# Nitrone Cycloadditions: Synthesis of (±)-Andrachamine

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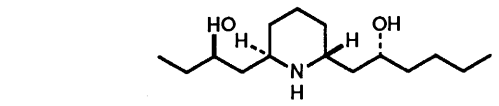
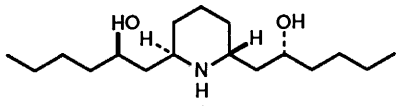
The usefulness of the cycloaddition of alkenes to 2-alkyl-2,3,4,5-tetrahydropyridine oxides for the preparation of *trans*-2,6-dialkylpiperidines is confirmed by a stereoselective synthesis of (±)-andrachamine. Peroxy acid oxidation of 9-oxa-1-azabicyclo[4.3.0]nonanes does not lead regioselectively to 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 recently[1] and the structure and stereochemistry (**1**) were assigned, largely on the basis of NMR and MS evidence. Nitrone 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 (±)-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 nitrone-cycloaddition route to *trans*.-2,6-dialkylpiperidines.[2] *exo*-Addition[4] 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 established[4] 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 $^1$H 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 $^1$H 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 $^1$H or the $^{13}$C 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 $^1$H 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**).


(1)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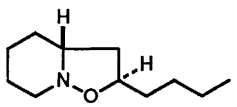
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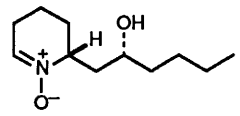
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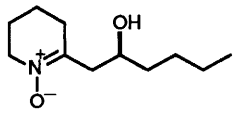
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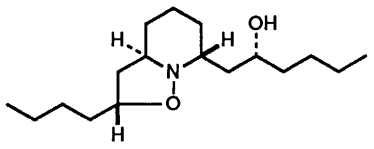
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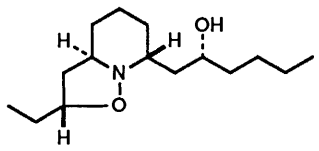
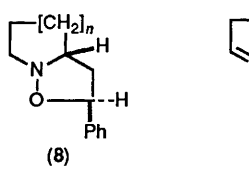

(7)

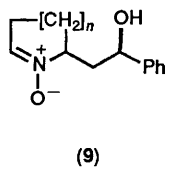
The structure of our synthetic compound corresponds to that reported for (−)-andrachamine. The *trans* configuration of the two alkyl substituents in the natural product was assigned by comparison of the $^{13}$C chemical shift of C-4 of the piperidine ring with values recorded for *cis*- and *trans*-2,6-dialkylpiperidines.[6] The $^{13}$C chemical shift for C-4 in our synthetic (**1**) ($\delta_C$ 19.12) is close to that reported for (−)-andrachamine ($\delta_C$ 18.7), and other $^{13}$C 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.

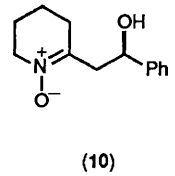
A disappointing feature in the synthesis of compound (**1**) was the lack of regioselectivity in the peroxy acid oxidation of the isoxazolidine (**3**), where the desired aldonitrone (**4**) was the minor component of the mixture of nitrones produced. An earlier report[7] had indicated that peroxy acid oxidation of the isoxazolidines (**8**; $n$ = 1,2), obtained by cycloaddition of styrene to $\Delta^1$-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 hands[3] 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 $^1$H 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 analogy[4] as before.



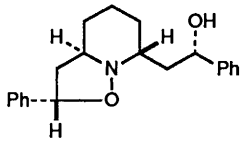
(**8**)



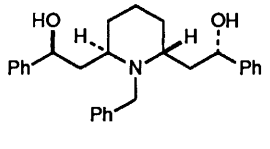
(**9**)



(**10**)

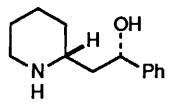


(**11**)

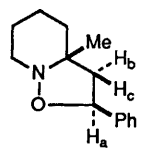


(**12**)

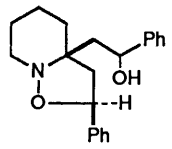
The major nitrone (**10**) from the oxidation of the isoxazolidine (**8**; $n$ = 2) was identified by IR absorption bands at 1 621 and 1 146 cm$^{-1}$, characteristic of the C–N and N–O stretch of nitrones, and by a signal at $\delta_C$ 149.56 in the $^{13}$C NMR spectrum, due to an olefinic quaternary carbon atom. The structure was confirmed by an alternative preparation by tungstate-catalysed peroxide oxidation[8] 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 $^1$H and $^{13}$C NMR spectra, particularly by a signal at $\delta_C$ 62.84 in the $^{13}$C 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 $^1$H NMR spectrum and is in line with the expected[4] *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-tetrahydropyridine oxide followed by addition of styrene, or directly from the adduct (**15**).



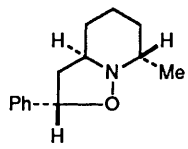
(**13**)



(**14**)



(**15**)



(**16**)

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

$^1$H NMR spectra (100 MHz) were determined using a JEOL JNM-MH 100 instrument, and 250 MHz $^1$H and 62.9 MHz $^{13}$C NMR spectra with a Bruker AM 250 spectrometer. Short-column chromatography[9] and dry column flash chromatography used Merck Kieselgel 60H (Merck No. 7736), and flash chromatography[10] 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); $\nu_{max}$ 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$^{-1}$; $\delta_H$(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); $\delta_C$(62.9 MHz; $CDCl_3$) 13.84 (Me), 22.59, 23.86, 24.68, 27.96, 29.36, and 34.94 (6 × $CH_2$), 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. $C_{11}H_{21}NO$ requires C, 72.08; H, 11.55; N, 7.64%; *M*, 183).

(2R*,6R*)-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–$CHCl_3$ (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); $\nu_{max}$ 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 $cm^{-1}$; $\delta_H$(250 MHz; $CDCl_3$) 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); $\delta_C$(62.9 MHz; $CDCl_3$) 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 × $CH_2$), 56.47, 59.58, 68.89, and 76.48 (4 × CH) (Found: $M^+$, 283.2502. $C_{17}H_{33}NO_2$ 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 $Et_3N$–MeOH–EtOAc, 1:1:18], gave the *piperidine* (**2**) as a pale yellow oil (340 mg) which crystallised on storage; $\nu_{max}$ 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 $cm^{-1}$; $\delta_H$(250 MHz; $CDCl_3$) 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 × OH), and 3.59–3.97 (2 H, m, 2 C*H*OH); $\delta_C$(62.9 MHz; $CDCl_3$) 14.01 (2 × Me), 19.92, 22.76, 28.22, 32.06, 37.33, and 39.08 (11 × $CH_2$), 47.14 (2 × CHN), and 69.05 (2 × CHOH); *m/z* 286 ($M^+$ + 1), 268, 184, and 166 (Found: C, 71.6; H, 12.1; N, 5.0. $C_{17}H_{35}NO_2$ 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 $NH_3$) the derivative was obtained as a pale yellow oil (142 mg, 63%); $\nu_{max}$ 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 $cm^{-1}$; $\delta_H$(250 MHz; $CDCl_3$) 0.89 (6 H, t, *J* 7 Hz, 2 × 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, C$H_2$Ph), 3.68–3.81 (2 H, m, 2 × C*H*OH), 4.11–4.76 (2 H, br s, 2 × OH), and 7.14–7.46 (5 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 13.79 (2 × Me), 20.84, 22.60, 24.07, 28.19, 36.64, and 37.21 (11 × $CH_2$), 48.89 (*C*$H_2$Ph), 50.06 (2 × CHN), 69.00 (2 × 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. $C_{24}H_{41}NO_2$ 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); $\nu_{max}$(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 $cm^{-1}$; $\delta_H$(250 MHz; $CDCl_3$) 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); $\delta_C$(62.9 MHz; $CDCl_3$) 9.82 and 13.97 (2 × Me), 18.46, 22.72, 27.75, 28.01, 29.46, and 37.65 (6 × $CH_2$), 25.46, 34.89, and 39.19 (3 × $CH_2$), and 56.48, 59.58, 68.82, and 77.63 (4 × CH); *m/z* 255 ($M^+$), *198* ($M^+$ − Bu), and 154 ($M^+$ − $C_6H_{12}O$) (Found: C, 70.8; H, 11.7; N, 5.6. $C_{15}H_{29}NO_2$ 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 (10M; 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; $\nu_{max}$ 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 $cm^{-1}$; $\delta_H$(250 MHz; $CDCl_3$) 0.86 (6 H, 2 × Me), 1.08–1.78 (18 H, m), 3.22–3.49 (2 H, m, CHNCH), 3.68–3.92 (2 H, m, 2 × C*H*OH), and 5.68–6.84 (3 H, br s, NH and 2 × OH); $\delta_C$(62.9 MHz; $CDCl_3$) 10.17 and 13.96 (2 × Me), 19.12, 22.65, 28.06, 30.04, 30.33, 30.36, 36.98, 37.62, and 37.94 (9 × $CH_2$), 47.69 and 47.74 (2 × CHN), and 68.22 and 69.60 (2 × CHOH); *m/z* 257 ($M^+$), 228 ($M^+$ − Et), 200 ($M^+$ − Bu), 184 ($M^+$ − $C_4H_9O$), and 156 ($M^+$ − $C_6H_{13}O$) (Found: C, 69.8; H, 12.0; N, 5.4. $C_{15}H_{31}NO_2$ 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 μl), and triethylamine (116 μl) 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); $\nu_{max}$ 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 $cm^{-1}$; $\delta_H$(250 MHz; $CDCl_3$) 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 × C*H*OH), 3.59 and 3.81 (2 H, q, *J* 12 Hz, C$H_2$Ph), 4.50–5.50 (2 H, br s), and 7.14–7.54 (5 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 10.45 and 14.01 (2 × Me), 20.84, 22.69, 28.33, 29.52, and 36.41 (5 × $CH_2$), 48.55 (Ph*C*$H_2$), 49.71 (CHNCH), 65.20 (2 × 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 ($M^+$ − $C_4H_9O$), and 248 ($M^+$ − $C_6H_{13}O$) (Found: C, 76.2; H, 10.6; N, 4.2. $C_{22}H_{37}NO_2$ 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); $\nu_{max}$ 2 939, 2 855, 1 605, 1 496, 1 452, 1 260, 1 009, 951, 759, and 699 $cm^{-1}$; $\delta_H$(250 MHz; $CDCl_3$) 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, C*H*Ph), and 7.11–7.54 (5 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 23.92, 24.84, and 29.40 (3 × $CH_2$), 43.19 ($CH_2$ of isoxazolidine), 55.25 ($CH_2$N), 66.77 (CHN), 77.61 (*C*HPh), 126.69, 127.58, and 128.37 (aromatic CH), and 142.02 (aromatic quat. C) (Found: $M^+$, 203. $C_{13}H_{17}NO$ 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 re-chromatography over 60 H silica [eluant ethyl acetate–light petroleum, (1:1)] afforded the isoxazolidine (**11**) as a yellow oil[7] (284 mg); $\nu_{max}$ 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$^{-1}$; $\delta_H$(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, PhC*H*OH), 5.19 (1 H, dd, *J* 4.6, 9.3 Hz, PhC*H*ON), and 7.14–7.57 (10 H, m); $\delta_C$(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 × 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: $\nu_{max}$(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$^{-1}$; $\delta_H$ (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) (PhCHC*H*$_2$), 3.76 (2 H, t, *J* 6.5 Hz), 5.14 (1 H, dd, *J* 3.2, 7.5 Hz, PhC*H*) 7.11–7.38 (5 H, m), and 7.38–7.59 (1 H, br s, OH); $\delta_C$ (62.9 MHz; $CDCl_3$) 18.37, 22.76, 31.12, 42.77, and 57.60 (5 × $CH_2$), 73.81 (*C*HPh), 125.15, 127.22, and 128.28 (aromatic CH), 144.64 (aromatic quat. C), and 149.56 (nitrone quat. C) (Found: $M^+$, 220.1337. $C_{13}H_{17}NO_2$ requires *M*, 220.1337).

The same ketonitrone was obtained by oxidation[8] 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; $\nu_{max}$ 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$^{-1}$; $\delta_H$(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 δ1.89–2.03; $\delta_C$(62.9 MHz; $CDCl_3$) 20.25 and 22.20 (2 × $CH_2$), 26.63 (br, Me), 32.50, 47.73, and 49.58 (3 $CH_2$), 62.83 (quat. C), 76.81 (*C*HPh), 125.80, 126.96, and 128.32 (aromatic CH), and 143.35 (aromatic quat. C) (Found: $M^+$, 217.1467. $C_{14}H_{19}NO$ 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**); $\delta_H$(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, C*H*Ph), and 7.00–7.65 (5 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 18.81 (C-4), 20.48 (Me), 25.46, 32.77, and 39.20 (3 × $CH_2$), 53.88 (*C*HMe), 60.50 (CHN), 78.28 (*C*HPh), 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.); $\nu_{max}$(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$^{-1}$; $\delta_H$(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 CH*H*), 3.27–3.54 (1 H, dd, *J* 8, 13.7 Hz, isoxazolidine CH*H*), 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, PhC$H_2$), 6.03 (1 H, t, *J* 8 Hz, PhC*H*), and 7.14–7.73 (10 H, m); $\delta_C$(62.9 MHz; $CDCl_3$) 17.15 and 20.36 (2 × $CH_2$), 22.36 (Me), 32.50, 40.89, 56.47, and 62.85, (4 × $CH_2$), 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. $C_{21}H_{26}BrNO$ 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 *product*[13] (8.1 g) formed needles from ethyl acetate–light petroleum, m.p. 111–114 °C; $\nu_{max}$(Nujol) 3 261, 2 925, 2 856, 1 602, 1 193, 1 148, 1 132, 1 080, 992, 775, 755, and 696 cm$^{-1}$; $\delta_H$(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, PhC*H*), and 7.08–7.57 (5 H, m) (Found: C, 76.3; H, 9.5; N, 6.7. $C_{13}H_{19}NO$ requires C, 76.1; H, 9.3; N, 6.8%).

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