The Synthesis and Reactions of 4-(2- and 3-Thienyl)-tetrahydroisoquinolines

David E. Tupper*, Terrence M. Hotten and William G. Prowse

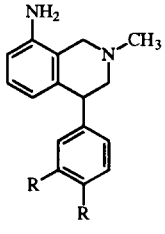
Lilly Research Centre Ltd., Eli Lilly and Co., Erl Wood Manor, Windlesham, Surrey, GU20 6PH, England

Received November 9, 1995

Tetrahydroisoquinoline derivatives substituted in the 4-position by either a 2- or 3-substituted thiophene ring have been synthesised. Simple electrophilic substitution reactions of these systems take place as expected in the α-position of the thiophene ring. Metalation reactions are more complex and take place at the benzylic 4-position of the tetrahydroisoquinoline nucleus in the case of the 2-substituted thiophene derivatives or at either the thiophene α-positions or the benzylic 4-position depending on the nature of the attacking electrophile in the case of the 3-substituted thiophene system.

J. Heterocyclic Chem., **33**, 1123 (1996).

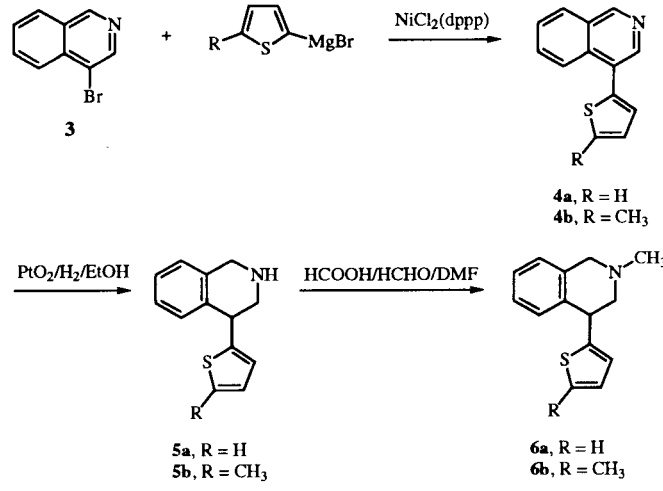
Recent programmes in these laboratories have sought to elucidate possible pharmacophores for antagonist activity at postsynaptic receptors of both the dopamine D_1 and D_2 subtypes [1-3]. During the course of these programmes we required synthetic routes to a number of tetrahydroisoquinoline derivatives substituted at the 4-position with a variety of heterocyclic systems. A number of synthetic routes have been developed for 4-aryl tetrahydroisoquinoline derivatives [4-6] because of the important biological activity of some of these compounds. Compounds such as nomifensin **1** are known to be effective antidepressant agents by virtue of their ability to inhibit dopamine and noradrenaline re-uptake mechanisms [7-11]. The dihydroxy derivative **2**, a metabolite of **1**, is also known to have activity at dopamine D_1 receptors [12].



R = H (nomifensin **1**)
R = OH (dihydroxynomifensin **2**)

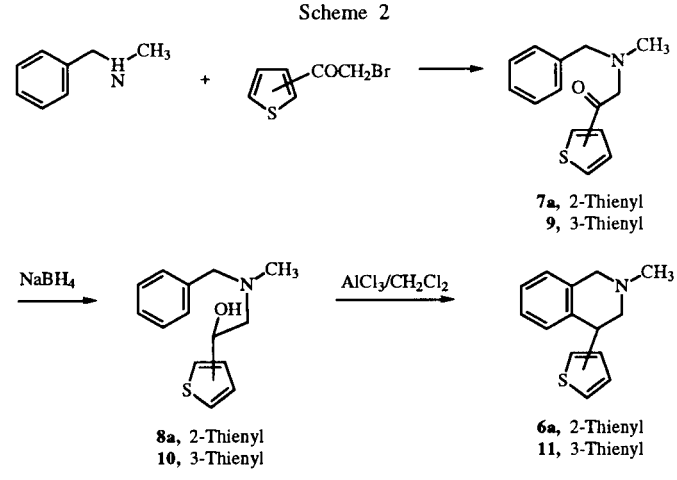
We report here the synthesis and reactions of tetrahydroisoquinoline derivatives substituted at the 4-position by either a 2- or 3-substituted thiophene ring. The synthesis of a number of aryl substituted isoquinoline derivatives has been reported using dichloro[1,3-bis(diphenylphosphino)propane]-nickel(II) [$NiCl_2$(dppp)] catalysed coupling of the appropriate haloisoquinoline with a Grignard reagent [13]. The Grignard reagents from 2-bromo and 2-bromo-5-methylthiophene were generated in ether using Red-Al as initiator. Coupling with 4-bromoisoquinoline **3** was achieved in dry THF using 5% by weight of $NiCl_2$(dppp) as catalyst. Yields of the coupled isoquinolines **4a** and **4b** were in the range 60-80%. Catalytic hydrogenation in the presence of Adams catalyst gave the parent tetrahydroisoquinoline systems **5a** and **5b**. Eschweiler-Clarke conditions yielded the required *N*-methyltetrahydroisoquinolines **6a** and **6b** (Scheme 1).

Scheme 1



Whilst convenient and high yielding, this method was not applicable to a number of the derivatives which we required. In particular it was unsuitable for the 3-substituted thiophene derivatives where the formation of Grignard reagents is notoriously unreliable. A second synthesis based on the reaction of bromoketone derivatives with *N*-methylbenzylamines was therefore used (Scheme 2)

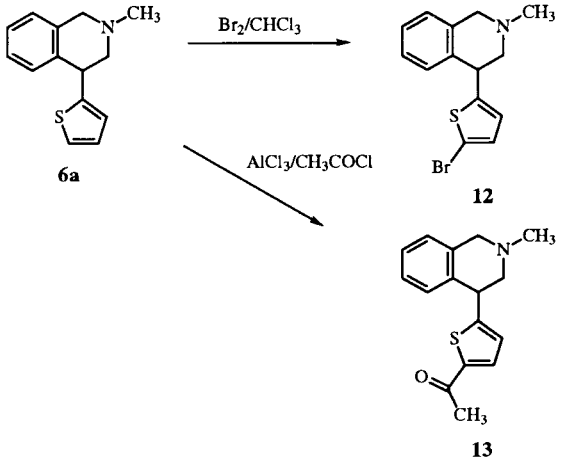
Scheme 2



[14]. The aminoketone intermediates **7a** and **9** were reduced to the aminoalcohols **8a** and **10** using sodium borohydride in ethanol and cyclised to the required tetrahydroisoquinolines **6a** and **11** in high yield using aluminium chloride in dichloromethane. The overall yields for the above process were usually in the range 60-90%.

As expected the parent 2-thienyltetrahydroisoquinoline derivative **6a** underwent electrophilic substitution reactions in the vacant 5-position of the thiophene ring to give both the 5-bromo and 5-acetyl derivatives **12** and **13** (Scheme 3). The ^{1}H nmr coupling constants for the thiophene ring protons, (J = 3.5 and 3.7 Hz respectively) were as expected for adjacent protons at the β-positions of the thiophene ring.

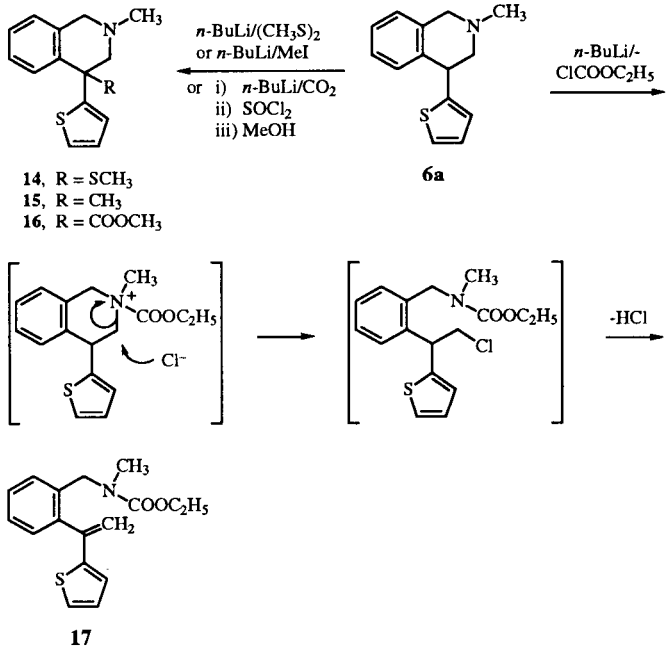
Scheme 3



6a **12** **13**

Metalation using *n*-butyl lithium and reaction with dimethyl disulphide, however, failed to yield the expected 5-methylthio derivative. Instead we obtained exclusively the 4-substituted tetrahydroisoquinoline derivative **14** (Scheme 4). Similarly, when the anion was treated with methyl iodide the corresponding 4-methyl derivative **15** was obtained. Use of solid carbon dioxide and esterification of the resultant carboxylic acid using thionyl chloride and methanol, lead to the tetrahydroisoquinoline ester derivative **16**. For **14**, **15** and **16** the appropriate signals for a monosubstituted thiophene ring were clearly seen in the ^{1}H nmr spectrum although conformational restraint due to the proximity of the 4-substituent caused some line broadening and loss of discernable coupling constants. For **15** and **16** the $J_{4,5}$ couplings of 5.4 and 5.8 Hz respectively were consistent with expected values, whilst for **16** a coupling constant of 3.5 Hz was also observed for the protons in the 3- and 4-positions. The expected tetrahydroisoquinoline methine signal at approximately 4.5-5.0 δ was absent in each case. The assignment was further confirmed for compound **16** by the ^{13}C nmr spectrum which exhibited a quaternary carbon at δ = 55.2 ppm, as was confirmed by a "DEPT 135" experiment.

Scheme 4

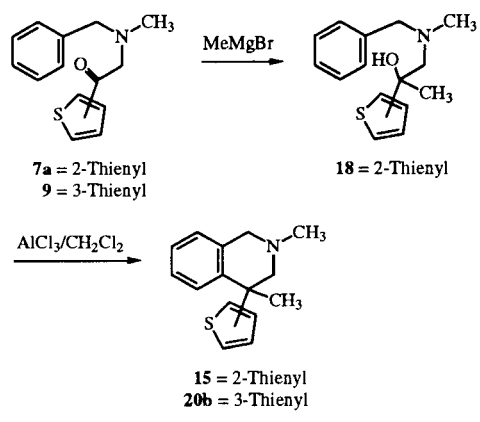


14, R = SCH_3
15, R = CH_3
16, R = $COOCH_3$

6a **17**

Treatment of the lithio derivative of **6a** with ethyl chloroformate resulted in another unexpected product, which was characterised as the ring opened derivative **17** on the basis of its ^{1}H and ^{13}C nmr spectra. A possible mechanism for this transformation would involve quaternisation of the tetrahydroisoquinoline nitrogen by the ethyl chloroformate, followed by attack at the adjacent 3-position by chloride ion with concomitant ring opening. Elimination of hydrogen chloride would then give the ring opened product observed (Scheme 4). A similar opening of a 1-benzyl tetrahydroisoquinoline using ethyl chloroformate and base has been reported [15].

Scheme 5



7a = 2-Thienyl
9 = 3-Thienyl

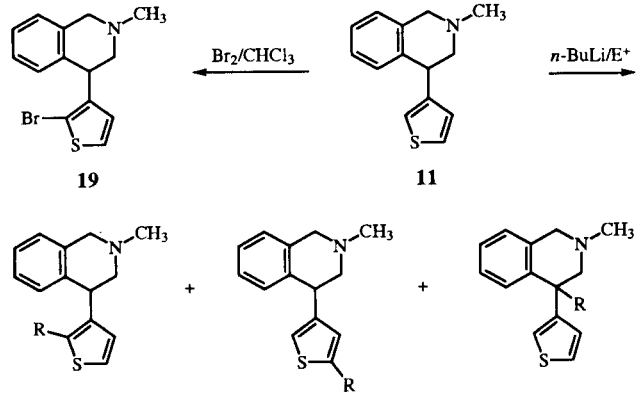
18 = 2-Thienyl

15 = 2-Thienyl
20b = 3-Thienyl

Compound **15** was unambiguously synthesised by reaction of the aminoketone **7a** with methylmagnesium bromide to give the carbinol **18**, followed by cyclisation using aluminium chloride in dichloromethane (Scheme 5).

The 3-thienyltetrahydroisoquinoline derivative **11** underwent bromination in the 2-position to give compound **19**, the structure of which was confirmed by the presence of the 4-proton at 5.39 δ and the coupling constant for the thiophene ring protons ($J_{4,5}$ = 5.2 Hz). None of the isomeric 5-substituted derivative was observed. The metalation reactions of **11** were, as might be expected, more complicated than those of compound **6a**. In this case two possible anions can be formed. An anion formed at the 4-position of the tetrahydroisoquinoline ring could react either in that position, or at the 2-position of the thiophene ring. An alternative anion can also be formed directly in the thiophene 5-position. Scheme 6 gives the yields and product ratios for the electrophiles attempted. Reaction with solid carbon dioxide, followed by esterification with oxalyl chloride and methanol, gave the product substituted in the 4-position of the tetrahydroisoquinoline ring **20a** and the thiophene ring substituted derivative **21a** in a ratio of approximately 1:2. Similarly reaction with iodomethane gave approximately equal amounts of **20b** and **21b**. Reaction of the anion with dimethyl disulphide gave all three of the possible substitution products **20c**, **21c** and **22c**, whilst on reaction with trimethylsilyl chloride only the two possible thiophene ring substituted derivatives **21d** and **22d** could be characterised. These two products both demonstrated significant instability and it is possible that any product substituted in the benzylic position that was formed may have been too unstable to isolate. This may also explain the lower yield of recovered products from this reaction. The 4-substituted products **20a-c** were initially characterised on the basis of the absence of the characteristic 4-proton. The 4-methyl derivative **20b** also gave characteristic coupling constants of 1.3, 3.0 and 5.0 Hz for the thiophene 2,4-, 2,5- and 4,5-protons respectively. Unambiguous structural assignment of the 4-substituted tetrahydroisoquinoline was provided by a detailed analysis of the ^{13}C and "DEPT 135" spectra of **20b**. These revealed two CH_3 signals (46.3, 28.9 ppm), two CH_2 signals (68.0, 59.1 ppm) and a quaternary carbon (42.0 ppm) in the aliphatic region of the spectrum. The protonated carbons were then correlated to their attached protons using an inverse-detected HMQC experiment. Confirmation that the CH_3 group (δ_H = 1.73 ppm, δ_{13C} = 28.9 ppm) was indeed attached to the C-4 position was obtained by analysis of long range proton-carbon couplings detected by an HMBC experiment. In this experiment the three proton singlet at 1.73 ppm showed the four ^2J and ^3J ^1H-^{13}C couplings expected for **20b**; to C-4 (42.0 ppm), C-3 (68.0 ppm), C-4a (141.9, ppm) and C-3' (150.6 ppm). The correlation to the thiophene carbon provides unambiguous evidence that the CH_3 and thiophene ring are attached to the same carbon (*ie.* C-4). A sample of **20b** was synthesised unambiguously by reaction of the aminoketone **9** with methylmagnesium bromide to give the carbinol, followed by cyclisation using aluminium chloride in dichloromethane (Scheme 5). The 2,4-substituted derivatives **21a** and **21d** gave characteristic coupling constants of 1.5 and 1.0 Hz respectively for the thiophene 2,4-protons. The methyl substituted derivative **21b** was insufficiently well resolved to observe any appropriate coupling constants. The 2,3-substituted derivatives **22c** and **22d** each exhibited a single coupling constant of 5.7 and 5.4 Hz respectively for the thiophene 4,5-positions.

Scheme 6



R	20	Ratio 21	22	%Yield (20 + 21 + 22)
a CO_2Me	37	63	0	65
b CH_3	45	55	0	49
c SCH_3	35	50	15	86
d $SiMe_3$	0	13	87	39

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. The ^1H-nmr and ^{13}C-nmr spectra were recorded on a Bruker AM300 spectrometer in either deuteriochloroform or perdeuteriomethanol or d_6-DMSO using TMS as reference, inverse-detected HMQC and HMBC spectra were acquired on a Bruker AC300 spectrometer. Mass spectra were recorded on a VG 7070E double focusing spectrometer using chemical ionisation with ammonia at 200eV. Column chromatography was carried out using Woelm alumina, Florisil or Sorbsil U30 grade silica gel. Magnesium sulphate was used as drying agent. 4-Bromoisoquinoline was obtained from Aldrich and used without purification.

4-(2-Thienyl)isoquinoline Hydrochloride (**4a**).

The Grignard reagent was prepared from 2-bromothiophene (2.0 g, 0.012 mole) and magnesium (0.3 g, 0.013 mole) in anhydrous diethyl ether (20 ml). The Grignard reagent thus prepared was added to a solution of 4-bromoisoquinoline (2.1 g, 0.01 mole) in THF (distilled from sodium/benzophenone) (50 ml) containing $NiCl_2$(dppp) (100mg). The reaction mixture was stirred at ambient temperature for 18 hours and then poured into

ice-cold dilute hydrochloric acid. After basification with dilute ammonia the solution was extracted several times with ether and the combined solvent layer washed with water, dried and concentrated. Purification by column chromatography on florisil using dichloromethane as eluent and crystallisation as the hydrochloride salt from ethanol/diethyl ether yielded 1.7 g (69%) of a yellow solid, mp 225-227°; ^{1}H nmr (methanol-d_4): δ 7.32 (1H, dd, $J_{4,5}$ = 5.1 Hz, $J_{3,4}$ = 3.6 Hz, 4'-H), 7.45 (1H, d, $J_{3,4}$ = 3.6 Hz, 3'-H), 7.68 (1H, d, $J_{4,5}$ = 5.1 Hz, 5'-H), 8.03 (1H, t, 6 or 7-H), 8.19 (1H, t, 6 or 7-H), 8.52 (1H, d, J = 8.2 Hz, 5 or 8-H), 8.58 (1H, s, 3-H), 8.62 (1H, d, J = 8.2 Hz, 5 or 8-H), 9.85 (1H, s, 1-H).

Anal. Calcd. for $C_{13}H_{10}NClS$: C, 63.03; H, 4.07; N, 5.65; Cl, 14.31; S, 12.94. Found: C, 63.20; H, 3.92; N, 5.88; Cl, 14.53, S, 12.75.

4-(5-Methyl-2-thienyl)isoquinoline Hydrochloride (**4b**).

This compound was similarly prepared from 2-bromo-5-methylthiophene [16] in a yield of 56% following column chromatography and was used without further purification.

4-(2-Thienyl)tetrahydroisoquinoline Hydrochloride (**5a**).

A mixture of compound **4a** (0.4 g, 0.0016 mole) and platinum oxide (0.1 g) in ethanol (20 ml) was shaken in an atmosphere of hydrogen at 60 psi for 18 hours. The catalyst was removed by filtration and the solution concentrated to a white solid. Crystallisation from ethanol/diethyl ether gave 0.3 g (74%) of white crystals, mp 220-225°; ^{1}H nmr (deuteriochloroform): δ 3.34 (1H, t, J = 12.5, 3-H), 3.80 (1H, dd, J = 7.2, 12.5 Hz, 3-H), 4.42 (1H, d, J = 15.8 Hz, 1-H), 4.50 (1H, d, J = 15.8 Hz, 1-H), 4.98 (1H, dd, 4-H), 7.0-7.24 (7H, m, Ar-H).

Anal. Calcd. for $C_{13}H_{14}NClS$: C, 62.02; H, 5.60, N, 5.56; Cl, 14.08; S, 12.73. Found: C, 61.92; H, 5.31; N, 5.26; Cl, 13.80, S, 12.78.

4-(5-Methyl-2-thienyl)tetrahydroisoquinoline Hydrochloride (**5b**).

This compound was similarly prepared (0.1 ml concentrated hydrochloric acid added to hydrogenation mixture) from **4b** in a yield of 90%, mp 232-234°; ^{1}H nmr (methanol-d_4): δ 2.44 (3H, s, CH_3), 3.50 (1H, dd, J = 9.7, 12.5 Hz, 3-H), 3.80 (1H, dd, J = 5.5, 12.5 Hz, 3-H), 4.41 (1H, d, J = 15.8 Hz, 1-H), 4.51 (1H, d, J = 15.8 Hz, 1-H), 4.76 (1H, dd, 4-H), 6.68 (1H, d, $J_{3,4}$ = 3.4 Hz, 3' or 4'-H), 6.78 (1H, d, $J_{3,4}$ = 3.4 Hz, 3' or 4'-H), 7.15-7.30 (4H, m, Ar-H).

Anal. Calcd. for $C_{14}H_{16}NClS$: C, 63.26; H, 6.07; N, 5.27; Cl, 13.34; S, 12.06. Found: C, 62.98; H, 5.83; N, 5.40; Cl, 13.06, S, 11.88.

2-Methyl-4-(2-thienyl)tetrahydroisoquinoline Hydrochloride (**6a**).

A solution of **5a** (0.2 g, 8 mmoles) in dimethylformamide (5 ml), 40% formaldehyde (2 ml) and 95% formic acid (2 ml) was heated at reflux for 2 hours. The reaction mixture was poured onto ice-water, made basic with dilute ammonia and extracted several times with diethyl ether. The combined ether layers were washed with water, dried and evaporated to dryness. Crystallisation of the hydrochloride salt from ethanol/diethyl ether gave 0.17 g (81%) of a white solid, mp 135-137°; ^{1}H nmr (methanol-d_4): δ 3.08 (3H, s, NCH_3), 3.64 (1H, t, J = 12.3 Hz, 3-H), 3.90 (1H, dd, J = 3.9, 12.3 Hz, 3-H), 4.57 (2H, s, 1-H), 5.00 (1H, dd, 4-H), 7.05 (1H, t, 4'-H), 7.08 (1H, dd, 3'-H), 7.12-7.35 (4H, m, Ar-H), 7.41 (1H, dd, $J_{4,5}$ = 5.1 Hz, $J_{3,5}$ = 1.4 Hz, 5'-H).

Anal. Calcd. for $C_{14}H_{16}NClS$: C, 63.26; H, 6.07; N, 5.27; Cl, 13.34; S, 12.06. Found: C, 63.43; H, 5.93; N, 5.21; C, 13.30, S, 12.30.

2-Methyl-4-(5-methyl-2-thienyl)tetrahydroisoquinoline Hydrochloride (**6b**).

This compound was similarly prepared from **5b** in a yield of 89%, mp 200-202°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.42 (3H, s, CH_3), 2.91 (3H, s, NCH_3), 3.5-3.9 (2H, bm, 3-H), 4.48 (2H, s, 1-H), 4.9 (1H, dd, 4-H), 6.90 (1H, d, $J_{3,4}$ = 3.3 Hz, 3' or 4'-H), 6.97 (1H, d, $J_{3,4}$ = 3.3 Hz, 3' or 4'-H), 7.0-7.3 (4H, m, Ar-H).

Anal. Calcd. for $C_{15}H_{18}NClS$: C, 64.38; H, 6.48; N, 5.01. Found: C, 64.12; H, 6.32; N, 5.03.

N-Benzyl-*N*-methyl-1-(2-thienyl)-2-aminoethanol (**8a**).

A mixture of 2-bromoacetylthiophene [17] (41 g, 0.2 mole) and *N*-methylbenzylamine (48.4 g, 0.4 mole) in dry toluene (300 ml) was stirred at ambient temperature for 2 hours. The *N*-methylbenzylamine hydrobromide formed was removed by filtration and the filtrate concentrated to a red oil (54.2 g). The crude aminoketone **7a** was dissolved in ethanol (300 ml) and sodium borohydride (7.6 g, 0.4 mole) added portionwise over 1 hour. The mixture was stirred for an additional 2 hours. The reaction was poured into ice-water, extracted with diethyl ether (3 x 100 ml), washed, dried and evaporated to a red oil. Distillation under reduced pressure gave 30 g (61%) of **8a** boiling at 125-130° and 0.05 mm Hg; ^{1}H nmr (deuteriochloroform): δ 2.29 (3H, s, NCH_3), 2.63 (1H, dd, J = 3.6, 12.4 Hz, NCH_2), 2.76 (1H, dd, J = 10.3, 12.4 Hz, NCH_2), 3.55, 3.71 (2H, AB system, J = 13 Hz, benzylic CH_2), 5.02 (1H, dd, J = 3.6, 10.3 Hz, C*H*OH), 6.97-7.35 (8H, m, ArH).

N-Benzyl-*N*-methyl-1-(3-thienyl)-2-aminoethanol (**10**).

This material was prepared in an identical manner from 3-bromoacetylthiophene [18] in a crude yield of 97%. The **10** thus formed was used without further purification.

2-Methyl-4(2-thienyl)tetrahydroisoquinoline (**6a**).

A solution of **8a** (30 g, 0.12 mole) in dichloromethane (50 ml) was added slowly to a stirred suspension of aluminium chloride (32.4 g, 0.24 mole) in dichloromethane (300 ml). The mixture was stirred for 2 hours at ambient temperature after which time water (200 ml) was added slowly. The mixture was made basic with aqueous ammonia and the solvent separated, washed with water, dried and concentrated to a red oil. Distillation under reduced pressure gave 24.3 g (88%) of the free base of **6a** boiling at 90-92° and 0.05 mm Hg; ^{1}H nmr (deuteriochloroform): δ 2.45 (3H, s, NCH_3), 2.80 (1H, dd, J = 6.9, 11.4 Hz, 3-H), 2.97 (1H, dd, J = 5.1, 11.4 Hz, 3-H), 3.65 (1H, AB system, 1-H), 3.67 (1H, AB system, 1-H), 4.53 (1H, t, 4-H), 6.92 (1H, d, 8-H), 6.93 (1H, dd, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 5.1 Hz, 4'-H), 7.00-7.20 (5H, m, Ar-H, 3'-H and 5'-H).

2-Methyl-4-(3-thienyl)tetrahydroisoquinoline Hydrochloride (**11**).

This compound was prepared in an identical manner from crude **10** in a yield of 71%. Crystallisation from ethanol/diethyl ether as the hydrochloride salt gave **11**, mp 136-138°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.90 (3H, s, NCH_3), 3.55 (1H, dd, J = 6.0, 12.1 Hz, 3-H), 3.68 (1H, dd, J = 12.1, 12.1 Hz, 3-H), 4.46 (2H, s, 1-H), 4.75 (1H, dd, 4-H), 6.87 (1H, d, 8-H), 6.97 (1H, d, $J_{4,5}$ = 4.8 Hz, 4'-H), 7.25 (3H, m, Ar-H), 7.53 (1H, bs, 2'-H), 7.58 (1H, d, $J_{4,5}$ = 4.8 Hz, 5'-H).

Anal. Calcd. for $C_{14}H_{16}NClS$: C, 63.26; H, 6.07; N, 5.27; Cl, 13.34; S, 12.06. Found: C, 62.97; H, 6.17; N, 5.23; Cl, 13.50, S, 12.02.

4-(5-Bromo-2-thienyl)-2-methyltetrahydroisoquinoline Hydrochloride (**12**).

A solution of bromine (0.8 g, 5 mmoles) in chloroform (10 ml) was added dropwise to a solution of **6a** (1.15 g, 5 mmoles) in chloroform (20 ml). The mixture was stirred for 4 hours at ambient temperature and then poured into 2*N* sodium hydroxide. The solvent was separated, washed with water, dried and concentrated under reduced pressure to a yellow oil. Chromatography on alumina using dichloromethane as eluent, followed by crystallisation as the hydrochloride salt from ethanol/diethyl ether gave 0.5 g (30%) of compound **12**, mp 260-264°; ^1H nmr (methanol-d_4): δ 3.08 (3H, s, N-CH_3), 3.63 (1H, dd, J = 12.3, 5.9 Hz, 3-H), 3.90 (1H, dd, J = 12.3, 11.0 Hz, 3-H), 4.56 (2H, s, 1-H), 4.95 (1H, dd, 4-H), 6.90 (1H, d, $J_{3,4}$ = 3.5 Hz, 4'-H), 7.05 (1H, d, $J_{3,4}$ = 3.5 Hz, 3'-H), 7.18 (1H, m, Ar-H), 7.23-7.40 (3H, m, Ar-H).

Anal. Calcd. for $C_{14}H_{15}BrClNS$: C, 48.78; H, 4.39; N, 4.06; Br, 23.18; S, 9.30. Found: C, 48.56; H, 4.33; N, 4.01; Br, 23.02; S, 9.21.

4-(5-Acetyl-2-thienyl)-2-methyltetrahydroisoquinoline Hydrochloride (**13**).

A solution of **6a** (0.46 g, 2 mmoles) in dichloromethane (10 ml) was added dropwise to a stirred suspension of aluminium chloride (0.53 g, 4 mmoles) in dichloromethane (10 ml). Acetyl chloride (0.23 g, 3 mmoles) in dichloromethane (10 ml) was added dropwise and the mixture stirred at ambient temperature for 48 hours. Water (10 ml) was added cautiously and the resultant mixture made basic with 2*N* sodium hydroxide. The solvent layer was separated, washed with water, dried and concentrated under reduced pressure. Chromatography on silica using 50% ethyl acetate/hexane as eluent and crystallisation as the hydrochloride salt from ethanol/diethyl ether gave 0.15 g (26%) of compound **13**, mp 208-210°; ^1H nmr (methanol-d_4): δ 2.54 (3H, s, CH_3CO), 3.05 (3H, s, N-CH_3), 3.63 (1H, dd, J = 12.5, 12.4 Hz, 3-H), 3.90 (1H, dd, J = 12.5, 5.3 Hz, 3-H), 4.53 (2H, s, 1-H), 4.98 (1H, dd, 4-H), 7.15 (1H, d, $J_{3,4}$ = 3.7 Hz, 3'-H), 7.80 (1H, d, $J_{3,4}$ = 3.7 Hz, 4'-H), 7.15 (1H, m, Ar-H), 7.20-7.40 (3H, m, Ar-H).

Anal. Calcd. for $C_{16}H_{18}ClNOS$: C, 62.43; H, 5.89; N, 4.55; S, 10.41. Found: C, 62.24; H, 5.79; N, 4.69; S, 10.12.

General Method for Preparation of the Anions of **6a** and **11**.

A stirred solution of **6a** or **11** (0.46 g, 2 mmoles) in dry tetrahydrofuran (25 ml) was cooled to -60°. *n*-Butyllithium (1.4 ml of a 1.6*M* solution in hexanes, 2.25 mmoles) was added dropwise to give an orange precipitate in the case of **6a** or a red solution in the case of **11**. The anion was stirred for 15 minutes to ensure complete formation.

2-Methyl-4-(2-thienyl)-4-thiomethyltetrahydroisoquinoline Hydrochloride (**14**).

Dimethyl disulphide (0.19 g, 2.0 mmoles) was added to the anion from **6a** and the precipitate redissolved to give a colourless solution. The reaction mixture was poured onto ice, extracted with diethyl ether, washed with water, dried and concentrated under reduced pressure. Chromatography on silica by elution with dichloromethane followed by crystallisation as the hydrochloride salt from ethanol/diethyl ether gave 0.27 g (35%) of compound **14**, mp 252-254°; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.03 (3H, s, SCH_3), 3.00 (3H, s, NCH_3), 3.99-4.21 (2H, broad, 1-H), 4.47 (2H, bs, 3-H),7.00-7.48 (7H, m, Ar-H).

Anal. Calcd. for $C_{15}H_{18}NClS_2$: C, 57.77; H, 5.82; N, 4.49; S, 20.56. Found: C, 57.58; H, 5.63; N, 4.23; S, 20.57.

2,4-Dimethyl-4-(2-thienyl)tetrahydroisoquinoline Hydrochloride (**15**).

Iodomethane (0.28 g, 2.0 mmoles) was added to the anion from **6a** and the precipitate redissolved to give a colourless solution. The reaction mixture was poured onto ice, extracted with diethyl ether, washed with water, dried and concentrated under reduced pressure. Chromatography on silica by elution with dichloromethane and crystallisation as the hydrochloride salt from ethanol/diethyl ether gave 0.47 g (84%) of compound **15**, mp 260-265°; ^1H nmr (methanol-d_4): δ 1.92 (3H, s, CH_3), 3.07 (3H, s, NCH_3), 3.7 (1H, d, 3-H), 3.90 (1H, br s, 3-H), 4.53 (2H, s, 1-H), approx 6.9 (1H, br, 3'-H), 6.99 (1H, t, 4'-H), 7.35 (1H, d, $J_{4,5}$ = 5.4 Hz, 5'-H), (4H, m, Ar-H).

Anal. Calcd. for $C_{15}H_{18}NClS$: C, 64.38; H, 6.48; N, 5.01. Found: C, 64.61; H, 6.67; N, 5.05.

Methyl 2-Methyl-4-(2-thienyl)tetrahydroisoquinoline-4-carboxylate Hydrochloride (**16**).

Carbon dioxide gas (from solid carbon dioxide pellets, passed through silica gel column) was passed into a suspension of the anion from **6a**. The precipitate redissolved and the colour was completely discharged. Evaporation to dryness under reduced pressure gave 0.57 g (100%) of the lithium salt as a white solid. The crude lithium salt was suspended in dichloromethane (10 ml) and thionyl chloride (1 ml) added dropwise. After 1 hour the solvent was removed and the resultant white solid dried under reduced pressure. The acid chloride was resuspended in dichloromethane (10 ml) and methanol (1 ml) added. After 1 hour the reaction was concentrated under reduced pressure and the product crystallised from cyclohexane to give 0.4 g (70%) of compound **16**, mp 98-100°, ^1H nmr (deuteriochloroform): δ 2.44 (3H, s, NCH_3), 2.78 (1H, d, J = 11.4 Hz, 3-H), 3.52 (1H, d, J = 15.0 Hz, 1-H), 3.60 (1H, d, J = 11.4 Hz, 3-H), 3.77 (3H, s, CO_2CH_3), 3.82 (1H, d, J = 15 Hz, 1-H), 6.85 (1H, d, $J_{3,4}$ = 3.5 Hz, 3'-H), 6.93 (1H, dd, $J_{4,5}$ = 5.8 Hz, $J_{3,4}$ = 3.5 Hz, 4'-H), 7.06-7.30 (5H, m, Ar-H and 5'-H); ^{13}C nmr (deuteriochloroform): δ 45.7 (NCH_3), 52.9 (CH_3), 55.2 (4-C), 58.4 (3-C), 65.0 (1-C), 124.7 (5'-C) 125.9, 126.1 (2 carbons), 126.2, 127.3, 131.2, 135.1, 135.4, 173.3 (CO).

Anal. Calcd. for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87; S, 11.16. Found: C, 66.64; H, 6.03; N, 4.80; S, 11.01.

Ethyl *N*-[2-(α-2-Thienyl)ethenylbenzyl]-*N*-methylcarbamate (**17**).

Ethyl chloroformate (0.19 ml, 2.0 mmoles) was added to the anion prepared from **6a**, the precipitate redissolved to give a colourless solution. The reaction mixture was poured onto ice, extracted with diethyl ether, washed with water, dried and concentrated under reduced pressure. Chromatography on silica gel by elution with dichloromethane gave 0.27 g (43%) of compound **17** after crystallisation from ethyl acetate/diethyl ether, mp 132-134°; ^1H nmr (deuteriochloroform): δ 1.20, 1.29 (3H, two m, CH_3CH_2), 2.71, 2.81 (3H, two s, NCH_3), 4.12, 4.14 (2H, two m, CH_3CH_2), 4.40, 4.46 (2H, two s, benzylic CH_2), 5.05 (1H, bs, C=CH), 5.79 (1H, bs, C=CH), 6.60 (1H, d, J = 3.5 Hz, 3'-H), 6.92 (1H, t, 4'-H), 7.1-7.4 (5H, m, Ar-H and 5'H); ^{13}C nmr

(deuteriochloroform): δ 14.8 (CH_3), 33.6, 34.2 (NCH_3), 49.6 (benzylic CH_2), 61.4 (OCH_2), 113.8 (=CH_2).

Anal. Calcd. for $C_{17}H_{19}NO_2S$: C, 67.71; H, 6.35; N, 4.65. Found: C, 67.97; H, 6.40; N, 4.38.

2,4-Dimethyl-4-(2-thienyl)tetrahydroisoquinoline Hydrochloride **15** from the aminoketone (**7a**).

A sample of the aminoketone **7a** was prepared as previously described from *N*-methylbenzylamine (4.84 g, 0.04 mole) and 2-bromoacetylthiophene (4.1 g, 0.02 mole). A solution of the resultant crude ketone **7a** in dry tetrahydrofuran (100 ml) was stirred under a nitrogen atmosphere at ambient temperature. A solution of methyl magnesium bromide (6.67 ml of a 3.0*M* solution in tetrahydrofuran. 0.02 mole) was added slowly over 10 minutes and the resultant mixture stirred for 18 hours. Water (5 ml) was added cautiously followed by anhydrous magnesium sulphate (5 g). The resultant solid was removed by filtration and well washed with diethyl ether. Concentration of the filtrates gave 5.2 g of the crude carbinol **18** as a red oil. This crude alcohol was dissolved in dichloromethane (20 ml) and added to a stirred suspension of aluminium chloride (5.3 g, 0.04 mole) in dichloromethane (100 ml) The reaction was stirred at ambient temperature for 18 hours. Water (20 ml) was added cautiously and the mixture made basic with 2*N* sodium hydroxide. The solvent was separated, washed with water, dried and concentrated to a red oil. Chromatography on silica gel by elution with 10% ethyl acetate in hexane and crystallisation as the hydrochloride salt from ethanol/diethyl ether gave 4.1 g (73% from 2-bromoacetylthiophene) of compound **15** which was identical with that prepared previously.

4-(2-Bromo-3-thienyl)-2-methyltetrahydroisoquinoline Hydrochloride (**19**).

A solution of bromine (0.64 g, 4 mmoles) in chloroform (10 ml) was added dropwise to a solution of **11** (1.06 g, 4 mmoles) in chloroform (20 ml). The mixture was stirred for 4 hours at ambient temperature and then poured into 2*N* sodium hydroxide. The solvent was separated, washed with water, dried and concentrated under reduced pressure to a yellow oil. Chromatography on alumina using dichloromethane as eluent, followed by crystallisation as the hydrochloride salt from ethanol/diethyl ether gave 1.1 g (72%) of compound **19**, mp 260-262°; ^{1}H nmr (methanol-d_4): δ 2.49 (2H, s, 1-H), 3.55 (3H, s, NCH_3), 4.03 (1H, dd, J = 12.3, 12.2, 3-H), 4.25 (1H, dd, J = 6.3, 12.3, 3-H), 5.39 (1H, dd, 4-H), 7.19 (1H, d, $J_{4,5}$ = 5.2 Hz, 5'-H), 7.32-7.73 (3H, m, Ar-H), 7.93 (1H, d, $J_{4,5}$ = 5.2 Hz, 4'-H).

Anal. Calcd. for $C_{14}H_{15}BrClNS$: C, 48.78; H, 4.39; N, 4.06; Br, 23.18; S, 9.30. Found: C, 48.91; H, 4.44; N, 4.07; Br, 23.15; S, 9.29.

Reaction of Lithium Derivative of **11** with Carbon Dioxide.

A solution of the above anion was saturated with dry carbon dioxide gas. The temperature was allowed to rise to ambient and oxalyl chloride (0.1 ml, 1.1 mmoles) was added. The mixture was stirred at ambient temperature for 1 hour, then excess methanol was added and the mixture stirred for an additional hour. The solution was concentrated under reduced pressure and partitioned between dilute aqueous ammonia solution and ethyl acetate. After removal of the solvent the crude product was chromatographed on silica gel by elution with diethyl ether to give **20a** and **21a** in 24 and 41% yield, respectively.

Methyl 2-Methyl-4-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (**20a**).

This compound was converted to the hydrochloride salt and crystallised from ethyl acetate, mp 209-209.5°; ^{1}H nmr (methanol-d_4): δ 3.10 (3H, s, NCH_3), 3.60 (1H, b hump, 3-H), 3.82 (3H, s, $COOCH_3$), 4.25 (1H, d, J = 12.7 Hz, 3-H), 4.52 (2H, s, 1-H), 6.90-7.50 (7H, Ar-H).

Anal. Calcd. for $C_{16}H_{18}NO_2SCl$: C, 59.39; H, 5.60; N, 4.33; Cl, 10.95; S, 9.90. Found: C, 59.46; H, 5.62; N, 4.54; Cl, 11.24; S, 9.64.

Methyl 4-(2-Methyl-1,2,3,4-tetrahydroisoquinol-4-yl)thiophene-2-carboxylate (**21a**).

This compound was also converted to the hydrochloride salt and crystallised from ethyl acetate, mp 204-208°; ^{1}H nmr (methanol-d_4): δ 3.16 (3H, s, NCH_3), 3.69 (1H, b hump, 3-H), 3.93 (1H, dd, J = 5.5, 12.5 Hz, 3-H), 3.94 (3H, s, $COOCH_3$), 4.65 (2H, s, 1-H), 4.85 (1H, dd, 4-H), 7.08-7.70 (4H, m, Ar-H), 7.73 (1H, d, $J_{2,4}$ = 1.5 Hz, 2'-H), 7.78 (1H, d, $J_{2,4}$ = 1.5 Hz, 4'-H).

Anal. Calcd. for $C_{16}H_{18}NO_2SCl$: C, 59.39; H, 5.60; N, 4.33. Found: C, 59.59; H, 5.85; N, 4.67.

Reaction of the Lithium Derivative of **11** with Iodomethane.

To a solution of the anion at -60° was added iodomethane (0.15 ml, 2.4 mmoles). The temperature of the solution was allowed to rise to ambient over 1 hour, the solution was poured onto ice and extracted with ethyl acetate. The combined extracts were washed with water, dried and the solvent removed under reduced pressure. The residue was chromatographed on silica gel by elution with 20 to 40% ethyl acetate in cyclohexane to give two isomeric products **20b** and **21b** in yields of 22 and 27% respectively.

2,4-Dimethyl-4-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**20b**).

This compound had ^{1}H nmr (deuteriochloroform): δ 1.73 (3H, s, 4-CH_3), 2.39 (3H, s, NCH_3), 2.61 (1H, d, J = 11.4 Hz, 3-H), 2.72 (1H, d, J = 11.4 Hz, 3-H), 3.57 (1H, d, J = 14.8 Hz, 1-H), 3.70 (1H, d, J = 14.8 Hz, 1-H), 6.86 (1H, dd, $J_{4,5}$ = 5.0 Hz, $J_{2,4}$ = 1.3 Hz, 4'H), 6.98-7.13 (5H, m, Ar-H), 7.19 (1H, dd, $J_{2,5}$ = 3.0 Hz, $J_{4,5}$ = 5.0 Hz, 5'H); ^{13}C nmr (deuteriochloroform): δ 28.9 (CH_3), 42.0 (quaternary carbon), 46.3 (NCH_3), 59.1, 68.0 (CH_2), 120.6 (2'-C), 124.9 (5'-C), 125.8, 126.2, 126.4, 127.7 (4'-C), 128.1 (8-C), 134.2 (8a-C), 141.9 (4a-C), 150.5 (3'-C). This compound was converted to the hydrochloride salt and crystallised from ethanol-ethyl acetate, mp 185-187°.

Anal. Calcd. for $C_{15}H_{18}NSCl$: C, 64.38; H, 6.48; N, 5.01. Found: C, 64.54; H, 6.71; N, 4.77.

2-Methyl-4-(5-methyl-3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**21b**).

This compound had ^{1}H nmr (deuteriochloroform): δ 2.42 (3H, d, J = 1 Hz, 5'-CH_3), 2.44 (3H, s, NCH_3), 2.61 (1H, dd J = 12.0, 8.5 Hz, 3-H), 2.96 (1H, dd J = 12.0, 6.5 Hz, 3-H), 3.59 (1H, d, J = 14.9 Hz, 1-H), 3.73 (1H, d, J = 14.9 Hz, 1-H), 4.28 (1H, dd, 4-H), 6.55 (1H, bs, 4'H), 6.79 (1H, d, J = 1.3 Hz, 2'H), 6.98-7.12 (4H, m, Ar-H); hrms: $C_{16}H_{18}NSCl$ requires 244.11600, observed: 244.11540, Dev: -2.43 ppm.

2,4-Dimethyl-4-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**20b**) from the Aminoketone **9**.

A sample of the aminoketone **9** (8.3 g, 0.034 mole) was prepared as previously described from *N*-methylbenzylamine and

3-bromoacetylthiophene. A solution of the resultant crude ketone **9** in dry tetrahydrofuran (100 ml) was stirred under a nitrogen atmosphere at ambient temperature. A solution of methyl magnesium bromide (11.5 ml of a 3.0*M* solution in tetrahydrofuran, 0.0335 mole) as added slowly over 10 minutes and the resultant mixture stirred for 2 hours. Ice-water (5 ml) was added cautiously followed by ether (20 ml). The magnesium salts were removed by filtration and well washed with diethyl ether. The filtrates were concentrated to give the crude carbinol which was dissolved in dichloromethane (20 ml) and added to a stirred suspension of aluminium chloride (7 g, 0.052 mole) in dichloromethane (100 ml). The reaction was stirred at ambient temperature for 18 hours. Water (20 ml) was added cautiously and the mixture made basic with 2*N* sodium hydroxide. The solvent was separated, washed with water, dried and concentrated to a red oil. Chromatography on silica gel by elution with 10% ethyl acetate in hexane gave 2.2 g (27%) of **20b** identical with that described above.

Reaction of the Lithium Derivative of **9** with Dimethyl Disulphide.

To a solution of the above anion at -70° was added dimethyl disulphide (0.2 ml, 2.7 mmoles). After the temperature of the colourless solution had been allowed to rise to ambient over 1 hour it was poured onto ice and extracted with ethyl acetate (x 3). The combined extracts were washed with water, dried and the solvent removed. The residue was chromatographed on silica gel eluting with 20 to 40% ethyl acetate in cyclohexane to give three isomeric products **20c**, **21c** and **22c** in yields of 23, 35 and 9% respectively, and recovered **11** (120 mg, 23%).

2-Methyl-4-methylthio-4-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**20c**).

This compound had ^{1}H nmr (deuteriochloroform): δ 1.90 (3H, s, SCH_3), 2.41 (3H, s, NCH_3), 2.98 (1H, d, J = 12.5 Hz, 3-H), 3.18 (1H, d, J = 12.5 Hz, 3-H), 3.59 (1H, d, J = 14.5 Hz, 1-H), 3.72 (1H, d, J = 14.5 Hz, 1-H), 7.06-7.45 (7H, m, Ar-H); hrms: $C_{15}H_{18}NS_2$ requires 276.08807, observed: 276.0896, Dev: +6.47 ppm.

2-Methyl-4-(5-methylthio-3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**21c**).

This compound had ^{1}H nmr (methanol-d_4): δ 2.45 (3H, s, SCH_3), 3.30 (3H, s, NCH_3), 3.58 (1H, dd, J = 12.0, 12.3 Hz, 3-H), 3.78 (1H, d, J = 6.2, 12.0 Hz, 3-H), 4.53 (2H, s, 1-H), 4.68 (1H, dd, 4-H), 6.90-7.40 (6H, m, Ar-H); hrms: $C_{15}H_{18}NS_2$ requires 276.08807, observed: 276.0858, Dev: -8.2 ppm.

2-Methyl-4-(2-methylthio-3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**22c**).

This compound had ^{1}H nmr (deuteriochloroform): δ 2.46 (3H, s, SCH_3), 2.46 (3H, s, NCH_3), 2.57 (1H, dd, J = 7.0, 12.0 Hz, 3-H), 2.99 (1H, dd, J = 12.0, 12.0 Hz, 3-H), 3.62 (1H, d, J = 14.5 Hz, 1-H), 3.78 (1H, d, J = 14.5 Hz, 1-H), 4.78 (1H, dd, 4-H), 6.71 (1H, d, $J_{4,5}$ = 5.7 Hz, 4'-H), 6.82-7.17 (4H, m, Ar-H), 7.21 (1H, d, $J_{4,5}$ = 5.7 Hz, 5'-H).; hrms: $C_{15}H_{18}NS_2$ requires 276.08807, observed: 276.09114, Dev: +11.11 ppm.

Reaction of the Lithium Derivative of **11** with Chlorotrimethylsilane.

To a solution of the above anion at -60° was added, dropwise, chlorotrimethylsilane (0.3 ml, 2.4 mmoles). After the temperature of the solution had been allowed to rise to ambient over 1 hour it was poured onto ice and extracted with ethyl acetate (x 3). The combined extracts were washed with water, dried and the solvent removed. The residue was chromatographed on silica gel eluting with 20 to 40% ethyl acetate in cyclohexane to give two isomeric products **21d** and **22d** in yields of 5 and 34% respectively.

2-Methyl-4-(5-trimethylsilyl-3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**21d**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.30 (9H, s, $Si(CH_3)_3$), 2.46 (3H, s, NCH_3), 2.64 (1H, dd, J = 11.0, 12.0 Hz, 3-H), 3.01 (1H, dd, J = 6.0, 12.0 Hz, 3-H), 3.61 (1H, d, J = 14.5 Hz, 1-H), 3.78 (1H, d, J = 14.5 Hz, 1-H), 4.43 (1H, dd, 4-H), 6.97 (1H, d, Ar-H), 7.05 (1H, d, $J_{2,4}$ = 1.0 Hz, 4'-H), 7.05-7.17 (3H, m, Ar-H), 7.27 (1H, d, $J_{2,4}$ = 1.0 Hz, 2'-H); hrms: $C_{17}H_{24}NSSi$ requires 302.13988, observed: 302.14150, Dev: +5.4 ppm.

2-Methyl-4-(2-trimethylsilyl-3-thienyl)-1,2,3,4-tetrahydroisoquinoline (**22d**).

This compound had ^{1}H nmr (deuteriochloroform): δ 0.42 (9H, s, $Si(CH_3)_3$), 2.46 (3H, s, NCH_3), 3.03 (1H, dd, J = 6.0, 12.0 Hz, 3-H), 3.56 (1H, t, J = 12.0 Hz, 3-H), 3.58 (1H, d, J = 14.5 Hz, 1-H), 3.86 (1H, d, J = 14.5 Hz, 1-H), 4.58 (1H, dd, 4-H), 6.76 (1H, d, $J_{4,5}$ = 5.4 Hz, 4'-H), 6.78 (1H, d, Ar-H), 7.02-7.17 (3H, m, Ar-H), 7.42 (1H, d, $J_{4,5}$ = 5.4 Hz, 5'-H); hrms: $C_{17}H_{24}NSSi$ requires 302.13988, observed: 302.14150, Dev: +5.4 ppm.

REFERENCES AND NOTES

[1] J. K. Chakrabarti, T. M. Hotten, S. E. Morgan, I. A. Pullar, D. M. Rackham, F. C. Risius, S. Wedley, M. O. Chaney and N. D. Jones, *J. Med. Chem.*, **25**, 1133 (1982).

[2] D. E. Tupper, J. A. Clemens, J. Fairhurst, I. A. Pullar, F. C. Risius, G. H. Timms and S. Wedley, *J. Med. Chem.*, **36**, 912 (1993).

[3] D. E. Tupper, M. S. Axton, B. P. Clark, T. M. Hotten, N. A. Moore, I. A. Pullar, G. H. Timms and S. Wedley, *J. Med. Chem.*, In press.

[4] P. A. Dandridge, C. Kaiser, M. Brenner, D. Gaitanopoulos, L. D. Davis, R. L. Webb, J. J. Foley and H. M. Sarau, *J. Med. Chem.*, **27**, 28 (1984).

[5] N. S. Narasimhan and P. A. Patil, *J. Chem. Soc., Chem. Commun.*, 191 (1987).

[6] P. F. Charifson, S. D. Wyrick, A. J. Hoffman, R. M. A. Simmons, J. P. Bowen, D. L. McDougald and R. B. Mailman, *J. Med. Chem.*, **31**, 1941 (1988).

[7] I. Hoffman, G. Erhart and K. Schmitt, *Arzneim.-Forsch. (Drug Res.)*, **21**, 1045 (1971).

[8] I. Hoffman, *Arzneim.-Forsch. (Drug Res.)*, **23**, 45 (1973).

[9] R. N. Brodgen, R. C. Heel, T. M. Speight and G. S. Avery, *Drugs*, **18**, 1 (1979).

[10] P. D. Stonier and P. Y. Wittels, *Int. Congr. Symp. Ser.,-R. Soc. Med.*, **25**, 131 (1980).

[11] W. Pöldinger and K. Taeuber, *Int. Pharmacopsychiat.*, **17**, Suppl 1 (1982).

[12] J. W. Kababian and D. B. Calne, *Nature (London)*, **277**, 93 (1979).

[13] L. N. Pridgen, *J. Heterocyclic Chem.*, **17**, 1289 (1980).

[14] E. Zára-Kaczián, L. György, G. Deák, A. Sergi and M. Dóda, *J. Med. Chem.*, **29**, 1189 (1986).

[15] J. Gadamer and F. Knoch, *Arch. Pharm.*, **259**, 135 (1921).

[16] S. Gronowitz, P. Moses and R. Håkansson, *Arkiv. Kemi*, **16**, 267 (1960).

[17] G. Carrara and G. Weitnauer, *Gazz. Chim. Ital.*, **81**, 142 (1951); *Chem. Abstr.*, **45**, 9029 (1951).

[18] D. W. H. MacDowell and T. D. Greenwood, *J. Heterocyclic Chem.*, **2**, 44 (1965).