CATALEPTIC AND NONCATALEPTIC NEUROLEPTIC AGENTS: SYNTHESIS AND PHARMACOLOGY OF 4-(2-CHLORO AND 8-CHLORO SUBSTITUTED 10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN-10-YL)PIPERAZINE--1-YLALKYL ETHERS AND SULFIDES

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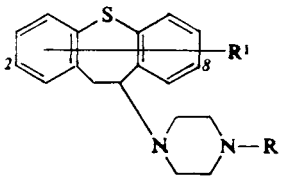
The title compounds *Iab*—*VIab* were prepared by substitution reactions of 2,11-dichloro- and 2,10--dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin with 1-(2-methoxyethyl)piperazine, 1-(3-methoxypropyl)piperazine, 1-(2-ethoxyethyl)piperazine, 1-(2-phenoxyethyl)piperazine, 1-(2-methylthioethyl)piperazine and 1-(2-phenylthioethyl)piperazine; they were transformed to hydrochlorides, maleates or methanesulfonates. Compounds of series *a* (8-chloro derivatives) are neuroleptics, with relatively strong cataleptic, antiapomorphine and central depressant activities (*Ia*, *IIa*, *IIIa*, *Va*) unless the volume and lipophilicity of the N-substituent exceeds certain limits (*IVa* and *VIa* are almost nontoxic and little active). Compounds of series *b* (2-chloro derivatives) are noncataleptic and devoid of the antiapomorphine potency; only two of them (*IIb*, *Vb*), however, showed a more pronounced effect in the test of influencing the turnover and metabolism of dopamine in the rat brain striatum.

In the group of cataleptic neuroleptics belonging to the series of 8-substituted 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins, the following N^4-substituents exerted a favourable influence on the activity: lower alkyls[1,2] and cyclopropyl[1], hydroxyalkyls with 2–4 carbon atom[1,3] and the corresponding acetoxyalkyls[1], 2-(1,3-dioxolan-2-yl)ethyl and 2-(1,3-dioxan-2-yl)ethyl[4,5], and some aliphatic residues with three carbon atoms[1]. On the other hand allyl and propargyl, 2-dimethylaminoethyl[1], phenyl[6], 2- and 4-pyridyl[7], aralkyls[7] (including 4-fluoroaralkyls[8,9]), acetyl[6], aminocarbonyl, methanesulfonyl[1] *etc.* had an unfavourable influence. Quite generally a negative effect was characteristic for very bulky residues, highly lipophilic residues and for groups which weakened or totally destroyed the basicity of the piperazine N^4 nitrogen atom. In the group of noncataleptic neuroleptics, *i.e.* the analogous 2-substituted substances[10], the knowledge about the influence of the N^4-substituent on activity is much more limited: The favourable influence of methyl and lower hydroxyalkyls is known; the work of another laboratory[11] indicated the positive effect of the 2-(2-oxo-oxazolidino)ethyl residue. Systematic investigation of the influence

of alkoxy-, aryloxy-, alkylthio- and arylthioalkyl groups as N-substituents on the anticonvulsant and central depressant activity of tricyclic 1,4-benzodiazepine analogues[12-14] led us to apply these fragments in the molecules of cataleptic and noncataleptic neuroleptics of the mentioned series. As substituent in position 8 of the skeleton ("neuroleptic substituent") and likewise in position 2 (in the noncataleptic series), chlorine[1,10,15,16] was used. The present paper describes the synthesis and pharmacology of the title compounds *Iab* – *VIab*.



a, R^1 = 8-Cl
b, R^1 = 2-Cl

I, R = $CH_2CH_2OCH_3$
II, R = $(CH_2)_3OCH_3$
III, R = $CH_2CH_2OC_2H_5$
IV, R = $CH_2CH_2OC_6H_5$
V, R = $CH_2CH_2SCH_3$
VI, R = $CH_2CH_2SC_6H_5$

The preparation of compounds *Iab* – *VIab* was carried out by substitution reactions of 2,11-dichloro-10,11-dihydrodibenzo-[*b*,*f*]thiepin[15] and 2,10-dichloro--10,11-dihydrodibenzo[*b*,*f*]thiepin[16] with 1-(2-methoxyethyl)piperazine[12], 1-(3-methoxypropyl)-piperazine[12], 1-(2-ethoxyethyl)piperazine[12], 1-(2-phenoxyethyl)piperarazine[12], 1-(2-methylthioethyl)piperazine[12] and 1-(2-phenylthioethyl)piperazine[12] in boiling chloroform. In method *A* the reaction mixture was diluted with chloroform and extracted with dilute sulfuric acid (in the case of compound *IIIb* with dilute hydrochloric acid), the aqueous layer was made alkaline, the released base was transformed to the maleate (in the case of compound *Va* to the methanesulfonate) and the salt was purified for analysis. Decomposition of the pure salts with aqueous ammonia gave homogeneous bases (with the exception of *Va* and *Vb* oils) which were used for recording the ^{1}H NMR spectra. In method *B* the diluted chloroform solution of the reaction mixture was shaken with diluted hydrochloric acid which extracted only the nonreacted starting secondary bases. The hydrochlorides of the strongly hydrophobic bases *IVa*, *VIa*, *IVb* and *VIb* remained in the chloroform layer from which they were obtained by evaporation and crystallization (in the case of compound *IVb* the crude hydrochloride was transformed to the maleate which was purified by crystallization). All compounds prepared are assembled in Table I. In the Experimental only the synthesis of compounds *Va* and *VIb* is being described as representative examples of carrying out the synthesis using methods *A* and *B*.

TABLE I

4-(2-Chloro and 8-chloro substituted 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine-1-ylalkyl ethers and sulfides and their salts

Compound	Method (% yield)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
Ia-M[a]	*A* (72)	177–178[b] (ethanol)	$C_{25}H_{29}ClN_2O_5S$ (505·0)	59·45 59·49	5·79 5·77	7·02 7·11	5·55 5·27	6·35 6·50
IIa-2 HM[c]	*A* (76)	144–145[d] (ethanol)	$C_{30}H_{35}ClN_2O_9S$ (635·1)	56·73 56·91	5·55 5·76	5·58 5·90	4·41 4·43	5·05 5·30
IIIa-M[a]	*A* (76)	149–152 (ethanol)	$C_{26}H_{31}ClN_2O_5S$ (519·1)	60·16 60·32	6·02 6·06	6·83 7·00	5·40 5·29	6·18 6·10
IVa-2 HCl[e]	*B* (64)	168–168·5[f] (aqueous ethanol)	$C_{26}H_{29}Cl_3N_2OS + H_2O$ (542·0)	57·62 57·51	5·77 5·87	19·62 19·46	5·17 5·00	5·92 6·30
Va	*A*[g] (67)	90–95 (benzene–light petroleum)	$C_{21}H_{25}ClN_2S_2$ (405·0)	62·27 62·56	6·22 6·35	8·75 8·67	6·92 6·98	15·84 15·59
Va-2 MS[h,e]	—	155–158 (2-propanol–ether)	$C_{23}H_{33}ClN_2O_6S_4 + H_2O$ (615·3)	44·90 44·88	5·73 5·51	5·76 5·75	4·55 4·59	20·85 20·85
VIa-2 HCl	*B* (58)	191–191·5 (ethanol–ether)	$C_{26}H_{29}Cl_3N_2S_2$ (540·0)	57·85 57·80	5·41 5·51	19·70 19·42	5·19 5·02	11·88 11·78
VIa-2 MS[h,i]	—	177·5[j] (2-propanol–ether)	$C_{28}H_{35}ClN_2O_6S_4 + 0·5\,H_2O$ (668·3)	50·32 50·42	5·43 5·62	5·31 5·42	4·19 4·15	19·19 19·26
Ib-2 HM[c]	*A* (77)	147–149 (ethanol)	$C_{29}H_{33}ClN_2O_9S$ (621·1)	56·08 55·94	5·36 5·57	5·71 5·92	4·51 4·69	5·16 5·14
IIb-M[a]	*A* (87)	155–157[k] (2-propanol)	$C_{26}H_{31}ClN_2O_5S$ (519·1)	60·16 60·04	6·02 6·08	6·83 6·90	5·40 5·32	6·18 5·80
IIIb-M[a]	*A* (75)	151–153[l] (ethanol)	$C_{26}H_{31}ClN_2O_5S$ (519·1)	60·16 60·24	6·02 5·98	6·83 6·90	5·40 5·35	6·18 6·25
IVb-M[a]	*B* (87)	142–144[m] (ethanol)	$C_{30}H_{31}ClN_2O_5S$ (567·1)	63·53 63·23	5·51 5·57	6·25 6·51	4·94 5·10	5·66 6·08
Vb	*A* (66)	67–70[n] (benzene–light petroleum)	$C_{21}H_{25}ClN_2S_2$ (405·0)	62·27 62·51	6·22 6·31	8·75 9·02	6·92 6·90	15·84 15·59
Vb-M	—	166–168 (2-propanol)	$C_{25}H_{29}ClN_2O_4S_2$ (521·0)	57·61 58·09	5·61 5·80	6·80 7·06	5·38 5·32	12·31 12·46
VIb-2 HCl	*B*[g] (38)	219–221 (95% ethanol–ether)	$C_{26}H_{29}Cl_3N_2S_2$ (540·0)	57·82 57·85	5·41 5·41	19·70 19·48	5·19 5·01	11·88 12·33

TABLE I
(*Continued*)

[a] Maleate. [b] The homogeneous oily base was released from the crystalline salt and used for recording the ^{1}H NMR spectrum: δ 7·65 (d, J = 2·5 Hz, 1 H, 1-H), 7·45 (bd, 1 H, 6-H), 7·30 (d, J = 8·0 Hz, 1 H, 4-H), *c*. 7·15 (m, 3 H, 7,8,9-H_3), 7·00 (q, J = 2·5; 8·0 Hz, 1 H, 3-H), 3·00 to 4·00 (m, 3 H, $ArCH_2CHAr$), 3·50 (t, J = 7·0 Hz, 2 H, CH_2O), 3·31 (s, 3 H, OCH_3), 2·65 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (bm, 6 H, remaining 3 CH_2N). [c] Hydrogen maleate. [d] ^{1}H NMR spectrum of the homogeneous oily base: δ 7·68 (d, J = 2·5 Hz, 1 H, 1-H), 7·48 (bd, 1 H, 6-H), 7·31 (d, J = 8·0 Hz, 1 H, 4-H), *c*. 7·15 (m, 3 H, 7,8,9-H_3), 7·00 (q, J = 2·5; 8·0 Hz, 1 H, 3-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·39 (t, J = 7·0 Hz, 2 H, CH_2O), 3·30 (s, 3 H, OCH_3), 2·65 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·40 (t, J = = 7·0 Hz, 2 H, NCH_2 in the chain), 1·80 (m, 2 H, CH_2 in the middle of the propane chain). [e] Monohydrate. [f] IR spectrum: 699, 754, 823, 833, 880, 890 (5, 4 and 2 adjacent, and solitary Ar—H), 1 239 (Ar—O—R), 1 503, 1 585, 1 599, 3 020 (Ar), 2 285 (NH^+), 3 125, 3 220 cm^{-1} (H_2O). [g] See Experimental. [h] Methanesulfonate. [i] Hemihydrate. [j] Mass spectrum, m/z: 466 (M^+ corresponding to $C_{26}H_{27}ClN_2S_2$, 0·5%), 464, 357, 343, 245 (100), 210, 137, 99, 56. [k] ^{1}H NMR spectrum of the homogeneous oily base: δ 7·60 (bd, 1 H, 9-H), 6·90—7·50 (m, 6 H, remaining ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·40 (t, J = 7·0 Hz, 2 H, CH_2O), 3·30 (s, 3 H, OCH_3), 2·65 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·45 (t, J = 7·0 Hz, 2 H, NCH_2 in the chain), 1·80 (m, 2 H, CH_2 in the middle of the propane chain). [l] ^{1}H NMR spectrum of the homogeneous oily base: δ 6·90—7·70 (m, 7 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·52 (t, 2 H, CH_2O in aminoethoxy), 3·45 (q, 2 H, CH_2O in ethoxyl), 2·55 (bm, 10 H, 5 CH_2N), 1·15 (t, 3 H, CH_3 in ethoxyl). [m] ^{1}H NMR spectrum of the homogeneous oily base: δ 6·70—7·70 (m, 12 H, ArH), 4·02 (t, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2$. .CHAr), 2·78 (t, 2 H, NCH_2 in the chain), 2·60 (bm, 8 H, 4 CH_2N of piperazine). [n] ^{1}H NMR spectrum: δ 7·60 (bd, 1 H, 9-H), 6·90—7·50 (m, 6 H, remaining ArH), 3·00—4·00 (m, 3 H,$ArCH_2$. .CHAr), 2·60 (bm, 8 H, $CH_2N^1CH_2$ of piperazine and NCH_2CH_2S), 2·48 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·10 (s, 3 H, SCH_3).

All compounds prepared were pharmacologically evaluated as potential neuroleptics in the form of salts, described in Table I; in the basic program all substances were administered orally and the doses given (in mg/kg) were calculated for bases. For most of the compounds the acute toxicity (AT) was determined and expressed as the medium lethal doses LD_{50}. The discoordinating activity was evaluated in the rotarod test (RR) in mice; medium effective doses ED_{50} bringing about ataxia in 50% mice in the time of maximum effect are given. For some of the compounds the inhibition of the spontaneous locomotor activity (ISM) of mice was investigated using the photo-cell method of Dews; medium inhibitory doses D_{50} are given. For all compounds the cataleptic effect in rats (CAT) was estimated; it is expressed by values of the medium effective doses (ED_{50}) bringing about a defined catalepsy in 50% rats. The antiapomorphine effect in rats was likewise estimated with all compounds; it was oriented toward the apomorphine stereotypies (AA): The D_{50} values are doses decreasing the occurrence of stereotypies to 50% of the control

value (*i.e.* apomorphine only). With the noncataleptic agents the main test was estimation of influencing the dopamine turnover and metabolism in the rat brain striatum (STR) after an oral dose of 80 mg/kg; the criterion was the rise of the level of homovanillic acid (HVA) as the main dopamine metabolite, which was determined by spectrofluorimetry and expressed as per cent of the control value (100%). Results of all just mentioned tests are assembled in Table II.

TABLE II

Pharmacological properties of compounds *Ia*—*VIa* and *Ib*—*VIb* (Explanation of the abbreviations is given in the general part of the paper)

Compound	AT LD_{50} mg/kg	RR ED_{50} mg/kg	ISM D_{50} mg/kg	CAT ED_{50} mg/kg	AA D_{50} mg/kg	STR HVA %
Ia	207	5·2[a]	—	8·5[b]	7·7[c]	—
IIa	179	4·2[c]	—	7·3[d]	7·5[c]	—
IIIa	355	7·8[e]	—	7·1[b]	7·3[c]	—
IVa	>500[f]	> 50[g]	24·4[h]	22·4[i]	30·6[c]	—
Va	311	6·4[c]	—	9·2[j]	4·0[c]	—
VIa	>500	>100	—	34·3[c]	*c.* 80[k]	—
Ib	148	3·9	3·4	>100	>100	100
IIb	—	—	—	> 50	> 50	148
IIIb	—	—	—	> 50[l]	> 50	100
IVb	780	33	27·3	>100	>100	100
Vb	—	—	—	> 50[m]	> 50	219
VIb	2 429	53·3	161	>100	>100	100[n]
Clorothepin	78	2·2	1·6	4·3	1·8	—
Docloxythepin	84	0·8		> 50	—	—

[a] In the interval of 24 h after the administration the effect was still found in 20% animals. [b] In the interval of 24 h after the administration of a dose of 25 mg/kg the effect persisted in 30% animals. [c] The effect disappears within 24 h after the administration. [d] In the interval of 24 h after the administration the effect persisted in 40% animals. [e] In the interval of 24 h after the administration the effect was still found in 30% animals. [f] The dose of 500 mg/kg does not bring about the death of the animals; a mild central depression was apparent. [g] In the rotarod test in mice the compound was inactive in doses of 10, 25 and 50 mg/kg. [h] In 24 h after the administration the doses of 25 and 50 mg/kg are without effect. [i] After a dose of 100 mg/kg the effect persists for 24 h in 20% animals. [j] After a dose of 25 mg/kg the effect persists for 24 h in 20% animals. [k] After this dose the chewing was inhibited to 52%, agitation to 30%; the significant central depressant effect disappeared within 24 h. [l] This dose brings about catalepsy in 20% rats. [m] The dose of 100 mg/kg brings about catalepsy in 20% rats. [n] There was a slight increase of the 5-hydroxyindole-3-acetic acid level (a metabolite of serotonin) in the rat brain striatum.

Four compounds were evaluated by methods of the general pharmacological screening, mostly on parenteral administration. In the first line their acute toxicities in mice on *i.v.* administration (LD_{50} in mg/kg) and their basic doses D (*i.v.*), used in the screening, are given: *Ia*, 60, 12; *IIIa*, 60, 12; *Ib*, 75, 15; *IVb*, 35, 7. Analgetic activity in Haffner's test, ED (an intravenous dose bringing about analgesia in 50% mice): *Ia*, 1; *IIIa*, 1 mg/kg. Analgesic activity in mice using chemical stimulation (intraperitoneal administration of acetic acid), ED in mg/kg orally: *Ia*, 1; *IIIa*, 1. Hypothermic effect in rats, ED (a dose in mg/kg decreasing the rectal temperature of rats by 1·0°C): *Ia*, 12 *i.v.*; *IIIa*, 12 *i.v.* Thiopental potentiation in mice, ED (a dose in mg/kg prolonging the duration of the thiopental sleeping time to 200% of the control value): *Ia*, 0·1 – 0·25 *i.v.*; *IIIa*, 0·05 – 0·1 *i.v.* Antiamphetamine effect in mice, ED (a dose in mg/kg protecting 100% mice from the lethal effect of a standard dose of amphetamine): *Ia*, 0·1 – 0·5 *i.v.*; *IIIa*, 0·1 – 0·5 *i.v.*; *Ib*, >15 *i.v.*; *IVb*, >7 *i.v.* Antihistamine activity in guinea pigs, ED (a dose in mg/kg protecting 50% animals from the lethal effect of 5 mg/kg histamine administered intrajugularly): *Ia*, 1 *s.c.*; *Ib*, 0·1 *s.c.*; *IVb*, 7 *s.c.* CNS depressant effect in known and unknown surroundings (inhibition of motor activity), ED in mg/kg: *Ia*, 0·05 – 0·5 *s.c.*; *IIIa*, 1 – 5 *s.c.*. Hypotensive effect in anesthetized normotensive rats, ED (a dose *i.v.* in mg/kg decreasing the pressure by 20% for at least 10 min): *Ia*, 0·05 – 0·1 (an oral dose of 60 mg/kg in nonanesthetized rats is without effect); *Ib*, 1; *IVb*, the dose D brings about deep and brief drops. Adrenolytic effect in rats, ED (a dose *i.v.* in mg/kg inhibiting the adrenaline pressor reaction by 50%): *Ia* 0·05; *Ib*, 0·01 – 0·1; *IVb*, 0·25.

In conclusion, compounds of series *a* with aliphatic ether or sulfide N^4-substituent have reasonable toxicity and high central depressant, discoordinating, cataleptic and antiapomorphine activity. They are also very potent in the tests of thiopental potentiation, antiamphetamine, antihistamine and peripheral α-adrenolytic activity. Compounds of the same series with aromatic ether or sulfide N^4-substients are very little toxic but at the same time less pharmacodynamically active. In the noncataleptic series *b* only the 3-methoxypropyl (*IIb*) and 2-methylthioethyl compound (*Vb*) showed clear dopamine metabolism increasing activity. Compounds of both series are less active than the standards – clorothepin[17] as a cataleptic compound and docloxythepin[18] as a noncataleptic agent – which are included in Table II.

The compounds prepared were also tested for antimicrobial activity *in vitro*; the microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *Ia* 25, *IIa* 25, *IIIa* 25, *Va* 25, *Ib* 12·5, *IIb* 50, *IIIb* 12·5, *Vb* 12·5; *Streptococcus faecalis*, *IIa* 100, *Ib* 50, *IIb* 100, *IIIb* 50, *Vb* 50; *Staphylococcus pyogenes aureus*, *Ia* 12·5, *IIa* 100, *IIIa* 6·25, *Va* 100, *Ib* 25, *IIb* 100, *IIIb* 100, *Vb* 100; *Escherichia coli*, *Ia* 50, *IIa* 50, *IIIa* 100, *Ib* 25, *IIb* 50, *IIIb* 25; *Saccharomyces pasterianus*, *IVb* 50; *Trichophyton mintagrophytes*, *Ia* 25, *IIa* 12·5, *IIIa* 25, *IVa* 50, *Va* 25, *VIa* 50, *Ib* 25, *IIb* 12·5, *IIIb* 6·25, *IVb* 50, *Vb* 12·5. It is thus clear that even in the line of antimicrobial effects the compounds with aliphatic, *i.e.* with sterically less pretention and simultaneously more hydrophilic N^4-substituents, are more effective.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The IR spectrum (in Nujol) was recorded with a Unicam SP 200G spectrophotometer, the ^1H NMR spectra (in C^2HCl_3) were registered with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with the spectrometers MCH 1320 and Varian MAT 44S. The homogeneity of the products and composition of the reaction mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-Chloro-11-[4-(2-methylthioethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Va*) (Method *A*)

A mixture of 5·0 g 1-(2-methylthioethyl)piperazine[12], 5 ml chloroform and 4·4 g 2,11-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[15] was stirred and refluxed for 6·5 h. It was diluted with 60 ml chloroform, washed with water and the product was extracted into 100 ml 1M-H_2SO_4. The aqueous layer with a little of the oily sulfate was made alkaline with NH_4OH, the base was extracted with benzene and obtained as an oil by evaporation of the extract; 4·2 g (67%). A part (2·9 g) was dissolved in 5 ml 2-propanol and the solution was neutralized with a solution of 1·45 g methanesulfonic acid in 4 ml ether; 3·4 g dimethanesulfonate monohydrate, m.p. 155–158°C (2-propanol–ether).

A sample of the dimethanesulfonate was decomposed with NH_4OH and the free base was isolated by extraction with ether. After evaporation of the extract, the base crystallized, m.p. 90–95°C (benzene–light petroleum). ^1H NMR spectrum: δ 7·70 (d, $J = 2·5$ Hz, 1 H, 1-H), 6·90–7·60 (m, 6 H, remaining ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·68 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·66 (s, 4 H, NCH_2CH_2S), 2·67 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·15 (s, 3 H, SCH_3). For analyses, *cf.* Table I.

2-Chloro-10-[4-(2-phenylthioethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIb*) (Method *B*)

A mixture of 5·6 g 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[16], 5·6 g 1-(2-phenylthioethyl)piperazine[12] and 5·8 ml chloroform was stirred and refluxed for 5·5 h. It was diluted with 40 ml chloroform, refluxed for further 4 h, cooled, washed with dilute NH_4OH and water, and then shaken with 50 ml 2·5M-HCl. The separated chloroform layer deposited on standing overnight 4·1 g (38%) dihydrochloride of *VIb*, m.p. 218–222°C with decomposition. Analytical sample, m.p. 219–221°C (95% ethanol–ether). For the analysis, *cf.* Table I. A sample of the salt was decomposed with NH_4OH, the oily base was isolated by extraction with ether and by complete evaporation of the solvent. It was used for recording the ^1H NMR spectrum: δ 6·80–7·60 (m, 12 H, ArH), 2·80–4·00 (m, 5 H, $ArCH_2CHAr$ and CH_2S), *c.* 2·50 (bm, 10 H, 5 CH_2N).

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REFERENCES

1. Jilek J. O., Pomykáček J., Metyšová J., Protiva M.: This Journal *36*, 2 226 (1971).
2. Šindelář K., Jílek J.O., Bártl V., Metyšová J., Kakáč B., Holubek J., Svátek E., Pomykáček J., Protiva M.: This Journal *41*, 910 (1976).
3. Jílek J. O., Červená I., Kopicová Z., Šindelář K., Svátek E., Metyšová J., Dlabač A., Pomykáček J., Protiva M.: This Journal *41*, 443 (1976).
4. Jílek J. O., Metyšová J., Protiva M.: This Journal *39*, 3 153 (1974).
5. Rajšner M., Svátek E., Metyšová J., Bartošová M., Mikšík F., Protiva M.: This Journal *42*, 3 079 (1977).
6. Jílek J. O., Svátek E., Metyšová J., Pomykáček J., Protiva M.: This Journal *32*, 3 186 (1967).
7. Jílek J. O., Metyšová J., Němec J., Šedivý Z., Pomykáček J., Protiva M.: This Journal *40*, 3 386 (1975).
8. Bártl V., Dlabač A., Protiva M.: This Journal *45*, 3 182 (1980).
9. Bártl V., Metyšová J., Protiva M.: This Journal *46*, 141 (1981).
10. Jílek J. O., Šindelář K., Rajšner M., Dlabač A., Metyšová J., Votava Z., Pomykáček J., Protiva M.: This Journal *40*, 2 887 (1975).
11. Aschwanden W., Kyburz E., Schönholzer P.: Helv. Chim. Acta *59*, 1 245 (1976).
12. Polívka Z., Ryska M., Holubek J., Svátek E., Metyš J., Protiva M.: This Journal *48*, 2 395 (1983).
13. Polívka Z., Holubek J., Metyš J., Šedivý Z., Protiva M.: This Journal *48*, 3 433 (1983).
14. Polívka Z., Holubek J., Svátek E., Metyš J., Protiva M.: This Journal *49*, 621 (1984).
15. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1 831 (1968).
16. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1 852 (1968).
17. Metyšová J., Metyš J., Dlabač A., Kazdová E., Valchář M.: Acta Biol. Med. Ger. *39*, 723 (1980).
18. Dlabač A., Metyš J., Metyšová J., Valchář M., Kazdová E.: Česk. Fysiol. *28*, 250 (1979).

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