1-[2-(2-HYDROXYMETHYLPHENYLTHIO)BENZYL]-4-METHYLPIPERAZINE AND RELATED COMPOUNDS AS POTENTIAL ANTIDEPRESSANTS: SYNTHESIS AND PHARMACOLOGICAL SCREENING

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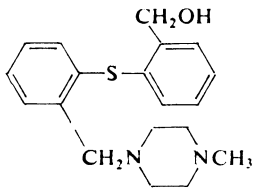
Heating of 1-(2-iodobenzoyl)-4-methylpiperazine (*II*) with thiophenol and its 2-methyl, 4-methyl, 4-chloro and 2-hydroxymethyl derivatives in dimethylformamide in the presence of potassium carbonate, copper and cuprous iodide gave the piperazides *IV*– *VIII*; compound *VIII* was transformed by reduction with lithium aluminium hydride to the title compound *I*. The acid *IX*, obtained by a reaction of 5-chloro-2-iodobenzoic acid with 2-methylthiophenol, was reduced to the alcohol *X*, which was transformed *via* the chloride *XI* to 1-[5-chloro-2-(2-methylphenylthio)-benzyl]-4-methylpiperazine (*XII*), an "open model" of the neuroleptic agent clorothepin. Heating of 2,5-dichloroacetophenone with thiosalicylic acid afforded the keto acid *XIII* whose reaction with 1-methylpiperazine was carried out with the help of N,N′-carbonyldiimidazole. The piperazide *XIV* obtained was reduced on the one hand with sodium borohydride to the secondary alcohol *XV*, and with lithium aluminium hydride to 1-(2-[4-chloro-2-(1-hydroxyethyl)phenylthio]benzyl)-4-methylpiperazine (*XVI*) on the other. None of the dibasic piperazines (*I*, *XII*, *XVI*) did show antireserpine activity. In the general screening, some of the piperazides displayed a mild hypotensive (*II*, *VIII*, *XIV*, *XV*), adrenolytic (*VIII*), mild stimulating and antitussic (*V*), and spasmolytic, antiinflammatory and negatively ino- and chronotropic (*XIV*) activities.

In spite of the great number of antidepressant drugs which are used in therapy[1], the research aiming at the development of better drugs is being further pursued. After having exhausted almost all possibilities in the series of tricyclic antidepressants, which represent the classical group and which display more or less undesirable cardiotoxic effects, the efforts are now concentrating in the area of nontricyclic antidepressants[2], denoted also as the second generation antidepressants. A comparison of structures, which are considered potential antidepressants on the basis of their pharmacological profiles, shows that the antidepressant effect is not too structurally specific and it is possible to search after it in broad areas of tertiary and secondary amines presenting a certain balance between the hydrophobic and hydrophilic parts of the molecules[3,4]. In this connection our attention was attracted by reports on the antitetrabenazine activity (which usually well correlates with the antidepressant activity) of substituted 2-(2-aminomethylphenylthio)benzyl alcohols, described in patents[5,6]. We were especially interested in the structure of the piperazine derivative *I* which belongs into a structural field investigated by our group for a long time[7]. It was the rea-

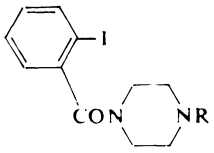
son of our having prepared compound *I* by a new procedure, as well as several new analogues. By their pharmacological testing we wanted to verify the correctness of the statement about the occurrence of antidepressant activity in this series. Report on this work forms the object of the present communication.

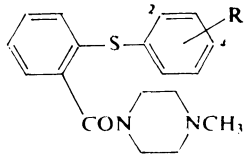


I

In the first part of our study, which included a new synthesis of compound *I*, we started from 1-(2-iodobenzoyl)-4-methylpiperazine (*II*) which is mentioned in the literature[8] especially from the point of view of its monoamine oxidase inhibitory activity (for the hydrochloride a melting point value was given which is completely different from the value we found). It has been prepared by a reaction of 2-iodobenzoyl chloride[9,10] with 1-methylpiperazine in chloroform. The crystalline hydrochloride of compound *II* was obtained as the primary product from which the base was then prepared and characterized. In an analogous manner the neutral 1-ethoxycarbonyl--4-(2-iodobenzoyl)piperazine (*III*) was obtained by a reaction of 2-iodobenzoyl chloride[9,10] with 1-ethoxycarbonylpiperazine. Compound *II* was subjected to reactions with thiophenol, 2-methylthiophenol[11,12] (for the method of preparation, *cf.*[13]), 4-methylthiophenol, 4-chlorothiophenol and 2-hydroxymethylthiophenol[14,15] in dimethylformamide at about 150°C in the presence of potassium carbonate, copper and cuprous iodide. The methylpiperazides *IV*– *VIII* were obtained out of which only compounds *VI* and *VII* crystallized as bases; all were characterized as crystalline maleates which were also used for pharmacological testing. Reduction of the piperazide *VIII* with lithium aluminium hydride in tetrahydrofuran afforded the oily base *I* which gave a crystalline dihydrochloride. The melting point of this compound differs greatly from a literature[5,6] value given for a "hydrochloride" of a product obtained by reduction of 1-(2-ethoxycarbonylbenzoyl)-4-methylpiperazine (the described product could be a monohydrochloride).

1-[5-Chloro-2-(2-methylphenylthio)benzyl]-4-methylpiperazine (*XII*) was prepared as a further potential antidepressant. 5-Chloro-2-iodobenzoic acid[16] was treated with 2-methylthiophenol[11,12] in boiling aqueous potassium hydroxide in the presence of copper. Acid *IX* was obtained in a high yield and was reduced with diborane, generated by a reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran (method[17]). Alcohol *X* was formed and transformed by treatment with thionyl chloride in pyridine to the oily chloro derivative *XI*. A substitution



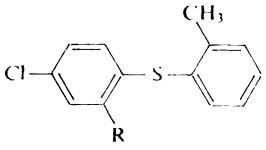


II, R = CH_3
III, R = $COOC_2H_5$

IV, R = H
V, R = 2-CH_3
VI, R = 4-CH_3

VII, R = 4-Cl
VIII, R = 2-CH_2OH

reaction with 1-methylpiperazine afforded the oily base *XII* which was converted to the crystalline bis(hydrogen maleate). The ^{1}H NMR spectrum of the base, released from the pure salt, confirmed the identity of the product.

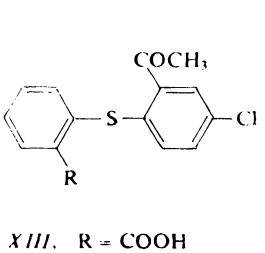


IX, R = COOH
X, R = CH_2OH

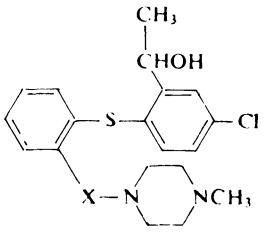
XI, R = CH_2Cl
XII, R = CH_2N NCH$_3$

2,5-Dichloroacetophenone[18] was treated with thiosalicylic acid[19] in the presence of dimethylformamide, potassium carbonate and copper at 120°C and gave the keto acid *XIII*. Because the attempts at proceeding further *via* the chloride of this acid met with difficulties (the reaction of the acid *XIII* with thionyl chloride is probably complicated by the presence of the keto group), N,N'-carbonyldiimidazole in dichloromethane-(method[20]) was used for the transformation of the acid *XIII* to the N-methylpiperazide *XIV*. In a yield of about 75% the oily base *XIV* was obtained which afforded a crystalline hydrochloride; the identity of the product was corroborated by spectra. The same product *XIV* was prepared by the mixed anhydride method[21]: the reaction of the acid *XIII* with ethyl chloroformate in dimethylformamide in the presence of 1-ethylpiperidine generated first the mixed anhydride of the acid *XIII* with the monoethyl carbonate which was treated *in situ* with 1-methylpiperazine. The base *XIV* was obtained in a yield of 55% and was transformed to the crystalline hydrogen maleate. Compound *XIV* was then reduced with sodium borohydride in a mixture of ethanol and benzene in the presence of water; only the keto group was reduced and there resulted the hydroxy piperazide *XV*. The oily base afforded a crystalline hydrogen maleate. The pure base *XV*, released from the salt, was used for recording the spectra which confirmed the structure. A reaction of compound *XIV* with lithium

aluminium hydride proceeded under reduction of both carbonyl groups and the oily derivative *XVI* was obtained which was characterized as the crystalline dihydrochloride.

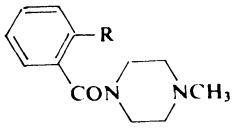


XIII, R = COOH
XIV, R = CON NCH$_3$



XV, X = CO
XVI, X = CH$_2$

As potential intermediates in the synthesis of similar compounds there were prepared 1-methyl-4-(2-nitrobenzoyl)piperazine (*XVII*) (by a reaction of 2-nitrobenzoyl chloride with 1-methylpiperazine in boiling benzene) and 1-(2-aminobenzoyl)-4-methylpiperazine (*XVIII*) (by reduction of the nitro compound by the Béchamp method[22]) which gave the N-acetyl derivative *XIX* by treatment with a boiling mixture of acetic acid and acetic anhydride.



XVII, R = NO$_2$
XVIII, R = NH$_2$
XIX, R = NHCOCH$_3$

The compounds prepared were pharmacologically tested in the form of salts, described in the Experimental, by methods of the pharmacological screening oriented especially to the expected central and neurovegetative effects. With all compounds, the acute toxicity in mice was determined in the first line; the LD_{50} values are given together with the basic dose D, used in the screening (all doses are in mg/kg and the compounds were administered intravenously unless stated otherwise): *I*, 34·6 (337 orally), 100 orally; *II*, 125, 25; *IV*, 75, 15; *V*, 50, 10; *VI*, 100, 20; *VII*, 125, 25; *VIII*, 175, 35; *XII*, 55, 10; *XIV*, 40, 8; *XV*, 90, 18; *XVI*, 34·8 (311 orally), 100 orally. All compounds administered in doses D were inactive in tests for antireserpine activity (ptosis and hypothermia in mice, reserpine gastric ulcers in rats), anticonvulsant activity (pentetrazole and electroshock in mice) and thiopental: potentiating activity in mice. Compounds *I* and *XVI* showed only a very weak indication of discoordinating

effect on the rotarod in mice (ataxia with 10% animals). The same compounds brought about a significant decrease of spontaneous motility in mice in the photo-cell method of Dews: *I* to 77% of the control value, *XVI* to 73%. On the other hand, compound *V* in the dose D (*s.c.*) increased clearly the motoric activity of mice. Compound *XII* which is an open model of the neuroleptic agent chlorothepin[23,24], was also tested with negative results for antiamphetamine, cataleptic and antiapomorphine activity (for other open models of clorothepin, *cf.*[18,25]). Some of the compounds (*II*, *VIII*, *XII*, *XIV* and *XV*) brought about sharp and brief drops of blood pressure in normotensive rats after the intravenously administered doses D. Compound *VIII* showed in addition an adrenolytic effect (the pressor action of adrenaline was decreased by 40%). Compound *V* displayed an antitussic effect in guinea-pigs: an oral dose of 25 mg/kg reduced the frequency of the cough attacks to 50% of the control value (the cough was elicited by chemical stimulation with an aerosol of citric acid); this activity corresponds to the effect of an oral dose of 10 mg/kg of codeine. Compound *XIV* had spasmolytic effect on the isolated rat duodenum agains the barium chloride contractions: a concentration of 10 μg/ml inhibited the contractions to 50% of the control. In a dose of 40 mg/kg orally it showed also an antiinflammatory effect in the test of kaolin arthritis in rats (twice as active as phenylbutazone). In a concentration of 25 μg/ml it decreased the heart inotropy and also frequency by 25% on the isolated rabbit atrium.

All compounds were also tested for antimicrobial activity *in vitro* but only three of them showed some inhibitory effects; microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceeded 100 μg/ml) are given: *Streptococcus β-haemolyticus XII* 25, *XVI* 100; *Streptococcus faecalis*, *XII* 50; *Staphylococcus pyogenes aureus*, *XII* 25, *XVI* 100; *Escherichia coli*, *XII* 25, *XVI* 100; *Proteus vulgaris*, *XII* 100; *Mycobacterium tuberculosis* H37Rv, *XII* 100; *Trichophyton mentagrophytes*, *VII* 50, *XII* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and 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, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer and the ^{1}N HMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and the composition of mixtures were checked by thin-layer chromatography on silica gel (Silufol).

1-(2-Iodobenzoyl)-4-methylpiperazine (*II*)

A stirred mixture of 75 ml 1-methylpiperazine and 25 ml chloroform was slowly treated with a mixture of 133 g 2-iodobenzoyl chloride[9,10] and 30 ml chloroform, the mixture was stirred for 1 h at room temperature and heated for 1 h under reflux in a bath of 120°C. It was allowed to stand overnight, the precipitated hydrochloride of *II* was filtered and recrystallized from ethanol; 143 g (78%), m.p. 245–250°C. Analytical sample, m.p. 248–252°C (ethanol). For $C_{12}H_{16}ClI.N_2O$ (366·6) calculated: 39·31% C, 4·40% H, 9·67% Cl, 34·62% I, 7·64% N; found: 39·70% C, 4·35% H, 9·84% Cl, 34·72% I, 7·72% N. Lit.[8], m.p. 163–165°C.

Treatment of the hydrochloride with aqueous NH_3 released the base which was isolated by extraction with benzene: m.p. 104–106°C (benzene–light petroleum). UV spectrum: inflex at 225 nm (log ε 4·13). IR spectrum (KBr): 730, 760 (4 adjacent ArH), 1 488, 1 580, 3 020 (Ar), 1 630 ($ArCONR_2$), 2 780 cm^{-1} ($N—CH_3$). For $C_{12}H_{15}IN_2O$ (330·2) calculated: 43·65% C, 4·58% H, 38·44% I, 8·49% N; found: 43·78% C, 4·58% H, 38·59% I, 8·59% N.

1-Ethoxycarbonyl-4-(2-iodobenzoyl)piperazine (*III*)

A solution of 3·99 g 2-iodobenzoyl chloride[9,10] in 4 ml chloroform was slowly added to 3·16 g 1-ethoxycarbonylpiperazine under stirring, the mixture was stirred for 30 min at room temperature and heated for 3·5 h under reflux in a bath of 120°C. After cooling the mixture was distributed between water and benzene, the benzene layer was washed with water, 2%NaOH and water, dried (Na_2SO_4) and evaporated. The inhomogeneous residue was chromatographed on a column of 150 g neutral Al_2O_3 (activity II). Elution with benzene and with a 4 : 1 mixture of benzene and ethanol gave 5·3 g (91%) homogeneous oily *III*. A sample for analysis was distilled; b.p. 218°C/0·24 Pa. UV spectrum: inflex at 226 nm (log ε 4·18). IR spectrum: 769 (4 adjacent Ar—H), 1 640 (ArCONRR'), 1 705 (NCOOR), 3 043 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·72 (bd, J = 8·0 Hz, 1 H, 6 H of benzoyl), 6·80–7·40 (m, 3 H, remaining ArH), 4·05 (q, J = 7·0 Hz, 2 H, OCH_2), 3·00–3·80 (m, 8 H, 4 CH_2N of piperazine), 1·19 (t, J = 7·0 Hz, CH_3 of ethyl). For $C_{14}H_{17}IN_2O_3$ (388·2) calculated: 43·31% C, 4·42% H, 32·09% I, 7·22% N; found: 43·87% C, 4·55% H, 33·00% I, 7·20% N.

1-Methyl-4-(2-nitrobenzoyl)piperazine (*XVII*)

A solution of 10 g 1-methylpiperazine in 100 ml benzene was stirred, cooled with ice and water and treated dropwise with a solution of 9·3 g 2-nitrobenzoyl chloride in 150 ml benzene, the mixture was then refluxed for 10 h, after cooling it was washed with water, 10% NaOH and water, dried (Na_2SO_4) and evaporated. The residue was crystallized from a mixture of benzene and light petroleum; 11·1 g (89%), m.p. 116–119°C. Analytical sample, m.p. 118–120°C (benzene–light petroleum). IR spectrum: 740, 778, 792 (4 adjacent Ar—H), 1 348, 1 530 ($ArNO_2$), 1 638 (Ar.CONRR'), 2 805 ($R_2N—CH_3$), 3 040, 3 095 cm^{-1} (Ar). For $C_{12}H_{15}N_3O_3$ (249·3) calculated: 57·82% C, 6·06% H, 16·86% N; found: 57·95% C, 5·83% H, 16·65% N.

Hydrochloride, m.p. 254–257°C (ethanol). For $C_{12}H_{16}ClN_3O_3$ (285·7) calculated: 50·44% C, 5·64% H, 12·41% Cl, 14·71% N; found: 50·50% C, 5·60% H, 12·47% Cl, 14·88% N.

1-(2-Aminobenzoyl)-4-methylpiperazine (*XVIII*)

A mixture of 24·9 g *XVII*, 60 g Fe, 80 ml 95% ethanol, 20 ml water and 1 ml hydrochloric acid was stirred and refluxed for 3 h. It was filtered while hot, the solid was washed with ethanol, the filtrate was evaporated, the residue distributed between water and benzene, the benzene layer was dried and evaporated; 22·7 g (100%) crude product. By longer standing it slowly crystallized, m.p. 76–79°C (benzene–light petroleum). UV spectrum: λ_{max} 305 nm (log ε 3·41), inflexes at 232 nm (4·06) and 252 nm (3·69). IR spectrum: 750, 756 (4 adjacent Ar—H), 1 478, 1 496, 3 008, 3 030, 3 060, 3 070 (Ar), 1 605 ($ArNH_2$), 1 630 (ArCONRR'), 3 180, 3 220, 3 335, 3 420 cm^{-1} (NH_2). ^1H NMR spectrum: δ 6·50–7·20 (m, 4 H, ArH), 4·28 (bs, 2 H, NH_2), 3 02 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 2·30 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3). For $C_{12}H_{17}N_3O$ (219·3) calculated: 65·72% C, 7·82% H, 19·16% N; found: 65·83% C, 8·14% H, 18·77% N.

1-(2-Acetamidobenzoyl)-4-methylpiperazine (*XIX*)

A mixture of 1·0 g *XVIII*, 2 ml acetic anhydride and 2 ml acetic acid was heated to the boiling point of the mixture, diluted with water and the solution was evaporated *in vacuo*. The residue was treated with a mixture of ethanol and benzene, evaporated again and then crystallized from acetone; 1·2 g (100%), m.p. 149–151°C. IR spectrum (KBr): 758, 780 (4 adjacent Ar—H), 1 500, 1 608 (Ar), 1 536, 1 690 (RCONH), 1 660 ($ArCONR_2$), 2 790 ($R_2N—CH_3$), 3 190, 3 238 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·60 (bs, 1 H, NH), 7·10–7·70 (m, 4 H, ArHz), 3·60 and 3·20 (2 bm, 4 H, $CH_2N^1CH_2$ of piperazine), c. 2·30 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3), 2·02 (s, 3 H, $COCH_3$). For $C_{14}H_{19}N_3O_2$ (261·3) calculated: 64·35% C, 7·33% H, 16·08% N; found: 64·53% C, 7·76% H, 16·14% N.

1-Methyl-4-[2-(phenylthio)benzoyl]piperazine (*IV*)

A mixture of 4·0 g thiophenol, 10 ml dimethylformamide, 9·9 g *II*, 6·4 g K_2CO_3, 0·2 g Cu and 0·2 g CuI was stirred and heated for 8 h under reflux in a bath of 150–160°C. After cooling it was distributed between water and benzene, the benzene layer was washed with water, dried and evaporated; 9·4 g crude oily *IV*. Neutralization with maleic acid (3·5 g) in 13 ml boiling ethanol and crystallization gave 10·7 g (83%) hydrogen maleate, m.p. 178–180°C (ethanol). For $C_{22}H_{24}.N_2O_5S$ (428·5) calculated: 61·66% C, 5·65% H, 6·54% N, 7·48% S; found: 61·71% C, 5·88% H, 6·43% N, 7·27% S.

1-Methyl-4-[2-(2-methylphenylthio)benzoyl]piperazine (*V*)

Was prepared similarly from 2·6 g 2-methylthiophenol[11,12] and 5·75 g *II* in the presence of 5 ml dimethylformamide, 3·7 g K_2CO_3, 0·1 g Cu and 0·1 g CuI; 5·7 g crude oily *V*. Neutralization with 2·3 g maleic acid in 13 ml ethanol gave 6·3 g (82%) hydrogen maleate, m.p. 179–181°C (ethanol). For $C_{23}H_{26}N_2O_5S$ (442·5) calculated: 62·42% C, 5·92% H, 6·33% N, 7·25% S; found: 62·41% C, 6·07% H, 6·20% N, 7·30% S.

1-Methyl-4-[2-(4-methylphenylthio)benzoyl]piperazine (*VI*)

A similar reaction of 2·24 g 4-methylthiophenol with 4·95 g *II* in the presence of 5 ml dimethylformamide, 3·2 g K_2CO_3, 0·1 g Cu and 0·1 g CuI gave 4·8 g crude oily *VI* which was neutralized with 1·75 g maleic acid in 35 ml ethanol and afforded 5·3 g (80%) hydrogen maleate, m.p. 146 to 149°C (ethanol–ether). For $C_{23}H_{26}N_2O_5S$ (442·5) calculated: 62·42% C, 5·92% H, 6·33% N, 7·25% S; found: 61·95% C, 5·86% H, 6·22% N, 7·00% S.

Treatment of the pure maleate with 10% NaOH and extraction with a mixture of ether and benzene gave the base *VI* which crystallized from a mixture of benzene and light petroleum; m.p. 87–89°C. IR spectrum: 750, 770, 820 (4 and 2 adjacent Ar—H), 1 491, 1 586, 1 596, 3 015, 3 030 (Ar), 1 628 cm^{-1} ($ArCONR_2$). ^1H NMR spectrum: δ 6·90–7·40 (m, 8 H, ArH), 3·80 and 3·22 (2 bt, 4 H, $CH_2N^4CH_2$ of piperazine), c. 2·40 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·28 (s, 3 H, $ArCH_3$), 2·22 (s, 3 H, NCH_3). For $C_{19}H_{22}N_2OS$ (326·5) calculated: 69·90% C, 6·79% H, 8·58% N, 9·82% S; found: 70·34% C, 6·73% H, 8·65% N, 10·16% S.

1-[2-(4-Chlorophenylthio)benzoyl]-4-methylpiperazine (*VII*)

A similar reaction of 2·60 g 4-chlorothiophenol with 4·95 g *II* in the presence of 6 ml dimethylformamide, 3·2 g K_2CO_3, 0·1 g Cu and 0·1 g CuI at 140–150°C gave 5·2 g (100%) crude oily base *VII* which was purified *via* the crystalline maleate similarly like in the preceding case. It was

then crystallized from hexane for analysis; m.p. 87–89°C. IR spectrum: 738, 776, 818, 839 (4 and 2 adjacent Ar—H), 1 478, 1 570, 1 590, 3 040, 3 055, 3 070 (Ar), 1 638 cm^{-1} ($ArCONR_2$). ^1H NMR spectrum: δ 7·30 (s, 8 H, ArH), 3·82 and 3·25 (2 bm, 4 H, $CH_2N^1CH_2$ of piperazine), c. 2·40 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{18}H_{19}ClN_2OS$ (346·9) calculated: 62·32% C, 5·52% H, 10·22% Cl, 8·08% N, 9·25% S; found: 62·05% C, 5·66% H, 10·37% Cl, 8·40% N, 9·22% S.

Hydrogen maleate, m.p. 145–149°C (ethanol). For $C_{22}H_{23}ClN_2O_5S$ (463·0) calculated: 57·07% C, 5·01% H, 7·66% Cl, 6·05% N, 6·93% S; found: 56·57% C, 5·16% H, 7·86% Cl, 5·82% N, 6·73% S.

1-[2-(2-Hydroxymethylphenylthio)benzoyl]-4-methylpiperazine (*VIII*)

A mixture of 11·2 g 2-hydroxymethylthiophenol[14,15], 19·8 g *II*, 12 ml dimethylformamide, 12·8 g K_2CO_3, 0·1 g Cu and 0·1 g CuI was stirred and refluxed for 8 h. After cooling the mixture was diluted with 200 ml benzene, the solid materials were filtered off, the filtrate was washed with water, dried and evaporated *in vacuo*; 20·5 g oily *VIII*. It was neutralized with 6·8 g maleic acid in 40 ml boiling ethanol, the solution was cooled and treated with ether; 23·3 g (85%) hydrogen maleate, m.p. 131–138°C. Analytical sample, m.p. 147–150°C (ethanol–ether). For $C_{23}H_{26}N_2O_6S$ (458·5) calculated: 60·24% C, 5·72% H, 6·11% N, 6·99% S; found: 59·68% C, 5·70% H, 5·78% N, 6·88% S.

The base released from the pure maleate did not show any tendency to crystallize. It was used for further work and for recording the ^1H NMR spectrum: δ 7·00–7·70 (m, 8 H, ArH), 4·70 (s, 2 H, $ArCH_2$), 3·75 and 3·20 (2 bm, 2 + 2 H, $CH_2N^1CH_2$ of piperazine), 3·40 (bs, 1 H, OH), c. 2·40 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3).

1-[2-(2-Hydroxymethylphenylthio)benzyl]-4-methylpiperazine (*I*)

A solution of 3·1 g *VIII* in 25 ml tetrahydrofuran was slowly added to a stirred suspension of 0·40 g $LiAlH_4$ in 10 ml tetrahydrofuran and the mixture was refluxed for 1·5 h. After cooling the mixture was decomposed under stirring with 0·5 ml 10% NaOH and 2 ml water, after 30 min stirring at room temperature the solid was filtered off, the filtrate was dried with K_2CO_3 and evaporated *in vacuo*; 1·9 g (64%) homogeneous oily *I*. Neutralization with HCl in a mixture of ethanol and ether gave the dihydrochloride, m.p. 213–216°C (ethanol). IR spectrum: 750, 777, 790 (4 adjacent Ar—H), 1 020 (CH_2OH), 1 568, 1 578, 3 015 (Ar), 2 428, 2 480, 2 508, 2 540, 2 610 (NH^+), 3 360 cm^{-1} (OH). For $C_{19}H_{26}Cl_2N_2OS$ (401·4) calculated: 56·85% C, 6·53% H, 17·66% Cl, 6·98% N, 7·99% S; found: 56·44% C, 6·56% H, 17·31% Cl, 6·77% N, 7·90% S. Lit.[5,6], m.p. 243–244°C for an unspecified "hydrochloride".

5-Chloro-2-(2-methylphenylthio)benzoic Acid (*IX*)

A solution of 12·1 g KOH in 130 ml water was stirred and treated with 7·9 g 2-methylthiophenol[11,12], 17·9 g 5-chloro-2-iodobenzoic acid[16] and 0·4 g Cu and the mixture was refluxed for 11 h. It was filtered while hot and the filtrate was acidified with hydrochloric acid. After standing overnight the crude product was filtered, washed with water and dried; 16·0 g (90%), m.p. 157 to 165°C. Analytical sample, m.p. 170–172°C (aqueous ethanol). UV spectrum: λ_{max} 260·5 nm (log ε 4·08), 327 nm (3·64). IR spectrum: 741, 759, 766, 789, 820, 895 (4 and 2 adjacent and solitary Ar—H), 933, 1 217, 1 258, 1 693, 2 472, 2 528, 2 592, 2 630, 2 655, 2 692, 2 715, infl. 3 110 cm^{-1} (ArCOOH). For $C_{14}H_{11}ClO_2S$ (278·8) calculated: 60·32% C, 3·98% H, 12·92% Cl, 11·50% S; found: 60·07% C, 4·02% H, 12·80% Cl, 11·36% S.

5-Chloro-2-(2-methylphenylthio)benzyl Alcohol (*X*)

A suspension of 11·2 g *IX* in 30 ml tetrahydrofuran was stirred and treated slowly with 1·8 g $NaBH_4$ and then at 15°C with 6 ml $BF_3.O(C_2H_5)_2$, added dropwise. The mixture was stirred for 3 h at room temperature, allowed to stand overnight, decomposed by a slow addition of 10 ml 1 : 1 dilute hydrochloric acid. After the addition of 100 ml water the product was extracted with benzene, the extract was washed with 5% NaOH and water, dried (Na_2SO_4) and evaporated *in vacuo*; 4·4 g (96% per conversion) crude *X* (6·3 g starting *IX* were recovered by acidification of the alkaline aqueous layers). The crude product was distilled, b.p. 166—168°C/0·1 kPa, and the distillate crystallized, m.p. 58—60°C (hexane). IR spectrum (KBr): 749, 753, 819, 873, 890 (4 and 2 adjacent and solitary Ar—H), 1 014, 1 038, 1 048, 1 060, 1 099 (CH_2OH), 1 470, 1 558, 1 585, 1 590 (Ar), 3 300 cm^{-1} (OH). ^1H NMR spectrum: δ 7·55 (bs, 1 H, 6-H), 7·00—7·30 (m, 6 H, remaining ArH), 4·72 (s, 2 H, $ArCH_2O$), 2·35 (s, 4 H, $ArCH_3$ and OH). For $C_{14}H_{13}ClOS$ (264·8) calculated: 63·50% C, 4·95% H, 13·39% Cl, 12·11% S; found: 63·42% C, 4·97% H, 13·22% Cl, 12·14% S.

5-Chloro-2-(2-methylphenylthio)benzyl Chloride (*XI*)

A stirred mixture of 7·7 g *X* and 3 ml pyridine was treated at 20°C with 4·7 g $SOCl_2$, added dropwise. The mixture was stirred for 2 h at 20°C, allowed to stand overnight, heated for 1 h to 35—40°C, cooled and decomposed by a slow addition of 25 ml water. The product was isolated by extraction with benzene. The extract was washed with dilute hydrochloric acid, 5% NaOH and water, dried with $CaCl_2$ and evaporated; 7·1 g (87%) crude product which was purified by distillation, b.p. 186—188°C/0·3 kPa. ^1H NMR spectrum: δ 6·70—7·90 (m, 7 H, ArH), 4·72 (s, 2 H, $ArCH_2Cl$), 2·40 (s, 3 H, $ArCH_3$). For $C_{14}H_{12}Cl_2S$ (283·2) calculated: 11·32% S; found: 11·37% S.

1-[5-Chloro-2-(2-methylphenylthio)benzyl]-4-methylpiperazine (*XII*)

A mixture of 4·6 g *XI*, 5·0 g 1-methylpiperazine and 5 ml chloroform was refluxed for 10 h, chloroform was evaporated *in vacuo*, the residue dstributed between water and benzene,from the benzene layer the product was extracted with 5% hydrochloric acid, the acid aqueous layer was treated with aqueous NH_3 and the base isolated by extraction with benzene; 3·5 g (62%) crude oily *XII*. Neutralization with 2·35 g maleic acid in 25 ml boiling ethanol gave 5·0 g bis(hydrogen maleate), m.p. 181—184°C (ethanol). For $C_{27}H_{31}ClN_2O_8S$ (579·1) calculated: 56·00% C, 5·40% H, 6·12% Cl, 4·84% N, 5·54% S; found: 56·12% C, 5·43% H, 5·94% Cl, 4·91% N, 5·69% S.

A sample of the pure salt was decomposed with aqueous ammonia and the base was isolated by extraction with ether. It was used for recording the ^1H NMR spectrum: δ 7·48 (d, J = 2·5 Hz, 1 H, 6-H), c. 7·20 (m, 4 H, ArH of methylphenylthio), 7·10 (q, J = 8·5; 2·5 Hz, 1 H, 4-H), 6·90 (d, J = 8·5 Hz, 1 H, 3-H), 3·60 (s, 2 H, $ArCH_2N$), 2·50 (bs, 8 H, 4 CH_2N of piperazine), 2·20 and 2·18 (2 s, 3+3 H, $ArCH_3$ and NCH_3).

2-(2-Acetyl-4-chlorophenylthio)benzoic Acid (*XIII*)

A mixture of 17·3 g thiosalicylic acid[19], 18·9 g 2,5-dichloroacetophenone[18], 20 ml dimethylformamide, 41·5 g K_2CO_3 and 0·3 g Cu was stirred and heated for 2 h to 120°C and then for 2 h to 150°C under reflux. It was diluted with water and washed with benzene, the aqueous layer was filtered and the filtrate was acidified with hydrochloric acid. After standing overnight the product was filtered, washed with water and crystallized from 400 ml methanol; 22·4 g (73%), m.p.194 to 200°C. Analytical sample, m.p. 200—202°C (methanol). UV spectrum: λ_{max} 317 nm (log ε 3·70),

inflexes at 235 nm (4·30) and 255 nm (4·03). IR spectrum: 738, 740, 817, 840, 897 (4 and 2 adjacent and solitary Ar—H), 915, 1 231, 1 260, 1 271, 1 691, 2 525, 2 570, 2 670, infl. 3 160 (ArCOOH), 1 562, 1 578, 1 588, 3 075 (Ar), 1 676 cm^{-1} (ArCOR). ^1H NMR spectrum [$C^2H_3SOC^2H_3$—$(CH_3)_3SiC^2H_2C^2H_2COO^2H$]: δ 7·82 (m, 2 H, 6-H and 3'-H), 7·40 (m, 3 H, 4,5,5'-H_3), 7·10 (m, 2 H, 3,6'-H_2), 2·50 (s, 3 H, $COCH_3$). For $C_{15}H_{11}ClO_3S$ (306·8) calculated: 58·72% C, 3·61% H, 11·56% Cl, 10·45% S; found: 59·08% C, 3·44% H, 11·72% Cl, 10·43% S.

1-[2-(2-Acetyl-4-chlorophenylthio)benzoyl]-4-methylpiperazine (*XIV*)

A) *XIII* (4·6 g) was added to a stirred solution of 2·5 g N,N'-carbonyldiimidazole in 20 ml dichloromethane under nitrogen, the mixture was treated with a solution of 1·5 g 1-methylpiperazine in 10 ml dichloromethane, stirred for 3 h at room temperature and allowed to stand for 48 h. It was diluted with dichloromethane, washed with water, 8% $NaHCO_3$, 15% Na_2CO_3 and water, dried with Na_2SO_4 and evaporated; 4·4 g (75%) oily base. Neutralization with HCl in a mixture of ethanol and ether gave 5·0 g hydrochloride, m.p. 203—215°C. Analytical sample, m.p. 217 to 220°C (ethanol). UV spectrum: λ_{max} 232·5 nm (log ε 4·32), 263 nm (3·89), 340 nm (3·50), infl. 286 nm (3·64). IR spectrum: 761, 775, 813, 868 (4 and 2 adjacent and solitary Ar—H), 1 542, 1 585, 3 015 (Ar), 1 631, 1 651 ($ArCONR_2$), 1 672, ArCOR), 2 380, 2 485, 2 530, 2 555 cm^{-1} (NH^+); in chloroform: 1 650 ($ArCONR_2$), 1 680 cm^{-1} (ArCOR). For $C_{20}H_{22}Cl_2N_2O_2S$ (425·4) calculated: 56·47% C, 5·21% H, 16·67% Cl, 6·59% N, 7·54% S; found: 55·84% C, 5·13% H, 16·32% Cl, 6·36% N, 7·59% S. The pure oily base, which was used for further work, was prepared by decomposition of this pure salt with aqueous ammonia and extraction with ether.

B) A mixture of 1·53 g *XIII*, 4 ml dimethylformamide and 0·6 g 1-ethylpiperidine was stirred and treated at 0—10°C with 0·54 g ethyl chloroformate. The mixture was stirred for 5 h and then treated with 0·6 g 1-methylpiperazine. It was stirred for 20 min at room temperature, allowed to stand overnight, evaporated *in vacuo* and the residue distributed between water and benzene. The benzene layer was washed with a solution of $NaHCO_3$ (acidification recovered 0·6 g starting *XIII*) and water, and the product was extracted into dilute hydrochloric acid. The acid aqueous layer was made alkaline with aqueous NH_3 and the base was isolated by extraction with ether. Processing of the extract gave 0·65 g (55% per conversion) homogeneous oily *XIV*, identical with the product obtained under *A* (TLC comparison). Neutralization with maleic acid in ethanol gave the hydrogen maleate, m.p. 160—162°C (ethanol–ether). For $C_{24}H_{25}ClN_2O_6S$ (505·0) calculated: 57·08% C, 4·99% H, 7·02% Cl, 5·55% N, 6·35% S; found: 57·66% C, 5·12% H, 6·99% Cl, 5·29% N, 6·20% S.

1-(2-[4-Chloro-2-(1-hydroxyethyl)phenylthio]benzoyl)-4-methylpiperazine (*XV*)

A solution of 7·1 g *XIV* in a mixture of 20 ml benzene and 75 ml ethanol was stirred and slowly treated with a solution of 0·6 g $NaBH_4$ in 5 ml water containing 0·1 ml 20% NaOH. The mixture was refluxed for 8·5 h, evaporated *in vacuo* and the residue was distributed between water and benzene. The benzene layer was washed with 5% NaOH and water, dried (Na_2SO_4) and evaporated *in vacuo*; 6·9 g crude oily *XV*. Neutralization with maleic acid (2·04 g) in a mixture of ethanol and ether gave 6·8 g (74%) hydrogen maleate, m.p. 154—160°C. Analytical sample, m.p. 158—162°C (ethanol–ether). For $C_{24}H_{27}ClN_2O_6S$ (507·0) calculated: 56·85% C, 5·37% H, 6·99% Cl, 5·53% N, 6·33% S; found: 56·64% C, 5·52% H, 7·30% Cl, 5·18% N, 6·42% S.

A sample of the pure maleate was decomposed with aqueous NH_3, the oily base was isolated by extraction with ether and used for recording the spectra. UV spectrum: λ_{max} 251 nm (log ε 4·08), 275 nm (3·78). IR spectrum: 752, 777, 822, 838, 895 (4 and 2 adjacent and solitary Ar—H), 1 105, 1 138 (CHOH), 1 585, 3 005 (Ar), 1 625 ($ArCONR_2$), 2 705, 2 760 (N—CH_2, N—CH_3), 3 320

cm^{-1} (OH). ^1H NMR spectrum: δ 7·60 (d, J = 2·0 Hz, 1 H, 3'-H), c. 7·15 (m, 6 H, remaining ArH), 5·29 (q, J = 6·0 Hz, 1 H, CH—O), 3·70 and 3·15 (2 bm, 4 H, $CH_2N^1CH_2$ of piperazine), 3·35 (bs, 1 H, OH), 2·20 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3), 1·31 (d, 3 H, CH_3 in hydroxyethyl).

1-(2-[4-Chloro-2-(1-hydroxyethyl)phenylthio]benzyl)-4-methylpiperazine (*XVI*)

A solution of 8·8 g *XIV* in 130 ml tetrahydrofuran was added dropwise over 8 min to a stirred suspension of 2·2 g $LiAlH_4$ in 50 ml tetrahydrofuran and the mixture was refluxed for 5 h. After cooling it was decomposed by a slow addition of a mixture of 8 ml water and 10 ml tetrahydrofuran and then 2·2 ml 10% NaOH. The mixture was stirred for 45 min, the solid was filtered off, the filtrate dried (Na_2SO_4) and evaporated; 8·2 g homogeneous oily base. Neutralization with HCl in a mixture of ethanol and ether gave 8·5 g (84%) dihydrochloride which was purified by crystallization from ethanol, m.p. 198—202°C. IR spectrum: 770, 820, 840, 895 (4 and 2 adjacent and solitary Ar-H), 1 110 (CHOH), 1 558, 1 580, 1 590 (Ar), 2 220, 2 265, 2 410, 2 535, 2 600 (NH^+), 3 325 cm^{-1} (OH). For $C_{20}H_{27}Cl_3N_2OS$ (449·9) calculated: 53·39% C, 6·05% H, 23·64% Cl, 6·23% N, 7·13% S; found: 53·33% C, 6·15% H, 23·07% Cl, 6·17% N, 7·40% S.

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