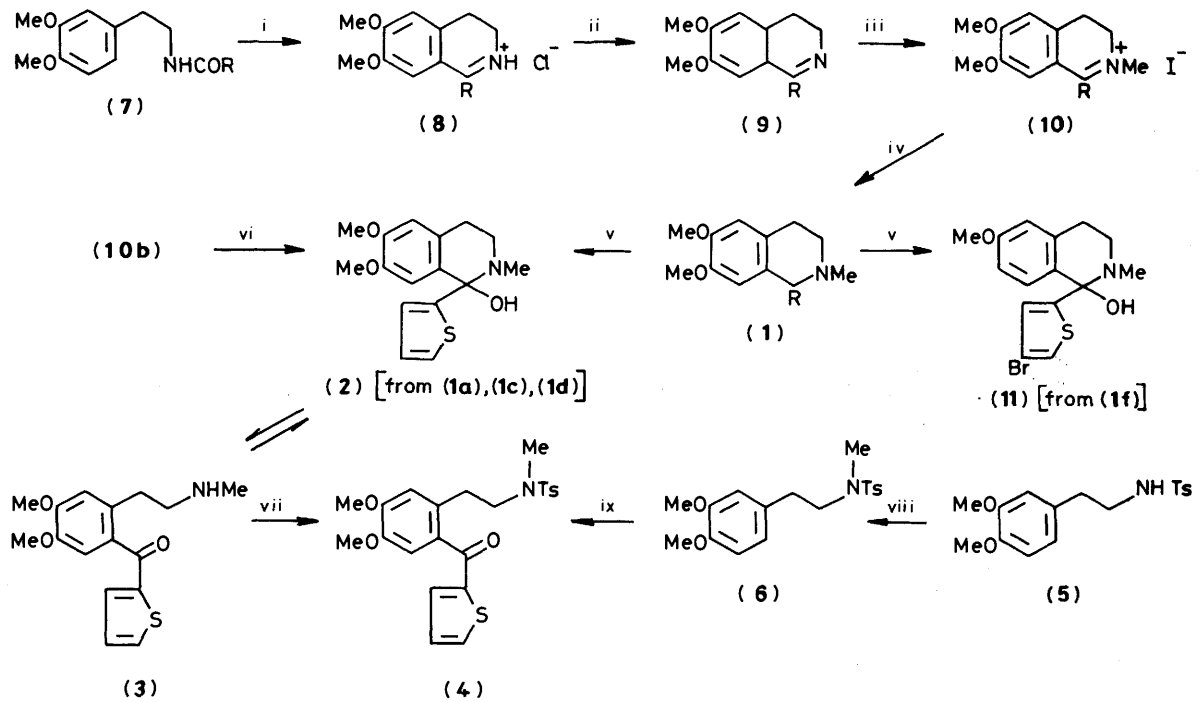
Dehalogenation of 1-Halogenothienyl-di- and -tetra-hydroisoquinolines by Sodium Methoxide in Dimethyl Sulphoxide

John M. Barker,* Patrick R. Huddleston, Jannette Clephane, Michael L. Wood, and (in part) David Holmes
Department of Physical Sciences, Trent Polytechnic, Clifton Lane, Nottingham NG11 8NS

On treatment with sodium methoxide–dimethyl sulphoxide (NaOMe–DMSO) 1-(5-halogeno-2-thienyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines suffer loss of halogen and are converted into the related 1-hydroxytetrahydroisoquinolines. The reaction fails with comparable 1-bromophenyl- and 1-(halogeno-3-thienyl)tetrahydroisoquinolines. A similar transformation takes place with (5-halogeno-2-thienyl)phenylmethoxymethanes, leading to the dimethyl acetal of the 5-dehalogenated-2-thienyl phenyl ketone. α-Halogenated-2- and 3-thienyl-3,4-dihydroisoquinolines undergo dehalogenation–aromatisation with NaOMe–DMSO. Mechanisms for these conversions are proposed.

We have already reported[1] that bromothiophenes undergo reductive debromination when treated with NaOMe–DMSO followed by addition to water. During the course of the work that led to these observations the reaction was applied to 1-(5-bromo-2-thienyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1a**). Debromination took place in this case also, but the product was not that of simple reduction, (**1b**). It was shown by a combination of elemental analysis, spectroscopic investigations, and an unambiguous synthesis to be the pseudo base (**2**). The aromatic region of the n.m.r. spectrum of the product in $CDCl_3$ was poorly resolved, but in the presence of trichloroacetyl isocyanate the two singlets due to 5-H and 8-H of the quinoline system and the typical 2-monosubstituted thiophene pattern were clearly defined. In $(CD_3)_2SO$ the aromatic region was also well resolved and in this solvent extra resonances were apparent which indicated that to a small extent (*ca.* 15%) the product exists in equilibrium with its open chain tautomer (**3**); the i.r. spectrum (KBr) gives a similar indication. Treatment of the pseudo base with toluene-*p*-sulphonyl chloride in pyridine led to the *N*-tosyl derivative of the ketoamine (**3**); the identity of this compound, (**4**), was confirmed by synthesis from the toluene-*p*-sulphonamide of homoveratrylamine.[2] In view of the interesting reaction of compound (**1a**) with NaOMe–DMSO we decided to investigate the behaviour of a variety of 1-substituted tetrahydroisoquinolines. These were prepared by a conventional route *via* the homoveratrylamides (**7**), the dihydroisoquinoline hydrochlorides (**8**), and their free bases (**9**), followed by reduction of the methiodides



a; R = 5-bromo-2-thienyl **b**; R = 2-thienyl **c**; R = 5-chloro-2-thienyl **d**; R = 5-iodo-2-thienyl **e**; R = 4-bromo-2-thienyl **f**; R = 4,5-dibromo-2-thienyl **g**; R = 5-bromo-3-thienyl **h**; R = 2,5-dibromo-3-thienyl **i**; R = 2,5-dichloro-3-thienyl **j**; R = 2-bromophenyl **k**; R = 3-bromophenyl **l**; R = 4-bromophenyl **m**; R = phenyl **n**; R = methyl

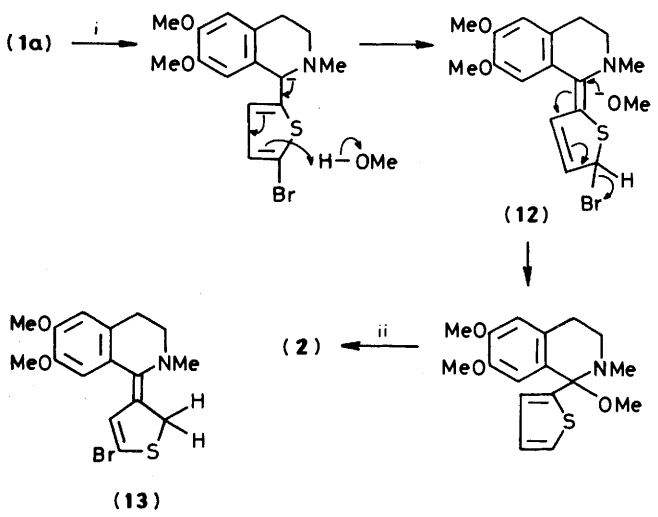
Scheme 1. *Reagents:* i, $POCl_3$–PhMe; ii, NaOH–H_2O; iii, MeI–DMF; iv, $NaBH_4$–EtOH–H_2O; v, NaOMe–DMSO, then H_2O; vi, 4M-NaOH–H_2O; vii, TsCl–pyridine; viii, Me_2SO_4–K_2CO_3–Me_2CO; ix, 2-thenoyl chloride–$SnCl_4$

(**10**). Each of the isoquinolines (**1b—n**) was also treated with two equivalents of NaOMe–DMSO and a definite pattern of behaviour became apparent. The dehalogenation–hydroxylation reaction only took place with those compounds containing the 5-halogeno-2-thienyl grouping, *i.e.* (**1a**), (**1c**), (**1d**), and (**1f**); in all other cases the starting material was recovered unchanged. The isoquinolines (**1a**), (**1c**), and (**1d**) all led to the pseudo base (**2**), while (**1f**) gave the 4-bromothienyl counterpart (**11**).

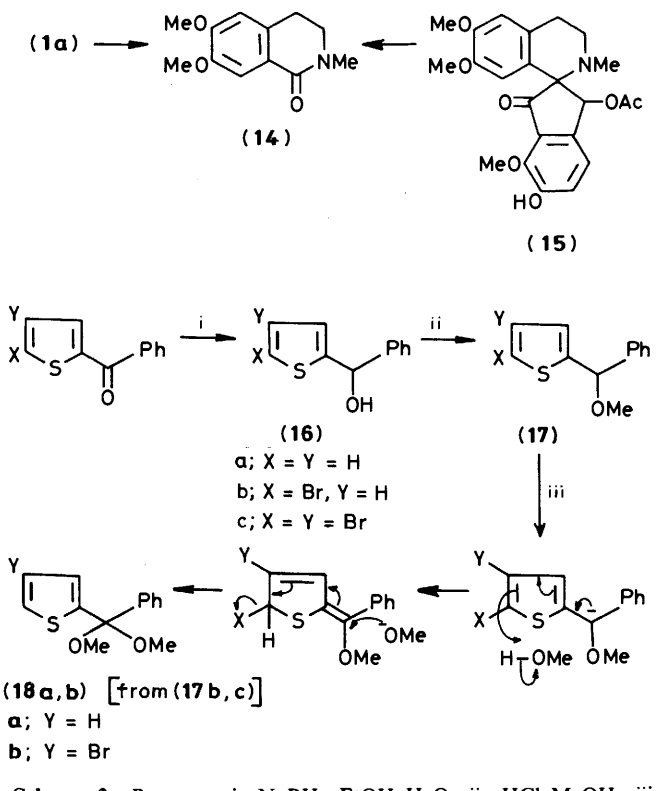
It is well known that halogen atoms at thiophene α-positions are more susceptible to removal (in metallation reactions, for example) than those at β-positions. The requirement that a halogen atom must be present at C-5 in the thiophene ring before the present reaction can proceed, and the observation that halogens at β-positions survive, are thus relatively easily accepted. The action of strong bases on halogenated thiophenes has received a good deal of attention.[3] In general, simple halogenated derivatives undergo rearrangement *via* the 'base-catalysed halogen dance', in which an ionic species generated by proton abstraction captures the halogen from a second molecule. This also takes place when the base is sodium methoxide, and occurs in a variety of solvents.[4] These facts led us to propose a mechanism involving as a key step the removal of halonium ion from thiophene α-positions in (**1a**), (**1c**), (**1d**), and (**1f**) by a dibenzylic anion. However, a referee has pointed out that there is no precedent for loss of Cl^+ from thiophene compounds under such circumstances, and has proposed that loss of halogen as the anion is a better alternative. We are grateful for this suggestion, which leads to the mechanism shown in Scheme 2 for the dehalogenation–hydroxylation reaction; the essential features of it also apply to some related transformations described later in this paper. The mechanism also accounts for the failure of the α-halogenated 3-thienyl compounds (**1g—i**) to undergo the reaction, since intermediates of type (**13**) are unable to lose halide in the way their 2-thienyl analogues [*e.g.* (**12**)] can.

The conversion of compound (**1a**) into (**2**) also took place when DMSO was replaced by dimethylformamide (DMF), albeit in rather poor yield. Although this change in solvent had only a minor effect, replacement of sodium methoxide by the methylsulphinyl anion resulted in the formation of a totally different product from (**1a**). After treatment with NaH–DMSO at 70 °C, or with Bu^{t}OK–DMSO (which contains an equilibrium concentration of the methylsulphinyl ion), followed by aqueous work-up, compound (**1a**) suffered oxidative cleavage of the C(1)–thiophene bond. The product (**14**) is an alkaloid[5] (*N*-methylcorydaldine), which has also been obtained on numerous occasions as a product of oxidative structure determinations on 1-benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline alkaloids. It is also formed when the methiodides of 1-benzyl-3,4-dihydroisoquinolines are treated with oxygen–copper(I) chloride–sodium hydroxide,[6] oxygen–sodium hydroxide–photosensitiser,[6] and rat-liver enzymes.[7] The intermediacy of a pseudo base in the formation of compound (**14**) as a minor product from the oxidation of a 1-benzyl-2-methyltetrahydroisoquinoline by Fremy's salt has been postulated by Castedo and co-workers.[8] The production of the ketone (**14**) by oxidative cleavage of 1-substituted isoquinolines under strongly basic conditions has been described recently by Blasko, Hussain, and Shamma,[9] who found that the spiro compound (**15**) gave some of the product (**14**) when treated with potassium t-butoxide in ethanol; it was obtained exclusively with the same reagent in isopropyl or t-butyl alcohol.

The 6,7-dimethoxyisoquinolines (**1a—n**) used in this study were also required for other purposes, and it was convenient to use them to examine some of the features of the dehalogenation–hydroxylation process. However, they are rather complex, and we sought to establish the essential structural requirements of the substrate by subjecting some simpler substances to the reaction conditions. We had hoped to obtain compounds containing the 2-thienyl-CH(NHMe)-phenyl system, but the introduction of the NHMe group into readily available starting materials proved to be difficult. Finally the more accessible ethers (**17a—c**) were prepared, by the route shown in Scheme 3. These contain the desired simpler 2-thienyl-CHX-phenyl system (X = OMe) which is like that present in the more elaborate isoquinolines (**1a—f**; X = NHMe). Compound (**17a**) did not react with NaOMe–DMSO, but in those two cases where C-5 of the thiophene ring carried a bromine atom dehalogenation occurred, and the methine proton was replaced.



Scheme 2. *Reagents:* i, MeO^-–DMSO; ii, H_2O–HO^-



Scheme 3. *Reagents:* i, $NaBH_4$–EtOH–H_2O; ii, HCl–MeOH; iii, MeO^-–DMSO

The isolated product was the dimethyl acetal of the related ketone [(**18a**) from (**17b**); (**18b**) from (**17c**)]. The mechanism that we suggest for these changes (Scheme 3) is, in its essential detail, the same as that for the conversions of the isoquinolines (**1a**), (**1c**), (**1d**), and (**1f**) into the appropriate pseudo bases.

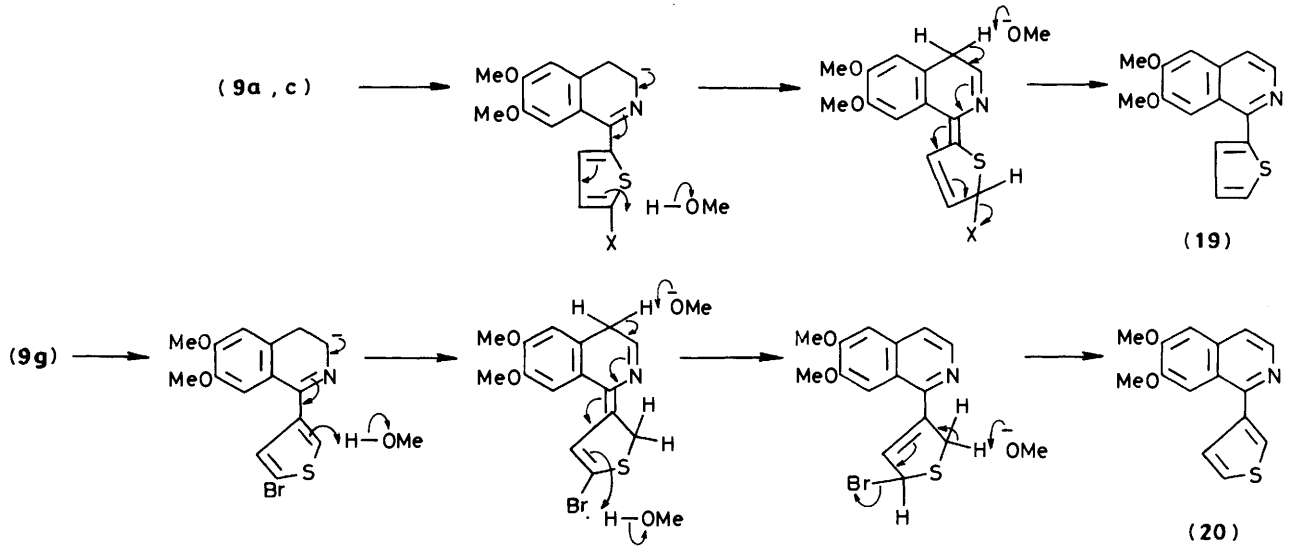
Another interesting reaction was revealed when the dihydroisoquinolines (**9a**) and (**9c**) were treated with NaOMe–DMSO or NaOMe–DMF. In both cases dehalogenation took place and the product, formed in good yield, was 6,7-dimethoxy-1-(2-thienyl)isoquinoline (**19**), identical with a sample prepared by the dehydrogenation of compound (**9b**). The same material was formed as one component of the mixtures arising from the interaction of compound (**9a**) with Bu^{t}OK–DMSO or with NaH–DMSO, or of 1-(5-bromo-2-thienyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with NaOMe–DMSO. In these transformations, linkage via the thiophene 2-position is not a *sine qua non*, since the brominated 3-thienyl-3,4-dihydroisoquinolines (**9g**) and (**9h**) also yielded a debromination–aromatisation product (**20**) with NaOMe–DMSO. 1-(2-Thienyl)- (**1b**) and 1-(bromophenyl)-3,4-dihydroisoquinolines (**9j**—**l**) were unaffected by NaOMe–DMSO. The mechanisms which we propose for these reactions are illustrated in Scheme 4. It will be noted that they account for the ability of the halogenated 3-thienyl compounds to participate in the reaction.

Experimental

M.p.s are uncorrected. Light petroleum refers to the fraction with b.p. 60—80 °C, and ether to diethyl ether. Organic solutions were dried over magnesium sulphate and were evaporated under reduced pressure.

Synthesis of the 1-*Substituted* 6,7-*Dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinolines* (**1a**—**n**).—The 1-phenyl- (**1m**)[10] and 1-methyl- (**1n**)[11] derivatives have previously been reported and (apart from n.m.r. data) no details of their synthesis are included here.

The Homoveratrylamides (**7a**—**n**).—In a typical run the acid chloride (0.19 mol) in chloroform (75 ml) was added dropwise to a stirred, ice-cooled solution of homoveratrylamine (0.19 mol) and triethylamine (0.25 mol) in chloroform (100 ml). The mixture was stirred at room temperature for 2 h, washed successively with water (× 1), 2M-hydrochloric acid (× 3), 2M-sodium hydroxide (× 3) and water, then dried and evaporated. This gave the essentially pure amide (yield 90—95%); analytical samples were crystallised from ethyl acetate–light petroleum. The m.p.s and analytical data for the new amides are presented in Table 1. The amide (**7b**) had m.p. 105—107 °C (lit.,[12] 105 °C). The n.m.r. spectra of the amides (in $CDCl_3$) all contained the



Scheme 4. X = Br or Cl

Table 1. Analytical data for the *homoveratrylamides* (**7a**—**l**)

Compound	M.p. (°C)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(**7a**)	100—102	$C_{15}H_{16}BrNO_3S$	48.2	4.7	3.7	48.7	4.3	3.8
(**7c**)	107—108	$C_{15}H_{16}ClNO_3S$	55.1	4.8	4.1	55.3	4.9	4.3
(**7d**)	121—123	$C_{15}H_{16}INO_3S$	43.5	4.0	3.4	43.2	3.8	3.4
(**7e**)	127—128	$C_{15}H_{16}BrNO_3S$	48.2	4.6	3.7	48.7	4.3	3.8
(**7f**)	120—121	$C_{15}H_{15}Br_2NO_3S$	40.6	3.4	3.1	40.1	3.3	3.1
(**7g**)	104—105	$C_{15}H_{16}BrNO_3S$	48.5	4.3	3.9	48.7	4.3	3.8
(**7h**)	108—110	$C_{15}H_{15}Br_2NO_3S$	39.6	3.4	3.1	40.1	3.3	3.1
(**7i**)	108—109	$C_{15}H_{15}Cl_2NO_3S$	49.9	4.2	4.0	50.1	4.2	3.9
(**7j**)	146—148	$C_{17}H_{18}BrNO_3$	56.0	4.9	3.8	56.0	5.0	3.8
(**7k**)	91—93	$C_{17}H_{18}BrNO_3$	55.6	5.3	3.7	56.0	5.0	3.8
(**7l**)	143—145	$C_{17}H_{18}BrNO_3$	55.9	5.0	3.7	56.0	5.0	3.8

Table 2. The *dihydroisoquinolines* and their *salts*

Compound	M.p. (°C)	Formula	Found (%) C	H	N	Required (%) C	H	N	M.p.s of salts (°C) *HCl (**8**)	*MeI (**10**)
(**9a**)	107—108	$C_{15}H_{14}BrNO_2S$	51.0	4.0	4.1	51.1	4.0	4.0	184—185	210—213
(**9b**)	138—139	$C_{15}H_{15}NO_2S$	65.5	5.4	5.3	65.9	5.5	5.1	187—188	176—177
(**9c**)	118—120	$C_{15}H_{14}ClNO_2S$	58.4	4.7	4.4	58.5	4.5	4.5	183—185*	199—201
(**9d**)	134—136	$C_{15}H_{14}INO_2S$	45.6	3.6	3.4	45.1	3.5	3.5	201—202	201—203
(**9e**)	131—133	$C_{15}H_{14}BrNO_2S$	51.6	4.1	3.9	51.1	4.0	4.0	188—191	198—200
(**9f**)	149—150	$C_{15}H_{13}Br_2NO_2S$	42.2	3.1	3.4	41.8	3.0	3.2	184—185	228—229
(**9g**)	118—120	$C_{15}H_{14}BrNO_2S$	50.5	3.9	3.8	51.1	4.0	4.0	213—215	208—210
(**9h**)	98—100	$C_{15}H_{13}Br_2NO_2S$	40.7	3.0	2.9	41.8	3.0	3.2	156—158	176—178
(**9i**)	92—93	$C_{15}H_{13}Cl_2NO_2S$	52.4	3.7	3.8	52.6	3.8	4.1	155—157	178—180
(**9j**)	72—73	$C_{17}H_{16}BrNO_2$	58.4	4.5	3.9	58.9	4.6	4.0	196—198	146—148
(**9k**)	Gum								202—204	218—220
(**9l**)	147—149†	$C_{17}H_{16}BrNO_2$	58.7	4.4	3.8	58.9	4.6	4.0	183—184	202—204

* Lit.,[12] 183.5 °C. † Lit.,[13] 142—143 °C.

Table 3. Analytical data for the *tetrahydroisoquinolines* (**1a**—**l**)

Compound	M.p. (°C)	Formula	Found (%) C	H	N	Required (%) C	H	N
(**1a**)	104—105	$C_{16}H_{18}BrNO_2S$	51.7	4.8	3.7	52.2	4.9	3.8
(**1b**)	85—87	$C_{16}H_{19}NO_2S$	66.2	6.5	4.9	66.4	6.6	4.8
(**1c**)	92—94	$C_{16}H_{18}ClNO_2S$	59.3	5.7	4.1	59.4	5.6	4.3
(**1d**)	103—104	$C_{16}H_{18}INO_2S$	46.6	4.4	3.3	46.3	4.3	3.4
(**1e**)	95—97	$C_{16}H_{18}BrNO_2S$	52.1	5.0	3.6	52.2	4.9	3.8
(**1f**)	104—105	$C_{16}H_{17}Br_2NO_2S$	43.3	3.9	3.2	42.9	3.8	3.1
(**1g**)	104—106	$C_{16}H_{18}BrNO_2S$	52.4	4.8	3.5	52.2	4.9	3.8
(**1h**)	101—103	$C_{16}H_{17}Br_2NO_2S$	42.7	3.5	2.8	42.9	3.8	3.1
(**1i**)	85—87	$C_{16}H_{17}Cl_2NO_2S$	53.8	4.8	3.7	53.8	4.8	3.9
(**1j**)	61—63	$C_{18}H_{20}BrNO_2$	59.7	5.5	3.5	59.7	5.5	3.9
(**1k**)	106—108	$C_{18}H_{20}BrNO_2$	60.4	6.0	3.8	59.7	5.5	3.9
(**1l**)	83—85	$C_{18}H_{20}BrNO_2 \cdot 0.5H_2O$	58.3	5.9	3.6	58.2	5.7	3.8

following features [$(MeO)_2C_6H_3\beta CH_2\alpha CH_2NHCOR$]: (a) two triplets ($J$ 7.5 Hz) in the regions δ 2.77—2.85 (β-H) and 3.49—3.63 (α-H); (b) two singlets in the region δ 3.72—3.89 (2 × MeO), and a broad singlet in the region δ 6.15—6.50 (NH).

The Dihydroisoquinoline Hydrochlorides (**8a**—**n**).—Typically the amide (0.06 mol) and phosphoryl chloride (20 ml) in toluene (100 ml) were heated on the steam-bath for 3.5 h. When cool the solution was added, with vigorous stirring, to ether (750 ml), and the yellow hydrochloride (*ca.* 100%) was filtered off and washed with ether. Small samples were crystallised to constant m.p. from ethanol–ether, but all gave consistently poor analytical results.

The 1-*Substituted* 6,7-*Dimethoxy*-3,4-*dihydroisoquinolines* (**9a**—**n**).—A solution of the foregoing hydrochloride in water was made basic by the addition of 4M-sodium hydroxide, the free base was isolated by extraction into ether and was crystallised from cyclohexane; the yields of the recrystallised material were *ca.* 80%.

The Methiodides (**10a**—**n**).—The dihydroisoquinoline (0.018 mol) and iodomethane (4 ml) were dissolved in DMF (20 ml) and the solution was heated under reflux on the steam-bath for 45 min. The cooled solution was added to ether (250 ml) with rapid and efficient stirring, to precipitate the canary-yellow methiodide as a solid (yield almost quantitative). It was collected by filtration and washed with ether, and a sample was crystallised to constant m.p. from ethanol–ether; few of the methiodides gave satisfactory microanalytical results. Details of the new dihydroisoquinolines (**9**), their hydrochlorides (**8**), and the methiodides (**10**) are collected in Table 2.

The ^1H n.m.r. spectra ($CDCl_3$) of the dihydroisoquinolines (**9a**—**n**) all possessed the following features due to the protons in the isoquinoline part of the molecule: (a) triplets in the regions δ 3.70—3.80 (2 H, 3-H) and 2.53—2.75 (2 H, 4-H) ($J_{3,4}$ 7.5 Hz); (b) singlets in the regions δ 6.80—7.30 (1 H) and 6.40—6.80 (1 H) (5-H/8-H); (c) singlets in the regions δ 3.90—3.98 (3 H) and 3.65—3.85 (3 H) (2 × MeO). In addition the following signals due to the protons in the substituent at C-1 in the individual compounds were observed: (**9a**) δ 7.28 (1 H, d, J 4.5 Hz, 4-H) and 7.05 (1 H, d, J 4.5 Hz, 3-H); (**9b**) δ 7.25 (3 H, m, 3-, 4-, and 5-H); (**9c**) δ 7.10 (1 H, d, J 4.5 Hz, 4-H) and 6.88 (1 H, d, J 4.5 Hz, 3-H); (**9d**) δ 7.28 (1 H, d, J 4.5 Hz, 4-H) and 7.06 (1 H, d, J 4.5 Hz, 3-H); (**9e**) δ 7.20 (1 H, d, J 1.5 Hz, 5-H) and 7.10 (1 H, d, J 1.5 Hz, 3-H); (**9f**) δ 7.14 (1 H, s, 3-H); (**9g**) δ 7.42 (1 H, d, J 1.5 Hz, 4-H) and 7.37 (1 H, d, J 1.5 Hz, 2-H); (**9h**) δ 7.00 (1 H, s, 4-H); (**9i**) δ 6.98 (1 H, s, 4-H); (**9j**) δ 7.40 (4 H, m, 3-, 4-, 5-, and 6-H); (**9k**) δ 6.65 (1 H, s, 2-H) and 7.40 (3 H, m, 4-, 5-, and 6-H); (**9l**) δ 7.52 (4 H, s, 2-, 3-, 5-, and 6-H); (**9m**) 7.48 (5 H, m, 2—6-H); (**9n**) δ 2.32 (3 H, s, Me).

The 1-*Substituted* 6,7-*Dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinolines* (**1a**—**n**).—In a typical case the methiodide (**10**) (12.5 mmol) was dissolved in ethanol–water (50 ml; 1:1), and an excess of sodium borohydride was added in small portions; the yellow colour of the solution was finally discharged. More water was added, the product was isolated by extraction into ether and [with the exception of the known[11] (**1n**), which is an oil] was crystallised from ethanol–water to give

the tetrahydroisoquinoline in *ca.* 90% yield. Microanalytical data and the m.p.s of the new bases are presented in Table 3; the 1-phenyl compound (**1m**) had m.p. 82—84 °C (lit.,[10] 81—82 °C).

The ^{1}H n.m.r. spectra ($CDCl_3$) of the tetrahydroisoquinolines (**1a**—**n**) all possessed the following features due to protons in the isoquinoline part of the molecule: (a) multiplets centred in the region δ 2.70—2.85 (4 H, 3- and 4-H); (b) singlets in the regions δ 6.50—6.61 (1 H) and 5.98—6.41 (1 H) due to 5-H/8-H; (c) a broad singlet (1 H) in the region δ 4.11—4.89 (1-H) [compounds (**1a**—**m**); in compound (**1n**) the 1-H signal was a quartet (δ 3.50, *J* 6.7 Hz)]; singlets in the regions δ 3.79—3.85 (3 H) and 3.50—3.77 (3 H) (2 × MeO): a singlet (3 H) in the region δ 2.15—2.38 (NMe). In addition the following signals due to the protons in the substituent at C-1 in the individual compounds were observed: (**1a**) δ 6.83 (1 H, d, *J* 4.5 Hz, 4-H) and 6.68 (1 H, d, *J* 4.5 Hz, 3-H); (**1b**) δ 7.10 (3 H, m, 3-, 4-, and 5-H); (**1c**) δ 6.80 (2 H, s, 3- and 4-H); (**1d**) δ 7.04 (1 H, d, *J* 4.5 Hz, 4-H) and 6.62 (1 H, d, *J* 4.5 Hz, 3-H); (**1e**) δ 7.05 (1 H, d, *J* 1.5 Hz, 5-H) and 6.82 (1 H, d, *J* 1.5 Hz, 3-H); (**1f**) δ 6.79 (1 H, s, 3-H); (**1g**) δ 7.04 (1 H, d, *J* 1.5 Hz, 4-H) and 6.88 (1 H, d, *J* 1.5 Hz, 2-H); (**1h**) δ 6.68 (1 H, s, 4-H); (**1i**) δ 6.58 (1 H, s, 4-H); (**1j**) δ 7.25 (4 H, m, 3—6-H); (**1k**) δ 7.20 (4 H, m, 2-, 4-, 5-, and 6-H); (**1l**) δ 7.20 (4 H, AA′XX′ system, $J_{2,3}$ 8.3 Hz, 2-, 3-, 5-, and 6-H); (**1m**) δ 7.22 (5 H, m, 2—6-H); (**1n**) δ 1.32 (3 H, d, *J* 6.7 Hz, Me).

Reaction of 1-(5-*Bromo*-2-*thienyl*)-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**1a**) *with* NaOMe–DMSO.—Sodium (0.4 g, 17.4 mg-atom) was dissolved in absolute methanol and the excess of methanol was removed under reduced pressure. Dry DMSO (30 ml) was added, the suspension was stirred magnetically and, after a short time, the isoquinoline (**1a**) (3 g, 7.85 mmol, suspended in a small volume of DMSO) was added. An exothermic reaction occurred, and the solution became orange. The mixture was stirred at room temperature overnight, then added to water (150 ml) and thoroughly extracted with dichloromethane. The combined extracts were washed repeatedly with water, dried, and evaporated to give a solid (2.4 g) which, on crystallisation from benzene–light petroleum (charcoal) afforded 1-*hydroxy*-6,7-*dimethoxy*-2-*methyl*-1-(2-*thienyl*)-1,2,3,4-*tetrahydroisoquinoline* (**2**) (1.6 g, 64%) as white crystals, m.p. 124—126 °C (Found: C, 62.3; H, 6.5; N, 5.0; S, 10.1. $C_{16}H_{19}NO_3S$ requires C, 62.9; H, 6.2; N, 4.6; S, 10.5%); $\nu_{max.}$(KBr) 3 500—2 100 (H-bonded OH), 1 660 (w, CO of open-chain isomer), and 1 020 cm^{-1} (diaryl alcohol); δ($CDCl_3$) 6.70—7.75 (5 H, diffuse m, all ArH), 4.12 (3 H, s, OMe), 3.79 (3 H, s, OMe), 2.80 (4 H, s, CH_2CH_2), and 2.31 (3 H, s, NMe); δ ($CDCl_3$–trichloroacetyl isocyanate) 6.85 (1 H, s, 5- or 8-H), 7.15 (1 H, s, 8- or 5-H), and 7.0—7.9 (3 H, ABC system, thiophene protons); δ[$(CD_3)_2SO$] 6.85—7.30 (3 H, ABC system, thiophene protons), 6.65 (2 H, s, 5- and 8-H), 5.1 (1 H, br s, OH), 3.73 (3 H, s, OMe), 3.53 (3 H, s, OMe), 2.6—3.3 (4 H, m, CH_2CH_2), and 2.22 (3 H, s, NMe). In addition, in this last solvent extra resonances were observed, distinct from those of the major isomer, due to the presence of *ca.* 15% of the open-chain form, at δ 8.05 (m, thiophene 3-H), 7.50 (m, thiophene 4-H), and 3.81 (s, OMe); *m/z* 305 (M^+), 287 (base peak; $M - H_2O$), and 204 (287 − C_4H_3S).

Reaction of 1-(5-*Chloro*-2-*thienyl*)- (**1c**) *and* 1-(5-*Iodo*-2-*thienyl*)-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**1d**) *with* NaOMe–DMSO.—Each of the isoquinolines (**1c**) and (**1d**) was treated with NaOMe–DMSO in the same manner as that described for (**1a**). In both cases the alcohol (**2**) was formed, in yields of 35% [from (**1c**)] and 20% [from (**1d**)], and the starting material was completely consumed.

Synthesis of Compound (**2**).—6,7-Dimethoxy-2-methyl-1-(2-thienyl)-3,4-dihydroisoquinolinium iodide (**10b**) (0.5 g) was stirred overnight with 4M-aqueous sodium hydroxide (30 ml). The buff solid was collected by filtration, washed with water, dried, and crystallised from benzene–light petroleum to give the pseudo base (**2**) (0.1 g, 27%), m.p. 127—128 °C, undepressed on admixture with the material obtained by the action of NaOMe–DMSO on compounds (**1a**), (**1c**), and (**1d**).

Toluene-p-*sulphonyl Derivative of Compound* (**2**).—The pseudo base (1.2 g) and toluene-*p*-sulphonyl chloride (0.57 g) were dissolved in pyridine (50 ml) and the solution was heated on the steam-bath for 10 min then, when cool, added to an excess of 2M-hydrochloric acid. The whole was extracted with dichloromethane (× 3), the extracts were washed with 2M-hydrochloric acid (× 2), with 4M-sodium hydroxide (× 2), and water, then dried and evaporated. The resulting oil (0.9 g) slowly crystallised; after two crystallisations from ethanol the *toluene*-p-*sulphonamide* (**4**) formed white crystals, m.p. 134—135 °C [Found (2 analyses): C, 60.15, 59.7; H, 5.9, 5.7; N, 3.5, 2.9. $C_{23}H_{25}NO_5S_2$ requires C, 60.1; H, 5.45; N, 3.05%]; $\nu_{max.}$(KBr) 1 620 cm^{-1} (diaryl CO); δ($CDCl_3$) 6.8—7.7 (9 H, m, all ArH), 3.96 (3 H, s, OMe), 3.76 (3 H, s, OMe), 2.8—3.4 (4 H, m, CH_2CH_2), 2.60 (3 H, s, NMe), and 2.36 (3 H, s, ArMe).

Synthesis of the Sulphonamide (**4**).—2-(3,4-*Dimethoxyphenyl*)-N-*methyl*-N-*tosylethylamine* (**6**). A solution of the tosyl derivative of homoveratrylamine[2] (3 g) and dimethyl sulphate (1.3 g) in acetone (50 ml) was stirred and boiled under reflux, in the presence of anhydrous potassium carbonate (2.5 g), for 4 h. The solids were filtered off and washed with acetone; evaporation of the combined acetone solutions left a solid, which was crystallised from ether–toluene to yield the title *sulphonamide* (**6**) (2.5 g, 80%), as a white solid, m.p. 80 °C (Found: C, 61.5; H, 6.9; N, 3.8; S, 9.1. $C_{18}H_{23}NO_4S$ requires C, 61.9; H, 6.6; N, 4.0; S, 9.2%); δ($CDCl_3$) 6.6—7.8 (7 H, m, all ArH), 3.68 (6 H, s, 2 × OMe), 2.60 (3 H, s, NMe), 2.26 (3 H, s, ArMe), and 2.8—3.7 (4 H, m, CH_2CH_2).

2-[4,5-*Dimethoxy*-2-(2-*thenoyl*)*phenyl*]-N-*methyl*-N-*tosylethylamine* (**4**). The foregoing sulphonamide (2.5 g, 7.2 mmol) and 2-thenoyl chloride (1.05 g, 7.2 mmol) were dissolved in dry dichloromethane (30 ml) and, with cooling, a solution of tin(IV) chloride (4.48 g, 17.1 mmol) in the same solvent (5 ml) was added slowly. The mixture was boiled under reflux for 3 h, cooled, washed with water (× 3) and with 2M-sodium hydroxide (× 2), then dried and evaporated. The resulting oil was triturated with ether to provide the impure product (3.8 g) as a grey-purple solid. After crystallisation from ether–toluene, then ethanol, the title compound (1.5 g, 46%) was obtained, identical in all respects with the sulphonamide prepared from the pseudo base (**2**).

Reaction of 1-(4,5-*Dibromo*-2-*thienyl*)-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**1f**) *with* NaOMe–DMSO.—When compound (**1f**) (2 g, 4.5 mmol) was treated with sodium methoxide [from sodium (0.22 g, 9.6 mg-atom)] in DMSO (15 ml) in the way described above for (**1a**) an oily solid (1.5 g) was obtained. It was crystallised from benzene–light petroleum to give 1-(4-*bromo*-2-*thienyl*)-1-*hydroxy*-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**11**) as a light-brown solid, m.p. 119—120 °C (decomp.) (Found: C, 50.3; H, 4.8; N, 3.6. $C_{16}H_{18}BrNO_3S$ requires C, 50.0; H, 4.7; N, 3.5%); $\nu_{max.}$(KBr) 3 500—2 100 (H-bonded OH) and 1 015 cm^{-1} (diaryl alcohol), δ[$(CD_3)_2SO$] 7.54 (1 H, d, *J* 1.5 Hz, thiophene 3-H), 7.06 (1 H, d, *J* 1.5 Hz, thiophene 5-H), 6.75 (2 H, s, 5- and 8-H), 6.20 (1 H, br s, OH), 3.82 (3 H, s, OMe), 3.60 (3 H, s, OMe), 2.9 (4 H, m, CH_2CH_2), and 2.35 (3 H, s, NMe).

Reaction of 1-(5-*Bromo*-2-*thienyl*)-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (**1a**) *with Dimethyl Sulphoxide Anion.*—(*a*) The isoquinoline (2.5 g) was added to a suspension of potassium *t*-butoxide (1.7 g) in DMSO (20 ml). After 24 h at room temperature the orange solution was poured into water and the whole was repeatedly extracted with ether. Evaporation of the washed (water; ×4) and dried extracts gave a semi-solid (0.6 g), which, on crystallisation from hexane, afforded 2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolin-1-(2H)-one (**14**), m.p. 121.5—123.5 °C (lit.,[14] 126 °C); $\nu_{max.}$(KBr) 1 640 cm^{-1} (CO) (lit.,[15] 1 630 cm^{-1}); δ($CDCl_3$) 7.70 (1 H, s, 8-H), 6.71 (1 H, s, 5-H), 3.97 (6 H, s, 2 × OMe), 3.16 (3 H, s, NMe), 3.59 (2 H, t, *J* 7.5 Hz, 4-H), and 3.05 (2 H, t, *J* 7.5 Hz, 3-H). These n.m.r. data are almost identical with those recorded previously for the amide (**14**).[15,16]

(*b*) Sodium hydride (0.35 g, 80% dispersion) was washed with dry light petroleum, then added to DMSO (15 ml); the suspension was stirred at 70 °C for 30 min, then cooled. The isoquinoline (**1a**) (1.5 g) was added in one portion; there was an immediate rise in temperature and a red colour (which quickly faded) developed. After 24 h the reaction mixture was worked up in the way described in (*a*) to give a small quantity of material, m.p. 115—117 °C, which had an i.r. spectrum identical with that of the sample of (**14**) obtained in experiment (*a*).

Synthesis of the Diarylmethoxymethanes (**17a—c**).—*The diarylmethanols* (**16a—c**). A solution of the appropriate ketone in ethanol was treated with enough water to give a suspension. An excess of sodium borohydride was added, in portions, and the mixture was set aside at room temperature for 15 min, then heated briefly on the steam-bath. When cool the solution was diluted with water and the product was isolated by extraction into ether. The crude products (yields *ca.* 100%) were sufficiently pure for use in the next stage; small samples were crystallised to constant m.p. from light petroleum, but only compound (**16a**) gave satisfactory microanalytical results. Details of the alcohols are given in Table 4.

The diarylmethoxymethanes (**17a—c**). The alcohol, in a small volume of methanol, was added to a large excess of methanol that had been saturated with dry hydrogen chloride. After 24 h at room temperature the solution was poured into an excess of 4M-ammonium hydroxide, containing ice; the product was isolated by extraction into ether, and distilled. The compounds deteriorated on standing, and none gave a satisfactory microanalysis. The properties of the new ethers are collected in Table 5.

Reaction of Compound (**17b**) *with* NaOMe–DMSO.—The ether (2.6 g) in DMSO (5 ml) was added to a suspension of sodium methoxide (2 equiv., from 0.45 g sodium) in DMSO (35 ml); the mixture became dark, and the temperature increased. The solution was stirred at room temperature for 24 h, then worked up in the usual way by addition to water and extraction with ether, to give an oil (2 g). The product was taken up in light petroleum (b.p. 40—60 °C) and passed through a short column of neutral alumina to provide *phenyl* 2-*thienyl ketone dimethyl acetal* (**18a**) (1.79 g, 84%), m.p. 59—60.5 °C (from aqueous ethanol) (Found: C, 66.7; H, 6.1. $C_{16}H_{14}O_2S$ requires C, 66.7; H, 6.0%); $\nu_{max.}$(KBr) 1 450, 1 085, and 1 050 cm^{-1}, δ($CDCl_3$) 6.8—7.7 (8 H, m, all ArH), and 3.15 (6 H, s, 2 × OMe). The bulk of the acetal (1.15 g) was heated on the steam-bath with 4M-hydrochloric acid (25 ml) for 1 h; the product was isolated by extraction into ether, and was crystallised from light petroleum (b.p. 40—60 °C) to give phenyl 2-thienyl ketone (0.74 g, 80%), m.p. and mixed m.p. 56—57 °C.

Reaction of Compound (**17c**) *with* NaOMe–DMSO.—This ether (2 g) was treated in the manner just described with sodium methoxide (from 0.28 g sodium) in DMSO (25 ml). The product obtained from the alumina column was the 4-*bromo*-2-*thienyl phenyl ketone dimethyl acetal* (**18b**) (1.46 g, 85%) as an oil, δ($CDCl_3$) 6.75—7.60 (7 H, m, all ArH), and 3.10 (6 H, s, 2 × OMe). The entire sample of crude acetal was hydrolysed as before to give 4-bromo-2-thienyl phenyl ketone (1.0 g, 80%) which, after crystallisation from light petroleum (b.p. 40—60 °C) had m.p. 79.5—80.5 °C (lit.,[17] 83—84 °C); $\nu_{max.}$(KBr) 1 633 cm^{-1} (CO); δ($CDCl_3$) 7.3—7.9 (m, all ArH). The i.r. and n.m.r. spectra were quite different from those of 5-bromo-2-thienyl phenyl ketone.

Reaction of Compound (**9a**) *with* NaOMe–DMSO.—A solution of 1-(5-bromo-2-thienyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (2 g, 5.7 mmol) in DMSO (10 ml) was added to a suspension of sodium methoxide [from sodium (0.57 g, 12.3 mg-atom)] in DMSO (15 ml) and the whole was stirred overnight at room temperature. The orange solution was added to water, and the solid produced was isolated by extraction into dichloromethane, then crystallised from cyclohexane to yield 6,7-*dimethoxy*-1-(2-*thienyl*)*isoquinoline* (**19**) (1.1 g, 71%); m.p. 119—121 °C (Found: C, 66.3; H, 4.7; N, 4.9. $C_{15}H_{13}NO_2S$ requires C, 66.4; H, 4.8; N, 5.2%); δ($CDCl_3$) 8.47 (1 H, d, *J* 5.7 Hz, quinoline 3-H), 7.82 (1 H, d, *J* 5.7 Hz, quinoline 5-H), 7.07—7.72 (4 H, m, C_4H_3S and quinoline 4-H), 7.07 (1 H, s, 8-H), 3.99 (3 H, s, OMe), and 3.95 (3 H, s, OMe).

Reaction of Compound (**9c**) *with* NaOMe–DMSO.—The dihydroisoquinoline (**9c**) (3 g) was treated with sodium methoxide (from 0.5 g sodium) in DMSO (25 ml) as just described to give (**19**) (1.74 g, 64%), m.p. 118—120 °C,

Table 4. The *diaryl methyl alcohols* (**16a—c**)

Compound	M.p. (°C)	$\nu_{max.}$(KBr) (cm^{-1})	δ($CDCl_3$) (p.p.m.)
(**16a**)*	57—59	3 250br, 1 440, 1 260, 1 010	7.1 (8 H, m, all ArH), 5.94 (1 H, s, C*H*OH), 2.70 (1 H, s, OH)
(**16b**)	63—64.5	3 430br, 1 440, 1 255, 1 010	7.45 (5 H, s, C_6H_5), 6.80 (1 H, d, thiophene 4-H), 6.50 (1 H, d, thiophene 3-H; $J_{3,4}$ 4 Hz), 5.80 (1 H, s, C*H*OH), 2.55 (1 H, s, OH)
(**16c**)	83—85	3 200br, 1 430, 1 255, 1 010	7.30 (5 H, s, C_6H_5), 6.58 (1 H, s, thiophene 3-H), 5.75 (1 H, s, C*H*OH), 3.30 (1 H, s, OH)

* Found: C, 69.6; H, 5.2. $C_{11}H_{10}OS$ requires C, 69.5; H, 5.3%.

Table 5. The *diarylmethoxymethanes* (**17a—c**)

Compound	Yield (%)	B.p. (°C/ mmHg)	$\nu_{max.}$(film) (cm^{-1})	δ($CDCl_3$) (p.p.m.)
(**17a**)	4	101/4	1 450, 1 090	7.1 (8 H, m, all ArH), 5.46 (1 H, s, C*H*OMe), 3.36 (3 H, s, OMe)
(**17b**)	53	145/0.04	1 450, 1 090	7.24 (5 H, s, C_6H_5), 6.60 (1 H, d, thiophene 4-H), 6.45 (1 H, d, thiophene 3-H; $J_{3,4}$ 4 Hz), 5.22 (1 H, s, C*H*OMe), 3.30 (3 H, s, OMe)
(**17c**)	72	155/0.05	1 450, 1 085	7.25 (5 H, s, C_6H_5), 6.53 (1 H, s, thiophene 3-H), 5.24 (1 H, s, C*H*OMe), 3.30 (3 H, s, OMe)

undepressed on admixture with the product of the foregoing experiment.

Reaction of Compound (**9c**) *with* NaOMe–DMF.—Treatment of compound (**9c**) (1.5 g, 4.9 mmol) with sodium methoxide [from sodium (0.25 g, 10.8 mg-atom)] in dry DMF (15 ml) by the procedure described in the above two experiments yielded the product (**19**) (0.9 g, 67%).

Reaction of Compound (**9a**) *with* Bu^{t}OK–DMSO.—The bromo compound (1 g, 2.85 mmol) was added to potassium t-butoxide (0.7 g, 6.2 mmol) in DMSO (10 ml). After 24 h at room temperature, the deep-yellow solution was processed in the usual way to yield an oil which was shown by t.l.c. (SiO_2; $CHCl_3$–EtOH) to contain unchanged (**9a**), the highly fluorescent product (**19**), and several other components. Eventually crystals were deposited; recrystallisation from cyclohexane (× 2) gave the product (**19**) (0.2 g, 26%), m.p. 118—120 °C.

Reaction of Compound (**9a**) *with* NaH–DMSO.—Sodium hydride (80% dispersion, 0.36 g, 11.8 mmol) was washed with dry light petroleum and suspended in DMSO. The dihydroisoquinoline (2 g, 5.7 mmol) in DMSO (10 ml) was added, and the mixture was stirred at room temperature for 24 h. The crude product (1.5 g), isolated in the usual way by extraction into dichloromethane, was digested with boiling cyclohexane. The solid (0.45 g) which crystallised from the solvent was shown by n.m.r. spectroscopy to be a mixture of unchanged compound (**9a**) (1 part) and the product (**19**) (2 parts).

1-(5-*Bromo*-2-*thienyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*.—The dihydroisoquinoline hydrochloride (**8a**) (7.1 g) was dissolved in ethanol–water (1:1; 100 ml) and an excess of sodium borohydride was added in portions. The solution was diluted with more water and extracted several times with chloroform to give a gum (6.5 g). A portion was digested with hot ethanol to yield, from the cooled alcohol solution, 1-(5-*bromo*-2-*thienyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinolinium chloride*, m.p 238—240 °C (Found: C, 46.2; H, 4.3; N, 3.5. $C_{15}H_{17}BrClNO_2S$ requires C, 46.1; H, 4.4; N, 3.6%). The remainder of the hydrochloride was dissolved in water, the solution was made basic with sodium hydroxide and the product was extracted into ether, giving 1-(5-*bromo*-2-*thienyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*, m.p. 108—110 °C (aqueous ethanol) (Found: C, 50.7; H, 4.5; N, 4.1. $C_{15}H_{16}BrNO_2S$ requires C, 50.8; H, 4.5; N, 3.95%), δ($CDCl_3$) 6.88 (1 H, d, *J* 4 Hz, thiophene 4-H), 6.63 (1 H, d, thiophene 3-H), 6.60 (1 H, s, 5- or 8-H), 6.50 (1 H, s, 8- or 5-H), 5.23 (1 H, br s, 1-H), 3.89 (3 H, s, OMe), 3.77 (3 H, s, OMe), 2.9 (4 H, m, 3- and 4-H), and 1.95 (1 H, br s, NH).

Reaction of 1-(5-*Bromo*-2-*thienyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline with* NaOMe–DMSO.—The tetrahydroisoquinoline (2.4 g, 6.8 mmol) was treated in the usual way with sodium methoxide [from sodium (0.37 g, 16.1 mg-atom)] in DMSO (25 ml). The crude product (1.3 g), a mixture of oil and solid, was shown by t.l.c. (SiO_2; $CHCl_3$–EtOH) to contain the product (**19**) and several other components, but no starting material. The mixture was extracted with boiling cyclohexane, and the solution was treated with decolourising carbon, cooled, seeded with a few crystals of (**19**), and set aside. Thus was obtained 6,7-dimethoxy-1-(2-thienyl)isoquinoline (**19**) (0.4 g, 21%), m.p. and mixed m.p. 115—117 °C.

Preparation of Compound (**19**) *by Dehydrogenation of* 6,7-*Dimethoxy*-1-(2-*thienyl*)-3,4-*dihydroisoquinoline*.—A solution of the title dihydro compound (**9b**) (1.85 g) and 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (1.53 g) in xylene (15 ml) was boiled under reflux for 15 h, then cooled and washed several times with 2M-hydrochloric acid. The washings were made basic (2M-sodium hydroxide) and the product was extracted with chloroform. Crystallisation from cyclohexane yielded the product (**19**) (0.4 g, 14%), m.p. 120—122 °C, having identical i.r. and n.m.r. spectra with those of the materials obtained above from compounds (**9a**) and (**9c**).

Reaction of Compound (**9h**) *with* NaOMe–DMSO.—Treatment of 1-(2,5-dibromo-3-thienyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**9h**) (1 g, 2.3 mmol) with sodium methoxide [from sodium (0.25 g, 10.9 mg-atom)] in DMSO (10 ml) in the usual fashion led to a yellow solid (0.5 g) which was crystallised first from cyclohexane, then from aqueous ethanol, to provide 6,7-*dimethoxy*-1-(3-*thienyl*)*isoquinoline* (**20**) (0.3 g, 48%) as pale-yellow crystals, m.p. 146—148 °C (Found: C, 66.0; H, 5.2; N, 5.0. $C_{15}H_{13}NO_2S$ requires C, 66.4; H, 4.8; N, 5.2%), δ($CDCl_3$) 8.41 (1 H, d, *J* 6 Hz, quinoline 3-H), 7.50 (1 H, s, quinoline 5-H), 7.40 (1 H, d, *J* 6 Hz, quinoline 4-H), 7.04 (1 H, s, 8-H), 7.40—7.65 (3 H, m, C_4H_3S), 4.00 (3 H, s, OMe), and 3.89 (3 H, s, OMe).

Reaction of Compound (**9g**) *with* NaOMe–DMSO.—When 1-(5-bromo-3-thienyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**9g**) (3 g, 8.5 mmol) was treated by the standard method with sodium methoxide [from sodium, 0.43 g (18.7 mg-atom)] a solid (2.2 g) which melted over a wide range was obtained; n.m.r. spectroscopy indicated that it was a 2:1 mixture of the product (**20**) and starting material (**9g**). When the reaction was repeated using a large excess of sodium methoxide the ratio of (**20**):(**9g**) rose to 4.4:1.

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