

Nitrone Cycloadditions: Synthesis of (\pm)-Andrachamine

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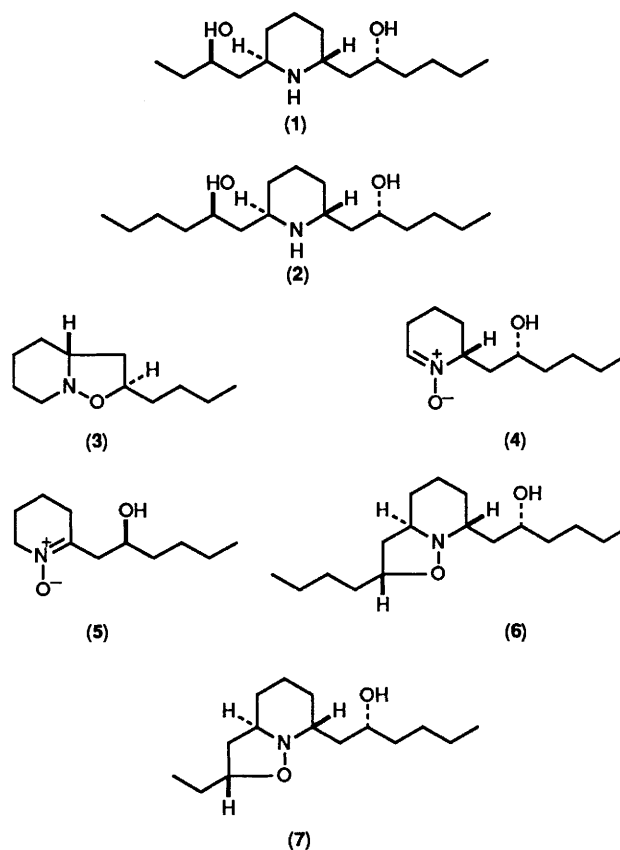
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The usefulness of the cycloaddition of alkenes to 2-alkyl-2,3,4,5-tetrahydropyridine oxides for the preparation of *trans*-2,6-dialkylpiperidines is confirmed by a stereoselective synthesis of (\pm)-andrachamine. Peroxy acid oxidation of 9-oxa-1-azabicyclo[4.3.0]nonanes does not lead regioselectively to the corresponding 2-alkyl-2,3,4,5-tetrahydropyridine oxide, as had previously been claimed.

The isolation of a new piperidine alkaloid, (–)-andrachamine, from the medicinal plant *Andrachne aspera* was reported recently¹ and the structure and stereochemistry (1) were assigned, largely on the basis of NMR and MS evidence. Nitronc cycloaddition chemistry lends itself to the synthesis of a compound of this structure and, because of our interest in this area,^{2,3} we undertook the synthesis of (\pm)-andrachamine in order to obtain further evidence bearing on its structure and stereochemistry.

We first prepared the homologous symmetrical *trans*-2,6-bis-(2-hydroxyhexyl)piperidine (2) in order to confirm the generality of our nitronc-cycloaddition route to *trans*-2,6-dialkylpiperidines.² *exo*-Addition⁴ of hex-1-ene to 2,3,4,5-tetrahydropyridine 1-oxide in boiling dichloromethane smoothly gave the isoxazolidine (3), which on oxidation with *m*-chloroperoxybenzoic acid (MCPBA) afforded a mixture of the aldo- and keto-nitrones (4) and (5) in the ratio *ca.* 2:5. These were not separated. On treatment of the mixture with a second molecule of hex-1-ene in dichloromethane only the aldonitrone reacted, to give the isoxazolidine (6) in 21 per cent yield from compound (3). Hydrogenolysis with hydrogen and Raney nickel yielded the disubstituted piperidine (2). Earlier work had established⁴ that cycloaddition of terminal alkenes to 2,3,4,5-tetrahydropyridine 1-oxide takes place in the *exo* mode leading, by analogy, to the stereochemistry for the hydroxy substituents shown in structure (2). The ¹H NMR spectrum of the corresponding *N*-benzyl derivative established the *trans* orientation of the alkyl substituents in compound (2). In *N*-benzyl derivatives of symmetrical piperidines such as (2) the ¹H NMR signal of the benzylic methylene protons appears as a singlet in the *cis*-isomer, while in the *trans*-compound it is a doublet of doublets.⁵ The NMR spectrum of the *N*-benzyl derivative of compound (2) showed considerable broadening at room temperature, but at 60 °C it was much sharper and included a doublet of doublets due to the benzylic protons centred at δ 3.62 (*J* 13 Hz) and δ 3.83 (*J* 13 Hz). No other isomer was detected in the ¹H or the ¹³C NMR spectrum. These experiments thus confirmed the stereoselectivity of this sequence for the preparation of *trans*-2,6-dialkylpiperidines from 2,3,4,5-tetrahydropyridine 1-oxide.

To prepare the unsymmetrical andrachamine (1) a similar approach was adopted. Reaction of the mixture of nitrones (4) and (5) with but-1-ene in chloroform at 110 °C gave the isoxazolidine (7), although in poorer yield (13%) than that obtained in the reaction with hex-1-ene. Reductive cleavage of the N–O bond with zinc and acetic acid then afforded the amino diol (1). The stereochemistry of the hydroxy substituents was based on analogy as before. The benzylic protons of the corresponding *N*-benzyl derivative again gave rise to a doublet of doublets in the ¹H NMR spectrum, at δ 3.59 (*J* 12 Hz) and δ

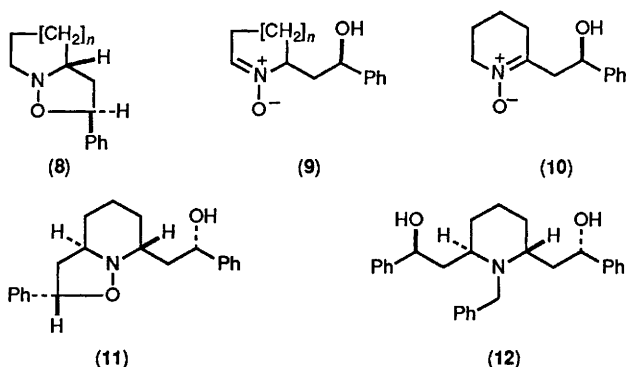


3.81 (*J* 12 Hz), but whether this criterion is sufficient to establish the *trans* orientation of the two different alkyl substituents in structure (1) is not certain. It seems likely that in compound (1) the two alkyl substituents are equivalent in the local environment of the benzylic protons, but in any case their *trans* orientation is highly probable on analogy with their orientation in the closely related homologue (2).

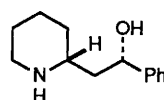
The structure of our synthetic compound corresponds to that reported for (–)-andrachamine. The *trans* configuration of the two alkyl substituents in the natural product was assigned by comparison of the ¹³C chemical shift of C-4 of the piperidine ring with values recorded for *cis*- and *trans*-2,6-dialkylpiperidines.⁶ The ¹³C chemical shift for C-4 in our synthetic (1) (δ_c 19.12) is close to that reported for (–)-andrachamine (δ_c 18.7), and other ¹³C chemical shifts and the mass spectrum fragmentation pattern are in agreement with those given for (–)-andrachamine, but we have not been able to obtain a specimen of the natural product for direct comparison.

† Deceased May 1990.

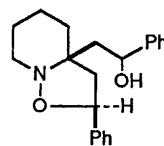
A disappointing feature in the synthesis of compound (1) was the lack of regioselectivity in the peroxy acid oxidation of the isoxazolidine (3), where the desired aldonitrone (4) was the minor component of the mixture of nitrones produced. An earlier report⁷ had indicated that peroxy acid oxidation of the isoxazolidines (8; $n = 1, 2$), obtained by cycloaddition of styrene to Δ^1 -pyrroline 1-oxide and to 2,3,4,5-tetrahydropyridine 1-oxide respectively, gave exclusively the aldonitrones (9; $n = 1, 2$). We have confirmed the regioselectivity of the oxidation of the isoxazolidine (8; $n = 1$) derived from pyrroline 1-oxide, but in our hands³ the homologue (8; $n = 2$) from tetrahydropyridine oxide gave a mixture of nitrones (9; $n = 2$) and (10) in which the aldonitrone (9; $n = 2$) was the minor component (ratio *ca.* 1 : 2). These products could not be separated, but only the aldonitrone (9; $n = 2$) reacted with styrene in boiling chloroform to give the adduct (11) as reported.⁷ The ketonitrone (10) was then readily separated by chromatography. Reaction of the adduct (11) with benzyl bromide gave the corresponding crystalline *N*-benzyl quaternary bromide, which on reduction with lithium aluminium hydride afforded the amino diol (12). In the ¹H NMR spectrum of this compound the signal due to the *N*-benzylic protons appeared as a doublet of doublets at δ 3.68 (*J* 13 Hz) and δ 3.97 (*J* 13 Hz), confirming the *trans* orientation of the two alkyl substituents in compound (12).⁵ The orientation of the hydroxy groups was based on analogy⁴ as before.



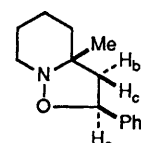
The major nitrone (10) from the oxidation of the isoxazolidine (8; $n = 2$) was identified by IR absorption bands at 1 621 and 1 146 cm^{-1} , characteristic of the C–N and N–O stretch of nitrones, and by a signal at δ_{C} 149.56 in the ¹³C NMR spectrum, due to an olefinic quaternary carbon atom. The structure was confirmed by an alternative preparation by tungstate-catalysed peroxide oxidation⁸ of the piperidine (13). The nitrone (10) did not react with styrene in chloroform (*vide supra*), but in boiling toluene it readily formed the isoxazolidine (14). The structure of this unexpected product was suggested by its ¹H and ¹³C NMR spectra, particularly by a signal at δ_{C} 62.84 in the ¹³C NMR spectrum, indicative of a non-aromatic quaternary carbon, and was supported by an alternative synthesis from reaction of 2-methyl-3,4,5,6-tetrahydropyridine oxide and styrene in boiling toluene. The stereochemistry shown was established from the ¹H NMR spectrum and is in line with the expected⁴ *exo* addition of styrene to the nitrone. The signal due to the benzylic proton (H_{a}) appears as a doublet of doublets at δ 5.22 and 5.41 (*J* 6, 10 Hz), and those of the methylene protons (H_{b}) and (H_{c}) as doublets of doublets centred at δ 2.62 (*J* 10, 12 Hz) and δ 1.96 (*J* 6, 12 Hz) respectively. Double irradiation established the proximity of H_{c} and the methyl group, allowing the assignment of the stereochemistry shown. It is uncertain whether compound (14) arises by a retro-aldol-type decomposition of the nitrone (10) with elimination of benzaldehyde, detected in the reaction mixture by isolation of its 2,4-dinitrophenylhydrazone, to give 2-methyl-3,4,5,6-tetra-



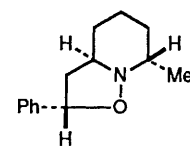
(13)



(15)



(14)



(16)

dropyridine oxide followed by addition of styrene, or directly from the adduct (15).

The tungstate-catalysed peroxide oxidation of the piperidine (13) and reaction of the product with styrene to give the isoxazolidine (14) led also to an isomeric product (ratio *ca.* 14 : 1) identified as the adduct (16) (see Experimental section), clearly formed from the alternative aldonitrone. It appears from this that tungstate-catalysed peroxide oxidation of 2-alkylpiperidines is not completely selective for the formation of the ketonitrone.

Experimental

¹H NMR spectra (100 MHz) were determined using a JEOL JNM-MH 100 instrument, and 250 MHz ¹H and 62.9 MHz ¹³C NMR spectra with a Bruker AM 250 spectrometer. Short-column chromatography⁹ and dry column flash chromatography used Merck Kieselgel 60H (Merck No. 7736), and flash chromatography¹⁰ used Camlab Kieselgel 60, 230–400 mesh. IR spectra were recorded with a Perkin-Elmer 881 spectrometer, as liquid films unless otherwise stated. High-resolution accurate mass spectra were determined at the SERC Mass Spectroscopy Centre, University College, Swansea. Gas-liquid chromatography (GLC) was carried out using a Pye-GCD, FID instrument. Light petroleum refers to that fraction boiling in the range 40–60 °C.

trans-8-Butyl-9-oxa-1-azabicyclo[4.3.0]nonane (3).—A solution of *N*-hydroxypiperidine (3.4 g) in dry dichloromethane (30 ml) was stirred with yellow mercury(II) oxide (24.8 g) at 0 °C for 30 min. Magnesium sulphate (2.5 g) was added and the slurry was filtered through Celite with the aid of dichloromethane (130 ml). The solvent was removed under reduced pressure and a solution of the recovered nitrone and hex-1-ene (4.8 g) in dichloromethane (10 ml) was refluxed under nitrogen for 18 h, after which the solvent was removed under reduced pressure, and the resulting oil was flash chromatographed over silica. Elution with hexane–diethyl ether (3:2) gave the isoxazolidine (3) as an oil (4.0 g, 65%), b.p. 62–66 °C at 0.1 mmHg (Kugelrohr); ν_{max} 2 935, 2 860, 1 468, 1 453, 1 377, 1 330, 1 260, 1 117, 1 087, 1 000, 904, 859, and 775 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.81 (3 H, t, Me), 0.95–1.35 (6 H, m), 1.35–1.97 (8 H, m), 1.97–2.14 (1 H, m), 2.24–2.43 (1 H, br d), 3.24–3.62 (1 H, br d, CHN), and 3.81–4.00 (1 H, br s, CHO); δ_{C} (62.9 MHz; CDCl_3) 13.84 (Me), 22.59, 23.86, 24.68, 27.96, 29.36, and 34.94 (6 \times CH_2), 40.01 (isoxazolidine CH_2), 55.02 (CH_2N), 66.25 (CHN), and 75.84 (Found: C, 71.8; H, 11.6; N, 8.0; M^+ , 183. $\text{C}_{11}\text{H}_{21}\text{NO}$ requires C, 72.08; H, 11.55; N, 7.64%; M , 183).

(2*R**,6*R**)-2,6-Bis[(2'*R**)-2-Hydroxyhexyl]piperidine (2).—A solution of MCPBA (670 mg, 80%) in dichloromethane (20 ml) was added dropwise to a solution of the foregoing isoxazolidine

(3) (520 mg) in dichloromethane (10 ml) under nitrogen. After 40 min the solution was washed with saturated aq. sodium hydrogen carbonate and the recovered yellow oil, shown by TLC [eluant MeOH-CHCl₃ (1:9)] to contain two products, was boiled for 18 h with hex-1-ene (10 ml) and chloroform (1 ml). The recovered product was chromatographed over 60 H silica to give the isoxazolidine (6) as a wax (170 mg, 21%) on elution with tetrahydrofuran (THF)-light petroleum (1:4); ν_{\max} 3 395, 2 937, 2 860, 1 716, 1 573, 1 467, 1 378, 1 289, 1 258, 1 124, 1 071, 962, and 754 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.92 (6 H, 2 superimposed t), 1.14–1.76 (18 H, m), 1.76–1.01 (3 H, m), 2.30 (1 H, app q, *J* 11 Hz), 2.73–3.08 (1 H, br s), 3.38–3.70 (1 H, m), 3.81–4.00 (1 H, m), 4.14–4.41 (1 H, m), and 4.41–4.84 (1 H, br s); δ_{C} (62.9 MHz; CDCl₃) 13.94 (Me), 14.03 (Me), 18.52, 22.65, 22.77, 25.51, 27.82, 28.02, 29.50, 35.09, 35.50, 37.67, and 39.25 (11 \times CH₂), 56.47, 59.58, 68.89, and 76.48 (4 \times CH) (Found: M^+ , 283.2502. C₁₇H₃₃NO₂ requires M , 283.2511).

Hydrogenation of the isoxazolidine (6) (510 mg) in methanol (20 ml) with Raney nickel at ambient temperature and pressure, and purification of the product by chromatography on 60 H silica [eluant Et₃N-MeOH-EtOAc, 1:1:18], gave the piperidine (2) as a pale yellow oil (340 mg) which crystallised on storage; ν_{\max} 3 375, 3 071, 2 930, 2 856, 1 460, 1 444, 1 380, 1 141, 1 112, 1 086, 1 060, 1 045, 1 002, 826, and 731 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.89 (6 H, t, *J* 7 Hz, 2 Me), 1.14–1.49 (15 H, m), 1.49–1.70 (5 H, m), 1.70–1.92 (2 H, m), 3.11–3.30 (2 H, m, CHNCH), 3.30–3.59 (3 H, br m, NH, and 2 \times OH), and 3.59–3.97 (2 H, m, 2 CHOH); δ_{C} (62.9 MHz; CDCl₃) 14.01 (2 \times Me), 19.92, 22.76, 28.22, 32.06, 37.33, and 39.08 (11 \times CH₂), 47.14 (2 \times CHN), and 69.05 (2 \times CHOH); m/z 286 (M^+ + 1), 268, 184, and 166 (Found: C, 71.6; H, 12.1; N, 5.0. C₁₇H₃₅NO₂ requires C, 71.5; H, 12.4; N, 4.9%).

The *N*-benzylpiperidine was obtained by reduction of the crude quaternary salt prepared from isoxazolidine (6) (170 mg) and benzyl bromide (500 mg) in boiling dichloromethane (40 ml), with lithium aluminium hydride (250 mg) in boiling THF (10 ml). After purification by chromatography on 60 H silica (eluant chloroform saturated with NH₃) the derivative was obtained as a pale yellow oil (142 mg, 63%); ν_{\max} 3 409, 3 030, 2 932, 1 605, 1 468, 1 379, 1 263, 1 207, 1 111, 1 065, 1 030, 852, 765, 720, and 698 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.89 (6 H, t, *J* 7 Hz, 2 \times Me), 1.03–1.54 (16 H, m), 1.54–1.89 (4 H, m), 2.00–2.30 (2 H, m), 3.27–3.49 (2 H, m, CHNCH), 3.62 and 3.84 (2 H, q, *J* 13 Hz, CH₂Ph), 3.68–3.81 (2 H, m, 2 \times CHOH), 4.11–4.76 (2 H, brs, 2 \times OH), and 7.14–7.46 (5 H, m); δ_{C} (62.9 MHz; CDCl₃) 13.79 (2 \times Me), 20.84, 22.60, 24.07, 28.19, 36.64, and 37.21 (11 \times CH₂), 48.89 (CH₂Ph), 50.06 (2 \times CHN), 69.00 (2 \times CHOH), 127.31, 128.42, and 129.59 (5 aromatic CH), and 139.10 (aromatic quaternary C); m/z 375 (M^+), 319, 276, 275, and 91 (Found: C, 76.6; H, 11.1; N, 3.5. C₂₄H₄₁NO₂ requires C, 76.8; H, 11.0; N, 3.7%).

(2R*,6R*,8R*)-8-Ethyl-[(2'R*)-2-hydroxyhexyl]-9-oxa-1-azabicyclo[4.3.0]-nonane (7).—A solution of MCPBA (5.8 g) in chloroform (50 ml) was added dropwise to a stirred slurry of the isoxazolidine (3) (4.9 g) and sodium hydrogen carbonate (7.2 g) in chloroform (50 ml) at 0 °C. After 10 min the mixture was allowed to come to ambient temperature and a solution of the recovered orange oil and excess of but-1-ene in chloroform (10 ml) was heated in a sealed tube at 110 °C for 18 h. Flash chromatography of the recovered product [eluant light petroleum-ethyl acetate (3:1)] gave the title compound (7) (881 mg) as nodules, m.p. 52–53 °C (from light petroleum); ν_{\max} (KBr) 3 391, 2 936, 2 846, 1 686, 1 466, 1 377, 1 263, 1 124, 1 085, 1 055, 971, 951, 901, 819, 735, and 702 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.86 (6 H, t, *J* 6 Hz, 2 Me), 1.03–1.70 (14 H, m), 1.70–2.00 (3 H, m), 2.24 (1 H, app q, *J* 12 Hz), 2.68–3.00 (1 H, br s), 3.30–3.68 (1 H, br s), 3.73–4.00 (1 H, m), 4.03–4.35 (1 H, m), and 4.38–

4.95 (1 H, br s, OH); δ_{C} (62.9 MHz; CDCl₃) 9.82 and 13.97 (2 \times Me), 18.46, 22.72, 27.75, 28.01, 29.46, and 37.65 (6 \times CH₂), 25.46, 34.89, and 39.19 (3 \times CH₂), and 56.48, 59.58, 68.82, and 77.63 (4 \times CH); m/z 255 (M^+), 198 (M^+ – Bu), and 154 (M^+ – C₆H₁₂O) (Found: C, 70.8; H, 11.7; N, 5.6. C₁₅H₂₉NO₂ requires C, 70.5; H, 11.4; N, 5.5%).

(2R*,6R*)-2-[(2'R*)-2-Hydroxybutyl]-6-[(2'R*)-2-hydroxyhexyl]piperidine, (±)-Andrachamine (1).—Zinc dust (1.9 g) was added to a solution of the foregoing adduct (7) (0.88 g) and ethylenediaminetetra-acetic acid (8.2 g) in ethanol (5 ml)-acetic acid (10 ml; 22 ml) at 55 °C, and the mixture was boiled for 45 min. The cooled solution was taken to pH 10 with aq. ammonia and extracted with chloroform. The recovered yellow oil (806 mg) on chromatography on 60 H silica gave andrachamine as a wax; ν_{\max} 3 394, 3 077, 2 929, 1 627, 1 442, 1 383, 1 352, 1 277, 1 131, 1 073, 1 050, 978, 815, 779, 766, and 731 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.86 (6 H, 2 \times Me), 1.08–1.78 (18 H, m), 3.22–3.49 (2 H, m, CHNCH), 3.68–3.92 (2 H, m, 2 \times CHOH), and 5.68–6.84 (3 H, br s, NH and 2 \times OH); δ_{C} (62.9 MHz; CDCl₃) 10.17 and 13.96 (2 \times Me), 19.12, 22.65, 28.06, 30.04, 30.33, 30.36, 36.98, 37.62, and 37.94 (9 \times CH₂), 47.69 and 47.74 (2 \times CHN), and 68.22 and 69.60 (2 \times CHOH); m/z 257 (M^+), 228 (M^+ – Et), 200 (M^+ – Bu), 184 (M^+ – C₄H₈O), and 156 (M^+ – C₆H₁₃O) (Found: C, 69.8; H, 12.0; N, 5.4. C₁₅H₃₁NO₂ requires C, 70.0; H, 12.1; N, 5.4%).

The *N*-benzyl derivative was obtained by reduction, with lithium aluminium hydride (1M in THF; 3 ml), of the corresponding *N*-benzoyl compound prepared from andrachamine (195 mg), benzoyl chloride (93 μ l), and triethylamine (116 μ l) in benzene (25 ml) at 25 °C for 48 h. Purification by chromatography on 60 H silica (eluant chloroform + 2% methanol, saturated with ammonia) gave the *N*-benzyl compound as an oil (107 mg); ν_{\max} 3 400, 2 938, 2 875, 1 605, 1 470, 1 382, 1 267, 1 200, 1 105, 1 070, 1 030, 850, 762, 719, and 700 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.84 (6 H, br t), 0.97–1.54 (10 H, m), 1.54–2.23 (5 H, br m), 3.16–3.41 (2 H, br s, CHNCH), 3.41–3.95 (2 H, m, 2 \times CHOH), 3.59 and 3.81 (2 H, q, *J* 12 Hz, CH₂Ph), 4.50–5.50 (2 H, br s), and 7.14–7.54 (5 H, m); δ_{C} (62.9 MHz; CDCl₃) 10.45 and 14.01 (2 \times Me), 20.84, 22.69, 28.33, 29.52, and 36.41 (5 \times CH₂), 48.55 (PhCH₂), 49.71 (CHNCH), 65.20 (2 \times CHOH), 127.47, 128.48, and 129.80 (5 aromatic CH), and 138.66 (aromatic quat. C); m/z 348 (M^+ + 1), 318 (M^+ – Et), 276 (M^+ – C₄H₈O), and 248 (M^+ – C₆H₁₃O) (Found: C, 76.2; H, 10.6; N, 4.2. C₂₂H₃₇NO₂ requires C, 76.5; H, 10.8; N, 4.1%).

trans-8-Phenyl-9-oxa-1-azabicyclo[4.3.0]nonane (8; *n* = 2).—A solution of 2,3,4,5-tetrahydropyridine 1-oxide, prepared as described above from 1-hydroxypiperidine (6.1 g), and styrene (9.4 g) in chloroform (50 ml) was refluxed under nitrogen for 24 h. Flash chromatography of the recovered product [eluant diethyl ether-hexane (1:3)] gave the isoxazolidine (8; *n* = 2) as a pale yellow oil (10.7 g); ν_{\max} 2 939, 2 855, 1 605, 1 496, 1 452, 1 260, 1 009, 951, 759, and 699 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.08–1.59 (3 H, m), 1.59–1.92 (3 H, m), 1.92–2.03 (1 H, m), 2.03–2.27 (1 H, m), 2.27–2.54 (1 H, m), 2.54–2.84 (1 H, m), 3.43–3.89 (1 H, 2 br s, invertomers, CHN), 4.86–5.54 (1 H, 2 br s, invertomers, CHPh), and 7.11–7.54 (5 H, m); δ_{C} (62.9 MHz; CDCl₃) 23.92, 24.84, and 29.40 (3 \times CH₂), 43.19 (CH₂ of isoxazolidine), 55.25 (CH₂N), 66.77 (CHN), 77.61 (CHPh), 126.69, 127.58, and 128.37 (aromatic CH), and 142.02 (aromatic quat. C) (Found: M^+ , 203. C₁₃H₁₇NO requires M , 203).

Peroxy Acid Oxidation of the Isoxazolidine (8; *n* = 2): 6-(2'-Hydroxy-2'-phenylethyl)-2,3,4,5-tetrahydropyridine 1-Oxide (10).—A solution of the foregoing isoxazolidine (8; *n* = 2) (880 mg) in dichloromethane (30 ml) was treated with a solution of

MCPBA (85%; 0.94 g) in dichloromethane (30 ml) at 0 °C, and then at ambient temperature for 90 min. The recovered yellow oil, which contained two components in the ratio 7:3 (^{13}C NMR), was refluxed under nitrogen for 48 h with styrene (1.03 g) in chloroform (50 ml). Removal of solvent and chromatography on 60 H silica (eluant chloroform + 5% methanol) gave, first, the ketonitrone (10), which formed a white powder from ethyl acetate–hexane, m.p. 121–122 °C (209 mg). Further elution gave an impure product, which on rechromatography over 60 H silica [eluant ethyl acetate–light petroleum, (1:1)] afforded the isoxazolidine (11) as a yellow oil⁷ (284 mg); ν_{max} 3 325, 3 060, 3 028, 2 935, 2 863, 1 605, 1 513, 1 494, 1 452, 1 248, 1 056, 1 029, 758, and 700 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.32–2.16 (7 H, m), 2.16–2.49 (1 H, m), 2.68 (1 H, app q, J 11.6 Hz), 2.86–3.24 (1 H, br d), 3.65–4.08 (1 H, br s), 5.08 (1 H, dd, J 4.6, 9.3 Hz, PhCHOH), 5.19 (1 H, dd, J 4.6, 9.3 Hz, PhCHON), and 7.14–7.57 (10 H, m); δ_{C} (62.9 MHz; CDCl_3) 18.53, 25.48, 29.62, 39.10, and 42.12 (5 CH_2), 56.74, 60.34, 71.72, and 78.25 (4 \times CH), 125.96, 126.59, 126.91, 127.72, 128.20, and 128.50 (aromatic CH), 142.24 and 145.57 (aromatic quaternary C).

The ketonitrone (10) (m.p. 121–122 °C) had: ν_{max} (KBr) 3 200, 2 960, 1 621, 1 600, 1 495, 1 443, 1 367, 1 332, 1 189, 1 146, 1 093, 1 001, 925, 814, 763, and 701 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.32–1.68 (2 H, m), 1.68–1.95 (3 H, m), 2.22 (1 H, dt, J 6.5, 19.4 Hz), 2.84 (1 H, dd, J 7.5, 13 Hz) and 3.08 (1 H, dd, J 3.3, 13 Hz) (PhCHCH_2), 3.76 (2 H, t, J 6.5 Hz), 5.14 (1 H, dd, J 3.2, 7.5 Hz, PhCH) 7.11–7.38 (5 H, m), and 7.38–7.59 (1 H, br s, OH); δ_{C} (62.9 MHz; CDCl_3) 18.37, 22.76, 31.12, 42.77, and 57.60 (5 \times CH_2), 73.81 (CHPh), 125.15, 127.22, and 128.28 (aromatic CH), 144.64 (aromatic quat. C), and 149.56 (nitrone quat. C) (Found: M^+ , 220.1337. $\text{C}_{13}\text{H}_{17}\text{NO}_2$ requires M , 220.1337).

The same ketonitrone was obtained by oxidation⁸ of 2-(2'-hydroxy-2'-phenylethyl)piperidine (13) (2.1 g) in methanol (30 ml) containing sodium tungstate (0.5 g) by slow addition of hydrogen peroxide (30%; 3 g) below 5 °C. After the addition the solution was brought to room temperature for 1 h and excess of hydrogen peroxide was destroyed by addition of sodium metabisulphite. The product was extracted into chloroform and, after chromatography on 60 H silica (eluant chloroform + 2% methanol), gave the nitrone (461 mg) as powder (from ethyl acetate–light petroleum), m.p. 120–121 °C, not depressed when mixed with a sample of the nitrone obtained as described immediately above.

cis-6-Methyl-8-phenyl-9-oxa-1-azabicyclo[4.3.0]nonane (14).—A solution of the above ketonitrone (218 mg) and styrene (2.74 g) in toluene (25 ml) was refluxed under nitrogen for 3 h. Removal of solvent and chromatography of the product over 60 H silica [eluant ethyl acetate–light petroleum, (1:1)] gave the product (14) (104 mg) as an oil which decomposed on attempted distillation; ν_{max} 3 028, 2 932, 1 604, 1 494, 1 451, 1 372, 1 279, 1 250, 1 131, 1 061, 950, 751, and 600 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.22 (3 H, s, Me) 1.30–1.65 (4 H, m), 1.65–1.89 (2 H, m), 1.89–2.03 (1 H, dd, J 6, 12 Hz, H_c), 2.51–2.73 (1 H, dd, J 10, 12 Hz, H_b), 2.97–3.22 (2 H, m), 5.22–5.41 (1 H, dd, J 6, 10 Hz, H_a), and 7.08–7.49 (5 H, m); irradiation of the Me signal at δ 1.22 led to a 10 per cent enhancement of the signal due to H_c at δ 1.89–2.03; δ_{C} (62.9 MHz; CDCl_3) 20.25 and 22.20 (2 \times CH_2), 26.63 (br, Me), 32.50, 47.73, and 49.58 (3 CH_2), 62.83 (quat. C), 76.81 (CHPh), 125.80, 126.96, and 128.32 (aromatic CH), and 143.35 (aromatic quat. C) (Found: M^+ , 217.1467. $\text{C}_{14}\text{H}_{19}\text{NO}$ requires M , 217.1467).

In a separate experiment, after careful removal of toluene, benzaldehyde was isolated from the reaction mixture by chromatography over 60 H silica (eluant light petroleum + 5% ethyl acetate) and identified as its 2,4-dinitrophenylhydrazone, m.p. 245–246 °C.

The isoxazolidine (14) was also obtained by reaction of 2-methyl-3,4,5,6-tetrahydropyridine 1-oxide [prepared from 2-methylpiperidine (10 g) and hydrogen peroxide (30%; 25 g) in the presence of sodium tungstate (1.32 g)]⁸ and styrene (20.5 g) in refluxing toluene (150 ml) for 18 h. Chromatography of the crude material (11.5 g) on 60 H silica (eluant light petroleum + 2–4% THF) gave mainly a product (6.67 g) identical in all respects with the oxazabicyclononane (14). A more polar component (0.46 g), obtained by continued elution, appeared to be the isomer (16); δ_{H} (250 MHz; CDCl_3) 1.22 (3 H, d, J 6.5 Hz, Me), 1.27–1.51 (2 H, m), 1.51–1.84 (2 H, br d), 1.84–2.22 (3 H, m), 2.51–2.97 (2 H, m), 3.70–4.03 (1 H, br quin., J 6.5 Hz, CHN), 5.30 (1 H, dd, J 4.3, 9.7 Hz, CHPh), and 7.00–7.65 (5 H, m); δ_{C} (62.9 MHz; CDCl_3) 18.81 (C-4), 20.48 (Me), 25.46, 32.77, and 39.20 (3 \times CH_2), 53.88 (CHMe), 60.50 (CHN), 78.28 (CHPh), 126.43, 127.46, and 128.37 (aromatic CH), and 142.75 (aromatic quat. C).

The *N*-benzyl quaternary bromide, prepared from the isoxazolidine (14) (48 mg) and benzyl bromide (1 g) in dichloromethane (15 ml), formed crystals (87 mg) from chloroform–diethyl ether, m.p. 162–163 °C (decomp.); ν_{max} (KBr) 3 032, 2 945, 2 892, 1 601, 1 585, 1 495, 1 454, 1 357, 1 251, 1 158, 949, 759, and 698 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.70–2.16 (4 H, m), 2.08 (3 H, s, Me), 2.16–2.57 (2 H, m), 3.00–3.27 (1 H, dd, J 8, 13.7 Hz, isoxazolidine CHH), 3.27–3.54 (1 H, dd, J 8, 13.7 Hz, isoxazolidine CHH), 3.68–4.00 (1 H, m), 4.00–4.22 (1 H, m), 4.84 and 5.46 (2 H, q, J 13 Hz, PhCH_2), 6.03 (1 H, t, J 8 Hz, PhCH), and 7.14–7.73 (10 H, m); δ_{C} (62.9 MHz; CDCl_3) 17.15 and 20.36 (2 \times CH_2), 22.36 (Me), 32.50, 40.89, 56.47, and 62.85 (4 \times CH_2), 80.89 (quat. C), 81.89 (PhCH), 127.17 (aromatic CH), 127.96 (aromatic quat. C), 128.61, 128.89, 129.19, 129.98, and 132.65 (aromatic CH), and 135.88 (aromatic quat. C) (Found: C, 64.6; H, 6.6; N, 3.5. $\text{C}_{21}\text{H}_{26}\text{BrNO}$ requires C, 65.0; H, 6.8; N, 3.6%).

2-(2'-Hydroxy-2'-phenylethyl)piperidine (13).—Zinc dust (13.6 g) was added cautiously to a solution of the isoxazolidine (8; $n = 2$) (10.7 g) in acetic acid (100 ml)–ethanol (50 ml) containing ethylenediaminetetra-acetic acid (61 g) at 50 °C. After being refluxed for 45 min, the cooled solution was neutralised with conc. ammonia and extracted with chloroform. The recovered product¹³ (8.1 g) formed needles from ethyl acetate–light petroleum, m.p. 111–114 °C; ν_{max} (Nujol) 3 261, 2 925, 2 856, 1 602, 1 193, 1 148, 1 132, 1 080, 992, 775, 755, and 696 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.24–1.49 (3 H, m), 1.49–1.68 (2 H, m), 1.68–2.00 (3 H, m), 2.43–2.68 (1 H, app. dt, J 3, 11 Hz), 2.68–2.92 (1 H, m), 2.92–3.19 (1 H, app. dd, J 2, 11 Hz), 4.95–5.14 (1 H, dd, J 4, 7 Hz, PhCH), and 7.08–7.57 (5 H, m) (Found: C, 76.3; H, 9.5; N, 6.7. $\text{C}_{13}\text{H}_{19}\text{NO}$ requires C, 76.1; H, 9.3; N, 6.8%).

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