TRICYCLIC ANALOGUES OF THE ANTIALLERGIC AGENT OXATOMIDE: 1-(3-(4-(10,11-DIHYDRO-5*H*-DIBENZO[*a*, *d*]-CYCLOHEPTENE-5-YL)-1-PIPERAZINYL)PROPYL)-1,3-DIHYDRO-2*H*--BENZIMIDAZOL-2-ONE AND THE RELATED 6,11-DIHYDRODIBENZO-[*b*, *e*]THIEPIN, 4,9-DIHYDROTHIENO[2,3-*c*]-2-BENZOTHIEPIN, AND 10,11-DIHYDRODIBENZO[*b*, *f*]THIEPIN DERIVATIVES

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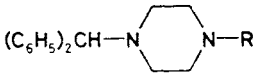
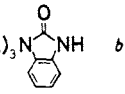
11-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin and its 2-methyl derivative *VI* were transformed via the 11-(4-(ethoxycarbonyl)-1-piperazinyl) compounds *IVc* and *Vc* to 11-(1-piperazinyl) compounds *IVb* and *Vb*. Their reactions with 1-(3-chloropropyl)-1,3-dihydro-2*H*-benzimidazol--2-one (*II*) afforded the title compounds *IVa* and *IVb*. Similar reactions and sequences in the series of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin, and 10,11-dihydrodibenzo[*b*,*f*]thiepin led to further oxatomide (*Ia*) analogues *IIIa* and *VIIa*—*XIa*. In the test of passive cutaneous anaphylaxis in rats, compound *VIIIa* was more active than *Ia*, and *IVa* had similar activity like *Ia*.

1-(3-(4-Benzhydryl-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*Ia*) (oxatomide) was developed by the Janssen group[1,2] as a potent inhibitor of allergic and anaphylactic reactions which found practical use especially in the treatment of chronic urticaria and allergic rhinitis[3–5]. Its structure, containing the benzhydryl-piperazine fragment, attracted our attention in connection with the known and pharmacologically active tricyclic piperazine derivatives whose molecules contain the skeletons, named in the title[6,7]. The present paper is devoted to the description of syntheses of these compounds and brings also some data on their pharmacology.

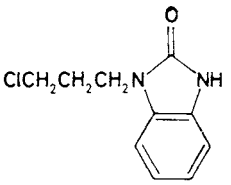


I

In formulae *I*, *III*–*V*, and *VII*–*XI*: *a*, R =  *b*, R = H

c, R = $COOC_2H_5$ *d*, R = $CH(C_6H_5)_2$

The synthesis of the common intermediate, i.e. *II*, was mentioned in patents[1,8] and in a recent article[9] but was not described with experimental details and the compound was not characterized. The procedure used here, consisting in alkylation of 1-(2-propenyl)-1,3-dihydro-2*H*-benzimidazol-2-one[10,11], metallated with sodium ethoxide, with 1-bromo-3-chloropropane and in the following hydrolysis with dilute sulfuric acid (for analogy, cf. ref.[12]), is described in the Experimental and the product was characterized by spectra. Only after the termination of our work, the synthesis (different method) and characterization of *II* have been described in a recent article[13]. A sample of *Ia* was needed as the standard for comparison with our products and was, therefore, synthesized. The synthesis of *Ia* was described in the mentioned patents[1], in some more recent ones[14–16], as well as in the mentioned recent article[13]. Conditions used in our work were different from those described and are disclosed in the Experimental. 1-(Ethoxycarbonyl)piperazine was treated with benzhydryl bromide[17] in boiling chloroform in the presence of sodium carbonate and gave 90% *Ic* (cf. ref.[18]). The following hydrolysis with 50% ethanolic potassium hydroxide at the boiling point of the mixture afforded 88% *Ib* (cf. refs[18,19]) having the melting point by 20° higher than the values reported[18,19]. The identity of our product was proven by analysis and by its successful use in the following synthetic step; the only explanation of the difference of melting points can thus be the difference of the crystal modification. The final step was the reaction of *Ib* with *II* in boiling toluene in the presence of triethylamine and a small amount of potassium iodide. The crude base *Ia* was chromatographed on aluminium oxide giving 64% of homogeneous *Ia* which was characterized by spectra and transformed to the dihydrochloride.

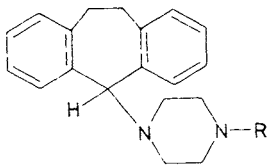


II

In the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene series we started from 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol[20] which was transformed by treatment with hydrogen chloride in benzene in the presence of calcium chloride to 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (for different procedures, cf. refs[21,22]). Its reaction with 1-(ethoxycarbonyl)piperazine in boiling chloroform in the presence of potassium carbonate gave *IIIc* which was hydrolyzed with ethanolic potassium hydroxide to *IIIb* (prepared formerly by reaction of the 5-chloro compound with piperazine[23]). The final reaction with *II* was carried out similarly like in the preceding

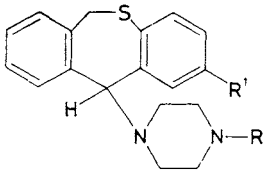
case and gave 60% of *IIIa* which was converted to the hydrochloride (ethanol solvate).

In the 6,11-dihydrodibenzo[*b*,*e*]thiepin series, 11-chloro-6,11-dihydrodibenzo-[*b*,*e*]thiepin[24] was transformed via *IVc* and *IVb* to *IVa* using similar methods like

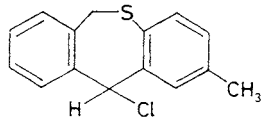


III

in the preceding cases. Compound *IVa* afforded the monohydrochloride (hemihydrate). Because of the outstanding antihistamine activity of (*E*)-N,N-dimethyl-3-(2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine (methiadene) (ref.[25]), our work included the 2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin derivatives. 2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[25] was treated with hydrogen chloride in benzene to give 11-chloro-2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VI*) which was transformed via *Vc* and *Vb* to *Va* (similar methods). Compound *Va* afforded the monohydrochloride (monohydrate).



IV, R^1 = H
V, R^1 = CH_3

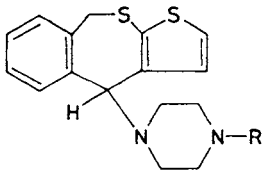


VI

The 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin skeleton proved a very convenient carrier system in the molecule of the antihistamine agent dithiadene[26] and was also included into the present study. 4,9-Dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol[27] was treated with methanesulfonyl chloride in pyridine and the methanesulfonate formed was reacted without isolation directly with 1-(ethoxycarbonyl)piperazine to give *VIIc* which crystallized from water as the monohydrate; its identity was confirmed by spectra. Its further transformation to *VIIa* via *VIIb* proceeded similarly like in the preceding cases. Compound *VIIa* afforded the monohydrochloride, solvated with ethanol.

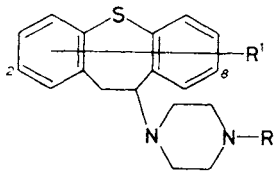
The 10,11-dihydrodibenzo[*b*,*f*]thiepin is not a diphenylmethane derivative but was, nevertheless, used also in the present study. The necessary intermediates *VIIIb*

(ref.[28]), *IXb* (ref.[29]), *Xb* (ref.[30]), and *XIb* (ref.[30]) were available and the synthesis of the final products consisted only in their reactions with *II*. Compounds *VIIIa–XIa* were characterized by spectra and were transformed to the dihydrochlorides (all of them solvates with water). Many 1-aralkyl-4-(10,11-dihydrodibenzo[*b*,*f*]thiepin-10-



VII

-yl)piperazines were prepared as potential neuroleptics (e.g. refs[28,30–33]) but the 1-benzhydryl derivatives have been unknown until now. They were prepared at this opportunity by reactions of *Ib* with 10-chloro-10,11-dihydrodibenzo[*b*,*f*]-thiepin[34], 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[35], and 10-chloro-8-(methylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin[36] in boiling chloroform; the crystalline bases *VIIId*, *Xd*, and *XId* were transformed to salts (hydrochlorides, methanesulfonates).



VIII, R^1 = H *X*, R^1 = 8-Cl
IX, R^1 = 2-Cl *XI*, R^1 = 8-SCH_3

The cyclic analogues of oxatomide (*Ia*) were tested as potential antiallergic agents. Results of the tests are assembled in Table I. Acute toxicity was determined in mice and oral administration was used for the new compounds. Most of the compounds were very little toxic (doses of 500–1 000 mg/kg did not bring about lethality). In addition to *Ia*, whose toxicity was determined on intravenous administration, only for two further compounds of the series (*VIIIa*, *IXa*) the LD_{50} values could be given. Histamine H_1 antagonistic activity was investigated using two most common tests in guinea pigs on oral administration: histamine aerosol test and histamine detoxication test. The results are expressed by the PD_{50} values or as response to a fixed dose (number of the protected animals out of the total number of animals in the experiment). In the histamine aerosol test, *Ia* was more active than the new compounds out of which only *VIIa–IXa* had significant activity. In the histamine

detoxication test, *IVa* was equipotent with *Ia*; the other compounds (as far as they were tested) were less active. The most important test used consisted in estimating the effect on passive cutaneous anaphylaxis (PCA) in rats[37] using oral administration. The results are expressed by the ED_{50} values or as response to the dose of 10 mg/kg in percents of the protected animals. Compound *VIIIa* (VÚFB-14 831) was clearly more active than oxatomide (*Ia*) and the activity of *IVa* (VÚFB-15 319) was approximately equal to that of *Ia*. The experimental material available is too limited for enabling a discussion of structure–activity relationships. The only observations in this line are the following ones: *1*) Only the nuclearly unsubstituted compounds (*IVa*, *VIIIa*) have significant activity. *2*) The thiophene-annelated compound(*VIIa*) in comparison with the benzene analogue (*IVa*) has some H_1 antihistamine activity but lacks the antianaphylactic effect.

Compounds *VIIId*, *Xd*, and *XId* were tested as potential neuroleptics. They are practically nontoxic, LD_{50} with all three compounds is above 1 000 mg/kg orally (in mice). In the rotarod test in mice, the oral doses of 100 mg/kg of all the three compounds were ineffective. In the test of catalepsy in rats the oral doses of 50 mg/kg were administered: *VIIId* and *XId* were inactive, *Xd* brought about catalepsy in 10% of the animals. There are no indications of neuroleptic character with these three compounds.

TABLE I

Pharmacological properties of the tricyclic analogues of oxatomide

Compound	Acute toxicity mice p.o. LD_{50}, mg/kg	Antihistamine activity guinea-pigs p.o. PD_{50}, mg/kg				PCA rat p.o.	
		Histamine aerosol		Histamine detoxication		ED_{50} mg/kg	10 mg/kg, % of protection
Ia	37·4[a]	1·6[b]		<10·0	(5/7)[c]	5·0	—
IIIa	>1 000	>3·0[d]		>10·0	(3/8)[c]	>10·0	21
IVa	>700	>3·0	(2/8)[c]	<10·0	(6/7)[c]	5·5	—
Va	>1 000	>3·0	(3/8)[c]	—		>10·0	19
VIIa	>1 000	3·0[b]		—		>10·0	8
VIIIa	180	4·6		>10·0	(2/8)[c]	1·9	80
IXa	800	3·3[b]		>10·0	(2/8)[c]	>10·0	42
Xa	>500	>3·0	(1/8)[c]	—		>10·0	—
XIa	>1 000	>3·0	(2/8)[c]	—		>10·0	—

[a] Intravenous administration. [b] Significant prolongation of the preconvulsant interval starting from the oral dose of 1 mg/kg. [c] Positive response to the dose given in the number of animals out of the total number. [d] This dose was without effect.

The compounds prepared were also tested for antimicrobial activity in vitro; minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml: *Streptococcus β-haemolyticus, Ia* 100; *Streptococcus faecalis, Ia* 50; *Staphylococcus pyogenes aureus, Ia* 25, *IIIa*, 50, *VIIIa* 12·5; *Trichophyton mentagrophytes, IIIa* 25, *Va* 50, *VIIa* 50, *VIIIa* 50, *Xa* 50, *XId* 50.

EXPERIMENTAL

The melting points were determined in a Mettler FP-5 melting point recorder; the samples were dried in vacuo of about 60 Pa at room temperature or at suitably elevated temperature. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (mostly in Nujol, ν in cm^{-1}) with a Unicam SP 200G spectrophotometer, ^1H NMR spectra (in C^2HCl_3, δ, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectrum (m/z, %) with a Varian MAT 44S (GC–MS) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with K_2CO_3 or $MgSO_4$ and evaporated under reduced pressure on a rotating evaporator. The column chromatography used neutral Al_2O_3 (activity II).

1-(3-Chloropropyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*II*)

1-(2-Propenyl)-1,3-dihydro-2*H*-benzimidazol-2-one[10] (75 g) was added to a solution of sodium ethoxide (9·8 g Na in 400 ml ethanol) and the stirred mixture was treated over 15 min with 94·5 g 1-bromo-3-chloropropane, added dropwise. The mixture was stirred and refluxed for 4 h, allowed to stand overnight at room temperature, treated with 43 ml 10M-H_2SO_4, stirred for 2 h at room temperature, diluted with 400 ml water, and ethanol was distilled off under reduced pressure (500 ml of distillate). The residue was cooled and stirred which induced crystallization of 79 g crude product. It was filtered, washed with water, dried, dissolved in 180 ml boiling benzene, the solution was filtered with charcoal, and the filtrate was treated with 90 ml light petroleum. There crystallized 50·0 g (55%) crude *II*, m.p. 109–112°C, which was used for further work. A sample was purified by crystallization from a mixture of ethyl acetate and light petroleum, m.p. 117–118°C. IR spectrum: 730, 752 (4 adjacent Ar—H); 1 615, 1 685 (ArNHCON); 3 010, 3 060, 3 130, 3 170 (NH). ^1H NMR spectrum: 2·20 m, 2 H (CH_2—CH_2—CH_2); 3·60 t, 2 H (CH_2Cl, J = 7·0); 4·03 t, 2 H (CH_2N, J = 7·0); 7·10 s, 4 H (4 ArH); 10·85 bs, 1 H (NH). Ref.[13], m.p. 118–120°C.

5-Chloro-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene

$CaCl_2$ (20 g) was added to a solution of 40·0 g 10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ol[20] in 250 ml benzene and the stirred suspension was saturated for 2·5 h with HCl. After standing overnight, the mixture was filtered with charcoal, the filtrate was evaporated, and the residue was crystallized from light petroleum (dissolved in 300 ml and a part of the solvent was distilled off); 40·2 g (93%), m.p. 103–106°C. Ref.[22], m.p. 104–105°C.

11-Chloro-2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin (*VI*)

A suspension of 36·3 g 2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol[25] and 20 g $CaCl_2$ in 450 ml benzene was saturated for 2·5 h with HCl and the mixture was processed similarly to

the preceding case. The crude product was crystallized from 65 ml cyclohexane; 37·4 g (96%), m.p. 117–118°C (cyclohexane). ^{1}H NMR spectrum: 2·18 s, 3 H (CH_3); 3·60 d, 1 H and 5·38 d, 1 H (ABq, $ArCH_2S$, J = 14·0); 6·10 s, 1 H (Ar_2CHCl); 6·80–7·40 m, 7 H (7 ArH). For $C_{15}H_{13}ClS$ (260·8) calculated: 69·09% C, 5·02% H, 13·59% Cl, 12·30% S; found: 69·46% C, 5·02% H, 13·73% Cl, 12·29% S.

1-Benzhydryl-4-(ethoxycarbonyl)piperazine (*Ic*)

A stirred mixture of 63·2 g 1-(ethoxycarbonyl)piperazine, 100 ml chloroform, and 22 g Na_2CO_3 was treated over 15 min with a solution of 50·0 g benzhydryl bromide[17] in 50 ml chloroform. After the exothermic reaction was over, the mixture was stirred and refluxed for 8 h. After cooling the inorganic salts were filtered off, the filtrate was washed with water, dried with $CaCl_2$, and evaporated. The residue was crystallized from 50 ml ethanol; 59·1 g (90%), m.p. 115–116°C. Ref.[18], m.p. 114–115°C.

1-(Ethoxycarbonyl)-4-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)piperazine (*IIIc*)

Reaction of 39·5 g 1-(ethoxycarbonyl)piperazine, 28·5 g 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, and 18·0 g K_2CO_3 in 80 ml chloroform was carried out similarly to the preceding case. The crude product was crystallized from 70 ml light petroleum; 35·0 g (80%), m.p. 107 to 109°C. IR spectrum: 760 (4 adjacent ArH); 1 240, 1 700 (NCOOR); 1 596, 3 020, 3 040, 3 064 (Ar); 2 760 (CH_2—N). ^{1}H NMR spectrum: 1·22 t, 3 H (CH_3, J = 7·0); 2·20 bt, 4 H ($CH_2N^4CH_2$ of piperazine); 3·38 bt, 4 H ($CH_2N^1CH_2$ of piperazine); 2·80 m, 2 H and 3·90 m, 3 H (Ar_2CH and $ArCH_2CH_2Ar$); 4·10 q, 2 H (OCH_2, J = 7·0); 7·10 s, 8 H (8 ArH). For $C_{22}H_{26}N_2O_2$ (350·5) calculated: 75·39% C, 7·48H %, 8·00% N; found: 75·47% C, 7·66% %, 7·78% N.

1-(Ethoxycarbonyl)-4-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)piperazine (*IVc*)

Reaction of 32·0 g 1-(ethoxycarbonyl)piperazine, 24·6 g 11-chloro-6,11-dihydrodibenzo[*b*,*e*]-thiepin[24], and 11·0 g Na_2CO_3 in 75 ml chloroform was carried out similarly. The crude oily product was extracted twice with 150 ml water at 60°C, the undissolved part was dissolved in 100 ml benzene, the solution was dried, and evaporated. The residue crystallized from 50 ml cyclohexane after the addition of light petroleum; 26·2 g (71%), m.p. 107–111°C. The analytical sample was obtained by further crystallization from the same mixture, m.p. 111–114°C. IR spectrum: 751 (4 adjacent Ar—H); 1 240, 1 692 (NCOOR); 1 490, 1 588 (Ar); 2 755, 2 800 (CH_2—N). ^{1}H NMR spectrum (at 60°C): 1·30 t, 3 H (CH_3, J = 7·0); 2·40 m, 4 H ($CH_2N^4CH_2$ of piperazine); 3·50 m, 4 H ($CH_2N^1CH_2$ of piperazine); 4·11 s, 1 H (Ar_2CH); 4·18 q, 2 H (OCH_2, J = 7·0); 3·58 d, 1 H and 5·95 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·90–7·40 m, 8 H (8 ArH). For $C_{21}H_{24}N_2O_2S$ (368·5) calculated: 68·45% C, 6·56% H, 7·60% N, 8·70% S;found:68·10% C, 6·64% H, 7·36% N, 8·69% S.

1-(Ethoxycarbonyl)-4-(2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)piperazine (*Vc*)

Similar reaction of 24·4 g 1-(ethoxycarbonyl)piperazine, 20·0 g *VI*, and 8·5 g Na_2CO_3 in 80 ml chloroform gave 26·3 g (90%) *Vc*, m.p. 151–152°C (ethanol). IR spectrum: 738, 765, 810, 840, 850, 895 (4 and 2 adjacent and solitary Ar—H); 1 124, 1 235, 1 690 (NCOOR); 1 480 (Ar). ^{1}H NMR spectrum: 1·20 t, 3 H (CH_3 of ethyl, J = 7·0); 2·18 s, 3 H ($ArCH_3$); 2·25 bt, 4 H ($CH_2N^4CH_2$ of piperazine); 3·40 m, 4 H ($CH_2N^1CH_2$ of piperazine); 4·00 s, 1 H (Ar_2CH); 4·08 q, 2 H (OCH_2, J = 7·0); 3·35 bd, 1 H and 5·98 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·70–7·30 m, 7 H (7 ArH). For $C_{22}H_{26}N_2O_2S$ (382·5) calculated: 69·08% C, 6·85% H, 7·32% N, 8·38% S; found: 69·45% C, 7·04% H, 7·23% N, 8·50% S.

1-(Ethoxycarbonyl)-4-(4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-yl)piperazine (*VIIc*)

A stirred solution of 16·2 g 4·9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol[27] in 32 ml pyridine was treated dropwise with 7·9 g methanesulfonyl chloride at 25—28°C (external cooling with ice and water) and the mixture was allowed to stand for 24 h at room temperature. 1-(Ethoxycarbonyl)piperazine (38 g) was added, the solution formed was stirred for 8 h and was allowed to stand for 16 h at room temperature. It was then distributed between 300 ml benzene and 250 ml water, the organic layer was washed with water, dried, and evaporated. The glassy residue was dissolved in benzene and chromatographed on a column of 500 g Al_2O_3. Benzene eluted 16·0 g (62%) homogeneous oily product which crystallized after trituration with water and was identified as the monohydrate of *VIIc*, m.p. 55—58°C. Mass spectrum: 374 (0·6) (M^+, $C_{19}H_{22}$·.$N_2O_2S_2$), 216 (100) ($C_{12}H_8S_2$), 184 (48) ($C_{12}H_8S$). IR spectrum: 760 (4 adjacent Ar—H); 845 (2 adjacent Ar—H of thiophene); 1 125, 1 220, 1 240, 1 290 (C—O in COOR); 1 686 (NCOOR); 2 745, 2 795 (CH_2—N); 3 018, 3 055, 3 108 (Ar). ^{1}H NMR spectrum: 1·28 t, 3 H (CH_3, J = 7·0); 2·30 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·40 bm, 4 H ($CH_2N^1CH_2$ of piperazine); 3·48 d, 1 H and 6·12 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 4·12 q, 2 H (OCH_2, J = 7·0); 4·12 s, 1 H (Ar_2CH); 6·75 d, 1 H (H-3, J = 5·0); 6·98 d, 1 H (H-2, J = 5·0); c. 7·20 m, 4 H (H-5, H-6, H-7, H-8). For $C_{19}H_{22}N_2O_2S_2 + H_2O$ (392·5) calculated: 7·14% N, 16·34% S; found: 7·15% N, 16·28% S.

1-Benzhydrylpiperazine (*Ib*)

A mixture of 59·0 g *Ic*, 30 g KOH, and 30 ml ethanol was stirred and heated for 6 h under reflux in a bath of 125—135°C. Ethanol was evaporated under reduced pressure, the residue was diluted with 500 ml water, and the separated oil crystallized. It was filtered, washed with water, dried, and recrystallized from 110 ml hexane; 40·4 g (88%), m.p. 91—92°C. A further recrystallization from hexane led to the analytical product, m.p. 92—92·5°C. For $C_{17}H_{20}N_2$ (252·4) calculated: 80·91% C, 7·99% H, 11·10% N; found: 81·08% C, 8·08% H, 11·15% N. Refs[18,19], m.p. 70—72°C.

1-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)piperazine (*IIIb*)

A mixture of 10·0 g *IIIc*, 6·0 g KOH, and 6 ml ethanol was processed similarly to the preceding case. After evaporation of ethanol the residue was distributed between 100 ml water and 100 ml benzene, the benzene layer was washed with water, dried, and evaporated; 7·7 g (97%) of *IIIb*, m.p. 109°C (light petroleum); ref.[23], m.p. 110°C. ^{1}H NMR spectrum: 1·45 s, 1 H (NH); 2·20 m, 4 H ($CH_2N^1CH_2$ of piperazine); 2·80 m, 4 H ($CH_2N^4CH_2$ of piperazine); 2·80 m, 2 H and 4·00 m, 2 H ($ArCH_2CH_2Ar$); 3·92 s, 1 H (Ar_2CH); 7·10 m, 8 H (8 ArH).

1-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)piperazine (*IVb*)

It was prepared similarly from 26·0 g *IVc* and 13·0 g KOH in 13 ml ethanol; 20·0 g (96%) crude oily product. Crystallization from a mixture of 20 ml benzene and 50 ml hexane gave 16·2 g (78%) of almost homogeneous *IVb*, m.p. 109—111°C. Analytical sample, m.p. 110—111°C (benzene–hexane). ^{1}H NMR spectrum: 1·45 bs, 1 H (NH); 2·25 bt, 4 H ($CH_2N^1CH_2$ of piperazine); 2·80 bt, 4 H ($CH_2N^4CH_2$ of piperazine); 3·37 bd, 1 H and 6·00 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 4·00 s, 1 H (Ar_2CH); 6·80—7·20 m, 8 H (8 ArH). For $C_{18}H_{20}N_2S$ (296·4) calculated: 72·93% C, 6·80% H, 9·45% N, 10·82% S; found: 73·14% C, 6·96% H, 9·41% N, 10·76% S.

Oxalate, m.p. 148—151°C (2-propanol). For $C_{20}H_{22}N_2O_4S$ (386·5) calculated: 62·15% C, 5·74% H, 7·25% N, 8·30% S; found: 62·33% C, 6·10% H, 7·27% N, 8·41% S.

1-(2-Methyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)piperazine (*Vb*)

It was prepared similarly from 24·7 g *Vc* and 12·5 g KOH in 20 ml ethanol; 17·0 g (85%), m.p. 164–166°C (ethanol). ^{1}H NMR spectrum: 1·52 bs, 1 H (NH); 2·18 s, 3 H ($ArCH_3$); 2·25 bt 4 H ($CH_2N^1CH_2$ of piperazine); 2·80 bt, 4 H ($CH_2N^4CH_2$ of piperazine); 3·35 bd, 1 H and 6·00 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 3·98 s, 1 H (Ar_2CH); 6·80–7·20 m, 7 H (7 ArH). For $C_{19}H_{22}N_2S$ (310·4) calculated: 73·51% C, 7·14% H, 9·02% N, 10·33% S; found: 73·07% C, 7·38% H, 8·88% N, 10·14% S.

1-(4,9-Dihydrothieno[2,3-*c*]-2-benzothiepin-4-yl)piperazine (*VIIb*)

Similarly from 20·4 g crude oily *VIIc* and 10·2 g KOH in 20 ml ethanol were obtained 14·2 g of oily product which crystallized from a mixture of 20 ml ether and 5 ml light petroleum (11·7 g, 71%), m.p. 132–135°C. IR spectrum: 755 (4 adjacent Ar—H); 810, 830, 839 (2 adjacent thiophene Ar—H); 1 595, 3 020, 3 060 (Ar); 2 748 (CH_2—N); 3 315 (NH). For $C_{16}H_{18}N_2S_2$ (302·4) calculated: 63·54% C, 6·00% H, 9·26% N, 21·20% S; found: 63·15% C, 6·15% H, 8·57% N, 20·92% S.

An attempt to prepare the maleate of *VIIb* by neutralization of 0·62 g *VIIb* with 0·46 g maleic acid in 5 ml ether gave 0·4 g substance melting at 191·5–192°C (aqueous ethanol) which was identified as piperazine bis(hydrogen maleate). For $C_{12}H_{18}N_2O_8$ (318·3) calculated: 45·28% C, 5·70% H, 8·80% N; found: 45·20% C, 5·82% H, 8·33% N.

1-(3-(4-Benzhydryl-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*Ia*)

A stirred mixture of 4·5 g *Ib*, 5·6 g *II*, 2·7 g triethylamine, 0·15 g KI, and 60 ml toluene was refluxed for 20 h. After cooling it was diluted with 60 ml toluene, decomposed with 60 ml water, stirred for 10 min, the organic layer was washed with water, dried, and evaporated. The inhomogeneous residue (9·0 g) was chromatographed on a column of 230 g Al_2O_3. Benzene eluted less polar components and a mixture of benzene with 3% ethanol eluted 4·85 g (64%) of *Ia*, which crystallized from ethanol, m.p. 152–154°C. IR spectrum: 710, 760 (5 and 4 adjacent Ar—H); 1 488, 3 060 (Ar); 1 655, 1 695 (ArNHCON); 3 200 (NH). ^{1}H NMR spectrum: 1·98 bm, 2 H ($CH_2CH_2CH_2$); 2·40 bs, 10 H (5 NCH_2 of piperazine and adjacent to piperazine); 3·91 t, 2 H (CH_2NCO, J = 7·0); 4·20 s, 1 H (Ar_2CH); 7·00 s, 4 H (4 ArH of benzimidazolone); 7·10 to 7·50 m, 10 H (remaining 10 ArH); 10·52 bs, 1 H (ArNHCO). Refs[1,13,38], m.p. 153–155 and 153·6°C, respectively.

Dihydrochloride, m.p. 200–202°C (ethanol–ether). For $C_{27}H_{32}Cl_2N_4O$ (499·5) calculated: 64·92% C, 6·46% H, 14·20% Cl, 11·22% N; found: 64·66% C, 6·54% H, 14·02% Cl, 11·00% N.

1-(3-(4-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-yl)-
-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*IIIa*)

It was prepared similarly from 7·2 g *IIIb*, 7·9 g *II*, 3·8 g triethylamine, and 0·3 g KI in 75 ml toluene. The crude product (14·7 g), obtained by evaporation of the organic solvent, crystallized from 20 ml ethanol; 7·0 g (60%), m.p. 175–182°C. Recrystallization from acetone afforded the product, m.p. 184–185°C. IR spectrum: 732, 758 (4 adjacent Ar—H); 1 690 (ArNHCON) 3 060, 3 140, 3 185 (NH). For $C_{29}H_{32}N_4O$ (452·6) calculated: 76·96% C, 7·13% H, 12·38% N; found: 76·99% C, 7·29% H, 12·35% N.

H ydrochloride, solvate 1 : 1 with ethanol, m.p. 221–222°C (aqueous ethanol). For $C_{29}H_{33}$·.ClN $_4O$ + C_2H_6O (535·1) calculated: 69·58% C, 7·35% H, 6·63% Cl, 10·47% N; found: 69·38% C, 7·47% H, 6·73% Cl, 10·36% N.

1-(3-(4-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)-1-piperazinyl)-propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*IVa*)

Similar preparation from 7·4 g *IVb*, 7·9 g *II*, 3·8 g triethylamine, and 0·3 g KI in 75 ml toluene. The crude product (15·0 g) was chromatographed on 250 g Al_2O_3. The product was eluted with benzene containing 3% ethanol; 9·70 g (83%), m.p. 180–181°C (ethanol–di(2-propyl) ether). UV spectrum: infl. 225 (4·39), 267 (4·05), 282 (3·98), 288 (3·92). IR spectrum: 730, 750 (4 adjacent Ar—H); 1 482, 1 558, 1 586, 3 043 (Ar); 1 621, 1 690 (ArNHCON in the cycle); 3 135, 3 180 (NH). ^{1}H NMR spectrum: 1·85 m, 2 H ($CH_2CH_2CH_2$); 2·30 bs, 10 H (5 NCH_2 of piperazine and adjacent to piperazine); 3·32 bd, 1 H and 6·00 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 3·88 bt, 2 H (CH_2NCO, J = 7·0); 4·00 s, 1 H (Ar_2CH); 6·80–7·30 m, 12 H (12 ArH); 10·62 bs, 1 H (CONH). For $C_{28}H_{30}N_4OS$ (470·6) calculated: 71·46% C, 6·43% H, 11·90% N, 6·81% S; found: 71·26% C, 6·63% H, 11·74% N, 6·72% S.

Monohydrochloride hemihydrate, m.p. 227–228°C and after new crystallization melting again at 250–260°C (aqueous ethanol). For $C_{28}H_{31}ClN_4OS + 0{\cdot}5\ H_2O$ (516·1) calculated: 65·16% C, 6·25% H, 6·87% Cl, 10·86% N, 6·21% S; found: 64·97% C, 6·54% H, 6·80% Cl, 10·33% N, 6·23% S.

1-(3-(4-(2-Methyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*Va*)

Compound *Vb* (6·2 g), 6·3 g *II*, 3·05 g triethylamine, and 0·15 g KI in 100 ml toluene gave similarly 11·1 g crude product which was chromatographed on 320 g Al_2O_3. Elution with benzene containing 3% ethanol, and the following crystallization from a mixture of ethanol, di(2-propyl) ether, and light petroleum afforded 6·2 g (65%) homogeneous *Va*, m.p. 196–198°C (ethanol). IR spectrum: 730, 750, 810, 845, 888 (4 and 2 adjacent and solitary Ar—H); 1 480, 1 575, 3 020, 3 060 (Ar); 1 620, 1 690 (ArNHCON in the cycle); 2 775, 2 788, 2 810 (CH_2—N); 3 130, 3 180 (NH). ^{1}H NMR spectrum: 1·85 m, 2 H ($CH_2CH_2CH_2$); 2·20 s, 3 H ($ArCH_3$); 2·30 bs, 10 H (5 NCH_2 of piperazine and adjacent to piperazine); 3·32 bd, 1 H and 6·00 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 3·88 bt, 2 H (CH_2NCO, J = 7·0); 4·00 s, 1 H (Ar_2CH); 6·70–7·30 m, 11 H (11 ArH); 10·62 bs, 1 H (CONH). For $C_{29}H_{32}N_4OS$ (484·6) calculated: 71·86% C, 6·66% H, 11·56% N, 6·62% S; found: 71·94% C, 6·94% H, 11·64% N, 6·74% S.

Monohydrochloride hydrate, m.p. 202–203°C (96% ethanol). For $C_{29}H_{33}ClN_4OS + H_2O$ (539·1) calculated: 64·60% C, 6·54% H, 6·58% Cl, 10·39% N, 5·95% S; found: 64·76% C, 6·41% H, 6·48% Cl, 10·26% N, 6·20% S.

1-(3-(4-(4,9-Dihydrothieno[2,3-*c*]-2-benzothiepin-4-yl)-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*VIIa*)

Compound *VIIb* (4·7 g), 4·9 g *II*, 2·4 g triethylamine, and 0·15 g KI in 70 ml toluene gave similarly 7·5 g crude product which crystallized from 10 ml ethanol; 3·7 g (50%), m.p. 205–206°C (acetone). IR spectrum: 730, 754 (4 adjacent Ar—H); 838, 842 (2 adjacent thiophene Ar—H); 1 481 (Ar); 1 689 (ArNHCON in the cycle); 3 130 (NH). ^{1}H NMR spectrum: 2·00 bm, 2 H ($CH_2CH_2CH_2$); 2·38 bs, 10 H (5 NCH_2 of piperazine and adjacent to piperazine); 3·41 d, 1 H and 6·18 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 3·98 bt, 2 H (CH_2NCO); 4·18 s, 1 H (Ar_2CH); 6·80 d, 1 H (H-3, J = 5·0); 6·98 d, 1 H (H-2, J = 5·0); c. 7·20 m, 4 H (H-5, H-6, H-7, H-8); 10·70 bs, 1 H (CONH). For $C_{26}H_{28}N_4OS_2$ (476·6) calculated: 65·51% C, 5·92% H, 11·76% N, 13·45% S; found: 65·21% C, 6·01% H, 11·42% N, 13·52% S.

Monohydrochloride, solvate 1 : 1 with ethanol, m.p. 187—188°C (98% ethanol). For $C_{26}H_{29}ClN_4OS_2 + C_2H_6O$ (559·2) calculated: 60·14% C, 6·31% H, 6·34% Cl, 10·02% N, 11·47% S; found: 60·25% C, 6·36% H, 6·32% Cl, 9·68% N, 11·53% S.

1-(3-(4-(10,11-Dihydrodibenzo[*b,f*]thiepin-10-yl)-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*VIIIa*)

Compound *VIIIb* (ref.[28]) (4·5 g), 4·8 g *II*, 2·3 g triethylamine, and 0·15 g KI in 50 ml toluene gave similarly 8·6 g of inhomogeneous product which was chromatographed on 230 g Al_2O_3. Elution with benzene, containing 3% ethanol, afforded 4·6 g (65%) *VIIIa*, m.p. 146—147°C (ethanol–di(2-propyl)ether). IR spectrum: 742, 760 (4 adjacent Ar—H); 1 489 (Ar); 1 690, (ArNHCON in the cycle); 2 810 (CH_2—N); 3 175, 3 460 (NH). ^{1}H NMR spectrum: 2·00 bm; 2 H ($CH_2CH_2CH_2$); c. 2·50 bm, 10 H (5 CH_2N of piperazine and adjacent to piperazine); 3·00—4·00 m, 3 H ($ArCH_2CHAr$); 3·98 bt, 2 H (CH_2NCO); 6·90—7·70 m, 12 H (12 ArH); 10·65 bs, 1 H (CONH). For $C_{28}H_{30}N_4OS$ (470·6) calculated: 71·46% C, 6·43% H, 11·90% N, 6·81% S; found: 71·37% C, 6·45% H, 11·89% N, 6·97% S.

Dihydrochloride monohydrate, m.p. 181—182°C (95% ethanol). For $C_{28}H_{32}Cl_2N_4OS + H_2O$ (561·6) calculated: 59·90% C, 6·10% H, 12·62% Cl, 9·97% N, 5·71% S; found: 60·12% C, 5·89% H, 12·90% Cl, 10·20% N, 6·10% S.

1-(3-(4-(2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*IXa*)

Compound *IXb* (ref.[29]) (6·2 g), 5·95 g *II*, 2·84 g triethylamine, and 0·15 g KI in 70 ml toluene gave the crude product which was chromatographed on 220 g Al_2O_3 to afford *IXa* in the yield of 73%, m.p. 113—114°C (acetone). IR spectrum: 735, 752, 812, 881 (4 and 2 adjacent and solitary Ar—H); 1 486, 1 560, 1 580 (Ar); 1 665, 1 702 (ArNHCON in the cycle); 2 810 (CH_2—N); 3 075, 3 145 (NH). ^{1}H NMR spectrum: 2·00 bm, 2 H ($CH_2CH_2CH_2$); 2·40 bm, 6 H ($CH_2N^1CH_2$ of piperazine and the adjacent NCH_2); 2·70 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·00—4·10 m, 5 H (CH_2NCO and $ArCH_2CHAr$); 6·90—7·80 m, 11 H (11 ArH); 11·80 s, 1 H (CONH). For $C_{28}H_{29}ClN_4OS$ (505·1) calculated: 66·58% C, 5·79% H, 7·02% Cl, 11·09% N, 6·35% S; found: 66·20% C, 5·92% H, 7·30% Cl, 10·59% N, 6·27% S.

Dihydrochloride sesquihydrate, m.p. 167—168°C (85% aqueous ethanol). For $C_{28}H_{31}Cl_3N_4OS + 1{\cdot}5\ H_2O$ (605·0) calculated: 55·58% C, 5·67% H, 17·58% Cl, 9·26% N, 5·30% S; found: 55·63% C, 5·48% H, 16·69% Cl, 9·33% N, 5·56% S.

1-(3-(4-(8-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*Xa*)

Compound *Xb* (ref.[30]) (6·6 g), 6·3 g *II*, 3·1 g triethylamine, and 0·15 g KI in 100 ml toluene gave similarly 11·0 g inhomogeneous product which crystallized from 20 ml ethanol; 7·65 g (76%), m.p. 177—178°C (ethanol–benzene). IR spectrum: 748, 765, 815, 885 (4 and 2 adjacent and solitary Ar—H); 1 490, 3 060 (Ar); 1 690 (ArNHCON in the cycle); 2 820 (CH_2—N); 3 150, 3 460 (NH). ^{1}H NMR spectrum: 2·00 m, 2 H ($CH_2CH_2CH_2$); c. 2·50 m, 10 H (5 CH_2N of piperazine and adjacent to piperazine); 3·00—4·00 m, 3 H ($ArCH_2CHAr$); 4·00 bt, 2 H ($CH_2N.CO$); 6·90—7·80 m, 11 H (11 ArH). For $C_{28}H_{29}ClN_4OS$ (505·1) calculated: 66·58% C, 5·79% H, 7·02% Cl, 11·09% N, 6·35% S; found: 66·77% C, 5·79% H, 7·17% Cl, 11·21% N, 6·44% S.

Dihydrochloride monohydrate, m.p. 178–179°C (95% ethanol). For $C_{28}H_{31}Cl_3N_4OS + H_2O$ (596·0) calculated: 56·42% C, 5·58% H, 17·85% Cl, 9·40% N, 5·38% S; found: 56·83% C, 5·60% H, 17·74% Cl, 9·57% N, 5·24% S.

1-(3-(4-(8-(Methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-1-piperazinyl)propyl)-1,3-dihydro-2*H*-benzimidazol-2-one (*XIa*)

Compound *XIb* (ref.[30]) (6·8 g), 6·3 g *II*, 3·1 g triethylamine, and 0·15 g KI in 100 ml toluene gave similarly 10·5 g inhomogeneous product which was chromatographed on 300 g Al_2O_3. Elution with benzene, containing 3% ethanol, afforded 6·9 g (67%) of *XIa* which crystallized from a mixture of di(2-propyl) ether and acetone; m.p. 109–111°C (acetone–light petroleum). IR spectrum: 740, 749, 760, 805, 810, 887, 894 (4 and 2 adjacent and solitary Ar—H); 1 490, 1 580, 3 060 (Ar); 1 690 (ArNHCON in the cycle); 2 810 (CH_2—N); 3 190, 3 465 (NH). ^{1}H NMR spectrum: 2·00 bm, 2 H ($CH_2CH_2CH_2$); 2·40 s, 3 H (SCH_3); c. 2·50 bm, 10 H (5 CH_2N of piperazine and adjacent to piperazine); 3·00–4·00 m, 3 H ($ArCH_2CHAr$); 4·00 bt, 2 H (CH_2NCO); 6·80–7·70 m, 11 H (11 ArH); 10·70 bs, 1 H (NH). For $C_{29}H_{32}N_4OS_2$ (516·7) calculated: 67·41% C, 6·24% H, 10·84% N, 12·41% S; found: 67·69% C, 6·42% H, 10·61% N, 12·27% S.

Dihydrochloride monohydrate, m.p. 198°C (85% ethanol). For $C_{29}H_{34}Cl_2N_4OS_2 + H_2O$ (607·6) calculated: 57·32% C, 5·97% H, 11·67% Cl, 9·22% N, 10·55% S; found: 57·37% C, 5·97% H, 11·59% Cl, 9·17% N, 10·70% S.

1-Benzhydryl-4-(10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine (*VIIId*)

A stirred mixture of 5·0 g 10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin[34], 40 ml chloroform, and 10·0 g *Ib* was refluxed for 15 h, chloroform was evaporated under reduced pressure and the residue was distributed between 120 ml benzene and 120 ml water at 50°C. The benzene layer was washed with water and then shaken with 150 ml 3M-HCl. The precipitated dihydrochloride (identified as the monohydrate) was filtered, washed with benzene, and dried; 7·60 g (70%), m.p. 172–176°C. Recrystallization from ethanol gave the product melting at 173–178°C. For $C_{31}H_{32}Cl_2N_2S + H_2O$ (553·6) calculated: 67·26% C, 6·19% H, 12·81% Cl, 5·06% N, 5·79% S; found: 67·33% C, 5·88% H, 12·32% Cl, 4·94% N, 5·90% S.

This salt was decomposed with NH_4OH and the base was isolated by extraction with benzene; microcrystalline and homogeneous (TLC) product melted at 73–76°C. IR spectrum (KBr): 704, 737, 755 (5 and 4 adjacent Ar—H); 1 465, 1 490, 1 558, 1 595, 3 020, 3 053 (Ar); 2 753, 2 805 (CH_2—N). ^{1}H NMR spectrum: 2·40 m, 4 H ($CH_2N^1CH_2$ of piperazine); 2·70 m, 4 H (CH_2N^4. .CH_2 of piperazine); 3·00–4·00 m, 3 H ($ArCH_2CHAr$); 4·25 s, 1 H (Ar_2CH); 7·00–7·70 m, 18 H (18 ArH). For $C_{31}H_{30}N_2S$ (462·3) calculated: 80·48% C, 6·54% H, 6·06% N, 6·93% S; found: 80·11% C, 6·71% H, 5·67% N, 7·05% S.

Dimethanesulfonate, m.p. 185–187°C (ethanol–ether). For $C_{33}H_{38}N_2O_6S_3$ (654·9) calculated: 60·52% C, 5·85% H, 4·28% N, 14·69% S; found: 60·52% C, 5·99% H, 4·21% N, 14·19% S.

Monomethanesulfonate, m.p. 236–237°C (ethanol). For $C_{32}H_{34}N_2O_3S_2$ (558·7) calculated: 68·78% C, 6·13% H, 5·01% N, 11·48% S; found: 68·66% C, 6·17% H, 4·89% N, 11·36% S.

1-Benzhydryl-4-(8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine (*Xd*)

A similar reaction of 5·6 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[35] with 10·0 g *Ib* in 40 ml boiling chloroform and similar processing gave 7·30 g (63%) *Xd* dihydrochloride hemihydrate, m.p. 178–182°C. For $C_{31}H_{31}Cl_3N_2S + 0·5\ H_2O$ (579·0) calculated: 64·30% C,

5·57% H, 18·37% Cl, 4·84% N, 5·45% S; found: 64·42% C, 5·45% H, 17·92% Cl, 4·73% N, 5·64% S.

The base, released with NH_4OH and isolated by extraction with ether, crystallized from a mixture of thanol and hexane, m.p. 157—158°C. ^{1}H NMR spectrum: 2·48 bm, 4 H ($CH_2N^1CH_2$ of piperazine); 2·70 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·00—4·00 m, 3 H ($ArCH_2CHAr$); 4·25 s, 1 H (Ar_2CH); 6·90—7·60 m, 16 H (16 ArH excluding H-9); 7·70 d, 1 H (H-9, $J = 2·5$). For $C_{31}H_{29}ClN_2S$ (497·1) calculated: 74·90% C, 5·88% H, 7·13% Cl, 5·64% N, 6·45% S; found: 75·34% C, 5·98% H, 7·52% Cl, 5·61% N, 6·85% S.

1-Benzhydryl-4-(8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine (*XId*)

A similar reaction of 5·8 g 10-chloro-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]thiepin[36] with 10·0 g *Ib* in 40 ml boiling chloroform and similar processing gave 9·0 g (76%) *XId* dihydrochloride hemihydrate, m.p. 183—187°C (aqueous ethanol). For $C_{32}H_{34}Cl_2N_2S_2 + 0·5\ H_2O$ (590·7) calculated: 65·07% C, 5·97% H, 12·01% Cl, 4·74% N, 10·86% S; found: 64·81% C, 5·99% H, 11·82% Cl, 4·39% N, 10·70% S.

The base, prepared similarly to the preceding case, crystallized from ethanol with a small amount of hexane, m.p. 67—70°C. ^{1}H NMR spectrum: 2·38 s, 3 H (SCH_3); 2·48 bm, 4 H ($CH_2N^1CH_2$ of piperazine); 2·70 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·00—4·00 m, 3 H ($ArCH_2CHAr$); 4·25 s, 1 H (Ar_2CH); 6·80—7·70 m, 17 H (17 ArH). For $C_{32}H_{32}N_2S_2$ (508·7) calculated: 75·74% C, 6·34% H, 5·51% N, 12·61% S; found: 75·63% C, 6·61% H, 5·04% N, 12·41% S.

Dimethanesulfonate hemihydrate, m.p. 156—158°C (ethanol). For $C_{34}H_{40}N_2O_6S_4 + 0·5\ H_2O$ (710·0) calculated: 57·51% C, 5·82% H, 3·95% N, 18·07% S; found: 57·42% C, 5·72% H, 3·71% N, 17·72% S.

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