Alkene Cyclisations of *N*-Alkenyl-α-(methylsulphinyl)acetamides and *N*-Alkenyl-α-chloro-α-(methylthio)acetamides: Novel Synthesis of Five-, Six-, and Seven-membered Lactams

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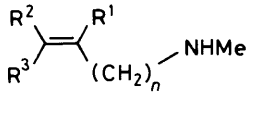
On being treated with trifluoroacetic anhydride, *N*-isopropenyl-*N*-methyl-α-(methylsulphinyl)acetamide (**4a**) underwent cationic alkene cyclisation to give the six-membered lactams (**6**) and (**7**), whereas the *N*-but-2-enyl (**4b**) and *N*-(3-methylbut-2-enyl) derivatives (**4c**) afforded the five-membered lactams (**8**) and (**9**), and (**10**), respectively. A similar treatment of the *N*-prop-2-enyl derivative (**4d**) gave only the Pummerer rearrangement product (**12**), which, on further treatment with trifluoroacetic acid, afforded the five-membered lactams (**13**) and (**14**). On the other hand, *N*-but-2-enyl-α-chloro-*N*-methyl-α-(methylthio)acetamide (**5b**), when treated with stannic chloride or silica gel, or when heated without solvent, gave the lactam (**8**). Treatment of *N*-prop-2-enyl derivative (**5d**) with stannic chloride yielded the lactams (**14**) and (**15**). The cyclisations of *N*-alk-3-enyl derivatives (**4e**), (**4f**), and (**5e**) giving seven-membered lactams are also described.

Considerable attention has recently been directed towards the use of α-thiocarbocations to accomplish carbon–carbon bond forming reactions.[1,2] Among several reactive species employed so far, the α-acyl substituted α-thiocarbocations (**1**)[2] are probably the most promising ones. These cations can be readily formed from α-acyl sulphoxides under the Pummerer reaction conditions or from α-acyl-α-chlorosulphides in the presence of a Lewis acid. Here, we wish to demonstrate the usefulness of the α-carbamoyl-α-thiocarbocation (**1**: R = NR^1R^2) as an initiator for cationic alkene cyclisation[3] which provides new routes to five-, six-, and seven-membered lactams.[4]

$$MeS\overset{+}{C}HCOR \longleftrightarrow Me\overset{+}{S}{=}CHCOR$$
(**1**)

Results

The *N*-alkenyl-α-(methylsulphinyl)acetamides (**4a**—**f**) were prepared by acylation of the corresponding *N*-alkenylamines (**2a**—**f**) with α-(methylthio)acetyl chloride and successive oxidation of the resultant sulphides (**3a**—**f**) with sodium metaperiodate.



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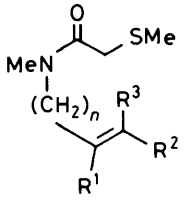

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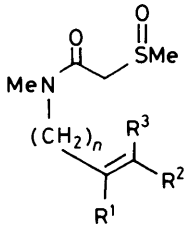


(**4**)

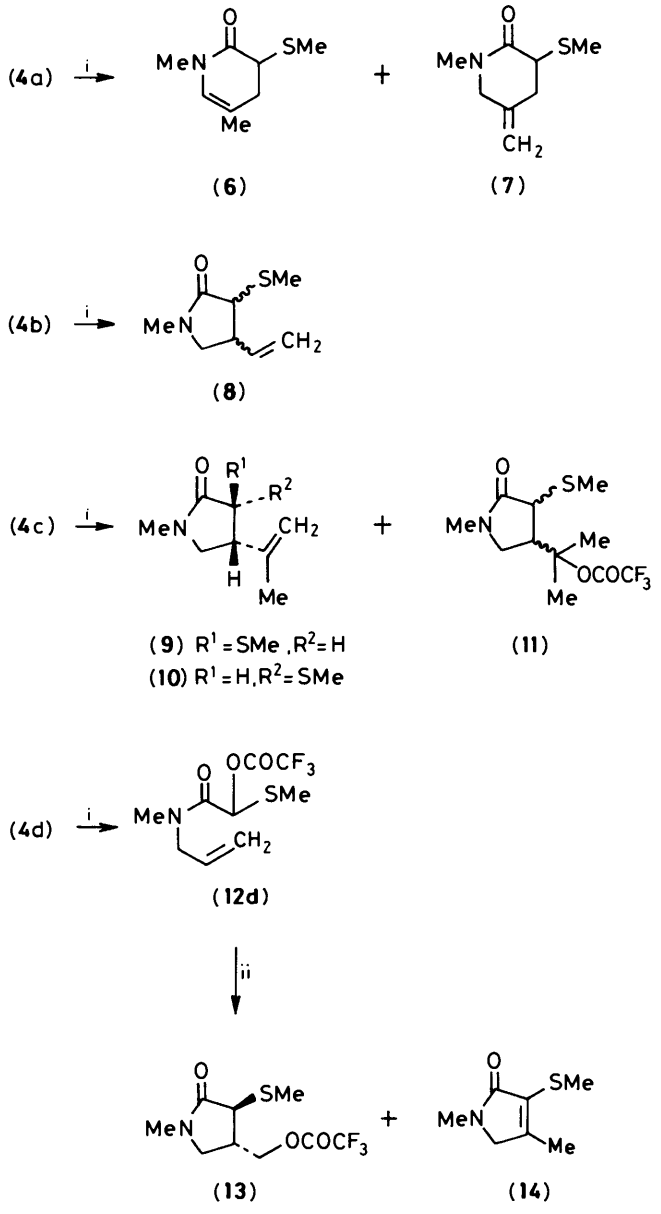
a; *n* = 1, R^1 = Me, R^2 = R^3 = H
b; *n* = 1, R^1 = R^3 = H, R^2 = Me
c; *n* = 1, R^1 = H, R^2 = R^3 = Me
d; *n* = 1, R^1 = R^2 = R^3 = H
e; *n* = 2, R^1 = R^2 = R^3 = H
f; *n* = 2, R^1 = Me, R^2 = R^3 = H

The sulphoxide (**4a**), on treatment with a stoicheiometric amount of trifluoroacetic anhydride (TFAA) in dichloromethane at 0 °C, gave two isomeric six-membered lactams (**6**) (35%) and (**7**) (43%). The structure assignment of these products rests mainly on their spectroscopic data. The i.r. spectra of (**6**) and (**7**) showed the carbonyl absorptions at 1 640 and 1 630 cm^{-1} respectively. The ^1H n.m.r. spectrum of (**6**) exhibited a broad singlet due to the vinylic methyl protons at δ 1.73 and double doublets (*J* 6 and 3 Hz) due to the proton α to carbonyl group at δ 3.29, while in the ^1H n.m.r. spectrum of (**7**) the signal due to the *exo*-methylene protons appeared at δ 4.98 as a broad singlet.

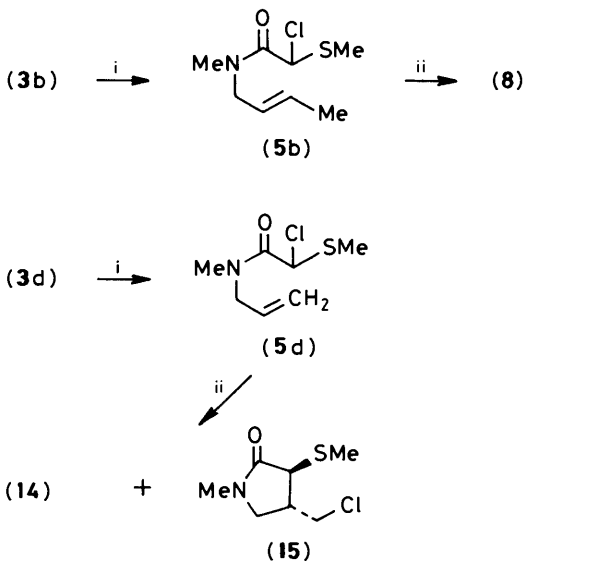
A similar treatment of the sulphoxide (**4b**), however, gave five-membered lactam (**8**) as a mixture of two stereoisomers (69:31 by g.l.c.) in 92% yield. The i.r. spectrum of the mixture showed the bands at 1 680 (five-membered lactam) and 920 cm^{-1} ($CH{=}CH_2$), and the ^1H n.m.r. spectrum revealed a multiplet signal due to three alkenic protons at δ 4.9—6.1. Treatment of this mixture with sodium ethoxide in refluxing ethanol resulted in an increase in the amount of the major isomer at the expense of the minor one (84:14 by g.l.c.), which suggests that the major isomer of the cyclisation products has a *trans*-structure and the minor one a *cis*-structure.

The cyclisation of the sulphoxide (**4c**) afforded a mixture of three products, the pyrrolidinones (**9**) and (**10**), and the trifluoroacetate (**11**) in a ratio of *ca.* 2:2:1 [by ^1H n.m.r. spectroscopy]. Since these products could not be separated by conventional means, the crude mixture was treated with 2% hydrochloric acid to hydrolyse the trifluoroacetate (**11**), then chromatographed, whereupon the lactams (**9**) and (**10**) were obtained pure. Since compound (**10**), when refluxed in ethanol in the presence of sodium ethoxide, was cleanly converted into its isomer (**9**), we were prompted to assign the stereochemistry of (**9**) and (**10**) as *trans* and *cis*, respectively.

In contrast, treatment of the sulphoxide (**4d**) with TFAA in CH_2Cl_2 gave no cyclised product but afforded only the normal Pummerer rearrangement product (**12**) [$\nu_{max.}$ 1 780 cm^{-1} ($OCOCF_3$); δ 6.34 (1 H, s, CF_3CO_2CHSMe)]. However, further treatment of the trifluoroacetate (**12**) with trifluoroacetic acid in the absence of CH_2Cl_2 caused the ring closure to yield the five-membered lactams (**13**) (9%) and (**14**) (39%). The ^1H n.m.r. spectrum of (**13**) (see the Experimental section) indicated it to be



Scheme 1. *Reagents:* i, $(CF_3CO)_2O$–CH_2Cl_2; ii, CF_3CO_2H



Scheme 2. *Reagents:* i, NCS–CCl_4; ii, $SnCl_4$–CH_2Cl_2

a single stereoisomer (probably *trans*). Direct treatment of the sulphoxide (**4d**) with TFAA in trifluoroacetic acid gave unsatisfactory results.

We next turned our attention to the cyclisation of the *N*-alk-2-enyl)-α-chloro-α-(methylthio)acetamides (**5b**) and (**5d**) in the presence of Lewis acid. The chlorides (**5b**) and (**5d**) were prepared in quantitative yields by reactions of the corresponding sulphides (**3b**) and (**3d**) with *N*-chlorosuccinimide (NCS).

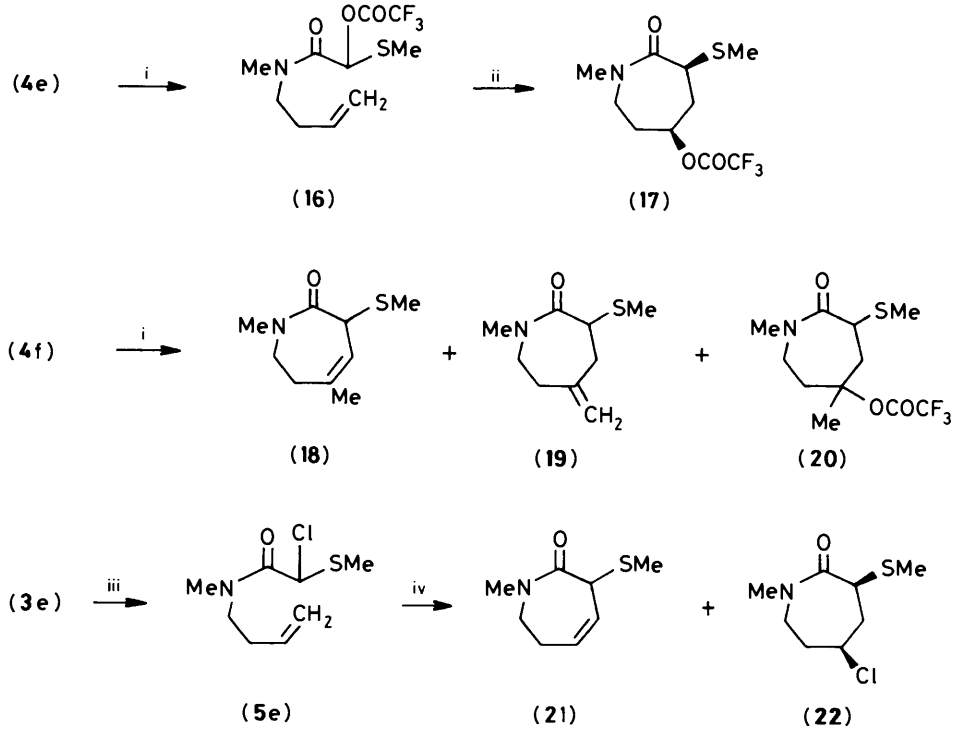
When the chloride (**5b**) was treated with a stoicheiometric amount of stannic chloride ($SnCl_4$) in CH_2Cl_2 at room temperature, the lactam (**8**) was obtained in 70% yield. The g.l.c. analysis of the product showed it to be a mixture of two stereoisomers (71:29), the ratio approximating to that seen in the products obtained from the sulphoxide (**4b**). Silica gel chromatography also effected the cyclisation of (**5b**), into the lactam (**8**) in 52% yield. More interestingly, the chloride (**5b**) was found to undergo cyclisation just by heating without solvent at 130 °C to afford the lactam (**8**) in 55% yield. The chloride (**5d**), when treated with $SnCl_4$, gave the lactams (**14**) and (**15**) in 18 and 42% yields, respectively. The ^1H n.m.r. spectrum of (**15**) (see the Experimental section) showed it to be a single stereoisomer (probably *trans*). Treatment of (**5d**) with silica gel or heating of (**5d**) gave polymeric materials.

Finally, in order to further define the scope of this cationic alkene cyclisation, we examined the behaviour of the homologous *N*-but-3-enyl systems, (**4e**), (**4f**), and (**5e**). When *N*-but-3-enyl-*N*-methyl-α-(methylsulphinyl)acetamide (**4e**) was treated with TFAA in CH_2Cl_2, only the Pummerer rearrangement product (**16**) was obtained. As in the case of the trifluoroacetate (**12**), the product (**16**) underwent cyclisation by treatment with trifluoroacetic acid in the absence of CH_2Cl_2 to afford the seven-membered lactam (**17**) in 12% yield. The i.r. spectrum of (**17**) showed the bands at 1 780 ($OCOCF_3$) and 1 640 cm^{-1} (CONMe). The ^1H n.m.r. spectrum revealed double doublets at δ 3.64 (1 H, *J* 9 and 3 Hz) due to C*H*SMe, two doublets of double doublets at δ 3.39 and 3.78 (1 H each, *J* 16, 8, and 3 Hz) due to NCH_2, and double triplets at δ 5.18 (1 H, *J* 8 and 4 Hz) due to $CHOCOCF_3$. The cyclisation of the *N*-(3-methylbut-3-enyl) derivative (**4f**) proceeded smoothly with TFAA in CH_2Cl_2 to give the seven-membered lactams (**18**) (6%), (**19**) (28%), and (**20**) (47%). The ^1H n.m.r. spectra of (**18**) and (**19**) revealed a broad doublet (1 H, *J* 8 Hz) at δ 5.45 due to the alkenic proton and a broad singlet (2 H) at δ 4.85 due to the *exo*-methylene protons, respectively. The i.r. spectrum of (**20**) showed bands at 1 780 ($OCOCF_3$) and 1 650 cm^{-1} (CONMe). In addition *N*-but-3-enyl-α-chloro-*N*-methyl-α-(methylthio)acetamide (**5e**), on treatment with stannic chloride, gave two lactams (**21**) (8%) and (**22**) (36%). The structure of (**22**) was confirmed by comparison of its ^1H n.m.r. spectrum with that of compound (**17**), and the structure of (**21**) was established by the following spectroscopic evidence. The i.r. spectrum showed the band at 1 635 cm^{-1} (CONMe) and the ^1H n.m.r. spectrum revealed a doublet at δ 3.99 (1 H, *J* 6 Hz) due to SCH and a multiplet at δ 5.6—5.8 (2 H) due to two alkene protons.

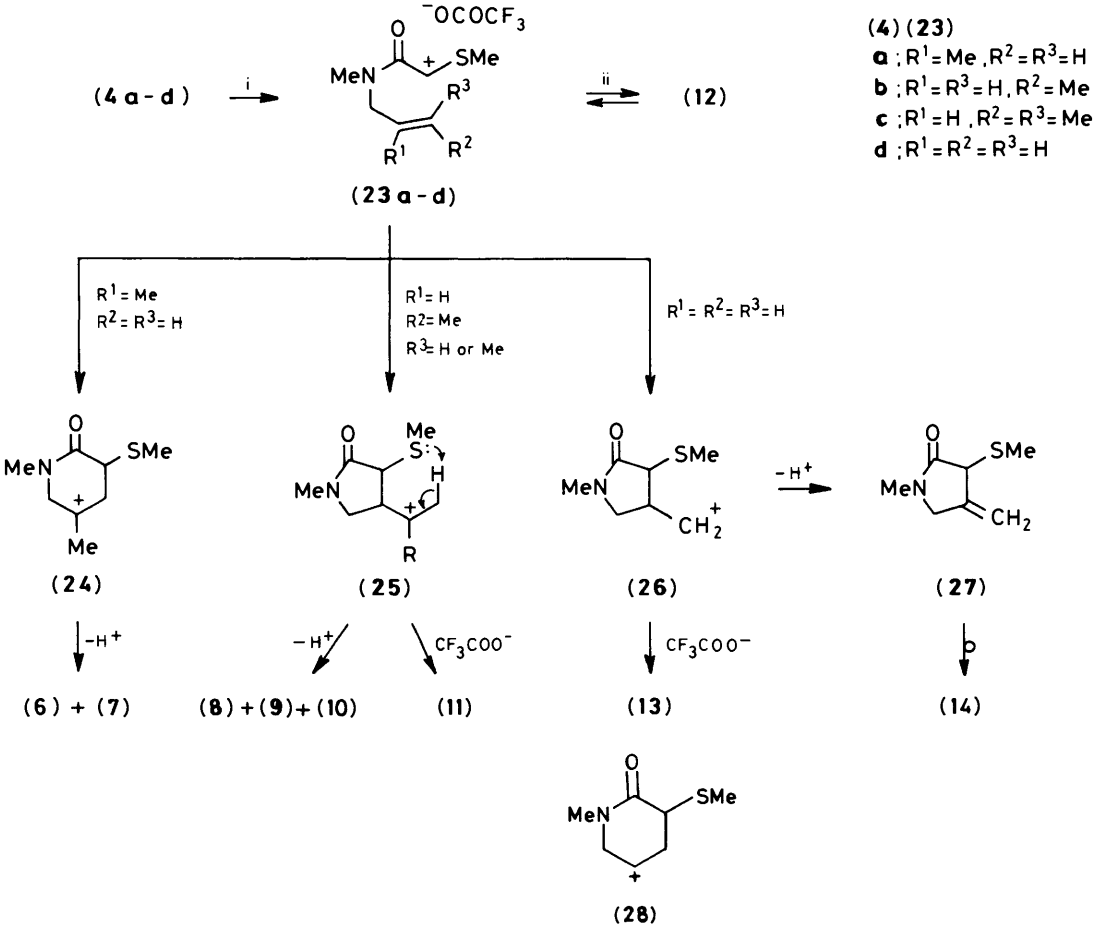
Discussion

We have confirmed that the lactams (**6**) and (**7**) were not interconverted and the trifluoroacetate (**13**) was not transformed into the lactam (**14**) under the reaction conditions we employed. These results suggest that all of the lactams obtained herein are the primary products of the reactions.

One possible mechanistic interpretation for the cyclisation



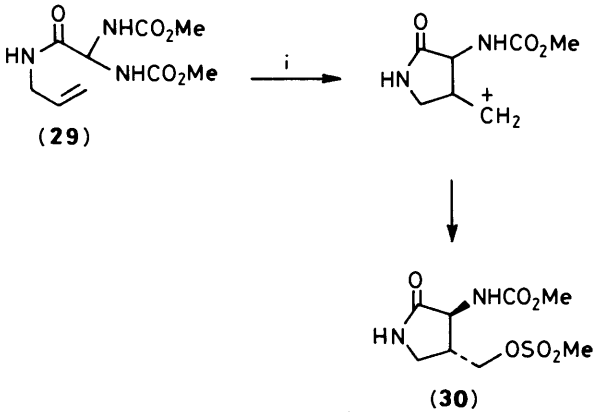
Scheme 3. *Reagents:* i, $(CF_3CO)_2O$–CH_2Cl_2; ii, CF_3CO_2H; iii, NCS–CCl_4; iv, $SnCl_4$–CCl_4



Scheme 4. *Reagents:* i, $(CF_3CO)_2O$; ii, CF_3CO_2H

reactions of *N*-alk-2-enyl systems is outlined in Scheme 4 in which the sulphoxides (**4a**—**c**) are initially converted to the Pummerer reaction intermediates (**23a**—**c**), which can undergo ring closure to yield the new cation (**24**) or (**25**). The only exception is the reaction of (**4d**) which gave the Pummerer rearrangement product (**12**). Apparently, an attack of trifluoroacetate anion on the carbocation (**23d**) competes with the ring-closure, perhaps because of the low nucleophilicity of the alkene double bond. However, the product (**12**) is labile in trifluoroacetic acid and undergoes ring closure either *via* a concerted *S*N2-like mechanism or by a stepwise manner involving the carbocation (**23d**) to generate the new carbocation (**26**). The cations (**24**)—(**26**) thus formed either lose a proton to afford the lactams (**6**)—(**10**) and (**14**) [*via* (**27**)], or are attacked by a trifluoroacetate anion to give the trifluoroacetate (**11**) or (**13**).

In principle, ring-closure of the Pummerer reaction intermediate (**23**) can occur in a 6-*endo-trig* or in a 5-*exo-trig* manner and many examples of the related processes indicate that the former is generally favoured over the latter during the cationic alkene cyclisation.[5] Our observations seem to point to a preference for forming five-membered rings, unless the carbocation formed is tertiary [*e.g.*, (**24**)]. In this context, the formation of the five-membered lactams (**13**) and (**14**) from (**4d**) is of particular interest, since it may involve the formation of the unstable primary carbocation (**26**) and not the secondary one (**28**). A similar ring-closure has been reported by Ben-Ishai who obtained the five-membered lactam (**30**) by treatment of α,α-bis(methoxycarbonylamino)acetamide (**29**) with methanesulphonic acid.[6] The reason for this abnormal behaviour is unclear, but it has been suggested that the carbonyl group incorporated into the ring system plays an important role.



(**29**) (**30**)

Scheme 5. *Reagents:* i, $MeSO_3H$

Another feature of this cyclisation reaction is the regiospecific formation of the double bond in the cyclised products (**8**)—(**10**). One possible explanation is that the lone pair electrons of the sulphur atom may take part in the proton abstraction of the cation (**25**) through a six-membered transition state.

The cyclisation of the chlorides (**5b**) and (**5d**) with $SnCl_4$ are similarly considered to proceed *via* the pathway involving the cationic species (**25**) (R^3 = H) and (**26**), although no evidence is available for the formation of the carbocations of type (**23**) in the presence of a Lewis acid. The thermal cyclisation of the chloride (**5b**) into the lactam (**8**) probably involves an *S*N2-like nucleophilic attack of the double bond on the carbon adjacent to the chlorine atom. In the case of the chloride (**5d**), such reaction does not occur because of low nucleophilicity of the alkene bond. The abundance of the chloride (**15**) as compared to the trifluoroacetate (**13**) may be ascribed to the difference in nucleophilicity of chloride and trifluoroacetate ions.

The formation of the seven-membered lactams (**17**), (**21**), and (**22**) from the *N*-but-3-enyl systems (**16**) and (**5e**) can be assumed to proceed *via* the carbocation (**31**). No product arising from the carbocation (**32**) was detected in the crude reaction mixture. This is in sharp contrast to the case of the *N*-prop-2-enyl systems (**12**) and (**5d**) where the unstable primary carbocation (**26**) is predominantly formed rather than the secondary one (**28**). The stability of the carbocation formed initially by ring closure is probably the dominant factor in the cyclisation of (**16**) and (**5e**). The high combined yields (81%) of the products (**18**), (**19**), and (**20**) from (**4f**) may be ascribed to the higher stability of the cationic intermediate (**33**).

(**31**) (**32**) (**33**)

Experimental

I.r. spectra were recorded with a JASCO-IRA-1 spectrophotometer, in $CHCl_3$. ^1H N.m.r. spectra were determined with a Hitachi R-22 (90 MHz) or JEOL JNM-PMX 60 (60 MHz) spectrometer in $CDCl_3$, and δ values quoted relative to tetramethylsilane. Exact mass determinations were obtained on a JEOL JMS-D-300 instrument operating at 70 eV. Chromatographic separation was performed with silica gel 60 (63—200 μm) (Merck).

General Procedure for the Preparation of N-*Alkenyl*-N-*methyl*-α-(*methylthio*)*acetamides* (**3a**—**f**).—To a solution of *N*-alkenyl-*N*-methylamine (**2a**—**f**) (30 mmol) and triethylamine (3.0 g, 30 mmol) in CCl_4 (30 ml), was added dropwise a solution of α-(methylthio)acetyl chloride[7] (3.75 g, 30 mmol) in CCl_4 (3 ml) at 0 °C and the mixture was stirred at room temperature for 30 min. Water (10 ml) was added to the reaction mixture and organic layer was separated. The aqueous layer was further extracted with CCl_4 and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated off and the residue was distilled under reduced pressure (for **3a**—**c**) or chromatographed on silica gel (ethyl acetate) (for **3d**—**f**) to give the *amides* (**3a**—**f**), whose yields and physical data are as follows.

N-*Methyl*-N-(2-*methylprop*-2-*enyl*)-α-(*methylthio*)*acetamide* (**3a**): (80%), b.p. 115—120 °C (bath temperature)/3 mmHg (Found: M^+, 173.0875. $C_8H_{15}NOS$ requires *M*, 173.0875); $\nu_{max.}$ 1 630 cm^{-1}; δ (60 MHz) 1.69 (3 H, br s), 2.21 (3 H, s), 2.93 and 2.99 (total 3 H, both s), 3.22 and 3.29 (total 2 H, both s), 3.8—4.0 (2 H, m), and 4.65—5.00 (2 H, m).

N-(*But*-2-*enyl*)-N-*methyl*-α-(*methylthio*)*acetamide* (**3b**): (83%), b.p. 140—150 °C (bath temperature)/11 mmHg (Found: M^+, 173.0880. $C_8H_{15}NOS$ requires *M*, 173.0875); $\nu_{max.}$ 1 630 cm^{-1}; δ (60 MHz) 1.55—1.80 (3 H, m), 2.20 (3 H, s), 2.90 and 2.99 (total 3 H, both s), 3.24 (2 H, s), 3.7—4.0 (2 H, m), and 5.1—5.8 (2 H m).

N-*Methyl*-N-(3-*methylbut*-2-*enyl*)-α-(*methylthio*)*acetamide* (**3c**): (85%), b.p. 130—140 °C (bath temperature)/3 mmHg (Found: M^+, 187.1030. $C_9H_{17}NOS$ requires *M*, 187.1030); $\nu_{max.}$ 1 630 cm^{-1}; δ (60 MHz) 1.71 (6 H, br s), 2.20 (3 H, s), 2.89 and 2.98 (total 3 H, both s), 3.24 (2 H, s), 3.7—4.1 (2 H, m), and 4.9—5.3 (1 H, m).

N-*Methyl*-N-*prop*-2-*enyl*-α-(*methylthio*)*acetamide* (**3d**): (94%), an oil (Found: M^+, 159.0717. $C_7H_{13}NOS$ requires *M*, 159.0717); $\nu_{max.}$ 1 630 cm^{-1}; δ (60 MHz) 2.20 (3 H, s), 2.92 and 3.00 (total 3 H, both s), 3.21 and 3.25 (total 2 H, both s), 3.85—

4.0 (2 H, m), 4.95—5.2 (2 H, m, CH=CH_2), and 5.4—5.9 (1 H, m, CH=CH$_2$).

N-*But*-3-*enyl*-N-*methyl*-α-(*methylthio*)*acetamide* (**3e**): (79%), an oil (Found: M^+, 173.0858. $C_8H_{15}NOS$ requires M, 173.0875); $\nu_{max.}$ 1 630 cm^{-1}; δ (60 MHz) 2.19 (3 H, s), 2.2—2.5 (2 H, m), 2.94 and 3.05 (total 3 H, both s), 3.2—3.6 (4 H, m), and 4.8—6.2 (3 H, m).

N-*Methyl*-N-(3-*methylbut*-3-*enyl*)-α-(*methylthio*)*acetamide* (**3f**): (83%), an oil (Found: M^+, 187.1001. $C_9H_{17}NOS$ requires M, 187.1028); $\nu_{max.}$ 1 630 cm^{-1}; δ (60 MHz) 1.78 (3 H, br s), 2.1—2.5 (2 H, m), 2.19 (3 H, s), 2.95 and 3.06 (total 3 H, both s), 3.2—3.7 (4 H, m), and 4.74 (2 H, br s).

General Procedure for the Preparation of N-*Alkenyl*-N-*methyl*-α-(*methylsulphinyl*)*acetamides* (**4a**—**f**).—A solution of sodium metaperiodate (4.50 g, 21 mmol) in water (50 ml) was added to a stirred solution of the sulphide (**3a**—**f**) (20 mmol) in methanol (50 ml) at 0 °C and stirring was continued at room temperature for 15 h. The precipitated salts were removed by filtration and the solvent was evaporated off. The residue was extracted with hot $CHCl_3$, the solvent was evaporated off, and the residue was chromatographed on silica gel (acetone) to give the *sulphoxides* (**4a**—**f**), whose yields and physical data are as follows.

N-*Methyl*-N-(2-*methylprop*-2-*enyl*)-α-(*methylsulphinyl*)*acetamide* (**4a**): (72%), an oil (Found: C, 50.5; H, 7.9; N, 7.1. $C_8H_{15}NO_2S$ requires C, 50.8; H, 8.0; N, 7.4%); $\nu_{max.}$ 1 630 (C=O) and 1 025 cm^{-1} (S=O); δ (60 MHz) 1.71 (3 H, br s), 2.76 (3 H, s), 2.96 and 3.03 (total 3 H, both s), 3.65—4.10 (4 H, m), and 4.6—5.0 (2 H, m).

N-*But*-2-*enyl*-N-*methyl*-α-(*methylsulphinyl*)*acetamide* (**4b**): (82%), an oil (Found: C, 50.5; H, 8.1; N, 7.6. $C_8H_{15}NO_2S$ requires C, 50.8; H, 8.0; N, 7.4%); $\nu_{max.}$ 1 635 (C=O) and 1 035 (S=O) cm^{-1}; δ (60 MHz) 1.60—1.85 (3 H, m), 2.77 (3 H, s), 2.94 and 3.02 (total 3 H, both s), 3.7—4.2 (4 H, m), and 5.1—5.8 (2 H, m).

N-*Methyl*-N-(3-*methylbut*-2-*enyl*)-α-(*methylsulphinyl*)*acetamide* (**4c**): (84%), an oil (Found: C, 53.1; H, 8.6; N, 6.9. $C_9H_{17}NO_2S$ requires C, 53.2; H, 8.4; N, 6.9%); $\nu_{max.}$ 1 635 (C=O) and 1 035 cm^{-1} (S=O); δ (60 MHz) 1.73 (6 H, br s), 2.77 (3 H, s), 2.92 and 3.02 (total 3 H, both s), 3.7—4.1 (2 H, m), 3.83 (2 H, s), and 4.9—5.3 (1 H, m).

N-*Methyl*-N-*prop*-2-*enyl*-α-(*methylsulphinyl*)*acetamide* (**4d**): (82%), an oil (Found: C, 47.4; H, 7.6; N, 7.85. $C_7H_{13}NO_2S$ requires C, 48.0; H, 7.5; N, 8.0%); $\nu_{max.}$ 1 635 (C=O) and 1 035 cm^{-1} (S=O); δ (60 MHz) 2.75 (3 H, s), 2.95 and 3.02 (total 3 H, both s), 3.73 and 3.80 (total 2 H, both s), 3.85—4.0 (2 H, m), 4.95—5.2 (2 H, m, CH=CH_2), and 5.4—5.9 (1 H, m, CH=CH$_2$).

N-*But*-3-*enyl*-N-*methyl*-α-(*methylsulphinyl*)*acetamide* (**4e**): (81%), an oil (Found: M^+, 189.0798. $C_8H_{15}NO_2S$ requires M, 189.0821); $\nu_{max.}$ 1 630 (C=O) and 1 035 cm^{-1} (S=O); δ (60 MHz) 2.1—2.6 (2 H, m), 2.76 (3 H, s), 2.96 and 3.03 (total 3 H, both s), 3.47 (2 H, t, J 7 Hz), 3.85 (2 H, s), and 4.8—6.1 (3 H, m).

N-*Methyl*-N-(3-*methylbut*-3-*enyl*)-α-(*methylsulphinyl*)*acetamide* (**4f**): (79%), an oil (Found: M^+, 203.0969. $C_9H_{17}NO_2S$ requires M, 203.0977); $\nu_{max.}$ 1 630 (C=O) and 1 035 cm^{-1} (S=O); δ (60 MHz) 1.77 (3 H, br s), 2.0—2.5 (2 H, m), 2.76 (3 H, s), 2.96 and 3.08 (total 3 H, both s), 3.3—3.7 (2 H, m), 3.86 (2 H, br s), and 4.75 (2 H, br s).

Cyclisation of the Sulphoxide (**4a**).—Trifluoroacetic anhydride (630 mg, 3.00 mmol) was added to a solution of (**4a**) (566 mg, 2.99 mmol) in CH_2Cl_2 (3 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation and the residue was chromatographed on silica gel [benzene–ethyl acetate (1:1)]. The first eluate gave 3,4-*dihydro*-1,5-*dimethyl*-3-*methylthiopyridin*-2(1H)-*one* (**6**) (179 mg, 35%) as an oil (Found: C, 56.0; H, 7.8; N, 8.15. $C_8H_{15}NOS$ requires C, 56.1; H, 7.65; N, 8.2%); $\nu_{max.}$ 1 640 cm^{-1} (C=O); δ (90 MHz) 1.73 (3 H, br s, CMe), 2.18 (1 H, dd, J 17 and 3 Hz, 4-H), 2.19 (3 H, s, SMe), 2.6—3.0 (1 H, m, 4-H), 3.01 (3 H, s, NMe), 3.29 (1 H, dd, J 6 and 3 Hz, 3-H), and 5.65—5.8 (1 H, m, 6-H). The second eluate gave 1-*methyl*-5-*methylene*-3-*methylthiopiperidin*-2-*one* (**7**) (242 mg, 43%) as an oil (Found: C, 55.9; H, 7.7; N, 8.1. $C_8H_{13}NOS$ requires C, 56.1; H, 7.65; N, 8.2%); $\nu_{max.}$ 1 630 cm^{-1} (C=O); δ (90 MHz) 2.27 (3 H, s, SMe), 2.58 (1 H, dd, J 14 and 4 Hz, 4-H), 2.8—3.1 (1 H, m, 4-H), 2.95 (3 H, s, NMe), 3.37 (1 H, t, J 4 Hz, 3-H), 3.96 (2 H, br s, 6-H), and 4.98 (2 H, br s, C=CH$_2$).

Cyclisation of the Sulphoxide (**4b**).—Trifluoroacetic anhydride (416 mg, 1.98 mmol) was added to a solution of (**4b**) (370 mg, 1.96 mmol) in CH_2Cl_2 (2 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation and the residue was chromatographed on silica gel (ethyl acetate) to give 4-*vinyl*-1-*methyl*-3-*methylthiopyrrolidin*-2(1H)-*one* (**8**) (310 mg, 92%), as an oil (Found: C, 55.9; H, 7.8; N, 8.0. $C_8H_{12}NOS$ requires C, 56.1; H, 7.65; N, 8.2%); $\nu_{max.}$ 1 680 (C=O) and 920 cm^{-1} (C=C); δ (90 MHz) 2.25 (3 H, s, SMe), 2.5—3.7 (4 H, m, 3-, 4-, and 5-H), 2.89 (3 H, s, NMe), 4.9—5.3 (2 H, m, CH=CH_2), and 5.6—6.1 (1 H, m, CH=CH$_2$). G.l.c. analysis [SCOT glass capillary column (50 ml) coated with Dexsil-300GC; 190 °C] of this product showed it to be a mixture of two isomers in a ratio of 69:31 (R_t 761 and 813 s, respectively).

Treatment of Compound (**8**) *with Base*.—The lactam (**8**) (173 mg, 1 mmol) was added to a solution of sodium ethoxide in ethanol, prepared from sodium (30 mg, 1.3 mmol) and ethanol (2 ml), and the mixture was heated under reflux for 15 min. The reaction mixture was poured into water (10 ml) and extracted with $CHCl_3$, then dried ($MgSO_4$). The solvent was removed by evaporation and the residue was subjected to g.l.c. analysis (on the same column as described above), which showed the product to be a mixture of two isomers in a ratio of 86:14 (R_t 755 and 812 s, respectively). This ratio of the products thus obtained remained unchanged even when treated with trifluoroacetic acid at room temperature.

Cyclisation of the Sulphoxide (**4c**).—Trifluoroacetic anhydride (550 mg, 2.62 mmol) was added to a solution of (**4c**) (521 mg, 2.57 mmol) in CH_2Cl_2 (3 ml) and the mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation and the residue was chromatographed on silica gel (diethyl ether) to give a mixture of three products (**9**), (**10**), and (**11**) (443 mg): $\nu_{max.}$ 1 780 [OCOCF$_3$ for (**11**)] and 1 675 cm^{-1} (CONMe); δ (90 MHz) (diagnostic data only) 1.65 [s, CMe$_2$ for (**11**) (*ca.* 20%)], 1.78 [s, C=CMe for (**9**) (*ca.* 40%)], and 1.82 [s, C=CMe for (**10**) (*ca.* 40%)]; m/z 299 [for (**11**) ($C_{11}H_{16}F_3NO_3S$)] and 185 [for (**9**) and (**10**) ($C_9H_{15}NOS$)]. This mixture was then added to hydrochloric acid (2%; 2 ml) and the mixture was heated at 70—80 °C for 30 min. The reaction mixture was neutralized with dilute aqueous MeOH and extracted with $CHCl_3$, then dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (diethyl ether). The first eluate gave trans-4-*isopropenyl*-1-*methyl*-3-*methylthiopyrrolidin*-2-*one* (**9**) (40 mg, 8%) as an oil (Found: M^+, 185.0866. $C_9H_{15}NOS$ requires M, 185.0872); $\nu_{max.}$ 1 675 cm^{-1} (C=O); δ (90 MHz) 1.77 (3 H, br s, CMe), 2.26 (3 H, s, SMe), 2.89 (3 H, s, SMe), 3.0—3.3 (2 H, m, 4-H and one of 5-H), 3.27 (1 H, d, J 6.5 Hz, 3-H), 3.51 (1 H, dd, J 9.5 and 8.5 Hz, one of 5-H), and 4.89 (2 H, br s, C=CH$_2$). The second eluate gave a mixture (247 mg, 52%) of the lactam (**9**) and cis-4-*isopropenyl*-1-methyl-3-*methylthiopyrrolidin*-2-*one* (**10**). The third eluate gave the *lactam* (**10**) (32 mg, 7%) as an oil (Found: M^+, 185.0866. $C_9H_{15}NOS$ requires M, 185.0872); $\nu_{max.}$ 1 675 cm^{-1} (C=O); δ (90 MHz) 1.82 (3 H, br s, CMe), 2.25 (3 H, s, SMe), 2.91 (3 H, s,

NMe), 3.0—3.7 (4 H, m, 3-, 4-, and 5-H), and 4.76 and 4.98 (1 H each, both br s, C=CH_2).

Attempted Epimerisation of Compounds (**9**) *and* (**10**).—The lactam (**10**) (25 mg, 0.14 mmol) was added to a solution of sodium ethoxide in ethanol [prepared from sodium (3.5 mg, 0.15 mmol) and ethanol (1 ml)], and the mixture was heated under reflux for 10 min. The reaction mixture was poured into water (10 ml) and extracted with $CHCl_3$, then dried ($MgSO_4$). The solvent was removed by evaporation to give the lactam (**9**) (22 mg, 88%) which was identical (by t.l.c. and ^1H n.m.r. spectroscopy) with that obtained by cyclisation of the sulphoxide (**4c**). Similar treatment of the lactam (**9**) with sodium ethoxide recovered only the starting material.

Cyclisation of the Sulphoxide (**4d**).—Trifluoroacetic anhydride (416 mg, 1.98 mmol) was added to a solution of (**4d**) (307 mg, 1.93 mmol) in CH_2Cl_2 (2 ml) at 0 °C. The mixture was stirred at room temperature for 1 h and the solvent was removed by evaporation. The i.r. and n.m.r. spectra showed that the residue consisted mainly of the Pummerer rearrangement product (**12**); $\nu_{max.}$ 1 780 ($OCOCF_3$) and 1 630 cm^{-1} (CONMe); δ (60 MHz) 2.27 (3 H, s, SMe), 3.04 and 3.14 (total 3 H, both s, NMe), 3.9—4.3 (2 H, m, NCH_2), 5.0—6.2 (3 H, m, CH=CH_2), and 6.34 (1 H, s, SCH). Trifluoroacetic acid (2 ml) was added to the residue and the mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation and the residue was chromatographed on silica gel (ethyl acetate). The first eluate gave 4-*trifluoroacetoxymethyl*-1-*methyl*-3-*methylthiopyrrolidin*-2-*one* (**13**) (44 mg, 9%) as an oil (Found: M^+, 271.0490. $C_9H_{12}F_3NO_3S$ requires M, 271.0489); $\nu_{max.}$ 1 785 ($OCOCF_3$) and 1 685 cm^{-1} (CONMe); δ (90 MHz) 2.25 (3 H, s, SMe), 2.89 (3 H, s, NMe), 2.6—3.9 (4 H, m, 3-, 4-, and 5-H), and 4.47 (2 H, d, J 6 Hz, OCH_2). The second eluate gave 1,4-*dimethyl*-3-*methylthio*-5H-*pyrrol*-2(1H)-*one* (**14**) (107 mg, 39%) as an oil (Found: C, 53.0; H, 7.1; N, 8.8. $C_7H_{11}NOS$ requires C, 53.5; H, 7.05; N, 8.9%); $\nu_{max.}$ 1 655 cm^{-1} (C=O); δ (90 MHz) 2.10 (3 H, s, CMe), 2.42 (3 H, s, SMe), 3.02 (3 H, s, NMe), and 3.82 (2 H, s, 4-H). The trifluoroacetate (**13**) was not converted into the lactam (**14**) when treated with trifluoroacetic acid at room temperature.

Cyclisation of the Chloride (**5b**).—(*a*) With $SnCl_4$. *N*-Chlorosuccinimide (NCS) (170 mg, 1.27 mmol) was added by portions to a stirred solution of the sulphide (**3b**) (201 mg, 1.16 mmol) in CCl_4 (5 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. The precipitated succinimide was filtered off and the filtrate was concentrated to give in almost quantitative yield, the *chloride* (**5b**) (Found: M^+, 207.0468. $C_8H_{14}ClNOS$ requires M, 207.0483); $\nu_{max.}$ 1 655 cm^{-1} (C=O); δ (60 MHz) 1.65—1.85 (3 H, m), 2.30 (3 H, s), 2.90 and 3.03 (total 3 H, both s), 3.8—4.0 (2 H, m), and 5.3—5.7 (3 H, m). This chloride (**5b**), without purification, was dissolved in CH_2Cl_2 (5 ml), and $SnCl_4$ (331 mg, 1.27 mmol) was added to the solution at 0 °C. The mixture was then stirred at room temperature for 1 h when it was quenched with water (10 ml) extracted with CH_2Cl_2, and the organic extract was dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate) to give the lactam (**8**) (140 mg, 70%) which was identical with that obtained by cyclisation of compound (**4b**).

(*b*) *With silica gel.* Using the same procedure as described above, the chloride (**5b**) was prepared from the sulphide (**3b**) (320 mg, 1.85 mmol) and NCS (272 mg, 2.00 mmol), and the crude chloride (**5b**) was dissolved in CCl_4 (10 ml). Silica gel (Merck 60 PF_{254}) (1 g) was added to the solution of (**5b**) and the mixture was stirred vigorously at room temperature for 10 h. Silica gel was filtered off, the solvent was evaporated off, and the residue was chromatographed on silica gel (ethyl acetate) to give the lactam (**8**) (165 mg, 52%).

(*c*) *By Heating.*—The chloride (**5b**), prepared from the sulphide (**3b**) (361 mg, 2.09 mmol) and NCS (307 mg, 2.3 mmol), was heated without solvent at 130 °C for 1 h and the reaction mixture was chromatographed on silica gel (ethyl acetate) to give the lactam (**8**) (194 mg, 55%).

Cyclisation of the Chloride (**5d**).—Using the same procedure as that described for the preparation of (**5b**) from (**3b**), the chloride (**5d**) was prepared from (**3d**) (278 mg, 1.75 mmol) and NCS (257 mg, 1.9 mmol). $SnCl_4$ (456 mg, 1.75 mmol) was added to a solution of the crude chloride (**5d**) in CH_2Cl_2 (5 ml) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water (10 ml) and the mixture was extracted with CH_2Cl_2, then dried ($MgSO_4$). The solvent was removed by evaporation and the residue was chromatographed on silica gel (ethyl acetate). The first eluate gave 4-*chloromethyl*-1-*methyl*-3-*methylthiopyrrolidin*-2-*one* (**15**) (143 mg, 42%) as an oil (Found: C, 43.5; H, 6.3; N, 7.1. $C_7H_{12}ClNOS$ requires C, 43.4; H, 6.25; N, 7.2%); $\nu_{max.}$ 1 685 cm^{-1} (C=O); δ (90 MHz) 2.25 (3 H, s, NMe), 2.4—2.7 (1 H, m, 4-H), 2.88 (3 H, s, NMe), 3.1—3.3 (2 H, m, CH_2Cl), 3.47 (1 H, d, J 8 Hz, 3-H), and 3.5—3.7 (2 H, m, 5-H). The second eluate gave the lactam (**14**) (48 mg, 18%) which was identical with that obtained by cyclisation of the sulphoxide (**4d**).

Cyclisation of the Sulphoxide (**4e**).—Trifluoroacetic anhydride (561 mg, 2.67 mmol) was added to a solution of (**4e**) (506 mg, 2.67 mmol) in CH_2Cl_2 (5 ml) at 0 °C and the mixture was stirred at the same temperature for 2 h. The solvent was removed by evaporation, and to the residue containing the trifluoroacetate (**16**) [δ 6.27 (1 H, s, SCH)] was added trifluoroacetic acid (1 ml), after which the mixture was stirred at room temperature for 1.5 h. $CHCl_3$ (10 ml) was added to the reaction mixture which was then washed successively with saturated aqueous $NaHCO_3$ and brine, before being dried ($MgSO_4$). The solvent was evaporated off and the residue was recrystallised to give 1-*methyl*-3-*methylthio*-5-*trifluoroacetoxyazepan*-2-*one* (**17**) (94 mg, 12%), m.p. 116—117.5 °C (from hexane–benzene) (Found: C, 42.1; H, 4.9; N, 5.0. $C_{10}H_{14}F_3NO_3S$ requires C, 42.1; H, 5.0; N, 4.9%); $\nu_{max.}$ 1 780 ($OCOCF_3$) and 1 640 cm^{-1} (CONMe); δ (90 MHz) 1.6—2.6 (4 H, m, 4- and 6-H), 2.14 (3 H, s, SMe), 3.04 (3 H, s, NMe), 3.39 (1 H, ddd, J 16, 8, and 3 Hz, 7-H), 3.64 (1 H, dd, J 9 and 3 Hz, 3-H), 3.78 (1 H, ddd, J 16, 8, and 3 Hz, 7-H), and 5.18 (1 H, d t, J 8 and 4 Hz, 5-H).

Cyclisation of the Sulphoxide (**4f**).—Trifluoroacetic anhydride (210 mg, 1 mmol) was added to a solution of compound (**4f**) (203 mg, 1 mmol) in CH_2Cl_2 (2 ml) at 0 °C and the mixture was stirred at room temperature for 1 h. Dichloromethane (10 ml) was added to the reaction mixture which was then washed successively with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel [benzene–ethyl acetate (1:1)]. The first eluate gave 1,5-*dimethyl*-3-*methylthio*-6,7-*dihydro*-1H-*azepin*-2(3H)-*one* (**18**) (11 mg, 6%) as an oil (Found: C, 58.4; H, 8.2; N, 7.55. $C_9H_{15}NOS$ requires C, 58.4; H, 8.1; N, 7.6%); $\nu_{max.}$ 1 635 cm^{-1} (C=O); δ (90 MHz) 1.75 (3 H, br s, CMe), 2.05—2.55 (2 H, m, 6-H), 2.22 (3 H, s, SMe), 2.95—3.45 (1 H, m, 7-H), 3.02 (3 H, s, SMe), 4.00 (1 H, br d, J 8 Hz, 3-H), 4.48 (1 H, ddd J 14.5, 10, and 4 Hz, 7-H), and 5.45 (1 H, br d, J 8 Hz, 4-H). The second eluate gave 1-*methyl*-5-*methylene*-3-*methylthioazepan*-2-*one* (**19**) (52 mg, 28%) as an oil (Found: M^+, 185.0865. $C_9H_{15}NOS$ requires M, 185.0872); $\nu_{max.}$ 1 630 (C=O) and 925 cm^{-1} (C=CH_2); δ (90 MHz) 2.17 (3 H, s, SMe), 2.2—2.9 (4 H, m, 4- and 6-H), 3.03 (3 H, s, NMe), 3.1—4.2 (3 H, m, 3- and 7-H), and 4.85 (2 H, s, C=CH_2). The third eluate gave 1,5-*dimethyl*-5-*trifluoroacetoxyazepan*-2-*one* (**20**) (141 mg, 47%),

m.p. 111—112 °C (from hexane–benzene) (Found: C, 44.3; H, 5.4; N, 4.7. $C_{11}H_{16}F_3NO_3S$ requires C, 44.15; H, 5.35; N, 4.7%); $\nu_{max.}$ 1 780 ($OCOCF_3$) and 1 650 cm^{-1} (CONMe); δ (90 MHz) 1.70 (3 H, s, CMe), 1.8—2.8 (4 H, m, 4- and 6-H), 2.08 (3 H, s, SMe), 3.02 (3 H, s, NMe), 3.13 (1 H, ddd, *J* 16, 6, and 3 Hz, 7-H), and 3.6—4.1 (2 H, m, 3- and 7-H).

Cyclisation of the Chloride (**5e**).—*N*-Chlorosuccinimide (238 mg, 1.7 mmol) was added to a solution of (**3e**) (308 mg, 1.7 mmol) in CCl_4 (11 ml) at 0 °C and the mixture was stirred at room temperature for 2 h. The precipitated succinimide was filtered off and $SnCl_4$ (443 mg, 1.7 mmol) was added to the filtrate containing the chloride (**5e**) at 0 °C. The mixture was stirred at room temperature for 1 h and the reaction was quenched with water (10 ml). The organic layer was separated and the aqueous layer was further extracted with CCl_4. The combined organic layers were dried ($MgSO_4$), the solvent was evaporated off, and the residue was chromatographed on silica gel [ethyl acetate–benzene (3:1)]. The first eluate gave 1-*methyl*-3-*methylthio*-6,7-*dihydro*-1H-*azepin*-2(3H)-*one* (**21**) (23 mg, 8%) as an oil (Found: M^+, 171.0725. $C_8H_{13}NOS$ requires *M*, 171.0718); $\nu_{max.}$ 1 635 cm^{-1} (C=O); δ (90 MHz) 2.0—2.5 (2 H, m, 6-H), 2.25 (3 H, s, SMe), 3.05 (3 H, s, NMe), 3.1—3.5 (1 H, m, 7-H), 3.99 (1 H, d, *J* 6 Hz, 3-H), 4.44 (1 H, ddd, *J* 14, 10, and 4 Hz, 7-H), and 5.6—5.8 (2 H, m, 4- and 5-H). The second eluate gave 5-*chloro*-1-*methyl*-3-*methylthioazepan*-2-*one* (**22**) (127 mg, 36%), m.p. 135.5—137 °C (Found: C, 46.4; H, 7.0; N, 6.7. $C_8H_{14}ClNOS$ requires C, 46.25; H, 6.8; N, 6.7%); $\nu_{max.}$ 1 640 cm^{-1} (C=O); δ (90 MHz) 1.7—2.7 (4 H, m, 4- and 6-H), 2.16 (3 H, s, SMe), 3.04 (3 H, s, NMe), 3.3—3.7 (3 H, m, 3-, 5-, and 7-H), and 4.09 (1 H, ddd *J* 14, 10, and 4 Hz, 7-H).

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