Bridged-ring Nitrogen Compounds. Part 5.[1] Synthesis of 2,6-Methano-3-benzazonine ring-systems

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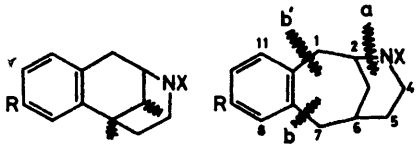
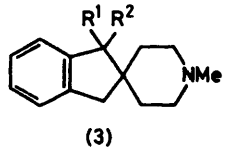
Syntheses of *cis*- and *trans*-4-benzyl- and 4-(3-methoxybenzyl)-2-methoxycarbonyl-1-methylpiperidines are described; amino-acids and amino-alcohols obtained from these compounds failed to cyclise. *cis*-2-Benzyl-4-ethoxycarbonyl-1-methylpiperidine has been made and its amino-acid hydrochloride cyclised in polyphosphoric acid at 160 °C to give 2,4,5,6,7-hexahydro-3-methyl-2,6-methano-1*H*-3-benzazonin-7-one which was converted into several derivatives. 4-Benzyl-4-ethoxycarbonyl-1-methylpiperidine, obtained by two routes, was hydrolysed and cyclised to give *N*-methylspiro[indane-2,4'-piperidine]-1-one which was also converted into several derivatives.

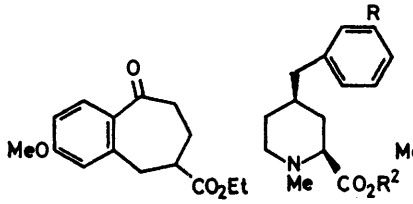
A STUDY of molecular models reveals that there is a strong similarity between the benzomorphan [2] ring-system (1) and the hitherto unknown hexahydro-2,6-methano-3-benzazonines (2). The subtle differences in bond angles of compounds (2) might be expected to lead to modified and, hopefully, useful pharmacological responses in tests for ' CNS ' activity. Accordingly, we have investigated several synthetic approaches to hexahydro-2,6-methano-3-benzazonines and have discovered



(1) (2)



(3)
a; R^1,R^2=O
b; R^1=OH, R^2=H
c; R^1=OH, R^2=Ph



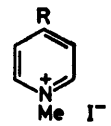
(4) (5) (6)
a; R^1=H, R^2=Me
b; R^1=R^2=H, HCl
c; R^1=OMe, R^2=Me

one which is not only successful for the expected products, but also, unexpectedly makes available isomeric materials having the spiro[indane-2,4'-piperidine] structure (3).

RESULTS AND DISCUSSION

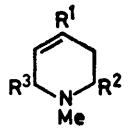
One synthetic route to the title compound from 8-ethoxycarbonyl-6,7,8,9-tetrahydro-2-methoxy-5*H*-benzocyclohepten-5-one (4) involved, as the final step, forming bond a in compounds (2). This approach proved tedious [1] and has now been abandoned. Alternative routes in which bonds b and b' [in compounds (2)] were formed during the ultimate step were next examined. The route involving b' is attractive because it suggests an intramolecular Friedel–Crafts cyclisation of a 4-benzylpiperidine-2-carboxylate [*e.g.* compounds (5)] in which a methoxy-group (5c) might aid cyclisation and so appear in the product (6) in a position analogous to the traditional bridged-ring analgesics.[2] Moreover, 4-phenylpiperidine-2-carboxylates have been cyclised to benzomorphans by May and his co-workers.[3,4] In the event, we had to use a modified procedure to introduce the required C≡N group into the 2-position of 4-benzylpyridines and thence were able to obtain the required 4-benzylpiperidine-2-carboxylates (5a) and (5c).

Commercially available 4-benzylpyridine was converted into the *N*-oxide [5] which reacted vigorously with dimethyl sulphate.[3] Further reaction with aqueous cyanides gave intractable materials. Likewise, the methiodide of 4-benzylpyridine reacted with cyanide to give unworkable mixtures. Unless air was excluded, 4-benzylpyridines treated with methyl iodide gave 4-



(7)

a; R = CH_2Ph
b; R = COPh
c; R = $CH_2C_6H_4OMe$-*m*
d; R = $CO{\cdot}C_6H_4OMe$-*m*
e; R = $CH(OH)C_6H_4OMe$-*m*
f; R = CO_2Et

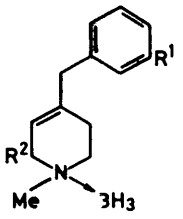


(8)

a; R^1 = CH_2Ph, R^2 = CN, R^3 = H
b; R^1 = CH_2Ph, R^2 = CO_2Me, R^3 = H
c; R^1 = CH_2Ph, R^2 = R^3 = H
d; R^1 = $CH_2C_6H_4OMe$-*m*, R^2 = CN, R^3 = H
e; R^1 = $CH_2C_6H_4OMe$-*m*, R^2 = CO_2Me, R^3 = H
f; R^1 = $CH_2C_6H_4OMe$-*m*, R^2 = R^3 = H
g; R^1 = $CH_2C_6H_4OMe$-*m*, R^2 = $CONH_2$, R^3 = H
h; R^1 = $CH(OH)C_6H_4OMe$-*m*, R^2 = CN, R^3 = H
i; R^1 = CO_2Et, R^2 = H, R^3 = CH_2Ph
j; R^1 = CO_2Et, R^2 = R^3 = H

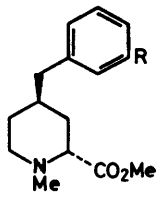
benzoyl-*N*-methylpyridinium iodides. The work of Fry [6] suggested a way round these problems: thus the pyridinium salt (7a) was treated with cyanide anion and sodium borohydride in ether–water. The products were

the tetrahydrocyano-compound (62%) and the borane complex (9a) (14%). Optimum methanolysis [7] of the cyano-compound occurred at 55 °C yielding the ester (8b) in 45% yield accompanied by the pyridine (8c) in 28% yield.



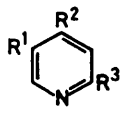
(9)

a; $R^1 = R^2 =$
b; $R^1 = OMe, R^2 = H$
c; $R^1 = OMe, R^2 = CN$



(10)

a; R = H
b; R = OMe



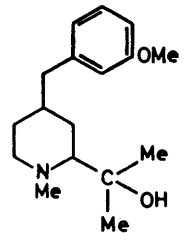
(11)

a; $R^1 = R^3 = H$, $R^2 = CH(OH)C_6H_4OMe$-*m*
b; $R^1 = R^3 = H$, $R^2 = CH_2C_6H_4OMe$-*m*
c; $R^1 = COPh$, $R^2 = CO_2Et$, $R^3 = C_6H_4OMe$-*m*
d; $R^1 = COPh$, $R^2 = CO_2H$, $R^3 = C_6H_4OMe$-*m*
e; $R^1 = H$, $R^2 = CO_2Et$, $R^3 = C_6H_4OMe$-*m*

Catalytic hydrogenation of the ester (8b) gave the desired *cis*-ester (5a) along with the *trans*-ester (10a). Epimerisation of the *trans*-ester into the *cis*-ester was completed by stirring the original mixture in acetic acid for 4 d. Short-path column chromatography separated the *cis*-ester (5a) (68%) from the *trans*-ester (10a) (22%); these were distinguished by n.m.r. spectroscopy. In particular, the *trans*-ester (10a) exhibited a double doublet (δ 3.3) with low coupling constant, indicative of an equatorial rather than an axial proton at C-2; this feature was absent from the *cis*-ester (5a). Repeated attempts to cyclise both the esters and their corresponding amino-acid hydrochlorides in polyphosphoric acid (PPA) failed; no ketonic material could be identified in the multicomponent mixtures obtained at temperatures of up to 160 °C.

4-(3-Methoxybenzyl)pyridine (11b) was obtained in two steps from pyridine-4-carbaldehyde. The latter, when treated with the Grignard reagent produced from 3-bromoanisole, yielded the pyridyl alcohol (11a) which was reduced by zinc in refluxing formic acid to give the desired pyridine. In this case, attempts to prepare the *N*-oxide gave only (in poor yield) the *N*-oxide of 4-(3-methoxybenzoyl)pyridine. Surprisingly, the pyridyl alcohol (11a) gave [5] the expected *N*-oxide in 60% yield. However, the latter compound could not be utilised in May's type [3,4] of synthesis, the sequence failing, as before, at the stage involving the cyanide ion. Our successful synthesis proceeded from the pyridinium salt (7c) which was reduced with sodium borohydride in presence of cyanide ion, as described above. In this case, the products were the required cyano-tetrahydropyridine (8a) (59%), the borane complex (9b) (12%), and the borane complex (9c) (4%). Thereafter the synthesis was analogous to that of the parent benzyl ester (see Experimental section) and yielded both the *cis*-ester (5c) and the *trans*-ester (10b), the stereochemistry of which was assigned by n.m.r. spectroscopy as before. Attempts to cyclise these esters or the amino-acid hydrochloride obtained from (5c) with PPA in the temperature range 100—190 °C all failed. The only product isolated was the decarboxylated 4-(3-methoxybenzyl)piperidine which was independently obtained by catalytic hydrogenation of the methiodide (7c)

It appeared that the well known tendency of α-amino-acid derivatives to decarboxylate is a lower-energy process than the alternative, desired cyclisation which requires inversion of the piperidine ring to place both the substituents in compounds (5) in axial positions.[3] The



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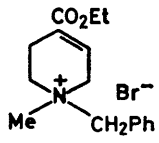

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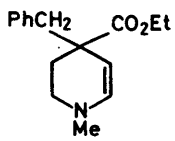

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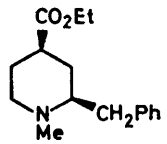

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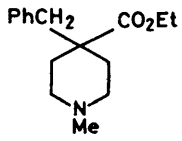

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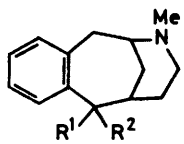
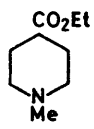


(17)

a; $R^1, R^2 = O$
b; $R^1 = OH, R^2 = H$



(18)

tertiary alcohol (12) was obtained from the corresponding *cis*-ester, but gave intractable materials with hot PPA. Accordingly, attention was directed to the synthesis of piperidine compounds carrying the substituent in reversed positions, *i.e* *cis*-2-benzylpiperidine-4-carboxylates.

2-Benzylpyridine-3-carboxylic acid is synthesized [8] in several steps, starting from 4-picoline and benzyl chloride. In our hands this reaction proved capricious at the stage involving oxidation of the methyl group with nitric acid, so we examined alternative methods, such as reaction of quaternary salts of ethyl isonico-

tinate (7f) with benzyl Grignard reagents.[9] This proved fruitless, as did other Grignard reactions [10-12] with the *N*-oxide of ethyl isonicotinate, although in model reactions (3-methoxyphenyl)magnesium bromide treated with the *N*-oxide in the presence of benzoyl chloride [10] gave the doubly substituted pyridine ester (11c). The same Grignard reagent treated with the acetate of the *N*-oxide [12] gave the ester (11e), both in low yield.

Finally, we turned to a synthesis depending upon the Stevens rearrangement.[13] This reaction has been applied [2,9] in benzomorphan syntheses using phenyllithium as the basic reagent. Our proposition was that since ester groups are probably incompatible with phenyllithium, a non-nucleophilic base would be required to convert the salt (13) into the amino-ester (8i) and it was thought [13] that, since this was a conjugated system, potassium t-butoxide might suffice.[14] This proved to be the case, the rearrangement giving >70% yield. Thus the synthesis of the required 2-benzylpiperidine-4-carboxylate (15) was achieved in moderate overall yield (see Experimental section) in four operationally simple steps from the quaternary salt (7f). The latter was reduced by $NaBH_4$ in mildly acidic medium to the tetrahydropyridine ester (8j), required to make the salt (13).

Interestingly, catalytic reduction of the Stevens-rearrangement product (8i) [later shown by g.l.c. to be a mixture including compound (14)] gave a mixture of isomeric esters (ratio *ca.* 5 : 1) which could be separated by column chromatography or by utilising their different rates of hydrolysis. Thus the minor isomer was comparatively resistant to hydrolysis by dilute alkali. The major isomer (15) was converted into the corresponding amino-acid hydrochloride, which cyclised in PPA at 160 °C during 24 h to give a ketone $C_{14}H_{17}NO$, which showed carbonyl absorption at $\nu_{max.}$ 1 680 cm^{-1}. The molecular formula was confirmed by conversion into a 2,4-dinitrophenylhydrazone, a methiodide, a perchlorate, and several other derivatives, including the corresponding alcohol by $NaBH_4$ reduction. Thus we conclude that this amino-ketone has structure (17a).

When the minor isomer (16), obtained from the above reduction, was converted into the corresponding amino-acid hydrochloride, the latter cyclised at 20 °C in methanesulphonic acid containing P_2O_5 [15,16] to give a different ketone, $C_{14}H_{17}NO$ ($\nu_{max.}$ 1 710 cm^{-1}). The molecular formula was confirmed by synthesis of the 2,4-dinitrophenylhydrazone methiodide, and *N*-pentyl iodide derivatives, the corresponding alcohol ($NaBH_4$ or H_2–Pd), and the Grignard product (PhMgBr). ^1H N.m.r. spectroscopy (particularly 360 MHz) revealed a 2-H singlet at δ 2.96 in the ketone, suggestive of structures (3) which, in turn, indicated that the precursor ester had structure (16). This deduction was confirmed by an alternative synthesis of compound (16) by benzylation of the ester (18) using benzyl bromide in the presence of lithium di-isopropylamide.[17] ^1H N.m.r. spin-decoupling experiments (300 MHz) on the ketones (3a) and (17a) confirmed the structures.

Thus it is concluded that the amino-ketone (3a) is a member of an almost unknown [18] class of spiro-compounds. Either of the syntheses of compound (16) mentioned here is convenient for precursors of the spiro[indane-2,4′-piperidine] (3) ring-system. Appearance of both the isomers (8i) and (14) in the Stevens rearrangement can be understood on the basis of an ambident radical-pair intermediate.[19] Only one 2-benzylpiperidine-4-carboxylic ester, (15), was isolated, although in a few 1,3-disubstituted piperidines, the *trans*-isomer (*eq,ax* or *ax,eq*) is found in significant proportions.[20-22] Normally [23] the *cis*-isomer (*eq,eq*) predominates as one would expect.[24]

Biological results on these compounds will be reported elsewhere.

EXPERIMENTAL

4-Benzylpyridine N-Oxide.—4-Benzylpyridine (3.2 g), glacial acetic acid (15 cm^3), and 30% hydrogen peroxide solution (4.5 cm^3) were stirred at 75 °C for 15 h. Another aliquot of hydrogen peroxide solution was added and the mixture was heated for a further 24 h. Evaporation of the volatile matter under reduced pressure, basification with 2M sodium hydroxide, and evaporation of the dried (Na_2SO_4) chloroform extracts yielded a yellow oil (2.95 g) which gave the *product* (2.8 g, 86%) on crystallisation from benzene, m.p. 107—108 °C (Found: C, 77.7; H, 6.0; N, 7.7. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%); $\nu_{max.}$ (Nujol) 1 615 and 1 385 cm^{-1} (ring-stretching modes of heterocyclic *N*-oxide); δ 3.8 (2 H, s, benzylic CH_2), 6.7—7.2 (7 H, m, aryl and pyridyl), and 7.9 (2 H, d, *J* 7 Hz, pyridyl).

4-Benzyl-1-methylpyridinium Iodide (7a).—Freshly distilled iodomethane (9 cm^3) was added in drops to 4-benzylpyridine (9.0 g) in dry acetone (50 cm^3) under nitrogen at room temperature and the resulting mixture was stirred for 10 h. The pale yellow, crystalline solids were filtered off and crystallised from acetone under nitrogen to give the *product* (7a) (15.15 g, 91%) as needles, m.p. 118—120 °C (Found: C, 49.7; H, 4.6; N, 4.4. $C_{13}H_{14}IN$ requires C, 50.0; H, 4.5; N, 4.5%); $\nu_{max.}$ (Nujol) 1 645, 1 600, and 1 520 cm^{-1} (ring-stretching modes of pyridinium ions); δ[$(CD_3)_2SO$] 3.35 (2 H, s, benzylic CH_2), 4.27 (3 H, s, $\overset{+}{N}Me$), 7.1—7.3 (5 H, m, aryl), 8.15 (2 H, d, *J* 7 Hz, 3- and 5-H), and 9.05 (2 H, d, *J* 7 Hz, 2- and 4-H).

4-Benzoyl-1-methylpyridinium Iodide (7b).—The preparation was carried out as above except aerobic conditions were used. The crude *product* (7b) crystallised from acetone as yellow prisms (65%), m.p. 181—182 °C (Found: C, 47.85; H, 3.6; N, 4.6. $C_{13}H_{12}INO$ requires C, 48.0; H, 3.7; N, 4.3%); $\nu_{max.}$ (Nujol) 1 665 (C=O) and 1 645, 1 605, and 1 520 cm^{-1} (ring-stretching modes of pyridinium ion); δ[$(CD_3)_2SO$] 4.35 (3 H, s, $\overset{+}{N}Me$), 7.3—7.7 (5 H, m, aryl), 8.15 (2 H, d, *J* 7 Hz, 3- and 5-H), and 9.05 (2 H, d, *J* 7 Hz, 2- and 6-H).

4-Benzyl-2-cyano-1,2,3,6-tetrahydro-1-methylpyridine (8a).[6] —A solution of potassium cyanide (4.0 g) in water (20 cm^3) layered with ether (35 cm^3) at 5 °C was treated in drops with 6M hydrochloric acid (4.5 cm^3). The methiodide (7a) (6.5 g, 20 mmol) was then dissolved in the cold solution and sodium borohydride (0.9 g) was added The mildly effervescing solution was stirred and allowed to come to room temperature during 4 h. The ethereal layer was separated, washed with water, dried (Na_2SO_4), and concentrated under re-

duced pressure to give a pale red oil (4.3 g). Column chromatography on silica gel (elution with ethanol in chloroform) isolated the *product* (8a) as a clear oil (2.35 g, 62%) (Found: C, 79.6; H, 7.6; N, 12.8. $C_{11}H_{16}N_2$ requires C, 79.2; H, 7.6; N, 13.2%); $\nu_{max.}$ (film) 2 200 (C≡N) and 1 665 cm^{-1} (C=C); δ 1.8—2.2 (1 H, m, 3-CH_2), 2.35 (3 H, s, NMe), 2.8—3.2 (2 H, m, 6-CH_2), 3.25 (2 H, s, benzylic CH_2), 3.6—3.75 (1 H, m, 2-H), 5.35 (1 H, m, olefinic), and 6.9—7.2 (5 H, m, aryl). A by-product of higher R_F, *4-benzyl-1,2,3,6-tetrahydro-1-methylpyridine*(N—B)*borane* (9a), was isolated as crystalline material (0.55 g, 14%), m.p. (from ether) 60—62 °C (Found: C, 77.4; H, 10.1; B, 4.4; N, 6.65%; *M*, 201.1677. $C_{13}H_{20}BN$ requires C, 77.6; H, 10.0; B, 5.4; N, 7.0%; *M*, 201.1689); $\nu_{max.}$ (Nujol) 2 360, 2 305, and 2 260 (BH_3-stretching modes) and 1 670 cm^{-1} (C=C); δ 1.9—2.15 (2 H, m, 3-CH_2), 2.45 (3 H, s, NMe), 2.8—3.2 (4 H, m, 2- and 6-CH_2), 3.25 (2 H, s, benzylic CH_2), 5.25 (1 H, m, olefinic), and 6.9—7.25 (5 H, m, aryl); δ_C 24.389 (t, benzylic C), 43.197 (q, NMe), 47.141 (t, 3-C), 55.877 (t, 6-C), 58.426 (t, 2-C), 117.216 (d, 4′-C), 126.438, 128.438, and 128.743 (d, 2′- and 6′-C; d, 3′- and 5′-C; and d, 5-C), 135.053 (s, 4-C), and 138.451 p.p.m. (s, 1′-C). A boron (^{11}B) n.m.r. spectrum was obtained in which the ^{11}B resonance appeared as a quartet, −2 650.1, −2 701.2, −2 849.1, and −2 945.6 p.p.m.

4-Benzyl-1,2,3,6-tetrahydro-2-methoxycarbonyl-1-methylpyridine (8b).—A solution of the foregoing nitrile (8a) (6 g) in methanol (200 cm^3) saturated with hydrogen chloride gas was heated at 55 °C for 50 h. The liquors were basified with sodium hydrogencarbonate and the liberated oil was shaken into chloroform. Concentration of the dried (Na_2SO_4) extracts gave a dark yellow oil which was purified by short-path column chromatography on silica gel (250 g) [elution with ethyl acetate in light petroleum (b.p. 60—80 °C)] to give the *product* (8b) as a yellow oil (3.7 g, 45%) (Found: C, 73.8; H, 8.1; N, 5.8. $C_{15}H_{19}NO_2$ requires C, 73.5; H, 7.8; N, 5.7%); $\nu_{max.}$ (film) 2 840, 2 810, and 1 740 cm^{-1} (C=O); δ 2.1—2.35 (2 H, m, 3-CH_2), 2.35 (3 H, s, NMe), 2.8—3.1 (3 H, m, 6-CH_2 and 2-H), 3.2 (2 H, s, benzylic CH_2), 3.55 (3 H, s, CO_2Me), 5.35 (1 H, br s, olefinic), and 6.9—7.2 (5 H, m, aryl). A component of lower R_F, *4-benzyl-1,2,3,6-tetrahydro-1-methylpyridine* (8c) was also isolated as a liquid (1.7 g, 28%), b.p. 125—130 °C at 0.2 Torr (Found: C, 83.3; H, 9.45; N, 7.5. $C_{13}H_{17}N$ requires C, 83.35; H, 9.15; N, 7.5%); $\nu_{max.}$ (film) 2 840, 2 780, 1 600, and 1 380 cm^{-1}; δ 2.0 (2 H, m, 2-CH_2), 2.2 (3 H, m, NMe), 2.35 (2 H, t, 3-CH_3), 2.8 (2 H, m, 6-CH_2), 3.15 (2 H, s, benzylic CH_2), 5.25 (1 H, m, olefinic), and 6.9—7.1 (5 H, m, aryl).

trans- *and* cis-*4-Benzyl-2-methoxycarbonyl-1-methylpiperidine* (10a) *and* (5a) *respectively*.—The amino-ester (8b) and 5% platinum-on-charcoal catalyst (150 mg) in acetic acid (65 cm^3) were shaken under hydrogen at room temperature and atmospheric pressure (1 mol equiv. of gas was absorbed during 5 h). The reaction mixture was then stirred for a further 92 h. After removal of the catalyst by filtration and of the solvent under reduced pressure, the residue was dissolved in water (25 cm^3), basified with sodium hydrogencarbonate, and the liberated oil was shaken into chloroform. The bulked and dried (Na_2SO_4) extracts, on concentration under reduced pressure gave a clear, pale yellow oil (2.2 g). Short-path column chromatography on silica gel (200 g) (elution with anhydrous ether) isolated the *product* (5a) as a pale yellow oil (1.48 g, 68%) (Found: C, 73.1; H, 8.75; N, 5.7%; *M*, 247.1575. $C_{15}H_{21}NO_2$ requires C, 72.9; H, 8.6; N, 5.7%; *M*, 247.1572); $\nu_{max.}$ (film) 1 742 cm^{-1} (C=O); δ 1.2—2.0 (6 H, m, methylene protons), 2.15 (3 H, s, NMe), 2.45 (2 H, d, benzylic CH_2), 2.6—3.0 (2 H, m, methylene protons), 3.65 (3 H, s, CO_2Me), and 6.9—7.2 (5 H, m, aryl).

A component of slightly higher R_F, the trans-*isomer* (10a), was isolated as an oil (0.47 g, 21.7%) (Found: C, 73.4; H, 8.4; N, 5.7%; *M*, 247.1572. $C_{15}H_{21}NO_2$ requires C, 72.9; H, 8.6; N, 5.7%; *M*, 247.1572); $\nu_{max.}$ (film) 1 745 cm^{-1} (C=O); δ 1.2—2.1 (6 H, m, methylene protons), 2.33 (3 H, s, NMe), 2.5 (2 H, d, benzylic), 2.7—2.95 (1 H, m), 3.25—3.4 (1 H, dd, 2-CH *eq*), 3.57 (3 H, s, CO_2Me), and 6.8—7.15 (5 H, m, aryl).

The *cis*-pipecolate ester (5a) (6.5 g) and 12M hydrochloric acid (80 cm^3) were refluxed for 10 h and then evaporated to dryness under reduced pressure. The brown solids, on washing with ether, gave *cis-4-benzyl-2-hydroxycarbonyl-1-methylpiperidine* as a pale brown, hygroscopic solid (4.7 g, 70%); $\nu_{max.}$ (Nujol) 3 310, 2 640, and 1 730 cm^{-1}. The pipecolic acid hydrochloride (5b) was used without further purification.

Attempted Cyclisation of the Hydrochloride (5b).—The pipecolic acid hydrochloride (5b) (1.5 g) and polyphosphoric acid (PPA) (35 g) were heated slowly to 130 °C and then held at 145 °C for 10 h. The cooled solution was basified to pH 7 with sodium hydroxide solution and extracted thoroughly with butanol–chloroform. The bulked and dried (Na_2SO_4) extracts, on concentration under reduced pressure, gave an intractable brown gum (0.77 g), which t.l.c. showed to be a multicomponent mixture. Similar results were obtained at 160 °C.

Attempted Cyclisation of the Piperidine (5a).—The *cis*-pipecolate ester (1.0 g) and PPA (40 g) were stirred at 145 °C for 10 h. Work-up as in the previous experiment gave a dark oil (0.27 g) which t.l.c. showed to be a multicomponent mixture containing much polar material. No separation was attempted.

4-(α-Hydroxy-3-methoxybenzyl)pyridine (11a).—A solution of pyridine-4-carbaldehyde (Aldrich Chemical Co.) (48.5 g, 0.45 mol) in anhydrous ether (100 cm^3) was added in drops during 1 h to the Grignard solution prepared from magnesium turnings (12.17 g, 0.5 mol), *m*-bromoanisole (92 g, 0.51 mol), and anhydrous ether (100 cm^3). The reaction mixture was refluxed for a further 0.5 h and the slurry was then poured into aqueous ammonium chloride. Filtration yielded the crude *product* (11a) which crystallised from dichloromethane as prisms (68.4 g, 71%), m.p. 120—121 °C (Found: C, 72.2; H, 6.2; N, 6.3. $C_{13}H_{13}NO_2$ requires C, 72.6; H, 6.1; N, 6.5%); $\nu_{max.}$ (Nujol) 3 350 (OH), 2 830, 1 260, and 1 050 cm^{-1}; δ 3.63 (3 H, s, OMe), 4.5 (1 H, br s, exchangeable OH), 5.55 (1 H, s, benzylic CH), 6.5—7.2 (6 H, m, aryl), and 8.1 (2 H, br s, 2- and 6-H).

4-(3-Methoxybenzyl)pyridine (11b).—The foregoing alcohol (11a) (50 g), granular zinc (120 g), and formic acid (625 cm^3) were refluxed (140 °C) for 36 h. The resultant mixture was cooled, the solids were filtered off and the filtrate was concentrated under reduced pressure. The residual oil was diluted with water and basified with 1M sodium hydroxide and the liberated oil shaken into chloroform. The bulked extracts were dried (Na_2SO_4) and concentrated, and the residue was distilled under reduced pressure to give the *product* (11b) (41.1 g, 88%) as a clear liquid, b.p. 140 °C at 0.4 Torr (Found: C, 78.7; H, 6.8; N, 6.8. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%); $\nu_{max.}$ (film) 2 840, 1 600, 1 415, and 1 260 cm^{-1}; δ 3.65 (3 H, s, OMe), 3.75 (2 H, s, benzylic CH_2), 6.5—7.1 (6 H, m, aryl and 3- and 5-H), and

8.25 (2 H, d, 2- and 6-H); δ_C 41.233 (benzylic-C), 54.916 (MeO), 111.814 (4'-C), 114.968 (2'-C), 121.279 (6'-C), 123.2 (3- and 5-C), 129.651 (5'-C), 140.271 (1'-C), 149.7 and 149.915 (4-C and 2- and 6-C), and 159.86 (3'-C) p.p.m.

4-(3-Methoxybenzyl)-1-methylpyridinium Iodide (7c).—Freshly distilled iodomethane (20 cm³) was added in drops to the pyridine (11b) (20 g) in dry acetone (100 cm³) under nitrogen at room temperature and the resulting mixture was stirred for 15 h. The crude solids were then filtered off and crystallised from acetone under nitrogen to give the *product* (7c) as prisms (32.6 g, 95%), m.p. 109—110 °C (Found: C, 48.9; H, 4.7; N, 1.1. $C_{14}H_{16}INO$ requires C, 49.3; H, 4.7; N, 4.1%); $\nu_{max.}$ (Nujol) 2 840 and 1 635, and 1 600 and 1 520 cm⁻¹ (ring-stretching modes of the pyridinium ion); δ[$(CD_3)_2SO$] 3.7 (3 H, s, OMe), 4.2 (2 H, s, benzylic CH_2), 4.25 (3 H, s, NMe), 6.6—7.2 (4 H, m, aryl), 7.9 (2 H, d, *J* 7 Hz, 3- and 5-H), and 8.75 (2 H, d, *J* 7 Hz, 2- and 6-H).

4-(3-Methoxybenzoyl)-1-methylpyridinium Iodide (7d).—Freshly distilled iodomethane (3 cm³) was added in drops to the pyridine (11b) (3 g) in dry acetone (25 cm³) under aerobic conditions and the resulting mixture was stirred at room temperature for 15 h. The solids were filtered off and crystallised from acetone to give the *product* (7d) as yellow prisms (4.2 g, 78%), m.p. 183—184 °C (Found: C, 47.5; H, 4.1; N, 3.7. $C_{14}H_{14}INO_2$ requires C, 47.3; H, 4.0; N, 3.9%); $\nu_{max.}$ (Nujol) 2 840, 1 668 (C=O), and 1 635, 1 600, and 1 520 cm⁻¹ (ring-stretching modes of pyridinium ion); δ[$(CD_3)_2SO$] 3.75 (3 H, s, OMe), 4.4 (3 H, s, $\overset{+}{N}$Me), 7.1—7.5 (4 H, m, aryl), 8.15 (2 H, d, *J* 7 Hz, 3- and 5-H), and 9.05 (2 H, d, *J* 7 Hz, 2- and 6-H); δ_C[$(CD_3)_2SO$] 48.293 (q, NMe), 55.635 (q, MeO), 114.240 (d, 4'-C), 120.735 (d, 6'-C), 122.919 and 126.316 (d, 5'-C and d, 2'-C), 130.200 (d, 3- and 5-C), 135.296 (s, 1'-C), 146.388 (d, 2- and 6-C), 150.866 (s, 4-C), 159.259 (s, 3'-C), and 191.72 p.p.m. (s, carbonyl).

4-(3-Methoxybenzoyl)pyridine N-*Oxide*.—The pyridine (11b) (2.5 g), glacial acetic acid (25 cm³), and 30% hydrogen peroxide solution (1.5 cm³) were stirred at 80 °C for 3 h. A further portion of hydrogen peroxide solution was added and the heating continued for another 16 h. Evaporation of the volatile matter under reduced pressure, dilution of the residue with water (30 cm³), basification with 2M sodium hydroxide, and evaporation of the dried (Na_2SO_4) chloroform extracts yielded a brown oil (2.4 g). Column chromatography on silica gel (MFC) (methanol–chloroform as eluant) isolated the *product* as a crystalline material (0.075 g, 2.8%), m.p. 179 °C (Found: C, 66.5; H, 5.7; N, 6.0. $C_{13}H_{11}NO_3$ requires C, 66.5; 5.7; N, 6.0%); $\nu_{max.}$ (Nujol) 1 665 (CO) and 1 610 and 1 380 cm⁻¹ (ring-stretching modes of heterocyclic *N*-oxide); δ 3.75 (3 H, s, OMe), 6.75—7.3 (6 H, m, aryl and pyridyl 3- and 5-H), and 8.05 (2 H, d, *J* 7 Hz, 2- and 6-H).

4-(α-Hydroxy-3-methoxybenzyl)pyridine N-*Oxide*.—The pyridyl alcohol (11a), (4 g), glacial acetic acid (35 cm³), and 30% hydrogen peroxide solution (5 cm³) were stirred at 70—80 °C for 3 h. A further aliquot of hydrogen peroxide solution was added and the heating was continued for another 10 h. Evaporation of the acetic acid under reduced pressure, dilution of the residue with water (30 cm³), basification with 2M sodium hydroxide solution, and concentration under reduced pressure of the dried (Na_2SO_4) chloroform extracts yielded a pale yellow oil (3.0 g) which gave the *product* (2.6 g, 60.5%) (from ethyl acetate), m.p. 112—114 °C (Found: C, 67.7; H, 5.6; N, 5.7%; *M*, 231.0904. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.7; N, 6.1%; *M*, 231.0895); $\nu_{max.}$ (Nujol) 3 350 (OH) and 1 610 and 1 375 cm⁻¹ (ring-stretching modes of heterocyclic *N*-oxide); δ 3.6 (3 H, m, aryl and pyridyl 3- and 5-H) and 7.6—7.75 (2 H, d, *J* 7 Hz, 2- and 6-H).

2-Cyano-1,2,3,6-tetrahydro-4-(3-methoxybenzyl)-1-methylpyridine (8d).—A solution of potassium cyanide (21.1 g, 0.32 mol) in water (35 cm³) layered with ether (50 cm³) at 10 °C was treated with 5M hydrochloric acid (50 cm³), added in drops. The methiodide (7c) (32 g, 0.094 mol) was then dissolved in the cold solution, sodium borohydride was added (3.9 g, 0.1 mol) as one portion, and the mildly effervescing solution was stirred and allowed to come to room temperature during 4 h. The ethereal layer was separated, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to give a pale red oil (22.5 g). Short-path column chromatography on silica gel (1 kg) [ethyl acetate in light petroleum (b.p. 60—80 °C) as eluant] isolated the *product* as a pale yellow oil (12.9 g, 59%) (Found: C, 73.8; H, 7.5; N, 11.3. $C_{15}H_{18}N_2O$ requires C, 74.3; H, 7.5; N, 11.6%); $\nu_{max.}$ (film) 2 840, 2 220 (C≡N), 1 260, and 1 050 cm⁻¹; δ 1.9—3.6 (6 H, m, benzylic CH_2 and 6- and 3-CH_2), 2.4 (3 H, s, NMe), 3.8 (4 H, s and m, OMe and 2-H), 5.61) H, m, olefinic), and 6.4—7.5 (4 H, m, aryl).

Two by-products were also isolated; *1,2,3,6-tetrahydro-4-(3-methoxybenzyl)-1-methylpyridine*(N—B)*borane* (9b) as a pale yellow oil (2.9 g, 12.1%) (Found: C, 72.3; H, 9.7; N, 6.05%. $C_{14}H_{22}BNO$ requires C, 72.7; H, 9.6; N, 6.1%); $\nu_{max.}$ (film) 2 840 and 2 380, 2 310 and 2 270 (BH_3-stretching modes), 1 260 and 1 045 cm⁻¹; δ 2.1—2.4 (2 H, m), 2.55 (3 H, s, NMe), 2.8—3.7 (6 H, m), 3.8 (3 H, s, OMe), 5.45 (1 H, m, olefinic), 6.6—7.0 (3 H, m, aryl), and 7.0—7.5 (1 H, m, 5'-H) and *2-cyano-1,2,3,6-tetrahydro-4-(3-methoxybenzyl)-1-methylpyridine*(N—B)*borane* (9c) as a red oil (1.1 g, 5.1%) (Found: C, 70.2; H, 9.3; N, 10.8. $C_{15}H_{21}BN_2O$ requires C, 70.3; H, 9.3; N, 10.9%); $\nu_{max.}$ (film) 2 440 and 2 360 (BH_3-stretching modes), 2 240 (C≡N), and 1 260 and 1 040 cm⁻¹; δ 2.1—2.5 (2 H, m), 2.55 (3 H, s, NMe), 2.8—3.7 (4 H, m), 3.8 (4 H, s and m, OMe and 6-H), 5.45 (1 H, m, olefinic), 6.6—7.0 (3 H, m, aryl), and 7.3 (1 H, m, 5'-H).

1,2,3,6-Tetrahydro-4-(3-methoxybenzyl)-2-methoxycarbonyl-1-methylpyridine (8e).—A solution of the foregoing nitrile (8d) (11.0 g) in methanol (250 cm³) saturated with anhydrous hydrogen chloride gas was heated at 54 °C for 60 h. The pale yellow filtrate was basified with sodium carbonate and the liberated oil shaken into chloroform. The bulked and dried (Na_2SO_4) extracts were concentrated under reduced pressure to give a red oil (12.3 g). Short-path column chromatography on silica gel (0.5 kg) [ethyl acetate in light petroleum (b.p. 60—80 °C) as eluant] isolated the *product* (8e) as a yellow oil (4.7 g, 40%) (Found: C, 69.6; H, 7.85; N, 5.1. $C_{16}H_{21}NO_3$ requires C, 70.0; H, 7.7; N, 5.1%); $\nu_{max.}$ (film) 2 840, 2 810, 2 780, 1 740 (C=O), 1 260, 1 250, and 780 cm⁻¹; δ 2.0—2.5 (3 H, m, 3-CH_2 and 2-H), 2.4 (3 H, s, NMe), 3.3 (4 H, s, benzylic CH_2 and 6-CH_2), 3.65 (3 H, s, CO_2Me), 3.8 (3 H, s, OMe), 5.5 (1 H, m, olefinic), 6.6—6.9 (3 H, m, aryl), and 7.2 (1 H, m, 5'-H). A component of lower R_F, *1,2,3,6-tetrahydro-4-(3-methoxybenzyl)-1-methylpyridine* (8f), was also isolated as a liquid (2.6 g, 25%) (Found: C, 77.3; H, 8.7; N, 6.4%; *M*, 217.1451. $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8; N, 6.5%; *M*,217.1467); $\nu_{max.}$ (film) 2840, 2 810, 2 780, 1 600, and 1 380 cm⁻¹; δ 2.0 (2 H, m, 2-CH_2), 2.2 (3 H, m, NMe), 2.35 (2 H, t, 3-CH_2), 2.8 (2 H, m, 6-CH_2), 3.15 (2 H, s, benzylic CH_2), 3.75 (2 H, s, OMe), 5.3 (1 H, m, olefinic), 6.7—7.0 (3 H, m, aryl), and 9.3 (1 H, m, 5'-H).

cis-4-(3-*Methoxybenzyl*)-2-*methoxycarbonyl*-1-*methylpiperidine* (5c) *and* trans-4-(3-*Methoxybenzyl*)-2-*methoxycarbonyl*-1-*methylpiperidine* (10b).—The foregoing amino-ester (8e) (2.4 g) and 5% platinum-on-charcoal catalyst (170 mg) in acetic acid (50 cm^3) were shaken under hydrogen at room temperature and atmospheric pressure; after 6 h 1 mol equiv. of gas was absorbed. The reaction mixture was then stirred for a further 92 h. After removal of the catalyst (filtration) and solvent (under reduced pressure), the oil was dissolved in water (25 cm^3), basified with sodium hydrogencarbonate, and the liberated oil shaken into chloroform. The bulked extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield a pale yellow oil (2.38 g). Short-path column chromatography on silica gel (200 g) (anhydrous ether as eluant) isolated the cis-*isomer* (5c) as a pale yellow oil (1.77 g, 73%) (Found: C, 69.6; H, 8.2; N, 4.9%; *M*, 277.1658. $C_{16}H_{23}NO_3$ requires C, 69.3; H, 8.35; N, 5.05%; *M*, 277.1678); $\nu_{max.}$ (film) 2 840, 2 780, 1 744 (C=O), 1 260, and 1 050 cm^{-1}; δ 1.2—2.05 (6 H, m, 3-, 5-, and 6-CH_2), 2.21 (3 H, s, NMe), 2.45 (2 H, d, benzylic CH_2), 2.5—3.0 (2 H, m, 2- and 4-H), 3.72 (3 H, s, CO_2Me), 3.79 (3 H, s, OMe), 6.5—6.7 (3 H, m, aryl), and 6.95—7.15 (1 H, m, 5′-H); δ_C 31.73 (t, benzylic C), 35.977 (q, NMe), 37.130 (d, 4-C), 43.015 (t, 5-C), 44.046 (t, 3-C), 51.873 (d, 6-C), 55.028 (d, 2-C), 55.635 (q, 3′-MeO), 68.436 (q, ester Me), 111.086 (d, 4′-C), 114.968 (d, 2′-C), 121.463 (d, 6′-C), 129.166 (d, 5′-C), 141.421 (s, 1′-C), 159.559 (s, 3′-C), and 173.761 p.p.m. (s, ester carbonyl).

A higher-R_F component, the trans-*isomer* (10b) (0.47 g, 19.5%) was isolated as an oil (Found: C, 69.6; H, 8.5; N, 5.3%; *M*, 277.1659. $C_{16}H_{23}NO_3$ requires C, 69.3; H, 8.35; N, 5.05%; *M*, 277.1678); $\nu_{max.}$ (film) 2 840, 2 780, 1 745 (C=O), 1 260, and 1 050 cm^{-1}; δ 1.2—2.2 (6 H, methylene 2-, 5-, and 6-CH_2), 2.41 (3 H, s, NMe), 2.45 (2 H, s, benzylic CH_2), 2.6—2.9 (1 H, m, 4-H), 3.25—3.40 (1 H, q, 2-H-*eq*), 3.65 (3 H, s, CO_2Me), 3.77 (3 H, s, OMe), 6.5—6.7 (3 H, m, aryl), and 6.95—7.15 (1 H, m, 5′-H).

1,2,3,6-*Tetrahydro*-4-(3-*methoxybenzyl*)-1-*methylpyridine*-2-*carboxamide* (8g).—A solution of the nitrile (8d) (1.3 g) in methanol (5 cm^3) (AnalaR) was saturated with anhydrous hydrogen bromide gas and stirred at 15 °C for 10 h. The pale yellow liquor was basified with sodium carbonate and the liberated oil shaken into chloroform. Concentration under reduced pressure of the bulked and dried (Na_2SO_4) extracts gave a yellow oil which solidified with time and was recrystallised from ether to give the *product* (8g) (0.72 g, 52%) as prisms, m.p. 128.5 °C (Found: C, 69.0; H, 8.1; N, 10.5. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.8; N, 10.8%); $\nu_{max.}$ (Nujol) 3 345 (bonded NH), 3 120 (free NH), 2 760, 2 695, and 1 645 cm^{-1} (C=O); δ 2.24 (2 H, br d, *J* 7 Hz, 3-CH_2) 2.36 (3 H, s, NMe), 3.1 (1 H, t, *J* 7 Hz, 2-H), 3.28 (4 H, br s, 6-CH_2 and benzylic CH_2), 3.79 (3 H, s, OMe), 5.45 (1 H, m, olefinic), 6.1 (1 H, br s, exchangeable NH), 6.4—7.0 (4 H, m, aryl and exchangeable NH), and 7.2 (1 H, m, 5′-H).

Attempted Cyclisation of the Piperidine (5c).—The *cis*-pipecolate ester (5c) (0.53 g) and PPA (17.5 g) were stirred at 75 °C for 4 h. T.l.c. examination showed only the starting material to be present. Heating at 85 °C for 16 h produced similar results, whilst heating at 105 °C for 4 h resulted in the formation of non-ketonic polar material. Heating at 115 °C for 8 h resulted in the formation of considerable quantities of non-ketonic material with no t.l.c. evidence for any starting material. After addition of ice, basification with 2M sodium hydroxide, and extraction with butanol–chloroform, the bulked and dried (Na_2SO_4) extracts, on concentration under reduced pressure, gave a dark oil (0.105 g) and, although comprising several components, the major component was found to have a molecular ion M^+, 219.1574 (whilst $C_{14}H_{21}NO$ requires *M*, 219.1623) and similar R_F and i.r. spectrum to 4-(3-methoxybenzyl)-1-methylpiperidine. Similar results were obtained at 140 °C with PPA.

Attempted Cyclisation of cis-2-*Hydroxycarbonyl*-4-(3-*methoxybenzyl*)-1-*methylpiperidine Hydrochloride*.—The *cis*-pipecolate ester (5c) (900 mg) and 12M hydrochloric acid (22.5 cm^3) were refluxed for 8 h and then evaporated to dryness under reduced pressure. The brown solids were washed with ether and the *product* was isolated as fawn hygroscopic solids (850 mg, 90%); $\nu_{max.}$ (Nujol) 3 350—2 650 and 1 725 cm^{-1} (C=O); the pipecolic acid hydrochloride (used without further purification) and PPA (50 g) were heated at 140 °C for 10 h. The cooled solution was basified (pH 7.0) with 2M sodium hydroxide and then extracted with butanol in chloroform. The bulked and dried (Na_2SO_4) extracts, on concentration under reduced pressure, gave a dark oil (131 mg) and although comprising several components (t.l.c. examination) the major component was found to have a molecular ion *M*, 219.1593 (whilst $C_{14}H_{21}NO$ requires *M*, 219.1623) and similar R_F and i.r. spectrum to 4-(3-methoxybenzyl)-1-methylpiperidine.

4-(3-*Methoxybenzyl*)-1-*methylpiperidine*.—The methiodide (7c) (6.4 g) and platinum oxide catalyst (300 mg) in methanol (120 cm^3) were shaken under hydrogen at 3 atm and room temperature for 18 h. After removal of the catalyst (filtration) and solvent under reduced pressure the grey solids were dissolved in water, basified with sodium hydrogencarbonate, and the liberated oil shaken into chloroform. The bulked and dried ($MgSO_4$) extracts were concentrated under reduced pressure to give *product* (3.5 g, 85%) as an oil (Found: C, 76.6; H, 9.6; N, 6.3. $C_{14}H_{21}NO$ requires C, 76.7; H, 9.6; N, 6.4%); $\nu_{max.}$ (film) 2 840, 2 780, 1 258, and 1 040 cm^{-1}; δ 1.0—2.0 (7 H, m, methylene protons), 2.23 (3 H, s, NMe), 2.52 (2 H, m, benzylic (CH_2), 2.85 (2 H, m, 2- and 6-H *eq*), 3.77 (3 H, s, OMe), 6.6—6.9 (3 H, m, aryl), and 7.1—7.25 (1 H, m, 5′-H).

2-(1-*Hydroxy*-1-*methylethyl*)-4-(3-*methoxybenzyl*)-1-*methylpiperidine* (12).—A solution of the *cis*-pipecolate ester (5c) (900 mg) in anhydrous ether (10 cm^3) was added in drops during 15 min to the Grignard solution prepared from iodomethane (2.0 g), magnesium turnings (0.6 g), and anhydrous ether (25 cm^3). The reaction mixture was stirred at room temperature for 18 h and the slurry poured onto aqueous ammonium chloride. The reaction liquors were then basified with sodium hydrogencarbonate and the bulked and dried (Na_2SO_4) chloroform extracts were concentrated under reduced pressure to yield a brown oil (800 mg). Short-path column chromatography on silica gel (40 g) (ethanol in chloroform as eluant) isolated the *product* (12) (250 mg, 28%) as a pale brown gum (Found: C, 73.7; H, 9.6; N, 5.2%; $M^+ - 1$, 276.1970. $C_{17}H_{27}NO_2$ requires C, 73.6; H, 9.8; N, 5.05%; *M* − 1 276.1963); $\nu_{max.}$ (film) 3 250 (OH), 2 840, 2 780, 1 602, and 1 250 cm^{-1}; δ 1.2—2.05 (6 H, m, methylene protons), 1.25 (6 H, s, 2 × isopropyl Me), 2.35—2.5 (5 H, s and d, benzylic CH_2 and NMe), 2.61—3.1 (2 H, m), 3.7 (3 H, s, OMe), 6.6—7.2 (4 H, m, aryl), and 8.75 (1 H, br s, exchangeable OH).

Attempted Cyclisation of the Piperidine (12).—The tertiary alcohol (12) (250 g) and PPA (20 g) were stirred at 180 °C for 5 h. The dark reaction mixture was cooled, treated with ice

and concentrated hydrochloric acid, and then stirred at 110 °C for 10 h. After addition of ice, basification with concentrated ammonium hydroxide, and extraction with butanol in chloroform, the bulked and dried (Na_2SO_4) extracts gave, on concentration under reduced pressure, a dark oil (112 mg). T.l.c. examination indicated a multicomponent mixture with considerable polar material. No separation was attempted.

4-(α-*Hydroxy*-3-*methoxybenzyl*)-1-*methylpyridinium Iodide* (7e).—Freshly distilled iodomethane (5 cm³) was added in drops to the pyridyl alcohol (11a) (6.0 g) in dry acetone (50 cm³) under nitrogen and the resulting mixture was stirred for 15 h. Recrystallisation from ethanol gave the *product* (7e) as prisms (7.35 g, 74%), m.p. 134—135 °C (Found: C, 47.15; H, 4.5; N, 3.5. $C_{14}H_{16}IN_2O$ requires C, 47.1; H, 4.5; N, 3.9%); $\nu_{max.}$ (Nujol) 3 350 (OH) and 1 640, 1 610 and 1 515 cm⁻¹ (ring-stretching modes of pyridinium ion); δ[$(CD_3)_2SO$] 3.7 (3 H, s, $\overset{+}{N}Me$), 4.25 (3 H, s, OMe), 5.85 (1 H, s, benzylic CH), 6.5—7.2 (4 H, m, aryl), 7.95 (2 H, d, *J* 7 Hz, 3- and 5-H), and 8.7 (2 H, d, *J* 7 Hz, 2- and 6-H).

2-*Cyano*-1,2,3,6-*tetrahydro*-4-(α-*hydroxy*-3-*methoxybenzyl*)-1-*methylpyridine* (8h).—A solution of potassium cyanide (4.4 g, 67 mmol) in water (20 cm³) and ether (35 cm³) at 5 °C, was treated with 6M hydrochloric acid (4.5 cm³), added in drops. The above methiodide (7e) (7.5 g, 21 mmol) was dissolved in the cold solution, followed by the addition of sodium borohydride (0.48 g, 12 mmol) as one portion, and the mildly effervescing solution was stirred and allowed to come to room temperature during 4 h. Combination of the interfacial solids with those obtained by concentration under reduced pressure of the dried (Na_2SO_4) ethereal extracts gave needles of the *pyridine* (8 h) (2.85 g, 54%), m.p. 108—109 °C (ether) (Found: C, 69.7; H, 7.0; N, 10.4. $C_{15}H_{18}N_2O_2$ requires C, 69.7; H, 7.0; N, 10.8%); $\nu_{max.}$ (Nujol) 3 350 (OH) and 2 220 cm⁻¹ (C≡N); δ 1.8—2.25 (3 H, m), 2.3 (3 H, s, NMe), 2.8 (1 H, s, exchangeable OH), 2.85—3.5 (2 H, m), 3.7 (3 H, s, OMe), 4.9 (1 H, s, benzylic CH_2), 5.65 (1 H, t, olefinic), and 6.6—7.2 (4 H, m, aryl).

5-*Benzoyl*-4-*ethoxycarbonyl*-2-(3-*methoxyphenyl*)*pyridine* (11c).—The Grignard solution from *m*-bromoanisole (4.5 g), magnesium (0.59 g), and ether (200 cm³) was cooled to −70 °C under nitrogen and to it was added slowly (10 min) a solution of ethyl isonicotinate *N*-oxide [10] (4 g), benzoyl chloride (3.6 g), ether (50 cm³), and dichloromethane (50 cm³). After 2.5 h at −70 °C and 20 h at 20 °C, aqueous ammonium chloride was added and the crude product was extracted from the organic layer. Extraction with concentrated hydrochloric acid gave the *product* (11c) (1.04 g), b.p. 190 °C/0.05 Torr (Found: C, 72.75; H, 5.6; N, 4.05%; M^+, 361.1291. $C_{22}H_{19}NO_4$ requires C, 73.15; H, 5.3; N, 3.9%; *M*, 361.1314); $\nu_{max.}$ (film) 1 715 (ester) and 1 660 cm⁻¹ (C=O); δ 1.05 (2 H, t, Me), 3.8 (3 H, s, OMe), 4.04 (2 H, q, CH_2Me), 6.8—7.7 (9 H, m, aryl H), 8.1 (1 H, s, 3-H), and 8.64 (1 H, s, 6-H). Hydrolysis gave the corresponding *acid* (11d), m.p. 189—190 °C (Found: C, 71.45; H, 4.7; N, 4.6. $C_{20}H_{15}NO_4$ requires C, 71.65; H, 5.1; N, 4.2%).

4-*Ethoxycarbonyl*-2-(3-*methoxyphenyl*)*pyridine* (11e).—The Grignard solution was made as above from *m*-bromoanisole (4.5 g) and cooled to −70 °C under nitrogen, after which the acetoxy-compound obtained from ethyl isonicotinate [10,12] (5 g) in dichloromethane (100 cm³) was added during 2 min. After 1 h at −70 °C and 24 h at 20 °C, the usual work-up gave the crude product (11e) (1 g), which was purified by extraction with 6M hydrochloric acid and by chromatography on silica plates, b.p. 60 °C/0.01 Torr [Found: C, 70.3; H, 5.95; N, 5.5%; M^+, 257.1038 (100%). $C_{15}H_{15}NO_3$ requires C, 70.1; H, 5.9; N, 5.45%; *M*, 257.1052]; δ 1.38 (3 H, t, *Me*CH_2), 3.8 (3 H, s, OMe), 4.35 (2 H, q, CH_2Me), 6.8—7.65 (5 H, m, aryl + 5-H), 2.1 (1 H, s, 3-H), and 2.63 (1 H, s, 6-H).

4-*Ethoxycarbonyl*-1,2,3,6-*tetrahydro*-1-*methylpyridine* (8i).—Ethyl *N*-methylisonicotinatium iodide [25] (14a) (15 g), ethanol (200 cm³), and glacial acid (10 ml) were stirred at 15 °C while sodium borohydride (3 g) was added in portions during 3 h. After being stirred for a further 24 h, the reaction mixture was diluted with water and, after 6 h, was basified with ammonium hydroxide solution (to pH 10) and extracted with chloroform. The *product* (8j) (6.26 g) was obtained in the usual way and was purified by distillation, b.p. 85—90 °C/0.05 Torr (Found: N, 8.05. $C_9H_{15}NO_2$ requires N, 8.3); δ 1.25 (3 H, t, *Me* CH_2), 2.31 (3 H, s, NMe), 2.25—2.55 (4 H, m, 2 × CH_2), 2.95—3.05 (2 H, m, CH_2), 4.1 (2 H, q, CH_2Me), and 6.7—6.8 (1 H, m, 5-H). The *picrate* derivative had m.p. 180—191 °C (from ethanol) (Found: C, 45.4; H, 4.65; N, 14.0. $C_{15}H_{18}N_4O_9$ requires C, 45.25; H, 4.55; N, 14.1%). Reaction with benzyl bromide in acetone gave the *quaternary salt* (13), m.p. 196 °C (from acetone–dichloromethane) (Found: C, 56.55; H, 6.5; N, 3.9; Br, 23.6. $C_{16}H_{22}BrNO_2$ requires C, 56.5; H, 6.5; N, 4.1; Br, 23.5%).

6-*Benzyl*-4-*ethoxycarbonyl*-1,2,3,6-*tetrahydro*-1-*methylpyridine* (8i).—The above quaternary salt (13) (6.8 g) was stirred with potassium t-butoxide (from 0.8 g potassium) and dry toluene (100 cm³) under nitrogen at 100—110 °C for 5 h. After cooling and filtration, the filtrate was washed with water, dried, and evaporated, leaving the product (4.1 g) which was further purified by chromatography on silica and by distillation, b.p. 150 °C/0.1 Torr (Found: C, 74.4; H, 8.15; N, 5.4%; M^+, 259.1574. $C_{16}H_{21}NO_2$ requires C, 74.2; H, 8.15; N, 5.4%; *M*, 259.1572); $\nu_{max.}$ (film) 1 705 cm⁻¹ (ester); δ 1.2 (3 H, t, *Me*CH_2), 2.42 (3 H, s, NMe), 2.2—3.15 (7 H, m, CH_2 + CH), 4.16 (2 H, q, CH_2Me), 6.6 (1 H, s, 5-H), and 7.0—7.2 (5 H, m, aryl H).

cis-2-*Benzyl*-4-*ethoxycarbonyl*-1-*methylpiperidine* (15) *and* 4-*Benzyl*-4-*ethoxycarbonyl*-1-*methylpiperidine* (16).—The crude pyridine (8i) [contaminated with (17b)] (53 g) was hydrogenated in ethanol (100 cm³) with platinum oxide (1 g) at 3.5—4.0 bar. A portion of the product was purified by short-path column chromatography on silica; after removing firstly traces of the starting material, the cis-*ester* (15) (major product, *ca.* 4 : 1) was eluted; it had b.p. 130 °C/0.03 Torr (Found: C, 73.95; H, 8.95; N, 5.8%; M^+, 261.1708. $C_{16}H_{23}NO_2$ requires C, 73.6; H, 8.9; N, 5.4%; *M*, 261.1729); $\nu_{max.}$ (film) 1 726 cm⁻¹ (ester); δ 1.14 (3 H, t, *Me*CH_2), 1.3—2.45 (8 H, m, 4 × CH_2), 2.35 (3 H, s, NMe), 2.9 (1 H, dt, CH), 3.13 (1 H, dd, CH), 3.96 (2 H, q, CH_2Me), and 6.96—7.2 (5 H, m, aryl H); δ_C 14.196 (q), 28.394 (t), 33.065 (t), 40.588 (q), 42.105 (t), 43.076 (d), 56.909 (t), 60.306 (t), 64.857 (d), 126.496 (d), 128.680 (2 C, d), 129.836 (2 C, d), 139.601 (s), and 175.334 (s) p.p.m.

This was followed by the 4-*benzyl ester* (16) (minor product), b.p. 150 °C/0.2 Torr (Found: C, 73.6; H, 9.1; N, 5.3%; M^+, 261.1720. $C_{16}H_{23}NO_2$ requires C, 73.6; H, 8.9; N, 5.4%; *M*, 261.1729); $\nu_{max.}$ (film) 1 720 cm⁻¹ (ester); δ 1.15 (3 H, t, *Me*CH_2), 1.4—2.15 (5 H, m, CH_2), 2.18 (3 H, s, NMe), 2.4—2.7 (3 H, m, CH_2 and CH), 2.75 (2 H, s, CH_2), 4.0 (2 H, q, CH_2Me), 6.8—7.2 (5 H, m, aryl); δ_C 14.135 (q), 33.611 (2 C, t), 46.352 (t), 46.595 (q), 46.777 (s), 53.390 (2 C, t), 60.306 (t), 126.923 (d), 128.316 (2 C, d) 130.321

(2 C, d), 137.174 (s), and 175.635 (s) p.p.m. The latter material was also obtained from 4-ethoxycarbonyl-1-methylpiperidine [26] using lithium di-isopropylamide [17] and benzyl bromide.

Hydrolysis and Re-esterification of the Piperidines (15) *and* (16).—The mixed esters (48 g, 0.15 mol), sodium hydroxide (5.7 g, 0.15 mol), water (50 cm^3), and ethanol (120 cm^3) were stirred and refluxed for 24 h. After cooling, extraction of the alkaline solution ($CHCl_3$) yielded 4-benzyl-4-ethoxycarbonyl-1-methylpiperidine (16) (10.9 g). The aqueous layer was acidified (concentrated HCl) and evaporated to dryness. A portion of the solid product was re-esterified (ethanol + concentrated H_2SO_4) to yield *cis*-2-benzyl-4-ethoxycarbonyl-1-methylpiperidine (15). Each ester was $<95\%$ pure by t.l.c. and n.m.r. spectroscopy. The remainder of the *cis*-acid hydrochloride was kept for cyclisation (see below).

N-*Methylspiro*[*indane*-2,4′-*piperidin*]-1-*one* (3a).—The piperidine (16) (2.18 g) was refluxed for 20 h with concentrated hydrogen chloride (20 cm^3). After evaporation under reduced pressure, the residue was stirred with methanesulphonic acid (15 cm^3) and phosphorus pentaoxide (2 g) for 7 d. After dilution with water and basification (NaOH), the *product* (3a) (1.37 g) was extracted and distilled, b.p. 130 °C/0.03 Torr (1.06 g) [Found: C, 78.35; H, 8.35; N, 6.25%; M^+, 215.1307 (100%). $C_{14}H_{17}NO$ requires C, 78.2; H, 7.95; N, 6.5%; *M*, 215.1310]; $\nu_{max.}$ (film) 1 715 cm^{-1} (C=O); δ 1.25—1.45 (2 H, br d, CH_2), 1.85—2.25 (4 H, m, 2 × CH_2), 2.28 (3 H, s, NMe), 2.6—2.95 (2 H, m, CH_2), 2.96 (2 H, s, CH_2), and 7.1—7.7 (4 H, m, aryl H); δ_C 33.551 (2 C, t) 38.889 (t), 46.595 (q), 47.990 (s), 52.662 (2 C, t), 124.997 (d), 126.982 (d), 127.773 (d), 135.112 (d), 136.325 (s), 152.585 (s), and 210.281 (s) p.p.m.

The 2,4-*dinitrophenylhydrazone* derivative had m.p. 210 °C (decomp.) (Found: C, 60.8; H, 5.15; N, 17.75. $C_{20}H_{21}N_5O_4$ requires C, 60.8; H, 5.35; N, 17.75%). The *methiodide* derivative had m.p. 282 °C (decomp.) (Found: C, 50.55; H, 5.35; N, 4.15. $C_{15}H_{20}INO$ requires C, 50.45; H, 5.65; N, 3.9%). The 1-*pentyl iodide* derivative had m.p. 192—193 °C (Found: C, 55.05; H, 6.65; N, 3.5. $C_{19}H_{28}INO$ requires C, 55.5; H, 6.85; N, 3.4%).

N-*Methylspiro*[*indane*-2,4′-*piperidin*]-1-*ol* (3b).—The ketone (3a) (1.8 g) was stirred at 20 °C with sodium borohydride (1.0 g) in ethanol (50 cm^3) overnight. The usual work-up gave the crude product (3b) (1.6 g), which was purified (with considerable loss) by chromatography on thick plates (SiO_2; elution with 40% ethanol–chloroform), to give the *product* (3b) b.p. 170 °C/0.03 Torr (boiling gave a glass) [Found: C, 77.5; H, 8.85; N, 6.45%; M^+, 217.1480 (100%) $C_{14}H_{19}NO$ requires C, 77.5; H, 8.85; N, 6.4%; *M*, 217.1467); δ 1.1—2.3 (6 H, m, 3 × CH_2), 2.16 (3 H, s, NMe), 2.4—2.9 (4 H, m, CH_2 + CH), 4.52 (1 H, s, CH), 4.62 (1 H, br s, exchangeable OH), and 3.0—3.4 (4 H, m, aryl H). The N-*methyl* iodide derivative was hygroscopic. The *benzoate* derivative was a wax, b.p. 200 °C/0.03 Torr (Found: C, 78.3; H, 7.45; N, 4.4. $C_{21}H_{23}NO_2$ requires C, 78.55; H, 7.2; N, 4.35%); $\nu_{max.}$ (film) 1 710 cm^{-1} (ester); δ 1.4—3.2 (10 H, m, 5 × CH_2), 2.25 (3 H, s, NMe), 6.1 (1 H, s, CHO), and 7.1—8.0 (9 H, m, aryl H).

N-*Methyl*-1-*phenylspiro*[*indane*-2,4′-*piperidin*]-1-*ol* (3c).—The ketone (3a) (0.52 g) was added to phenylmagnesium bromide [from magnesium (0.13 g), bromobenzene (0.75 g), and ether (100 cm^3)] under nitrogen with stirring. The whole was refluxed overnight, cooled, and treated with an excess of saturated aqueous ammonium chloride, separated, and the organic layer dried and evaporated. The *product* (3c) (100 mg) was crystallised from light petroleum (b.p. 60—80 °C), m.p. 153 °C (Found: C, 82.0; H, 8.05; N, 5.15. $C_{20}H_{23}NO$ requires C, 81.85; H, 7.9; 4.8%); δ 1.7—2.4 (6 H, m, 3 × CH_2), 2.15 (s, exchangeable OH), 2.18 (3 H, s, NMe), 2.4—2.8 (2 H, m, 2 × CH), 2.95 (2 H, s, CH_2), and 7.1—7.4 (9 H, m, aryl H). Better yields were obtained using a 5-molar excess of phenylmagnesium bromide.

2,3,4,5,6,7-*Hexahydro*-3-*methyl*-2,6-*methano*-1H-3-*benzazonin*-7-*one* (17a).—The hydrochloride of the acid of compound (15) (2.57 g), described previously, and PPA (130 g) were stirred at 160 ± 5 °C for 24 h. The reaction mixture was cooled to *ca.* 50 °C, poured into ice (excess), and basified (NaOH). Extraction with chloroform gave the *product* (17a), b.p. 150—155 °C/0.05 Torr (Found: C, 78.2; H, 8.2; N, 6.35%; M^+, 215.1314. $C_{14}H_{17}NO$ requires C, 78.2; H, 7.95; N, 6.5%; *M*, 215.1310); $\nu_{max.}$ (film) 1 675 cm^{-1} (C=C) δ 1.9—2.0 (1 H, m), 2.05 (2 H, dq), 2.35 (1 H, br d), 2.36 (3 H, s, NMe), 2.42 (1 H, dd), 2.48 (1 H, dd), 2.55 (1 H, m), 2.72 (1 H, dd), 3.08 (1 H, dd), 3.45 (1 H, m), 7.0—7.4 (4 H, m, aryl H); δ_C 28.272 (t), 30.396 (t), 31.124 (t), 42.651 (q), 42.894 (d), 45.745 (t), 54.664 (d), 126.982 (d), 127.952 (d), 129.772 (d), 131.593 (d), 138.631 (s), 140.878 (s), and 211.378 (s) p.p.m.

The *methiodide hydrate* had m.p. 240 °C (Found: C, 48.6; H, 5.75; N, 3.8. $C_{15}H_{20}INO{\cdot}H_2O$ requires C, 48.1; H, 5.9; N, 3.75%). The N-*pentyl iodide* had m.p. 181 °C (Found: C, 54.7; H, 6.95; N, 3.1. $C_{19}H_{28}INO$ requires C, 55.25; H, 6.85; N, 3.4%). The 2,4-*dinitrophenylhydrazone* had m.p. 192—193 °C (Found: C, 60.75; H, 5.45; N, 18.0. $C_{20}H_{21}N_5O_4$ requires C, 60.8; H, 5.35; N, 17.75%). The *chloroplatinate* had no distinct m.p. [Found: C, 40.55; H, 4.65; N, 3.3 $(C_{14}H_{17}NO)_2{\cdot}H_2PtCl_6$ requires C, 40.05; H, 4.3; N, 3.35%]. The *hydrobromide* had m.p. 235 °C (Found: C, 56.8; H, 6.25; N, 4.35. $C_{14}H_{17}NO{\cdot}HBr$ requires C, 56.8; H, 6.2; N, 4.75%). The *perchlorate* had m.p. 130 °C (Found: C, 53.2; H, 5.95; N, 4.35. $C_{14}H_{17}NO{\cdot}HClO_4$ requires C, 53.3; H, 5.75; N, 4.45%).

2,3,4,5,6,7-*Hexahydro*-7(α *or* β)-*hydroxy*-3-*methyl*-2,6-*methano*-(1H)-3-*benzazonine* (17b).—The previously described ketone (21a) (1.5 g) was treated with sodium borohydride in ethanol as described above for the isomer (3a). The *product* (17b) (1.0 g) was purified by chromatography on silica (elution with 20% ethanol—chloroform) and by vacuum distillation, b.p. 190—200 °C/0.01 Torr (Found: C, 77.4; H, 9.1; N, 6.4%; M^+, 217.1465. $C_{14}H_{19}NO$ requires C, 77.5; H, 8.25; N, 6.4%; *M*, 217.1467).

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REFERENCES

[1] Part 4, G. R. Proctor and F. J. Smith, *J. Chem. Res.*, 1980, (*S*) 286; (*M*) 3544.
[2] D. C. Palmer and M. J. Strauss, *Chem. Rev.*, 1977, **1**, 1.
[3] K. Kanematsu, R. T. Parfitt, A. E. Jacobson, J. H. Ager, and E. L. May, *J. Am. Chem. Soc.*, 1968, **90**, 1064.
[4] K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, 1969, **12**, 405.
[5] E. Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[6] E. M. Fry, *J. Org. Chem.*, 1964, **29**, 1647.

[7] E. N. Zilberman, *Russ. Chem. Rev.* (*Engl. Transl.*), 1962, **31**, 615.
[8] J. A. Phelisse, B. Brossard, and M. Gaignon, Fr.P., 1,468,611 (*Chem. Abstr.*, 1968, **68**, 87170f).
[9] J. H. Ager and E. L. May, *J. Org. Chem.*, 1962, **27**, 245.
[10] T. Kametani and T. Suzuki, *J. Chem. Soc. C*, 1971, 1053.
[11] O. Cervinka, *Collect. Czech. Chem. Commun.*, 1962, **27**, 567.
[12] C. W. Muth and R. S. Darlak, *J. Org. Chem.*, 1965, **30**, 1912.
[13] T. S. Stevens, personal communication.
[14] J. M. Paton, P. L. Pauson, and T. S. Stevens, *J. Chem. Soc., C*, 1969, 2130.
[15] P. E. Eaton and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, **94**, 1016.
[16] K. S. Kim, E. Vanotti, A. Suarato, and F. Johnson, *J. Am. Chem. Soc.*, 1979, **101**, 2483.
[17] R. J. Cregge, J. L. Hermann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 1973, 2425.
[18] L. M. Rice, C. F. Geschickter, and C. H. Grogan, *J. Med. Chem.*, 1963, **6**, 388.
[19] (*a*) U. Schollkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, 1969, 3415; (*b*) W. D. Ollis, M. Rey, I. O. Sutherland, and G. L. Closs, *J. Chem. Soc., Chem. Commun.*, 1975, 543.
[20] P. Stern, P. Trska, and M. Ferles, *Collect. Czech. Chem. Commun.*, 1970, **39**, 2267.
[21] M. Balasubramanian and N. Padma, *Tetrahedron*, 1968, **24**, 5395.
[22] M. Balasubramanian and N. Padma, *Tetrahedron*, 1963, **19**, 2135.
[23] D. E. Caddy and J. H. P. Utley, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1258.
[24] Dr. J. H. P. Utley, personal communication.
[25] T. Tsukamoto and T. Komori, *Pharm. Bull. Jpn.*, 1955, **3**, 243 (*Chem. Abstr.*, 1956, **50**, 6565b).
[26] N. Sugimoto and H. Kugita, *J. Pharm. Soc. Jpn.*, 1953, **73** 71.