MODIFIED SYNTHESES OF 2-(METHYLTHIO)-10-(2-(1-METHYL-2--PIPERIDINYL)ETHYL)PHENOTHIAZINE (THIORIDAZINE) AND 1-(3-(2-(METHYLSULFONYL)-10-PHENOTHIAZINYL)PROPYL)-PIPERIDINE-4-CARBOXAMIDE (METOPIMAZINE)

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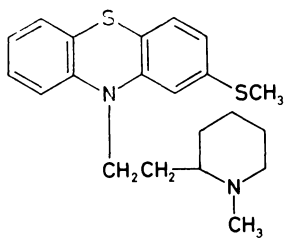
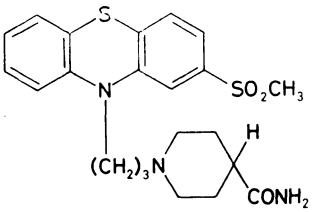
Modified syntheses of the title compounds used the enhanced reactivity of the aromatic fluorine atom in exchange reactions and proceeded via fluorinated intermediates. 2-(2-Fluorophenylthio)-5-(methylthio)nitrobenzene (*III*) was synthesized, reduced to the amine *IV* which was alkylated with 2-(2-chloroethyl)-1-methylpiperidine to compound *VI*. This was cyclized with sodium hydride in dimethyl sulfoxide to thioridazine (*I*) in excellent yield. The last two steps could be combined and thioridazine resulted from *IV* in one step. Synthesis of metopimazine (*II*) started similarly from 4-(2-fluorophenylthio)-3-nitrophenyl methyl sulfone (*XII*) which was reduced to the amine *XIV* and cyclized to 2-(methylsulfonyl)phenothiazine (*XVII*). Alkylation of *XIV* with 1-(3-chloropropyl)piperidine-4-carboxamide (*X*) proceeded with simultaneous cyclization and afforded metopimazine (*II*).

Thioridazine (*I*) is a mild neuroleptic agent[1,2] with very low incidence of the unpleasant side effects (e.g. sedation, extrapyramidal syndrome). It is much used in schizophrenic patients with milder disturbances, very often in children and geriatric patients[3,4]. Metopimazine (*II*) is a very potent antiemetic agent[5-7]. Both agents belong to the phenothiazine series of antidopaminergic compounds, their molecules show the presence of a sulfur containing nuclear substituent in position 2 and of an atypical basic side chain encompassing the piperidine fragment. Their syntheses use partly either in the stage of intermediates[8] or in the final step[9] cyclization of the correspondingly substituted *o*-bromo-*o'*-aminodiphenyl sulfides under the hard conditions of the Ullmann reaction[10]. It is well known that in the nucleophilic displacement reactions of activated aryl halides the atom of fluorine is much more reactive than the other halogen atoms[11]. On the other hand our team made some very positive experiences with such displacement reactions of aryl fluorides in which the fluorine atom was activated by the *ortho*-standing sulfide sulfur atom[12-16]. These facts led us to the idea to carry out syntheses of *I* and *II* via fluorinated intermediates. The description of the results is the object of the present communication.



I

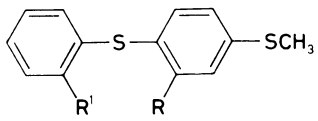


II

Thioridazine (*I*) was prepared by the following main synthetic methods: (i) alkylation of 2-(methylthio)phenothiazine[8,17] with 2-(2-chloroethyl)-1-methylpiperidine[1,18–20] in boiling xylene in the presence of sodium amide[21]; (ii) thermal cleavage of 10-((2-(1-methyl-2-piperidinyl)ethoxy)carbonyl)-2-(methylthio)phenothiazine[22,23]; (iii) reaction of 2-(methylthio)phenothiazine[8,17] with 2-(1-methyl-2-piperidinyl)-ethanol[24–26] and diethyl carbonate either in 1,2-dichlorobenzene at 175°C or in the presence of sodium methoxide at 135°C (ref.[27]); (iv) reaction of N-(2-(1-methyl-2--piperidinyl)ethyl)-3-(methylthio)diphenylamine with sulfur monochloride[1,28]; (v) cyclization of N-(2-(1-methyl-2-piperidinyl)ethyl)-2-(2-bromophenylthio)-5-(methylthio)aniline by refluxing in dimethylformamide in the presence of copper and calcium carbonate[9]. Our work was concentrated to attempts at improving the synthesis of 2-(methylthio)phenothiazine and at modifying method (v) by making use of fluorinated intermediates.

The work was started with the reaction of 2-fluorothiophenol[29] with 2-chloro-5--(methylthio)nitrobenzene[30,31] ,carried out either in boiling ethanol in the presence of sodium hydroxide or better in dimethyl formamide at 60°C in the presence of potassium carbonate. The crystalline *IIIa* was obtained in excellent yield and was characterized by spectra. The nitro group in *IIIa* was reduced by the following three methods: (i) with sodium sulfide in boiling aqueous methanol in the presence of sodium hydrogen carbonate (yield 60%), (ii) with iron in boiling aqueous acetic acid (yield 77%), and (iii) with hydrazine hydrate in boiling ethanol in the presence of ferric chloride and active carbon (almost theoretical yield) (for the method, cf.[32,33]). The crystalline *IVa* was characterized by spectra and was transformed by treatment with acetic anhydride to *Va*. Compound *IVa* was cyclized with sodium hydride in boiling xylene and gave *VIII* in a satisfactory yield. Similar cyclization with sodium hydride in boiling dimethylformamide gave *VIII* in a moderate yield only. Cyclization of *Va* with potassium carbonate in boiling dimethylformamide and the following hydrolysis with ethanolic potassium hydroxide (in analogy to ref.[34]) gave a mixture from which *VIII* could be obtained only in the yield of 13%.

For getting a comparison with the described procedures, we proceeded also in the bromo series. Reaction of 2-bromothiophenol with 2-chloro-5-(methylthio)-

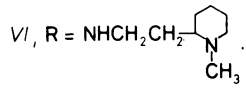


a, $R^1 = F$ *b*, $R^1 = Br$

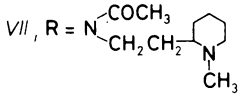
III, $R = NO_2$

IV, $R = NH_2$

V, $R = NHCOCH_3$

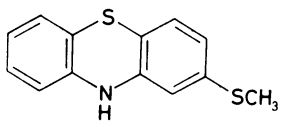


VI, $R = NHCH_2CH_2$-(N-methylpiperidin-2-yl)

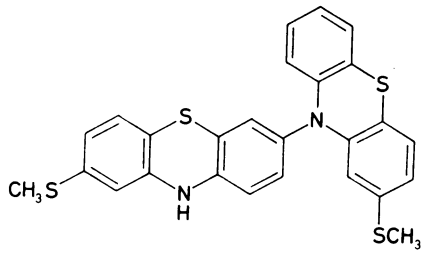


VII, $R = N(COCH_3)CH_2CH_2$-(N-methylpiperidin-2-yl)

nitrobenzene[30] in boiling ethanol in the presence of sodium hydroxide[34] gave *IIIb* which melted constantly by 10°C lower (82–83°C) in comparison with the literature[34] value (90–92°C). For this reason it was fully characterized by spectra which confirmed its identity. It was reduced with hydrazine hydrate in boiling ethanol in the presence of ferric chloride and carbon (method[32,33]) giving 88% of *IVb* (for different reduction method, cf. ref.[34]). Acetylation with acetic anhydride[35] afforded the known *Vb*. Cyclization of *IVb* with potassium carbonate in boiling dimethylformamide in the presence of copper[34] gave *VIII* in a yield by 10% lower than in the fluoro series (see Experimental under *A*). Cyclization of *Vb* in a similar fashion[34] followed by hydrolysis with ethanolic potassium hydroxide gave an inhomogeneous *VIII* from which crystallization separated a small amount of an insoluble and high-melting compound $C_{26}H_{20}N_2S_4$ (analysis and mass spectrum) which was identified by the ^1H NMR spectrum as *IX*. It is evidently a product of oxidation of *VIII* with air oxygen taking place under the hard reaction conditions (the mixture was not protected from the air). The assigned structure is in good agreement with structures assigned to products of oxidation of phenothiazine with dimethyl sulfoxide–acetic anhydride[36] and of oxidation of 2-chlorophenothiazine with iodine in dimethyl sulfoxide[37].



VIII

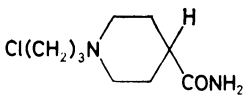


IX

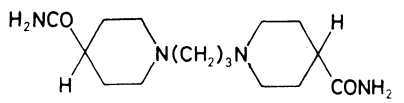
Compound *IVa* was alkylated with 2-(2-chloroethyl)-1-methylpiperidine[1,18–20] in boiling xylene in the presence of sodium hydride. An oily mixture was obtained

which was chromatographed on silica gel. The homogeneous oily *VIa* was obtained in a rather low yield, its identity was verified by the ^{1}H NMR spectrum and it was transformed to the crystalline 2,4,6-trinitrobenzoate. Compound *Va* was alkylated similarly, the crude product was inhomogeneous and its chromatography on aluminium oxide gave the homogeneous oily *VIIa* which afforded a crystalline hydrochloride (its IR spectrum was recorded). Cyclization of *VIa* with sodium hydride in dimethyl sulfoxide at 150°C gave *I*, isolated as the crystalline hydrochloride, in a very high yield. The use of pulverized potassium hydroxide instead of sodium hydride led to the same product (*I*.HCl) but the yield was considerably lower. Reaction of *IVa* with 2-(2-chloroethyl)-1-methylpiperidine and 2 equivalents of sodium hydride in dimethyl sulfoxide at 130°C combined the steps of alkylation and cyclization and afforded directly *I* (isolated as hydrochloride) in a reasonable yield of 58%. The hydrochloride of thioridazine (*I*) has the tendency to form crystalline solvates; two of them were characterized: hemihydrate (analysis) and 1 : 1 solvate with ethanol (analysis and mass spectrum).

The synthesis of metopimazine (*II*) was described[38] only by alkylation of 2-(methylsulfonyl)phenothiazine[8] with 1-bromo-3-chloropropane and by the following reaction of the intermediate obtained with piperidine-4-carboxamide[39]. Our work was started by the synthesis of *X*, the precursor of the metopimazine side chain. Piperidine-4-carboxamide[39] was reacted with 1-bromo-3-chloropropane in dioxane at 90°C. The precipitated mixture of salts was filtered off and processing of the filtrate gave *X* in a moderate yield. It was characterized by spectra and gave a crystalline hydrochloride. The mentioned mixture of salts was decomposed on a column of Amberlyst A-26 (OH^- cycle) and the bases were separated by crystallization from dioxane. The soluble fraction consisted mainly of the starting piperidine-4-carboxamide. The insoluble minor product had a high melting point (245–250°C with decomposition), corresponded to $C_{15}H_{28}N_4O_2$ (analysis and mass spectrum) and was evidently *XI* (IR spectrum in agreement). A similar reaction in ethanol in the presence of potassium carbonate gave a much better yield of the desired *X*.



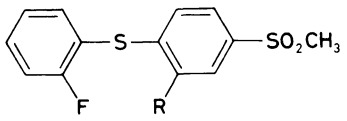
X



XI

Reaction of 2-fluorothiophenol[29] with 4-chloro-3-nitrophenyl methyl sulfone[40] in dimethylformamide at 60°C in the presence of potassium carbonate gave 63% of *XII* whose identity was corroborated by spectra. In a larger batch the yield was lower (56%) and the mother liquors were subjected to chromatographic separation on a column of aluminium oxide. No further quantity of *XII* was obtained but

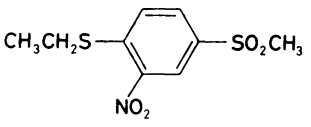
benzene and chloroform eluted successively three unexpected by-products. The most important of them was the first one, eluted with benzene. It was un unsharply melting solid (m.p. about 120°C) with the elemental composition $C_{19}H_{14}F_2O_2S_3$ (analysis and mass spectrum). The absence of nitrogen and presence of three sulfur atoms and two fluorine atoms indicated that in the starting 4-chloro-3-nitrophenyl methyl sulfone not only the atom of chlorine but also the nitro group was substituted by the fluorophenylthio residue. The resulting formula *XIII* was fully confirmed by the IR and ^{1}H NMR spectra. The second, less important by-product was eluted with chloroform (m.p. 145–147°C). According to the mass spectrum and analysis the elemental composition was $C_9H_{11}NO_4S_2$. The ^{1}H NMR spectrum proved the presence of the SO_2CH_3 group, of three aromatic protons, and of five further protons of an ethyl group connected to a heteroatom. The only plausible structure is represented by formula *XV* but the source of ethanethiol, which must have intervened, is obscure. The last crystalline substance, eluted with chloroform, was the minor by-product $C_{14}H_{12}N_2O_8S_3$ (mass spectrum and analysis) melting at 208–212°C. After considering the IR and ^{1}H NMR spectra, the formula *XVI* for this product was the only possibility. We have to presume here an interchange of the reactive atom of chlorine and of the SH group in a small amount of the starting materials which opened the way to *XVI*.



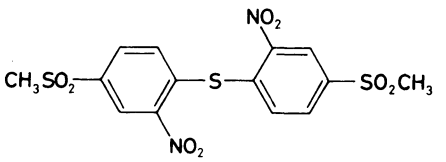
XII, R = NO_2
XIII, R = S–C$_6$H$_4$F
XIV, R = NH_2

Compound *XII* was reduced (i) with hydrazine in boiling ethanol in the presence of ferric chloride and carbon and (ii) with iron in boiling aqueous acetic acid. The amine *XIV* was obtained, the crystalline base was characterized by spectra and transformed to the hydrochloride. It was cyclized with sodium hydride in dimethyl sulfoxide at 140°C or in boiling xylene (less favourable) and gave *XVII* which was fully characterized by spectra. Its preparation by different methods was described in the literature[8,41,42]. The final step of the synthesis of *II* consisted in alkylation of *XIV* with *X* in the presence of sodium hydride in dimethyl sulfoxide at 100°C which proceeded under simultaneous cyclization. The crystalline base *II* (cf. also ref.[38]) was obtained and its spectra were recorded.

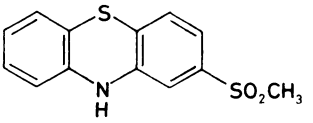
Some time ago[43] we carried out the first test of reactivity of carbanions as nucleophiles in reactions with fluoroarenes in which the fluorine atom was activated by the



XV

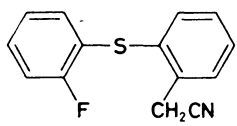


XVI

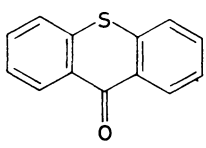


XVII

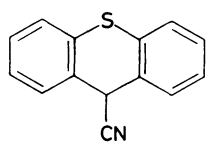
o-standing sulfide sulfur atom; these experiments were at the same time attempts at a new synthesis of the dibenzo[*b*,*f*]thiepin skeleton: treatment of diethyl 2-(2-fluorophenylthio)benzylmalonate and ethyl 2-(2-fluorophenylthio)benzylcyanoacetate with sodium hydride in dimethylformamide at 90°C, however, did not lead to any reactions and the starting compounds were recovered. Now, a new attempt in the same line was carried out. The nitrile *XVIII* was prepared from the known 2-(2-fluorophenylthio)benzyl chloride[43] and its cyclization with sodium hydride in dimethyl sulfoxide at 50–60°C was attempted. A mixture was obtained from which thioxanthone (*XIX*) (refs[44–46]) was isolated as the only crystalline product. The presence of the unchanged *XVIII* in the crude product was indicated by TLC. The appearance of *XIX* is the proof of the fact that the desired cyclization – at least partly – really took place. The primary product was likely the nitrile *XX* which apparently cleaved the cyanide anion and the remained thioxanthylium cation (*XXI*)



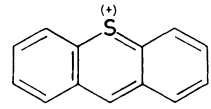
XVIII



XIX



XX



XXI

was hydrolyzed under disproportionation[46,47] to a mixture of *XIX* and thioxanthene, from which only *XIX*, which is easily to be isolated, was obtained. Our previous conclusion on the insufficient reactivity of carbanions in nucleophilic exchange reactions with activated fluoroarenes[43] was thus not completely justified.

EXPERIMENTAL

The melting points of analytical samples were determined in the Mettler FP-5 melting point recorder; the samples were dried in vacuo of about 60 Pa at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in NUJOL, ν in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) with a CW-NMR TESLA BS 487C (80 MHz) spectrometer, and the mass spectra (m/z, fragments and /or %) with MCH 1320 and Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

2-(2-Fluorophenylthio)-5-(methylthio)nitrobenzene (*IIIa*)

A) 2-Fluorothiophenol[29] (79·2 g) and 126 g 2-chloro-5-(methylthio)nitrobenzene[30,31] were added to a solution of 27·2 g NaOH in 700 ml ethanol and the mixture was stirred and refluxed for 6 h. Ethanol was evaporated in vacuo, the residue was diluted with 300 ml water and the mixture was extracted with chloroform. The extract was washed with water, 1M-NaOH, 5% hydrochloric acid, and water, dried, and evaporated. The residue was crystallized from ethanol with active carbon; total yield on *IIIa* (including the processing of the mother liquors) was 151 g (83%), m.p. 85–86°C (ethanol). UV spectrum: 261 (4·35), 286 (4·15), 400 (3·49). IR spectrum: 764, 819, 824, 876, 884 (4 and 2 adjacent and solitary Ar–H); 1 326, 1 505 ($ArNO_2$); 1 537, 1 594, 3 060, 3 085, 3 106 (Ar). ^1H NMR spectrum: 2·51 s, 3 H (SCH_3); 6·75 dd, 1 H (H-4, J = 8·5; 2·5); 7·00–7·70 m, 5 H (H-3 and 4 × ArH of fluorophenyl); 8·03 d, 1 H (H-6, J = 2·5). For $C_{13}H_{10}FNO_2S_2$ (295·3) calculated: 52·86% C, 3·41% H, 6·43% F, 4·74% N, 21·71% S; found: 53·14% C, 3·51% H, 6·49% F, 4·48% N, 21·90% S.

B) A solution of 29·0 g 2-fluorothiophenol[29] in 100 ml dimethylformamide was treated with 33·3 g K_2CO_3 and 46·1 g 2-chloro-5-(methylthio)nitrobenzene[30,31] and the stirred mixture was heated for 3·5 h to 60°C. After cooling the mixture was filtered, the filtrate was evaporated in vacuo, the residue was diluted with 100 ml water and the mixture was extracted with chloroform. The extract was washed with water and processed. The crude product was crystallized from 300 ml ethanol; 59·2 g (89%), m.p. 84–86°C. The product was found identical with that obtained under *A*.

2-(2-Bromophenylthio)-5-(methylthio)nitrobenzene (*IIIb*)

2-Bromothiophenol (150 g) and 161 g 2-chloro-5-(methylthio)nitrobenzene[30,31] were added to a solution of 34·8 g NaOH in 800 ml ethanol and the mixture was refluxed for 6 h. Processing gave 223 g (79%) of *IIIb* melting constantly on repeated recrystallizations from ethanol at 82 to 83°C. Ref.[34], m.p. 90–92°C. Because of this difference, our product was fully characterized. UV spectrum: 261 (4·33), infl. 285 (4·12), 404 (3·48). IR spectrum: 750, 820, 860, 885 (4 and 2 adjacent and solitary Ar–H); 1 330, 1 510 ($ArNO_2$); 1 530, 1 589, 3 054, 3 093 (Ar). ^1H NMR

spectrum: 2·50 s, 3 H (SCH_3); 6·65 d, 1 H (H-3, $J = 9·0$); 7·20 dd, 1 H (H-4, $J = 9·0$; 2·0); 7·25–7·80 m, 4 H (ArH of bromophenyl); 8·01 d, 1 H (H-6, $J = 2·0$). For $C_{13}H_{10}BrNO_2S_2$ (356·3) calculated: 43·83% C, 2·83% H, 22·43% Br, 3·93% N, 18·00% S; found: 43·78% C, 2·83% H, 22·72% Br, 3·76% N, 17·96% S.

2-(2-Fluorophenylthio)-5-(methylthio)aniline (*IVa*)

A) A mixture of 49·2 g *IIIa* and 1·3 l methanol was stirred and treated over 1·5 h with a solution of 302 g $Na_2S.9\,H_2O$ and 38·1 g $NaHCO_3$ in 390 ml water, added dropwise. The mixture was refluxed for 12 h, methanol was distilled off, the residue was extracted with chloroform, the extract was washed with water and processed. The residue was crystallized from 40 ml ethanol; 26·7 g (60%) of *IVa*, m.p. 67–68°C (benzene–light petroleum). UV spectrum: 240 (4·54), 272 (4·16), 314 (3·81). IR spectrum: 752, 785, 850 (4 and 2 adjacent and solitary Ar–H); 1 545, 1 561, 1 570, 1 580 (Ar); 1 608 ($ArNH_2$); 3 360, 3 450 (NH_2). ^{1}H NMR spectrum: 2·46 s, 3 H (SCH_3); 4·30 bs, 2 H ($ArNH_2$); 6·50–7·40 m, 7 H (ArH). For $C_{13}H_{12}FNS_2$ (265·4) calculated: 58·84% C, 4·56% H, 7·16% F, 5·28% N, 24·16% S; found: 58·96% C, 4·59% H, 7·42% F, 4·89% N, 24·33% S.

B) A refluxing mixture of 450 ml acetic acid, 45 ml water, and 49·0 g *IIIa* was treated over 1 h with 46·6 g Fe. The mixture was refluxed for 45 min, acetic acid was evaporated in vacuo, the residue was diluted with 400 ml water and extracted with dichloromethane. The mixture was filtered and the filtrate was separated. Processing of the organic layer gave a semisolid residue which was crystallized first from ethanol and then from a mixture of benzene and light petroleum; 34·0 g (77%) of *IVa*, m.p. 64–67°C, identical with the product under *A*.

C) A solution of 118 g *IIIa* in 930 ml ethanol was treated with 18·6 g active carbon and 70 ml 99% $N_2H_4.H_2O$ and the stirred mixture was treated over 10 min with a solution of 4·8 g $FeCl_3.6\,H_2O$ in 90 ml ethanol. The reaction was exothermic (after heating to the boiling point of ethanol further heating was discontinued but refluxing continued spontaneously for 30 min). It was then refluxed for 10 h, filtered, ethanol was evaporated under reduced pressure, the residue was diluted with 500 ml water and neutralized with acetic acid. The precipitated product was filtered, washed with water, and dried in vacuo; 105 g (99%) of *IVa*, m.p. 66–67·5°C, identical with the product under *A* and *B*.

2-(2-Fluorophenylthio)-5-(methylthio)acetanilide (*Va*)

A mixture of 26·5 g *IVa* and 16 ml acetic anhydride was heated under reflux for 4 h in a bath of 170°C. Volatile components were evaporated in vacuo, and the residue was distilled; 29·8 g, b.p. about 260°C/0·13 kPa. The distillate crystallized after trituration with a mixture of benzene and light petroleum; 27·3 g (89%), m.p. 66–71°C. Analytical sample, m.p. 72–73°C (benzene–light petroleum). IR spectrum: 760, 815, 821, 860 (4 and 2 adjacent Ar–H); 1 515, 1 585, 3 070 (Ar); 1 560, 1 669 (CONH); 3 310 (NH). ^{1}H NMR spectrum: 2·12 s, 3 H ($COCH_3$); 2·50 s, 3 H (SCH_3); 6·80–7·30 m, 5 H (H-4 and 4 × ArH of fluorophenyl); 7·45 d, 1 H (H-3, $J = 8·0$); 1 H (CONH); 8·40 d, 1 H (H-6, $J = 2·0$). For $C_{15}H_{14}FNOS_2$ (307·4) calculated: 58·61% C, 4·59% H, 6·18% F, 4·56% N, 20·86% S; found: 58·90% C, 4·69% H, 6·42% F, 4·35% N, 21·00% S.

2-(2-Bromophenylthio)-5-(methylthio)aniline (*IVb*)

A refluxing solution of 221 g *IIIb* in 1·75 l ethanol was treated with a solution of 9·1 g $FeCl_3.6\,H_2O$ in 175 ml ethanol and with 35 g active carbon. The heating was discontinued and the stirred mixture was treated over 1·5 h with 170 ml 80% $N_2H_4.H_2O$, added dropwise. It was

then stirred and refluxed for 10 h. The mixture was filtered while hot, the active carbon was extracted with 400 ml ethanol and the extract was combined with the ethanolic filtrate. Crystallization by cooling and processing of the mother liquor gave 178 g (88%) of *IVb*, m.p. 114–115°C. Ref.[34], m.p. 115–117°C.

N-*Acetyl derivative* (Vb) (ref.[35]), m.p. 98–100°C (ethanol). Ref.[35], m.p. 99–101°C.

2-(Methylthio)phenothiazine (*VIII*)

A) A mixture of 5·30 g *IVa*, 40 ml xylene, and 0·7 g 80% NaH (oil suspension) was refluxed for 10 h. After cooling the xylene solution was separated by decantation from the solid material which was extracted with 100 ml water and the suspension was filtered. The crude product was dried in vacuo and crysallized from ethanol; 3·17 g (65%), m.p. 137–140°C. Refs[8,17], m.p. 138–139°C and 138–140°C, respectively (different method).

B) A solution of 5·30 g *IVa* in 40 ml dimethylformamide was treated with 0·7 g 80% NaH (oil suspension) and the mixture was refluxed for 13 h. Dimethylformamide was evaporated in vacuo, the residue was diluted with water and extracted with benzene. Processing of the extract and crystallization of the crude product from ethanol with active carbon gave 1·75 g (36%) of *VIII*, m.p. 137–139°C. It was identical with the product obtained under *A*.

C) A mixture of 5·0 g *Va*, 35 ml dimethylformamide, and 5·0 g K_2CO_3 was refluxed for 15 h. After cooling it was diluted with 120 ml water and extracted with benzene. Processing of the extract gave 6·4 g residue which was dissolved in 20 ml ethanol, a solution of 1·6 g KOH in 30 ml ethanol was added and the mixture was refluxed for 6 h. Ethanol was evaporated, the residue was diluted with water and extracted with benzene. Processing of the extract gave 4·3 g of an inhomogeneous residue from which the product was obtained by extraction with ethanol; 0·5 g (13%), m.p. 136–138°C.

D) A mixture of 37·5 g *IVb*, 35 g K_2CO_3, 1·0 g Cu, and 225 ml dimethylformamide was refluxed for 15 h. After cooling it was filtered, the filtrate was evaporated in vacuo and the residue was crystallized from ethanol; 15·4 g (55%) of *VIII*, m.p. 136–139°C. The procedure used was in principle the same like described in ref.[34].

E) A mixture of 49·7 g *Vb*, 265 ml dimethylformamide, 41·1 g K_2CO_3, and 1·2 g Cu was refluxed for 15 h (cf. ref.[34]). After cooling the mixture was filtered, the filtrate was evaporated in vacuo, the residue was treated with 200 ml 20% ethanolic KOH and the mixture was refluxed for 5 h. Ethanol was evaporated, the residue was diluted with water and extracted with benzene. Processing of the extract gave 31·8 g of a residue which gave by crystallization from benzene 21·6 g (65%) of not completely homogeneous *VIII*, m.p. 129–135°C, and 3·02 g of an insoluble substance which was crystallized from a mixture of 50 ml benzene and 20 ml ethanol, m.p. 208·5–210°C. This was assigned to be 2-(methylthio)-7-(2-(methylthio)phenothiazine-10-yl)-phenothiazine (*IX*). Mass spectrum: 488 (M^+, $C_{26}H_{20}N_2S_4$, 100), 473, 456, 440, 426, 394, 244, 197. UV spectrum: infl. 236 (4·57), 267·5 (4·87), 336 (3·93). IR spectrum: 732, 744, 795, 826, 850 (4 and 2 adjacent and solitary Ar–H); 1 560, 1 575, 1 584, 3 048 (Ar); 3 360 (NH). ^{1}H NMR spectrum: 2·22 s and 2·30 s, 3 and 3 H (2 × SCH_3); 5·98 d, 1 H (H-6, J = 2·5); 6·20 dd, 1 H (H-8, J = 8·0; 2·5); 6·50–7·00 m, 11 H (H-1, H-3, H-4, H-9, and 7 × ArH of 10-phenothiazinyl); 8·88 bs, 1 H (NH). For $C_{26}H_{20}N_2S_4$ (488·7) calculated: 63·90% C, 4·12% H, 5·73% N, 26·25% S; found: 64·03% C, 4·20% H, 5·44% N, 25·97% S.

N-(2-(1-Methyl-2-piperidinyl)ethyl)-2-(2-fluorophenylthio)-
-5-(methylthio)aniline (*VIa*)

A mixture of 5·3 g *IVa*, 30 ml xylene, and 0·72 g 80% NaH (suspension in mineral oil) was stirred for 15 min at room temperature and then treated over 5 min with a solution of 3·9 g 2-(2-chloroethyl)-1-methylpiperidine[1,18–20] in 5 ml xylene, added dropwise. The mixture was refluxed for 3 h, after cooling it was washed with water and then extracted with 50 ml of a 10% solution of (+)-tartaric acid. The separated aqueous extract was made alkaline with 20% NaOH and the base was extracted with benzene. Processing of the extract gave 7·0 g of an inhomogeneous oil which was chromatographed on 150 g silica gel. Elution with chloroform removed some components and elution with ethyl acetate gave 1·8 g (23%) of homogeneous oily *VIa*. ^{1}H NMR spectrum: 2·12 s, 3 H (SCH_3); 2·49 s, 3 H (NCH_3); 1·00–3·00 m, 11 H ($CH_2CH(CH_2)_4N$); 3·18 m, 2 H (CH_2NAr); 5·52 bt, 1 H (NHAr); 6·40–7·10 m, 6 H (H-4, H-6, and 4 × ArH of fluorophenyl); 7·34 d, 1 H (H-3, J = 8·5).

2,4,6-Trinitrobenzoate, m.p. 101–105°C with decomposition (ethanol). For $C_{28}H_{30}FN_5O_8S_2$ (647·7) calculated: 51·92% C, 4·67% H, 2·93% F, 10·81% N, 9·90% S; found: 51·63% C, 4·66% H, 3·08% F, 10·54% N, 10·11% S.

N-(2-(1-Methyl-2-piperidinyl)ethyl)-2-(2-fluorophenylthio)-
-5-(methylthio)acetanilide (*VIIa*)

A mixture of 6·6 g *Va*, 40 ml xylene, and 0·80 g 80% NaH (oil suspension) was stirred for 10 min at room temperature, treated with a solution of 4·0 g 2-(2-chloroethyl)-1-methylpiperidine[1,18–20] in 5 ml xylene and refluxed for 3 h. After cooling it was washed with water, and the base was extracted with a 10% solution of (+)-tartaric acid. The aqueous extract was made alkaline with 10% NaOH and the bases were extracted with benzene. Processing of the extract gave 9·75 g of an inhomogeneous oil which was chromatographed on a column of 200 g neutral Al_2O_3 (activity II). Benzene eluted first some contaminants and a mixture of benzene and chloroform eluted then 5·82 g (63%) of homogeneous oily *VIIa*.

Hydrochloride, m.p. 153·5–156·5°C (ethanol–ether). IR spectrum: 760, 840, 870 (4 and 2 adjacent and solitary Ar–H); 1 460, 1 540, 1 570, 1 590, 3 020, 3 065, 3 080 (Ar); 1 660 (RCON); 2 500 (NH^+). For $C_{23}H_{30}ClFN_2OS_2$ (469·1) calculated: 58·89% C, 6·45% H, 7·56% Cl, 4·05% F, 5·97% N, 13·67% S; found: 58·99% C, 6·58% H, 7·50% Cl, 4·17% F, 5·74% N, 13·37% S.

2-(Metylthio)-10-(2-(1-methyl-2-piperidinyl)ethyl)phenothiazine (*I*)

A) A mixture of 2·55 g *VIa*, 30 ml dimethyl sulfoxide, and 0·30 g 80% NaH (oil suspension) was stirred under reflux in nitrogen atmosphere for 6·5 h at 150°C (bath temperature). After cooling the stirred mixture was decomposed by 30 ml water, added dropwise, and the mixture was extracted with benzene. The extract was washed with water and processed. The residue (2·3 g) represented practically homogeneous *I* (TLC). It was dissolved in benzene, the solution was filtered through a column of 20 g neutral Al_2O_3, the filtrate was evaporated and the residue was transformed to the hydrochloride (HCl in ether–acetone); 2·55 g (96%), m.p. 157–161°C. Ref.[1], m.p. 158–160°C. It has to be mentioned for comparison that the described[9] cyclization of *VIb* with K_2CO_3 in boiling dimethylformamide in the presence of Cu gave in our hands 71% of *I*.

Hydrochloride hemihydrate, m.p. 99–102°C (95% ethanol–acetone). For $C_{21}H_{27}ClN_2S_2$ + 0·5 H_2O (416·1) calculated: 60·62% C, 6·78% H, 8·52% Cl, 6·73% N, 15·41% S; found: 60·79% C, 6·99% H, 8·40% Cl, 6·46% N, 15·12% S.

Hydrochloride, 1 : 1 solvate with ethanol, m.p. 90–92°C (ethanol). Mass spectrum: 370 (M^+, $C_{21}H_{26}N_2S_2$, 9), 258 ($C_{14}H_{12}NS_2$, 4), 244 ($C_{13}H_{10}NS_2$, 3), 126 ($C_8H_{16}N$, 10), 98 ($C_6H_{12}N$, 100). For $C_{21}H_{27}ClN_2S_2 + C_2H_6O$ (453·1) calculated: 60·97% C, 7·34% H, 7·83% Cl, 6·18% N, 14·15% S; found: 60·96% C, 7·44% H, 8·03% Cl, 5·91% N, 14·22% S.

B) A mixture of 15·2 g crude *VIa*, 100 ml dimethyl sulfoxide, and 5·0 g pulverized KOH was stirred and heated for 5 h to 150°C (bath temperature). After cooling it was diluted with water and extracted with a mixture of benzene and ether. The extract was washed with water and processed giving 10·2 g (71%) of practically homogeneous *I* (TLC). The hydrochloride, which was crystallized from ethanol and dried in vacuo at 110°C, melted at 156–162°C.

C) A mixture of 160 g *IVa*, 1·3 l dimethyl sulfoxide, and 44 g 80% NaH (oil suspension) was stirred under nitrogen, heated to 125°C, and treated over 5 min with 107 g 2-(2-chloroethyl)-1-methylpiperidine[1,18–20], added dropwise. The mixture was stirred and heated for 6 h to 130°C, dimethyl sulfoxide was evaporated in vacuo, the residue was diluted with 1 l water and extracted with benzene. The base was transferred from the organic solvent by extraction with 1 l 10% solution of (+)-tartaric acid into the aqueous layer. This layer was made alkaline with NH_4OH and the base was extracted with benzene. Processing of the extract gave 212 g of inhomogeneous residue which was dissolved in 300 ml benzene and the solution was filtered through a column of 400 g neutral Al_2O_3 (activity II) which was washed with further 400 ml benzene. The filtrate was evaporated, the residue (196 g) was dissolved in 300 ml acetone and the solution was neutralized with HCl in ether. After 4 days of standing the hydrochloride of *I* was filtered and recrystallized from 250 ml ethanol; 144 g (58%), m.p. 156–161°C.

1-(3-Chloropropyl)piperidine-4-carboxamide (*X*)

A) A stirred solution of 9·6 g piperidine-4-carboxamide[39] in 75 ml dioxane was treated over 10 min at 90°C with a solution of 6·3 g 1-bromo-3-chloropropane in 5 ml dioxane. The mixture was stirred for 15 min at 90°C, cooled, and after 2 h standing the precipitated substance (9·1 g) was filtered off. Evaporation of the filtrate and trituration of the residue with ether gave 2·6 g (24% per conversion) of *X*, m.p. 109–113°C. Analytical sample, m.p. 114·5–117°C (ether). IR spectrum: 640, 705 (C–Cl); 1 620 (NH_2); 1 655 ($RCONH_2$); 2 735, 2 760, 2 800 ($N–CH_2$); 3 160, 3 340 (NH_2). ^{1}H NMR spectrum (CD_3SOCD_3): 1·50–2 10 bm, 8 H (CH_2CH(ax)NCH. (ax)CH_2 of piperidine and CH_2 in position 2 of propyl); 2·35 t, 2 H (CH_2N, J = 6·5); 2·82 bm, 2 H (2 × H-eq in positions 2 and 6 of piperidine); 3·61 t, 2 H (CH_2Cl, J = 6·5); 4·20 bt, 1 H (H-4 of piperidine); 6·70 bs and 7·25 bs, 1 and 1 H ($CONH_2$). For $C_9H_{17}ClN_2O$ (204·7) calculated: 52·81% C, 8·37% H, 13·69% N; found: 52·76% C, 8·24% H, 13·50% N.

Hydrochloride, m.p. 186–194°C (acetone–ethanol–ether). For $C_9H_{18}Cl_2N_2O$ (241·2) calculated: 44·82% C, 7·52% H, 11·62% N; found: 44·59% C, 7·55% H, 11·35% N.

The mixture of salts, which was filtered off (9·1 g), was decomposed by filtration through a column of 250 g Amberlyst A-26 using the OH^- cycle. The mixture of bases (5·8 g) obtained was separated on the basis of different solubility in dioxane. The soluble fraction, which crystallized from dioxane, was the recovered starting piperidine-4-carboxamide (2·8 g), m.p. 138·5 to 141°C (ref.[39], m.p. 150–152°C). The insoluble fraction (1·3 g) was crystallized from ethanol and was identified as 1,3-bis(4-aminocarbonyl-1-piperidinyl)propane (*XI*), m.p. 249–252°C with decomposition. Mass spectrum: 296 (M^+, $C_{15}H_{28}N_4O_2$), 168 ($C_9H_{16}N_2O$, 38), 153. ($C_8H_{13}N_2O$, 30), 142 ($C_7H_{13}N_2O$, 100), 124 ($C_8H_{14}N$, 65). IR spectrum: 1 650 ($RCONH_2$); 2 675, 2 760, 2 810 ($N–CH_2$); 3 200, 3 365, 3 400 (NH_2). For $C_{15}H_{28}N_4O_2$ (296·4) calculated: 60·78% C, 9·52% H, 18·90% N; found: 60·54% C, 9·75% H, 18·92% N.

B) A mixture of 9·6 g piperidine-4-carboxamide[39], 75 ml ethanol, and 7·0 g 1-bromo-3-chloropropane was stirred for 4 h at 40–45°C. 1-Bromo-3-chloropropane (4·8 g) and 13·0 g K_3CO_3 were added and the mixture was stirred at the same temperature for further 2 h. It was then filtered, the filtrate was evaporated in vacuo at 40°C and the residue was extracted with 80 ml dioxane at room temperature. Evaporation of the extract gave 5·3 g (35%) of almost homogeneous *X*, m.p. 108–113°C (ether).

4-(2-Fluorophenylthio)-3-nitrophenyl Methyl Sulfone (*XII*)

A) A mixture of 35·8 g 2-fluorothiophenol[29], 125 ml dimethylformamide, and 41·2 g K_2CO_3 was stirred at 40°C and treated over 45 min with 65·8 g 4-chloro-3-nitrophenyl methyl sulfone[40]; the temperature rose spontaneously to 60–70°C. It was stirred for 3·5 h at 60°C. After cooling the precipitated substance was filtered off, the filtrate was evaporated in vacuo and the residue was combined with the insoluble substance. It was stirred with 750 ml water and extracted with chloroform. The extract was washed with water, 1M-NaOH, 5% hydrochloric acid, and water and processed. The residue was crystallized from a mixture of ethanol and chloroform or from acetic acid giving 57·6 g (63%) of *XII*, m.p. 182–183°C (ethanol–chloroform). UV spectrum: 251 (4·32), 277 (4·20), 354 (4·73). IR spectrum: 742, 761, 770, 789, 830, 889 (4 and 2 adjacent and solitary Ar–H); 1 154, 1 320 (SO_2); 1 320, 1 520 ($ArNO_2$); 1 475, 1 552, 1 595, 3 025, 3 100 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 3·30 s, 3 H (SO_2CH_3); 6·90–7·90 s, 5 H (H-5 and 4 × ArH of fluorophenyl); 8·08 dd, 1 H (H-6, J = 8·5; 2·0); 8·71 t, 1 H (H-2, J = 2·0). For $C_{13}H_{10}FNO_4S_2$ (327·3) calculated: 47·70% C, 3·08% H, 5·80% F, 4·28% N, 19·59% S; found: 47·87% C, 3·13% H, 5·84% F, 4·37% N, 19·61% S.

B) Similar reaction of 61·8 g 2-fluorothiophenol[29], 113·6 g 4-chloro-3-nitrophenyl methyl sulfone[40], and 71 g K_2CO_3 in 230 ml dimethylformamide and similar processing gave 89·8 g (56%) of *XII*, m.p. 179–183°C.

The mother liquors were evaporated in vacuo, the residue was dissolved in 200 ml benzene and the solution was chromatographed on a column of 1 kg neutral Al_2O_3 (activity II). The first benzene eluates containing inhomogeneous substances were followed by fractions containing 8·03 g of homogeneous crystalline material, crystallizing from ethanol and melting at 112–120°C. It was identified as 3,4-bis(2-fluorophenylthio)phenyl methyl sulfone (*XIII*). Mass spectrum: 408 (M^+, $C_{19}H_{14}F_2O_2S_3$, 59), 329 ($C_{18}H_{11}F_2S_2$, 4), 296 ($C_{18}H_{10}F_2S$, 4), 233 (10), 218 (12) 202 ($C_{12}H_7FS$, 100), 189 (16), 170 (16), 157 (23). UV spectrum: 276 (4·24). IR spectrum: 750, 757, 762, 820, 832, 900 (4 and 2 adjacent and solitary Ar–H); 1 140, 1 155, 1 305 ($ArSO_2R$); 1 570, 1 594, 3 005, 3 060 (Ar). ^{1}H NMR spectrum: 2·95 s, 3 H (SO_2CH_3); 6·80–7·80 m, 11 H (ArH). For $C_{19}H_{14}F_2O_2S_3$ (408·5) calculated: 55·86% C, 3·46% H, 9·30% F, 23·55% S; found: 56·08% C, 3·55% H, 9·61% F, 23·31% S.

Elution with chloroform gave 4·96 g of a different homogeneous solid which crystallized from a mixture of chloroform and ethanol and melted at 145–147°C, to which the structure of 4-(ethylthio)-3-nitrophenyl methyl sulfone (*XV*) was assigned. Mass spectrum: 261 (M^+, $C_9H_{11}NO_4S_2$, 24), 233 ($C_7H_7NO_4S_2$, 5), 216 ($C_7H_6NO_3S_2$, 43), 184 ($C_7H_6NO_3S$, 20), 154 ($C_6H_4NO_2S$, 44), 63 (100). UV spectrum: 257·5 (4·22), 284 (4·13), 360 (3·60). IR spectrum: 788, 890 (2 adjacent and solitary Ar–H); 1 150, 1 170, 1 312 ($ArSO_2R$); 1 345, 1 518 ($ArNO_2$); 1 550, 1 594, 3 000, 3 115 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 1·32 t, 3 H (CH_3 of ethyl); 3·15 q, 2 H (CH_2S of S-ethyl, J = 7·0); 3·30 s, 3 H (SO_2CH_3); 7·81 d, 1 H (H-5, J = 8·5); 8·15 dd, 1 H (H-6, J = 8·5; 2·0); 8·59 d, 1 H (H-2, J = 2·0). For $C_9H_{11}NO_4S_2$ (261·3) calculated: 41·36% C, 4·24% H, 5·36% N; found: 41·62% C, 4·11% H, 5·31% N.

Last chloroform fractions contained 1·50 g of the last homogeneous crystalline substance from this experiment. It crystallized from acetic acid, melted at 208–212°C and was assigned

to be di(4-(methylsulfonyl)-2-nitrophenyl) sulfide (*XVI*). Mass spectrum: 432 (M^+, $C_{14}H_{12}N_2O_8S_3$, 2), 416 (0·5), 386 ($C_{14}H_{12}NO_6S_3$, 1·5), 338 ($C_{13}H_{10}N_2O_5S_2$, 2), 324 (18), 200 ($C_7H_7NO_4S$, 24), 79 (90), 63 (100). UV spectrum: 250 (4·29), infl. 271 (4·02), 350 (3·71). IR spectrum: 781, 886 (2 adjacent and solitary Ar–H); 1 150, 1 305 ($ArSO_2R$); 1 345, 1 535 ($ArNO_2$); 1 560, 1 600, 3 000, 3 090 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 3·32 s, 6 H (2 × SO_2CH_3); 7·72 d, 2 H (H-6 and H-6′, J = 8·5); 8·15 dd, 2 H (H-5 and H-5′, J = 8·5; 2·0); 8·65 d, 2 H (H-3 and H-3′, J = 2·0). For $C_{14}H_{12}N_2O_8S_3$ (432·4) calculated: 38·88% C, 2·80% H, 6·48% N; found: 39·18% C, 2·79% H, 6·53% N.

2-(2-Fluorophenylthio)-5-(methylsulfonyl)aniline (*XIV*)

A) A mixture of 5·0 g *XII*, 100 ml ethanol, 3 ml 99% $N_2H_4.H_2O$, and 0·7 g active carbon was refluxed and treated dropwise with a solution of 0·2 g $FeCl_3.6\,H_2O$ in 5 ml ethanol. The refluxing was continued for 10 h, after cooling the mixture was filtered and the filtrate was evaporated in vacuo. The residue was diluted with water and extracted with benzene. Processing of the extract gave 4·7 g of the oily product which crystallized from methanol; 4·25 g (94%) of *XIV*, m.p. 88·5–89·5°C. UV spectrum: 242 (4·23), 275 (3·68), 328 (3·78). IR spectrum: 760, 795, 803, 886 (4 and 2 adjacent and solitary Ar–H); 1 149, 1 289, 1 299 (SO_2); 1 470, 1 555, 1 570 (Ar); 1 612 ($ArNH_2$); 3 353, 3 450 (NH_2). ^{1}H NMR spectrum: 3·05 s, 3 H (SO_2CH_3); 4·70 bs, 2 H ($ArNH_2$); 6·90–7·60 m, 7 H (ArH). For $C_{13}H_{12}FNO_2S_2$ (297·4) calculated: 52·51% C, 4·07% H, 6·39% F, 4·71% N, 21·56% S; found: 52·68% C, 4·13% H, 6·66% F, 4·66% N, 21·56% S.

Hydrochloride, m.p. 100–107°C (ethanol). For $C_{13}H_{13}ClFNO_2S_2$ (333·8) calculated: 46·77% C, 3·93% H, 10·62% Cl, 5·69% F, 4·20% N, 19·21% S; found: 47·04% C, 3·92% H, 10·75% Cl, 5·99% F, 4·16% N, 19·51% S.

B) Compound *XII* (89·5 g) was added in portions over 1·5 h to a refluxing mixture of 90 ml acetic acid, 800 ml water, and 90 g Fe. The mixture was refluxed for 4 h, after cooling made alkaline with 350 ml 20% NaOH, and extracted with chloroform. It was filtered, the filtrate was separated, and the organic layer was processed. The residue was crystallized from a mixture of 40 ml ether and 15 ml methanol; 61·9 g (76%), m.p. 81–86°C.

2-(Methylsulfonyl)phenothiazine (*XVII*)

A) A solution of 19·3 g *XIV* in 150 ml dimethyl sulfoxide was stirred and treated at 100°C over 15 min with 2·4 g 80% NaH (oil suspension). The mixture was heated for 4 h to 140°C, cooled. diluted with water, and extracted with chloroform. Processing of the extract gave 16·8 g of a semisolid residue which was crystallized from benzene; 11·7 g (65%) of *XVII*, m.p. 160 to 161·5°C (benzene). UV spectrum: 266 (4·62), 328 (3·62). IR spectrum: 759, 760, 795, 857, 865 (4 and 2 adjacent and solitary Ar–H); 1 191, 1 290, 1 315 (SO_2); 1 509, 1 566, 1 600, 3 010, 3 040, 3 050, 3 100 (Ar); 3 335 (NH). ^{1}H NMR spectrum (CD_3SOCD_3): 3·10 s, 3 H (SO_2CH_3); 6·50 to 7·30 m, 7 H (ArH); 8·90 bs, 1 H (NH). Refs[8,41,42], m.p. 156·6–158°C, 164°C, and 162°C, respectively (different methods).

B) A solution of 16·2 g *XIV* in 120 ml xylene was stirred and treated over 15 min at 100 to 130°C with 2·0 g 80% NaH (oil suspension) and the mixture was refluxed for 6·5 h. After cooling, xylene was removed by decantation and the residue was extracted with chloroform. The extract was processed, the residue was dissolved in benzene and the solution was filtered through a column of 30 g neutral Al_2O_3. Evaporation of the filtrate and crystallization of the residue from benzene gave 0·65 g of *XII*, m.p. 154–161°C. The decanted xylene solution was evaporated and the residue was also crystallized from benzene giving further 4·1 g of *XVII*, m.p. 154·5–160°C. The total yield was thus 4·75 g (31%) of *XVII*.

1-(3-(2-(Methylsulfonyl)-10-phenothiazinyl)propyl)piperidine-4-carboxamide (*II*)

A stirred solution of 7·0 g *XIV* in 60 ml dimethyl sulfoxide was treated under nitrogen over 5 min at 60—70°C with 1·7 g 80% NaH (oil suspension) and after 30 min with the solution of 5·3 g *X* in 20 ml dimethyl sulfoxide, added over 15 min. The mixture was heated for 6 h to 100°C, poured into 500 ml ice-cold water, and extracted with ethyl acetate. The extract was filtered and the basic product was re-extracted with 120 ml 10% solution of methanesulfonic acid. The acid aqueous solution was made alkaline with 20% NaOH and the base was isolated by extraction with ethyl acetate. The extract was filtered through a column of 20 g silica gel and evaporated. Trituration of the residue with a mixture of acetone and ethyl acetate gave 2·6 g (25%) of *II*, m.p. 164—170°C. Analytical sample, m.p. 167—170°C (ethyl acetate). Mass spectrum: 445 (M^+, $C_{22}H_{27}N_3O_3S_2$, 4·7), 316 ($C_{16}H_{14}NO_2S_2$), 169 (23), 155 (20), 151 (21), 141 ($C_7H_{13}N_2O$, 100), 123 ($C_7H_{11}N_2$, 45). UV spectrum: 238 (4·22), 265 (4·27), 320 (3·56). IR spectrum: 740, 760, 799, 815, 871 (4 and 2 adjacent and solitary Ar–H); 1 150, 1 296, 1 306 (SO_2); 1 566, 1 588, 1 600, 3 010 (Ar); 1 650 ($RCONH_2$); 3 175, 3 340, 3 470 (NH_2). ^{1}H NMR spectrum (in CD_3.$SOCD_3$ at 60°C): 1·30—3·90 m, 13 H (CH_2CH_2N, 4 × CH_2 and CH of piperidine); 3·18 s, 3 H (SO_2CH_3); 3·98 t, 2 H (CH_2NAr_2, J = 6·0); 6·50 bs, 2 H ($CONH_2$); 6·80—7·50 m, 7 H (ArH). Ref.[38], m.p. 170—171°C (different method).

(2-(2-Fluorophenylthio)phenyl)acetonitrile (*XVIII*)

A solution of 43·1 g 2-(2-fluorophenylthio)benzyl chloride[43] in 130 ml dimethylformamide was treated with 25 g NaCN and the mixture was stirred for 4·5 h and heated to 110—120°C. The solvent was evaporated in vacuo, the residue was diluted with 200 ml water and extracted with benzene. Processing of the extract and distillation of the residue gave 33·8 g (82%) of *XVIII*, b.p. 162—165°C/40 Pa. IR spectrum: 752 (4 adjacent Ar–H); 1 220, 1 260 (Ar–F); 1 470, 1 573, 1 590, 3 015, 3 060 (Ar); 2 250 (R–CN). ^{1}H NMR spectrum: 3·94 s, 2 H ($ArCH_2CN$); 6·90 to 7·70 m, 8 H (ArH). For $C_{14}H_{10}FNS$ (243·3) calculated: 69·11% C, 4·14% H, 7·81% F, 5·76% N, 13·18% S; found: 69·40% C, 4·29% H, 7·86% F, 5·77% N, 12·88% S.

Cyclization of the nitrile *XVIII*

A solution of 6·0 g *XVIII* in 50 ml dimethyl sulfoxide was treated with 0·75 g 80% NaH (oil suspension) under nitrogen and the mixture was stirred for 5 h at 50—60°C. After cooling it was diluted with water and extracted with benzene. Evaporation of the extract gave 5·9 g semisolid residue which was crystallized from benzene and gave 1·0 g thioxanthone (*XIX*), m.p. 215 to 217°C. Ref.[44], m.p. 213—215°C. The identity was confirmed also by comparison (TLC) with an authentic sample[44–46].

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