# POTENTIAL ANTIDEPRESSANTS: 2-(FLUORO-, CHLORO-, BROMO- AND CYANOPHENYLTHIO)BENZYLAMINES AS INHIBITORS OF 5-HYDROXYTRYPTAMINE AND NORADRENALINE RE-UPTAKE IN BRAIN

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*Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.*

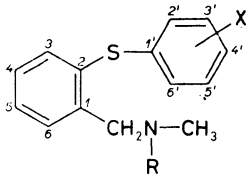
2-, 3- and 4-Fluorothiophenol, 2-, 3- and 4-chlorothiophenol, and 2-bromothiophenol were converted in two steps into the corresponding 2-(halogenphenylthio)benzoyl chlorides *IV* which afforded amides *V* and *VI* by reaction with dimethylamine and N,N,N′-trimethylethylenediamine. The amides were reduced either by lithium aluminium hydride or by diborane to benzylamines *Ia—Ig* and *IIa—IIc*. The reaction of 2-chlorobenzaldehyde with 3-bromothiophenol or 4-bromothiophenol afforded aldehydes *VIIh* and *VIIi* yielding subseuently benzylamines *Ih* and *Ii* by subsequent reducing amination. Cyano analogs *Ij* and *Il* were obtained from the bromo derivatives *Ig* and *Ii* by their reaction with cuprous cyanide in hexamethylphosphoric triamide. The synthesis of compound *Ik* was effected via aldehyde acid *VIIm* affording amino acid *Im* on reducing amination. The conversion of the latter to amide *In* and its dehydration yielded nitrile *Ik*. Some of the compounds synthesized, especially *Ic*, *Id*, *Ie* and *If*, are efficient and selective inhibitors of re-uptake of 5-hydroxytryptamine in brain structures. The most interesting from this aspect is compound *If* (hydrochloride VÚFB-17649) of this series which was chosen for detailed pharmacological testing.

In our earlier communications[1-3] we described substituted 2-(phenylthio)benzylamines of which several, predominantly 2-(methoxy- and hydroxyphenylthio)benzylamines show properties characteristic of potential antidepressants: they possess a typical antireserpine activity, they potentiate yohimbine toxicity, they show a high activity toward imipramine and desimipramine binding sites of rat brain, and they strongly inhibit the re-uptake of 5-hydroxytryptamine and noradrenaline in rat brain structures. The most interesting compound of this series, N,N-dimethyl-2-(3-hydroxyphenylthio)benzylamine hydrogen maleate (VÚFB-15468, moxyfetin) (ref.[2]), is an efficient inhibitor of re-uptake of 5-hydroxytryptamine and is in the preclinical stage of development at present.

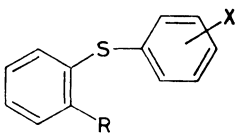
The results described above made us launch an extensive synthetic program in an effort to find other moxyfetin structure analogs with more convenient pharmaco-

logical features and to cast more light on the structure–activity relationship of this series of compounds. The present communication reports on 2-(phenylthio)benzylamines with phenylthio group bearing an atom of fluorine, chlorine, bromine or a cyano group in various positions. These compounds are mostly N,N-dimethyl derivatives. Since we have observed that more lipophilic substituents on the nitrogen atom resulted as a rule in a decrease of the effect of these compounds[2], we replaced in this series the N-methyl group in several cases by the more hydrophilic 2-dimethylaminoethyl group.

For the synthesis of the fluorinated analogs in the *m*-series 3-fluorothiophenol was used to start with[4]. The latter was converted to acid *IIIb* (see ref.[5] for method) by reaction with 2-iodobenzoic acid in boiling potassium hydroxide solution in the presence of copper powder. The corresponding 2-(2-fluoro- and 4-fluorophenylthio)-benzoic acids (*IIIa* and *IIIc*) were prepared by known procedures[6,7]. Acids *IIIa–IIIc* were converted into chlorides *IVa–IVc* by treatment with thionyl chloride in boiling benzene in the presence of a small quantity of N,N-dimethylformamide. The reaction of the latter chlorides with dimethylamine or N,N,N′-trimethylenediamine[8] yielded the corresponding amides. Compounds *Vc* and *VIa–VIc* were fully characterized and reduced either by lithium aluminium hydride in ether or by diborane in situ in tetrahydrofuran. Oily amides *Va* and *Vb* were reduced also by diborane without being isolated. The oily bases *Ia–Ic* and *IIa–IIc* obtained were converted into water soluble salts, mostly hydrochlorides, for the physiological testing.




*Ia–In*, R = $CH_3$
*IIa–IIc*, R = $CH_2CH_2N(CH_3)_2$




*IIIa–IIIc*, *IIIg*, R = COOH
*IVa–IVg*, R = COCl
*Va–Vg*, R = $CON(CH_3)_2$
*VIa–VIc*, R = $CONCH_2CH_2N(CH_3)_2$ ($CH_3$)
*VIIh*, *VIIi*, *VIIm*, R = CHO

In formulae *I–VII*: *a*, X = 2-F ; *b*, X = 3-F ; *c*, X = 4-F ; *d*, X = 2-Cl ; *e*, X = 3-Cl ; *f*, X = 4-Cl ; *g*, X = 2-Br ; *h*, X = 3-Br ; *i*, X = 4-Br ; *j*, X = 2-CN ; *k*, X = 3-CN ; *l*, X = 4-CN ; *m*, X = 3-COOH ; *n*, X = 3-$CONH_2$

For the synthesis of the chlorinated compounds series substituted benzoyl chlorides *IVd* (ref.[9]), *IVe* (ref.[10]), and *IVf* (ref.[11]), prepared by the procedures described, were

used as starting material. In analogy to the preceding cases compounds *IVd*–*IVf* were converted into dimethyl amides *Vd*–*Vf* by reactions with a toluene solution of dimethylamine. The resulting amides were reduced by lithium aluminium hydride in ether. The final benzylamines *Id*–*If* were characterized and used in the form of hydrochlorides for pharmacological purposes. N,N-Dimethyl-2-(2-bromophenylthio)benzylamine (*Ig*) was prepared in an analogous manner. Acid *IIIg* (ref.[12]) afforded the unstable chloride *IVg* which was converted without being isolated into crystalline amide *Vg* by treatment with dimethylamine. Reduction of the latter in tetrahydrofuran yielded crystalline base *Ig* which was characterized by its spectra and which was also converted into its crystalline hydrochloride for pharmacological testing.

The preparation of 3-bromophenylthio and 4-bromophenylthio analogs *Ih* and *Ii* was effected via aldehydes *VIIh* and *VIIi* which were synthesized by the reaction of 2-chlorobenzaldehyde with 3-bromothiophenol[13] or 4-bromothiophenol[14], respectively in dimethylformamide in the presence of potassium carbonate at 100 to 110°C. Aldehydes *VIIh* and *VIIi* were converted into benzylamines *Ih* and *Ii* by the Leuckart reaction[15] using treatment with dimethylformamide and formic acid at 170°C (cf. ref.[16]). The products were fully characterized and used as hydrochlorides for pharmacological testing.

Cyano derivatives *Ij* and *Il* were prepared by nucleophilic substitution of the corresponding aryl bromides *Ig* and *Ii* by treatment of the latter with freshly prepared cuprous cyanide in hexamethylphosphoric triamide at 160°C in yields ranging around 60% (cf. ref.[17]). The oily bases formed were converted into their salts (*Ij* – hydrogen maleate, *Il* – hydrochloride) which were characterized and used for pharmacological testing. The preparation of nitrile *Ik* by this method was not successful. A mixture of products was formed even after the reaction conditions had been modified and therefore another procedure was employed. Aldehyde acid *VIIm* was obtained by the reaction of 3-mercaptobenzoic acid[18] with 2-chlorobenzaldehyde in N,N-dimethylformamide in the presence of potassium carbonate. When the latter was subjected to the Leuckart reaction (N,N-dimethylformamide, formic acid, 170°C) it afforded crystalline hydrochloride *Im* in a yield of 86%. The latter was converted directly into the hydrochloride of the acid chloride which yielded without being isolated benzamide *In* by treatment with ammonia in dichloromethane. The dehydration of the latter by thionyl chloride at 0°C gave the required nitrile in a yield of 74%. The crystalline hydrogen maleate was prepared for pharmacological testing.

The substituted 2-(phenylthio)benzylamines described here were tested as their salts (listed in Experimental) and by methods of biochemical pharmacology (concentrations used 100, 1 000 and 10,000 $nmol^{-1}$) and also by some tests on animals (the compounds were administered orally and the doses given are calculated for the bases).

Acute toxicity tested on mice (the compounds were administered in doses of 100

and 500 mg/kg, the figures designate the mortality rate of animals in %): *Ia*, 0, 90; *Ib*, 0, 100; *Ic*, 0, 100; *Id*, 0, 100; *Ig*, 0, 100; *Ih*, 0, 80; *Ii*, 0, 80; *Ik*, 0, 100; *Il*, 0, 100; *IIa*–*IIc*, 0, 100.

The code numbers and the IC50-values of the compounds synthesized, which characterize their effect on the re-uptake of 5-hydroxytryptamine in rat brain in vitro and of noradrenaline in synaptosomes of the rat brain cortex in vitro, and the affinity of some compounds for the imipramine binding sites in membranes isolated from rat brain cortex, are listed in Table I. The data in Table I were complemented by the following in vivo tests: inhibition of reserpine-induced ptosis in mice (dose in mg/kg which will significantly antagonize ptosis): *Ie*, 100; *If*, 100; *Ig*, 100; *Ih*, 100; *Ii*, 10; *Ik*, 30; *Il*, 100; *IIc*, 30.

TABLE I

Biochemical pharmacology of some 2-(phenylthio)benzylamines and standards

| Compound | Code number VÚFB | IC50 in nM | | |
|---|---|---|---|---|
| | | IMI[a] | 5-HT[b] | NA[c] |
| *Ia* | 17786 | 282 | 82·8 | <1 000 |
| *Ib* | 17737 | [e] | <1 000 | >1 000 |
| *Ic* | 17738 | 55·5 | 2·2 | 281 |
| *Id* | 17642 | [e] | 0·65 | 6·5 |
| *Ie*[d] | 17643 | [e] | 2·3 | 6 243 |
| *If* | 17649 | 130·8 | 0·16 | 222 |
| *Ig* | 17700 | [e] | >100 | >1 000 |
| *Ih* | 17666 | [e] | 1·34 | 4·2 |
| *Ii*[d] | 17665 | [e] | 109·8 | 4 397 |
| *Ij* | 17702 | [e] | >100 | >1 000 |
| *Ik* | 17699 | [e] | >100 | >1 000 |
| *Il* | 17667 | [e] | 0·59 | 921 |
| *IIa* | 17772 | [e] | 2 130 | <1 000 |
| *IIb* | 17766 | [e] | >1 000 | <1 000 |
| *IIc* | 17784 | [e] | 1 860 | >1 000 |
| Amitriptyline | | 20·2 | 15·4 | 16·4 |
| Nortriptyline | | 391·8 | 517 | 1·7 |
| Imipramine | | 10·9 | 3·8 | 23·2 |
| Desipramine | | 317·5 | 52·8 | 0·7 |

[a] Inhibition of binding of 4 nM [$^3$H]imipramine in hypothalamus of rat brain; [b] inhibition of re-uptake of 10 nM [$^3$H]5-hydroxytryptamine in rat brain; [c] inhibition of re-uptake of 10 nM [$^3$H]noradrenaline in cortex of rat brain; [d] inhibition of binding of 1 nM [$^3$H]ketanserine in cortex of rat brain (IC 50), *Ie* (52·5), *Ii* (24·7); [e] not determined.

Potentiation of yohimbine toxicity in mice (dose in mg/kg and response): *Ia*, dose of 50 mg/kg efficient in 30% of animals; *Ic*, ED50 13·5 mg/kg, very efficient; *Id* and *Ie*, dose of 100 mg/kg efficient in 50% of animals; *If*, ED50 15 mg/kg, very efficient; *Ig*, dose of 100 mg/kg efficient in 50% of animals; *Ih*, doses of 100 and 10 mg/kg efficient in 50 and 10% of animals, respectively; *Ii*, ED50 27·5 mg/kg; *Ij*, doses of 100 and 50 mg/kg efficient in 75 and 25% of animals, respectively; *Ik*, ED50 52·2 mg/kg; *Il*, dose of 100 mg/kg efficient in 90% of animals; *IIb*, dose of 50 mg/kg efficient in 30% of animals; *IIc*, ED50 12·5 mg/kg, very efficient. Most of the compounds are ataxically and incoordinately inefficient in doses up to 100 mg/kg.

Chlorinated compounds *Id*, *Ie*, *If* and also fluorinated analog *Ic* are selective inhibitors of 5-hydroryptamine re-uptake in brain structures. The most interesting compound of this series, N,N-dimethyl-2-(4-chlorophenylthio)benzylamine (*If*, VÚFB-17649), was chosen for a more detailed pharmacological testing. Interest deserve also compounds *Ia*, *Ii* and *Il* which also show a certain selectivity in their effect, and the bromo analog *Ih* which acts as a strong inhibitor of noradrenaline re-uptake. The activity of the compounds in tests on animals does not correspond in some cases to the results obtained by methods of biochemical pharmacology.

## EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder or in a Kofler block. The samples were dried in vacuo at 60 Pa over $P_2O_5$ at 80°C or at room temperature. The UV spectra were measured in methanol ($\lambda_{max}$ in nm ($\log \varepsilon$) with a Unicam SP 8000 Spectrophotometer. The infrared spectra were measured in Nujol unless stated otherwise ($\nu$ in $cm^{-1}$) with a Perkin–Elmer 298 or a Shimadzu IR-4351 Spectrophotometer. For the determination, of the NMR spectra (in $CD_3SOCD_3$ unless stated otherwise, chemical shifts in ppm ($\delta$-scale), $\tilde{\nu}$ in Hz) a FT-NMR Tesla BS 567 A Spectrophotometer ($^1H$ NMR at 100 MHz, $^{13}C$ NMR at 25·14 MHz) was employed. The mass spectra were measured with Varian MAT 44S (GC MS) Spectrometer. The purity of the products and the composition of the reaction mixtures were checked by thin layer chromatography on silica gel (Silufol). The extracts were dried by $MgSO_4$ or $K_2CO_3$ and taken to dryness at low pressure in a rotary evaporator.

### 2-(3-Fluorophenylthio)benzoic Acid (*IIIb*)

3-Fluorothiophenol[4] (42·7 g; 0·33 mol) was added to a solution of 85% KOH (67 g; 0·33 mol) in water (500 ml) with stirring at 50°C. The solution was stirred for 15 min and then copper powder (8 g) and 2-iodobenzoic acid (81·8 g; 0·33 mol) were added. The mixture was refluxed for 10 h, was then diluted with water (200 ml) and filtered over active charcoal. The cooled-down filtrate was acidified with hydrochloric acid and the crystalline precipitate which had separated was filtered off in vacuo and washed with cold water. The crude product (74 g) was recrystallized from ethanol (175 ml). Yield 60 g (74%), m.p. 175–176°C. Sample for analysis 176°C (ethanol–water). UV spectrum: 251 (3·94), 273 (3·64), 283 (3·63), 312 (3·62). IR spectrum: 690, 700, 746, 780, 880 (4 and 3 adjacent and solitary Ar-H); 900, 1 256, 1 674, 2 560, 2 650, 3 150 infl. (COOH); 1 560, 1 580, 1 586, 1 598 (Ar); 1 219 (Ar-F). $^1H$ NMR spectrum: 7·95 dd, 1 H (H-6); 7·10 bd,

1 H (H-3); 7·30—7·70 m, 6 H (remaining Ar-H). $^{13}$C NMR spectrum: 167·47 s (COOH); 162·61 s (C-3′, $J$(F, C) = 247); 130·13 s (C-2); 135·12 s (C-1′, $J$(F, C) = 7·5); 132·51 d (C-4); 131·73 d (C-5′, $J$(F, C) = 9·3); 130·87 d (C-6); 130·64 d (C-6′); 128·55 s (C-1′); 127·73 d (C-3); 125·34 d (C-5); 120·89 d (C-4′, $J$(F, C) = 22·6); 116·11 d (C-2′, $J$(F, C) = 22). For $C_{13}H_9FO_2S$ (248·3) calculated: 62·89% C, 3·66% H, 7·65% F, 12·91% S; found 62·70% C, 3·83% H, 7·74% F, 12·91% S.

General Procedure for Preparation of Chlorides *IVa—IVc*

A mixture of the acid (0·12 mol), benzene (300 ml) and 2 drops of N,N-dimethylformamide was treated dropwise 5 min with thionyl chloride (29 ml; 0·16 mol). The mixture was refluxed and stirred for 2 h. Benzene and excess thionyl chloride were distilled off afterwards under reduced pressure and the residue was crystallized from hexane.

2-(2-*Fluorophenylthio)benzoyl chloride* (IVa). Acid *IIIa* (ref.[6]; 30 g) was converted into chloride *IVa* (19·5 g; 61%), m.p. 50—51°C. UV spectrum: 219 (4·39), 251 (3·94), 270 infl. (3·70), 313 (3·66). IR spectrum: 759 (4 adjacent Ar-H); 1 719, 1 759 (ArCOCl); 1 551, 1 587, 1 591, 2 050 (Ar). $^1$H NMR spectrum: 8·00 m, 1 H (H-6); 6·70 m, 1 H (H-3); 7·10—7·90 m, 6 H (remaining Ar-H). $^{13}$C NMR spectrum: 167·47 s (COCl); 162·57 s (C-2′, $J$(F, C) = 250); 140·35 s (C-2); 137·66 d (C-4); 132·81 d, 132·66 d (C-4′, $J$(F, C) = 7·5); 131·31 d, 127·43 s (C-1); 126·09 d (C-6′, $J$(F, C) = = 8); 126·09 d, 124·67 d (C-5′); 118·99 s (C-1′, $J$(F, C) = 19); 116·67 d (C-3′, $J$(F, C) = 22). For $C_{13}H_8ClFOS$ (266·7) calculated: 58·54% C, 3·02% H, 13·30% Cl, 7·12% F, 12·02% S; found 58·74% C, 3·07% H, 13·17% Cl, 7·39% F, 12·13% S.

2-(3-*Fluorophenylthio)benzoyl chloride* (IVb). Acid *IIIb* (30 g) was converted into chloride *IVb* (25·9 g; 81%), m.p. 77°C (cyclohexane). UV spectrum: 218 (4·35), 250 (3·91), 312 (3·63). IR spectrum: 722, 746, 700, 783, 790, 880 (4 and 3 adjacent and solitary Ar-H); 1 599, 1 578, 1 585, 1 595, 3 060 (Ar); 1 673 (COOH); 1 717, 1 750 (Ar-COCl). $^1$H NMR spectrum: 8·00 dd, 1 H (H-6); 6·90 bd, 1 H (H-3); 7·10—7·80 m, 6 H (remaining Ar-H). $^{13}$C NMR spectrum: 167·39 s (COCl); 162·54 s (C-3′, $J$(F, C) = 244); 140·13 s (C-2); 135·20 s (C-1′, $J$(F, C) = 7·5); 132·58 d (C-4); 131·84 d (C-5′, $J$(F, C) = 7·5); 130·79 d (C-6′, $J$(F, C) = 3·7); 128·55 s (C-1, C-6); 128·80 d (C-5); 125·41 d (C-3); 120·97 d (C-4′, $J$(F, C) = 20·6); 116·19 d (C-2′, $J$(F, C) = = 20·7). For $C_{13}H_8ClFOS$ (266·7) calculated: 58·54% C, 3·02% H, 13·30% Cl, 7·12% F, 12·02% S; found: 58·30% C, 3·02% H, 13·14% Cl, 7·39% F, 12·18% S.

2-(4-*Fluorophenylthio)benzoyl chloride* (IVc). Acid *IIIc* (ref.[7]; 30 g) was converted into chloride *IVc* (24·3 g; 76%), m.p. 74°C. UV spectrum: 218 (4·38), 251 (3·95), 270 infl. (3·68), 3·15 (3·67). IR spectrum: 748, 830, (4 and 2 adjacent Ar-H); 1 222, 1 233 (Ar-F); 900, 1 255, 2 640 (COOH); 1 489, 1 559, 1 588 (Ar); 1 677 (Ar-COOH); 1 740, 1 760 (ArCOCl). $^1$H NMR spectrum: 7·97 dd, 1 H (H-6, $J$ = 8 and 2); 7·20—7·70 m (H-4, H-5); 7·65 dd (H-2′ and H-6′, $J$(H, H) = 9·5, $J$(H, F) = 5); 7·38 t, $\sum$ 6 H (H-3′, H-5′, $J$(H, H) = $J$(H, F) = 9·5); 6·72 dd, 1 H (H-3, $J$ = 8 and 2). For $C_{13}H_8ClFOS$ (266·7) calculated: 58·54% C, 3·02% H, 13·30% Cl, 7·12% F, 12·02% S; found: 58·61% C, 3·10% H, 13·32% Cl, 7·34% F, 12·02% S.

N,N-Dimethyl-2-(4-fluorophenylthio)benzamide (*Vc*)

Dimethylamine vapors (13·5 g; 0·3 mol) were passed through a solution of *IVc* (10 g; 37·5 mmol) in benzene (100 ml) at 10—15°C. The reaction mixture was then stirred 1 h at room temperature, was washed with water (2 × 100 ml) and dried by $CaCl_2$. After the solution had been taken to dryness under reduced pressure 9·4 g (77%) of amide *Vc* was obtained m.p. 69—72°C. The m.p. of the analytical sample was 72—73°C (cyclohexane). UV spectrum: 247 (3·96), 195·6 (3·73).

IR spectrum (KBr pellets): 753, 772, 818, 822, 846 (4 and 2 adjacent Ar-H); 1 221 (Ar-F); 1 489, 1 500, 1 589, 3 000, 3 010, 3 055, 3 080 (Ar); 1 635 ($ArCONR_2$). $^1H$ NMR spectrum ($CDCl_3$): 7·43 dd, 2 H (H-2′ and H-6′, $J(H, H) = 8$, $J(H, F) = 5$); 7·25 m, 4 H (H-3, H-4, H-5, H-6); 7·03 t, 2 H (H-3′, H-5′, $J(H, H) = J(H, F) = 8$); 3·13 s, 3 H, 2·85 s, 3 H ($N(CH_3)_2$). For $C_{15}H_{14}$. .FNOS (275·3) calculated: 65·43% C, 5·13% H, 6·90% F, 5·09% N, 11·64% S; found: 65·43% C, 5·14% H, 6·93% F, 5·01% N, 11·61% S.

N,N-Dimethyl-2-(4-chlorophenylthio)benzamide (*Vf*)

Compound *Vf* was prepared from *IVf* (ref.[11]; 20 g; 0·07 mol) as described above. Yield 18 g (88%), m.p. 80—82°C (methanol–water). IR spectrum: 757, 820 (4 and 2 adjacent Ar-H); 1 500, 1 560, 1 570, 1 585, 3 010, 3 060, 3 080 (Ar); 1 634 ($ArCONR_2$). $^1H$ NMR spectrum ($CDCl_3$): 7·28 s, 8 H (Ar-H); 3·10 s, 3 H, 2·82 s, 3 H ($N(CH_3)_2$). For $C_{15}H_{14}ClNOS$ (291·8) calculated: 61·74% C, 4·84% H, 12·15% Cl, 4·80% N, 10·99% S; found: 61·47% C, 4·90% H, 12·01% Cl, 4·84% N, 10·98% S.

N,N-Dimethyl-2-(2-bromophenylthio)benzamide (*Vg*)

A suspension (22·5 g; 0·072 mol) of acid *IIIg* (ref.[12]) in toluene (160 ml) was treated first with 0·5 ml of N,N-dimethylformamide and then at 80°C dropwise with thionyl chloride (12 ml; 0·17 mol) for 15 min. The mixture was refluxed 2 h, toluene and excess thionyl chloride were distilled off in vacuo and the remaining thionyl chloride was evaporated off with 50 ml of toluene. The dark product representing crude chloride *IVg* (24 g) was dissolved in toluene (60 ml) and the solution was added dropwise to a dimethylamine solution (8·7 g; 0·19 mol) in 60 ml of toluene during 20 min at 0—5°C. The mixture was then heated at 40°C and stirred 2 h at this temperature. The reaction mixture was then extracted with water, 50% NaOH (2 × 30 ml) and finally with water (30 ml). The toluene solution was dried by $Na_2SO_4$, evaporated and the residue crystallized from a mixture of methanol and water (1 : 1). Yield 17·4 g (72%), m.p. 72—74°C. UV spectrum: 243 (3·95), 292 (3·93), 302 (4·01). IR spectrum: 750, 759, 775 (4 adjacent Ar-H); 1 492, 1 503, 1 560, 1 627 (Ar-$CONR_2$). $^1H$ NMR spectrum ($CDCl_3$): 7·59 m, 1 H (H-6); 7·00—7·40 m, 7 H (remaining Ar-H); 3·10 s, 3 H, 2·86 s, 3 H ($N(CH_3)_2$). For $C_{15}H_{14}BrNOS$ (336·3) calculated: 53·57% C, 4·20% H, 23·77% Br, 4·16% N, 9·54% S; found: 53·71% C, 4·34% H, 23·57% Br, 4·07% N, 9·47% S.

General Procedure for Preparation of Amides *VIa*—*VIb*

A solution of N,N,N′-trimethylethylenediamine[8] (12 g; 0·117 mol) in benzene (50 ml) was treated 10 min dropwise with stirring and cooling at +10°C with the chloride solution (9·4 g; 0·0468 mol) in benzene (150 ml). The mixture was stirred 4 h at room temperature and was then extracted with water (2 × 150 ml), dried and taken to dryness. The oily amide was dissolved in ether (100 ml) and was converted into the hydrogen maleate by the addition of the equivallent quantity of maleic acid in ethanol (20 ml).

N-(2-*Dimethylaminoethyl*)-N-*methyl*-2-(2-*fluorophenylthio*)*benzamide* (VIa). Chloride *IVa* (9·4 g) was converted into amide *VIa* (14·6 g; 94%). Hydrogen maleate m.p. 104—107°C (ethanol–ether). $^1H$ NMR spectrum: 7·00—7·50 m, 8 H (Ar-H); 3·07 s, 2 H (CH=CH); 2·88 s, 6 H ($N(CH_3)_2$); 2·82 s, 3 H (CON—$CH_3$). For $C_{22}H_{25}FN_2O_5S$ (448·5) calculated: 58·91% C, 5·62% H, 4·24% F, 6·25% N, 7·15% S; found: 58·95% C, 5·59% H, 4·40% F, 6·21% N, 7·20% S.

N-(2-*Dimethylaminoethyl*)-N-*methyl*-2-(3-*fluorophenylthio*)*benzamide* (VIb). Chloride *IVb* (9·4 g) was converted into amide *VIb* (14·3 g; 96%). Hydrogen maleate m.p. 86—87°C (acetone–

–ether). Mass spectrum: 332 ($M^+$, $C_{18}H_{21}FN_2OS$, 0·1), 262 (0·3), 71 (29), 58 (100). For $C_{22}H_{25}$. .$FN_2O_5S$ (448·5) calculated: 58·91% C, 5·62% H, 4·24% F, 6·25% N, 7·15% S; found: 58·66% C, 5·59% H, 4·16% F, 6·21% N, 7·43% S.

N-(2-*Dimethylaminoethyl*)-N-*methyl*-2-(4-*fluorophenylthio*)*benzamide* (VIc). Chloride *IVc* (9·4 g) was converted into amide *VIc* (14·2 g; 95%). Hydrogen maleate m.p. 111—112°C (ethanol–ether). Mass spectrum: 332 ($M^+$, $C_{18}H_{21}FN_2OS$, 0·1), 202 (2), 71 (29), 58 (100). For $C_{22}H_{25}$. .$FN_2O_5S$ (448·5) calculated: 58·91% C, 5·62% H, 4·24% F, 6·25% N, 7·15% S; found: 59·01% C, 5·52% H, 4·37% F, 6·05% N, 7·42% S.

General Procedure for Preparation of Amines *Ic*, *If* and *IIa*

A suspension of $LiAlH_4$ (3·4 g; 0·09 mol) in ether (100 ml) was treated dropwise with stirring in an atmosphere of nitrogen with the solution of the amide (0·03 mol) in 100 ml of ether. The mixture was then refluxed with stirring for 8 h. Subsequently the reaction mixture was cooled down and decomposed by stepwise addition of water (3·5 ml), 15% NaOH solution (3·5 ml) and water (10 ml). The solid products which had separated after 1 h were filtered off in vacuo, washed with ether (2 × 40 ml) and the pooled ethereal extracts were dried. The oily amide obtained after evaporation was converted into its hydrochloride by dissolving in ether and precipitation with a solution of hydrogen chloride in ether.

N,N-*Dimethyl*-2-(4-*fluorophenylthio*)*benzylamine* (Ic). Amide *Vc* (8·3 g) was converted into amine *Ic* (7·3 g; 93%). Hydrochloride m.p. 180—182°C (ethanol–ether). UV spectrum: 245·5 (3·99), 266 (3·67). IR spectrum: 765, 843 (4 and 2 adjacent ArH); 1 220 (Ar-F); 1 490, 1 588, 3 020, 3 045, 3 088 (Ar); 2 465, 2 555 ($NH^+Cl^-$). $^1$H NMR spectrum: 8·00 m, 1 H, 7·20 to 7·60 m, 7 H (Ar-H); 4·50 s, 2 H ($ArCH_2N$); 2·76 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}ClFNOS$ (297·8) calculated: 60·49% C, 5·76% H, 11·90% Cl, 6·38% F, 4·70% N, 10·77% S; found: 60·23% C, 5·68% H, 11·93% Cl, 6·62% F, 4·59% N, 11·00% S.

N,N-*Dimethyl*-2-(4-*chlorophenylthio*)*benzylamine* (If). Amide *Vf* (8·8 g) was converted into amine *If* (5·6 g; 67%). Hydrochloride m.p. 230—232°C (ethanol). $^1$H NMR spectrum: 7·15 to 8·00 m, 6 H (H-3, H-4, H-5, H-6, H-3′, H-5′); 7·12 d, 2 H (H-2′, H-6′, $J$ = 8·5); 4·48 bs, 2 H ($ArCH_2N$); 3·76 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314·3) calculated: 57·32% C, 5·45% H, 22·56% Cl, 14·46% N, 10·20% S; found: 57·39% C, 5·56% H, 22·58% Cl, 4·81% N, 10·30% S.

N-(2-*Dimethylaminoethyl*)-N-*methyl*-2-(2-*fluorophenylthio*)*benzylamine* (IIa). Amide *VIa* (10 g) was converted into amine *IIa* (7·2 g; 75%). Dihydrochloride m.p. 189—192°C (ethanol). $^1$H NMR spectrum: 8·10 m, 7·20—7·60 m, $\sum$ 6 H (Ar-H); 4·60 bs, 2 H ($ArCH_2N$); 3·60 bm, 4 H ($CH_2CH_2$); 2·86 s, 6 H ($N(CH_3)_2$); 2·70 s, 3 H (N—$CH_3$). For $C_{18}H_{25}Cl_2FN_2S$ (391·4) calculated: 55·24% C, 6·44% H, 18·12% Cl, 4·85% F, 7·16% N, 8·19% S; found: 54·96% C, 6·70% H, 18·34% Cl, 4·67% F, 7·27% N, 7·90% S.

General Procedure for Preparation of Amines *Ig*, *IIb* and *IIc*

A mixture of the amide (0·033 mol), $NaBH_4$ (2·8 g; 0·075 mol) and tetrahydrofuran (120 ml), was treated with stirring in an atmosphere of nitrogen at 20—25°C dropwise with $BF_3.(C_2H_5)_2O$ (12·6 ml; 0·1 mol). The mixture was stirred 1 h at this temperature and then refluxed with stirring 3 h. After this period the reaction mixture was cooled down and dilute hydrochloric acid (25 ml; 1 : 1) was added dropwise during 1 h. The reaction mixture was repeatedly refluxed for 3 h. It was then cooled down to 10°C and made alkaline by the addition of 20% NaOH (55 ml). The base was extracted with ether. The pooled extracts were dried and evaporated under reduced pressure.

N,N-*Dimethyl*-2-(2-*bromophenylthio*)*benzylamine* (Ig). Amide *Vg* (11·1 g) was converted into amine *Ig* (10·3 g; 98%), b.p. 152—154°C/0·4 kPa. $^1$H NMR spectrum ($CDCl_3$): 7·00—7·50 m, 8 H (Ar-H); 3·53 s, 2 H ($ArCH_2N$); 2·23, 6 H ($N(CH_3)_2$). For $C_{15}H_{16}BrNS$ (332·3) calculated: 55·90% C, 5·00% H, 24·80% Br, 4·35% N, 9·95% S; found: 55·80% C, 5·12% H, 24·94% Br, 4·22% N, 10·05% S. The hydrochloride hemihydrate was precipitated from the solution of base *Ig* (9·6 g; 0·033 mol) in ether (80 ml) by the addition of a solution of hydrogen chloride in ether. Yield 9·5 g (86%), m.p. 106—108°C (ethanol–ether). Mass spectrum: 321 ($M^+$, $C_{15}H_{16}$·.BrNS, 7), 306 (12), 242 (22), 197 (43), 175 (2), 132 (37), 91 (12), 58 (100), 36 (55). IR spectrum: 763, 772 (4 adjacent Ar-H); 1 553, 1 566, 1 587, 3 055, 3 070 (Ar); 2 370, 2 475, 2 570, 2 600 ($NH^+$); 3 400, 3 420 (NH, $H_2O$). $^1$H NMR spectrum: 2·80 s, 2·75 s, $\sum$ 6 H ($N(CH_3)_2$); 4·46 bd, 2 H ($ArCH_2N$); 8·05 m, 1 H (H-6); 7·10—7·80 m, 7 H (remaining Ar-H). For $C_{15}H_{17}BrClNS$ + 0·5 $H_2O$ (367·7) calculated: 48·99% C, 4·93% H, 9·64% Cl, 3·81% N, 8·72% S; found: 48·76% C, 5·00% H, 9·38% Cl, 3·72% N, 8·72% S.

N-(2-*Dimethylaminoethyl*)-N-*methyl*-2-(3-*fluorophenylthio*)*benzylamine* (IIb). Amide *VIb* (11 g) was converted into amine *IIb*. The dry residue was chromatographed on a column of 160 g of silica gel Fluka 60 (0·063—0·20 mm). Unpolar side products were washed off with benzene and subsequent elution with a mixture of benzene and ethanol (9 : 1) afforded 5·4 g (52%) of oily amine *IIb*. The dihydrochloride was precipitated from the ethereal solution of the base by the addition of a solution of hydrogen chloride in ether (4·8 g; m.p. 185—187°C). The analytical sample was obtained by crystallization from a mixture of ethanol and ether, m.p. 186—187°C. $^1$H NMR spectrum: 7·00—7·70 m, 8 H (Ar-H); 4·56 bs, 2 H ($ArCH_2N$); 3·20—3·60 m ($CH_2CH_2$); 2·85 s, 6 H ($N(CH_3)_2$); 2·72 s, 3 H ($NCH_3$). For $C_{18}H_{25}Cl_2FN_2S$ (391·4) calculated: 55·24% C, 6·44% H, 18·12% Cl, 6·16% N, 8·18% S; found: 55·53% C, 6·35% H, 18·05% Cl, 7·53% N, 8·30% S.

N-(2-*Dimethylaminoethyl*)-N-*methyl*-2-(4-*fluorophenylthio*)*benzylamine* (IIc). Amide *VIc* (11 g) was converted into amine *IIc*. Chromatography of the crude dry product under the conditions described for the preceding compound afforded 4·2 g (40%) of crude oily amine *IIc*. Dihydrochloride m.p. 195—198°C (ethanol). $^1$H NMR spectrum 7·20—8·00 m, 8 H (Ar-H); 4·58 s, 2 H ($ArCH_2N$); 3·20—3·60 m, 4 H ($CH_2CH_2$); 2·84 s, 6 H ($N(CH_3)_2$); 2·72 s, 3 H ($NCH_3$). For $C_{18}H_{25}Cl_2FN_2S$ (391·4) calculated: 55·24% C, 6·44% H, 18·12% Cl, 4·85% F, 7·16% N, 8·19% S; found: 55·47% C, 6·40% H, 18·04% Cl, 5·18% F, 7·54% N, 8·25% S.

N,N-Dimethyl-2-(2-fluorophenylthio)benzylamine (*Ia*)

Dimethylamine vapors (13·5 g; 0·3 mol) were passed 1 h through a solution of chloride *IVa* (10 g; 0·0375 mol) in benzene (100 ml) at 10—15°C. The reaction mixture was stirred for 1 more hour at room temperature, then washed with water (2 × 100 ml) and the solution was dried by anhydrous $CaCl_2$. The evaporation of the solution under reduced pressure afforded 10 g (97%) of chromatographically homogeneous oil representing amide *Va*. The latter was dissolved in 120 ml of absolute tetrahydrofuran and $NaBH_4$ (2·8 g; 0·075 mol) was added. The mixture was treated in an atmosphere of nitrogen dropwise 30 min with $BF_3.(C_2H_5)_2O$ (15 g; 0·1 ml) at 20—25°C. The mixture was stirred for 1 additional hour at the same temperature and was then refluxed for 4·5 h. It was cooled down afterwards, decomposed by dilute hydrochloric acid (1 : 1) and repeatedly refluxed for 4·5 h. The mixture was then cooled down to 10°C and made alkaline by the addition of 20% NaOH solution. The bases were extracted with ether (4 × 50 ml), the extracts were dried and evaporated. The oily residue was dissolved in ether and the crystalline hydrochloride was precipitated by the addition of an ethereal solution of hydrogen chloride. Yield 8·6 g (80%), m.p. 151—153°C. Analytical sample, m.p. 152—153°C

(ethanol–ether). $^1$H NMR spectrum: 8·00, 1 H (H-6); 7·10—7·60 m, 7 H (remaining ArH); 4·52 s, 2 H ($ArCH_2N$); 2·78 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}ClFNS$ (297·8) calculated: 60·49% C, 5·76% H, 11·90% Cl, 6·38% F, 4·70% N, 10·77% S; found: 60·76% C, 5·83% H, 12·06% Cl, 6·63% F, 4·73% N, 10·66% S.

General Procedure for Preparation of Amines *Ib*, *Id* and *Ie*

Dimethylamine (10 g; 0·22 mol) was dissolved in toluene (50 ml) which had been precooled to −20°C and this solution was treated dropwise 30 min with a solution of the chloride (0·073 mol) in toluene (100 ml). The temperature was maintained during the reaction at 0—5°C. Subsequently the reaction mixture was heated 1 h at 40°C, then extracted with 5% NaOH solution and water and dried. After evaporation of the solvent the crude amide was obtained, dissolved in ether (150 ml) and the solution added dropwise to a suspension of $LiAlH_4$ (6·8 g; 0·18 mol) in ether (100 ml). The mixture was refluxed 10 h, then cooled down and decomposed by 20% NaOH solution (35 ml). The inorganic salts were filtered off and washed with toluene. The bases were extracted with 10% hydrochloric acid, the acidic extracts were made alkaline by the addition of 20% NaOH solution and the bases extracted with dichloromethane. The extracts yielded an oily base which was dissolved in ethanol (20 ml) and converted into its crystalline salt.

N,N-*Dimethyl*-2-(3-*fluorophenylthio*)*benzylamine* (Ib). Chloride *IVb* (19·6 g) was converted into amine (*Ib*) (16·4 g; 86%). Hydrogen maleate m.p. 130°C (ethanol–ether). Mass spectrum: 261 (10), 246 (16), 215 (20), 165 (14), 132 (21), 58 (10). $^1$H NMR spectrum: 6·90—7·80 m, 8 H (ArH); 6·08 s, 2 H (CH=CH); 4·38 s, 2 H ($ArCH_2N$); 2·78 s, 6 H ($N(CH_3)_2$). For $C_{19}H_{20}F.NO_4S$ (377·4) calculated: 60·46% C, 5·34% H, 5·03% F, 3·71% N, 8·50% S; found: 60·46% C, 5·20% H, 5·09% F, 3·58% N, 8·61% S.

N,N-*Dimethyl*-2-(2-*chlorophenylthio*)*benzylamine* (Id). Chloride *IVd* (ref.[9]; 20·7 g) was converted into amine *Id* (12·4 g; 61%). Hydrochloride hemihydrate m.p. 90—92°C (ethanol–ether). Mass spectrum: 277 (19), 276 (8), 262 (32), 231 (10), 197 (31), 165 (50), 132 (37), 91 (12), 58 (100). $^1$H NMR spectrum: 8·10 m, 1 H, 7·40—7·70 m, 6 H, 7·05 m, 1 H (Ar-H); 4·48 s, 2 H ($ArCH_2N$); 2·77 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS + 0·5\ H_2O$ (323·3) calculated: 55·73% C, 5·61% H, 21·94% Cl, 4·33% N, 9·92% S; found: 55·80% C, 5·56% H, 22·37% Cl, 4·34% N, 9·98% S.

N,N-*Dimethyl*-2-(3-*chlorophenylthio*)*benzylamine* (Ie). Chloride *IVe* (ref.[10]; 20·7 g) was converted into amine *Ie* (17·2 g; 85%). Hydrochloride m.p. 145—147°C (ethanol–ether). $^1$H NMR spectrum: 8·04 m, 1 H (H-6); 7·10—7·70 m, 7 H (remaining Ar-H); 4·50 bm ($ArCH_2N$); 7·76 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314·3) calculated: 57·32% C, 5·45% H, 22·56% Cl, 4·46% N, 10·20% S; found: 57·54% C, 5·26% H, 22·59% Cl, 4·33% N, 10·32% S.

2-(3-Bromophenylthio)benzaldehyde (*VIIh*)

To a solution of 3-bromothiophenol[13] (34·2 g; 0·18 mol) in N,N-dimethylformamide (60 ml) was added $K_2CO_3$ (26 g) in an atmosphere of nitrogen and after 10 min of stirring 2-chlorobenzaldehyde (25·3 g; 0·18 mol). The mixture was heated at 105°C with stirring for 5 h. After this period the reaction mixture was cooled down and poured into water (400 ml). The product was extracted with dichloroethane (3 × 40 ml). The pooled extracts were washed with 5% $Na_2CO_3$ solution, water, were dried and taken to dryness. Crystallization of the residue from methanol afforded 25·9 g (49%) of aldehyde *VIIh*, m.p. 38—42°C. Analytical sample m.p. 40—42°C (methanol). UV spectrum: 231 infl. (4·19), 247 infl. (4·05), 330 (3·27). IR spectrum: 680, 757, 770, 780, 886, (4 and 3 adjacent and solitary Ar-H); 1 551, 1 583, 1 671, 1 690 (doublet, Ar-CHO); 2 755, 2 825 (CHO); 3 050, 3 080 (Ar). $^1$H NMR spectrum: 10·40 s, 1 H (CHO);

7·90 m, 1 H (H-6); 7·10—7·60 m, 7 H (remaining Ar-H). For $C_{13}H_9BrOS$ (293·2) calculated: 53·25% C, 3·09% H, 27·26% Br, 10·94% S; found: 53·17% C, 3·10% H, 27·36% Br, 10·60% S.

2-(4-Bromophenylthio)benzaldehyde (*VIIi*)

Compound *VIIi* was prepared from 4-bromothiophenol[14] (35 g; 0·186 mol) and 2-chlorobenzaldehyde (26·1 g; 0·186 mol) by the procedure described above. Yield 39·2 g (72%), m.p. 80—82°C (methanol). For $C_{13}H_9BrOS$ (293·2) calculated: 53·25% C, 3·09% H, 27·26% Br, 10·94% S; found: 53·18% C, 3·11% H, 27·20% Br, 10·93% S.

N,N-Dimethyl-2-(3-bromophenylthio)benzylamine (*Ih*)

A mixture of aldehyde *VIIh* (20 g; 0·068 mol) in N,N-dimethylformamide (25 g; 0·34 mol) and 100% formic acid (15·6 g; 0·34 mol) was heated 8 h at 170°C. The reaction mixture was then cooled down, poured into a solution of hydrochloric acid (30 ml) in water (200 ml) and the neutral portions were extracted with toluene. The aqueous phase was made alkaline by the addition of $Na_2CO_3$ and the base was extracted with dichloroethane (3 × 40 ml). The pooled extracts were washed with a NaCl solution, dried and evaporated. The oily residue (21 g; 96%) was converted in the usual manner into the crystalline hydrochloride, m.p. 156—158°C (ethanol–ether). $^1$H NMR spectrum: 8·04 m, 1 H (H-6); 7·10—7·70 m, 7 H (remaining Ar-H); 4·50 bs, 2 H ($ArCH_2N$); 2·76 s, 6 H ($N(CH_3)_2$). For $C_{14}H_{17}BrClNS$ (358·7) calculated: 50·22% C, 4·78% H, 22·28% Br, 9·88% Cl, 3·90% N, 8·94% S; found: 50·21% C, 4·89% H, 22·45% Br, 9·68% Cl, 3·92% N, 9·05% S.

N,N-Dimethyl-2-(4-bromophenylthio)benzylamine (*Ii*)

A mixture of aldehyde *VIIi* (35·2 g; 0·12 mol), N,N-dimethylformamide (46·5 ml; 0·6 mol) and 100% formic acid (22 ml; 0·6 mol) was refluxed for 6 h. The reaction mixture was then poured into a solution of concentrated hydrochloric acid (50 ml) in water (400 ml). The crystalline product which had separated after cooling was filtered off and dried. Yield 39·2 g (91%), m.p. 225—227°C. Analytical sample m.p. 229—231°C (ethanol). Mass spectrum: 321 (8), 306 (13), 275 (6), 197 (39), 165 (52), 132 (31), 91 (16), 58 (100). IR spectrum: 760, 811, 881, (4 and 2 adjacent Ar-H); 1 500, 1 590, 1 611, 3 000, 3 040 (Ar); 2 370, 2 460, 2 500, 2 555 ($NH^+$). $^1$H NMR spectrum: 8·00 m, 1 H and 7·55 m, 5 H (H-3, H-4, H-5, H-6, H-2′, H-6′); 7·18 d, 2 H (H-3′, H-5′, $J$ = 8·5); 4·47 s, 2 H ($ArCH_2N$); 2·75 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}BrClNS$ (358·7) calculated: 50·22% C, 4·78% H, 22·28% Br, 9·88% Cl, 3·90% N, 8·94% S; found: 50·29% C, 4·86% H, 22·38% Br, 9·99% Cl, 3·91% N, 8·75% S. Base liberated from the hydrochloride b.p. 168—170°C/0·25 kPa. $^1$H NMR spectrum ($CDCl_3$): 7·40 d, 2 H (H-3′, H-5′, $J$ = 9); 7·20—7·40 m, 4 H (H-3, H-4, H-5, H-6); 7·23 d, 2 H (H-2′, H-6′, $J$ = 9), 3·54 s, 2 H ($ArCH_2N$); 2·26 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{16}BrNS$ (332·3) calculated: 55·90% C, 5·00% H, 24·80% Br, 4·35% N, 9·95% S; found: 55·70% C, 5·05% H, 24·98% Br, 4·25% N, 9·79% S.

2-(2-(Dimethylaminomethyl)phenylthio)benzonitrile (*Ij*)

A mixture of bromide *Ig* (8·5 g; 26·6 mmol), CuCN (1·5 g; 16·7 mmol) and hexamethylphosphoric triamide (40 ml) was heated 8 h at 150—155°C. An additional portion of CuCN (1·5 g; 16·7 mmol) was added afterwards and the mixture was again heated at the same temperature. The addition was repeated twice more (total quantity added 6·0 g of CuCN; 67 mmol) during 32 h. The reaction mixture was then cooled down and treated with 15% $NH_4OH$ (50 ml) and toluene (50 ml). After 4 h of stirring the solid moiety was filtered off, the organic layer was

separated and washed with water. Treatment of the toluene solution in the usual manner afforded 5·7 g of oily nitrile *Ij* which was dissolved in ethanol (15 ml) and converted into the hydrogen maleate by the addition of maleic acid (2·5 g) in ethanol (10 ml). Yield 6·0 g (59%), m.p. 118 to 126°C. Analytical sample m.p. 128—130°C (ethanol–ether). Mass spectrum: 268 ($M^+$, $C_{16}H_{16}N_2S$, 23), 267 (11), 253 (18), 224 (14), 222 (13), 165 (20), 132 (24). IR spectrum: 755, 1 030 (4 adjacent Ar-H); 1 193 (CN); 1 434, 1 462 ($CH_3$, $CH_2$); 1 584 (Ar); 2 220 (CN); 2 770, 2 816 (N—$CH_3$); 2 941, 2 972, 3 057 ($CH_3$, $CH_2$). $^1$H NMR spectrum: 7·00—8·00 m, 8 H (Ar); 6·08s, 2 H (CH=CH); 4·40 s, 2 H ($ArCH_2N$); 2·82 s, 6 H ($N(CH_3)_2$). For $C_{20}H_{20}N_2O_4S$ (384·4) calculated: 62·48% C, 5·24% H, 7·29% N, 8·34% S; found: 62·11% C, 5·41% H, 6·98% N, 7·97% S.

4-(2-(Dimethylaminomethyl)phenylthio)benzonitrile (*Il*)

Compound *Il* was prepared from *Ii* (6·5 g; 0·22 mol) and CuCN (3·6 g; 0·04 mol) as described above. The oily nitrile obtained (3·9 g) was converted into the hydrochloride in the usual manner. Yield 3·2 g (60%) of hydrochloride *Il*, m.p. 205—207°C (ethanol–ether). IR spectrum: 761, 823 (4 and 2 adjacent Ar-H); 1 485, 1 590, 3 000, 3 015, 3 040 (Ar); 2 223 (Ar-CN); 2 465, 2 510, 2 564 ($NH^+$). $^1$H NMR spectrum: 8·10 m, 1 H (H-6); 7·80 d, 2 H (H-3′, H-5′, $J$ = 8·5); 7·70 m, 3 H (H-2, H-3, H-4); 7·20 d, 2 H (H-2′, H-6′, $J$ = 8·5); 4·47 bs, 2 H ($ArCH_2N$); 2·74 s, 6 H ($N(CH_3)_2$). For $C_{16}H_{17}ClN_2S$ (304·8) calculated: 63·04% C, 5·62% H, 11·63% Cl, 9·19% N, 10·52% S; found: 62·76% C, 5·55% H, 11·80% Cl, 9·02% N, 10·60% S.

3-(2-Formylphenylthio)benzoic Acid (*VIIm*)

To a solution of 3-mercaptobenzoic acid[18] (23·2 g; 0·15 mol) in N,N-dimethylformamide (80 ml) were added $K_2CO_3$ (55·2 g; 0·4 mol) and then 2-chlorobenzaldehyde (21 g; 1·15 mol). The mixture was stirred 0·5 h at 45°C and then 6 h at 100°C. It was cooled down afterwards and was poured into water (400 ml) and acidified with hydrochloric acid with cooling and stirring. The crystalline product which had separated was filtered off, was washed with water and recrystallized from aqueous ethanol. Yield 36 g (93%), m.p. 150—152°C. UV spectrum: 218 (4·38), 250 infl. (4·06), 330 (3·38). IR spectrum: 710, 750, 812, 826, 850 (4 and 3 adjacent and solitary Ar-H); 880, 1 254, 1 713, 2 625, 3 110 infl. (Ar-COOH); 1 545, 1 590 (Ar); 1 647 (Ar-CHO...HOCOAr). $^1$H NMR spectrum ($CDCl_3$): 10·48 s, 1 H (CHO); 8·50 s, 1 H (COOH); 8·21 dd, 1 H (H-2′, $J$ = 2·0 and 2·3); 7·21 bd, 1 H (H-5′, $J$ = 7); 7·40—8·15 m, 6 H (remaining Ar-H). For $C_{14}H_{10}O_3S$ (258·3) calculated: 65·19% C, 3·90% H, 12·41% S; found: 64·86% C, 3·98% H, 12·20% S.

3-(2-(Dimethylaminomethyl)phenylthio)benzoic Acid (*Im*)

A mixture of aldehyde acid *VIIm* (25·8 g; 0·1 mol), N,N-dimethylformamide (36·6 g; 0·5 mol) and 100% formic acid (23 g; 0·5 mol) was refluxed for 8 h. The reaction mixture was then cooled down and decomposed by being poured into a solution of concentrated hydrochloric acid (30 ml) in water (300 ml). The neutral products were extracted with toluene, the aqueous solution was evaporated under reduced pressure and the dry residue was extracted with hot ethanol (3 × 100 ml). The pooled ethanolic extracts were concentrated to a volume of approximately 50 ml and were cooled down. The crystalline product which had separated was filtered off and washed with ethanol–ether. Yield 24·6 g (86%) of hydrochloride *Im*, m.p. 175—180°C. Analytical sample obtained by recrystallizatim from ethanol–ether, m.p. 186—188°C. Mass spectrum: 287 ($M^+$, $C_{16}H_{18}NO_2S$, 14), 272 (20), 197 (33), 165 (28), 132 (21), 91 (13), 58 (100), 44 (25), 42 (29). $^1$H NMR spectrum: 7·40—8·10 m, 8 H (Ar-H); 4·50 s, 2 H ($ArCH_2N$); 2·76 s, 6 H, ($N(CH_3)_2$). For $C_{16}H_{18}ClNO_2S$ (323·8) calculated: 59·34% C, 5·60% H, 10·95% Cl, 4·32% N, 9·90% S; found: 59·33% C, 5·81% H, 11·74% Cl, 4·28% N, 9·85% S.

3-(2-(Dimethylaminomethyl)phenylthio)benzamide (*In*)

A few drops of N,N-dimethylformamide were added to a suspension of hydrochloride *In* (5·8 g; 0·018 mol) in dichloromethane (50 ml). The reaction mixture was then treated dropwise with a solution of 3·6 g of thionyl chloride (2·2 ml; 0·03 mol) in dichloromethane (20 ml) at 40°C. The mixture was refluxed for 3 h, was then cooled down and added dropwise with stirring to an ammonia solution (1·7 g; 0·1 mol) in dichloromethane (80 ml) at 0—4°C. The mixture was stirred for additional 30 min at the same temperature, was then heated at 40°C and stirred for 30 min more. The mixture was set aside overnight and was then washed with aqueous ammonia (25 ml), dried and evaporated. Yield 4·6 g (92%), m.p. 124—129°C. Analytical sample, m.p. 127—129°C (ethanol–hexane). UV spectrum: 249 infl. (4·03), 274 (3·72). IR spectrum: 690, 747, 769, 850 (4 and 3 adjacent and solitary Ar-H); 1 553, 1 587, 1 608, 3 000 (Ar); 1 647 ($ArCONH_2$); 2 755, 2 783, 2 810 ($N(CH_3)_2$); 3 185, 3 400 ($NH_2$). $^1$H NMR spectrum ($CDCl_3$): 7·73 bs, 1 H (H-2'); 7·65 m, 1 H (H-4'); 7·20—7·60 m, 6 H (remaining Ar-H); 6·12 bs, 2 H ($CONH_2$); 3·58 s, 2 H ($ArCH_2N$); 2·28 s, 6 H ($N(CH_3)_2$). For $C_{16}H_{18}N_2OS$ (286·4) calculated: 67·10% C, 6·33% H, 9·78% N, 11·20% S; found: 66·85% C, 6·57% H, 9·37% N, 11·17% S.

3-(2-(Dimethylaminomethyl)phenylthio)benzonitrile (*Ik*)

A solution of *In* (3·6 g; 12·5 mmol), in N,N-dimethylformamide (40 ml) was treated dropwise at 0°C 15 min with thionyl chloride (1·8 ml; 25 mmol). The mixture was stirred for additional 30 min at the same temperature, then 4 h at room temperature. It was set aside overnight and then it was decomposed by pouring over ice. The reaction mixture was neutralized with solid $Na_2CO_3$ and the product was extracted with dichloromethane. The extracts yielded oily nitrile *Ik* which was converted into its hydrogen maleate. Yield 3·5 g (74%) of hydrogen maleate *Ik*, m.p. 108—112°C. Analytical sample m.p. 117—119°C (ethanol–ether). Mass spectrum: 268, ($M^+$, $C_{16}H_{16}N_2S$, 31), 267 (15), 253 (30), 224 (6), 222 (20), 165 (12), 132 (17), 58 (100). For $C_{20}H_{20}N_2O_4S$ (384·4) calculated: 62·48% C, 5·24% H, 7·29% N, 8·34% S; found: 62·10% C, 5·43% H, 7·32% N, 8·28% S. The base was liberated from the hydrogen maleate. $^1$H NMR spectrum: 7·20—7·60 m, 8 H (Ar-H); 3·56 s, 2 H ($ArCH_2N$); 2·24 s, 6 H ($N(CH_3)_2$).

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## REFERENCES

1. Jílek J., Urban J., Taufmann P., Holubek J., Dlabač A., Valchář M., Protiva M.: Collect. Czech. Chem. Commun. *54*, 1995 (1989).
2. Jílek J., Šindelář K., Pomykáček J., Kmoníček V., Šedivý Z., Hrubantová M., Holubek J., Svátek E., Ryska M., Koruna I., Valchář M., Dlabač A., Metyšová J., Dlohožková N., Protiva M.: Collect. Czech. Chem. Commun. *54*, 3294 (1989).
3. Šindelář K., Pomykáček J., Holubek J., Svátek E., Valchář M., Dobrovský K., Metyšová J., Polívka Z.: Collect. Czech. Chem. Commun. *56*, 459 (1991).
4. Rajšner M., Protiva M.: Collect. Czech. Chem. Commun. *32*, 2021 (1967).
5. Jílek J., Seidlová V., Svátek E., Protiva M.: Monaths. Chem. *96*, 182 (1965).
6. Šindelář K., Holubek J., Ryska M., Svátek E., Urban J., Grimová J., Červená I., Hrubantová M., Protiva M.: Collect. Czech. Chem. Commun. *48*, 1187 (1983).

7. Jílek J., Metyšová J., Pomykáček J., Protiva M.: Collect. Czech. Chem. Commun. *33*, 1831 (1968).
8. Abe K.: J. Pharm. Soc. Jpn. *75*, 153 (1955).
9. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: Collect. Czech. Chem. Commun. *33*, 1852 (1968).
10. Sandoz Ltd.: Belg. 617 251; Chem. Abstr. *58*, 12518 (1963).
11. Jílek J., Pomykáček J.: Cesk. Farm. *14*, 294 (1965).
12. Adrina, L. J., Martin J. C.: J. Org. Chem. *42*, 4006 (1977).
13. Bordwell F. G., Andersen H. M.: J. Am. Chem. Soc. *75*, 6019 (1953).
14. Jílek J., Pomykáček J.: Cesk. Farm. *11*, 451 (1962).
15. Moore M. L.: Org. React. *5*, 301 (1949).
16. Weilmuenster E. A., Jordan C. N.: J. Am. Chem. Soc. *67*, 415 (1945).
17. Šindelář K., Holubek J., Matoušová O., Svátek E., Valchář M., Dlabač A., Dlohožková N., Hrubantová M., Protiva M.: Collect. Czech. Chem. Commun. *53*, 340 (1988).
18. Thurber J. C., Prince A., Halpers O.: J. Heterocycl. Chem. *19*, 961 (1982).

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