8-ALKYLTHIO-10-PIPERAZINODIBENZO[*b*,*f*]THIEPINS*

J.O.JÍLEK, J.METYŠOVÁ, J.POMYKÁČEK and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

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Starting from the corresponding alkyl phenyl sulfides *V*, 11-step syntheses were applied for the preparation of higher homologues of metitepin (*Ia*), containing as substituents in position 8 an ethylthio (*Ib*), propylthio (*Ic*), isobutylthio (*Id*) and dodecylthio (*Ie*) group. In the 8-isobutylthio series, also the amino alcohol *IId* and the enamine *IV* were prepared. Of the compounds obtained, only the ethylthio derivative *Ib* retains the high degree of neuroleptic activity; with increasing the alkyl in the alkylthio group this activity drops rapidly.

Some time ago we described the preparation and the high degree of neuroleptic activity of 8-methylthio-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[1,2] (*Ia*) which underwent under the name „methiothepin" (or „metitepin"[3]) a series of pharmacological and biochemical tests[4–9] as an antiserotonin neuroleptic[10–13]. The methylthio group was then used as a „neuroleptic" 8-substituent in a number of cases[14–17], its presence being always accompanied by the high degree of activity. The effect of higher alkylthio groups on the activity was not known and for this reason the present study was carried out (for analogous studies in the series of 8-alkyl and 8-alkoxy derivatives see ref.[18,19]) where the preparation and properties of 8-ethylthio (*Ib*), 8-propylthio (*Ic*), 8-isobutylthio (*Id*) and 8-dodecylthio (*Ie*) analogues of compound *Ia* are described. An improved synthesis of *Ia*, involving thiol *Va*, characterization of the disulfide[20] *IXa*, of the alcohol *XIIa* and the final product *Ia* are also presented. Preparation of *Ia via* reduction of the corresponding enamine with diborane was in the meantime described in a patent application[21]. Another note in the experimental part deals with the secondary amine[15] *IIIa*. In the 8-isobutylthio series we describe also the preparation of aminoalcohol *IId* and enamine *IV*.

In the preparation of *I*–*IV* we used the usual procedure[1,18]. The starting compounds were alkyl phenyl sulfides *V*, the preparation of which was described before[22–25]. In analogy, using cyclooctyl bromide, the previously unknown cyclooctyl sulfide *X* was prepared. The alkyl phenyl sulfides *V* were converted in a reaction with chlorosulfonic acid in chloroform (for method see ref.[26]) to the sulfonyl chlorides *VI* which were processed further in the crude state. To characterize them, the corre-

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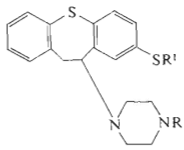
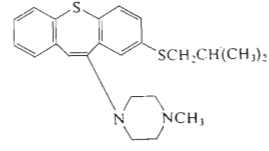
sponding sulfonamides *VIIc*, *VIId* and *VIIe* were prepared in three cases. The sulfonyl chlorides *VIb* and *VIc* were reduced with zinc in sulfuric acid (for method see ref.[26]) to 4-(ethylthio)thiophenol (*VIIIb*) and 4-(propylthio)thiophenol (*VIIIc*), respectively. 4-(Isobutylthio)thiophenol (*VIIId*) was obtained by reduction of the sulfonyl chloride *VId* with lithium aluminium hydride in ether. For the preparation of 4-(n-dodecylthio)thiophenol (*VIIIe*), the most suitable procedure was the reduction of sulfonyl chloride *VIe* with iodine and phosphorus in acetic acid (method[27]). The same method was found to be useful for the preparation of larger batches of 4-(methylthio)thiophenol[1,26] (*VIIIa*) using reduction of 4-(methylthio)benzenesulfonyl chloride[28] (*VIa*). After steam-distillation of thiol *VIIIa*, a considerable amount of disulfide[20] *IXa* is left over.

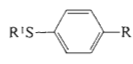
The thiophenols *VIII* were converted by a reaction with 2-iodobenzoic acid[29] in boiling potassium hydroxide in the presence of copper to 2-(4-alkylthiophenylthio)benzoic acids *XI* (method *A*). Reduction of acids *XI* with sodium bis(2-methoxyethoxy)dihydroaluminate[30] in benzene yielded 2-(4-alkylthiophenylthio)benzyl alcohols *XII* (method *B*), including the basic member of the series *XIIa* (*cf.*[1]). Reaction



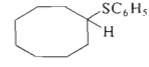
I, R = CH_3
II, R = $(CH_2)_3OH$
III, R = H



IV



V, R = H
VI, R = SO_2Cl
VII, R = SO_2NH_2
VIII, R = SH



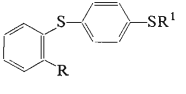
X

IX, R = SS— —SR^1

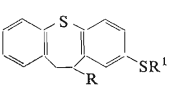
In all formulas: *a*, $R^1 = CH_3$; *b*, $R^1 = CH_2CH_3$; *c*, $R^1 = (CH_2)_2CH_3$; *d*, $R^1 = CH_2CH(CH_3)_2$ *e*, $R^1 = (CH_2)_{11}CH_3$.

of alcohols *XII* with thionyl chloride in the presence of pyridine resulted in 2-(4-alkylthiophenylthio)benzyl chlorides *XIII* (method *C*). Chlorides *XIIIb*–*XIIId* were converted in a reaction with sodium cyanide in aqueous ethanol to nitriles *XIVb* to *XIVd* (method *D*); for the conversion of chloride *XIIIe* to nitrile *XIVe* sodium cyanide in dimethylformamide was used. Preparation of the dodecylthio derivatives was generally markedly complicated by the lipophilic character of the products which did not crystallize readily and which had to be purified generally by chromatography. Nitriles *XIV* were hydrolyzed to the substituted phenylacetic acids *XV* by an aqueous–-alcoholic solution of potassium hydroxide (method *E*). Cyclization of acids *XVb* to *XVd* to the ketones *XVIb*–*XVId* was done by polyphosphoric acid in boiling toluene (method *F*). Ketone *XVIe* was obtained in the absence of toluene, by heating to 130°C. The next step was the reduction of ketones *XVI* to alcohols *XVII* with sodium borohydride in aqueous ethanol (method *G*). The alcohols *XVII* were treated with hydrogen chloride in benzene to convert them to chlorides *XVIII* (method *H*). The subsequent substitution reaction with 1-methylpiperazine or with 1-(3-hydroxypropyl)piperazine[31], was done in boiling chloroform and yielded the bases *I* and *II* (method *J*). It is demonstrated on the example of *Ia* which was previously obtained in a small yield (*cf.*[32]). The substitution reactions are accompanied even here by elimination; compounds *XIXb* and *XIXc* were isolated from the products and characterized. Ketone *XVI* was converted in a reaction with 1-methylpiperazine and titanium tetrachloride in boiling benzene (ref.[14]) to enamine *IV*. Compounds *I*, *II*, *IV* and *XI*–*XIX* are shown in Table I with the usual experimental data.

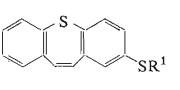
In the form of methanesulfonates and maleates the compounds were subjected to pharmacological tests, being applied either parenterally or orally. The acute toxicity for mice was determined and expressed by the mean lethal dose LD_{50}. The incoordinating effect in the rotating-rod test was studied in mice and expressed by the mean effective dose ED_{50}, this being taken as an indicator of the central depressant activity. Finally, the cataleptic effect on rats (for pharmacological methods see ref.[33]) was examined, this being an indicator of neuroleptic activity and is expressed by the mean effective doses ED_{50}. Data on toxicity and activity (in mg/kg) referring to the corresponding base are shown in Table II. For comparison, the table includes metitepin (*Ia*) which was administered parenterally, as well as orally.



XI, R = COOH
XII, R = CH_2OH
XIII, R = CH_2Cl
XIV, R = CH_2CN
XV, R = CH_2COOH



XVI, R = =O
XVII, R = OH
XVIII, R = Cl



XIX

Table II shows that only the ethylthio derivative *Ib* retains the full activity or even exceeds that of the standard (in case of the central depressant activity). Increasing the alkyl group in the alkylthio substituent by a single further carbon decreases the depressant effect by 90%, the cataleptic effect by 70%. The isobutylthio derivatives are little effective, this being in agreement with results obtained in the series of 8-alkyl[18] and 8-alkoxy derivatives[19].

The compounds prepared were also tested for antimicrobial activity *in vitro*; Table III shows the minimum inhibitory concentrations for several typical microorganisms. One may observe an increase in antibacterial activity as the alkyl is prolonged from ethyl (*Ib*) to propyl (*Ic*) and particularly to isobutyl in combination with the N-(3-hydroxypropyl) group (*IId*). This trend motivated the synthesis of the 8-dodecylthio derivative *Ie* which was found to be completely ineffective at concentrations up to 125 μg/ml. A similar lack of effect was found with enamine *Ig*.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 0·5 Torr over P_2O_5 at a suitable temperature (maximally at 100°C). The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer or in an Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss Jena) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on alumina.

Ethyl Phenyl Sulfide (*Vb*)

Thiophenol (110 g) was added to a solution of 23 g sodium in 600 ml ethanol, followed over an hour by 172 g ethyl iodide. The mixture was refluxed for 4 h, ethanol was evaporated, the residue diluted with 600 ml water and extracted with ether. The extract was washed with 10% NaOH, water and 10% H_2SO_4, dried with $CaCl_2$ and distilled; 114 g (83%), b.p. 84—85°C/16 Torr. For a compound prepared using diethyl sulfate, ref.[22] gives a b.p. of 204·5°C/760 Torr.

In analogy, the phenyl propyl sulfide (*Vc*) was prepared by using propyl bromide; the yield was 87%, b.p. 90°C/12 Torr. For a compound prepared using propyl iodide, ref.[22] reports a b.p. of 74·5°C/3Torr, using propyl bromide in aqueous ethanol[23,24] boiling points of 218·5—219·5°C/750 Torr and 218—219°C/760 Torr.

In analogy, the phenyl isobutyl sulfide (*Vd*) was prepared by using isobutyl iodide; the yield was 86%, b.p. 98°C/10 Torr or 103—105°C/15 Torr. Ref.[23] gives a b.p. of 85—87°C/4 Torr for a compound prepared with the aid of isobutyl bromide in aqueous ethanol.

Cyclooctyl Phenyl Sulfide (*X*)

Reaction of 11·0 g thiophenol with a solution of 2·3 g sodium in 60 ml ethanol and 21·0 g cyclooctyl bromide yielded 17·3 g (72%) sulfide *X*, b.p. 180°C/12 Torr or 172°C/8 Torr. NMR spectrum: δ 7·35 (m, 5 H, aromatic protons), 3·40 (m, 1 H, S—CH in a ring), c. 1·80 (m, 4 H, CH_2—C(—S)—CH_2 in the ring), 1·56 (bs, 10 H, remaining CH_2 groups of cyclooctane). For $C_{14}H_{20}S$ (220·4) calculated: 76·30% C, 9·15% H, 14·55% S; found: 75·81% C, 9·02% H, 15·18% S.

TABLE I

8-Alkylthiodibenzo[*b*,*f*]thiepins *I*, *II*, *IV*, *XVI*—*XIX* and Intermediates *XI*—*XV*[a]

Compound[b]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (m. w.)	Calculated/Found			
				% C	% H	% N (Cl)	% S
XIb	*A* (85)	202—204[c] (ethanol)	$C_{15}H_{14}O_2S_2$ (290·4)	62·04 62·12	4·86 4·87	— —	22·08 21·85
XIc	*A*[d] (80)	188—189 (ethanol)	$C_{16}H_{16}O_2S_2$ (304·3)	63·15 62·85	5·30 5·40	— —	21·04 21·08
XId	*A* (90)	163—165[e] (ethanol)	$C_{17}H_{18}O_2S_2$ (318·4)	64·12 64·43	5·69 5·62	— —	20·14 20·21
XIe	*A* (36)	105—108[f] (ethanol)	$C_{25}H_{34}O_2S_2$ (430·6)	69·72 69·70	7·96 8·27	— —	14·89 15·02
XIIa	*B* (95)	52—54[g] (benzene–light petroleum)	—	—	—	—	—
XIIb	*B* (96)	165/0·1[h]	$C_{15}H_{16}OS_2$ (276·4)	65·18 65·29	5·83 5·92	— —	23·20 22·82
XIIc	*B*[d] (84)	193—195/0·1	$C_{16}H_{18}OS_2$ (290·3)	66·19 66·01	6·25 6·32	— —	22·06 21·90
XIId	*B* (91)	179—180/0·1	$C_{17}H_{20}OS_2$ (304·5)	67·06 66·99	6·62 6·64	— —	21·06 21·01
XIIe	*B* (60)	51—52[i] (light petroleum)	$C_{25}H_{36}OS_2$ (416·7)	72·07 72·10	8·71 8·66	— —	15·38 14·94
XIIIc	*C*[d] (90)	54 (ethanol)	$C_{16}H_{17}ClS_2$ (308·9)	62·21 62·57	5·55 5·67	11·48 11·44	20·76 20·56
XIIId	*C* (79)	182—185/0·15	$C_{17}H_{19}ClS_2$ (322·9)	63·23 63·65	5·93 5·98	10·98 10·62	19·86 19·56
XIIIe	*C* (70)	38—39[j] (light petroleum)	$C_{25}H_{35}ClS_2$ (435·1)	69·01 69·55	8·11 8·38	8·15 7·90	14·73 14·85
XIVb	*D* (70)	185—188/0·15	$C_{16}H_{15}NS_2$ (285·4)	67·33 66·68	5·30 5·44	—	—
XIVc	*D* (78)	203—205/0·1	$C_{17}H_{17}NS_2$ (299·3)	—	—	4·68 4·09	21·38 21·25
XIVd	*D*[d] (82)	190—192/0·05	$C_{18}H_{19}NS_2$ (313·5)	68·97 69·09	6·11 6·42	4·47 3·85	20·45 20·63
XIVe	[d]	66 (light petroleum)	$C_{26}H_{35}NS_2$ (425·7)	73·36 73·44	8·29 8·52	3·29 3·14	15·06 15·14
XVb	*E* (87)	90—92[k] (benzene–light petroleum)	$C_{16}H_{16}O_2S_2$ (304·4)	63·12 63·26	5·30 5·27	— —	21·07 21·00

TABLE I
(*Continued*)

Compound[b]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (m. w.)	Calculated/Found			
				% C	% H	% N(Cl)	% S
XVc	*E*[d] (94)	114 (ethanol)	$C_{17}H_{18}O_2S_2$ (318·3)	64·14 63·74	5·70 5·72	— —	20·11 20·06
XVd	*E* (80)	108 (benzene–light petroleum)	$C_{18}H_{20}O_2S_2$ (332·5)	65·03 64·78	6·06 6·10	— —	19·29 18·96
XVIb	*F* (85)	78—78·5[m] (ethanol)	$C_{16}H_{14}OS_2$ (286·4)	67·10 67·22	4·92 5·01	— —	22·39 22·52
XVIc	*F*[d] (78)	68—70 (ethanol)	$C_{17}H_{16}OS_2$ (300·3)	67·99 68·32	5·37 5·52	— —	21·32 21·17
XVId	*F* (80)	182—183/0·1[n] m.p. 64—65	$C_{18}H_{18}OS_2$ (314·4)	68·75 68·72	5·77 5·75	— —	20·39 20·03
XVIIb	*G* (85)	84—85· (cyclohexane)	$C_{16}H_{16}OS_2$ (288·4)	66·63 66·30	5·59 5·57	— —	22·23 21·97
XVIIc	*G*[d] (97)	88—90 (methanol)	$C_{17}H_{18}OS_2$ (302·3)	67·54 67·64	6·00 6·14	— —	21·20 20·92
XVIId	*G* (90)	76 (aqueous ethanol)	$C_{18}H_{20}OS_2$ (316·5)	68·31 68·54	6·37 6·58	— —	20·26 20·05
XVIIe	*G* (87)	71—72 (ethanol–light petroleum)	$C_{26}H_{36}OS_2$ (428·7)	72·84 72·68	8·47 8·22	— —	14·96 14·79
XVIIIb	*H* (93)	68—70 (light petroleum)	$C_{16}H_{15}ClS_2$ (306·8)	62·62 62·81	4·93 5·09	11·55 11·66	20·90 20·60
XVIIIc	*H*[d] (98)	80—81 (cyclohexane)	$C_{17}H_{17}ClS_2$ (320·9)	63·63 64·05	5·34 5·49	11·05 11·13	19·98 19·88
XVIIId	*H* (92)	67—68[p] (light petroleum)	$C_{18}H_{19}ClS_2$ (334·9)	64·55 64·58	5·72 5·83	10·59 10·83	19·14 19·00
Ib-M	*J*[d] (71)	164—165 (ethanol)	$C_{25}H_{30}N_2O_4S_2$ (486·6)	61·70 61·47	6·21 6·34	5·76 5·61	13·18 13·33
Ib-2MS	—	188—189 (ethanol–ether)	$C_{23}H_{34}N_2O_6S_4$ (562·7)	49·09 48·59	6·09 6·36	4·98 5·15	22·79 22·78
Ic-M	*J* (80)	153—154 (ethanol)	$C_{26}H_{32}N_2O_4S_2$ (500·5)	62·39 62·32	6·44 6·03	5·60 5·52	12·78 12·88
Ic-MS	—	128—129 (ethanol–ether)	$C_{23}H_{32}N_2O_3S_3$ (480·7)	57·47 57·44	6·71 6·66	5·83 5·97	20·01 20·24
Ic-2MS[q]	—	110—113 (ethanol–ether)	$C_{24}H_{38}N_2O_7S_4$ (594·8)	48·46 48·49	6·44 6·32	4·71 4·76	21·56 21·96

TABLE I
(*Continued*)

Compound[b]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (m. w.)	Calculated/Found			
				% C	% H	% N (Cl)	% S
Id-2MS[r]	*J* (69)	121—123[s] (ethanol)	$C_{25}H_{41}N_2O_{7.5}S_4$ (617·8)	48·60 48·78	6·69 6·58	4·53 4·12	20·76 20·79
Ie-2HM	*J* (38)	122—125[t] (ethanol–ether)	$C_{39}H_{54}N_2O_8S_2$ (742·9)	63·04 63·27	7·33 7·52	3·77 3·63	8·63 8·78
IId-MS	*J* (74)	150—151 (ethanol)	$C_{26}H_{38}N_2O_4S_3$ (538·7)	57·96 57·99	7·11 6·86	5·20 4·86	17·85 17·92
XIXb	*J*[d]	61—62 (ethanol)	$C_{16}H_{14}S_2$ (270·4)	71·07 71·01	5·22 5·30	— —	23·71 23·89
XIXc	*J*	73—74[u] (ethanol)	$C_{17}H_{16}S_2$ (284·3)	71·82 71·55	5·67 5·65	— —	22·51 22·46
IV	[d]	109—110 (ethanol)	$C_{23}H_{28}N_2S_2$ (396·6)	69·65 69·89	7·12 7·26	7·06 6·96	16·17 16·26
IV-M[v]		99—101 (ethanol)	$C_{27}H_{33}N_2O_{4.5}S_2$ (521·7)	62·16 62·24	6·37 6·27	5·38 5·23	12·29 12·38

[a] Of the intermediates, chloride *XIIIb*, acid *XVe*, ketone *XVIe* and chloride *XVIIIe* were not obtained as chemical individuals and are not included in the table. [b] M maleate, HM hydrogen maleate, MS methanesulfonate. [c] UV spectrum: λ_{max} 266 nm (log ε 4·15); IR spectrum (Nujol): 750, 820 (4 and 2 adjacent Ar-H), 940, 1 260 (COOH), 1 575 (Ar), 1 670 cm^{-1} (ArCOOH). [d] See Experimental. [e] IR spectrum: 750, 818 (4 and 2 adjacent Ar-H), 920, 1 260 (COOH), 1 578 (Ar), 1 648 cm^{-1} (ArCOOH). [f] IR spectrum (Nujol): 748, 820 (4 and 2 adjacent Ar—H), 905, 1 258, 1 318 (COOH), 1 564, 1 580 (Ar), 1 680 cm^{-1} (ArCOOH); NMR spectrum: δ 11·52 (bs, disappears after deuteration, 1 H, COOH), 8·20 (m, 1 H, aromatic proton in the vicinity of carboxyl), 7·45 and 7·25 (2d, J = 9·0 Hz, 4 H, aromatic protons of phenylene disulfide), 6·70—7·30 (m, 3 H remaining aromatic protons), 2·85 (t, J = 6·0 Hz, 2 H, SCH_2), c. 1·50 (m, 2 H, CH_2 next to terminal methyl), 1·20 (s, 18 H, remaining 9 CH_2 of dodecyl), 0·85 (t, 3 H, CH_3). [g] For an analytical sample we reported previously[1] a m.p. of 56—58°C. [h] IR spectrum (film): 754, 816 (4 and 2 adjacent Ar—H), 1012 (CH_2OH), 3380 cm^{-1} (OH). [i] Pure compound was obtained by chromatography on alumina (activity II); IR spectrum (Nujol): 742, 808 (4 and 2 adjacent Ar—H), 1040, 1052 (CH_2OH), 1580, 1590 (Ar), 3360 cm^{-1} (OH); NMR spectrum: δ 7·00—7·50 (m, 8 H, aromatic protons), 4·71 (d, after D_2O s, 2 H, $ArCH_2O$), 2·85 (t, J = 9·0 Hz, 2 H, SCH_2), 2·20 (t, disappears after D_2O, 1 H, OH). c. 1·50 (m, 2 H, CH_2 next to terminal methyl), 2·21 (bs, 18 H, remaining 9 CH_2 of dodecyl), 0·85 (t, 3 H, CH_3). [j] Pure compound was obtained by chromatography of crude product on alumina (activity II) on elution with benzene; NMR spectrum: δ 7·15—7·65 (m, 8 H, aromatic protons), 4·75 (s, 2 H, $ArCH_2Cl$), 2·86 (t, J = 7·0 Hz, 2 H, SCH_2), 1·20 (bs, 20 H, remaining 10 CH_2 of dodecyl), 0·85 (t, 3 H, CH_3). [k] IR spectrum: 758, 809 (4 and 2 adjacent Ar—H), 946, 1236, 1703, 2600 cm^{-1} (COOH). [m] UV spectrum: λ_{max} 234·5 nm (log ε 4·20), 253·5 nm (4·30), 282 nm (4·19), 358 nm (3.47); IR spectrum: 743, 766, 797, 819, 899 (4 and 2 adjacent and solitary Ar—H), 1570 (Ar), 1670 cm^{-1} (ArCO); NMR

Dodecyl Phenyl Sulfide (*Ve*)

Thiophenol (44 g) was added to a solution of 27 g KOH in 150 ml 95% ethanol, followed over 30 min at 60°C with 100 g dodecyl bromide. The mixture was refluxed under stirring for 1·5 h, cooled, diluted with 300 ml water and the product extracted with benzene. After processing the extract, a product was obtained which crystallized and was filtered after mixing with a small amount of ethanol; 94 g (84%), m.p. 32—33°C, b.p. 145—147°C/0·2 Torr. A similar procedure was used for the preparation by Takahashi and coworkers[24] but they did not characterize the substance. Another procedure was employed by Adams and Ferretti[25] who reported a m.p. of 33—34°C.

4-(Ethylthio)benzenesulfonyl Chloride (*VIb*)

Chlorosulfonic acid (480 g) was added dropwise over 45 min at 0—5°C to a solution of 114 g *Vb* in 410 ml chloroform. The mixture was stirred for 1 h at 10°C and poured onto ice. The oily sulfonyl chloride was extracted with chloroform. The product obtained by evaporation (150 g, 77%) was used for reduction. In analogy, *VIc* (84% yield), *VId* (almost 100% yield) and *VIe* (66% yield) were prepared.

4-(n-Propylthio)benzenesulfonamide (*VIIc*)

A mixture of 2·0 g crude *VIc* and 5 ml concentrated NH_4OH was agitated for 2 h at room temperature, heated for 20 min to 50—60°C, cooled and acidified with 3M-HCl. On the following day, 1·8 g product was filtered; m.p. 129—130°C (methanol). For $C_9H_{13}NO_2S_2$ (231·2) calculated: 46·75% C, 5·67% H, 6·06% N, 27·68% S; found: 46·76% C, 5·88% H, 6·31% N, 27·58% S.

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spectrum: δ 8·17 (d, J = 2·0 Hz, 1 H, 9-H), 7·10—7·80 (m, 6 H, remaining aromatic protons), 4·35 (s, 2 H, $ArCH_2CO$), 2·92 (q, J = 7·0 Hz, 2 H, SCH_2), 1·26 (t, J = 7·0 Hz, 3 H, CH_3). [n] UV spectrum: λ_{max} 250 nm (log ε 4·34), 282·5 nm (4·23), 360 nm (3·54); IR spectrum (Nujol): 750, 818, 858, 900 (4 and 2 adjacent and solitary Ar—H), 1580, 1620 (Ar), 1675 cm^{-1} (Ar—CO); NMR spectrum: δ 8·12 (d, 1 H, aromatic 9-H), 6·95—7·85 (m, 6 H, remaining aromatic protons), 4·32 (s, 2 H, $ArCH_2CO$), 2·82 (d, 2 H, SCH_2), 1·20—2·10 (m, 1 H, CH of isobutyl), 0·98 (d, 6 H, 2 CH_3). [o] IR spectrum: 751, 815, 891 (4 and 2 adjacent and solitary Ar—H), 1052 and 1069 (CHOH), 1574 (Ar), 3340 cm^{-1} (OH). [p] NMR spectrum: δ 7·00—7·80 (m, 7 H, aromatic protons), 5·81 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·01 and 3·66 (2dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$), 2·81 (d, J = 7·0 Hz, 2 H, SCH_2), 1·90 (m, 1 H, CH of isobutyl), 1.03 (d, J = 6·0 Hz, 6 H, 2 CH_3). [q] Monohydrate. [r] Sesquihydrate. [s] NMR spectrum: δ 7·00—7·65 (m, 7 H, aromatic protons), 5·10 (m, 1 H, Ar—CH—N), 2·80—3·60 (m, after deuteration 15 H, $ArCH_2$, 4 NCH_2, SCH_2 and NCH_3), 2·77 (s, 6 H, 2 CH_3 of methanesulfonic acid), 1·80 (m, 1 H, CH of isobutyl), 0·98 (d, J = 6·0 Hz, 6 H, CH_3—C—CH_3). [t] NMR spectrum (CD_3SOCD_3): δ 6·90—7·50 (m, 7 H, aromatic protons), 6·14 (s, 4 H, 2 CH=CH of maleic acid), 2·50—4·10 (m, 16 H, $ArCH_2CHAr$, 4 NCH_2, SCH_2, NCH_3), c. 1·40 (m, 2 H, CH_2 next to terminal methyl), 1·20 (s, 18 H, remaining CH_2 of dodecyl), 0·85 (t, 3 H, C—CH_3). [u] NMR spectrum: δ 7·10—7·70 (m, 7 H, aromatic protons), 7·02 (s, 2 H, olefinic CH=CH), 2·85 (t, J = 8·0 Hz, 2 H, SCH_2), 1·65 (m, 2 H, CH_2 in the middle of propyl), 0·98 (t, J = 7·0 Hz, 3 H, CH_3). [v] Hemihydrate.

TABLE II

Pharmacological Activity (mg/kg) of the Prepared Compounds

Compound	Type of administration	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
Ia	*i.v.*	51	0·09	2·0[a]
Ia	*p.o.*	94	1·9	10·5
Ib	*i.v.*	25	0·04	2·3[a]
Ic	*i.v.*	41	0·3	6·9[a]
Id	*p.o.*	215	19·5	41·0
IId	*p.o.*	375	25·0	>100[b]
IV	*p.o.*	270	20·0	21

[a] Intraperitoneally; [b] a dose of 100 mg/kg brings about catalepsy in 30% animals.

TABLE III

Antimicrobial Activity of *Ib*—*Id* and *IId in vitro* (μg/ml)

Microorganism	*Ib*[a]	*Ic*[a]	*Id*[a]	*IId*[b]
Streptococcus β-haemolyticus	25	12·5	12·5	1·58
Staphylococcus pyogenes aureus	25	12·5	25	1·58
Mycobacterium tuberculosis H37Rv	12·5	12·5	12·5	12·5
Saccharomyces pasterianus	62·3	62·3	125	12·5
Trichophyton mentagrophytes	62·3	62·3	125	62·3
Candida albicans	125	125	—	125
Aspergillus niger	125	125	—	62·3

[a] Tested as bismethanesulfonate; [b] tested as monomethanesulfonate.

4-(Isobutylthio)benzenesulfonamide (*VIId*)

Preparation was analogous to the above, but starting from *VId*; m.p. 89—91°C (cyclohexane). For $C_{10}H_{15}NO_2S_2$ (245·3) calculated: 48·95% C, 6·16% H, 5·71% N, 26·14% S; found: 49·38% C, 6·30% H, 5·66% N, 25·99% S.

4-(n-Dodecylthio)benzenesulfonamide (*VIIe*)

Using 3·0 g *VIe*, 2·5 g product was obtained; m.p. 117°C (ethanol). NMR spectrum (CD_3SOCD_3): δ 7·80 (d, J = 9·0 Hz, 2 H, aromatic protons in the vicinity of the sulfonamide group), 7·45 (d, J = 9·0 Hz, 2 H, remaining two aromatic protons), 7·35 (s, disappears after D_2O, 2 H,

SO_2NH_2), 2·99 (t, J = 6·0 Hz, 2 H, SCH_2), 1·20 (s, 20 H, C—$(CH_2)_{10}$—C of dodecyl), 0·85 (t, J = 5·0 Hz, 3 H, CH_3). For $C_{18}H_{31}NO_2S_2$ (357·6) calculated: 60·46% C, 8·74% H, 3·92% N, 17·93% S; found: 60·49% C, 8·75% H, 3·77% N, 17·73% S.

4-(Ethylthio)thiophenol (*VIIIb*)

Crude *VIb* (143 g) was added to a solution of 415 g H_2SO_4 in 1280 g water at 0°C and then combined over a period of 15 min with 200 g zinc powder. The mixture was stirred for 15 min at 0°C and for 2·5 h at 20°C, heated to 95°C and the product was steam-distilled. The distillate (6 liters) was extracted with chloroform; 52·4 g (51%), b.p. 140—142°C/10 Torr.

In analogy, the 4-(n-propylthio)thiophenol (*VIIIc*) was prepared; b.p. 145—150°C/10 Torr. For $C_9H_{12}S_2$ (184·2) calculated: 58·69% C, 6·57% H, 34·75% S; found: 59·01% C, 6·59% H, 34.39% S.

4-(Isobutylthio)thiophenol (*VIIId*)

A solution of 26·5 g crude *VId* in 300 ml ether was added dropwise to a solution of 9·5 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 4 h, left to stand overnight and then decomposed with a small amount of water and with 350 ml 2M-HCl. The ether layer was washed with water, dried with $CaCl_2$ and distilled; 9·4 g (48%), b.p. 145—146°C/10 Torr. For $C_{10}H_{14}S_2$ (198·3) calculated: 60·56% C, 7·11% H, 32·33% S; found: 60·90% C, 7·27% H, 32·04% S.

4-(Methylthio)thiophenol (*VIIIa*)

A solution of 103 g *VIa* (ref.[28]) in 150 ml acetic acid was added dropwise to a refluxing mixture of 250 ml acetic acid, 45 g red phosphorus and 2·5 g iodine over a period of 30 min. The mixture was then refluxed for 3 h, left to stand overnight, combined with 50 ml water, refluxed for 1 h and steam-distilled. A total of 5 liters of distillate was collected from which the product was obtained partly by separation, partly by extraction with chloroform; a total of 47·5 g (66%), b.p. 120°C/10 Torr. For $C_7H_8S_2$ (156·3) calculated: 53·81% C, 5·16% H, 41·03% S; found: 53·94% C, 5·10% H, 41·14% S.

The residue after steam-distillation was extracted with hot benzene. A sample of the residue extract (1·5 g) was dissolved in benzene and the solution was chromatographed on a column of 30 g neutral alumina (activity II). Elution with benzene produced in the first fractions 0·80 g yellow compound, m.p. 85—86°C (cyclohexane). The compound melts without depression after mixing with the oxidation product of *VIIIa* (using H_2O_2 in aqueous-ethanolic sodium hydroxide); m.p. 90°C (cyclohexane). The compound in question is bis(4-methylthiophenyl)disulfide (*IXa*), for which the literature[20] reports a m.p. of 84—86°C.

4-(n-Dodecylthio)thiophenol (*VIIIe*)

Similarly to the above case, 26·5 g *VIe* was reduced with a mixture of 5·0 g red phosphorus, 2·6 g iodine and 65 ml acetic acid. After adding 6·5 ml water and 1 h of refluxing, the phosphorus was filtered, the filtrate was diluted with water and extracted with benzene. Processing of the extract yielded 12·6 g (58%) product boiling at 176—180°C/0·3 Torr. The distillate crystallized and was purified for analysis by crystallization from acetone; m.p. 77—80°C. NMR spectrum: δ 7·46 (d, J = 9·0 Hz, 2 H, aromatic protons in the vicinity of sulfide S), 7·25 (d, J = 9·0 Hz, 2 H, remaining two aromatic protons), 2·86 (t, J = 6·0 Hz, 2 H, SCH_2), 1·21 (s, 21 H, remaining 10 CH_2 of dodecyl and SH), 0·85 (t, J = 5·0 Hz, 3 H, CH_3). For $C_{18}H_{30}S_2$ (310·5) calculated: 69·61% C, 9·74% H, 20·65% S; found: 69·71% C, 9·47% H, 20·34% S.

2-(4-n-Propylthiophenylthio)benzoic Acid (*XIc*) (Method *A*)

Compound *VIIIc* (42·5 g), 75 g 2-iodobenzoic acid[29] and 3·0 g copper powder were added under stirring to a solution of 48 g KOH in 400 ml water and the mixture was refluxed for 7 h. After cooling, it was filtered, the filtrate made acid with hydrochloric acid, and the precipitated crude acid was purified by precipitation from an alkaline solution by another acidification; 55·6 g (80%), m.p. 188—190°C (ethanol). IR spectrum: 750 and 821 (4 and 2 adjacent Ar—H), 930, 1259, 2600 (COOH), 1574 (Ar), 1675 cm^{-1} (Ar—COOH). Compounds *XIb*, *XId* and *XIe* were prepared analogously.

2-(4-n-Propylthiophenylthio)benzyl Alcohol (*XIIc*) (Method *B*)

Sodium bis(2-methoxyethoxy)dihydroaluminate[30] (150 ml of a 50% benzene solution) was added dropwise under stirring over a period of 1 h to a suspension of 56 g *XIc* in 350 ml benzene. The solution formed was stirred for 3 h at room temperature, cooled with ice water and decomposed with 300 ml 10% NaOH. The benzene layer was dried and distilled; 44·7 g (84%), b.p. 193 to 195°C/0·1 Torr. Alcohols *XIIa* (ref.[1]) *XIIb*, *XIId* and *XIIe* were prepared analogously.

2-(4-n-Propylthiophenylthio)benzyl Chloride (*XIIIc*) (Method *C*)

Thionyl chloride (21·0 g) was added dropwise under stirring at 10—20°C over a period of 1 h to a mixture of 43·7 g *XIIc* and 15 g pyridine. The mixture was stirred for 3 h at room temperature, left to stand overnight and heated for 2 h to 40°C; it was cooled again, diluted with 200 ml benzene and decomposed by adding dropwise 120 ml water. After shaking, the benzene layer was washed, dried and evaporated. The residue weighed 42 g (90%), m.p. 53—55°C (ethanol). Chlorides *XIIIb*, *XIIId* and *XIIIe* were prepared analogously.

[2-(4-Isobutylthiophenylthio)phenyl]acetonitrile (*XIVd*) (Method *D*)

A solution of 19·3 g NaCN in 35 ml water was combined with a solution of 63·5 g *XIIId* in 80 ml ethanol and the mixture was refluxed for 8 h. After evaporation of ethanol, the residue was diluted with 140 ml water and the product extracted with benzene; 50·7 g (82%), b.p. 210—212°C/0·4 Torr or 190—192°C/0·05 Torr. Nitriles *XIVb* and *XIVc* were prepared analogously.

[2-(4-n-Dodecylthiophenylthio)phenyl]acetonitrile (*XIVe*)

Sodium cyanide (2·4 g) was added to a solution of 7·0 g *XIIIe* in 17 ml dimethylformamide and the mixture was heated under stirring for 8 h to 100—110°C. On the following day, the dimethylformamide was evaporated *in vacuo*, the residue was diluted with 100 ml water and extracted with benzene. The extract was washed with water, dried with $CaCl_2$ and evaporated to dryness. The residue (6·4 g, 93%), melted at 66°C (light petroleum). NMR spectrum: δ 7·40 (m, 4 H, aromatic protons of phenylacetonitrile), 7·30 and 7·10 (2 d, $J = 9{\cdot}0$ Hz, 4 H, aromatic protons of phenylene disulfide), 3·83 (s, 2 H, $ArCH_2CN$), 2·86 (t, $J = 7{\cdot}0$ Hz, SCH_2), 1·20 (s, 20 H, 10 CH_2 of dodecyl), 0·86 (t, 3 H, CH_3).

[2-(4-n-Propylthiophenylthio)phenyl]acetic Acid (*XVc*) (Method *E*)

A solution of 30 g *XIVc* in 100 ml ethanol was refluxed with a solution of 30 g KOH in 30 ml water for 4 h. The ethanol was evaporated, the residue dissolved in 300 ml water and the solution

washed with benzene. Acidification with hydrochloric acid precipitated the product; 29·7 g (94%), m.p. 114°C (ethanol). Acids *XVb*, *XVd* and *XVe* were prepared analogously.

8-(n-Propylthio)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVIc*) (Method *F*)

A mixture of 100 g polyphosphoric acid, 10·0 g *XVc* and 30 ml toluene was refluxed under stirring for 4 h. After cooling, it was diluted with benzene, 100 ml water was added, the benzene layer separated after agitation, washed with 5% solution of NaOH and evaporated; 7·30 g (78%), b.p. 195°C/0·1 Torr, m.p. 68—70°C (ethanol). UV spectrum: λ_{max} 250·5 nm (log ε 4·32), 274·5 nm (4·21), 360 nm (3·46). IR spectrum: 744, 766 and 815 (4 and 2 adjacent and solitary Ar—H), 1 570 (Ar), 1 664 cm^{-1} (Ar—CO). NMR spectrum: δ 8·15 (ms, J = 2·0 Hz, 1 H, 9-H), 7·00—7·80 (m, 6 H, remaining aromatic protons), 4·33 (s, 2 H, $ArCH_2CO$), 2·90 (t, J = 3·0 Hz, 2 H, SCH_2), 1·60 (m, 2 H, central CH_2 of propyl), 0·98 (t, J = 7·0 Hz, 3 H, CH_3). Ketones *XVIb* and *XVId* were prepared analogously.

8-(n-Dodecylthio)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XVIe*)

A mixture of polyphosphoric acid (32 g P_2O_5 and 22·5 ml 85% H_3PO_4) and 5·0 g *XVe* was heated under stirring for 5 h to 130°C. After cooling, benzene was added, the mixture was decomposed with water and processed as in the preceding case. A total of 4·16 g (86%) oil was obtained, a part of which was converted for characterization to the 2,4-dinitrophenylhydrazone, m.p. 142—143°C (ethanol–benzene). UV spectrum: λ_{max} 277 and 382 nm. IR spectrum: 744, 766, 820, 836 (4 and 2 adjacent and solitary Ar—H), 1 340 and 1 507 (NO_2), 1 597 (Ar), 1 613 (C=N), 3 320 cm^{-1} (NH). For $C_{32}H_{38}N_4O_4S_2$ (606·8) calculated: 9·23% N, 10·58% S; found: 9·17% N, 10·73% S.

8-(n-Propylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XVIIc*) (Method *G*)

A solution of 1·9 g $NaBH_4$ in 20 ml water with 0·5 ml 20% NaOH was added dropwise over a period of 30 min to a solution of 18·0 g *XVIc* in 300 ml ethanol. The mixture was refluxed under stirring for 2 h, ethanol was evaporated and the residue was divided between 200 ml water and 200 ml benzene. The benzene layer was washed with 3% NaOH and water, filtered and evaporated. The residue weighed 17·6 g (97%), m.p. 88—90°C (methanol). IR spectrum: 749, 821, 831, 882 (4 and 2 adjacent and solitary Ar—H), 1051 (CHOH in a ring), 1573 (Ar), 3325 cm^{-1} (OH). Alcohols *XVIIb*, *XVIId* and *XVIIe* were prepared analogously.

8-(n-Propylthio)-10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVIIIc*) (Method *H*)

Powdery $CaCl_2$ (20 g) was added to a solution of 16·7 g *XVIIc* in 170 ml benzene and the suspension was saturated with anhydrous HCl. After standing overnight, it was filtered and the filtrate was evaporated at reduced pressure; 17·3 g (98%), m.p. 82—84°C (needles from cyclohexane). Chlorides *XVIIIb*, *XVIIId* and *XVIIIe* were prepared analogously.

8-Methylthio-10-(4-methylpiperazino)-10,11-dihydrodibenzo [*b*,*f*]thiepin (*Ia*) (Method *J*)

A mixture of 293 g *XVIIIa* (ref.[1]), 300 ml chloroform and 250 g 1-methylpiperazine was refluxed under stirring for 7 h, the solvent was evaporated and the residue was diluted with 1 liter benzene. The solution was washed several times with water, shaken with excess 3M-HCl, the precipitated hydrochloride was filtered, washed with benzene, suspended in the acid–aqueous phase of the filtrate and the base was liberated by treatment with NH_4OH. It was extracted with benzene;

284 g (80%) crude base. In a previous paper[1] where no chloroform was used as the medium and where less pure 1-methylpiperazine was used, a yield of only 45% was reported. The base crystallized, m.p. 88—89°C (ethanol). For $C_{20}H_{24}N_2S_2$ (356·5) calculated: 67·38% C, 6·78% H, 7·85% N, 17·99% S; found: 67·07% C, 6·81% H, 7·94% N, 17·65% S.

Maleate, for which a m.p. of 160—161°C was previously reported[1] melted now at 171—173°C (ethanol). For $C_{24}H_{28}N_2O_4S_2$ (472·6) calculated: 60·99% C, 5·97% H, 5·93% N, 13·57% S; found: 60·93% C, 6·06% H, 6·04% N, 13·42% S.

4,4'-*Methylenebis*(3-*hydroxy*-2-*naphthoate*) (*monohydrate*), m.p. 180—190°C. For $C_{43}H_{42}N_2O_7S_2$ (762·9) calculated: 67·70% C, 5·55% H, 3·67% N, 8·40% S; found: 67·36% C, 5·35% H, 3·48% N, 8·60% S.

8-Ethylthio-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ib*)

The oily base was obtained from *XVIIIb* by method *J* in a 71% yield. Maleate m.p. 164—165°C (ethanol). NMR spectrum: δ 7·15—7·65 (m, 5 H, aromatic 1,2,3,4,9-H_5), 7·42 (d, J = 9·0 Hz, 1 H, 6-H), 7·08 (q, J = 9·0; 2·0 Hz, 1 H, 7-H), 6·31 (s, 2 H, CH=CH of maleic acid), 3·20—4·10 (m, 3 H, $ArCH_2CHAr$), 2·60—3·20 (m, 10 H, SCH_2 and 4 NCH_2 of piperazine), 2·75 (s, 3 H, NCH_3), 1·25 (t, 3 H, $C—CH_3$). Dimethanesulfonate, m.p. 188—189°C (ethanol–ether). The analytical data for both salts are shown in Table I.

Washing of the benzene solution with hydrochloric acid and evaporation produced a 25% yield of 2-ethylthiodibenzo [*b*,*f*]thiepin (*XIXb*), m.p. 61—62°C (ethanol). UV spectrum: λ_{max} 267 nm (log ε 4·52). IR spectrum: 746, 809 and 880 (4 and 2 adjacent and solitary Ar—H), 782 (CH=CH cis), 1569 cm^{-1} (Ar). NMR spectrum: δ 7·10—7·70 (m, 7 H, aromatic protons), 7·02 (s, 2 H, olefinic CH=CH), 2·92 (q, J = 7·0 Hz, 2 H, SCH_2), 1·27 (t, J = 7·0 Hz, 3 H, CH_3). Bases *Ic*, *Id*, *Ie* and *IId*, as well as *XIXc* were prepared analogously.

8-Methylthio-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IIIa*)

The compound was prepared similarly as before[1,5] but the maleate previously reported to melt at 162—163°C (ethanol–ether) melted now at 171—172°C (aqueous ethanol). For $C_{23}H_{26}N_2O_4S_2$ (458·5) calculated: 60·25% C, 5·72% H, 6·11% N, 13·98% S; found: 60·35% C, 5·92% H, 6·38% N, 14·13% S.

8-Isobutylthio-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*IV*)

A solution of 3·32 g $TiCl_4$ in 20 ml benzene was added dropwise under stirring to a solution of 11·1 g *XVId* and 17·5 g 1-methylpiperazine in 80 ml benzene and the mixture was refluxed for 24 h. After cooling, 100 ml water were added, the precipitate was filtered and the filtrate separated. The benzene phase was washed with water and evaporated. Crystallization of the residue from 20 ml light petroleum yielded 8·25 g (59%) base, m.p. 109—110°C (ethanol). UV spectrum: λ_{max} 274 nm (log ε 4·34), 312 nm (3·92). IR spectrum (Nujol): 750, 785, 818, 836 and 865 (4 and 2 adjacent and solitary Ar—H), 1570, 1604 (Ar), 2790 cm^{-1} (N—CH_3). NMR spectrum: δ 7·00—7·70 (m, 7 H, aromatic protons), 6·32 (s, 1 H, ArCH=C), 2·96 (m, 4 H, $CH_2N^1CH_2$), 2·74 (d, 2 H, SCH_2), 2·52 (m, 4 H, $CH_2N^4CH_2$), 2·31 (s, 3 H, N—CH_3), c. 1·90 (m, 1 H, CH of isobutyl), 1·00 (d, 6 H, 2 C—CH_3). Maleate (hemihydrate), m.p. 99—101°C (ethanol).

The spectra were registered and interpreted by Drs B. Kakáč, E. Svátek and J. Holubek of the physicochemical department. Analyses were done in the analytical laboratory of this institute by

Mr K. Havel, Mrs J. Komancová, Mrs. V. Šmídová, Mrs A. Slavíková and Mrs J. Hrdá. The antimicrobial activity was estimated by Dr J. Turinová and Dr A. Čapek of the bacteriological department of this institute. Mr Z. Šedivý assisted with the preparation of some of the compounds.

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