Reductive alkylation of pyridinium salts. Part 1. Synthesis of di-, tetra- and hexa-hydropyridine esters

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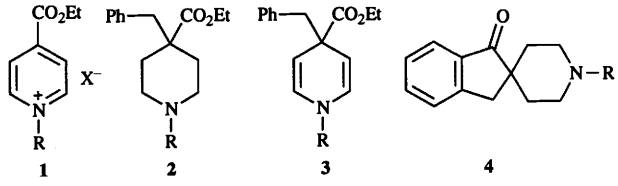
Reaction of 1-methyl-, 1-benzyl- and 1-benzoyl-4-ethoxycarbonylpyridinium salts 1 with zinc and benzyl bromide produce regioselectively the 4,4-disubstituted 1,4-dihydropyridines 3 (R = CH_3, $PhCH_2$, PhCO); only the latter is stable but all are reduced catalytically to piperidines 2 (R = CH_3, $PhCH_2$, PhCO). 1-Benzoyl-4-ethoxycarbonylpyridinium chloride with zinc and benzoyl chloride or ethyl bromoacetate gives respectively 4-benzoyl- 18 or 4-ethoxycarbonylmethyl-1-benzoyl-4-ethoxycarbonyl-1,4-dihydropyridine 17, but 1-methyl-4-ethoxycarbonylpyridinium iodide 1 (R = CH_3, X = I) with benzoyl chloride gives 3-benzoyl-4-ethoxycarbonyl-1-methyl-1,2-dihydropyridine 21. The action of zinc and benzyl bromide on 1-methyl- and 1-benzyl-3-ethoxycarbonylpyridinium salts 5 gives, after catalytic hydrogenation, mixtures of 2- and 4-benzyl-5-ethoxycarbonyl-1,2,3,4-tetrahydropyridines 6 and 7 (R = CH_3 or $PhCH_2$) but similar treatment of 1-benzoyl-3-ethoxycarbonylpyridinium chloride 5 (R = PhCO, X = Cl) yields selectively the stable 4-benzyl-3-ethoxycarbonyl-1,4-dihydropyridine 9. Treatment of 1-methyl- or 1-benzoyl-3-ethoxycarbonylpyridinium salts 5 with zinc and benzoyl chloride gives a mixture of products. 1-Methyl-2-ethoxycarbonylpyridinium iodide 11 (R = CH_3, X = I) reacts with zinc and benzyl bromide giving, after catalytic hydrogenation, 2-, 4- and 6-benzyl-2-ethoxycarbonyl-1-methylpiperidines 12, 13 and 14 (R = CH_3) in the ratio 2:7:1, but 1-benzyl-2-ethoxycarbonylpyridinium bromide 11 (R = $PhCH_2$, X = Br) gives only 1,4-dibenzyl-2-ethoxycarbonylpiperidine 13 (R = $PhCH_2$).

In previous work [1,2] it was shown that when *N*-methylisonicotinate ester **1** (R = CH_3, X = I) was treated with zinc and benzyl



1 **2** **3** **4**

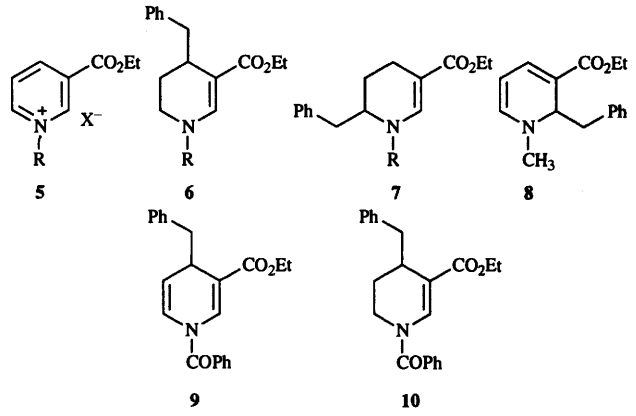
bromide in acetonitrile followed by *immediate* catalytic reduction, the product was the ester **2** (R = CH_3). It was, therefore, deduced that this reductive alkylation had produced initially the dihydropyridine **3** (R = CH_3) which was unstable. It was demonstrated that polyphosphoric acid (PPA) treatment of **2** (R = CH_3) yielded the spiro compound **4** (R = CH_3).[1] This interesting discovery seemed worthy of exploitation; we report here our investigation into reductive alkylations of various pyridinium esters.

Discussion

Firstly, the reductive benzylation of the isonicotinate **1** (R = CH_3, X = I) was re-examined using the conditions previously employed [2] which were based on publications by Kosower and co-workers concerning stable pyridinyl radicals.[3–8] The initially capricious results were much improved by standardising certain features: vacuum drying the pyridinium salt, activating the zinc,[9] degassing the acetonitrile and use of fresh platinum oxide in all catalytic hydrogenations (see Experimental section). In this way, crude dihydropyridine **3** (R = CH_3) could be specifically detected by ^1H NMR spectroscopy which, in particular, revealed vinyl proton doublets (each 2 H) at δ 4.55 and 5.85 along with all other expected signals. However, the areas under the peaks were out of balance and the material **3** (R = CH_3) was certainly unstable. Nevertheless, *immediate* (within 1 h) catalytic hydrogenation gave consistently 41% overall yield of almost pure piperidine **2** (R = CH_3) which cyclised satisfactorily to spiroketone **4** (R = CH_3).[1,2] A similar series of reactions was applied to the *N*-benzyl salt **1** (R = $PhCH_2$, X = Br) giving ultimately **4** (R = $PhCH_2$) from which the benzyl group could be removed if required for structural modifications in this rare ring system.[1,2,10]

Because both dihydropyridines **3** (R = CH_3, $PhCH_2$) are enamines, it was reasoned that *N*-acyl substitution (*e.g.* **3**: R = R'CO) would perhaps confer some stability,[11,12] thus allowing more detailed study of dihydropyridine chemistry. *N*-Benzoyl salt **1** (R = COPh, X = Cl), chosen for its steric similarity to the *N*-benzyl case above, was made and used *in situ* (as it was unstable). Reductive benzylation yielded a stable crystalline dihydropyridine **3** (R = PhCO) in 75% yield accompanied by a minor impurity, possibly dimeric, which could not be properly identified. Process modifications showed that carrying out the reaction at 0 °C rather than −40 °C increased the rate of reaction without deleterious effect on the yield: moreover the amount of impurity diminished to negligible amounts at the higher temperature. In all cases, dihydropyridines are accompanied by variable quantities of bibenzyl, reinforcing the view that radicals are involved in reductive benzylations.[2–8] We have not established whether or not organozinc intermediates are involved. ^1H and ^{13}C NMR spectra of dihydropyridines **3** (R = PhCO) were entirely consistent with the proposed structure: line broadening of the vinyl hydrogen signals (δ 5.2 and 6.95) can be attributed to the presence of rotamers in the amidic structure.

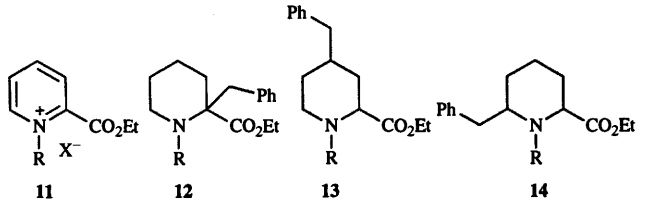
Turning to the salts of ethyl nicotinate **5**, reductive benzylation by the standardised method used above yielded mixtures of products when alkyl groups (R = CH_3 and $PhCH_2$) were present. In the *N*-methyl case, immediate catalytic hydrogenation gave a mixture of tetrahydropyridines, initially inseparable by chromatography. Eventually the major isomer **6** (R = CH_3) crystallised and its structure was confirmed by 2-D, ^1H and ^{13}C NMR spectroscopy; reversed-phase HPLC gave



5 6 7 8 9 10

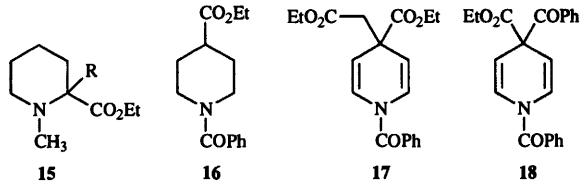
one peak only. The minor product was not obtained in a pure state but its structure seemed likely to have been **7** (R = CH_3) on steric grounds and because the alternative intermediate dihydropyridine **8** would have lacked the stabilising simple β-aminoacryl moiety[13] and would, therefore, have been expected to give a hexahydropyridine on hydrogenation. The *N*-benzyl salt **5** (R = $PhCH_2$, X = Br) gave similar results: an inseparable mixture of **6** and **7** (R = $PhCH_2$) was obtained in a 4:1 ratio. It might be possible to use the crude product for further work but this was not explored.

In situ formation and reductive benzylation of the salt **5** (R = COPh, X = Cl) gave a single main product (68%) as a viscous oil: its structure was confirmed as **9** in the usual ways although the probable presence of rotamers (N–COPh) caused line broadening of vinyl signals as previously described and not all 22 carbons could be distinguished in ^{13}C and J_{mod} spectra, presumably for the same reason (see Experimental section). Reduction of the dihydropyridine **9** gave the expected tetrahydropyridine **10**.



11 12 13 14

In the case of the picolinate salt **11** (R = CH_3, X = I) reductive benzylation followed by *immediate* catalytic hydrogenation yielded three separable products **12**, **13** and **14** (R = CH_3) in a 2:7:1 ratio. The major isomer **13** (R = CH_3) is the higher homologue of the methyl ester reported previously.[1] The novel isomer **12** (R = CH_3) was also synthesised by lithium diisopropylamide (LDA)[14] induced benzylation of *N*-methylpipecolinic ester **15** (R = H): the product **15** (R = $PhCH_2$) was identical to that [**12** (R = CH_3)] obtained by reductive

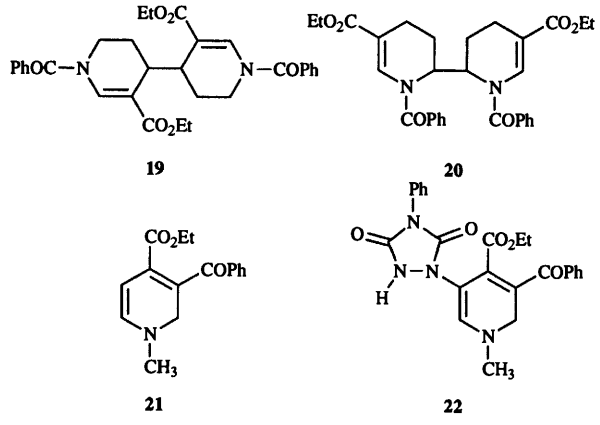


15 16 17 18

benzylation and catalytic hydrogenation of **11** (R = CH_3, X = I), and was obtained in 92% yield. Regrettably the reductive benzylation in this case was, although informative, not synthetically useful. On the other hand, reductive benzylation and hydrogenation of *N*-benzylpicolinic ester **11** (R = $PhCH_2$, X = Br) gave in 52% yield (after purification) only one product which proved to be the 4-benzyl isomer **13** (R = $PhCH_2$). The latter is an improvement on the method previously published for the analogous case of **13** (R = CH_3). Unfortunately attempts to achieve *in situ* benzoylation of ethyl picolinate [to give **11** (R = PhCO, X = Cl)] failed: the subsequent introduction of zinc and benzyl bromide did not give a benzylated product; only ethyl picolinate was recovered.

Accordingly it appears that only pyridine-3- and -4-carboxylate esters are amenable to conversion to stable *N*-benzoyldihydropyridine esters by this protocol.

Substitution of methyl iodide for benzyl bromide in the reaction of **1** (R = COPh, X = Cl) with zinc in acetonitrile did not lead to a methylated product, since catalytic hydrogenation of the reaction mixture produced only *N*-benzoylisonipecotic ester (ethyl *N*-benzoylpiperidine-4-carboxylate) **16**. On the other hand, ethyl bromoacetate in place of benzyl bromide gave the dihydropyridine **17** in very poor (11%) yield while substitution of benzoyl chloride for benzyl bromide led to **18** in 20% yield. Contrastingly, the nicotinate salt **5** (R = COPh, X = Cl) did not give a monomeric product when subjected to benzoyl chloride and zinc in acetonitrile: after hydrogenation, a viscous inseparable mixture was obtained along with two dimers, possibly **19** and **20**. In other cases, some dimeric



19 20 21 22

products have been seen but in all cases definitive structural elucidation has not been carried out. However, the appearance of dimers is further evidence for the presence of radicals during these reactions.

Although *N*-methyl ester **1** (R = CH_3, X = I) had reacted regioselectively with benzyl bromide and zinc to yield 1,4-dihydropyridine **3** (R = CH_3), surprisingly it reacted with benzoyl bromide to give the 1,2-dihydropyridine **21** (34% yield). This unusual structure was supported by elemental analysis, mass spectroscopy and J_{mod} ^{13}C spectroscopy (16 C). The ^1H NMR spectrum revealed two methylene protons as a sharp singlet (δ 4.81) and the two vinyl protons were sharp doublets (δ 6.57 and 6.60; J = 3 Hz). Hydrogen, carbon correlation bird-pulse (HCCOBI) and heteronuclear multiple bond correlation (HMBC) spectra confirmed the vinyl protons to be α and β to the nitrogen atom. Further support for the structure of **21** was found when it reacted with 4-phenyl-1,2,4-triazoline-3,5-dione to provide, not a Diels–Alder product, but an 'ene' compound **22** in which the β-vinyl proton had disappeared and the α-vinyl proton reduced to a sharp singlet.

By comparison with this result, the isomeric *N*-methyl ester **5** (R = CH_3, X = I) reacted with benzoyl chloride and zinc in acetonitrile giving very poor yields of three polysubstituted products which appear to be one pentabenzoylhexahydropyridine and two tribenzoyltetrahydropyridines. Although elemental analysis and mass spectroscopy support this contention, NMR spectroscopy does not permit precise establishment of structure (see Experimental section).

In conclusion, the technique of reductive alkyation applied to pyridinium salts has made available both novel and known

reduced alkylated pyridines in a very convenient way. Several of the products would appear to be synthetically useful: this will be described in the following paper.

Experimental

Melting points were obtained on a Gallenkamp melting point apparatus in open capillaries and are uncorrected. Microanalytical data for carbon, hydrogen and nitrogen were determined on a Carlo Erba 1106 Analyser and on a Perkin Elmer 2400 Analyser using a technique based on the classical Pregl Dumas method. Mass spectra were recorded on a AEI MS9 double focussing mass spectrometer, modified with solid state console, using a GEC-905 computer based data system. Infrared spectra were recorded on a Perkin Elmer 397 spectrometer with the samples prepared as liquid films, Nujol mulls or KBr discs. ^{1}H NMR spectra were recorded on a Bruker SM 250 spectrometer operating at 250.13 MHz in Fourier transform mode or (where stated) on a Perkin Elmer R32 spectrometer operating at 90 MHz. ^{13}C NMR, COSY, HMBC and HCCOBI spectra were obtained on a Bruker AMX400 spectrometer operating at 100.625 MHz for ^{13}C and 400.13 MHz for ^{1}H in Fourier transform mode. All spectra were recorded using deuteriochloroform as solvent with tetramethylsilane as the internal reference, unless otherwise stated. Coupling constants are given in Hz.

Flash chromatographic columns were run using Camlab Art. Nr 81538 MN Kieselgel 60 (0.04–0.06 mm) and samples were applied to the column in solution. Thin layer chromatography (TLC) was performed on pre-covered plastic sheets of 0.25 mm silica gel containing fluorescent indicator UV254 supplied by Camlab. High pressure liquid chromatography was carried out with a Milton Roy pump and a Cecil detector operating at 280 nm. The column used was 25 cm long, with an external diameter of 4.5 mm and was packed with octadecylsilane (ODS). Ether refers to diethyl ether.

4-Ethoxycarbonyl-1-methylpyridinium iodide 1 (R = CH_3, X = I)

Iodomethane (15.1 g, 0.1 mol) was added dropwise to ethyl isonicotinate (ethyl pyridine-4-carboxylate) (13.49 g, 0.89 mol) in dry acetone (30 cm^3) and stirred, under nitrogen, for 20 h. The crude product was filtered, washed with ether and recrystallised (acetone), to produce orange needles (23.4 g, 90%), mp 122–124 °C (lit.,[15] mp 122–124 °C).

4-Benzyl-4-ethoxycarbonyl-1-methylpiperidine 2 (R = CH_3)

Vacuum dried 4-ethoxycarbonyl-1-methylpyridinium iodide **1** (R = CH_3, X = I) (5.86 g, 20 mmol) and acetonitrile† (100 cm^3) were stirred, under nitrogen, for 1 h. Benzyl bromide (3.42 g, 20 mmol) was then added and the system was cooled to −40 °C. After stirring for 1 h, activated zinc[9] (2 g) was added over 10 min. The stirred reaction mixture was left to come to room temperature overnight, then added to ice–ammonia and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*, to produce a mobile red oil (5.0 g, 96%). Some of the crude product (3.47 g) was *immediately* (within 1 h) hydrogenated in ethanol (200 cm^3) over platinum oxide (200 mg), in a Cook hydrogenator (room temp., 45 psi). The catalyst was then removed by filtration through kieselguhr and the filtrate was concentrated *in vacuo*, to give the crude product (2.92 g, 84%). Purification by Kugelrohr distillation afforded the title compound as a mobile oil (1.48 g, 41%), bp 130 °C/0.01 mmHg (lit.,[1] bp 85–90 °C/0.05 mmHg).

1-Benzyl-4-ethoxycarbonylpyridinium bromide 1 (R = $PhCH_2$, X = Br)

Benzyl bromide (18.81 g, 13.1 cm^3, 0.11 mol) was added, dropwise, to a solution of ethyl isonicotinate (15.12 g, 0.1 mol) in dry acetone (30 cm^3) under nitrogen. The mixture was stirred for 18 h then the crude product was filtered, washed with ether and recrystallised (ethanol–ether), to give yellow plates (29.8 g, 93%), mp 163–165 °C (Found: C, 56.0; H, 5.15; Br, 24.7; N, 4.35%. $C_{15}H_{16}BrNO_2$ requires C, 55.9; H, 5.0; Br, 24.8; N, 4.35%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.40 (3 H, t, *J* 7.1, CH_2CH_3), 4.45 (2 H, q, *J* 7.1, CH_2CH_3), 6.44 (2 H, s, $PhCH_2$), 7.35 (3 H, m, aryl), 7.78 (2 H, m, aryl), 8.44 (2 H, d, *J* 6.6, 3-H and 5-H), 9.96 (2 H, d, *J* 6.6, 2-H and 6-H).

1,4-Dibenzyl-4-ethoxycarbonylpiperidine 2 (R = $PhCH_2$)

1-Benzyl-4-ethoxycarbonylpyridinium bromide **1** (R = $PhCH_2$, X = Br) (3.22 g, 10 mmol) and acetonitrile (100 cm^3) were stirred under nitrogen for 2 h. Benzyl bromide (1.71 g, 10 mmol) was added and the system was cooled to −15 °C. The mixture was stirred for 0.5 h and activated zinc[9] (1 g) was added over 10–15 min. The reaction was then stirred for 4 h, added to ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The orange oil produced was *immediately* hydrogenated in ethanol (100 cm^3) over platinum oxide (100 mg) at atmospheric temperature and pressure. The catalyst was removed by filtration through kieselguhr and the filtrate was concentrated *in vacuo*. Purification by column chromatography (eluent: 20% ethyl acetate–hexane) produced a viscous, colourless oil (1.53 g, 45%), bp 150 °C/0.2 mmHg (Found: M^+, 337.2040. $C_{22}H_{27}NO_2$ requires *M*, 337.2042) [the methiodide salt had mp 225 °C (Found: C, 57.5; H, 6.15; I, 26.3; N, 3.0%. $C_{23}H_{30}INO_2$ requires C, 57.6; H, 6.3; I, 26.5; N, 2.9%)]; ν_{max}(film)/cm^{-1} 1725 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.16 (3 H, t, *J* 7.1, CH_2CH_3), 1.59 (2 H, dt, *J* 3.4 and 12.0, 3-H and 5-H), 1.9–2.2 (4 H, m, 2-H, 3-H, 5-H and 6-H), 2.73 (2 H, dd, *J* 3.4 and 11.9, 2-H and 6-H), 2.81 (2 H, s, $PhCH_2$), 3.44 (2 H, s, $N\text{-}CH_2Ph$), 4.07 (2 H, q, *J* 7.1, CH_2CH_3), 7.04 (2 H, m, aryl), 7.18–7.35 (8 H, m, aryl).

1-Benzoyl-4-benzyl-4-ethoxycarbonyl-1,4-dihydropyridine 3 (R = PhCO)

Benzoyl chloride (4.22 g, 3.5 cm^3, 30 mmol) was added slowly to a stirred solution of ethyl isonicotinate (4.54 g, 30 mmol) and acetonitrile (100 cm^3) under nitrogen. After 2 h, benzyl bromide (5.13 g, 30 mmol) was added and the stirred mixture was cooled to 0 °C. After 15 min, activated zinc[9] (2 g) was added over 10–15 min and the reaction was stirred for 5 h. The reaction mixture was then poured onto ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*, to produce an orange oil which crystallised slowly. Purification by column chromatography (eluent: 18% ethyl acetate–hexane) yielded a colourless crystalline solid (7.81 g, 75%), mp 55–57 °C (Found: C, 76.6; H, 6.4; N, 3.95%; M^+, 347.1511. $C_{22}H_{21}NO_3$ requires C, 76.1; H, 6.1; N, 4.0%; *M*, 347.1522); ν_{max}(film)/cm^{-1} 1730 and 1670 (C=O str); δ_H(400 MHz, $CDCl_3$) 1.26 (3 H, t, *J* 7.1, CH_2CH_3), 3.02 (2 H, s, $PhCH_2$), 4.19 (2 H, q, *J* 7.1, CH_2CH_3), 5.20 (2 H, br s, 3-H and 5-H), 6.95 (2 H, br s, 2-H and 6-H), 7.1–7.5 (10 H, m, aryl); δ_C(100.625 MHz, $CDCl_3$) 14.21 (CH_2CH_3), 47.81 ($PhCH_2$), 48.20 (C-4), 61.36 (CH_2CH_3), 126.89, 127.98, 128.40, 128.54, 130.63, 131.13 (C–H aryl), 133.50 and 135.77 (*ipso*-aryl), 167.23, 173.27 (C=O).

3-Ethoxycarbonyl-1-methylpyridinium iodide 5 (R = CH_3, X = I)

Methyl iodide (19.87 g, 0.14 mol) was added, dropwise, to a stirred solution of ethyl nicotinate (ethyl pyridine-3-carboxylate) (10.58 g, 70 mmol) in propan-2-ol (15 cm^3) under nitrogen. The mixture was stirred for 18 h then the crude product (17.8 g,

† Degassed on rotary evaporator for not less than 10 min/20 °C.

87%) was filtered, washed with ether and recrystallised (propan-2-ol) to form yellow needles, mp 95 °C (lit.,[16] mp 97 °C).

Reductive alkylation of 3-ethoxycarbonyl-1-methylpyridinium iodide 5 (R = CH_3, X = I) in the presence of zinc and benzyl bromide

3-Ethoxycarbonyl-1-methylpyridinium iodide (5.86 g, 20 mmol) and acetonitrile (100 cm^3) were stirred under nitrogen for 1 h. Benzyl bromide (3.42 g, 20 mmol) was added and the system was cooled to −40 °C. After a further 1 h, activated zinc (2 g)[9] was added over 10 min. The stirred reaction mixture was left to come to room temperature overnight, then added to ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The orange oil produced was *immediately* hydrogenated in ethanol (200 cm^3) over platinum oxide (200 mg) at atmospheric pressure. The catalyst was then removed by filtration through kieselguhr and the filtrate was concentrated *in vacuo*. Purification by column chromatography (eluent: 30% ethyl acetate–hexane) produced a colourless oil (2.70 g, 52%), bp 115 °C/0.01 mmHg. Microanalysis and mass spectrometry indicated a molecular formula corresponding to a tetrahydropyridine (*m/z* = 259). However, the ^1H NMR spectrum indicated that a mixture of tetrahydro isomers **6** (R = CH_3) and **7** (R = CH_3) respectively had formed, in a *ca.* 3:1 ratio. The major isomer **6** (R = CH_3) partially crystallised from light petroleum (bp 40–60 °C) as colourless needles, mp 78–80 °C. HPLC indicated that the sample consisted of a single component [retention time 15 min, (eluent: 60% acetonitrile–water)].

4-Benzyl-3-ethoxycarbonyl-1-methyl-1,4,5,6-tetrahydropyridine 6 (R = CH_3) (Found: C, 74.5; H, 8.3; N, 5.3%; M^+, 259.1579. $C_{16}H_{21}NO_2$ requires C, 74.1; H, 8.2; N, 5.4%; *M*, 259.1572); ν_{max}(Nujol)/cm^{-1} 1677 (C=O str); δ_H(400 MHz, $CDCl_3$) 1.30 (3 H, t, *J* 7.1, CH_2CH_3), 1.55 (1 H, m, 5-H), 1.67 (1 H, m, 5-H), 2.27 (1 H, dd, *J* 10.7 and 13.5, $PhCH_2$), 2.86 (1 H, m, 4-H), 2.96 (1 H, m, 6-H), 2.97 (3 H, s, $N-CH_3$), 3.08 (1 H, dd, *J* 3.5 and 13.5, $PhCH_2$), 3.16 (1 H, dt, *J* 4 and 12.7, 6-H), 4.17 (2 H, ddq, *J* 7.1, 10.7 and 16.8, CH_2CH_3), 7.17–7.31 (5 H, m, aryl), 7.38 (1 H, s, 1-H); δ_C(100.625 MHz, $CDCl_3$) 14.91 (CH_2CH_3), 23.25 (C-5), 31.64 (C-4), 41.83 ($PhCH_2$), 42.96 ($N-CH_3$), 43.76 (C-6), 59.03 (CH_2CH_3), 98.56 (C-3), 125.98, 128.39 and 129.56 (*o*-, *m*- and *p*-aryl), 141.28 (*ipso*-aryl), 146.36 (C-2), 168.66 (C=O).

1-Benzyl-3-ethoxycarbonylpyridinium bromide 5 (R = $PhCH_2$, X = Br)

Benzyl bromide (10.26 g, 60 mmol) was added, dropwise, to a stirred solution of ethyl nicotinate (6.05 g, 40 mmol) in propan-2-ol (15 cm^3) under nitrogen. The mixture was stirred for 18 h and then the crude product was filtered and washed with ether (12.63 g, 98%), mp 132 °C (Found: C, 55.5; H, 4.9; N, 4.2%. $C_{15}H_{16}BrNO_2$ requires C, 55.9; H, 5.0; N, 4.35%); ν_{max}($CHCl_3$)/cm^{-1} 1720 (C=O str); δ_H(90 MHz, $CDCl_3$) 1.43 (3 H, t, CH_2CH_3), 4.45 (2 H, q, CH_2CH_3), 6.6 (2 H, s, $PhCH_2$), 7.4 (3 H, m, aryl), 7.8 (2 H, m, aryl), 8.4 (1 H, t, 5-H), 8.95 (1 H, d, 4-H), 9.9 (1 H, s, 2-H), 10.15 (1 H, d, 6-H).

Reductive alkylation of 1-benzyl-3-ethoxycarbonylpyridinium bromide 5 (R = $PhCH_2$, X = Br) in the presence of zinc and benzyl bromide

A solution of 1-benzyl-3-ethoxycarbonylpyridinium bromide (3.22 g, 10 mmol) and acetonitrile (100 cm^3) was stirred under nitrogen for 2 h. Benzyl bromide (1.71 g, 10 mmol) was then added and the system was cooled to −15 °C. Stirring was continued for a further 0.5 h, before adding activated zinc[9] (1 g) over 10–15 min. The mixture was stirred for a further 4 h at −15 °C and then added to ice–ammonia and extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The orange oil produced was immediately hydrogenated in ethanol (100 cm^3) over platinum oxide (100 mg), in a Cook hydrogenator (room temp., 45 psi). The catalyst was then removed by filtration through kieselguhr and the filtrate was concentrated *in vacuo*. Some of the crude product (2.5 g) was then purified by column chromatography (eluent: 20% ethyl acetate–hexane), to afford a colourless oil (1.15 g, 38%). Microanalysis and mass spectrometry indicated a molecular formula corresponding to a tetrahydropyridine (*m/z* = 335). However, the ^1H NMR spectrum indicated a mixture of tetrahydro isomers **6** (R = $PhCH_2$) and **7** (R = $PhCH_2$) had formed, in a *ca.* 4:1 ratio, respectively, bp 130 °C/0.01 mmHg (Found: C, 78.8; H, 7.5; N, 4.2%; M^+, 335.1904. $C_{22}H_{25}NO_2$ requires C, 78.4; H, 7.5; N, 4.2%; *M*, 335.1885); ν_{max}(film)/cm^{-1} 1727 (C=O str).

1-Benzoyl-4-benzyl-3-ethoxycarbonyl-1,4-dihydropyridine 9

Benzoyl chloride (2.11 g, 1.74 cm^3, 15 mmol) was added to a stirred solution of ethyl nicotinate (2.27 g, 15 mmol) and acetonitrile (50 cm^3) under nitrogen. After 2 h, benzyl bromide (2.57 g, 1.78 cm^3, 15 mmol) was added and the stirred mixture was cooled to 0 °C. Activated zinc[9] (1 g) was added after 15 min, over 10–15 min and stirred for 5 h. The reaction mixture was allowed to come to room temperature and then added to ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*, to produce a yellow oil. Purification by column chromatography (eluent: 15% ethyl acetate–hexane) afforded a colourless, viscous oil (3.56 g, 68%) (Found: M^+, 347.1522. $C_{22}H_{21}NO_3$ requires *M*, 347.1511); ν_{max}(film)/cm^{-1} 1735 and 1675 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.30 (3 H, t, *J* 7.1, CH_2CH_3), 2.80 (1 H, dd, *J* 7.6 and 13.0, $PhCH_2$), 2.96 (1 H, dd, *J* 3.7 and 13.0, $PhCH_2$), 3.69 (1 H, m, 4-H), 4.24 (2 H, q, *J* 7.1, CH_2CH_3), 5.12 (1 H, dd, *J* 5.0 and 8.0, 5-H), 6.85 (1 H, br s, 6-H), 7.14–7.5 (10 H, m, aryl), 7.86 (1 H, br s, 2-H).

2-Ethoxycarbonyl-1-methylpyridinium iodide 11 (R = CH_3, X = I)

Methyl iodide (28.4 g, 0.2 mol) was added dropwise to a stirred solution of ethyl pyridine-2-carboxylate (ethyl picolinate) (15.2 g, 0.1 mol) in dry acetone (15 cm^3) under nitrogen. The mixture was stirred for 18 h, then the crude product was filtered, washed with ether and recrystallised (acetone), to produce yellow needles (23.9 g, 81%), mp 106 °C (lit.,[17] mp 108 °C).

Reductive alkylation of 2-ethoxycarbonyl-1-methylpyridinium iodide 11 (R = CH_3, X = I) in the presence of zinc and benzyl bromide

2-Ethoxycarbonyl-1-methylpyridinium iodide (5.86 g, 20 mmol) and acetonitrile (100 cm^3) were stirred under nitrogen for 1 h. Benzyl bromide (3.42 g, 2 mmol) was then added and the system was cooled to −40 °C. Stirring was continued for a further 1 h, before adding activated zinc[9] (2 g), over 10 min. The stirred reaction mixture was left to come to room temperature overnight, added to ice–ammonia and extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The orange oil produced was *immediately* hydrogenated in ethanol (200 cm^3) over platinum oxide (200 mg), at atmospheric temperature and pressure. The catalyst was then removed by filtration through kieselguhr and the filtrate concentrated *in vacuo*, to give the crude product (4.61 g, 88%). Some of the crude product (2.25 g) was then purified by Kugelrohr distillation and column chromatography (eluent: 10% ethyl acetate–hexane) to yield piperidines **12** (R = CH_3) (0.2 g, 8%), **13** (R = CH_3) (0.7 g, 28%) and **14** (R = CH_3) (0.1 g, 4%), as colourless oils, bp 130 °C/0.01 mmHg.

2-Benzyl-2-ethoxycarbonyl-1-methylpiperidine 12 (R = CH_3) (Found: C, 73.0; H, 8.8; N, 5.2%; M^+, 261.1722. $C_{16}H_{23}NO_2$ requires C, 73.5; H, 8.9; N, 5.4%; *M*, 261.1729) [the methiodide salt had mp 206 °C (Found: C, 50.6; H, 6.5; I, 31.6; N, 3.4%. $C_{17}H_{26}INO_2$ requires C, 50.6; H, 6.5; I, 31.5; N, 3.5%)];

ν_{max}(film)/cm^{-1} 1740 (C=O str); δ_H(400 MHz, $CDCl_3$) 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 1.38 (1 H, m, 3-H), 1.53 (4 H, m, 4-H and 5-H), 1.78 (1 H, m, 3-H), 2.6–2.75 (5 H, m and s, 6-H and N–CH_3), 2.88 (1 H, d, *J* 13.5, PhCH_2), 3.28 (1 H, d, *J* 13.5, PhCH_2), 4.18 (2 H, dq, *J* 4.5 and 7.1, CH_2CH$_3$), 7.16–7.28 (5 H, m, aryl); δ_C(100.625 MHz, $CDCl_3$) 14.56 (CH_2CH_3), 21.49 (C-4), 25.34 (C-5), 32.52 (C-3), 39.73 (N–CH_3), 42.65 (PhCH_2), 52.33 (C-6), 60.13 (CH_2CH$_3$), 66.54 (C-1), 126.54, 128.01 and 130.74 (*o*-, *m*- and *p*-aryl), 137.16 (*ipso*-aryl), 174.01 (C=O).

4-Benzyl-2-ethoxycarbonyl-1-methylpiperidine 13 (R = CH_3) (Found: C, 74.1; H, 9.3; N, 5.6%; M$^+$, 261.1725. $C_{16}H_{23}NO_2$ requires C, 73.5; H, 8.9; N, 5.4%; *M*, 261.1729); ν_{max}(film)/cm^{-1} 1705 (C=O str); δ_H(400 MHz, $CDCl_3$) 1.27 (3 H, t, *J* 7.1, CH_2CH_3), 1.43 (2 H, m, 3-H and 5-H), 1.60 (2 H, m, 4-H and 5-H), 1.84 (1 H, ddd, *J* 2.8, 5.9 and 12.6, 3-H), 1.99 (1 H, dt, *J* 2.6 and 12, 6-H), 2.23 (3 H, s, N–CH_3), 2.53 (2 H, d, *J* 6.8, PhCH_2), 2.59 (1 H, dd, *J* 2.8 and 11.6, 2-H), 2.94 (1 H, ddd, *J* 2.6, 3.9 and 12, 6-H), 4.20 (2 H, dq, *J* 1.0 and 7.1, CH_2CH$_3$), 7.11–7.29 (5 H, m, aryl); δ_C(100.625 MHz, $CDCl_3$) 14.38 (CH_2CH_3), 31.74 (C-5), 36.16 (C-2), 37.38 (C-4), 43.17 (PhCH_2), 44.13 (N-CH_3), 55.86 (C-6), 60.93 (CH_2CH$_3$), 68.75 (C-2), 126.15, 128.42, 129.24 (*o*-, *m*- and *p*-aryl), 140.09 (*ipso*-aryl), 173.59 (C=O).

2-Benzyl-6-ethoxycarbonyl-1-methylpiperidine 14 (R = CH_3) (Found: C, 74.1; H, 9.3; N, 5.8%; M$^+$, 261.1707. $C_{16}H_{23}NO_2$ requires C, 73.5; H, 8.9; N, 5.4%; *M*, 261.1729); ν_{max}(film)/cm^{-1} 1725 (C=O str); δ_H(400 MHz, $CDCl_3$) 1.15–1.30 (5 H, m and t, *J* 7.1, 4-H, 5-H, CH_2CH_3), 1.45 (1 H, m, 5-H), 1.68 (2 H, m, 4-H and 3-H), 1.83 (1 H, m, 6-H), 2.17 (1 H, m, 6-H), 2.38 (3 H, s, N–CH_3), 2.47 (1 H, dd, *J* 9.9 and 13.2, PhCH_2), 2.83 (1 H, dd, *J* 2.8 and 11.4, 2-H), 3.29 (1 H, dd, *J* 3.9 and 13.2, PhCH_2), 4.23 (2 H, q, *J* 7.1, CH_2CH$_3$), 7.15–7.30 (5 H, m, aryl); δ_C(100.625 MHz, $CDCl_3$) 14.41 (CH_2CH_3), 23.76 (C-4), 30.11 (C-3), 30.27 (C-5), 40.35 (PhCH_2), 41.23 (N–CH_3), 60.85 (CH_2CH$_3$), 65.39 (C-6), 69.93 (C-2), 126.15, 128.41 and 129.64 (*o*-, *m*- and *p*-aryl), 139.86 (*ipso*-aryl), 174.19 (C=O).

1-Benzyl-2-ethoxycarbonylpyridinium bromide 11 (R = PhCH_2, X = Br)

Benzyl bromide (10.26 g, 60 mmol) was added, dropwise, to a stirred solution of ethyl pyridine-2-carboxylate (4.54 g, 30 mmol) in propan-2-ol (15 cm^3) under nitrogen. The mixture was stirred for 18 h and the crude product was filtered and washed with ether, to produce a colourless, microcrystalline powder (8.3 g, 86%), mp 94–96 °C (Found: C, 55.8; H, 4.9; N, 4.2%. $C_{15}H_{16}BrNO_2$ requires C, 55.9; H, 5.0; N, 4.35%); ν_{max}(CDCl$_3$)/cm^{-1} 1725 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.30 (3 H, t, *J* 7, CH_2CH_3), 4.42 (2 H, q, *J* 7, CH_2CH$_3$), 6.54 (2 H, s, PhCH_2), 7.35 (5 H, s, aryl), 8.42 (1 H, ddd, *J* 2, 6 and 8, 5-H), 8.53 (1 H, dd, *J* 2 and 8, 3-H), 9.03 (1 H, dt, *J* 1 and 8, 4-H), 10.38 (1 H, d, *J* 6, 6-H).

1,4-Dibenzyl-2-ethoxycarbonylpiperidine 13 (R = PhCH_2)

1-Benzyl-2-ethoxycarbonylpyridinium bromide **11** (R = PhCH_2, X = Br) (3.22 g, 10 mmol) and acetonitrile (100 cm^3) were stirred under nitrogen, for 1 h. Benzyl bromide (1.71 g, 10 mmol) was then added and the system was cooled to −70 °C. The mixture was stirred for 0.5 h, then activated zinc[9] (1 g) was added over 10–15 min. The stirred reaction was left to come to room temperature overnight, then added to ice–ammonia and extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The red oil produced was *immediately* hydrogenated in ethanol (100 cm^3) over platinum oxide (100 mg), in a Cook hydrogenator (room temp., 45 psi). The catalyst was removed by filtration through kieselguhr and the filtrate was concentrated *in vacuo* to give the crude product (3.17 g, 94%). Purification (1 g) by column chromatography (eluent: 15% ethyl acetate–hexane) produced the title compound as a colourless, viscous oil (0.56 g, 52%), bp 120 °C/0.01 mmHg (Found: C, 78.3; H, 8.5; N, 4.0%; M$^+$, 337.2040. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.1; N, 4.15%; *M*, 337.2042) [the methiodide salt had mp 155–157 °C (Found: C, 57.6; H, 6.4; I, 26.3; N, 2.9%. $C_{23}H_{30}INO_2$ requires C, 57.6; H, 6.3; I, 26.5; N, 2.9%)]; ν_{max}(film)/cm^{-1} 1720 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.2–1.6 (7 H, m and t, *J* 7.1, ring C–H and CH_2CH_3), 1.87 (2 H, m, ring C–H), 2.51 (2 H, d, *J* 5.6, PhCH_2), 2.88 (2 H, m, ring C–H), 3.17 (1 H, d, *J* 13.0, PhCH_2), 3.78 (1 H, d, *J* 13.0, PhCH_2), 4.21 (2 H, q, *J* 7.1, CH_2CH$_3$), 7.08–7.39 (10 H, m, aryl).

***N*-Benzylspiro[indane-2,4′-piperidin]-1-one 4 (R = PhCH_2)**

1,4-Dibenzyl-4-ethoxycarbonylpiperidine **2** (R = PhCH_2) (0.65 g, 1.93 mmol) was added to polyphosphoric acid (20 g) and stirred for 24 h at 150 °C. The reaction mixture was then cooled to 60 °C, poured onto ice–water, basified with aqueous sodium hydroxide and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to produce a dark viscous oil. Purification by column chromatography (eluent: 3% ethanol–$CHCl_3$) produced a colourless, crystalline solid (0.28 g, 50%), mp 102–105 °C (Found: C, 82.45; H, 7.6; N, 4.8%; M$^+$, 291.1629. $C_{20}H_{21}NO$ requires C, 82.4; H, 7.3; N, 4.8%; *M*, 291.1623); ν_{max}(KBr)/cm^{-1} 1730 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.1–1.4 (2 H, m, 3-H and 5-H), 2.0–2.25 (4 H, m, 2-H, 3-H, 5-H and 6-H), 2.94 (2 H, dd, *J* 3.9 and 11.7, 2-H and 6-H), 3.04 (2 H, s, PhCH_2), 3.58 (2 H, s, PhCH_2), 7.2–7.4 (6 H, m, aryl), 7.46 (1 H, dd, *J* 1 and 7.6, aryl), 7.6 (1 H, dt, *J* 1 and 7.4, aryl), 7.78 (1 H, d, *J* 7.6, aryl).

2-Ethoxycarbonyl-1-methylpiperidine 15 (R = H)

Ethyl piperidine-2-carboxylate (ethyl pipecolinate) (9.08 g, 60 mmol), water (200 cm^3), glacial acetic acid (70 cm^3, 125 mmol), 36% aqueous formaldehyde (60 cm^3, 72 mmol) and 10% palladium on charcoal (250 mg), were hydrogenated in a Cook hydrogenator, at room temperature and 50 psi. The catalyst was then removed by filtration through kieselguhr and the filtrate was basified with ammonia and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*, to afford a residual oil. Purification by Kugelrohr distillation produced the title compound as a volatile, colourless oil (8.25 g, 80%), bp 60 °C/0.01 mmHg (lit.,[18] bp 94 °C/16 mmHg) [the methiodide salt had mp 127–129 °C (lit.,[19] mp 129 °C)].

2-Benzyl-2-ethoxycarbonyl-1-methylpiperidine 15 (R = PhCH_2)

Butyllithium in hexanes (55 cm^3, 88 mmol) was added, dropwise, to a stirred solution of diisopropylamine (8.905 g, 12.35 cm^3, 88 mmol) in THF (50 cm^3), under nitrogen, at 0 °C. The solution was then cooled to −78 °C and ethyl 1-methylpipecolinate (13.7 g, 14.05 cm^3, 80 mmol) added dropwise, over 15 min. The solution was stirred for a further 30 min, before adding benzyl bromide (16.42 g, 11.42 cm^3, 96 mmol) dropwise. The reaction was left to come to room temperature overnight, then basified with dilute aqueous ammonia and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by Kugelrohr distillation produced the product as a colourless, mobile oil (19.13 g, 92%), bp 115 °C/15 mmHg. This material was identical to compound **12** (R = CH_3).

Reductive alkylation of ethyl nicotinate in the presence of activated zinc and benzoyl chloride

Benzoyl chloride (2.82 g, 20 mmol) was added to a stirred solution of ethyl nicotinate (1.51 g, 10 mmol) and acetonitrile (50 cm^3), under nitrogen, at 0 °C. Activated zinc[9] (2 g) was added after 1 h, over 15 min. After being stirred for 3 d, the reaction mixture was poured onto ice–ammonia and extracted with chloroform. The extracts were then washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product, a dark oil (3.1 g), was *immediately* hydrogenated in ethyl acetate

(100 cm^3) over platinum oxide (150 mg), at atmospheric temperature and pressure, for 3 days. The catalyst was then removed by filtration through kieselguhr and the filtrate was concentrated *in vacuo*. Purification by column chromatography (eluent: 40% ethyl acetate–hexane) yielded bipyridines **19** and **20**.

1,1′-Dibenzoyl-3,3′-ethoxycarbonyl-1,1′,4,4′,5,5′,6,6′-octahydro-4,4′-bipyridine 19. Mp 194–195 °C (Found: C, 69.7; H, 6.1; N, 5.5%; M^+, 516.2267. $C_{30}H_{32}N_2O_6$ requires C, 69.75; H, 6.2; N, 5.4%; *M*, 516.2260); ν_{max}(KBr)/cm^{-1} 1700, 1676 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.21 (6 H, t, *J* 7.1, CH_2CH_3), 1.68 (2 H, br d, ring C–H), 1.90 (2 H, br d, ring C–H), 2.92 (2 H, br s, 4-H and 4′-H), 3.83 (2 H, td, *J* 3.5 and 13.4, ring C–H), 4.14 (6 H, q, *J* 7.1, ring C–H and CH_2CH_3), 7.5 (10 H, m, aryl), 8.05 (2 H, br s, 2-H and 2′-H).

1,1′-Dibenzoyl-5,5′-ethoxycarbonyl-1,1′,2,2′,3,3′,4,4′-octahydro-2,2′-bipyridine 20. Mp 166–168 °C (Found: C, 69.3; H, 6.65; N, 5.4%; M^+, 516.2263. $C_{30}H_{32}N_2O_6$ requires C, 69.75; H, 6.2; N, 5.4%; *M*, 516.2260); ν_{max}(KBr)/cm^{-1} 1702 and 1675 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.14 (6 H, t, *J* 7.1, CH_2CH_3), 1.75 (2 H, br d, ring C–H), 1.95 (2 H, br d, ring C–H), 2.73 (2 H, br s, 6-H and 6′-H), 3.74 (2 H, br t, ring C–H), 3.95–4.15 (4 H, m, CH_2CH_3), 4.35 (2 H, br s, ring C–H), 7.5 (10 H, m, aryl), 7.85 (2 H, br s, 2-H and 2′-H).

3-Benzoyl-4-ethoxycarbonyl-1-methyl-1,2-dihydropyridine 21

4-Ethoxycarbonyl-1-methylpyridinium iodide **1** (R = CH_3, X = I) (2.93 g, 10 mmol) and acetonitrile (75 cm^3) were stirred for 1 h, under nitrogen. Benzoyl chloride (3.09 g, 22 mmol) was added and the system was cooled to −40 °C, stirred for 1 h, then activated zinc[9] (2 g) was added over 10 min. The stirred reaction was then left to come to room temperature overnight, added to ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*, to produce a dark, viscous oil (2.45 g). Half of the crude product was purified by column chromatography (eluent: 20% ethyl acetate–hexane), to yield the product as a yellow–orange solid (0.46 g, 34%), mp 123–125 °C (Found: C, 70.8; H, 6.4; N, 5.05%; M^+, 271.1210. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%; *M*, 271.1209); ν_{max}(KBr)/cm^{-1} 1675 (C=O str); δ_H(400 MHz, $CDCl_3$) 1.26 (3 H, t, *J* 7.1, CH_2CH_3), 3.54 (3 H, s, N–CH_3), 4.21 (2 H, q, *J* 7.1, CH_2CH_3), 4.81 (2 H, s, 2-H), 6.57 (1 H, d, *J* 3.0, vinyl C–H), 6.6 (1 H, d, *J* 3.0, vinyl C–H), 7.49 (2 H, tt, *J* 1.5 and 7.6, *m*-aryl), 7.59 (1 H, tt, *J* 1.5 and 7.4, *p*-aryl), 8.09 (2 H, dt, *J* 1.6 and 8.3, *o*-aryl); δ_C(100.625 MHz, $CDCl_3$) 14.58 (CH_2CH_3), 34.40 (N–CH_3), 35.79 (C-2), 59.55 (CH_2CH_3), 109.80 (C-5), 113.77 (C-3), 122.45 (C-6), 128.58 (*m*-aryl), 128.85 (*o*-aryl), 132.52 (C-4), 133.54 (*p*-aryl), 136.69 (*ipso*-aryl), 165.52 (C=O), 196.29 (C=O).

Attempted Diels–Alder reaction of 3-benzoyl-4-ethoxycarbonyl-1-methyl-1,2-dihydropyridine 21 with 4-phenyl-1,2,4-triazoline-3,5-dione

To a stirred solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.064 g, 0.368 mmol) in dry dichloromethane (10 cm^3) was added, dropwise, a solution of the dihydropyridine (0.1 g, 0.368 mmol) in dry dichloromethane (10 cm^3), under nitrogen, at −50 °C. The mixture was allowed to come to room temperature and the solvent was removed *in vacuo*. The brown solid produced was washed with ether, filtered and concentrated *in vacuo*. Purification by column chromatography (eluent: 2% ethanol–chloroform), produced the unstable 'ene' adduct **22** (0.09 g, 55%), mp 245 °C (decomp.) (Found: M^+, 446.1604. $C_{24}H_{22}N_4O_5$ requires *M*, 446.1590); ν_{max}(KBr)/cm^{-1} 3300–2800 (N–H str), 1769, 1708 and 1700 (C=O str); δ_H(250 MHz, [$^2H_6$]DMSO) 1.11 (3 H, t, *J* 7.1, CH_2CH_3), 3.47 (3 H, s, N–CH_3), 4.08 (2 H, q, *J* 7.1, CH_2CH_3), 4.95 (2 H, s, 2-H), 6.71 (1 H, s, 6-H), 7.4–7.8 (8 H, m, aryl), 8.09 (2 H, d, *J* 8.2, aryl), 11.46 (1 H, br s, N–H); δ_C(100.625 MHz, [$^2H_6$]DMSO) 14.13 (CH_2CH_3), 30.31 (N–CH_3), 35.75 (C-2), 59.13 (CH_2CH_3), 105.37 (C-6), 111.47 (C), 126.53, 128.14, 128.82, 128.88 and 133.58 (aryl and vinyl C–H), 123.19, 131.61, 133.02 and 136.17 (*ipso*-aryl and vinyl C), 151.34, 151.98, 163.68, 195.59 (C=O).

Reductive alkylation of 3-ethoxycarbonyl-1-methylpyridinium iodide 5 (R = CH_3, X = I) in the presence of activated zinc and benzoyl chloride

3-Ethoxycarbonyl-1-methylpyridinium iodide (2.93 g, 10 mmol) and acetonitrile (75 cm^3) were stirred under nitrogen for 1 h. Benzoyl chloride (1.69 g, 12 mmol) was added and the system was cooled to −40 °C, stirred for 1 h, then activated zinc[9] (1 g) was added over 10 min. The stirred reaction was left to come to room temperature overnight, then added to ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (eluent: 30% ethyl acetate–hexane) yielded components **A** (0.07 g, 4%), mp 170–173 °C, **B** (0.13 g, 7%), mp 160 °C and **C** (0.16 g, 9%), mp 150–151 °C. The ^1H NMR spectrum of **A** was too complex to allow determination of the structural formula.

Component A: Pentabenzoyl-5-ethoxycarbonyl-1-methylpiperidine. (Found: C, 76.05; H, 5.6; N, 1.9%; M^+, 691.2555. $C_{44}H_{37}NO_7$ requires C, 76.4; H, 5.4; N, 2.0%; *M*, 691.2570); ν_{max}(KBr)/cm^{-1} 1740, 1712 and 1676 (C=O str).

2,3,3-Tribenzoyl-5-ethoxycarbonyl-1-methyl-1,2,3,4-tetrahydropyridine (B). (Found: C, 74.6; H, 5.5; N, 2.8%; M^+, 481.1889. $C_{30}H_{27}NO_5$ requires C, 74.8; H, 5.65; N, 2.9%; *M*, 481.1889); ν_{max}(Nujol)/cm^{-1} 1730 and 1675 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.34 (3 H, t, *J* 7.1, CH_2CH_3), 2.40 (1 H, d, *J* 10.5, 4-H), 2.58 (1 H, d, *J* 10.5, 4-H), 2.68 (3 H, s, N–CH_3), 4.28 (2 H, q, *J* 7.1, CH_2CH_3), 5.08 (1 H, s, 6-H), 7.02–7.7 (12 H, m, 2-H and aryl), 8.03 (2 H, dd, *J* 1.5 and 8.6, aryl), 8.16 (2 H, dd, *J* 1.6 and 8.6, aryl).

3,3,4-Tribenzoyl-5-ethoxycarbonyl-1-methyl-1,2,3,4-tetrahydropyridine (C). (Found: C, 74.9; H, 5.6; N, 2.8%; M^+, 481.1887. $C_{30}H_{27}NO_5$ requires C, 74.8; H, 5.65; N, 2.9%; *M*, 481.1889); ν_{max}(KBr)/cm^{-1} 1728, 1695 and 1670 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.01 (3 H, t, *J* 7.1, CH_2CH_3), 2.08 (1 H, d, *J* 9.7, 6-H), 3.10 (1 H, *J* 9.7, 6-H), 3.23 (3 H, s, N–CH_3), 3.95 (2 H, dq, *J* 3.5 and 7.1, CH_2CH_3), 4.91 (1 H, s, ring C–H), 7.2–7.6 (12 H, m, 2-H and aryl), 7.99 (2 H, dd, *J* 1.3 and 8.3, aryl), 8.2 (2 H, dd, *J* 1.3 and 8.2, aryl).

1,4-Dibenzoyl-4-ethoxycarbonyl-1,4-dihydropyridine 18

Benzoyl chloride (5.62 g, 40 mmol) was added to a stirred solution of ethyl isonicotinate (1.51 g, 10 mmol) and acetonitrile (50 cm^3), under nitrogen. After 1 h, the system was cooled to −40 °C and activated zinc[9] (2 g) was added, over 10–15 min. The stirred mixture was left to come to room temperature overnight, then poured onto ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*, to produce a dark viscous oil. Purification by column chromatography (eluent: 25% ethyl acetate–hexane), yielded a colourless solid (0.72 g, 20%), mp 92–94 °C (Found: C, 72.7; H, 5.6; N, 3.9%; M^+, 361.1310. $C_{22}H_{19}NO_4$ requires C, 73.1; H, 5.3; N, 3.9%; *M*, 361.1314); ν_{max}(KBr)/cm^{-1} 1753 and 1675 (C=O str); δ_H(250 MHz, $CDCl_3$) 1.17 (3 H, t, *J* 7.1, CH_2CH_3), 4.21 (2 H, q, *J* 7.1, CH_2CH_3), 5.42 (2 H, br d, 3-H and 5-H), 7.2 (2 H, br s, 2-H and 6-H), 7.4–7.7 (8 H, m, aryl), 7.92 (2 H, dd, *J* 1.5 and 7.1, aryl).

1-Benzoyl-4-ethoxycarbonyl-4-ethoxycarbonylmethyl-1,4-dihydropyridine 17

Benzoyl chloride (1.40 g, 10 mmol) was added to a stirred solution of ethyl isonicotinate (1.51 g, 10 mmol) and acetonitrile (50 cm^3), under nitrogen and stirring was continued for 2 h at room temperature. Ethyl bromoacetate (1.84 g, 10 mmol) was added and the mixture was cooled to −40 °C. After 15 min, activated zinc[9] (2 g) was added. The stirred mixture was left to

come to room temperature overnight, then poured into ice–ammonia and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Some of the crude product (2.90 g) was purified by column chromatography (eluent: 20% ethyl acetate–hexane), yielding ethyl isonicotinate (0.25 g) and the title compound (0.31 g, 11%), as a colourless oil (Found: C, 66.2; H, 6.25; N, 3.85%; M^+, 343.1420. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%; *M*, 343.1420); ν_{max}(film)/cm^{-1} 1730 and 1675 (C=O str); δ_H(400 MHz, $CDCl_3$) 1.25 (3 H, t, *J* 7.1, CH_2CH_3), 1.29 (3 H, t, *J* 7.1, CH_2CH_3), 2.79 (2 H, s, CH_2), 4.12 (2 H, q, *J* 7.1, CH_2CH_3), 4.21 (2 H, q, *J* 7.1, CH_2CH_3), 5.16 (2 H, br s, 3-H and 5-H), 7.05 (2 H, br s, 2-H and 6-H), 7.4–7.55 (5 H, m, aryl); δ_C(100 MHz, $CDCl_3$) 14.27 (CH_2CH_3), 14.36 (CH_2CH_3), 44.82 (CH_2), 45.98 (CH_2), 60.9 (CH_2CH_3), 61.85 (CH_2CH_3), 128.57, 128.78 and 131.43 (*o*-, *m*- and *p*-aryl), 128.62, 130.30 and 133.44 (*ipso*-aryl and vinyl C–H), 167.5, 170.0 and 172.73 (C=O).

Acknowledgements

J. MacTavish thanks Organon Laboratories Ltd. for a studentship.

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Paper 6/01653G
Received 8*th March* 1996
Accepted 4*th June* 1996