POTENTIAL ANTICONVULSANTS: SUBSTITUTED N-BENZYLIDENE DERIVATIVES OF 10-(4-AMINOPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS*

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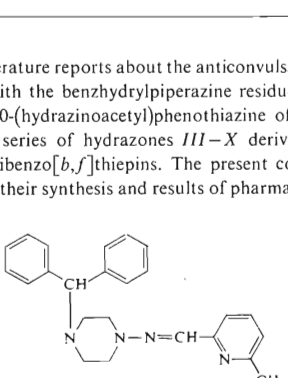
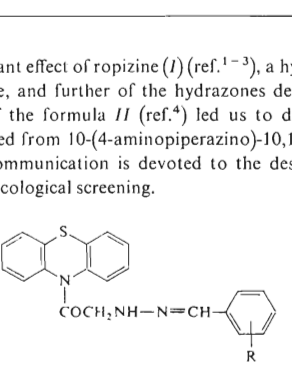
Reactions of 10-(4-aminopiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepins *XIVa*–*XIVd* with benzaldehyde, 3,4-dimethoxybenzaldehyde, 4-dimethylaminobenzaldehyde, salicylaldehyde, 3-ethoxy-4-hydroxybenzaldehyde, 2-(2-dimethylaminoethoxy)benzaldehyde, 3-(2-dimethylaminoethoxy)benzaldehyde and 3-ethoxy-4-(2-dimethylaminoethoxy)benzaldehyde afforded a series of 19 hydrazones *IIIa*–*Xc*. Some of them showed the expected anticonvulsant effect but only towards pentetrazole; antagonism of maximal electroshock seizures was not observed. In general, the products have a character of tranquillizers: in higher doses they produce central depression, potentiate the thiopental sleeping time, have hypothermic action; in single cases antiamphetamine, antireserpine, antihistamine and cataleptic effects were observed. The water-soluble salts of the basic hydrazones *VIIIa*, *VIIIc*, *IXc* and *Xc*, administered parenterally, showed a rather high acute toxicity and revealed also adrenolytic and hypotensive activity.

The literature reports about the anticonvulsant effect of ropizine (*I*) (ref.[1–3]), a hydrazone with the benzhydrylpiperazine residue, and further of the hydrazones derived from 10-(hydrazinoacetyl)phenothiazine of the formula *II* (ref.[4]) led us to design a new series of hydrazones *III*–*X* derived from 10-(4-aminopiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepins. The present communication is devoted to the description of their synthesis and results of pharmacological screening.



I



II

The starting compounds for the synthesis of hydrazones *III*–*X* were 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIa*) (ref.[5]), its 2-chloro derivative *XIb* (ref.[6])

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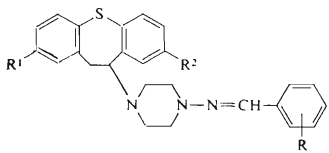
8-chloro derivative *XIc* (ref.[7,8]) and the new 2,8-dichloro derivative *XId* which was obtained by alkaline hydrolysis of the carbamate *XIId*. In a previous communication[5] we described the transformation of the secondary amine *XIa* by treatment with nitrous acid to the N-nitroso derivative *XIIIa* which was reduced with lithium aluminium hydride to the N-amino derivative *XIVa*. This reduction reaction has now been carried out in ether and similarly – *via* the nitroso derivatives *XIIIb*–*XIIId* – the hydrazine derivatives *XIVb*–*XIVd* were prepared.



III, R = H
IV, R = 3,4-$(OCH_3)_2$
V, R = 4-$N(CH_3)_2$
VI, R = 2-OH
VII, R = 3-OC_2H_5-4-OH
VIII, R = 2-$OCH_2CH_2N(CH_3)_2$
IX, R = 3-$OCH_2CH_2N(CH_3)_2$
X, R = 3-OC_2H_5-4-$OCH_2CH_2N(CH_3)_2$

In formulae III–XV: *a*, $R^1 = R^2 = H$; *b*, $R^1 = Cl$, $R^2 = H$; *c*, $R^1 = H$, $R^2 = Cl$; *d*, $R^1 = R^2 = Cl$

The hydrazones *III*–*X* (in series *a*–*d*) were obtained by reactions of the hydrazine derivatives *XIV* with benzaldehyde, 3,4-dimethoxybenzaldehyde, 4-dimethylaminobenzaldehyde, salicylaldehyde, 3-ethoxy-4-hydroxybenzaldehyde, 2-(2-dimethylaminoethoxy)benzaldehyde[9], 3-(2-dimethylaminoethoxy)benzaldehyde (*XVI*) and 3-ethoxy-4-(2-dimethylaminoethoxy)benzaldehyde (*XVII*) in boiling ethanol. The last two of the aldehydes were prepared from 3-hydroxybenzaldehyde and 3-ethoxy-4-hydroxybenzaldehyde by reactions with sodium methoxide and 2-dimethylaminoethyl chloride in boiling chlorobenzene (method, *cf.*[9]). The hydrazones crystallize by cooling of the reaction mixtures and were isolated as bases. The hydrazones *III*–*VII* do not afford salts by reactions with organic acids and they were used for pharmacological testing as bases. The strongly basic hydrazones *VIII*–*X* were tested in the form of hydrochlorides. All hydrazones prepared are assembled in Table I; the Experimental describes only the preparation of compound *IVb* (general method) and further the somewhat anomalous case of the compound *VIIb*. In this case the use of the general method (*i.e.* equimolecular quantities of the hydrazine derivative *XIVb* and 3-ethoxy-4-hydroxybenzaldehyde) led to precipitation of the molecular complex 1 : 1 of the product *VIIb* with the starting hydrazine *XIVb* and the desired substance *VIIb* could be obtained only by repeated treatment of this molecular complex with the aldehyde.

TABLE I

Substituted 10-[4-(Benzylideneamino)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepins (All compounds were prepared by the general method described in the Experimental for compound *IVb*)

Compound (yield, %)	M.p., °C (Solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% Cl	% N	% S
IIIa	175–177[a]	$C_{25}H_{25}N_3S$	75·15	6·31	—	10·25	8·02
(90)	(ethanol)	(399·6)	75·15	6·27	—	10·74	8·15
IIIb	157–160[b]	$C_{25}H_{24}ClN_3S$	69·19	5·57	8·17	9·68	7·39
(84)	(ethanol)	(434·0)	69·52	5·56	8·25	10·03	7·41
IIIc	176–177[c]	$C_{25}H_{24}ClN_3S$	69·19	5·57	8·17	9·68	7·39
(85)	(ethanol)	(434·0)	69·38	5·58	8·17	9·70	7·82
IIId	163–166[d]	$C_{25}H_{23}Cl_2N_3S$	64·10	4·95	15·14	8·97	6·84
(70)	(ethanol)	(468·5)	64·30	4·88	15·08	9·34	6·85
IVa	164–165[e]	$C_{27}H_{29}N_3O_2S$	70·56	6·34	—	9·14	6·97
(95)	(ethanol)	(459·6)	70·56	6·74	—	8·99	7·10
IVb	204–206	$C_{27}H_{28}ClN_3O_2S$	65·64	5·71	7·18	8·50	6·49
(84)[f]	(dioxane)	(494·1)	66·03	5·77	7·18	8·44	6·20
IVc	138–140[g]	$C_{27}H_{28}ClN_3O_2S$	65·64	5·71	7·18	8·50	6·49
(90)	(ethanol)	(494·1)	65·65	5·71	7·34	8·33	6·48
Va	225–227[h]	$C_{27}H_{30}N_4S$	73·27	6·83	—	12·66	7·24
(86)	(dioxane)	(442·6)	72·91	6·67	—	12·32	7·18
VIa	179–182[i]	$C_{25}H_{25}N_3OS$	72·26	6·06	—	10·11	7·72
(92)	(ethanol)	(415·6)	72·51	6·40	—	10·24	7·29
VIb	195–197[j]	$C_{25}H_{24}ClN_3OS$	66·73	5·38	7·88	9·34	7·13
(86)	(ethanol)	(450·0)	67·00	5·32	8·10	9·63	7·19
VIc	184–185[k]	$C_{25}H_{24}ClN_3OS$	66·73	5·38	7·88	9·34	7·13
(89)	(ethanol)	(450·0)	67·24	5·50	7·80	9·23	7·14
VId	143–145[l]	$C_{25}H_{23}Cl_2N_3OS$	61·98	4·79	14·64	8·67	6·62
(70)	(ethanol)	(484·5)	61·95	4·56	14·82	8·36	6·77
VIIa	133–135[m]	$C_{27}H_{29}N_3O_2S$	70·56	6·56	—	9·14	6·97
(92)	(ethanol)	(459·6)	70·47	6·48	—	9·49	6·85
VIIb	127–129	$C_{27}H_{28}ClN_3O_2S$	65·64	5·71	7·17	8·51	6·49
f	(ethanol)	(494·1)	65·65	5·70	7·53	8·68	6·38
VIIc[n]	94–95[o]	$C_{27}H_{28}ClN_3O_2S$	67·20	6·39	6·61	7·83	5·99
(86)	(cyclohexane)	$+ 0{\cdot}5\ C_6H_{12}$ (536·1)	67·29	6·35	6·92	7·94	6·37
VIIIa	113–116[p]	$C_{29}H_{34}N_4OS$	71·57	7·04	—	11·51	6·59
(90)	(ethanol)	(486·7)	71·28	7·25	—	11·46	6·98

TABLE I
(*Continued*)

Compound (yield, %)	M.p., °C (Solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% Cl	% N	% S
VIIIa.3 HCl	199–202 (ethanol–ether)	$C_{29}H_{38}Cl_3N_4OS$ (597·1)	58·34 58·14	6·42 6·26	17·81 17·74	9·38 9·31	5·37 5·70
VIIIc (95)	154–156[q] (ethanol)	$C_{29}H_{33}ClN_4OS$ (521·1)	66·84 66·99	6·38 6·34	6·80 7·19	10·75 10·72	6·15 6·60
VIIIc.HCl	132–136 (ethanol–ether)	$C_{29}H_{34}Cl_2N_4OS$ (557·6)	62·47 62·03	6·15 6·53	12·72 12·96	10·05 9·79	5·75 5·73
IXc (91)	108–111[r] (methanol)	$C_{29}H_{33}ClN_4OS$ (521·1)	66·84 67·11	6·38 6·40	6·80 6·81	10·75 10·69	6·15 6·29
IXc.HCl[s]	120–124 (95% ethanol–ether)	$C_{29}H_{34}Cl_2N_4OS + H_2O$ (575·6)	60·51 60·76	6·30 6·38	12·32 12·96	9·73 9·56	5·57 5·92
Xc (75)	83–86[t] (light petroleum)	$C_{31}H_{37}ClN_4O_2S$ (565·2)	65·88 65·19	6·60 6·87	6·27 6·34	9·91 9·77	5·67 5·70
Xc.2 HCl[s]	194–199 (ethanol)	$C_{31}H_{39}Cl_3N_4O_2S + H_2O$ (656·1)	56·75 56·66	6·30 6·14	16·21 17·02	8·54 8·42	4·89 5·10
Xc.3 HCl[s]	155–159 (ethanol)	$C_{31}H_{40}Cl_4N_4O_2S + H_2O$ (692·6)	53·75 53·79	6·11 6·08	20·48 19·90	8·09 8·09	4·63 5·10

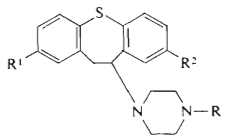
[a] UV spectrum: λ_{max} 290 nm (log ε 4·32); IR spectrum: 700, 755, 769 (5 and 4 adjacent Ar—H), 1 572, 1 598, 3 055 cm^{-1} (Ar); ^1H NMR spectrum: δ 6·90–7·80 (m, 14 H, ArH and ArCH=), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·12 and 2·71 (2 def. t, 8 H, 4 CH_2N of piperazine). [b] UV spectrum: λ_{max} 289 nm (log ε 4·38); IR spectrum: 696, 759, 821, 878, 898 (5, 4 and 2 adjacent and solitary Ar—H), 1 569, 1 589, 1 604 (Ar), 1 644 cm^{-1} (C=N); ^1H NMR spectrum: δ 7·00 to 7·80 (m, 13 H, ArH and ArCH=), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·20 and 2·85 (2 def. t, 8 H, 4 CH_2N of piperazine). [c] UV spectrum: λ_{max} 285 nm (log ε 4·35); IR spectrum (KBr): 692, 753, 829, 889 (5, 4 and 2 adjacent and solitary Ar—H), 1 555, 1 572, 1 596, 3 005, 3 045 (Ar), 1 635 cm^{-1} (C=N); ^1H NMR spectrum: δ 7·68 (d, 1 H, 1-H), 6·90–7·60 (m, 12 H, remaining ArH and ArCH=), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·20 and 2·85 (2 def. t, 8 H, 4 CH_2N of piperazine). [d] UV spectrum: λ_{max} 287 nm (log ε 4·40); IR spectrum (KBr): 696, 757, 817, 884 (5 and 2 adjacent and solitary Ar—H), 1 563, 1 580, 1 595, 3 020, 3 060, 3 075 (Ar), 1 633 cm^{-1} (C=N); ^1H NMR spectrum: δ 6·90–7·80 (m, 12 H, ArH and ArCH=), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·20 and 2·85 (2 def. t, 8 H, 4 CH_2N of piperazine). [e] UV spectrum: λ_{max} 290 nm (log ε 4·35), 308 nm (4·36); IR spectrum: 754, 765, 813, 865 (4 and 2 adjacent and solitary Ar—H), 1 261 ($ArOCH_3$), 1 513, 1 570, 1 601, 3 048, 3 070 (Ar), 1 650 cm^{-1} (C=N); ^1H NMR spectrum: δ 6·70–7·70 (m, 12 H, ArH and ArCH=), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·88 and 3·85 (2 s, 6 H, 2 OCH_3), 3·10 and 2·80 (2 m, 8 H, 4 CH_2N of piperazine). [f] See Experimental. [g] UV

TABLE I
(*Continued*)

spectrum: λ_{max} 285—290 nm (log ε 4·36), 308 nm (4·37); IR spectrum: 766, 821, 889 (4 and 2 adjacent and solitary Ar—H), 1 159, 1 250, 1 270, 2 820 ($ArOCH_3$), 1 521, 1 583 (Ar), 1 610 cm^{-1} (C=N); ^1H NMR spectrum: δ 7·68 (d, 1 H, 1-H), 6·70—7·60 (m, 10 H, remaining ArH and ArCH=), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·90 and 3·85 (2 s, 6 H, 2 OCH_3), 3·12 and 2·80 (2 def. t, 8 H, 4 CH_2N of piperazine). [h] UV spectrum: λ_{max} 313 nm (log ε 4·13), infl. at 334 nm (4·08); IR spectrum: 763, 821 (4 and 2 adjacent Ar—H), 1 537 (Ar), 1 618 cm^{-1} (C=N); ^1H NMR spectrum: δ 7·45 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of benzylidene), 6·62 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of benzylidene), 7·00—7·70 (m, 9 H, remaining ArH and ArCH=), 3·00—4·00 (m, 3 H, $ArCH_2$·.$CHAr$), 3·09 and 2·78 (2 def. t, 8 H, 4 CH_2N of piperazine), 2·90 (s, 6 H, CH_3NCH_3). [i] UV spectrum: λ_{max} 281 nm (log ε 4·33), 288 nm (4·32), 312 nm (4·22); IR spectrum (KBr): 763 (4 adjacent Ar—H), 1 277 (ArOH), 1 499, 1 572, 1 600, 3 000, 3 055 (Ar), 1 624 (C=N), 3 420 cm^{-1} (OH); ^1H NMR spectrum: δ 11·68 (s, 1 H, OH), 6·70—7·70 (m, 13 H, ArH and ArCH=), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·10 and 2·80 (2 m, 8 H, 4 CH_2N of piperazine). [j] UV spectrum: λ_{max} 281·5 nm (log ε 4·35), 312 nm (4·21), infl. at 288 nm (4·34); IR spectrum: 756, 809, 814, 909 (4 and 2 adjacent and solitary Ar—H), 1 271 (ArOH), 1 570, 1 601 (Ar), 1 630 cm^{-1} (C=N); ^1H NMR spectrum: δ 11·70 (s, 1 H, OH), 7·70 (s, 1 H, ArCH=), 6·70—7·60 (m, 11 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·15 and 2·85 (2 def. t, 8 H, 4 CH_2N of piperazine). [k] UV spectrum: λ_{max} 230 nm (log ε 4·26), 275 nm (4·32), 311 nm (4·18); IR spectrum: 760, 838, 898 (4 and 2 adjacent and solitary Ar—H), 1 146, 1 154, 1 280, (ArOH), 1 500, 1 538, 1 579, 1 603, 3 010, 3 060 (Ar), 1 628 cm^{-1} C=N); ^1H NMR spectrum: δ 11·64 (s, 1 H, OH), 6·70 to 7·70 (m, 12 H, ArH and ArCH=), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·12 and 2·80 (2 def. t, 8 H, 4 CH_2N of piperazine). [l] UV spectrum: λ_{max} 281 nm (log ε 4·38), 311 nm (4·24), inflexes at 288 nm (4·35) and 320 nm (4·20); IR spectrum: 756, 807, 819, 828, 880, 898 (4 and 2 adjacent and solitary Ar—H), 1 270 (ArOH), 1 572, 1 601 (Ar), 1 629 cm^{-1} (C=N); ^1H NMR spectrum: δ 11·70 (s, 1 H, OH), 7·73 (s, 1 H, ArCH=N), 7·72 (d, J = 2·5 Hz, 1 H, 9-H), 6·80—7·60 (m, 9 H, remaining ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·20 and 2·82 (2 def. t, 8 H, 4 CH_2N of piperazine). [m] ^1H NMR spectrum: δ 6·70—7·70 (m, 12 H, ArH and ArCH=), 5·78 (bs, 1 H, OH), 4·11 (q, J = 7·0 Hz, 2 H, OCH_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·12 and 2·80 (2 def. t, 8 H, 4 CH_2N of piperazine), 1·40 (t, J = 7·0 Hz, 3 H, CH_3). [n] Solvate with 0·5 molecule of cyclohexane. [o] UV spectrum: λ_{max} 280 nm (log ε 4·36), 307 nm (4·35); IR spectrum: 759, 820, 832, 902 (4 and 2 adjacent and solitary Ar—H), 1 244 (ArOH), 1 268, 1 278 (ArOR), 1 516, 1 552, 1 582 (Ar), 1 611 cm^{-1} (C=N); ^1H NMR spectrum: δ 7·75 (d, 1 H, 1-H), 6·90—7·60 (m, 10 H, remaining ArH and ArCH=), 5·85 (bs, 1 H, OH), 4·10 (q, J = 7·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·18 and 2·85 (2 def. t, 8 H, 4 CH_2N of piperazine), 1·48 (t, J = 7·0 Hz, 3 H, CH_3), 1·48 (s, 6 H, 3 CH_2 of cyclohexane). [p] UV spectrum: λ_{max} 235 nm (log ε 4·30), 280 nm (4·25), 313 nm (4·25), infl. at 290 nm (4·24); IR spectrum: 754 (4 adjacent Ar—H), 1 143, 1 246 (ArOR), 1 492, 1 567, 1 603, 3 000, 3 045 (Ar), 2 760, 2 815 cm^{-1} (CH_3—N—CH_3); ^1H NMR spectrum: δ 6·70—8·00 (m, 13 H, ArH and ArCH=), 4·10 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00 to 4·00 (m, 3 H, $ArCH_2CHAr$), 3·12 and 2·80 (2 m, 8 H, 4 CH_2N of piperazine), 2·72 (t, J = 6·0 Hz, 2 H, CH_2N in dimethylaminoethoxy), 2·30 (s, 6 H, CH_3NCH_3). [q] Mass spectrum, m/z: 520 (M^+ corresponding to $C_{29}H_{33}ClN_4OS$), 505, 448, 344, 327, 244, 209, 190, 178, 164; UV spectrum: λ_{max} 397 nm (log ε 4·15), 312·5 nm (4·28); IR spectrum: 750, 812, 900 (4 and 2 adjacent and solitary Ar—H), 1 142 (ArOR), 1 491, 1 567, 1 604, 3 035, 3 055 (Ar), 2 760, 2 813 cm^{-1} (CH_3NCH_3); ^1H NMR spectrum: δ 6·70—8·00 (m, 12 H, ArH and ArCH=), 4·10 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·12 and 2·80 (2 m, 8 H, 4 CH_2N of piperazine), 2·71 (t, J = 6·0 Hz, 2 H, CH_2N in dimethylaminoethoxy), 2·30 (s, 6 H, CH_3NCH_3). [r] UV

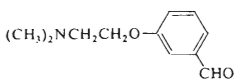
TABLE I
(*Continued*)

spectrum: λ_{max} 294 nm (log ε 4·38); IR spectrum (KBr): 691, 756, 780, 790, 820, 832, 887, 900 (4, 3 and 2 adjacent and solitary Ar—H), 1 132, 1 270 (ArOR), 1 490, 1 570, 1 594, 3 048 (Ar), 1 609 (C=N), 2 755, 2 805 cm^{-1} (CH_3NCH_3); ^1H NMR spectrum: δ 7·66 (d, J = 2·5 Hz, 1 H, 1-H), 6·70—7·60 (m, 11 H, remaining ArH and ArCH=), 4·08 (t, J = 5·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·15 and 2·80 (bm, 8 H, 4 CH_2N of piperazine), 2·70 (t, J = 7·0 Hz, 2 H, CH_2N in dimethylaminoethoxy), 2·30 (s, 6 H, CH_3NCH_3). [s] Monohydrate. [t] UV spectrum: λ_{max} 291 nm (log ε 4·35), 308 nm (4·35), infl. at 280 nm (4·33); IR spectrum: 755, 816, 890 (4 and 2 adjacent and solitary Ar—H), 1 144, 1 262 (ArOR), 1 514, 1 576, 1 600 (Ar), 1 674 (C=N), 2 740 cm^{-1} (CH_3—N—CH_3); ^1H NMR spectrum: δ 7·72 (d, J = 2·0 Hz, 1 H, 1-H), 6·80—7·70 (m, 10 H, remaining ArH and ArCH=), 4·15 (m, 4 H, 2 CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·22 and 2·88 (2 m, 8 H, 4 CH_2N of piperazine), 2·80 (t, 2 H, remaining CH_2N), 2·40 (s, 6 H, CH_3NCH_3), 1·49 (t, J = 7·0 Hz, 3 H, CH_3 in ethoxyl).

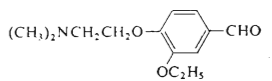


XI, R = H
XII, R = $COOC_2H_5$

XIII, R = NO
XIV, R = NH_2
XV, R = $N{=}C(CH_3)_2$



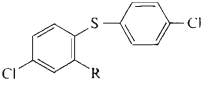
XVI



XVII

In series *d* (2,8-dichloro derivatives) the starting compounds were obtained by the following way: A reaction of 2,5-dichloroacetophenone[10] with 4-chlorothiophenol in the presence of potassium carbonate and copper as catalyst at 150°C resulted in the acetophenone derivative *XVIII* which was processed by a Willgerodt reaction (method, *cf.*[10,11]). Treatment with sulfur and an excess of boiling morpholine gave a mixture of two products which were separated by crystallization from a mixture of benzene and light petroleum and identified as thiomorpholide *XIX* and oxothiomorpholide *XX*. By increasing the quantity of sulfur, prolonging the reaction time and direct crystallization of the crude product from ethanol it was possible to obtain the desired product *XIX* in yields of 50—70%, while the by-product *XX* remained

in the mother liquor. The alkaline hydrolysis of the thiomorpholide *XIX* gave the acid *XXI* whose preparation by hydrolysis of the nitrile has been described by us previously[12]. The cyclization to the ketone *XXII* with polyphosphoric acid has been carried out similarly like in our previous work[12] and its reduction to the alcohol *XXIII* followed the described procedure[12]. The following treatment with hydrogen chloride in benzene affords the chloro derivative *XXIV* (ref.[12]) described as an unstable substance eliminating hydrogen chloride during crystallization; the previously described[12] product was, clearly, inhomogeneous and contaminated by the product of elimination. In the present study a homogeneous substance, melting by 20°C higher than the previous product, was obtained. Its substitution reaction with an excess of 1-(ethoxycarbonyl)piperazine at 110°C afforded the carbamate *XIId* whose further use has already been mentioned.

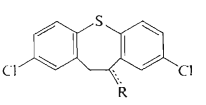


XVIII, R = $COCH_3$

XIX, R = CH_2CSN O

XX, R = $COCSN$ O

XXI, R = CH_2COOH



XXII, R = =O

XXIII, R = OH

XXIV, R = Cl

The hydrazones *IIIa–Xc* (Table I) were pharmacologically tested using methods of the general screening. Compounds *IIIa–VIIc* were tested as the very little water-soluble bases and were administered orally; compounds *VIIIa–Xc* were tested in the form of hydrochlorides (Table I) and were administered parenterally (mostly intravenously). There is a big difference between these two subgroups: while the orally administered simple hydrazones have very low toxicity and the character of mild tranquillizers with anticonvulsant activity in some cases, the parenterally administered hydrazones with the basic aryl ether moiety reveal high acute toxicity, strong hypothermic and partly also adrenolytic and hypotensive effects. First of all the acute toxicity in mice (LD_{50}) and the screened doses (D) (all doses in mg/kg) are given. Oral administration: *IIIabcd*, *IVabc*, *Va*, *VIbcd*, *VIIab*, LD_{50} above 2 500 mg/kg and D = 300 mg/kg; *VIa*, 1 250, 300; *VIIc*, 1 500, 300. Intravenous administration: *VIIIa*, 15, 3; *VIIIc*, 3·0, 0·6; *IXc*, 1·5, 0·3; *Xc*, 50, 10. In doses higher than D, most of the compounds show central depressant effects in mice manifested by the inhibition of activity and reactivity. Toxic doses produce ataxia, tremor and con-

vulsions. Some of the compounds bring about at the doses D or at lower doses the expected anticolvulsant effect and central depressant effects in the form of inhibition of spontaneous motility, potentiation of the thiopental sleeping time, hypothermic effect and ataxia.

The anticolvulsant effect was found in mice and only towards pentetrazole (oral doses prolonging significantly the latency of clonic convulsions elicited by pentetrazole and oral doses protecting from the lethal action of pentetrazole are given): *IIIc*, 200, 75; *IVa*, 75, 25; *Va*, 75, 25; *VId*, 200, 75; *VIIb* 200, 75 (for phenytoine, ED = = 100 mg/kg). All compounds were ineffective towards the maximal electroshock seizures. The inhibition of spontaneous motility was examined also in mice (oral doses decreasing significantly the motility in unknown surroundings are given): *IIIb*, 100; *IIIc*, 300; *IIId*, 300; *IVa*, 10–100; *IVb*, 10; *VIa*, 5; *VIIa*, 100; *VIIb*, 10–100; *VIIc*, 10–100. The same effect in known surroundings: *IIIb*, 300; *IVa*, 100. Thiopental potentiation was followed also in mice (doses prolonging the duration of the thiopental sleeping time to 200% of the control value are given): *IIIb*, 300 *p.o.*; *IVa*, 300 *p.o.*; *VIa*, 10–50 *p.o.*; *VIIa*, 10–50 *p.o.*; *VIIb*, 300 *p.o.*; *VIIc*, 50–100 *p.o.*; *VIIIa*, 1–3 *i.v.*; *Xc*, 0·5–1·0 *i.v.* (for chlorpromazine, ED = 1·0 *p.o.* and 0·5 *i.v.*). Hypothermic effect was evaluated by decrease of the rectal temperature of rats (doses decreasing the temperature by 1°C given): *IIIa*, 300 *p.o.*; *IIIb*, 100–300 *p.o.*; *IVa*, 100 *p.o.*; *Va*, 100 *p.o.*; *VIa*, 100–300 *p.o.*; *VIIa*, 100 *p.o.*; *VIIIc*, 0·3–0·6 *i.v.*; *IXc*, 0·1–0·3 *i.v.* (for chlorpromazine, ED = 5–10 *p.o.* and 0·5–1·0 *i.v.*). The discoordinating effect was examined in the rotarod test in mice (doses bringing about ataxia in approximately 50% animals are given): *IVa*, 300 *p.o.*; *VIa*, 50–100 *p.o.*; *Xc*, 1 *i.v.* Some effects were observed only with single compounds: *VIa* had antiamphetamine effect at oral doses between 50 and 100 mg/kg (these doses protected 100% mice from the lethal effect of a standard dose of amphetamine; for chlorpromazine, ED = 1·5 mg/kg *p.o.*). *VIIc* showed cataleptic activity in rats at a dose of 300 mg/kg *p.o.* (ED_{50} for chlorpromazine 10 mg/kg *p.o.*). *VIIIa* had antihistamine effect in guinea-pigs at a dose of 3 mg/kg *s.c.* (dose protecting 50% animals from the lethal effect of 5 mg/kg histamine administered intrajugularly). *Xc* showed some antireserpine activity at a dose of 10 mg/kg *i.p.* (the dose antagonizing significantly the reserpine ptosis in mice). Two compounds reduced the blood pressure of normotensive rats by 20% for at least 10 min in the following doses: *VIIIa*, 1·5 mg/kg *i.v.*; *Xc*, 5 mg/kg *i.v.*; *Xc* had an α-adrenolytic effect at a dose of 10 mg/kg *i.v.* (inhibited the adrenaline pressor reaction in rats by 50%).

The water-soluble substances (hydrochlorides) were also tested for the antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute). Microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml are given: *Streptococcus β-haemolyticus*, *VIIIa* 6·2, *VIIIc* 12·5, *IXc* 6·2, *Xc* 6·2; *Streptococcus faecalis*, *VIIIa* 12·5, *VIIIc* 50, *IXc* 6·2, *Xc* 12·5; *Staphylococcus pyogenes aureus*, *VIIIa* 12·5, *VIIIc* 25, *IXc* 6·2, *Xc* 6·2; *Escherichia coli*, *VIIIa* 6·2; *Proteus vulgaris*, *VIIIa* 100; *Mycobacterium tuberculosis* H37Rv,

VIIIa 25, *VIIIc* 25, *IXc* 12·5, *Xc* under 12·5; *Saccharomyces pasterianus*, *VIIIc* 50, *IXc* 50, *Xc* 50; *Trichophyton mentagrophytes*, *VIIIc* 50, *IXc* 50, *Xc* 25; *Candida albicans*, *Xc* 50.

EXPERIMENTAL

The melting points 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 spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer 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).

5-Chloro-2-(4-chlorophenylthio)acetophenone (*XVIII*)

A stirred mixture of 202 g 2,5-dichloroacetophenone[10], 173 g 4-chlorothiophenol, 268 g K_2CO_3 and 5 g Cu was heated to 150°C for 1 h. After cooling to 80°C the mixture was diluted with 1 l benzene, the undissolved material was filtered off and the filtrate was evaporated under reduced pressure. The residue was extracted with 1·5 l boiling ethanol, filtered and the filtrate allowed to crystallize by standing and cooling; 223 g (70%), m.p. 99–101°C. Analytical sample, m.p. 101–102°C (ethanol). UV spectrum: λ_{max} 230 nm (log ε 4·38), 263 nm (3·99), 345 nm (3·63), infl. at 285 nm (3·83). IR spectrum: 829, 878 (2 adjacent and solitary Ar–H), 1 546, 1 572, 3 053, 3 085 (Ar), 1 678 cm^{-1} (ArCO). ^{1}H NMR spectrum: δ 7·72 (d, J = 2·5 Hz, 1 H, 6-H), 7·38 (s, 4 H, ArH of 4-chlorophenylthio), 7·18 (q, J = 8·5; 2·5 Hz, 1 H, 4-H), 6·76 (d, J = 8·5 Hz, 1 H, 3-H), 2·61 (s, 3 H, $COCH_3$). For $C_{14}H_{10}Cl_2OS$ (297·2) calculated: 56·58% C, 3·39% H, 23·86% Cl, 10·79% S; found: 56·93% C, 3·55% H, 23·73% Cl, 10·56% S.

2-[5-Chloro-2-(4-chlorophenylthio)phenyl]acetic Acid Thiomorpholide (*XIX*)

A) A mixture of 29·7 g *XVIII*, 4·9 g S and 17·3 g morpholine was stirred and refluxed for 4·5 h (bath temperature 140–150°C). After cooling it was diluted with 100 ml chloroform and filtered with charcoal, the filtrate was washed with water, 1M-HCl and water, dried with K_2CO_3 and evaporated *in vacuo*. The residue was dissolved in 45 ml boiling benzene, the solution was treated with 75 ml light petroleum and the mixture allowed to crystallize; 7·8 g (20%) 5-chloro-2-(4-chlorophenylthio)phenylglyoxylic acid thiomorpholide (*XX*), m.p. 180–192°C. Analytical sample, m.p. 194–196°C (benzene–light petroleum). UV spectrum: λ_{max} 272 nm (log ε 4·34), 354 nm (3·86). IR spectrum: 768 (C–Cl), 822, 827, 840, 872 (2 adjacent and solitary Ar–H), 1 231 (R–O–R in morpholine), 1 500 (S=C–NR_2), 1 660 (ArCOCSNR_2), 3 080 cm^{-1} (Ar). For $C_{18}H_{15}Cl_2NO_2S_2$ (412·4) calculated: 52·43% C, 3·67% H, 17·20% Cl, 3·40% N, 15·55% S; found: 52·99% C, 3·78% H, 17·06% Cl, 3·18% N, 15·42% S.

The mother liquor was evaporated and the residue gave by crystallization 14·0 g (35%) of *XIX*, m.p. 102–105°C. Analytical sample, m.p. 110–111°C (benzene–light petroleum). UV spectrum: λ_{max} 256·5 nm (log ε 4·31), 280 nm (4·35). IR spectrum: 820, 873, 890 (2 adjacent and solitary Ar–H), 1 480 (S=C–NR_2), 1 559, 1 580, 3 045, 3 065 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·20 to 7·50 (m, 3 H, ArH of the phenylacetic acid residue), 7·20 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in chlorophenylthio), 7·02 (d, J = 8·5 Hz, 2 H, 3,5-H_2 in chlorophenylthio), 4·22 (s, 2 H, $ArCH_2CS$), 4·30 and 3·70 (2 t, 8 H, CH_2NCH_2 and CH_2OCH_2 of morpholine). For $C_{18}H_{17}Cl_2NOS_2$ (398·4) calculated: 54·27% C, 4·30% H, 17·80% Cl, 3·52% N, 16·10% S; found: 54·52% C, 4·44% H, 17·93% Cl, 3·35% N, 16·24% S.

B) A mixture of 62·0 g *XVIII*, 13·5 g S and 63 g morpholine was stirred and refluxed for 9 h (bath temperature 180°C). After cooling the mixture was diluted with 250 ml chloroform and processed like in the preceding case. The residue (67·1 g) was crystallized from 250 ml ethanol; 56·8 g (68%) crude *XIX*, m.p. 100–105°C, which was used without further purification.

2-[5-Chloro-2-(4-chlorophenylthio)phenyl]acetic Acid (*XXI*)

A mixture of 90 g *XIX*, 65 g 85% KOH and 130 ml ethanol was stirred and refluxed (bath temperature 120°C) for 2 h, then diluted with 250 ml water and extracted with chloroform. The extract was washed with water, dried with $MgSO_4$ and evaporated under reduced pressure. The solid residue was crystallized from a mixture of benzene and light petroleum; 58·9 g (83%), m.p. 123–125°C. Lit.[12], m.p. 124–126°C.

2,8-Dichlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXII*)

XXI (58·5 g) was cyclized with polyphosphoric acid (prepared from 100 ml 88% H_3PO_4 and 150 g P_2O_5) by stirring and heating to 140°C for 3 h. After cooling the mixture was decomposed with 250 g ice and water and the product was extracted with chloroform. Processing of the extract and crystallization of the residue from benzene gave 48·6 g (89%) *XXII*, m.p. 170–172°C. Analytical sample, m.p. 170·5–171·5°C (benzene). ^{1}H NMR spectrum: δ 8·13 (d, J = 2·0 Hz, 1 H, 9-H), 7·55 (d, J = 8·0 Hz, 1 H, 4-H), 7·52 (d, J = 8·0 Hz, 1 H, 6-H), 7·45 (d, J = 2·0 Hz, 1 H, 1-H), 7·35 (q, J = 8·0; 2·0 Hz, 1 H, 7-H), 7·15 (q, J = 8·0; 2·0 Hz, 1 H, 3-H), 4·28 (s, 2 H, $ArCH_2CO$). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·73% H, 24·02% Cl, 10·86% S; found: 57·36% C, 2·81% H, 23·87% Cl, 10·99% S. Lit.[12], m.p. 165–167°C.

2,8,10-Trichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXIV*)

$CaCl_2$ (20 g) was added to a solution of 47·9 g *XXIII* (ref.[12]) in 500 ml benzene and the suspension was saturated under stirring for 5 h with HCl at room temperature. After 48 h standing $CaCl_2$ was filtered off and the filtrate was evaporated *in vacuo*; 50·1 g (99%), m.p. 135°C. A sample was recrystallized twice from light petroleum without any sign of decomposition, m.p. 135 to 138°C. ^{1}H NMR spectrum: δ 7·50 (d, J = 2·5 Hz, 2 H, 1,9-H_2), 7·41 and 7·33 (2 d, J = 8·5 Hz, 2 H, 4,6-H_2), 7·11 and 7·09 (2 q, J = 8·5; 2·5 Hz, 2 H, 3,7-H_2), 5·70 (dd, J = 8·0; 4·0 Hz, 1 H, Ar–CH–Cl), 3·93 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_9Cl_3S$ (315·7) calculated: 53·27% C, 2·87% H, 33·70% Cl, 10·16% S; found: 53·00% C, 3·04% H, 33·41% Cl, 10·34% S. Lit.[12], m.p. 115–117°C for an inhomogeneous product.

2,8-Dichloro-10-(4-ethoxycarbonylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXIId*)

A mixture of 50·0 g *XXIV* and 70 g 1-(ethoxycarbonyl)piperazine was stirred and heated to 110°C for 6 h. After cooling the mixture was diluted with 300 ml water and extracted with benzene. The extract was repeatedly washed with water, dried with K_2CO_3 and evaporated. The residue was crystallized from ethanol; 57·5 g (83%), m.p. 114–117°C. IR spectrum: 777 (C–Cl), 829, 882, 897 (2 adjacent and solitary Ar–H), 1 260, 1 286 (C–O of carbamate), 1 490, 1 569, 1 583, 3 070 (Ar), 1 700 cm^{-1} (NCOOR). For $C_{21}H_{22}Cl_2N_2O_2S$ (437·4) calculated: 57·67% C, 5·07% H, 16·20% Cl, 6·41% N, 7·33% S; found: 57·69% C, 5·01% H, 16·04% Cl, 6·33% N, 7·01% S.

2,8-Dichloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin (*XIId*)

A mixture of 20·0 g *XIId*, 20 g 85% KOH and 40 ml ethanol was stirred and refluxed for 3 h (bath 120°C). After cooling it was dissolved in water and extracted with benzene. The extract was filtered with charcoal, dried with K_2CO_3 and evaporated; 13·3 g (80%), m.p. 124–126°C. Analytical sample, m.p. 130–132°C (cyclohexane). ^{1}H NMR spectrum: δ 7·70 (d, J = 2·5 Hz, 1 H, 9-H), 7·40 and 7·30 (2 d, J = 8·0 Hz, 2 H, 4,6-H_2), 7·25 (d, J = 2·5 Hz, 1 H, 1-H), 7·04 and 7·02 (2 q, J = 8·0; 2·5 Hz, 2 H, 3,7-H_2), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·85 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·58 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 1·50 (bs, 1 H, NH). For $C_{18}H_{18}Cl_2N_2S$ (365·3) calculated: 59·18% C, 4·97% H, 19·41% Cl, 7·67% N, 8·78% S; found: 59·57% C, 5·14% H, 19·10% Cl, 7·36% N, 8·69% S.

2-Chloro-10-(4-nitrosopiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIb*)

A stirred mixture of 10·0 g *XIb* (ref.[6]) and 10 ml 1 : 1 dilute hydrochloric acid in 50 ml water was treated dropwise at 75°C with a solution of 2·8 g $NaNO_2$ in 10 ml water. The mixture was stirred for 3 h at 75–80°C, allowed to stand overnight at room temperature, diluted with 100 ml water, neutralized with a saturated solution of Na_2CO_3 and extracted with chloroform. Processing of the extract gave an oil which crystallized from ethanol; 8·3 g (76%), m.p. 133–134°C. Analytical sample, m.p. 136–138°C (ethanol). IR spectrum: 758, 831, 888 (4 and 2 adjacent and solitary Ar–H), 1 370 (R_2N–N=O), 1 556, 1 584, 3 050 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·25 (d, J = 2·5 Hz, 1 H, 1-H), 7·00–7·60 (m, 6 H, remaining ArH), 2·50–4·30 (m, 11 H, $ArCH_2$.CHAr and 4 NCH_2 of piperazine). For $C_{18}H_{18}ClN_3OS$ (359·9) calculated: 60·08% C, 5·04% H, 9·85% Cl, 11·68% N, 8·91% S; found: 59·68% C, 5·23% H, 9·86% Cl, 11·62% N, 8·68% S.

2-Chloro-11-(4-nitrosopiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIIc*)

Was prepared similarly from 53 g *XIc* (ref.[7,8]), 14·5 g $NaNO_2$ and 26·5 ml hydrochloric acid in 90 ml water; 43·6 g (75%), m.p. 121–125°C (ethanol). IR spectrum: 770, 811, 825, 835, 894 (4 and 2 adjacent and solitary Ar–H), 1 360, 1 370 (R_2N–N=O), 1 555, 1 581, 3 060 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·59 (d, J = 2·5 Hz, 1 H, 1-H), 7·00–7·50 (m, 6 H, remaining ArH), 2·50–4·30 (m, 11 H, $ArCH_2CHAr$ and 4 CH_2N of piperazine). For $C_{18}H_{18}ClN_3OS$ (359·9) calculated: 60·08% C, 5·04% H, 9·85% Cl, 11·68% N, 8·91% S; found: 60·22% C, 5·26% H, 9·78% Cl, 11·93% N, 8·80% S.

2,8-Dichloro-10-(4-nitrosopiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIId*)

Similarly from 28·3 g *XId*, 6·9 g $NaNO_2$ and 16 ml hydrochloric acid in 175 ml water; 20·3 g (72%), m.p. 148–151°C (ethanol). Polarographic reduction in 0·5M-HCl (towards a saturated calomel electrode), $E_{1/2}$ = −0·38 V (corresponds to reduction of the R_2N–N=O group). IR spectrum: 826, 892 (2 adjacent and solitary Ar–H), 1 379 (R_2N–N=O), 1 571, 1 590, 3 060 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·60 (d, J = 2·5 Hz, 2 H, 1,9-H_2), 7·42 and 7·35 (2 d, J = 8·5 Hz, 2 H, 4,6-H_2), 7·05 and 7·04 (2 q, J = 8·5; 2·5 Hz, 2 H, 3,7-H_2), *c.* 4·00 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), *c.* 2·70 (m, 4 H, $CH_2N^1CH_2$ of piperazine). For $C_{18}H_{17}Cl_2N_3OS$ (394·3) calculated: 54·83% C, 4·35% H, 17·98% Cl, 10·66% N, 8·13% S; found: 55·57% C, 4·70% H, 17·80% Cl, 10·63% N, 8·06% S.

10-(4-Aminopiperazino)-2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIVb*)

XIIIb (27·4 g) was added over 20 min to a stirred suspension of 7·5 g $LiAlH_4$ in 250 ml ether and the mixture was stirred for 5 h at room temperature. After standing overnight it was diluted

with 200 ml benzene and decomposed under stirring by a slow addition of 9 ml water, 9 ml 15% NaOH and 30 ml water. A part of ether (some 100 ml) was distilled off, the separated solid was filtered off and the filtrate was evaporated *in vacuo*; 25·6 g (97%), m.p. 120—124°C (cyclohexane). ^{1}H NMR spectrum: δ 6·90—7·70 (m, 7 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·00 (bs, 2 H, N—NH_2), 2·60 (bs, 8 H, 4 CH_2N of piperazine). For $C_{18}H_{20}ClN_3S$ (345·9) calculated: 62·50% C, 5·83% H, 10·25% Cl, 12·15% N, 9·27% S; found: 62·51% C, 5·95% H, 10·25% Cl, 11·76% N, 9·31% S.

11-(4-Aminopiperazino)-2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIVc*)

Was prepared similarly from 16·5 g *XIIIc* and 4·4 g $LiAlH_4$ in 200 ml ether; 12·2 g (77%), m.p. 146—148°C (cyclohexane). IR spectrum: 761, 769, 829, 843, 905 (4 and 2 adjacent and solitary Ar—H), 1 611, 3 142, 3 288 (NH_2), 3 015, 3 070, 3 090 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·62 (d, J = 2·5 Hz, 1 H, 1-H), 7·48 (m, 1 H, 6-H), 7·32 (d, J = 8·5 Hz, 1 H, 4-H), *c.* 7·20 (m, 3 H, 7,8,9-H_3), 7·0 (q, J = 8·5; 2·5 Hz, 1 H, 3-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·10 (bs, 2 H, N—NH_2), 2·65 (s, 8 H, 4 CH_2N of piperazine). For $C_{18}H_{20}ClN_3S$ (345·9) calculated: 62·50% C, 5·83% H, 10·25% Cl, 12·15% N, 9·27% S; found: 63·16% C, 6·31% H, 10·06% Cl, 12·20% N, 8·87% S.

10-(4-Aminopiperazino)-2,8-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIVd*)

VIIId (19·8 g) was similarly reduced with 4·6 g $LiAlH_4$ in 150 ml ether. Similar processing gave 18 g inhomogeneous oily product which was chromatographed on a column of 600 g neutral Al_2O_3 (activity II). Elution with benzene recovered 5·1 g starting *VIIId*. Elution with chloroform afforded 11·7 g (88% per conversion) oily *XIVd* which crystallized from cyclohexane as an 3 : 2 solvate with this solvent, m.p. 71—73°C. Mass spectrum, *m/z*: 379 (M^+ corresponding to C_{18}·$H_{19}Cl_2N_3S$). ^{1}H NMR spectrum: δ 7·65 (d, J = 2·5 Hz, 1 H, 9-H), 7·45 and 7·35 (2 d, J = 8·5 Hz, 2 H, 4,6-H_2), 7·30 (d, J = 2·5 Hz, 1 H, 1-H), 7·10 and 7·08 (2 q, J = 8·5; 2·5 Hz, 2 H, 3,7-H_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·15 (s, 2 H, N—NH_2), 2·70 (bs, 8 H, 4 CH_2N of piperazine), 1·47 (s, 8 H, 4 CH_2 of cyclohexane). For $C_{18}H_{19}Cl_2N_3S + 2/3\ C_6H_{12}$ (436·4) calculated: 60·54% C, 6·23% H, 16·25% Cl, 9·62% N, 7·35% S; found: 60·98% C, 6·36% H, 16·20% Cl, 9·32% N, 7·50% S.

Neutralization of a sample with maleic acid in ether and crystallization of the product from acetone led to 2,8-dichloro-10-(4-isopropylideneaminopiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XVd*) bis(hydrogen maleate), m.p. 142—149°C with decomposition. Mass spectrum, *m/z*: 419 (M^+ corresponding to $C_{21}H_{23}Cl_2N_3S$). For $C_{29}H_{31}Cl_2N_3O_8S$ (652·6) calculated: 53·37% C, 4·79% H, 10·87% Cl, 6·44% N, 4·91% S; found: 53·13% C, 4·71% H, 10·79% Cl, 6·40% N, 5·44% S.

3-(2-Dimethylaminoethoxy)benzaldehyde (*XVI*)

A solution of 40·0 g 3-hydroxybenzaldehyde in 330 ml chlorobenzene was treated with 35 g *c.* 50% sodium methoxide and 35·4 g 1-chloro-2-dimethylaminoethane. Methanol was removed by distillation and the mixture was refluxed for 15 h. After cooling the solid was filtered off and the filtrate was distilled; 32·7 g (56%), b.p. 136°C/0·4 kPa, n_D^{24} 1·5351. For $C_{11}H_{15}NO_2$ (193·2) calculated: 68·37% C, 7·82% H, 7·25% N; found: 68·69% C, 7·98% H, 7·13% N.

3-Ethoxy-4-(2-dimethylaminoethoxy)benzaldehyde (*XVII*)

Was prepared similarly from 8·3 g 3-ethoxy-4-hydroxybenzaldehyde, 5·5 g 1-chloro-2-dimethylaminoethane and 6·0 g *c.* 50% sodium methoxide in 50 ml chlorobenzene; 5·9 g (50%), b.p. 146°C/0·3 kPa. UV spectrum: λ_{max} 230 nm (log ε 4·26), 274 nm (4·10), 308 nm (3·99). IR spectrum (film): 811, 870 (2 adjacent and solitary Ar—H), 1 038, 1 137, 1 270 (Ar—O—R), 1 512, 1 537, 1 599 (Ar), 1692, 2 720 (ArCHO), 2 762, 2 815 cm^{-1} (CH_3—N—CH_3). ^1H NMR spectrum: δ 9·86 (s, 1 H, CHO), 7·42 (q, J = 8·0; 2·0 Hz, 1 H, 6-H), 7·39 (d, J = 2·0 Hz, 1 H, 2-H), 6·97 (d, J = 8·0 Hz, 1 H, 5-H), 4·19 (t, J = 6·0 Hz, 2 H, OCH_2 in 2-dimethylaminoethoxy), 4·10 (q, J = 7·0 Hz, 2 H, OCH_2 in ethoxy), 2·86 (t, J = 6·0 Hz, 2 H, CH_2N), 2·35 (s, 6 H, CH_3.NCH_3), 1·45 (t, J = 7·0 Hz, 3 H, CH_3 in ethoxyl). For $C_{13}H_{19}NO_3$ (237·3) calculated: 65·80% C, 8·07% H, 5·90% N; found: 65·71% C, 8·19% H, 5·63% N.

2-Chloro-10-[4-(3,4-dimethoxybenzylideneamino)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IVb*) (General method)

A solution of 3·5 g *XIVb* in 30 ml ethanol was treated with a solution of 1·2 g 3,4-dimethoxybenzaldehyde in 10 ml ethanol and the mixture was refluxed for 15 min. It was allowed to stand overnight and the product was filtered; 4·2 g (84%), m.p. 197—200°C. Analytical sample, m.p. 204—206°C (dioxane). UV spectrum: λ_{max} 290 nm (log ε 4·18), 307·5 nm (4·17). IR spectrum: 751, 825, 862, 883, 908 (4 and 2 adjacent and solitary Ar—H), 1 262 (Ar—OCH_3), 1 518, 1 570, 1 576, 1 589 (Ar), 1 606 cm^{-1} (C=N). ^1H NMR spectrum: δ 6·70—7·80 (m, 11 H, ArH and ArCH=), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·91 and 3·86 (2 s, 6 H, 2 $ArOCH_3$), 3·15 (def. t, 4 H, CH_2.N^4CH_2 of piperazine), 2·85 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine). Analysis in Table I.

2-Chloro-10-[4-(3-ethoxy-4-hydroxybenzylideneamino)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIb*)

A solution of 3·5 g *XIVb* in 30 ml ethanol was treated with a solution of 1·2 g 3-ethoxy-4-hydroxybenzaldehyde in 10 ml ethanol and the mixture was refluxed for 15 min. After standing overnight there were isolated by filtration 3·9 g (92%) compound, m.p. 156—158°C, which was identified as the molecular complex of *VIIb* and starting *XIVb*. The mass spectrum confirmed the presence of *XIVb*, *m/z* (%): 345 (M^+ corresponding to $C_{18}H_{20}ClN_3S$, 11%), 329 (20), 247 (42), 245 (100), 210 (61), 178 (20), 165 (23), 100 (62), 83 (75). UV spectrum: λ_{max} 282 nm (log ε 4·47), infl. 310 nm (4·38). IR spectrum indicates the presence of *VIIb*: 758, 824, 880, 907 (4 and 2 adjacent and solitary Ar—H), 1 272, 1 289 (ArOH, ArOR), 1 515, 1 569, 1 586 (Ar), 1 610 cm^{-1} (C=N). For $C_{27}H_{28}$.ClN_3O_2S + $C_{18}H_{20}ClN_3S$ (840·0) calculated: 64·35% C, 5·76% H, 8·44% Cl, 10·01% N, 7·63% S; found: 64·68% C, 5·87% H, 8·36% Cl, 9·75% N, 7·49% S.

The preceding molecular complex of *VIIb* and *XIVb* (3·4 g) was refluxed for 1 h with 0·6 g 3-ethoxy-4-hydroxybenzaldehyde in 30 ml ethanol. Cooling and standing overnight gave 3·3 g (83%) of *VIIb*, m.p. 127—129°C (ethanol). UV spectrum: λ_{max} 216 nm (log ε 4·59), 287 nm (4·33), infl. at 307 nm (4·29). IR spectrum (KBr): 750, 813, 820, 900 (4 and 2 adjacent and a solitary Ar—H), 1 195 (ArOH), 1 267 (ArOR), 1 510, 1 580, 1 609, 3 040 (Ar), 1 635 (C=N), 3 410 cm^{-1} (OH). ^1H NMR spectrum: δ 6·80—7·70 (m, 11 H, ArH and ArCH=), 5·30 (bs, 1 H, OH), 4·15 (q, J = 7·0 Hz, 2 H, OCH_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·11 (def. t, 4 H, CH_2.N^4CH_2 of piperazine), 2·80 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 1·45 (t, J = 7·0 Hz, 3 H, CH_3). Analysis in Table I.

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