2.238 (q, *J* 12 Hz, 0.6H); 2.048, 1.978, 1.895, 1.834 (d, *J* 12 Hz, 2H); 1.598, 1.504 (d, *J* 12/9 Hz, 2H); 1.30–1.00 (m, 1H); 0.925, 0.895, 0.895 (s, *t*-butyl, 9H). δ (100 MHz, ¹³C): 131.46, 131.23 (s, C-11a); 128.73 (d, C-9); 128.62, 124.22 (d, C-11); 128.44 (d, C-8); 127.76, 126.67 (d, C-10); 63.44, 58.36 (d, C-11b); 55.71 (t, C-4); 51.31 (t, C-6); 44.74, 31.09 (d, C-2); 29.58 (t, C-1); 26.88, 26.47 (m, C-*t*-butyl); 25.86, 24.01 (d, C-7); 23.52, 19.04 (t, C-3). ν (KBr): 2900; 2500; 1620; 800; 785 cm⁻¹. *m/z*: 243.199 (M⁺ (31%), C₁₇H₂₅N requires 243.199). Found (%) C, 70.66; H, 9.29; N, 4.94; Cl, 12.87. C₁₇H₂₆NCl requires (%) C, 72.92; H, 9.36; N, 5.01; Cl, 12.67. The hydrated salt (0.5 H₂O) requires (%) C, 70.67; H, 9.07; N, 4.85; Cl, 12.30.

Acknowledgements. We are grateful to the S.E.R.C. for a CASE studentship (to P.D.P.) in collaboration with Pfizer Central Research and also to the Royal Society and the University of London Central Research Fund for equipment grants. NMR spectra were measured by the ULIRS WH-400 N.M.R. Service at Queen Mary College.

REFERENCES

- Ross, S. D., Finkelstein, M. and Petersen, R. C. *J. Org. Chem.* **31** (1966) 128; Nyberg, K. and Servin, R. *Acta Chem. Scand. B* **30** (1976) 640.

- Nyberg, K., Malmberg, M. and Servin, R. *AIChE Symp. Ser.* **75** (1979) 36.
- Dean, R. T., Padgett H. C. and Rapoport, H. *J. Am. Chem. Soc.* **98** (1976) 7449; Bates, H. A. and Rapoport, H. *Ibid.* **101** (1979) 1259.
- Malmberg, M. and Nyberg, K. *Acta Chem. Scand. B* **38** (1984). *In press.*; Okika, M., Wakamatsu, T., Mori, M. and Ban, Y. *Heterocycles* **14** (1980) 1089.
- Palasz, P. D. and Utley, J. H. P. *Abstracts, 10th Scandinavian Meeting on Organic Electrochemistry, Sandbjerg, June 1982*; Palasz, P. D. *Ph.D. Thesis*, London University, London 1982.
- Okita, M., Wakamatsu, T. and Ban, Y. *Heterocycles* **20** (1983) 401.
- Blum, Z., Ekström, M. and Wistrand, L.-G. *Acta Chem. Scand. B* **38** (1984). *In press.*
- Malmberg, M. and Nyberg, K. *J. Chem. Soc. Chem. Commun.* (1969) 167.
- Shono, T., Matsumura, Y. and Tsubata, K. *J. Am. Chem. Soc.* **103** (1981) 1172.
- Malmberg, M. and Nyberg, K. *Acta Chem. Scand. B* **33** (1979) 69.
- Palasz, P. D., Utley, J. H. P. and Hardstone, J. D. *J. Chem. Soc. Perkin Trans. II* (1983). *In press.*
- Malmberg, M. and Nyberg, K. *Acta Chem. Scand. B* **38** (1984). *In press.*
- Hawkes, G. E., Palasz, P. D., Utley, J. H. P. and Hardstone, J. D. *J. Chem. Res. (S)* (1983) 208.
- Franciso, J. *Sec. Chem. Mineral. Physics* **6** (1937) 1; *Chem. Abstr.* **32** (1938) 2125.
- Maier, L. *Helv. Chim. Acta* **56** (1973) 1252.
- Satoda, I., Murayama, M., Tsuji, J. and Yoshi, E. *Tetrahedron Lett.* (1962) 1199.
- Vetuschi, C., Ottolino, A. and Tortorella, V. *Gazz. Chim. Ital.* **105** (1975) 935.

Received June 27, 1983.