POTENTIAL NONCATALEPTIC NEUROLEPTIC AGENTS; 2,6-DICHLORO-, 2,7-DICHLORO- AND 2,8-DICHLORO--10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS

Miroslav PROTIVA, Antonín DLABAČ, Martin VALCHÁŘ, Stanislav WILDT, Irena ČERVENÁ and Zdeněk ŠEDIVÝ

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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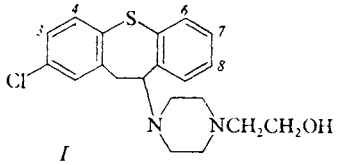
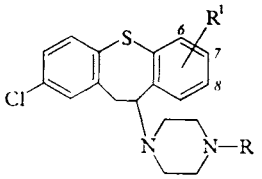
Substitution reactions of 2,6,10-trichloro-, 2,7,10-trichloro- and 2,8,10-trichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Vabc*) with 1-(2-hydroxyethyl)piperazine, 1-methylpiperazine and 1-benzylpiperazine gave the title compounds *IIabc*, *IIIab* and *IVab*. The new chloro compounds *Va* and *Vb* were obtained in 6 steps starting from reactions of 2,5-dichloroacetophenone with 2-chlorothiophenol or 3-chlorothiophenol. Compounds *IIabc* are 6-chloro, 7-chloro and 8-chloro derivatives of the noncataleptic neuroleptic agent docloxythepin (*I*). They are almost devoid of cataleptic activity and do not inhibit the apomorphine stereotypies in rats. Compounds *IIab* have a clozapine-like affinity to dopaminergic receptors in the rat brain striatum; the affinity of *IIc* is much higher. On the other hand only compounds *IIb* and *IIIa* prove a significant antidopaminergic activity *in vivo* (increase significantly the homovanillic acid level in the rat brain striatum).

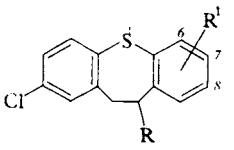
In two previous communications[1,2] the synthesis of 3-chloro and 4-chloro derivatives of the noncataleptic neuroleptic agent docloxythepin (*I*) (refs[3-5]) were described. Docloxythepin (*I*) proved a somewhat similar pharmacological profile[6,7] like the well-known antipsychotic clozapine[8] but it was dropped because of the serious side effects[9] and indications of hepatotoxicity in dogs. The mentioned 3-chloro and 4-chloro derivatives of compound *I* were not only noncataleptic but they were in general devoid of the neuroleptic character[1,2]. In the search after further noncataleptic neuroleptic agents we have recently prepared the 6-chloro (*IIa*), 7-chloro (*IIb*) and 8-chloro (*IIc*) derivatives of docloxythepin (*I*), as well as some further related compounds. The present paper discloses the syntheses and pharmacological properties of these substances.



I

Synthesis of compounds *IIabc*, *IIIab* and *IVab* used in the final step the substitution reaction of 2,6,10-trichloro-, 2,7,10-trichloro- and 2,8,10-trichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Vabc*) with excessive 1-(2-hydroxyethyl) piperazine, 1-methylpiperazine and 1-benzylpiperazine[10] in boiling chloroform. The products were isolated (with the exception of compound *IVa*; *cf.* Experimental) by crystallization of the bases which were then transformed to salts [dimethanesulfonates and in one case bis(hydrogen maleate)]. Compounds *II*–*IV* are assembled in Table I with the usual experimental data. The procedure for preparing compound *IIa* is described in the Experimental as an example.





II, R = CH_2CH_2OH
III, R = CH_3
IV, R = $CH_2C_6H_5$

V, R = Cl
VI, R = OH

In formulae *II*–*XI*: *a*, R^1 = 6(2′)-Cl; *b*, R^1 = 7(3′)-Cl; *c*, R^1 = 8(4′)-Cl

Synthesis of compounds *Vabc* was carried out by methods used previously in similar cases[11,12]. In series *a* 2,5-dichloroacetophenone[11] was reacted with 2-chlorothiophenol[13] in the presence of potassium carbonate, copper and a small amount of boiling ethanol; 5-chloro-2-(2-chlorophenylthio)acetophenone (*VIIa*) was obtained in a yield of 70%. Heating of the ketone *VIIa* with an excess of morpholine and sulfur (*cf.*[14]) gave the thiomorpholide *VIIIa* in yields of 50–60%; its hydrolysis with boiling ethanolic potassium hydroxide gave (5-chloro-2-(2-chlorophenylthio)--phenyl)acetic acid (*IXa*). This acid was cyclized with polyphosphoric acid at 150°C to give 2,6-dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xa*) in very good yields. Reduction of compound *Xa* with sodium borohydride in aqueous ethanol resulted in the alcohol *VIa* which was transformed to *Va* by treatment with hydrogen chloride in benzene. The final substitution reactions with the mentioned piperazines, leading to compounds *IIa*, *IIIa* and *IVa*, were accompanied by elimination reactions and the isolated neutral product was identified as the new 2,6-dichlorodibenzo[*b*,*f*]thiepin (*XIa*). The identity of all the intermediates and of the final products was confirmed by spectra.

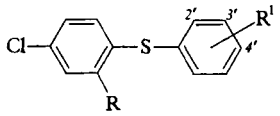
In series *b* the synthesis started from 2,5-dichloroacetophenone[11] and 3-chlorothiophenol[15] and proceeded similarly like in series *a via* the intermediates *VIIb*, *VIIIb*, *IXb*, *Xb* and *VIb* to the desired chloro compound *Vb*. The neutral by-product of the final substitution reactions, *i.e.* 2,7-dichlorodibenzo[*b*,*f*]thiepin (*XIb*), was

TABLE I

2,6-, 2,7- and 2,8-Dichloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins

Compound[a] (yield %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% Cl	% N	% S
IIa[b] (65)	139–141 (benzene)	$C_{20}H_{22}Cl_2N_2OS$ (409·4)	58·67 58·80	5·42 5·45	17·32 17·18	6·84 6·74	7·83 8·06
IIa-BHM	161–162 (ethanol–ether)	$C_{28}H_{30}Cl_2N_2O_9S$ (641·5)	52·42 52·35	4·71 4·75	11·05 11·30	4·37 4·12	5·00 5·20
IIb[c] (79)	56–58 (benzene)	$C_{20}H_{22}Cl_2N_2OS + C_6H_6$ (487·5)	64·06 64·47	5·80 5·84	14·56 14·71	5·76 5·70	6·59 6·80
IIb-2 MS	188–190 (ethanol–ether)	$C_{22}H_{30}Cl_2N_2O_7S_3$ (601·6)	43·92 43·54	5·02 5·10	11·79 11·78	4·66 4·47	15·99 15·73
IIc[d] (60)	97–101 (cyclohexane)	$C_{20}H_{22}Cl_2N_2OS + 1/3\ C_6H_{12}$ (437·4)	60·40 60·37	5·99 6·07	16·21 16·43	6·41 6·39	7·33 7·48
IIc-2 MS[e]	161–163 (ethanol)	$C_{22}H_{30}Cl_2N_2O_7S_3 + H_2O$ (619·6)	42·64 42·94	5·21 5·10	11·44 11·23	4·52 4·71	15·53 15·43
IIIa[f] (64)	98–99 (hexane)	$C_{19}H_{20}Cl_2N_2S$ (379·3)	60·15 60·26	5·31 5·44	18·69 18·55	7·39 7·34	8·45 7·97
IIIa-2 MS	211–212 (ethanol–ether)	$C_{21}H_{28}Cl_2N_2O_6S_3$ (571·6)	44·13 44·04	4·93 5·09	12·41 12·53	4·90 4·81	16·83 16·74
IIIb[g] (60)	130–132 (benzene)	$C_{19}H_{20}Cl_2N_2S$ (379·3)	60·15 60·34	5·31 5·44	18·69 18·70	7·39 7·24	8·45 8·37
IIIb-2 MS	216–218 (ethanol–ether)	$C_{21}H_{28}Cl_2N_2O_6S_3$ (571·6)	44·13 43·88	4·93 5·00	12·41 12·53	4·90 4·60	16·83 16·56
IVa-2 MS[b,e] (21)	148–151 (ethanol–ether)	$C_{27}H_{32}Cl_2N_2O_6S_3 + H_2O$ (665·7)	48·71 48·93	5·15 4·92	10·65 10·27	4·21 3·96	14·45 14·00
IVb (67)	134–136 (benzene)	$C_{25}H_{24}Cl_2N_2S$ (455·4)	65·92 65·89	5·31 5·26	15·57 15·48	6·15 5·84	7·04 6·94
IVb-2 MS	158–159 (ethanol)	$C_{27}H_{32}Cl_2N_2O_6S_3$ (647·7)	50·07 49·85	4·98 5·30	10·95 10·77	4·32 4·82	14·85 14·64

[a] BHM bis(hydrogen maleate), 2 MS dimethanesulfonate. [b] See Experimental. [c] Solvate with benzene 1 : 1; IR spectrum: 800, 813, 830, 870, 900 (2 adjacent and solitary Ar—H), 1 006, 1 059 (CH_2OH), 1 549, 1 560, 1 580, 3 030 (Ar), 2 670, 2 690, 2 755, 2 765 (CH_2—N), 3 170, 3 400 cm^{-1} (OH); ^1H NMR spectrum: δ 6·90–7·70 (m, ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, J = 6·0 Hz, 2 H, CH_2O), 2·75 (bs, 1 H, OH), c. 2·50 (m, 10 H, 5 CH_2N). [d] Solvate 3 : 1

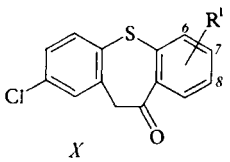


VII, R = $COCH_3$

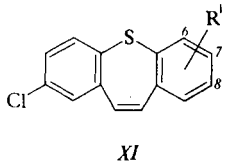
VIII, R = CH_2CSN O

IX, R = CH_2COOH

described in one of our previous communications[16]. In series *c* the chloro compound *Vc* was known[17,18] and was obtained similarly like in series *a* and *b*. The product of elimination, formed in the final stage, *i.e.* 2,8-dichlorodibenzo[*b*,*f*]thiepin(*XIc*), has also been previously described[17].



X



XI

The compounds prepared were pharmacologically tested in the form of salts, described in Table I; unless stated otherwise, they were administered orally and the doses (in mg/kg) were calculated per base. The testing was oriented in the first line towards the expected neuroleptic activity. A part 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 determined only for some of the compounds. LD_{50}: *IIa*, 300; *IIb*, 60 *i.v.*; *IIc*, 40 *i.v.*; *IVb*, 150 i.v. Symptoms observed during these tests: With the orally administered compound *IIa* the toxic symptoms started to appear

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with cyclohexane; IR spectrum: 818, 822, 876 (2 adjacent and solitary Ar—H), 1 048, 1 052 (CH_2OH), 1 560, 1 580 (Ar), 3 150 cm^{-1} (OH); ^1H NMR spectrum: δ 7·58 (d, J = 2·5 Hz, 1 H, 9-H), 7·35 (d, J = 8·0 Hz, 1 H, 4-H), 7·25 (d, J = 8·0 Hz, 1 H, 6-H), 7·09 (d, J = 2·5 Hz, 1 H, 1-H), 6·98 (dd, J = 8·0; 2·5 Hz, 1 H, 3-H), 6·97 (dd, J = 8·0; 2·5 Hz, 1 H, 7-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·52 (t, J = 7·0 Hz, 2 H, CH_2O), 2·80 (s, 1 H, OH), c. 2·50 (bm, 10 H, 5 CH_2N), 1·35 (3, 4 H, 2 CH_2 of cyclohexane). [e] Monohydrate. [f] IR spectrum: 709, 773, 790, 808, 864, 900 (3 and 2 adjacent and solitary Ar—H), 1 550, 1 560, 1 580, 3 049 (Ar), 2 665, 2 690, 2 740, 2 760, 2 790, 2 815 cm^{-1} (CH_3—N, CH_2—N); ^1H NMR spectrum: δ 6·90—7·50 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·35 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·21 (s, 3 H, CH_3N). [g] IR spectrum: 800, 810, 837, 868, 874 (2 adjacent and solitary Ar—H), 1 550, 1 578, 3 050 (Ar), 2 685, 2 740, 2 755 cm^{-1} (CH_3—N, CH_2—N); ^1H NMR spectrum: δ 6·90—7·70 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (bt, 4 H, $CH_2N^1CH_2$ of piperazine). 2·35 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, CH_3N).

in 20 min after the administration as long lasting decrease of activity and reactivity connected with ptosis and hypothermia; the perishing proceeded with delay in the 2nd till the 5th day after the administration. With the intravenously administered compounds *IIb*, *IIc* and *IVb*, the perishing in convulsions proceeded shortly after the administration. The surviving animals showed long lasting decrease of activity and reactivity, and ptosis. Affinity to dopaminergic receptors in the rat brain striatum *in vitro* determined by inhibition of binding of 0·5 nanomol [^{3}H]spiperone[19], IC_{50} in nanomol: *IIa*, 460 (for clorothepin 8·0, for clozapine 288·5); *IIb*, 490; *IIc*, 21·06 (in tuberculum olfactorium 8·58); *IIIa*, 2 662. Influence on the dopamine turnover and metabolism in the rat brain striatum *in vivo* checked in the interval of 3 h by the increase of homovanillic acid (HVA) level after a dose of 80 mg/kg[20]; percent of HVA in comparison with the control (100%): *IIa*, 206 (for clozapine 289); *IIb*, 380; *IIc*, 135 (insignificant); *IIIa*, 393 (a dose of 20 mg/kg had still a significant effect – increase to 260%; the effect of a dose of 5 mg/kg was no more significant – increase to 220%); *IVa* and *IVb* are inactive. Compounds *IIa*, *IIb*, *IIIa* and *IVb* brought about an insignificant decrease of dopamine level (by 15–20%). Catalepsy in rats: The dose of 50 mg/kg was used with all compounds tested. Compound *IIIa* was completely inactive, compounds *IIa*, *IIb* and *IVb* brought about catalepsy in 10% animals, *IIc* in 30% and *IIIb* in 40%. The last compound is thus somewhat cataleptogenic. The other are considered noncataleptic. Antiapomorphine activity in rats: The dose of 50 mg/kg was used with all compounds tested (*IIabc*, *IIIab*, *IVab*). None of the compounds did influence the apomorphine stereotypies (chewing). *IIa* and *IIIb* significantly antagonized the apomorphine agitation (*IIIb* reduced the agitation to 69% of the control value). The agitation was also reduced with compounds *IIa*, *IIb*, and *IIIc* but this was explained by the concomitant central myorelaxant and sedative action. Antiamphetamine effect in mice (ED is the dose protecting 100% of the animals from the lethal effect of a standard dose of amphetamine): *IIa*, 25; *IIb*, 12 *i.v.*; *IIc*, <1 *i.v.* Reduction of spontaneous locomotor activity of mice in the photo-cell test by Dews: Three compounds were administered in doses of 10 mg/kg and reduced the motility from the control 100% to 5·1% (*IIa*), 1·9% (*IIIa*), 2·1% (*IIIb*). Compound *IIb* was administered in the dose of 6 mg/kg and reduced the motility to 4·9%. Compound *IIc* reduced the motility significantly in the dose of 1 mg/kg *s.c.* The motility was also significantly decreased in unknown surroundings, ED given: *IIa*, 5–10; *IIb*, 1–5 *s.c.*; *IIc*, <1 *s.c.* The CNS depressant activity of compounds in the test of the traction wire corresponds to central myorelaxant activity, ED given: *IIa*, 5–10; *IIb*, 12 *s.c.*; *IIc*, 1 *s.c.* Compound *IIc* showed in addition a very high myorelaxant activity on the rat gastrocnemium muscle; a dose of 1 mg/kg *i.v.* blocked completely and without the need of artificial ventilation contractions elicited by electric stimulation of the nervus ischiadicus and prevented the death in the 2 h interval. Discoordinating activity in the rotarod test in mice: the ED_{50} values for compounds *IIab* and *IIIab* were within the range of 3·0 to

3·5 mg/kg. Compounds *IVa* and *IVb* in doses of 10 mg/kg brought about ataxia in 20–30% animals. Thiopental potentiation in mice (ED is the dose prolonging the duration of the thiopental sleeping time to 200% of the control value): *IIa*, 5–10 *p.o.*; *IIb*, 0·5–1·0 *i.v.*; *IIc*, 0·1 *i.v.* Hypothermic effect in rats (ED is the dose decreasing rectal temperature by 1·0°C): *IIc*, 1 mg/kg *i.p.* Antihistamine activity (ED is the dose protecting 50% of the guinea-pigs from the lethal effect of 5 mg/kg histamine, administered intrajugularly): *IIa*, 10 orally; *IIc*, 8 *s.c.* Spasmolytic activity on the isolated rat duodenum: Compound *IIc* in concentrations of 10 μg/ml reduced the acetylcholine and barium chloride contractions by 50% (a papaverine-like effect). Hypotensive effect in normotensive rats: Compound *IIa* in oral doses of 30 to 60 mg/kg brought about a significant hypotensive effect. Brief and deep drops of blood pressure were noted after the *i.v.* administration (compound and dose given): *IIb*, 6; *IIc*, 8. Adrenolytic effect (inhibition of the adrenaline pressor reaction in rats by 50%, *i.v.* doses given): *IIb*, 1; *IVb*, 10. Compound *IIc* was extremely active: full blockade of the adrenaline effect was brought about by the dose of 0·005 mg/kg *i.v.*; the inhibition was still indicated in the dose of 0·05 μg/kg *i.v.* Antiarrhythmic effect in rats towards aconitine (doses prolonging significantly the latency of ventricular extrasystoles): *IIa*, 25–60 orally; *IIc*, 2·8–8·0 *i.v.*

The following conclusions can be drawn on the basis of results described: *1*) The 2,8-dichloro compound *IIc* (VÚFB-15 573) has the character of a multipotent psychotropic and neurotropic agent. Being almost noncataleptic and free of the antiapomorphine effect, it has an extremely high affinity to dopaminergic receptors (in this line it almost equals the activity of the cataleptic neuroleptics), it has the highest antiamphetamine effect, a high tranquillizing activity, a clear myorelaxant activity in two tests, potentiates most potently thipental, has a clear hypothermic effect and moreover antihistamine, antispasmodic, antiarrhythmic and an extremely high α-adrenolytic action. On the other hand, it showed only a weak antidopaminergic effect *in vivo* (insignificant increasing dopamine metabolism in the rat brain) which is probably due to its difficult penetration through the blood-brain barrier. For this reason this agent was dropped. *2*) The 2,7-dichloro compound *IIb* (VÚFB-15 325) seems to be a more suitable candidate for further testing as the noncataleptic neuroleptic agent. Its antidopaminergic activity *in vitro* and *in vivo* is similar like that of clozapine. It is noncataleptic and free of the antiapomorphine actions. It has a clear antiamphetamine effect, tranquillizing and myorelaxant activities, a high discoordinating activity and potentiates significantly thiopental. Its adrenolytic effect is not so striking like with *IIc* which is an advantage. *3*) The 2,6-dichloro compound *IIa* (VÚFB-15 323) is also noncataleptic and free of the antiapomorphine action. On the other hand, it is weaker in the most important tests than clozapine and *IIb*. *4*) The N-methyl analogue of *IIa*, *i.e.* compound *IIIa* (VÚFB-15 320), has a high antidopaminergic activity *in vivo* but its affinity to dopamine receptors is lower. Typical is its high central depressant activity in several tests. *5*) The N-benzyl com-

pounds *IVa* and *IVb* did not show any antidopaminergic activity *in vitro* and are inactive in tests for central depressant activity.

The compounds prepared were also tested for antimicrobial activity *in vitro*; minimum inhibitory concentration in μg/ml are given unless they exceed 100 μg/ml: *Streptococcus β-haemolyticus*, *IIa* 10, *IIb* 5, *IIc* 12·5, *IIIa* 5, *IIIb* 2·5; *Streptococcus faecalis*, *IIa* 10, *IIb* 10, *IIIa* 10, *IIIb* 10; *Staphylococcus pyogenes aureus*, *IIa* 5, *IIb* 5, *IIIa* 5, *IIIb* 5; *Proteus vulgaris*, *IIa* 100, *IIb* 100, *IIIa* 100, *IIIb* 100; *Saccharomyces pasterianus*, *IIa* 25, *IIb* 12·5, *IIc* 25, *IIIa* 12·5, *IIIb* 12·5; *Trichophyton mentagrophytes*, *IIa* 12·5, *IIb* 6·2, *IIc* 12·5, *IIIa* 25, *IIIb* 12·5, *IVa* 50, *IVb* 50; *Aspergillus niger*, *IIb* 50, *IIIb* 25. The activity against cocci is worth mentioning.

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 spectrophorometer, IR spectra (in Nujol) with the Perkin–Elmer 298 spectrophotometer, and ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol). Processing of the extracts consisted in drying with K_2CO_3 or $MgSO_4$ and evaporation on rotating evaporator under reduced pressure.

5-Chloro-2-(2-chlorophenylthio)acetophenone (*VIIa*)

A stirred mixture of 31·7 g 2-chlorothiophenol[13] and 37·8 g 2,5-dichloroacetophenone[11] was treated with 1·0 g Cu and 55 g K_2CO_3. Addition of 10 ml ethanol enabled continuation of the stirring and the mixture was heated under reflux for 6 h (bath temperature 120°C). The warm mixture was treated with 100 ml water and 100 ml benzene, stirred, filtered and the aqueous layer was extracted with benzene. The organic solutions were combined and processed. The oily product slowly crystallized on standing and was recrystallized from 35 ml ethanol; 41·2 g (69%), m.p. 86–87°C. Analytical sample, m.p. 87–88·5°C (ethanol). In a larger batch the yield was 78% (including the processing of the mother liquors). UV spectrum: λ_{max} 234 nm (log ε 4·38), 266 nm (3·92), 341 nm (3·62), infl. 284 nm (3·75). IR spectrum: 758, 820, 870 (4 and 2 adjacent and solitary Ar–H), 1 355, **1 665** ($ArCOCH_3$), 1 540, 1 560, 1 570, 1 580 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·80 (d, J = 2·5 Hz, 1 H, 6-H), 7·10–7·70 (m, 5 H, remaining ArH 3-H excluded), 6·71 (d, J = 8·5 Hz, 1 H, 3-H), 2·65 (s, 3 H, $COCH_3$). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·57% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·51% C, 3·37% H, 23·71% Cl, 10·68% S.

5-Chloro-2-(3-chlorophenylthio)acetophenone (*VIIb*)

A stirred mixture of 31·7 g 3-chlorothiophenol[15] and 37·8 g 2,5-dichloroacetophenone[11] was treated with 1·0 g Cu, 55 g K_2CO_3 and 10 ml ethanol, and was heated under reflux for 6 h. Similar processing like in the preceding case gave 38·0 g (64%) *VIIb*, m.p. 56–57°C. Analytical sample, m.p. 57–58°C (ethanol). UV spectrum: λ_{max} 233 nm (log ε 4·37), 263 nm (3·90), 341 nm (3·58), infl. 289 nm (3·69). IR spectrum: 695, 781, 792, 805, 880 (3 and 2 adjacent and solitary Ar–H), 1 360, **1 670** ($ArCOCH_3$), 1 548, 1 562, 1 575 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·80 (d, J = 2·5 Hz, 1 H, 6-H), 7·50 (bs, 1 H, 2′-H), 7·35 (bs, 3 H, 4′,5′,6′-H_3), 7·28 (q, J = 8·5; 2·5 Hz, 1 H, 4-H), 6·88 (d, J = 8·5 Hz, 1 H, 3-H), 2·70 (s, 3 H, $COCH_3$). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·57% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·88% C, 3·38% H, 23·57% Cl, 10·96% S.

(5-Chloro-2-(2-chlorophenylthio)phenyl)acetothiomorpholide (*VIIIa*)

A mixture of 140 g *VIIa*, 22·5 g S and 81 g morpholine was stirred and heated under reflux for 4·5 h (bath temperature 145—150°C). After standing overnight the mixture was diluted with 500 ml chloroform, it was thoroughly shaken and filtered with charcoal. The filtrate was washed with water, 1 : 9 dilute hydrochloric acid and water, dried with $MgSO_4$, filtered and evaporated. The residue was dissolved by warming in 250 ml benzene and the solution was allowed to crystallize; 111 g (60%) *VIIIa*, m.p. 134—137°C. Analytical sample, m.p. 142—143°C (benzene). IR spectrum: 763, 818, 880, 890 (4 and 2 adjacent and solitary Ar—H), 1 115 (C—O—C), 1 463, 1 490 (N—C—S), 1 580 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60—7·60 (m, 7 H, ArH), 4·30 (s, 2 H, $ArCH_2CS$), 4·30 (t), 3·70 (t), 3·50 (s) (2 + 2 + 4 H, 4 CH_2 of morpholine). For $C_{18}H_{17}Cl_2NOS_2$ (398·4) calculated: 54·27% C, 4·30% H, 17·80% Cl, 3·52% N, 16·10% S; found: 54·44% C, 4·31% H, 17·74% Cl, 3·40% N, 16·10% S.

(5-Chloro-2-(3-chlorophenylthio)phenyl)acetothiomorpholide (*VIIIb*)

A mixture of 99 g *VIIb*, 16·0 g S and 58 g morpholine was processed similarly like in the preceding case. The crude product crystallized from a mixture of 150 ml benzene and 200 ml light petroleum; 75 g (56%), m.p. 107—109°C. Analytical sample, m.p. 110—111°C (benzene). IR spectrum: 685, 780, 822, 872, 882, 890 (3 and 2 adjacent and solitary Ar—H), 1 118 (C—O—C), 1 462, 1 495 (N—C=S), 1 555, 1 565, 1 575 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·90—7·60 (m, 7 H, ArH), 4·35 (s, 2 H, $ArCH_2CS$), 4·37 (t), 3·80 (t), 3·50 (s) (2 + 2 + 4 H, 4 CH_2 of morpholine). For $C_{18}H_{17}Cl_2NOS_2$ (398·4) calculated: 54·27% C, 4·30% H, 17·80% Cl, 3·52% N, 16·10% S; found: 54·46% C, 4·31% H, 17·65% Cl, 3·42% N, 15·60% S.

(5-Chloro-2-(2-chlorophenylthio)phenyl)acetic Acid (*IXa*)

VIIIa (40 g) was added to a hot solution of 28 g KOH in 100 ml ethanol and the mixture was refluxed for 3 h. While warm it was diluted with 1 l water, the solution was filtered with charcoal and the filtrate was acidified with hydrochloric acid. The oily separated product crystallized on standing overnight. It was filtered, washed with water and dried *in vacuo*; 24 g (76%), m.p. 135—138°C. Analytical sample, m.p. 139—141°C (70% ethanol). IR spectrum: 760, 835, 875 (4 and 2 adjacent and solitary Ar—H), 920, 1 285, **1 720** (RCOOH), 1 560, 1 573, 1 585 (Ar), 2 540, 2 640, 2 720, infl. 3 100 cm^{-1} (COOH). ^1H NMR spectrum: δ 11·40 (bs, 1 H, COOH), 6·70—7·50 (m, 7 H, ArH), 3·85 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{10}Cl_2O_2S$ (313·2) calculated: 53·68% C, 3·22% H, 22·64% Cl, 10·24% S; found: 53·47% C, 3·16% H, 22·45% Cl, 10·47% S.

(5-Chloro-2-(3-chlorophenylthio)phenyl)acetic Acid (*IXb*)

VIIIb (400 g) was similarly hydrolyzed with 28 g KOH in 80 ml ethanol; 27 g (86%) *IXb*, m.p. 113—115°C. Analytical sample, m.p. 115—116°C (70% ethanol). IR spectrum: 690, 785, 830, 878 (3 and 2 adjacent and solitary Ar—H), 920, 1 105, 1 235, **1 712** (RCOOH), 1 575 (Ar), 2 530, 2 630, 2 730, infl. 3 200 cm^{-1} (COOH). ^1H NMR spectrum: δ 11·40 (bs, 1 H, COOH), 6·90 to 7·60 (m, 7 H, ArH), 3·85 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{10}Cl_2O_2S$ (313·2) calculated: 53·68% C, 3·22% H, 22·64% Cl, 10·24% S; found: 53·39% C, 3·15% H, 22·47% Cl, 10·06% S.

2,6-Dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xa*)

A stirred mixture of 50 g *IXa* and 500 g polyphosphoric acid was heated for 4 h to 150°C and poured into 2·5 l water. The precipitate was filtered and the oily layer in the filtrate was extracted twice with 500 ml benzene. The solid product was dissolved in the extract with some warming,

the solution was filtered, washed at 40°C with water, 5% NaOH and water, dried and evaporated; 42·5 g (89%), m.p. 159—162°C. Analytical sample, m.p. 164—165°C (benzene). UV spectrum: λ_{max} 240 nm (log ε 4·30), inflexes at 262 nm (4·62), 268 nm (3·98), and 273 nm (3·87). IR spectrum: 705, 768, 800, 819, 875, 892 (3 and 2 adjacent and solitary Ar—H), 1 560, 1 575, 3 060, 3 070 (Ar), **1 665** cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·10 (q, J = 8·0; 1·5 Hz, 1 H, 9-H), 7·60 (d, J = 8·0 Hz, 1 H, 4-H), 7·58 (q, J = 8·0; 1·5 Hz, 1 H, 7-H), 7·45 (*d*, J = 2·5 Hz, 1 H, 1-H), 7·22 (t, J = 8·0 Hz, 1 H, 8-H), 7·18 (q, J = 8·0; 2·5 Hz, 1 H, 3-H), 4·32 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·73% H, 24·02% Cl, 10·86% S; found: 56·87% C, 2·68% H, 24·30% Cl, 11·10% S.

2,7-Dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xb*)

IXb (53 g) was similarly treated with 530 g polyphosphoric acid; 45·7 g (91%), m.p. 155—157°C. Analytical sample, m.p. 157—158°C (benzene). UV spectrum: λ_{max} 249 nm (log ε 4·35), 327 nm (3·57), infl. 278 nm (3·94). IR spectrum: 811, 830, 865, 896 (2 adjacent and solitary Ar—H), 1 580, 3 065, 3 083 (Ar), **1 685** cm^{-1} (ArCOR). ^1H NMR spectrum: δ 8·18 (d, J = 8·5 Hz, 1 H, 9-H), 7·60 (d, J = 2·5 Hz, 1 H, 1-H), 7·58 (d, J = 8·5 Hz, 1 H, 4-H), 7·47 (d, J = 2·5 Hz, 1 H, 6-H), 7·30 (q, J = 8·5; 2·5 Hz, 1 H, 8-H), 7·18 (q, J = 8·5; 2·5 Hz, 1 H, 3-H), 4·39 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·73% H, 24·02% Cl, 10·86% S; found: 56·77% C, 2·63% H, 24·20% Cl, 10·96% S.

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

A suspension of 42·5 g *Xa* in 900 ml ethanol was stirred and treated at 65—70°C over 15 min with a solution of 27·2 g $NaBH_4$ in 270 ml water containing 1 ml 20% NaOH. It was then refluxed for 6 h, ethanol was evaporated and the residue was distributed between 600 ml benzene and 250 ml water. The organic layer was washed with 250 ml 2% NaOH and with 250 ml water, it was dried with $MgSO_4$, filtered with charcoal and evaporated. The residue contained still some *Xa* (TLC) and was crystallized from 90 ml benzene; 33·6 g (79%), m.p. 132—134°C. Analytical sample, m.p. 134—135°C (ethanol). IR spectrum: 706, 790, 820, 875 (3 and 2 adjacent and solitary Ar—H), 1 035, 1 060 (CHOH in the ring), 1 547, 1 560, 1 577, 3 050, 3 065 (Ar), 3 555 cm^{-1} (OH). ^1H NMR spectrum: δ 7·00—7·60 (m, 6 H, ArH), 5·60 (bm, 1 H, Ar—CH—O), 3·65 and 3·20 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·28 (bd, 1 H, OH). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·57% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·84% C, 3·40% H, 23·88% Cl, 10·81% S.

2,7-Dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*VIb*)

Xb (45·7 g) was reduced with 29·1 g $NaBH_4$ in 1 l ethanol and 290 ml water; 36·9 g (80%) recrystallized product, m.p. 123—125°C. Analytical sample, m.p. 125—126°C (ethanol). IR spectrum: 818, 825, 835, 885 (2 adjacent and solitary Ar—H), 1 091, 1 105 (CHOH in the ring), 1 559, 1 560, 1 580, 3 045, 3 070 (Ar), 3 290, 3 360 cm^{-1} (OH). ^1H NMR spectrum: δ 7·00 to 7·50 (m, 6 H, ArH), 5·25 (m, 1 H, Ar—CH—O), 3·69 and 3·36 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·08 (d, J = 7·0 Hz, 1 H, OH). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·57% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·85% C, 3·39% H, 24·08% Cl, 10·58% S.

2,6,10-Trichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Va*)

A solution of 36·5 g *VIa* in 1 l benzene was treated with 50 g powdered $CaCl_2$ and the stirred suspension was saturated for 7·5 h with HCl at 20°C. The solid was filtered off and washed with 50 ml benzene. Evaporation of the filtrate gave 38·6 g (100%) of *Va*, m.p. 115—116°C.

Analytical sample, m.p. 115·5—116°C (benzene–light petroleum). ^{1}H NMR spectrum: δ 6·90 to 7·50 (m, 6 H, ArH), 5·90 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·86 and 3·48 (2 dd, J = 13·0; 4·0 and 13·0; 8·0 Hz, 1 + 1 H, $ArCH_2$). For $C_{14}H_9Cl_3S$ (315·6) calculated: 53·27% C, 2·87% H, 33·70% Cl, 10·16% S; found: 53·54% C, 2·89% H, 33·52% Cl, 10·23% S.

2,7,10-Trichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Vb*)

Similar treatment of 39·5 g *VIb* in 1·3 l benzene with 50 g $CaCl_2$ and then with HCl for 16 h gave by similar processing 40·3 g crude product which was contaminated with the starting *VIb*. Crystallization from 130 ml benzene gave 35·8 g (85%) homogeneous *Vb*, m.p. 155·5—156°C. Analytical sample, m.p. 157—158°C (benzene), ^{1}H NMR spectrum: δ 7·00—7·50 (m, 6 H, ArH), 5·65 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·92 and 3·47 (2 dd, J = 13·0; 4·0 and 13·0; 8·0 Hz, 1 + 1 H, $ArCH_2$). For $C_{14}H_9Cl_3S$ (315·6) calculated: 53·27% C, 2·87% H, 33·70% Cl, 10·16% S; found: 53·35% C, 2·88% H, 33·72% Cl, 10·23% S.

2,6-Dichloro-10-(4-(2-hydroxyethyl)piperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IIa*)

A mixture of 13·0 g *Va*, 20 ml chloroform and 16 g 1-(2-hydroxyethyl)piperazine was stirred and refluxed for 7 h, chloroform was evaporated *in vacuo* and the residue was distributed between water and benzene. The organic layer was washed with 5% NaOH and water, the base was extracted into 1·25M-H_2SO_4, the aqueous solution was washed with benzene and treated with NH_4OH. The base was isolated by extraction with benzene. Processing of the extract gave 11·0 g (65%) *IIa*, m.p. 135—137°C. Analytical sample, m.p. 139—141°C (benzene). IR spectrum: 721, 775, 821, 840, 873, 902 (3 and 2 adjacent and solitary Ar—H), 1 004, 1 043 (CH_2OH), 1 550, 1 560, 1 580, 3 070 (Ar), 2 670, 2 690, 2 765, 2 825 (N—CH_2), 3 150 cm^{-1} (OH). ^{1}H NMR spectrum: δ 6·90—7·50 (m, 6 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·55 (t, J = 6·0 Hz, 2 H, CH_2O), 2·85 (bs, 1 H, OH), c. 2·50 (m, 10 H, 5 CH_2N). Neutralization of 8·4 g base with 4·7 g maleic acid in 30 ml boiling ethanol gave by standing and cooling 12·5 g bis(hydrogen maleate), m.p. 161—162°C (ethanol–ether). For analyses *cf.* Table I.

The benzene solution, from which the base was extracted with H_2SO_4, was washed with water and evaporated; 3·9 g (34%) of 2,6-dichlorodibenzo[*b*,*f*]thiepin (*XIa*), m.p. 97—98°C (benzene). UV spectrum: λ_{max} 267·5 nm (log ε 4·34), 305 nm (3·70). IR spectrum: 711, 753, 800, 813, 881 (3 and 2 adjacent and solitary Ar—H), 1 550, 1 577, 3 015 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 6·80—7·60 (m, ArH and CH=CH). For $C_{14}H_8Cl_2S$ (279·2) calculated: 60·23% C, 2·89% H, 25·40% Cl, 11·48% S; found: 60·13% C, 2·93% H, 25·50% Cl, 11·60% S.

2,6-Dichloro-10-(4-benzylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IVa*)

A mixture of 11·3 g *Va*, 30 ml chloroform and 18·9 g 1-benzylpiperazine[10] was stirred and refluxed for 8 h. Chloroform was evaporated, the residue was diluted with 60 ml benzene and the solution was washed three times with 3% NaOH. The bases were extracted into 1·25M-H_2SO_4, the aqueous layer was treated with NH_4OH and the bases were extracted with benzene. Processing of the extract gave 21·2 g mixture of *IVa* and 1-benzylpiperazine. The mixture was extracted twice with 30 ml boiling water. After separation of the aqueous layer, the base was dissolved in benzene, the solution was dried and evaporated *in vacuo*; 12·4 g oily base. It was dissolved in 20 ml ethanol, the solution was treated with 5·1 g methanesulfonic acid and 30 ml ether. The precipitated salt (8·0 g) was filtered and crystallized from 50 ml ethanol; 7·2 g 1-benzylpiperazine dimethanesulfonate, m.p. 204—206°C (ethanol). For $C_{13}H_{24}N_2O_6S_2$ (368·5) calculated: 42·37% C, 6·57% H, 7·60% N, 17·40% S; found: 42·42% C, 6·60% H, 7·52% N, 17·10% S. A sample of this salt was decomposed with NH_4OH, the base was isolated by extraction with ether

and used for recording the ^{1}H NMR spectrum: δ 7·25 (s, 5 H, C_6H_5), 3·42 (s, 2 H, $ArCH_2N$), 2·80 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·42 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 1·52 (s, 1 H, NH).

The mother liquors after the preceding methanesulfonate were combined and evaporated. The residue was dissolved in water, the solution was filtered with charcoal, evaporated *in vacuo* and the residue was treated with NH_4OH. Extraction with benzene gave 5·3 g oily base which was dissolved in 12 ml ethanol, the solution was treated with 2·24 g methanesulfonic acid and ether. The methanesulfonate crystallized over 12 h and proved to be the dimethanesulfonate monohydrate of *IVa*; 5·1 g (21%), m.p. 148–151°C (ethanol–ether). For the analysis, *cf.* Table I.

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REFERENCES

1. Urban J., Dlabač A., Valchář M., Protiva M.: This Journal *49*, 992 (1984).
2. Valenta V., Dlabač A., Protiva M.: This Journal *46*, 781 (1981).
3. Jílek J. O., Šindelář K., Rajšner M., Dlabač A., Metyšová J., Protiva M.: Activ. Nerv. Super. *17*, 215 (1975).
4. Jílek J. O., Šindelář K., Rajšner M., Dlabač A., Metyšová J., Votava Z., Pomykáček J., Protiva M.: This Journal *40*, 2 887 (1975).
5. Dlabač A., Metyšová J., Kazdová E., Metyš J.: Activ. Nerv. Super. *17*, 217 (1975).
6. Valchář M., Metyšová J., Dlabač A. in the book: *Developments in Neuroscience.* Vol. 7. *Phenothiazines and Structurally Related Drugs*; *Basic and Clinical Studies* (E. Usdin, H. Eckert, I. S. Forrest, Eds), p. 79. Elsevier/North-Holland, New York–Amsterdam–Oxford 1980.
7. Náhunek K., Kulísková O., Mišurec J., Sláma B., Švestka J.: Activ. Nerv. Super. *26*, 16 (1984).
8. Schmutz J., Eichenberger K. in the book: *Chronicles of Drug Discovery* (J. S. Bindra, D. Lednicer, Eds), Vol. 1, p. 39. Wiley, New York 1982.
9. Mišurec J., Náhunek K., Kulísková O., Švestka J.: Activ. Nerv. Super. *26*, 17 (1984).
10. Cymerman Craig J., Young R. J.: Org. Syn., Coll. Vol. *5*, 88 (1973).
11. Rajšner M., Mikšík F., Protiva M.: This Journal *43*, 1 276 (1978).
12. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1 831 (1968).
13. Godt H. C., jr, Wann R. E.: J. Org. Chem. *26*, 4 047 (1961).
14. Carmack M.: Org. Reactions *3*, 85 (1946).
15. Daccomo G.: Jahresber. Fortschr. Chem. *1891*, 1 375.
16. Šindelář K., Kopicová Z., Metyšová J., Protiva M.: This Journal *40*, 3 530 (1975).
17. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1 852 (1968).
18. Bártl V., Holubek J., Svátek E., Bartošová M., Protiva M.: This Journal *48*, 1 173 (1983).
19. Titeler M.: Biochem. Pharmacol. *30*, 3 031 (1981).
20. Westering B. H. C., Korf J.: Eur. J. Pharmacol. *38*, 281 (1976).

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