POTENTIAL ANTIDEPRESSANTS AND INHIBITORS OF 5-HYDROXYTRYPTAMINE AND NORADRENALINE RE-UPTAKE IN THE BRAIN: N,N-DIMETHYL-(ARYLTHIO)THENYLAMINES AND N,N-DIMETHYL-2-(THIENYLTHIO)BENZYLAMINES

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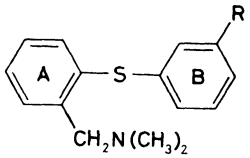
3-(3-Methoxyphenylthio)thiophene-2-carboxylic acid (*IV*) and 2-(3-methoxyphenylthio)thiophene-3-carboxylic acid (*VII*) were transformed via acid chlorides and dimethylamides to the amines *V* and *VIII* which were demethylated to the phenolic amines *VI* and *IX*. N,N-Dimethyl-4-bromothiophene-3-carboxamide (*XI*) was reacted with 3-methoxythiophenol and the amide *XII* was reduced and demethylated to the amine *XIV*. 2-(2-Thienylthio)benzoic acid (*XVa*) and 2-(5-bromo-2-thienylthio)benzoic acid (*XVb*) were transformed via the isolated acid chlorides and N,N-dimethylamides to the amines *XVIIIa* and *XVIIIb*. The amines *VI*, *IX*, and *XIV* are thiophene isosters of moxifetin, the potent inhibitor of 5-hydroxytryptamine re-uptake in the brain structures. Out of the compounds prepared, only the methoxy amine *VIII* (VÚFB-17697) showed a similar type of activity. The intermediate *V*, the phenolic amine *VI*, and the hydroxyl group lacking amine *XVIIIa* are selective inhibitors of noradrenaline re-uptake in the brain.

In previous communications[1,2] the synthesis and properties of compounds *I* and *II* were described; both compounds appear to be promising potential antidepressants. These compounds are active in tests for antireserpine activity, they potentiate the toxicity of yohimbine and *I* has significant affinity to the imipramine and desipramine binding sites in the rat brain and moreover it is a strong inhibitor of 5-hydroxytryptamine as well as noradrenaline re-uptake in the rat brain structures. Introduction of the hydroxyl group to position 3′ of the benzene ring (compound *II*, moxifetin) leads to disappearing of affinity to desipramine binding sites and the product inhibits less the noradrenaline re-uptake. Moxifetin (*II*) is thus a highly potent inhibitor of the 5-hydroxytryptamine re-uptake. In the effort to find even more active substances of this type, the present study was undertaken describing the synthesis of isosteric analogues of *I* and *II* in whose molecules the A or B benzene ring is substituted by a thiophene ring.

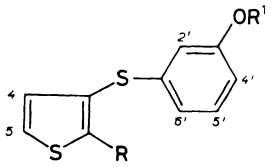
Key intermediates in the series of 2,3-disubstituted thiophenes were the correspondingly substituted thiophenecarboxylic acids. Synthesis of the first of them started from 3-bromothiophene[3] which reacted with 3-methoxythiophenol[4] in

boiling dimethylformamide in the presence of potassium carbonate and copper and afforded *III*. Proton abstraction by treatment with butyllithium in ether at −60°C followed by reaction with carbon dioxide led to *IV*. The synthesis of the isomeric acid

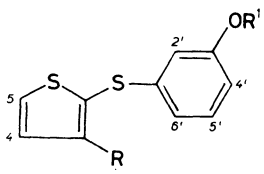


I, R = H
II, R = OH

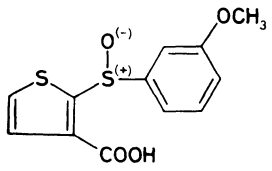
VII started from thiophene-3-carboxylic acid[5] which also was treated with butyllithium leading to abstraction of proton in position 2 of the thiophene ring. The following reaction with 3-methoxyphenylsulfenyl chloride (obtained by the action of N-chlorosuccinimide on 3-methoxythiophenol) gave the acid *VII*. As a by-product of this reaction, the sulfoxide *X* was isolated. The acids *IV* and *VII* were transformed to the acid chlorides by treatment with thionyl chloride in boiling benzene, the crude chlorides afforded by treatment with aqueous solutions of dimethylamine the corresponding dimethylamides which were not isolated in pure state but immediately reduced with diborane, generated "in situ" by reaction of sodium borohydride with boron trifluoride etherate. The obtained oily bases *V* and *VIII* were converted to crystalline hydrochlorides for characterization and for pharmacological testing.



III, R = H ; R^1 = CH_3
IV, R = COOH ; R^1 = CH_3
V, R = $CH_2N(CH_3)_2$; R^1 = CH_3
VI, R = $CH_2N(CH_3)_2$; R^1 = H



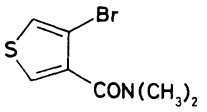
VII, R = COOH ; R^1 = CH_3
VIII, R = $CH_2N(CH_3)_2$; R^1 = CH_3
IX, R = $CH_2N(CH_3)_2$; R^1 = H



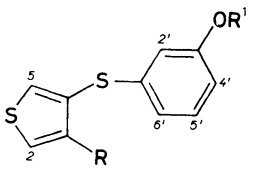
X

Synthesis of *XIII* started from 4-bromothiophene-3-carboxylic acid[6]. Treatment with thionyl chloride gave the acid chloride which was not isolated but subjected directly to treatment with aqueous dimethylamine. The obtained N,N-dimethyl-4--bromothiophene-3-carboxamide (*XI*) was reacted with 3-methoxythiophenol in dimethylformamide in the presence of potassium carbonate and copper and gave *XII* which was reduced with diborane similarly like in the preceding cases. The obtained oily *XIII* was characterized as hydrochloride and also submitted to pharmacological testing.

The methoxy compounds *V*, *VIII*, and *XIII* were demethylated by heating with 48% hydrobromic acid to 120°C. The resulting oily hydroxy compounds *VI*, *IX*, and *XIV* were transformed to crystalline hydrogen oxalates.

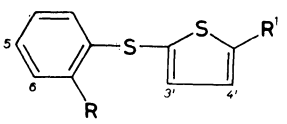


XI



XII, R = $CON(CH_3)_2$; $R^1 = CH_3$
XIII, R = $CH_2N(CH_3)_2$; $R^1 = CH_3$
XIV, R = $CH_2N(CH_3)_2$; R^1 = H

Synthesis of the last type of thiophene derivatives investigated started from 2-(2--thienylthio)benzoic acid (*XVa*) (ref.[7]). Its reaction with bromine in chloroform in the presence of pyridine gave *XVb*. The acids *XVa* and *XVb* afforded by treatment with thionyl chloride the acid chlorides *XVIa* and *XVIb* which were transformed by the action of aqueous dimethylamine to the dimethylamides *XVIIa* and *XVIIb*. Their reduction (in the former case with lithium aluminium hydride and with diborane "in situ" in the latter) gave the oily bases *XVIIIa* (characterized as hydrochloride) and *XVIIIb* (isolated as the maleate). All new compounds were analyzed and characterized by spectra.



a, R^1 = H
b, R^2 = Br

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

Compounds *V*, *VI*, *VIII*, *IX*, *XIII*, *XIV*, *XVIIIa*, and *XVIIIb* were tested in the form of salts described in the Experimental by methods of biochemical pharmacology

(the compounds were used in concentrations of 100, 1 000 or 10 000 nmol l^{-1}) and animal pharmacology (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 and the lethality in % of animals is given: *V*, 0, 80; *VI*, 0, 0; *VIII*, 0, 90; *IX*, 0, 30; *XIII*, 0, 90; *XIV*, 0, 0; *XVIIIa*, 0, 100; *XVIIIb*, 0, 70.

Table I assembles the code numbers of the compounds tested and the IC_{50} values in nmol l^{-1} characterizing the affinities of the compounds to the binding sites of imipramine in the membrane fraction isolated from the rat cerebral cortex (inhibition of binding of 5 nM [^3H]imipramine) and the influence on re-uptake of 5-hydroxytryptamine in the rat brain in vitro (inhibition of binding of 10 nM [^3H]5-hydroxytryptamine) and of noradrenaline in synaptosomes of the rat brain cortex in vitro (inhibition of binding of 10 nM [^3H]noradrenaline).

The following tests were used (results given):

– ataxic activity in the rotarod test in mice: all the compounds tested were inactive in doses of 50 and 100 mg/kg;

– antireserpine activity in the test of reserpine-induced ptosis in mice (the threshold active doses in mg/kg are given): *V*, *VI*, *XIV* and *XVIIIa*, 100; *XIII* and *XVIIIb*, 30; *VIII* and *IX*, inactive at 100 mg/kg;

– potentiation of the yohimbine toxicity in mice (doses in mg/kg and response given): *V* and *IX*, inactive at 100; *XIII*, inactive at 50; *XIV*, inactive at 125; *VI*, *VIII* and *XVIIIa*, at 100 mg/kg active in 20% of the animals; *XVIIIb*, very active, ED_{50} = 17·3 mg/kg.

TABLE I

Biochemical pharmacology of the N,N-dimethyl-(arylthio)thenylamines and N,N-dimethyl-2-(thienylthio)benzylamines

Compound	Code number	IC_{50}, nmol l^{-1}		
		IMI[a]	5-HT[b]	NA[c]
V	VÚFB-17729	129	226·9	81·1
VI	VÚFB-17728	487	1 830	83·0
VIII	VÚFB-17697	935	16·9	832
IX	VÚFB-17698	[d]	>10 000	>1 000
XIII	VÚFB-17730	1 499	>100	>100
XIV	VÚFB-17707	[d]	>100	>1 000
XVIIIa	VÚFB-17679	[d]	80·3	6·7
XVIIIb	VÚFB-17703	[d]	>100	>1 000

[a] Imipramine; [b] 5-hydroxytryptamine; [c] noradrenaline; [d] not estimated.

In conclusion: Compound *VIII* (VÚFB-17697) is a selective 5-hydroxytryptamine re-uptake inhibitor. Compounds *V*, *VI* and *XVIIIa* are selective noradrenaline re--uptake inhibitors. The activity of these compounds in the animal tests does not correspond to results obtained by methods of biochemical pharmacology.

EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder and they were not corrected; 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 (in NUJOL, ν in cm^{-1}) with a Perkin--Elmer 298 spectrophotometer, ^1H NMR spectra (in CD_3SOCD_3 unless stated otherwise, δ in ppm, J in Hz) with the FT-NMR spectrometer TESLA BS 567A (100 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 (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$, $CaCl_2$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

3-Methoxyphenyl 3-Thienyl Sulfide (*III*)

A mixture of 24·6 g 3-methoxythiophenol[3], 100 ml dimethylformamide, 25 g K_2CO_3, 28·6 g 3-bromothiophene[4], and 10 g Cu was stirred and refluxed for 13 h, after partial cooling it was poured to water, extracted with benzene, and filtered. The benzene extract was evaporated and the residue was distilled; 23·8 g (61%) of *III*, b.p. 145—150°C/133 Pa. ^1H NMR spectrum ($CDCl_3$): 3·73 s, 3 H (OCH_3); 6·60—7·40 m, 7 H (ArH). For $C_{11}H_{10}OS_2$ (222·3) calculated: 59·43% C, 4·53% H, 28·84% S; found: 59·83% C, 4·67% H, 28·46% S.

3-(3-Methoxyphenylthio)thiophene-2-carboxylic Acid (*IV*)

A solution of 26·1 g *III* in 200 ml ether was cooled (dry ice–acetone) to −70°C and over 5 min there were added dropwise 100 ml of a 7% solution of butyllithium in hexane. The mixture was stirred for 1·5 h at −60°C and poured to a mixture of solid CO_2 and ether. The solution was washed with water and 5% NaOH; the organic layer was processed by distillation which led to recovery of 16·6 g *III*. The aqueous layer was acidified with hydrochloric acid, the precipitated product was filtered, washed with water and crystallized from aqueous ethanol; 7·8 g (69% per conversion) of *IV*, m.p. 177—180°C. UV spectrum: 268 (3·96), 306 (4·03). IR spectrum: 687, 784, 851, 902 (Ar–H); 933, 1 250, 1 283, 1 646, 2 530, 2 610, infl. 3 100 (ArCOOH); 1 480, 1 489, 1 590, 3 000, 3 050 (Ar). ^1H NMR spectrum: 3·80 s, 3 H (OCH_3); 6·36 d, 1 H (H-4, J = 5·0); 7·15 m, 3 H (H-2′, H-4′, H-6′); 7·45 t, 1 H (H-5′, J = 3·0); 7·76 d, 1 H (H-5, J = 5·0). For $C_{12}H_{10}O_3S_2$ (266·3) calculated: 54·11% C, 3·78% H, 24·08% S; found: 53·80% C, 3·85% H, 24·28% S.

2-(3-Methoxyphenylthio)thiophene-3-carboxylic Acid (*VII*)

A solution of 7·7 g thiophene-3-carboxylic acid[5] in 150 ml tetrahydrofuran was cooled to −10°C and treated with 100 ml 15% butyllithium in hexane. The mixture was stirred without cooling for 1 h, cooled and at −10°C treated with a solution of 3-methoxyphenylsulfenyl chloride which was prepared from 17·6 g 3-methoxythiophenol[3] and 17·0 g N-chlorosuccinimide in 140 ml ether

by refluxing for 3 h and filtering off of the precipitated succinimide. The mixture was stirred for 2 h at room temperature, allowed to stand for 3 days and extracted with water. The aqueous layer was acidified with hydrochloric acid and extracted with ether. Processing of the extract and crystallization of the residue from aqueous ethanol gave 8·2 g (51%) of *VII*, m.p. 151 to 152·5°C. Literature[8] does report neither the yield nor any characterization. UV spectrum: 249 (3·87), 278 (3·57). IR spectrum: 717, 780, 849, 861 (Ar–H); 946, 1 250, 1 286, 1 669, 2 520, 2 600 (ArCOOH); 1 489, 1 504, 1 572, 1 590, 3 080, 3 095 (Ar). ^{1}H NMR spectrum: 3·82 s, 3 H (OCH_3); 7·00—7·60 m, 6 H (ArH). For $C_{12}H_{10}O_3S_2$ (266·3) calculated: 54·11% C, 3·78% H, 24·08% S; found: 54·06% C, 3·86% H, 24·00% S.

Processing of the mother liquor afforded 0·36 g (2%) of 2-(3-methoxyphenylthio)thiophene-3-carboxylic acid S-oxide (*X*), m.p. 192—193°C (benzene). Mass spectrum: 282 (M^+, $C_{12}H_{10}O_4S_2$), 234 (100). UV spectrum: 246 (4·01), 283 (3·82). IR spectrum: 700, 770, 870 (Ar–H); 1 012, 1 033, 1 230 ($ArOCH_3$); 1 230, 1 700, 2 440, 2 560, 2 620, infl. 3 130 (ArCOOH); 1 480, 1 519, 1 576, 3 020, 3 080, 3 100 (Ar). ^{1}H NMR spectrum: 3·82 s, 3 H (OCH_3); 7·00 to 8·00 m, 6 H (ArH). For $C_{12}H_{10}O_4S_2$ (282·3) calculated: 51·05% C, 3·57% H, 22·71% S; found 51·19% C, 3·66% H, 22·59% S.

2-(5-Bromo-2-thienylthio)benzoic Acid (*XVb*)

A stirred solution of 10·0 g *XVa* (ref.[7]) in 120 ml chloroform was treated with 3·3 g pyridine and then over 20 min with a solution of 7·4 g Br in 150 ml chloroform. The mixture was stirred for 1·5 h at room temperature, the crystalline product was filtered and washed with ether; 10·7 g (80%) of *XVb*, m.p. 222—225°C. Analytical sample, m.p. 224—225°C (ethanol). UV spectrum: 251 (4·21), 310 (3·72). IR spectrum: 750, 793 (Ar–H); 923, 1 260, 1 273, 1 318, 1 678, 2 565, 2 655, infl. 3 100 (ArCOOH); 1 560, 1 587, 3 090 (Ar). ^{1}H NMR spectrum: 6·92 dd, 1 H (H-3, J = 8·0; 2·0); 7·28 dt, 1 H (H-5, J = 8·0; 2·0); 7·38 d and 7·43 d (ABq), 1 and 1 H (H-3′, H-4′, J = 3·5); 7·53 dt, 1 H (H-4, J = 8·0; 2·0); 8·00 dd, 1 H (H-6, J = 8·0; 2·0). For $C_{11}H_7BrO_2S_2$ (315·2) calculated: 41·91% C, 2·24% H, 25·36% Br, 20·34% S; found: 41·71% C, 2·27% H, 25·52% Br, 20·01% S.

2-(2-Thienylthio)benzoyl Chloride (*XVIa*)

A mixture of 47·2 g *XVa* (ref.[7]), 400 ml benzene and 2 drops of dimethylformamide was stirred and treated over 10 min with 78·5 g $SOCl_2$, added dropwise. The mixture was stirred and refluxed for 2 h, the volatile components were evaporated; the oily residue (48·4 g, 95%) is the crude *XVIa*; a sample for analysis was distilled, b.p. 150—152°C/33 Pa. For $C_{11}H_7ClOS_2$ (254·7) calculated: 51·86% C, 2·77% H; found: 51·86% C, 2·72% H.

2-(5-Bromo-2-thienylthio)benzoyl Chloride (*XVIb*)

A mixture of 10·7 g *XVb*, 100 ml benzene and 1 drop of dimethylformamide was treated over 5 min with 13·3 g $SOCl_2$ and stirred and refluxed for 2 h. The volatile components were evaporated and the oily residue was crystallized from cyclohexane; 8·6 g (76%) of *XVIb*, m.p. 72 to 73°C. UV spectrum: 260 (4·25), 307 (3·79). IR spectrum: 725, 800, 875 (Ar–H); 1 509, 1 551, 1 585, 3 068, 3 088 (Ar); 1 720, 1 757 (ArCOCl). ^{1}H NMR spectrum ($CDCl_3$): 7·00 dd, 1 H (H-3, J = 8·0; 2·0); 7·15 s, 2 H (H-3′, H-4′); 7·27 dt, 1 H (H-5, J = 8·0; 2·0); 7·48 dt, 1 H (H-4, J = 8·0; 2·0); 8·32 dd, 1 H (H-6, J = 8·0; 2·0). For $C_{11}H_6BrClOS_2$ (333·7) calculated:39·60% C, 1·81% H, 23·95% Br, 10·62% Cl, 19·22% S; found: 39·42% C, 1·87% H, 23·81% Br, 10·62% Cl, 19·02% S.

N,N-Dimethyl-4-bromothiophene-3-carboxamide (*XI*)

A stirred mixture of 12·8 g 4-bromothiophene-3-carboxylic acid[6] and 130 ml benzene was treated dropwise over 15 min with 20 g $SOCl_2$ and the mixture was refluxed for 2 h. Volatile components were evaporated in vacuo, the residue was dissolved in 50 ml benzene and the solution was treated at 5—10°C with 50 ml 40% aqueous dimethylamine. The mixture was stirred with cooling for 5 h, the benzene layer was washed with water and evaporated. Crystallization of the residue from ethanol gave 10·5 g (73%) of *XI*, m.p. 84—86°C. IR spectrum: 850, 865 (Ar–H); 1 501, 1 560, 3 080 (Ar); 1 616 ($ArCONR_2$). ^1H NMR spectrum ($CDCl_3$): 2·92 s and 3·14 s, 3 and 3 H ($N(CH_3)_2$); 7·25 d, 1 H (H-5, $J = 3·0$); 7·38 d, 1 H (H-2, $J = 3·0$). For C_7H_8BrNOS (234·1) calculated: 35·91% C, 3·44% H, 34·13% Br, 5·98% N, 13·79% S; found: 35·90% C, 3·50% H, 34·21% Br, 5·99% N, 13·59% S.

N,N-Dimethyl-4-(3-methoxyphenylthio)thiophene-3-carboxamide (*XII*)

A mixture of 11·65 g *XI*, 25 ml dimethylformamide, 8·8 g 3-methoxythiophenol[3], 7·5 g K_2CO_3, and 2 g Cu was stirred and refluxed for 14 h, after cooling it was poured into water and extracted with benzene. Processing of the extract gave 15·2 g of oily residue which was chromatographed on 150 g silica gel. The main product (oily *XII*) was eluted with chloroform, 11·2 g (77%). ^1H NMR spectrum ($CDCl_3$): 2·72 bs and 2·90 bs, 3 and 3 H ($N(CH_3)_2$); 3·70 s, 3 H (OCH_3); 6·60—7·10 m, 4 H (H-2′, H-4′, H-5′, H-6′); 7·25 d, 1 H (H-5, $J = 2·8$); 7·35 d, 1 H (H-2, $J = 2·8$).

N,N-Dimethyl-2-(2-thienylthio)benzamide (*XVIIa*)

A solution of 40 g *XVIa* in 300 ml benzene was treated with 58 g gaseous dimethylamine which was introduced over 1·5 h at 10—20°C. The mixture was stirred for 1 h at 10°C, was washed with water and evaporated in vacuo. The residue was crystallized from a mixture of ethanol and hexane; 29·5 g (71%) of *XVIIa*, m.p. 92°C. UV spectrum: infl. 240 (4·12), infl. 275 (3·67). IR spectrum: 739, 769, 850 (Ar–H); 1 498, 1 587, 3 065, 3 085, 3 100 (Ar); 1 629 ($ArCONR_2$). ^1H NMR spectrum ($CDCl_3$): 2·92 s and 3·17 s, 3 and 3 H ($N(CH_3)_2$); 7·00—7·40 m, 7 H (ArH). For $C_{13}H_{13}NOS_2$ (263·4) calculated: 59·29% C, 4·97% H, 5·32% N, 24·35% S; found: 59·27% C, 5·01% H, 5·12% N, 24·25% S.

N,N-Dimethyl-2-(5-bromo-2-thienylthio)benzamide (*XVIIb*)

A similar reaction of 15·0 g *XVIb* in 120 ml benzene with 16 g dimethylamine gave 15·1 g (98%) of *XVIIb*, m.p. 50—51°C (cyclohexane). UV spectrum: 244 (4·15), infl. 288 (3·75). IR spectrum: 750, 800 (Ar–H), 1 499, 1 510, 1 583, 3 085, 3 095 (Ar); 1 629 ($ArCONR_2$). ^1H NMR spectrum ($CDCl_3$): 2·88 bs and 3·14 bs, 3 and 3 H ($N(CH_3)_2$); 7·02 d and 7·08 d, 1 and 1 H (H-3′, H-4′, $J = 4·5$); 7·12 m, 4 H (remaining ArH). For $C_{13}H_{12}BrNOS_2$ (342·3) calculated: 45·62% C, 3·54% H, 23·35% Br, 4·09% N, 18·73% S; found: 45·93% C, 3·54% H, 23·30% Br, 4·13% N, 18·79% S.

N,N-Dimethyl-3-(3-methoxyphenylthio)-2-thenylamine (*V*)

A mixture of 7·7 g *IV* and 80 ml benzene was stirred and treated dropwise over 15 min with 10 g $SOCl_2$, the mixture was refluxed for 2 h, volatile components were evaporated, the oily residue (8·9 g of the crude acid chloride) was dissolved in 50 ml benzene and the solution was treated at 5—10°C with 30 ml 40% aqueous dimethylamine. The mixture was stirred vigorously for 5 h at room temperature, the benzene layer was washed with water and evaporated in vacuo.

The oily residue (8·4 g of the crude dimethylamide) was dissolved in 50 ml tetrahydrofuran and the solution (under nitrogen) was treated first with 2·15 g $NaBH_4$ and then at 20—25°C with 7·5 g $BF_3.O(C_2H_5)_2$, added dropwise. The mixture was stirred for 1 h, refluxed for 4 h, cooled, treated with 10 ml hydrochloric acid, and refluxed for 3 h. After cooling it was made alkaline with 50 ml 20% NaOH and extracted with ether. The extract was evaporated, the oily residue was dissolved in ether, and neutralized with HCl in ether; 6·5 g (71%) of *V*.HCl, m.p. 125·5 to 126·5°C (ethanol–ether). Mass spectrum: 279 (M^+, $C_{14}H_{17}NOS_2$, 62), 264 (89), 235 (54), 202 (44), 172 (41), 138 (61), 58 (100). ^{1}H NMR spectrum: 2·74 s, 6 H ($N^+(CH_3)_2$); 3·74 s, 3 H (OCH_3); 4·62 s, 2 H ($ArCH_2N$); 6·75 m, 3 H (H-2′, H-4′, H-6′); 7·16 d, 1 H (H-4, J = 5·0); 7·26 t, 1 H (H-5′, J = 8·0); 7·94 d, 1 H (H-5, J = 5·0). For $C_{14}H_{18}ClNOS_2$ (315·9) calculated: 53·23% C, 5·74% H, 11·22% Cl, 4·43% N, 20·30% S; found: 53·51% C, 5·92% H, 11·18% Cl, 4·44% N, 20·27% S.

N,N-Dimethyl-2-(3-methoxyphenylthio)-3-thenylamine (*VIII*)

Similarly like in the preceding case, 7·0 g *VII* reacted with 9·0 g $SOCl_2$ in 80 ml benzene and gave the crude oily acid chloride which was treated in 60 ml cyclohexane under stirring with 30 ml 40% aqueous dimethylamine. Similar processing gave the crude oily dimethylamide which was reduced in 50 ml tetrahydrofuran under nitrogen with 2·15 g $NaBH_4$ and 7·5 g $BF_3.O(C_2H_5)_2$. Processing gave the crude oily *VIII* which was transformed to the hydrochloride (6·1 g, 73%), m.p. 130—131°C (ethanol–ether). ^{1}H NMR spectrum (D_2O): 3·68 s, 6 H ($N^+(CH_3)_2$); 3·73 s, 3 H (OCH_3); 4·34 s, 2 H ($ArCH_2N$); 6·80 m, 3 H (H-2′, H-4′, H-6′); 7·30 t, 1 H (H-5′, J = 8·0); 7·75 d, 1 H (H-4, J = 5·0); 8·00 d, 1 H (H-5, J = 5·0). For $C_{14}H_{18}ClNOS_2$ (315·9) calculated: 53·23% C, 5·74% H, 11·22% Cl, 4·43% N, 20·30% S; found: 53·21% C, 5·85% H, 11·18% Cl, 4·34% N, 20·11% S.

N,N-Dimethyl-4-(3-methoxyphenylthio)-3-thenylamine (*XIII*)

A stirred solution of 10·5 g *XII* in 60 ml tetrahydrofuran was treated under nitrogen with 2·0 g $NaBH_4$ and then at 20—25°C with 9·3 g $BF_3.O(C_2H_5)_2$, which was added dropwise. The mixture was stirred for 1 h and refluxed for 5 h, 12 ml hydrochloric acid were added and the mixture was refluxed for further 3 h. After cooling it was made alkaline with 60 ml 20% NaOH and extracted with ether. The extract was evaporated, the residue was dissolved in ether and neutralized with HCl in ether. Crystallization of the crude product from a mixture of ethanol and ether afforded 4·7 g (42%) of *XIII*.HCl, m.p. 135—138°C. Mass spectrum: 279 (M^+, $C_{14}H_{17}NOS_2$), 42 (100). IR spectrum: 690, 786 (Ar–H); 1 034, 1 250 ($ArOCH_3$); 1 478, 1 572, 1 586, 3 050, 3 070 (Ar); 2 380, 2 485, 2 510, 2 555 (NH^+). ^{1}H NMR spectrum: 2·88 s, 6 H ($N^+(CH_3)_2$); 3·72 s, 3 H (OCH_3); 4·21 s, 2 H ($ArCH_2N$); 6·60—6·80 m, 3 H (H-2′, H-4′, H-6′); 7·25 t, 1 H (H-5′, J = 9·0); 8·05 d, 1 H (H-5, J = 3·0); 8·38 d, 1 H (H-2, J = 3·0). For $C_{14}H_{18}ClNOS_2$ (315·9) calculated: 53·23% C, 5·74% H, 11·22% Cl, 4·43% N, 20·30% S; found: 53·08% C, 5·82% H, 11·22% Cl, 4·45% N, 20·15% S.

N,N-Dimethyl-2-(2-thienylthio)benzylamine (*XVIIIa*)

A suspension of 24·4 g *XVIIa* in 450 ml ether was added over 45 min to a stirred solution of 10·5 g $LiAlH_4$ in 200 ml ether and the mixture was refluxed for 7 h. After cooling it was decomposed under stirring by slow addition of 10·5 ml water, 10·5 ml 15% NaOH and 32 ml water. After 20 min of stirring the precipitated solid was filtered off, washed with ether, the filtrate was dried and evaporated. The residue, representing the almost homogeneous *XVIIIa* (21·3 g, 92%), was transformed to the hydrochloride, m.p. 194—195°C (ethanol–ether). For $C_{13}H_{16}ClNS_2$

(285·8) calculated: 54·62% C, 5·64% H, 12·40% Cl, 4·90% N, 22·44% S; found: 54·64% C, 5·79% H 12·67% Cl, 4·89% N, 22·42% S.

A sample of the hydrochloride was decomposed with NH_4OH and the released oily *XVIIIa* was isolated by extraction with ether. ^{1}H NMR spectrum ($CDCl_3$): 2·30 s, 6 H ($N(CH_3)_2$), 3·46 s, 2 H ($ArCH_2N$); 6·90—7·50 m, 7 H (ArH). For $C_{13}H_{15}NS_2$ (249·4) calculated: 62·61% C, 6·06% H, 5·62% N, 25·71% S; found: 61·98% C, 6·15% H, 5·66% N, 25·54% S.

N,N-Dimethyl-2-(5-bromo-2-thienylthio)benzylamine (*XVIIIb*)

A solution of 12·0 g *XVIIb* in 100 ml tetrahydrofuran was treated under nitrogen with 2·05 g $NaBH_4$ and under stirring at 20—25°C with 10·3 g $BF_3.O(C_2H_5)_2$, added dropwise. The mixture was stirred for 1 h at room temperature and was refluxed for 3 h. After cooling, 30 ml 5M-HCl, were added and refluxing was continued for 3 h. After cooling it was made alkaline with 66 ml 20% NaOH and extracted with ether. The extract was evaporated giving 11·5 g (theoretical) of almost homogeneous oily *XVIIIb*.

Hydrogen maleate, m.p. 127—127·5°C (ethanol–ether). Mass spectrum: 327 (M^+, $C_{13}H_{14}BrNS_2$, 1), 281 (0·5), 203 (12), 165 (100), 150 (15), 132 (20), 58 (65). ^{1}H NMR spectrum: 2·80 s, 6 H ($N^+(CH_3)_2$); 4·40 s, 2 H ($ArCH_2N$); 6·12 s, 2 H (CH=CH of maleic acid); 7·30 to 7·60 m, 6 H (ArH). For $C_{17}H_{18}BrNO_4S_2$ (444·4) calculated: 45·95% C, 4·08% H, 17·99% Br, 3·15% N, 14·43% S; found: 45·97% C, 4·19% H, 17·66% Br, 3·08% N, 14·54% S.

N,N-Dimethyl-3-(3-hydroxyphenylthio)-2-thenylamine (*VI*)

A stirred mixture of 3·95 g *V*.HCl and 25 ml 48% hydrobromic acid was heated for 7 h under reflux to 120°C. After cooling it was diluted with water, made alkaline with NH_4OH and extracted with chloroform. Processing of the extract gave 2·55 g (77%) of crystalline *VI*, m.p. 113—115°C. IR spectrum: 689, 773, 844, 896 (Ar–H); 1 259 (ArOH); 1 486, 1 572, 3 040, 3 105 (Ar); 2 560, 2 655 (NH^+); 2 780 (N–CH_3). ^{1}H NMR spectrum ($CDCl_3$): 2·19 s, 6 H ($N(CH_3)_2$); 3·69 s, 2 H ($ArCH_2N$); 6·12 bs, 1 H (H-2′); 6·70 m, 2 H (H-4′, H-6′); 7·05 d, 1 H (H-4, J = 5·0); 7·18 t, 1 H (H-5′, J = 8·0); 7·32 d, 1 H (H-5, J = 5·0). For $C_{13}H_{15}NOS_2$ (265·4) calculated: 58·83% C, 5·70% H, 5·28% N, 24·16% S; found: 58·56% C, 5·75% H, 5·19% N, 24·05% S.

Hemioxalate, m.p. 217—219·5°C (aqueous ethanol). For $C_{13}H_{15}NOS_2 + 0{\cdot}5\ C_2H_2O_4$ (310·4) calculated: 54·17% C, 5·20% H, 4·51% N, 20·66% S; found: 53·92% C, 5·36% H, 4·42% N, 20·42% S.

N,N-Dimethyl-2-(3-hydroxyphenylthio)-3-thenylamine (*IX*)

A similar reaction of 3·8 g *VIII*.HCl with 25 ml 48% hydrobromic acid and similar processing gave 3·2 g (theoretical) of almost homogeneous oily *IX*. It was transformed to the hydrogen oxalate, m.p. 145—149°C (ethanol). Mass spectrum: 265 (M^+, $C_{13}H_{15}NOS_2$, 26), 250 (15), 221 (23), 219 (25), 188 (31), 187 (41), 140 (22), 137 (19), 128 (16), 97 (32), 65 (27), 58 (100), 45 (93), 44 (54). ^{1}H NMR spectrum: 2·63 s, 6 H ($N^+(CH_3)_2$); 4·18 s, 2 H ($ArCH_2N$); 6·60 m, 3 H (H-2′, H-4′, H-6′); 7·16 t, 1 H (H-5′, J = 8·0); 7·44 d, 1 H (H-4, J = 5·0); 7·96 d, 1 H (H-5, J = = 5·0). For $C_{15}H_{17}NO_5S_2$ (355·4) calculated: 50·69% C, 4·82% H, 3·94% N; found: 50·37% C, 5·12% H, 3·96% N.

N,N-Dimethyl-4-(3-hydroxyphenylthio)-3-thenylamine (*XIV*)

A similar reaction of 3·35 g *XIII*.HCl with 25 ml 48% hydrobromic acid and similar processing gave 2·8 g (99%) of *XIV*, m.p. 143—145°C (methanol). IR spectrum: 687, 771, 865, 900 (Ar–H);

1 000, 1 266 (ArOH); 1 496, 1 522, 1 591, 3 100 (Ar); 2 475, 2 500, 2 560, 2 665 (NH^+); 2 780 (N–CH_3). ^{1}H NMR spectrum: 2·14 s, 6 H ($N(CH_3)_2$); 3·32 s, 2 H ($ArCH_2N$); 6·55 m, 3 H (H-2′, H-4′, H-6′); 7·12 t, 1 H (H-5′); 7·56 d, 1 H (H-5, $J = 3·0$); 7·76 d, 1 H (H-2, $J = 3·0$). For $C_{13}H_{15}NOS_2$ (265·4) calculated: 58·83% C, 5·70% H, 5·28% N; found: 58·93% C, 5·80% H, 5·15% N.

Hemioxalate, m.p. 230–232°C (ethanol–ether). Mass spectrum: 265 (M^+, $C_{13}H_{15}NOS_2$), 250, 221, 220, 219, 171, 128, 97, 58 (100). For $C_{13}H_{15}NOS_2 + 0·5\ C_2H_2O_4$ (310·4) calculated: 54·17% C, 5·20% H, 4·51% N, 20·66% S; found: 53·95% C, 5·30% H, 4·53% N, 20·46% S.

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