POTENTIAL ANTIDEPRESSANTS: 1-(2-(METHOXY- AND HYDROXY--PHENYLTHIO)PHENYL)-2-PROPYLAMINES

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2-(Methoxyphenylthio)benzaldehydes *Xa*—*Xd* were reacted with nitroethane in boiling acetic acid to give the corresponding 1-aryl-2-nitropropenes *XIIa*—*XIId*; benzonitriles *XIIIa* and *XIIIc* and benzaldoximes *XXIc* and *XXId* were isolated as by-products. Chromatographed compounds *XIIa*—*XIId* were reduced with lithium aluminium hydride to the primary amines *VIIa*—*VIId*, and formylated by heating with ethyl formate to the formamides *XIVa*, *XIVc*, and *XIVd*. Reduction of the formamides with lithium aluminium hydride afforded the secondary amines *VIIIa*, *VIIIc*, and *VIIId*, and methylation of the primary amines with formic acid and formaldehyde gave the tertiary amines *IXa*, *IXc*, and *IXd*. Compound *VIIIa* was prepared also by an alternative route starting from the nitrile *XIIIa* and proceeding via *XIXa* and *XIVa*. Some of the methoxylated amines were demethylated either by heating with pyridine hydrochloride or by treatment with boron tribromide to the title compounds *IVa*, *IVc*, *Vc*, *Vd*, *VIa*, and *VIc*. The amines prepared were transformed to salts for characterization and for pharmacological testing. Compound *VIIIa* (hydrogen oxalate VÚFB-15 475) showed clearly the character of a potential antidepressant.

In a recent communication[1] the antireserpine activity (in all the three common tests in rodents) and some anorectic activity of N-methyl-1-(2-(phenylthio)phenyl)-2--propylamine (*I*) has been described by our team. In the same communication[1], N,N-dimethyl-2-(phenylthio)benzylamine (*II*) has been reported to have high affinity to the imipramine as well as desipramine binding sites in the rat brain, and antireserpine activity in two tests. It potentiated significantly the toxicity of yohimbine and inhibited strongly the reuptake of 5-hydroxytryptamine as well as of noradrenaline in the rat brain structures. More recently it has been reported[2] that N,N-dimethyl-2-(3-hydroxyphenylthio)benzylamine (*III*) is a highly active and extremely selective inhibitor of 5-hydroxytryptamine reuptake in the brain structures having at the same time the typical antireserpine activity. These are promising indications that we arrived at the structural field of potential antidepressants of a new generation.

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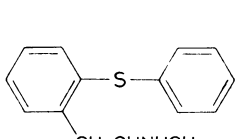
This fact was considered to warrant a continuation of studies along this line. The next step should be the synthesis and testing of the title compounds *IVa–VId* and of their O-methylated precursors and the present communication describes our efforts in this direction and the results attained.



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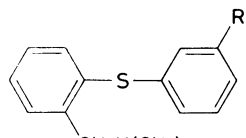
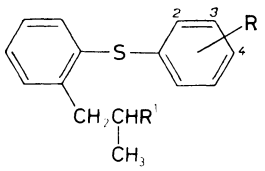


II, R = H
III, R = OH

It was the intention to prepare compounds *IV–VI* by demethylation of the corresponding methoxy compounds *VII–IX*. The first task was thus the synthesis of *VIIa–IXd* or at least some of them. We tried to use to this end both methods used and described by us in the nonmethoxylated series[1]. The work proceeded in four series (*a–d*) and the starting products were the aldehydes *Xa–Xd* which were obtained by reactions of 2-chlorobenzaldehyde with the corresponding thiophenols, i.e. 2-methoxythiophenol[3], 3-methoxythiophenol[4], 4-methoxythiophenol[5], and 3,4-dimethoxythiophenol[6]. The reactions were carried out in hexamethylphosphoric triamide or dimethylformamide at 100°C in the presence of sodium carbonate or potassium carbonate (for analogy, cf. refs[2,7]). Working in the presence of aqueous sodium hydroxide (cf. ref.[1]) resulted in lower yield (cf. the case of *Xc*). The aldehydes were characterized by spectra and by crystalline semicarbazones (*XIa–XId*). Two of the aldehydes were described earlier: *Xa* (ref.[8], different method), *Xb* (ref.[2], similar method).

The work on the synthesis of *VII–IX* proceeded in the individual series (*a–d*) differently and it is thus necessary to describe the experiments in the individual series separately. In series *a* the aldehyde *Xa* was reacted with nitroethane in boiling acetic acid in the presence of ammonium acetate (method, refs[1,9]). The oily product obtained was found to be inhomogeneous and was separated by chromatography on silica gel or on aluminium oxide. The first to be eluted was the homogeneous oily *XIIa* which was followed by a crystalline compound $C_{14}H_{11}NOS$ identified by analysis and spectra as the known nitrile *XIIIa* (ref.[8]). Compounds *XIIa* and *XIIIa* were formed in the ratio of approximately 2 : 1. We thus meet again the formation of a nitrile from an aromatic aldehyde by refluxing with nitroethane in acetic acid (cf. refs[1,10]) which was described in the literature[11] as being specific for this reaction, carried out in the presence of sodium acetate. We have to repeat the most likely explanation of this strange reaction; it assumes the following steps: (i) rearrangement of nitroethane to ethanehydroxamic acid in the acid medium[12], (ii) cleavage of

ethanehydroxamic acid to hydroxylamine, (iii) formation of the oxime of the starting aldehyde, and (iv) dehydration of the oxime. Reaction of *Xa* with nitroethane in boiling acetic acid in the presence of butylammonium acetate (instead of ammonium acetate) gave a higher yield on the desired *XIIa* (88% after chromatography) and the formation of *XIIIa* was suppressed. Compound *XIIa* was reduced with lithium aluminium hydride in ether and gave the oily base *VIIa* which was transformed to the hydrochloride appearing to be the monohydrate. The mass spectrum confirmed the elemental composition of the base $C_{16}H_{19}NOS$ and the ^{1}H NMR spectrum verified the structure of *VIIa* hydrochloride including the presence of the crystal water. Compound *VIIa* was formylated by heating with ethyl formate in autoclave to 150°C and gave the crystalline *XIVa* in a high yield. The ^{1}H NMR spectrum of this compound showed the usual cleavage of the formyl hydrogen signal; more surprising was the splitting of the signal of the C—CH_3 group. Reduction of *XIVa* with lithium aluminium hydride in a mixture of ether and benzene afforded the oily *VIIIa* which was transformed to the hydrogen oxalate crystallizing from ethanol and ether and melting constantly at 71–73°C. It gave correct analysis and spectra (IR and ^{1}H NMR) were in agreement with the structure. This oxalate was considered the "crystal modification A". A single recrystallization of this form from the same mixture of solvents was connected with rise of melting point to 97–100°C. This "crystal modification B" of *VIIIa* hydrogen oxalate gave also correct analysis and spectra of the released base were identical with those of the base released from the modification A. Methylation of *VIIa* with a refluxing mixture of aqueous formic acid and formaldehyde (Eschweiler–Clarke reaction[13]) afforded the oily *IXa* which was transformed to the crystalline hydrochloride; ^{1}H NMR spectrum of the released base confirmed the structure.



IV, R^1 = NH_2
V, R^1 = $NHCH_3$
VI, R^1 = $N(CH_3)_2$

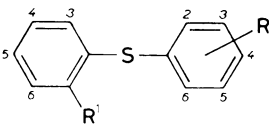
In formulae *IV* – *VI*: *a*, R = 2-OH *b*, R = 3-OH *c*, R = 4-OH
d, R = 3,4-$(OH)_2$

A different approach in series *a* aimed only at *VIIIa*. The aldehyde *Xa* was reduced with sodium borohydride in aqueous ethanol to *XVa* (for a different method, cf. ref.[8]). This alcohol was transformed by treatment with thionyl chloride in benzene

to *XVIa* which was reacted without characterization with potassium cyanide in boiling aqueous ethanol and gave *XVIIa*. The transformation of *XVIIa* to *XIXa* proceeded in analogy to refs[1,14]. Compound *XVIIa* was treated with sodium ethoxide in toluene and the anion formed was acylated with ethyl acetate to give the oily *XVIIIa* which was cleaved without purification by heating with 85% phosphoric acid and afforded the oily *XIXa*. This was purified by distillation and its structure was corroborated by spectra. Compound *XIXa* was subjected to the Leuckart–Wallach reaction[13], i.e. it was refluxed with a mixture of formamide and formic acid. An inhomogeneous oily product was obtained which was separated by chromatography on aluminium oxide. The first to be eluted with benzene was an important amount of an oil which was purified by distillation and identified as *XVIIa*. Further elution with chloroform afforded then 44% of the crystalline formamido derivative *XIVa* which proved identical with the product mentioned above. The last chloroform fractions eluted a minor amount of a crystalline compound $C_{15}H_{15}NO_2S$ (analysis and mass spectrum) which was identified by IR and ^{1}H NMR spectra as the amide *XXa*. We prefer not to consider *XVIIa* and *XXa* by-products of the Leuckart–Wallach reaction described; because the intermediates *XVIIIa* and *XIXa* were oily, the used *XIXa* probably contained some starting *XVIIa* which mostly remained unchanged under the conditions of the Leuckart–Wallach reaction. Only a small part was hydrated to *XXa* which thus appeared as a further and unexpected product of the reaction. Compound *XIVa*, obtained by this method, was reduced with diborane, generated "in situ" by reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran (method[15,16]). The oily base obtained was transformed to the hydrogen oxalate melting at 114 – 115°C which is being considered „crystal modification C" of *VIIIa* hydrogen oxalate. Its analysis was correct and the released base afforded a fully satisfying ^{1}H NMR spectrum.

In series *b* *Xb* was reacted with nitroethane in boiling acetic acid in the presence of butylammonium acetate. The inhomogeneous oily product was chromatographed on silica gel giving 81% of homogeneous *XIIb* with satisfactory analysis and spectra. The minor by-product was not isolated in pure state. Compound *XIIb* was reduced with lithium aluminium hydride in ether and the purified oily base *VIIb* was obtained via the crude hydrochloride and by chromatography on aluminium oxide. It was not completely homogeneous because the ^{1}H NMR spectrum showed splitting of signals of OCH_3 and C—CH_3. The character of the contaminant is unclear; it hardly could be the expected 2-(3-methoxyphenylthio)benzylamine (cf. ref.[2]). The alternative approach started again by reduction of the aldehyde *Xb* with sodium borohydride in aqueous ethanol giving *XVb* (different method[17]). This was transformed to *XVIIb* via *XVIb* by the described procedure[17]. Reaction of *XVIIb* with sodium ethoxide and ethyl acetate in toluene gave an oily product considered to be the expected *XVIIIb* and it was attempted to cleave it by heating with 85% phosphoric acid. An inhomogeneous product (according to TLC consisting of four main com-

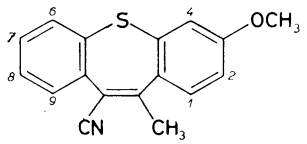
ponents) was obtained and was separated by chromatography on silica gel. The first two components were eluted with a mixture of benzene and light petroleum, were oily and were not identified. The major product was eluted with benzene, it was crystalline and had the composition $C_{17}H_{13}NOS$ (analysis and mass spectrum).



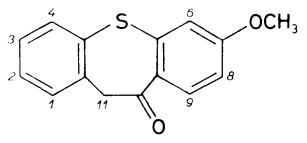
VII, $R^1 = CH_2CH(CH_3)NH_2$
VIII, $R^1 = CH_2CH(CH_3)NHCH_3$
IX, $R^1 = CH_2CH(CH_3)N(CH_3)_2$
X, $R^1 = CHO$
XI, $R^1 = CH{=}N{-}NHCONH_2$
XII, $R^1 = CH{=}C(CH_3)NO_2$
XIII, $R^1 = CN$
XIV, $R^1 = CH_2CH(CH_3)NHCHO$
XV, $R^1 = CH_2OH$
XVI, $R^1 = CH_2Cl$
XVII, $R^1 = CH_2CN$
XVIII, $R^1 = CH(CN)COCH_3$
XIX, $R^1 = CH_2COCH_3$
XX, $R^1 = CH_2CONH_2$
XXI, $R^1 = CH{=}NOH$
XXII, $R^1 = CH_2NHCH_3$

In formulae *VII*–*XXII*: *a*, R = 2-OCH_3 *b*, R = 3-OCH_3 *c*, R = 4-OCH_3 *d*, R = 3,4-$(OCH_3)_2$

It showed a high degree of conjugation (UV spectrum), the presence of the C=C—CN fragment (the band at 2 200 cm^{-1} in the IR spectrum) and the ^1H NMR spectrum showed in addition to 7 aromatic protons the presence of $ArOCH_3$ and of a further methyl group (singlet at 2·70 ppm). A cyclodehydration of the interme diate *XVIIIb* must have taken place instead of the cleavage to *XIXb*. The structure of 3-methoxy-11-methyldibenzo[*b*,*f*]thiepin-10-carbonitrile (*XXIII*) was proposed for the product and is in agreement with all data available. The cyclodehydration of *XVIIIb* to *XXIII* was evidently promoted by the presence of the methoxy group activating strongly the *p*-standing hydrogen. A similar case was the repeatedly encountered formation of 3-methoxythioxanthone in the series of analogous 2-(3-methoxyphenylthio)benzylamines[2]. The last product which was eluted with benzene was identified as the known 7-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXIV*, ref.[17]). In this case the cyclization occurred under the loss of two carbon atoms



XXIII



XXIV

which must be explained by the primary hydrolysis of CN to COOH and by the following acid-forming cleavage of the β-keto acid formed; the last step was the cyclization of the intermediate substituted ((phenylthio)phenyl)acetic acid with phosphoric acid. The synthetic route via *XIXb* appeared thus to be unreal.

In series *c* reaction of the aldehyde *Xc* with nitroethane in boiling acetic acid in the presence of butylammonium acetate gave an inhomogeneous product which was separated by chromatography on silica gel. The first to be eluted with a mixture of benzene and light petroleum was the rather homogeneous oily *XIIc* in the yield of 83%. Elution with benzene gave a small amount of a crystalline compound $C_{14}H_{11}NOS$ (analysis and mass spectrum) which was identified as the nitrile *XIIIc*. The last component of the crude product which was eluted with a mixture of benzene and ether was a further crystalline substance identified as the oxime *XXIc*. In this way we had in our hands a second intermediate of the sequence leading from the benzaldehydes to the benzonitriles like mentioned in series *a*, in fact the immediate precursor of *XIIIc*. The oxime *XXIc* was prepared for comparison also directly from *Xc* and the identity of both products was proved. At the time of these experiments we considered a different possibility for the formation of benzaldoximes (and benzonitriles likewise) from benzaldehydes and nitroethane. According to this hypothesis the first step of the sequence could be the reduction of nitroethane to acetaldoxime (such reductions of nitroalkanes with various agents were really described[18-20]); the aldehydes *X* could be the reduction agents. The other step could then be the transoximation reaction between acetaldoxime and the corresponding benzaldehydes *X* which should lead, presumably, to the oximes *XXI* and by their dehydration the nitriles *XIII* could be formed. For supporting this hypothesis we subjected *Xc* to interaction with butyraldoxime (ref.[21]) in boiling acetic acid. Separation of the crude product by chromatography on silica gel gave 50% of *XXIc*, identical with the authetic product. So far, this hypothesis could not be simply rejected. On the other hand, the reduction of nitroethane with the aldehydes *X* was not proven and so the explanation, mentioned for series *a* should be preferred. Reduction of *XIIc* with lithium aluminium hydride in ether gave the oily base *VIIc* which could be transformed to crystalline hydrochloride and formate. The base *XIIc*, released from the purified hydrochloride, was found to be completely homogeneous by the ^{1}H NMR spectrum. Formylation of the crude base *VIIc* by heating with ethyl formate in autoclave to 150°C gave the crystalline amide *XIVc* with satisfactory analysis. The ^{1}H NMR spectrum, however, showed inhomogeneity by splitting of some signals. The inhomogeneity of *XIVc* became clear in the following step which was the reduction with lithium aluminium hydride in a mixture of benzene and ether. The oily amine was transformed to the oxalate whose analysis corresponded to *VIIIc* hydrogen oxalate but the mass spectrum indicated the presence of an impurity $C_{15}H_{17}NOS$. Processing of the mother liquors after crystallization of *VIIIc* hydrogen oxalate gave a different oxalate which was identified as

XXIIc hydrogen oxalate. This shows that the crude *VIIc* contained some 2-(4-methoxyphenylthio)benzylamine which was N-formylated and the product reduced to *XXIIc*. The key, of course, is the presence of some *XIIIc* in the crude *XIIc* used. The amine *VIIIc* was also transformed to the crystalline hydrochloride which was carefully purified by crystallization and the base, released from the purified hydrochloride, proved complete homogeneity (^{1}H NMR spectrum). The Eschweiler–Clarke methylation[13] of *VIIc* afforded *IXc*, isolated in the form of hydrogen oxalate. Whereas the mass spectrum indicated the presence of N,N-dimethyl-2-(4-methoxyphenylthio)benzylamine as the contaminant, the ^{1}H NMR spectrum confirmed the identity of *IXc* without any doubts as to the homogeneity.

In series *d*, likewise, reaction of *Xd* with nitroethane in boiling acetic acid in the presence of butylammonium acetate gave inhomogeneous *XIId* which was chromatographed on silica gel. A mixture of benzene and ether (18 : 1) eluted first the almost homogeneous *XIId* and in the last fractions some 5% of *XXId*. Reduction of *XIId* with lithium aluminium hydride in ether afforded *VIId*, isolated as the hydrochloride hemihydrate. The mass spectrum confirmed the identity and together with the ^{1}H NMR spectrum of the released base confirmed the homogeneity. The following formylation with ethyl formate gave the crystalline amide *XIVd* (doubts about homogeneity through the ^{1}H NMR spectrum). Reduction with lithium aluminium hydride in a mixture of benzene and ether afforded *VIIId*, characterized and purified in the form of crystalline hydrogen oxalate. The released oily base *VIIId* was homogeneous (^{1}H NMR spectrum). The Eschweiler–Clarke methylation[13] of *VIId* gave *IXd*, isolated and purified again in the form of hydrogen oxalate. The released oily base *IXd* was, likewise, homogeneous (^{1}H NMR spectrum).

Methoxy amines *VIIa*, *VIIc*, *VIIIc*, *IXa*, *IXc*, and *VIIId* were demethylated to the corresponding phenolic amines *IVa*, *IVc*, *Vc*, *VIa*, *VIc*, and *Vd*. In the first five cases the demethylation was carried out by heating with pyridine hydrochloride to 210 to 215°C (method *A*), the products were isolated and purified in the form of crystalline salts, and characterized by spectra. In the last case the demethylation was carried out with boron tribromide in chloroform at room temperature (method *B*), the product was isolated and purified as the hydrogen maleate and the released base crystallized as the hemihydrate. Even in this case, the identity was confirmed by spectra. The phenolic amines obtained are assembled in Table I with the usual experimental data and their spectra are assembled in Table II. The preparations of *IVa* and *Vd* are described in the Experimental.

The compounds prepared were pharmacologically tested on the one hand as potential antidepressants, and by methods of the general screening on the other. They were administered orally (unless otherwise stated) in the form of salts, described in Experimental (*VIIIa* was tested in the form of modifications A and C of the hydrogen oxalate); the doses given were calculated per bases.

TABLE I

1-(2-(Hydroxyphenylthio)phenyl)-2-propylamines and their salts

Compound[a]	Method (yield, %)	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
IVa-HCl	*A*[b]	182–183	$C_{15}H_{18}ClNOS$	60·89	6·15	11·98	4·74	10·84
	(56)	(ethanol–ether)	(295·9)	60·65	6·00	12·20	4·96	10·60
IVc-HO	*A*	220–221	$C_{16}H_{18}NO_3S$	63·15	5·96	—	4·61	10·52
	(90)	(ethanol–ether)	(304·3)	62·85	5·90	—	4·31	10·65
Vc-HCl	*A*	189–191	$C_{16}H_{20}ClNOS$	62·01	6·52	11·44	4·52	10·35
	(69)	(ethanol–ether)	(309·9)	61·93	6·65	11·56	4·52	10·27
Vd-HH	*B*	86–87	$C_{16}H_{19}NO_2S + 0{\cdot}5\ H_2O$	64·40	6·75	—	4·69	10·75
	(68)	(water)	(298·4)	64·70	6·45	—	4·62	10·66
Vd-HM	*B*[b]	164	$C_{20}H_{23}NO_6S$	59·24	5·72	—	3·45	7·91
		(ethanol–ether)	(405·4)	59·13	5·76	—	3·37	7·75
VIa-HCl-HH	*A*	181–182	$C_{17}H_{22}ClNOS + 0{\cdot}5\ H_2O$	61·33	6·96	10·65	4·21	9·63
	(65)	(ethanol–ether)	(332·9)	61·53	6·89	10·95	4·51	9·92
VIc-HCl-E	*A*	79–81	$C_{19}H_{28}ClNO_2S + C_2H_6O$	61·67	7·62	9·58	3·79	8·67
	(94)	(ethanol–ether)	(370·0)	61·36	7·36	9·63	3·97	8·90

[a] HO hemioxalate, HH hemihydrate, E solvate with ethanol, HM hydrogen maleate; [b] see Experimental.

TABLE II

Spectra of 1-(2-(hydroxyphenylthio)phenyl)-2-propylamines and salts

Compound	Spectrum	Data
IVa-HCl	MS	259 (M^+, $C_{15}H_{17}NOS$, 0·7), 216 (0·8), 213 ($C_{13}H_9OS$, 0·7), 44 (100)
	IR	749 (4 adjacent Ar–H); 1 195, 1 255, 1 271, 1 287, 1 350, 1 360, 1 387 (ArOH); 1 503, 1 589, 1 600, 3 050 (Ar); 2 465, 2 495, 2 550, 2 685, 2 735 (NH_3^+); 3 130, 3 195 (NH_2)
IVc-HO[a]	MS	259 (M^+, $C_{15}H_{17}NOS$, 1·5), 216 (5·5), 44 (100)
	^{1}H NMR[b]	1·19 d, 3 H (C–CH_3, J = 6·0); 2·90–3·60 m, 3 H ($ArCH_2CHN$); 6·80–7·30 m, 8 H (ArH); 7·40 bs (NH_3^+, OH)
Vc-HCl	MS	273 (M^+, $C_{16}H_{19}NOS$, 0·5), 216 ($C_{13}H_{12}OS$, 0·7), 213 ($C_{13}H_9OS$, 1·6), 58 (C_3H_8N, 100)
	IR	737, 835 (4 and 2 adjacent Ar–H); 1 220, 1 264 (ArOH); 1 493, 1 581, 1 600, 3 058 (Ar); 2 455, 2 740, 2 760 (NH_3^+); 3 235 (OH)
Vd[c]	MS	289 (M^+, $C_{16}H_{19}NO_2S$, 0·3), 213 (0·4), 184 ($C_{12}H_8S$, 0·5); 58 (100)
	UV	249 (4·08), infl. 285 (3·73)
	IR	750, 810, 869 (4 and 2 adjacent and solitary Ar–H); 1 260 (ArOH); 1 562, 1 585 (Ar); 2 480, 2 660 (NH_2^+); infl. 3 280 (NH, OH, H_2O)
	^{1}H NMR[b]	0·98 bd, 3 H (C–CH_3, J = 5·0); 2·30 s, 3 H (NCH_3); 2·90 bm, 3 H ($ArCH_2CHN$); 6·20 bs, 3 H (2 × OH and NH); 6·60–7·20 m, 7 H (ArH)
Vd[d]	MS	289 (M^+, $C_{16}H_{19}NO_2S$, 0·4), 229 ($C_{13}H_9O_2S$, 0·3), 213 ($C_{13}H_9OS$, 0·4), 58 (C_3H_8N, 100)
VIa-HCl[c]	MS	287 (M^+, $C_{17}H_{21}NOS$, 0·3), 272, 243, 72
	IR	760 (4 adjacent Ar–H); 1 200, 1 293 (ArOH); 1 496, 1 585 (Ar); 2 480, 2 510, 2 585, 2 650 (NH^+); 3 120 (OH)
VIc-HCl[e]	MS	287 (M^+, $C_{17}H_{21}NOS$, 0·3), 272, 243, 72 (presence of ethanol proven)
	UV	234 (4·19), 247 (4·24), infl. 274 (3·76)
	IR	758, 835 (4 and 2 adjacent Ar–H); 1 045 (CH_2OH of ethanol); 1 165, 1 270 (ArOH); 1 492, 1 600 (Ar); 2 485, 2 515, 2 640 (NH^+); 3 120, 3 220 (OH)

[a] HO hemioxalate; [b] in CD_3SOCD_3; [c] hemihydrate; [d] HM hydrogen maleate; [e] solvate with C_2H_5OH.

Acute toxicity in mice (LD_{50} in mg/kg): *IVa*, 371; *IVc*, 400; *Vc*, 264; *Vd*, 529; *VIa*, 261; *VIc*, 199 (25 i.v.); *VIIa*, 239; *VIIc*, 259 (35 i.v.); *VIId*, 341 (40 i.v.); *VIIa*, 361; *VIIIc*, 320 (25 i.v.); *VIIId*, 256 (40 i.v.); *IXa*, 228 (17·5 i.v.); *IXc*, 156 (31 i.v.); *IXd*, 360. Doses i.v. (D in mg/kg) used in the acreening: *VIc*, 5; *VIIc*, 7; *VIId*, 8; *VIIIc*, 5; *VIIId*, 8; *IXa*, 3.

Antireserpine activities: (i) Inhibition of reserpine-induced ptosis in mice: At 25 mg/kg significant effect with *IVa*, *VIIa*, *VIIIa* (threshold dose 10 mg/kg, i.e. equipotent with desipramine and prothiadene); *VIIIc*, *IXc* (threshold dose 3 mg/kg, i.e. equipotent with imipramine); the other compounds were ineffective at 25 mg/kg. (ii) Antagonization of the ulcerogenic effect of reserpine in rats: *IVa*, *VIIa*, *VIIc*, *VIId*, and *VIIIc* were significantly active at 50 mg/kg; *VIIIa* was still active at 12·5 mg/kg. Compound *VIIIa* inhibited also the formation of gastric lesions after indomethacin in rats, ED_{50} 13 mg/kg. (iii) Antagonization of reserpine hypothermia in mice: the effect was found only with *VIIIa* at 10 mg/kg in the whole interval investigated, i.e. in 1–4 h after the administration. Potentiation of yohimbine toxicity in mice, ED_{50}: *VIIIa*, 27·2 mg/kg.

Inhibition of binding of 4 nM[^{3}H]imipramine in the rat hypothalamus, IC_{50} in nmol l^{-1}: *Vc*, 69·1; *VIId*, 249·9; *VIIIa*, inhibited at 100 nmol l^{-1} by 72%; *IXc*, 20·9; *IVc*, *Vd*, *VIc*, *VIIa*, *VIIc*, *VIIIc*, *VIIId*, *IXa*, and *IXd* inhibited at 100 nmol l^{-1} less than by 50%. Inhibition of binding of 4 nM [^{3}H]desipramine in the rat hypothalamus, IC_{50} in nmol l^{-1}: *Vc*, 292; *VIId*, 6 992; *VIIIa*, 237·3; *VIIIc*, >100; *IXc*, 982·2; *IVc*, *Vd*, *VIa*, *VIc*, *VIIa*, *VIIc*, *VIIId*, *IXa*, and *IXd* did not inhibit the binding at 100 nmol l^{-1}. For *VIIIa* the inhibition of reuptake of 10 mM [^{3}H]5-hydroxytryptamine in the rat brain (IC_{50} 18·4 nmol l^{-1}) and of the uptake of 10 nM [^{3}H]-noradrenaline in the rat brain cortex in vitro (IC_{50} 353·75 nmol l^{-1}) was estimated. Compound *VIIIa* was also investigated from the point of view of the influence of an oral dose of 100 mg/kg on the levels of 5-hydroxytryptamine (5 HT) and of 5-hydroxyindoleacetic acid (5 HIAA) in the hypothalamus of male rats; *VIIIa* brought about a significant drop of 5HT and a significant increase of 5HIAA levels. The same compound in the dose of 100 mg/kg did not antagonize the adrenaline toxicity in mice, in the dose of 50 mg/kg (administered 30 min prior to 5 mg/kg of perphenazine i.p.) had not anticataleptic effect, and in the dose of 30 mg/kg it did not show anticholinergic activity in the oxotremorine test in mice.

Anorectic activity in male rats: *VIIc* in the dose of 100 mg/kg had the effect in the interval of 1 h after the administration; *VIIIa* in the dose of 50 mg/kg had the effect during the whole interval of 1–4 h after the administration; *IXc* at 100 mg/kg was active in the interval of 1–4 h; *VIIId*, ED_{50} 40 mg/kg (tested in mice); compounds *VIIa*, *VIId*, *VIIIc*, and *IXa* were inactive at 100 mg/kg (rats). Influence on the spontaneous locomotor activity of mice in the test of Dews in the dose of 10 mg/kg: only *VIIIc* and *IXd* significantly inhibited the activity, the other were inactive. Compounds *IVa*, *Vc*, *Vd*, *VIIIa*, *VIIId*, and *IXc* were tested for the possible dopa-

minergic activity by inhibition of binding of 0.5nM [^{3}H]spiperone in the rat corpus striatum; in the concentration of 200 nmol l^{-1} none of the compounds did inhibit the binding. Hypotensive effect in normotensive anaesthetized rats (brief and sharp drops of the blood pressure after the doses D i.v.): *VIc*, *VIIc*, *VIIIc*, *VIIId*, *IXa*. Spasmolytic effects on the isolated rat duodenum (concentration in mg/l reducing the contractions to 50%) against contractions induced by (i) acetylcholine: *VIc*, 1; *VIIc*, 1–10; *VIIIc*, 1–10; *VIIId*, 1–10; *IXa*, 1–10; (ii) barium chloride: 1–10 for *VIc*, *VIIc*, *VIIIc*, *VIIId*, and *IXa*.

In conclusion, only compound *VIIIa* (hydrogen oxalate VÚFB – 15 475) showed clearly the character of a potential antidepressant (antireserpine activity in three tests, significant potentiation of yohimbine toxicity, affinity to imipramine as well as desipramine binding sites in the hypothalamus, indication of selective inhibition of the 5HT reuptake in the brain structures). Due to some signs of cardiotoxicity in rats (arrhythmogenic effect similar to that of amitriptyline), its testing was discontinued.

EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder or in a Koffer 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 ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in NUJOL, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in $CDCl_3$ unless otherwise stated, δ in ppm, J in Hz) with a CW-NMR spectrometer Tesla BS 487C (80 MHz) and the mass spectra (m/z, fragments and/or %) with MCH 1 320 and/or Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

2-(2-Methoxyphenylthio)benzaldehyde (*Xa*)

A stirred mixture of 14·0 g 2-methoxythiophenol[3], 30 ml dimethylformamide, 10·6 g Na_2CO_3, and 13·2 g 2-chlorobenzaldehyde was heated under nitrogen for 3·5 h to 100°C. The mixture was poured to 350 ml ice-cold water and the separated semi-solid product was extracted with benzene. Processing of the extract gave 22·8 g of solid residue which was crystallized from 20 ml ethanol; 13·8 g (60%) of *Xa*, m.p. 107–108°C (ethanol). The analysis and spectra confirmed the identity. Réf.[8], m.p. 107·5–109·5°C (different synthetic method). Using K_2CO_3 instead of Na_2CO_3 led to the same product in the yield of 58%.

Semicarbazone (*XIa*), m.p. 216–218°C (ethanol). UV spectrum: 287 (4·36), infl. 331 (4·00). IR spectrum: 750, 759 (4 adjacent Ar–H); 1 249, 1 373 ($ArOCH_3$); 1 475, 1 571, 1 580, 3 048 (Ar); 1 708 ($NHCONH_2$); 3 140, 3 210, 3 260, 3 450 (NH, NH_2). For $C_{15}H_{15}N_3O_2S$ (301·4) calculated: 59·78% C, 5·02% H, 13·94% N, 10·64% S; found: 59·51% C, 5·09% H, 14·24% N, 10·80% S.

2-(3-Methoxyphenylthio)benzaldehyde (*Xb*)

A stirred mixture of 14·0 g 3-methoxythiophenol[4], 30 ml hexamethylphosphoric triamide, 10·6 g Na_2CO_3, and 13·2 g 2-chlorobenzaldehyde was heated under nitrogen for 3·5 h to 100°C and processed similarly as in the preceding case. The solid residue was crystallized from 20 ml ethanol giving 18·1 g (79%) of *Xb*, m.p. 63–64°C (ethanol). UV spectrum: infl. 231 (4·28), infl. 248 (4·09), infl. 269 (3·83), infl. 285 (3·73), 338 (3·45). IR spectrum: 755, 786, 828, 860 (4 and 2 adjacent and solitary Ar–H); 1 255 ($ArOCH_3$); 1 482, 1 590, 3 000, 3 060 (Ar); 1 681, 2 760 (ArCHO). Ref.[2], m.p. 63·5–64·5°C (similar reaction but in dimethylformamide in the presence of K_2CO_3).

Semicarbazone (*XIb*), m.p. 210–212°C (ethanol). For $C_{15}H_{15}N_3O_2S$ (301·4) calculated: 59·78% C, 5·02% H, 13·94% N, 10·64% S; found: 59·60% C, 5·02% H, 13·78% N, 10·50% S.

2-(4-Methoxyphenylthio)benzaldehyde (*Xc*)

A) 4-Methoxythiophenol[5] (240 g) was added over 10 min to a stirred mixture of 510 ml dimethylformamide and 180 g Na_2CO_3. After 15 min of stirring 225 g 2-chlorobenzaldehyde were added over 10 min and the mixture was heated under nitrogen for 6 h to 100°C under stirring. After standing overnight at room temperature it was poured into 3·5 l water, the suspension obtained was stirred for 1 h, the product was filtered, washed with 300 ml water and crystallized from 1 l ethanol giving 345 g (88%) of *Xc*, m.p. 104–105°C (ethanol. UV spectrum: 231 (4·43), infl. 266 (3·98), 341 (3·58). IR spectrum: 770, 800, 820, 850 (4 and 2 adjacent Ar–H); 1 490, 1 558, 1 569, 1 590 (Ar); 1 669, 2 740 (ArCHO). ^{1}H NMR spectrum: 3·82 s, 3 H (OCH_3); 6·80–7·50 m, 7 H (ArH with the exception of H-6); 7·80 m, 1 H (H-6); 10·30 s, 1 H (CHO). For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·82% C, 4·95% H, 13·13% S; found: 69·09% C, 4·94% H, 12·86% S.

B) A Stirred solution of 14·0 g 4-methoxythiophenol[5] in 31 ml hexamethylphosphoric triamide was treated with a solution of 4·0 g NaOH in 11 ml water, after 10 min stirring 13·2 g 2-chlorobenzaldehyde were added, and the mixture was heated for 3·5 h under nitrogen to 100°C with stirring. After cooling the mixture was poured into 300 ml water and *Xc* was isolated by extraction with benzene. Processing of the extract gave a crystalline residue which was suspended in a mixture of benzene and light petroleum (1 : 1), filtered, and dried in vacuo; 11·0 g (48%), m.p. 100–103°C. Crystallization from ethanol gave pure *Xc* melting at 104–105°C, identical with the product obtained under *A*).

Semicarbazone, m.p. 219–222°C (ethanol). UV spectrum: 232 (4·32), 251 (4·26), 286 (4·29), infl. 335 (4·00). IR spectrum: 751, 830 (4 and 2 adjacent Ar–H); 1 252 ($ArOCH_3$); 1 493, 1 570, 1 590 (Ar); 1 719 ($NHCONH_2$); 3 160, 3 240, 3 468 (NH_2). For $C_{15}H_{15}N_3O_2S$ (301·4) calculated: 59·78% C, 5·02% H, 13·94% N, 10·64% S; found: 59·56% C, 5·14% H, 14·13% N, 10·72% S.

2-(3,4-Dimethoxyphenylthio)benzaldehyde (*Xd*)

A) A suspension of 53 g Na_2CO_3 in 150 ml hexamethylphosphoric triamide was stirred and treated with 85 g 3,4-dimethoxythiophenol[6]. Affter 10 min of stirring, 69 g 2-chlorobenzaldehyde were added and the mixture was heated for 3·5 h under nitrogen to 100°C with stirring. After standing overnight the mixture was poured into 1·5 l water, the product was extracted with benzene and after processing of the extract, the crude product was crystallized from 250 ml ethanol; 95 g (70%) of *Xd* (crystal modification A), m.p. 84–85°C. Analytical sample, m.p. 87–88°C (ethanol). UV spectrum: 234 (4·33), infl. 271 (3·99), 283 (3·78), 340 (3·54). IR spectrum: 769, 770, 801, 820, 840, 880, 888 (4 and 2 adjacent and solitary Ar–H); 1 029, 1 190, 1 232, 1 253

($ArOCH_3$); 1 502, 1 550, 1 591 (Ar); 1 670, 1 689, 2 740 (ArCHO). ^{1}H NMR spectrum: 3·82 s and 3·90 s, 3 and 3 H (2 × OCH_3); 6·80–7·70 m, 6 H (ArH with the exception of H-6); 7·80 m, 1 H (H-6); 10·30 s, 1 H (CHO). For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·67% C, 5·14% H, 11·69% S; found: 65·91% C, 4·84% H, 11·47% S.

B) A similar reaction of 53 g 3,4-dimethoxythiophenol[6], 41·0 g 2-chlorobenzaldehyde, and 32·8 g Na_2CO_3 in 120 ml dimethylformamide and similar processing gave 47·5 g of crude product melting at 93–94°C. Crystallization from 50 ml ethanol gave 44·0 g (55%) of the crystal modification B of *Xd*, m.p. 95–95·5°C. The UV spectrum is practically identical with that of modification A (under *A*). On the other hand, the IR spectrum showed some differences: 760, 814, 845, 874, 880 (4 and 2 adjacent and solitary Ar–H); 1 228, 1 249 ($ArOCH_3$); 1 500, 1 554, 1 583, 3 000, 3 070 (Ar); 1 673, 1 691, 2 740 (ArCHO). The ^{1}H NMR spectrum is identical with that of modification A. For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·67% C, 5·14% H, 11·69% S; found: 65·64% C, 5·29% H, 11·57% S.

Semicarbazone (*XId*), m.p. 179–181°C (ethanol). UV spectrum: 250 (4·26), 288 (4·38), infl. 330 (4·10). IR spectrum: 759, 800, 812, 860, 870, 879 (4 and 2 adjacent and solitary Ar–H); 1 230, 1 253 ($ArOCH_3$); 1 500, 1 530, 1 591 (Ar); 1 718 ($NHCONH_2$); 3 150, 3 275, 3 440, 3 460 (NH, NH_2). For $C_{14}H_{17}N_3O_3S$ (331·4) calculated: 57·99% C, 5·17% H, 12·68% N, 9·68% S; found: 58·12% C, 5·30% H, 12·98% N, 9·72% S.

1-(2-(2-Methoxyphenylthio)phenyl)-2-nitropropene (*XIIa*)

A) A mixture of 60 g *Xa*, 210 ml acetic acid, 37·8 g nitroethane, and 21 g ammonium acetate was stirred and refluxed for 4 h. After cooling the mixture was diluted with water and extracted with ether. The extract was washed with water, 5% Na_2CO_3, dried, and evaporated. From the residue (69·1 g) a part (6·91 g) was chromatographed on a column of 250 g silica gel. Elution with a mixture of benzene and light petroleum (2 : 1) gave 0·27 g of little polar components. This fraction was followed by 3·5 g (corresponds to 47%) of homogeneous oily *XIIa* which did not crystallize and was used for analysis as the chromatographic fraction. ^{1}H NMR spectrum: 2·18 bs, 3 H (=C–CH_3); 3·80 s, 3 H (OCH_3); 6·70–7·40 m, 8 H (ArH); 8·29 bs, 1 H (ArCH=C). For $C_{16}H_{15}NO_3S$ (301·4) calculated: 63·76% C, 5·03% H, 4·65% N, 10·64% S; found: 64·09% C, 5·10% H, 4·49% N, 10·87% S.

Continued elution with the same mixture of solvents afforded 1·14 g (19%) of 2-(2-methoxyphenylthio)benzonitrile (*XIIIa*), m.p. 81–82°C (acetone–methanol). Mass spectrum: 241·0557 (M^+, for $C_{14}H_{11}NOS$ calculated 241·0562, 100), 226 (6), 198 (19), 171 (11), 154 (12), 116 (20). UV spectrum: 223 (4·27), 255 (3·93), 285 (3·77), 312 (3·63). ^{1}H NMR spectrum: 3·79 s, 3 H (OCH_3); 6·70–7·60 m, 8 H (ArH). Ref.[8], m.p. 82–83·5°C.

The remaining crude product (62·2 g) was chromatographed on 2·5 kg neutral Al_2O_3 (activity II). Elution with the same mixture of solvents afforded 23·0 g of *XIIa* and 12·9 g of *XIIIa*.

B) A mixture of 30 g *Xa*, 120 ml acetic acid, 18·9 g nitroethane, and 6·0 g butylamine was processed similarly as under *A*). There were obtained 36·1 g of crude product which was chromatographed on 500 g silica gel. A mixture of benzene and light petroleum (1 : 1) eluted 32·5 g (88%) of oily *XIIa*, identical with the product obtained under *A*) (TLC).

1-(2-(3-Methoxyphenylthio)phenyl)-2-nitropropene (*XIIb*)

A mixture of 60 g *Xb*, 220 ml acetic acid, 38 g nitroethane, and 11·5 g butylamine was stirred and refluxed for 4 h. Similar processing as described for the preparation of *XIIa* gave 74 g of the crude product which was chromatographed on 1·5 kg silica gel. Elution with a mixture of

benzene and light petroleum afforded 60 g (81%) of practically homogeneous oily *XIIb*. UV spectrum: infl. 246 (3·87), infl. 265 (3·78), infl. 282 (3·70), infl. 291 (3·63), infl. 335 (3·17). IR spectrum (film): 690, 765, infl. 780, 870 (4 and 3 adjacent and solitary Ar–H); 1 040, 1 232, 1 250, 1 286 ($ArOCH_3$); 1 327, 1 524 ($C{=}C{-}NO_2$); 1 480, 1 550, 1 588, 1 592, 3 025, 3 080 (Ar); 1 655 (conjugated C=C). ^{1}H NMR spectrum: 2·18 d, 3 H ($=C{-}CH_3$, J = 1·0); 3·70 s, 3 H (OCH_3); 6·60–7·50 m, 8 H (ArH); 8·20 bm, 1 H (Ar—CH=). For $C_{16}H_{15}NO_3S$ (301·4) calculated: 63·76% C, 5·03% H, 4·65% N, 10·64% S; found: 64·05% C, 5·09% H, 4·65% N, 10·36% S.

2-(4-Methoxyphenylthio)benzaldoxime (*XXIc*)

A) A mixture of 4·5 g *Xc*, 6·0 g hydroxylamine hydrochloride, 15 ml pyridine, and 30 ml ethanol was refluxed for 2 h. The solvents were evaporated in vacuo, the residue was diluted with 40 ml water, the separated solid was filtered, washed with water, and crystallized twice from ethanol to give the analytical sample of *XXIc*, m.p. 124–125°C. UV spectrum: 244 (4·37), infl. 310 (3·42). IR spectrum: 750, 759, 813 (4 and 2 adjacent Ar–H); 1 020, 1 249 ($ArOCH_3$); 1 580, 1 599, 3 010, 3 053 (Ar); 1 629, 1 660 (CH=N); 3 270 (OH). ^{1}H NMR spectrum (at 60°C): 3·70 s, 3 H (OCH_3); 6·79 d, 2 H (H-3 and H-5 of methoxyphenyl, J = 8·5); 7·10 m, 3 H (H-3, H-4, H-5); 7·20 d, 2 H (H-2 and H-6 of methoxyphenyl, J = 8·5); 7·65 m, 1 H (H-6); 8·29 bs, 1 H (=NOH); 8·61 s, 1 H (Ar—CH=N). For $C_{14}H_{13}NO_2S$ (259·3) calculated: 64·83%C, 5·06% H, 5·40% N, 12·36% S; found: 64·54% C, 5·13% H, 5·30% N, 12·66% S.

B) A mixture of 14 g *Xc*, 5·1 g butyraldoxime[21] and 55 ml acetic acid was refluxed for 2 h, poured into water, and extracted with ether. The extract was washed with water and 5% Na_2CO_3, dried, and evaporated. The residue represented according to TLC a mixture of *Xc* and *XIXc* approximately 1 : 1. A sample (1·5 g) was chromatographed on 60 g silica gel. Benzene eluted 0·65 g of *Xc* and the mixture of benzene and ether (6 : 1) eluted 0·75 g of *XXIc*, m.p. 124–125°C (acetone–heptane). The mixture of products obtained under *A*) and *B*) melted without depression.

1-(2-(4-Methoxyphenylthio)phenyl)-2-nitropropene (*XIIc*)

A mixture 60 g *Xc*, 220 ml acetic acid, 37·8 g nitroethane, and 13·5 g butylamine was refluxed for 4 h and processed similarly like in the preceding cases; 74 g of inhomogeneous product. A part (7·4 g) was chromatographed on 200 g silica gel. A mixture of benzene and light petroleum (1 : 1) elued 5·5 g (corresponds to 74%) of the almost homogeneous oily *XIIc*. UV spectrum: 250 (4·26), infl. 350 (3·51). IR spectrum (film): 760, 829 (4 and 2 adjacent Ar–H); 1 029, 1 245 ($ArOCH_3$); 1 345, 1 518 ($C{=}C{-}NO_2$); 1 491, 1 580, 3 000, 3 050 (Ar); 1 655 (C=C). ^{1}H NMR spectrum: 2·20 d, 3 H ($=C{-}CH_3$, J = 1·0); 3·80 s, 3 H (OCH_3); 6·87 d, 2 H (H-3 and H-5 of methoxyphenyl, J = 8·0); 7·20 m, 4 H (H-3, H-4, H-5, and H-6); 7·30 d, 2 H (H-2 and H-6 of methoxyphenyl, J = 8·0); 8·25 bm, 1 H (Ar—CH=C). For $C_{16}H_{15}NO_3S$ (301·4) calculated: 63·76% C, 5·03% H, 4·65% N, 10·64% S; found: 63·95% C, 4·95% H, 4·75% N, 10·61% S.

The chromatography was continued by elution with benzene affording 0·31 g of 2-(4-methoxyphenylthio)benzonitrile (*XIIIc*), m.p. 98·5–100°C (acetone–heptane). Mass spectrum: 241 (M^+, $C_{14}H_{11}NOS$, 100), 226 ($C_{13}H_8NOS$, 46), 198 (14), 171 ($C_{11}H_7S$, 10), 154 ($C_{11}H_8N$, 23). UV spectrum: 255 (4·08), 315 (3·63). IR spectrum: 769, 820 (4 and 2 adjacent Ar–H); 1 025, 1 251 ($ArOCH_3$); 1 490, 1 590 (Ar); 2 210 (ArCN). ^{1}H NMR spectrum: 3·80 s, 3 H (OCH_3); 6·90 to 7·60 m, 4 H (H-3, H-4, H-5, and H-6); 6·90 d, 2 H (H-3 and H-5 of methoxyphenyl, J = 8·0); 7·40 d, 2 H (H-2 and H-6 of methoxyphenyl, J = 8·0). For $C_{14}H_{11}NOS$ (241·2) calculated: 69·70% C, 4·59% H, 5·80% N, 13·26% S; found: 69·40% C, 4·71% H, 5·89% N, 13·32% S.

The chromatography was concluded by elution with a mixture of benzene and ether (8 : 1) which yielded 0·68 g of 2-(4-methoxyphenylthio)benzaldoxime (*XXIc*), m.p. 125—126°C (acetone–heptane). Direct comparison with authetic *XXIc* (cf. above) confirmed the identity.

1-(2-(3,4-Dimethoxyphenylthio)phenyl)-2-nitropropene (*XIId*)

A mixture of 10·0 g *Xd*, 45 ml acetic acid, 5·8 g nitroethane, and 2·3 g butylamine was refluxed for 5 h and processed similarly like in the preceding cases. There were obtained 11·7 g of inhomogeneous product, a part of which (6·1 g) was chromatographed on 190 g silica gel. Elution with a mixture of benzene and ether (18 : 1) gave first 4·8 g of practically homogeneous oily *XIId*. UV spectrum: 248 (4·24), infl. 285 (4·07). IR spectrum (film): 765, 808, 870 (4 and 2 adjacent and solitary Ar–H); 1 025, 1 230, 1 255 ($ArOCH_3$); 1 320, 1 513 ($C{=}C{-}NO_2$); 1 500, 1 582, 3 000, 3 050 (Ar); 1 655 (C=C). ^{1}H NMR spectrum: 2·20 d, 3 H ($=C{-}CH_3$, J = 1·0); 3·78 s and 3·85 s, 3 and 3 H (2 × OCH_3); 6·70—7·30 m, 7 H (ArH); 8·25 bm, 1 H (ArCH=). For $C_{17}H_{17}NO_4S$ (331·4) calculated: 61·61% C, 5·18% H, 4·23% N, 9·67% S; found: 61·69% C, 5·48% H, 4·03% N, 9·90% S.

The elution with the same mixture of solvents was continued and gave 0·55 g of 2-(3,4-dimethoxyphenylthio)benzaldoxime (*XXId*), m.p. 131—133°C (acetone–heptane). Mass spectrum: 289 (M^+, $C_{15}H_{15}NO_3S$, 90), 272 ($C_{15}H_{14}NO_2S$, 100), 256 ($C_{14}H_{10}NO_2S$, 35), 138 ($C_8H_{10}O_2$, 58), 136 (23), 123 (24), 79 (34). UV spectrum: 245 (4·32), 320 (3·48). IR spectrum: 755, 805, 859, 870, 877 (4 and 2 adjacent and solitary Ar–H), 1 017, 1 250 ($ArOCH_3$); 1 500, 1 580, 3 010, 3 070 (Ar); 3 420 (NOH). ^{1}H NMR spectrum: 3·74 s and 3·80 s, 3 and 3 H (2× OCH_3); 6·70—7·30 m, 6 H (ArH with the excception of H-6); 7·65 m, 1 H (H-6); 8·60 s, 1 H (ArCH=); 8·93 s, 1 H (NOH, disappears after D_2O addition). For $C_{15}H_{15}NO_3S$ (289·4) calculated: 62·26% C, 5·24% H, 4·84% N, 11·08% S; found: 62·47% C, 5·44% H, 4·82% N, 11·06% S.

1-(2-(2-Methoxyphenylthio)phenyl)-2-propylamine (*VIIa*)

A solution of 18·6 g *XIIa* in 200 ml ether was added dropwise over 2 h to a stirred solution of 12·4 g $LiAlH_4$ in 400 ml ether and the mixture was stirred for 3 h at room temperature. After standing overnight the excess of $LiAlH_4$ was decomposed by slow addition of 10 ml ethanol and then 10 ml water with stirring. The mixture was filtered, the filtrate was washed with water, dried, and evaporated. The oily residue (14·6 g, 87%) represented the crude base *VIIa*. It was transformed by ethanolic HCl to the hydrochloride crystallizing from a mixture of 95% ethanol and ether as the monohydrate, m.p. 125°C. Mass spectrum: 273 (M^+, $C_{16}H_{19}NOS$, 1), 230 (8), 150 (5), 44 (100). ^{1}H NMR spectrum (at 60°C): 1·40 d, 3 H ($C{-}CH_3$, J = 6·5); 3·20 bm, 2 H ($ArCH_2$); 3·75 s and 3·75 bm, 3 and 1 H (OCH_3 and CHN); 6·60—7·50 m, 8 H (ArH); 8·40 bs, (NH_3^+, H_2O). For $C_{16}H_{20}ClNOS + H_2O$ (327·9) calculated: 58·60% C, 6·78% H, 4·27% N, 10·81% Cl, 9·78% S; found: 58·67% C, 6·48% H, 4·18% N, 11·08% Cl, 10·03% S.

1-(2-(3-Methoxyphenylthio)phenyl)-2-propylamine (*VIIb*)

Similar reduction of 8·1 g *XIIb* with 5·4 g $LiAlH_4$ in 240 ml ether gave 6·9 g (94%) of crude oily *VIIb*, a sample of which was purified by chromatography on neutral Al_2O_3 (activity II). Even then, the oily product was not completely homogeneous as shown by the ^{1}H NMR spectrum. IR spectrum (film): 690, 754, 776, 821 (4 and 3 adjacent Ar–H); 1 038, 1 053, 1 248, 1 283 ($ArOCH_3$); 1 488, 1 590, 3 000, 3 055 (Ar); 3 280, 3 360 (NH_2). ^{1}H NMR spectrum: 0·95 d and 1·10 d, $\sum$ 3 H ($C{-}CH_3$); 1·35 bs, 2 H (NH_2); 2·50—3·60 m, 3 H ($ArCH_2CHN$); 3·69 s and 3·75 s, $\sum$ 3 H (OCH_3); 6·50—7·50 m, 8 H (ArH). For $C_{16}H_{19}NOS$ (273·4) calculated: 5·12% N, 11·73% S; found: 5·28% N, 11·78% S.

1-(2-(4-Methoxyphenylthio)phenyl)-2-propylamine (*VIIc*)

Similar reduction of 24·9 g *XIIc* with 15·9 g $LiAlH_4$ in 730 ml ether gave 21·9 g (97%) of crude oily *VIIc* which was transformed to the hydrochloride, m.p. 184—185°C (ethanol–ether). For $C_{16}H_{20}ClNOS$ (309·9) calculated: 62·01% C, 6·52% H, 11·44% Cl, 4·52% N, 10·35% S; found: 61·71% C, 6·51% H, 11·74% Cl, 4·38% N, 10·35% S.

The released base was used for recording the spectra. IR spectrum (film): 745, 815, 825 (4 and 2 adjacent Ar–H); 1 026, 1 248, 1 282 ($ArOCH_3$); 1 487, 1 567, 1 585, 3 010, 3 055 (Ar); 1 630, infl. 3 265, 3 350 (NH_2). ^1H NMR spectrum: 1·18 d, 3 H ($C-CH_3$, J = 6·5); 1·55 s, 2 H (NH_2); 2·50—3·50 m, 3 H ($ArCH_2CHN$); 3·82 s, 3 H (OCH_3); 6·89 d, 2 H (H-3 and H-5 in methoxyphenyl, J = 8·5); 7·10 m, 4 H (H-3, H-4, H-5, and H-6); 7·35 d, 2 H (H-2 and H-6 of methoxyphenyl, J = 8·5).

Neutralization of the base with formic acid in ethanol gave the formate which crystallized after the addition of ether, m.p. 137—140°C (ethanol–ether). For $C_{17}H_{21}NO_3S$ (319·5) calculated: 63·91% C, 6·64% H, 4·39% N, 10·04% S; found: 63·61% C, 6·56% H, 4·47% N, 10·34% S.

1-(2-(3,4-Dimethoxyphenylthio)phenyl)-2-propylamine (*VIId*)

Similar reduction of 7·3 g *XIId* with 4·5 g $LiAlH_4$ in 215 ml ether gave 5·8 g (87%) of crude oily base *VIId* which was transformed to the hydrochloride crystallizing from a mixture of 95% ethanol and ether as the hemihydrate, m.p. 202—205°C. Mass spectrum: 303 (M^+, $C_{17}H_{21}NO_2S$, 2·5), 260 ($C_{15}H_{16}O_2S$, 5), 44 (C_2H_6N, 100). IR spectrum: 759, 810, 832, 877 (4 and 2adjacent and solitary Ar–H); 1 045, 1 230, 1 250 ($ArOCH_3$); 1 500, 1 580, 1 597, 3 030, 3 050, 3 080 (Ar); 1 610 (NH_2); 2 505, 2 585, 2 700 (NH_3^+); 3 220 (H_2O). For $C_{17}H_{22}ClNO_2S + 0·5\ H_2O$ (348·9) calculated: 58·51% C, 6·66% H, 10·16% Cl, 4·02% N, 9·19% S; found: 58·81% C, 6·53% H, 10·46% Cl, 4·00% N, 9·16% S.

Treatment of the hydrochloride with NH_4OH released the base which was isolated by extraction with ether; homogeneous oil. IR spectrum (film): 751, 808, 878 (4 and 2 adjacent and solitary Ar–H); 1 025, 1 230, 1 256 ($ArOCH_3$); 1 505, 1 586, 3 000, 3 050 (Ar); 3 190, 3 290, 3 350 (NH_2). ^1H NMR spectrum: 1·18 d, 3 H ($C-CH_3$, J = 6·0); 2·00 bs, 2 H (NH_2); 2·50—3·60 m, 3 H ($ArCH_2CHN$); 3·78 s and 3·85 s, 3 and 3 H (2 × OCH_3); 6·70—7·30 m, 7 H (ArH).

2-(2-Methoxyphenylthio)benzyl Alcohol (*XVa*)

A solution of 106 g *Xa* in 1·7 l ethanol was stirred and treated with a solution of 8·25 g $NaBH_4$ in 80 ml water containing 0·8 ml 20% NaOH, added dropwise at 70°C. The mixture was refluxed for 6 h, ethanol was evaporated and the residue was distributed between 800 ml water and 800 ml benzene and the organic layer was processed by distillation, 100·3 g (94%) of *XVa*, b.p. 170—172°C/60 Pa. Ref.[8], b.p. 178—180°C/0·1 kPa.

2-(3-Methoxyphenylthio)benzyl Alcohol (*XVb*)

Similar reduction of 27·3 g *Xb* in 400 ml ethanol with a solution of 2·1 g $NaBH_4$ in 20 ml water containing 0·2 ml 20% NaOH gave 27 g (98%) of *XVb*, b.p. 168—174°C/0·2 kPa. Ref[17], b.p. 163—164°C/0·9 kPa.

(2-(2-Methoxyphenylthio)phenyl)acetonitrile (*XVIIa*)

A boiling solution of 100·3 g *XVa* in 230 ml benzene was treated dropwise with 54·6 g $SOCl_2$ and the mixture was refluxed for 2 h. Benzene with the excess of $SOCl_2$ were distilled off, the

remaining crude *XVIa* was dissolved in 185 ml ethanol, a solution of 54·6 g KCN in 75 ml water was added, and the mixture was refluxed for 9 h. It was poured to 750 ml water and the product was extracted with chloroform. Processing of the extract gave 90·3 g (86%) of *XVIIa*, b.p. 171 to 175°C/40 Pa. Analytical sample, b.p. 171°C/40 Pa. For $C_{15}H_{13}NOS$ (255·3) calculated: 70·56% C, 5·13% H, 5·49% N, 12·56% S; found: 70·86% C, 5·33% H, 5·26% N, 12·86% S.

(2-(2-Methoxyphenylthio)phenyl)acetone (*XIXa*)

A stirred suspension of 13·7 g NaH (suspension in mineral oil) in 225 ml toluene was treated dropwise over 45 min with 53 ml ethanol at 70°C and the sodium ethoxide suspension formed was treated over 10 min with a solution of 89·8 g *XVIIa* in 53 ml ethyl acetate, added dropwise. The mixture was refluxed under stirring for 2 h during which time it became so thick that it was necessary to dilute it with 100 ml toluene for enabling continuous stirring. After cooling the precipitated sodium salt of the enol form of *XVIIIa* was dissolved in 600 ml water, the toluene layer was extracted with 2 × 200 ml water, the aqueous solutions were combined, acidified with dilute hydrochloric acid, and *XVIIIa* was isolated by extraction with toluene. Processing of the extract gave 78·8 g (75%) of crude oily *XVIIIa*.

This crude intermediate (78·8 g) was treated with 62 g 85% H_3PO_4 and the mixture was stirred for 8 h under reflux in a silicon oil bath heated to 200°C. After cooling the mixture was diluted with 375 ml water and the product was extracted with ether. The extract was washed with water, dried, evaporated, and the residue was distilled; 54·3 g of *XIXa* (57% per starting *XVIIa*) b.p. 188—193°C/50 Pa. Analytical sample, b.p. 188°C/50 Pa. IR spectrum (film): 750 (4 adjacent Ar–H); 1 020, 1 240, 2 835 ($ArOCH_3$); 1 578, 3 000, 3 055 (Ar); 1 720 (RCOR'). ^{1}H NMR spectrum: 2·10 s, 3 H ($COCH_3$); 3·80 s, 3 H (OCH_3); 3·88 s, 2 H ($ArCH_2CO$); 6·60—7·50 m, 8 H (ArH). For $C_{16}H_{16}O_2S$ (272·4) calculated: 70·56% C, 5·92% H, 11·77% S; found: 70·56% C, 5·83% H, 11·68% S.

3-Methoxy-11-methyldibenzo[*b,f*]thiepin-10-carbonitrile (*XXIII*)

Sodium ethoxide suspension was prepared by reaction of 10·7 g 80% NaH (suspension in mineral oil) in 250 ml toluene with 41 ml ethanol), which was added dropwise under stirring over 45 min at 70°C. The suspension was then treated with a mixture of 70 g *XVIIb* and 37 g ethyl acetate, refluxed with stirring for 2 h, and processed similarly like in the preceding case; 42·4 g (52%) of crude oily *XVIIIb*.

This crude intermediate (42·4 g) was treated with 33·1 g 85% H_3PO_4 and the mixture was stirred and heated under reflux for 8 h (bath temperature 200°C). After cooling the mixture was diluted with 200 ml water and extracted with ether. Processing of the extract gave 19·2 g of inhomogeneous product boiling at 160—165°C/0·13 kPa. According to TLC it consisted of four main components. It was chromatographed on 500 g silica gel. A mixture of benzene and light petroleum (1 : 1) eluted first 7·25 g of component *A* and then 0·2 g of component *B*; both substances did not crystallize and they were not identified. Benzene eluted then 7·4 g (10% per the starting *XVIIb*) of component *C* which was identified as *XXIII*, m.p. 115—117°C (benzene–hexane). Mass spectrum: 279 (M^+, $C_{17}H_{13}NOS$, 100), 264 ($C_{16}H_{10}NOS$, 24), 247 ($C_{17}H_{13}NO$, 36), 236 ($C_{15}H_{10}NS$, 43), 204 ($C_{15}H_{10}N$, 30), 203 ($C_{15}H_9N$, 20), 177 ($C_{13}H_7N$, 14). UV spectrum: 237 (3·87), 266·5 (4·23), 302 (4·03), infl. 326 (3·75). IR spectrum: 760, 812, 830, 875 (4 and 2 adjacent and solitary Ar–H); 1 045, 1 228 ($ArOCH_3$); 1 490, 1 545, 1 595, 3 015, 3 055 (Ar); 2 200 (C≡C—CN). ^{1}H NMR spectrum: 2·70 s, 3 H (C≡C—CH_3); 3·75 s, 3 H (OCH_3); 6·70 dd, 1 H (H-2, J = 2·0; 8·5); 7·04 d, 1 H (H-4, J = 2·0); 7·10 d, 1 H (H-1, J = 8·5); 7·10—7·60 m, 4 H (H-6, H-7, H-8, and H-9). For $C_{17}H_{13}NOS$ (279·3) calculated: 73·11% C, 4·69% H, 5·02% N, 11·46% S; found: 73·26% C, 4·79% H, 4·89% N, 11·17% S.

Continued elution with benzene afforded 2·8 g of component *D* which was identified as 7--methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXIV*), m.p. 133—135°C (ethanol). ^{1}H NMR spectrum: 3·81 s, 3 H (OCH_3); 4·30 s, 2 H ($ArCH_2CO$); 6·75 dd, 1 H (H-8, J = 8·5; 2·5); 7·02 d, 1 H (H-6, J = 2·5); 7·10—7·70 m, 4 H (H-1, H-2, H-3, and H-4); 8·11 d, 1 H (H-9, J = 8·5). The analysis was in agreement with $C_{15}H_{12}O_2S$. Ref.[17], m.p. 131—132°C (different way of formation).

N-(1-(2-(2-Methoxyphenylthio)phenyl)-2-propyl)formamide (*XIVa*)

A) A mixture of 8·5 g *VIIa* and 50 ml ethyl formate was heated for 6·5 h in the autoclave to 150°C. After cooling the mixture was dissolved in ether, the solution was washed with dilute hydrochloric acid and 5% Na_2CO_3, dried, and evaporated. There were obtained 8·8 g (94%). of the curde crystalline *XIVa* which was purified by crystallization from a mixture of benzene and heptane; m.p. 101—102°C. IR spectrum: 755 (4 adjacent Ar–H); 1 020, 1 250, 1 275 ($ArOCH_3$); 1 473, 1 581, 3 060 (Ar); 1 555, 1 650, 1 675 (RNHCHO); 3 245 (NH), ^{1}H NMR spectrum: 1·34 d and 1·36 d, $\sum$ 3 H (C–CH_3); 3·00 m, 2 H ($ArCH_2$); 3·85 s, 3 H (OCH_3); 4·40 m, 1 H (CHN); 5·90 bm, 1 H (NH); 6·70—7·40 m, 8 H (ArH); 7·72 bd, and 7·95 bs, $\sum$ 1 H (CHO). For $C_{17}H_{14}NO_2S$ (301·4) calculated: 67·73% C, 6·37% H, 4·65% N, 10·64% S; found: 67·78% C, 6·42% H, 4·67% N, 10·56% S.

B) A mixture of 53·8 g *XIXa*, 120 g formamide, and 23·5 g formic acid was stirred and heated under reflux for 10 h (bath temperature 190—200°C). After partial cooling the mixture was poured to 500 ml water nd extracted with benzene. The extract was washed with water, dried, and evaporated. There were obtained 56 g of oily inhomogeneous residue which was chromatographed on 1·4 kg neutral Al_2O_3 (activita II). Benzene eluted 14·1 g of almost homogeneous oil which was distilled; 10·95 g of *XVIIa*, b.p. 193—198°C/0·1 kPa. It gave correct analysis for $C_{15}H_{13}NOS$ and the boiling point corresponds to that of authetic *XVIIa*, described above.

The elution was continued with chloroform and afforded 26·50 g (44%) of crystalline *XIVa*, m.p. 101·5—102°C, which was found identical with the product obtained under A (comparison by TLC).

The last chloroform fractions contained 1·31 g of a different crystalline product which was identified as (2-(2-methoxyphenylthio)phenyl)acetamide (*XXa*), m.p. 110·5—111·5°C (benzene). Mass spectrum: 273 (M^+, $C_{15}H_{15}NO_2S$), 227, 213, 197, 184, 165, 152, 134 (100), 121, 91, 76, 44. UV spectrum: 249 (4·03), 284·5 (3·77). IR spectrum: 752 (4 adjacent Ar–H); 1 247, 1 274 ($ArOCH_3$); 1 581, 1 612, 3 005 ,3 050 (Ar); 1 648 ($CONH_2$); 3 200, 3 395 (NH_2). ^{1}H NMR spectrum: 3·70 s, 2 H ($ArCH_2CO$); 3·80 s, 3 H (OCH_3); 5·80 bs and 6·20 bs, 1 and 1 H (NH_2); 6·60—7·50 m, 8 H (ArH). For $C_{15}H_{15}NO_2S$ (273·4) calculated: 65·91% C, 5·53% H, 5·12% N, 11·73% S; found: 66·19% C, 5·63% H, 5·15% N, 11·70% S.

N-(1-(2-(4-Methoxyphenylthio)phenyl)-2-propyl)formamide (*XIVc*)

In analogy to *XIVa* under *A*: Reaction of 40·0 g *VIIc* with 70 ml ethyl formate at 150°C in autoclave gave 39·9 g (91%) of crystalline *XIVc* which was purified by crystallization from a mixture of benzene and heptane, m.p. 96—97°C. IR spectrum: 755, 818, 828 (4 and 2 adjacent Ar–H); 1 015, 1 250 ($ArOCH_3$); 1 490, 1 570, 1 593, 3 010, 3 050 (Ar); 1 550, 1 650 (RNHCHO); 3 250 (NH). ^{1}H NMR spectrum: 1·25 d and 1·31 d, $\sum$ 3 H (C–CH_3); 2,98 m, 2 H ($ArCH_2$); 3·80 s, 3 H (OCH_3); 4·45 m, 1 H (CHN); 5·90 bd and 6·25 bs, $\sum$ 1 H (NH); 6·89 d, 2 H (H-3 and H-5 of methoxyphenyl, J = 8·5); 7·10 m, 4 H (H-3, H-4, H-5, and H-6); 7·30 d, 2 H (H-2 and H-6 of methoxyphenyl, J = 8·5); 7·75 d and 8·00 bs, $\sum$ 1 H (CHO). For $C_{17}H_{19}NO_2S$ (301·4) calculated: 67·73% C, 6·37% H, 4·65% N, 10·64% S; found: 67·49% C, 6·41% H, 4·47% N,10·40% S.

N-(1-(2-(3,4-Dimethoxyphenylthio)phenyl)-2-propyl)formamide (*XIVd*)

In analogy to *XIVa* under *A*: Reaction of 25·6 g *VIId* with 70 ml ethyl formate at 150°C in autoclave gave 21·3 g (76%) of crude oily *XIVd* which was chromatographed on 430 g silica gel. Elution with chloroform gave the main crystalline fraction which seemed to be practically homogeneous and which was crystallized from a mixture of chloroform and heptane to the constant melting point; 16·2 g, m.p. 109—110°C. IR spectrum: 750, 765, 820, 850, 880 (4 and 2 adjacent and solitary Ar–H); 1 020, 1 030, 1 230, 1 250 ($ArOCH_3$); 1 465, 1 500, 1 585, 3 005, 3 075 (Ar); 1 515, 1 680 (RNHCHO); 2 750 (CHO); 3 350 (NH). ^{1}H NMR spectrum: 1·21 d and 1·25 d, $\sum$ 3 H ($C-CH_3$); 2·90 m, 2 H ($ArCH_2$); 3·76 s and 3·82 s, 3 and 3 H (2 × OCH_3); 4·40 m, 1 H (CHN); 5·80 bm and 6·25 bm, $\sum$ 1 H (NH); 6·70—7·30 m, 7 H (ArH); 7·70 d (J = 12·0) and 7·98 bs, $\sum$ 1 H (CHO). For $C_{18}H_{21}NO_3S$ (331·5) calculated: 65·22% C, 6·40% H, 4·23% N, 9·67% S; found: 64·92% C, 6·39% H, 4·05% N, 9·86% S.

N-Methyl-1-(2-(2-methoxyphenylthio)phenyl)-2-propylamine (*VIIIa*)

A) A solution of 10·2 g *XIVa* in 60 ml benzene was added dropwise to a stirred solution of 5·6 g $LiAlH_4$ in 70 ml ether and the mixture was refluxed for 5·5 h. After standing overnight the excess of $LiAlH_4$ was decomposed by slow addition of 10 ml ethanol and 10 ml water under stirring. The mixture was filtered, the filtrate was washed with water, dried, and evaporated. There were obtained 6·2 g (64%) of crude oily *VIIIa*. Neutralization with oxalic acid dihydrate in ethanol and addition of ether led to the crystalline hydrogen oxalate, crystal modification A, m.p. 71—73°C (ethanol–ether). For $C_{19}H_{23}NO_5S$ (377·5) calculated: 60·45% C, 6·15% H, 3·71% N, 8·49% S; found: 60·73% C, 6·25% H, 3·99% N, 8·19% S.

The released oily base was used for measuring the spectra. IR spectrum (film): 750 (4 adjacent Ar–H); 1 025, 1 042, 1 241 ($ArOCH_3$); 1 475, 1 575, 3 000, 3 058 (Ar); 3 315 (NH). ^{1}H NMR spectrum: 1·05 d, 3 H ($C-CH_3$, J = 6·0); 1·70 bs, 1 H (NH); 2·39 s, 3 H (NCH_3); 2·88 m, 3 H ($ArCH_2CHN$); 3·85 s, 3 H (OCH_3); 6·70—7·40 m, 8 H (ArH).

A single crystallization of the modification A of hydrogen oxalate from a mixture of ethanol and ether raised suddenly the melting point to 97—100°C which then did not change by further recrystallization. The substance was considered crystal modification B of *VIIIa* hydrogen oxalate. For $C_{19}H_{23}NO_5S$ (377·5) calculated: 60·45% C, 6·15% H, 3·71% N, 8·49% S; found: 60·45% C, 6·19% H, 4·01% N, 8·19% S. The IR and ^{1}H NMR spectra of the base, released from this crystal form B, were identical with those of the base released from the form A of the hydrogen oxalate.

B) A solution of 26·5 g *XIVa* (under *B*) in 250 ml tetrahydrofuran was treated under nitrogen with 9·6 g $NaBH_4$ and then under stirring with 30·5 ml $BF_3.O(C_2H_5)_2$, added dropwise. The mixture was stirred for 1 h at room temperature and then refluxed for 3 h (nitrogen atmosphere). After cooling it was decomposed with 150 ml dilute hydrochloric acid (1 : 1), diluted with 250 ml benzene, and made alkaline with 20% NaOH. The organic layer was separated, dried, and evaporated. The oily residue was dissolved in 100 ml ether, the solution was filtered and neutralized with a solution of 11·0 g oxalic acid dihydrate in 50 ml acetone. Crystallization by standing overnight gave 25·9 g (78%) of hydrogen oxalate melting at 112—115°C. Analytical sample, m.p. 114—115°C (ethanol–ether). The substance is considered modification C of *VIIIa* hydrogen oxalate. For $C_{19}H_{23}NO_5S$ (377·5) calculated: 60·45% C, 6·15% H, 3·71% N, 8·49% S; found: 60·33% C, 6·26% H, 3·65% N, 8·56% S. The ^{1}H NMR spectrum of the released base was almost identical with the spectrum described under *A*: 1·08 d, 3 H ($C-CH_3$, J = 6·0); 1·48 bm, 1 H (NH); 2·40 s, 3 H (NCH_3); 2·90 m, 3 H ($ArCH_2CHN$); 3·88 s, 3 H (OCH_3); 6·70—7·40 m, 8 H (ArH).

N-Methyl-1-(2-(4-methoxyphenylthio)phenyl)-2-propylamine (*VIIIc*)

XIVc (11·0 g) was similarly reduced with 4·1 g $LiAlH_4$ in a mixture of 50 ml ether and 50 ml benzene. Similar processing gave 9·0 g of crude oily *VIIIc* which was transformed to the hydrogen oxalate melting at 149—152°C. This salt was shown by the mass spectrum to be a mixture of oxalates of *VIIIc* and *XXIIc*: 287 (M^+, $C_{17}H_{21}NOS$), 230, 148, 58 (100), and 259 (M^+, $C_{15}H_{17}NOS$), 227, 151, 150, 137, 118.

Further crystallization of this salt from ethanol–ether led to the hydrogen oxalate melting at 151—154°C which was nearly homogeneous (TLC). For $C_{19}H_{23}NO_5S$ (377·5) calculated: 60·45% C, 6·15% H, 3·71% N, 8·49% S; found: 60·15% C, 5·89% H, 3·87% N, 8·80% S.

The released base was transformed to the hydrochloride whose crystallization from ethanol–ether proved more suitable for separating the contaminant, m.p. 129—131°C. For $C_{17}H_{22}ClNOS$ (323·9) calculated: 63·03% C, 6·86% H, 10·94% Cl, 4·33% N, 9·90% S; found: 62·73% C, 6·87% H, 11·25% Cl, 4·72% N, 9·85% S.

Spectra of the base, released from the hydrochloride, were recorded. IR spectrum (film): 750, 829 (4 and 2 adjacent Ar–H); 1 030, 1 245, 1 285 ($ArOCH_3$); 1 495, 1 570, 1 590, 3 055 (Ar); 2 790 ($N–CH_3$); 3 320 (NH). ^{1}H NMR spectrum: 1·05 d, 3 H ($C–CH_3$, J = 6·0); 1·60 bs, 1 H (NH); 2·40 s, 3 H (NCH_3); 2·88 m, 3 H ($ArCH_2CHN$); 3·80 s, 3 H (OCH_3); 6·80 d, 2 H (H-3 and H-5 of methoxyphenyl, J = 8·5); 7·00 m, 4 H (H-3, H-4, H-5, and H-6); 7·28 d, 2 H (H-2 and H-6 of methoxyphenyl, J = 8·5).

Processing of the mother liquors after crystallization of hydrogen oxalate of *VIIIc* gave a small amount of N-methyl-2-(4-methoxyphenylthio)benzylamine (*XXIIc*) hydrogen oxalate, m.p. 173—176°C (ethanol–ether). Mass spectrum: 259 (M^+, $C_{15}H_{17}NOS$, 41), 227 (23), 151 (32), 150 (32), 137 (100), 118 (60). ^{1}H NMR spectrum (CD_3SOCD_3): 2·65 s, 3 H (NCH_3); 3·80 s, 3 H (OCH_3); 4·30 s, 2 H ($ArCH_2$); 6·92 d, 2 H (H-3 and H-5 of methoxyphenyl, J = 8·0); 7·10—7·70 m, 6 H (remaining ArH). For $C_{17}H_{19}NO_5S$ (349·4) calculated: 58·43% C, 5·49% H, 4·01% N, 9·17% S; found: 58·84% C, 5·70% H, 3·98% N, 9·12% S.

N-Methyl-1-(2-(3,4-dimethoxyphenylthio)phenyl)-2-propylamine (*VIIId*)

Formamide *XIVd* ((16·2 g) was similarly reduced with 9·0 g $LiAlH_4$ in a mixture of 110 ml ether and 110 ml benzene. Similar processing gave 11·2 g (72%) of crude oily *VIIId* which was transformed to the hydrogen oxalate, m.p. 135·5—137·5°C (ethanol–ether). For $C_{20}H_{25}NO_6S$ (407·5) calculated: 58·94% C, 6·20% H, 3·44% N, 7·87% S; found: 58·99% C, 6·29% H, 3·23% N, 7·85% S.

^{1}H NMR spectrum of the released base was recorded: 1·18 d, 3 H ($C–CH_3$, J = 6·0); 2·59 s, 3 H (NCH_3); 2·60—3·30 m, 3 H ($ArCH_2CHN$); 3·78 s and 3·84 s, 3 and 3 H (2 × OCH_3); 6·70—7·30 m, 7 H (ArH).

N,N-Dimethyl-1-(2-(2-methoxyphenylthio)phenyl)-2-propylamine (*IXa*)

A mixture of 8·3 g *VIIa*, 6·5 ml water, 9·5 ml formic acid, and 16 ml 28% aqueous formaldehyde was refluxed for 10 h and poured into excess of dilute NaOH. The product was extracted with ether and the extract was processed giving 8·3 g (91%) of crude oily *IXa* which was transformed to the hydrochloride, m.p. 183·5—184·5°C (ethanol–ether). For $C_{18}H_{24}ClNOS$ (337·9) calculated: 63·97% C, 7·17% H, 10·49% Cl, 4·15% N, 9·49% S; found: 64·21% C, 6·97% H, 10·67% Cl, 4·19% N, 9·74% S.

^{1}H NMR spectrum of the released base: 0·91 d, 3 H ($C–CH_3$, J = 6·5); 2·30 s, 6 H ($N(CH_3)_2$); 2·50—3·40 m, 3 H ($ArCH_2CHN$); 3·85 s, 3 H (OCH_3); 6·70—7·40 m, 8 H (ArH).

N,N-Dimethyl-1-(2-(4-methoxyphenylthio)phenyl)-2-propylamine (*IXc*)

In analogy to *IXa*: Reaction of 35 g *VIIc*, 36·5 ml 80% formic acid and 64 ml 28% aqueous formaldehyde in 30 ml water gave 32·4 g (84%) of the crude oily *IXc* which was transformed to the hydrogen oxalate, m.p. 78·5—80·5°C (ethanol–ether). ^{1}H NMR spectrum: 1·32 d, 3 H (C–CH_3, J = 6·0); 2·90 s, 6 H ($N(CH_3)_2$); 2·80—3·70 m, 3 H ($ArCH_2CHN$); 3·81 s, 3 H (OCH_3); 6·80—7·40 m, 8 H (ArH). For $C_{20}H_{25}NO_5S$ (391·5) calculated: 61·35% C, 6·45% H, 3·58% N, 8·19% S; found: 61·13% C, 6·28% H, 3·17% N, 8·36% S.

N,N-Dimethyl-1-(2-(3,4-dimethoxyphenylthio)phenyl)-2-propylamine (*IXd*)

In analogy to *IXa*: Reaction of 8·5 g *VIId*, 9·5 ml 80% formic acid, 16 ml 28% aqueous formaldehyde, and 6·5 ml water gave 6·8 g (73%) of practically homogeneous oily *IXd* which was transformed to hydrogen oxalate, m.p. 107—110°C (ethanol–ether). For $C_{21}H_{27}NO_6S$ (421·6) calculated: 59·83% C, 6·47% H, 3·32% N, 7·61% S; found: 59·96% C, 6·47% H, 3·24% N, 7·76% S.

^{1}H NMR spectrum of the released base: 0·98 d, 3 H (C–CH_3, J = 6·0); 2·35 s, 6 H ($N(CH_3)_2$); 2·50—3·20 m, 3 H ($ArCH_2CHN$); 3·80 s and 3·88 s, 3 and 3 H (2 × OCH_3); 6·70—7·30 m, 7 H (ArH).

1-(2-(2-Hydroxyphenylthio)phenyl)-2-propylamine (*IVa*) (Method *A*)

From a mixture of 51 ml hydrochloric acid, 45 ml ethanol, and 43·5 ml pyridine the volatile components were distilled off, 7·0 g *VIIa* were added to the remaining pyridine hydrochloride and the mixture was heated under stirring for 1·5 h to 215°C (bath temperature) in an open flask. After cooling a solution of 23 g NaOH in 200 ml water was added, water was evaporated, the residue was dissolved in water, and the solution was neutralized with dilute hydrochloric acid, the separated oily base was isolated by decantation, dissolved in ethanol, the solution was boiled for several min with active carbon, filtered, and the filtrate was evaporated in vacuo giving 3·7 g (56%) of the crude oily *IVa*. It was transformed to the hydrochloride, m.p. 182—183°C (ethanol–ether). Analysis and spectra are given in Tables I and II.

N-Methyl-1-(2-(3,4-dihydroxyphenylthio)phenyl)-2-propylamine (*Vd*) (Method *B*)

A stirred solution of 5·0 g *VIIId* in 35 ml chloroform was treated at +10°C with a solution of 8·0 g BBr_3 in 10 ml chloroform, added dropwise over 10 min. The mixture was stirred for 5 h at room temperature, treated under cooling (at 15—20°C) with 40 ml ethanol, the solution formed was stirred for 6 h at room temperature and allowed to stand overnight. The solvents were evaporated under reduced pressure at max. 50°C, the residue was dissolved in 120 ml water, the solution was filtered with active carbon, and the filtrate was neutralized with dilute NH_4OH, approximately to pH 8. The separated semi-solid product slowly solidified, was filtered, washed with water, and dried in vacuo; 3·1 g (68%) of the crude *Vd*.

A part of the product (1·0 g) was dissolved together with 0·4 g maleic acid in 5 ml ethanol. After the addition of 3 ml ether, the hydrogen maleate of *Vd* slowly crystallized. After 2 h standing the salt was filtered; 0·8 g, m.p. 161—162°C. Analytical sample, m.p. 164°C (ethanol–ether). A solution of 0·4 g of the purified hydrogen maleate in 40 ml water was treated with 4 drops of NH_4OH and at the pH 8 the hemihydrate of the base *Vd* crystallized, m.p. 86—87°C. Analyses and spectra of both crystalline substances are given in Tables I and II.

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