2-CHLORO-7-FLUORO- AND 2-CHLORO-3,7-DIFLUORO--11-[4-(4-FLUOROARALKYL)PIPERAZINO]-10,11-DIHYDRODIBENZO-[*b*,*f*]THIEPINS AND RELATED COMPOUNDS; LONG ACTING TRANQUILLIZERS*

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Substitution reactions of 2,11-dichloro-7-fluoro- (series *a*) and 2,11-dichloro-3,7-difluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin (series *b*) with 1-(4-fluorobenzyl)piperazine, 1-[2-(4-fluorophenyl)-ethyl]piperazine, 1-[2-(4-fluorophenoxy)ethyl]piperazine, 1-[2-(4-fluorophenylthio)ethyl]piperazine, 1-[3-(4-fluorobenzoyl)propyl]piperazine and 1-[4,4-bis-(4-fluorophenyl)butyl]piperazine gave the title compounds *Ia,b*—*VIa,b*. Compounds of the series *a* are little toxic, have low cataleptic activity and display a relatively high central depressant activity, being fully developed only after 4 h and persisting until the 3rd—7th day after the oral administration. Compounds of series *b* are less active and the protracted depressant effects are shown only by substances *IIIb* and *Vb*.

In one of the recent communications of this series[1] we described the synthesis of six 2-chloro-11-[4-(4-fluoroaralkyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepins as potential tricyclic neuroleptics in the effort to estimate the influence of the *para*-fluorinated phenyl in the side chain on the activity and its duration. With the exception of the 4-[3-(4-fluorobenzoyl)propyl]piperazino derivative, these products did not reveal at all the neuroleptic character. In the present communication, we are describing the synthesis of similar substances in which we attempted to increase the intensity and duration of effect by introducing a fluorine atom into position 7 of the skeleton, or by a simultaneous fluorination in positions 3 and 7, *i.e.* substances *Ia*—*VIa* and *Ib*—*VIb*. The positive influence of fluorination in these positions in the analogous N-methyl and N-(hydroxyalkyl) derivatives was confirmed[2–4].

The acids *VIIa* (refs[2,3]) and *VIIb* (ref.[4]) were the starting products; they have now been prepared by reactions of (4-fluoro-2-iodophenyl)acetic acid[5] with 4-chlorothiophenol and 4-chloro-3-fluorothiophenol[6], respectively, in a boiling aqueous solution of potassium hydroxide and in the presence of a copper catalyst (for analogy, *cf.*[7]). Both acids were cyclized with polyphosphoric acid to ketones *VIIIa* and *VIIIb*. Using described methods, the ketones *VIIIa,b* were transformed in two-steps to 2,11-dichloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[2] and 2,11-di-

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TABLE I
Compound *Ia*—*VIa* and *Ib*—*VIb*

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found					
				% C	% H	% Cl	% F	% N	% S
Ia	*A-I* (49)	140—141·5[a] (acetone)	$C_{25}H_{23}ClF_2N_2S$ (457·0)	65·71 65·54	5·07 5·21	7·76 7·80	8·31 8·19	6·13 6·08	7·02 7·29
Ib	*A-I* (50)	153—156[b] (acetone)	$C_{25}H_{22}ClF_3N_2S$ (475·0)	63·22 63·81	4·67 4·84	7·47 7·71	12·00 11·50	5·90 5·90	6·75 7·27
Ib-M[c,d]		183—185 (ethanol)	$C_{29}H_{26}ClF_3N_2O_4S$ + 0·5 H_2O (600·1)	58·05 57·86	4·54 4·74	5·91 5·97	9·50 9·67	4·67 4·90	5·34 5·63
IIa-2M[e]	*A-I* (49)	150—152[f] (aqueous ethanol)	$C_{34}H_{33}ClF_2N_2O_8S$ (703·2)	58·08 58·12	4·79 5·06	5·04 5·17	5·40 5·21	3·98 4·06	4·56 4·71
IIb-A[g]	*A-I*[h] (66)	114—115 (cyclohexane–light petroleum)	$C_{26}H_{24}ClF_3N_2S$ (489·0)	63·86 64·07	4·95 5·11	7·25 7·33	11·66 11·94	5·73 5·71	6·56 6·66
IIb-B[i]		144—146 (cyclohexane–light petroleum)	$C_{26}H_{24}ClF_3N_2S$ (489·0)	63·86 63·82	4·95 4·90	7·25 7·31	11·66 11·86	5·73 5·78	6·56 6·78
IIIa-2 M[e]	*A-II*[h] (39)	148—149 (ethanol–ether)	$C_{34}H_{33}ClF_2N_2O_9S$ (719·2)	56·78 56·79	4·63 4·66	4·93 5·02	5·28 5·10	3·90 3·72	4·46 4·57
IIIb-M[c]	*A-I* (72)	181—184[j] (acetone)	$C_{30}H_{28}ClF_3N_2O_5S$ (621·1)	58·02 58·25	4·54 4·62	5·70 5·89	9·18 9·38	4·51 4·55	5·16 5·20
IVa-M[c]	*A-I* (41)	170—172[k] (ethanol)	$C_{30}H_{29}ClF_2N_2O_4S_2$ (619·2)	58·20 58·19	4·72 4·61	5·73 6·00	6·14 6·12	4·52 4·59	10·36 10·37
Vb-M[c]	*A-II* (48)	189—192[l] (acetone)	$C_{30}H_{28}ClF_3N_2O_4S_2$ (637·3)	56·55 56·41	4·43 4·33	5·56 5·86	8·95 9·69	4·40 4·48	10·06 10·20
IVa-M[c]	*A-I* (53)	169—173[m] (aqueous ethanol)	$C_{32}H_{31}ClF_2N_2O_5S$ (629·1)	61·09 61·21	4·97 5·16	5·64 5·80	6·04 5·77	4·45 4·42	5·10 5·11
Vb	*A-II* (57)	129—132[n] (cyclohexane)	$C_{28}H_{26}ClF_3N_2OS$ (531·0)	63·33 63·08	4·94 4·86	6·68 6·90	10·73 10·67	5·28 5·41	6·04 6·22
Vb-M[c]		181—183 (ethanol)	$C_{32}H_{30}ClF_3N_2O_5S$ (647·1)	59·39 60·00	4·67 5·12	5·48 5·25	8·81 8·58	4·33 4·77	4·95 4·93
VIa-2M[e]	*A-I* (38)	152—154[o] (ethanol–ether)	$C_{42}H_{40}ClF_3N_2O_8S$ (825·3)	61·12 61·21	4·89 4·98	4·30 4·10	6·91 6·98	3·39 3·43	3·89 3·82
VIb-2 M[e]	*A-II* (50)	161—163[p] (acetone–ether)	$C_{42}H_{39}ClF_4N_2O_8S$ (843·3)	59·82 59·86	4·66 4·84	4·20 4·40	9·01 9·20	3·32 3·40	3·80 4·08

chloro-3,7-difluoro-10,11-dihydrodibenzo[*b,f*]thiepin[4]. These chloro derivatives were processed by substitution reactions with 1-(4-fluorobenzyl)piperazine[1], 1-[2-(4-fluorophenyl)ethyl]piperazine[1], 1-[2-(4-fluorophenoxy)ethyl]piperazine[1], 1-[2-(4-fluorophenylthio)ethyl]piperazine[1], 1-[3-(4-fluorobenzoyl)propyl]piperazine[8] and 1-[4,4-bis(4-fluorophenyl)butyl]piperazine[1] (used in an excess of 100%) in boiling chloroform (method *A-I*); the products were the compounds *Ia,b*–*VIa,b* which, in some cases,

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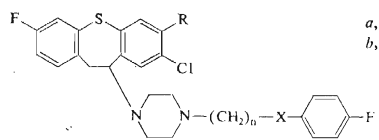
[a] ^{1}H-NMR spectrum: δ 7·60 (mcs, J = 2·5 Hz, 1 H, 1-H), 7·27 (d, J = 8·0 Hz, 1 H, 4-H), 6·70—7·20 (m, 8 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·40 (s, 2 H, $ArCH_2N$) 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine). [b] ^{1}H-NMR spectrum: δ 7·70 (d, J_{H-F} = 8·0 Hz, 1 H, 1-H), 6·70—7·40 (m, 8 H, remaining Ar—H), 3·00 to 4·00 (m, 3 H, $ArCH_2CHAr$), 3·45 (s, 2 H, $ArCH_2N$), 2·60 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine); ^{19}F-NMR spectrum: δ —116·4 (dt, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz, 1 F, 7-F), —116·6 (m, F of fluorophenyl), —118·6 (dd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·5 Hz, 3-F). [c] Maleate. [d] Hemihydrate. [e] Bis(hydrogen maleate). [f] ^{1}H-NMR spectrum of the base released from the pure salt: δ 7·64 (mcs, J = 2·5 Hz, 1 H, 1-H), 6·70—7·40 (m, 9 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), *c.* 2·55 (m, 12 H, 5 NCH_2 and $ArCH_2$). [g] Crystal modification *A*. [h] See Experimental. [i] Crystal modification B. [j] ^{1}H-NMR spectrum of the base released from the pure salt: δ 7·70 (d, J_{H-F} = 8·0 Hz, 1 H, 1-H), 6·70—7·30 (m, 8 H, remaining Ar—H), 4·05 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·78 (t, J = 6·0 Hz, 2 H, NCH_2 in the chain), 2·15 (bs, 8 H, 4 NCH_2 of piperazine). [k] ^{1}H-NMR spectrum of the base released from the pure salt: δ 7·62 (mcs, J = 2·5 Hz, 1 H, 1-H), 6·70—7·40 (m, 9 H, remaining Ar—H), 2·80—4·00 (m, 5 H, $ArCH_2CHAr$ and CH_2S), *c.* 2·55 (m, 10 H, 5 NCH_2); ^{19}F-NMR spectrum: δ —116·3 (m, F in fluorophenyl), —116·6 (dt, $J_{F(o-H)}$ = 9·0 Hz; $J_{F(m-H)}$ = 5·5 Hz, 7-F). [l] ^{1}H-NMR spectrum of the base released from the pure salt: δ 7·70 (d, J_{H-F} = 8·0 Hz, 1 H, 1-H), 6·70—7·50 (m, 8 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·00 (t, 2 H, CH_2S), 2·30—2·80 (m, 10 H, 5 NCH_2). [m] ^{1}H-NMR spectrum of the base released from the pure salt: δ 7·98 (m, 2 H, 2 Ar—H in the fluorophenyl adjacent to CO), 7·60 (mcs, J = 2·5 Hz, 1 H, 1-H), 6·70—7·40 (m, 7 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·92 (t, 2 H, CH_2CO), *c.* 2·55 (m, 10 H, 5 NCH_2), 1·95 (m, 2 H, CH_2 in the middle of the propane chain); ^{19}F-NMR spectrum: δ —106·5 (m, F in the fluorophenyl), —116·6 (dt, $J_{F(o-H)}$ = 9·0 Hz; $J_{F(m-H)}$ = 5·5 Hz, 7-F). [n] ^{1}H-NMR spectrum: δ 8·00 (m, 2 H, 2 Ar—H in the fluorophenyl adjacent to CO), 7·71 (d, J = 8·0 Hz, 1 H, 1-H), 7·16 (d, J = 10·0 Hz, 1 H, 4-H), 6·80—7·40 (m, 5 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·98 (t, J = = 7·0 Hz, 2 H, CH_2CO), 2·50 (m, 8 H, 4 NCH_2 of piperazine), 2·45 (t, J = 8·0 Hz, 2 H, NCH_2 in the chain), 2·00 (m, 2 H, CH_2 in the middle of the propane chain); ^{19}F-NMR spectrum: δ —106·5 (m, F in the fluorophenyl), —116·3 (dt, $J_{F(o-H)}$ = 8·0 Hz, $J_{F(m-H)}$ = 5·5 Hz, 7-F), —118·7 (dd, $J_{F(o-H)}$ = 8·5 Hz; $J_{F(m-H)}$ = 6·5 Hz, 3-F). [o] ^{1}H-NMR spectrum of the base released from the pure salt: δ 7·62 (mcs, J = 2·0 Hz, 1 H, 10-H), 6·80—7·40 (m, 13-H, remaining Ar—H), 3·00—4·00 (m, 4 H, $ArCH_2CHAr$ and Ar_2CH), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·38 (m, 6 H, remaining 3 NCH_2), 1·98 (m, 2 H, C^3H_2 in the butyl chain), 1·45 (m, 2 H, C^2H_2 in the butyl). [p] ^{1}H-NMR spectrum of the base released from the pure salt: δ 7·70 (d, J_{H-F} = 8·0 Hz, 1 H, 1-H), 6·70—7·40 (m, 8 H, remaining Ar—H in the tricycle and 4 Ar—H in 2,6,2′,6′-positions of benzhydryl), 6·90 (t, 4 H, 4 Ar—H in benzhydryl adjacent to F), 3·00 to 4·00 (m, 4 H, $ArCH_2CHAr$ and Ar_2CH), 2·60 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (m, 6 H, remaining 3 NCH_2), 2·00 (m, 2 H, C^3H_2 in the butyl chain), 1·40 (m, 2 H, C^2H_2 in the butyl).

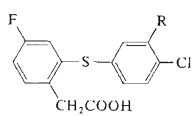
had to be separated from the starting monosubstituted piperazines by chromatography (method *A-II*). The final products are assembled in Table I with the experimental data.



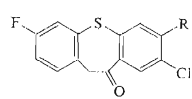
a, R = H
b, R = F

I, n = 1, X = –
II, n = 2, X = –
III, n = 2, X = O

IV, n = 2, X = S
V, n = 3, X = CO
VI, n = 3, X = CH—F



VII



VIII

The compounds *Ia,b*–*VIa,b* were pharmacologically evaluated as potential neuroleptics in the form of salts described in the Experimental and in Table I. Results are summarized in Table II; the doses given were calculated for bases. The Table II includes for comparison data on octoclothepin[9] and chlorpromazine. All compounds were administered orally. The acute toxicity was estimated in mice and is expressed as the usual LD_{50}. The Table II shows further the medium effective doses (ED_{50}) bringing about ataxia in the rotarod test in mice and the medium effective doses (ED_{50}) exhibiting catalepsy in rats. The new compounds are less toxic and less active than octoclothepin[9]. Compounds of the series *a* (7-fluoro derivatives) are more active than compounds of the series *b* (3,7-difluoro derivatives): the *p*-fluorophenethyl compound *IIa* and the *p*-fluorobenzoylpropyl compound *Va* are neuroleptics with strong tranquillizing and mild cataleptic (chlorpromazine-like) activity. Both activities show a high degree of prolongation; the incoordinating effect persists until the 4th-7th day after the administration, the catalepsy is still apparent after 48 – 72 h after the administration. Even the incoordinating effect of the less active compounds (*Ia*, *IIIa*, *IIIb*, *IVa*, *Vb*) is clearly protracted and lasts for 3–4 days. This is an important difference in comparison with octoclothepin[9], the effect of which disappears within the first 24 h.

The compounds were also tested for antimicrobial activity *in vitro* (Dr L. Langšádl and Dr J. Turinová, bacteriological department of this institute). The used microorganisms, numbers

of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Mycobacterium tuberculosis* H37Rv, *Ib* 50, *IIa* 6·25, *IIIa* 25, *IIIb* 50, *IVa* 100, *Va* 3·12, *Vb* 12·5, *VIa* 100; *Trichophyton mentagrophytes*, *Ib* 50, *IIa* 50, *IIIa* 50, *IVa* 50, *Va* 50, *VIa* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra were recorded with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra ($CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer and the ^{19}F-NMR spectra

TABLE II

Pharmacological Properties of Compounds *Ia,b—VIa,b*

Oral administration, doses in mg/kg, numbers in parentheses are percent of animals responding to the dose given.

Compound	Code number	Acute toxicity LD_{50}	Ataxia rotarod ED_{50} [a]	Catalepsy ED_{50}
Ia	VÚFB-12.430	>1 000 (10)	31 [b]	>100 [c]
Ib	VÚFB-12.483	>1 000 (40)	>100	>100
IIa	VÚFB-12.431	340	< 10 (60 [d])	15 [e]
IIb	VÚFB-12.484	[f]	>100	>100
IIIa	VÚFB-12·432	370	6·5 [g]	>100 [c]
IIIb	VÚFB-12·485	[f]	35 [b]	>100
IVa	VÚFB-12.433	660	24·5 [h]	>100 [c]
IVb	VÚFB-12.486	[f]	>100	>100
Va	VÚFB-12.434	410	5·4 [i]	19 [j]
Vb	VÚFB-12.487	[f]	88 [k]	>100
VIa	VÚFB-12.435	>1 000 (0)	>100 (4)	>100 [c]
VIb	VÚFB-12.488	>1 000 (0)	>100	>100
Octoclothepin[9]		78	2·2	4·3
Chlorpromazine		198	8·2	16

[a] The data given refer to the maximum activity in the interval of 3—4 h after the administration. [b] The effect of a dose of 100 mg/kg persits until the 3rd day after the administration. [c] This dose brings about a strong depression persisting over 24 h. [d] The effect of a dose of 100 mg/kg persists until the 7th day after the administration. [e] After 24 h, ED_{50} = 36 mg/kg; after 48 h and a dose of 100 mg/kg, 20% animals are still in the cataleptic state. [f] Not estimated. [g] The effect of a dose of 50 mg/kg persists until the 4th day after the administration. [h] The effect of a dose of 100 mg/kg persists until the 4th day after the administration. [i] The effect of a dose of 25 mg/kg persists until the 4th day after the administration. [j] After 24 h, ED_{50} = 85 mg/kg; after 48 h 100 mg/kg; after 72 h >100 mg/kg (30%). [k] After 24 h, ED_{50} = 130 mg/kg; the effect persists until the 4th day after the administration.

(in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol). The column chromatography was carried out on neutral alumina (activity II).

[2-(4-Chlorophenylthio)-4-fluorophenyl]acetic Acid (*VIIa*)

A solution of 22·0 g 4-chlorothiophenol, 38·4 g (4-fluoro-2-iodophenyl)acetic acid[5] and 20 g KOH in 300 ml water was treated with 1·5 g Cu and refluxed for 12 h. The warm solution was filtered, acidified with hydrochloric acid and extracted with benzene. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue crystallized from a mixture of benzene and light petroleum; 29·3 g (73%), m.p. 118—123°C. A sample was recrystallized from aqueous ethanol, m.p. 121—124°C (lit[2], m.p. 124—125°C).

[2-(4-Chloro-3-fluorophenylthio)-4-fluorophenyl]acetic Acid (*VIIb*)

A mixture of 52·0 g (4-fluoro-2-iodophenyl)acetic acid[5], 35·0 g 4-chloro-3-fluorothiophenol[6], 52 g 85% KOH, 400 ml water and 1·0 g Cu was refluxed for 12 h, filtered, the filtrate acidified with hydrochloric acid and extracted with dichloromethane. Processing of the extract and crystallization of the residue from cyclohexane gave 38·6 g (66%) crude *VIIb*, m.p. 83—87°C. Analytical sample, m.p. 84—88°C (cyclohexane). IR spectrum (Nujol): 810, 831, 867, 883, 903 (2 adjacent and solitary Ar—H), 932, 1239, 1700, 2553, 2665, 2745 (COOH), 1488, 1579, 1600, 1610, 3083, 3092, 3110 cm^{-1} (Ar). For $C_{14}H_9ClF_2O_2S$ (314·7) calculated: 53·43% C, 2·88% H, 11·26% Cl, 12·07% F, 10·17% S; found: 53·58% C, 2·92% H, 11·70% Cl, 12·41% F, 10·44% S. The literature[4] described a different procedure and the product was not characterized.

8-Chloro-3,7-difluorodibenzo[*b,f*]thiepin-10(11*H*)-one (*VIIIb*)

A mixture of 38·6 g *VIIb* and 250 g polyphosphoric acid was stirred and heated for 8 h to 120 to 130°C. After cooling it was decomposed with 1 kg ice and water and extracted with benzene. The extract was washed with 5% NaOH and water, dried ($MgSO_4$) and evaporated; 32·3 g (88%), m.p. 129—133°C (lit.[4], m.p. 131—133°C).

2-Chloro-3,7-difluoro-11-[4-(2-[4-fluorophenyl]ethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IIb*) (Method *A*—*I*)

A mixture of 5·0 g 2,11-dichloro-3,7-difluoro-10,11-dihydrodibenzo[*b,f*]thiepin[4], 8·5 g 1-[2-(4-fluorophenyl)ethyl]piperazine[1] and 10 ml chloroform was stirred and refluxed for 8 h. It was then diluted with chloroform, washed with 10% NaOH, the organic solution was dried with K_2CO_3 and evaporated. The residue was dissolved in ether and the solution treated with a slight excess of anhydrous HCl in ether. The precipitated hydrochloride was filtered, suspended in warm water, filtered after cooling, decomposed with 20% NaOH and extracted with ether. Processing of the extract gave 5·1 g (66%) base crystallizing from ethanol. For analysis, the sample was crystallized from a mixture of cyclohexane and light petroleum, modification *A*, m.p. 114—115°C. IR spectrum (KBr): 770, 822, 870, 900 (2 adjacent and solitary Ar—H), 1236, 1240 (Ar—F), 1480, 1492, 1512, 1535, 1600, 3050, 3073 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·70 (d, J_{H-F} =, = 8·0 Hz, 1 H, 1-H), 6·70—7·30 (m, 8 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·30—2·90 (m, 12 H, 5 NCH_2 and $ArCH_2$). ^{19}F-NMR spectrum: δ —116·3 (dt, $J_{F(o-H)}$ = 8·0 Hz; $J_{F(m-H)}$ = 5·5 Hz, 7-F), —118·0 (m, F in fluorophenyl), —118·6 (dd, $J_{F(o-H)}$ = 8·5 Hz $J_{F(m-H)}$ = 6·5 Hz, 3-F). Crystallization of another sample from a mixture of cyclohexane

and light petroleum and standing for 2 days led to modification *B*, m.p. 144—146°C. The IR spectrum (KBr) shows differences in comparison with that of modification A: 770, 820, 861, 874 (2 adjacent and solitary Ar-—H), 1219, 1236 (Ar—F), 1472, 1490, 1512, 1581, 1599, 3045, 3073 cm^{-1} (Ar). In CCl_4, the IR spectra of both modifications are identical. Analyses in Table I.

2-Chloro-7-fluoro-11-[4-(2-[4-fluorophenoxy]ethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IIIa*) (Method *A*—*II*)

A mixture of 3·0 g 2,11-dichloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[2], 4·5 g 1-[2-(4-fluorophenoxy)ethyl]piperazine[1] and 5 ml chloroform was stirred and heated under reflux to 70°C for 8 h. It was diluted with chloroform and shaken with a saturated solution of K_2CO_3. The organic layer was washed with water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was chromatographed on a column of 250 g alumina. Elution with light petroleum removed the least polar components. Elution with benzene gave 1·9 g (39%) homogeneous oily base. Neutralization with 1·0 g maleic acid in ethanol gave 2·1 g bis(hydrogen maleate), m.p. 148—149°(ethanol–ether). Decomposition of a sample with NH_4OH and extraction with ether gave pure oily base *IIIa*, used for recording the spectra. ^{1}H-NMR spectrum: δ 7·60 (mcs, J = = 2·5 Hz, 1 H, 1-H), 6·70—7·40 (m, 9 H, remaining Ar—H), 4·00 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·78 (t, J = 6·0 Hz, 2 H, NCH_2 in the chain), 2·60 (m, 8 H, 4 NCH_2 of piperazine). ^{19}F-NMR spectrum: δ —116·6 (dt, $J_{F(o-H)}$ = 9·0 Hz, $J_{F(m-H)}$ = = 5·5 Hz, 7-F), —124·6 (m, F in fluorophenyl). Analysis in Table I.

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