6-SUBSTITUTED AND 2-CHLORO-6-SUBSTITUTED 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS AS POTENTIAL ANTIDEPRESSANTS; SYNTHESIS AND PHARMACOLOGY

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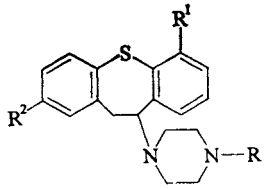
6-Substituted and 2-chloro-6-substituted 10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepins *XIIIa–f* were reacted with 1-(ethoxycarbonyl)piperazine and the carbamates *IIIa–f* obtained were hydrolyzed to the title compounds *Ia–f*. The new chlorides *XIIIa–c* were obtained from 2-(2-arylthiophenyl)acetic acids *VIIIa–c via* ketones *XIa–c* and alcohols *XIIa–c*. Reactions of the chlorides *XIIIa* and *XIIIc* with 1-methylpiperazine afforded compounds *IIa* and *IIc*. All compounds *I* are devoid of antireserpine and cataleptic activity; they are neither typical antidepressants nor neuroleptics.

The title compounds *Ia–f* were designed as potential antidepressants on the basis of following structural relations: The dibenz[*b*,*f*]-1,4-oxazepine derivative amoxapine (*IV*), which is the N-demethyl analogue of the strong neuroleptic agent loxapine[1], exhibits some properties of thymoleptic agents and is used in therapy as an antidepressant[2–4]. The simple N-demethylation seems to be connected in this case with the reversal of a neuroleptic into an antidepressant agent. On the other hand it was observed that amoxapine (*IV*) also possesses many typical properties of neuroleptic agents, their undesirable side effects included[5,6]. In the series of antidepressant 3-(dibenzo[*a*,*d*]cycloheptene-5-ylidene)propylamines (ptylinoids), the team of Hoffmann–La Roche[7] found the substitution in position 1 (Cl, CH_3) as especially suitable for obtaining high activity. This led to detailed examination of the 1-chloro derivative of amitriptyline (*V*) (refs[8,9]), as well as of compounds Ro 8-1998 (*VI*) (refs[10,11]) and Ro 8-0254 (benzaprinoxide, *VII*) (refs[12,13]). Combination of N-demethylation with substitution in position 6 (corresponding to position 1 in compounds *V–VII*), applied to the neuroleptic series of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins[14–17], led to structures *Ia–f*. The corresponding compounds were considered potential antidepressants or at least a mixed type between antidepressants and neuroleptics.

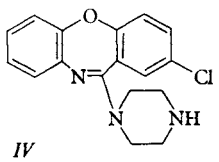
Compounds *Ia–f* were synthesized by methods described in our previous communications[18–21] for similar cases. (2-Arylthiophenyl)acetic acids *VIII* were

cyclized with polyphosphoric acid to dibenzo[*b*,*f*]thiepin-10(11*H*)-ones *XI* which were reduced with sodium borohydride to alcohols *XII*. Treatment with hydrogen chloride gave the 10-chloro compounds *XIII*. Heating of these compounds with an excess of 1-(ethoxycarbonyl)piperazine in boiling chloroform (method *A*) resulted

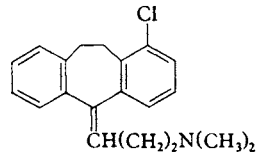


I, R = H
II, R = CH_3
III, R = $COOC_2H_5$

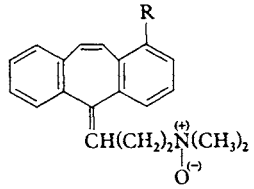
In formulae *I*–*III*, *VIII*–*XIII* and *XV*: *a*, R^1 = CH_3, R^2 = H; *b*, R^1 = CH_3, R^2 = Cl; *c*, R^1 = C_2H_5, R^2 = H; *d*, R^1 = Cl, R^2 = H; *e*, R^1 = OCH_3, R^2 = H; *f*, R^1 = OCH_3, R^2 = Cl



IV



V



VI, R = CH_3
VII, R = Cl

in the basic carbamates *III*, which were hydrolyzed with potassium hydroxide in boiling ethanol (method B) to the title compounds *Ia*–*f*. Chloro compounds *XIIIa* and *XIIIc* were also subjected to substitution reactions with 1-methylpiperazine using method *A* and gave the methylpiperazino derivatives *IIa* and *IIc*. Compounds *I*–*III*, prepared by the general methods *A* and *B*, are assembled in Table I. Most of the bases *I* and *II* were crystalline and all of them were transformed to dimethanesulfonates. The bases *I*–*III* were characterized by spectra; the salts of *I* and *II* are included in Table I.

TABLE I

6-Substituted and 2-chloro-6-substituted 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins (*I*), their N-methyl (*II*) and N-ethoxycarbonyl derivatives (*III*)

Compound[a]	Method (% yield)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
Ia-2 MS	B[b] (95)	206–209 (ethanol)	$C_{21}H_{30}N_2O_6S_3$ (502·7)	50·17 50·57	6·02 6·18	— —	5·57 5·59	19·14 18·97
Ib-2 MS[c]	B[d,e] (98)	210–213 (methanol)	$C_{21}H_{29}ClN_2O_6S_3 + H_2O$ (555·2)	45·43 45·77	5·63 5·60	6·39 6·18	5·05 5·03	17·33 16·82
Ic-2 MS	B (96)	207–210 (ethanol–ether)	$C_{22}H_{32}N_2O_6S_3$ (516·7)	51·14 50·99	6·26 6·35	— —	5·42 5·44	18·62 18·52
Id	B[f] (95)	102–104 (benzene–hexane)	$C_{18}H_{19}ClN_2S$ (330·9)	65·33 65·87	5·79 5·87	10·72 10·66	8·47 8·38	9·69 9·31
Id-2 MS		234–236 (95% ethanol–ether)	$C_{20}H_{27}ClN_2O_6S_3$ (523·1)	45·92 46·12	5·20 5·32	6·78 6·80	5·36 5·29	18·39 18·34
Ie	B[g] (84)	119–121 (benzene–hexane)	$C_{19}H_{22}N_2OS$ (326·5)	69·90 70·26	6·79 6·84	— —	8·58 8·59	9·82 9·80
Ie-2 MS[h]		202–204 (methanol)	$C_{21}H_{30}N_2O_7S_3 + 0{\cdot}5\ H_2O$ (527·7)	47·80 47·81	5·92 5·83	— —	5·31 5·08	18·23 18·23
If	B[i] (94)	134–136 (benzene–light petroleum)	$C_{19}H_{21}ClN_2OS$ (360·9)	63·23 63·28	5·87 5·95	9·82 9·94	7·76 7·64	8·89 8·94
If-2 MS		162–166 (95% ethanol)	$C_{21}H_{29}ClN_2O_7S_3$ (553·1)	45·60 45·59	5·28 5·62	6·41 6·38	5·07 4·80	17·39 16·85
IIa	A[j] (78)	83–85 (hexane)	$C_{20}H_{24}N_2S$ (324·5)	74·03 73·88	7·45 7·55	— —	8·64 8·60	9·88 9·84
IIa-2 MS		195–197 (ethanol)	$C_{22}H_{32}N_2O_6S_3$ (516·7)	51·14 50·92	6·24 6·28	— —	5·42 5·30	18·62 18·48
IIc-2 MS[h]	A[k] (80)	175–178 (95% ethanol–ether)	$C_{23}H_{34}N_2O_6S_3 + 0{\cdot}5\ H_2O$ (539·7)	51·18 51·27	6·54 6·39	— —	5·19 5·38	17·82 18·38
IIIa	A[l] (50)	107–109 (ethanol)	$C_{22}H_{26}N_2O_2S$ (382·5)	69·07 69·02	6·85 7·05	— —	7·33 7·16	8·38 8·55

TABLE I
(*Continued*)

Compound[a]	Method (% yield)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
IIIb	A[i] (69)	133–136 (ethanol)	$C_{22}H_{25}ClN_2O_2S$ (417·0)	63·37 63·59	6·04 6·07	8·50 8·73	6·72 6·81	7·70 7·81
IIIc	A[m] (53)	83–86 (ethanol)	$C_{23}H_{28}N_2O_2S$ (396·5)	69·66 70·35	7·11 7·27	— —	7·07 7·19	8·09 8·13
IIId	A[n] (68)	138–140 (ethanol)	$C_{21}H_{23}ClN_2O_2S$ (402·0)	62·59 62·61	5·75 5·81	8·80 8·89	6·95 7·17	7·96 8·18
IIIe	A (85)	[o]	—	—	—	—	—	—
IIIf	A[p] (71)	117–118 (cyclohexane)	$C_{22}H_{25}ClN_2O_3S$ (433·0)	61·02 61·42	5·82 5·93	8·19 8·25	6·47 6·41	7·41 7·58

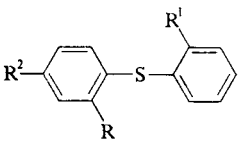
[a] 2 MS di(methanesulfonate). [b] The homogeneous oily base was obtained by decomposition of the salt with NH_4OH and by extraction with ether; it was used for recording the spectra; IR spectrum (film): 679, 750, 776 (4 and 3 adjacent Ar—H), 1 475, 1 570, 3 010, 3 055 (Ar), 2 740, 2 808 (NCH_2), 3 300 cm^{-1} (NH); ^1H NMR spectrum: δ 6·80–7·50 (m, 7 H, ArH), 3·00–4·20 (m, 3 H, $ArCH_2CHAr$), 2·80 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·48 (s, 3 H, $ArCH_3$), 2·12 (bs, 1 H, NH). [c] Monohydrate. [d] Mass spectrum, *m/z* (% and composition): 344 (M^+ corresponding to $C_{19}H_{21}ClN_2S$, 2%), 258 (70, $C_{15}H_{11}ClS$), 225 (26), 223 (19, $C_{15}H_{11}S$), 208 (17, $C_{14}H_8S$), 190 (44), 85 (52), 56 (44, C_3H_6N), 44 (100, C_2H_6N). [e] The homogeneous oily base, released from the salt, was used for recording the ^1H NMR spectrum: δ 6·80–7·50 (m, 6 H, ArH), 3·00–4·20 (m, 3 H, $ArCH_2CHAr$), 2·80 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·68 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·47 (s, 3 H, $ArCH_3$), 2·20 (s, 1 H, NH). [f] ^1H NMR spectrum: δ 6·80–7·60 (m, 7 H, ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·80 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·52 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 1·40 (bs, 1 H, NH). [g] IR spectrum: 750, 783, 802 (4 and 3 adjacent Ar—H), 1 133, 1 250 ($ArOCH_3$), 1 565, 1 590, 3 040, 3 055 (Ar), 2 790, 2 805 (CH_2—N), 3 330 cm^{-1} (NH); ^1H NMR spectrum: δ 6·60–7·60 (m, 7 H, ArH), 3·00–4·20 (m, 3 H, $ArCH_2CHAr$), 3·90 (s, 3 H, OCH_3), 2·80 and 2·55 (2 bm, 4 + 4 H, 4 CH_2 of piperazine), 1·45 (s, 1 H, NH). [h] Hemihydrate. [i] See Experimental. [j] ^1H NMR spectrum: δ 6·80–7·50 (m, 7 H, ArH), 3·00–4·20 (m, 3 H, $ArCH_2$. .CHAr), 2·62 and 2·38 (2 m, 4 + 4 H, 4 CH_2 of piperazine), 2·48 (s, 3 H, $ArCH_3$), 2·20 (s, 3 H, NCH_3). [k] The homogeneous oily base, released from the salt, was used for recording the ^1H NMR spectrum: δ 6·80–7·50 (m, 7 H, ArH), 4·20 (dd, J = 9·0; 5·0 Hz, 1 H, Ar—CH—N), 2·20 to 3·80 (m, 12 H, 6 CH_2), 2·16 (s, 3 H, NCH_3), 1·18 (t, 3H, CH_3 of ethyl). [l] IR spectrum: 750, 769, 780 (4 and 3 adjacent Ar—H), 1 128, 1 240 (C—O), 1 575, 3 050 (Ar). 1 681 cm^{-1} (NCOOR); ^1H NMR spectrum: δ 6·90–7·60 (m, 7 H, ArH), 4·15 (q, J = 7·0 Hz, 2 H, OCH_2), 3·00–4·15 (m, 3 H, $ArCH_2CHAr$), 3·40 and 2·60 (2 bm, 4 + 4 H, 4 CH_2 of piperazine), 2·48 (s, 3 H, $ArCH_3$), 1·25 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). [m] IR spectrum: 750, 770, 809 (4 and 3 adjacent Ar—H), 1 111, 1 130, 1 240, 1 685 (NCOOR), 1 570, 1 585, 3 050 cm^{-1} (Ar); ^1H NMR spectrum: δ 6·90–7·60 (m, 7 H, ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 4·10 (q, J = 7·0 Hz, 2 H,

TABLE I

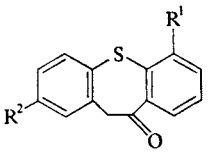
(*Continued*)

OCH_2), 3·40 and 2·55 (2 m, 4 + 4 H, 4 CH_2 of piperazine), 2·90 (q, J = 7·0 Hz, 2 H, $ArCH_2$ in ethyl), 1·21 (t, J = 7·0 Hz, 6 H, 2 CH_3 in the ethyl groups). [n] IR spectrum: 722, 755, 770, 780, 800 (4 and 3 adjacent Ar—H), 1 134, 1 245, 1 680 (NCOOR), 1 485, 1 550, 3 050 cm^{-1} (Ar); ^1H NMR spectrum: δ 6·80—7·60 (m, 7 H, ArH), 4·09 (q, J = 7·0 Hz, 2 H, OCH_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·38 and 2·52 (2 bm, 4 + 4 H, 4 CH_2 of piperazine), 1·21 (t, J = 7·0 Hz, 3 H, CH_3 in ethyl). [o] This product was oily and was used for hydrolysis in crude state. [p] UV spectrum: λ_{max} 280 nm (log ε 3·80), 294 nm (3·86), 300 nm (3·86); IR spectrum: 780, 813, 899 (3 and 2 adjacent and solitary Ar—H), 1 125, 1 254 (C—O in $ArOCH_3$ and NCOOR), 1 565, 1 580 (Ar), 1 690 cm^{-1} (NCOOR); ^1H NMR spectrum: δ 6·50—7·50 (m, 6 H, ArH), 4·10 (q, J = 7·0 Hz, OCH_2), 3·91 (s, 3 H, OCH_3), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·44 and 2·55 (2 m, 4 + 4 H, 4 CH_2 of piperazine), 1·24 (t, J = 7·0 Hz, 3 H, CH_3 in ethyl).

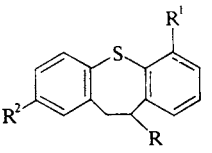
The synthesis of compounds *Ia* and *IIa* started by the reaction of (2-iodophenyl)-acetic acid[22] with 2-methylthiophenol in boiling aqueous potassium hydroxide in the presence of copper giving the acid *VIIIa*. Its cyclization with polyphosphoric acid to the ketone *XIa* was carried out in boiling toluene. The reaction proceeds rather slowly and a part of the starting acid *VIIIa* is recovered. Heating of *VIIIa* with polyphosphoric acid without toluene to 130—140°C led to a mixture from which the heptacyclic furan *XIV* was isolated; its identity was confirmed by the mass spectrum (for similar reactions, *cf.*[23]). The ketone *XIa* was reduced with sodium borohydride in a boiling mixture of benzene and aqueous ethanol to the alcohol *XIIa* in a high yield. The conversion to the 10-chloro compound *XIIIa* used the treatment with hydrogen chloride in benzene in the presence of calcium chloride. The final substitution reactions (method *A*) were accompanied by hydrogen chloride



VIII, R = CH_2COOH
IX, R = $COCH_3$
X, R = CH_2CSN O



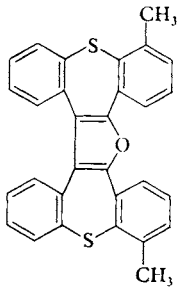
XI



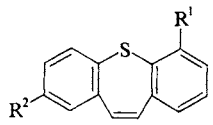
XII, R = OH
XIII, R = Cl

elimination and chromatography of the neutral by-product yielded 4-methyldibenzo-[*b*,*f*]thiepin (*XVa*).

The synthesis of compound *Ib* used in the starting steps a different approach (*cf.*[24]). Reaction of 2,5-dichloroacetophenone[24] with 2-methylthiophenol in the presence of potassium carbonate and copper at 140–160°C gave 5-chloro-2-(2-methylphenylthio)acetophenone (*IXb*) which was processed by the Willgerodt reaction in Kindler's modification (*cf.*[25]). Heating with an excess of morpholine and sulfur gave the thiomorpholide *Xb* in yields of about 50%; its hydrolysis with boiling ethanolic potassium hydroxide resulted in the acid *VIIIb*. Cyclization to 2-chloro-6-methyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIb*) was carried out with polyphosphoric acid at 110–120°C. Its transformation to the alcohol *XIIb* and the chloride *XIIIb* proceeded similarly like in series *a*. 2-Chloro-6-methyldibenzo[*b*,*f*]thiepin (*XVb*) was isolated as the elimination by-product from the reaction of *XIIIb* with 1-(ethoxycarbonyl)piperazine (method *A*).



XIV



XV

The work in series *c* proceeded similarly like in series *a*. Reaction of (2-iodophenyl)-acetic acid[22] with 2-ethylthiophenol[26] gave the acid *VIIIc* which was cyclized to the ketone *XIc* by heating with polyphosphoric acid to 110–120°C. Conversion to the chloride *XIIIc via* the alcohol *XIIc* was carried out analogously like in series *a* and *b*. The neutral by-product, isolated during the preparation of compound *IIIc*, was identified as 4-ethyldibenzo[*b*,*f*]thiepin (*XVc*). In series *d* the chloro compound *XIIId* was described previously[18] and the described synthesis was followed with the exception of preparation of the acid *VIIId* which has now been prepared by reaction of (2-iodophenyl)acetic acid[22] with 2-chlorothiophenol[27]. In series *e*, the synthesis of the chloro compound *XIIIe* used also the described procedure[20]. In series *f* the chloro compound *XIIIf*, likewise, was known[21]. An improved procedure for preparing the acetophenone *IXf* is being described in the Experimental. Substitution reaction of *XIIIf* with 1-(ethoxycarbonyl)piperazine (method *A*) gave 2-chloro-6-methoxydibenzo[*b*,*f*]thiepin (*XVf*) as the neutral by-product.

Compounds *I* and *II* were pharmacologically tested in the first line from the point

of view of the expected antidepressant and/or neuroleptic activity. Unless stated otherwise they were administered orally in the form of salts described in Table I; the doses, given in mg/kg, were calculated per base. Most of the compounds underwent also a general pharmacological screening which supplemented further data on the neurotropic activities and provided information about other lines of efficacy. Acute toxicity in mice was estimated only with some compounds, LD_{50} and the screened doses D are given: *Ib*, 30 *i.v.*, 6 *i.v.*; *Ic*, 50 *i.v.*, 10 *i.v.*; *Id*, 80 *i.v.*, 15 *i.v.*; *If*, 60 *i.v.*, 12 *i.v.*; *IIc*, 40 *i.v.*, 8 *i.v.* Toxic symptoms of doses higher than D: *Ib*, inhibition of activity, ptosis of long duration; *Ic*, ataxia, convulsions; *Id*, ataxia and ptosis; *If*, inhibition of activity and reactivity, ptosis of long duration. Discoordinating activity in the rotarod test in mice: *Ia*, the dose of 25 mg/kg brought about ataxia in 40% animals; *Ib*, ED_{50} 3·6 mg/kg; *Ic*, the dose of 200 mg/kg – ataxia in 40% animals; *Id*, the dose of 10 mg/kg – ataxia in 30% animals; *Ie*, ED_{50} 20·3 mg/kg; *If*, ED_{50} 8·8 mg/kg; *IIc*, ED_{50} 59·5 mg/kg. Antireserpine effect in the test of ptosis in mice: Compounds *Ia* and *Ie* inactive at doses of 100 mg/kg; *Ib*, *Ic*, *Id*, and *If* are inactive at 30 mg/kg; *IIc*, in the dose of 30 mg/kg antagonizes significantly the reserpine ptosis. Test of catalepsy in rats: compounds *Ia*, *Ib*, and *IIa* in doses of 50 mg/kg inactive; *Id*, inactive in the dose of 15 mg/kg *i.p.*; *Ie*, catalepsy with 20% of animals after the dose of 50 mg/kg.

Potentiation of yohimbine toxicity in mice[28] (the compounds were administered 60 min prior to a practically nontoxic dose of 20 mg/kg *s.c.* of yohimbine; toxicity was assessed 16 h after yohimbine; ED_{50} is the dose producing lethality in 50% of the mice): *Ia*, 4·6 (for nortriptyline, ED_{50} 2·7); *Ib*, 3·8; *Ic*, 36·1; *Ie*, 7·8 mg/kg. Release of [^{3}H] imipramine from its binding sites in the rat hypothalamus[29], IC_{50} in nanomol: *Ia*, 335·8 (for desipramine 317·5); *Ib*, >100; *Id*, >100; *Ie*, 1 520 (for nomifensine 1 049). Effect on locomotor activity in mice: *Ia*, the dose of 30 mg/kg decreases first the activity to 41% of the control group, this decrease is then followed by a rise of motility to 200–400% (similarly like with amitriptyline); *Id*, the dose of 15 mg/kg *s.c.* was without effect; *Ie*, the dose of 30 mg/kg reduced first the activity to 30% and this reaction was followed by hypermotility (200–400%); *IIa*, the dose of 10 mg/kg significantly inhibits the locomotor activity. Antagonism against climbing behaviour (verticalization) induced by apomorphine (2 mg/kg *s.c.*) in mice[30] (PD_{50}, the dose blocking this reaction in 50% of the animals): *Ib*, 9·7 mg/kg (for chlorpromazine 4·6, for thioridazine 6·6); *Ie*, 30 mg/kg. The effect of the dose of 30 mg/kg (percent of animals given in which the reaction was blocked): *Ia*, 40; *Ic*, 0; *IIc*, 0. The effect of the dose of 10 mg/kg: *Id*, 60; *If*, 80; *IIa*, 60 (with compounds *Id* and *If* the doses of 30 mg/kg were too sedative and caused myorelaxation which interfered with the antiapomorphine effect in this test). Peripheral antiadrenergic effect in mice (protection from the lethal effect of adrenaline): *Ia*, PD_{50} 10·5; *Ib*, PD_{50} 3·8 mg/kg (a high effect); *Id*, the *i.v.* dose of 0·05 mg/kg is significantly effective; *Ie*, subtoxic doses of 10 and 25 mg/kg are effective in 20% of animals. Influence on dopamine turnover

and metabolism in striatum of the rat brain evaluated by the increase of the homovanillic acid (HVA) level (or decrease of dopamine (DA) level) (ref.[31]): *Ia*, the dose of 25 mg/kg does not influence the HVA level; *Ib*, the HVA level is significantly increased starting from the dose of 0·5 mg/kg, even the dose of 25 mg/kg does not influence dopamine level; *Ie*, the dose of 25 mg/kg increases significantly HVA level and does not influence DA level; *IIa*, 80 mg/kg do not influence HVA and DA levels. Inhibition of [^{3}H]spiperone binding in rat brain striatum[32], IC_{50} in nanomol: *Ib*, >200; *IIa*, 170 (its affinity to dopamine receptors is higher than that of clozapine but lower than that of chlorpromazine). Hypothermic effect in rats (ED is the dose decreasing rectal temperature by 1·0°C): *Ib*, 1 mg/kg *i.p.*; *Ic*, 5–10 *i.p.* (for chlorpromazine 0·5–1·0 *i.v.*). Thiopental potentiation in mice (ED is the dose prolonging the duration of the thiopental sleeping time to 200% of the control value): *Ib* 0·5–1·0 mg/kg *i.v.* (for chlorpromazine 0·5 mg/kg *i.v.*); *Id*, 0·1–1·0 mg/kg *i.v.*; *If*, 2·5 mg/kg *i.v.* Antiamphetamine effect in mice (ED is the dose protecting 100% of the animals from the lethal effect of a standard dose of amphetamine): *Ib*, 2·5 mg/kg *i.v.* (for chlorpromazine 1 mg/kg *i.v.*); *Id*, 15 mg/kg *i.v.* Antihistamine activity (ED is the dose protecting 50% of the guinea-pigs from the lethal effect of 5 mg/kg histamine, administered intrajugularly): *Ib*, 0·5–1·0 mg/kg *s.c.* (for mebrophenhydramine 0·25 mg/kg *s.c.*); *Id*, 1 mg/kg *s.c.*; *If*, 1 mg/kg *s.c.*; *IIc*, 1 mg/kg *s.c.* Spasmolytic activity on the isolated rat duodenum: Compounds *Ib*, *Ic*, *Id*, *If*, and *IIc* in concentrations of 1–10 μg/ml reduce the acetylcholine and barium chloride contractions by 50% (a papaverine-like effect). Antitussive action in rats (oral doses and percent of the coughing activity when 100% is the activity of the untreated control group; the cough was elicited by the aerosol of an aqueous citric acid solution): *Id*, 75 mg/kg by 57%; *If*, 60 mg/kg by 39%; *IIc*, 40 mg/kg by 28%. Hypotensive effect (short and deep drops of blood pressure in normotensive rats after the *i.v.* doses given): *Ib*, 6; *Ic*, 5; *Id*, 5; *If*, 12; *IIc*, 8 mg/kg. Doses (*i.v.*) inhibiting the adrenaline pressor reaction in rats by 50%: *Ib*, 0·05–0·1; *Id*, 0·05; *If*, 0·1–0·5 mg/kg. Antiarrhythmic effect in rats towards aconitine (doses prolonging significantly the latency of ventricular extrasystoles): *Id*, 5–15 *i.v.*; *If*, 5–12 *i.v.*; *IIc*, 2·5 mg/kg *i.v.*

In conclusion there is only a low evidence of thymoleptic (antidepressant) character of the compounds prepared. In this line only compound *Ia* is an exception being comparable with some known antidepressants in the test of potentiation of yohimbine toxicity and showing a clear affinity to the imipramine binding sites, and only the atypical compound *IIc* showed antireserpine activity in the test of ptosis. On the other hand, compound *Ib*, differing from *Ia* by the presence of atom of chlorine in position 2 of the skeleton (position of the clozapine substituent), has properties of a noncataleptic neuroleptic agent: discoordinating, hypothermic, thiopental potentiating and antiamphetamine effects, blockade of the apomorphine-induced climbing behaviour and a strong elevation of the HVA level in the rat striatum after a low dose.

It is interesting to compare with amoxapine (*IV*) on the basis of our own experimental findings (oral administration): LD_{50} 106 mg/kg. Thymoleptic properties: antireserpine activity in the test of ptosis (significant effect starting with the dose of 10 mg/kg on preventive application); potentiates yohimbine toxicity, ED_{50} 17·6 mg/kg. Neuroleptic properties: inhibits the apomorphine-induced verticalization, PD_{50} 15·8 mg/kg; has cataleptic activity, ED_{50} 35·6 mg/kg; the dose of 20 mg/kg increases the HVA level in rat striatum to 218% and in tuberculum olfactorium to 368%; it inhibits the binding of 0·5 nanomol [^{3}H]spiperone in the rat striatum, IC_{50} 144 nanomol (its dopaminergic affinity is lower than that of chlorpromazine but higher than that of clozapine). With amoxapine, likewise, the neuroleptic character predominates over the thymoleptic one.

The compounds prepared were also tested for antimicrobial activity *in vitro*; minimum inhibitory concentrations in μg/ml are given (unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *Ia* 50, *Ib* 6·2, *Ic* 50, *Id* 6·2, *If* 25, *IIa* 50, *IIc* 50; *Streptococcus faecalis*, *Ia* 25, *Ib* 12·5, *Ic* 25, *Id* 12·5, *If* 25, *IIa* 100, *IIc* 100; *Staphylococcus pyogenes aureus*, *Ia* 12·5, *Ib* 3·1, *Ic* 3·1, *Id* 3·1, *Ie* 100, *If* 6·2, *IIa* 25, *IIc* 6·2; *Pseudomonas aeruginosa*, *Id* 50, *If* 100, *IIc* 100; *Escherichia coli*, *Ia* 50, *Ib* 25, *Ic* 50, *Id* 25, *If* 50, *IIa* 100, *IIc* 100; *Proteus vulgaris*, *Ia* 25, *Ib* 25, *Ic* 25, *Id* 25, *If* 50, *IIa* 100, *IIc* 100; *Saccharomyces pasterianus*, *Ia* 50, *Ib* 25, *Id* 25; *Trichophyton mentagrophytes*, *Ia* 50, *Ib* 50, *Ic* 50, *Id* 50, *If* 50, *IIa* 50, *IIc* 25.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block (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 (almost exclusively in Nujol) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer, and mass spectra 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 Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure in rotating evaporators.

5-Chloro-2-(2-methylphenylthio)acetophenone (*IXb*)

A stirred mixture of 37·3 g 2-methylthiophenol, 53·0 g 2,5-dichloroacetophenone[24], 66·5 g K_2CO_3, and 1·3 g Cu was heated for 5 h under nitrogen in a bath of 140–160°C. After partial cooling the mixture was diluted with 100 ml benzene, the inorganic salts were filtered off and washed with warm benzene, and the filtrate was evaporated. The residue was dissolved in 300 ml ethanol, the solution was filtered with charcoal, and the filtrate was evaporated again. The residue was crystallized from 100 ml ethanol: 58·1 g (75%), m.p. 61–65°C. The first crystals, which were then used for seeding, were obtained by distillation of a sample, b.p. 168–172°C/0·8 kPa. Analytical sample was obtained by recrystallization from ethanol, m.p. 64–66°C. UV spectrum: λ_{max} 273 nm (log ε 3·95), 347 nm (3·56). IR spectrum: 757, 853, 870 (4 and 2 adjacent and solitary Ar—H), 1 540, 1 588, 3 060, 3 080 (Ar), 1 670 cm^{-1} (ArCOR). ^{1}H NMR spectrum: δ 7·80 (d, J = 2·5 Hz, 1 H, 6-H), 7·20–7·60 (m, 4 H, ArH of *o*-tolyl), 7·15 (dd, J = 8·5; 2·5 Hz, 1 H, 4-H), 6·60 (d, J = 8·5 Hz, 1 H, 3-H), 2·68 (s, 3 H, $COCH_3$), 2·30 (s, 3 H, $ArCH_3$). For $C_{15}H_{13}ClOS$ (276·8) calculated: 65·09% C, 4·73% H, 12·81% Cl, 11·59% S; found: 64·89% C, 4·77% H, 12·86% Cl, 11·58% S.

5-Chloro-2-(2-methoxyphenylthio)acetophenone (*IXf*)

A mixture of 34·4 g 2-methoxythiophenol[33], 44·9 g 2,5-dichloroacetophenone[24], 52·7 g K_2CO_3, 1·1 g Cu, and 14 ml dimethylformamide was stirred for 3 h under nitrogen and heated to 110°C (bath temperature). After partial cooling the mixture was diluted with 150 ml benzene, the suspension was stirred for 20 min, the salts were filtered off and washed with warm benzene. The filtrate was evaporated *in vacuo*, the residue was distributed between benzene and water, the organic layer was dried and evaporated *in vacuo*. The residue was dissolved in 400 ml boiling ethanol, the solution was filtered with charcoal, the filtrate was partly evaporated and allowed to crystallize; 47·9 g (69%), m.p. 78—80°C. Ref.[21], yield 28%, m.p. 81—82°C.

(5-Chloro-2-(2-methylphenylthio)phenyl)acetic Acid Thiomorpholide (*Xb*)

A mixture of 5·5 g *IXb*, 1·3 g S and 6·0 g morpholine was stirred and heated under reflux for 10 h to 140—160°C (bath temperature). It was then diluted with 60 ml ethanol, filtered with charcoal and evaporated *in vacuo*. The residue was dissolved in ether and the solution was washed with water, 2% NaOH, water, 1·5M-HCl and water. After drying ether was evaporated and the residue was crystallized from ethanol; 4·1 g (55%), m.p. 127—131°C. Analytical sample, m.p. 131—133°C (ethanol). IR spectrum: 755, 818, 845, 880, 889 (4 and 2 adjacent and solitary Ar—H), 1 110 (R—O—R), 1 460, 1 490 (RCSN), 1 580 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·90—7·50 (m, 7 H, ArH), 4·30 (s, 2 H, $ArCH_2CS$), 4·32 (t), 3·75 (t) and 3·40 (s) (together 8 H, 4 CH_2 of morpholine), 2·35 (s, 3 H, $ArCH_3$). For $C_{19}H_{20}ClNOS_2$ (378·0) calculated: 60·38% C, 5·33% H, 9·38% Cl, 3·71% N, 16·97% S; found: 60·52% C, 5·40% H, 9·52% Cl, 3·73% N, 17·17% S.

(2-(2-Methylphenylthio)phenyl)acetic Acid (*VIIIa*)

A stirred solution of 32·7 g KOH in 350 ml water was treated with 21·3 g 2-methylthiophenol, and after 10 min stirring there were added 45·1 g (2-iodophenyl)acetic acid[22] and 2·0 g Cu. The mixture was stirred and refluxed for 17 h, filtered, the solid was washed with hot water and the filtrate was acidified with hydrochloric acid. After standing overnight at 0°C, the crude product was filtered, dissolved in benzene and the solution was extracted with 60 ml 15% Na_2CO_3 in three portions. The combined aqueous solutions were filtered with charcoal, the filtrate was acidified with hydrochloric acid, the product was filtered after standing overnight at 4°C, and dried *in vacuo*; 27·2 g (61%), m.p. 77—83°C. Analytical sample, m.p. 87—89°C (aqueous ethanol). IR spectrum: 740, 755 (4 adjacent Ar—H), 940, 1 239, **1 707**, 2 550, 2 630, 2 730, infl. 3 100 (R—COOH), 1 590, 3 010, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·25 (bs, 1 H, COOH), 6·80—7·40 (m, 8 H, ArH), 3·80 (s, 2 H, $ArCH_2CO$), 2·30 (s, 3 H, $ArCH_3$). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·74% C, 5·46% H, 12·41% S; found: 69·73% C, 5·52% H, 12·33% S.

(5-Chloro-2-(2-methylphenylthio)phenyl)acetic Acid (*VIIIb*)

Xb (14·5 g) was added to a solution of 11·6 g KOH in 40 ml ethanol, the mixture was refluxed for 4 h and evaporated *in vacuo*. The residue was dissolved in 50 ml water, the solution was washed with benzene and ether, and acidified with hydrochloric acid. After standing overnight the product was filtered, washed with water and dried *in vacuo*: 9·8 g (87%), m.p. 123—127°C. Analytical sample, m.p. 127—129°C (benzene – light petroleum). IR spectrum: 750, 830, 870 (4 and 2 adjacent and solitary Ar—H), 916, 1 230, **1 710**, 2 540, 2 600, 2 720, infl. 3 150 (R—COOH), 1 483, 1 553, 1 583, 3 010 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·05 (bs, 1 H, COOH), 6·90—7·40 (m, 7 H, ArH), 3·75 (s, 2 H, $ArCH_2CO$), 2·25 (s, 3 H, $ArCH_3$). For $C_{15}H_{13}ClO_2S$ (292·8) calculated: 61·53% C, 4·47% H, 12·11% Cl, 10·95% S; found: 61·57% C, 4·50% H, 12·09% Cl, 10·95% S.

(2-(2-Ethylphenylthio)phenyl)acetic Acid (*VIIIc*)

2-Ethylthiophenol[26] (34·2 g) was dissolved in a stirred solution of 47·5 g KOH in 500 ml water at 50°C, the solution was treated with 64·7 g (2-iodophenyl)acetic acid[22] and 2·5 g Cu and the mixture was refluxed for 14 h. A similar processing, like described for *VIIIa*, gave 65·5 g oily product which crystallized from a mixture of benzene and light petroleum: 44·8 g (67%), m.p. 47–54°C. Analytical sample, m.p. 56–58°C (benzene–light petroleum). IR spectrum: 743, 760 (4 adjacent Ar—H), 925, 1 234, 1 277, **1 700**, 2 650, infl. 3 160 (R—COOH), 1 565, 1 585 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·20 (bs, 1 H, COOH), 6·80–7·30 (m, 8 H, ArH), 3·75 (s, 2 H, $ArCH_2CO$), 2·68 (q, J = 7·0 Hz, 2 H, $ArCH_2$ in ethylphenyl), 1·24 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{16}H_{16}O_2S$ (272·4) calculated: 70·55% C, 5·92% H, 11·77% S; found: 70·77% C, 6·03% H, 11·90% S.

(2-(2-Chlorophenylthio)phenyl)acetic Acid (*VIIId*)

A mixture of 112 g KOH in 900 ml water, 71 g 2-chlorothiophenol[27], 128·4 g (2-iodophenyl) acetic acid[22] and 6·0 g Cu was stirred and refluxed for 12 h. Processing like in the preceding cases gave the oily product which crystallized from aqueous ethanol; 70 g (51%), m.p. 99–101°C. Ref.[18], m.p. 100–102°C.

6-Methyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XIa*)

A) A mixture of 37·3 g *VIIIa*, 160 ml toluene and 350 g polyphosphoric acid was stirred and refluxed for 4·5 h. After cooling the mixture was decomposed with 1 000 ml water and extracted with benzene. The organic layer was washed with 5% NaOH and acidification of the aqueous washings with hydrochloric acid recovered 15·2 g of *VIIIa*. The washed organic layer was dried and evaporated *in vacuo*; 17·6 g (86% per conversion) crude *XIa* which was crystallized from cyclohexane, m.p. 103–106°C. UV spectrum: λ_{max} 241 nm (log ε 4·29), 332 nm (3·59), infl. 265 nm (3·97). IR spectrum: 728, 756, 791 (4 and 3 adjacent Ar—H), 1 575, 3 030 (Ar), 1 663 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·00 (dd, 1 H, 9-H), 7·00–7·70 (m, 6 H, remaining ArH), 4·31 (s, 2 H, $ArCH_2CO$), 2·58 (s, 3 H, $ArCH_3$). For $C_{15}H_{12}OS$ (240·3) calculated: 74·96% C, 5·03% H, 13·34% S; found: 75·00% C, 5·03% H, 13·21% S.

B) A stirred mixture of 38·8 g *VIIIa* and 238 g polyphosphoric acid was heated for 5·5 h to 130–140°C. Processing like under *A*) gave 34·2 g deeply orange mixture of *XIa* and a less soluble compound. Repeated crystallization from a mixture of benzene and light petroleum led to purification of the by-product whereas *XIa* remained in the mother liquors. The pure by-product melted at 333–336°C and was identified as 6,14-dimethylfuro[2,3-*m*; 4,5-*m'*]bis(dibenzo-[*b,f*]thiepin) (*XIV*). Mass spectrum, *m/z* (%): 460 (M^+ corresponding to $C_{30}H_{20}OS_2$, 100%), 428 (18, $C_{30}H_{20}OS$), 230 (25), 205 (22), 191 (19), 190 (19), 197 (16), 185 (15). UV spectrum: λ_{max} 258 nm (log ε 4·74), 320 nm (4·49), inflexes 276 nm (4·58) and 335 nm (4·42). IR spectrum: 700, 760, 786 (4 and 3 adjacent Ar—H), 1 553, 1 570, 1 593, 3 050 cm^{-1} (Ar). For $C_{30}H_{20}OS_2$ (460·6) calculated: 78·22% C, 4·38% H, 13·93% S; found: 78·65% C, 4·49% H, 13·64% S.

2-Chloro-6-methyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XIb*)

A mixture of 7·3 g *VIIIb* and 40 g polyphosphoric acid was stirred for 5 h and heated to 100 to 120°C (bath temperature). After cooling it was decomposed with 100 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, was dried and evaporated; 6·8 g (99%) crude neutral product. Crystallization from benzene gave 4·6 g (67%) pure *XIb*, m.p. 115 to 117°C. UV spectrum: λ_{max} 235 nm (log ε 4·33), 260 nm (4·00), 335 nm (3·58). IR spectrum: 710,

768, 810, 815, 870, 880, 895 (3 and 2 adjacent and solitary Ar—H), 1 560, 1 580, 3 060 (Ar), 1 665 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·02 (dd, J = 8·0; 2·0 Hz, 1 H, 9-H), 7·54 (d, J = 8·0 Hz, 1 H, 4-H), 7·40 (d, J = 2·0 Hz, 1 H, 1-H), 7·00—7·30 (m, 3 H, 3,7,8-H_3), 4·30 (s, 2 H, $ArCH_2CO$), 2·58 (s, 3 H, $ArCH_3$). For $C_{15}H_{11}ClOS$ (274·8) calculated: 65·56% C, 4·04% H, 12·90% Cl, 11·67% S; found: 65·71% C, 3·93% H, 12·92% Cl, 11·82% S.

6-Ethyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIc*)

A mixture of 13·2 g *VIIIc* and 68 g polyphosphoric acid was processed similarly like in the preceding case. There were obtained 11·5 g (93%) crude product which was crystallized from 20 ml ethanol; 9·4 g (76%), m.p. 72—76°C. Analytical sample, m.p. 76—78°C (ethanol). UV spectrum: λ_{max} 241 nm (log ε 4·31), 330 nm (3·60), infl. 260 nm (4·04). IR spectrum: 732, 753, 768, 810 (4 and 3 adjacent Ar—H), 1 575, 3 030, 3 060 (Ar), 1 280, **1 664** cm^{-1} ($ArCOCH_2$). ^1H NMR spectrum: δ 7·99 (dd, J = 8·5; 2·5 Hz, 1 H, 9-H), 7·55 (bd, J = 8·5 Hz, 1 H, 4-H), 6·90—7·40 (m, 5 H, remaining ArH), 4·30 (s, 2 H, $ArCH_2CO$), 3·95 (q, J = 7·0 Hz) and 1·25 (t, J = 7·0 Hz) (2 + 3 H, $ArCH_2CH_3$). For $C_{16}H_{14}OS$ (254·3) calculated: 75·55% C, 5·55% H, 12·61% S; found: 75·14% C, 5·49% H, 12·77% S.

6-Methyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIa*)

A solution of 29 g *XIa* in 60 ml benzene and 300 ml ethanol was treated with a solution of 6·6 g $NaBH_4$ in 60 ml water containing 1·5 ml 10% NaOH, the mixture was refluxed for 5 h and evaporated *in vacuo*. The residue was distributed between water and benzene, the organic layer was washed with 3% NaOH and water, dried and evaporated. The residue was dissolved in ethanol, the solution was filtered with charcoal and the filtrate was evaporated again; 19·2 g (91%), m.p. 85—89°C. Analytical sample, m.p. 88—90°C (cyclohexane). IR spectrum: 750, 772, 777 (4 and 3 adjacent Ar—H), 1 068, 3 300 (CHOH in the ring), 1 470, 1 567, 1 585, 3 000, 3 040, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·90—7·60 (m, 7 H, ArH), 5·70 (m, after ^2H_2O dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—O), 3·60 and 3·20 (2 dd, J = 13·0; 4·0 and 13·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·61 (d, J = 6·0 Hz, disappears after ^2H_2O, 1 H, OH), 2·47 (s, 3 H, $ArCH_3$). For $C_{15}H_{14}OS$ (242·3) calculated: 74·34% C, 5·82% H, 13·23% S; found: 74·20% C, 5·62% H, 13·16% S.

2-Chloro-6-methyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIb*)

A solution of 17·1 g *XIb* in 45 ml benzene and 250 ml ethanol was similarly reduced with 5·7 g $NaBH_4$ in 50 ml water containing 1·4 ml 10% NaOH. Similar processing gave 14·8 g (86%) almost pure *XIIb*, m.p. 119—124°C. Analytical sample, m.p. 120—123°C (benzene). IR spectrum: 705, 785, 810, 880 (3 and 2 adjacent and solitary Ar—H), 1 065 (CHOH in the ring), 1 580, 3 040, 3·070 (Ar), 3 560 cm^{-1} (OH). ^1H NMR spectrum: δ 6·80—7·40 (m, 6 H, ArH), 5·70 (m, 1 H, Ar—CH—O), 3·55 and 3·08 (2 dd, J = 16·0; 4·0 and 16·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·55 (d, J = 6·0 Hz, 1 H, OH), 2·48 (s, 3 H, $ArCH_3$). For $C_{15}H_{13}ClOS$ (276·8) calculated: 65·09% C, 4·73% H, 12·81% Cl, 11·59% S; found: 65·49% C, 4·66% H, 13·08% Cl, 11·72% S.

6-Ethyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIc*)

A solution of 27·2 g *XIc* in 110 ml benzene and 220 ml ethanol was similarly reduced with a solution of 2·5 g $NaBH_4$ in 20 ml water containing 0·5 ml 10% NaOH. Similar processing gave 21·8 g (80%) *XIIc*, m.p. 107—109°C. Analytical sample, m.p. 108—110°C (ethanol). IR spectrum: 735, 758, 790, 798 (4 and 3 adjacent Ar—H), 1 050, 1 075 (CHOH in the ring), 1 477, 1 560, 1 580, 3 040, 3 060 (Ar), 3 300 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90—7·50 (m, 7 H, ArH),

5·80 (m, 1 H, Ar—CH—O), 3·60 and 3·10 (2 dd, J = 13·0; 4·0 and 13·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·90 (q, J = 7·0 Hz) and 1·16 (t, J = 7·0 Hz) (2 + 3 H, $ArCH_2CH_3$), 2·60 (d, J = = 4·0 Hz, OH). For $C_{16}H_{16}OS$ (256·3) calculated: 74·96% C, 6·29% H, 12·51% S; found: 75·39% C, 6·47% H, 12·43% S.

11-Chloro-4-methyl-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIa*)

A solution of 19·1 g *XIIa* in 250 ml benzene was treated with 25 g powdered $CaCl_2$ and saturated at room temperature with HCl. After standing overnight $CaCl_2$ was filtered off, washed with benzene and the filtrate was evaporated *in vacuo*. The solid residue (20·3 g, 99%) was crystallized from 25 ml acetone; 15·8 g (77%), m.p. 74—77°C. Analytical sample, m.p. 75—78°C (acetone). ^{1}H NMR spectrum: δ 6·90—7·60 (m, 7 H, ArH), 6·12 (dd, J = 4·0; 6·0 Hz, 1 H, Ar—CH—Cl), 3·91 and 3·60 (2 dd, J = 13·0; 4·0 and 13·0; 8·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·53 (s, 3 H, $ArCH_3$). For $C_{15}H_{13}ClS$ (260·8) calculated: 69·08% C, 5·02% H, 13·60% Cl, 12·30% S; found: 69·04% C, 4·93% H, 13·37% Cl, 12·19% S.

2,10-Dichloro-6-methyl-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIb*)

A similar reaction of 14·8 g *XIIb* in 210 ml benzene gave 13·7 g (87%) *XIIIb*, m.p. 90—93°C (acetone). ^{1}H NMR spectrum: δ 6·90—7·50 (m, 6 H, ArH), 6·04 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·82 and 3·48 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 1 + 1 H, $ArCH_2$ in the ring), 2·48 (s, 3 H, $ArCH_3$). For $C_{15}H_{12}Cl_2S$ (295·2) calculated: 61·02% C, 4·10% H, 24·02% Cl, 10·86% S; found: 60·97% C, 4·06% H, 24·07% Cl, 10·93% S.

11-Chloro-4-ethyl-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIc*)

A similar reaction of 18·2 g *XIIc* in 200 ml benzene gave 17·1 g (88%) *XIIIc*, m.p. 92—94°C. Analytical sample, m.p. 93—95°C (acetone). For $C_{16}H_{15}ClS$ (274·8) calculated: 69·93% C, 5·50% H, 12·90% Cl, 11·67% S; found: 69·12% C, 5·41% H, 12·50% Cl, 11·54% S.

2-Chloro-10-(4-ethoxycarbonylpiperazino)-6-methyl-10,11-dihydrodibenzo[*b,f*]thiepin (*IIIb*) (Method *A*)

A mixture of 3·3 g *XIIIb*, 4·3 g 1-(ethoxycarbonyl)piperazine and 4 ml chloroform was stirred and heated for 9·5 h under reflux (bath temperature 115—120°C). It was then evaporated *in vacuo*, the residue was distributed between benzene and water and from the benzene layer the product was extracted into 1 : 1 dilute hydrochloric acid. The aqueous solution was made alkaline with NH_4OH, the base was extracted with benzene, the extract was washed with water, dried and evaporated. A single crystallization of the residue from ethanol gave 3·2 g (69%) pure *IIIb*, m.p. 133—136°C. IR spectrum: 710, 768, 780, 810, 895 (3 and 2 adjacent and solitary Ar—H), 1 128, 1 242 (COOR), 1 580, 3 040 (Ar), 1 685 cm^{-1} (NCOOR). ^{1}H NMR spectrum: δ 6·80 to 7·40 (m, 6 H, ArH), 3·00—4·20 (m, 3 H, $ArCH_2CHAr$), 4·05 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·40 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·55 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 2·48 (s, 3 H, $ArCH_3$), 1·21 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For analysis, *cf.* Table I.

The benzene layers after the extraction with hydrochloric acid from several batches were combined (totally from 19·6 g *XIIIb*), washed with 3M-HCl and water, dried and evaporated. The residue was dissolved in cyclohexane and the solution was chromatographed on a column of 85 g neutral Al_2O_3 (activity II). There were eluted 1·5 g (9%) 2-chloro-6-methyldibenzo-[*b,f*]thiepin (*XVb*), m.p. 56—58°C (ethanol). UV spectrum: λ_{max} 224 nm (log ε 4·51), 267 nm (4·30), 303 nm (3·71). IR spectrum: 687, 720, 780, 810, 816, 887 (3 and 2 adjacent and solitary

Ar—H), 1 545, 1 574, 3 020, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80—7·60 (m, 8 H, ArH and CH=CH), 2·62 (s, 3 H, $ArCH_3$). For $C_{15}H_{11}ClS$ (258·8) calculated: 69·62% C, 4·29% H, 13·70% Cl, 12·39% S; found: 69·79% C, 4·35% H, 13·48% Cl, 12·35% S.

4-Methyldibenzo[*b,f*]thiepin (*XVa*)

Was obtained similarly like *XVb* as the neutral by-product of preparation of *IIIa*; m.p. 52—54°C (ethanol). UV spectrum: λ_{max} 223 nm (log ε 4·62), 264 nm (4·47), 302 nm (3·88). ^1H NMR spectrum: δ 7·05—7·60 (m, 7 H, ArH), 7·00 (s, 2 H, CH=CH). 2·59 (s, 3 H, $ArCH_3$). For C_{15}. $.H_{12}S$ (324·3) calculated: 80·31% C, 5·39% H, 14·30% S; found: 80·16% C, 5·41% H, 13·41% S.

4-Ethyldibenzo[*b,f*]thiepin (*XVc*)

Was obtained similarly like *XVa* and *XVb* as the neutral by-product of preparation of *IIIc*; m.p. 65—67°C (hexane). UV spectrum: λ_{max} 261·5 nm (log ε 4·31), 300 nm (3·74), ^1H NMR spectrum: δ 6·90—7·60 (m, 9 H, ArH and CH=CH), 3·00 (q, J = 7·0 Hz) and 1·25 (t, J = = 7·0 Hz) (2 + 3 H, $ArCH_2CH_3$). For $C_{16}H_{14}S$ (238·3) calculated: 80·62% C, 5·92% H, 13·46% S; found: 80·60% C, 5·95% H, 13·36% S.

2-Chloro-6-methoxydibenzo[*b,f*]thiepin (*XVf*)

Was obtained similarly like *XVa—XVc* as the neutral by-product of preparation of *IIIf*; m.p. 93—95°C (ethanol). UV spectrum: λ_{max} 263 nm (log ε 4·24), 313 nm (3·89). IR spectrum: 721, 780, 809, 870, 890 (3 and 2 adjacent and solitary Ar—H), 1 077, 1 260 ($ArOCH_3$), 1 560, 3 000, 3 020, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·52 (d, J = 8·5 Hz, 1 H, 4-H), 6·70—7·40 (m, 7 H, remaining ArH and CH=CH), 3·90 (s, 3 H, OCH_3). For $C_{15}H_{11}ClOS$ (274·8) calculated: 65·56% C, 4·04% H, 12·90% Cl, 11·67% S; found: 65·54% C, 4·20% H, 13·02% Cl, 11·81% S.

2-Chloro-6-methoxy-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin (*If*) (Method *B*)

IIIf (11·3 g) was added to a solution of 7·2 g KOH in 17 ml ethanol and the mixture was stirred and refluxed for 6 h (bath temperature 115°C). It was then evaporated *in vacuo*, the residue was distributed between water and benzene and from the benzene layer the base was extracted into 3M-HCl. The solution of hydrochloride was made alkaline with NH_4OH and the base was extracted with benzene. The extract was washed with water, dried and evaporated *in vacuo*. The residue was crystallized from a mixture of benzene and light petroleum and gave 8·8 g (94%) pure *If*, m.p. 134—136°C. ^1H NMR spectrum: δ 7·48 (d, J = 8·5 Hz, 1 H, 4-H), 7·00—7·30 (m, 4 H, 1,3,8,9-H_4), 6·72 (dd, J = 8·5; 3·0 Hz, 1 H, 7-H), 3·92 (s, 3 H, OCH_3), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·82 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·55 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 1·48 (bs, 1 H, NH).

A solution of 9·9 g base in 30 ml ethanol was treated with 5·4 g methanesulfonic acid. There crystallized 15·0 g crude dimethanesulfonate which was recrystallized twice from 95% ethanol; 12·9 g, m.p. 162—166°C. For analytical data of the base and this salt, *cf.* Table I.

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