Bridged-ring Nitrogen Compounds. Part 3.[1] Synthesis of Representatives of the 1,5-Methano-4-benzazonine Ring System

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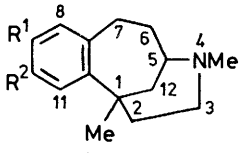
Reaction of arylaldehydes with 2,4-dimethylpyridine and n-butyl-lithium gives in good yield 1-aryl-2-(4-methylpyridyl)ethanols which, after dehydration with polyphosphoric acid and catalytic hydrogenation, give 2-phenethyl-4-methylpyridines. Cyclisation of the derived tetrahydropyridines gives 1,4-dimethyl-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-4-benzazonines except when cyclisation is attempted *meta* to a methoxy-group.

HEXAHYDRO-1,5-METHANO-1*H*-4-BENZAZONINES [*e.g.* (1)] have not to our knowledge been reported: they are homologues of the benzomorphans (2) [2] and are, therefore, of interest as potential analgesics. It seemed that



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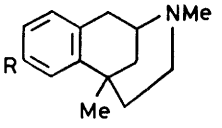

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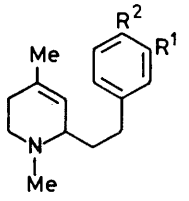

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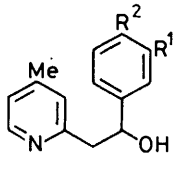

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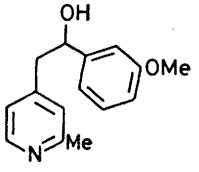

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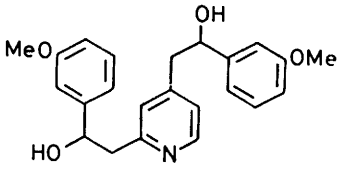

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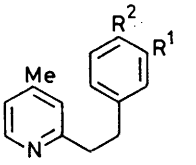
they might be available by cyclisation of 2-phenethyltetrahydropyridines (3); this proved to be the case and this paper is concerned with the synthesis and cyclisation of the latter.

We examined first the reaction of phenethylmagnesium bromide with 1,4-dimethylpyridinium iodide, an approach modelled on one of May's benzomorphan syntheses.[3] This reaction did give the expected unstable dihydropyridine (4) in 32% yield, but the subsequent hydrogenation gave the hexahydropyridine rather than the expected tetrahydropyridine (3; $R^1 = R^2 = H$).

An alternative approach towards 2,4-dialkylated pyridines was suggested by the work of Arens [4] and his co-workers who showed that 2,4-dimethylpyridine could be lithiated in the 2-position by reaction with phenyllithium in ether–hexane. We found, however, that the lithium salt thus formed, reacted with *m*-methoxybenzaldehyde to give two isomeric alcohols (5; $R^1 = OMe$, $R^2 = H$) and (6) in 14% and 12% yields respectively. These were separated and characterised. On the other hand, reaction of n-butyl-lithium [5] and 2,4-dimethylpyridine at −78 °C followed by slow addition of *m*-methoxybenzaldehyde gave an improved yield of compound (5; $R^1 = OMe$, $R^2 = H$) (34%) along with the isomer (6) (5%) and the dihydric alcohol (7) (5%). When 2,4-dimethylpyridine and *m*-methoxybenzaldehyde were added rapidly but sequentially to n-butyl-lithium, the only product obtained was the desired compound (5; $R^1 = OMe$, $R^2 = H$) (55%). It is fortunate that n-butyl-lithium exhibits this selective metallation in the 2-position (presumably due to complexation of the lithium cation with the ring nitrogen atom [6]) since it has been shown that the hydrogen atoms on the 4-methyl group are more acidic than those on the 2-methyl group.[7]

Reduction of the alcohol (5; $R^1 = OMe$, $R^2 = H$) with zinc in formic acid at 135 °C gave the phenethylpyridine (8; $R^1 = OMe$, $R^2 = H$) (57%) but contaminated with the formate of alcohol (5; $R^1 = OMe$, $R^2 = H$); at lower temperatures, the latter compound predominated. Although separation by chromatography was possible, it was tedious. Catalytic (palladium) hydrogenolysis only



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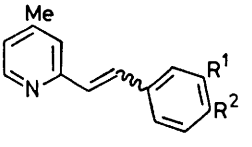

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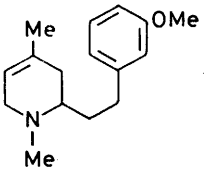

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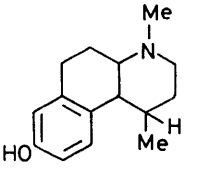

(11)

worked very slowly on a microscale. Alternatively, treatment of the alcohol (5; $R^1 = OMe$, $R^2 = H$) with polyphosphoric acid gave the alkene (9; $R^1 = OMe$, $R^2 = H$) which, on palladium-catalysed hydrogenation, gave

the phenethylpyridine (8; R^1 = OMe, R^2 = H) in 93% overall yield.

The quanternary methiodide of the pyridine (8; R^1 = OMe, R^2 = H) was reduced by sodium borohydride in alkaline medium to give a mixture of tetrahydropyridines (10) and (3; R^1 = OMe, R^2 = H); these were separated for characterisation by thick layer chromatography. For subsequent work, the mixture of isomers was used since, on protonation, they would give the same tertiary carbenium ion. The best of several media investigated for cyclisation was found to be polyphosphoric acid at 150 °C for a relatively short time (3 h). The product thus obtained was a crystalline hydroxy-compound, $C_{15}H_{21}NO$, which was deemed to have structure (1; R^1 = OH, R^2 = H) for the following reasons. Demethylated starting materials are excluded for two main reasons: first, absence of alkene-H resonances in the ^1H n.m.r. spectrum, and secondly, appearance of four singlet signals in the ^{13}C n.m.r. spectrum instead of three singlets). The latter evidence also excludes the plausible alternative cyclisation product (11) as does the appearance of a singlet for a methyl group in the ^1H n.m.r. spectrum. Mass spectroscopy of compound (1; R^1 = OH, R^2 = H) confirmed the molecular formula ($C_{15}H_{21}NO$) (47%) and, most significantly, revealed that the base peak was attributable to $M - CH_3$, typical of structures containing a tertiary methyl group. None of the precursors showed this phenomenon.

Considering that the ring being formed in the above cyclisation is seven-membered, the 40% yield of the hydroxy-amine (1; R^1 = OH, R^2 = H) is reasonably good compared with related 2-benzyltetrahydropyridine cyclisations.[8] The methoxy-group which is *para* to the point of electrophilic attack exerts a beneficial effect, for in the unsubstituted example, cyclisation of compound (3; R^1 = R^2 = H) proceeded in only 18% yield at 175 °C in polyphosphoric acid, and when the methoxy-group was *meta* to the point of attack as in compound (3; R^1 = H, R^2 = OMe), the reaction failed entirely. This pattern is in accord with previous experience (*cf.* ref. 9) with δ-arylpentanoic acid cyclisations. Compounds (3; R^1 = R^2 = H) and (3; R^1 = H, R^2 = OMe) were made as described above for compound (3; R^1 = OMe, R^2 = H), but starting ultimately with benzaldehyde and *p*-methoxybenzaldehyde, respectively, instead of *m*-methoxybenzaldehyde. Identification of the product (1; R^1 = R^2 = H) which was an oil, depended on the same type of arguments already presented for compound (1; R^1 = OH, R^2 = H) (see Experimental section).

Preliminary analgesic tests on compound (1; R^1 = OH, R^2 = H) showed that it had approximately a quarter of the activity of pentazocine.

EXPERIMENTAL

1,4-Dimethyl-2-phenethyl-1,2-dihydropyridine (4).—A stirred suspension of 1,4-dimethylpyridinium iodide (18.7 g, 0.08 mol) in anhydrous ether was treated at room temperature during 0.5 h with 0.35M-ethereal phenethylmagnesium bromide (275 cm³). The mixture was stirred for an additional 1.5 h and then poured into a vigorously stirred ice–ammonium chloride slurry. The ethereal layer was separated and extracted with 2M-hydrochloric acid. The combined extracts were made alkaline with ice–ammonium hydroxide and the liberated oil shaken into ether. The combined dried (Na_2SO_4) extracts on concentration *in vacuo* gave a yellow oil (5.5 g, 32%); $\nu_{max.}$ (film) 1 625 (C=C) and 1 600 cm^{-1}; δ 1.4—2.9 (4 H, m, methylene protons), 1.75 (3 H, s, 4-CH_3), 2.7 (3 H, s, NCH_3), 3.7—4.1 (1 H, m, 6-H), 4.65 (1 H, dd, $J_{2.3}$ 7, $J_{3.5}$ 1.5 Hz, 3-H), 4.6—4.8 (1 H, m, 5-H), 5.9 (1 H, d, $J_{2.3}$ 7 Hz, 2-H) and 7.1 (5 H, s, aryl). This material was unstable.

1,4-Dimethyl-2-phenethylpiperidine.—The above dihydropyridine (4; 3.7 g, 0.017 mol) was dissolved in 1N-hydrochloric acid and the solution was shaken under hydrogen with 5% Pd–$BaSO_4$ catalyst (1 g) for 15 h during which 1.65 mol. equiv. of hydrogen were absorbed. After removal of catalyst (filtration) the liquors were basified with ammonium hydroxide. The liberated oil was shaken with ether. The combined dried extracts yielded, on concentration under reduced pressure, a liquid (3.4 g) which on distillation (150—155 °C at 0.3 mmHg) gave a colourless *oil* (1.9 g, 50%) (Found: C, 82.9; H, 10.9; N, 6.5. $C_{15}H_{23}N$ requires C, 82.9; H, 10.7; N, 6.5%); $\nu_{max.}$ (film) 2 860, 2 770, and 1 605 cm^{-1}; δ 0.95 (3 H, d, 4-CH_3), 1.05—2.15 (8 H, m, methylene protons), 2.2 (3 H, s, NCH_3), 2.25—3.0 (4 H, m, methylene protons), and 6.5—7.2 (5 H, m, aryl).

The *methiodide* crystallised from ethanol as colourless *prisms*, m.p. 229—230 °C (Found: C, 54.0; H, 7.6; N, 3.9. $C_{16}H_{26}IN$ requires C, 53.7; H, 7.6; N, 3.9%); $\nu_{max.}$ (film) 2 860 and 1 605 cm^{-1}; δ [$(CD_3)_2SO$] 1.05 (3 H, d, 4-CH_3), 1.4—2.7 (8 H, m, methylene protons), 2.85 (3 H, s, $\overset{+}{N}CH_3$), 3.05 (3 H, s, $\overset{+}{N}CH_3$), 3.1—3.5 (4 H, m, methylene protons), and 7.0—7.2 (5 H, m, aryl).

1-(3-Methoxyphenyl)-2-(4-methyl-2-pyridyl)ethanol (5; R^1 = OMe, R^2 = H).—(*a*) Anhydrous diethyl ether (600 cm³) at −78 °C was treated *via* a syringe with 1.5M-n-butyllithium (200 cm³, 0.3 mol) followed immediately with 2,4-dimethylpyridine (32.1 g, 0.3 mol) in anhydrous ether (250 cm³) all under nitrogen. After stirring for 3 h at −78 °C, the red solution was treated with *m*-methoxybenzaldehyde (34 g, 0.3 mol) in anhydrous ether (200 cm³) dropwise over 1 h. The colourless solution was poured onto ice, stirred for 1 h, then extracted with chloroform. The extracts were washed with 2N-hydrochloric acid and the aqueous extracts basified and back-washed with chloroform. The bulked dried (Na_2SO_4) extracts were then concentrated *in vacuo* to give a pale red oil (54.5 g). Short-path column chromatography on silica gel (CT, 1 kg), eluting with anhydrous ether, gave (5; R^1 = OMe, R^2 = H) (24.6 b, 34%) which crystallised from light petroleum (b.p. 60—80 °C as *prisms*, m.p. 73.74 °C (Found: C, 74.4; H, 7.3; N, 5.6. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.0; N, 5.8%); $\nu_{max.}$ ($CHBr_3$) 3 580 (OH, free), 3 300 (OH, bonded), 1 040, and 789 cm^{-1}; δ 2.27 (3 H, s, pyridyl CH_3) 3.1 (2 H, d, *J* 6 Hz, 2-CH_2), 3.75 (3 H, s, OCH_3), 5.1—5.2 (1 H, t, *J* 6 Hz, 1-H), 5.5br (1 H, s, exchangeable, OH), 6.7—7.6 (6 H, m, aryl), and 8.3 (1 H, m, pyridyl 6-H). Two by-products were also isolated, the first of slightly higher R_F, *1-(3-methoxyphenyl)-2-(2-methyl-4-pyridyl)ethanol*, as a colourless *oil* (6; 3.35 g, 4.6%) (Found: C, 73.9; H, 7.2; N, 5.7. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.0; N, 5.8%); $\nu_{max.}$ ($CHBr_3$) 3 580 (OH, free), 3 300 (OH, bonded), 1 270, 835, and 790 cm^{-1}; δ 2.17 (3 H, s, pyridyl CH_3), 3.05 (2 H, d, benzylic CH_2), 3.8 (3 H, s, OCH_2), 5.1—

5.4 (1 H, overlapping d, 1-H), 5.5br (1 H, s, exchangeable OH), 6.7—7.6 (6 H, m, aryl), and 8.3 (1 H, m, pyridyl 6-H).

The second by-product 1,1'-(*3-methoxyphenyl*)-2,2'-(*pyridine*-2,4-*diyl*)*diethanol* (7), was of lower R_F and was isolated as colourless crystalline *needles*, m.p. 147—148 °C (Found: C, 72.4; H, 6.7; N, 3.8%; *M*, 379.170 5. $C_{23}H_{25}NO_4$ requires C, 72.8; H, 6.5; N, 3.6%; *M*, 379.178 3); $\nu_{max.}$ (KBr) 3 350 (OH), 1 600, and 1 585 cm^{-1}; δ 1.36 (4 H, s, 2 × benzylic CH_2), 3.5 (3 H, s, OCH_3), 3.55 (3 H, s, OCH_3), 5.2—5.6 [2 H, m, 2 of $-CH(OH)-$], 6.4—7.1 (10 H, m, aryl), and 8.2—8.3 (1 H, m, aryl).

(*b*) To anhydrous diethyl ether (150 cm^3) under nitrogen at −78 °C was added, *via* a syringe, 1.5M-n-butyl-lithium (50 cm^3, 0.075 mol) followed immediately by a steady stream of 2,4-dimethylpyridine (8.1 g, 0.075 mol) in anhydrous ether (75 cm^3) under nitrogen. After stirring at −78 °C for 3 h the deep red solution was treated with *m*-methoxybenzaldehyde (10.2 g, 0.075 mol) in anhydrous ether (100 cm^3) added as a single aliquot. Work-up as above gave a pale brown oil which crystallised from light petroleum (b.p. 80—80 °C) as colourless prisms of (5; R^1 = OMe, R^2 = H) (10.2 g, 55.5%), m.p. 74 °C. No isomeric alcohol was produced.

2-(*4-Methyl-2-pyridyl*)-1-*phenylethanol* (5; $R^1 = R^2$ = H).—Preparation as in (*b*) above, but using benzaldehyde (8.1 g, 0.05 mol), gave a single product (5; $R^1 = R^2$ = H) as a waxy solid which crystallised from light petroleum (b.p. 60—80 °C) as colourless *prisms* (8.9 g, 55.7%), m.p. 91—92 °C (Found: C, 78.4; H, 7.2; N, 6.5. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.1; N, 6.6%); $\nu_{max.}$ (Nujol) 3 170 (OH) and 1 600 cm^{-1}; δ 2.2 (3 H, s, pyridyl CH_3), 2.95 (2 H, d *J* 7 Hz, 2-CH_2), 5.0 (1 H, t, *J* 6 Hz, 1-H), 5.4br (1 H, s, exchangeable, OH), 6.7—8.4 (7 H, m, aryl), and 8.15 (1 H, d, *J* 5 Hz, pyridyl 6-H).

2-(*3-Methoxyphenethyl*)-*4-methylpyridine* (8; R^1 = OMe, R^2 = H).—(*a*) The above alcohol (5; R^1 = OMe, R^2 = H) (328 mg, 1.35 mmol) in 10% palladium–charcoal (75 mg) in ethanol containing 12M-hydrochloric acid (0.22 cm^3) was shaken with hydrogen at room temperature and atmospheric pressure for 4 days. After removal of catalyst (filtration) and solvent (*in vacuo*), dilution of the residue with water, basification with sodium hydrogencarbonate, extraction with chloroform, and concentration of the bulked dried (Na_2SO_4) extracts under reduced pressure, the product was isolated as a colourless *oil* (298 mg, 97.3%) (Found: C, 78.85; H, 7.6; N, 6.0. $C_{15}H_{17}NO$ requires C, 79.3; H, 7.5; N, 6.2%); $\nu_{max.}$ (film) 1 260, 1 050, 820, and 780 cm^{-1}; δ 2.30 (3 H, s, 4-CH_3), 3.05 (4 H, s, methylene protons), 3.8 (3 H, s, OCH_3), 6.6—7.4 (6 H, m, aryl), and 8.45 (1 H, m, 6-H).

(*b*) The foregoing alcohol (5; R^1 = OMe, R^2 = H) (2 g, 82 mmol), granular zinc, and 90% formic acid (50 cm^3) were heated at 135—140 °C for 56 h. The resultant pale yellow reaction mixture was cooled and filtered and the filtrate was concentrated under reduced pressure. The residual oil was diluted with water, basified with sodium carbonate, and the liberated oil shaken into chloroform. The bulked extracts were dried and concentrated under reduced pressure to give a pale yellow oil (1.7 g) which was purified by short-path column chromatography on silica gel (CT, 100 g). Elution with ethyl acetate in light petroleum (b.p. 60—80 °C) allowed isolation of *product* (8; R^1 = OMe, R^2 = H) (1.07 g, 57.3%), which showed identical spectral characteristics to an authentic sample. Also isolated, of lower R_F, was 1-(*3-methoxyphenyl*)-2-(*4-methyl-2-pyridyl*)*ethyl formate* [formate of (5; R^1 = OMe, R^2 = H)] as a yellow *oil* (0.48 g, 21.5%) (Found: C, 71.1; H, 6.2; N, 5.2%; *M*, 271.122 6. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%; *M*, 271.120 8); $\nu_{max.}$ (film) 1 722 cm^{-1} (C=O); δ 2.23 (3 H, s, pyridyl CH_3), 2.9—3.25 (2 H, m, 2-CH_2), 3.7 (3 H, s, OCH_3), 5.0—5.2 (1 H, m, 1-H), 6.6—7.3 (6 H, m, aryl), 7.9 (1 H, s, formyl), and 8.2—8.2 (1 H, m, pyridyl 6-H).

2-(*3-Methoxystyryl*)-*4-methylpyridine* (9; R^1 = OMe, R^2 = H).—The alcohol (5; R^1 = OMe, R^2 = H) (12 g, 0.05 mol) and polyphosphoric acid (240 g) were stirred at 100 °C for 1 h. The usual work-up gave a pale yellow *oil* (10.4 g, 95%) (Found: C, 80.3; H, 6.9; N, 6.6. $C_{15}H_{15}NO$ requires C, 80.0; H, 6.7; N, 6.2%); $\nu_{max.}$ (Nujol) 1 635 (C=C), 1 600, 1 260, 1 040, 815, and 720 cm^{-1}; δ 2.25 (3 H, s, 4-CH_3), 3.75 (3 H, s, OCH_3), 6.6—7.6 (8 H, m, aryl and olefinic), and 8.3 (1 H, d, *J* 5 Hz, 6-H).

2-(*3-Methoxyphenethyl*)-*4-methylpyridine* (8; R^1 = OMe, R^2 = H).—The aforementioned alkene (9; R^1 = OMe, R^2 = H) (10.3 g, 0.048 mol) and 10% palladium–charcoal in AnalaR ethanol were shaken with hydrogen at room temperature and atmospheric pressure for 10 h. After removal of catalyst (filtration) and solvent (*in vacuo*) the product (10.5 g, 95%) was isolated as a pale yellow oil which showed identical spectral characteristics to those of the sample prepared previously.

4-Methyl-2-phenethylpyridine (8; $R^1 = R^2$ = H).—The alkene (9; $R^1 = R^2$ = H) (7.3 g, 0.037 mol) and 10% palladium–charcoal in ethanol were shaken with hydrogen at room temperature and atmospheric pressure for 7 h. Work-up as above gave a pale yellow *oil* (7.35 g, 99%) (Found: C, 85.3; H, 7.4; N, 7.0. $C_{14}H_{15}N$ requires C, 85.25; H, 7.65; N, 7.1%); $\nu_{max.}$ 1 600 and 1 520 cm^{-1}; δ 2.25 (3 H, s, 4-CH_3), 2.9 (4 H, s, methylene protons), 6.8—7.2 (7 H, m, aryl), and 8.25 (1 H, d, *J* 6 Hz, 6-H).

4-Methyl-2-styrylpyridine (9; $R^1 = R^2$ = H).—The alcohol (5; $R^1 = R^2$ = H) (8.7 g, 0.04 mol) and polyphosphoric acid (100 g) were stirred at 100 °C for 1.5 h. After cooling to room temperature the mixture was diluted with water and basified with ammonium hydroxide. The liberated oil was shaken with chloroform and the bulked dried (Na_2SO_4) extracts concentrated under reduced pressure to give a yellow oil which crystallised from light petroleum (b.p. 80—80 °C) to give colourless *prisms* (7.3 g, 91%), m.p. 92—93 °C (Found: C, 86.3; H, 5.6; N, 7.1. $C_{14}H_{13}NO$ requires C, 86.1; H, 6.7; N, 7.2%); $\nu_{max.}$ (film) 1 635 (C=C) and 1 600 cm^{-1}; δ 2.3 (3 H, s, 4-CH_3), 6.8—7.6 (9 H m, aryl and olefinic), and 8.35 (1 H, d, *J* 5 Hz, 6-H).

Methiodide of 2-(*3-Methoxyphenethyl*)-*4-methylpyridine* (8; R^1 = OMe, R^2 = H).—Freshly distilled iodomethane (1 cm^3) was added dropwise to the dialkylated pyridine (8; R^1 = OMe, R^2 = H) (245 mg, 1.08 mmol) in dry acetone (3 cm^3), and the resulting solution was stirred at 20 °C for 16 h. The *methiodide* (364 mg, 99.2%) crystallised from acetone as colourless *prisms*, m.p. 199 °C (Found: C, 52.0; H, 5.5; N, 3.8. $C_{16}H_{20}INO$ requires, C, 52.05; H, 5.5; N, 3.8%); $\nu_{max.}$ (Nujol) 1 640, 1 600, 1 590, and 1 570 cm^{-1} (ring stretching modes of the pyridinium ion); δ [$(CD_3)_2SO$] 2.59 (3 H, s, 4-CH_3), 2.95—3.6 (4 H, m, methylene protons), 3.78 (3 H, s, OCH_3), 4.27 (3 H, s, $\overset{+}{N}CH_3$), 6.8—8.0 (6 H, m, aryl), and 8.75 (1 H, d, *J* 5.5 Hz, 6-H).

2-(*3-Methoxyphenethyl*)-1,*4-dimethyl*-1,2,3,6-*tetrahydropyridine* (10) *and* 2-(*3-Methoxyphenethyl*)-1,*4-dimethyl*-1,2,5,6-*tetrahydropyridine* (3; R^1 = OMe, R^2 = H).—The previous methiodide (533 mg, 1.44 mmol), sodium hydroxide

(900 mg), water (1.5 cm³), methanol (2 cm³), and sodium borohydride (8 mg) were stirred at 60 °C for 1.5 h. After dilution with water, the bulked, dried (Na_2SO) chloroform extracts were concentrated *in vacuo* and the pale brown oil was purified by thick plate chromatography on silica (ethanol–chloroform double elution). First eluted was the 1,2,5,6-*tetrahydropyridine* (3; R^1 = OMe, R^2 = H) (135 mg, 39%) (Found: C, 78.75; H, 9.6; N, 5.4%; *M*, 24.175 8. $C_{16}H_{23}NO$ requires C, 78.35; H, 9.5; N, 5.7%; *M*, 245.178 0); $\nu_{max.}$ (film) 2 900, 2 820, 2 760, 1 595, and 1 580 cm⁻¹; δ 1.3—2.9 (9 H, m, methylene protons), 1.66 (3 H, s, NCH_3), 2.28 (3 H, s, 4-CH_3), 3.7 (3 H, s, OCH_3), 5.2br (1 H, s, 5-H), 6.5—6.8 (3 H, m, aryl), and 6.9—7.15 (1 H, m, aryl); also isolated at a lower R_F was the 1,2,3,6-*tetrahydro-isomer* (10) (60 mg, 17%) (Found: C, 78.6; H, 9.5; N, 5.4%; *M*, 245.176 7. $C_{16}H_{23}NO$ requires C, 78.35; H, 9.5; N, 5.7%; *M*, 245.178 0 $\nu_{max.}$(film) 2 900, 2 820, 2 760, 1 595, and 1 580 cm⁻¹; δ 1.3—2.9 (9 H, m, methylene protons), 1.64 (3 H, s, NCH_3), 2.27 (3 H, s, 4-CH_3), 3.7 (3 H, s, OCH_3), 5.2br (1 H, s, 3-H), 6.5—6.8 (3 H, m, aryl), and 6.95—7.15 (1 H, m, aryl).

Considerably higher yields of these tetrahydropyridines were obtained when the reaction was repeated on a larger scale.

1,4-*Dimethyl*-2,3,4,5,6,7-*hexahydro*-1,5-*methano*-1H-4-*benzazonin*-9-*ol* (1; R^1 = OH, R^2 = H).—(*a*) The above tetrahydropyridines (125 mg) and 48% hydrobromic acid (3 cm³) were stirred at room temperature for 48 h. The reaction mixture was basified with potassium carbonate and the bulked, dried (Na_2SO_4) chloroform extracts were concentrated *in vacuo* to give a dark oil (75 mg) which t.l.c. showed to be a multicomponent mixture.

(*b*) The above tetrahydropyridines (250 mg) and polyphosphoric acid (8 g) were stirred at room temperature for 24 h. T.l.c. showed only starting material.

(*c*) The above tetrahydropyridines (625 mg) and 48% hydrobromic acid (10 cm³) were stirred at 135 °C for 3 h. Work-up as in (*a*) gave a dark oil (210 mg) which although t.l.c. showed to be a multicomponent mixture had mass spectral evidence indicating the presence of a molecular ion *M*, 231.162 8 ($C_{15}H_{21}NO$ requires *M*, 231.162 3).

(*d*) The above tetrahydropyridines (700 mg, 2.85 mmol) and polyphosphoric acid (40 g) were stirred at 190—195 °C for 10 h. The dark red reaction mixture was cooled and treated with ice–water (150 cm³) and 12M-hydrochloric acid (100 cm³), and stirred at 115 °C for 10 h. After addition of ice, basification with ammonium hydroxide, and extraction with butanol–chloroform, the bulked, dried (Na_2SO_4) extracts gave on concentration *in vacuo* a dark oil (375 mg). Recrystallisation from methanol gave fawn *prisms* (127 mg, 17.1%), m.p. 235—236 °C (Found: C, 77.8; H, 9.05; N, 5.8%; *M*, 231.162 6. $C_{15}H_{21}NO$ requires C, 77.85; H, 9.15; N, 6.1%; *M*, 231.162 3); $\nu_{max.}$ (Nujol) 3 250 (OH), 2 600, 1 605, and 1 570 cm⁻¹; δ 1.25 (3 H, s, 1-CH_3), 1.5—1.9 (6 H, m, 2-CH_2, 6-CH_2, and 12-CH_2), 2.17 (3 H, s, NCH_3), 2.2—2.5 (3 H, m, 3-CH_2 and 5-H), 2.9—3.3 (2 H, m, 7-CH_2), 4.85br (1 H, s, exchangeable, 9-OH), and 6.8—7.25 (3 H, m, aryl); δ_C (C_5D_5N) 26.270 (t, 7-C), 34.218 (q, 1-CH_3), 35.431 (q, N-CH_3), 38.288 (t, 6-C), 39.214 (s, 1-C), 42.044 and 43.076 (t, 2-C, and t, 12-C), 45.624 (t, 3-C), 56.181 (d, 5-C), 114.668 (d, 10-C), 118.245 (d, 8-C), 130.864 (d, 11-C), 136.446 (s, 7-C), 143.969 (s, 1-C), and 156.345 p.p.m. (s, 9-C).

(*e*) Reaction of the mixture of tetrahydropyridines (6 g) in polyphosphoric acid (250 g) at 150 °C for 3 h gave the product, m.p. 235—236 °C (2.1 g) as in (*d*).

Methiodide of 4-*Methyl*-2-*phenethylpyridine* (8; R^1 = R^2 = H).—Prepared as described previously, the *methiodide* crystallised from acetone as colourless *prisms*, m.p. 194—195 °C; (Found: C, 52.8; H, 5.4; N, 4.1. $C_{15}H_{18}IN$ requires C, 53.1; H, 5.3; N, 4.1%); $\nu_{max.}$ (Nujol) 1 638, 1 595, and 1 570 cm⁻¹ (ring stretching modes of the pyridinium ion); $\delta(C_5D_5N)$ 2.38 (3 H, s, 4-CH_3), 3.05—3.60 (4 H, m, methylene protons), 4.41 (3 H, s, $\overset{+}{N}CH_3$), 7.1—7.8 (7 H, m, aryl), and 9.0—9.2 (1 H, m, 6-H).

Reduction of Methiodide of 4-*Methyl*-2-*phenethylpyridine* (8; R^1 = R^2 = H).—To the methiodide (7.0 g, 0.021 mol) and sodium hydroxide (8 g) in water (20 cm³) and methanol (25 cm³) was added sodium borohydride (0.96 g) in one portion, and the resultant solution was stirred at 60 °C for 1 h. The usual work-up gave a product comprising principally one component with some material of slightly higher R_F (Found: *M*, 215.167 4. $C_{15}H_{21}N$ requires *M*, 215.167 4); $\nu_{max.}$ (film) 1 635 (C=C) and 1 600 cm⁻¹; δ 1.66 (3 H, s, NCH_3), 1.5—3.0 (9 H, m, methylene protons), 2.25 (s, 4-CH_3), 2.26 (s, 4-CH_3) (the combined integral of these singlets was equivalent to 3 H), 5.2br (1 H, s, olefinic), and 7.0—7.2 (5 H, m, aryl).

1,4-*Dimethyl*-2,3,4,5,6,7-*hexahydro*-1,5-*methano*-1H-4-*benzazonine* (1; R^1 = R^2 = H).—(*a*) The above tetrahydropyridines (1.5 g 7.0 mmol), and polyphosphoric acid were stirred at 192 °C for 5 h. Work-up as previously described gave a colourless *oil* (115 mg, 7%), b.p. 145—150 °C at 0.25 mmHg (Found: C, 83.4; H, 9.9; N, 6.5%; *M*, 215.168 4. $C_{15}H_{21}N$ requires C, 83.7; H, 9.8; N, 6.5%; *M*, 215.167 4); $\nu_{max.}$ (film) 3 060, 3 020, 2 930, 2 805, 1 605, and 1 230 cm⁻¹; δ 1.25 (3 H, s, 1-CH_3), 1.55—2.0 (6 H, m, 2-CH_2, 6-CH_2, and 12-CH_2), 2.2 (3 H, s, N-CH_3), 2.4—3.4 (5 H, m, 3-CH_2, 5-H, and 7-CH_2), and 6.85—7.25 (4 H, m, aryl); δ_C 24.875 (t, 7-C), 33.551 (q, 1-CH_3), 34.885 (q, N-CH_3), 38.465 (s, 1-C), 38.889 (t, 6-C), 41.620 and 42.833 (t, 2-C, and t, 12-C), 44.959 (t, 3-C), 55.392 (d, 5-C), 125.647 and 126.132 (d, 8-C and d, 11-C), 128.258 (s, 7-C) 129.287 and 130.685 (d, 9-C, and d, 10-C), and 141.906 (s, 1-C).

(*b*) The above tetrahydropyridines (3.8 g, 18 mmol) and polyphosphoric acid (160 g) were stirred at 175 °C for 1 h. Work-up gave a pale yellow oil (0.67 g, 18%) which had identical spectral and analytical characteristics to those of an authentic sample from (*a*).

1-(4-*Methoxyphenyl*)-2-(4-*methyl*-2-*pyridyl*)*ethanol* (5; R^1 = H, R^2 = OMe).—As described in (*b*) for the *meta*-isomer, *p*-methoxybenzaldehyde, n-butyl-lithium, and 2,4-dimethylpyridine were allowed to react at −78 °C to give the *product* (9 g), m.p. 54 °C (Found: C, 74.0; H, 7.2; N, 5.7. $C_{15}H_{17}NO_2$ requires C, 74.15; H, 7.05; N, 5.75%); δ 2.23 (3 H, s, pyridyl CH_3), 2.95—3.05 (2 H, dd, 2-CH_2), 3.77 (3 H, s, OCH_3), 4.9—5.05 (1 H, dd, 1-H), 6.7—7.3 (6 H, m, aryl), and 8.2 (1 H, d, pyridyl 6-H).

2-(4-*Methoxystyryl*)-4-*methylpyridine* (9; R^1 = H, R^2 = OMe).—The above alcohol (18 g) and polyphosphoric acid (800 g) were stirred at 60 °C for 30 min. Work-up gave the *product*, m.p. 76—78 °C (14 g) (Found: C, 79.7; H, 6.9; N, 6.35%; M^+, 225.112 6. $C_{15}H_{15}NO$ requires C, 80.05; H, 6.7; N, 6.25%; *M*, 225.115 3); δ 2.25 (3 H, s, 4-CH_3), 3.7 (3 H, s, OCH_3), 6.7—7.55 (8 H, m, aryl and olefinic), and 8.3 (1 H, d, *J* 5 Hz, 6-H).

2-(4-*Methoxyphenethyl*)-4-*methylpyridine* (8; R^1 = H, R^2 = OMe).—Hydrogenation of the above ethene (300 mg) in ethanol (40 ml) with palladium–charcoal (10%; 150 mg) gave the *product*, b.p. 150 °C at 0.03 mmHg (290 mg) (Found: C, 79.35; H, 7.95; N, 6.3. $C_{15}H_{17}NO$ requires C,

79.35; H, 7.55; N, 6.15%). δ 2.2 (3 H, s, 4-CH_3), 2.9 (4 H, s, methylene protons), 3.67 (3 H, s, OCH_3), 6.65—7.15 (6 H, m, aryl), and 8.27 (1 H, d, *J* 6 Hz, 6-H). The *methiodide* had m.p. 110 °C (from ethanol) (Found: C, 51.6; H, 5.35; N, 3.8. $C_{16}H_{20}INO$ requires C, 50.9; H, 4.85; N, 3.95%).

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