# New Synthesis of Sulphides from Vinylic Ethers. Application to the Syntheses of 3-Alkylsulphenyl-, 3-Alkylsulphinyl- and 3-Alkylsulphonyl-piperidinium Chlorides

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A synthesis of 3-alkylsulphenyl-, 3-alkylsulphinyl- and 3-alkylsulphonyl-1-methylpiperidinium hydrochlorides has been carried out starting from 3-hydroxypyridine and alkanethiols. These piperidyl derivatives described herein are monoconformational compounds in solution and their magnetic parameters can be used as reference standards for the conformational analysis of related cyclic and acyclic compounds with sulphur and nitrogen heteroatoms in a 1,3-relationship.

The synthesis of 3-alkylsulphenyl-, 3-alkylsulphinyl- and 3-alkylsulphonyl-piperidines has not been described in the literature. Their preparation was of our interest since these compounds could be used as rigid models to carry out conformational analysis of related cyclic and acyclic compounds with sulphur and nitrogen heteroatoms in a 1,3-relationship. Furthermore, the piperidine ring is present in many products with pharmaceutical activity. Several 1-alkylpiperidines having a functional group containing sulphur have shown anticholinergic,[1] spasmolitic,[2] antiarrhythmic[3] and analgesic[4] activities. These piperidyl derivatives have been also widely used in the synthesis of metallic complexes,[5–9] which are useful substrates for several organic syntheses.

In this paper an efficient synthesis of 3-alkylsulphenyl-, 3-alkylsulphinyl- and 3-alkylsulphonyl-1-methylpiperidinium chlorides by acid-catalysed addition of several thiols to 3-methoxy-1-methyl-1,2,5,6-tetrahydropyridine **1** in the presence of traces of water (Scheme 1) is described for the first time.

The obvious approach to the synthesis of these compounds, the nucleophilic substitution of the 3-tosyl derivative of the commercially available 3-hydroxy-1-methylpiperidine, failed to give the desired products. An alternative route to 1-methyl-3-methylsulphenylpiperidine **7** was attempted (Scheme 2) by the same procedure described for the synthesis of the 1-methyl-4-methylsulphenylpiperidine,[10–12] but the overall yield was only 3%. The key steps in this synthesis were the isolation of the 1-methyl-3-piperidone from aqueous media in low yield (because of the easy formation of its hydrate that highly increases its solubility in water) and the formation of variable amounts of the corresponding disulphide of 3-mercapto-1-methylpiperidine in its purification process. These problems were resolved by application of a new strategy, which is indicated in Scheme 1.

3-Methoxy-1-methyl-1,2,5,6-tetrahydropyridine **1** was prepared according to the procedure described by Lyle[10] and converted into its toluene-*p*-sulphonate **2** by reaction with anhydrous toluene-*p*-sulphonic acid (PTSA). When the synthesis was carried out with monohydrated PTSA, the 1-methyl-3-oxopiperidinium toluene-*p*-sulphonate **3** was the major product (69%), compound **2** being the minor reaction product (31%).

The reaction of compound **2** or **3** with an appropriate alkanethiol led to the corresponding thioacetals **4–6**, which were reduced to 3-alkylsulphenyl-1-methylpiperidines **7–9** in good yield with sodium borohydride. These compounds could be stored at 0 °C under nitrogen, but they turned dark within a few hours at room temperature. They were converted into their more stable hydrochlorides **10–12** by bubbling $HCl_g$ in diethyl ether at room temperature.

Oxidation of salts **10**, **11** and **12** to the respective sulphoxides **13**, **14** and **15** was attempted with several reagents (*m*-$ClC_6H_4CO_2OH$, $F_3CCO_2H$–$H_2O_2$, $H_2O_2$–acetone and $NaIO_4$). Best results were obtained by treatment with $NaIO_4$ (1 mol equiv.) in aq. ethanol.

Oxidation of free bases **7–9** under the same conditions led to a complex mixture, in which small amounts of sulphoxide and sulphone products were detected. For this reason, the oxidation was carried out with ammonium salts.

Sulphoxides **13–15** were obtained as a mixture of two products, epimeric with respect to the configuration of the sulphoxide group (**13**α + **13**β, **14**α + **14**β and **15**α + **15**β), which were separated by fractional recrystallization from a suitable solvent. A poor-to-moderate diastereoisomeric excess (d.e.) was observed with the size of the alkyl group (d.e. 10, 24 and 40 for methyl, ethyl and isopropyl, respectively), isomer α being the major one in all cases.

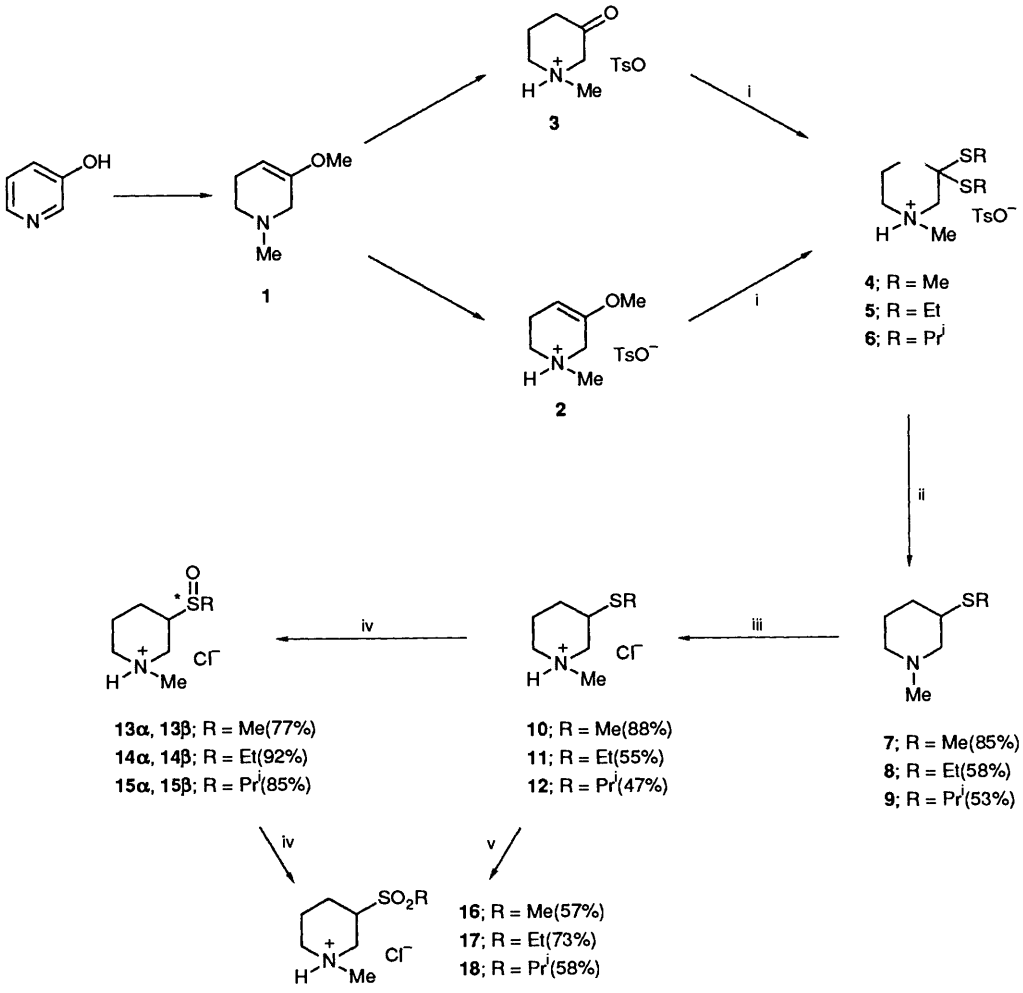
Sulphides **7–9** were also converted into their toluene-*p*-sulphonates, which were oxidized to the corresponding sulphoxides in good yield, but the diastereoisomeric sulphoxides (α and β) could not be separated by fractional recrystallization, because they were very insoluble in the majority of organic solvents and for this reason the corresponding hydrochlorides were used in the oxidation. Sulphones **16–18** were obtained by oxidation of the sulphides **10–12** or sulphoxides **13–15** with $NaIO_4$ (excess or limited amount, respectively).

All products were fully characterized by $^1H$ NMR and $^{13}C$ NMR spectroscopy.

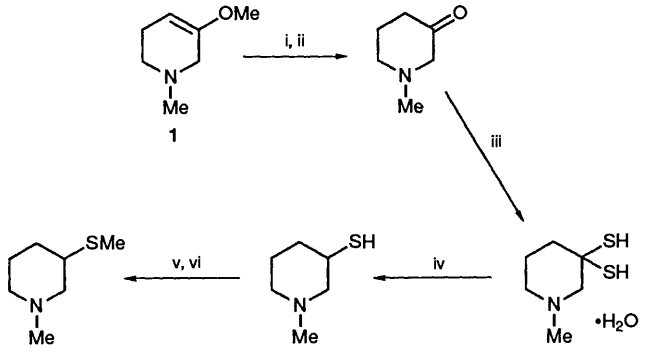
Only the *cis*-isomer was obtained in the synthesis of sulphides **10–12**, sulphoxides **13–15** and sulphones **16–18**. The *trans*-isomer was not detected by NMR spectroscopy of the reaction mixture. The conformational equilibrium in the *cis*-isomer is shifted toward the diequatorial conformer (Fig. 1).

In the $^1H$ NMR spectra of these compounds, the signal of the proton attached to carbon C-3 appears as a triplet of triplets with vicinal couplings of 12.3 and 3.9 Hz, indicating that the major conformer has an axial 3-H, hence the (S)R group is equatorial. On the other hand, in the $^1H$ NMR spectrum of compound **10** the signal of the axial proton at C-2 appears as a double triplet with vicinal couplings of 12.3 and 9.6 Hz. This last coupling constant is in agreement with an axial arrangement for the proton attached to nitrogen. The same value for this vicinal coupling was found for the axial 6-H proton.

These facts indicate that the protons attached to nitrogen and C-3 should be preferably in the axial position, and all




**Scheme 1** *Reagents:* i, RSH, $HCl_g$; ii, $NaBH_4$; iii, $HCl_g$, $Et_2O$; iv, $NaIO_4$ (1 mol equiv.); v, $NaIO_4$ (2 mol equiv.)




**Scheme 2** *Reagents:* i, HBr; ii, $Na_2CO_3$; iii, $H_2S$; iv, $NaBH_4$; v, MeI, MeOH; vi, $K_2CO_3$

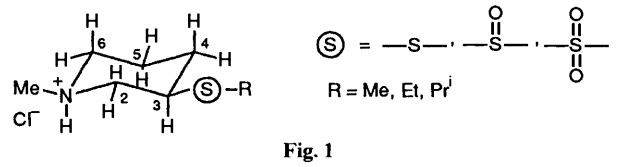



**Fig. 1**

compounds described herein are monoconformational. The spectrometric data are consistent with a (1*S*,3*R*)/(1*R*,3*S*) absolute configuration in the ring moiety for all the piperidinium chloride derivatives described.

The observed pattern of the $^{13}C$ NMR spectra of sulphoxides **13–15** named as 'α' is the same for C-4, C-5 and C-2, C-6, being very different to the observed pattern for the three sulphoxides named as 'β' for the same carbons. This fact indicates that all 'α' sulphoxides have the same stereochemistry, and that the same occurs for all the 'β' sulphoxides. However, the absolute configuration of both the α and the β series cannot be assigned with the parameters at present available to us.

## Experimental

M.p.s are determined in open capillaries on a Büchi apparatus and are uncorrected IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. $^1H$ NMR spectra were recorded on a Varian T-60A or a Varian VXR 300 spectrometer (*J*-values are given in Hz), and $^{13}C$ NMR spectra were recorded on a Varian FT 80 or a Varian VXR 300 spectrometers with $SiMe_4$ as internal standard. Solvents were purified by the usual procedure.[13]

*3-Methoxy-1-methyl-1,2,5,6-tetrahydropyridine* **1**.—The methyl ether **1** was prepared from 3-hydroxypyridine according to the method of Lyle *et al.*[10] B.p. 60–63 °C at 11 mmHg; yield 41%; $\nu_{max}$(neat)/$cm^{-1}$ 3060–3010, 3000–2900, 2840, 2780, 1680, 1230, 1070 and 820; $\delta_H$(60 MHz; $CDCl_3$) 2.0–2.6 (4 H, m, $CH_2CH_2$), 2.3 (3 H, s, Me), 2.8 (2 H, m, $NCH_2C{=}C$), 3.5 (3 H, s, MeO) and 4.6 (1 H, t, *J* 4.0, C=CH); $\delta_C$(20 MHz; $CDCl_3$) 23.72 (C-5), 45.41 (NMe), 52.35 (C-6), 54.49 (C-2), 55.64 (MeO), 90.69 (C-4) and 153.10 (C-3).

*3-Methoxy-1-methyl-1,2,5,6-tetrahydropyridinium Toluene-p-sulphonate* **2**.—To a solution of anhydrous PTSA (2.35 g,

13.65 mmol) in dry acetone (40 $cm^3$) was added a solution of compound **1** (1.58 g, 12.4 mmol) in dry acetone (43 $cm^3$) and the mixture was stirred for 15 min. The solvent was removed to yield compound **2** (3.92 g, 100%); $\nu_{max}$(KBr)/$cm^{-1}$ 3020–2920, 2700–2560, 1680, 1600, 1485, 1450, 1230, 1120, 1160, 1030, 820 and 780; $\delta_H$(60 MHz; $CDCl_3$) 2.2 (3 H, s, *Me*Ar), 2.5–2.8 (2 H, m, 5-$H_2$), 2.7 (3 H, s, NMe), 2.9–3.4 (4 H, m, 2- and 6-$H_2$), 3.3 (3 H, s, MeO), 4.4 (1 H, m, C=CH), 6.6 (2 H, m, ArH), 7.2 (2 H, m, ArH) and 10.2 (1 H, br s, NH); $\delta_C$(20 MHz; $CDCl_3$) 19.4 (C-5), 20.8 (*Me*Ar), 42.1 (NMe), 50.3 (C-6), 51.3 (C-2), 54.2 (MeO), 90.5 (C-4), 125.3, 128.4, 139.6 and 142.2 (four signals due to six aromatic carbons) and 146.6 (C-3).

1-*Methyl*-3-*oxopiperidinium Toluene*-p-*sulphonate* **3**.—To a solution of PTSA monohydrate (18.47 g, 97.2 mmol) in acetone (40 $cm^3$) was added a solution of compound **1** (12.35 g, 97.2 mmol) in acetone (40 $cm^3$), and the mixture was stirred for 15 min. The solution was concentrated, then cooled, and the solid product formed was filtered off and identified as compound **2** (8.98 g, 31%). The filtrate was evaporated under reduced pressure to yield compound **3** (19.14 g, 69%); $\nu_{max}$(KBr)/$cm^{-1}$ 3020–2950, 2750–2600, 1730, 1600, 1500, 1480, 1180, 1035 and 790; $\delta_H$(60 MHz; $CDCl_3$) 2.1 (3 H, s, *Me*Ar), 2.3 (3 H, s, NMe), 2.5–3.0 (4 H, m, 4- and 5-$H_2$), 3.1–3.9 (4 H, m, 2- and 6-$H_2$), 7.1 (2 H, m, ArH), 7.6 (2 H, m, ArH) and 10.0 (1 H, br s, NH); $\delta_C$(20 MHz; $CDCl_3$) 20.33 (C-5), 21.26 (*Me*Ar), 36.58 (C-4), 43.85 (NMe), 52.00 (C-6), 61.46 (C-2), 125.87, 129.10, 140.76 and 141.57 (four signals due to six aromatic carbons) and 199.56 (CO).

3-*Alkylsulphenyl*-1-*methylpiperidines. General Procedure.*—1-*Methyl*-3-*methylsulphenylpiperidine* **7**. Hydrogen chloride was bubbled into a stirred solution of compound **3** (18.91 g, 66 mmol) in dichloromethane (1200 $cm^3$) for 5 min. Methanethiol (45.75 g, 0.95 mol) was then slowly bubbled into the solution and the mixture was stirred for 18 h. The solvent was removed under reduced pressure to give 1-methyl-3,3-bis(methylsulphenyl)piperidinium toluene-*p*-sulphonate **4** (23.97 g). The same result was obtained by treatment of compound **2** with methanethiol.

To a stirred solution of the dithioacetal **4** (20.25 g, 55 mmol) in methanol (50 $cm^3$) was slowly added $NaBH_4$ (3.61 g) and the mixture was stirred for 24 h. Dil. hydrochloric acid was added until all the solid had dissolved and the solution was then made alkaline (pH 8) by addition of aq. sodium hydroxide. The aq. mixture was extracted with diethyl ether and the extract was dried over anhydrous magnesium sulphate, filtered and evaporated. The crude oily product was distilled under reduced pressure to yield compound **7** (6.84 g, 85%), b.p. 65 °C at 14 mmHg); $\delta_H$(80 MHz; $CDCl_3$) 1.65–2.04 (4 H, m, 4- and 5-$H_2$), 2.09 (3 H, s, SMe), 2.24 (3 H, s, NMe), 2.50–2.90 (3 H, m, 3-H and 6-$H_2$) and 3.46 (2 H, m, 2-$H_2$); $\delta_C$(20 MHz; $CDCl_3$) 13.59 (SMe), 25.45 (C-5), 30.42 (C-4), 42.86 (C-3), 46.29 (NMe), 55.71 (C-6) and 61.73 (C-2).

3-*Ethylsulphenyl*-1-*methylpiperidine* **8**. Treatment of compound **2** (8.85 g, 30 mmol), ethanethiol (26.34 g, 0.43 mol) and dichloromethane (650 $cm^3$) by the same procedure as used in the synthesis of compound **7**, gave title product **8** (2.75 g, 58%), b.p. 80–84 °C at 48 mmHg; $\delta_H$(60 MHz; $CDCl_3$) 1.2 (3 H, t, *J* 7.0, *Me*$CH_2$), 1.6-2.2 (4 H, m, 4- and 5-$H_2$), 2.3 (3 H, s, NMe) and 2.3–3.2 (7 H, m, 2-$H_2$, 3-H and S$CH_2$); $\delta_C$(20 MHz; $CDCl_3$) 15.57 (*Me*$CH_2$), 23.86 (S$CH_2$), 24.90 (C-5), 30.30 (C-4), 40.53 (C-3), 45.75 (NMe), 54.99 (C-6) and 61.69 (C-2).

3-*Isopropylsulphenyl*-1-*methylpiperidine* **9**. Prepared by the same procedure used for compound **7**, starting from compound **3** (5.0 g, 17.5 mmol) and propane-2-thiol (19.11 g, 0.251 mol), yield 53%; b.p. 80 °C at 50 mmHg; $\delta_H$(60 MHz; $CDCl_3$) 1.3 (6 H, d, *J* 7.0, $Me_2$CH), 1.4–2.0 (4 H, m, 4- and 5-$H_2$), 2.2 (3 H, s, NMe) and 2.4–3.2 (6 H, m, 2- and 6-$H_2$, 3-H and C*H*$Me_2$); $\delta_C$(20 MHz; $CDCl_3$) 23.00 and 23.14 ($Me_2$CH), 24.67 (C-5), 30.58 (C-4), 32.85 (*C*H$Me_2$), 39.35 (C-3), 45.57 (NMe), 54.70 (C-6) and 61.89 (C-2).

3-*Alkylsulphenyl*-1-*methylpiperidinium Chlorides. General Procedure.*—1-*Methyl*-3-*methylsulphenylpiperidinium chloride* **10**. Dry hydrogen chloride was bubbled into a solution of compound **7** (4.36 g, 30 mmol) in diethyl ether (100 $cm^3$) for 2 h. The solvent was removed and the product was recrystallized from ethyl acetate–ethanol (93:3) to afford *title compound* **10** (4.8 g, 88%) as a white solid; m.p. 160–162 °C; $\delta_H$(300 MHz; $CDCl_3$) 1.36 (1 H, dq, *J* 12.9 and 3.6, 4-$H^{ax}$), 1.96 (1 H, dquin, *J* 14.5 and 3.3, 5-$H^{eq}$), 2.18 (3 H, s, SMe), 2.20 (1 H, m, 4-$H^{eq}$), 2.35 (1 H, dtt, *J* 14.4, 13.2 and 3.9, 5-$H^{ax}$), 2.65 (1 H, dt, *J* 12.3 and 9.6, 2-$H^{ax}$), 2.71 (1 H, tdd, *J* 12.6, 9.6 and 3,3, 6-$H^{ax}$), 2.82 (3 H, d, *J* 4.8, NMe), 3.34 (1 H, tt, *J* 12.3 and 3.9, 3-$H^{ax}$), 3.50 (1 H, dm, *J* 12.0, 6-$H^{eq}$), 3.64 (1 H, ddd, *J* 11.9, 3.7 and 1.8, 2-$H^{eq}$) and 12.38 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 12.60 (SMe), 22.22 (C-5), 27.46 (C-4), 38.17 (C-3), 42.87 (NMe), 53.03 (C-6) and 57.56 (C-2) (Found: C, 45.9; H, 8.8; N, 7.3; S, 17.4; Cl, 19.4. $C_7H_{16}$ClNS requires C, 46.26; H, 8.88; N, 7.71; S, 17.64; Cl, 19.51%).

3-*Ethylsulphenyl*-1-*methylpiperidinium chloride* **11**. Prepared similarly, starting from compound **8**. Recrystallized yield from ethyl acetate was 55%; m.p. 164–166 °C; $\delta_H$(300 MHz; $CDCl_3$) 1.29 (3 H, t, *J* 7.5, *Me*$CH_2$), 1.40 (1 H, qd, *J* 13.1 and 3.9, 4-$H^{ax}$), 1.97 (1 H, dm, *J* 14.4, 5-$H^{eq}$), 2.17 (1 H, br d, *J* 12.9, 4-$H^{eq}$), 2.31 (1 H, dtt, *J* 14.4, 13.2 and 3.9, 5-$H^{ax}$), 2.16–2.73 (2 H, AB portion of an $ABX_3$ spectrum, $\delta_A$ 2.67, $\delta_B$ 2.62, $J_{AB}$ 12.3, $J_{AX} = J_{BX} = 7.5$, C$H_2$Me), 2.74–2.82 (2 H, m, 2- and 6-$H^{ax}$), 2.85 (3 H, s, NMe), 3.40 (1 H, tt, *J* 12.3 and 3.9, 3-$H^{ax}$), 3.49 (1 H, br d, *J* 11.6, 6-$H^{eq}$), 3.61 (1 H, br d, *J* 11.7, 2-$H^{eq}$) and 12.18 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 14.82 (*Me*$CH_2$), 22.68 (C-5), 24.75 (S$CH_2$), 28.79 (C-4), 37.19 (C-3), 43.38 (NMe), 53.70 (C-6) and 58.97 (C-2); $\delta_C$(ADEPT) Me 14.82 and 43.38; $CH_2$ 22.68, 24.75, 28.79, 53.70 and 58.97; CH 37.19 (Found: C, 49.0; H, 9.3; Cl, 18.3; N, 6.9; S, 16.1. $C_8H_{18}$ClNS requires C, 44.08; H, 9.27; Cl, 18.11; N, 7.16; S, 16.38%).

3-*Isopropylsulphenyl*-1-*methylpiperidinium chloride* **12**. Prepared similarly, starting from compound **9**. Recrystallized yield from ethyl acetate was 47%; m.p. 176–178 °C; $\delta_H$(300 MHz; $CDCl_3$) 1.28 and 1.33 each (3 H, d, *J* 6.8, together CH$Me_2$), 1.35 (1 H, qd, *J* 13.2 and 3.9, 4-$H^{ax}$), 1.94 (1 H, dm, *J* 14.4, 5-$H^{eq}$), 2.17 (1 H, br d, *J* 13.2, 4-$H^{eq}$), 2.36 (1 H, dtt, *J* 14.7, 13.2 and 3.9, 5-$H^{ax}$), 2.53–2.74 (2 H, m, 6- and 2-$H^{ax}$), 2.79 (3 H, d, *J* 4.2, NMe), 3.09 (1 H, sept, *J* 6.6, C*H*$Me_2$), 3.45 (1 H, tt, *J* 12.3 and 3.9, 3-$H^{ax}$), 3.48 (1 H, br d, *J* 12.3, 6-$H^{eq}$), 3.59 (1 H, br d, *J* 11.7, 2-$H^{eq}$) and 12.47 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 22.35 (C-5), 23.02 and 23.21 (CH$Me_2$), 28.64 (C-4), 34.10 (*C*H$Me_2$), 35.87 (C-3), 42.74 (NMe), 52.81 (C-6) and 58.49 (C-2) (Found: C, 51.3; H, 9.4; Cl, 16.8; N, 6.25; S, 15.1. $C_9H_{20}$ClNS requires C, 51.53; H, 9.61; Cl, 16.90; N, 6.68; S, 15.28%).

3-*Alkylsulphinyl*-1-*methylpiperidinium Chlorides. General Procedure.*—1-*Methyl*-3-*methylsulphinylpiperidinium chloride* **13**. To a solution of compound **10** (1.5 g, 8.27 mmol) in ethanol (37 $cm^3$) was added a solution of sodium metaperiodate (1.77 g, 8.27 mmol) in water (24 $cm^3$) and the mixture was stirred for 24 h. The solvent was removed and the solid product was stirred in dichloromethane for 2 h, and then filtered off. The filtrate was dried over anhydrous magnesium sulphate, filtered and evaporated to give title product **13** (1.25 g, 77%) as a yellow solid. A 55:45 mixture of the two diastereoisomeric sulphoxides was observed by $^{13}C$ NMR and $^1H$ NMR spectroscopy. The solid was repeatedly recrystallized from ethyl acetate–ethanol (~82:18) to yield the major diastereoisomer **13α** as a pure product (m.p. 190–192 °C). From the mother liquors was isolated the other isomeric product **13β** (purity 66%).

Compound **13α**. $\delta_H$(300 MHz; $CDCl_3$) 1.81 (1 H, dq, *J* 13.0 and 3.9, 4-$H^{ax}$), 2.07 (1 H, dm, *J* 14.4, 5-$H^{eq}$), 2.17 (1 H, br d, *J* 12.6, 4-$H^{eq}$), 2.44 (1 H, dtt, *J* 14.7, 12.9 and 3.6, 5-$H^{ax}$), 2.70 (3 H, s, MeSO), 2.78 (1 H, br t, *J* 12.0, 6-$H^{ax}$), 2.92 (3 H, s, NMe), 3.12 (1 H, t, *J* 11.9, 2-$H^{ax}$), 3.50 (1 H, tt, *J* 12.0 and 3.9, 3-$H^{ax}$), 3.54 (1 H, dm, *J* 11.7, 6-$H^{eq}$), 3.78 (1 H, dm, *J* 12.0, 2-$H^{eq}$) and 12.60 (1 H, br s, NH); $\delta_C$(20 MHz; $CDCl_3$) 21.75 and 23.37 (C-4 and -5), 36.06 (MeSO), 44.05 (NMe), 50.70 and 53.91 (C-2) and -6) and 52.02 (C-3); $\delta_C$(ADEPT) Me 36.06 and 44.05; $CH_2$ 21.75, 23.37, 50.70 and 53.91; CH 52.02.

Compound **13β**. $\delta_H$(300 MHz; $CDCl_3$) 1.85 (1 H, br q, *J* 12.9, 4-$H^{ax}$), 2.06–2.20 (2 H, m, 4- and 5-$H^{eq}$), 2.40 (1 H, m, 5-$H^{ax}$), 2.64 (3 H, s, MeSO), 2.90 (1 H, m, 6-$H^{ax}$), 2.91 (3 H, s, NMe), 3.10 (t, 1 H, t, *J* 12.0, 2-$H^{ax}$), 3.40–3.60 (2 H, m, 6-$H^{eq}$) and 3-$H^{ax}$), 3.75 (1 H, br d, *J* 11.7, 2-$H^{eq}$) and 12.33 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 16.12 and 20.87 (C-4 and -5), 34.93 (MeSO), 43.62 (NMe), 52.32 (C-3) and 53.67 and 53.73 (C-6 and -2).

3-*Ethylsulphinyl*-1-*methylpiperidinium chloride* **14**. Prepared similarly, starting from compound **11** (yield 92%). Repeated recrystallization of the obtained 62:38 diastereoisomeric mixture from ethyl acetate–ethanol (~92:8) yielded the major diastereoisomer **14α** as a pure product (m.p. 194–196 °C). The mother liquors were then evaporated and the residue was recrystallized from ethyl acetate–ethanol (~94:6) to afford the minor diastereoisomer **14β** as a pure product (m.p. 180–182 °C).

Compound **14α**. $\delta_H$(300 MHz; $CDCl_3$) 1.39 (3 H, t, *J* 7.5, *Me*$CH_2$), 1.85 (1 H, dq, *J* 13.2 and 13.9, 4-$H^{ax}$), 2.06 (1 H, dm, *J* 14.4, 5-$H^{eq}$), 2.16 (1 H, dm, *J* 13.2, 4-$H^{eq}$), 2.44 (1 H, dtt, *J* 14.1, 13.5 and 3.6, 5-$H^{ax}$), 2.70–2.98 (3 H, m, 6-$H^{ax}$ and C$H_2$Me), 2.89 (3 H, s, NMe), 3.09 (1 H, t, *J* 11.7, 2-$H^{ax}$), 3.05–3.64 (2 H, m, 6-$H^{eq}$ and 3-$H^{ax}$), 3.68 (1 H, dm, *J* 12.0, 2-$H^{eq}$) and 12.56 (1 H, br s, NH); $\delta_C$(20 MHz; $CDCl_3$) 7.23 (*Me*$CH_2$), 21.79 and 23.35 (C-4 and -5), 43.44 (MeC$H_2$), 43.86 (NMe), 49.77 (C-3) and 50.91 and 53.69 (C-2 and -6) (Found: C, 45.1; H, 8.6; Cl, 16.5; N, 6.3; S, 14.9. $C_8H_{18}ClNOS$ requires C, 45.38; H, 8.57 Cl, 16.74; N, 6.61; S, 15.14%).

Compound **14β**. $\delta_H$(300 MHz; $CDCl_3$) 1.37 (3 H, t, *J* 7.5, *Me*$CH_2$), 1.86 (1 H, dq, *J* 13.0 and 3.9, 4-$H^{ax}$), 2.07 (1 H, br d, *J* 12.3, 4-$H^{eq}$), 2.12 (1 H, br d, *J* 15.0, 5-$H^{eq}$), 2.40 (1 H, m, 5-$H^{ax}$), 2.73 (1 H, dq, *J* 12.9 and 7.5, MeC*H* H), 2.87 (1 H, dq, *J* 13.1 and 7.5, MeCH*H*), 2.88–2.94 (1 H, m, 6-$H^{ax}$), 2.91 (3 H, s, NMe), 3.15 (1 H, t, *J* 11.7, 2-$H^{ax}$), 3.44–3.60 (2 H, m, 6-$H^{eq}$ and 3-$H^{ax}$), 3.72 (1 H, br d, *J* 11.7, 2-$H^{eq}$) and 12.68 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 7.32 (*Me*$CH_2$), 16.70 and 20.97 (C-4 and -5), 42.79 (*C*$H_2$Me), 43.62 (NMe), 50.85 (C-3) and 53.67 and 53.90 (C-2 and -6); $\delta_C$(ADEPT) Me 7.32 and 43.62; $CH_2$ 16.70, 20.97, 42.79, 53.67 and 53.90; CH 50.85.

3-*Isopropylsulphinyl*-1-*methylpiperidinium chloride* **15**. Prepared similarly, starting from compound **12** (yield 85%). The solid (a 70:30 mixture of the two distereoisomeric sulphoxides) was repeatedly recrystallized from ethyl acetate–ethanol (~94:6) to yield the major diastereoisomer **15α** as a pure product (m.p. 196–198 °C). From the mother liquors was isolated the other isomeric product **15β** (purity 90%; m.p. 168–172 °C).

Compound **15α**. $\delta_H$(300 MHz; $CDCl_3$) 1.32 and 1.39 (each 3 H, d, *J* 6.9, together $Me_2$CH), 1.89 (1 H, qd, *J* 13.0 and 3.9, 4-$H^{ax}$), 2.07 (1 H, dm, *J* 14.7, 5-$H^{eq}$), 2.14 (1 H, dm, *J* 12.9, 4-$H^{eq}$), 2.43 (1 H, dtt, *J* 14.4, 13.2 and 3.9, 5-$H^{ax}$), 2.76–2.90 (1 H, m, 6-$H^{ax}$), 2.88 (1 H, s, NMe), 2.99 (1 H, sept, *J* 6.9, C*H*$Me_2$), 3.08 (1 H, t, *J* 11.4, 2-$H^{ax}$), 3.55 (1 H, br d, *J* 14.7, 6-$H^{eq}$), 3.61 (1 H, br d, *J* 11.7, 2-$H^{eq}$), 3.71 (1 H, tt, *J* 12.3 and 3.9, 3-$H^{ax}$) and 12.56 (1 H, br s, NH); $\delta_C$(20 MHz; $CDCl_3$) 15.20 and 15.67 ($Me_2$CH), 21.54 and 23.35 (C-4 and -5), 43.27 (NMe), 47.17 and 47.83 (*C*H$Me_2$ and C-3) and 50.58 and 53.03 (C-6 and -2).

Compound **15β**. $\delta_H$(300 MHz; $CDCl_3$) 1.20 and 1.37 (each 3 H, d, *J* 6.9, together $Me_2$CH), 1.78–2.14 (3 H, m, 4-$H_2$ and 5-$H^{eq}$), 2.46 (1 H, dm, *J* 14.4, 5-$H^{ax}$), 2.78 (1 H, m, 6-$H^{ax}$), 2.83 (3 H, s, NMe), 2.97 [1 H, sept, *J* 6.9, C*H*($Me_2$)], 3.00 (1 H, m, 2-$H^{ax}$), 3.50 (1 H, br d, *J* 12.0, 6-$H^{eq}$), 3.54–3.74 (2 H, m, 3-$H^{ax}$ and 2-$H^{eq}$) and 12.8 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 15.95 and 16.15 ($Me_2$CH), 16.88 and 21.17 (C-4 and -5), 43.98 (NMe), 48.21 and 48.74 (*C*H$Me_2$ and C-3) and 54.11 and 54.84 (C-2 and -6).

3-*Alkylsulphonyl*-1-*methylpiperidinium Chlorides*.—1-*Methyl*-3-*methylsulphonylpiperidinium chloride* **16**. Prepared by the same procedure as used for compound **13**, starting from compound **10** (0.4 g, 2.2 mmol) and sodium metaperiodate (1.41 g, 6.6 mmol). Recrystallized yield from ethanol was 57%; m.p. 192–196 °C; $\delta_H$(300 MHz; $CDCl_3$) 1.77 (1 H, qd, *J* 12.9 and 3.9, 4-$H^{ax}$), 2.09 (1 H, br d, *J* 14.7, 5-$H^{eq}$), 2.30–2.56 (2 H, m, 4-$H^{eq}$ and 5-$H^{ax}$), 2.73 (1 H, t, *J* 12.3, 2-$H^{ax}$), 2.88 (3 H, s, NMe), 2.90 (1 H, m, 6-$H^{ax}$), 3.00 (3 H, s, $MeSO_2$), 3.53 (1 H, dm, *J* 12.0, 2-$H^{eq}$), 3.84 (1 H, dm, *J* 11.7, 6-$H^{eq}$), 4.12 (1 H, tt, *J* 12.3 and 3.9, 3-$H^{ax}$) and 13.12 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 21.15 and 21.35 (C-4 and -5), 39.75 ($MeSO_2$), 44.12 (NMe), 51.97 and 54.08 (C-2 and -6) and 55.96 (C-3).

3-*Ethylsulphonyl*-1-*methylpiperidinium chloride* **17**. Prepared similarly, starting from compound **14** (0.41 g, 1.96 mmol) and sodium metaperiodate (0.46 g, 2.15 mmol). Recrystallized yield from ethanol was 73%; m.p. 204–210 °C (decomp.); $\delta_H$[300 MHz; $(CD_3)_2SO$] 1.25 (3 H, t, *J* 7.5, *Me*$CH_2$), 1.57 (1 H, qd, *J* 12.0 and 4.5, 4-$H^{ax}$), 1.80–2.02 (2 H, m, 5-$H_2$), 2.14 (1 H, br d, *J* 12.6, 4-$H^{eq}$), 2.78 (3 H, s, NMe), 2.93 (1 H, t, *J* 12.0, 6-$H^{ax}$), 3.08 (1 H, t, *J* 12.0, 2-$H^{ax}$), 3.21 (2 H, q, *J* 7.5, C$H_2$Me), 3.38 (1 H, br d, *J* 12.3, 6-$H^{eq}$), 3.70–3.82 (2 H, m, 3-$H^{ax}$ and 2-$H^{eq}$) and 11.2 (1 H, br s, NH); $\delta_C$[75 MHz; $(CD_3)_2SO$] 5.77 (*Me*$CH_2$), 20.32 and 20.90 (C-4 and -5), 42.56 (*C*$H_2$Me), 44.51 (NMe), 50.20 and 52.28 (C-2 and -6) and 53.61 (C-3); $\delta_C$(ADEPT) Me 5.77 and 44.51; $CH_2$ 20.32, 20.90, 42.56, 50.20 and 52.28; CH 53.61.

3-*Isopropylsulphonyl*-1-*methylpiperidinium chloride* **18**. Prepared similarly, starting from compound **15** (0.31 g, 1.36 mmol) and sodium metaperiodate (0.32 g, 1.5 mmol). Recrystallized yield from ethyl acetate–ethanol (~96:4) was 58%; m.p. 204–210 °C (decomp.); $\delta_H$(300 MHz; $CDCl_3$) 1.42 and 1.44 (each 3 H, d, *J* 6.9, together $Me_2$CH), 1.79 (1 H, qd, *J* 12.7 and 3.9, 4-$H^{ax}$), 2.06–2.36 (3 H, m, 4-$H^{eq}$ and 5-$H_2$), 2.81 (1 H, td, *J* 12.6 and 3.0, 6-$H^{ax}$), 2.91 (3 H, s, NMe), 3.01 (1 H, t, *J* 12.0, 2-$H^{ax}$), 3.22 (1 H, sept, *J* 6.9, C*H*$Me_2$), 3.57 (1 H, br d, *J* 11.0, 2-$H^{eq}$), 3.81 (1 H, br d, *J* 11.4, 6-$H^{eq}$), 4.06 (1 H, tt, *J* 12.3 and 3.6, 3-$H^{ax}$) and 12.00 (1 H, br s, NH); $\delta_C$(75 MHz; $CDCl_3$) 14.53 and 15.19 ($Me_2$CH), 20.95 and 21.51 (C-4 and -5), 44.22 (NMe), 51.37 and 52.20 (*C*H$Me_2$ and C-3) and 52.77 and 54.05 (C-2 and -6); $\delta_C$(DEPT) Me and CH 14.53, 15.19, 44.22, 51.37 and 52.20; $CH_2$ 20.95, 21.51, 52.77 and 54.05.

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