Cycloaddition of 2,3,4,5-Tetrahydropyridine *N*-Oxide to Isobutyl Vinyl Ether and Allyl Alcohol; Methyl 2-Formylmethylpiperidine-1-carboxylate

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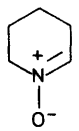
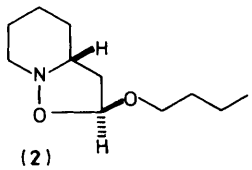
2,3,4,5-Tetrahydropyridine *N*-oxide undergoes cycloaddition with isobutyl vinyl ether and allyl alcohol to give the hexahydroisoxazolo[2,3-*a*]pyridines (**3**) and (**4**). In model experiments these were converted into methyl 2-formylmethylpiperidine-1-carboxylate (**9**).

In connection with other work we required a method to introduce a formylmethyl group into the α-position of a piperidine nucleus. It seemed that this might be possible *via* nitrone cycloaddition, and we record here results of our model experiments using 2,3,4,5-tetrahydropyridine *N*-oxide (**1**).

It has been reported[1] that oxidation of piperidine with hydrogen peroxide, catalysed by sodium tungstate, in the presence of butyl vinyl ether affords the cycloadduct (**2**) through the intermediate formation of the nitrone (**1**). We obtained similar results using isobutyl vinyl ether, although the yield of adduct (**3**) (30%) was considerably less than that reported for the reaction with butyl vinyl ether. The stereochemistry of the adduct (**3**) is based on analogy.[2] The ^1H and ^{13}C n.m.r. spectra



(**1**)



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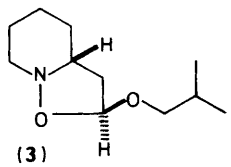
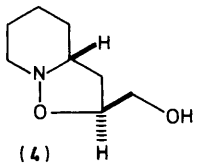


(**3**)

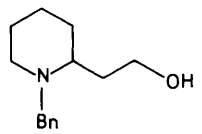


(**4**)

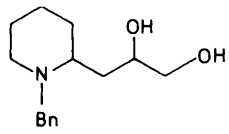
of (**3**) were complicated by slow nitrogen inversion, and were consistent with the presence of a mixture of two forms which interchange at a rate of *ca.* 10 s^{-1} at 30 °C, giving rise to broadened peaks; at −10 °C the spectra are much sharper and clearly show two distinct forms. Similar behaviour has been noted before[3] in isoxazolidines and we observed it also in the adduct (**4**) which we obtained in poor yield by reaction of 2,3,4,5-tetrahydropyridine *N*-oxide with allyl alcohol. Allyl alcohol is noticeably less reactive than the vinyl ethers and a higher temperature was required to induce reaction with the nitrone (**1**).

Attempted cleavage of the isoxazolidine ring of the adduct (**3**) with zinc and acetic acid gave only a very poor yield of an impure product, possibly due to chelation of the metal with the amino alcohol produced, but reduction of the corresponding *N*-benzyl bromide salt with lithium aluminium hydride[4] afforded an excellent yield of the 2-(*N*-benzyl-2-piperidyl)-ethanol (**5**). The *N*-benzyl bromide salt of (**4**) similarly gave the diol (**6**) in high yield. The ^{13}C n.m.r. spectrum of compound (**6**) showed the presence of *ca.* 15% of a diastereoisomer arising from incomplete stereoselectivity in the reaction of allyl alcohol with the nitrone (**1**).

Since there was evidence from the periodate oxidation of the diol (**6**) that the *N*-benzyl aldehyde (**7**) rapidly undergoes a

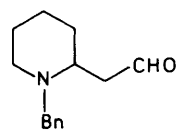


(**5**)

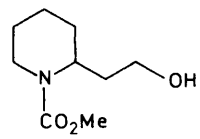


(**6**)

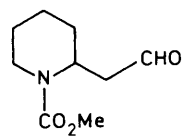
Bn = Benzyl



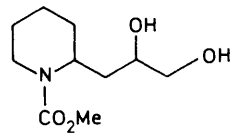
(**7**)



(**8**)



(**9**)



(**10**)

reverse Michael reaction, before proceeding further the *N*-benzyl compounds (**5**) and (**6**) were converted into the corresponding *N*-methoxycarbonyl derivatives by cleavage of the *N*-benzyl groups with palladium and ammonium formate and reaction of the free amine with methyl chloroformate. Swern oxidation[5] of the piperidylethanol (**8**) then afforded the required aldehyde (**9**) in excellent yield, and the same compound was obtained by periodate oxidation of the diol (**10**). The aldehyde group in (**9**), of course, provides an excellent handle for further elaboration of the piperidyl side-chain.

Experimental

100 MHz ^1H N.m.r. spectra were determined using a Jeol JNM-MH 100 instrument, and 250 MHz ^1H and 62.9 MHz ^{13}C n.m.r. spectra with a Brüker AM250 instrument. The degree of substitution at carbon atoms in the ^{13}C spectra was obtained by the DEPT technique. I.r. spectra were recorded on a Perkin-Elmer 398 spectrometer interfaced to a Perkin-Elmer 3600 data station. Low resolution mass spectra were obtained with a VG-Micromass MM16F mass spectrometer; high resolution mass spectra were determined at the S.E.R.C. Mass Spectrometry Unit, University College, Swansea. Flash chromatography used Camlab Kieselgel 60, 230—400 mesh, and 'dry column' chromatography was performed with Merck Kieselgel 60H (Merck No. 7736).

Cycloaddition of 2,3,4,5-*Tetrahydropyridine* N-*Oxide with Isobutyl Vinyl Ether:* 2-*Isobutoxyhexahydroisoxazolo*[2,3-a]-*pyridine* (**3**).—Hydrogen peroxide (100 vol., 17.4 g) was added dropwise to a stirred solution of sodium tungstate dihydrate (0.92 g), piperidine (5.95 g), and isobutyl vinyl ether (14.0 g) in methanol (13 ml) at such a rate that the temperature of the solution did not rise above 5 °C. The reaction mixture was then allowed to warm to room temperature and methanol (60 ml) was added to provide a homogeneous solution. After 24 h the reaction mixture was partitioned between brine (200 ml) and dichloromethane (200 ml) and the recovered product was purified by flash chromatography (eluant chloroform) and bulb-to-bulb distillation, affording the hexahydroisoxazolopyridine (**3**) as a yellow oil (4.2 g, 30%), b.p. 90 °C (oven temp.) at 0.3 mmHg; δ_H(250 MHz, $CDCl_3$, 30 °C) 0.90 (d, 6 H, *J* 6.7 Hz, 2-CH_3), 1.10—2.30 [m, 9 H, 4-CH_2 and $(CH_3)_2CHCH_2O$], 2.31—2.65 and 3.02—3.21 (m, 3 H, CH_2NCHR), 3.39—3.65 [m, 2 H, $OCH_2CH(CH_3)_2$], 5.06—5.22 (br m, 1 H, OCHO); at −10 °C the spectrum is similar but much sharper; δ_C(62.9 MHz, $CDCl_3$, −10 °C) 19.5 (4-CH_3), 21.2 (2 signals), 23.5, 25.0, and 26.0 (5-CH_2), 28.2 (2-CH), 28.9, 40.9, 41.5, 51.2, and 55.5 (5-CH_2), 58.0 and 64.0 (2-CH), 75.2 (2-CH_2), and 101.0 and 102.0 (2-CH) (Found: M^+, 199.1573. $C_{11}H_{21}NO_2$ requires *M*, 199.1572).

Reaction of the hexahydroisoxazolopyridine (3.0 g) with benzyl bromide (2.8 g) in dichloromethane (40 ml) under reflux for 12 h gave the corresponding *N*-benzylammonium bromide as colourless crystals (3.8 g), m.p. 132—134 °C (from chloroform–ether) (Found: $M^+ - {}^{80}Br + 1$, 291. $C_{18}H_{28}NO_2{}^{80}Br$ requires 370). The ^1H and ^{13}C n.m.r. spectra were complex presumably due to the formation of a quaternary salt from each of the nitrogen-inversion isomers; δ_H[250 MHz, $(CD_3)_2SO$] 0.88—0.091 [two overlapping doublets, 6 H, $CH(CH_3)_2$], 1.06—2.01 (m, 7 H), 2.86—2.98 (m, 2 H), 3.09—3.25 (m, 1.4 H), 3.33 (s, 0.8 H), 3.37—3.74 (m, 1.7 H), 3.88 (t, 2 H, *J* 6.8 Hz), 4.18—4.39 (m, 1.4 H), 4.69 (d, 0.6 H), 7.45—7.47 (m, 3 H), 7.62—7.70 (m, 2 H), and 8.87 (br d, 0.5 H); δ_C[62.9 MHz, $(CD_3)_2SO$] 18.36 (CH_2), 18.73 (CH_3), 19.53, 20.50 (2 signals), 21.31 and 24.86 (5-CH_2), 27.10 (CH), 27.65 (2 signals), 31.94, 35.55, 47.74, 50.10, 50.21, 52.29, 55.54, and 55.61 (10-CH_2), 56.35, 59.25, and 59.36 (3-CH), 70.42 (CH_2), 128.7—131.42 (5-CH and 2-C), and 169.40 and 169.70 (2-C).

Reaction of 2,3,4,5-*Tetrahydropyridine* N-*Oxide with Allyl Alcohol:* 2-*Hydroxymethylhexahydroisoxazolo*[2,3-a]*pyridine* (**4**).—A solution of 2,3,4,5-tetrahydropyridine *N*-oxide was prepared from piperidine (5.95 g) in the presence of allyl alcohol (8.13 g) as in the experiment described above. On completion of the addition of hydrogen peroxide the reaction mixture was refluxed for 12 h. Extractive work-up, flash chromatography, and bulb-to-bulb distillation of the product as described above afforded the hexahydroisoxazolopyridine (**4**) as a viscous oil (1.9 g, 17%), b.p. 90 °C (oven temp.) at 0.5 mmHg; δ_H(250 MHz, $CDCl_3$, 30 °C) 1.10—2.60 (m, 10 H, 5-CH_2), 2.71—2.92 and 2.97—3.07 (m, 1 H), 3.41—3.63 (m, 2 H, CH_2OH), 4.74—4.81 (m, 1 H), and 4.12—4.29 and 4.39—4.46 (m, 1 H); δ_C(62.9 MHz, $CDCl_3$, 30 °C) 19.58, 23.17, 23.84,* 24.83,* 25.72, 29.43,* 33.12, 36.63,* 50.29, and 55.27 (10-CH_2), 60.07 (CH), 64.16* and 64.85 (2-CH_2), and 67.04,* 76.33,* and 77.20 (3-CH). These signals are divided into two distinct sets indicating an approximately 2:1 ratio of inversion isomers. The same behaviour is shown to an extent in the ^1H n.m.r. spectrum (Found: C, 60.9; H, 9.6; N, 9.0%; M^+, 157. $C_8H_{15}NO_2$ requires C, 61.1; H, 9.6; N, 8.9%; *M*, 157).

The corresponding *N*-benzyl quaternary bromide was prepared from the hexahydroisoxazolopyridine (3.0 g) and benzyl bromide (3.6 g) as described above. It formed colourless crystals in chloroform, m.p. 163—165 °C, and again showed complex ^1H and ^{13}C n.m.r. spectra (Found: $M^+ - {}^{80}HBr$, 247. $C_{15}H_{22}NO_2{}^{80}Br$ requires *M*, 328).

2-(1-*Benzyl*-2-*piperidyl*)*ethanol* (**5**).—The benzylammonium bromide (2.0 g) of the hexahydroisoxazolopyridine (**3**) was added portionwise to a stirred solution of lithium aluminium hydride (0.52 g) in THF (50 ml) at 0 °C and the resulting mixture was refluxed for 3 h. The recovered product was distilled (Kugelröhr) and gave the ethanol (**5**) as an oil (1.1 g, 94%), b.p. 140 °C (oven temp.) at 0.02 mmHg; δ_H(250 MHz, $CDCl_3$), 1.24—2.01 (m, 8 H, 4-CH_2), 2.14—2.24 (m, 1 H), 2.69—2.77 (m, 1 H), 2.90—3.00 (m, 1 H, CH_2NCH), 3.46 and 4.16 (q, 2 H, *J* 13.0 Hz, $PhCH_2N$), 3.70—3.96 (m, 2 H, CH_2OH), 4.90 (br s, 1 H, OH), and 7.31—7.47 (m, 5 H); δ_C(62.9 MHz, $CDCl_3$) 22.63 (2-CH_2), 27.44, 31.89, 49.32, and 57.75 (4-CH_2), 59.81 (CH), 62.05 (CH_2 of CH_2Ph), 127.08, 128.40, and 129.07 (3-CH), and 138.85 (C) (Found: C, 76.4; H, 9.65; N, 6.3%; M^+, 219. $C_{14}H_{21}NO$ requires C, 76.7; H, 9.65; N, 6.4%; *M*, 219).

3-(1-*Benzyl*-2-*piperidyl*)*propane*-1,2-*diol* (**6**).—Reduction of the benzylammonium bromide (2.0 g) of the hexahydroisoxazolopyridine (**4**) with lithium aluminium hydride (0.58 g) as described above gave the title compound as an oil (1.4 g, 91%), b.p. 180—190 °C (oven temp.) at 0.12 mmHg. The n.m.r. spectra of this compound showed the presence of a mixture of diastereoisomers arising from the lack of complete stereoselectivity in the dipolar addition to give (**4**) but previously undetected due to the complication of the n.m.r. spectra of (**4**) caused by the dynamic nitrogen inversion; the minor diastereoisomer accounts for *ca.* 15% of the mixture; δ_H(250 MHz, $CDCl_3$) 1.26—1.75 (m, 7.5 H), 1.88—1.99 (m, 1 H), 2.13—2.27 (m, 1 H), 2.66 (m, 1 H), 2.85—2.92 (m, 1 H), 3.16 and 4.36 (q, 2 H, *J* 12.8 Hz, $PhCH_2$), 3.40—3.47 (m, 1 H), 3.58—3.64 (m, 1 H), 3.88 (d, 0.3 H), 4.11—4.20 (m, 1 H), and 7.31—7.45 (m, 5 H); δ_C(62.9 MHz, $CDCl_3$) (major diastereoisomer) 23.64, 24.27, 29.07, 32.24, 51.58, and 58.34 (6-CH_2), 59.40 (CH), 66.78 (CH_2OH), 70.08 (CHOH), 127.19, 128.40, and 129.19 (3-CH), and 138.03 (C) (Found: M^+, 249.1729. $C_{15}H_{23}NO_2$ requires *M*, 249.1729).

Methyl 2-(2-*Hydroxyethyl*)*piperidine*-1-*carboxylate* (**8**).—A solution of 3-(1-benzyl-2-piperidyl)propane-1,2-diol (**6**) (1.1 g) and ammonium formate (3.2 g) in methanol (20 ml) containing palladium–charcoal (10%, 1.1 g) was refluxed under nitrogen for 12 h. The solution was cooled, filtered, evaporated under reduced pressure and the resulting crude debenzylated piperidine (0.71 g) stirred in saturated aqueous sodium hydrogen carbonate (50 ml) and treated with methyl chloroformate (3.9 ml) at 0 °C. After 2 h the mixture was allowed to warm to room temperature and stirred for a further 18 h. The recovered product was purified by short column chromatography (eluant, chloroform–methanol, 49:1) and bulb-to-bulb distillation, affording the *N*-carboxylate as an oil (0.29 g), b.p. 140 °C (oven temp.) at 0.03 mmHg; δ_H(250 MHz, $CDCl_3$) 1.39—1.72 (m, 7 H, 3-CH_2 and 1-H of ring CH_2), 1.91—2.02 (m, 1 H of ring CH_2), 2.76 (d t, 1 H, J_t 13.1 and J_d 2.4 Hz, 6-H), 3.40—3.57 (m, 3 and 1 H exchangeable in D_2O, CH_2OH), 3.70 (s, 3 H, OCH_3), 3.97—4.02 (br d, 1 H, *J* 12.6 Hz, 6-H), and 4.41—4.45 (m, 1 H, 2-H); δ_C(62.9 MHz, $CDCl_3$) 19.13, 25.52, 29.15, 32.59, and 39.31 (5-CH_2), 47.32 (CH), 52.74 (OCH_3), 58.95 (CH_2OH), and 157.02 (CO) (Found: C, 57.4; H, 9.0; N, 7.3%; M^+, 187. $C_9H_{17}NO_3$ requires C, 57.7; H, 9.2; N, 7.5%; *M*, 187).

Methyl (2-*Formylmethyl*)*piperidine*-1-*carboxylate* (**9**).—The above alcohol (0.25 g) in THF (2 ml) was added dropwise at

* Due to the major isomer.

−70 °C to a stirred solution prepared from oxalyl chloride (139 μl) and dimethyl sulphoxide (131 μl) in THF (6 ml). After 2 h at −50 °C to −60 °C, triethylamine (923 μl) was added and stirring continued at room temperature for 1 h. The mixture was diluted with ether (100 ml), filtered, and the recovered product was purified by short column chromatography (eluant chloroform) and bulb-to-bulb distillation, affording the aldehyde as an oil (0.18 g, 73%), b.p. 120 °C (oven temp.) at 0.03 mmHg; δ_H(250 MHz, $CDCl_3$) 1.50—1.70 (m, 6 H, 3-CH_2), 2.59—2.85 (m, 3 H, CH_2CHO and 6-H), 3.69 (s, 3 H, OCH_3), 4.04 (br d, 1 H, *J* 13.2 Hz, 6-H), 4.84—4.95 (m, 1 H, 2-H), and 9.72 (s, 1 H, C*H*O); δ_C(62.5 MHz, $CDCl_3$) 18.91, 25.22, 28.74, 39.63, and 44.60 (5-CH_2), 46.26 (CH), 52.66 (OCH_3), and 200.43 (*C*HO) (the carbonyl of the carboxylate group was not detected and is presumably masked in the background noise) (Found: C, 58.0; H, 8.1; N, 7.4%; M^+, 185. $C_9H_{15}NO_3$ requires C, 58.4; H, 8.2; N, 7.6%; *M*, 185).

Methyl 2-(2,3-*Dihydroxypropyl*)*piperidine*-1-*carboxylate* (**10**).—The *N*-benzyl compound (**6**) (2.4 g) was debenzylated with ammonium formate in the presence of palladium-on-charcoal as described above for the analogue (**5**). The crude debenzylated compound (0.73 g) was converted directly into the carboxylate derivative with methyl chloroformate as described above for compound (**8**); after short column chromatography (eluant, chloroform–methanol, 49:1) it was obtained as an oil (0.14 g), b.p. 140—150 °C (oven temp.) at 0.02 mmHg. This product was a *ca.* 10:1 mixture of stereoisomers, as judged by the intensity of ^{13}C signals in the n.m.r.; δ_H(250 MHz, $CDCl_3$) 1.31—1.89 (m, 7 H, 3-CH_2 and 1 H of CH_2), 1.93 (t, 1 H, *J* 13.4 Hz), 2.70—2.82 (m, 1 H), 2.96 (br s, 1 H, OH), 3.49—3.53 (m, 3 H, CH_2OH and C*H*OH), 3.71 (s, 3 H, OCH_3), 3.98 (br d, 1 H, *J* 13.6 Hz, 6-H), 4.36 (br s, 1 H, O*H*), and 4.47—4.52 (m, 1 H, 2-H); δ_C(62.9 MHz, $CDCl_3$) (major diastereoisomer) 19.5, 25.43, 29.45, 33.49, and 39.32 (5-CH_2), 47.31 (CH), 52.94 (CH_3), 66.52 (CH_2OH), 68.57 (*C*HOH), and 157.47 (*C*O) (Found: $M^+ + 1$, 218.1388. $C_{10}H_{19}NO_4$ requires $M + 1$, 218.1392).

Oxidation of this compound (0.14 g) with sodium periodate (0.35 g) in aqueous ethanol (1:1, 10 ml) and purification of the product by short column chromatography (eluant, chloroform–methanol, 49:1) afforded the aldehyde (**9**) (0.076 g, 64%), identical in all respects with that obtained as above.

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