POTENTIAL ANTIDEPRESSANTS AND SELECTIVE INHIBITORS OF 5-HYDROXYTRYPTAMINE RE-UPTAKE IN THE BRAIN: SYNTHESIS OF SEVERAL POTENTIAL METABOLITES OF MOXIFETIN AND OF TWO A-RING FLUORINATED ANALOGUES

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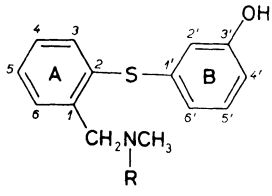
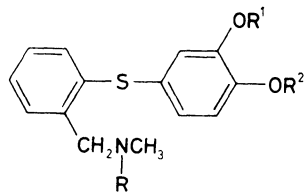
A series of potential metabolites of the potent inhibitor of 5-hydroxytryptamine re-uptake in the brain structures — moxifetin (*I*) — i.e. the O-methylated and hydroxylated, further methoxylated, and N-monodemethylated analogues (*III*—*VII*, *IX*, and *X*) was synthesized from the acids *XV*, *XIX*, *XXIIIa*, *XXIIIb*, *XXVIIa*, and *XXVIIb*. The synthesis of *III* and *V* proceeded with protection of one hydroxyl group by benzyl and by the final debenzylation by short heating with hydrobromic acid. Compound *IV* was obtained by partial demethylation of N,N-dimethyl-(3,4-dimethoxyphenylthio)benzylamine with sodium 4-toluenethiolate. Synthesis of *VI*, *VII*, *IX*, and *X* proceeded without protection of the hydroxyl group via the mixed anhydrides of the mentioned acids and methanesulfonic acid which were coupled with dimethylamine and the dimethylamides obtained were directly reduced to the final products. Two A-ring fluorinated analogues of *I*, i.e. *VIII* and *XI* were prepared from the acids *XXIIIc* and *XXVIIc* via acid chlorides, dimethylamides, and amines *XXVIc* and *XXXc*. The final step was demethylation by heating with hydrobromic acid. The N-oxide *XII* was obtained by oxidation of *I* with hydrogen peroxide in ethanol. Compounds *III* (VÚFB-18285) and especially *XI* (VÚFB-17724) were found to be selective inhibitors of the 5-hydroxytryptamine re-uptake in the brain. Some compounds (*IV*, *VI*, *VII*, *X*) indicate a similar type of activity. In addition to *II* (described previously), compounds *IV* and *V* were found to be moxifetin metabolites in the animals.

In previous communications[1,2] our team tried to find new potential antidepressants in series of 2-(arylthio)aralkylamines and in N,N-dimethyl-2-(3-hydroxyphenylthio)-benzylamine (*I*, hydrogen maleate VÚFB-15468, moxifetin), a compound was found which is an extremely potent inhibitor of 5-hydroxytryptamine re-uptake in the brain structures having at the same time the typical antireserpine activity[3-6]. The preferred conformation of the molecule of *I* was determined by the X-ray structure analysis[7] and the agent is undergoing the usual stages of preclinical testing[8-10]. The preliminary metabolic study of moxifetin (*I*) in rats and dogs[10] using mass spectrometry for identification of the separated metabolites[11] indicated the following metabolic pathways in the biotransformation of *I*: (i) N-monodemethylation (compound *II* (cf. ref.[3])) was identified as a metabolite); (ii) hydroxylation in the side

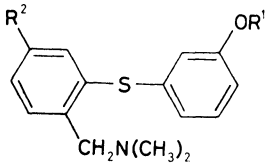
chain to the N-(hydroxymethyl)analogue was indicated as a metabolic process; (iii) hydroxylation combined with O-methylation in undetermined positions of the rings A and B (compound *IV* was identified as a metabolite by comparison with the authentic synthetic sample described in the present paper); (iv) hydroxylation combined with O-methylation and S-oxidation (position of the oxygen functions unknown). The object of the present paper is to describe the synthesis of seven hydroxy--methoxy derivatives *III*–*VII*, *IX*, and *X* as potential metabolites, of two A-ring fluorinated analogues *VIII* and *XI*, compounds with partial blockade against the metabolic hydroxylation, and finally of the N-oxide *XII*.



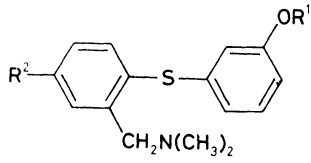
I, R = CH_3
II, R = H



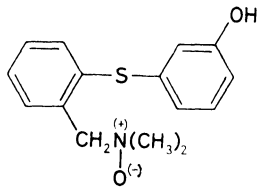
III, R = R^2 = CH_3 ; R^1 = H
IV, R = R^1 = CH_3 ; R^2 = H
V, R = R^2 = H ; R^1 = CH_3



VI, R^1 = H ; R^2 = OCH_3
VII, R^1 = CH_3 ; R^2 = OH
VIII, R^1 = H ; R^2 = F



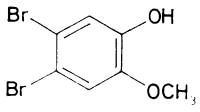
IX, R^1 = H ; R^2 = OCH_3
X, R^1 = CH_3 ; R^2 = OH
XI, R^1 = H ; R^2 = F



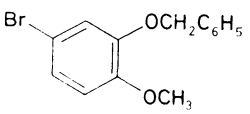
XII

The first to be described is the synthesis of the B-ring hydroxy-methoxy compounds *III*–*V*. The synthesis of *III* started from 1-bromo-3-hydroxy-4-methoxy-

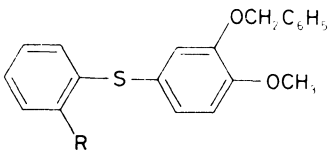
benzene[12] which was obtained by bromination of guaiacol carbonate and by the following alkaline hydrolysis[12]. Treatment of guaiacol acetate[13] with bromine in chloroform at room temperature resulted in a very inhomogeneous oily product whose alkaline hydrolysis gave the crystalline 1,2-dibromo-4-hydroxy-5-methoxybenzene (*XIII*); its structure was definitely established by spectra. The literature[12] mentioned a "dibromoguaiacol" with unclear position of the bromine atoms which is evidently identical with our product. 1-Bromo-3-hydroxy-4-methoxybenzene was transformed to *XIV* by the procedure described[14]. Its reaction with thiosalicylic acid in boiling dimethylformamide in the presence of potassium carbonate and copper gave the acid *XV* in moderate yield. Treatment with thionyl chloride in boiling benzene effected the conversion to the acid chloride *XVI* which was fully characterized and was further transformed to the dimethylamide *XVII*. This was reduced with diborane, generated from sodium borohydride and boron trifluoride etherate in boiling tetrahydrofuran. The amine *XVIII* was obtained and was debenzylated to *III* by refluxing with 48% hydrobromic acid for 3 min. The crystalline base *III* was characterized by spectra and was transformed to the crystalline hydrogen maleate. The same compound was obtained in a very low yield from *XVIII* by treatment with butylmagnesium bromide in a mixture of ether and tetrahydrofuran followed by cobaltous chloride and by refluxing the mixture (for the method, cf. ref.[15]).



XIII



XIV

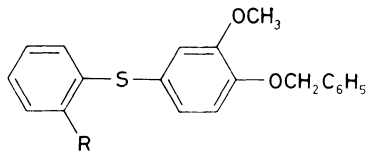


XV, R = COOH
XVI, R = COCl
XVII, R = $CON(CH_3)_2$
XVIII, R = $CH_2N(CH_3)_2$

In a recent paper[16] we described an unexpected selective mono-demethylation during reduction of the nitrile, containing a 1,4-dimethoxybenzene residue, with aluminium hydride (prepared from lithium aluminium hydride and aluminium chloride in ether). We tried to explain this reaction by the presence of some unreacted

aluminium chloride in the reagent. For obtaining *IV* we subjected now the known N,N-dimethyl-2-(3,4-dimethoxyphenylthio)benzamide[3] to treatment with a similar aluminium hydride reagent in a boiling mixture of ether and tetrahydrofuran. No demethylation took place and chromatography of the crude product separated the known N,N-dimethyl-2-(3,4-dimethoxyphenylthio)benzylamine which was transformed to the crystalline hydrochloride[3]. Its melting point was distinctly lower than that of the substance which was prepared by us previously[3] and for this reason, it was fully characterized (analysis and spectra); its identity was confirmed. It was then found that the base of this compound is demethylated by heating with sodium 4-toluenethiolate in toluene with a limited amount of hexamethylphosphoric triamide (for the method, cf. ref.[17]). The crude product was a mixture of two major components (evidently *IV* and *III*). Chromatography on aluminium oxide separated the less polar component and crystallization of the more polar one (elution with ethanol) from ether gave the crystalline base *IV* in a low yield. Its difference from *III* was clear and the identity was corroborated by spectra. It also was transformed to the hydrogen maleate.

The synthesis of the secondary amine *V* started from the known 2-benzyloxy-5--bromoanisole[18] which was reacted with thiosalicylic acid similarly like in the synthesis of *III*. The isomeric acid *XIX* was obtained and transformed to the acid chloride *XX*. This also was crystalline and was fully characterized. Its reaction in benzene with an aqueous solution of methylamine under vigorous stirring gave the crystalline methylamide *XXI*. Reduction with diborane "in situ" gave the oily *XXII* which was transformed to the crystalline hydrochloride and this was characterized by spectra. The final debenzylation with hydrobromic acid was similar like in the preparation of *III*. A mixture of bases was obtained which was separated by chromatography. The more polar fractions afforded a hydrogen oxalate which was identified as the salt of the desired *V*.

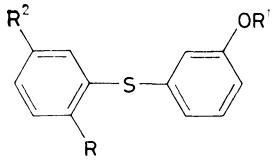


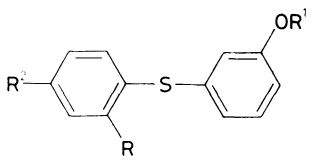
XIX, R = COOH
XX, R = COCl
XXI, R = $CONHCH_3$
XXII, R = CH_2NHCH_3

The synthesis of *VI* started from the reaction of 2-iodo-4-methoxybenzoic acid[19] with 3-hydroxythiophenol[20], carried out by refluxing in an aqueous solution of potassium hydroxide in the presence of copper. Processing gave 56% of the desired

hydroxy acid *XXIIIa*. Methanesulfonyl chloride reacted with *XXIIIa* in pyridine under formation of the corresponding mixed anhydride (cf. ref.[21]) which was subjected "in situ" to treatment with dimethylamine. The inhomogeneous product was separated by chromatography. The less polar fractions contained the methanesulfonic ester of *XXVa*; the more polar product was *XXVa*. Both of these amides were oily and were characterized only by the ^{1}H NMR spectra. Both amides were reduced with lithium aluminium hydride in ether or tetrahydrofuran and gave the same *VI*, isolated as hydrogen maleate and characterized by spectra in this form.

The synthesis of *VII*, *IX* and *X* proceeded similarly without protection of the free hydroxyl group. 4-Hydroxy-2-iodobenzoic acid[22] was reacted with 3-methoxythiophenol[23] in boiling aqueous potassium hydroxide in the presence of copper and the obtained *XXIIIb* was transfomed via the mixed anhydride with methanesulfonic acid to the dimethylamide *XXVb*. This compound crystallized after chromatography and in crude state contained probably also the corresponding methanesulfonic ester. It was reduced to *VII* with lithium aluminium hydride. The base *VII* was crystalline, its spectra were recorded and it was transformed to the crystalline hydrochloride. 2-Bromo-5-methoxybenzoic acid[24] reacted similarly like in the preceding cases with 3-hydroxythiophenol[20] and the obtained *XXVIIa* was transformed to *IX* via *XXIXa*. The crystalline *XXIXa* was reduced to *IX* which gave a hydrogen maleate. The synthesis of *X* started from 2-bromo-5-hydroxybenzoic acid[25] which reacted with the sodium salt of 3-methoxythiophenol[23] in boiling dimethylformamide in the presence of copper. The acid *XXVIIb* was transformed to *X* via the crude *XXIXb*. The final *X* was crystalline, the spectra were recorded and it was transformed to the hydrochloride.





XXIII, R = COOH
XXIV, R = COCl
XXV, R = $CON(CH_3)_2$
XXVI, R = $CH_2N(CH_3)_2$

XXVII, R = COOH
XXVIII, R = COCl
XXIX, R = $CON(CH_3)_2$
XXX, R = $CH_2N(CH_3)_2$

In formulae *XXIII*–*XXX*: *a*, R^1 = H ; R^2 = OCH_3 *b*, R^1 = CH_3 ; R^2 = OH
c, R^1 = CH_3 ; R^2 = F

The synthesis of the A-ring fluorinated analogues *VIII* and *XI* proceeded via the methoxy compounds *XXVIc* and *XXXc*. Reaction of 4-fluoro-2-iodobenzoic acid[26] with 3-methoxythiophenol[23] gave *XXIIIc* which was transformed to *XXVc* via the

acid chloride *XXIVc*. Reduction of *XXVc* with diborane "in situ" afforded *XXVIc* which was characterized in the form of hydrochloride. Demethylation to *VIII* was carried out by heating with 46% hydrobromic acid to 120°C. The base *VIII* was crystalline, its spectra recorded and it afforded a crystalline hydrogen maleate. The synthesis of *XI* started by reaction of 5-fluoro-2-iodobenzoic acid[26] and proceeded similarly via *XXVIIc*–*XXXc*. The characterization of *XI* was similar like with *VIII*.

In addition to the sulfoxide, sulfone, and sulfone N-oxide derived from moxifetin[3], the N-oxide (*XII*) has now been prepared in a low yield by oxidation of *I* with hydrogen peroxide in ethanol at room temperature and by separation of the mixture formed by chromatography and crystallization. Its IR spectrum shows bands at 970 and 990 cm^{-1}, corresponding to the N-oxide.

Compounds *III*, *IV*, *V*–*X*, *XI*, *XXVIc*, and *XXXc* were pharmacologically tested in the form of salts, described in the Experimental. A series of tests which used the methods of biochemical pharmacology were applied (the compounds were used in concentration of 1 000 nmol l^{-1}). The animal tests used oral administration and the doses given were calculated per bases.

Inhibition of binding of 5 nM [^3H]imipramine in the rat brain cortex: IC_{50} values in nmol l^{-1} are given: *III*, 15·1, *IV*, 97; *XI*, 80·1; *XXXc*, 4 882.

Inhibition of re-uptake of 10 nM [^3H]5-hydroxytryptamine in synaptosomes of the rat brain: *III* and *IV* showed significant inhibition; IC_{50} values (in nM) were determined with the following compounds: *V*, 137; *VI*, 115; *VII*, 36·8; *IX*, 13·0; *X*, 10·4; *XI*, 4·84; *VIII*, *XXVIc*, and *XXXc* were practically inactive.

Inhibition of re-uptake of 10 nM [^3H]noradrenaline in the rat brain cortex: *VIII* and *XXVIc* were inactive; the following compounds were active (IC_{50} in nM given); *V*, 18·5; *VI*, 21; *VII*, 89; *IX*, 0·94; *X*, 270; *XI*, 491; *XXXc* had some activity.

Affinity to $GABA_A$-ergic receptors in homogenates of the rat brain (inhibition of binding of 5 nM [^3H]muscimol): *III*, *IV*, *VI*, and *XXXc* were inactive; *VIII* and *XXVIc* showed some activity.

Affinity to α_2-adrenergic receptors in membranes of the rat brain (inhibition of binding of 1 nM [^3H]clonidine): *III*, *IV*, *VI*, and *XXXc* were inactive; *VIII*, *XI*, and *XXVIc* showed significant activity.

Acute toxicity in mice: *VIII*, *XI*, and *XXVIc* were not toxic at 100 mg/kg, doses of 500 mg/kg were lethal for 100% of the animals; *XXXc* at 500 mg/kg was lethal for 70% of the animals.

Ataxic activity (rotarod test in mice): *VIII*, *XI*, and *XXVIc* at 50 and 100 mg/kg were inactive.

Antireserpine activity in the test of ptosis in mice; doses in mg/kg are given which significantly antagonized the ptosis: *VIII*, 100; *XI*, 30; *XXVIc*, 100; *XXXc*, 30.

Antireserpine activity in the test of reserpine-induced gastric ulcers in rats: *XI* in the dose of 100 mg/kg significantly inhibited the formation of the ulcers.

Potentiation of yohimbine toxicity in mice: *VIII* in the dose of 50 mg/kg potentiated in 50% of the animals; *XI* was inactive at 100 mg/kg.

In conclusion: Compounds *III* (VÚFB-18285) and especially *XI* (VÚFB-17724) are selective inhibitors of the 5-hydroxytryptamine re-uptake in the brain structures and potential antidepressants. Compounds *IV*, *VI*, *VII*, and *X* indicate the activity in the same line. It seems that fluorination in position 4 blocks a site of metabolic introduction of an oxygen function (hydroxy or methoxy); the 4-fluoro compound (*VIII*) is inactive whereas the 4-hydroxy and 4-methoxy compounds (*VI*, *VII*) are active. The 5-fluoro compound (*XI*), which leaves the critical position 4 free, is very active.

EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder; 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 8000 spectrophotometer, IR spectra (mostly in NUJOL, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, NMR spectra (in CD_3SOCD_3 unless stated otherwise, δ in ppm, J in Hz) with the FT-NMR spectrometer TESLA BS 567A (^1H 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 and compositions 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.

1,2-Dibromo-4-hydroxy-5-methoxybenzene (*XIII*)

A stirred solution of 122 g guaiacol acetate[13] in 265 ml chloroform was treated over 7 h with 117 g Br in 210 ml chloroform at room temperature. After standing overnight the mixture was washed with 5% NaOH and water, dried, and distilled. There were obtained 115·4 g of a lower-boiling fraction (b.p. 115–118°C/1·5 kPa) and 54 g of the fraction boiling at 165–172°C/1·5 kPa. The higher boiling fraction was dissolved in 180 ml ethanol, a solution of 90 g NaOH in 90 ml water was added and the mixture was refluxed for 30 min. Ethanol was distilled off, the residue was diluted with 225 ml water, the mixture was acidified with 170 ml hydrochloric acid, and the product was extracted with ether. Processing of the extract and repeated crystallization of the residue from mixtures of benzene and light petroleum gave 11·45 g (6%) of *XIII*, m.p. 90·5–93°C. IR spectrum: 861 (solitary Ar–H); 1 199, 1 248, 1 260 ($ArOCH_3$, ArOH); 1 487, 1 570, 1 598 (Ar); 3 350 (OH). ^1H NMR spctrum ($CDCl_3$): 3·88 s, 3 H (OCH_3); 5·58 s, 1 H (OH); 7·07 s, 1 H (H-3); 7·18 s, 1 H (H-6). For $C_7H_6Br_2O_2$ (282·0) calculated: 29·82% C, 2·14% H, 56·69% Br; found: 30·10% C, 2·20% H, 56·79% Br. Ref.[12] gave the m.p. of 95°C for a product of uncertain structure (3,4(or 4,5)-dibromoguaiacol) which is probably identical with our substance.

2-(3-Benzyloxy-4-methoxyphenylthio)benzoic Acid (*XV*)

A mixture of 21·6 g thiosalicylic acid, 41·1 g *XIV* (ref.[14]), 42 g K_2CO_3, 2 g Cu, and 200 ml dimethylformamide was stirred and refluxed for 6·5 h. It was poured into 1 l water and the precipitated recovered bromo compound was filtered off, washed with water, and dried (15 g, m.p.

100—105°C). The filtrate was acidified with hydrochloric acid, the product was filtered, washed with water, and dried; 9·05 g (28% per conversion) of *XV* which was purified by crystallization from ethanol, m.p. 179—182°C. Mass spectrum: 366 (M^+, $C_{21}H_{18}O_4S$, 5), 348 (0·1), 333 (0·2), 315 (0·5), 275 (2), 213 (8), 187 (2), 139 (3), 137 (5), 115 (3), 111 (8), 91 (100), 65 (9). IR spectrum (KBr): 699, 747, 809, 900 (5, 4 and 2 adjacent and solitary Ar–H); 907, 1 250, 1 673, 2 555, 2 635, infl. 3 100 (ArCOOH); 1 500, 1 558, 1 580 (Ar). For $C_{21}H_{18}O_4S$(366·4) calculated: 68·83%C, 4·95% H, 8·75% S; found: 68·80% C, 4·96% H, 8·83% S.

2-(4-Benzyloxy-3-methoxyphenylthio)benzoic Acid (*XIX*)

Similar reaction of 14·2 g thiosalicylic acid, 27·0 g 2-benzyloxy-5-bromoanisole[18], and 35 g K_2CO_3 in 150 ml dimethylformamide in the presence of 1·5 g Cu (refluxing for 13 h) gave 13·6 g (40%) of *XIX*, m.p. 168—169°C (ethanol). UV spectrum: infl. 222 (4·47), infl. 250 (4·13), 280 (3·90); 313 (3·71). IR spectrum: 698, 732, 749, 807, 847, 852 (5, 4 and 2 adjacent and solitary Ar–H), 920, 1 263, 1 313, 1 687, 2 520, 2 555, infl. 3 050 (ArCOOH); 1 021, 1 131, 1 220, 1 245 (ArOR); 1 499, 1 559, 1 579, 3 030, 3 050 (Ar). ^{1}H NMR spectrum: 3·76 s, 3 H (OCH_3); 5·16 s, 2 H (OCH_2Ar); 6·75 m, 1 H (H-3); 7·00—7·60 m, 10 H (remaining ArH with the exception of H-6); 7·92 m, 1 H (H-6). ^{13}C NMR spectrum: 55·72 q (OCH_2), 69·99 t (OCH_3); 114·36 d (C-5′); 118·84 d (C-2′); 122·58 s (C-1′); 124·22 d (C-6′); 126·09 d (C-3); 126·76 s (C-1); 127·95 d (C-4 of benzyl); 127·95 d (C-2 and C-6 of benzyl); 128·48 d (C-3 and C-5 of benzyl); 128·70 d (C-5); 130·94 d (C-6); 132·44 d (C-4); 136·77 s (C-1 of benzyl); 143·12 s (C-2); 149·17 s (C-4′); 149·99 s (C-3′); 167·39 s (COOH). For $C_{21}H_{18}O_4S$ (366·4) calculated: 68·83% C, 4·95% H, 8·74% S; found: 68·65% C, 5·07% H, 8·73% S.

2-(3-Hydroxyphenylthio)-4-methoxybenzoic Acid (*XXIIIa*)

3-Hydroxythiophenol[20] (8·4 g) was dissolved in a solution of 13·8 g KOH in 140 ml water at 50°C, the solution was treated with 14·0 g 2-iodo-4-methoxybenzoic acid[19] and 5 g Cu and the stirred mixture was refluxed for 7·5 h. It was diluted with 100 ml water and filtered with 5 g active carbon while warm. The filtrate was acidified with hydrochloric acid under stirring and cooling. After 1 h standing the precipitated product was filtered and crystallized from aqueous ethanol; 7·78 g (56%) of *XXIIIa*, m.p. 213—215°C. UV spectrum: 236 (4·51), infl. 259 (4·11), infl. 273 (3·91), infl. 307 (3·64). IR spectrum: 691, 772, 819, 854, 874, 890 (3 and 2 adjacent and solitary Ar–H); 1 025, 1 269 ($ArOCH_3$); 1 269 (ArOH); 1 230, 1 683, 2 508, 2 565, 2 650, infl. 3 100 (ArCOOH); 1 547, 1 580, 1 590, 3 060(Ar); 3 485 (OH). ^{1}H NMR spectrum: 3·65 s, 3 H (OCH_3); 6·90—7·40 m, 6 H (ArH with the exception of H-3); 6·28 bs, 1 H (H-3). For $C_{14}H_{12}O_4S$ (276·3) calculated: 60·86% C, 4·38% H, 11·60% S; found: 60·40% C, 4·38% H, 11·44% S.

4-Hydroxy-2-(3-methoxyphenylthio)benzoic Acid (*XXIIIb*)

3-Methoxythiophenol[23] (5·05 g) was added to a warm solution of 10 g KOH in 150 ml water and after 10 min stirring at 50—60°C it was followed by 3·5 g Cu and 7·8 g 4-hydroxy-2-iodobenzoic acid[22]. The mixture was stirred and refluxed for 8 h and processed similarly like in the preceding case; 7·25 g (85%) of *XXIIIb*, m.p. 202—205°C (aqueous ethanol). UV spectrum: 235 (4·38), infl. 261 (3·98), infl. 288 (3·76), infl. 303 (3·55). IR spectrum: 681, 770, 849, 852, 909 (3 and 2 adjacent and solitary Ar–H); 883, 1 676, 2 530, 2 640, 3 050(ArCOOH); 1 019, 1 221 ($ArOCH_3$); 1 229, 1 270, 1 302 (ArOH and ArCOOH); 1 477, 1 583 (Ar); 3 320 (OH). ^{1}H NMR spectrum: 3·80 s, 3 H (OCH_3); 7·82 d, 1 H (H-6, J = 9·0); 7·00—7·40 m, 4 H (4 ArH of methoxyphenyl); 6·55 dd, 1 H (H-5, J = 9·0; 2·0); 6·16 d, 1 H (H-3, J = 2·0). ^{13}C NMR spectrum:

55·35 q (OCH_3); 111·89 d (C-5); 12·87 d (C-3); 115·48 d (C-2′); 117·50 s (C-1), 120·63 d (C-4′); 127·80 d (C-6′); 131·02 d (C-5′); 133·18 s (C-1′); 133·41 d (C-6); 145·13 s (C-2); 160·22 s (C-3′); 161·12 s (C-4); 167·09 s (COOH). For $C_{14}H_{12}O_4S$ (276·3) calculated: 60·86% C, 4·38% H, 11·60% S; found: 60·47% C, 4·47% H, 11·41% S.

2-(3-Hydroxyphenylthio)-5-methoxybenzoic Acid (*XXVIIa*)

A stirred mixture of 140 ml dimethylformamide, 12·0 g 2-bromo-4-methoxybenzoic acid[24], 8·2 g 3-hydroxythiophenol[20], and 3 g Cu was heated to 80—100°C and slowly treated with 23 g K_2CO_3. It was then refluxed for 10 h. Dimethylformamide was evaporated in vacuo and the residue was diluted with 250 ml water. The mixture was filtered and the filtrate was acidified with hydrochloric acid. The separated oily product was extracted with benzene, the extract was processed and the residue was chromatographed on 120 g silica gel. The product was eluted with chloroform and with chloroform containing 5% of ethanol. The crude product was dissolved in dilute NH_4OH, the solution was filtered with active carbon and the filtrate was acidified with 3M-HCl. The separated oil was isolated by decantation and it crystallized after the addition of water. Recrystallization from ethanol gave 8·15 g (57%) of *XXVIIa*, m.p. 140°C. UV spectrum: infl. 220 (4·40), 251 (3·99), 283 (3·80), 333 (3·44). IR spectrum: 696, 780, 820, 866, 895 (3 and 2 adjacent and solitary Ar–H); 880, 1 698, infl. 2 660, 3 200 (ArCOOH); 1 020, 1 200, 1 300 ($ArOCH_3$); 1 184, 1 220, 1 274 (ArOH and ArCOOH); 3 425 (OH). ^{1}H NMR spectrum: 3·78 s, 3 H (OCH_3); 6·70—7·30 m, 6 H (ArH with the exception of H-6); 7·37 d, 1 H (H-6, $J = 2·0$). ^{13}C NMR spectrum: 55·50 q (CH_3O); 114·96 d (C-6); 115·33 d (C-4′); 118·69 d (C-4); 119·14 d (C-2′); 123·17 d (C-6′); 129·00 s (C-2); 130·57 d (C-5′); 131·54 d (C-3); 132·21 s (C-1); 135·50 s (C-1′); 157·46 s (C-3′); 158·28 s (C-5); 167·54 s (COOH). For $C_{14}H_{12}O_4S$ (276·3) calculated: 60·85% C, 4·38% H, 11·61% S; found: 60·86% C, 4·41% H, 11·69% S.

5-Hydroxy-2-(3-methoxyphenylthio)benzoic Acid (*XXVIIb*)

A mixture of 45 ml dimethylformamide, 4·15 g K_2CO_3, 1·42 g 3-methoxythiophenol[23], 0·8 g Cu, and 2·0 g 2-bromo-5-hydroxybenzoic acid[25] was stirred and refluxed for 15 h. Similar processing like in the preceding cases gave 0·75 g (30%) of crude *XXVIIb* which was purified by chromatography on silica gel and crystallization from toluene, m.p. 158—160°C. UV spectrum: infl. 250 (4·01), 282 (3·79), 336 (3·50). IR spectrum (KBr): 685, 770, 781, 820, 858, 878 (3 and 2 adjacent and solitary Ar–H); 928, 1 685, 2 530, 2 610 (ArCOOH); 1 029, 1 041, 1 213, 1 230, 1 264 ($ArOCH_3$, ArOH); 1 472, 1 575, 1 584 (Ar); 3 392 (OH). ^{1}H NMR spectrum: 3·74 s, 3 H (OCH_3); 6·80—7·40 m, 7 H (ArH). ^{13}C NMR spectrum: 55·13 q (OCH_3); 113·16 d (C-6); 116·52 d (C-4); 116·82 d (C-4′); 119·59 d (C-2′); 123·70 d (C-6′); 125·26 s (C-2); 130·42 d (C-5′); 132·66 d (C-3); 133·33 s (C-1); 136·84 s (C-1′); 156·19 s (C-5); 159·85 s (C-3′); 167·69 s (COOH). For $C_{14}H_{12}O_4S$ (276·3) calculated 60·86% C, 4·38% H, 11·60% S; found: 61·09% C, 4·52% H, 11·46% S.

4-Fluoro-2-(3-methoxyphenylthio)benzoic Acid (*XXIIIc*)

A solution of 10·6 g KOH in 115 ml water was treated at 50°C with 8·06 g 3-methoxythiophenol[23], after 10 min stirring with 0·9 g Cu and 15·0 g 4-fluoro-2-iodobenzoic acid[26] and the mixture was stirred and refluxed for 9 h. It was filtered while hot, the solid was washed with 25 ml hot water, and the filtrate was acidified with dilute hydrochloric acid (1 : 1). After cooling and 2 h standing the product was filtered and crystallized from 80 ml 80% aqueous ethanol; 14·15 g (90%) of *XXIIIc*, m.p. 177—179°C. UV spectrum: 254 (3·96), infl. 278 (3·82), infl. 286 (3·78),

infl. 302 (3·63). IR spectrum: 690, 774, 790, 860, 890 (3 and 2 adjacent and solitary Ar–H); 925, 1 237, 1 259, 1 270, 1 672, 2 510, 2 530, 2 563, 2 650, infl. 3 100 (ArCOOH); 1 057, 1 211 ($ArOCH_3$); 1 473, 1 567, 1 590, 3 000, 3 055, 3 075 (Ar). ^1H NMR spectrum: 3·80 s, 3 H (OCH_3); 6·38 dd, 1 H (H-3, $J_{H-H} = 2·5$; $J_{H-F} = 10·0$); 6·95—7·60 m, 5 H (H-5 and 4 ArH of methoxyphenyl); 8·05 dd, 1 H (H-6, $J_{H-H} = 9·0$; $J_{H-F} = 6·0$); For $C_{14}H_{11}FO_3S$ (278·3) calculated: 60·42% C, 3·98% H, 6·83% F, 11·52% S; found: 60·72% C, 4·13% H, 7·00% F, 11·59% S.

5-Fluoro-2-(3-methoxyphenylthio)benzoic Acid (*XXVIIc*)

This compound was prepared similarly by reaction of 8·06 g 3-methoxythiophenol[23] with 15·0 g 5-fluoro-2-iodobenzoic acid[26] and 10·6 g KOH in 115 ml water in the presence of 0·9 g Cu; 14·9 g (95%), m.p. 159·5—161°C (ethanol). UV spectrum: 250 (3·76), 280 (3·58), 324 (3·53). IR spectrum: 695, 769, 781, 814, 865, 872, 893 (3 and 2 adjacent and solitary Ar–H); 936, 1 682, 2 555, 2 585, 2 615, 2 725, infl. 3 140 (COOH); 1 040, 1 230, 1 252, 1 269, 1 283 ($ArOCH_3$, COOH); 1 570, 1 590, 3 010, 3 065 (Ar). ^1H NMR spectrum: 3·80 s, 3 H (OCH_3); 6·80—7·80 m, 7 H (ArH). For $C_{14}H_{11}FO_3S$ (278·3) calculated: 60·42% C, 3·98% H, 6·83% F, 11·52% S; found: 60·57% C, 4·09% H, 6·89% F, 11·59% S.

2-(3-Benzyloxy-4-methoxyphenylthio)benzoyl Chloride (*XVI*)

A mixture of 9·15 g *XV*, 100 ml benzene, and 10 ml $SOCl_2$ was refluxed for 3 h. It was filtered, the filtrate was evaporated and the residue was crystallized from cyclohexane, 9·0 g (94%) of *XVI*, m.p. 70—72·5°C. IR spectrum: 691, 723, 769 (Ar–H); 1 087, 1 133, 1 228, 1 253 ($ArOCH_3$); 1 500, 1 550, 1 582, 3 023, 3 062, 3 080 (Ar); 1 720, 1 753 (ArCOCl). ^1H NMR spectrum: 3·84 s, 3 H (OCH_3); 5·10 s, 2 H (OCH_2Ar); 6 65 bd, 1 H (H-3); 7·00—7·50 m, 10 H (remaining ArH with the exception of H-6); 7·92 bd, 1 H (H-6). ^{13}C NMR spectrum: 55·72 q (OCH_2); 70·06 t (OCH_3); 113·24 d (C-5′); 120·63 d (C-2′); 122·05 s (C-1′); 124·14 d (C-6′); 124·44 d (C-3); 126·09 d (C-4 of benzyl); 126·61 s (C-1); 127·88 d (C-2 and C-6 of benzyl); 128·48 d (C-3 and C-5 of benzyl); 129·30 d (C-5); 130·94 d (C-6); 132·44 d (C-4); 136·84 s (C-1 of benzyl); 143·49 s (C-2); 143·57 s (C-3′); 150·66 s (C-4′); 167·32 s (COCl). For $C_{21}H_{17}ClO_3S$ (384·9) calculated: 65·53% C, 4·45% H, 9·21% Cl, 8·33% S; found: 65·44% C, 4·42% H, 9·43% Cl, 8·51% S.

2-(4-Benzyloxy-3-methoxyphenylthio)benzoyl Chloride (*XX*)

Compound *XX* was prepared similarly from 13·5 g *XIX* and 14 ml $SOCl_2$ in 100 ml benzene; 13·6 g (96%), m.p. 110—111·5°C (cyclohexane). UV spectrum: infl. 224 (4·47), infl. 252 (4·12), infl. 278 (3·89), infl. 284 (3·86), 317 (3·73). IR spectrum: 691, 745, 800, 766 (5, 4 and 2 adjacent and solitary Ar–H); 1 000, 1 031, 1 129, 1 137, 1 190, 1 220, 1 249 ($ArOCH_3$); 1 499, 1 550, 3 030, 3 055, 3 080 (Ar); 1 712, 1 745 (COCl). ^1H NMR spectrum: 3·76 s, 3 H (OCH_3); 5·16 s, 2 H (OCH_2Ar); 6·72 bd, 1 H (H-5′); 7·00—7·50 m, 10 H (remaining ArH with the exception of H-6); 7·92 bd, 1 H (H-6). For $C_{21}H_{17}ClO_3S$ (384·9) calculated: 65·43% C, 4·45% H, 9·21% Cl, 8·33% S; found: 65·29% C, 4·50% H, 9·35% Cl, 8·29% S.

4-Fluoro-2-(3-methoxyphenylthio)benzoyl Chloride (*XXIVc*)

This compound was prepared similarly by reaction of 14·0 g *XXIIIc* and 19·3 g $SOCl_2$ in 100 ml benzene; 12·78 g (86%), m.p. 78—79°C (cyclohexane). UV spectrum: 244 (3·98), infl. 268 (3·85), infl. 276 (3·80), infl. 293 (3·70). IR spectrum: 691, 789, 819, 861, 881 (3 and 2 adjacent and solitary Ar–H); 1 037, 1 193, 1 218, 1 259 ($ArOCH_3$); 1 481, 1 561, 1 591, 3 000, 3 060, 3 070, 3 090 (Ar);

1 731, 1 757 (ArCOCl). ^{1}H NMR spectrum ($CDCl_3$): 3·84 s, 3 H (OCH_3); 6·52 dd, 1 H (H-3, J = 10·0; 3·0); 6·80—7·50 m, 5 H (remaining ArH with the exception of H-6); 8·38 dd, 1 H (H-6, J = 8·0; 6·0). For $C_{14}H_{10}ClFO_2S$ (296·7) calculated: 56·66% C, 3·40% H, 11·95% Cl, 6·40% F, 10·80% S; found: 56·39% C, 3·54% H, 11·55% Cl, 6·58% F, 10·65% S.

5-Fluoro-2-(3-methoxyphenylthio)benzoyl Chloride (*XXVIIIc*)

Compound *XXVIIIc* was prepared similarly from 14·75 g *XXVIIc* and 20·3 g $SOCl_2$ in 110 ml benzene; 15·1 g (96%), m.p. 72—73·5°C (cyclohexane). For $C_{14}H_{10}ClFO_2S$ (296·7) calculated: 56·66% C, 3·40% H, 11·95% Cl, 6·40% F, 10·80% S; found: 56·68% C, 3·48% H, 12·05% Cl, 6·48% F, 10·66% S.

N,N-Dimethyl-2-(3-benzyloxy-4-methoxyphenylthio)benzamide (*XVII*)

A solution of 9·5 g *XVI* in 50 ml benzene was slowly added to 25 ml 50% aqueous dimethylamine under vigorous stirring. The stirring was continued for 2 h, the benzene layer was separated, washed with water, dried with K_2CO_3, filtered, and evaporated. The residue was crystallized from a mixture of benzene and cyclohexane; 8·65 g (89%) of *XVII*, m.p. 104—105°C. UV spectrum: 247 (4·11), infl. 275 (3·91). IR spectrum: 699, 750, 770, 810, 830, 899 (5, 4 and 2 adjacent and solitary Ar–H); 1 003, 1 025, 1 131, 1 220, 1 247 ($ArOCH_3$); 1 499, 1 579, 3 000, 3 010, 3 045, 3 065, 3 095 (Ar); 1 630 ($ArCONR_2$). ^{1}H NMR spectrum ($CDCl_3$): 2·87 s and 3·12 s, 3 and 3 H ($N(CH_3)_2$); 3·88 s, 3 H (OCH_3); 5·09 s, 2 H (OCH_2Ar); 6·80—7·40 m, 12 H (ArH). ^{13}C NMR spectrum ($CDCl_3$): 34·58 q and 38·20 q ($N(CH_3)_2$); 56·02 q (OCH_3); 70·96 t (OCH_2); 112·27 d (C-5′); 119·59 d (C-2′); 123·62 s (C-1′); 126·24 d (C-6′); 126·61 d (C-5); 127·36 d (C-3); 127·36 d (C-2 and C-6 in benzyl); 127·88 d (C-4 in benzyl); 128·48 d (C-3 and C-5 in benzyl); 129·22 d (C-6); 129·52 d (C-4); 135·05 s and 136·54 s (C-1 and C-2); 136·84 s (C-1 in benzyl); 148·42 s (C-4′); 150·29 s (C-3′); 169·78 s (CON). For $C_{23}H_{23}NO_3S$ (393·5) calculated: 70·20% C, 5·89% H, 3·56% N, 8·15% S; found: 70·23% C, 5·89% H, 3·10% N, 8·05% S.

N-Methyl-2-(4-benzyloxy-3-methoxyphenylthio)benzamide (*XXI*)

A similar reaction of 13·4 g *XX* in 100 ml benzene with 50 ml 40% aqueous methylamine gave 11·0 g (83%) of *XXI*, m.p. 153·5—154·5°C (benzene). UV spectrum: infl. 247 (4·44), 279 (4·24). IR spectrum: 700, 749, 807, 851, 861 (5, 4 and 2 adjacent and solitary Ar–H); 994, 1 029, 1 131, 1 231, 1 250 ($ArOCH_3$); 1 500, 1 581, 3 020, 3 040, 3 065 (Ar); 1 549, 1 629 (ArCONHR); 3 275 (NH). ^{1}H NMR spectrum ($CDCl_3$): 3·82 s, 3 H (OCH_3); 5·16 s, 2 H (OCH_2Ar); 6·25 bs, 1 H (CONH); 6·80—7·60 m, 12 H (ArH). ^{13}C NMR spectrum ($CDCl_3$): 26·59 q ($NHCH_3$); 56·02 q (OCH_3); 70·89 t (OCH_2); 114·43 d (C-5′); 117·50 d (C-2′); 124·29 s (C-1′); 125·49 d (C-6′); 125·95 d (C-4 of benzyl); 127·28 d (C-2 and C-6 of benzyl); 128·55 d (C-3 and C-5 of benzyl); 127·28 d, 128·18 d, and 128·92 d (C-3, C-5, and C-6); 130·42 d (C-4); 134·53 s (C-1); 136·62 s (C-2); 137·59 s (C-1 of benzyl); 148·87 s (C-4′); 150·21 s (C-3′); 168·66 s (CON). For $C_{22}H_{21}NO_3S$ (379·5) calculated: 69·63% C, 5·58% H, 3·69% N, 8·45% S; found: 69·54% C, 5·69% H, 3·60% N, 8·78% S.

N,N-Dimethyl-4-hydroxy-2-(3-methoxyphenylthio)benzamide (*XXVb*)

A solution of 7·25 g *XXIIIb* in 60 ml pyridine was stirred and treated under external cooling (ice and water) with 6·0 g methanesulfonyl chloride over 30 min. The temperature of the mixture was kept at 5—8°C. The cooling was continued and gaseous dimethylamine (11·8 g) was introduced over 1 h. The mixture was stirred for 4·5 h at room temperature, allowed to stand overnight, poured into 200 ml water, and the solution formed was extracted with benzene. Processing

of the extract gave 6·6 g (83%) of crude *XXVb* which was contaminated by a less polar component (TLC), probably the corresponding methanesulfonic ester. A sample of the crude product was chromatographed on silica gel. A fraction, obtained by elution with chloroform containing 7% of ethanol, crystallized; m.p. 109—110°C (benzene). ^{1}H NMR spectrum ($CDCl_3$): 2·80 s and 3·04 s, 3 and 3 H ($CON(CH_3)_2$); 3·70 s, 3 H (OCH_3); 6·40—7·30 m, 7 H (ArH); 8·85 bs, 1 H (OH). ^{13}C NMR spectrum ($CDCl_3$): 34·96 q and 38·84 q ($N(CH_3)_2$); 55·27 q (OCH_3); 113·54 d (C-4′); 115·26 d (C-5); 117·05 d (C-2′); 119·14 d (C-3); 124·22 d (C-6′); 128·03 d (C-5′); 128·55 s (C-1); 129·97 d (C-6); 133·93 s (C-1′); 135·50 s (C-2); 158·28 s (C-4); 160·00 s (C-3′); 171·20 s (CON). For $C_{16}H_{17}NO_3S$ (303·4) calculated: 63·34% C, 5·65% H, 4·62% N, 10·57% S; found: 63·35% C, 5·65% H, 4·85% N, 10·61% S.

N,N-Dimethyl-2-(3-hydroxyphenylthio)-5-methoxybenzamide (*XXIXa*)

A similar reaction of 7·6 g *XXVIIa* with 6·3 g methanesulfonyl chloride in 65 ml pyridine and the following treatment with 12·4 g dimethylamine gave 8·1 g (97%) of crude *XXIXa*. Chromatography of a sample on silica gel afforded the homogeneous *XXIXa*, m.p. 154—155°C (acetone–light petroleum). UV spectrum: infl. 243 (4·13), 283 (3·86). IR spectrum: 701, 780, 827, 869, 881, 890 (3 and 2 adjacent and solitary Ar–H); 1 019, 1 221, 1 231 ($ArOCH_3$ and ArOH); 1 500, 1 579, 1 590, 1 600 (Ar); 1 620 ($ArCONR_2$); 3 200 (OH). ^{1}H NMR spectrum ($CDCl_3$): 2·72 s and 3·03 s, 3 and 3 H ($CON(CH_3)_2$); 3·74 s, 3 H (OCH_3); 6·50—7·40 m, 7 H (ArH). ^{13}C NMR spectrum ($CDCl_3$): 33·54 q and 37·80 q ($N(CH_3)_2$); 55·13 q (CH_3O); 111·97 d (C-6); 113·46 d (C-4′); 115·26 d (C-2′); 115·78 d (C-4); 119·51 d (C-6′); 120·48 s (C-2); 129·22 d (C-5′); 135·80 d (C-3); 136·99 s (C-1); 142·22 s (C-1′); 157·53 s (C-3′); 159·25 s (C-5); 167·77 s (CON). For $C_{16}H_{17}NO_3S$ (303·4) calculated: 63·34% C, 5·65% H, 4·62% N, 10·57% S; found: 63·31% C, 5·60% H, 4·67% N, 10·62% S.

N,N-Dimethyl-2-(3-benzyloxy-4-methoxyphenylthio)benzylamine (*XVIII*)

A solution of 8·4 g *XVII* in 50 ml tetrahydrofuran was stirred and treated with 1·7 g $NaBH_4$ and then dropwise over 15 min with 6·0 g $BF_3.O(C_2H_5)_2$. The mixture was stirred for 30 min at room temperature and refluxed for 3 h. It was cooled, decomposed with 20 ml dilute hydrochloric acid (1 : 1), added dropwise, and refluxed for further 3 h. After cooling it was made alkaline with 40 ml 20% NaOH, the organic layer was separated, the aqueous layer was extracted with ether, organic layers were combined, dried with K_2CO_3, evaporated, and the residue was crystallized from methanol; 7·35 g (91%) of *XVIII*, m.p. 79—82°C. IR spectrum (KBr): 694, 745, 800, 870, 897 (5, 4 and 2 adjacent and solitary Ar–H); 1 000, 1 016, 1 217, 1 245 (ArOR); 1 499, 1 572, 3 000, 3 040, 3 060 (Ar); 2 760, 2 780, 2 810 ($N–CH_3$, OCH_3). ^{1}H NMR spectrum ($CDCl_3$): 3·24 s, 6 H ($N(CH_3)_2$); 3·50 s, 2 H ($ArCH_2N$); 3·86 s, 3 H (OCH_3); 5·05 s, 2 H (OCH_2Ar); 6·80—7·20 m, 7 H (ArH of the diphenyl sulfide moiety); 7·30 s, 5 H (C_6H_6 of benzyl). ^{13}C NMR spectrum ($CDCl_3$): 45·67 q ($N(CH_3)_2$); 55·95 q (OCH_3); 62·07 t (CH_2N); 70·81 t (OCH_2); 112·27 d (C-5′); 118·99 d (C-2′); 125·12 s (C-1′); 125·49 d (C-6′); 127·28 d (C-2 and C-6 of benzyl); 127·80 d (C-4 of benzyl); 128·48 d (C-3 and C-5 of benzyl); 126·76 d, 127·58 d, and 129·07 d (C-3, C-4, and C-5); 129·82 d (C-6); 136·54 s (C-1 of benzyl); 137·51 s (C-1); 138·26 s (C-2); 148·42 s (C-4′); 149·76 s (C-3′). For $C_{23}H_{25}NO_2S$ (379·5) calculated: 72·79% C, 6·64% H, 3·69% N, 8·45% S; found: 72·63% C, 6·63% H, 3·34% N, 8·57% S.

N-Methyl-2-(4-benzyloxy-3-methoxyphenylthio)benzylamine (*XXII*)

Similar reduction of 12·0 g *XXI* with 2·5 g $NaBH_4$ and 9·2 g $BF_3.O(C_2H_5)_2$ in 70 ml tetrahydrofuran under nitrogen gave 10·6 g of oily *XXII* which was transformed to the hydrochloride

(9·7 g, 76%), m.p. 124·5—126°C (ethanol–ether). IR spectrum: 700, 749, 768, 796, 842, 859, 875, 888 (5, 4 and 2 adjacent and solitary Ar–H); 1 009, 1 021, 1 143, 1 213, 1 253 (ArOR); 1 500, 1 580, 3 040 (Ar); 2 404, 2 540, 2 680, 2 710, 2 755 (NH_2^+); 3 360 (NH). ^{1}H NMR spectrum: 2·62 s, 3 H (NCH_3); 3·76 s, 3 H (OCH_3); 4·27 s, 2 H ($ArCH_2N$); 5·12 s, 2 H (OCH_2Ar); 6·90 to 7·80 m, 12 H (ArH). ^{13}C NMR spectrum: 32·34 q (NCH_3); 48·55't (CH_2N); 55·80 q (OCH_3); 69·99 t (OCH_2); 114·43 d (C-5′); 115·15 d (C-2′); 124·14 s (C-1′); 125·34 d (C-6′); 127·95 d (C-4 of benzyl); 127·95 d (C-2 and C-6 of benzyl); 128·48 d (C-3 and C-5 of benzyl); 127·36 d, 129·90 d, 130·64 d, and 131·09 d (C-3, C-4, C-5, and C-6); 131·61 s (C-1); 136·84 s (C-2 and C-1 of benzyl): 148·27 s (C-4′); 149·76 s (C-3′). For $C_{22}H_{24}ClNO_2S$ (402·0) calculated: 65·74% C, 6·02% H, 8·82% Cl, 3·48% N; 7·98% S; found: 65·48% C, 6·19% H, 8·89% Cl, 3·20% N, 7·87% S.

N,N-Dimethyl-2-(3,4-dimethoxyphenylthio)benzylamine (cf. ref.[3])

A solution of 3·0 g $LiAlH_4$ in 60 ml ether was treated under stirring with a solution of 9·0 g $AlCl_3$ in 60 ml ether and the mixture was stirred under nitrogen for 15 min. A solution of 9·0 g N,N-dimethyl-2-(3,4-dimethoxyphenylthio)benzamide[3] in 30 ml tetrahydrofuran was added and the mixture was refluxed for 4 h. After cooling it was decomposed by slow addition of 100 ml 10% hydrochloric acid, the aqueous layer was made alkaline with NH_4OH and extracted with chloroform. Processing of the extract gave 7·4 g of oil which was chromatographed on 50 g neutral Al_2O_3 (activity II). Main part of the product was obtained by elution with chloroform and ethanol. It was oily and was transformed to the hydrochloride; 3·6 g (37%), m.p. 162·5 to 164°C (ethanol–ether). Mass spectrum: 303 (M^+, $C_{17}H_{21}NO_2S$, 13), 288 (4), 257 (21), 243 (5), 227 (32), 181 (22), 165 (93), 132 (13), 109 (13), 91 (22), 58 (100), 44 (61). IR spectrum: 767, 779, 819, 856 (4 and 2 adjacent and solitary Ar–H); 1 022, 1 235, 1 258 ($ArOCH_3$); 1 504, 1 584, 3 000, 3 010, 3 075 (Ar); 2 320, 2 400, 2 435, 2 493, 2 540 (NH^+). ^{1}H NMR spectrum: 2·91 s, 6 H ($N^+(CH_3)_2$); 3·76 s and 3·81 s, 3 and 3 H (2 × OCH_3); 4·49 bs, 2 H ($ArCH_2N^+$); 7·00—7·50 m and 7·95 m, 6 and 1 H (ArH). ^{13}C NMR spectrum: 41·90 q ($N(CH_3)_2$); 55·65 q (2 × OCH_3); 56·54 t (CH_2N); 112·87 d (C-5′); 116·30 d (C-2′); 123·25 s (C-1′); 126·01 d (C-6′); 129·67 s (C-1); 127·21 d, 130·42 d, and 130·72 d (C-3, C-4, and C-5); 132·44 d (C-6); 138·49 s (C-2); 149·47 s C-3′ and C-4′). For $C_{17}H_{22}ClNO_2S$ (339·9) calculated: 60·07% C, 6·52% H, 10·43% Cl, 4·12% N, 9·43% S; found: 60·09% C, 6·52% H, 10·77% Cl, 4·24% N, 9·64% S. Ref.[3], m.p. 175—176°C.

N,N-Dimethyl-4-fluoro-2-(3-methoxyphenylthio)benzylamine (*XXVIc*)

A solution of 32·3 g dimethylamine hydrochloride in 20 ml water was treated under stirring at 4—7°C with a solution of 12·7 g NaOH in 30 ml water and at the same temperature with a solution of 12·65 g *XXIVc* in 90 ml benzene. The mixture was stirred vigorously at room temperature for 2 h, allowed to stand overnight, the benzene layer was washed with water, dried, and evaporated. The residue (12·0 g of the crude *XXVc*) was dissolved in 80 ml tetrahydrofuran and the stirred solution was treated under nitrogen first with 3·26 g $NaBH_4$ and then at 22—27°C with 10·2 ml $BF_3.O(C_2H_5)_2$ over 45 min. The mixture was stirred for 1 h at room temperature and refluxed for 3 h. After cooling to 15°C it was decomposed by the addition of 32 ml dilute hydrochloric acid (1 : 1) and the mixture was refluxed for 3 h. After cooling it was made alkaline with 70 ml 20% NaOH, the aqueous layer was extracted with benzene, the combined organic layers were dried and evaporated. The residue was dissolved in ethanol and the solution was treated with HCl in ether giving 9·75 g (70%) of *XXVIc*.HCl, m.p. 120—122°C (ethanol–ether). IR spectrum: 780, 809, 859, 899 (3 and 2 adjacent and solitary Ar–H); 1 039, 1 229, 1 284 ($ArOCH_3$); 1 479, 1 573, 1 588, 1 600, 3 006, 3 045 (Ar); 2 460, 2 508, 2 560 (NH^+). ^{1}H NMR spectrum: 2·79 s, 6 H ($N^+(CH_3)_2$); 3·79 s, 3 H (OCH_3); 4·46 s, 2 H ($ArCH_2N$); 6·85—7·50 m,

6 H (ArH with the exception of H-6); 8·02 dd, 1 H (H-6, $J_{H-H} = 8·0$; $J_{H-F} = 6·0$). For $C_{16}H_{19}ClFNOS$ (327·8) calculated: 58·61% C, 5·84% H, 10·82% Cl, 5·80% F, 4·27% N, 9·78% S; found: 58·79% C, 6·01% H, 10·78% Cl, 5·98% F, 4·38% N, 9·75% S.

N,N-Dimethyl-5-fluoro-2-(3-methoxyphenylthio)benzylamine (*XXXc*)

A similar reaction of 38·3 g dimethylamine hydrochloride with 15 g NaOH in 60 ml water and 15·0 g *XXVIIIc* in 100 ml benzene gave 15 g oily *XXIXc* which was reduced with 4·07 g $NaBH_4$ and 12·8 ml $BF_3.O(C_2H_5)_2$ in 100 ml tetrahydrofuran under nitrogen. Similar processing gave 13·5 g (82%) of *XXXc*.HCl, m.p. 164–167°C (ethanol–ether). Mass spectrum: 291 (M^+, $C_{16}H_{18}$·.FNOS, 40), 276 (15), 245 (40), 215 (20), 183 (15), 150 (30), 58 (100). IR spectrum: 690, 780, 820, 838, 863, 899 (3 and 2 adjacent and solitary Ar–H); 1 030, 1 230 ($ArOCH_3$); 1 569, 1 580, 1 590, 1 602, 3 000, 3 010, 3 070, 3 090 (Ar); 2 370, 2 410, 2 445 (NH^+). ^1H NMR spectrum: 2·75 s, 6 H ($N^+(CH_3)_2$); 3·73 s, 3 H (OCH_3); 4·52 s, 2 H ($ArCH_2N$); 6·80–8·20 m, 7 H (ArH). For $C_{16}H_{19}ClFNOS$ (327·8) calculated: 58·61% C, 5·84% H, 10·82% Cl, 5·80% F, 4·27% N, 9·78% S; found: 58·53% C, 5·96% H, 10·73% Cl, 5·96% F, 4·21% N, 10·00% S.

N,N-Dimethyl-2-(3-hydroxy-4-methoxyphenylthio)benzylamine (*III*)

A mixture of 3·4 g *XVIII* and 10 ml 48% hydrobromic acid was refluxed for 3 min. After cooling the solution was washed with ether, made alkaline with NH_4OH and extracted with ether. Processing of the extract gave 2·1 g (81%) of *III*, m.p. 115–117°C (methanol). Mass spectrum: 289 (M^+, $C_{16}H_{19}NO_2S$, 27), 274 (14), 244 (16), 243 (30), 227 (14), 213 (23), 184 (12), 167(30), 165 (65), 164 (42), 150 (21), 132 (49), 91 (24), 58 (100), 46 (30), 44 (58), 42 (27). UV spectrum: 245 (4·11), 281 (3·85). IR spectrum: 752, 800, 840, 865 (4 and 2 adjacent and solitary Ar–H); 1 003, 1 019, 1 220, 1 270 ($ArOCH_3$, ArOH); 1 496, 1 567, 1 589 (Ar); 2 600 (NH^+); infl. 3 100 (OH). ^1H NMR spectrum ($CDCl_3$): 3·28 s, 6 H ($N(CH_3)_2$); 3·55 s, 2 H ($ArCH_2N$); 3·98 s, 3 H (OCH_3); 6·70–7·40 m, 7 H (ArH). ^{13}C NMR spectrum ($CDCl_3$): 45·27 q ($N(CH_3)_2$); 55·95 q (OCH_3); 61·85 t (CH_2N); 111·37 d (C-5′); 119·29 d (C-2′); 124·97 d (C-6′); 126·53 s (C-1′); 126·01 d, 127·73 d, 130·12 d (C-3, C-4, and C-5); 130·12 d (C-6); 137·89 s (C-1 and C-2); 146·40 s (C-3′); 148·85 s (C-4′). For $C_{16}H_{19}NO_2S$ (289·4) calculated: 66·40% C, 6·62% H, 4·84% N, 11·08% S; found: 66·58% C, 6·66% H, 4·82% N, 11·02% S.

Hydrogen maleate, m.p. 143·5–145°C (ethanol–ether). For $C_{20}H_{23}NO_6S$ (405·5) calculated: 59·24% C, 5·72% H, 3·45% N, 7·91% S; found: 59·27% C, 5·83% H, 3·34% N, 7·93% S.

N-Methyl-2-(4-hydroxy-3-methoxyphenylthio)benzylamine (*V*)*

Similar debenzylation of 7·6 g *XXII*.HCl with 20 ml 48% hydrobromic acid by refluxing for 2 min and similar processing (extraction with chloroform) gave 2·55 g (49%) of oily *V* which was transformed to the hydrogen oxalate, m.p. 147·5–148·5°C (ethanol). ^1H NMR spectrum: 2·64 s, 3 H (N^+CH_3); 3·74 s, 3 H (OCH_3); 4·27 s, 2 H ($ArCH_2N^+$); 6·90–7·60 m, 7 H (ArH). For $C_{17}H_{19}NO_6S$ (365·4) calculated: 55·88% C, 5·24% H, 3·83% N, 8·78% S; found: 55·59% C, 5·56% H, 3·49% N, 8·73% S.

* Recently[27], a direct comparison of the mass spectra of this compound and of the „N--hydroxymethyl" metabolite of moxifetin (*I*), mentioned above[10,11], proved the identity; the „hydroxymethyl" structure is thus ruled out and compound *V* is the third moxifetin metabolite with determined structure.

N,N-Dimethyl-2-(4-hydroxy-3-methoxyphenylthio)benzylamine (*IV*)

A solution of 8·35 g N,N-dimethyl-2-(3,4-dimethoxyphenylthio)benzylamine[3] in 25 ml toluene was added to a mixture of 4·5 g 4-methylthiophenol, 6·5 g hexamethylphosphoric triamide, 75 ml toluene, and 1·1 g 80% NaH (suspension in oil), and the mixture formed was refluxed for 10 h. After cooling it was washed with water and dilute NaOH. The combined aqueous layers were acidified with hydrochloric acid and washed with ether. The clear aqueous layer was made alkaline with NH_4OH, extracted with dichloromethane, and the extract was processed. There were obtained 8·0 g of inhomogeneous oil which was chromatographed on 100 g neutral Al_2O_3 (activity II). After the separation of the benzene and first chloroform eluates, further chloroform and ethanol eluates were combined giving 3·35 g (42%) of crude *IV*, which was purified by crystallization from methanol, m.p. 141—143°C. IR spectrum: 748, 783, 805, 819, 862, 882 (4 and 2 adjacent and solitary Ar–H); 1 019, 1 218, 1 262 ($ArOCH_3$, ArOH); 1·498, 1 570, 1 585, 3 050 (Ar); 2 360, 2 440, 2 500, 2 560, 2 620, 2 700 (NH^+); infl. 3 100 (OH). ^{1}H NMR spectrum ($CDCl_3$): 2·29 s, 6 H ($N(CH_3)_2$); 3·54 s, 2 H ($ArCH_2N$); 3·92 s, 3 H (OCH_3); 6·80—7·40 m, 7 H (ArH). ^{13}C NMR spectrum ($CDCl_3$): 45·27 q ($N(CH_3)_2$); 55·95 q (OCH_3); 61·92 t (CH_2N); 115·63 d (C-5′); 116·60 d (C-2′); 123·62 s (C-1′); 125·34 d (C-6′); 127·73 d, 127·88 d, 128·48 d (C-3, C-4, and C-5); 130·05 d (C-6); 136·69 s (C-1); 139·16 s (C-2); 146·40 s (C-4′); 147·37 s (C-3′). For $C_{16}H_{19}NO_2S$ (289·4) calculated: 66·40% C, 6·62% H, 4·84% N, 11·08% S; found: 66·22% C, 6·59% H, 4·62% N, 11·07% S.

Hydrogen maleate, m.p. 143·5—144·5°C (ethanol–ether). For $C_{20}H_{23}No_6S$ (405·5) calculated: 59·24% C, 5·72% H, 3·45% N; 7·91% S; found: 59·13% C, 5·81% H, 3·54% N, 7·83% S.

N,N-Dimethyl-4-hydroxy-2-(3-methoxyphenylthio)benzylamine (*VII*)

A solution of 2·1 g *XXVb* in 60 ml tetrahydrofuran was added dropwise to a stirred solution of 0·85 g $LiAlH_4$ in 40 ml tetrahydrofuran and the mixture was refluxed under nitrogen for 8 h. After cooling it was decomposed with 4·5 ml water, added dropwise. After 30 min stirring the solid was filtered off, washed with tetrahydrofuran, the filtrate was dried and evaporated. The residue crystallized on standing (1·15 g (53%) of *VII*), m.p. 113—114°C (benzene). UV spectrum: infl. 214·5 (4·49), infl. 231 (4·25), infl. 248 (4·08), 283 (3·82). IR spectrum: 683, 689, 778, 799, 817, 845, 866, 903 (3 and 2 adjacent and solitary Ar–H); 1 041, 1 230, 1 263, 1 280 ($ArOCH_3$, ArOH); 1 489, 1 573, 1 590, 3 005, 3 020, 3 073 (Ar); 2 540, 2 640, 2 740 (NH^+). ^{1}H NMR spectrum ($CDCl_3$): 2·24 s, 6 H ($N(CH_3)_2$); 3·50 s, 2 H ($ArCH_2N$); 3·79 s, 3 H (OCH_3); 6·50—7·30 m, 7 H (ArH); 7·30 bs, 1 H (OH). ^{13}C NMR spectrum ($CDCl_3$): 44·82 t ($N(CH_3)_2$); 55·27 q (OCH_3); 60·43 t (CH_2N); 112·79 d (C-4′); 115·55 d (C-5); 116·23 d (C-2′); 119·59 d (C-3); 123·25 d (C-6′); 128·85 s (C-1); 130·05 d (C-5′); 131·99 d (C-6); 136·54 s and 137·07 s (C-2 and C-1′); 156·86 s (C-4); 160·07 s (C-3′). For $C_{16}H_{19}NO_2S$ (289·4) calculated: 66·41% C, 6·62% H, 4·84% N, 11·07% S; found: 65·99% C, 6·66% H, 4·95% N, 11·09% S.

Hydrochloride, m.p. 162—163°C (ethanol–ether). ^{1}H NMR spectrum: 2·72 s, 6 H ($N^+(CH_3)_2$); 3·74 s, 3 H (OCH_3); 4·32 bs, 2 H ($ArCH_2N^+$); 6·80—7·30 m, 7 H (ArH). For $C_{16}H_{20}ClNO_2S$ (325·8) calculated: 58·98% C, 6·19% H, 10·88% Cl, 4·30% N, 9·83% S; found: 58·91% C, 6·30% H, 10·85% Cl, 4·15% N, 9·98% S.

N,N-Dimethyl-2-(3-hydroxyphenylthio)-5-methoxybenzylamine (*IX*)

The amide *XXIXa* (3·5 g) was similarly reduced with 1·4 g $LiAlH_4$ in 160 ml tetrahydrofuran under nitrogen. Similar processing gave 1·54 g (47%) of *IX*, m.p. 151°C (benzene–light petroleum). UV spectrum: infl. 230 (4·26), infl. 243 (4·17), infl. 277 (3·82), 284 (3·82), infl. 292 (3·72). IR

spectrum: 685, 770, 821, 840, 861, 890 (3 and 2 adjacent and solitary Ar–H); 1 010, 1 029, 1 229, 1 260, 1 310 ($ArOCH_3$, ArOH); 1 480, 1 580, 1 593 (Ar); 2 570, 2 660 (NH^+); infl. 3 040 (OH). ^1H NMR spectrum ($CDCl_3$): 2·08 s, 6 H ($N(CH_3)_2$); 3·44 s, 3 H (OCH_3); 3·58 s, 2 H ($ArCH_2N$); 5·94 bs, 1 H (H-4′); 6·60 bt, 1 H (H-2′); 7·46 d, 1 H (H-3, J = 9·0); 6·74—7·20 m, 4 H (H-3, H-6, H-5′, H-6′). ^{13}C NMR spectrum ($CDCl_3$): 44·82 q ($N(CH_3)_2$); 55·27 q (OCH_3); 60·80 t (CH_2N); 113·16 d and 113·31 d (C-4 and C-2′); 114·65 d (C-6); 115·63 d (C-4′); 118·39 d (C-6′); 122·95 s (C-2); 130·05 d (C-5′); 138·04 d (C-3); 140·35 s (C-1′); 143·19 s (C-1); 157·61 s (C-3′); 160·97 s (C-5). For $C_{16}H_{19}NO_2S$ (289·4) calculated: 66·41% C, 6·62% H, 4·84% N, 11·07% S; found: 66·70% C, 6·60% H, 4·76% N, 11·18% S.

Hydrogen maleate, m.p. 78—81°C (benzene–ether). Mass spectrum: 289 (M^+, $C_{16}H_{19}NO_2S$, 24), 274 (19), 244 (20), 243 (45), 227 (8), 213 (5), 200 (6), 195 (11), 162 (13), 152 (8), 137 (17), 1 321 (11), 98 (13), 58 (100), 54 (27), 46 (22), 44 (52). For $C_{20}H_{23}NO_6S$ (405·4) calculated: 59·24% C, 5·72% H, 3·45% N, 7·91% S; found: 59·33% C, 5·81% H, 3·36% N, 7·94% S.

N,N-Dimethyl-2-(3-hydroxyphenylthio)-4-methoxybenzylamine (*VI*)

A stirred and cooled solution of 7·0 g *XXIIIa* in 60 ml pyridine was treated with 5·8 g methanesulfonyl chloride, added dropwise over 30 min at 5—8°C. After 5 min stirring, 11·4 g gaseous dimethylamine was introduced at 10—13°C over 1 h and the mixture was stirred for 4·5 h at room temperature. After standing overnight it was poured into 200 ml water and extracted with benzene. Processing of the extract gave 5·85 g inhomogeneous oil which was chromatographed on 70 g silica gel. Benzene and benzene–chloroform (1 : 1) eluted minute amounts of oily substances which were discarded. Chloroform eluted then 2·8 g of a rather homogeneous oily substance which was characterized by the ^1H NMR spectrum ($CDCl_3$) as the methanesulfonic ester of *XXV*: 2·78 s, 3 H (SO_2CH_3); 2·84 bs and 3·06 bs, 3 and 3 H ($N(CH_3)_2$); 3·78 s, 3 H (OCH_3); 6·80—7·40 m, 7 H (ArH). The chromatography was continued by elution with chloroform containing 6% of ethanol and gave 2·15 g of oily *XXVa*. ^1H NMR spectrum ($CDCl_3$): 2·87 bs and 3·08 bs, 3 and 3 H ($N(CH_3)_2$); 3·65 s, 3 H (OCH_3); 6·70—7·20 m, 7 H (ArH).

A) A solution of 2·1 g of the crude methanesulfonic ester of *XXVa* in 40 ml ether and 10 ml tetrahydrofuran was added dropwise to a stirred solution of 1·0 g $LiAlH_4$ in 40 ml ether and the mixture was stirred and refluxed for 8·5 h under nitrogen. After cooling it was decomposed by successive addition of 1 ml water, 1 ml 15% NaOH and 3 ml water. The solvents were evaporated in vacuo, the residue was diluted with 10 ml water and the mixture was neutralized with 15 ml 1M-HCl to pH 8—8·5. Extraction with chloroform and processing of the extract gave 0·95 g (60%) of the oily *VI* which was transformed to the hydrogen maleate, m.p. 119—120°C (ethanol–ether). Mass spectrum: 289 (M^+, $C_{16}H_{19}NO_2S$, 40), 274 (19), 243 (100), 227 (8), 213 (13), 200 (10), 195 (22), 162 (23), 152 (13), 137 (27), 121 (14), 107 (12), 98 (19), 77 (11), 58 (56). ^1H NMR spectrum: 2·76 s, 6 H ($N^+(CH_3)_2$); 3·75 s, 3 H (OCH_3); 4·30 s, 2 H ($ArCH_2N$); 6·04 s, 2 H (CH=CH of maleic acid); 6·60—6·80 m and 7·20 m (4 ArH of hydroxyphenyl); 6·92 d, 1 H (H-3, J = 3·0); 7·10 dd, 1 H (H-5, J = 8·0; 3·0); 7·60 d, 1 H (H-6, J = 8·0). ^{13}C NMR spectrum: 42·28 q ($N(CH_3)_2$); 55·42 q (OCH_3); 57·29 t (CH_2N); 114·28 d (C-5); 114·66 d (C-4′); 116·30 d (C-2′); 119·06 d (C-3); 120·33 d (C-6′); 124·14 s (C-1); 130·57 d (C-5′); 133·85 d (C-6); 135·35 s (C-2); 135·82 d (CH=CH of maleic acid); 136·77 s (C-1′); 158·22 s (C-3′); 160·45 s (C-4); 167·32 s (2 × COOH of maleic acid). For $C_{20}H_{23}NO_6S$ (405·4) calculated: 59·24% C, 5·72% H, 3·45% N, 7·91% S; found: 58·92% C, 5·70% H, 3·09% N, 7·94% S.

B) Oily *XXVa* (1·3 g) was similarly reduced with 0·8 g $LiAlH_4$ in 80 ml tetrahydrofuran and gave 0·65 g (52%) of oily *VI*, identical with the product obtained under *A*) (TLC). It afforded the hydrogen maleate melting at 118·5—120°C (ethanol).

N,N-Dimethyl-5-hydroxy-2-(3-methoxyphenylthio)benzylamine (*X*)

A solution of 3·35 g *XXVIIb* in 30 ml pyridine was treated similarly like in the preceding case with 2·8 g methanesulfonyl chloride and then with 5·5 g dimethylamine. Similar processing gave 3·3 g of crude oily *XXIXb* (containing evidently some methanesulfonic ester) which was similarly reduced with 1·6 g $LiAlH_4$ in 90 ml ether and 10 ml tetrahydrofuran. Processing gave 1·5 g (43%) of crystalline *X*, m.p. 129—130°C (benzene–light petroleum). UV spectrum: infl. 216 (4·73), infl. 244 (4·48), 278 (4·11), 283 (4·12), infl. 304 (4·04). IR spectrum: 690, 771, 782, 829, 849, 861 (3 and 2 adjacent and solitary Ar–H); 1 040, 1 227, 1 240, 1 280, 1 314 ($ArOCH_3$, ArOH); 1 571, 1 589, 3 000, 3 080 (Ar); 2 480 (NH^+). ^1H NMR spectrum: 2·13 s, 6 H ($N(CH_3)_2$); 3·44 s, 2 H ($ArCH_2N$); 3·67 s, 3 H (OCH_3); 6·50—7·40 m, 7 H (ArH). ^{13}C NMR spectrum: 45·12 q ($N(CH_3)_2$); 54·98 q (OCH_3); 60·88 t (CH_2N); 110·70 d (C-4′); 111·89 d (C-2′); 115·26 d (C-4); 116·75 d (C-6); 118·62 d (C-6′); 119·29 s (C-2); 129·97 d (C-5′); 137·59 d (C-3); 140·28 s (C-1′); 144·24 s (C-1); 158·75 s (C-5); 159·70 s (C-3′). For $C_{16}H_{19}NO_2S$ (289·4) calculated: 66·41% C, 6·62% H, 4·84% N, 11·07% S; found: 66·76% C, 6·79% H, 4·75% N, 11·04% S.

Hydrochloride hemihydrate, m.p. 58—60°C (ethanol–ether). For $C_{16}H_{20}ClNO_2S + 0{\cdot}5\ H_2O$ (325·8) calculated: 57·38% C, 6·34% H, 10·59% Cl, 4·18% N, 9·57% S; found: 57·26% C, 6·71% H, 10·35% Cl, 3·90% N, 9·41% S.

N,N-Dimethyl-4-fluoro-2-(3-hydroxyphenylthio)benzylamine (*VIII*)

A mixture of 6·5 g *XXVIc*.HCl and 26 ml 48% hydrobromic acid was stirred and heated for 8 h to 120°C under reflux. After cooling it was poured into 50 ml water, neutralized with 10% NaOH and extracted with dichloromethane. Processing gave 4·55 g (83%) of crystalline *VIII*, m.p. 122—123°C (methanol). IR spectrum: 789, 823, 867, 891, 901 (3 and 2 adjacent and solitary Ar–H); 1 153, 1 171, 1 260 (ArOH); 1 489, 1 583, 1 600, 3 060 (Ar); 2 470, 2 570, 2 660, 2 710 (NH^+). ^1H NMR spectrum ($CDCl_3$): 4·24 s, 6 H ($N(CH_3)_2$); 3·55 s, 2 H ($ArCH_2N$); 6·50 to 7·40 m, 7 H (ArH). For $C_{15}H_{16}FNOS$ (277·4) calculated: 64·95% C, 5·82% H, 6·85% F, 5·05% N, 11·56% S; found: 64·63% C, 5·85% H, 7·07% F, 5·07% N, 11·62% S.

Hydrogen maleate, m.p. 154—155°C (ethanol). For $C_{19}H_{20}FNO_5S$ (393·4) calculated: 58·00% C, 5·12% H, 4·83% F, 3·56% N; 8·15% S; found: 57·87% C, 5·20% H, 4·85% F, 3·55% N, 8·24% S.

N,N-Dimethyl-5-fluoro-2-(3-hydroxyphenylthio)benzylamine (*XI*)

Similar demethylation of 9·3 g *XXXc*.HCl with 37 ml 48% hydrobromic acid and similar processing gave 6·3 g (80%) of crystalline *XI*, m.p. 103—104°C (methanol). IR spectrum: 685, 770, 840, 879 (3 and 2 adjacent and solitary Ar–H); 1 012, 1 220, 1 235, 1 274 (ArOH); 1 574, 1 600, 3 068 (Ar); 2 540, 2 630 (NH^+); 1 750 ($N-CH_3$). ^1H NMR spectrum ($CDCl_3$): 2·22 s, 6 H ($N(CH_3)_2$); 3·60 s, 2 H ($ArCH_2N$); 6·68 bs, 1 H (OH); 6·40—7·50 m, 7 H (ArH). For $C_{15}H_{16}$-.FNOS (277·4) calculated: 64·95% C, 5·82% H ,6·85% F, 5·05% N, 11·56% S; found: 65·11% C, 5·92% H, 7·00% F, 5·19% N, 11·59% S.

Hydrogen maleate, m.p. 115—116°C (ethanol). For $C_{19}H_{20}FNO_5S$ (393·4) calculated: 58·00% C, 5·12% H, 4·83% F, 3·56% N, 8·15% S; found: 58·12% C, 5·20% H, 4·85% F, 3·52% N, 8·33% S.

N,N-Dimethyl-2-(3-hydroxyphenylthio)benzylamine N-Oxide (*XII*)

A solution of 2·6 g *I* (ref.[3]) in 30 ml ethanol was treated with 2 ml 30% H_2O_2, the mixture was allowed to stand for 24 h at room temperature and extracted with benzene. Processing of the

extract gave 3·13 g of crude product which was chromatographed on 50 g neutral Al_2O_3 (activity II). Evaporation of the first fraction, eluted with chloroform containing 10% of ethanol, gave 0·92 g of crude *XII* which was crystallized from a mixture of chloroform, ethanol and ether, m.p. 165–168°C. Mass spectrum: 275 (M^+, $C_{15}H_{17}NO_2S$, 1), 259 (1), 258 (1), 231 (3), 215 (67), 214 (29), 213 (100). IR spectrum: 692, 759, 783 (4 and 3 adjacent Ar–H); 970, 990 (R_2N–O); 1 261, 1 271 (ArOH); 1 505, 1 577, 3 028 (Ar); 3 370 (OH). ^{1}H NMR spectrum: 2·50 s, 6 H ($N(CH_3)_2$); 4·74 s, 2 H ($ArCH_2N$); 6·50–7·50 m, 7 H (ArH). For $C_{15}H_{17}NO_2S$ (275·4) calculated: 65·43% C, 6·22% H, 5·09% N, 11·64% S; found: 65·29% C, 6·28% H, 5·21% N, 11·34% S.

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