Intramolecular Cyclisation of Arylalkyl Isothiocyanates. Part 3.[1] Synthesis of 4,5-Dihydro-3*H*-2-benzazepines and 7,8-Dihydro-6H-thieno[3,2-*c*]-azepines †

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The 4,5-dihydro-3*H*-benzazepine-1-thiones (6) and (7), prepared by cyclisation of 3-phenylpropyl isothiocyanate (2) and its 3,4-dimethoxy-derivative (3) with polyphosphoric acid or aluminium chloride, were alkylated with triethyloxonium tetrafluoroborate, dimethyl sulphate, or methyl fluorosulphate to yield the 1-alkylthio-compounds (8)—(10). 3-(2-Thienyl)propyl isothiocyanate (12) reacted with polyphosphoric acid to give a thione (13) which was prepared also from the corresponding lactam (14) and phosphorus pentasulphide. The thione (13) and the lactam (14) were ethylated with triethyloxonium tetrafluoroborate and each of the products, (15) and (16), respectively, was converted into 4-cyclopropylamino-7,8-dihydro-6*H*-thieno[3,2-*c*]azepine (17) by reaction with cyclopropylamine. With aluminium chloride 3-(2-thienyl)propyl isothiocyanate (12) gave a product (18) arising from intermolecular condensation. Attempts to cyclise the isothiocyanates (1)—(5), (12), (26), and (29) with triethyloxonium tetrafluoroborate succeeded only in the case of compound (3), which gave 1-ethylthio-4,5-dihydro-7,8-dimethoxy-3*H*-2-benzazepine (10).

We have reported the syntheses of 1-alkylthio-3,4-dihydroisoquinolines [2] and thienopyridines [1] by cyclisation of 2-arylethyl isothiocyanates and have extended our investigation to other arylalkyl isothiocyanates in an attempt to prepare larger and smaller heterocyclic systems.

4,5-*Dihydro*-3H-2-*benzazepines*.—Cyclisation of 3-phenylpropyl isothiocyanate (2) with aluminium chloride or polyphosphoric acid gave moderate yields (*ca.* 30%) of 4,5-dihydro-3*H*-benzazepine-1-thione (6), which reacted with triethyloxonium tetrafluoroborate, methyl sulphate, or methyl fluorosulphate to give high yields of the corresponding 1-alkylthio-4,5-dihydro-3*H*-2-benzazepine, (8) or (9), respectively. Various attempts were made to improve the yield of the thione (6). A reaction at high dilution in polyphosphoric acid, for example, did not give an increased yield, which suggests that intermolecular condensation of the isothiocyanate (2) is not a significant side reaction.

† Part of this work is the subject of patent applications: M. W. Gittos, J. James, and J. P. Verge, Ger.P. Offen. 1,911,519/1969 (*Chem. Abs.*, 1970, **72**, 12601).

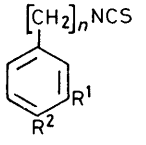
[1] Part 2, R. V. Davies, B. Iddon, T. McC. Paterson, M. W. Pickering, H. Suschitzky, and M. W. Gittos, *J.C.S. Perkin I*, 1976, 138.

[2] Part 1, M. W. Gittos, M. D. Robinson, J. P. Verge, R. V. Davies, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1976, 33.

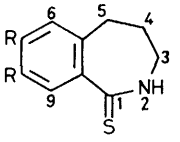
Cyclisation of 3-(3,4-dimethoxyphenyl)propyl isothiocyanate (3) with polyphosphoric acid proceeded rapidly to give a high yield of the thione (7). With triethyloxonium tetrafluoroborate this thione (7) yielded the isolable hydrotetrafluoroborate salt (11) of 1-ethyl-4,5-dihydro-7,8-dimethoxy-3*H*-2-benzazepine (10) or the free base (10), depending on the work-up procedure.

Attempts to cyclise 3-(*p*-bromophenyl)propyl isothiocyanate (4) with aluminium chloride or polyphosphoric acid did not give the corresponding thione; unidentified solids were obtained in each case.

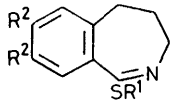
While 3-(3,4-dimethoxyphenyl)propyl isothiocyanate (3) reacted with triethyloxonium tetrafluoroborate to give 1-ethylthio-4,5-dihydro-7,8-dimethoxy-3*H*-2-benzazepine (10) (62% yield) directly, 3-phenylpropyl isothiocyanate (2) gave a complex oily mixture, which



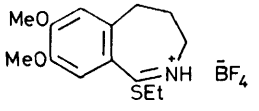
(1) $n = 1$, $R^1 = R^2 = H$
(2) $n = 3$, $R^1 = R^2 = H$
(3) $n = 3$, $R^1 = R^2 = OMe$
(4) $n = 3$, $R^1 = H$, $R^2 = Br$
(5) $n = 4$, $R^1 = R^2 = H$



(6) R = H
(7) R = OMe



(8) $R^1 = Et$, $R^2 = H$
(9) $R^1 = Me$, $R^2 = H$
(10) $R^1 = Et$, $R^2 = OMe$



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chromatography did not separate. (By contrast 2-phenylethyl isothiocyanate under the same conditions gave high yields of 1-ethylthio-3,4-dihydroisoquinoline.[2]) Distillation of this oil resulted mainly in decomposition; chromatography of the small amount of clear distillate obtained again did not separate its components. I.r. absorptions at 2 260 and 2 280 cm^{-1} suggested the presence of an isocyanate, and absorptions in the 3 000—3 100 cm^{-1} region suggested the presence of a monosubstituted benzene, thus indicating that cyclisation had not occurred. The complex ^1H n.m.r. spectrum of the distillate was consistent with the presence of a monosubstituted benzene and two ethyl groups. 3-Phenylpropyl isothiocyanate (2) also gave an intractable mixture with methyl fluorosulphate.

3-(*p*-Bromophenyl)propyl isothiocyanate (4) reacted with triethyloxonium tetrafluoroborate or methyl fluorosulphate more slowly than either of the isothiocyanates (2) and (3) and gave complex mixtures similar to those obtained by reaction of the parent compound (2) with these alkylating agents.

It is possible, therefore, to synthesise 4,5-dihydro-3*H*-2-benzazepines by our procedures; reactions are facilitated by the presence of electron-donating groups in the benzene ring of the starting isothiocyanate. Interestingly, an attempt to prepare 4,5-dihydro-1-methylthio-3*H*-2-benzazepine (9) by a procedure analogous to the Lora–Tomayo procedure (see ref. 2 and references cited therein), namely by reaction of 3-phenylpropyl chloride with methyl thiocyanate in the presence of tin(IV) chloride, yielded 3,4-dihydro-3-methyl-1-methylthioisoquinoline together with an unidentified compound. The isoquinoline is formed presumably by rearrangement of the 3-phenylpropylium ion prior to condensation with the methyl thiocyanate and cyclisation.[2]

7,8-*Dihydro*-6H-*thieno*[3,2-c]*azepines*.—In connection with other work concerning the potential pharmacological activity of thienoazepines[3,4] it became of interest to study the cyclisation of 3-(2-thienyl)propyl isothiocyanate (12). Initially we hoped that the thiophen ring would facilitate cyclisation of this compound. With polyphosphoric acid, however, it gave the thione (13) in only 13% yield. A higher yield (71%) of this thione was obtained by reaction of the lactam (14) {prepared from 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one oxime by means of a Beckmann rearrangement[5]} with phosphorus pentasulphide. Triethyloxonium tetrafluoroborate alkylated both the thione (13) and the lactam (14) to give 4-ethylthio- (15) and 4-ethoxy-7,8-dihydro-6*H*-thieno[3,2-*c*]azepine (16), respectively. These compounds (or their hydrochloride salts) reacted with cyclopropylamine hydrochloride (or the free base, respectively) to give the 4-cyclopropylamino-derivative (17). In general, the 4-ethylthio-compound (15) gave a better yield than the ethoxy-compound (16).

3-(2-Thienyl)propyl isothiocyanate (12) reacted vigorously with aluminium chloride. At room temperature in tetrachloroethane it gave 2-(3-isothiocyanatopropyl)-5-{*N*-[3-(2-thienyl)propyl]thiocarbamoyl}thiophen (18) (20% yield) as the only isolable product. This arises by intermolecular attack of the initially generated intermediate, $R[CH_2]_3{\cdot}N{=}C^+{-}S^-{-}AlCl_3$ (R = 2-thienyl), in the electron-rich 5-position of the starting isothiocyanate (12).

With triethyloxonium tetrafluoroborate 3-(2-thienyl)-propyl isothiocyanate (12) gave an oily mixture which chromatography did not separate. After 24 h, a white solid separated from this oil, and this was filtered off and purified. Elemental analysis and mass spectrometry showed it to have the molecular formula $C_{20}H_{26}N_2S_4$, which suggests structure (19), although the polymeric structure (20) cannot be ruled out on this evidence alone.

[3] B. Iddon, H. Suschitzky, and D. S. Taylor, *J.C.S. Perkin I*, 1974, 579.

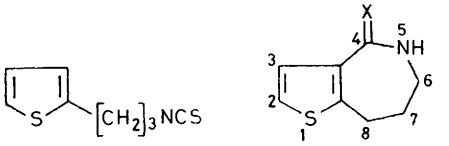
[4] B. Iddon, M. W. Pickering, and H. Suschitzky, *J.C.S. Chem. Comm.*, 1974, 759; B. Iddon, M. W. Pickering, H. Suschitzky, and D. S. Taylor, *J.C.S. Perkin I*, 1975, 1686.

[5] B. P. Fabrichnyi, I. F. Shalavina, and Ya. L. Gol'dfarb, *J. Org. Chem.* (*U.S.S.R.*), 1965, **1**, 1526.

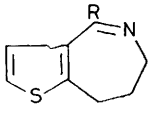
The i.r. spectrum of this compound is consistent with either structure, and in the ^1H n.m.r. spectrum two doublets are seen at τ 3.33 and 4.15 (J 6.0 Hz in each case). The high-field resonance of the aromatic protons is more consistent with structure (19) than (20).[6]

Attempts to cyclise 4-phenylbutyl isothiocyanate (5) and benzyl isothiocyanate (1) with triethyloxonium tetrafluoroborate or methyl fluorosulphate in the hope that they would yield the benzazocines (21) and the benzo[*c*]pyrroles (22) (R = Et or Me in both cases) gave only intractable mixtures. Attempts to trap the identified solid. *cis*-Cinnamyl isothiocyanate (29) also gave intractable mixtures with triethyloxonium tetrafluoroborate and was not studied further.

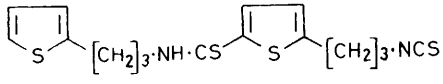
Preparation of Starting Materials.—Isothiocyanates were prepared by the Hodgkins–Ettlinger[7,8] modification of the Andreasch–Kaluza procedure (Scheme). They were contaminated, as we have reported previously,[2] with small amounts of carbonyl-containing impurities (i.r.), inseparable by distillation, which probably arise by incomplete breakdown of the intermediates (30) (Scheme). An attempt to separate the



(12) (13) X = S (14) X = O



(15) R = SEt
(16) R = OEt
(17) R = $H_2\overset{+}{N}$—⟨▷⟩ Cl^-



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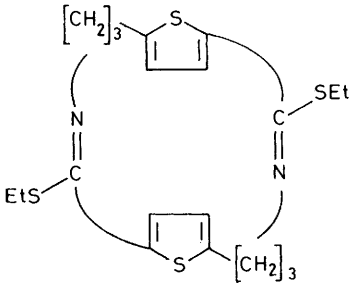

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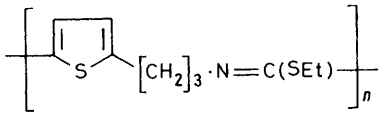


(20)

benzo[*c*]pyrroles by addition of maleic anhydride were unsuccessful too.

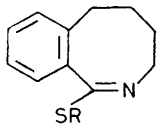
In order to study the effect of a bulky substituent or the presence of a double bond in the side-chain we prepared the isothiocyanates (26) and (29). We hoped that such structural constraints would facilitate cyclisation. The acetal isothiocyanate (26) was chosen because the desired product would contain a useful carbonyl function which we hoped to modify. With alkylating agents, however, isothiocyanate (26) gave intractable oils similar to those mentioned before. With polyphosphoric acid it gave a small amount of an uncarbonyl-containing impurity present in 3-phenylpropyl isothiocyanate (2) by chromatography on silica resulted in decomposition and led to a poor recovery (*ca.* 5%) of organic material. An attempt to prepare 3-phenylpropyl isothiocyanate (2) on a moderately large scale (2 molar) gave *NN'*-bis-(3-phenylpropyl)thiourea as the major product. Its formation can be rationalised by competition between the triethylamine and 3-phenylpropylamine in the second step of the Scheme, which excludes the protonated primary amine from further

[6] B. H. Smith, 'Bridged Aromatic Compounds,' Academic Press, New York and London, 1964, p. 407.

[7] J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, 1956, **21**, 404.

[8] E. E. Reid, 'Organic Chemistry of Bivalent Sulfur,' Vol. VI, Chemical Publ. Co., New York, 1966, p. 64.

reaction until alkali is added during work-up, when it is set free only to react with the isothiocyanate produced. This problem was overcome by reverse addition, *i.e.* addition of 3-phenylpropylamine to a solution of carbon



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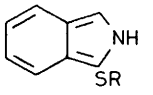

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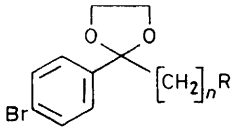
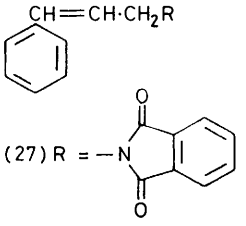


(23) $n = 1$, R = Br
(24) $n = 1$, R = CN
(25) $n = 2$, R = NH_2
(26) $n = 2$, R = NCS



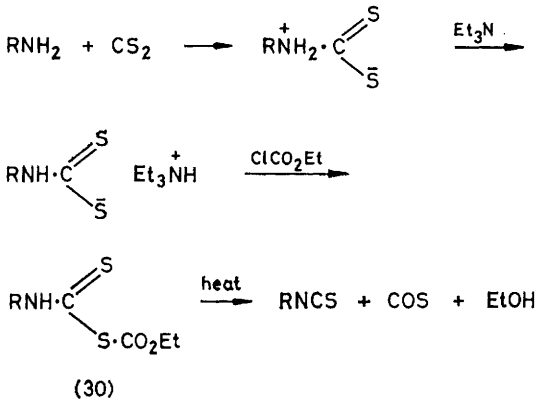
(27) R = —N

(28) R = NH_2
(29) R = NCS

disulphide and triethylamine in methylene chloride prior to addition of ethyl chloroformate.

3-(3,4-Dimethoxyphenyl)propylamine was synthesised by condensation of veratraldehyde with malonic acid, conversion of the resulting 3,4-dimethoxycinnamic acid into its amide, and reduction of the amide.

3-(*p*-Bromophenyl)propylamine and 3-amino-4′-bromopropiophenone ethylene acetal (25) were prepared by reduction of 3-(*p*-bromophenyl)propiononitrile and 3-(*p*-bromophenyl)-3-oxopropiononitrile ethylene acetal (24), respectively. The former nitrile was obtained by



(30)

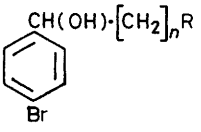
SCHEME

successive reaction of *p*-dibromobenzene with n-butyllithium and ethylene oxide, conversion of the 2-(*p*-bromophenyl)ethanol produced into 2-(*p*-bromophenyl)-ethyl bromide, and reaction of the bromide with cyanide ion. In agreement with a report by Sontag,[9] elemental bromination of 2-phenylethyl bromide gave a mixture (g.l.c.) of approximately equal amounts of 2-(*o*- and *p*-bromophenyl)ethyl bromide, which proved difficult to separate.

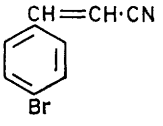
3-(*p*-Bromophenyl)-3-oxopropiononitrile ethylene acetal (24) was synthesised from *p*-bromophenacyl cyanide and ethylene glycol in the presence of toluene-*p*-sulphonic acid. The yield of this nitrile (24) increased as the amount of toluene-*p*-sulphonic acid was increased. Treatment of the corresponding bromide (23) with cyanide ion in either dimethyl sulphoxide or dimethylformamide resulted in 100% recovery of starting material under all the conditions employed.[10] In aqueous ethanol hydrolysis of the acetal occurred. The ethylene acetal (23) was prepared without difficulty from *p*-bromophenacyl bromide and ethylene glycol.

Hydrogenation of *N*-(3-phenylprop-2-ynyl)phthalimide in the presence of 5% palladium–barium sulphate gave *cis*-*N*-cinnamylphthalimide (27). The use of a Lindlar catalyst as recommended in a patent [11] was unsatisfactory. Hydrazinolysis of *cis*-*N*-cinnamylphthalimide (27) gave *cis*-cinnamylamine (28).[11]

Attempts to prepare the amine (32) by selective reduction of *p*-bromophenacyl cyanide failed. Use of



(31) $n = 1$, R = CN
(32) $n = 2$, R = NH_2



(33)

lithium aluminium hydride yielded mixtures containing at least five components (t.l.c.), and sodium borohydride gave mainly mixtures of 3-(*p*-bromophenyl)-3-hydroxypropiononitrile (31) and the product (33) of dehydration of the nitrile. Reduction of both 3-(*p*-bromophenyl)-3-hydroxypropiononitrile (31) and *p*-bromocinnamonitrile (33) with lithium aluminium hydride gave 3-(*p*-bromophenyl)propylamine. The nitrile (31) readily dehydrated in the presence of toluene-*p*-sulphonic acid to give a *p*-bromocinnamononitrile (33).

EXPERIMENTAL *

^{1}H N.m.r. spectra were recorded with a Varian A60 or HA100 spectrometer (Me_4Si as internal standard), i.r. spectra (liquids as films and solids as Nujol mulls) with a Perkin-Elmer 257 instrument, and mass spectra with an A.E.I. MS12 or MS902S instrument. Mass spectra of all new compounds were consistent with the assigned structures. Calculated M^+ values for mass spectra are for the ions containing ^{79}Br and ^{32}S. For g.l.c. a Pye 104 Chromatograph was used, fitted with a flame-ionisation detector and 5 ft × 5.0 mm (i.d.) columns.

Light petroleum had b.p. 60—80 °C unless stated otherwise.

* N.m.r. spectroscopic and elemental analysis data are available as Supplementary Publication No. SUP 22101 (5 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1976, Index issue.

[9] D. Sontag, *Ann. Chim.* (*France*), 1934, **1**, 359 (*Chem. Abs.*, 1934, **28**, 4716).
[10] R. V. Davies, Ph.D. Thesis, University of Salford, 1973.
[11] R. P. Mull, U.S.P. 3,332,988/1967 (*Chem. Abs.*, 1967, **67**, 108427).

3,4-Dimethoxycinnamamide (73%), m.p. 169—171 °C (from water) (lit.,[12] 164—166 °C) was prepared from 3,4-dimethoxycinnamic acid [13] in the normal way.

p-Bromophenacyl cyanide (93%), m.p. 166 °C (lit.,[14] 158 °C), was prepared by a procedure similar to that reported.[14]

3-Phenylprop-2-yn-1-ol (94%),[15] $\nu_{max.}$ 3 330br (OH) and 2 250 cm^{-1} (C≡C), prepared from phenylacetylene by successive treatment with n-butyl-lithium and paraformaldehyde, was converted into 3-chloro-1-phenylprop-1-yne (95%), b.p. 118 °C at 16.0 mmHg (lit.,[16] 99 °C at 7.0 mmHg), $\nu_{max.}$ 2 240 cm^{-1} (C≡C), with thionyl chloride (1 equiv.) in chloroform by heating under reflux for 1 h and then storing overnight at ambient temperature before work-up in the usual way.

3-(2-Thienyl)propylamine (71%), b.p. 60—75 °C at 0.4 mmHg (lit.,[17] 110—112 °C at 19 mmHg) was synthesised by the method of Blicke and Burkhalter.[17]

4-Phenylbutylamine (38%), b.p. 82 °C at 1.5 mmHg (lit.,[18] 123—124 °C at 17.0 mmHg), $\nu_{max.}$ 3 300 and 3 380 cm^{-1} (NH_2), was prepared by the method of von Braun.[18]

3-(3,4-*Dimethoxyphenyl*)*propylamine*.— 3,4-Dimethoxycinnamamide (20.7 g, 0.1 mol) was placed in the thimble of a Soxhlet apparatus and added by extraction during *ca.* 48 h to a suspension of lithium aluminium hydride (7.6 g, 0.2 mol) in tetrahydrofuran (200 ml) heated under reflux (this procedure was used because the amide was extremely insoluble in ethers, and it gave higher yields). Work-up in the usual way gave the amine (15.8 g, 81%), b.p. 140—150 °C at 3.5 mmHg (lit.,[19] 125—130 °C at 1.5 mmHg), $\nu_{max.}$ 3 300 and 3 360 cm^{-1} (NH_2).

2-(p-*Bromophenyl*)*ethanol*.—A solution of n-butyl-lithium (1.0 mol) in hexane (456 ml) was added dropwise during 1.5 h to a stirred solution of *p*-dibromobenzene (236.0 g, 1.0 mol) in anhydrous ether (500 ml) at −40 °C under nitrogen and the resulting mixture was allowed to warm slowly to ambient temperature. It was recooled to −40 °C and a solution of ethylene oxide (44.0 g, 1.0 mol) in anhydrous ether (800 ml) was added dropwise during 1 h. Then the mixture was allowed to warm slowly to room temperature again and was stirred at this temperature for a further 1 h. Work-up in the usual way gave starting material (8.0 g, 3% recovery) and 2-(*p*-bromophenyl)-ethanol (157.5 g, 84%), b.p. 117—120 °C at 1.0 mmHg (lit.,[20] 154—155 °C at 18.5 mmHg), $\nu_{max.}$ 3 320br cm^{-1} (OH).

2-(*p*-Bromophenyl)ethyl bromide (78%), b.p. 98 °C at 0.8 mmHg (lit.,[20] 124.5—125.5 °C at 5—5.5 mmHg), was prepared from the alcohol by the method of Griffin *et al.*[20]

3-(p-*Bromophenyl*)*propylamine*.—(*a*) A solution of 2-(*p*-bromophenyl)ethyl bromide (63.2 g, 0.24 mol) in ethanol (400 ml) was added dropwise to a stirred solution of sodium cyanide (12.0 g, 0.25 mol) in water (100 ml) at ambient temperature and the resulting mixture was heated under reflux for 20 h. An excess of water was added and extraction with ether gave 3-(p-*bromophenyl*)*propiononitrile* (46.7 g, 93%), b.p. 126 °C at 0.6 mmHg, $\nu_{max.}$ 2 260 cm^{-1} (C≡N), *m/e* 209 (M^+).

(*b*) A solution of the nitrile (46.0 g, 0.22 mol) in ether (500 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (8.3 g, 0.22 mol) in ether (100 ml) heated under reflux at a rate such that gentle boiling continued with the heating source removed, and the resulting mixture was then heated under reflux for a further 1.5 h. Work-up in the usual way gave 3-(p-*bromophenyl*)-*propylamine* (25.0 g, 53%), b.p. 108 °C at 1.0 mmHg, $\nu_{max.}$ 3 300 and 3 380 cm^{-1} (NH_2), *m/e* 213 (M^+); *hydrochloride*, m.p. 181 °C (from ethanol–chloroform).

2,4′-*Dibromoacetophenone Ethylene Acetal* (23).—A mixture of *p*-bromophenacyl bromide (27.8 g, 100 mmol), ethylene glycol (10 ml; excess), toluene-*p*-sulphonic acid (1.0 g, 5.8 mmol), and toluene (1.5 l) was heated under reflux for 1 h with azeotropic removal of water (1.8 ml). The toluene was distilled off under reduced pressure, and the residue was shaken with ether (500 ml). The ethereal solution was filtered and the solvent distilled off to yield the acetal (23) (27.3 g, 85%), m.p. 76 °C (from ethanol) (lit.,[21] 78—80 °C), *m/e* 320 (M^+).

3-(p-*Bromophenyl*)-3-*oxopropiononitrile Ethylene Acetal* (24).—A rapidly stirred mixture of *p*-bromophenacyl cyanide (12.15 g, 54.2 mmol), ethylene glycol (6.3 g, 101.6 mmol), toluene-*p*-sulphonic acid (19.2 g, 111.6 mmol), and anhydrous toluene (500 ml) (it is important that this be pre-dried with sodium) was heated under reflux for 6 h with azeotropic distillation of water. The resulting mixture was washed with saturated aqueous sodium hydrogen carbonate (2 × 200 ml), then with water (3 × 500 ml), and dried ($MgSO_4$). Distillation under reduced pressure and crystallisation of the residue from ethanol gave the *product* (9.5 g, 66%), m.p. 95 °C, $\nu_{max.}$ 2 260 cm^{-1} (C≡N).

3-*Amino*-4′-*bromopropiophenone Ethylene Acetal* (25). This was prepared (35%) by reduction of the nitrile synthesised as described in the preceding experiment with lithium aluminium hydride in ether in the usual way. It had b.p. 130 °C at 0.1 mmHg, $\nu_{max.}$ 3 310 and 3 380 cm^{-1} (NH_2), *m/e* 271 (M^+). This compound was treated with hot acetic anhydride for 10 min, to give N-*acetyl*-3-*amino*-4′-*bromopropiophenone* (32%), m.p. 138—139 °C (from aqueous ethanol), $\nu_{max.}$ 1 635 (amide C=O), 1 680 (C=O), and 3 260 cm^{-1} (NH), *m/e* 269 (M^+).

Reduction of p-*Bromophenacyl Cyanide*.—(*a*) A solution of sodium borohydride (0.25 g, 6.6 mmol) and 2M-sodium hydroxide (0.2 ml) in water (1.8 ml) was added dropwise to a stirred suspension of the nitrile (2.24 g, 10.0 mmol) in methanol (15 ml) heated under reflux and the resulting mixture was heated under reflux for a further 1 h. Then it was poured into water (500 ml); extraction with ether followed by distillation gave 3-(p-*bromophenyl*)-3-*hydroxypropiononitrile* (31) (2.0 g, 88%), b.p. 200 °C at 1.0 mmHg (Kugelrohr apparatus), m.p. 60 °C, $\nu_{max.}$ 3 425 (OH) and 2 275 cm^{-1} (C≡N), *m/e* 225 (M^+), characterised as the product of dehydration (see later).

(*b*) A reaction similar to that described in (*a*) was carried out on ten times the scale in ethanol. Distillation gave a complex mixture (6.3 g), b.p. 100—140 °C at 1.00 mmHg, which contained olefinic compounds (^1H n.m.r.) (not

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examined further), and 3-(*p*-bromophenyl)-3-hydroxypropiononitrile (31) (13.4 g, 59%), identical (m.p. and i.r. and ^{1}H n.m.r. spectra) with the sample prepared as described in (*a*).

(*c*) The reaction described in (*a*) was repeated on twenty times the scale. Concentration of the combined ethereal extracts under reduced pressure gave *trans-p*-bromocinnamonitrile (33) (21.3 g, 51%), m.p. 106—108 °C (lit.,[22] 105—106 °C), $\nu_{max.}$ 2 235 (C≡N) and 1 630 cm^{-1} (C=C), *m/e* 207 (M^+).

Other reactions analogous to those described in (*a*)—(*c*) gave mainly mixtures (^{1}H n.m.r.) of compounds (31) and (33). Treatment of one such mixture (11.9 g) with toluene-*p*-sulphonic acid (0.5 g) in toluene (250 ml) with azeotropic distillation of the eliminated water, removal of the solvent under reduced pressure, addition of water (100 ml) to the residue, and extraction with ether gave *p*-bromocinnamonitrile (33) (7.2 g), b.p. 120 °C at 0.2 mmHg, m.p. 101 °C, identical (i.r.) with the sample prepared as described in (*c*).

Reduction of 3-(p-*Bromophenyl*)-3-*hydroxypropiononitrile* (31).—Reduction with lithium aluminium hydride in ether and work-up in the usual way gave 3-(*p*-bromophenyl)-propylamine (38%), identical (i.r.) with the sample prepared as described before.

Reduction of p-*Bromocinnamononitrile* (33).—Reduction with lithium aluminium hydride in ether, work-up in the usual way, and distillation of the brown oil obtained also gave 3-(*p*-bromophenyl)propylamine (61%), identical (i.r.) with the samples prepared as described before. The residue (3.1 g) of the distillation was triturated with light petroleum, which left an unidentified solid, m.p. 140 °C (from ethanol).

cis-*Cinnamylamine* (28).—(*a*) *N*-(3-Phenylprop-2-ynyl)-phthalimide was prepared (76%) by the method of Mull.[11] It had m.p. 157—159 °C (from aqueous ethanol) (lit.,[11] 158—160 °C), $\nu_{max.}$ 1 710 cm^{-1} (C=O).

(*b*) A mixture of *N*-(3-phenylprop-2-ynyl)phthalimide (22.0 g, 85.0 mmol), ethyl acetate (500 ml), methanol (500 ml), and 5% palladium–barium sulphate (4 g) was hydrogenated (1 880 ml of hydrogen taken up in 8 h). The catalyst was filtered off and the solvents distilled off under reduced pressure to give *cis-N*-cinnamylphthalimide (27) (18.8 g, 86%), m.p. 100—105 °C (from aqueous ethanol) (lit.,[11] 110—111 °C), $\nu_{max.}$ 1 710 cm^{-1} (C=O), *J* (olefinic protons) 12 Hz.

(*c*) Hydrazinolysis of *cis-N*-cinnamylphthalimide (27) (8.9 g, 34.0 mmol) according to the procedure reported by Mull [11] gave *cis*-cinnamylamine (28) (3.4 g, 74%), b.p. 80 °C at 0.3 mmHg, $\nu_{max.}$ 3 290 and 3 365 cm^{-1} (NH_2), *J* (olefinic protons) 12 Hz; hydrochloride, m.p. 173—175 °C (lit.,[11] 177—178 °C).

Arylalkyl Isothiocyanates.—The following isothiocyanates were prepared by the general method given in Part 1: [2] benzyl isothiocyanate (1) (63%), b.p. 112 °C at 4.5 mmHg (lit.,[23] 90—91 °C at 1.3 mmHg), $\nu_{max.}$ 2 100 and 2 185 cm^{-1} (NCS); 3-phenylpropyl isothiocyanate (2) (92%), b.p. 130 °C at 2.0 mmHg (lit.,[24] 156—160 °C at 12.0 mmHg), $\nu_{max.}$ 2 100 and 2 190 cm^{-1} (NCS); 4-phenylbutyl isothiocyanate (5) (80%), b.p. 130 °C at 0.5 mmHg (lit.,[24] 166—174 °C at 12.0 mmHg), $\nu_{max.}$ 2 110 and 2 190 cm^{-1} (NCS); 3-(3,4-*dimethoxyphenyl*)*propyl isothiocyanate* (3) (86%), b.p. 180—190 °C at 1.3 mmHg, $\nu_{max.}$ 2 110 and 2 190 cm^{-1} (NCS), *m/e* 237 (M^+); characterised as a thiourea derivative (see later); 3-(p-*bromophenyl*)*propyl isothiocyanate* (4) (76%), b.p. 160 °C at 1.5 mmHg, $\nu_{max.}$ 2 100 and 2 190 cm^{-1} (NCS), *m/e* 255 (M^+); 3-(2-*thienyl*)*propyl isothiocyanate* (12) (94%), b.p. 110—112 °C at 4.0 mmHg, $\nu_{max.}$ 2 120 and 2 200 cm^{-1} (NCS), *m/e* 183 (M^+); 3-(p-*bromophenyl*)-3-*oxopropyl isothiocyanate ethylene acetal* (26) (71%), b.p. 120 °C at 0.5 mmHg, m.p. 48—50 °C (from n-pentane), $\nu_{max.}$ 2 120 and 2 220 cm^{-1} (NCS); and cis-*cinnamyl isothiocyanate* (29) (20%), b.p. 140 °C at 2.0 mmHg, $\nu_{max.}$ 2 100 and 2 180 cm^{-1} (NCS), *m/e* 175 (M^+), characterised as a thiourea derivative (see later).

N-*Benzyl*-N′-(3-*phenylpropyl*)*thiourea*.[25]—A solution of benzylamine (5.35 g, 50 mmol) in ethanol (25 ml) was added dropwise to a stirred solution of 3-phenylpropyl isothiocyanate (8.85 g, 50 mmol) in ethanol (25 ml), and the resulting mixture was heated under reflux for 5 min. It was then cooled and water was added to precipitate the *thiourea* (14.0 g, 99%), m.p. 80 °C (from ethanol), $\nu_{max.}$ 3 320 and 3 290 cm^{-1} (NH), *m/e* 284 (M^+).

The following thioureas were prepared similarly: *N*-[3-(p-*bromophenyl*)*propyl*]-N′-*butylthiourea* (55%), m.p. 102—106 °C (from 70% aqueous ethanol), $\nu_{max.}$ 3 220 cm^{-1} (NH), *m/e* 328 (M^+); NN′-*bis*-[3-(p-*bromophenyl*)*propyl*]*thiourea* (60%), m.p. 121—123 °C (from 70% aqueous ethanol), $\nu_{max.}$ 3 240 and 3 340 cm^{-1} (NH), *m/e* 468 (M^+); N-*cyclohexyl*-N′-[3-(3,4-*dimethoxyphenyl*)*propyl*]*thiourea*, m.p. 129 °C (from aqueous ethanol); N-*benzyl*-N′-[3-(2-*thienyl*)-*propyl*]*thiourea*, m.p. 74 °C; and N-cis-*cinnamyl*-N′-*phenylthiourea*, m.p. 85—87 °C (from ethyl acetate–light petroleum).

Cyclisation of 2-*Phenylpropyl Isothiocyanate* (2).—(a) *With aluminium chloride*. A solution of the isothiocyanate (2) (5.4 g, 30.0 mmol) in tetrachloroethane (20 ml) was added dropwise to a stirred suspension of aluminium chloride (8.0 g, 60.0 mmol) in tetrachloroethane (50 ml) at 20 °C. The resulting mixture was heated at 120 °C for 1 h, then poured on a mixture of crushed ice and hydrochloric acid. The resulting black solid was filtered off and triturated with tetrachloroethane. The washings were combined and evaporated almost to dryness; addition of light petroleum gave 4,5-*dihydro*-3H-2-*benzazepine*-1-*thione* (6) (1.7 g, 32%), m.p. 128 °C (from ethanol), $\nu_{max.}$ 3 120 cm^{-1} (NH) (Found: M^+, 177.0612. $C_{10}H_{11}NS$ requires *M*, 177.0612).

(b) *With polyphosphoric acid*. Several reactions were carried out at different temperatures and for different periods of time. The optimum yield was obtained by heating a mixture of the isothiocyanate (2) (10.0 g, 56 mmol) and polyphosphoric acid (100 g) at 130 °C for 48 h. The mixture was poured into ice-cold water (500 ml), whereupon 4,5-dihydro-3*H*-2-benzazepine-1-thione (6)(2.6 g, 26%) separated, m.p. 127 °C (from ethanol), identical (i.r.) with the sample prepared as described in (a). Continuous extraction of the remaining aqueous solution with chloroform for 24 h yielded no organic product. Addition of 2M-sodium hydroxide to the aqueous solution and subsequent extraction with chloroform gave an intractable tar, and continuous extraction of the basified aqueous solution with chloroform for 24 h gave more tar.

(c) *With triethyloxonium tetrafluoroborate*. A mixture of the isothiocyanate (2) (13.4 g, 75.0 mmol) and triethyl-

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oxonium tetrafluoroborate (14.5 g, 76.0 mmol) in methylene chloride (15 ml) was heated under reflux for 3 h and then worked up as described before.[2] This gave an acid-soluble material (5.3 g) and an acid-insoluble material (6.2 g). The latter was shown by i.r. spectroscopy and t.l.c. to be largely starting material. The acid-soluble material was recovered in the usual way and one part was chromatographed on silica. Light petroleum eluted a mixture containing at least eight components. Since only about 20% of the material placed on the column was recovered, chromatography was abandoned. Distillation (Kugelrohr apparatus) of a second part gave an oil, b.p. 100 °C at 0.1 mmHg, which remains unidentified.

(d) *With methyl fluorosulphate.* A mixture of the isothiocyanate (2) (8.8 g, 50.0 mmol), methyl fluorosulphate (5.7 g, 50.0 mmol), and methylene chloride (10 ml) was stirred and heated under reflux for 1 h. Then it was cooled and stirred at 20 °C for 24 h. Work-up in the usual way gave an acid-soluble oil (1.6 g) similar (t.l.c. and i.r. and ^{1}H n.m.r. spectra) to that obtained in (c). This was not studied further.

1-*Ethylthio*-4,5-*dihydro*-3H-2-*benzazepine* (8).—A mixture of 4,5-dihydro-3*H*-2-benzazepine-1-thione (6) (1.77 g, 10.0 mmol) and triethyloxonium tetrafluoroborate (1.99 g, 10.0 mmol) in chloroform (50 ml) was heated under reflux for 3 h. Work-up as described before gave the *product* (8) (1.62 g, 78%), b.p. 103 °C at 0.6 mmHg, $\nu_{max.}$ 1 610 cm^{-1} (C=N), *m/e* 205 (M^+). This compound was not subjected to microanalysis but gave with amines the same 1-amino-derivatives as the 1-methylthio-compound, prepared as described in the following paragraph. (The 1-amino-derivatives are described in patents; see footnote on title page.)

4,5-*Dihydro*-1-*methylthio*-3H-2-*benzazepine* (9).—(*a*) Dimethyl sulphate (3.0 ml, 30.0 mmol) was added dropwise to a solution of the thione (6) (5.2 g, 30.0 mmol) in benzene (25.0 ml) heated under reflux and the resulting mixture was heated under reflux for a further 1.5 h. Water was added and the benzene was separated off. Addition of potassium carbonate to the aqueous layer and extraction with ether gave the *product* (9) (4.0 g, 70%), b.p. 90 °C at 0.05 mmHg, $\nu_{max.}$ 1 610 cm^{-1} (C=N).

(*b*) A solution of methyl fluorosulphate (1.14 g, 10.0 mmol) in methylene chloride (5 ml) was added dropwise to a solution of the thione (6) (1.77 g, 10.0 mmol) in methylene chloride (50 ml) heated under reflux and the resulting mixture was heated under reflux for a further 2 h. Work-up in the usual way gave an acid-soluble oil (1.61 g, 84%), identical (i.r.) with the product prepared as described in (*a*).

Attempt to Prepare 4,5-*Dihydro*-1-*methylthio*-3H-2-*benzazepine* (9) *from* 3-*Phenylpropyl Chloride and Methyl Thiocyanate* (*Lora-Tomayo Procedure*).—Tin(IV) chloride (104.3 g, 47 ml, 0.4 mol was added dropwise to a stirred mixture of 3-phenylpropyl chloride (61.8 g, 0.4 mol) and methyl thiocyanate (29.2 g, 27.2 ml, 0.4 mol) at ambient temperature. The mixture was heated at 110 °C for 1.5 h, then the temperature was allowed to rise to 135 °C during 3.5 h. The cooled mixture was poured into 3M-sodium hydroxide (450 ml) and worked up as described before.[2] Distillation gave two fractions: (i) 3,4-dihydro-3-methyl-1-methylthioisoquinoline (3.1 g), b.p. 82—84 °C at 0.05 mmHg, with acceptable i.r. and ^{1}H n.m.r. spectra [different from those of compound (9)]; and (ii) an unidentified compound (3.7 g), b.p. 85—120 °C at 0.1 mmHg (Found: C, 60.5; H, 7.0; N, 5.6%).

1-*Ethylthio*-4,5-*dihydro*-7,8-*dimethoxy*-3H-2-*benzazepine* (10).—(*a*) (i) A mixture of 3-(3,4-dimethoxyphenyl)propyl isothiocyanate (3) (3.0 g, 12.7 mmol) and polyphosphoric acid (100 g) was stirred at 120 °C for 10 min. Then it was poured into water and 4,5-*dihydro*-7,8-*dimethoxy*-3H-2-*benzazepine*-1-*thione* (7) (2.6 g, 87%) was filtered off, m.p. 165 °C (from ethanol), $\nu_{max.}$ 3 130 cm^{-1} (NH), *m/e* 237 (M^+).

(ii) A stirred mixture of the thione (7) (2.2 g, 9.3 mmol), triethyloxonium tetrafluoroborate (4.0 g, 21.0 mmol), and chloroform (5 ml) was heated under reflux for 1 h, then kept overnight at ambient temperature. It was poured into water and stirred, and the resulting aqueous layer was made alkaline with 2M-sodium hydroxide. Extraction with ether gave 1-*ethylthio*-4,5-*dihydro*-7,8-*dimethoxy*-3H-2-*benzazepine* (10) (1.52 g, 62%), b.p. 100 °C at 0.05 mmHg (Kugelrohr apparatus), *m/e* 265 (M^+); *hydrotetrafluoroborate salt* (11) (this salt was prepared by adding a similar reaction mixture to ether), m.p. 185 °C (from propan-2-ol–light petroleum), $\nu_{max.}$ 3 310 cm^{-1} ($^+$NH), mass spectrum identical with that of the free base.

(*b*) A mixture of 3-(3,4-dimethoxyphenyl)propyl isothiocyanate (3) (2.37 g, 10.0 mmol), triethyloxonium tetrafluoroborate (1.91 g, 10.0 mmol), and chloroform (3 ml) was stirred and heated under reflux for 1 h. Work-up in the usual way gave an acid-insoluble fraction (1.9 g), which was not examined further, and an acid-soluble fraction, which was distilled to give 1-ethylthio-4,5-dihydro-7,8-dimethoxy-3*H*-2-benzazepine (10) (0.6 g, 23%), b.p. 100 °C at 0.05 mmHg, identical (i.r., ^{1}H n.m.r., and mass spectra) with the sample prepared as described in (*a*).

Reactions of 3-(p-*Bromophenyl*)*propyl Isothiocyanate* (4).—(a) *With aluminium chloride.* A solution of the isothiocyanate (4) (2.7 g, 10.5 mmol) in tetrachloroethane (10 ml) was added dropwise to a stirred suspension of aluminium chloride (3.9 g, 30.0 mmol) in tetrachloroethane (100 ml) at ambient temperature and the resulting mixture was stirred at this temperature for 38 h. Water was added followed by 2M-hydrochloric acid, and extraction with ether yielded a tar which was chromatographed on silica. Chloroform eluted an unidentified solid (0.83 g), m.p. 300 °C, $\nu_{max.}$ 3 200—2 500br cm^{-1}, τ($CDCl_3$) 2.50—2.90 (m, aromatic), 6.10—6.30 (m), and 7.80—8.40 (m).

(b) *With polyphosphoric acid.* The isothiocyanate (4) (5.4 g, 21.1 mmol) was added dropwise to polyphosphoric acid (50 g) stirred and heated at 180 °C. The resulting mixture was heated at 180 °C for a further 1 h, then poured into water. An unidentified solid (1.3 g) separated and was filtered off, m.p. 280 °C (with decomp.), $\nu_{max.}$ 3 000—3 500br cm^{-1}. Extraction of the aqueous layer with ether gave starting material (1.0 g, 18.5% recovery).

5,6,7,8-*Tetrahydrothieno*[3,2-c]*azepine*-4-*thione* (13).—(*a*) A vigorously stirred mixture of 3-(2-thienyl)propyl isothiocyanate (12) (3.0 g, 16.4 mmol) and polyphosphoric acid (30 g) was heated to 135—140 °C during 20 min, then heated at this temperature for 10 min, cooled, and poured into water. Extraction with ether gave the *thienoazepine* (13) (0.4 g, 13%) as an oil which rapidly solidified, m.p. 93—94 °C (yellow needles from aqueous acetone), $\nu_{max.}$ 3 150 cm^{-1} (NH), *m/e* 183 (M^+).

(*b*) An intimate mixture of 5,6,7,8-tetrahydrothieno-[3,2-*c*]azepin-4-one [5] (14) (4.9 g, 29.0 mmol) and phosphorus pentasulphide (3.6 g, 16.0 mmol) was heated to 80 °C. The source of heat was then removed, and the temperature of the mixture continued to rise to 130 °C. After the initial exothermic reaction was over, the mixture was

heated at 140 °C for 30 min. Warm water (150 ml at 50 °C) was added to hydrolyse the red glass-like product, the precipitate was filtered off, and the aqueous filtrate was extracted with ether, to give more solid. The two solids were combined, placed in the thimble of a Soxhlet apparatus, and extracted for 12 h with ether, to yield a yellow solid which was chromatographed on alumina. Acetone eluted the thienoazepine (3.8 g, 71%), identical (m.p. and i.r. spectrum) with the sample prepared as described in (*a*).

4-*Ethylthio*-7,8-*dihydro*-6H-*thieno*[3,2-c]*azepine* (15).—A stirred mixture of 5,6,7,8-tetrahydrothieno[3,2-*c*]azepine-4-thione (13) (1.0 g, 5.5 mmol), triethyloxonium tetrafluoroborate (1.25 g, 6.5 mmol), and dry dichloromethane (20 ml) was heated under reflux for 1 h. Work-up in the usual way gave 4-*ethylthio*-7,8-*dihydro*-6H-*thieno*[3,2-c]*azepine* (15) (1.1 g, 95%), b.p. 95—99 °C at 1.75 mmHg (Kugelrohr apparatus), $\nu_{max.}$ 1 605 cm^{-1} (C=N), *m/e* 211 (M^+); *hydrochloride*, m.p. 139—141 °C (from butan-2-one).

4-*Ethoxy*-7,8-*dihydro*-6H-*thieno*[3,2-c]*azepine* (16).—A mixture of 5,6,7,8-tetrahydrothieno[3,2-*c*]azepin-4-one (14) [5] (0.5 g, 3.0 mmol), triethyloxonium tetrafluoroborate (0.57 g, 3.0 mmol), and hexamethylphosphoramide (5 ml) was heated to 90 °C, then stirred at this temperature for 35 min. Work-up in the usual way gave an oil which was chromatographed on silica. Ether eluted 4-*ethoxy*-7,8-*dihydro*-6H-*thieno*[3,2-c]*azepine* (16) (0.5 g, 85%), b.p. 100—103 °C at 2.00 mmHg (Kugelrohr apparatus), $\nu_{max.}$ 1 660 cm^{-1} (C=N) (Found: M^+, 195.0735. $C_{10}H_{13}NOS$ requires *M*, 195.0718); *hydrochloride*, m.p. 89—90 °C (from butan-2-one).

Reactions of 3-(2-*Thienyl*)*propyl Isothiocyanate* (12).—(a) *With aluminium chloride*. Aluminium chloride (2.9 g, 21.8 mmol) was added in portions to a stirred solution of the isothiocyanate (12) (2.0 g, 10.9 mmol) in tetrachloroethane (20 ml) at ambient temperature. The resulting mixture was stirred at this temperature for 3 h, then water (50 ml) was added and the mixture was made alkaline with 2M-sodium hydroxide. The organic layer yielded a black solid which was chromatographed on silica. Light petroleum–chloroform (9 : 1) eluted 2-(3-*isothiocyanatopropyl*)-5-{N-[3-(2-*thienyl*)*propyl*]*thiocarbamoyl*}*thiophen* (18) (0.4 g, 20%), m.p. 71—72 °C (from light petroleum), $\nu_{max.}$ 2 140 and 2 200 (NCS) and 3 370 cm^{-1} (NH).

(b) *With triethyloxonium tetrafluoroborate*. A stirred mixture of the isothiocyanate (12) (4.0 g, 21.8 mmol), triethyloxonium tetrafluoroborate (3.6 g, 19.0 mmol), and dichloromethane (20 ml) was heated under reflux for 5 h. Work-up in the usual way gave an oil from which a solid had separated after 12 h. The whole product was triturated with cold (0 °C) ether; the precipitate was filtered off, washed with cold (0 °C) ether, and recrystallised from carbon tetrachloride to give a compound (0.4 g) with m.p. 180 °C (decomp.), $\nu_{max.}$ (Nujol) 1 615 cm^{-1} (C=N), τ ($CDCl_3$) 3.33 (1 H, d, *J* 6.0 Hz), 4.15 (1 H, d, *J* 6.0 Hz), 6.10—6.47 (2 H, m), 7.18 (2 H, q, *J* 7.5 Hz, CH_2), 7.71—8.33 (4 H, m), and 8.78 (3 H, t, *J* 7.5 Hz, Me) (Found: C, 56.7; H, 6.2; N, 6.5%; M^+, 422. $C_{20}H_{26}N_2S_4$ requires C, 56.8; H, 6.2; N, 6.6%; *M*, 422) (see main text for a discussion of its structure).

4-*Cyclopropylamino*-7,8-*dihydro*-6H-*thieno*[3,2-c]*azepine Hydrochloride* (17).—A stirred mixture of 4-ethoxy- (16) or 4-ethylthio-7,8-dihydro-6*H*-thieno[3,2-*c*]azepine (15) (or the hydrochloride salt of either compound) (3.0 mmol), cyclopropylamine hydrochloride (or its free base, respectively) (3.0 mmol), and dimethylformamide (3 ml) was heated at 100 °C for 3 h. Ether (15 ml) was added to the cooled mixture to give the *hydrochloride salt* (17) (88%), m.p. 199—200 °C (from propan-2-ol–acetone), $\nu_{max.}$ 1 620 (C=N) and 2 500—3 200br cm^{-1} (amine salt), *m/e* 206 (M^+ of free base).

We thank the S.R.C. (C.A.P.S. award to R. V. D. and a research studentship to P. T. G.) and The Nicholas Research Institute, Slough (research scholarship to M. W. P.), for financial support, Dr. Rex Clark and Synthetic Chemicals Ltd., Four Ashes, Wolverhampton, for gifts of thiophen, Dr. Roger P. Napier and Mobil Chemical Company, Edison, New Jersey, for gifts of 6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one, and Mr. T. McC. Paterson for help with the experimental work.

[7/683 *Received*, 25*th April*, 1977]