Intramolecular Cyclisation of Arylalkyl Isothiocyanates. Part I. Synthesis of 1-Substituted 3,4-Dihydroisoquinolines [1]

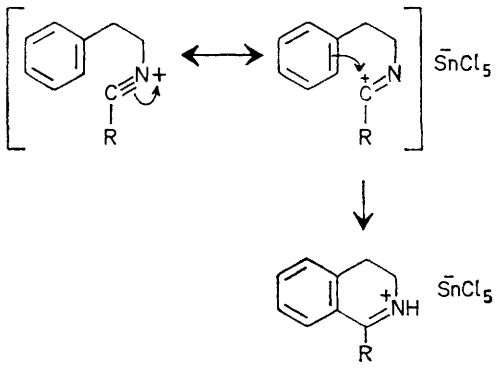
By **Maurice W. Gittos, Malcolm R. Robinson,** and **John P. Verge,** Nicholas Research Institute, 225 Bath Road, Slough, Buckinghamshire SL1 4AU
Roy V. Davies, Brian Iddon,* and **Hans Suschitzky,** The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, Lancashire M5 4WT

With triethyloxonium tetrafluoroborate or ethyl or methyl fluorosulphonate. 2-arylethyl isothiocyanates cyclised to give a 1-ethylthio- or 1-methylthio-3,4-dihydroisoquinoline, respectively. These compounds were prepared also by successive cyclisation of the isothiocyanates with aluminium chloride or polyphosphoric acid and alkylation of the resultant 3,4-dihydroisoquinoline-1(2*H*)-thione. They are useful starting materials for the synthesis of other 1-substituted 3,4-dihydroisoquinolines, *e.g.* 1-amino-compounds.

A SERIES of 1-amino-3,4-dihydroisoquinolines was prepared for pharmacological evaluation as potential cardiovascular and pressor agents by nucleophilic displacement of the 1-alkylthio-group in a 1-alkylthio-3,4-dihydroisoquinoline with an amine.[2-4] In this paper we report the preparations of the 1-alkylthio-compounds (15)—(24). 1-Amino-3,4-dihydroisoquinolines may be prepared also by cyclisation of thiourea derivatives with phosphoryl chloride [5] or mercury(II) chloride [6] and by cyclisation of the corresponding urea derivatives under Bischler-Napieralski conditions.[7,†]

Lora-Tomayo *et al.*[8-11] showed that the nitrilium salts prepared [12] by reaction of nitrile–tin(IV) chloride complexes ($RC\equiv\overset{+}{N}-\overset{-}{SnCl_4}$) with simple arylalkyl halides cyclise when heated to give 1-substituted 3,4-dihydroisoquinolines (Scheme 1). With the exception of benzyl thiocyanate, aliphatic and aromatic thiocyanates react similarly to yield 1-alkylthio- (50—80% yields) and 1-arylthio-3,4-dihydroisoquinolines (40—60%), respectively.[10,11] We prepared 1-methylthio-3,4-dihydroisoquinoline (15) and similar compounds by this route. On a pilot scale (0.5 kg), however, the reactions were extremely exothermic at the cyclisation temperature (110 °C) and, consequently, difficult to control.

Therefore, we examined an alternative synthesis of the 1-alkylthio-compound (15) which involves alkylation of 3,4-dihydroisoquinoline-1(2*H*)-thione (10), previously prepared [13] by cyclisation of phenethyl isothiocyanate (1) with aluminium chloride in carbon disulphide. Replacement of the hazardous solvent was desirable for large-scale work. Surprisingly, cyclisation of the isothiocyanate (1) with aluminium chloride failed in tetrachloroethane (an intractable tar was obtained) but gave a reasonable yield (40—58%) of the thione (10) in tetrachloroethylene. This method was extended to the synthesis of 4,4-dimethyl- (11), 7-chloro- (12), and



SCHEME 1

6,7-dichloro-3,4-dihydroisoquinoline-1(2*H*)-thione (13) from the isothiocyanates (5), (7), and (8), respectively. The chloro-compounds (12) and (13) were obtained in good yield in tetrachloroethane. Under similar conditions, however, cyclisation of 2-methyl-2-phenylpropyl isothiocyanate (5) gave the corresponding thione (11) in only 8.5% yield. The use of polyphosphoric acid in this case increased the yield of the thione (11) to 63%. Other Lewis acids gave yields comparable to that obtained with aluminium chloride. Polyphosphoric acid also cyclised the isothiocyanates (1) and (9) to the

†At approximately the time our first patent application [2] was published another appeared in which compounds (12), (14), and the hydroiodide of compound (17) are described along with several 1-amino-3,4-dihydroisoquinolines [C. Jeanmart, M. N. Messer, and P. E. Simon, S. Afr. P. 6,901,552/1969 (*Chem. Abs.*, 1970, **72**, 111 309); see also G. Seidl, R. Kunstmann, and E. Granzer, Ger. P. Offen. 2,143,745/1973 (*Chem. Abs.*, 1973, **78**, 147 823)].

[1] Presented at the VIth International Symposium on Organic Sulphur Chemistry, Bangor, July 1st—5th, 1974, abstract no. D7; see also Aspro-Nicholas Ltd., French P. 2,180,066/1973.

[2] M. W. Gittos, J. W. James, and J. P. Verge, Ger. P. Offen., 1,911,519/1969 (*Chem. Abs.*, 1970, **72**, 12601).

[3] M. W. Gittos, Ger. P. Offen., 2,318,399/1973 (*Chem. Abs.*, 1974, **80**, 14857).

[4] M. W. Gittos, J. W. James, and J. P. Verge, B.P. 1,244,501/1971.

[5] I. M. Roushdi, A. M. M. E. Omar, and A. A. B. Hazzaa, *Egypt. J. Pharm. Sci.*, 1972, **13**, 101 (*Chem. Abs.*, 1974, **80**, 59839).

[6] I. M. Roushdi, A. M. M. E. Omar, and A. A. B. Hazzaa, *Egypt. J. Pharm. Sci.*, 1972, **13**, 109 (*Chem. Abs.*, 1974, **80**, 59838).

[7] L. M. Mohunta and J. N. Rây, *J. Chem. Soc.*, 1934, 1263.

[8] M. Lora-Tomayo, R. Madroñero, and G. García Muñoz, *Chem. and Ind.*, 1959, 657.

[9] M. Lora-Tomayo, R. Madroñero, and G. Garcia Muñoz, *Chem. Ber.*, 1960, **93**, 289.

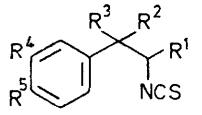
[10] M. Lora-Tomayo, R. Madroñero, D. Gracían, and V. Gómez-Parra, *Tetrahedron*, 1966, Suppl. 8, Part I, 305.

[11] F. Johnson and R. Madroñero, *Adv. Heterocyclic Chem.*, 1966, **6**, 112.

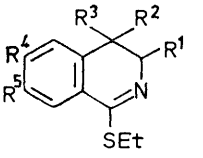
[12] H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, 1956, **89**, 209.

[13] P. A. S. Smith and R. O. Kan, *J. Amer. Chem. Soc.*, 1960, **82**, 4753; *J. Org. Chem.*, 1964, **29**, 2261.

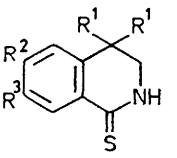
corresonding thione, (10) or (14). In the latter case cyclisation occurred under particularly mild conditions.



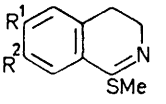
(1) R^1–R^5 = H
(2) R^1 = Me, R^2–R^5 = H
(3) R^2 = Bu^n, R^1 and R^3–R^5 = H
(4) R^2 = Ph, R^1 and R^3–R^5 = H
(5) R^2 = R^3 = Me, R^1 = R^4 = R^5 = H
(6) R^4 = Br, R^1–R^3 and R^5 = H
(7) R^5 = Cl, R^1–R^4 = H
(8) R^4 = R^5 = Cl, R^1–R^3 = H
(9) R^4 = R^5 = OMe, R^1–R^3 = H



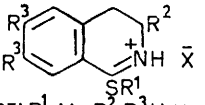
(18) R^1–R^5 = H
(19) R^1 = Me, R^2 – R^5 = H
(20) R^2 = Bu^n, R^1 and R^3–R^5 = H
(21) R^2 = Ph, R^1 and R^3–R^5 = H
(22) R^2 = R^3 = Me, R^1 = R^4 = R^5 = H
(23) R^4 = Br, R^1–R^3 and R^5 = H
(24) R^4 = R^5 = OMe, R^1–R^3 = H



(10) R^1–R^3 = H
(11) R^1 = Me, R^2 = R^3 = H
(12) R^3 = Cl, R^1 = R^2 = H
(13) R^2 = R^3 = Cl, R^1 = H
(14) R^2 = R^3 = OMe, R^1 = H



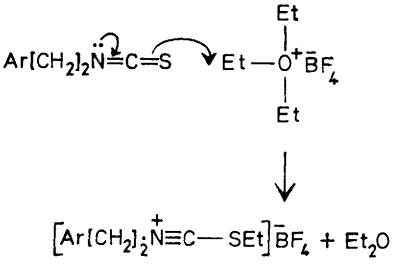
(15) R^1 = R^2 = H
(16) R^1 = R^2 = Cl
(17) R^1 = R^2 = OMe



(25) R^1 = Me, R^2 = R^3 = H, X = SO_3F
(26) R^1 = Et, R^2 = R^3 = H, X = BF_4
(27) R^1 = Et, R^2 = H, R^3 = OMe, X = BF_4
(28) R^1 = cyclopropylamino, R^2 = Me, R^3 = H, X = SO_3F
(29) R^1 = NH·CH_2C:CH, R^2 = H, R^3 = OMe, X = Cl

On large scales, however, the use of either aluminium chloride or polyphosphoric acid (particularly the former) led to difficulties during work-up and an alternative method of synthesis of the alkylthio-compounds (15)—(24) was sought. They may be prepared, however, by alkylation of the thiones (10)—(14) with dimethyl sulphate, methyl fluorosulphonate, or triethyloxonium tetrafluoroborate.

We have found that the 2-arylethyl isothiocyanates (1)—(6) and (9) are converted directly into 1-alkylthio-3,4-dihydroisoquinolines with triethyloxonium tetrafluoroborate or with ethyl or methyl fluorosulphonate, presumably by *S*-alkylation of the isothiocyanate (Scheme 2) and spontaneous cyclisation of the resultant nitrilium salt (Scheme 1). These new reactions proceed rapidly at 40 °C in methylene chloride, are easy to work up, and, in contrast to Lora-Tomayo's procedure, are not noticeably exothermic on a large scale (0.5 kg). Under these conditions phenethyl isothiocyanate (1) reacted with triethyloxonium tetrafluoroborate or methyl fluorosulphonate to give precipitates of 1-ethylthio-3,4-dihydroisoquinolinium tetrafluoroborate (26) or 1-methylthio-3,4-dihydroisoquinolinium fluorosulphonate (25), respectively. The structure of the tetrafluoroborate (26)



SCHEME 2

was confirmed by conversion into the free base (18) with aqueous sodium carbonate and by its synthesis from the free base and fluoroboric acid.

Cyclisation of a 2-arylethyl isothiocyanate proceeds in high yield whether the aromatic ring contains an electron-withdrawing [*e.g.* (6) ⟶ (23)] or an electron-donating [*e.g.* (9) ⟶ (24)] substituent. Usually, work-up involves addition of alkali and isolation of the free base. The particularly mild reaction conditions allow cyclisation without affecting functional groups [such as OMe in (9)] or chiral centres in the side-chain. Thus, (+)-1-ethylthio-3,4-dihydro-3-methylisoquinoline (19) was obtained from (+)-1-methyl-2-phenylethyl isothiocyanate (2) with ethyl fluorosulphonate or triethyloxonium tetrafluoroborate.

N.m.r. data (τ values)

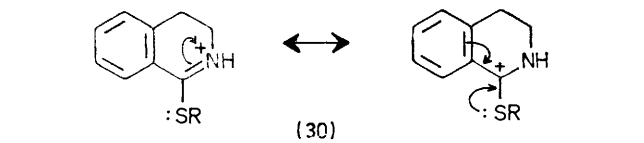
Compd.	3-H_2	4-H_2	5-, 6-, and 7-H	8-H	S·CH_3	Me	Others
(15) [a]	6.30 (t, *J* 7.0 Hz)	7.46 (t, *J* 7.0 Hz)	2.60—3.05 (m)	2.25—2.45 (m)		7.60 (s)	
(15) [b]	6.29	7.37	2.55—3.00	2.29—2.55		7.61	
(18) [a]	6.53 (t, *J* 7.0 Hz)	7.72 (t, *J* 7.0 Hz)	2.80—3.30 (m)	2.40—2.70 (m)	7.12 (q, *J* 7.5 Hz)	8.90 (t, *J* 7.5 Hz)	
(18) [b]	6.29	7.32	2.50—3.00	2.25—2.50	6.98	8.67	
(22) [b]	6.53 (s)		2.60—3.15 (m)	2.29—2.55 (m)	7.02 (q, *J* 7.5 Hz)	8.75 (t, *J* 7.5 Hz)	8.90 (s, CMe_2)
(25) [a]	6.10 (t, *J* 7.0 Hz)	6.87 (t, *J* 7.0 Hz)	2.10—2.60 (m)	1.80—2.10 (m)		7.12 (s)	0.70br (s, NH)
(26) [a]	6.03 (t, *J* 7.5 Hz)	6.88 (t, *J* 7.5 Hz)	2.20—2.70 (m)	1.95—2.20 (m)	6.59 (q, *J* 7.0 Hz)	8.50 (t, *J* 7.0 Hz)	−0.05br(s, NH)

[a] In $(CD_3)_2SO$. [b] In CCl_4.

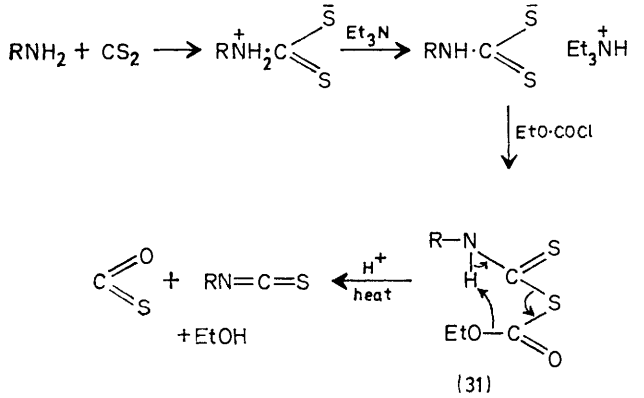
A comparison (Table) of the ^1H n.m.r. spectra of the 1-alkylthio-3,4-dihydroisoquinolines (15), (18), and (22) with those of the salts (25) and (26) is of interest. The signals at τ 6.30 and 6.53 in the spectra of compounds (15) and (18) are assigned to the 3-protons by analogy with the signal at τ 6.53 for the 3-protons in the 4,4-dimethyl compound (22). On this basis the signals at τ 7.46 and 7.72 can be assigned to the 4-protons of compounds (15) and (18), respectively. These assignments are consistent with values given in correlation tables [14]

[14] L. M. Jackman and S. Sternhell, in 'Applications of NMR Spectroscopy in Organic Chemistry,' vol. 5 of International Series of Monographs in Organic Chemistry, Pergamon, London, 2nd edn., 1969.

and for methylene groups in similar environments.[15] For the salts (25) and (26), however, the signals assigned to the 4-protons are shifted downfield to a greater extent than the signals assigned to the 3-protons. We attribute this to extensive delocalisation of the charge on nitrogen in the salts over the sulphur atom and particularly over the aromatic ring, as shown in (30). In the i.r. spectra of the salts a sharp single peak in the 3 200—3 300 cm^{-1} region is consistent with this suggestion.[16] Such extensive delocalisation of charge on the nitrogen atom of a base has been observed in other systems.[16,17]



(30)



SCHEME 3

As examples of the preparation of 1-amino-3,4-dihydroisoquinolines we describe in the Experimental section the preparations of compounds (28) and (29) from (+)-1-ethylthio-3,4-dihydro-3-methylisoquinolinium fluorosulphonate and 3,4-dihydro-6,7-dimethoxy-1-methylthioisoquinoline (17), respectively.

Preparation of Starting Materials.—The isothiocyanates required for this work were prepared by a standard procedure (Scheme 3). In most cases they were contaminated with small quantities of carbonyl compounds which were separated only with difficulty on distillation. These probably arise by incomplete breakdown of the intermediates (31).

EXPERIMENTAL

^1H N.m.r. spectra were recorded with a Varian A60 or HA100 spectrometer (tetramethylsilane 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.

Light petroleum refers to the fraction b.p. 60—80° unless stated otherwise. Unless specified later the 2-arylethylamines required as starting materials were available commercially.

2-Phenylhexylamine was prepared by reduction of the corresponding nitrile [18] with lithium aluminium hydride in ether (procedure of Benington *et al.*[19]). It had b.p. 80—81° at 0.2 mmHg (Found: C, 81.0; H, 10.7; N, 7.7. $C_{12}H_{19}N$ requires C, 81.3; H, 10.8; N, 7.9%).

The following amines were prepared similarly: 2-(3-bromophenyl)ethylamine, b.p. 127—132° at 12.0 mmHg; hydrochloride, m.p. 226—227° (from propan-2-ol) (lit.,[20] m.p. 225°); and 2-(4-chlorophenyl)ethylamine (aluminium chloride–lithium aluminium hydride in ether used in this case), b.p. 117–119° at 12.0 mmHg (lit.,[21] b.p. 120° at 15.0 mmHg).

2-(3,4-Dichlorophenyl)ethylamine, b.p. 147–152° at 12.0 mmHg (lit.,[22] b.p. 143—148° at 15.0 mmHg) [hydrochloride, m.p. 165—166° (from ethanol) (lit.,[22] m.p. 163—164°)], was prepared by reduction of the corresponding nitrile with sodium borohydride in bis-(2-methoxyethyl) ether in the presence of aluminium chloride.

2-Methyl-2-phenylpropiononitrile.—A solution of phenylacetonitrile (40.0 g, 342 mmol) in anhydrous ether (80 ml) was added dropwise during 30 min to a stirred solution of freshly prepared sodamide (25 g) in anhydrous ether (300 ml) at ambient temperature, and the resulting mixture was heated under reflux for 1 h. It was then cooled to 0 °C and a solution of methyl iodide (100 g, 704 mmol) in anhydrous ether (100 ml) was added dropwise during 45 min. The resulting mixture was heated under reflux for a further 2 h, then cooled, whereupon sufficient water was added to dissolve any precipitated sodium iodide. Extraction with ether gave 2-methyl-2-phenylpropiononitrile (35 g, 70%), b.p. 80—82° at 0.4 mmHg (lit.,[23] 92—93° at 5.5 mmHg), $\nu_{max.}$ 2 245 cm^{-1} (C⋮N), τ (CCl_4) 2.40—2.80 (5 H, m, aromatic) and 8.29 (6 H, s, 2 × CH_3) (Found: C, 82.4; H, 7.6; N, 9.5. $C_{10}H_{11}N$ requires C, 82.7; H, 7.6; N, 9.65%).

2-Methyl-2-phenylpropylamine.—A solution of 2-methyl-2 phenylpropiononitrile (25 g, 172 mmol) in anhydrous ether (40 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (8.5 g, 224 mmol) in anhydrous ether (175 ml) heated at a rate just sufficient to maintain boiling, and the resulting mixture was heated under reflux for 1.5 h. Work-up in the usual way gave 2-methyl-2-phenylpropylamine (24.5 g, 98%), b.p. 80—81° at 0.3 mmHg (lit.,[24] 106—108° at 15 mmHg), $\nu_{max.}$ 3 310 and 3 400 cm^{-1} (NH_2), τ (CCl_4) 2.58—2.95 (5 H, m, aromatic), 7.30 (2 H, s, CH_2), 8.70 (6 H, s, 2 × CH_3), and 9.22br (2 H, s, exchangeable, NH_2) (Found: M^+, 149.1216. $C_{10}H_{15}N$ requires M, 149.1205); *phenylsulphonyl derivative*, m.p.

[15] N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, in 'High Resolution NMR Spectra Catalogue,' Varian Associates Ltd., Palo Alto, California, 1963, vol. 2.
[16] K. Nakanishi, in 'Infrared Absorption Spectroscopy,' Holden-Day, San Francisco, 1964, pp. 38 and 39.
[17] H. Möhrle, D. Schittenhelm, and P. Gundlach, *Arch. Pharm.*, 1972, **305**, 108.
[18] L. H. Baldinger and J. A. Nieuwland, *J. Amer. Chem. Soc.*, 1933, **55**, 2851.
[19] F. Benington, R. D. Morin, L. C. Clark, and R. P. Fox, *J. Org. Chem.*, 1958, **23**, 1979.
[20] H. Kondo and S. Ishiwata, *Ber.*, 1931, **64B**, 1533.
[21] A. McCoubrey and D. W. Mathieson, *J. Chem. Soc.*, 1949, 696.
[22] A. Brossi and O. Schnider, Ger. P. 1,109,700/1961 (*Chem. Abs.*, 1962, **56**, 12802).
[23] C. R. Hauser and W. R. Brasen, *J. Amer. Chem. Soc.*, 1956, **78**, 494.
[24] J. H. Short, C. W. Ours, and W. J. Ranus, *J. Medicin. Chem.*, 1968, **11**, 1129.

83—84° (from aqueous ethanol) (Found: C, 66.05; H, 6.6; N, 4.75. $C_{16}H_{19}NO_2S$ requires C, 66.4; H, 6.6; N, 4.8%).

Arylalkyl Isothiocyanates.—A solution of carbon disulphide (6.0 ml, 0.1 mol) in methylene chloride (15 ml) was added dropwise during 15 min to a stirred mixture of 2-methyl-2-phenylpropylamine (14.9 g, 0.1 mol), triethylamine (10.0 g, 0.1 mol), and methylene chloride (15 ml) at 0 °C, and the resulting mixture was allowed to warm slowly to room temperature. It was then cooled to 0 °C and ethyl chloroformate (10.85 g, 0.1 mol) was added dropwise during 15 min at this temperature and the mixture was allowed to warm slowly to ambient temperature again. More triethylamine (13 ml) was added and the mixture was stirred for a further 1.5 h at ambient temperature, and finally heated under reflux for 15 min. Water (200 ml) was added and the mixture was made alkaline with 2M-sodium hydroxide. Extraction with ether gave *2-methyl-2-phenylpropyl isothiocyanate* (5) (18.1 g, 95%), b.p. 100° at 0.08 mmHg, $\nu_{max.}$ 2 110 and 2 200 cm^{-1} (NCS), τ (CCl_4) 2.58—2.88 (5 H, m, aromatic), 6.55 (2 H, s, CH_2), and 8.69 (6 H, s, 2 × CH_3) (Found: M^+, 191.0765. $C_{11}H_{13}NS$ requires M, 191.0769).

The following isothiocyanates were prepared similarly: phenethyl isothiocyanate (1) (81%), b.p. 99—101° at 0.6 mmHg (lit.,[25] 141—144° at 11 mmHg), $\nu_{max.}$ 2 100 and 2 190 cm^{-1} (NCS); *2-(3-bromophenyl)ethyl isothiocyanate* (6) (42%), b.p. 120—123° at 0.1 mmHg, $\nu_{max.}$ 2 100 and 2 190 cm^{-1} (Found: C, 44.6; H, 3.5; N, 5.7. C_9H_8BrNS requires C, 44.6; H, 3.3; N, 5.8%); 2-(4-chlorophenyl)ethyl isothiocyanate (7) (81%), b.p. 123—125° at 0.5 mmHg (lit.,[26] 144—145° at 0.9 mmHg), $\nu_{max.}$ 2 100 and 2 190 cm^{-1} (NCS) (Found: C, 55.1; H, 4.1; N, 7.1. C_9H_8ClNS requires C, 54.7; H, 4.1; N, 7.1%); *2-(3,4-dichlorophenyl)ethyl isothiocyanate* (8)* (89%), b.p. 124—127° at 0.1 mmHg, $\nu_{max.}$ 2 100 and 2 190 cm^{-1} (Found: C, 46.7; H, 3.0; N, 6.0. $C_9H_7Cl_2NS$ requires C, 46.6; H, 3.0; N, 6.0%); 2-(3,4-dimethoxyphenyl)ethyl isothiocyanate (9) (83.5%), b.p. 138—140° at 0.2 mmHg (lit.,[27] b.p. 140—145° at 0.2 mmHg), $\nu_{max.}$ 2 110 and 2 200 cm^{-1}; (+)-1-methyl-2-phenylethyl isothiocyanate (2) (81%), $[\alpha]_D^{22}$ 130° (*c* 5 in EtOH), b.p. 81—84° at 0.2 mmHg (lit.,[28] 84.5° at 0.4 mmHg) (Found: C, 67.8; H, 6.4; N, 7.9. $C_{10}H_{11}NS$ requires C, 67.8; H, 6.3; N, 7.9%); *2-phenylhexyl isothiocyanate* (3) (70%), b.p. 115—117° at 0.2 mmHg, $\nu_{max.}$ 2 110 and 2 200 cm^{-1} (NCS) (Found: C, 71.3; H, 7.6; N, 6.4. $C_{13}H_{17}NS$ requires C, 71.2; H, 7.8; N, 6.4%); and *2,2-diphenylethyl isothiocyanate* (4) (90%), b.p. 151° at 0.25 mmHg, $\nu_{max.}$ 2 100 and 2 190 cm^{-1} (NCS) (Found: C, 75.6; H, 5.7; N, 5.7. $C_{15}H_{13}NS$ requires C, 75.3; H, 5.5; N, 5.85%).

Cyclisation of Phenethyl Isothiocyanate (1).—(a) *With aluminium chloride.* Phenethyl isothiocyanate (1) (30 g, 185 mmol) was added during 10 min to a stirred suspension of powdered aluminium chloride (54.4 g, 407 mmol) in dry tetrachloroethylene (190 ml) at 20 °C. The mixture was heated at 70—75 °C for 3 h, then kept overnight at 20 °C. 2M-Hydrochloric acid (80 ml) was added to the cooled (0 °C) mixture and the black solid remaining was filtered off and triturated with more 2M-hydrochloric acid (80 ml). Recrystallisation of the residue from methanol (charcoal) gave yellow crystals of 3,4-dihydroisoquinoline-1(2*H*)-thione (10) (17.4 g, 58%), m.p. 99—102° (lit.,[13] 98—99°).

The use of tetrachloroethane in place of tetrachloroethylene in the previous experiment gave an intractable black tar from which no product was isolated.

(b) *With polyphosphoric acid.* The isothiocyanate (1) (40.8 g, 0.25 mol) was added dropwise to polyphosphoric acid (359 g) stirred and heated at 70 °C. The mixture was stirred and heated at 130 °C for a further 2.5 h and then poured on to ice, to give 3,4-dihydroisoquinoline-1(2*H*)-thione (10) (16.3 g, 40%), identical (m.p. and i.r. spectrum) with the sample prepared as described in (a).

Cyclisation of 2-Methyl-2-phenylpropyl Isothiocyanate (5).—(a) *With aluminium chloride.* Anhydrous aluminium chloride (6.7 g, 50 mmol) was added in small amounts during 2 h to a stirred solution of the isothiocyanate (5) (4.75 g, 25 mmol) in trichloroethane (5 ml) at 0 °C, and the mixture was stirred at 0 °C for a further 8 h. It was then allowed to warm slowly to room temperature, the solvent was distilled off under reduced pressure, water (100 ml) was added, and the mixture was made alkaline with 2M-sodium hydroxide. Ether extracted a black oil which was chromatographed on silica. Chloroform–light petroleum (20 : 80) eluted *4,4-dimethyl-3,4-dihydroisoquinoline-1(2H)-thione* (11) (0.4 g, 8.5%), m.p. 108° (from aqueous ethanol), $\nu_{max.}$ 3 180 cm^{-1} (NH), τ (CCl_4) 0.00br (1 H, exchangeable, NH), 1.30—1.60 (1 H, m, 8-H), 2.40—2.80 (3 H, m, 5-, 6-, and 7-H), 6.72 (2 H, d, collapsed to s on addition of D_2O, 3-H_2), and 8.71 (6H, s, 2 × CH_3) (Found: C, 69.2; H, 6.8; N, 7.3%; M^+, 191. $C_{11}H_{13}NS$ requires C, 69.1; H, 6.85; N, 7.3%; M, 191).

(b) *With polyphosphoric acid.* The isothiocyanate (5) (4.75 g, 25 mmol) was added dropwise during 30 min to polyphosphoric acid (4.7 g) stirred and heated at 200 °C, and the mixture was stirred at this temperature for 20 h. The hot mixture was poured into cold (0 °C) water (100 ml) and extraction with ether gave a black tar, trituration of which with light petroleum gave 4,4-dimethyl-3,4-dihydroisoquinoline-1(2*H*)-thione (11) (3 g, 63%) as a yellow solid, identical (m.p. and i.r. spectrum) with the sample prepared as described in (a).

(c) *With tin*(IV) *chloride.* The reaction described in (a) was repeated but with tin(IV) chloride (5.6 ml, 50 mmol) in place of the aluminium chloride. Work-up gave the same product (11) in the same yield (*ca.* 9%).

(d) *With boron trifluoride.* The reaction described in (a) was repeated but with boron trifluoride–diethyl ether complex (7.0 g, equivalent to 50 mmol of BF_3) in place of the aluminium chloride. Work-up gave the same product (11) (0.9 g, 19%).

Cyclisation of 2-(4-Chlorophenyl)ethyl Isothiocyanate (7) *with Aluminium Chloride.*—The isothiocyanate (7) (9.9 g, 50 mmol) was added dropwise to a stirred suspension of powdered aluminium chloride (15 g, 112 mmol) in tetrachloroethane (50 ml) at 10—20 °C. The mixture was heated at 110 °C for 15 min and then poured on to a mixture of ice and 5M-hydrochloric acid (30 ml). The residue was filtered off and washed with tetrachloroethane; evaporation of the separated and dried organic layer gave *7-chloro-3,4-dihydroisoquinoline-1(2H)-thione* (12) (6.0 g, 60%), m.p.

* See A. F. McKay, *Chem. Products*, 1961, **24**, 148, in which this compound is mentioned without experimental details.

[25] J. von Braun and H. Deutsch, *Ber.*, 1912, **45**, 2188.

[26] Ceskoslovenska Akademie Ved., B.P. 1,141,586/1969 (*Chem. Abs.*, 1969, **70**, 96384); K. Antos, P. Nemec, and M. Hrdina, *Coll. Czech. Chem. Comm.*, 1972, **37**, 3339.

[27] N. Gruenfeld, B.P. 1,131,191/1968 (*Chem. Abs.*, 1969, **70**, 47457).

[28] K. A. Jensen, G. Cederberg, R. B. Jensen, and E. Larsen, *Acta Chem. Scand.*, 1970, **24**, 2264.

189.5—190.5° (from propan-2-ol) (Found: C, 54.5; H, 4.0; N, 6.9. C_9H_8ClNS requires C, 54.7; H, 4.1; N, 7.1%).

Cyclisation of 2-(3,4-*Dichlorophenyl*)*ethyl Isothiocyanate* (8) *with Aluminium Chloride*.—The isothiocyanate (47.3 g, 0.2 mol) was added to aluminium chloride (57 g, 0.42 mol) in tetrachloroethane (200 ml) as described before. The temperature was kept below 40 °C. The resultant mixture was heated at 110 °C for 5 min and worked-up as in the preceding experiment to give crude 6,7-dichloro-3,4-dihydroisoquinoline-1(2*H*)-thione (13) (28 g, 59%), m.p. 196—201°, which was used without further purification as described later.

Cyclisation of 2-(3,4-*Dimethoxyphenyl*)*ethyl Isothiocyanate* (9) *with Polyphosphoric Acid*.—The isothiocyanate (9) (54.3 g, 243 mmol) was stirred with polyphosphoric acid (350 g) at 75 °C for 1.5 h and the resultant blood-red mixture was poured into water (1.5 l). Extraction of the yellow precipitate with chloroform gave 6,7-*dimethoxy*-3,4-*dihydroisoquinoline*-1(2H)-*thione* (14) (49 g, 90%), m.p. 223° (Found: C, 59.1; H, 5.85; N, 6.4; S, 14.3. $C_{11}H_{13}NO_2S$ requires C, 59.2; H, 5.9; N, 6.3; S, 14.4%).

3,4-*Dihydro*-1-*methylthioisoquinoline* (15).—(a) *From phenethyl isothiocyanate* (1). A mixture of the isothiocyanate (1) (16.3 g, 0.1 mol), methyl fluorosulphonate (11.4 g, 0.1 mol), and methylene chloride (20 ml) was stirred and heated under reflux for 4 h. After 5 min, the solution was red in colour, but after 30 min it became colourless and a small amount of solid precipitated. After 4 h the mixture had solidified. More solvent (100 ml) was added and 3,4-*dihydro*-1-*methylthioisoquinolinium fluorosulphonate* (25) (25.6 g, 92%) was filtered off; m.p. 188° (from ethanol) $\nu_{max.}$ 3230 (NH) and 1630 cm^{-1} (C:N) (see Table for n.m.r. data) (Found: C, 43.5; H, 4.4; N, 4.8; S, 22.7. $C_{10}H_{12}FNO_3S_2$ requires C, 43.3; H, 4.4; N, 5.1; S, 23.1%), M^+ for free base (15) 177.0604 ($C_{10}H_{11}NS$ requires 177.0612). Treatment of the salt with dilute aqueous sodium hydroxide and subsequent extraction with ether gave 3,4-dihydro-1-methylthioisoquinoline (15), b.p. 80—84° at 0.05 mmHg, $\nu_{max.}$ 1 620 cm^{-1} (C:N) (see Table for n.m.r. data).

(b) *From phenethyl chloride*. Methyl thiocyanate (19.5 g, 0.27 mol) was added carefully to stirred anhydrous tin(IV) chloride (69.6 g, 0.27 mol) to give a white solid complex. Phenethyl chloride (37.5 g, 0.27 mol) was added to the stirred mixture, which was heated to 110 °C; the internal temperature then immediately increased to 135 °C. The mixture was heated at 110 °C for a further 3 h and then poured into vigorously stirred 5M-sodium hydroxide. The separated oil was extracted with ether and the extracts were combined and washed with 5M-hydrochloric acid (100 ml); the acidic washings were made alkaline with 10M-sodium hydroxide. Extraction with ether and distillation gave 3,4-dihydro-1-methylthioisoquinoline (15) (29 g, 61%), b.p. 82—83° at 0.05 mmHg, identical (i.r.) with the sample prepared as described in (a).

(c) *From* 3,4-*dihydroisoquinoline*-1(2H)-*thione* (10). A mixture of the thione (10) (8.15 g, 50 mmol), dimethyl sulphate (6.3 g, 4.8 ml, 50 mmol), and anhydrous methanol (50 ml) was heated under reflux for 1.5 h. The solvent was distilled off under reduced pressure and the residue was dissolved in water. Addition of 5M-sodium hydroxide liberated an oil which was extracted with ether. Distillation gave 3,4-dihydro-1-methylthioisoquinoline (15) (5.6 g, 63%), b.p. 74—76° at 0.01 mmHg, identical with the samples prepared as described before.

6,7-*Dichloro*-3,4-*dihydro*-1-*methylthioisoquinoline* (16).—A mixture of 6,7-dichloro-3,4-dihydroisoquinoline-1(2*H*)-thione (13) (28 g, 120 mmol), dimethyl sulphate (15.1 g, 12.1 ml, 120 mmol), and benzene (250 ml) was heated under reflux for 2.5 h, then cooled and treated successively with water and 5M-sodium hydroxide. The organic layer was separated and dried ($MgSO_4$), and the solvent was distilled off; sublimation of the residue gave 6,7-*dichloro*-3,4-*dihydro*-1-*methylthioisoquinoline* (16) (15 g, 50%), m.p. 87.5° (Found: C, 49.0; H, 3.65; N, 5.7. $C_{10}H_9Cl_2NS$ requires C, 48.8; H, 3.7; N, 5.7%).

3,4-*Dihydro*-6,7-*dimethoxy*-1-*methylthioisoquinoline* (17) (88%) was prepared similarly; m.p. 94—96° (from ethyl acetate–light petroleum); *hydrochloride*, m.p. 190—192° (from ethanol–ether) (Found: C, 52.3; H, 6.0; N, 5.0; S, 11.8. $C_{12}H_{16}ClNO_2S$ requires C, 52.6; H, 5,9; N, 5.1; S, 11.7%).

Cyclisation of Phenethyl Isothiocyanate (1) *with Triethyloxonium Tetrafluoroborate*.—(*a*) A mixture of phenethyl isothiocyanate (1) (16.3 g, 0.1 mol), triethyloxonium tetrafluoroborate (19.1 g, 0.1 mol), and methylene chloride (20 ml) was heated under reflux for 48 h; the mixture remained clear during this time [see (*b*)]. The solvent was distilled off under reduced pressure and ethanol was added to the residue, to give a precipitate of 1-*ethylthio*-3,4-*dihydroisoquinolinium tetrafluoroborate* (26) (14.9 g, 54%), m.p. 125° (from ethanol), $\nu_{max.}$ 3 300 (NH), 1 627 (C:N), and 1 100br cm^{-1} (BF_4^-) (see Table for n.m.r. data) (Found: C, 47.4; H, 5.1; N, 4.8. $C_{11}H_{14}BF_4NS$ requires C, 47.3; H, 5.1; N, 5.0%), M^+ (free base) 191.0755 ($C_{11}H_{13}NS$ requires 191.0769). Treatment of the salt with dilute aqueous sodium carbonate and subsequent extraction with chloroform gave a quantitative yield of 1-ethylthio-3,4-dihydroisoquinoline (18), b.p. 100—102° at 0.2 mmHg (lit.,[10] 89—90° at 0.5 mmHg), $\nu_{max.}$ 1 620 cm^{-1} (C:N) (see Table for n.m.r. data).

(*b*) Phenethyl isothiocyanate (132.7 g, 0.815 mol) was added dropwise to a stirred solution of triethyloxonium tetrafluoroborate (190 g, 1.0 mol) in methylene chloride (350 ml) and the resulting mixture was heated under reflux for a further 30 min. The solvent was distilled off and the residue heated on a water-bath for 1 h. The solid residue was made alkaline with 5M-sodium hydroxide, and extracted with ether. The extracts were combined and washed with 2M-hydrochloric acid. 2M-Sodium hydroxide was added to the combined acidic washings and extraction with ether followed by distillation gave 1-ethylthio-3,4-dihydroisoquinoline (18) (135 g, 87%), b.p. 109—111° at 0.7 mmHg, identical (spectra) with the sample prepared as described in (*a*).

The following compounds were prepared similarly: 1-ethylthio-3,4-dihydro-4,4-dimethylisoquinoline (22) (80%), b.p. 160° at 0.4 mmHg, or 92—94° at 0.1 mmHg, $\nu_{max.}$ 1 615 cm^{-1} (C:N) (see Table for n.m.r. data), characterised as the *picrate*, m.p. 186—188° (from ethanol) (Found: C, 51.0; H, 4.5; N, 12.5. $C_{19}H_{20}N_4O_7S$ requires C, 50.9; H, 4.5; N, 12.5%); 6-*bromo*-1-*ethylthio*-3,4-*dihydroisoquinoline* (23) (57%), b.p. 126—129° at 0.1 mmHg (Found: C, 48.6; H, 4.7; N. 4.9. $C_{11}H_{12}BrNS$ requires C, 48.9; H, 4.5; N, 5.2%); 1-*ethylthio*-3,4-*dihydro*-6,7-*dimethoxyisoquinolinium tetrafluoroborate* (27) (95%), m.p. 174—176° (Found: C, 46.0; H, 5.4; N, 4.2. $C_{13}H_{18}BF_4NO_2S$ requires C, 46.0; H 5.35; N, 4.1%); free base (24), b.p. 142—145° at 0.25 mmHg; 4-*butyl*-1-*ethylthio*-3,4-*dihydroisoquinoline* (20) (70%), b.p. 122—124° at 0.2 mmHg (Found: C, 72.8; H, 8.5; N, 5.7. $C_{15}H_{21}NS$ requires C, 72.8; H, 8.6; N, 5.7%); and 1-*ethylthio*-3,4-*dihydro*-4-*phenylisoquinoline* (21) (45%),

b.p. 161° at 0.15 mmHg (Found: C, 76.65; H, 6.6; N, 5.0. $C_{17}H_{17}NS$ requires C, 76.4; H, 6.4; N, 5.2%).

(+)-1-*Ethylthio*-3,4-*dihydro*-3-*methylisoquinoline* (19).—A mixture of (+)-1-methyl-2-phenylethyl isothiocyanate (2) (8.86 g, 0.05 mol) and ethyl fluorosulphonate (6.4 g, 0.05 mol) was kept at ambient temperature overnight. Crystallisation of the residue from acetonitrile gave (+)-1-*ethylthio*-3,4-*dihydro*-3-*methylisoquinolinium fluorosulphonate* (10.5 g, 68%), m.p. 110—111°, $[\alpha]_D^{22}$ −84° (*c* 5 in $Me_2N{\cdot}CHO$) (Found: C, 47.3; H, 5.2; N, 4.6. $C_{12}H_{16}FNO_3S_2$ requires C, 47.2; H, 5.3; N, 4.6%); free base (19), b.p. 83° at 0.01 mmHg, $n_D^{26.4}$ 1.5787.

1-*Ethylthio*-3,4-*dihydroisoquinolinium Tetrafluoroborate* (26).—A mixture of 1-ethylthio-3,4-dihydroisoquinoline (18) (19.1 g, 0.1 mol) and aqueous 40% w/v tetrafluoroboric acid (17.0 ml, 0.1 mol) was stirred for 3 h at ambient temperature. Addition of an excess of ether and filtration gave the salt (24 g, 88%), identical (m.p. and i.r. spectrum) with the sample prepared as described before.

(+)-1-*Cyclopropylamino*-3,4-*dihydro*-3-*methylisoquinolinium Fluorosulphonate* (28).—A stirred mixture of (+)-1-ethylthio-3,4-dihydro-3-methylisoquinolinium fluorosulphonate (6.1 g, 0.02 mol), cyclopropylamine (1.4 g, 1.25 mol), and dimethylformamide (20 ml) was heated under reflux for 1.5 h while the ethanethiol distilled off. The resulting mixture was diluted with ether and the precipitate filtered off to give the *salt* (4.9 g, 80%), m.p. 140—142° (from propan-2-ol), $[\alpha]_D^{22}$ −21.6° (*c* 5 in $Me_2N{\cdot}CHO$) (Found: C, 52.0; H, 5.7; N, 9.3. $C_{13}H_{17}FN_2O_3S$ requires C, 52.0; H, 5.7; N, 9.3%).

3,4-*Dihydro*-6,7-*dimethoxy*-1-(*prop*-2-*ynylamino*)*isoquinolinium Chloride* (29).—A solution of 3,4-dihydro-6,7-dimethoxy-1-methylthioisoquinoline (17) (7.12 g, 0.03 mol) and prop-2-ynylamine hydrochloride (2.75 g, 0.03 mol) in dimethylformamide (25 ml) was heated at 120 °C for 1.5 h while the methanethiol was evolved. Work-up as in the preceding experiment gave the *salt* (5 g, 60%), m.p. 210° (Found: C, 59.8; H, 6.2; Cl, 12.4; N, 10.1. $C_{14}H_{17}ClN_2O_2$ requires C, 59.9; H, 6.1; Cl, 12.6%; N, 9.9%).

We thank the S.R.C. (C.A.P.S. to R. V. D.) and the Nicholas Research Institute for financial support.

[5/1186 *Received*, 18*th June*, 1975]