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Original paper

Sulphonium analogues of some piperidine analgesics

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Summary — A number of hexahydrothiapyrylium analogues of piperidine analgesics have been synthesised and examined for biological activity. All inhibited the electrically-stimulated contractions of the guinea pig ileum at micromolar concentrations; naloxone reversed this effect only for an analogue of sufentanil. Some compounds exhibited activity *in vivo*, but not at a sufficiently high level to warrant further investigation.

Résumé — **Analogues à fonction sulfonium de quelques analgésiques pipéridiniques.** *Un certain nombre d'analogues hexahydrothiapyrylium d'analgésiques pipéridiniques ont été synthétisés puis examinés afin d'en déterminer l'activité biologique. A des concentrations micromolaires, ils ont tous inhibé les contractions de l'iléon du cobaye stimulé électriquement ; la naloxone n'a pu inverser cet effet que pour un analogue du sufentanil. Certains composés ont montré une activité* in vivo, *activité toutefois insuffisante pour justifier d'autres études.*

analgesics / opiates / sulphonium salts / pentanyl / fethidine / sufentanil

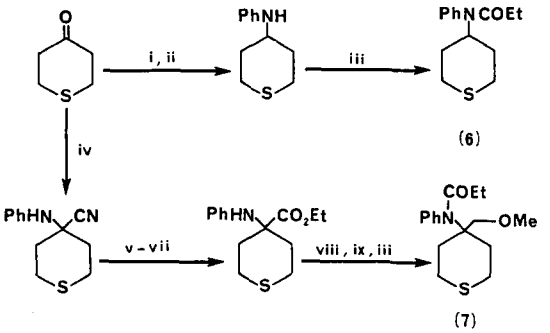
Introduction

A considerable number of opiate analgesics derived from piperidine have been prepared [1]. It is generally assumed that the protonated tertiary amine, prevalent at physiological pH, is the species bound at the receptor [2]. Thus it is of interest to investigate the effect of replacing the ammonium function with a permanently charged group, for example by the substitution of a stereo-electronically similar hexahydrothiapyrylium ring for the piperidine moiety. If ion-pairing makes a significant contribution to the receptor—ligand interaction, and this substitution is compatible with productive binding, such compounds could represent prototype hydrophilic opiate agonists with reduced CNS penetration.

The sulphonium analogues (**1b**, **2b**) of pethidine (meperidine, **1a**) and methadone (**2a**) have been prepared by Hofmann and Weiss [3] and were reported to be inactive as analgesic agents; however, no pharmacological data were provided. More recently, three sulphonium analogues (**3b**) of isolevorphanol (**3a**) were prepared in an attempt to clarify the nature of the interaction of the tertiary amine site with the receptor [4, 5]. We have prepared a number of hexahydrothiapyrylium derivatives and have examined their effects on both the electrically-stimulated guinea pig ileum longitudinal muscle and acetic acid-induced writhing in mice.

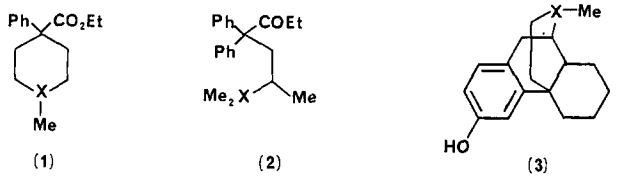
Chemistry

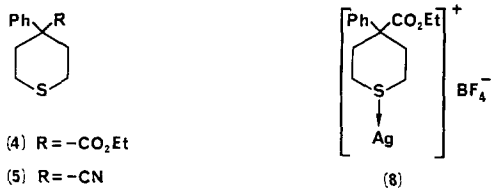
The tetrahydrothiapyran analogue of norpethidine (**4**) was prepared by a modification of the method of Hofmann and Weiss [3]. In this case the intermediate nitrile (**5**) was obtained in crystalline form and fully characterised. Both 4-(*N*-phenylpropionamido)tetrahydrothiapyran (**6**) and 4-(methoxymethyl)-4-(*N*-phenylpropionamido)tetrahydrothiapyran (**7**) were prepared from tetrahydrothiapyran-4-one as shown in Scheme 1 [6—8].

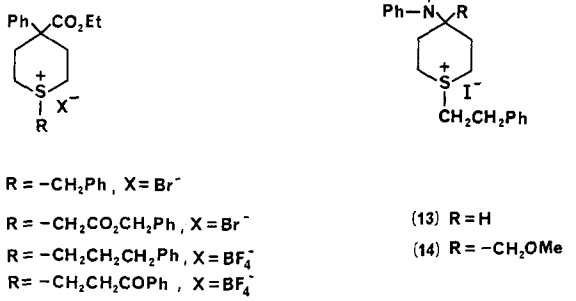


Scheme 1. Reagents: i: $PhNH_2$, $PhCH_3$, Δ; ii: $NaBH_4$, MeOH; iii: $[EtCO]_2O$; iv: KCN, $PhNH_2$, HOAc; v: cH_2SO_4; vi: KOH, $HOCH_2CH_2OH$; vii: EtBr, HMPA, NaOH, 1 eq; viii: $LiAlH_4$, THF; ix: Me_2SO_4, PhH, 60% NaOH aq, Adogen 464.

S-Alkylation was achieved by reaction of the respective tetrahydrothiapyran (**4**, **6** or **7**) with an excess of the appropriate halide either alone, or, for the less reactive species, in the presence of silver tetrafluoroborate [9]. In the latter case, an intermediate silver—tetrahydrothiapyran complex, *e.g.* (**8**), could be isolated. This complex subsequently reacted with the halide to form the desired product. In all, six novel sulphonium analogues of known [1, 10—12] analgesic piperidine derivatives were prepared. Their structures (**9—14**) are shown below.







The NMR spectra of some of the sulphonium salts showed clear evidence for the presence of axial and equatorial S-alkyl groups (*cis* and *trans* with respect to the equatorial 4-substituents). For example, the 360 MHz spectrum of the sufentanil analogue (**14**) is shown in Fig. 1. Duplicate signals appear for the ethyl (0.75—1.88 δ) and methoxy (3.0—3.4δ) groups. The ratio of the integrals for these duplicate peaks is the same as that observed for some of the ring proton signals (65:35). In view of the poor biological activity, a detailed analysis of the data for assignment of the conformations has not been carried out, although the conformational equilibria of many simple hexahydrothiapyrylium salts have been studied [21].

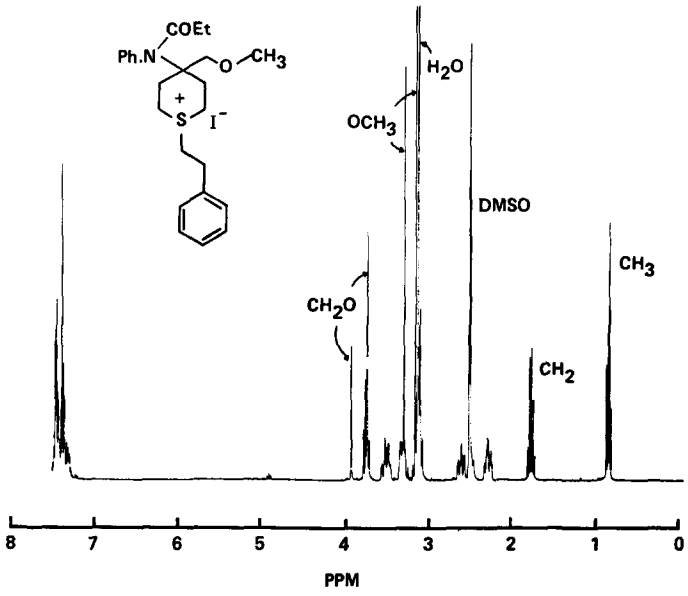


Fig. 1.

Biological Activity

The sulphonium analogues were tested for opiate activity by suppression of the co-axially-stimulated contractions of the guinea pig ileum *in vitro* [13]. Opiate activity was characterised by full reversal of the electrically-induced twitch by the specific opiate antagonist naloxone (1 μg ml^{-1}); *i.e.*, compounds whose effects were wholly antagonised by naloxone were assumed to be pure opiate agonists.

Anti-nociceptive activity *in vivo* was assessed in the acetic acid-induced writhing test in mice [14]. This peripherally selective analgesic test was chosen rather than a centrally mediated anti-nociceptive model *e.g.*, hotplate, since polar sulphonium salts would not be expected readily to penetrate the blood—brain barrier into the CNS. The use of writhing assays to detect peripherally mediated anti-nociceptive effects of opioids has been discussed elsewhere [15, 16].

For comparative purposes, pethidine (**1a**) and fentanyl were investigated in the same assays. The effects of pethidine on the guinea pig ileum did not appear to be wholly mediated *via* opiate receptors, since only a partial reversal of the twitch by naloxone was observed. This finding is in agreement with Paton [13] who described the effects of pethidine on the ileum to be mediated by both atropinic and morphine-like effects.

Results and Discussion

The S-alkylated analogues of pethidine retained biological activity on the guinea pig ileum, the ED_{50}'s for the inhibition of the electrically-stimulated contractions ranging from 0.08 to 23.1 μM. For comparison, the activity of

pethidine itself also lies within this range: $ED_{50} = 2.7$ μM. Unlike pethidine, however, where the inhibitory effects of the opiate in the guinea pig ileum are at least partially antagonised by naloxone, none of the S-alkylated analogues showed any degree of reversal by the opiate receptor antagonist on this tissue. The introduction of the hexahydrothiapyrylium ring, therefore, appears to favour the introduction of non-opioid properties into the molecules. Since pethidine itself possesses some atropine-like activity and acetylcholine receptor blockade induces inhibition of the electrically-induced contractions of the guinea pig ileum, atropinic activity may represent the major pharmacological property of the sulphonium analogues of pethidine described. In agreement with the apparent loss of opioid activity in these analogues, anti-nociceptive activity was generally not observed in the mouse writhing model.

In contrast to pethidine, fentanyl is a potent selective opioid receptor agonist. The sulphonium analogue (**13**) of fentanyl prepared, however, also failed to produce a naloxone-reversible inhibition of the electrically-induced contractions of the guinea pig ileum, although this was achieved by a sulphonium analogue (**14**) of sufentanil. In comparison with fentanyl, however, this latter analogue displayed very weak biological activity both *in vitro* and *in vivo* (see Table I).

Table I. Biological activities.

Compound	G.P.I.[a] ED_{50} (μM)	Naloxone[b] antagonism	A.A.W.[c](s.c.) ED_{50} (mg/kg)
1b	9.5	No	N.E. at 100
9	23.1	No	N.E. at 10
10	3.3	No	N.E. at 10
11	1.1	No	N.E. at 10
12	0.08	No	*ca.* 3
13	0.83	No	33% at 10
14	0.22	Yes	19.8
1a	2.73	Partial	10.7
Fentanyl	0.013	Yes	0.01

[a]Inhibition of electrically-induced contractions of the guinea pig ileum.
[b]Antagonism of ileum effect by naloxone at 1 μg ml^{-1}.
[c]Acetic acid-induced writhing in mice. N.E. = < 20% inhibition at the stated dose.

In general, therefore, the replacement in opiates of the amine function with a sulphonium species appears to lead to a considerable loss of opiate receptor activity which may also be accompanied by the introduction of non-opioid properties. That opiate activity is not completely lost may indicate that ion-pairing at the receptor plays a small but significant role in determining activity [4, 5], although there is insufficient evidence to give an unequivocal answer. Similar effects to those described here have been identified following the quaternisation of opiates [17].

Experimental protocols

Chemistry

Reaction products were purified by crystallisation from suitable solvents or by chromatography on silica gel (Merck). Identity and purity of products were confirmed by IR, NMR and mass spectrometry. Elemental analyses for C, H, N, Br and S were determined in the Physical Chemistry Department of the Wellcome Research Laboratories, Beckenham, Kent, U.K. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Commercial grade solvents and reagents were used throughout. Solutions in organic solvents were dried over anhydrous magnesium sulphate and evaporated using a Buchi Rotavapor.

4-Cyano-4-phenyltetrahydrothiapyran **5**
A solution of sodium sulphide nonahydrate (16 g; 66 mmol) in water (40 ml) was added to a solution of 1,5-dichloro-3-cyano-3-phenylpentane [18] (16 g; 66 mmol) in ethanol (75 ml). The turbid solution was heated at reflux for 22 h, allowed to cool, then poured onto ice (500 ml). The mixture was extracted with ether (3 × 120 ml). The combined extracts were dried, filtered and evaporated to give the crude product as a pale yellow oil (9.9 g). Purification was achieved by adsorbing the oil onto silica gel (25 g), packing this material onto a column of silica gel (250 g) in dichloromethane and eluting with increasing amounts of methanol in dichloromethane to a maximum of 10%. Fractions containing the major product were pooled and evaporated to leave a pale yellow oil (4.2 g). Crystallisation from hexane gave the pure product. Yield 3.6 g (27%), mp = 55—56°C. Analysis $C_{12}H_{13}NS$ calculated: C: 70.89; H: 6.45; N: 6.89; S: 15.77%. Found: C: 71.15; H: 6.26; N: 6.85; S: 15.24%. Mass spectrum: *m/z* 203 (M^+, 55%) 115 (M^+—C_4H_6S, 100%). NMR: 60 MHz, $CDCl_3$: δ 2.0—3.6 (8H, m, 4 × CH_2); 7.4 (5H, s, Ph).

4-Carbethoxy-4-phenyltetrahydrothiapyran **4**
The method of Daum [19] was adapted. The nitrile (**5**) (3.2 g; 15.7 mmol) was heated to 150°C (internal temperature) in a mixture of conc. sulphuric acid (4.4 ml; 8 g) and water (4 ml) for 1.5 h. The mixture was cooled, ethanol (10 ml) was added and the suspension heated at reflux for 3.5 h. The resulting oily suspension was poured onto ice and basified to *ca.* pH 12 with 2 M NaOH. The mixture was extracted with ether (3 × 100 ml) and the combined extracts dried and evaporated. The product was obtained as a pale brown oil which exhibited a single spot on TLC (SiO_2, CH_2Cl_2—hexane (1:1), R_f = 0.4). Yield 2.0 g (51%). Mass spectrum *m/z* 250 (M^+, 52%), 91 ($C_7H_7^+$, 100%). NMR 60 MHz $CDCl_3$: δ 1.16 (3H, t, CH_3), 1.68—3.04 (8H, m, 4 × CH_2); 4.05 (2H, q, CH_2); 7.12 (5H, s, Ph). This material was used directly in subsequent stages.

4-Ethoxycarbonyl-1-methyl-4-phenylhexahydrothiapyrylium iodide **1b**
This material was prepared on a 1.2 mmol scale as described by Hofmann and Weiss [3], except that the product was isolated from the reaction mixture by precipitation with ether to give a 90% yield of crude product. Recrystallisation from ethanol gave the pure product. Yield 0.21 g (45%), mp = 141—142°C (Lit. [3] 138—139°C). Analysis $C_{15}H_{21}IO_2S$ calculated: C: 45.92; H: 5.40; S: 8.17%. Found: C: 45 96; H: 5.31; S: 8.68%.

4-Ethoxycarbonyl-4-phenyl-1-(3-phenylpropyl) hexahydrothiapyrylium tetrafluoroborate **11**
Silver tetrafluoroborate (0.32 g; 1.2 mmol) was added to a stirred suspension of the thiapyran (**4**) (0.3 g, 1.2 mmol) in 3-phenylpropyl bromide (1.5 ml). An exothermic reaction occurred with precipitation of silver bromide. The mixture was stirred for 18 h at ambient temperature then diluted with CH_2Cl_2 and filtered. The solid was washed with several portions of CH_2Cl_2 and the combined filtrates were evaporated. The residue was dissolved in EtOH—H_2O (1:1, 20 ml) and extracted with petroleum ether (bp = 80—100°C, 3 × 5 ml) to remove the starting bromide. The aqueous phase was evaporated and the residue crystallised twice from EtOH to give the pure product. Yield 70 mg (12.7%), mp = 150—151°C. Analysis $C_{23}H_{29}SO_2BF_4$ calculated: C: 60.53; H: 6.40; S: 7.03%. Found: C: 60.41; H: 6.34; S: 6.61%. NMR 80 MHz DMSO-d_6: δ 1.12 (3H, t, CH_3), 1.9—3.9 (complex, 7 × CH_2 + solvent), 4.18 (2H, q, CH_2Me), 7.35 (5H, s, Ph), 7.48 (5H, s, Ph).

1-Benzyl-4-ethoxycarbonyl-4-phenylhexahydrothiapyrylium bromide **9**
A solution of the thiapyran (**4**) (0.1 g; 0.4 mmol) in benzyl bromide (0.3 g; 1.75 mmol) was stirred at ambient temperature for 5 h during which time the mixture solidified. The solid was triturated with ether and collected by filtration. Yield 0.12 g (71%). Recrystallisation from

EtOH—Et_2O gave the pure product. Yield 90 mg (53%), mp = 112—113°C. Analysis $C_{21}H_{25}O_2SBr$ calculated: C: 59.85; H: 5.98; S: 7.61; Br: 18.96%. Found: C: 59.95; H: 5.94, S: 7.84; Br: 18.94%. NMR 90 MHz DMSO-d_6, 80°C: δ 1.14 (3H, t, CH_3); 2.5—3.0 (complex, 4 × CH_2 + solvent), 4.14 (2H, q, CH_2Me), 4.67 (2H, s, $PhCH_2S$); 7.34—7.58 (10H, s + m, 2 × Ph).

1-Benzyloxycarbonylmethyl-4-ethoxycarbonyl-4-phenylhexahydrothiapyrylium bromide **10**

A solution of the thiapyran (**4**) (0.1 g; 0.4 mmol) in benzyl bromoacetate (0.3 g, 1.3 mmol) was stirred at ambient temperature for 30 days. During this time a crystalline precipitate formed slowly. The mixture was diluted with ether, triturated and the solid collected by filtration. Yield 0.12 g (21%), mp = 97—98°C. Analysis $C_{23}H_{27}O_4SBr$ calculated: C: 57.62; H: 5.68; S: 6.69%. Found: C: 57.24, H: 5.68; S: 6.66%. NMR 90 MHz DMSO-d_6 (the spectrum showed a doubling of several peaks due to the existence of two conformations, ratio *ca.* 1:1): δ 1.14 (3H, t + t, CH_3); 2.3—2.8 (complex, CH_2—C—CH_2 + solvent); 3.4—3.9 4H, complex, CH_2—S—CH_2); 4.14 (2H, q + q, CH_2CH_3); 4.79—4.86 (2H, s + s, S—CH_2—CO_2); 5.15—5.27 (2H, s + s, O—CH_2—Ph); 7.37 (10H, s, 2 × Ph).

(4-Ethoxycarbonyl-4-phenyltetrahydrothiapyran) silver (I) tetrafluoroborate **8**

A mixture of the thiapyran (**4**) (110 mg; 0.44 mmol), β-chloropropiophenone (120 mg; 0.66 mmol) and silver(I) tetrafluoroborate (130 mg; 0.66 mmol) in dichloromethane (2 ml) was stirred at ambient temperature for *ca.* 18 h. The solution was diluted with dichloromethane (20 ml) and filtered. The filtrate was evaporated to leave a pale brown gum. The gum was dissolved in dichloromethane (*ca.* 1 ml) and diluted with ether to initiate crystallisation. The mixture was cooled to 5°C and further portions of ether added periodically (*ca.* 4 ml total). After a further 18 h at 5°C, the solid was collected by filtration, washed with dichloromethane—ether (1:5) and dried *in vacuo*. Yield 70 mg, mp = (120—195°C blackens) 200°C. Analysis $C_{14}H_{18}O_2SAgBF_4$ calculated: C: 37.78; H: 4.08%. Found: C: 37.90; H: 3.94%. NMR 90 MHz DMSO-d_6 60°C: δ 1.14 (3H, t, CH_3); 2.09—2.87 (8H, m, 4 × CH_2 + solvent); 4.14 (2H, q, CH_2Me); 7.35 (5H, s, Ph).

1-(2-Benzoylethyl)-4-ethoxycarbonyl-4-phenylhexahydrothiapyrylium tetrafluoroborate **12**

A. Silver(I) tetrafluoroborate (350 mg; 1.8 mmol) was added to a stirred mixture of the thiapyran (**4**) (425 mg; 1.7 mmol) and β-chloropropiophenone (1.8 g; 10 mmol). A thick precipitate of the above complex (**8**) formed rapidly. The mixture was heated on a steam bath for 1 h during which time the solid was converted to a heavy precipitate of silver chloride. The suspension was diluted with dichloromethane (30 ml), filtered and the filtrate evaporated to leave a brown gum. The gum was triturated with dry ether (2 × 40 ml) and the resulting sticky solid heated in dichloromethane to complete crystallisation. The product was collected by filtration, washed with dichloromethane and ether and dried *in vacuo*. Yield 680 mg, mp = 158—160°C. An analytical sample was recrystallised from methanol, mp = 158—160°C. $C_{23}H_{27}O_3SBF_4$ calculated: C: 57.83; H: 5.79; S: 6.82%. Found: C: 57.96; H: 5.79; S: 6.71%. NMR 80 MHz DMSO-d_6 70°C: δ 1.14 (3H, t, CH_3); 2.2—3.05 (4H, m + solvent, 2 × CH_2); 3.05—3.95 (9H, complex, 4 × CH_2 + HOD); 4.14 (2H, q, CH_2Me); 7.35—8.10 (10H, s + m, 2 × Ph)

B. The silver complex (**8**) (40 mg, 0.09 mmol) and β-chloropropiophenone (0.4 g, 2.2 mmol) were heated as a melt with stirring on a steam bath for 30 min. The mixture was diluted with dichloromethane (10 ml), filtered and evaporated. The residue was triturated with ether (2 × 5 ml) then crystallised from dichloromethane—ether to yield 32 mg (80%) of product, mp = 156—158°C, identical with that obtained above.

4-(N-Phenylamino)tetrahydrothiapyran

A mixture of tetrahydrothiapyran-4-one (5.0 g; 43 mmol) and aniline (3.8 g; 41 mmol) in toluene was heated at reflux, in a Soxhlet apparatus containing calcium hydride, for 18 h. The solvent was evaporated *in vacuo*, and the residue taken up in dry methanol (50 ml). Sodium borohydride (3.2 g; 84 mmol) was added over 0.5 h and the mixture stirred at ambient temperature for a further 2 h. The mixture was acidified with dilute hydrochloric acid, made alkaline with dilute sodium hydroxide solution and concentrated *in vacuo*. Water was added and the mixture extracted with chloroform (3 × 100 ml). The combined extracts were dried and evaporated to give the crude product (7.25 g, 91%). A sample was crystallised from ethanol to give the pure material: mp = 59—62°C. Analysis $C_{11}H_{15}NS$ calculated: C: 68.35; H: 7.82; N: 7.25%. Found: C: 68.59; H: 7.99; N: 7.23%. Mass spectrum: *m/z* 193 (M^+, 71%), 132 (M^+—C_2H_5S, 100%). 60 MHz NMR $CDCl_3$: δ 1.2—2.9 (8H, m, 4 × CH_2); 3.0—3.9 (2H, t × t and broad, CH, NH); 6.4—7.4 (5H, m, Ph).

4-(N-Phenylpropionamido)tetrahydrothiapyran **6**

4-(*N*-Phenylamino)tetrahydrothiapyran (3.0 g; 15.5 mmol) in propionic anhydride (50 ml) was heated at reflux under an atmosphere of nitrogen for 1.5 h. The solution was cooled and the solvent evaporated *in vacuo*. The residue was taken up in 5% sodium hydrogen carbonate solution and extracted with chloroform (3 × 100 ml). The combined extracts were dried and concentrated *in vacuo* to leave the product as a crystalline solid (4.06 g). Recrystallisation from petroleum ether (bp = 60—80°C) gave analytically pure material. Yield 3.1 g (80%), mp = 55—57°C. Analysis $C_{14}H_{19}NSO$ calculated: C: 67.43; H: 7.68; N: 5.62%. Found: C: 67.42; H: 7.76; N: 5.51%. Mass spectrum: *m/z* 249 (M^+, 22%), 149 (M^+—C_5H_8S, 100%). NMR 80 MHz $CDCl_3$: δ 1.0 (3H, t, CH_3); 1.17—3.13 (10H, m, 5 × CH_2); 4.4—4.9 (1H, t × t, CH); 6.9—7.5 (5H, m, Ph).

1-(2-Phenylethyl)-4-(N-phenylpropionamido)hexahydrothiapyrylium iodide **13**

The above product (**6**) (0.5 g; 2 mmol) was dissolved in (2-iodoethyl)-benzene (5 ml) and stirred overnight at ambient temperature. The mixture was then heated to 60°C for 2 h, and stirred again at ambient temperature for 48 h. The resulting solid was collected by filtration and dried in high vacuum (0.05 mm Hg). Yield 38 mg. Analysis $C_{22}H_{28}$-NSOI calculated: C: 54.89; H: 5.86; N: 2.91%. Found: C: 55.24; H: 5.79; N: 2.86%. FAB—mass spectrum: *m/z* 354 (M^+, 100%) NMR 90 MHz DMSO-d_6: δ 0.88 (3H, t, CH_3); 1.07—2.65 (6H, m + q, 3 × CH_2 + solvent); 3.0 (2H, t-partially obscured by HOD, CH_2Ph); 3.49—3.93 (6H, m, 3 × CH_2—S^+); 5.12 (1H, t × t, CH); 7.19—7.56 (10H, m, 2 × Ph).

4-Cyano-4-(N-phenylamino)tetrahydrothiapyran

The following method was modified from that described in [20]. A solution of potassium cyanide (0.56 g; 8.6 mmol) in water (2 ml) was added slowly to a mixture of tetrahydrothiapyran-4-one (1.0 g; 8.6 mmol) and aniline (0.8 g; 8.6 mmol) in glacial acetic acid (6 ml). An exothermic reaction occurred and a precipitate was formed. After stirring at ambient temperature for 4 h, the solid was collected by filtration, washed with cold, aqueous acetic acid and dried *in vacuo* (0.05 mm Hg). Yield 1.52 g (81%). An analytical sample was obtained by recrystallisation from methanol, mp = 136—139°C. Analysis $C_{12}H_{14}N_2S$ calculated: C: 66.02; H: 6.46; N: 12.83%. Found: C: 66.34; H: 6.85; N: 12.72%. Mass spectrum: *m/z* 218 (M^+, 47%), 135 ($PhNCS^+$, 100%). NMR 60 MHz $CDCl_3$: δ 1.6—3.4 (9H, m, 4 × CH_2 + NH); 6.6—7.4 (5H, m, Ph).

4-(N-Phenylamino)tetrahydrothiapyran-4-carboxamide

The above nitrile (1.0 g; 4.6 mmol) was added, with stirring, to conc. sulphuric acid (50 ml). The solid dissolved within 1 h and the resulting solution was stirred at ambient temperature for 20 h. The solution was added to a mixture of aqueous ammonia (s.g. 0.88) and crushed ice. The mixture was extracted with dichloromethane (4 × 50 ml) and the combined extracts dried and evaporated to leave a white solid (0.72 g; 66%). An analytical sample was obtained by crystallisation from ethanol, mp = 215—218°C. Analysis $C_{12}H_{16}N_2OS$ calculated: C: 60.99; H: 6.82; N: 11.85%. Found: C: 60.90; H: 6.92, N: 11.79%. Mass spectrum: *m/z* 236 (M^+, 9%), 192 (M^+—$CONH_2$, 100%). NMR 60 MHz DMSO-d_6: δ 1.9—3.0 (*ca.* 8H, m, 4 × CH_2 + DOH + solvent); 4.7 (1H, br s, exch, NH); 6.0—7.1 (7H, m, Ph + NH_2).

Ethyl-4-(N-phenylamino)tetrahydrothiapyran-4-carboxylate

The above carboxamide (2.76 g; 11.7 mmol) and potassium hydroxide (1.4 g; 25 mmol) in ethylene glycol (20 ml) was heated at reflux for 10 h. The resulting orange solution was cooled, poured into water (70 ml) and glacial acetic acid added to pH 6. The precipitated solid was collected by filtration and washed with water and acetone. The crude acid (2.4 g; 10.8 mmol) was dissolved in water containing sodium

hydroxide (0.4 g; 10 mmol) and the dark brown solution freeze dried. The sodium salt was dissolved in HMPA (hexamethylphosphoramide, 20 ml), ethyl bromide (1.3 g; 12 mmol) was added and the solution stirred at ambient temperature for 72 h. The solvent was removed *in vacuo*, water added and the mixture extracted with dichloromethane (3 × 50 ml). The combined extracts were dried and evaporated to leave a dark oil (2.3 g). Purification was achieved by elution through a short column of silica gel, using ether as the eluant, to give the product as a pale yellow solid (1.1 g, 35%). An analytical sample was obtained by crystallisation from aqueous ethanol, mp = 63—67°C. Analysis $C_{14}H_{19}NO_2S$ calculated: C: 63.37; H: 7.22; N: 5.28%. Found: C: 63.40; H: 7.07; N: 5.14%. Mass spectrum: *m/z* 265 (M^+, 27%), 192 (M^+—CO_2Et, 100%). NMR 60 MHz $CDCl_3$: δ 1.1 (3H, t, CH_3); 2.1—3.2 (8H, m, 4 × CH_2); 3.7 (1H, br s, NH); 4.1 (2H, q, CH_2CO); 6.4—7.2 (5H, m, Ph).

4-Hydroxymethyl-4-phenylaminotetrahydrothiapyran

The above ester (0.96 g; 3.6 mmol) was dissolved in THF (5 ml) and added to a stirred suspension of lithium aluminium hydride (0.28 g; 7.4 mmol) in THF (20 ml) under an atmosphere of nitrogen. After stirring at ambient temperature for 4 h, water (0.3 ml), 10% aqueous sodium hydroxide (0.3 ml) and water (1.0 ml) were added, in order, then the mixture was filtered. The solvent was evaporated to leave a viscous oil (0.8 g; 99%) which was redissolved in 1 M HCl—HOAc and freeze dried to give the hydrochloride salt. A sample of the salt was recrystallised from ethanol—ether to give a hygroscopic solid. Analysis $C_{12}H_{17}NOS \cdot HCl \cdot 0.25\ H_2O$ calculated: C: 54.53; H: 7.06; N: 5.30%. Found: C: 54.48; H: 7.11; N: 4.88%. Mass spectrum: *m/z* 223 (M^+, 6%), 192 (M^+—CH_2OH, 100%). NMR 200 MHz DMSO-d_6: δ 1.9—2.1 (4H, br, 2 × CH_2); 2.6—2.8 (4H, br, 2 × CH_2); 3.45 (*ca.* 2H, s, CH_2 + H_2O); 6.9—7.7 (5H, br, Ph); > 10 (br, exch).

4-Methoxymethyl-4-phenylaminotetrahydrothiapyran

Dimethyl sulphate (0.2 g; 1.6 mmol) was added to a mixture of the above salt (0.64 g; 2.9 mmol), benzene (6 ml), 60% aqueous sodium hydroxide (6 ml) and Adogen 464 (2 drops). The mixture was shaken vigorously for 4 h, a second portion of dimethyl sulphate was added (0.2 g; 1.6 mmol) and shaking continued for a further 2 h. The phases were separated and the aqueous phase extracted with benzene (3 × 10 ml). The combined organic phases were washed with water, dried and evaporated to give a pale yellow oil. This material was converted to the hydrochloride salt and crystallised from ethanol—ether. Yield 0.45 g (66%), mp = 193—198°C (dec). Analysis $C_{13}H_{19}NOS \cdot HCl \cdot 0.5\ H_2O$ calculated: C: 55.20; H: 7.48; N: 4.95%. Found: C: 55.14; H: 7.48, N: 4.69%. Mass spectrum: *m/z* 237 (M^+, 5%), 192 (M^+—CH_2OCH_3, 100%). NMR 200 MHz DMSO-d_6: δ 1.95—2.27 (4H, br, 2 × CH_2); 2.60—2.83 (4H, br, 2 × CH_2); 3.35 (3H, s, OCH_3); 3.4 (*ca.* 2H, s + s, CH_2O + H_2O); 7.1—7.7 (5H, br, Ph), > 10 (br, exch).

4-Methoxymethyl-4-(N-phenylpropionamido)tetrahydrothiapyran 7

The above methoxymethylthiapyran (0.4 g; 1.4 mmol) was acylated by heating to 100°C in a mixture of propionic anhydride (5 ml) and pyridine (5 ml) under an atmosphere of nitrogen for 4 h and then under reflux for 1.5 h. The cooled solution was evaporated. The residue in dichloromethane (50 ml) was washed with 5% aqueous sodium hydrogen carbonate, dried and evaporated to leave a gum. Purification was achieved by flash chromatography, using ethyl acetate—hexane (3:1) as the eluant, to give a pale yellow oil. Yield 240 mg (58%). Mass spectrum: *m/z* 293 (M^+, 2%); found 293.1449, $C_{16}H_{23}NO_2S$ requires 293.1450. NMR 80 MHz $CDCl_3$: δ 0.88 (3H, t, CH_3); 1.55—2.9 (10H, m, 4 × CH_2 + CH_2CO); 3.35 (3H, s, OCH_3); 4.01 (2H, s, CH_2O); 7.28 (5H, s, Ph).

1-(2-Phenylethyl)-4-methoxymethyl-4-(N-phenylamino)hexahydrothiapyrylium iodide 14

The above propionamide (7) (138 mg; 0.47 mmol) was dissolved in (2-iodoethyl)benzene (2 ml) and stirred under an atmosphere of nitrogen for 10 days. The solid formed was collected by filtration, washed with ether and dried. Yield 38 mg, mp = 127—130°C. Analysis $C_{24}H_{32}NO_2SI$ calculated: C: 54.81; H: 6.14; N: 2.67%. Found: C: 55.01; H: 6.02; N: 2.67%. FAB—mass spectrum: *m/z* 398 (M^+, cation). NMR 360 MHz DMSO-d_6 80°C: δ 0.75—0.95 (3H, t + t, CH_3); 1.68—1.88 (2H, q + q, CH_2Me); 2.18—2.37 (2H, m, 2 × CH); 2.40—2.67 (*ca.* 4H, m, 2 × CH_2 + H_2O); 3.03—3.20 (*ca.* 4H, m, OCH_3 + CH_2Ph + H_2O); 3.20—3.37 (*ca.* 3H, m, OCH_3 + 2 × CH); 3.41—3.58 (2H, m, 2 × CH); 3.64—3.81 (3.3H, m, CH_2 + OCH_2); 3.91 (0.7H, s, OCH_2); 7.18—7.60 (10H, m, 2 × Ph).

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