4-SUBSTITUTED 1-(1-(2-(ARYLTHIO)-5-HALOGENOPHENYL)ETHYL)-PIPERAZINES; SYNTHESIS AND BIOLOGICAL SCREENING

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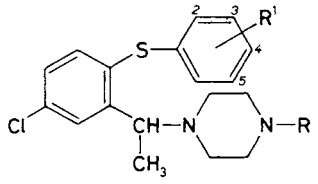
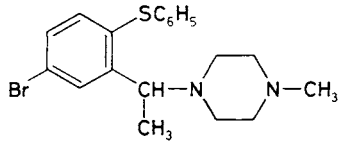
Reactions of 2,5-dichloroacetophenone and 2,5-dibromoacetophenone with a series of thiophenols gave the 2-(arylthio)-5-halogenoacetophenones *VII* and *VIII* which were reduced with sodium borohydride in ethanol to the secondary alcohols *IX* and *X*. Treatment with thionyl chloride afforded the chloro compounds *XI* and *XII* which were transformed by substitution reactions with correspondingly monosubstituted piperazines by two methods to the title compounds *I*—*V*. Their salts (maleates and hydrochlorides) showed in addition to antitussic activity some anthelmintic effects towards a series of the helminth species.

Some time ago our research team[1] described the synthesis of 1-(1-(5-chloro-2-(phenylthio)phenyl)ethyl)-4-methylpiperazine (*Ia*) which was prepared as an open model of the neuroleptic agent clorothepin (octoclothepin) (ref.[2]). The substance *Ia* ("fethiozine", VÚFB-12 257) did not reveal any neuroleptic activity but in addition to some peripheral neurotropic effects it showed within a screening programme, outlined more recently, an important anthelmintic effect against *Trichocephalus muris* and in lesser extent towards *Fasciola hepatica* and *Heterakis spumosa*. These findings induced us to use the structure *Ia* as a prototype for preparing a series of fethiozine analogues (title compounds *I*—*V*) modified on the one hand by chlorination in the phenylthio residue, and in the N^4 piperazine substituent on the other.



I, R = CH_3
II, R = CH_2CH_2OH
III, R = $CH_2CH_2OCH_3$
IV, R = C_6H_5
V, R = 

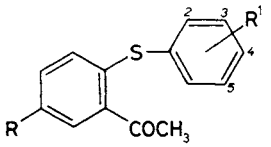


VI

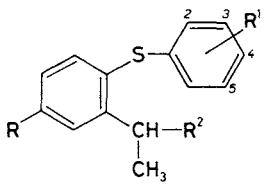
(In formulae *I*–*V*, *VII*–*XII*: *a*, R^1 = H; *b* R^1 = 2-Cl; *c* R^1 = 4-Cl; *d*, R^1 = 3,4-Cl_2; *e*, R^1 = 2,5-Cl_2)

The description of syntheses of these compounds and results of their biological screening are the subjects of the present communication.

The synthesis of the title compounds *I* – *VI* started from the 2-(arylthio)-5-halogenoacetophenones (*VII*, *VIII*), out of which *VIIa* (ref.[1]), *VIIb* (ref.[3]) and *VIIc* (ref.[4]) were known. The remaining ketones *VIId*, *VIIe* and *VIII* were obtained by reactions of 2,5-dichloroacetophenone[1] and 2,5-dibromoacetophenone[5] with 3,4-dichlorothiophenol[6], 2,5-dichlorothiophenol[7], and thiophenol, respectively, in the presence of potassium carbonate and copper at 150°C. The ketones *VII* and *VIII* were reduced with sodium borohydride in boiling ethanol to the secondary alcohols *IX* and *X*, out of which only *IXa* had been described previously[1]. The following treatment with thionyl chloride in boiling benzene led to the chloro compounds *XI* and *XII* which were oily and distilled under partial decomposition (*XIa* described previously[1]); for this reason they were used without characterization as crude products. In the final step, these chloro compounds were processed by substitution reactions with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine, 1-(2-methoxyethyl)piperazine[8], 1--phenylpiperazine[9] and 1-(3-chlorophenyl)piperazine[10]. For carrying out these reactions, two methods were used. In the case of hydrophilic piperazines with aliphatic substituents, the chloro compounds *XI* and *XII* were refluxed for 7 h with a four--fold excess of the corresponding piperazine in chloroform, the excess of the monosubstituted piperazine was removed by washing with water, the desired crude bases were transformed to maleates which were purified by crystallization (method A). The bases released from the pure maleates (some of the bases crystallized) were used for recording the spectra. In cases of the rather hydrophobic arylpiperazines, the chloro compounds *XI* were reacted with equimolecular quantities of the monosubstituted piperazines in dimethylformamide at 120–130°C in the presence of potassium carbonate; the crude bases were isolated by treatment with dilute hydrochloric acid and purified by crystallization of the hydrochlorides (method B). Most of the released bases crystallized and their spectra were also recorded. All of the title compounds, prepared by methods A and B, are assembled in Table I with the usual experimental data. The Experimental describes the synthesis of all new intermediates (*VII*–*XII*)



VII, R = Cl
VIII, R = Br



IX, R = Cl; R^2 = OH
X, R = Br; R^2 = OH
XI, R = Cl; R^2 = Cl
XII, R = Br; R^2 = Cl

TABLE I

4-Substituted 1-(1-(2-(arylthio)-5-halogenophenyl)ethyl)piperazines *I*—*VI*

Compound[a]	Method (yield %)	M.p., °C	Formula (mol.wt.)	Calculated/found				
				% C	% H	% Cl	% N	% S
Ib-2 HM	A (76)	141—143·5[b] (2-propanol)	$C_{27}H_{30}Cl_2N_2O_8S$ (613·5)	52·85 52·70	4·93 5·00	11·56 11·80	4·57 4·15	5·23 5·40
Ic-2 HM	A (47)	154·5—155·5[c] (ethanol)	$C_{27}H_{30}Cl_2N_2O_8S$ (613·5)	52·85 52·52	4·94 4·94	11·56 11·73	4·57 4·56	5·23 5·35
Id-2 HM[d]	A (48)	146—147·5[e] (acetone)	$C_{27}H_{29}Cl_3N_2O_8S + H_2O$ (666·0)	48·69 49·22	4·69 4·40	15·97 15·61	4·21 4·20	4·82 4·99
Ie-2 HM	A (54)	153—154·5[f] (acetone–ether)	$C_{27}H_{29}Cl_3N_2O_8S$ (648·0)	50·04 49·83	4·51 4·62	16·42 16·30	4·32 4·28	4·95 5·12
IIa-2 HM[g]	A (70)	134—136 (2-propanol)	$C_{28}H_{33}ClN_2O_9S$ (609·1)	55·21 55·12	5·46 5·63	5·82 6·20	4·60 4·33	5·27 5·45
IIa[g]	—	72—76 (benzene–hexane)	$C_{20}H_{25}ClN_2OS$ (377·0)	63·72 63·18	6·69 6·70	9·41 9·33	7·43 6·97	8·51 8·67
IIb-2 HM	A (75)	134—135 (2-propanol)	$C_{28}H_{32}Cl_2N_2O_9S$ (643·5)	52·25 51·87	5·01 5·12	11·02 11·04	4·35 4·01	4·98 5·10
IIb[d]	—	90—92[h] (benzene–light petroleum)	$C_{20}H_{24}Cl_2N_2OS + H_2O$ (429·4)	55·94 56·18	6·10 6·01	16·51 16·20	6·53 6·30	7·47 7·40
IId-2 HM	A (70)	135—135·5[i] (acetone–ether)	$C_{28}H_{31}Cl_3N_2O_9S$ (678·0)	49·60 49·73	4·61 4·57	15·69 15·65	4·13 3·97	4·73 4·98

IIa-2 HM	A (78)	130–132[j] (acetone)	$C_{28}H_{31}Cl_3N_2O_9S$ (678·0)	49·60 49·68	4·61 4·67	15·69 15·44	4·13 3·95	4·73 4·90
IIId-2 HM	A (36)	148–149[k] (ethanol–ether)	$C_{29}H_{33}Cl_3N_2O_9S$ (692·0)	50·33 50·53	4·81 4·82	15·37 15·13	4·05 3·72	4·63 4·97
IVa-HCl	B (56)	163–164 (ethanol)	$C_{24}H_{26}Cl_2N_2S$ (445·5)	64·71 64·33	5·88 5·97	15·92 15·91	6·29 6·15	7·20 7·47
IVa	—	87–91[l] (benzene–hexane)	$C_{24}H_{25}ClN_2S$ (443·7)	70·48 70·45	6·16 6·28	8·67 8·82	6·85 6·53	7·84 7·87
IVb-2 HCl	B (79)	207–207·5[m] (ethanol–ether)	$C_{24}H_{26}Cl_4N_2S$ (516·4)	55·82 55·39	5·07 4·90	27·47 26·91	5·43 5·18	6·21 6·20
IVc-HCl	B (67)	202–205·5 (ethanol)	$C_{24}H_{25}Cl_3N_2S$ (479·9)	60·06 60·04	5·25 5·34	22·17 22·01	5·84 5·68	6·68 6·60
IVc	—	142–146[n] (benzene–light petroleum)	$C_{24}H_{24}Cl_2N_2S$ (443·4)	65·00 65·18	5·46 5·63	15·99 15·75	6·32 5·85	7·23 7·18
IVd-2 HCl	B (51)	167–169 (ethanol–ether)	$C_{24}H_{25}Cl_5N_2S$ (550·8)	52·33 52·28	4·57 4·51	32·18 32·47	5·09 4·69	5·82 5·84
IVd	—	143–146[o] (cyclohexane)	$C_{24}H_{23}Cl_3N_2S$ (477·9)	60·32 60·52	4·85 4·95	22·26 21·66	5·86 5·54	6·71 6·88
Va-HCl	B[p] (64)	153–155[q] (2-propanol)	$C_{24}H_{25}Cl_3N_2S$ (479·9)	60·06 60·01	5·26 5·26	22·17 22·11	5·84 5·64	6·68 6·80
Vc-HCl[g]	B (62)	175–177 (2-propanol)	$C_{24}H_{24}Cl_4N_2S$ (514·4)	56·04 56·04	4·70 4·83	27·57 27·32	5·45 5·22	6·42 6·50
Vc	—	133–136 (benzene–light petroleum)	$C_{24}H_{23}Cl_3N_2S$ (477·9)	60·32 60·85	4·85 5·01	22·26 22·03	5·86 5·67	6·71 6·63

TABLE I
(*Continued*)

Compound[a]	Method (yield %)	M.p., °C	Formula (mol.wt.)	Calculated/found				
				% C	% H	% Cl	% N	% S
Vd-2 HCl	B (35)	145—147 (ethanol–ether)	$C_{24}H_{24}Cl_6N_2S$ (583·3)	49·25 49·46	4·13 4·18	36·35 36·38	4·79 4·49	5·48 5·30
Vd	—	120—124[r] (benzene–light petroleum)	$C_{24}H_{22}Cl_4N_2S$ (512·3)	56·26 56·46	4·33 4·45	27·68 27·34	5·47 5·12	6·26 6·40
Ve-HCl	B (40)	170—172 (acetone–2-propanol)	$C_{24}H_{23}Cl_5N_2S$ (548·8)	52·52 52·19	4·22 4·28	32·30 31·94	5·11 5·10	5·84 5·91
VI-2 HM	A (84)	157—158 (ethanol–ether)	$C_{27}H_{31}BrN_2O_8S$ (623·5)	52·01 51·40	5·01 5·04	12·82[s] 13·08	4·49 4·13	5·13 5·20

[a] 2 HM bis(hydrogen maleate). [b] The oily base *Ib* was released from the salt with NH_4OH, isolated by extraction with ether, and was used for recording the ^1H NMR spectrum (the other bases were obtained similarly): δ 7·55 (bs, 1 H, 6-H), 6·70—7·45 (m, 6 H, remaining ArH), 3·90 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 2·40 (bs, 8 H, 4 CH_2N of piperazine), 2·20 (s, 3 H, NCH_3), 1·24 (d, J = 7·0 Hz, 3 H, C—CH_3). [c] Oily base *Ic*, ^1H NMR spectrum: δ 7·50 (bs, 1 H, 6-H), c. 7·10 (m, 6 H, remaining ArH), 3·90 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 2·35 (bs, 8 H, 4 CH_2N of piperazine), 2·19 (s, 3 H, NCH_3), 1·20 (d, J = 7·0 Hz, 3 H, C—CH_3). [d] Monohydrate. [e] Oily base *Id*, ^1H NMR spectrum: δ 6·80—7·60 (m, 6 H, ArH), 3·88 (q, J = 6·5 Hz, 1 H, Ar—CH—N), 2·35 (bs, 8 H, 4 CH_2N of piperazine), 2·20 (s, 3 H, NCH_3), 1·25 (d, J = 6·5 Hz, 3 H, C—CH_3). [f] Oily base *If*, ^1H NMR spectrum: δ 7·60 (bs, 1 H, 6-H), c. 7·25 (m, 3 H, 3,4,3′-H_3), 7·00 (dd, J = 8·0; 3·0 Hz, 1 H, 6′-H), 6·70 (d, J = 3·0 Hz, 1 H, 4′-H), 3·81 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 2·32 (bs, 8 H, 4 CH_2N of piperazine), 2·18 (s, 3 H, NCH_3), 1·22 (d, J = 7·0 Hz, 3 H, C—CH_3). [g] See Experimental. [h] Mass spectrum, m/z: 410 (M^+ corresponding to $C_{20}H_{24}Cl_2N_2OS$), 395, 392, 379. ^1H NMR spectrum: δ 7·59 (bs, 1 H, 6-H), 6·80—7·40 (m, 6 H, remaining ArH), 3·98 (q, J = 6·0 Hz, 1 H, Ar—CH—N), 3·60 (bt, J = 6·0 Hz, 2 H, CH_2O), 2·80 (bs, 3 H, H_2O and OH), 2·50 (bs, 10 H, 5 CH_2N), 1·30 (d, J = 6·0 Hz, 3 H, CH_3). [i] Oily base *IId*, ^1H NMR spectrum: δ 6·70—7·60 (m, 6 H, ArH), 3·90 (q, J = 6·5 Hz, 1 H, Ar—CH—N), 3·58 (t, J = 6·0 Hz, 2 H, CH_2O), 2·98 (bs, 1 H, OH), 2·48 (bs, 10 H,

5 CH_2N), 1·25 (d, J = 6·5 Hz, 3 H, CH_3). [j] Oily base *IIa*, ^{1}H NMR spectrum: δ 7·58 (bs, 1 H, 6-H), c. 7·25 (m, 3 H, 3,4,3′-H_3), 7·00 (dd, J = 8·0; 3·0 Hz, 1 H, 4′-H), 6·68 (d, J = 3·0 Hz, 1 H, 6′-H), 3·82 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 3·52 (t, J = 6·0 Hz, 2 H, CH_2O), 2·90 (bs, 1 H, OH), 2·40 (bs, 10 H, 5 CH_2N), 1·20 (d, J = 7·0 Hz, 3 H, CH_3). [k] Oily base *IIId*, ^{1}H NMR spectrum: δ 6·70—7·60 (m, 6 H, ArH), 3·90 (q, J = 6·5 Hz, 1 H, Ar—CH—N), 3·48 (t, J = 6·0 Hz, 2 H, CH_2O), 3·32 (s, 3 H, OCH_3), 2·52 (t, J = 6·0 Hz, 2 H, NCH_2 in the chain), 2·48 (s, 8 H, 4 CH_2N of piperazine), 1·25 (d, J = 6·5 Hz, 3 H, C—CH_3). [l] ^{1}H NMR spectrum: δ 7·55 (bs, 1 H, 6-H), 6·60—7·40 (m, 12 H, remaining ArH), 4·02 (q, J = 6·0 Hz, 1 H, Ar—CH—N), 3·15 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·31 (d, J = 6·0 Hz, 3 H). [m] Oily base *IVb*, ^{1}H NMR spectrum: δ 7·58 (bs, 1 H, 6-H), 6·60—7·40 (m, 11 H, remaining ArH), 3·95 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 3·08 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·52 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·25 (d, J = 7·0 Hz, 3 H, CH_3). [n] ^{1}H NMR spectrum: δ 6·60—7·60 (m, 12 H, ArH), 3·95 (q, J = 6·0 Hz, 1 H, Ar—CH—N), 3·10 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·52 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·25 (d, J = 6·0 Hz, 3 H, CH_3). [o] ^{1}H NMR spectrum: δ 6·70—7·70 (m, 11 H, ArH), 3·98 (q, J = 6·5 Hz, 1 H, Ar—CH—N), 3·15 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 1·30 (d, J = 6·5 Hz, 3 H, CH_3). [p] When using method A in this case, a mixture of bases was obtained, which was chromatographed on Al_2O_3 and the only homogeneous fraction obtained was identified as the starting 1-(3-chlorophenyl)piperazine[10]. Maleate, m.p. 147—148·5°C (ethanol). For $C_{14}H_{17}ClN_2O_4$ (312·8) calculated: 53·76% C, 5·48% H, 11·34% Cl, 8·96% N; found: 53·72% C, 5·54% H, 11·45% Cl, 9·01% N. [q] Oily base *Va*, ^{1}H NMR spectrum: δ 7·55 (bs, 1 H, 6-H), 6·60—7·30 (m, 11 H, remaining ArH), 3·98 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 3·09 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·50 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·24 (d, J = 7·0 Hz, 3 H, CH_3). [r] ^{1}H NMR spectrum: δ 6·60—7·70 (m, 10 H, ArH), 3·98 (q, J = 6·5 Hz, 1 H, Ar—CH—N), 3·10 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·52 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·30 (d, J = = 6·5 Hz, 3 H, CH_3). [s] Content of bromine.

and of compounds *IIa* and *Vc* as examples of carrying out the preparation by the general methods A and B.

Compounds *I* – *V* in the form of salts, described in Table I, were subjected to biological screening. First of all the acute toxicities in mice (LD_{50} in mg/kg), way of administration and doses (D in mg/kg), used in the general pharmacological screening, are given: *Ib*, 60, *i.v.*, 12; *Ic*, 80, *i.v.*, 16; *Id*, 87·5, *i.v.*, 15; *Ie*, 75–100, *i.v.*, 20; *IIa*, 60, *i.v.*, 12; *IIb*, 30, *i.v.*, 6; *IId*, 125, *i.v.*, 25; *IIe*, 2 000, *p.o.*, 300; *IIId*, 100, *i.v.*, 20; *IVa*, >2 500, *p.o.*, 300; *IVb*, 2 500, *p.o.*, 300; *IVc*, >2 500, *p.o.*, 300; *IVd*, >2 500, *p.o.*, 300; *Vb*, >2 500, *p.o.*, 300; *Vc*, >2 500, *p.o.*, 300; *VI*, 363, *p.o.*

Some of the compounds proved to have antitussive action in rats (the coughing activity was elicited by the aerosol of citric acid solution and the oral ED (in mg/kg) given inhibited the frequency of cough attacks approximately to 50% of the control value): *Ib*, 60 (equipotent to 10 mg/kg *p.o.* of codeine); *Id*, 75;*IIa*, 60; *IId*, 125; *IVa*, 300; *Vb*, 300. Two of the compounds potentiated the thiopental effect in mice (ED in mg/kg *i.v.* prolonged the sleeping time to 200% of the control): *Id*, >10; *IIId*, 10–20. Compound *IIe* showed diuretic effect in mice: oral dose of 100 mg/kg increased diuresis by 100% (hydrochlorothiazidelike effect) in comparison with the control.

Compound *VI* was tested as a potential antidepressant (doses calculated *per* base). In the oral dose of 50 mg/kg it showed some antireserpine action in the test of reserpine-induced gastric ulcers in rats. On the other hand, it was inactive (25 mg/kg *p.o.*) in the test of reserpine ptosis in mice. In the concentration of 500 nmol l^{-1} it did not inhibit the binding of [^{3}H]imipramine and in the concentration of 100 nmol l^{-1} the binding of [^{3}H]desipramine, both in rat hypothalamus. It cannot be considered a potential antidepressant.

In the anthelmintic screening, the compounds showed some effects towards the following species: *Nippostrongylus brasiliensis* (*Ic, Id, Ie, IIb, IId, IIe, IIId, IVa, IVb, IVd, Vb, Vd, VI*), *Hymenolepis nana* (*Id, Ie, IIa, IIb, IId, IIe, IIId, IVa, IVb, IVd, Vb, Vd*), *Nematospiroides dubius* (*IIb*), *Aspiculuris tetraptera* (*IVb*), *Trichocephalus muris* (*IVb*), *Heterakis spumosa* (*IVb*). In all cases, the effects were lower than those of standards and the results did not warrant some more detailed studies.

The compounds prepared were also tested for antimicrobial activity *in vitro* (the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *Ib* 10, *Ic* 5, *Id* 5, *Ie* 5, *IIa* 50, *IIb* 25, *IId* 5, *IIe* 5, *IIId* 25, *VI* 6·2; *Streptococcus faecalis*, *Ib* 12·5, *Ic* 12·5, *Id* 10, *Ie* 10, *IIa* 100, *IIb* 50, *IId* 10, *IIe* 10, *IIId* 100, *VI* 25; *Staphylococcus pyogenes aureus*, *Ib* 10, *Ic* 5, *Id* 5, *Ie* 5, *IIa* 50, *IIb* 25, *IIa* 10, *IIe* 10, *IIId* 25, *VI* 12·5; *Proteus vulgaris*, *Id* 100, *IId* 100, *VI* 100; *Saccharomyces pasterianus*, *Ic* 50, *Id* 50, *IId* 50, *IIe* 50, *VI 50*; *Trichophyton mentagrophytes*, *Ib* 25, *Ic* 25, *Id* 12·5, *Ie* 12·5, *IIa* 50, *IIb* 25, *IId* 12·5, *IIe* 12·5, *IIId* 25, *VI* 12·5.The inactivity of the N-arylpiperazino compounds is probably due to their very low water-solubility.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectrum with MCH 1320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3, and evaporated under reduced pressure on a rotating evaporator.

5-Chloro-2-(3,4-dichlorophenylthio)acetophenone (*VIId*)

A stirred mixture of 37·8 g 2,5-dichloroacetophenone[1], 39·4 g 3,4-dichlorothiophenol[6], 47·0 g K_2CO_3 and 1·0 g Cu catalyst was heated to 150—155°C. The mixture solidified and the heating without stirring was continued for 1 h. After cooling to 80°C, the mixture was diluted with 150 ml benzene, the inorganic salts were filtered off and washed with benzene, and the filtrate was evaporated. The solid residue was recrystallized from 700 ml methanol; 51·1 g (77%), m.p. 98—105°C. Analytical sample, m.p. 104·5—106°C (methanol). UV spectrum: λ_{max} 232 nm (log ε 4·45), 263 nm (4·02), 287 nm (3·79), 340 nm (3·64). IR spectrum: 820, 889, 895 (2 adjacent and solitary Ar—H), 1 546, 3 070, 3 090 (Ar), 1 670 cm^{-1} (ArCOR). ^{1}H NMR spectrum: δ 7·75 (d, J = = 2·5 Hz, 1 H, 6-H), 7·10—7·60 (m, 4 H, 4,2′,5′,6′-H_4), 6·82 (d, J = 8·5 Hz, 1 H, 3-H), 2·60 (s, 3 H, $COCH_3$). For $C_{14}H_9Cl_3OS$ (331·7) calculated: 50·70% C, 2·73% H, 32·07% Cl, 9·67% S; found: 50·89% C, 2·79% H, 31·89% Cl, 9·80% S.

5-Chloro-2-(2,5-dichlorophenylthio)acetophenone (*VIIe*)

A similar reaction of 28·4 g 2,5-dichloroacetophenone[1], 29·6 g 2,5-dichlorothiophenol[7], 35·0 g K_2CO_3 and 0·6 g Cu gave 18·5 g (37%) crude *VIIe*, m.p. 125—130°C. Analytical sample. m.p. 131·5—132·5°C (2-butanone). UV spectrum: λ_{max} 233 nm (log ε 4·47), 260 nm (3·94), 340 nm (3·57), infl. 286 nm (3·64). IR spectrum: 811, 817, 858, 880 (2 adjacent and solitary Ar—H), 1·535, 1 550, 1 572, 3 075 (Ar), 1 662 cm^{-1} (ArCOR). ^{1}H NMR spectrum: δ 7·70 (d, J = 2·0 Hz, 1 H, 6-H), 7·10—7·50 (m, 4 H, 4,3′,4′,6′-H_4), 6·81 (d, J = 8·5 Hz, 1 H, 3-H), 2·60 (s, 3 H, $COCH_3$). For $C_{14}H_9Cl_3OS$ (331·7) calculated: 50·70% C, 2·73% H, 32·07% Cl, 9·67% S; found: 50·93% C, 2·74% H, 32·02% Cl, 9·63% S.

5-Bromo-2-(phenylthio)acetophenone (*VIIIa*)

A mixture of 30·0 g 2,5-dibromoacetophenone[5], 12·5 g thiophenol, 23·5 g K_2CO_3 and 0·4 g Cu was stirred for 10 min at room temperature, heated for 1 h without stirring to 100°C, cooled to 50°C, and diluted with 140 ml benzene. Inorganic salts were filtered off, washed with 50 ml benzene, the filtrate was washed with 50 ml 10% $NaHCO_3$ and with water, it was dried and evaporated. Crystallization from 20 ml hexane gave 12·2 g inhomogeneous product (TLC) which was recrystallized from a mixture of 10 ml cyclohexane and 13 ml hexane; 8·4 g (26%), m.p. 59—64°C. Analytical sample, m.p. 65·5—66·5°C (hexane). UV spectrum: λ_{max} 246 nm (log ε 4·27), 337 nm (3·75), infl. 275 nm (4·03). IR spectrum: 699, 708, 760, 799, 810, 862, 872 (5 and 2 adjacent and solitary Ar—H), 1 537, 1 572, 3 060, 3 085 (Ar), 1 668 cm^{-1} (ArCOR). ^{1}H NMR spectrum: δ 7·70 (d, J = 8·5 Hz, 1 H, 6-H), 7·25 (dd, J = 8·5; 2·0 Hz, 1 H, 4-H), 7·46 (m, 5 H, C_6H_5), 6·95 (d, J =

= 2·0 Hz, 1 H, 3-H), 2·67 (s, 3 H, $COCH_3$). For $C_{14}H_{11}BrOS$ (307·2) calculated: 54·73% C 3·61% H, 26·01% Br, 10·44% S; found: 54·83% C, 3·63% H, 26·23% Br, 10·48% S.

1-(5-Chloro-2-(2-chlorophenylthio)phenyl)ethanol (*IXb*)

A solution of 25·0 g *VIIb* (ref.[3]) in 100 ml ethanol was stirred and treated at 60°C with 3·8 g $NaBH_4$ (added in small portions), and the mixture was refluxed for 1·5 h. Ethanol was evaporated, the residue was diluted with 100 ml water and the suspension was heated to 100°C for several minutes. After cooling, the product was extracted with benzene, and the extract was processed: 24·8 g (98%) crude product, m.p. 82—85°C. Analytical sample, m.p. 84—85·5°C (cyclohexane–light petroleum). IR spectrum: 740, 825, 879 (4 and 2 adjacent, and solitary Ar—H), 1 088, 1 098 (CHOH), 1 550, 1 560, 1 570, 1 577, 3 050 (Ar), 3 350 cm^{-1} (OH). ^1H NMR spectrum: δ 6·60—7·70 (m, 7 H, ArH), 5·22 (m, 1 H, Ar—CH—O), 2·20 (bd, 1 H, OH), 1·38 (d, J = 6·0 Hz, 3 H, CH_3). For $C_{14}H_{12}Cl_2OS$ (299·2) calculated: 56·19% C, 4·04% H, 23·70% Cl, 10·72% S; found: 56·21% C, 4·10% H, 23·32% Cl, 10·78% S.

1-(5-Chloro-2-(4-chlorophenylthio)phenyl)ethanol (*IXc*)

Similar reduction of 23·0 g *VIIc* (ref.[4]) with 3·0 g $NaBH_4$ in 100 ml ethanol gave 22·7 g (99%) crude oily *IXc*. A sample for analysis was distilled, b.p. 187°C/0·1 kPa. IR spectrum (film): 812, 895 (2 adjacent and solitary Ar—H), 1 092 (CHOH), 1 472, 1 552, 1 579, 3 060, 3 075 (Ar), 3 350 cm^{-1} (OH). ^1H NMR spectrum: δ 7·65 (d, 1 H, 6-H), 6·80—7·40 (m, 6 H, remaining ArH), 5·32 (bq, J = 7·0 Hz, 1 H, Ar—CH—O), 2·30 (bs, 1 H, OH), 1·48 (d, J = 7·0 Hz, 3 H, CH_3). For $C_{14}H_{12}Cl_2OS$ (299·2) calculated: 56·19% C, 4·04% H, 23·70% Cl, 10·72% S; found: 56·27% C, 4·05% H, 23·48% Cl, 10·87% S.

1-(5-Chloro-2-(3,4-dichlorophenylthio)phenyl)ethanol (*IXd*)

Similar reduction of 49·0 g *VIId* with 7·0 g $NaBH_4$ in 200 ml boiling ethanol afforded 44·0 g (89%) crude oily *IXd*. A sample for analysis was distilled, b.p. 205°C/1·1 kPa. For $C_{14}H_{11}Cl_3OS$ (333·7) calculated: 50·39% C, 3·32% H, 31·88% Cl, 9·61% S; found: 50·70% C, 3·38% H, 31·28% Cl, 9·87% S.

1-(5-Chloro-2-(2,5-dichlorophenylthio)phenyl)ethanol (*IXe*)

A stirred suspension of 22·5 g *VIIe* in 100 ml ethanol was treated at 50°C with 4·0 g $NaBH_4$, added in small portions. The solution formed was stirred for 1 H at 50—60°C, and refluxed for 3·5 h. After evaporation, the residue was distributed between 130 ml water and 100 ml benzene. The organic layer was dried and evaporated, the residue (20·7 g) was crystallized from a mixture of 20 ml cyclohexane and 40 ml light petroleum; 17·6 g (60%), m.p. 75—79°C. Analytical sample, m.p. 77·5—80°C (cyclohexane–light petroleum). IR spectrum: 798, 810, 872, 882 (2 adjacent and solitary Ar—H), 1 090 (CHOH), 1 550, 1 565, 1 578, 3 052, 3 070 (Ar), 3 330, 3 410 cm^{-1} (OH). ^1H NMR spectrum: δ 7·65 (bs, 1 H, 6-H), 6·90—7·40 (m, 4 H, 3,4,3′,4′-H_4), 6·55 (bs, 1 H, 6′-H), 5·20 (bm, 1 H, Ar—CH—O), 2·10 (bd, 1 H, OH), 1·39 (d, J = 6·0 Hz, 3 H, CH_3). For $C_{14}H_{11}Cl_3OS$ (333·7) calculated: 50·39% C, 3·32% H, 31·88% Cl, 9·61% S; found: 50·28% C, 3·38% H, 31·58% Cl, 9·61% S.

1-(5-Bromo-2-(phenylthio)phenyl)ethanol (*Xa*)

Reduction of 8·4 g *VIIIa* with 1·2 g $NaBH_4$ in 40 ml ethanol was carried out similarly like in the

preparation of *IXb*; 6·8 g (81%) crude *Xa* (oil). Distillation gave 5·1 g product, b.p. 164—166°C/66 Pa. IR spectrum (film): 690, 740, 750, 798, 822, 899 (5 and 2 adjacent, and solitary Ar—H), 1 050, 1 070, 1 086 (CHOH), 1 552, 1 575, 3 060, 3 075 (Ar), 3 350 cm^{-1} (OH). ^1H NMR spectrum: δ 7·10—7·60 (m, 8 H, ArH), 5·31 (bq, J = 6·5 Hz, 1 H, Ar—CH—O), 2·30 (bs, 1 H, OH), 1·45 (s, J = 6·5 Hz, 3 H, CH_3). For $C_{14}H_{13}BrOS$ (309·2) calculated: 54·37% C, 4·24% H, 25·84% Br, 10·37% S; found: 54·90% C, 4·33% H, 25·97% Br, 10·43% S.

4,4′-Dichloro-2-(1-chloroethyl)diphenyl Sulfide (*XIc*)

A stirred solution of 20·5 g *IXc* in 45 ml benzene was treated over 15 min at 45—50°C with a solution of 8·3 g $SOCl_2$ in 15 ml benzene, the mixture was stirred at this temperature for 30 min, and refluxed for 1·5 h. The volatile components were completely evaporated *in vacuo*; 21·9 g (100%) crude oily *XIc*. A sample was distilled with partial decomposition; b.p. 171°C/80 Pa. ^1H NMR spectrum: δ 7·70 (bs, 1 H, 3-H), 7·00—7·40 (m, 6 H, remaining ArH), 5·70 (q, J = 7·0 Hz, 1 H, Ar—CH—Cl), 1·80 (d, J = 7·0 Hz, 3 H, CH_3). For $C_{14}H_{11}Cl_3S$ (317·7) calculated: 10·10% S; found: 9·88% S. Compounds *XIb*, *XId*, *XIe* and *XIIa* were prepared similarly as oily crude products in yields of 95—100% and were used without characterization.

1-(1-(5-Chloro-2-(phenylthio)phenyl)ethyl)-4-(2-hydroxyethyl)piperazine (*IIa*) (Method A)

A stirred mixture of 5·7 g *XIa* (ref.[1]), 13·0 g 1-(2-hydroxyethyl)-piperazine and 15 ml chloroform was refluxed for 6 h, diluted with 120 ml benzene and washed repeatedly with water. The organic layer was dried and evaporated. The residue (7·4 g crude oily base *IIa*) was dissolved in 40 ml ethanol and the solution was neutralized with a solution of 4·64 g maleic acid in 15 ml ethanol. Treatment with 120 ml ether and standing overnight led to crystallization of 8·6 g (70%) bis(hydrogen maleate), m.p. 135—137°C. Crystallization from 2-propanol gave the analytical sample melting at 134—136°C.

Decomposition of a sample of the maleate with NH_4OH released the base which was isolated by extraction with benzene and crystallized from a mixture of benzene and hexane, m.p. 72—76°C. ^1H NMR spectrum: δ 7·50 (bs, 1 H, 6-H), 7·00—7·30 (m, 7 H, remaining ArH), 3·91 (q, J = = 7·0 Hz, 1 H, Ar—CH—N), 3·55 (t, J = 7·0 Hz, 2 H, CH_2O), 3·02 (bs, 1 H, OH), 2·40 (bs, 10 H, 5 CH_2N), 1·20 (d, J = 7·0 Hz, 3 H, CH_3). For analyses of the maleate and of the base, *cf.* Table I.

1-(1-(5-Chloro-2-(4-chlorophenylthio)phenyl)ethyl)-4-(3-chlorophenyl)piperazine (*Vc*) (Method B)

A mixture of 6·9 g crude *XIc*, 10 ml dimethylformamide, 4·3 g 1-(3-chlorophenyl)piperazine[10] and 3·5 g K_2CO_3 was stirred for 5 h at 120°C. After cooling it was diluted with 100 ml benzene, the inorganic salts were filtered off and washed with benzene, the filtrate was washed with water and then shaken with 100 ml 2·5M-HCl. The organic layer was evaporated to the volume of 80 ml and allowed to stand for 2 days in a refrigerator. The solution deposited 7·0 g (62%) *Vc* hydrochloride which proved rather insoluble in water and in dilute hydrochloric acid but soluble in benzene. It was recrystallized from 2-propanol, m.p. 175—177°C.

The base was released from the hydrochloride with NH_4OH and isolated by extraction with benzene; m.p. 133—136°C (benzene–light petroleum). ^1H NMR spectrum: δ 6·50—7·60 (m, 11 H, ArH), 3·98 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 3·10 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·55 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 1·28 (d, J = 7·0 Hz, 3 H, CH_3). For analyses of the hydrochloride and of the base, *cf.* Table I.

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