POTENTIAL NEUROLEPTICS; N-ARALKYL, N-(AROYLALKYL) AND N-PYRIDYL DERIVATIVES OF 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*]THIEPINS*

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Substitution reactions of 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin with 1-aralkylpiperazines (*XIId–XIIi*) yielded the N-aralkyl derivatives *Ib–VIb*. Alkylation of 8-chloro and 8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin by phenacyl halogenides and 4-chloro--1-(4-fluorophenyl)-1-butanone led to *VIIb*, *VIIc* and *VIIIc*. Reactions of 10-chloro, 8,10-dichloro and 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b,*]thiepin with 1-(2-pyridyl)piperazine and 1-(4-pyridyl)piperazine resulted in *IXa–IXc*, *Xb* and *Xc*. The prepared compounds are little toxic, their central depressant activity appears only at high doses and only some of them (*Ib*, *IIb*, *IVb*, *VIIIc*) are clearly cataleptic. The most interesting of all is the 3-(4-fluorobenzoyl)propyl derivative *VIIIc* which is minimally toxic but has the same cataleptic effect as chlorpromazine while being practically free of any depressant action.

In the group of neuroleptics derived from 10-piperazinodibenzo[*b,f*]thiepins relatively little attention has been devoted to compounds which carry a larger and lipophilic group as the piperazine N^4-substituent, involving an aromatic ring, *i.e.* aryl or aralkyl. The present experience in this respect is limited to the N-phenyl analogues of "perathiepin"[1] and "octoclothepin"[2] which were practically free of central activity, further to the N-benzyl analogues of the mentioned compounds[1,2] which were clearly active as central depressants, and finally to the N-(4-methoxybenzyl) analogue of octoclothepin[3] described also in patents[4] which possessed a remarkably reduced depressant activity while its cataleptic effect was preserved. It was thought to be of interest to supplement the existing information along this line, the results being reported here.

First of all we prepared a series of N-aralkyl analogues of octoclothepin *Ib–VIb*, the molecules of which contain a chain of 2–3 methylene groups between the piperazine nitrogen atom N^4 and the aryl group. The compounds were prepared by heating 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2] with the appropriate 1-aralkylpiperazines (*XIId–XIIi*) to 100–110°C (Method *A*). The starting aralkylpiperazines were prepared by alkylation of 1-(ethoxycarbonyl)piperazine[5] with 2-phenylethyl

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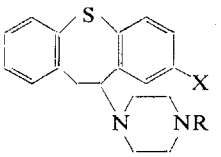
bromide[6], 2-(4-tolyl)ethyl bromide[7], 2-(4-chlorophenyl)ethyl bromide[8], 2-(4-methoxyphenyl)ethyl bromide[9], 2-(1-naphthyl)ethyl bromide[10] and 3-phenylpropyl bromide[11] (Method *B*) and subsequent alkaline hydrolysis of the carbamates formed *XId–XIi* (Method *C*). Of these carbamates, references are found[12] only on *XIg* which was prepared by a procedure somewhat different from ours. Of the aralkylpiperazines, references may be found on 1-(2-phenylethyl)piperazine[13–18] (*XIId*), 1-[2-(4-methoxyphenyl)ethyl]piperazine[12] (*XIIg*) and 1-(3-phenylpropyl)piperazine[16] (*XIIi*), only *XIIg* having been obtained by a procedure resembling ours. Of the arylalkanols[7,8,19–21] used for the preparation of the bromides, 2-phenylethanol and 3-phenylpropanol were of commercial origin; the others were prepared by reduction of the appropriate arylacetic acids (ref.[22]) with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene[23]. During preparation of 4-methoxyphenylacetic acid[22] by alkaline hydrolysis of crude 4-methoxyphenylacetonitrile, a by-product was isolated and characterized as ethyl 4-methoxybenzyl ether (for another route of formation see ref.[24]); the compound is apparently contained in the starting nitrile which, in contrast with the more recent procedure[25], was prepared by an analogy of the preparative procedure for phenylacetonitrile[26], *i.e.* by a reaction of 4-methoxybenzyl chloride[25] with potassium cyanide in aqueous ethanol.

The molecule of the antidepressant "lopramine"[27–29] contains as the N-substituent a 4-chlorophenacyl group which, apparently due to biotransformation, is readily cleaved off by an enzymic oxidative N-dealkylation. This brought us to using phenacyl as the N-substituent in the present series. Hence we alkylated 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[3] with phenacyl bromide and 8-methylthio--10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[3] with phenacyl chloride in the presence of potassium carbonate, in the first case in 1-butanol, in the other in dimethylformamide (Method *D*) and thus obtained the phenacylpiperazine derivatives *VIIb* and *VIIc*. A typical N-substituent in the molecules of psychotropic substances

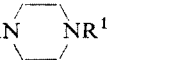


a, X = H
b, X = Cl
c, X = SCH_3

I, R = $CH_2CH_2C_6H_5$ (*d*)
II, R = 4-$CH_2CH_2C_6H_4CH_3$ (*e*)
III, R = 4 $CH_2CH_2C_6H_4Cl$ (*f*)
IV, R = 4-$CH_2CH_2C_6H_4OCH_3$ (*g*)
V, R = CH_2CH_2– (*h*)

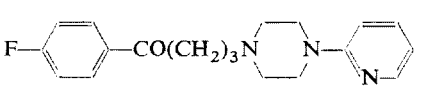
VI, R = $(CH_2)_3C_6H_5$ (*i*)
VII, R = $CH_2COC_6H_5$
VIII, R = 4-$(CH_2)_3COC_6H_4F$
IX, R = –
X, R = –

is 3-(4-fluorobenzoyl)propyl, occurring in the piperidine and piperazine derivatives with a high neuroleptic activity[30-32]. This residue was hence introduced into the molecules of our series, using alkylation of 8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[3] by 4-chloro-1-(4-fluorophenyl)-1-butanone[33] by Method *D*; the product was *VIIIc*.


[R has the same meaning as in formulas *I*—*VI* (see *d*—*i*)]

XI, $R^1 = COOC_2H_5$
XII, $R^1 = H$

A model for the last type of compounds prepared here was the tranquilizer "azaperone"[34-38], *i.e.* the N-(2-pyridyl)piperazine derivative *XIII*. 1-(2-Pyridyl)piperazine[39] prepared in a described fashion and the analogously synthesized 1-(4-pyridyl)-piperazine (for another method of preparation see ref.[40]) were converted by substitution reactions with 10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[41], its 8-chloro derivative[2] and its 8-methylthio derivative[42] in boiling chloroform (Method *E*) to the pyridylpiperazine derivatives *IXa*—*IXc*, *Xb* and *Xc*. For comparison, a sample of *XIII* (ref.[35]) was synthesized in the form of dimaleate.



XIII

All the compounds prepared are collected together with experimental data in Table I. The experimental section shows only examples of preparation by the general methods (*A* — *E*) and preparations carried out by other methods.

Most of the 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin derivatives were evaluated pharmacologically with main emphasis on the expected neuroleptic activity. All the results are shown in Table II and in the corresponding notes. As to the desired activity, the results may be summarized as follows. *1*) The N-aralkyl derivatives of noroctoclothepin (*Ib*—*VIb*) are all little toxic and little centrally active; on the other hand, some of them retain a relatively high degree of cataleptic activity (*Ib*, *IIb*, *IVb*) wherein they resemble the N-(4-methoxybenzyl) derivative of noroctoclothepin[3,4] *2*) The N-phenacyl derivative of noroctoclothepin *VIIb* has practically no central activity. *3*) The 3-(4-fluorobenzoyl)propyl derivative *VIIIc*, the structure of which represents a combination of two neuroleptic structural types[1-3,30,31], is a generally attractive compound which, at a very low toxicity and practical absence of the centrally depressant component, has practically the same cataleptic activity as chlorpromazine. It may be of special interest particularly because of the duration

of its neuroleptic effect. *4*) The 2-pyridyl derivatives *IXa–IXc* are all little toxic and practically inactive centrally; the analogous 4-pyridyl derivatives *Xb* and *Xc* are somewhat more toxic and become clearly centrally depressant at high doses.

As to other types of effects, mention should be made of the antihistamine effect of *Ib* and *IIb*, of the hypotensive effect of *IVb* and the antimicrobial activity of the 4-pyridyl derivatives *Xb* and *Xc* (in contrast with the lack of activity of analogous 2-pyridyl derivatives *IXa–IXc*). The other effects mentioned are only indications of the actual activities, being observed only at very high doses.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at room temperature or at a suitably raised temperature (not higher than 100°C). The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol) in a Unicam SP 200 G spectrophotometer and NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on alumina. Analyses of *I–XIII* are shown in Table I.

4-Methoxyphenylacetic Acid

A solution of 27·5 g 4-methoxybenzyl chloride[25] in 50 ml ethanol was added to a solution of 23·0 g KCN in 35 ml water and the mixture was refluxed under stirring for 7 h. After cooling, it was diluted with 500 ml water and the crude 4-methoxyphenylacetonitrile was isolated by extraction with ether; 21·5 g, b.p. 92–95°C/3 Torr. The total amount of product was dissolved in 135 ml ethanol and refluxed for 6 h under addition of a solution of 48 g 85% KOH in 40 ml water. After cooling, it was diluted with 1 litre water, the oily substance was extracted with benzene and the aqueous phase was acidified with hydrochloric acid. Filtration yielded 12·0 g 4-methoxyphenylacetic acid melting at 82°C; ref.[22] reports a m.p. of 81–83°C. Distillation of the benzene solution of the neutral compound resulted in 9·0 g ethyl 4-methoxybenzyl ether, b.p. 93–96°C/5 Torr. NMR spectrum: δ 7·40 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2), 6·97 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2), 4·46 (s, 2 H, $ArCH_2$), 3·79 (s, 3 H, OCH_3), 3·55 (q, J = 7·5 Hz, 2 H, OCH_2 in ethoxyl), 1·21 (t, J = 7·5 Hz, 3 H, C–CH_3). For $C_{10}H_{14}O_2$ (166·2) calculated: 72·26% C, 8·49% H; found 72·20% C, 8·52% H. Preparation of this compound was described by using various methods[24,43,44] and the boiling points reported are 111–113°C/11 Torr, 109–110°C/9 Torr and 90–92°C/4 Torr. According to ref.[45] the compound (b.p. 125–127°C/30 Torr was obtained as the sole product of a reaction of 4-methoxybenzyl chloride with KCN in ethanol; no proof of its identity has been provided.

2-(1-Naphthyl)ethanol

A 50% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate[23] (75 ml) was added dropwise under stirring over a period of 30 min to a solution of 16·7 g 1-naphthylacetic acid in 150 ml benzene. After 3 h of stirring at room temperature, the mixture was decomposed with 170 ml 10% solution of NaOH and processing of the benzene phase yielded 11·0 g (71%) product boiling at 195–200°C/25 Torr. For a product of the analogous reduction with $LiAlH_4$ ref.[21] reports a b.p. of 174–175°C/13 Torr. In analogy, 2-(4-tolyl)ethanol (85% of a crude

TABLE I

Piperazine Derivatives I—XIII

Compound[a] (method/% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% N	% S	% Hal
XId (*B*/81)	155—158/2·5	$C_{15}H_{22}N_2O_2$ (262·3)	68·67 68·20	8·45 8·45	10·68 10·61	—	—
XId-M	147—149 (ethanol)	$C_{19}H_{26}N_2O_6$ (378·4)	60·30 60·25	6·92 7·05	7·40 7·28	—	—
XIe (*B*/85)	162—164/0·7	$C_{16}H_{24}N_2O_2$ (276·4)	69·53 68·91	8·75 8·92	—	—	—
XIf (*B*/88[b])	168—172/1	$C_{15}H_{21}ClN_2O_2$ (296·8)	60·70 60·49	7·13 7·39	9·44 9·39	—	11·95 12·11
XIf-M	133 (ethanol)	$C_{19}H_{25}ClN_2O_6$ (412·9)	55·27 55·23	6·10 6·15	6·79 6·49	—	8·59 8·82
XIg (*B*/81)	170—173/1[c]	$C_{16}H_{24}N_2O_3$ (292·4)	65·72 65·74	8·27 8·39	9·58 9·52	—	—
XIg-M	123—125 (ethanol–ether)	$C_{20}H_{28}N_2O_7$ (408·4)	58·81 59·00	6·91 7·15	6·86 7·11	—	—
XIh-M (*B*/90)	149—152 (ethanol)	$C_{23}H_{28}N_2O_6$ (428·5)	64·47 64·46	6·59 6·77	6·54 6·43	—	—
XIi (*B*/89)	160—163/2	$C_{16}H_{24}N_2O_2$ (276·4)	69·53 69·61	8·75 8·99	10·14 10·38	—	—
XIi-M	117—120 (ethanol)	$C_{20}H_{28}N_2O_6$ (392·4)	61·21 61·06	7·19 7·33	7·13 7·32	—	—
XIId (*C*/78)	170—173/30[d]	—	— —	— —	— —	— —	— —
XIId-2 M	173—175 (aqueous ethanol)	$C_{20}H_{26}N_2O_8$ (422·4)	56·86 56·58	6·20 6·50	6·63 6·47	—	—
XIIe-2 MS (*C*/65[e])	212—214 (ethanol)	$C_{15}H_{28}N_2O_6S_2$ (396·5)	45·43 45·59	7·12 7·46	7·07 7·04	16·17 16·21	—
XIIf (*C*/79[b])	140—145/2	$C_{12}H_{17}ClN_2$ (224·7)	64·13 63·63	7·62 7·76	12·46 12·33	—	15·78 15·50
XIIf-2 M	168—170 (aqueous ethanol)	$C_{20}H_{25}ClN_2O_8$ (456·9)	52·57 51·64	5·52 5·71	6·13 6·24	—	7·76 7·91
XIIg (*C*/42)	58—60[f] (light petroleum)	—	— —	— —	— —	— —	— —

TABLE I
(*Continued*)

Compound[a] (method/% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% N	% S	% Hal
XIIh-M (*C*/82)	218–219 (dimethyl-formamide)	$C_{20}H_{24}N_2O_4$ (356·4)	67·39 67·04	6·79 7·18	7·86 7·89	— —	— —
XIIi (*C*/82)	100–105/2[g]	—	— —	— —	— —	— —	— —
XIIi-2 M	162–165 (ethanol)	$C_{21}H_{28}N_2O_8$ (436·5)	57·79 57·31	6·46 6·70	6·42 6·32	— —	— —
Ib-2 MS (*A*/76)	201–203 (ethanol)	$C_{28}H_{35}ClN_2O_6S_3$ (627·2)	53·61 54·10	5·62 5·90	4·46 4·55	15·34 15·58	5·65 5·55
IIb (*A*/85)	134–137[h] (benzene–light petroleum)	$C_{27}H_{29}ClN_2S$ (449·0)	72·21 72·68	6·51 6·89	6·24 6·09	7·14 7·20	7·90 7·88
IIb-2 MS	206–209 (ethanol–ether)	$C_{29}H_{37}ClN_2O_6S_3$ (641·3)	54·31 53·65	5·82 5·93	4·37 4·19	15·00 14·74	5·53 5·52
IIIb (*A*/89[b])	142–145 (benzene)	$C_{26}H_{26}Cl_2N_2S$ (469·5)	66·52 66·62	5·58 5·68	5·97 5·89	6·83 7·07	15·10 15·27
IIIb-MS	165–169 (ethanol–ether)	$C_{27}H_{30}Cl_2N_2O_3S_2$ (565·6)	57·33 57·16	5·35 5·48	4·95 4·90	11·34 11·57	12·54 12·67
IVb-M (*A*/50)	194–197 (ethanol–ether)	$C_{31}H_{33}ClN_2O_5S$ (581·1)	64·07 63·88	5·72 5·76	4·82 4·60	5·52 5·70	6·10 6·17
Vb-M (*A*/61)	210–212 (dimethyl-formamide)	$C_{34}H_{33}ClN_2O_4S$ (601·1)	67·93 68·23	5·53 5·80	4·66 4·64	5·33 5·75	5·90 5·77
VIb-2 M (*A*/84)	155–159 (ethanol–acetone)	$C_{35}H_{37}ClN_2O_8S$ (681·2)	61·71 61·48	5·47 5·64	4·11 4·08	4·71 4·75	5·20 5·45
VIb-2 M[i]	147–149 (ethanol)	$C_{35}H_{39}ClN_2O_9S$ (699·2)	60·12 60·35	5·62 5·89	4·01 4·36	— —	— —
VIIb[b]	142–145 (benzene–light petroleum)	$C_{26}H_{25}ClN_2OS$ (449·0)	69·55 69·27	5·61 5·60	6·24 6·11	7·14 7·18	7·90 8·09
VIIb-MS	164–166 (ethanol–ether)	$C_{27}H_{29}ClN_2O_4S_2$ (545·1)	— —	— —	5·14 4·83	11·76 11·99	6·50 6·55
VIIc-M (*D*/20[j])	138–142 (ethanol)	$C_{31}H_{32}N_2O_5S_2$ (576·7)	— —	— —	4·86 4·73	11·12 11·46	— —

TABLE I
(*Continued*)

Compound[a] (method/% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% N	% S	% Hal
VIIIc (*D*/69[b])	120—122 (ethanol–benzene)	$C_{29}H_{31}FN_2OS_2$ (506·7)	68·74 68·88	6·16 6·19	— —	12·65 12·43	3·75 3·61
VIIIc-2 MS	124—126 (aqueous acetone)	$C_{31}H_{39}FN_2O_7S_4$ (698·9)	53·27 53·33	5·62 5·79	— —	18·35 18·04	2·72 2·69
IXa (*E*/65)	178—179[k] (ethanol)	$C_{23}H_{23}N_3S$ (373·5)	73·96 74·09	6·21 6·30	11·25 11·04	8·58 8·30	— —
IXa-2 M[m]	118—120 (ethanol)	$C_{33}H_{37}N_3O_9S$ (651·7)	— —	— —	6·45 6·50	4·92 5·15	— —
IXb (*E*/77[b])	123—124 (ethanol)	$C_{23}H_{22}ClN_3S$ (407·9)	67·71 67·86	5·44 5·48	10·30 10·14	7·86 8·07	8·69 8·76
IXb-2 MS	234 (ethanol–ether)	$C_{25}H_{30}ClN_3O_6S_3$ (600·1)	50·03 49·80	5·04 5·09	7·00 6·85	16·02 15·80	5·91 5·85
IXc (*E*/73)	156—157[n] (ethanol–benzene)	$C_{24}H_{25}N_3S_2$ (419·5)	68·72 68·86	6·01 5·98	10·02 9·64	15·26 15·13	— —
IXc-2 MS[i]	146—150 (ethanol–ether)	$C_{26}H_{35}N_3O_7S_4$ (629·8)	49·58 49·70	5·60 5·54	6·67 6·59	20·36 20·73	— —
Xb (*E*/45)	159—160[o] (ethanol)	$C_{23}H_{22}ClN_3S$ (407·9)	67·71 67·93	5·44 5·76	10·30 9·96	7·86 7·95	8·69 8·92
Xb-2 M	159—160 (ethanol)	$C_{31}H_{30}ClN_3O_8S$ (640·1)	58·17 58·14	4·72 4·85	6·56 6·69	5·01 5·14	5·54 5·42
Xc (*E*/41)	194—195 (ethanol)	$C_{24}H_{25}N_3S_2$ (419·6)	68·70 69·06	6·01 6·20	10·01 9·78	15·28 15·19	— —
Xc-2 M	158—159 (ethanol)	$C_{32}H_{33}N_3O_8S_2$ (651·7)	58·97 58·88	5·10 5·20	6·45 6·39	9·84 9·68	— —
XIII-2 M[p]	160—163 (ethanol)	$C_{27}H_{30}FN_3O_9$ (559·5)	57·95 58·22	5·40 5·32	— —	— —	3·39 3·13

[a] M maleate, MS methanesulfonate. [b] See the experimental section. [c] Ref.[12] reports the preparation of the compound by a similar procedure and gives a b.p. for the base of 180°C/0·5 Torr. [d] Ref.[13–18] report the preparation of the compound by different procedures; a b.p. of 156 to 158°C/10 Torr was reported for the base; only hydrochloride is mentioned as salt. [e] The yield refers to the base melting at 62—64°C (light petroleum). [f] Ref.[12] describes the preparation of the compound by an analogous procedure and reports a b.p. of 136°C/0·1 Torr for the base. [g] Ref.[16] describes the preparation of the compound by a different procedure and reports a b.p. of 122 to

product, see ref.[7]), 2-(4-chlorophenyl)ethanol (65%, b.p. 150–153°C/30 Torr; ref.[8] reports 144–153°C/30–34 Torr) and 2-(4-methoxyphenyl)ethanol (89% of a crude product, see ref.[19,20]) were prepared.

1-[2-(4-Chlorophenyl)ethyl]-4-(ethoxycarbonyl)piperazine (*XIf*) (Method *B*)

A mixture of 32 g 2-(4-chlorophenyl)ethyl bromide[8] (b.p. 123–126°C/18 Torr) and 71 g 1-(ethoxycarbonyl)piperazine[5] was kept for 3 h at 120–125°C. After cooling, it was decomposed with 200 ml 10% solution of NaOH and extracted with benzene. The extract was washed with water, dried and distilled; 38 g (88%), b.p. 168–172°C/1 Torr. Neutralization of the base with maleic acid in ethanol yielded the hydrogen maleate melting at 133°C (ethanol).

1-[2-(4-Chlorophenyl)ethyl]piperazine (*XIIf*) (Method *C*)

A solution of 36·5 g *XIf* in 50 ml ethanol was treated with 40 g 85% KOH, the mixture was stirred while being heated up to boiling temperature and then (without stirring) refluxed for 3 h on a 110–120°C bath. After cooling, it was diluted with 70 ml water and extracted with benzene. Processing of the extract yielded 21·8 g (79%) base boiling at 180–190°C/25 Torr; after redistillation 140–145°C/2 Torr; m.p. 42–45°C. Di(hydrogen maleate), m.p. 168–170°C (aqueous ethanol).

8-Chloro-10-(4-[2-(4-chlorophenyl)ethyl]-piperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IIIb*) (Method *A*)

A mixture of 7·5 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2] and 12·0 g *XIIf* was heated for 3 h to 100°C. After cooling, 70 ml water was added and the whole extracted with benzene. The benzene solution was washed with water and shaken with excess dilute hydrochloric acid (1 : 3). The precipitated solid hydrochloride was filtered, combined with the acid aqueous phase of the filtrate and the suspension made alkaline with NH_4OH; the base was obtained by extrac-

Explanation to Table I

128°C/0·5 Torr for the base. [h] NMR spectrum δ 7·62 (d, J = 3·0 Hz, 1 H, 9-H in the tricycle), 6·80–7·50 (m, 6 H, remaining aromatic protons in the tricycle), 6·98 (s, 4 H, aromatic protons in the aralkyl), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$ in the tricycle), 2·60 (m, 12 H, remaining CH_2 groups), 2·25 (s, 3 H, $Ar-CH_3$). [i] Monohydrate. [j] Phenacyl chloride was used for the alkylation and under these conditions most of the secondary base remained intact. [k] NMR spectrum: δ 8·23 (dd, 1 H, 6-H of pyridine), 6·90–7·95 (m, 9 H, aromatic protons of the tricycle and 3-H of pyridine), 6·45–6·80 (m, 2H, 4,5-H_2 of pyridine), 3·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·90 to 3·00 (m, 3 H, $ArCH_2CHAr$), 2·71 (t, 4 H, $CH_2N^1CH_2$ of piperazine). [m] Solvate with a molecule of ethanol. [n] NMR spectrum: δ 8·20 (m, 1 H, 6-H of pyridine), 6·45–7·70 (m, 9 H, remaining aromatic protons with the exception of the next), 6·95 (*q*, J = 9·0; 2·5 Hz, 1 H, 7-H in the tricycle), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·70 (t, 4 H, CH_2. .N^1CH_2 of piperazine), 2·36 (s, 3 H, SCH_3). [o] NMR spectrum: δ 8·36 (d, J = 7·0 Hz, 2 H, 2,6-H_2 of pyridine), 7·75 (d, J = 2·0 Hz, 1 H, 9-H in the tricycle), 7·25–7·70 (m, 5 H, 1,2,3,4,6-H_5 in the tricycle), 7·12 (q, J = 9·0; 2·0 Hz, 1 H, 7-H in the tricycle), 6·70 (d, J = 7·0 Hz, 2 H, 3,5-H_2 of pyridine), 3·00–4·10 (m, 3 H, $ArCH_2CHAr$), 3·28 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·78 (m, 4 H, $CH_2N^1CH_2$ of piperazine). [p] The base was prepared according to ref.[35] and was converted to the novel dimaleate.

TABLE II

Pharmacological Properties (mg/kg) of Piperazine Derivatives *I*–*X* and of Reference Compounds on Oral Administration[a]

Compound[b]	Toxicity[c] LD_{50}	Rotating rod[d] ED_{50}	Catalepsy[e] ED_{50}	Hypothermia[f] ED	Antiamphetamine[g] ED_{50}	Potentiation of thiopental sleep ED[h]	Locomotor activity ED[i]
Ib-2 MS[j]	2·500	50	25–50	10	—	50–100	25
IIb-2 MS[k]	>2·500	10–50	5	1–5	5	2·5–5	5
IIIb-MS[m]	>2·500	>300	>300	50–100	5	1–2·5	>300
IVb-M[n]	1·500	300	5–10	5–10	1–2·5	2·5–5	25
Vb-M[o]	>2·500	>300	>300	100–300	10–25	10–25	>300
VIb-2 M[p]	200[+]	36[+]	> 50[q]	—	—	—	—
VIIb-MS	> 500[r]	260[+]	>100[q]	—	—	—	—
VIIIc	>1·000	>100[s]	19·5[+]	—	—	—	—
IXa-2 M	1·000	>500[s]	> 50[t]	—	—	—	—
IXb-2 MS	>1·000[u]	>500[v]	> 50[t]	—	—	—	—
IXc-2 MS	>1·000[r]	>500[w]	> 50[y]	—	—	—	—
Xb-2 M[z]	240[+]	88[+]	> 50[t]	—	—	—	—
Xc-2 M[aa]	> 500[r]	100	> 50[t]	—	—	—	—
XIII-2 M[bb]	62·5	6·5	> 13	13	13	6·5	13
OCT[cc]	78[+]	2·2[+]	4·3[+]	2·5[ee]	1·0[ff]	0·25[gg]	1·6[hh]
CPZ[dd]	198[+]	8·2[+]	16[+]	5·0[ee]	5·6[ff]	2·5[gg]	4·8[hh]

Explanation to Table II

[a] Values of LD_{50} and ED (or ED_{50}) are the results of orientation experiments carried out in connection with a general pharmacological screening; the meaning of ED is defined for the individual columns separately; values marked with $^+$ represent LD_{50} and ED_{50} determined in detailed experiments using groups of ten animals; they refer to the corresponding bases. [b] MS methanesulfonate, M maleate. [c] Acute toxicity determined in mice. [d] The dose bringing about ataxia in mice at the time of maximum effect has been determined (incoordinating effect taken as the criterion of central depressant activity). [e] Cataleptic effect determined in rats. [f] A hypothermic effect was examined in rats when taking the rectal temperature; ED is the dose causing the body temperature to drop by 1·0°C. [g] Determined in a test on mice; ED_{50} is the dose which protects 50% mice against the lethal effect of 30 mg amphetamine/kg, after *i.p.* application 60 min prior to administering the tested compound *p.o.* [h] Estimated in mice; ED is the dose which prolongs thiopental sleep (40 mg/kg thiopental *i.v.* in the form of 0·4% solution applied 60 min prior to an oral administration of the tested compound) to twice the control value. [i] Inhibition of locomotor activity estimated in mice; ED is the dose which causes a significant drop of motility in known (or unknown) surroundings. [j] The compound has an antihistamine effect in the histamine detoxication test in guinea-pigs; ED_{50} (dose protecting 50% guinea-pigs from the lethal effect of 5 mg histamine/kg administered intrajugularly 60 min after oral application of the tested compound) is 5 mg/kg; the compound prolongs the survival time of an asphyctic mouse myocard, ED = 100—300 mg/kg (dose extending survival with statistical significance); at a concentration of 25 μg/ml it inhibits the growth of *Mycobacterium tuberculosis* H37Rv *in vitro*. [k] The compound has an antihistamine effect (see [j]), ED_{50} = 25 mg/kg; it brings about miosis of mouse pupil at a dose of 100—300 mg/kg; it has an analgesis effect in Haffner's test on mice, ED_{50} = 100—300 mg/kg; it extends the survival time of an asphyctic mouse myocard (see [j]), ED = 25—50 mg/kg; it had an antiarrhythmic effect toward aconitine in rats in pentobarbital narcosis, ED = 100—300 mg/kg (dose which prolongs significantly the latency of occurrence of chamber extrasystoles following infusion of a solution of aconitine, applied 60 min after oral administration of the tested compound). [m] The compound has a slight anticonvulsant effect toward pentetrazol in mice, ED = 100—300 mg/kg (dose which prolongs significantly the period of latency of convulsions and delays exitus following infusion of a 0·5% solution of pentetrazol applied 60 min after an oral administration of the tested compound); it has no anticonvulsant action in the electroshock test in mice; at a dose of 100—300 mg/kg is depresses the blood pressure of normotensive rats by 10%. [n] At a dose of 300 mg/kg the compound has an antiarrhythmic effect toward aconitine in a test on rats (see [k]) and raises the blood sugar level of rats by 20%; at a dose of 25—50 mg/kg it reduces the blood pressure of normotensive rats by 10%. [o] The compound brings about miosis of the mouse pupil at a dose of 300 mg/kg. [p] At a concentration of 25 μg/ml it inhibits growth of *Mycobacterium tuberculosis* H37Rv *in vitro*. [q] The dose caused catalepsy of 30% animals of a group. [r] The dose shown has no lethal effect. [s] The dose shown does not cause ataxia. [t] The dose shown caused catalepsy in one rat out of ten. [u] The dose shown has a lethal effect on 40% animals. [v] The dose shown brought about ataxia in 10—20% animals. [w] The dose shown brings about ataxia in 40% animals. [y] The dose shown brings about catalepsy in 20% animals. [z] The compound has an antibacterial effect *in vitro* (the minimum inhibitory concentrations in μg/ml are shown): *Streptococcus β-haemolyticus*, 6·25; *Staphylococcus pyogenes aureus*, 6·25; *Mycobacterium tuberculosis* H37Rv, 12·5. [aa] The compound has the same antibacterial effect as *Xb*; in addition, it inhibits at the concentrations shown the growth of the following microorganisms *in vitro*: *Saccharomyces pasterianus*, 31·2; *Trichophyton mentagrophytes*, 31·2; *Candida albicans*, 125; *Aspergillus niger*, 125. [bb] In contrast with the other compounds in the table, this was applied parenterally, *i.e.* intravenously (unless stated otherwise); in tests

tion with benzene, 11·2 g (89%), m.p. 142—145°C (benzene). NMR spectrum: δ 7·74 (d, J = = 3·0 Hz, 1 H, aromatic 9-H), 7·70—7·00 (m, remaining aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$ in the tricycle), c. 2·63 (m, 12 H, remaining CH_2 groups). Neutralization of the base with methanesulfonic acid in ethanol yielded the methanesulfonate, m.p. 165—169°C (ethanol–ether).

8-Chloro-10-(4-phenacylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*VIIb*)

A mixture of 8·3 g 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[3], 5·0 g K_2CO_3, 6·0 g phenacyl bromide and 70 ml 1-butanol was heated under stirring for 8 h to 130°C. The inorganic salts were filtered off from the hot mixture and the filtrate was left to stand for 24 h at room temperature. 3·0 g hydrobromide of the starting base then precipitated (m.p. 260—265°C) and was filtered. Evaporation of the filtrate yielded 5·9 g (52%) crude product which crystallized after mixing with ethanol, m.p. 142—145°C (benzene–light petroleum). UV spectrum: λ_{max} 241 nm (log ε 4·30), 265 nm (4·07). IR spectrum: 689, 750, 758, 815, 825, 885 (5, 4 and 2 adjacent and solitary Ar—H), 1572, 1590 (Ar), 1682 cm^{-1} (COAr). NMR spectrum: δ 8·02 (m, 2 H, 2,6-H_2 in phenacyl), 7·70 (d, J = 2·5 Hz, 1 H, 9-H in the tricycle), 7·15—7·65 (m, 8 H, remaining aromatic protons except the next), 7·02 (q, J = 9·0; 2·5 Hz, 1 H, 7-H in the tricycle), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·78 (s, 2 H, $ArCOCH_2$), 2·65 (bs, 8 H, 4 CH_2 of piperazine). Methanesulfonate, m.p. 164—166°C (ethanol–ether).

8-Methylthio-10-(4-[3-(4-fluorobenzoyl)propyl]piperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*VIIIc*) (Method *D*)

A mixture of 8·50 g 8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[3], 8·0 g 4-chloro-1-(4-fluorophenyl)-1-butanone[33], 5·0 g K_2CO_3 and 25 ml dimethylformamide was heated under stirring for 6 h to 100°C. Filtration of the hot mixture removed inorganic salts and the filtrate was evaporated at reduced pressure. The residue was dissolved in benzene and the solution chromatographed on a column of 300 g neutral alumina (activity II). Elution with benzene yielded 8·6 g (69%) homogeneous product which crystallized from a mixture of ethanol and benzene, m.p. 120—122°C. UV spectrum: λ_{max} 239 nm (log ε 4·31), 275 nm (4·24), 309 nm (3·09), 334 nm (2·91). IR spectrum: 758, 803, 838, 885 (4 and 2 adjacent and solitary Ar—H), 1005

Explanation to Table II (continued)

done *in vivo* the compound was applied at a dose of 13 mg/kg, in some tests at half the dose, *i.e.* 6·5 mg/kg; in these doses the compound was effective in all the tests (with the exception of catalepsy) which does not exclude the possibility of its being effective even in lower doses; in the doses shown it has a pronounced analgesic effect in Haffner's test (see[k]),a protracted hypotensive and adrenolytic effect on rats, it prolongs the bleeding time in mice without affecting coagulation, on *i.p.* administration it has a protracted vasodilating effect evaluated on the basis of increased temperature of the guinea-pig ear-lobe; it has a more pronounced anaesthetic effect in the rabbit cornea test than trimecaine; it has a positively inotropic effect on isolated rabbit atrium. [cc] Octoclothepin, *i.e.* 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[2]. [dd] Chlorpromazine. [ee] Threshold dose bringing about a statistically significant drop of body temperature in mice. [ff] Like[g] but amphetamine was applied here intravenously. [gg] Threshold dose which prolongs with statistical significance the narcotic effect of thiopental (1·4—1·7 times) when applied prophylactically. [hh] Dose which decreeases locomotor activity of mice to 50% of the average control value when using the photo-cell method.

(Ar—F), 1230 (C—O), 1502, 1596 (Ar), 1682 cm^{-1} (COAr). NMR spectrum: δ 8·12 (m, 2 H, 2,6-H_2 of benzoyl), 7·62 (d, J = 2·0 Hz, 1 H, 9-H in the tricycle), 7·15 (m, 2 H, 3,5-H_2 of 4-fluorobenzoyl), 7·00—7·55 (m, 6 H, remaining aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·95 (t, J = 6·0 Hz, 2 H, $COCH_2$), c. 2·50 (m, 10 H, 5 NCH_2), 2·41 (s, 3 H, SCH_3), 1·98 (m, 2 H, middle CH_2 in the propane chain). Dimethanesulfonate, m.p. 124—126°C (aqueous ethanol).

1-(4-Pyridyl)piperazine

A mixture of 63·2 g anhydrous piperazine, 58·3 g 4-bromopyridine, 35 g Na_2CO_3 and 240 ml 3-methylbutanol was refluxed under stirring for 5 h (in a 180°C bath) using a water separator for the water separating from the condensate. The inorganic salts were filtered from the hot solution and the filtrate was left to stand overnight. A total of 12·7 g piperazine hydrobromide crystallized (m.p. 196—198°C) which was filtered and the filtrate evaporated; 28·2 g (47%) base, crystallizing from heptane and melting at 138—141°C. NMR spectrum: δ 8·32 (dd, 2 H, 2,6-H_2 of pyridine), 6·66 (dd, 2 H, 3,5-H_2 of pyridine), 3·25 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·95 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 1·88 (s, 1 H, NH). Ref.[40] described the preparation of the compound by a catalytic debenzylation of 1-benzyl-4-(4-pyridyl)piperazine on palladium and reports a m.p. of 140°C.

8-Chloro-10-[4-(2-pyridyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IXb*) (Method *E*)

A mixture of 5·6 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2], 9·75 g 1-(2-pyridyl)piperazine[39] (b.p. 132°C/2·3 Torr) and 8 ml chloroform was refluxed for 7 h. After evaporation of the chloroform the residue was mixed with 100 ml water and extracted with benzene. The benzene solution was washed with water and shaken with 70 ml 3M-HCl. The acid aqueous phase was separated and made alkaline with NH_4OH to liberate the base which was isolated by extraction with benzene; 6·25 g (77%), m.p. 123—124°C (ethanol). NMR spectrum: δ 8·20 (q. 1 H, 6-H of pyridine), 6·50—7·80 (m, 10 H, remaining aromatic protons), 3·91 (s, 1 H, Ar—CH—N), 3·70 and 3·10 (2 d, J = 9·0 Hz, 2 H, $ArCH_2$), 3·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·70 (t, 4 H, $CH_2N^1CH_2$ of piperazine). Dimethanesulfonate, m.p. 234°C (ethanol–ether).

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