Tetrahedron Vol. 44, No. 10, pp. 3025 to 3036, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00
Pergamon Press plc

SYNTHESES OF ALKYL (E)-(1-ARYL-2-PYRROLIDINYLIDENE)ACETATES

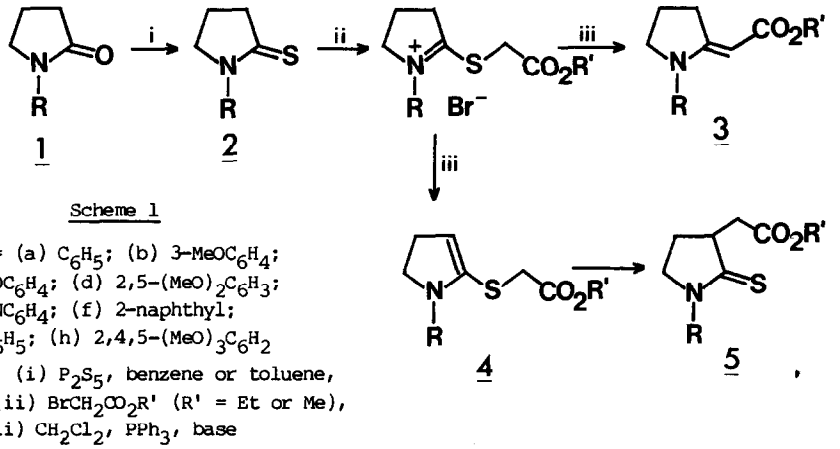
Joseph P. Michael,* Gladys D. Hosken and Arthur S. Howard

Department of Chemistry, University of the Witwatersrand,
Wits 2050, South Africa

(*Received in UK* 9 *March* 1988)

Two methods for the synthesis of the title compounds [3] are presented. The first, and less satisfactory, method uses the sulphide contraction, which involves salt formation between alkyl bromoacetates and N-aryl-pyrrolidine-2-thiones [2] followed by sulphur extrusion. By-products include N-arylpyrrolidin-2-ones [1] and 3-alkoxycarbonylmethylpyrrolidine-2-thiones [5]. A better route is by way of condensation between ethyl 6-chloro-3-oxohexanoate [6] and substituted anilines, followed by intramolecular cyclisation. An unusual Reformatsky reaction with methyl bromoacetate and 1-phenylpyrrolidine-2-thione [2a] is also reported.

The 3-carboxylic acids of certain 4-quinolinones and a number of their aza analogues are assuming increasing importance as antibacterial agents[1]. For some model studies relating to the synthesis of 4-quinolinone antibiotics, we needed a convenient, general preparation of alkyl (1-aryl-2-pyrrolidinylidene)acetates [3]. The Eschenmoser sulphide contraction sequence[2], in which exocyclic enamines (vinylogous urethanes) of this sort are prepared by extruding sulphur from the salts derived by S-alkylation of thiolactams with alkyl α-haloacetates, was an obvious route to investigate. This route was particularly attractive because we[3] (and others[4]) had previously used it with success to prepare vinylogous urethanes as intermediates for alkaloid synthesis. The presence of the N-aryl group is, however, a novel feature in the sulphide contraction, since relevant documented examples deal with thiolactams bearing hydrogen or alkyl groups on nitrogen. The reaction sequence envisaged is outlined in Scheme 1.



Scheme 1

Series: R = (a) C_6H_5; (b) 3-$MeOC_6H_4$; (c) 4-$MeOC_6H_4$; (d) 2,5-$(MeO)_2C_6H_3$; (e) 4-$O_2NC_6H_4$; (f) 2-naphthyl; (g) $CH_2C_6H_5$; (h) 2,4,5-$(MeO)_3C_6H_2$

Conditions: (i) P_2S_5, benzene or toluene, reflux; (ii) $BrCH_2CO_2R'$ (R' = Et or Me), 50°C; (iii) CH_2Cl_2, PPh_3, base

The thiolactams [2] needed as precursors were obtained in good yield (73 - 96%) from the corresponding lactams [1] and phosphorus pentasulphide in boiling benzene or toluene. The lactams [1] were in turn made by slightly modifying a published method[5] involving reaction between butyrolactone and the appropriate aniline. Most of the thiolactams prepared are new compounds, though several of them have previously been reported in the patent literature[6].

To our dismay, the sulphide contraction of N-arylthiolactams [2] with ethyl (or methyl) bromoacetate did not proceed at all well. We had expected that mesomeric interaction between the thioamide group and the N-aryl substituent would diminish the nucleophilicity of sulphur in the salt-formation step. The extent of the effect, however, surprised us; the only N-aryl thiolactam to form a salt satisfactorily at room temperature was [2a]. Other workers have overcome the problem of poor nucleophilicity of thiocarbonyl compounds by using special reaction conditions[7] or more reactive alkylating agents[8]. We did not examine these options because we found that salt formation between the reactants, though very slow, could be forced essentially to completion (as judged by TLC) if left for prolonged periods at 50°C, and preferably in the absence of solvent.

The problems encountered during the extrusion step of the sulphide contraction were of greater consequence. Sequential treatment of the unpurified salts in dichloromethane first with triphenylphosphine and then with a tertiary amine gave the desired vinylogous urethanes [3], but mostly in poor yields (Table 1). The distribution of products appeared to be variable. The major by-product was the lactam [1], but this was frequently accompanied by the 3-alkylated thiolactam [5]. Rapoport's explanation[4c,8b] for similar findings (deprotonation at an alternative acidic position, C-3 of the ring, to give a ketene-S,N-acetal [4] which may either be involved in transalkylation, or undergo hydrolysis during workup) seems appropriate in the present case as well. The question of alternative sites for deprotonation and the equilibrium distribution of products in the sulphide contraction has recently been discussed by Hart[4e], who has optimised

Table 1. Sulphide contraction with N-aryl thiolactams

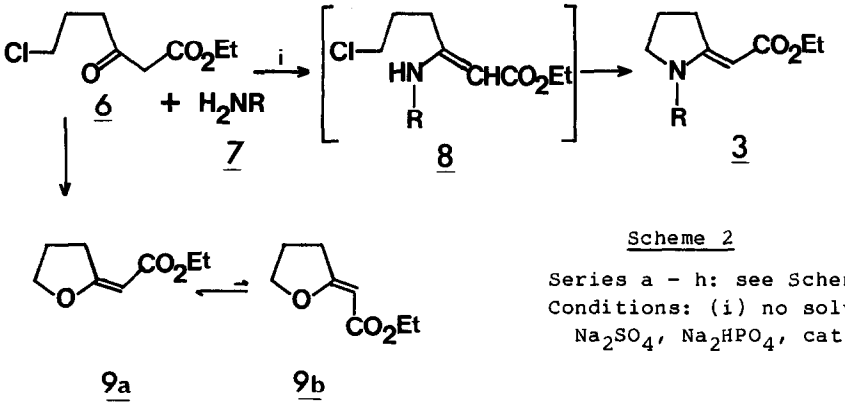
Entry	Thiolactam	R'	Conditions for salt formation	Base used in contraction[a]	Products[b]
1	2a	Me	Acetone, rt, 24 h	$(iPr)_2NEt$	1a 42%; 3a 11%; 5a 15%
2	2a	Me	Acetone/NaI; remove solvent; rt, 19 h	$(iPr)_2NEt$	1a 40%; 3a 33%
3	2a	Me	Acetone/NaI, rt, 4 h	NEt_3	1a 46%; 3a 8%
4	2a	Me	CH_2Cl_2, rt, 80 min	NEt_3	1a 26%; 3a (c); 5a 31%
5	2a	Me	CH_2Cl_2, rt, 25 h	DABCO[d]	1a 62%; 3a 5%;[e] 5a 14%[e]
6	2b	Et	50°C/ 92 h	NEt_3	1b 47%; 3b 37%; 5b <3%
7	2c	Me	50°C/189 h	NEt_3	1c 33%; 3c 26%; 5c 10%
8	2d	Me	50°C/ 74 h	NEt_3	3d 65%
9	2e	Me	50°C/ 78 h	NEt_3	1e 52%; (Z)-3e 17%
10	2f	Et	50°C/ 24 h	NEt_3	1f 84%; 3f 14%[e]
11	2g	Et	rt / 19 h	NEt_3	3g 73%

(a) In CH_2Cl_2 with PPh_3 at room temperature; (b) Yields refer to isolated, chromatographically pure products. In most cases, fractions containing mixtures of products were also obtained; (c) Contaminated with substantial quantities of [1a] and [5a, R'=Me]; (d) In boiling chloroform; (e) Determined by NMR

conditions for sulphide contraction (refluxing chloroform, triphenylphosphine, diazabicyclo[2.2.2]octane as base) with quinolizidine-4-thiones. In a solitary attempt under these conditions (Table 1, entry 5), we found no improvement. The disappointing results described above do appear to be associated with the N-aryl substituent, since salt formation between ethyl bromoacetate and N-benzylthiolactam [2g], and the subsequent extrusion of sulphur, proceed smoothly under the normal conditions to produce [3g] in 73% yield.

The structure and stereochemistry of the alkyl (E)-(1-aryl-2-pyrrolidinylidene)acetates [3] described in this work were established mainly by proton and ^{13}C-NMR spectroscopy. The assignment of (E) geometry - and more specifically, of trans-s-cis structures - to the compounds is on the basis of the chemical shifts of the signals for the methylene protons at C-3 of the heterocyclic ring (δ approximately 3.3; cf. δ 2.7 for cis-s-cis structures[2]), a phenomenon whose origins and implications we have previously discussed[3]. The only exception seems to be the p-nitro compound [3e] (a compound that we were in any case unable to characterise entirely satisfactorily owing to its easy decomposition to lactam [1e]), for which the signal appears at δ 2.7.

In view of the unsatisfactory yields of [3] from the sulphide contraction, we sought alternative methods for the synthesis of N-aryl vinylogous urethanes. Carrié and co-workers[9] have recently prepared vinylogous urethanes similar to [3], but unsubstituted on nitrogen, by treating ethyl 6-chloro-3-oxohexanoate [6] with azide ion followed by cyclisation involving an aza-Wittig reaction. We felt that treatment of the same chloro-ester with substituted anilines [7] might lead to an acceptable alternative synthesis of [3] (Scheme 2). The sequence of events (condensation of the amine with the keto group followed by nucleophilic displacement of chloride, or vice versa) was not of great concern, although we suspected that the former was more likely in view of the easy condensation of anilines with β-ketoesters (such as occurs, for example, in the first step of the Conrad-Limpach synthesis of 4-quinolinones[10]). It has been reported[11] that condensation of anilines at the keto group of β-ketoesters is promoted by molecular iodine. We accordingly devised a procedure in which reactants [6] and [7] were heated at 65°C in the presence of a trace of iodine as catalyst, a drying agent (Na_2SO_4), and a base (Na_2HPO_4) to facilitate the elimination of hydrochloric acid.



Scheme 2

Series a - h: see Scheme 1
Conditions: (i) no solvent, Na_2SO_4, Na_2HPO_4, cat I_2

Table 2. Reaction of ethyl 6-chloro-3-oxohexanoate [6] with amines

Entry	Amine	Conditions[a]	Products[b]	Yields by S-contraction[c]
1	7a	i, 65°C, 66 h	3a 52%	3a 33%
2	7b	i, 65°C, 96 h	3b 41%	3b 37%
3	7c	i, 65°C, 40 h	3c 65%	3c 26%
4	7d	i, 65°C, 96 h	3d 62%	3d 65%
5	7e	i, 65°C, 18 days	3e 0%	3e 17%
6	7f	i, 65°C, 96 h	3f 80%	3f 14%
7	7g	i, 65°C, 96 h	3g 46%	3g 73%
8	7h	i, 65°C, 96 h	3h 54%; 8h 4%	
9	7c	ii	(d)	
10	7c	iii	3c 20%; 9a 7% + mixtures	
11	7c	iv	3c 12%; 9b 47%	

(a) Conditions i: no solvent, I_2 (cat), Na_2SO_4, Na_2HPO_4; ii, as for i, without Na_2HPO_4, 42°C/7 h, then rt/55 h; iii, I_2 (cat), Na_2SO_4, K_2CO_3, 70°C/10 h, then rt/60 h; iv, NaI/ acetone, then benzene/NEt_3, reflux, 11.5 h; (b) In most cases, [6], [7], [8] and [9] were detected by ^{1}H-NMR spectroscopy & TLC, but could not be separated cleanly; (c) From Table 1; (d) 2:1 mixture of [3c] and [8c] obtained; latter cyclises to former (effective yield 52%) on heating

Inspection of the results, which are summarised in Table 2, shows that, for the N-aryl cases, the yields of the vinylogous urethanes are generally better than those obtained by the sulphide contraction. The method thus does constitute a useful alternative to the synthesis of N-aryl vinylogous urethanes. The failure with p-nitroaniline is not surprising, since iodine-catalysed condensation of nitroanilines with ethyl acetoacetate is known to be unsuccessful[11]. The desired products [3] were always accompanied by several by-products, which could seldom be obtained pure. The identities of these by-products were tentatively assigned from certain diagnostic signals in the ^{1}H-NMR spectra of mixtures containing them. In most cases there was evidence for the presence of the acyclic vinylogous urethanes [8] and for the products of the intramolecular cyclisation of chloro-ester [6], compounds [9a] and [9b]. In one case (Table 2, entry 9), we intercepted a substantial quantity of [8c] by lowering the reaction temperature and omitting the base. Conversion to [3c] was achieved simply by heating [8c] in in acetonitrile. Only once - for [8h] - could the acyclic intermediate be isolated in a relatively pure state; even so, it rapidly cyclised to [3h] just on standing. Detection of these acyclic vinylogous urethanes [8] provides support for the pathway depicted in Scheme 2 rather than the alternative displacement of halide followed by condensation with the carbonyl group. In all these reactions, incidentally, there is no evidence for cyclisation occurring through the nucleophilic carbon atom of [8] rather than through nitrogen.

Pure samples of [9a] and [9b] were obtained from reactions performed under modified conditions. Thus, conversion of chloride to a better leaving group was accomplished by treating [6] with sodium iodide in acetone; intramolecular cyclisation was promoted, and the Z isomer [9b] was isolated in 47% yield (Table 2, entry 11). On standing in solution, [9b] isomerised to [9a], which was also isolated from a reaction performed at 70°C with potassium carbonate as base (Table 2, entry 10). Confirmation of the identities of [9a] and [9b] by ^{1}H-NMR spectroscopy was unexceptional in the light of data published for them by Carrié and co-workers[9].

One final group of experiments deserves mention. It is known that carbonyl groups in imides can undergo alkylidenation by the Reformatsky reaction[12]; but similar reactions on amides and lactams, not to mention their thiocarbonyl analogues, appear to be unrecorded. It was therefore of considerable interest to discover that heating a solution of 1-phenylpyrrolidine-2-thione [2a] in THF with the reagent prepared from a zinc-copper couple[13] and methyl bromoacetate gave a 47% isolated yield of vinylogous urethane [3a, R'=Me], together with 1-phenylpyrrolidin-2-one [1a] (43%). It is not yet clear whether this represents a genuine Reformatsky reaction or merely a peculiar variation of the sulphide contraction, since the pre-formed salt from [3a] and methyl bromoacetate also gave [3a, R'=Me] (26%) and [1a] (59%) when sonicated in the presence of zinc-copper couple; without sonication, only the lactam [1a] (84%) was obtained. From the p-methoxy and p-nitro thiolactams [2c] and [2e], however, only the corresponding lactams [1c] and [1e] were isolated after treatment with the organozinc species.

EXPERIMENTAL

Melting points are uncorrected. All solvents were distilled before use. Column chromatography was on Merck Kieselgel 60 (particle size 0.063 - 0.200 mm). The R_F values quoted are for thin-layer chromatography (TLC) on pre-coated silica gel plates (Merck F254). IR spectra were recorded on a Pye-Unicam SP3-300 spectrometer in chloroform solution; only strong peaks are listed. UV spectra were obtained on a Cary model 2300 spectrometer in ethanol solution, and are quoted as λ_{max} (ε_{max}). NMR spectra were obtained on Varian EM-360A and Bruker AC200 FT instruments. Unless otherwise stated, spectra were recorded in $CDCl_3$ solution, ^1H spectra were measured at 200.13 MHz, and ^{13}C spectra at 50.32 MHz. The DEPT technique and, if necessary, H-C correlated spectra were used to assign ^{13}C signals. Mass spectra were recorded on an AEI MS-9 instrument.

N-Aryllactams

1-Phenylpyrrolidin-2-one [1a], 1-(3-methoxyphenyl)pyrrolidin-2-one [1b], 1-(4-methoxyphenylpyrrolidin-2-one [1c], 1-(4-nitrophenyl)pyrrolidin-2-one [1e], and 1-(2-naphthyl)pyrrolidin-2-one [1f] were prepared by heating the appropriate aniline with butyrolactone in a modification of Reppe's procedure[5]; m.p.s agree with those reported, and proton NMR spectra are as expected. The following procedure is typical of the method used.

1-(2,5-Dimethoxylphenyl)pyrrolidin-2-one [1d].- 2,5-Dimethoxyaniline (11.58 g, 75.60 mmol) and butyrolactone (6.20 ml, ca. 81.3 mmol) were stirred together at 200-210°C (oil bath temperature) for 3 h. The mixture was cooled, and sulphuric acid (18 M, 1 ml) was added. Heating was resumed for a further 2 h. The dark mixture was cooled to room temperature and dissolved in chloroform (80 ml). The solution was washed successively with aqueous hydrochloric acid (2 M, 80 ml), water (80 ml), aqueous ammonia solution (2 M, 50 ml), and saturated sodium chloride solution (150 ml). The organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a dark liquid that was purified by bulb-to-bulb distillation at 1 mm Hg/210°C (oven temperature), then 1 mm Hg/185-190°C. The product (9.27 g, 55%) solidified on standing; m.p. 58-59°C (from hexane - ethyl acetate); R_F (ether) 0.24; IR 1680 (C=O) cm^{-1}; ^1H-NMR 6.9-6.75 (3H, m, ArH), 3.78, 3.76 and 3.76 (8H, overlapping s, s, and t, J ca. 7.5 Hz, 2 x OMe and CH_2N); 2.55 (2H, t, J 8.1 Hz with further fine coupling, $CH_2C{=}O$), 2.17 (2H, quintet, J 7.6 Hz with further fine coupling, $CH_2CH_2CH_2$); ^{13}C-NMR 174.60 (C=O), 153.27, 148.68 (arom C-2, C-5), 127.60 (arom C-1), 113.93, 113.23, 112.91 (remaining arom C), 55.99, 55.37 (2 x OMe), 49.58 (CH_2N), 30.85 ($CH_2C{=}O$), 18.58 ($CH_2CH_2CH_2$) (Found: C, 64.77; H, 7.15; N, 6.39. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%).

Conversion of N-substituted pyrrolidin-2-ones to pyrrolidine-2-thiones

The lactams [1] were dissolved in benzene (ca. 10 ml per g) unless otherwise stated, and phosphorus pentasulphide (ca. 2.5-3 eq S per C=O group) was added in portions with stirring. The mixture was heated under reflux (ca. 2 - 8 h), after which the solvent was decanted. The residue was boiled with dichloromethane for 30 min to extract additional product. This extract was decanted, and the residue was then stirred with concentrated ammonia liquor to dissolve the inorganic material. The basic mixture was extracted with dichloromethane; all organic ex-

tracts were combined, evaporated under reduced pressure, and chromatographed on silica gel with hexane-ethyl acetate mixtures. The following products (isolated yields given in brackets) were prepared and characterised:

1-Phenylpyrrolidine-2-thione [2a] (73%, together with recovered lactam [1a], 25%; reaction carried out with ultrasonic irradiation instead of reflux): colourless needles, m.p. 76°C (from acetone - hexane); R_F (ether) 0.76; IR 1485, 1432, 1415, 1290, 1255, 1140 cm^{-1}; ^{1}H-NMR 7.55-7.25 (5H, m, ArH), 4.12 (2H, t, J 7.2 Hz, CH_2N), 3.24 (2H, t, J 7.9 Hz, CH_2CS), 2.23 (2H, quintet, J 7.6 Hz, $CH_2\underline{CH}_2CH_2$); ^{13}C-NMR 202.17 (C=S), 140.13 (arom C-1), 128.56, 127.15 and 124.50 (remaining arom C), 58.33 (CH_2N), 45.97 ($\underline{C}H_2C=S$), 20.18 ($CH_2\underline{C}H_2CH_2$); MS 179 (4), 178 (11), 177 (M^+, 55), 176 (100) (Found: C, 67.99; H, 6.64; N, 7.91. $C_{10}H_{10}NS$ requires C, 67.76; H, 6.25; N, 7.90%).

1-(3-Methoxyphenyl)pyrrolidine-2-thione [2b] (87%, together with recovered lactam [1b], 5%): colourless needles, m.p. 88.5-89°C (from benzene): R_F (ether) 0.62; IR 1605, 1590, 1495, 1488, 1440, 1418, 1300, 1285, 1267, 1135 cm^{-1}; ^{1}H-NMR 7.36 (1H, t, J 8.1 Hz, ArH-5), 7.15 (1H, t, J 2.2 Hz, ArH-2), 7.04 (1H, ddd, J 8.0, 2.0, and 0.9 Hz, ArH-4 or ArH-6), 6.87 (1H, ddd, J 8.3, 2.5, and 0.9 Hz, ArH-4 or ArH-6), 4.11 (2H, t, J 7.2 Hz, CH_2N), 3.82 (3H, s, OMe), 3.25 (2H, t, J 7.9 Hz, CH_2CS), 2.23 (2H, quintet, J 7.4 Hz, $CH_2\underline{CH}_2CH_2$); ^{13}C-NMR 202.30 (C=S), 159.63 (arom C-3), 141.32 (arom C-1), 129.45 (arom C-5), 116.55, 113.03, and 110.65 (remaining arom C), 58.49 (CH_2N), 55.13 (OMe), 46.20 ($\underline{C}H_2C=S$), 20.33 ($CH_2\underline{C}H_2CH_2$) (Found: C, 63.75; H, 6.61; N, 6.93. $C_{11}H_{13}NOS$ requires C, 63.74; H, 6.32; N, 6.76%).

1-(4-Methoxyphenyl)pyrrolidine-2-thione [2c] (77%, together with recovered lactam [1c], 13%): colourless plates, m.p. 90-91°C (from ethyl acetate-hexane); R_F (ether) 0.63; IR 1515, 1490, 1463, 1450, 1298, 1253, 1147 cm^{-1}; ^{1}H-NMR 7.40 (2H, d, J 9.1 Hz with further fine coupling, ArH-2 and ArH-6), 6.96 (2H, d, J 9.1 Hz with further fine coupling, ArH-3 and ArH-5), 4.08 (2H, t, J 7.2 Hz, CH_2N), 3.82 (3H, s, OMe), 3.23 (2H, t, J 7.9 Hz, CH_2CS), 2.22 (2H, quintet, J 7.5 Hz, $CH_2\underline{CH}_2CH_2$); ^{13}C-NMR 201.71 (C=S), 157.97 (arom C-4), 132.85 (arom C-1), 125.65 (arom C-2, C-6), 113.63 (arom C-3, C-5), 58.42 (CH_2N), 54.91 (OMe), 45.61 ($\underline{C}H_2CS$), 19.91 ($CH_2\underline{C}H_2CH_2$)(Found: C, 63.37; H, 6.33; N, 6.77. $C_{11}H_{13}NOS$ requires C, 63.74; H, 6.32; N, 6.76%).

1-(2,5-Dimethoxyphenyl)pyrrolidine-2-thione [2d] (78%; reaction carried out in toluene): colourless needles, m.p. 122.5-123.5°C (from dichloromethane-acetone); R_F (ether) 0.65; IR 1510, 1488, 1462, 1440, 1422, 1300, 1275, 1207 cm^{-1}; ^{1}H-NMR 7.0-6.85 (3H, m, ArH), 4.01 (2H, t, J 7.3 Hz, CH_2N), 3.80 (3H, s, OMe), 3.77 (3H, s, OMe), 3.21 (2H, t, J 7.9 Hz, $CH_2C=S$), 2.25 (2H, quintet, J 7.5 Hz, $CH_2\underline{CH}_2CH_2$); ^{13}C-NMR 203.48 (C=S), 153.22 and 147.96 (arom C-2, C-5), 129.26 (arom C-1), 114.39, 113.82, 113.31 (arom C-3, C-4, C-6), 57.26 (CH_2N), 56.03 and 55.43 (2 x OMe), 44.89 ($\underline{C}H_2C=S$), 20.65 ($CH_2\underline{C}H_2CH_2$) (Found: C, 61.06; H, 6.41; N, 6.04. $C_{12}H_{15}NO_2S$ requires C, 60.73; H, 6.37; N, 5.90%).

1-(4-Nitrophenyl)pyrrolidine-2-thione [2e] (96%), yellow spars, m.p. 148.5-149.5°C (from benzene); R_F (hexane - acetone 1:1) 0.44; IR 1495, 1480, 1455, 1430, 1340, 1330, 1295, 1285 cm^{-1}; ^{1}H-NMR 8.31 (2H, d, J 9.3 Hz with further fine coupling, ArH-3 and ArH-5), 7.89 (2H, d, J 9.3 Hz with further fine coupling, ArH-2 and ArH-6), 4.21 (2H, t, J 7.2 Hz, CH_2N), 3.26 (2H, t, J 7.8 Hz, $CH_2C=S$), 2.28 (2H, quintet, J 7.5 Hz, $CH_2\underline{CH}_2CH_2$); ^{13}C-NMR 204.18 (C=S), 145.66 and 145.45 (arom C-1 and C-4), 124.72 and 124.12 (arom C-2,C-6 and C3,C5), 57.78 (CH_2N), 46.81 ($\underline{C}H_2CS$), 20.52 ($CH_2\underline{C}H_2CH_2$)(Found: C, 54.01; H, 4.39; N, 12.69. $C_{10}H_{10}N_2O_2S$ requires C, 54.04; H, 4.53; N, 12.60%).

1-(2-Naphthyl)pyrrolidine-2-thione [2f] (94%); colourless needles, m.p. 154 C (from ethyl acetate - hexane); R_F (ether) 0.74; IR 1480, 1445, 1415, 1290, 1135 cm^{-1}; ^{1}H-NMR 7.9-7.75 (4H, m, ArH-1, -4, -5 and -8), 7.64 (1H, dt, J 8.7 and 1.0 Hz, ArH-3), 7.55-7.2 (2H, m, ArH-6, ArH-7), 4.09 (2H, t, J 7.2 Hz, CH_2N), 3.20 (2H, t, J 7.9 Hz, $CH_2C=S$), 2.15 (2H, quintet, J 7.6 Hz, $CH_2\underline{CH}_2CH_2$); ^{13}C-NMR 202.57 (C=S), 137.86 (arom C-2), 132.96 and 132.04 (arom C-5a, C-8a), 128.51, 127.65, 127.46, 126.27, 122.99, 122.94 (remaining arom C), 58.59 (CH_2N), 46.14 ($\underline{C}H_2C=S$), 20.45 ($CH_2\underline{C}H_2CH_2$)(Found: C, 73.23; H, 5.81; N, 6.10. $C_{14}H_{13}NS$ requires C, 73.97; H, 5.76; N, 6.16%).

1-Benzylpyrrolidine-2-thione [2g] (82% yield), colourless crystals, m.p. 70-71 C (lit.[14] m.p. 71°C); R_F (ether) 0.83; IR 1500, 1450, 1305 cm^{-1}; ^{1}H-NMR 7.33 (5H, s, ArH), 4.99 (2H, s, $ArCH_2N$), 3.59 (2H, t, J 7.3 Hz, CH_2CH_2N), 3.10 (2H, t, J 7.9 Hz, $CH_2C=S$), 2.02 (2H, quintet, J 7.6 Hz, $CH_2\underline{CH}_2CH_2$); ^{13}C-NMR 201.17 (C=S), 134.71 (arom C-1), 128.38, 127.81, and 127. 56 (remaining aromatic C), 53.62 ($CH_2\underline{C}H_2N$), 51.09 ($Ar\underline{C}H_2N$), 44.51 ($\underline{C}H_2CS$), 19.04 ($CH_2\underline{C}H_2CH_2$).

General procedure for the sulphide contraction

N-Arylpyrrolidine-2-thione (0.5-15 mmol scale) was dissolved in a small quantity of dichloromethane (2-20 ml) and the appropriate alkyl bromoacetate (1.1 eq) was added. Solvent was removed by evaporation at atmospheric pressure on an oil bath. The mixture was kept at 50°C for the times indicated in Table 1. The salt thus formed was dissolved in dichloromethane (10 - 50 ml, depending on solubility), and triphenylphosphine (1.1-1.2 eq) was added, followed by triethylamine (1.1-2.0 eq). The ensuing reaction was usually exothermic, and the colour tended to darken. The solution was stirred at room temperature for no longer than 2h, after which the solvent was removed under reduced pressure. Trituration of the residue with ether left the bulk of the triethylammonium bromide undissolved. Evaporation of the filtrate followed by chromatography on silica gel with hexane - ethyl acetate mixtures gave the following (isolated yields in brackets):

From 1-(3-methoxyphenyl)pyrrolidine-2-thione [2b] (0.443 g, 2.13 mmol) and ethyl bromoacetate (0.25 ml, 2.3 mmol) were obtained ethyl (E)-(1-(3-methoxyphenyl)-2-pyrrolidinylidene)acetate [3b, R'=Et] (207 mg, 37%), 1-(3-methoxyphenyl)pyrrolidin-2-one [1b] (190 mg, 47%), and an impure sample of 3-ethoxycarbonylmethyl-1-(3-methoxyphenyl)pyrrolidine-2-thione [5b, R'=Et] (20 mg, <3%).

Compound [3b, R'=Et]: colourless prisms, m.p. 63.5-64°C (from dichloromethane - hexane); R_F (hexane - ethyl acetate 2:1) 0.41; UV 300(16110), 245(8350) nm; IR 1675, 1668, 1608, 1575, 1488, 1135, 1043 cm^{-1}; ^{1}H-NMR 7.29 (1H, td, J 7.9 and 0.8 Hz, ArH-5), 6.84 (1H, ddd, J 7.9, 1.9 and 1.1 Hz, ArH-4 or ArH-6), 6.80-6.72 (2H, m, ArH-2 and ArH-4 or ArH-6), 4.96 (1H, t, J 1.4 Hz, C=CH), 4.07 (2H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 3.80 (3H, s, OMe), 3.71 (2H, t, J 7.0 Hz, CH_2N), 3.31 (2H, td, J 7.7, 1.4 Hz, $CH_2C{=}C$), 2.07 (2H, quintet, J 7.4 Hz, $CH_2\underline{CH}_2CH_2$), 1.21 (3H, t, J 7.1 Hz, $OCH_2\underline{CH}_3$) (irradiation at 4.96 causes collapse of 3.31 signal to t, J 7.8 Hz); ^{13}C-NMR 169.44 ($N\underline{C}{=}CH$), 163.58 (C=O), 160.32 (arom C-3), 142.54 (arom C-1), 130.04 (arom C-5), 116.74, 111.24, and 110.46 (remaining aromatic C), 81.59 ($NC{=}\underline{C}H$), 58.38 ($O\underline{C}H_2CH_3$), 55.30 (OMe), 54.45 (CH_2N), 32.53 ($\underline{C}H_2C{=}C$), 21.45 ($CH_2\underline{C}H_2CH_2$), 14.59 ($OCH_2\underline{C}H_3$) (Found: C, 68.58; H, 7.45; N, 5.38. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36%).

Compound [5b, R'=Et]: R_F (ether) 0.79; IR 1730, 1603, 1490, 1298, 1263 cm^{-1}; ^{1}H-NMR 7.34 (1H, t, J 8.1 Hz, ArH-5), 7.10 (1H, t, J 2.2 Hz, ArH-2), 7.01 (1H, ddd, J 7.9, 1.9 and 0.9 Hz, ArH-4 or ArH-6), 6.86 (1H, ddd, J 8.2, 2.5 and 0.8 Hz, ArH-4 or ArH-6), 4.3-3.9, 4.17 and 4.16 (4H, superimposed m and 2 x q, J 7.2 Hz, CH_2N and $OC\underline{H}_2CH_3$), 3.80 (3H, s, OMe), 3.5-3.25 and 3.36 (2H, superimposed m and dd, J 17.5 and 3.6 Hz, CHC=S and $C\underline{H}_aH_bCO_2Et$), 2.7-2.45 and 2.60 (2H, superimposed m and dd, J 17.5 and 10.0 Hz, $CH_2C\underline{H}_cH_dCH$ and $CH_a\underline{H}_bCO_2Et$), 1.95 (1H, ddd, J 18.4, 12.7 and 9.1 Hz, $CH_2CH_c\underline{H}_dCH$), 1.27 (3H, t, J 7.1 Hz, $OCH_2\underline{CH}_3$).

From 1-(4-methoxyphenyl)pyrrolidine-2-thione [2c] (1.143 g, 5.52 mmol) and methyl bromoacetate (0.57 ml, 6.0 mmol) were obtained methyl (E)-(1-(4-methoxyphenyl)-2-pyrrolidinylidene)acetate [3c, R'=Me] (0.361 g, 26%), 1-(4-methoxyphenyl)pyrrolidin-2-one [1c] (0.354 g, 33%), and 3-methoxycarbonylmethyl-1-(4-methoxyphenyl)pyrrolidine-2-thione [5c, R'=Me] (0.155 g, 10%).

Compound [3c, R'=Me]: colourless plates, m.p. 114-115°C (from dichloromethane - hexane); R_F (ether) 0.76; UV 288(20080), 247(sh, 5860), 226(8980) nm; IR 1680, 1618, 1595, 1515, 1300, 1250, 1190, 1150, 1045 cm^{-1}; ^{1}H-NMR 7.14 (2H, d, J 9.1 Hz with further fine coupling, ArH-2 and ArH-6), 6.91 (2H, d, J 9.1 Hz with further fine coupling, ArH-3 and ArH-5), 4.71 (1H, t, J 1.2 Hz, C=CH), 3.80 (3H, s, ArOMe), 3.68 (2H, t, J 7.0 Hz, CH_2N), 3.58 (3H, s, CO_2Me), 3.30 (2H, td, J 7.8 and 1.2 Hz, $CH_2C{=}C$), 2.08 (2H, quintet, J 7.5 Hz, $CH_2\underline{CH}_2CH_2$) (irradiation at 4.71 causes collapse of 3.30 signal to t, J 7.8 Hz; irradiation at 3.30 causes collapse of 4.71 signal to s); ^{13}C-NMR 169.75 ($N\underline{C}{=}CH$), 164.88 (C=O), 157.81 (arom C-4), 134.07 (arom C-1), 126.31 (arom C-2, C6), 114.69 (arom C-3, C5), 80.07 ($NC{=}\underline{C}$), 55.42 (ArOMe), 54.98 (CH_2N), 49.88 ($CO_2\underline{Me}$), 32.41 ($\underline{C}H_2C{=}C$), 21.49 ($CH_2\underline{C}H_2CH_2$) (Found: C, 67.52; H, 6.74; N, 5.73. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%).

Compound [5c, R'=Me]: colourless prisms, m.p. 99-99.5°C (from dichloromethane - hexane); R_F (ether) 0.73; IR 1725, 1510, 1440, 1292, 1250 cm^{-1}; ^{1}H-NMR 7.37 (2H, d, J 9.1 Hz with further fine coupling, ArH-2 and Ar-H6), 6.95 (2H, d, J 9.1 Hz with further fine coupling, ArH-3 and ArH-5), 4.08 and 3.97 (2H, 2 x dddd by JRES technique; J 10.9, 9.0, 7.3 and 0.7 Hz; and J 11.1, 9.1, 3.4 and 0.6 Hz respectively; $C\underline{H}_xH_yN$ and $CH_x\underline{H}_yN$), 3.81(3H, s, ArOMe), 3.72 (3H, s, CO_2Me), 3.45-3.25 and 3.35 (2H, superimposed m and dd, J 17.6 and 3.7 Hz, CHC=S and $C\underline{H}_aH_bCO_2Me$), 2.75-2.5 and 2.63 (2H, superimposed m and dd, J 17.4 and 9.8 Hz, $CH_2C\underline{H}_cH_dCH$ and $CH_a\underline{H}_bCO_2Me$), 1.94 (1H, ddd, J 18.4, 12.7, and 9.1 Hz, $CH_2CH_c\underline{H}_dCH$); ^{13}C-NMR 203.67 (C=S), 172.30 (C=O), 158.54 (arom C-4), 133.46 (arom C-1), 126.16 (arom C-2, C-6), 114.18 (arom C-3, C-5), 56.42 (CH_2N), 55.28 (ArO$\underline{Me}$), 51.57 ($CO_2\underline{Me}$), 50.63 ($\underline{C}HC{=}S$), 38.42 ($\underline{C}H_2CO_2Me$), 26.98 ($CH_2\underline{C}H_2CH$) (Found: C, 60.01; H, 5.95; N, 5.11. $C_{14}H_{17}NO_3S$ requires C, 60.19; H, 6.13; N, 5.01%).

From 1-(2,5-dimethoxylphenyl)pyrrolidine-2-thione [2d] (3.712 g, 15.64 mmol) and methyl bromoacetate (1.63 ml, ca. 17.2 mmol) was obtained methyl (E)-(1-(2,5-dimethoxyphenyl)-2-pyrrolidinylidene)acetate [3d, R'=Me] (2.808 g, 65%); colourless needles, m.p. 126-127°C (from hexane - ethyl acetate); R_F (ether) 0.72; UV 283(18960), 262(sh, 12530), 224(10210) nm; IR 1575, 1505, 1045 cm^{-1}; ^{1}H-NMR 6.95 -6.7 (3H, m, ArH), 4.45 (1H, t, J 1.3 Hz, C=CH), 3.9-3.55, 3.76, and 3.58 (11H, overlapping m and 2 x s, CH_2N, 2 x ArOMe and CO_2Me), 3.29 (2H, td, J 7.8 and 1.2 Hz, CH_2C=C), 2.11 (2H, quintet, J 7.4 Hz, $CH_2CH_2CH_2$) (irradiation at 4.45 causes collapse of 3.29 signal to t, J 7.8 Hz); ^{13}C-NMR 169.73 (NC=CH), 165.70 (C=O), 153.88, 149.44 (arom C-2, C-5), 129.85 (arom C-1), 114.43, 113.77, 113.64 (remaining arom C), 79.96 (NC=CH), 56.31, 55.74 (2 x ArOMe), 53.69 (CH_2N), 49.81 (CO_2Me), 31.99 (CH_2C=C), 21.93 ($CH_2CH_2CH_2$) (Found: C, 65.30; H, 6.91; N, 5.10. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%).

From 1-(4-nitrophenyl)pyrrolidine-2-thione [2e] (0.563 g, 2.53 mmol) and methyl bromoacetate (0.30 ml, ca. 3.2 mmol) were obtained 1-(4-nitrophenyl)pyrrolidin-2-one [1e] (273 mg, 52%), methyl (Z)-(1-(4-nitrophenyl)-2-pyrrolidinylidene)-acetate [Z-3e, R'=Me] (113 mg, 17%), and a fraction (110 mg) containing a 2:1 mixture of lactam [1e] and vinylogous urethane [Z-3e]. Compound [3e] hydrolysed to the lactam [1e] on standing and on attempted purification; R_F (ether) 0.60; ^{1}H-NMR 8.03 (2H, d, J 9.2 Hz, ArH-3 and ArH-5), 6.54 (2H, d, J 9.2 Hz, ArH-2 and ArH-6), 3.75 and 3.73 (4H, 2 x s, superimposed CO_2Me and C=CH), 3.30 (2H, t, J 6.9 Hz, CH_2N), 2.77 (2H, t, J 7.0 Hz, CH_2C=C), 2.04 (2H, quintet, J 7.0 Hz, $CH_2CH_2CH_2$).

From 1-(2-naphthyl)pyrrolidine-2-thione [2f] (0.108 g, 0.473 mmol) and ethyl bromoacetate (0.06 ml, ca. 0.5 mmol) were obtained 1-(2-naphthyl)pyrrolidin-2-one [1f] (84 mg, 84%) and impure ethyl (E)-(1-(2-naphthyl)-2-pyrrolidinylidene)-acetate [3f, R'=Et] (23 mg; 83% pure by NMR, <14%). Data for the latter compound are given below.

Methyl (E)-(1-phenyl-2-pyrrolidinylidene)acetate [3a, R'=Me].-
(i) Methyl bromoacetate (0.15 ml, ca. 1.6 mmol) was added to a solution of 1-phenylpyrrolidine-2-thione [2a] (250 mg, 1.41 mmol) in acetone (0.5 ml). Solvent was removed in a stream of compressed air, and the mixture was kept at room temperature for 23.5 h, after which it was dissoved in dichloromethane (10 ml). Triphenylphosphine (415 mg, 1.58 mmol) was added, followed by diisopropylethylamine (0.27 ml, ca. 1.6 mmol). After 1 h the mixture was worked up according to the general procedure to give methyl (E)-(1-phenyl-2-pyrrolidinylidene)-acetate [3a, R'=Me] (33 mg, 11%), 1-phenylpyrrolidin-2-one (1a] (96 mg, 42%) and 3-methoxycarbonylmethyl-1-phenylpyrrolidine-2-thione [5a, R'=Me] (54 mg, 15%). Compound [3a] was sublimed at 110°C/23 mm Hg to give colourless needles, m.p. 82.5-83.5°C; R_F (ether) 0.77; UV 296(15720), 244(6990) nm; IR 1680, 1607, 1580, 1497, 1310, 1153 cm^{-1}; ^{1}H-NMR 7.4-7.3 (2H, m, ArH), 7.25-7.1 (3H, m, ArH), 4.92 (1H, t, J 1.3 Hz, C=CH), 3.71 (2H, t, J 7.0 Hz, CH_2N), 3.58 (3H, s, CO_2Me), 3.31 (2H, td, J 7.7 and 1.2 Hz, CH_2C=C), 2.06 (2H, quintet, J 7.4 Hz, $CH_2CH_2CH_2$) (irradiation at 4.92 causes collapse of 3.31 signal to t, J 7.8 Hz); ^{13}C-NMR 169.59 (NC=CH), 163.72 (C=O), 141.19 (arom C-1), 129.20 (arom C-3, C-5), 125.75 (arom C-4), 124.29 (arom C-2, C-6), 80.66 (NC=CH), 54.31 (CH_2N), 49.83 (CO_2Me), 32.40 (CH_2C=C), 21.27 ($CH_2CH_2CH_2$) (Found: C, 71.73; H, 6.93; N, 6.38. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45%).

Compound [5a, R'=Me]: m.p. 74-75°C; R_F (ether) 0.74; IR 1730, 1496, 1438, 1295, 1265 cm^{-1}; ^{1}H-NMR 7.55-7.25 (5H, m, ArH), 4.2-3.9 (2H, m, CH_2N), 3.73 (3H, s, CO_2Me), 3.5-3.3 and 3.38 (2H, superimposed m and dd, J 17.6 and 3.7 Hz, CHCS and $CH_aH_bCO_2Me$), 2.75-2.5 and 2.65 (2H, superimposed m and dd, J 17.5 and 9.9 Hz, $CH_2CH_cH_dCH$ and $CH_aH_bCO_2Me$), 1.97 (1H, ddd, J 18.4, 12.7, and 9.1 Hz, $CH_2CH_cH_dCH$); ^{13}C-NMR 204.08 (C=S), 172.50 (C=O), 140.79 (arom C-1), 129.18 (arom C-3 and C-5), 127.85 (arom C-4), 125.05 (arom C-2 and C-6), 56.31 (CH_2N), 51.77 (CO_2Me), 50.96 (CHC=S), 38.55 (CH_2CO_2Me), 27.24 (CH_2CH_2CH) (Found, M^+, 249.0785. $C_{13}H_{15}NO_2S$ requires 249.0802).
(ii) Methyl bromoacetate (0.15 ml, ca. 1.6 mmol) was added to a solution of sodium iodide (283 mg, 1.89 mmol) in acetone (1 ml). The precipitate formed was filtered off after 100 min at room temperature, and 1-phenylpyrrolidine-2-thione [2a] (250 mg, 1.41 mmol) was added to the filtrate. Solvent was removed in a stream of compressed air, and the mixture was kept at room temperature for 19 h prior to the addition of dichloromethane (10 ml), triphenylphosphine (411 mg, 1.57 mmol) and diisopropylethylamine (0.27 ml, ca. 1.55 mmol). After 70 min the mixture was worked up as above to give methyl (E)-(1-phenyl-2-pyrrolidinylidene)-acetate [3a, R'=Me](101 mg, 33%) and 1-phenylpyrrolidin-2-one [1a] (92 mg, 40%).
(iii) A solution of 1-phenylpyrrolidine-2-thione [2a] (267 mg, 1.51 mmol) and methyl bromoacetate (0.16 ml, 1.7 mmol) in dry dichloromethane (0.4 ml) was kept at room temperature under nitrogen for 80 min. The solution was diluted with

dichloromethane (10 ml), then triphenylphosphine (438 mg, 1.67 mmol) was added over 3 min. After 8 min, dry triethylamine (0.23 ml, 1.7 mmol) was added. After 45 min, work-up and column chromatography according to the general procedure yielded 1-phenylpyrrolidin-2-one [1a] (63 mg, 26%), 3-methoxycarbonylmethyl-1-phenylpyrrolidine-2-thione [5a, R'=Me] (116 mg, 31%), and mixed fractions (173 mg) containing [1a], [3a, R'=Me] and [5a, R'=Me].

(iv) Methyl bromoacetate (0.15 ml, ca. 1.6 mmol) and 1-phenylpyrrolidine-2-thione [2a] (248 mg, 1.40 mmol) were kept in dichloromethane (0.25 ml) at room temperature for 25 h. Chloroform (10 ml) was added, followed by triphenylphosphine (372 mg, 1.42 mmol) and 1,4-diazabicyclo[2.2.2]octane (162 mg, 1.42 mmol). The solution was heated under reflux for 1 h under a blanket of nitrogen. Workup and chromatography according to the general procedure gave 1-phenylpyrrolidin-2-one [1a] (143 mg, 63%) and a mixture of methyl (E)-(1-phenyl-2-pyrrolidinylidene)-acetate [3a, R'=Me] and 3-methoxycarbonylmethyl-1-phenylpyrrolidine-2-thione [5a, R'=Me] (62 mg, 7:2 ratio by NMR).

Ethyl (E)-(1-benzyl-2-pyrrolidinylidene)acetate [3g, R'=Et].- Ethyl bromoacetate (0.50 ml, ca. 4.5 mmol) was added to a solution of 1-benzylpyrrolidine-2-thione [2g] (794 mg, 4.15 mmol) in dichloromethane (1.5 ml). The mixture was kept at room temperature for 19 h, after which it was diluted with more dichloromethane (10 ml). Triphenylphosphine (1.178 g, 4.49 mmol) was added, followed by triethylamine (0.60 ml, ca. 4.3 mmol). The mixture was worked up according to the general procedure after 25 min. The sole product isolated was ethyl (E)-(1-benzyl-2-pyrrolidinylidene)acetate [3g, R'=Et] (745 mg, 73%) as colourless needles, m.p. 61-63°C (after sublimation at 70°C/0.5 mm Hg); R_F (ether) 0.81; UV 282 (31810), 279(31430), 227(sh, 2630), 205(10620) nm; IR 1665, 1580, 1135, 1055 cm^{-1}; ^{1}H-NMR 7.4 - 7.15 (5H, m, ArH), 4.69 (1H, s with further fine coupling, C=CH), 4.36 (2H, s, $PhC\underline{H}_2N$), 4.08 (2H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 3.35 (2H, t, J 7.1 Hz, $CH_2C\underline{H}_2N$), 3.24 (2H, td, J 7.8 and 1.2 Hz, CH_2C=C), 1.97 (2H, quintet, J 7.4 Hz, $CH_2C\underline{H}_2CH_2$), 1.24 (3H, t, J 7.1 Hz, $OCH_2C\underline{H}_3$) (irradiation at 3.24 causes collapse of 4.69 signal to t, J 7.8 Hz); ^{13}C-NMR 169.50 (N$\underline{C}$=CH), 165.15 (C=O), 136.04 (arom C-1), 128.69, 127.43 and 127.16 (remaining arom C), 78.43 (NC=$\underline{C}$H), 58.25 ($O\underline{C}H_2CH_3$), 52.37 ($CH_2\underline{C}H_2N$), 49.99 ($Ph\underline{C}H_2N$), 32.57 ($\underline{C}H_2C$=C), 21.07 $CH_2\underline{C}H_2CH_2$), 14.68 ($OCH_2\underline{C}H_3$) (Found: C, 73.62; H, 8.12; N, 8.72. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71%).

General procedure for the synthesis of ethyl (E)-(1-aryl-2-pyrrolidinylidene)-acetates [3] from ethyl 6-chloro-3-oxohexanoate [6]

The chloro-ester [6][9] and the appropriate amine or aniline [7] (approximately equimolar quantities) were heated together gently until the latter had dissolved. If the amine failed to dissolve, dichloromethane was added to ensure dissolution. A small crystal of iodine was added, followed by solid disodium hydrogen phosphate (1 eq) and anhydrous sodium sulphate (1 eq). The resulting heterogeneous mixture was stirred in an oil bath at ca. 65°C for 40-96 h. Once it had cooled, dichloromethane (100-150 ml) was added and the mixture was washed with water (100-150 ml). The aqueous phase was extracted with dichloromethane, after which the combined organic phases were washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated under reduced pressure. The solid obtained was chromatographed on silica gel with ethyl acetate - hexane mixtures. Numerous by-products were noted, but generally not obtained sufficiently pure for characterisation. The following products were prepared in this way:

Ethyl (E)-(1-phenyl-2-pyrrolidinylidene)acetate [3a, R'=Et] (225 mg, 52%), from aniline (0.16 ml, 1.76 mmol) and the chloro-ester [6] (337 mg, 1.75 mmol); colourless needles, m.p. 59-60°C (from hexane - dichloromethane); R_F (hexane - ethyl acetate 2:1) 0.52; UV 296(17070), 245(7490) nm; IR 1673, 1605, 1580, 1498, 1305, 1140 cm^{-1}; ^{1}H-NMR 7.45-7.10 (5H, m, ArH), 4.90 (1H, t, J 1.5 Hz, C=CH), 4.07 (2H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 3.73 (2H, t, J 7.0 Hz, CH_2N), 3.32 (2H, td, J 7.8 and 1.5 Hz, CH_2C=C), 2.09 (2H, quintet, J 7.4 Hz, $CH_2C\underline{H}_2CH_2$), 1.21 (3H, t, J 7.1 Hz, $OCH_2C\underline{H}_3$) (irradiation at 3.32 causes collapse of 4.90 signal to s); ^{13}C-NMR 169.36 (N$\underline{C}$=CH), 163.70 (C=O), 141.29 (arom C-1), 129.28 (arom C-3, C-5), 125.81 (arom C-4), 124.43 (arom C-2, C-6), 81.10 (NC=$\underline{C}$H), 58.29 ($O\underline{C}H_2CH_3$), 54.36 (CH_2N), 32.47 ($\underline{C}H_2C$=C), 21.39 ($CH_2\underline{C}H_2CH_2$), 14.52 ($OCH_2\underline{C}H_3$) (Found: C, 72.03; H, 7.46; N, 6.01. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%).

Ethyl (E)-(1-(3-methoxyphenyl)-2-pyrrolidinylidene)acetate [3b, R'=Et] (171 mg, 41%), from m-anisidine (220 mg, 1.78 mmol) and the chloro-ester [6] (310 mg, 1.61 mmol). Data are quoted above.

Ethyl (E)-(1-(2,5-dimethoxyphenyl)-2-pyrrolidinylidene)acetate [3d, R'=Et] (300 mg, 62%), together with recovered amine (82 mg, 32%), from 2,5-dimethoxyaniline (253 mg, 1.65 mmol) and the chloro-ester [6] (318 mg, 1.65 mmol). Colourless needles, m.p. 103.5 - 104°C (from hexane - ethyl acetate); R_F (hexane - ethyl

acetate 2:1) 0.35; UV 283(18800), 262(sh, 12340), 223(10260) nm; IR 1673, 1665 (sh), 1575, 1505, 1135, 1040 cm^{-1}; ^{1}H-NMR 7.0-6.7 (3H, m, ArH), 4.45 (1H, s, C=CH), 4.04 (2H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 3.9-3.55 and 3.74 (8H, superimposed m and s, CH_2N and 2 x OMe), 3.28 (2H, td, J 7.7 and 0.8 Hz, CH_2C=C), 2.09 (2H, quintet, J 7.4 Hz, $CH_2\underline{CH}_2CH_2$), 1.19 (3H, t, J 7.1 Hz, $OCH_2\underline{CH}_3$) (irradiation at 4.45 causes collapse of 3.28 signal to t, J 7.8 Hz); ^{13}C-NMR 169.14 (N$\underline{C}$=CH), 165.38 (C=O), 153.53, 149.15 (arom C-2, C-5), 129.47 (arom C-1), 114.25, 113.29 113.22 (remaining arom C), 79.95 (NC=$\underline{C}$H), 57.88 ($O\underline{C}H_2CH_3$), 55.91, 55.39 (Ar$O\underline{Me}$), 53.35 (CH_2N), 31.76 ($\underline{C}H_2$C=C), 21.67 ($CH_2\underline{C}H_2CH_2$), 14.36 ($OCH_2\underline{C}H_3$) (Found: C, 65.76; H, 7.26; N, 4.78. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.26; N, 4.81%).

Ethyl (E)-(1-(2-naphthyl)-2-pyrrolidinylidene)acetate [3f, R'=Et] (840 mg, 80%), from 2-naphthylamine (531 mg, 3.71 mmol) and the chloro-ester [6] (715 mg, 3.71 mmol); colourless plates, m.p. 107-108°C (from ethyl acetate - hexane); R_F (2:1 hexane - ethyl acetate) 0.47; UV 312(15960), 281(19830), 272(sh, 16725), 252(sh 9415) nm; IR 1670, 1578, 1400, 1297, 1130 cm^{-1}; ^{1}H-NMR 7.85-7.7 (3H, m, ArH-4, ArH-5, ArH-8), 7.59 (1H, d, J 2.1 Hz, ArH-1), 7.5-7.35 (3H, m, ArH-3, ArH-6, ArH-7), 5.02 (1H, s, C=CH), 4.08 (2H, q, J, 7.1 Hz, $OC\underline{H}_2CH_3$), 3.75 (2H, t, J 7.0 Hz, CH_2N), 3.35 (2H, td, J 7.7 and 1.0 Hz, CH_2C=C), 2.07 (2H, quintet, J. 7.3 Hz, $CH_2\underline{CH}_2CH_2$), 1.20 (3H, t, J 7.1 Hz, $OCH_2\underline{CH}_3$) (irradiation at 5.02 causes col-collapse of 3.35 signal to t, J 7.7 Hz); ^{13}C-NMR 169.27 (N$\underline{C}$=CH), 163.52 (C=O), 138.73 (arom C-2), 133.56, 131.21 (arom C-4a, C-8a), 129.03, 127.51, 127.31 (arom C-4, C-5, C-8), 126.41, 125,70, 123.07 (arom C-3, C-6, C-7), 121.84 (arom C-1), 81.45 (NC=$\underline{C}$H), 58.29 ($O\underline{C}H_2CH_3$), 54.36 (CH_2N), 32.44 ($\underline{C}H_2$C=C), 21.35 ($CH_2\underline{C}H_2CH_2$), 14.48 ($OCH_2\underline{C}H_3$) (Found: C, 76.16; H, 6.79; N, 4.82. $C_{18}H_{19}NO_2$ requires C, 76.84; H, 6.81; N, 4.98%).

Ethyl (E)-(1-benzyl-2-pyrrolidinylidene)acetate [3g, R'=Et] (188 mg, 46%), from benzylamine (0.20 ml, 1.8 mmol) and the chloro-ester [6] (321 mg, 1.67 mmol). Data are quoted above.

Ethyl (E)-(1-(2,4,5-trimethoxyphenyl)-2-pyrrolidinylidene)acetate [3h, R'=Et] (475 mg, 54%), together with ethyl 6-chloro-3-(2,4,5-trimethoxyphenylamino)hex-2-enoate [8h, R'=Et] (36 mg, 4%), were obtained from 2,4,5-trimethoxyaniline [7h][15] (499 mg, 2.72 mmol) and the chloro-ester [6](542 mg, 2.81 mmol). Compound [3h, R'=Et]: colourless prisms, m.p. 138-138.5°C (from hexane-dichloromethane); R_F (ethyl acetate) 0.76; UV 282(23805), 231(9700) nm; IR 1662, 1612, 1582, 1512, 1465, 1457, 1232, 1202, 1142, 1040 cm^{-1}; ^{1}H-NMR 6.70 (1H, s, ArH-6), 6.58 (1H, s, ArH-3), 4.39 (1H, t, J 1.2 Hz, C=CH), 4.05 (2H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 4.0-3.5, 3.90, 3.82 and 3.78 (11H, superimposed m and 3 x s, CH_2N and 3 x OMe), 3.28 (2H, t, J 7.6 Hz, CH_2C=C), 2.10 (2H, quintet, J 7.4 Hz, $CH_2\underline{CH}_2CH_2$), 1.20 (3H, t, J 7.1 Hz $OCH_2\underline{CH}_3$) (irradiation at 3.28 causes collapse of 4.39 signal to s); ^{13}C-NMR 168.99 (N$\underline{C}$=CH), 165.70 (C=O), 149.30, 148.73, 142.90 (arom C-2, C-4, C-5), 120.53 (arom C-1), 112.00 (arom C-6), 98.61 (arom C-3), 79.50 (NC=$\underline{C}$H), 57.69 ($O\underline{C}H_2CH_3$), 56.22, 56.14, 55.80 (3 x OMe), 53.41 (CH_2N), 31.58 ($\underline{C}H_2$C=C), 21.46 ($CH_2\underline{C}H_2CH_2$), 14.24 ($OCH_2\underline{C}H_3$) (Found: C, 63.60; H, 7.24; N, 4.38. $C_{17}H_{23}NO_5$ requires C, 63.54; H, 7.21; N, 4.36%).
Compound [8h, R'=Et]: obtained as an oil, and not purified; R_F (hexane - ethyl acetate 2:1) 0.35; ^{1}H-NMR (60 MHz) 9.78 (1H, br s, NH), 6.60 (1H, s, ArH-6), 6.45 (1H, s, ArH-3), 4.53 (1H, s, C=CH), 4.07 (2H, q, J 7 Hz, $OC\underline{H}_2CH_3$), 3.78, 3.75, 3.72 (9H, 3 x s, 3 x OMe), 3.42 (2H, t, J 6 Hz, CH_2C=C), 2.5 - 1.7 (4H, m, CH_2Cl and $CH_2\underline{CH}_2CH_2$), 1.23 (3H, t, J 7 Hz, $OCH_2\underline{CH}_3$); ^{13}C-NMR 170.56 (N$\underline{C}$=CH), 163.02 (C=O), 148.78, 148.02, 142.75 (arom C-2, C-4, C-5), 119.65 (arom C-1), 112.25 (arom C-6), 98.25 (arom C-3), 84.27 (NC=$\underline{C}$H), 58.66 ($O\underline{C}H_2CH_3$), 56.60, 56.55, 56.22 (3 x OMe), 43.98 (CH_2Cl), 30.36 ($\underline{C}H_2$C=C), 29.49 ($CH_2\underline{C}H_2CH_2$), 14.52 ($OCH_2\underline{C}H_3$).

Ethyl (E)-(1-(4-methoxyphenyl)-2-pyrrolidinylidene)acetate [3c, R'=Et].-
(i) When the general procedure described above was followed with p-anisidine (610 mg, 4.95 mmol) and the chloro-ester [6] (993 mg, 5.16 mmol) for 40 h, compound [3c, R'=Et] (845 mg, 65%) was produced; colourless needles, m.p. 72.5-73.5°C (from hexane - dichloromethane); R_F (hexane - ethyl acetate 2:1) 0.39; UV 289(21070), 247(sh, 5370), 226(8580) nm; IR 1675, 1610, 1582, 1507, 1294, 1242, 1142, 1132, 1044 cm^{-1}; ^{1}H-NMR 7.15 (2H, d, J 9.1 Hz with further fine coupling, ArH-2 and ArH-6), 6.91 (2H, d, J 9.1 Hz with further fine coupling, ArH-3 and ArH-5), 4.70 (1H, t, J 1.4 Hz, C=CH), 4.05 (2H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 3.81 (3H, s, OMe), 3.67 (2H, t, J 7.0 Hz, CH_2N), 3.30 (2H, td, J 7.8 and 1.3 Hz, CH_2C=C), 2.08 (2H, quintet, J 7.4 Hz, $CH_2\underline{CH}_2CH_2$), 1.20 (3H, t, J 7.1 Hz, $OCH_2\underline{CH}_3$) (irradiation at 4.70 causes collapse of 3.30 signal to t, J 7.8 Hz; irradiation at 3.30 causes collapse of 4.70 signal to s); ^{13}C-NMR 169.32 (N$\underline{C}$=CH), 164.67 (C=O), 157.66 (arom C-4), 133.95 (arom C-1), 126.25 (arom C-2, C-6), 114.54 (arom C-3, C-5), 80.26 (NC=$\underline{C}$H), 58.11 ($O\underline{C}H_2CH_3$), 55.26 (OMe), 54.82 (CH_2N), 32.30 ($\underline{C}H_2$C=C), 21.38 ($CH_2\underline{C}H_2CH_2$), 14.48 ($OCH_2\underline{C}H_3$) (Found: C, 68.63; H, 7.58; N, 5.40. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36%).

(ii) The above reaction was repeated with p-anisidine (720 mg, 5.84 mmol) and chloro-ester [6] (1.124 g, 5.84 mmol) in the absence of disodium hydrogen phosphate at 42°C for 7.3 h followed by room temperature for 55 h. Work-up by the general procedure led to the isolation of an oily solid (1.581 g) consisting of a 2:1 mixture of the vinylogous urethane [3c, R'=Et] and the acyclic compound ethyl 6-chloro-3-(4-methoxyphenyl)hex-2-enoate [8c, R'=Et], the following ^{1}H-NMR (60 MHz, CCl_4) signals for which were clearly assignable: 10.11 (1H, br s, NH), 7.00 (2H, d, J 9 Hz with further fine coupling, ArH-2 and ArH-6), 6.74 (2H, d, J 9 Hz with further fine coupling, ArH-3 and ArH-5), 4.58 (1H, s, C=CH), 3.97 (2H, q, J 7 Hz, $OC\underline{H}_2CH_3$), 3.72 (3H, s, OMe), 3.7-3.1 (2H, m, CH_2C=C), 2.8-1.6 (4H, m, CH_2Cl and $CH_2C\underline{H}_2CH_2$), 1.23 (3H, t, J 7 Hz, $OCH_2C\underline{H}_3$). A portion of the above mixture (1.226 g) was heated under reflux in acetonitrile (25 ml) for 80 min. The solvent was removed under reduced pressure, the residue was dissolved in dichloromethane (100 ml), and the solution was washed with aqueous saturated sodium hydrogencarbonate (100 ml). The aqueous phase was extracted with dichloromethane (50 ml); the organic layers were combined, dried ($MgSO_4$), and evaporated to a dark solid (1.031 g) which was chromatographed on silica gel with hexane - ethyl acetate mixtures to yield the vinylogous urethane [3c, R'=Et] (0.626 g, effective yield 52%), ethyl 6-chloro-3-oxohexanoate [6] (96 mg, 11%), and p-anisidine (7 mg, 1%).

(iii) The general procedure was repeated with p-anisidine (475 mg, 3.86 mmol) and chloro-ester [6] (737 mg, 3.82 mmol), but substituting potassium carbonate (342 mg, 2.47 mmol) for disodium hydrogen phosphate. The mixture was stirred at 75°C for 10 h, and at room temperature for 60 h. Workup and chromatography as usual gave vinylogous urethane [3c, R'=Et] (200 mg, 20%), p-anisidine (31 mg, 6.5%), ethyl (E)-(2-tetrahydrofuranylidene)acetate [9a] (41 mg, 7%), and a mixed fraction (446 mg) containing approximately 4:1:1 of [9a], [8c] and p-anisidine (by NMR). Compound [9a]: yellow liquid, R_F (hexane - ether 1:1) 0.41; ^{1}H-NMR (60 MHz, CCl_4) 5.13 (1H, t, J 2 Hz, C=CH), 4.15 and 4.02 (4H, superimposed t and q, J 7 Hz and 7 Hz, ring-CH_2O and $OC\underline{H}_2CH_3$), 3.05 (2H, td, J 7 and 2 Hz, CH_2C=C), 2.05 (2H, quintet, J 7 Hz, $CH_2C\underline{H}_2CH_2$), 1.22 (3H, t, J 7 Hz, $OCH_2C\underline{H}_3$); compare data in reference[9].

(iv) A solution of sodium iodide (107 mg, 0.71 mmol) and the chloro-ester [6] (112 mg, 0.58 mmol) in acetone (0.5 ml) was stirred in the dark for 70 min. Benzene (10 ml) and p-anisidine (70 mg, 0.57 mmol) were added, and a heavy white precipitate formed. Triethylamine (0.09 ml, 0.6 mmol) was added, after which the mixture was heated under reflux for 5.5 h. Additional ester [6] (41 mg, 0.21 mmol) was added, heating was continued for 6 h, and then kept at room temperature for 15 h. The solvent was removed under reduced pressure, and the residue was partitioned between water (10 ml) and dichloromethane (25 ml). Evaporation of the organic phase gave a crude product (260 mg) that was separated by column chromatography on silica gel with hexane - ethyl acetate mixtures to give the vinylogous urethane [3c, R'=Et] (18 mg, 12%), p-anisidine (10 mg, 14%) and ethyl (Z)-(2-tetrahydrofuranylidene)acetate [9b] (59 mg, 47% based on [6]) as an oil, R_F (ether) 0.43; ^{1}H-NMR (60 MHz, CCl_4) 4.67 (1H, t, J 1.5 Hz, C=CH), 4.30 (2H, t, J 6.5 Hz, ring-CH_2O), 4.00 (2H, q, J 7 Hz, $OC\underline{H}_2CH_3$), 2.65 (2H, t, J 7 Hz with further fine coupling, CH_2C=C), 2.3-1.7 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.20 (3H, t, J 7 Hz, $OCH_2C\underline{H}_3$); compare data in reference[9].

Reformatsky reactions on 1-phenylpyrrolidine-2-thione [2a]

(i) Methyl bromoacetate (0.07 ml, 0.7 mmol) was added to a vigorously stirred suspension of zinc-copper couple[13] (89 mg) in dry THF (1 ml). After 45 min, a solution of 1-phenylpyrrolidine-2-thione [2a] (100 mg, 0.56 mmol) in dry THF (1.5 ml) was added. The mixture was heated under reflux for 45 min, then stirred at room temperature for 15 h. Sulphuric acid (10 M, 2 ml) and water (20 ml) were added, and the solution was neutralised with ammonia liquor. Extraction with ether (3 x 40 ml), followed by drying ($MgSO_4$) and evaporation of the extracts under reduced pressure yielded an oil (139 mg), which was separated by column chromatography on silica gel with hexane - ethyl acetate mixtures. Methyl (E)-(1-phenyl-2-pyrrolidinylidene)acetate [3a, R'=Me] (57 mg, 47%) and 1-phenylpyrrolidin-2-one [1a] (39 mg, 43%) were obtained as pale yellow solids.

(ii) 1-Phenylpyrrolidine-2-thione [2a] (100 mg, 0.56 mmol) and methyl bromoacetate (0.07 ml, 0.7 mmol) were dissolved in dry THF (1 ml). Salt formation was allowed to proceed at room temperature for 130 min. The reaction vessel was immersed in a laboratory ultrasonic cleaning bath. More THF (5 ml) and the zinc-copper couple[13] (68 mg) were added, after which the mixture was sonicated for 5.75 h. The bath temperature rose to 55°C during the reaction. Work-up and chromatography as described above yielded methyl (E)-(1-phenyl-2-pyrrolidinylidene)acetate [3a, R'=Me] (32 mg, 26%) and 1-phenylpyrrolidin-2-one [1a] (54 mg, 59%).

Acknowledgements

We thank the Foundation for Research Development for financial assistance (JPM), the FRD and the University of the Witwatersrand for post-graduate bursaries (GDH), and Dr L Carlton and Mrs S Heiss for invaluable assistance in obtaining NMR spectra. The efforts of an able group of undergraduate students (B Bartels, S-F Chang, I Hindmarch, A Leins and E Scopelitis) in the preparation of certain substrates for this project are gratefully acknowledged.

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