TRICYCLIC POTENTIAL NEUROLEPTICS: 2-CHLORO-11-[4-(4-FLUOROARALKYL)PIPERAZINO]--10,11-DIHYDRODIBENZO[*b,f*]THIEPINS AND RELATED COMPOUNDS*

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Alkylation of 1-ethoxycarbonylpiperazine with 4-fluorobenzyl bromide, 2-(4-fluorophenyl)ethyl bromide and 4,4-bis(4-fluorophenyl)butyl bromide gave the carbamates *IIa*, *IIb* and *IIf*. Two further similar compounds (*IIc*, *IId*) were obtained by reactions of 1-(2-chloroethyl)-4-ethoxycarbonylpiperazine with 4-fluorophenol, and with 4-fluorothiophenol, respectively. Hydrolysis of carbamates *IIa—f* resulted in piperazine derivatives *IIIa—f* affording the title compounds by substitution reactions with 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin. Out of the compounds prepared only the fluorophenethyl derivative *Ib* and the fluorobenzoylpropyl derivative *Ie* maintain the neuroleptic character, *i.e.* clear central depressant and cataleptic activity.

In the series of analogues of the neuroleptic agent octoclothepin[1,2], *i.e.* 2-chloro--11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]-thiepin, relatively little attention was paid to the N-aralkyl analogues (N-methyl substituted by N-aralkyl). The investigated compounds of this type include the N-benzyl[1], N-(4-methoxybenzyl)[3], some N-(2-arylethyl)[4] and N-(3-phenylpropyl) analogues[4]. A mild degree of neuroleptic activity was preserved only by the 4-methoxybenzyl derivative[3] and the 2-arylethyl derivatives[4]. The experimental work described now started from our efforts to determine the influence of fluorination in the aromatic nuclei of neuroleptics of the 10-piperazinodibenzo[*b,f*]thiepin series on activity; whereas the effect of fluorination in aromatic nuclei of the tricyclic skeleton was rather thoroughly investigated[5], the effect of fluorination in the benzene nucleus in the side chain has been practically unknown. The N-[3-(4-fluorobenzoyl)propyl]derivative of 2-methylthio-11-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[4], representing a structural combination of an ω-amino-4-fluorobutyrophenone type of neuroleptic and a tricyclic neuroleptic of our series, was the only exception in this area showing a chlorpromazine--like cataleptic activity with negligible central depressant effects. The present paper describes the synthesis of six title compounds *Ia – f*.

2,11-Dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1] was a common intermediate in the synthesis of compounds *Ia – f* which was processed by substitution reactions

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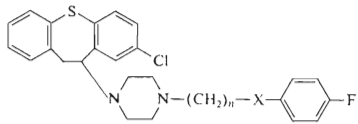
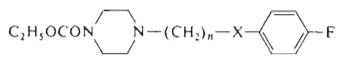
with piperazine derivatives *IIIa – f*. Out of these compounds, the literature mentioned 1-[3-(4-fluorobenzoyl)propyl]piperazine (*IIIe*) (ref.[6]) and 1-[4,4-bis(4-fluorophenyl)-butyl]piperazine (*IIIf*) (ref.[7]). In our work we used in the first case (*IIIe*) the described procedure[6] but in the second case (*IIIf*) we proceeded independently. In general, the N-ethoxycarbonyl derivatives *II* were used as precursors of compounds *III*.



I



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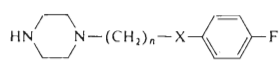

III

a, $n = 1$, X = —
b, $n = 2$, X = —
c, $n = 2$, X = O
d, $n = 2$, X = S
e, $n = 3$, X = CO
f, $n = 3$, X = 

Three of them (*IIa, IIb, IIf*) were obtained by alkylations of 1-ethoxycarbonylpiperazine with 4-fluorobenzyl bromide[8], 2-(4-fluorophenyl)ethyl bromide[9] and 4,4-bis-(4-fluorophenyl)butyl bromide[10]. The remaining two carbamates (*IIc, IId*) were prepared by condensation reactions of 1-(2-chloroethyl)-4-ethoxycarbonylpiperazine[11] with 4-fluorophenol[12] and 4-fluorothiophenol[13] in acetone in the presence of potassium carbonate. 4-Fluorophenol was obtained by demethylation of 4-fluoroanisol[14] by heating with pyridine hydrochloride. The carbamates *IIa – d* and *IIf* were transformed to the monosubstituted piperazines *IIIa – d* and *IIIf* by hydrolysis with 50% potassium hydroxide in ethanol. The final substitution reactions of 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1] with piperazine derivatives *IIIa – f* were carried out in boiling chloroform using a 100% excess of the piperidine derivatives.

The prepared compounds *Ia – f* were pharmacologically evaluated as potential neuroleptics in the form of salts described in the Experimental. Results are summarized in Table I; the doses given were calculated for bases. The Table includes for comparison data on octoclothepin[2] and chlorpromazine. The new compounds are very little toxic so that the medium lethal doses (LD_{50}) for mice are higher than 1 g/kg. The Table shows 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. All compounds were administered orally. It is apparent that the new compounds *Ia – f* are at least 10 times less active than octoclothepin in the test of ataxia and a similar relation exists also in the test of catalepsy. The neuroleptic character is maintained virtually only with the 4-fluorophenethyl compound *Ib* and the 4-fluorobenzoylpropyl compound *Ie*. Only in these two cases the ED_{50} in the test of catalepsy could be estimated. All of the compounds *Ia – f* were inactive in the test of antiapomorphine activity in rats: a dose of 50 mg/kg orally did influence neither the apomorphine stereotypies (chewing), nor the agitation. In comparison with the nonfluorinated analogues[1,3,4], the fluorinated ones *Ia – f* did not show any improvement of the pharmacological profile.

Some of the compounds were also tested for antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this institute). The used microorganisms, numbers of compounds and the minimum inhibitory concentrations (unless they exceed 100 μg/ml) are given: *Mycobacterium tuberculosis* H37Rv, *Ib* 25, *Ic* 50, *Ie* 50; *Saccharomyces pasterianus*. *Ic* 50, *Ie* 50, *If* 50; *Trichophyton mentagrophytes*, *Ib* 50, *Ic* 50, *Ie* 50, *If* 50.

TABLE I

Pharmacological Properties of Compounds *Ia—f*

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}	Catalepsy ED_{50}
Ia	VÚFB-12.331	>1 000 (20)	>200 (30)	>50 (20)
Ib	VÚFB-12.332	>1 000 (0)	61	56
Ic	VÚFB-12.333	>1 000 (20)	43	>20 (10)
Id	VÚFB-12.334	>1 000 (20)	90	>20 (10)
Ie	VÚFB-12·335	>1 000 (40)	25	36
If	VÚFB-12.336	>1 000 (20)	>200 (20)	>50 (0)
Octoclothepin[2]		78	2·2	4·3
Chlorpromazine		198	8·2	16

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 UV spectrum was recorded with a Unicam SP 8000 spectrophotometer, the IR spectrum with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra with a Tesla BS 487C (80 MHz) spectrometer, ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument, and the mass spectra with the MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

4-Fluorophenol

Pyridine hydrochloride (prepared from 173 g pyridine) was heated with 47 g 4-fluoroanisole[14] for 10 h to 200°C (under reflux). The melt was diluted with 250 ml water, treated with 100 ml hydrochloric acid and the mixture extracted with ether. The extract was shaken with 400 ml 10% NaOH, the alkaline solution was separated, acidified with hydrochloric acid and extracted with ether. The extract was dried with $MgSO_4$ and distilled; 38·2 g (92%), b.p. 83°C/2·0 kPa, m.p. 44—46°C. The literature[12] reported the b.p. of 185°C and the m.p. of 48°C.

1-Ethoxycarbonyl-4-(4-fluorobenzyl)piperazine (*IIa*)

1-Ethoxycarbonylpiperazine (73·5 g) was stirred and treated under cooling over 30 min with 44·0 g 4-fluorobenzyl bromide[8], added dropwise. The mixture was stirred for 2 h at 90°C, cooled and diluted with 250 ml benzene. The solution was washed with water and extracted with 60 ml 1 : 1 dilute hydrochloric acid. The aqueous layer was separated, made alkaline with NH_4OH and extracted with benzene. The extract was washed with saturated NaCl, dried with K_2CO_3 and evaporated; 61·2 g (99%) crude *IIa*. A sample was distilled, b.p. 184°C/0·33 kPa; For $C_{14}H_{19}FN_2O_2$ (266·3) calculated: 63·14% C, 7·19% H, 10·52% N; found: 62·64% C, 7·49% H, 11·16% N.

Hydrobromide, m.p. 207—208°C (acetone). For $C_{14}H_{20}BrFN_2O_2$ (347·2) calculated: 48·43% C, 5·80% H, 5·47% F, 8·07% N; found: 48·63% C, 5·90% H, 5·20% F, 8·36% N.

1-Ethoxycarbonyl-4-[2-(4-fluorophenyl)ethyl]piperazine (*IIb*)

A mixture of 90 g 1-ethoxycarbonylpiperazine and 46·7 g 2-(4-fluorophenyl)ethyl bromide[9] was allowed to stand overnight at room temperature and then heated to 110°C for 1 h under stirring. After cooling the mixture was diluted with 250 ml benzene and washed with water. The organic layer was shaken with 200 ml 10% hydrochloric acid, the precipitated hydrochloride was filtered, decomposed with NH_4OH and the base isolated by extraction with benzene; 50·3 g (79%). A sample was distilled, b.p. 198°C/0·4 kPa. For $C_{15}H_{21}FN_2O_2$ (280·3) calculated: 64·26% C, 7·55% H, 6·78% F, 9·99% N; found: 65·17% C, 7·96% H, 6·45% F, 10·24% N.

1-Ethoxycarbonyl-4-[2-(4-fluorophenylthio)ethyl]piperazine (*IId*)

A mixture of 12·8 g 4-fluorothiophenol[13], 25·7 g 1-(2-chloroethyl)-4-ethoxycarbonylpiperazine hydrochloride[11], 20 g K_2CO_3 and 200 ml acetone was srtirred and refluxed for 13 h. After cooling the solid was filtered and washed with acetone, the filtrate evaporated, the residue dissolved in ether and the solution extracted with dilute hydrochloric acid. The aqueous layer was made alkaline with NH_4OH and the base isolated by extraction with ether; 26·4 g (85%) crude *IId*.

A sample was distilled, b.p. 205°C/0·27 kPa. For $C_{15}H_{21}FN_2O_2S$ (312·4) calculated: 57·67% C, 6·77% H, 8·97% N; found: 56·78% C, 7·04% H, 9·34% N.

1-(4-Fluorobenzyl)piperazine (*IIIa*)

A mixture of 61·2 g crude *IIa*, 70 g KOH and 75 ml ethanol was stirred and refluxed for 3 h in a bath of 120°C. After cooling it was diluted with 100 ml water and extracted with benzene. The extract was dried with K_2CO_3 and distilled; 32·0 g (72%), b.p. 108°C/0·31 kPa. The distillate crystallized on standing, m.p. 64—65°C (light petroleum). For $C_{11}H_{15}FN_2$ (194·3) calculated: 68·02% C, 7·78% H, 9·78% F, 14·42% N; found: 67·63% C, 7·88% H, 9·58% F, 14·31% N.

Bis(hydrogen maleate), m.p. 167—168°C (water). For $C_{19}H_{23}FN_2O_8$ (426·4) calculated: 53·52% C, 5·44% H, 4·45% F, 6·57% N; found: 52·95% C, 5·55% H, 4·23% F, 6·64% N.

Dimethanesulfonate monohydrate, m.p. 202—204°C (ethanol). For $C_{13}H_{23}FN_2O_6S_2 + H_2O$ (404·5) calculated: 38·60% C, 6·23% H, 4·70% F, 6·93% N, 15·85% S; found: 39·04% C, 5·99% H, 4·66% F, 6·76% N, 15·45% S.

1-[2-(4-Fluorophenyl)ethyl]piperazine (*IIIb*)

A mixture of 48·6 g crude *IIb*, 50 g KOH and 50 ml ethanol was refluxed for 3 h (bath of 120°C) and processed similarly like in the preceding case; 21·5 g (60%), b.p. 135—145°C/0·4 kPa. For analysis a sample was redistilled, b.p. 142°C/0·4 kPa. For $C_{12}H_{17}FN_2$ (208·3) calculated: 69·20% C, 8·23% H, 9·12% F, 13·45% N; found: 69·01% C, 8·48% H, 9·01% F, 13·53% N.

Bis(hydrogen maleate), m.p. 154—156°C (ethanol). For $C_{20}H_{25}FN_2O_8$ (440·4) calculated: 54·54% C, 5·72% H, 4·31% F, 6·36% N; found: 54·51% C, 5·72% H, 4·04% F, 5·88% N.

Bis(hydrogen maleate) hemihydrate, m.p. 164·5—166·5°C (ethanol). For $C_{20}H_{25}FN_2O_8 +$ + 0·5 H_2O (449·4) calculated: 53·45% C, 5·83% H, 4·23% F, 6·23% N; found: 53·65% C, 6 02% H, 3·90% F, 6·23% N.

1-[2-(4-Fluorophenoxy)ethyl]piperazine (*IIIc*)

A mixture of 8·0 g 4-fluorophenol, 18·4 g 1-(2-chloroethyl)-4-ethoxycarbonylpiperazine hydrochloride[11], 12 g K_2CO_3 and 150 ml acetone was stirred and refluxed for 7 h. After cooling the solid was filtered and washed with acetone, the filtrate was evaporated, the residue was dissolved in ether, the solution was washed with 5% NaOH and water, dried with K_2CO_3 and evaporated. The residue (14·4 g crude *IIc*) was treated with 16 g KOH and 16 ml ethanol and the mixture stirred and refluxed for 4 h (bath of 120°C). Similar processing like in the preceding cases gave 9·0 g (56%) base, b.p. 125—127°C/0·17 kPa. The analytical sample was redistilled, b.p. 125°C : : 0·17 kPa. Fro $C_{12}H_{17}FN_2O$ (224·3) calculated: 8·47% F, 12·49% N; found: 7·78% F, 12·12% N.

Bis(hydrogen maleate), m.p. 152—154°C (ethanol). For $C_{20}H_{25}FN_2O_9$ (456·4) calculated: 52·63% C, 5·52% H, 4·16% F, 6·14% N; found: 52·19% C, 5·58% H, 3·77% F, 5·86% N.

1-[2-(4-Fluorophenylthio)ethyl]piperazine (*IIId*)

A mixture of 5·0 g *IId*, 5·0 g KOH and 5 ml ethanol was heated for 3 h to 110°C and processed similarly like in the preceding cases. The crude base was dissolved in 30 ml ethanol and the solution was neutralized with 4·4 g maleic acid in 10 ml ethanol; 7·0 g (91%) bis(hydrogen maleate) hemihydrate, m.p. 143—145°C (ethanol). For $C_{20}H_{25}FN_2O_8S + 0·5\ H_2O$ (481·5) calculated: 49·89% C, 5·44% H, 3·95% F, 5·82% N, 6·66% S; found: 49·48% C, 5·35% H, 3·30% F, 5·66% N,

6·29% S. Decomposition of this salt with NH_4OH and extraction with ether gave the purified base *IIId* which was used for further work.

1-[4,4-Bis(4-fluorophenyl)butyl]piperazine (*IIIf*)

A mixture of 30 g 4,4-bis(4-fluorophenyl)butyl bromide[10] and 44 g 1-ethoxycarbonylpiperazine was heated for 6 h to 120°C. After cooling it was diluted with 250 ml benzene and washed with water. The benzene layer was extracted with 5% hydrochloric acid, the aqueous layer with the oily hydrochloride was made alkaline with NH_4OH and extracted with benzene. Processing of the extract gave 37·1 g (100%) crude *IIf* which was heated for 2·5 h with 35 g KOH and 35 ml ethanol to 120°C. The melt was diluted with water and the product extracted with benzene. The extract was dried with K_2CO_3 and evaporated; 18·1 g (60%) crude *IIIf*, m.p. 42—51°C. A sample of the base was transformed to the dihydrochloride, m.p. 174—180°C (ether). The literature[7] reported for the dihydrochloride of *IIIf*, prepared differently, a m.p. of 175—180°C.

Bis(hydrogen maleate), m.p. 166—168°C (ethanol). For $C_{28}H_{32}F_2N_2O_8$ (562·6) calculated: 59·78% C, 5·73% H, 6·76% F, 4·98% N; found: 60·65% C, 5·73% H, 6·56% F, 5·13% N.

2-Chloro-11-[4-(4-fluorobenzyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Ia*)

A mixture of 8·0 g *IIIa*, 5·6 g 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1] and 10 ml chloroform was refluxed for 8 h, cooled, decomposed with 50 ml water and extracted with benzene. The extract was shaken with 1 : 1 dilute hydrochloric acid, the solid hydrochloride was filtered, decomposed with 20% NaOH and the base extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The oily residue (7·1 g) was dissolved in 50 ml ethanol and the solution was neutralized with 3 ml methanesulfonic acid in 50 ml ether. Crystallization gave 6·6 g (50%) dimethanesulfonate dihydrate, m.p. 197—200°C (ethanol). For $C_{27}H_{32}Cl.FN_2O_6S_3 + 2\,H_2O$ (667·3) calculated: 48·60% C, 5·44% H, 5·31% Cl, 2·85% F, 4·20% N, 14·42% S; found: 49·06% C, 5·23% H, 5·26% Cl, 3·35% F, 4·27% N, 14·60% S.

Decomposition of the salt with NH_4OH and extraction with ether gave the base, m.p. 116 to 118°C (n-hexane). ^{1}H-NMR spectrum ($CDCl_3$): δ 7·65 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·45 (mcd, 1 H, 6-H), 7·30 (d, J = 8·0 Hz, 1 H, 4-H), 6·70—7·30 (m, 8 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·40 (s, 2 H, $ArCH_2N$), 2·62 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·45 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine). ^{19}F-NMR spectrum: δ —116·5 (m). For $C_{25}H_{24}.ClFN_2S$ (439·0) calculated: 68·40% C, 5·51% H, 8·08% Cl, 4·33% F, 6·38% N, 7·30% S; found: 68·65% C, 5·57% H, 8·01% Cl, 4·10% F, 6·26% N, 7·20% S.

2-Chloro-11-[4-(2-[4-fluorophenyl]ethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Ib*)

A mixture of 6·3 g 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1], 10·5 g *IIIb* and 10 ml chloroform was refluxed for 6 h. After cooling it was decomposed with water and extracted with benzene. The extract was washed with water, filtered with charcoal and evaporated. The residue was dissolved in ether and the hydrochloride was precipitated by treatment with a slight excess of a solution of HCl in ether. It was filtered, dried *in vacuo*, heated with 100 ml water, cooled and filtered again. Decomposition with NH_4OH and extraction with benzene gave 4·8 g (47%) base, m.p. 110—112°C (n-hexane). ^{1}H-NMR spectrum ($CDCl_3$): δ 7·70 (mcs, J = 2·5 Hz, 1 H, 1-H), 7·50 (mcd, 1 H, 6-H), 7·35 (d, J = 8·0 Hz, 1 H, 4-H), 6·80—7·30 (m, 8 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), *c.* 2·60 (m, 12 H, remaining 6 CH_2). ^{19}F-NMR spectrum: δ —117·9 (m), For $C_{26}H_{26}ClFN_2S$ (453·0) calculated: 68·93% C, 5·78% H, 7·83% Cl, 4·19% F, 6·18% N, 7·08% S; found: 69·07% C, 5·81% H, 7·64% Cl, 3·91% F, 6·04% N, 7·10% S.

2-Chloro-11-[4-(2-[4-fluorophenoxy]ethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Ic*)

A mixture of 7·0 g 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1], 12·4 g *IIIc* and 15 ml chloroform was refluxed for 8 h and processed similarly like in the preceding case; 7·0 g (60%) oily base. ^{1}H-NMR spectrum ($CDCl_3$): δ 7·62 (mcs, J = 2·5 Hz, 1 H, 1-H), 6·70—7·50 (m, 10H, remaining Ar—H), 4·00 (t, J = 7·0 Hz, 2 H, OCH_2), 3·00—3·90 (m, 3 H, $ArCH_2CHAr$), 2·75 (t, J = 7·0 Hz, 2 H, NCH_2 in the chain), 2·60 (m, 8 H, 4 NCH_2 of piperazine).

Bis(hydrogen maleate), m.p. 160—163°C (ethanol). For $C_{34}H_{34}ClFN_2O_9S$ (701·2) calculated: 58·24% C, 4·89% H, 5·06% Cl, 2·71% F, 4·00% N, 4·58% S; found: 58·29% C, 4·86% H, 5·14% Cl, 2·79% F, 3·90% N, 4·76% S.

2-Chloro-11-[4-(2-[4-fluorophenylthio]ethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Id*)

A mixture of 3·9 g 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1], 6·5 g *IIId* and 10 ml chloroform was refluxed for 8 h and processed similarly like in the preceding cases; 3·6 g (54%) crude oily base. Bis(hydrogen maleate), m.p. 147—150°C (ethanol). Mass spectrum, *m/e*: 484·1 230 (M^+ corresponding to $C_{26}H_{26}ClFN_2S_2$), 357, 343, 245. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·80—7·50 (m, 11 H, Ar—H), 3·40—4·20 (m, 3 H, $ArCH_2CHAr$), 2·40—3·30 (m, 12 H, 5 NCH_2 and SCH_2). For $C_{34}H_{34}ClFN_2O_8S_2$ (717·2) calculated: 56·94% C, 4·78% H, 4·94% Cl, 2·65% F, 3·91% N, 8·94% S; found: 56·80% C, 4·91% H, 4·94% Cl, 2·66% F, 4·01% N, 8·82% S.

2-Chloro-11-[4-(3-[4-fluorobenzoyl]propyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Ie*)

A mixture of 7·0 g 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1], 14·7 g *IIIe* (ref.[6]) and 15 ml chloroform was processed similarly like in the preceding cases; 9·2 g (63%) dihydrochloride hydrate, m.p. 169—172°C (95% ethanol). Mass spectrum, *m/e*: 494·1 594 (M^+ corresponding to $C_{28}H_{28}ClFN_2OS$), 245, 165, 123. UV spectrum (methanol): λ_{max} 242·5 nm (log ε 4·26), infl. 264 nm (4·01). IR spectrum (Nujol): 727, 740, 751, 819, 826, 890 (4 and 2 adjacent and solitary Ar—H), 1 109, 1 212, 1 229 (C—F, C—N and CO), 1 377 (C—H in CH_2CO), 1 505, 1 597 (Ar), 1 689 (ArCO), 2 410 (NH^+), 3 420 cm^{-1} (H_2O). For $C_{20}H_{30}Cl_3FN_2OS + H_2O$ (586·0) calculated: 57·39% C, 5·50% H, 18·15% Cl, 3·24% F, 4·78% N, 5·47% S; found: 57·00% C, 5·23% H, 17·94% Cl, 3·23% F, 4·97% N, 5·97% S.

2-Chloro-11-[4-(4,4-bis[4-fluorophenyl]butyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*If*)

A mixture of 2·6 g 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1], 6·3 g *IIIf* and 10 ml chloroform was refluxed for 8 h, diluted with benzene and washed with water. It was dried with K_2CO_3, filtered with charcoal and evaporated. The residue (7·0 g) was chromatographed on a column of 250 g neutral Al_2O_3 (activity II). Elution with benzene gave 2·2 g (40%) homogeneous oily base. Bis(hydrogen maleate), m.p. 144—146°C (ethanol). For $C_{42}H_{41}ClF_2N_2O_8S$ (807·3) calculated: 62·49% C, 5·12% H, 4·39% Cl, 4·71% F, 3·47% N, 3·97% S; found: 62·36% C, 5·16% H, 4·31% Cl, 4·75% F, 3·61% N, 4·11% S.

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