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STUDIES ON LACTAMS—XXX[1]

SYNTHESIS OF DIHYDROPYRROLES AND TETRAHYDROPYRIDINES AS INTERMEDIATES FOR BICYCLIC β-LACTAMS

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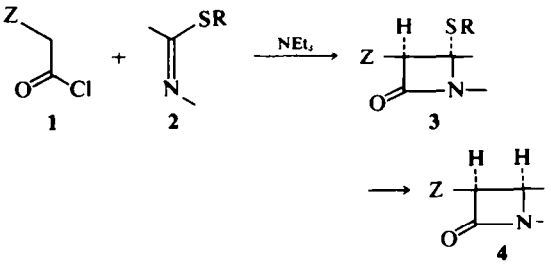
Abstract—N-Acetyl derivatives of 5,6 or 7-membered lactams were condensed with aromatic aldehydes, deacetylated and allowed to react with P_2S_5 in refluxing pyridine. The thio-lactams so obtained were methylated with MeI to give 5- and 6-membered thioimidates which were convenient intermediates for the synthesis of penam and cepham derivatives.

In recent years we have utilized the reaction of acid chlorides (**1**) with imines in the presence of an organic base as a convenient synthetic route to β-lactams with various α-substituents.[2] When a thioimidate (**2**) is used as the imine component[3,4] there occurs stereoselective formation of a β-lactam (**3**) which can be desulfurized to a *cis*-2-azetidinone[4] (**4**).



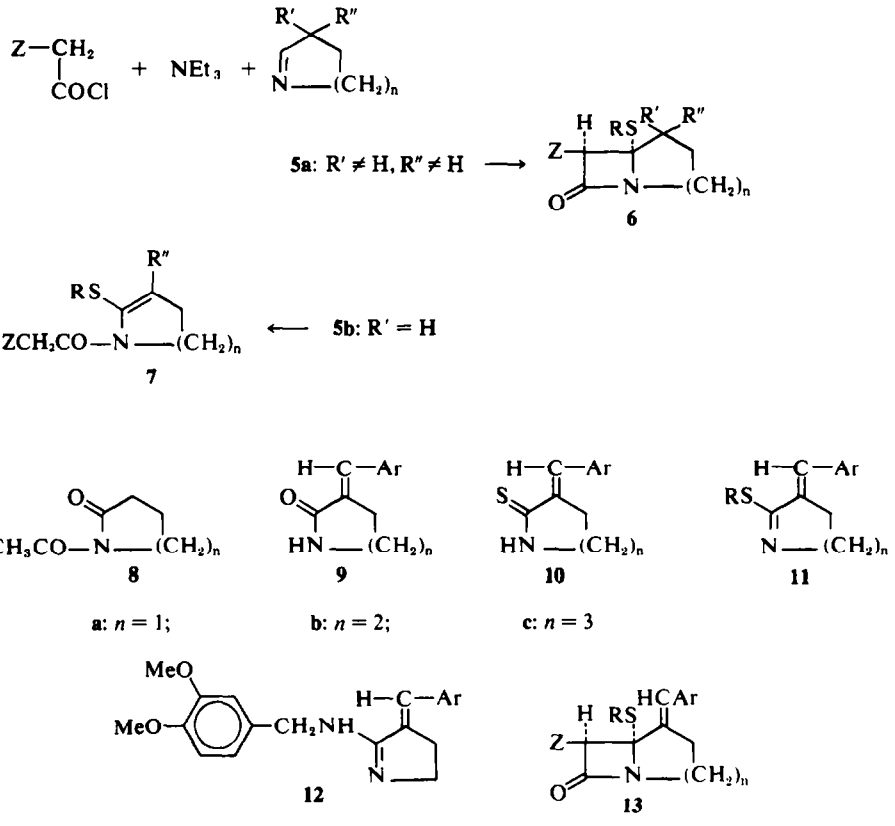
The above sequence of reactions could be used for the preparation of bicyclic β-lactams (**6**) if appropriate 2-alkylthio cyclic imines (**5**) are available. To prevent an alternative mode of reaction between an acid chloride, triethylamine and (**5**) leading to the byproduct (**7**), it is necessary that no hydrogen be available at the 3-position in (**5**).

It has been shown[6] that aldol condensation of 2-pyrrolidones with aromatic aldehydes can be successfully achieved when the lactam nitrogen function is protected with a sufficiently strong electron withdrawing group, such as the acetyl group, which enhances the acidity of the hydrogens alpha to the carbonyl and simultaneously protects the nitrogen from reaction. The acetyl group is easily removed to provide 3-arylidene-2-pyrrolidones (**9a**). We have therefore investigated the possibility of converting γ- and δ-lactams to arylidene derivatives of type **9** and their further modification to the desired cyclic thioimidates of type **11**.

Following the method of Zimmer *et al.*[6] N-acetylpyrrolidone (**8a**) was condensed with several aromatic and heterocyclic aldehydes. This condensation is competitive with the condensation between the aldehyde and the acetyl group to yield cinnamic acids or analogs[7] which, however, could be removed with sodium bicarbonate solution leaving the desired cyclic amides (**9a**) in the organic phase. From their NMR spectra these products were considered to be the more stable *trans* isomers since the vinyl proton exhibited an allylic coupling with J = 2–3 Hz. It has been reported that in the *trans* system **A** the allylic coupling is 0·5 to 2·5 Hz whereas in the *cis* isomer such as **B** the allylic coupling constant is essentially zero.[8]

N-Acetyl-2-piperidone (**8b**) prepared from 2-piperidone and acetic anhydride was condensed with aromatic aldehydes to produce the lactam derivatives (**9b**). The homologous 7-membered lactam derivative (**9c**) was obtained in a low yield from the reaction between N-acetyl-2H-azepin-3-one (**8c**) and veratraldehyde.

Amides have been converted to thioamides by reaction with phosphorus pentasulphide (often employed in large excess) in various solvents.[9-11] We found the usual solvents unsatisfactory as the reaction medium for the conversion of the arylidene-2-pyrrolidones and piperidones to thioamides; the yields were low and erratic and the products difficult to purify. An adaptation of a method in the literature[9] was eventually found to be convenient for preparing pure thioamides in nearly quantitative yield: refluxing pyridine was employed as the solvent and a stoichiometric quantity (1/5 mole) of phosphorus pentasulphide was utilized. After refluxing for about 1 h the hot reaction mixture was poured through a filter paper into warm water when the product separated as yellow crystals. The PMR spectra of the thiolactams were similar to those for



The novel thioimidates (**11**) described here were utilized for the synthesis of a variety of penam and cepham derivatives of type (**13**). A description of these β-lactams will be the subject of a future publication.

the starting lactams except that the NH absorption was shifted downfield by *ca* 60–70 Hz.

After some investigation it was found that a convenient method for preparing the S-methyl compounds (**11**) was to reflux (**10**) with methyl iodide in tetrahydrofuran. In less than 1 h the pure hydroiodide of **11** (R=Me) crystallized out. The analogous S-benzyl compounds (**11**, R=$PhCH_2$) have been prepared using benzyl bromide; a longer reaction time (*ca* 6 h) was required. The free bases (**11**, R=Me) were obtained as stable solids by neutralization of the hydroiodides with triethylamine.

The methylthiopyrroline (**11**) is easily converted to the parent amide **9** with traces of water when the hydroiodide of (**11a**) is subjected to reflux in alcohol. Upon heating **11a** hydroiodide with a primary amine the hydroiodide of the primary amine was formed in preference to the replacement of the methylthio group. However, 3-benzylidene-2-(3′, 4′-dimethoxybenzylamine)-2-pyrroline (**12**) could be prepared in low yield from **11a** hydroiodide and veratrylamine.

EXPERIMENTAL

M.ps were determined on a Mel-Tamp apparatus. IR spectra were recorded on a Perkin-Elmer 247 Grating Spectrophotometer. PMR spectra in $CDCl_3$ solns containing TMS as an internal standard were recorded on a Varian A-60A spectrometer; chemical shifts are reported in δ units (ppm downfield from TMS). Mass spectra were obtained with a Hitachi RMU-7 spectrometer. Elemental analyses were performed by Bernhardt, Max-Planck Institute. Mülheim, West Germany. Florisil from Fisher Scientific Company was used for chromatography. Dichloromethane or $CHCl_3$ extracts of reaction mixtures were dried over anhyd. Na_2SO_4 or $MgSO_4$.

N-Acetyl-2-pyrrolidone (**8**, n = 1) was prepared by the method of Zimmer *et al.*[6]

N-Acetyl-2-piperidone (**8**, n = 2)

A solution of 2-piperidone (49·6 g, 0·50 mole) and Ac_2O (51 g, 0·50 mole) was heated under reflux for 2 h. The AcOH was evaporated and the remaining oil distilled to give the product, 57·4 g (82%), b.p. 74–75°/0·5 mm; IR (film); 1700 (C=O) cm^{-1}; NMR ($CDCl_3$): 1·8–2·2 (m, 4, CH_2CH_2), 2·4–2·8 (m, 2, CH_2), 2·46 (s, 3, CH_3), 3·5–3·9 (m, 2, CH_2) ppm.

N-Acetyl-hexahydro-2H-azepin-2-one (**8**, n = 3)

Hexahydro-2H-azepin-2-one (45·3 g, 0·40 mole) and Ac_2O (40·8 g, 0·40 mole) were heated under reflux for 2 h. The AcOH was evaporated and the product distilled to give 48·9 g (79%), of the title compound, b.p. 85–86°/0·05 mm; IR (film); 1730 (C=O) cm^{-1}; NMR ($CDCl_3$): 1·5–2·0 (m, 6, $CH_2CH_2CH_2$), 2·4 (s, 3, CH_3), 2·5–3·0 (m, 2, CH_2), 3·7–4·0 (m, 2, CH_2) ppm.

General method for the synthesis of 3-arylidene lactams (**9a–9j**)*

A general condensation procedure is described below. A 3l 3-neck flask was equipped with a mechanical stirrer, a thermometer reaching down into the flask and a 1l pressure equalizing dropping funnel. The sodium hydride-mineral oil dispersion was added to the THF and the resulting suspension cooled to about 5–8° but no lower. Into the dropping funnel was placed a soln of the N-acetyl lactam, aromatic aldehyde and THF. The soln was added dropwise to the flask at a rate that maintained steady H_2 evolution and a temp of 10–14°. The H_2 evolved was removed *via* the top of the dropping funnel and was passed through a small flask containing THF so that the rate could be easily monitored. Constant attention was necessary since the reaction seemed to require an induction period and a vigorous exothermic reaction occurred after addition of about a third of the solution at which point the reaction mixture turned yellow or brown. After addition was complete the mixture was stirred at ice-bath temp for 1 h more. A small quantity of MeOH in THF soln sufficient to decompose the excess sodium hydride, was slowly added from the dropping funnel. The mixture was poured into twice its volume of ice-water, acidified to pH 5 with 20% HCl and, after the mineral oil layer was separated, extracted with $CHCl_3$, washed several times with sat $NaHCO_3$ aq, washed once with water, dried and evaporated to give the solid product which was then crystallized (Table 1). The yields, m.ps and analytical data on these pyrrolidones and piperidones are recorded in Table 1; spectral information is given below.

3-Benzylidene-2-pyrrolidone (**9a**). IR (nujol): 3250 (NH), 1680 (C=O), 1650 (C=CH) cm^{-1}; NMR (d_6-DMSO): 3·3–3·9 (m, 2, CH_2), 3·47 (t, 2, J = 6 Hz, CH_2), 7·2 (t, 1, J = 3 Hz, C=CH), 7·3–7·7 (m, 5, aromatics), 8·4–8·7 (br. s, 1, NH) ppm; M^+ at *m/e* 173.

3-Veratrylidene-2-pyrrolidone (**9b**). IR (nujol): 3120 (NH), 1680 (C=O), 1650 (C=C) cm^{-1}; NMR (d_6-DMSO): 3·0–3·4 (t, 2, J = 7 Hz, CH_2), 3·4–3·8 (t, 2, J = 7 Hz, CH_2), 3·97 (s, 6, CH_3), 6·9–7·8 (m, 4, aromatics and C=CH), 8·4–8·7 (br. s, 1, NH) ppm; M^+ at *m/e* 233.

3-(4′-Chlorobenzylidene)-2-pyrrolidone (**9c**). IR (nujol): 3100, 3200 (NH), 1690 (C=O), 1640 (C=CH) cm^{-1}; NMR (d_6-DMSO): 2·8–3·4 (m, 2, CH_2), 3·4 (t, 2, J = 6 Hz, CH_2), 7·1 (t, 1, J = 3 Hz, C=CH), 7·4 (s, 4, aromatics), 8·4–8·7 (br. s, 1, NH) ppm; M^+ at *m/e* 207.

3-(3′-Nitrobenzylidene)-2-pyrrolidone (**9d**). IR (nujol): 3250 (NH), 1725 (C=O), 1650 (C=C), 1550 (NO_2) cm^{-1}; NMR (d_6-DMSO): 3·1–3·6 (m, 2, CH_2), 3·9 (t, 2, J = 6 Hz, CH_2), 7·5–8·5 (m, 5, aromatics and C=CH), 8·4–8·7 (br. s, 1, NH) ppm; M^+ at *m/e* 218.

3-(2′-Pyridinecarboxylidene)-2-pyrrolidone (**9e**). IR (nujol): 3200 (NH), 1720 (C=O), 1680 (C=CH) cm^{-1}; NMR (d_6-DMSO): 3·2–3·6 (m, 4, CH_2CH_2), 7·0–7·8 (m, 5, aromatic and C=CH), 8·0–8·3 (br. s, 1, NH) ppm; M^+ at *m/e* 174.

3-(2′-Thiophenecarboxylidene)-2-pyrrolidone (**9f**). IR (nujol): 3330 (NH), 1740 (C=O), 1660 (C=CH) cm^{-1}; NMR (d_6-DMSO): 2·7–3·3 (m, 2, CH_2), 3·7 (t, 2, J = 6 Hz, CH_2, 6·9–7·7 (m, 5, aromatics, C=CH and NH) ppm; M^+ at *m/e* 179.

3-(2′-Furancarboxylidene)-2-pyrrolidone (**9g**). IR (nujol): 3300 (NH), 1720 (C=O), 1675 (C=CH) cm^{-1}; NMR (d_6-DMSO): 2·9–3·4 (m, 2, CH_2), 3·7 (t, 2, J = 6 Hz, CH_2), 6·4–6·7 (m, 2, beta-furanyl protons), 7·2 (t, 1, J = 2 Hz, C=CH), 7·6 (s, 1, alpha-furanyl proton), 8·4–8·8 (br. s, 1, NH) ppm; M^+ at *m/e* 163.

3-Benzylidene-2-piperidone (**9h**). IR (nujol): 3300 (NH), 1660 (C=O), 1600 (C=CH) cm^{-1}; NMR ($CDCl_3$): 1·6–2·1 (m, 2, CH_2), 2·5–3·0 (m, 2, CH_2), 3·2–3·6 (m, 2, CH_2), 7·35 (s, 5, phenyl), 7·6–7·8 (br. s, 1, NH), 7·82 (t, 1, J = 2 Hz, C=CH) ppm; M^+ at *m/e* 187.

3-Veratrylidene-2-piperidone (**9i**). IR (nujol): 3300 (NH), 1660 (C=O), 1600 (C=CH) cm^{-1}; NMR ($CDCl_3$): 1·6–2·1 (m, 2, CH_2), 2·6–3·0 (m, 2, CH_2), 3·2–3·6 (m, 2, CH_2), 3·88 (s, 6, CH_3), 6·9–7 (br. s, 3, aromatics), 7·7–7·9 (br. s, 2, NH and C=CH) ppm; M^+ at *m/e* 247.

3-Veratrylidene-hexahydro-2H-azepin-2-one (**9j**). IR (nujol): 3200 (NH), 1650 (C=O), 1600 (C=CH) cm^{-1}; NMR ($CDCl_3$): 1·6–2·0 (m, 4, CH_2CH_2), 2·3–2·8 (m, 2, CH_2), 3·0–3·5 (m, 2, CH_2), 3·85 (s, 6, CH_3), 6·8–7·2 (br. m, 5, aromatic, C=CH and NH) ppm; M^+ at *m/e* 261.

Synthesis of 3-arylidene-2-thiolactams (**10a–10b**). A suspension of 3-arylidene lactams (**9**, 0·1 mole) P_2S_5 (0·02 mole) and pyridine (300 ml) was heated under reflux for 1 h and the resulting soln poured through a filter paper into water at 50°. On cooling the thiolactams crystallized out and were collected. Table 2 shows the m.ps, yields and analytical data on these thiolactams. The spectroscopic information is given below:

3-Benzylidene-2-thiopyrrolidone (**10a**). IR (nujol): 3120 (NH), 1640 (C=C) cm^{-1}; NMR (d_6-DMSO): 3·15 (t, 2, J = 8 c/s, CH_2), 3·68 (t, 2, J = 8 c/s, CH_2), 7·2–7·8 (m, 7, phenyl, C=CH and NH) ppm; M^+ at *m/e* 189.

3-Veratrylidene-2-thiopyrrolidone (**10b**). IR (nujol): 3330 (SH), 1600 (C=C) cm^{-1}; M^+ at *m/e* 249.

3-(4′-Chlorobenzylidene)-2-thiopyrrolidone (**10c**). IR (nujol): 3140 (NH), 1640 (C=C) cm^{-1}; NMR (d_6-DMSO): 2·9–3·3 (m, 2, CH_2), 3·6 (t, 2, J = 7 Hz, CH_2), 7·5 (s, 5, aromatics an),C!X7q(·7 (br. s, 1, NH) ppm; M^+ at *m/e* 235.

3-(3′-Nitrobenzylidene)-2-thiopyrrolidone (**10d**). IR (nujol): 3130 (NH), 1640 (C=C), 1515 (NO_2) cm^{-1}; M^+ at *m/e* 234.

3 - (2′ - Thiophenecarboxylidene) - 2 - thiophenecarboxylidene (**10e**). IR (nujol): 3130 (NH), 1640 (C=C) cm^{-1}; NMR (d_6-DMSO): 2·8–3·3 (m, 2, CH_2), 3·4–3·9 (m, 2, CH_2), 7·0–8·0 (m, 5, thienyl protons, C=CH and NH) ppm; M^+ at *m/e* 195.

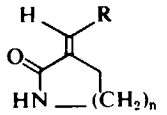
3-Furfurylidene-2-thiopyrrolidone (**10f**). IR (nujol): 3220 (NH), 1640 (C=C) cm^{-1}; NMR (d_6-DMSO): 2·9–3·3 (m, 2, CH_2), 3·65 (t, 2, J = 7 Hz, CH_2), 6·3–7·7 (m, 2, beta-furanyl protons), 7·37 (t, 1, J = 2 Hz, C=CH), 7·5 (s, 1, alpha-furanyl proton), 10·0 (br. s, 1, NH) ppm; M^+ at *m/e* 179.

3-Benzylidene-2-thiopiperidone (**10g**). IR (nujol): 3220 (NH), 1640 (C=C) cm^{-1}; NMR ($CDCl_3$): 1·7–2·2 (m, 2, CH_2), 2·6–3·0 (m, 2, CH_2), 3·2–3·6 (m, 2, CH_2), 7·35 (s, 5, phenyl), 8·46 (s, 1, C=CH), 9·2–9·7 (br. s, 1, NH) ppm.

3-Veratrylidene-2-thiopiperidone (**10h**). IR (nujol): 3150 (NH), 1620, 1600, 1580 (C=C, aromatic) cm^{-1}; NMR

*Compounds **9a–9d** were previously reported by Zimmer (ref. 6) in low yield. Yields quoted apply to analytically pure material.

Table 1.



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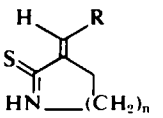
	n	R	Yield %	m.p.	Solvent of recrystallization	Formula	Analysis calc. (found)
	1	phenyl	15	172–173°	EtOAc	$C_{11}H_{11}NO$	C 76·77, H 6·40, N 8·09 (C 76·80, H 6·49, N 7·87)
b	1	3,4-Dimethoxyphenyl	26	182–183°	2-PrOH	$C_{13}H_{15}NO_3$	C 66·93, H 6·48, N 6·00 (C 66·80, H 6·56, N 6·23)
c	1	4-Chlorophenyl	20	229–230°	2-PrOH	$C_{11}H_{10}ClNO$	C 62·33, H 4·85, N 5·51 (C 62·38, H 5·04, N 5·57)
d	1	3-Nitrophenyl	29	235–237°	DMF	$C_{11}H_{10}N_2O_3$	C 60·53, H 4·62, N 12·84 (C 60·58, H 4·69, N 12·71)
e	1	2-Pyridyl	25	162–165°	CH_3CN	$C_{11}H_{10}N_2O$	C 68·94, H 5·79, N 16·09 (C 68·91, H 5·89, N 16·23)
f	1	2-Thienyl	45	198–200°	EtOH	C_9H_9NOS	C 60·31, H 5·06, N 7·83 (C 60·53, H 5·13, N 7·98)
g	1	2-Furyl	24	142–144°	$CHCl_3$	$C_9H_9NO_2$	C 66·23, H 5·56, N 8·58 (C 66·21, H 5·63, N 8·55)
h	2	Phenyl	30	160–161°	EtOAc	$C_{12}H_{13}NO$	C 77·00, H 7·00, N 7·48 (C 77·01, H 7·07, N 7·39)
i	2	3,4-Dimethoxyphenyl	20	168–170°	EtOAc	$C_{14}H_{17}NO_3$	C 68·00, H 6·93, N 5·67 (C 67·96, H 7·08, N 5·79)
j	3	3,4-Simethoxyphenyl	4	166–168°	EtOAc	$C_{15}H_{19}NO_3$	C 68·95, H 7·33, N 5·36 (C 68·85, H 7·28, N 5·41)

Table 2.



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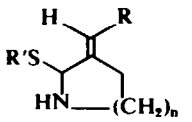
	n	R	Yield %	m.p.	Solvent of recrystallization	Formula	Analysis calc. (found)
a	1	Phenyl	100	163–165°	Benzene	$C_{11}H_{11}NS$	C 69·79, H 5·85, N 7·40 (C 69·86, H 5·70, N 7·47)
b	1	3,4-Dimethoxyphenyl	80	213–214°	Pyridine	$C_{13}H_{15}NO_2S$	C 62·61, H 6·07, N 5·62 (C 62·86, H 6·21, N 5·85)
c	1	4-Chlorophenyl	72	212–215°	Benzene	$C_{11}H_{10}ClNS$	C 59·04, H 4·51, N 6·26 (C 59·40, H 4·82, N 6·24)
d	1	3-Nitrophenyl	77	250–251°	Pyridine	$C_{11}H_{10}N_2O_2S$	C 56·38, H 4·30, N 11·95 (C 56·50, H 4·55, N 11·76)
e	1	2-Thienyl*	25	144–148°	—	$C_9H_9NS_2$	
f	1	2-Furyl	53	162–163°	Benzene	C_9H_9NOS	C 60·31, H 5·06, N 7·82 (C 60·80, H 5·39, N 7·90
g	2	Phenyl	70	113–115°	Benzene	$C_{12}H_{13}NS$	C 70·90, H 6·44, N 6·89 (C 70·81, H 6·53, N 7·01)
h	2	3,4-Dimethoxyphenyl	56	155–156°	Pyridine	$C_{14}H_{17}NO_2S$	

*Xylene used as solvent.

Table 3.



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	n	R	R'	Yield %	Solvent of m.p.	recrystallization	Formula	Aanlysis calc. (found)
a	1	Phenyl		72	94–95°	b.p. (0·05 mm) 124°	$C_{12}H_{13}NS$	C 70·90, H 6·44, N 6·89 (C 70·73, H 6·44, N 6·80)
b	1	3,4-Dimethoxyphenyl	CH_3	67	95–96°	2–PrOH	$C_{14}H_{17}NO_2S$	C 63·84, H 6·50, N 5·32 (C 64·10, H 6·67, N 5·58)
c	1	3-Nitrophenyl	CH_3	77	156–157°	EtOAc	$C_{12}H_{12}N_2O_2S$	C 58·03, H 4·87, N 11·28 (C 58·04, H 4·95, N 11·10)
d	1	2-Thienyl	CH_3	75	196–197°	Benzene	$C_{10}H_{11}NS_2$	
e	1	4-Chlorophenyl	$C_6H_5CH_2$	65	83–84°		$C_{18}H_{16}ClNS$	C 68·91, H 5·14, N 4·47 (C 68·80, H 5·24, N 4·47)
f	1	2-Furyl	$C_6H_5CH_2$	54	140/0·01 mm		$C_{16}H_{15}$-NOS	C 62·84, H 5·28, N 4·58 (C 62·50, H 5·24, N 4·39)
g	2	Phenyl	CH_3	89	57–58°	Benzene	$C_{13}H_{15}NS$	C 71·83, H 6·96, N 6·45 (C 72·10, H 7·08, N 6·39)
h	2	3,4-Dimethoxyphenyl	CH_3	90	94–95°	Benzene	$C_{15}H_{19}NO_2S$	

*Converted to the hydrochloride salt and analyzed as such.

($CDCl_3$): 1·7–2 (m, 2, CH_2), 2·6–3·0 (m, 2, CH_2), 3·82 (s, 6, CH_3), 6·8–7·0 (m, 3, aromatics), 8·3 (s, 1, C=CH), 9·3 (br. s, 1, NH) ppm; M^+ at *m/e* 263.

S-*Alkylation of arylidenethiolactams* (**11**). A soln of 3-arylidene-2-thiolactams (**10**, 0·05 mole), MeI or benzyl bromide (0·07 mole) and THF (600 ml) was refluxed. In the case of **11b** DMF was used as the solvent. Reflux time varied from 1–16 h in different cases. On cooling to room temp the product separated out as its hydroiodide and was collected. To liberate the free base the salt was dissolved in water, neutralized with thriethylamine and extracted with CH_2Cl_2. The organic phase was separated, washed with water, dried and evaporated to afford the pyrrolines or pyridines (**11**, see Table 3). The free bases were recrystallized from appropriate solvents.

3-*Benzylidene-2-methylthio-pyrroline* (**11a**). IR (nujol): 1590 (C=C), 1540 (C=N) cm^{-1}; NMR ($CDCl_3$): 2·49 (s, 3, methyl), 2·6–3·0 (m, 2, CH_2), 3·8–4·2 (m, 2, CH_2), 6·76 (t, 1, J = 3 Hz, C=CH), 7·1–7·5 (m, 5, phenyl) ppm; M^+ at *m/e* 203.

2-*Methylthio-3-veratrylidene-1-pyrroline* (**11b**). IR (nujol): 1620 (C=C), 1550 (C=N) cm^{-1}; NMR ($CDCl_3$): 2·52 (s, 3, CH_3), 2·7–3·2 (m, 2, CH_2), 3·7–4·2 (m, 2, CH_2), 3·86 (s, 6, methoxyls), 6·7–7·2 (m, 4, aromatics and C=CH) ppm.

2-*Methylthio-3-(3'-nitrobenzylidene)-1-pyrroline* (**11c**). IR (nujol): 1610 (C=C), 1550 (C=N), 1530 (NO_2) cm^{-1}; NMR ($CDCl_3$): 2·55 (s, 3, CH_3), 2·8–3·2 (m, 2, CH_2), 3·9–4·2 (m, 2, CH_2) 6·77 (s, 1, C=CH), 7·2–8·3 (m, 4, aromatics) ppm; M^+ at *m/e* 248.

2 - *Methylthio* - 3 - (2' - *thiophenecarboxylidene*) - 1 - *pyrroline* (**11d**). IR (nujol): 1600 (C=C), 1550 (C=N) cm^{-1}; NMR ($CDCl_3$): 2·50 (s, 3, CH_3), 2·7–3·1 (m, 2, CH_2), 3·9–4·2 (m, 2, CH_2), 6·9–7·6 (m, 4, thienyl proton and C=CH) ppm.

2-*Benzylthio-3-(4'-chlorobenzylidene)-1-pyrroline* (**11e**). IR (nujol): 1580 (C=C), 1540 (C=N) cm^{-1}; NMR ($CDCl_3$): 2·7–3·0 (m, 2, CH_2), 3·9–4·2 (m, 2, CH_2), 4·36 (s, 2, benzyl CH_2), 6·22 (t, 1, J = 3 Hz, C=CH), 7·0–7·4 (m, 4, aromatics) ppm; M^+ at *m/e* 394. For elemental analysis the product was converted to the hydrochloride by treating a THF soln of the free base in with a THF soln of HCl.

2-*Benzylthio-3-furfurylidene-1-pyroline* (**11f**). IR (film): 1600 (C=C), 1540 (C=N) cm^{-1}; NMR ($CDCl_3$): 2·8–3·1 (m, 2, CH_2), 3·9–4·2 (m, 2, CH_2), 4·40 (s, 2, benzyl CH_2), 6·40 (s, 2, beta-furanyl protons), 6·65 (t, 1, J = 3 Hz, C=CH), 7·1–7·7 (m, 6, phenyl and alpha-furanyl proton) ppm; M^+ at *m/e* 254. The product was converted to the hydrochloride and was analyzed as this salt.

3-*Benzylidene-2-methylthio-3, 4, 5, 6-tetrahydropyridine* (**11g**). IR (nujol): 1600 (C=C), 1580 (C=N) cm^{-1}; NMR ($CDCl_3$): 1·4–1·9 (m, 2, CH_2), 2·33 (s, 3, CH_3), 2·4–2·8 (m, 2, CH_2), 3·6–3·9 (t, 2, J = 5 Hz, CH_2), 7·3 (s, 6, phenyl and C=CH) ppm; M^+ at *m/e* 217.

2-*Methylthio-3-veratrylidene-3, 4, 5, 6-tetrahydropyridine* (**11h**). IR (nujol): 1590 (C=C), 1570 (C=N) cm^{-1}; NMR ($CDCl_3$) 1·5–2·0 (m, 2, CH_2), 2·32 (s, 3, CH_3S), 2·70 (t, 2, J = 7 Hz, each peak further split into doublets J = 2 Hz, CH_2), 3·75 (t, 2, J = 7 Hz, CH_2), 3·84 (s, 6, CH_3O), 6·83 (s, 3, aromatics), 7·14 (t, 1, J = 2 Hz, C=CH) ppm; M^+ at *m/e* 277.

3-*Benzylidene-2-(3', 4'- dimethoxybenzylamino)-2-pyrroline* (**12**). A soln of **11a** (4·0 g; 0·012 mole), veratrylamine (2·0 g, 0·012 mole) and 2-propanol (200 ml) was heated under reflux for 3 days. A crystalline ppt was removed from the hot soln, yield 1·3 g (25%), m.p. 235–236°. This product was neutralized with KOH in water, extracted with chloroform, dired and evaporated to give a white solid that was crystallized from EtOAc to give the title compound as white needles, m.p. 132–133°. IR (nujol): 3200 (NH), 1590 (C=N, C=C) cm^{-1}; NMR ($CDCl_3$) 2·7–3·1 (m, 2, CH_2), 3·6–4·0 (m, 2, CH_2), 3·8 (s, 6, CH_3O), 4·5 (s, 2, benzylic CH_2), 4·8 (s, 1, NH), 6·54 (t, 1, J = 3 Hz, C=CH, 6·7–6·9 (m, 3, aromatic), 7·1–7·4 (m, 5, phenyl) ppm; M^+ at 450. (Found: C, 74·44; H 6·87. $C_{20}H_{22}N_2O_2$ requires: C 74·50, H 6·88%).

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