SUBSTITUTED N,N-DIMETHYL-3-(PHENYLTHIO)- AND -4-(PHENYLTHIO)BENZYLAMINES

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(Arylthio)benzoic acids *IIa—IIe* and *VIb—VId* were transformed via the acid chlorides to the N,N-dimethylamides which were reduced either with diborane "in situ" or with lithium aluminium hydride to N,N-dimethyl-(arylthio)benzylamines *Ia—Ie* and *Vb—Vd*. Leuckart reaction of the aldehydes *IX* and *X* with dimethylformamide and formic acid afforded directly the amines *Va* and *Ve*. Demethylation of the methoxy compounds *Ia* and *Ve* with hydrobromic acid resulted in the phenolic amines *If* and *Vf*. The most interesting N,N-dimethyl-4-(phenylthio)benzylamine (*Va*) hydrochloride showed affinity to cholinergic and 5-HT_2 serotonin receptors in the rat brain and some properties considered indicative of antidepressant activity (inhibition of serotonin re-uptake in the brain and potentiation of yohimbine toxicity in mice).

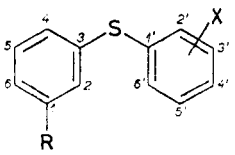
In some previous communications[1-4] series of substituted 2-(phenylthio)benzylamines were described and some of them vere shown to be strong inhibitors of 5-hydroxytryptamine (5-HT) and noradrenaline re-uptake in brain structures. N,N-Dimethyl-2-(3-hydroxyphenylthio)benzylamine (VÚFB - 15 468) (ref.[2]) was selected for preclinical and clinical research as a potential antidepressant[5-8]. The steric structure of molecules of some of these compounds was investigated by the X-ray structure analysis[9,10] and the energetic minima of such molecules in dependence on conformation were calculated[11].

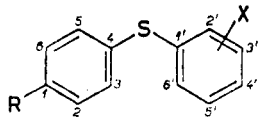
The object of the work described now was to prepare selected 3-(phenylthio)benzylamine and 4-(phenylthio)benzylamine derivatives and to determine the influence of these structural manipulations (positional isomerism) on the biological activity. The interest was concentrated to analogues of the biologically most active 2-(phenylthio)benzylamines : (3-methoxy- and 3-hydroxyphenylthio)benzylamines and (2-, 3- and 4-chlorophenylthio)-benzylamines.

In the synthesis of the new compounds, similar methods like described in the previous papers[1-4], were used. Starting materials in the synthesis of N,N-dimethyl--3-(arylthio)benzylamines *Ia—Ie* were the corresponding 3-(arylthio)benzoic acids *IIa—IIe*. With the exception of *IIa*, which was prepared by a described[12] procedure, these acids were obtained by reactions of 3-iodobenzoic acid with 2-chlorothiophenol, 3-chlorothiophenol, 4-chlorothiophenol, and 3-methoxythiophenol in

boiling solutions of potassium hydroxide in the presence of copper. The acids were transformed by treatment with thionyl chloride in benzene to the acid chlorides *IIIa–IIIe* which were reacted with dimethylamine in benzene and gave the amides *IVa–IVe*. Their reduction either with diborane "in situ" in tetrahydrofuran or with lithium aluminium hydride in ether afforded the final products *Ia–Ie*. Demethylation of *Ie* with boiling hydrobromic acid resulted in the phenolic amine *If*.

The N,N-dimethyl-4-(chlorophenylthio)benzylamines *Vb–Vd* were prepared similarly. The starting materials were the acids *VIb*, *VIc* and *VId* (ref.[13]), obtained by reactions of 4-iodobenzoic acid with chlorothiophenols under similar conditions like in the preceding cases. The transformation of these acids to the final amines proceeded also similarly like in the 3-(arylthio)benzylamine series (treatment with thionyl chloride to give *VIIb–VIId*, their transformation to dimethylamides *VIIIb–VIIId* and finally reduction with diborane to *Vb–Vd*).



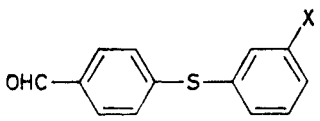


I, R = $CH_2N(CH_3)_2$
II, R = COOH
III, R = COCl
IV, R = $CON(CH_3)_2$

V, R = $CH_2N(CH_3)_2$
VI, R = COOH
VII, R = COCl
VIII, R = $CON(CH_3)_2$

In formulae *I–VIII*: *a*, X = H; *b*, X = 2-Cl; *c*, X = 3-Cl; *d*, X = 4-Cl; *e*, X = 3-OCH_3; *f*, X = 3-OH

The syntheses of N,N-dimethyl-4-(phenylthio)benzylamine (*Va*) and N,N-dimethyl-4-(3-methoxyphenylthio)benzylamine (*Ve*) started from 4-bromobenzaldehyde which was reacted with thiophenol and 3-methoxythiophenol in dimethylformamide in the presence of potassium carbonate at 110°C and gave the aldehydes *IX* (ref.[14]) and *X*. These were processed by Leuckart reaction with dimethylformamide and formic acid at 170°C and thus directly converted to *Va* and *Ve*. N,N-Dimethyl-4-(3-hydroxyphenylthio)benzylamine (*Vf*) was obtained by demethylation of *Ve* with hydrobromic acid.



IX, X = H
X, X = OCH_3

The prepared amines *Ia–If* and *Vb–Vf* were tested in the form of salts described in the Experimental by methods of biochemical and behavioural pharmacology (in the in vivo tests the compounds were administered orally and the doses given were calculated per bases).

Acute toxicity in mice (the compounds were administered in doses of 100 and 500 mg/kg): LD_{50}, *Ia–Ic*, *Va*, *Vc*, *Ve* ,and *Vf* over 100 mg/kg- *Id*, *Ie*, *Vb*, and *Vd* over 500 mg/kg.

Inhibition of the re-uptake of 10 nM [^{3}H] 5-HT in the rat brain: IC_{50} in nmol l^{-1}: *Ic* 123, *Va* 14·3; the other compounds were slightly active or inactive.

Compound *Va* has also significant affinity to cholinergic receptors in the rat brain (inhibition of binding of 0·5 nM [^{3}H] quinuclidinyl benzilate, $IC_{50} = 6{\cdot}7 \cdot 10^{-6}$ mol l^{-1}) and further to 5-HT_2 serotonin receptors (inhibition of binding of 1 nM [^{3}H]ketanserine, IC_{50} = 30·6 nmol l^{-1}).

In tests in vivo in mice the following compounds displayed significant activity in doses of 100 mg/kg: *Ib*, *Id*, *Vd* (potentiation of toxicity of yohimbine) and further *Ia* and *If* (antagonization of the reserpine-induced ptosis).

In conclusion: the substitution of N,N-dimethylbenzylamine with various arylthio groups in position 2 has the most favourable influence on activity in the line of possible antidepressant effects but even substitution in positions 3 and 4 maintains some activity.

EXPERIMENTAL

Melting points were determined in the Mettler FP-5 melting point recorder or in a Kofler block; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm (log ε)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra in NUJOL (ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) with the FT-NMR spectrometer TESLA BS 567A (^{1}H at 100 MHz, ^{13}C at 25·14 MHz), and the mass spectra (*m/z*, %) with a Varian MAT 44S (GC-MS) spectrometer. The homogeneity of the products was checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure (about 3 kPa) on a rotary evaporator.

General Procedure for Preparation of Acids *IIb—IIe*, *VIb*, and *VIc*

Dusty Cu (1·0 g, 15·7 mmol), the corresponding thiophenol (70 mmol) and the corresponding iodobenzoic acid (65 mmol) were added to a solution of KOH (13·0 g, 230 mmol) in water (140 ml) and the mixture was refluxed for 9 h. After cooling to 80–90°C it was filtered and the filtrate was acidified with 5M-HCl. The precipitated product was filtered, washed with water and crystallized from ethanol.

3-(2-*Chlorophenylthio)benzoic acid* (IIb). 3-Iodobenzoic acid (17·2 g) and 2-chlorothiophenol (10·1 g) afforded 13·9 g (76%) of *IIb*, m.p. 197–199°C. For $C_{13}H_9ClO_2S$ (264·7) calculated: 58·98% C, 3·43% H, 13·39% Cl, 12·11% S; found: 59·27% C, 3·33% H, 13·25% Cl, 11·90% S.

3-(3-*Chlorophenylthio)benzoic acid* (IIc). 3-Iodobenzoic acid (17·2 g) and 3-chlorothiophenol (10·1 g) gave 13·0 g (71%) of *IIc*, m.p. 109—109·5°C. UV spectrum: infl. 215 (4·44), 250 (4·04), 275 (3·74). IR spectrum: 721, 749, 779, 868, 896 (ArH): 1 265, 1 316, 1 679, 2 553, 2 660 (COOH); 1 557, 1 570, 1 589, 3 060 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 7·95 m, 2 H (H-2, H-6); 7·20—7·70 m, 6 H (remaining ArH). ^{13}C NMR spectrum (CD_3SOCD_3): 166·50 s (CO); 137·07 s (C-3); 135·5 d (C-4); 134·45 s (C-1′); 134·08 s (C-3′); 132·36 s (C-1); 131·70 d, 129·07 d, 127·58 d (C-2′, C-4′, C;6′); 131·31 d (C-5′); 130·12 d (C-5); 129·60 d, 128·85 d (C-2, C-6). For $C_{13}H_9ClO_2S$ (264·7) calculated: 58·98% C, 3·43% H, 13·39% Cl, 12·11% S; found: 58·82% C, 3·42% H, 13·28% Cl, 11·91% S.

3-(4-*Chlorophenylthio)benzoic acid* (IId). 3-Iodobenzoic acid (17·2 g) and 4-chlorothiophenol (10·1 g) gave 14·2 g (78%) of *IId*, m.p. 177—178°C. UV spectrum: 223 (4·33), 253 (4·09), 276 (3·87). IR spectrum: 700, 716, 740, 826, 986 (ArH); 1 269, 1 290, 1 300, 1 678, 2 540, 2 640 (COOH); 1 569, 1 590, 3 040, 3 060 (Ar). ^{13}C NMR spectrum (CD_3SOCD_3): 166·57 s (CO); 135·50 s (C-3); 134·60 d (C-4); 132·96 s and d (C-1′, C-3′, C-4′, C-5′); 132·21 s (C-1); 130·79 d, 128·33 d (C-2, C-6); 129·97 d (C-5); 129·75 d (C-2′, C-6′). For $C_{13}H_9ClO_2S$ (264·7) calculated: 58·98% C, 3·43% H, 13·39% Cl, 12·11% S; found: 58·34% C, 3·34% H, 13·42% Cl, 11·74% S.

3-(3-*Methoxyphenylthio)benzoic acid* (IIe). 3-Iodobenzoic acid (17.2 g) and 3-methoxythiophenol (9·8 g) afforded 14·0 g (73%) of *IIe*, m.p. 94—96°C. ^{1}H NMR spectrum: 11·05 bs, 1 H (COOH); 8·10 bs, 1 H (H-6, J = 7·5); 7·35 m, 3 H (H-4, H-5, H-5′); 6·92 m, 3 H (H-2′, H-4′, H-6′); 3·80 s, 3 H (OCH_3). For $C_{14}H_{12}O_3S$ (260·3) calculated: 64·60% C, 4·65% H, 12·32% S; found: 64·80% C, 4·88% H, 12·08% S.

4-(2-*Chlorophenylthio)benzoic acid* (VIb), 4-Iodobenzoic acid (17·2 g) and 2-chlorothiophenol (10·1 g) gave 15·6 g (86%) of *VIb*, m.p. 152·5—155°C. ^{1}H NMR spectrum (CD_3SOCD_3): 7·95 d, 2 H (H-2, H-6; J = 8·5); 7·34 d, 2 H (H-3, H-5; J = 8·5); 7·40—7·80 m, 4 H (remaining ArH). For $C_{13}H_9ClO_2S$ (264·7) calculated: 13·39% Cl, 12·11% S; found: 13·42% Cl, 11·74% S.

4-(3-*Chlorophenylthio)benzoic acid* (VIc). 4-Iodobenzoic acid (17·2 g) and 3-chlorothiophenol (10·1 g) gave 12·7 g (69%) of *VIc*, m.p. 177—178°C. ^{1}H NMR spectrum (CD_3SOCD_3): 7·95 d, 2 H (H-2, H-6; J = 8·5); 7·50 m, 4 H (H-2′, H-4′, H-5′, H-6′); 7·38 d, 2 H (H-3, H-5; J = 8·5). ^{13}C NMR spectrum (CD_3SOCD_3): 166·72 s (CO); 140·80 s (C-4); 135·26 s (C-1′); 134·15 s (C-3′); 131·46 d (C-5′); 131·24 d, 128·40 d (C-2′, C-4′, C-6′); 130·42 d (C-2, C-6); 129·37 s (C-1); 129·15 d (C-3, C-5). For $C_{13}H_9ClO_2S$ (264·7) calculated: 58·98% C, 3·43% H, 13·39% Cl, 12·11% S; found: 58·60% C, 3·42% H, 13·34% Cl, 11·81% S.

General Procedure for Preparation of the Acid Chlorides *IIIb* and *VIIb—VIId*

A stirred mixture of the acid (50 mmol), benzene (100 ml) and dimethylformamide (2 drops) was treated dropwise with $SOCl_2$ (19·6 g, 165 mmol) and refluxed for 2 h. Volatile components were evaporated in vacuo and the residue was crystallized from a mixture of cyclohexane and light petroleum.

3-(2-*Chlorophenylthio)benzoyl chloride* (IIIb). The acid *IIb* (13·2 g) was converted to *IIIb* (10·5 g, 74%), m.p. 57—58°C. IR spectrum: 684, 709, 742, 800, 887 (ArH); 1 578, 3 055, 3 080 (Ar); 1 756 (ArCOCl). For $C_{13}H_8Cl_2OS$ (283.2) calculated: 55·14% C, 2·85% H, 25·04% Cl, 11·32% S; found: 54·92% C, 2·84% H, 24·91% Cl, 11·29% S.

4-(2-*Chlorophenylthio)benzoyl chloride* (VIIb). The acid *VIb* (13·2 g) was transformed to *VIIb* (10·8 g, 76%), m.p. 81—81·5°C. For $C_{13}H_8Cl_2OS$ (283·2) calculated: 55·14% C, 2·85% H, 25·04% Cl, 11·32% S; found: 54·98% C, 2·90% H, 25·07% Cl, 11·44% S.

4-(3-*Chlorophenylthio)benzoyl chloride* (VIIc). The acid *VIc* (13·2 g) was transformed to *VIIc* (11·8 g, 84%), m.p. 40—41°C. For $C_{13}H_8Cl_2OS$ (283·2) calculated: 55·14% C, 2·85% H, 25·04% Cl, 11·32% S; found: 55·13% C, 2·89% H, 24·78% Cl, 11·25% S.

4-(4-*Chlorophenylthio)benzoyl chloride* (VIId). The acid *VId* (ref.[13]) was transformed to *VIId* (11·4 g, 81%), m.p. 56—57°C. For $C_{13}H_8Cl_2OS$ (283·2) calculated: 55·14% C, 2·85% H, 25·04% Cl, 11·32% S; found: 55·15% C, 2·87% H, 24·88% Cl, 11·48% S.

N,N-Dimethyl-3-(2-chlorophenylthio-)benzamide (*IVb*)

A solution of *IIIb* (8·3 g, 29 mmol) in benzene (65 ml) was treated at 7°C with gaseous dimethylamine (3·9 g, 87 mmol), the mixture was stirred for 2h, washed with water, dried, and evaporated. The residue (8·55 g, 100%) was further used without purification . For analysis, a sample was crystallized from benzene, m.p. 68—70°C. UV spectrum: 246 (4·10), 276 (3·70). IR spectrum: 688, 740, 760, 814, 896 (ArH); 1 500, 1 560, 3 018, 3 040, 3 072 (Ar); 1 603 ($ArCONR_2$). ^{1}H NMR spectrum: 7·10—7·50 m, 8 H (ArH); 3·00 s, 6 H ($N(CH_3)_2$). ^{13}C NMR spectrum: 170·60 s (CO); 137·96 s (C-3); 135·05 s (C-1'); 133·18 s (C-1); 132·81 d (C-4); 132·14 d, 130·27 d, 130·12 d, 127·43 d (C-3', C-4', C-5', C-6'); 129·52 d (C-2); 128·33 d, 126·53 d (C-2, C-6); 38·09 g ($N(CH_3)_2$). For $C_{15}H_{14}ClNOS$ (291·8) calculated: 4·80% N, 10·99% S; found: 4·49% N, 10·98% S.

N,N-Dimethyl-4-(4-chlorophenylthio)benzamide (*VIId*)

A similar procedure starting form *VIId* (5·4 g, 19 mmol) afforded 5·5 g (99%) of *VIId*, m. p. 107—107·5°C (cyclohexane). UV spectrum: infl. 219 (4·27), 257 (4·18), infl. 278 (4·04). IR spectrum: 819, 840, 846 (ArH); 1 500, 1 590, 3 000, 3 040, 3 060 (Ar); 1 627 ($ArCONR_2$). ^{1}H NMR spectrum: 7·37 s, 8 H (ArH); 3·06 s, 6 H ($N(CH_3)_2$). ^{13}C NMR spectrum: 170·90 s (CO); 138·11 s (C-4); 134·83 s (C-1) 134·00 s (C-1'); 133·33 d (C-3', C-5'); 132·96 s (C-4'); 129·75 d (C-2, C-6); 129·60 d (C-2', C-6'); 128·10 d (C-3, C-5); 39·77 q ($N(CH_3)_2$). 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: 61·65% C, 4·76% H, 12·22% Cl, 4·41% N, 11·10% S.

N,N-Dimethyl-3-(4-chlorophenylthio)benzamide (*IVd*)

A stirred mixture of *IId* (13·85 g, 52 mmol), benzene (110 ml) and dimethylformamide (2 drops) was treated dropwise with $SOCl_2$ (20·3 g, 170 mmol) and it was refluxed for 2 h. The volatile components were evaporated in vacuo, the residue was dissolved in benzene (110 ml) and at 7°C gaseous dimethylamine (7·0 g, 155 mmol) was introduced, the mixture was stirred for 2h, washed with water, dried, and evaporated; 14·8 g (98%) of *IVd*, m.p. 102·5—104°C (ethanol). UV spectrum: 252 (4·15), 277 (3·85). IR spectrum: 700, 770, 800, 825, 883 (ArH); 1 475, 1 500, 1 560, 1 590, 3 000, 3 018, 3 025, 3 060 (Ar); 1 622 ($ArCONR_2$). 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: 62·12% C, 4·85% H, 12·39% Cl, 5·27% N, 11·15% S.

N,N-Dimethyl-3-(3-methoxyphenylthio)benzamide (*IVe*)

A similar procedure starting from *IIe* (9·3 g, 36 mmol) gave 10·0 g (98%) of oily *IVe* which was further used without purification. ^{1}H NMR spectrum: 7·05 m, 8 H (ArH); 3·86 s, 3 H (OCH_3); 3·06 bs and 2·94 bs, 2 × 3 H ($N(CH_3)_2$).

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

A stirred solution of the amide (30 mmol) in tetrahydrofuran (60 ml) under nitrogen was treated with $NaBH_4$ (2·5 g, 66 mmol) and then at 20–27°C with $BF_3 . O(C_2H_5)_2$ (8·5 g, 60 mmol), added dropwise. The mixture was stirred for 1 h at room temperature and then refluxed for 3 h. After cooling it was decomposed with 5M-HCl (25 ml), refluxed for further 3 h, cooled, made alkaline with 20% NaOH (50 ml), and extracted with benzene. The extract was dried and evaporated, the residue was dissolved in ethanol (10 ml), the solution was neutralized with an ethanolic solution of HCl and diluted with ether. The hydrocyhloride of the product crystallized and was recrystallized from a mixture of ethanol and ether.

N,N-*Dimethyl*-3-(2-*chlorophenylthio*)*benzylamine* (Ib). The amide *IVb* gave 5·8 g (62%) of *Ib*. HCl, m.p. 173–174°C. IR spectrum: 709, 755, 786, 971 (ArH); 1 559, 1 570, 3 000, 3 015, 3 060 (Ar); 2 395, 2 433, 2 460, 2 498, 2 545 (NH^+). ^1H NMR spectrum (CD_3SOCD_3): 7·00–7·80 m, 8 H (ArH); 4·32 s, 2 H (CH_2); 2·69 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314·3) calculated: 57·32% C, 5·45% H, 22·57% Cl, 4·46% N, 10·20% S; found: 57·25% C, 5·39% H, 22·53% Cl, 4·27% N, 10·41% S.

N,N-*Dimethyl*-3-(4-*chlorophenylthio*)*benzylamine* (Id). The amide *IVd* afforded 4·7 g (50%) of *Id*. HCl, m.p. 151–152°C. IR spectrum: 690, 790, 810, 902 (ArH); 1 555, 1 570, 1 590, 3 005, 3 060 (Ar); 2 400, 2 465, 2 500, 2 550 (NH^+). ^1H NMR spectrum (CD_3SOCD_3): 7·30–7·70 m: 8 H (ArH); 4·28 s, 2 H (CH_2); 2·68 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314·3) calculated. 57·32% C, 5·45% H, 22·57% Cl, 4·46% N, 10·20% S; found: 57·35% C, 5·47% H, 22·74% Cl, 4·10% H, 10·38% S.

N,N-*Dimethyl*-3-(3-*methoxyphenylthio*)*benzylamine* (Ie). The amide *IVe* (8·6 g) gave 5·7 g (61%) of *Ie*. HCl, m.p. 129–131°C. IR spectrum: 685, 703, 776, 781, 860, 880, 900 ArH); 1 033, 1 246 ($ArOCH_3$): 1 477, 1 583, 3 010, 3 030, 3 050 (Ar); 2 475, 2 510, 2 550 (NH^+). ^1H NMR spectrum: 6·80–7·80 m, 8 H (ArH); 4·16 bs, 2 H (CH_2); 3·80 s, 3 H (OCH_3); 2·76 bs, 6 H ($N(CH_3)_2$). For $C_{16}H_{20}ClNOS$ (309·9) calculated: 62·02% C, 6·51% H, 4·52% N, 10·35% S; found: 61·65% C, 6·62% H, 4·69% N, 10·12% S.

N,N-*Dimethyl*-4-(4-*chlorophenylthio*)*benzylamine* (Vd). The amide *VIIId* (8·7 g) gave 7·05 g (75%) of *Vd*. HCl, m.p. 222–224°C. UV spectrum: infl. 220 (4·21), 256 (4·19), infl. 277 (3·93). IR spectrum: 821 (ArH); 1 569, 1 597, 3 010, 3 028, 3 059, 3 090 (Ar); 2 380, 2 468, 2 518, 2 550 (NH^+). ^1H NMR spectrum (CD_3SOCD_3): 7·62 d and 7·38 d (ABq); 2 and 2 H (4 ArH, J = = 8·5); 7·53 and d 7·42 d (ABq), 2 and 2 H (4 ArH, H = 8·5); 4·28 s, 2 H (CH_2); 2·70 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314·3) calculated: 57·32% C, 5·45% H, 22·57% Cl, 4·46% N, 10·20% S; found: 56·93 %C, 5·42% H, 22·68% Cl, 4·11% N, 10·31% S.

N,N-Dimethyl-3-(phenylthio)benzylamine (*Ia*)

A stirred mixture of *IIa* (ref.[12]) (11·5 g, 50 mmol), toluene (100 ml) and dimethylformamide (2 drops) was treated dropwise with $SOCl_2$ (11·9 g, 100 mmol) and then refluxed for 3 h. The volatile components were evaporated in vacuo, the residue was dissolved in toluene (50 ml) and the solution was dropped at 5°C to the stirred 10% aqueous dimethylamine (70 g, 155 mmol). It was stirred for 2 h at 40°C, the toluene layer was separated, dried and toluene was evaporated. The residue (11·3 g) was dissolved in ether (50 ml) and the solution was dropped to a stirred solution of $LiAlH_4$ (4·0 g, 106 mmol) in ether (100 ml). The mixture was refluxed for 10 h, decomposed with 20% NaOH (30 ml), the precipitated solid was filtered off and washed with ether. The filtrate was dried, evaporated, and the residue was distilled in vacuo, 5·5 g (45%)

of *Ia*, b.p. 152–154°C/0·25 kPa. ^{1}H NMR spectrum: 7·25 m, 9 H (ArH); 3·35 s 2 H (CH_2); 2·18 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}NS$ (243·4) calculated: 74·02% C, 7·04% H, 5·75% N, 13·18% S; found: 73·92% C, 7·26% H, 5·79% N, 13·18% S. The base was converted to the hydrochloride, m.p. 161–163°C (ethanol–ether). For $C_{15}H_{18}ClNS$ (279·6) calculated: 64·38% C, 6·48%H, 12·67% Cl, 5·00% N, 11·46% S; found: 64·11% C, 6·59% H, 12·75% Cl, 4·92% N, 11·54% S.

N,N-Dimethyl-3-(3-chlorophenylthio)benzylamine (*Ic*)

A stirred mixture of *IIc* (12·7 g, 48 mmol), benzene (100 ml) and dimethylformamide (2 drops) was treated dropwise with $SOCl_2$ (18·6 g, 156 mmol) and it was refluxed for 2 h. The volatile components were evaporated, the residue was dissolved in benzene (100 ml) and at 7°C gaseous dimethylamine (5·9 g, 131 mmol) was introduced into the stirred solution. The mixture was stirred for 2 h, washed with water and dried. The residue (11·7 g) was dissolved in tetrahydrofuran (75 ml) and under nitrogen the stirred solution was treated first with $NaBH_4$ (3·2 g, 85 mmol) and then at 20–27°C with $BF_3 . O(C_2H_5)_2$ (11·2 g, 79 mmol), added dropwise. The mixture was stirred for 1 h at room temperature and then refluxed for 3 h. After cooling it was decomposed with 5M HCl (30 ml), refluxed for 3 h, cooled, made alkaline with 20% NaOH (70 ml), and extracted with benzene. The exctrat was dried, evaporated, the residue was dissolved in ethanol (15 ml), the solution was neutralized with an ethanolic solution of HCl, and diluted with ether. Crystallization gave 8·8 g (58%) of *Ic*. HCl, m.p. 171–172°C (ethanol–ether). UV spectrum: 252 (4·12), infl. 277 (3·83). IR spectrum: 741, 800, 855 (ArH); 1 559, 1 570, 3 020, 3 040, 3 068 (Ar); 2 385, 2 470, 2 500, 2 555 (NH^+). ^{1}H NMR spectrum (CD_3SOCD_3): 7·10–7·80 m, 8 H (ArH); 4·12 s, 2 H (CH_2); 2·71 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314·3) calculated: 57·32% C, 5·54% H, 22·57% Cl, 4·46% N, 10·20% S; found: 57·44% C, 5·48% H, 22·37% Cl, 4·20% N, 10·38% S.

N,N-Dimethyl-4-(2-chlorophenylthio)benzylamine (*Vb*)

Gaseous dimethylamine (5·9 g, 131 mmol) was introduced at 7°C into a stirred solution of the acid chloride *VIIb* (12·1 g, 43 mmol) in benzene (100 ml). The mixture was stirred for 2 h, washed with water, dried, and evaporated. The residue was dissolved in tetrahydrofuran (85 ml) and the stirred solution under nitrogen was treated first with $NaBH_4$ (3·5 g, 93 mmol) and then dropwise at 20–27°C with $BF_3 . O(C_2H_5)_2$ (12·3 g, 87 mmol). The reaction mixture was stirred for 1 h at room temperature and then refluxed for 3 h. After cooling it was decomposed with 5M HCl (35 ml) and the mixture was refluxed for another 3 h. After cooling it was made alkaline with 20% NaOH (80 ml) and extracted with benzene. The extract was dried and evaporated, the residue was dissolved in ethanol (15 ml), the solution was neutralized with ethanolic HCl and diluted with ether; 10·5 g (78%) of *Vb*. HCl, m.p. 204–206°C (ethanol–ether). IR spectrum: 725, 743, 803, 856 (ArH); 1 480, 1 559, 1 570, 3 020, 3 048, 3 065 (Ar); 2 470, 2 500, 2 555 (NH^+). ^{1}H NMR spectrum: 7·20–7·80 m, 8 H (ArH); 4·42 s, 2 H (CH_2); 2·72 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314·3) calculated: 57·32% C, 5·45% H, 22·57% Cl, 4·46% N, 10·20% S; found: 56·99% C, 5·47% H, 22·65% Cl, 4·20% N, 10·16% S.

N,N-Dimethyl-4-(3-chlorophenylthio)benzylamine (*Vc*)

A similar procedure starting from *VIIc* (11·0 g, 39 mmol) gave 10·4 g (83%) of *Vc*. HCl, m.p. 184–186°C (ethanol–ether). IR spectrum: 681, 789, 880, 889 (ArH); 1 480, 1 490, 1 573, 1 598, 3 000, 3 018, 3 050, 3 070 (Ar); 2 380, 2 470, 2 510, 2 555 (NH^+). ^{1}H NMR spectrum: 7·20–7·70 m, 8 H (ArH); 4·08 d and 4·32 d (ABq), 1 and 1 H ($ArCH_2N$, $J = 13·0$); 2·76 s and 2·82 s, 3

and 3 H ($NCH_3)_2$). For $C_{15}H_{17}Cl_2NS$ (314.3) calculated: 57·32 %C, 5·54% H, 22·57% Cl, 4·46% N, 10·20% S; found: 57·40% C, 5·42% H, 22·31% Cl, 4·20% N, 10·30% S.

4-(Phenylthio)benzaldehyde (*IX*)

A stirred mixture of 4-bromobenzaldehyde (18·5 g, 100 mmol), thiophenol (11·0 g, 100 mmol), K_2CO_3 (14·5 g, 105 mmol) and dimethylformamide (60 ml) was heated under nitrogen for 6 h to 110°C. It was poured into water (300 ml) and extracted with 1,2-dichloroethane. The extract was dried and evaporated, the residue was dissolved in ether (100 ml) and the solution was shaken for 1 h with a solution of $K_2S_2O_5$ (40 g, 180 mmol) in water (100 ml). The precipitated addition product was filtered, suspended in 20% H_2SO_4 (100 ml) and the mixture was shaken until the complete transformation of the solid into oily material. It was then extracted with 1,2-dichloroethane, the extract was dried and evaporated, 20·4 g (95%) of *IX*, m.p. 54°C. Ref.[14], m.p. 53–54°C (different synthetic method).

4-(3-Methoxyphenylthio)benzaldehyde (*X*)

A similar procedure starting from 4-bromobenzaldehyde (17·5 g, 95 mmol) and 3-methoxythiophenol (13·4 g, 96 mmol) resulted in 19·4 g (84%) of *X*, m.p. 64–66°C (ethanol–hexane). UV spectrum: 309 (4·21). IR spectrum: 685, 694, 782, 815, 836, 854 (ArH); 1 035, 1 214, 1 250 ($ArOCH_3$); 1 480, 1 555, 1 574, 1 590, 3 010, 3 060 (Ar); 1 691, 2 740 (ArCHO); 2 830, 2 850 ($ArOCH_3$). ^{1}H NMR spectrum: 9·94 s, 1 H (CHO); 7·73 d, 2 H (H-2, H-6; J = 9·0); 7·28 d, 2 H (H-3, H-5; J = 9·0); 6·90–7·40 m, 4 H (H-2′, H-4′, H-5′, H-6′); 3·82 s, 3 H (OCH_3). For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·82% C, 4·95% H, 13·13% S; found: 69·11% C, 5·17% H, 13·07% S.

N,N-Dimethyl-4-(phenylthio)benzylamine (*Va*)

A mixture of *IX* (18·3 g, 85 mmol), dimethylformamide (40·6 g, 556 mmol) and formic acid (19·6 g, 426 mmol) was refluxed for 8 h, poured into 1M-HCl (400 ml), the solution formed was made alkaline with 20% NaOH and extracted with 1,2-dichloroethane. The extract was dried and evaporated, the residue was distilled in vacuo; 15·9 g (76%) of *Va*, b.p. 140–142°C/0·15 kPa ^{1}H NMR spectrum: 7·30 m, 9 H (ArH); 3·40 s, 2 H (CH_2); 2·25 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{17}NS$ (243·4) calculated: 74·03% C, 7·04% H, 5·76% N, 13·18% S; found: 74·07% C, 7·23% H, 5·62% N, 13·17% S. The base was transformed to the hydrochloride melting at 203–205°C (ethanol–ether). For $C_{15}H_{18}ClNS$ (279·8) calculated: 64·38% C, 6·48% H, 12·67% Cl, 5·00% N, 11·46% S; found: 64·34% C, 6·69% H, 12·78% Cl, 4·81% N, 11·60% S.

N,N-Dimethyl-4-(3-methoxyphenylthio)benzylamine (*Ve*)

A similar procedure starting from *X* (17·0 g, 70 mmol) gave 13·2 g (69%) of *Ve*, b.p. 180–182°C/0·25 kPa. ^{1}H NMR spectrum: 7·37 d, 2 H (H-2, H-6; J = 8·5); 7·25 d, 2 H (H-3, H-5; J = 8·5); 7·20 bt, 1 H (H-5′); 6·70–6·90 m, 3 H (H-2′, H-4′, H-6′); 3·74 s, 3 H (OCH_3); 2·25 s, 6 H ($N(CH_3)_2$). For $C_{16}H_{19}NOS$ (273·4) calculated: 70·29% C, 7·00% H, 5·12% N, 11·73% C; found: 69·98% C, 7·25% H, 5·11% N, 11·61% S. The base was transformed to the hydrochloride, m.p. 157–159°C (ethanol–ether). For $C_{16}H_{20}ClNOS$ (309·9) calculated: 62·02% C, 6·51% H, 11·44% Cl, 4·52% N, 10·35% S; found: 61·79% C, 6·62% H, 11·32% Cl, 4·32% N, 10·39% S.

N,N-Dimethyl-3-(3-hydroxyphenylthio)benzylamine (*If*)

A solution of *Ie* (8·3 g, 30 mmol) in 48% HBr (60 g, 330 mmol) was refluxed for 3 h, poured into water (150 ml), made alkaline with 20% NaOH to pH 9, and extracted with 1,2-dichloroethane. The extract was dried and evaporated, the residue was dissolved in ethanol (20 ml), the solution was neutralized with ethanolic HCl and diluted with ether. Crystallization gave 6·2 g (69%) of *If*. HCl m.p. 168—170°C (ethanol–ether). Mass spectrum: 259 (M^+, $C_{15}H_{17}NOS$, 40), 216 (42), 200 (7), 122 (15), 91 (25), 58 (100). IR spectrum: 700, 786, 882 (ArH); 1 210 (ArOH); 1 571, 1 593, 3 015 (Ar); 2 680 (NH^+); 3 205 (OH). ^{1}H NMR spectrum (CD_3SOCD_3): 6·70—8·70 m, 8 H (ArH); 4·26 s, 2 H (CH_2); 2·68 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{18}ClNOS$ (295·8) calculated: 60·90% C, 6·13% H, 11·99% Cl, 4·73% N, 10·84% S; found 60·76% C, 6·19% H, 12·06% Cl, 4·56% N, 10·99% S.

N,N-Dimethyl-4-(3-hydroxyphenylthio)benzylamine (*Vf*)

Similar demethylation of *Ve* (16·3 g, 60 mmol) gave *Vf* which was transformed to the hydrochloride (11·2 g, 64 %), m.p. 128—130°C (ethanol–ether). Mass spectrum: 259 (M^+, $C_{15}H_{17}NOS$, 63), 215 (100), 200 (4), 183 (6), 134 (12), 91 (8), 58 (68). IR spectrum: 690, 784, 805, 870, 890 (ArH); 1 222 (ArOH); 1 527, 1 594, 3 000, 3 020 (Ar); 2 468, 2 575, 2 650 (NH^+); 3 100 (OH). ^{1}H NMR spectrum (CD_3SOCD_3): 7·60 d, 2 H (H-3, H;5- J = 8·5); 7·30 d, 2 H (H-2, H-6; J = 8·5); 7·18 bt, 1 H (H-5′); 6·80 m, 3 H (H-2′, H-4′, H;6′); 4·24 s, 2 H (CH_2); 2·67 s, 6 H ($N(CH_3)_2$). For $C_{15}H_{18}ClNOS$ (295·8) calculated: 60·90% C, 6·13% H, 11·99% Cl, 4·73% N, 10·84% S; found: 60·88% C, 6·28% H, 11·95% Cl, 4·70% N, 10·76% S.

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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. Kmoníček V., Pomykáček J., Holubek J., Svátek E., Valchář M., Metyšová J., Polívka Z.: Collect. Czech. Chem. Commun. *56*, (1991).
5. Valchář M., Dobrovský K., Dlohožková N., Dlabač A.: Activ. Nerv. Super. *32*, 224, 227 (1990).
6. Metyšová J., Tynková J.: Activ. Nerv. Super. *32*, 222 (1990).
7. Lapka R., Šmolík S., Brejcha A.: Activ. Nerv. Super. *32*, 225 (1990); Cesk. Farm. *39*, 258 (1990).
8. Poláková L., Ryska M., Koruna I., Metyšová J., Lapka R., Šišpera K., Svátek E., Šindelář K.: Activ. Nerv. Super. *32*, 228 (1990); Cesk. Farm. *39*, 254 (1990).
9. Schneider B., Hašek J., Ječný J.: Collect. Czech. Chem. Commun. *55*, 1529 (1990).

10. Schneider B., Hašek J., Ječný J.: Acta Crystalogr., C *47*, 232 (1991).
11. Schneider B., Rejholec V., Kuchař V.: Collect. Czech. Chem. Commun. *55*, 2590 (1990).
12. Ponec R., Procházka M.: Collect. Czech. Chem. Commun. *39*, 2088 (1974).
13. Leandri G., Maioli L., Ruzzier L.: Boll. Sci. Fac. Chim. Ind. Bologna *15*(3), 57 (1957); Chem. Abstr. *52*, 7291 (1958).
14. Szmant H. H., Segedi M. J., Dudek J.: J. Org. Chem. *18*, 754 (1953).

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