2(8)-CHLORO-10(11)-(DIMETHYLAMINOALKYL)DIBENZO[*b*,*f*]THIEPINS AS POTENTIAL CNS AGENTS; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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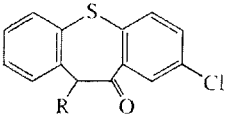
Received January 21st, 1976

Alkylation of 2-(4-chlorophenylthio)phenylacetonitrile (*IVa*) with butyl bromide, benzyl chloride 2-dimethylaminoethyl chloride, 3-dimethylaminopropyl chloride and 2-methyl-3-dimethylaminopropyl chloride in the presence of sodium amide yielded nitriles *IVb—f* which underwent alkaline hydrolysis to amides *Vb—f*. Heating with polyphosphoric acid results in cyclization of the amides to ketones *Ib—f* which were reduced with sodium borohydride in aqueous ethanol to *cis*-alcohols *VIc—f*. In three cases, the corresponding *trans*-isomers were also prepared (*VIIc—e*). Alcohols *VIc—f* were treated with thionyl chloride to yield hydrochlorides of chlorides *VIIId—f* and chloride *VIIIc* which are assumed to be of *trans* configuration. Dehydrochlorination reactions further yielded olefins *IXc—f*. Exposure of the hydrochlorides of chlorides *VIIId* and *VIIIe* in chloroform to 1-methylpiperazine leads to cyclic quaternary salts *X* and *XI* which can be degraded to olefins *IXd* and *IXe*. During cyclization of amide *Vc* the thiepinone *Ic* formed is accompanied by indanone *XII*. Pharmacologically, ketones *Id* and *Ie* appear to be most interesting, showing central depressant, antireserpine, hypothermic and antihistamine activities. Olefins *IXd* and *IXe* are cataleptic. Quaternary salts *X* and *XI* are highly toxic, possess anticholinergic and in high doses peripheral myorelaxant activity.

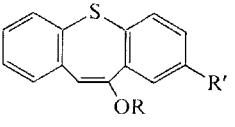
Of the series of dibenzo[*b*,*f*]thiepin amines, pharmacologists attach importance to 11-(3-dimethylaminopropyl)dibenzo[*b*,*f*]thiepin-10(11*H*)-one and its monodemethyl analogue[1] which, in animal tests, showed antireserpine and antitetrabenazine activity and hence properties similar to those of imipramine and desipramine[2]. It was necessary to take them into account as potential antidepressants. Their use is prevented by their difficult availability. Patents of Geigy[3] described compounds of this type and of type *I* as the only isolated products of alkylation of dibenzo[*b*,*f*]thiepin-10(11*H*)-one and of ketone *Ia* by 2-dimethylaminoethyl chloride or 3-dimethylaminopropyl chloride in the presence of sodium amide but in most of the patents mentioned the yield is not shown; if reported, it lies mostly at about 10%.

* Part CIII in the series Neurotropic and Psychotropic Agents; Part CII: This Journal *41*, 2771 (1976).

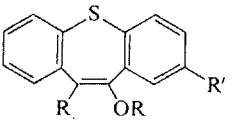
In contrast with the above, Fujisawa[4] describe as the sole products of the same reaction under practically identical reaction conditions enol-ethers of type *II*. We studied a similar reaction[5,6]; using chromatography of the primary products we separated and identified enol-ethers of type *II* and 11-alkylated enol-ethers of type *III*. Only acid hydrolysis of compounds of type *III* (patents by Geigy[3] report hydrolysis of crude reaction products) permitted to obtain ketones of type *I* in a satisfactory way[7]. It was the aim of the present work to develop a new and preparatively applicable method of obtaining C-alkylated ketones of type *I* and to take up their chemistry.



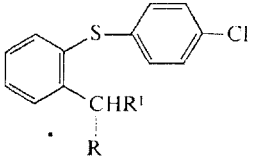
I



II



III



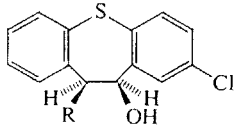
IV, R = CN
V, R = $CONH_2$

Formulae in the series:

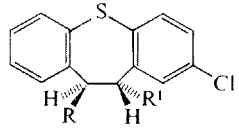
a, R = H
b, R = $(CH_2)_3CH_3$
c, R = $CH_2C_6H_5$
d, R = $(CH_2)_2N(CH_3)_2$
e, R = $(CH_2)_3N(CH_3)_2$
f, R = $CH_2CHCH_2N(CH_3)_2$ (with CH_3 branch)

The starting compound for all the work was 2-(4-chlorophenylthio)phenylacetonitrile[8] (*IVa*) which was alkylated in the presence of sodium amide in boiling toluene with n-butyl bromide, benzyl chloride, 2-dimethylaminoethyl chloride, 3-dimethylaminopropyl chloride and 2-methyl-3-dimethylaminopropyl chloride[9] (method *A*). The products were oily α-alkylated nitriles *IVb–f* of which *IVb* and *IVc* were processed further in the crude state while the aminoalkylated nitriles (*IVd–f*) were characterized as hydrochlorides. In the nitriles prepared here the CN group is sterically hindered so that hydrolysis by boiling with aqueous–ethanolic potassium hydroxide (method *B*) does not result in carboxylic acids[8] but only in the corresponding amides *Vb–f*. As it had been found before[10] that the amides can be used for the present purpose equally well as carboxylic acids it was not considered necessary to attempt to achieve complete hydrolysis. Molecules of nitrile *IVf* and amide *Vf* contain two centres of chirality each; the compounds were isolated only in the form of diffusely melting hydrochlorides so that they are likely to represent mixtures of both racemates. On heating with polyphosphoric acid to 120–140°C for 4–16 h (method *C*) amides *Vb–f* cyclize in satisfactory yields to ketones *Ib–f*. Of these ketones, *Id* and *Ie* were prepared in a yield of 14 and 8%, respectively, by the previously mentioned[3] amino-

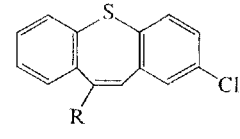
alkylation of ketone *Ia*. The present method of their preparation is thus substantially better and renders it possible to prepare them for potential biological studies. In the case of amide *Vc*, cyclization resulted in a nonhomogeneous product which was separated by chromatography on a column of silica gel into two approximately equal fractions. The less polar one crystallized and was characterized with the aid of spectra as the desired ketone *Ic*. The more polar product is oily and was characterized with the aid of ^{1}H-NMR spectrum as a second very probable cyclization product, *viz* the indanone derivative *XII*. The molecule of ketone *If* again contains two centres of chirality and, in spite of the fact that the substance crystallized as a base to a "constant melting point", it represents even then a mixture of approximately equal parts of two stereoisomers as shown by the ^{1}H-NMR spectrum.



VI



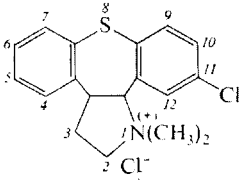
VII, $R^1 = OH$
VIII, $R^1 = Cl$



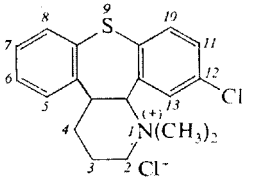
IX

Reduction of ketones *Ic–f* with sodium borohydride in boiling aqueous ethanol (method *D*) results in the corresponding alcohols which are homogeneous and, according to ^{1}H-NMR spectra (cases *c–e*, and *f* per analogy) they are of the *cis*-configuration and hence have the structures shown by *VIc–f*. These reductions take place stereospecifically. On heating the *cis*-alcohols *VId* and *VIe* with 30% sulfuric acid (method *E*) no dehydration takes place but the resulting products are isomeric with the starting compounds. Without further evidence they are ascribed the structure of *trans*-alcohols *VIId* and *VIIe*. Reactions of *cis*-alcohols *VIc–f* with thionyl chloride in toluene yielded the corresponding chlorides; in the reactions a Walden inversion is assumed to take place and the products are ascribed the structures of *VIIIc–f*. This is very probable in cases *d–f* when the reaction is carried out in boiling toluene (method *F*) and when the amino alcohols are converted to aminoalkyl chlorides. Certain doubt can be entertained in the case of the benzyl derivative when the reaction of alcohol *VIc* with thionyl chloride in toluene was conducted at room temperature; at higher temperatures hydrogen chloride was eliminated with concomitant formation of olefin *IXc*. In the reaction of the chloride which is formulated as *VIIIc*, with potassium hydroxide in aqueous ethanol a back substitution of the chlorine atom with a hydroxyl group takes place since the resulting substance is isomeric with alcohol *VIc*; it is ascribed the structure of *trans*-alcohol *VIIc* and the reaction is assumed to proceed under equilibration giving a mixture from which the *trans* isomer could be

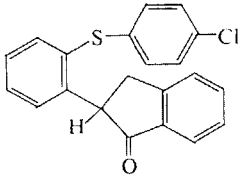
isolated. In a similar reaction of a mixture of ethanol with benzene (a small amount of water was present in the potassium hydroxide used) an ethanolysis takes place, giving rise to the ethoxy derivative *XIII*, apparently as a mixture of the two stereoisomers. Dehydrochlorination of chlorides *VIIId–f* was effected by heating with an ethanolic solution of potassium hydroxide (method *G*). In the case of aminoalkyl chlorides no ethanolysis takes place but rather an elimination reaction with resulting olefins *IXd–f*. Preparation of *IXe* was described in a patent[11] using a completely different procedure. Since the compound was not characterized and no intermediates were sufficiently described one can assume that it has not been prepared at all. Preparation of some similar compounds, although different from the present products, was described in a very complex manner in patents of Geigy[12].



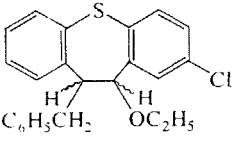
X



XI



XII



XIII

In an attempt to apply a substitution reaction for introducing the N-methylpiperazine residue into the molecule, hydrochlorides of *VIIId* and *VIIIe* reacted with excess 1-methylpiperazine in chloroform at room temperature (method *H*). After decomposition of the reaction mixtures with water products of ammonium salt character crystallized from the aqueous layers which, however, did not yield bases on treatment with alkali. According to analysis, they contain one nitrogen atom per one sulfur atom and two chlorine atoms. The empirical formulas $C_{18}H_{21}Cl_2NOS$ and $C_{19}H_{23}$. $.Cl_2NOS$ suggest that we are dealing here with monohydrates of cyclic quaternary ammonium chlorides *X* and *XI*. On exposure to one equivalent of picric acid in aqueous solutions they are converted to the corresponding ammonium picrates. The identity of *X* was verified by means of its ^{1}H-NMR spectrum and further by its mass spectrum where the substance appears as a mixture of the corresponding tertiary

TABLE I

Dibenzo[*b*,*f*]thiepin Derivatives and Intermediates

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% N	% Cl	% S
IVd-HCl	*A* (63)	206–210 (ethanol)	$C_{18}H_{20}Cl_2N_2S$ (367·3)	58·86 59·26	5·48 5·60	7·62 8·25	19·31 19·11	8·73 9·15
IVe-HCl	*A* (50)	153–155[a] (ethanol–ether)	$C_{19}H_{22}Cl_2N_2S$ (381·4)	59·83 59·95	5·81 5·95	7·34 7·40	18·63 18·57	8·39 8·68
IVf-HCl	*A*[b] (91)	179–187 (2-propanol)	$C_{20}H_{24}Cl_2N_2S$ (395·4)	60·76 61·03	6·12 6·34	7·08 7·08	17·93 17·79	— —
Vb	*A* + *B*[b] (62)	115–118 (ethanol)	$C_{18}H_{20}ClNOS$ (333·9)	64·75 64·74	6·04 6·35	4·20 4·07	10·62 10·96	9·60 9·50
Vc	*A* + *B* (31)	150–152[c] (ethanol)	$C_{21}H_{18}ClNOS$ (367·9)	68·65 68·66	4·93 4·97	3·81 3·90	9·64 9·73	8·72 8·71
Vd-HCl	*B* (82)	188–195[d] (ethanol)	$C_{18}H_{21}Cl_2N_2OS$ (385·4)	56·10 56·38	5·76 5·80	7·27 7·20	18·40 18·59	8·35 8·63
Ve	*B*[b] (69)	98–99 (ethanol–ether)	$C_{19}H_{23}ClN_2OS$ (362·9)	62·88 62·80	6·39 6·77	7·72 7·71	9·77 9·89	8·83 8·59
Ve-HCl	—	184–186 (ethanol–ether)	$C_{19}H_{24}Cl_2N_2OS$ (399·4)	57·14 56·71	6·05 6·12	7·01 7·02	17·76 17·74	8·03 8·08
Vf-HCl	*B* (80)	168–(187)[e] (ethanol–ether)	$C_{20}H_{26}Cl_2N_2OS$ (413·4)	58·11 58·29	6·34 6·90	6·77 6·87	17·15 16·80	7·76 7·72
Ib	*C*[b] (87)	73–76 (ethanol)	$C_{18}H_{17}ClOS$ (316·8)	68·23 68·53	5·41 5·67	— —	11·19 11·38	10·12 9·96
Ic	*C*[b] (44)	130–131 (ethanol)	$C_{21}H_{15}ClOS$ (350·9)	71·89 72·21	4·31 4·37	— —	10·10 10·32	9·14 9·33

Id	*C*[b] (70)	107—108·5 (ether)	$C_{18}H_{18}ClNOS$ (331·9)	65·15 65·29	5·47 5·25	4·22 4·10	— —	— —
Id-HCl	—	275 (decomp.) (ethanol)	$C_{18}H_{19}Cl_2NOS$ (368·3)	58·70 58·41	5·20 5·25	3·80 3·63	19·25 19·10	8·71 8·71
Ie-HCl	*C* (68)	239·5—243[f] (ethanol)	$C_{19}H_{21}Cl_2NOS$ (382·3)	59·69 59·67	5·35 5·61	3·66 3·64	18·54 18·71	8·38 8·38
If	*C* (87)	142·5—145[g] (benzene)	$C_{20}H_{22}ClNOS$ (359·9)	66·74 66·79	6·16 5·87	3·89 4·09	9·85 10·10	8·91 9·26
If-HCl[h]	—	238—243 (ethanol–ether)	$C_{20}H_{24}Cl_2NO_{1.5}S$ (405·4)	59·26 59·37	5·97 5·56	3·46 3·59	— —	7·91 7·31
VIc	*D*[b] (84)	51—53 (ether)	$C_{21}H_{17}ClOS$ (352·9)	71·48 71·00	4·85 5·14	— —	10·05 9·88	9·10 9·11
VId	*D* (70)	108—110[i] (aqueous ethanol)	$C_{18}H_{20}ClNOS$ (333·9)	64·75 64·72	6·04 6·16	4·20 4·19	10·62 10·90	9·60 9·90
VId-HCl	—	231—234 (ethanol–ether)	$C_{18}H_{21}Cl_2NOS$ (370·3)	58·38 57·51	5·72 5·50	3·78 3·80	19·15 19·31	8·65 8·53
VIe-A	*D*[b] (70)	145—147 (ether)	$C_{19}H_{22}ClNOS$ (347·9)	65·59 65·80	6·37 6·46	4·03 3·80	10·19 10·34	9·22 9·35
VIe-B[b]	—	113—116 (ethanol)	$C_{19}H_{22}ClNOS$ (347·9)	65·59 65·80	6·37 6·69	4·03 3·82	10·19 10·57	9·22 9·21
VIe-HM[j]	—	156—159 (ethanol–ether)	$C_{23}H_{26}ClNO_5S$ (463·9)	59·54 59·46	5·65 5·66	3·02 2·79	7·64 7·61	6·91 7·04
VIf-HCl[k]	*D* (86)	132—136 (ethanol)	$C_{20}H_{27}Cl_2NO_2S$ (416·4)	57·69 57·97	6·53 6·60	3·36 3·42	17·03 16·61	7·70 7·64
VIIc	*b*	141—142·5 (cyclohexane–light petroleum)	$C_{21}H_{17}ClOS$ (352·9)	71·48 70·55	4·85 4·85	— —	10·05 9·82	9·10 8·80
VIId-HCl	*E* (62)	204—208 (ethanol)	$C_{18}H_{21}Cl_2NOS$ (370·3)	58·38 58·56	5·72 5·71	3·78 3·83	19·15 19·34	8·65 8·57

TABLE I
(*Continued*)

Compound	Method (yield, %)	M.p. °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% N	% Cl	% S
VIIe	*E*[b] (80)	132–134 (ether)	$C_{19}H_{22}ClNOS$ (347·9)	65·59 65·47	6·37 6·62	4·03 3·98	10·19 10·34	9·22 9·04
VIIIc	*b*	43–45 (2-propanol)	$C_{21}H_{16}Cl_2S$ (371·3)	67·93 67·78	4·34 4·61	— —	— —	8·63 8·70
VIIId-HCl	*F*[b] (73)	178–183 (ethanol–ether)	$C_{18}H_{20}Cl_3NS$ (388·8)	55·61 56·07	5·18 5·33	3·60 3·42	27·36 27·53	8·25 8·27
VIIIe-HCl	*F* (74)	170–174 (ethanol–ether)	$C_{19}H_{22}Cl_3NS$ (402·8)	56·65 56·73	5·51 5·77	3·48 3·27	26·40 26·45	7·96 7·97
VIIIf-HCl	*F* (52)	179–185 (ethanol–ether)	$C_{20}H_{24}Cl_3NS$ (416·8)	57·63 58·47	5·80 5·47	3·36 3·38	— —	7·69 8·06
IXc	*b*	96–97 (ethanol)	$C_{21}H_{15}ClS$ (334·9)	75·32 75·08	4·52 4·54	— —	10·58 10·82	9·58 9·64
IXd-HCl	*G* (66)	256–259[m,n] (ethanol–ether)	$C_{18}H_{19}Cl_2NS$ (352·3)	61·36 61·37	5·44 5·57	3·98 3·68	20·13 20·09	9·10 9·29
IXd-HCl	*J* (63)	256–259 (ethanol)	$C_{18}H_{19}Cl_2NS$ (352·3)	61·36 60·78	5·44 5·41	3·98 4·08	20·13 20·18	9·10 9·02
IXe-HCl	*G*[b] (73)	215–217 (ethanol–ether)	$C_{19}H_{21}Cl_2NS$ (366·3)	62·29 61·80	5·78 5·85	3·82 3·63	19·35 19·18	8·76 8·82
IXe-HCl	*J*[b] (75)	210–212 (ethanol–ether)	$C_{19}H_{21}Cl_2NS$ (366·3)	62·29 61·56	5·78 5·73	3·82 3·60	19·35 19·76	8·76 8·61
IXf-HCl[h]	*G* (68)	253–255[o] (ethanol–ether)	$C_{20}H_{24}Cl_2NO_{0.5}S$ (389·4)	61·69 61·87	6·21 5·74	3·60 3·66	— —	8·23 8·72

X[k]	*H*[b] (72)	166—167 (ethanol)	$C_{18}H_{21}Cl_2NOS$ (370·3)	58·38 57·47	5·72 5·59	3·78 3·66	19·15 19·13	8·65 8·63
X-P[p]	*b*	228—236 (ethanol)	$C_{24}H_{21}ClN_4O_7S$ (545·0)	52·89 53·21	3·89 4·20	10·28 10·49	6·51 6·49	5·88 5·73
XI[k]	*H* (63)	184—186 (ethanol–ether)	$C_{19}H_{23}Cl_2NOS$ (384·4)	59·30 58·73	6·03 5·93	3·64 3·44	18·43 18·50	8·33 8·23
XI-P[p]	—	238—242 (ethanol)	$C_{25}H_{23}ClN_4O_7S$ (559·0)	53·72 53·77	4·15 3·90	10·02 10·22	6·34 6·27	5·73 5·78
XIII	*b*	105—106 (2-propanol)	$C_{23}H_{21}ClOS$ (380·9)	72·52 72·48	5·55 5·56	— —	9·30 9·43	8·41 8·58

[a] IR spectrum: 776, 825 (4 and 2 adjacent Ar—H), 2290 (R—CN), 2715 cm^{-1} (NH^+). [b] See Experimental. [c] IR spectrum: 710, 770, 821 (5, 4 and 2 adjacent Ar—H), 1480, 1592, 1610 (Ar), 1662, 3195, 3415 cm^{-1} ($CONH_2$). [d] IR spectrum: 752, 760, 823 (4 and 2 adjacent Ar—H), 1627, 1675 ($CONH_2$), 2480, 2590, 2640 (NH^+), 3170, 3190, 3310, 3365 cm^{-1} ($CONH_2$). [e] IR spectrum: 775, 830 (4 and 2 adjacent Ar—H), 1485 (Ar), 1630, 1686 ($CONH_2$), 2708 (NH^+), 3190, 3205, 3270, 3320, 3375 cm^{-1} ($CONH_2$). [f] UV spectrum: λ_{max} 341 nm (log ε 3·65, infl. 265 nm (4·07), 242 nm (4·32), 227 nm (4·31); IR spectrum: 750, 811, 887 (4 and 2 adjacent and solitary Ar—H), 1450, 1470, 1575 (Ar), 1678 (CO—Ar), 2470, 2580 (NH^+), 2950 cm^{-1} (CH_2); literature[3] gave the m.p. for the base (62—63°C). [g] UV spectrum: λ_{max} 223·5 nm (log ε 4·32), 242 nm (4·28), infl. 262·5 nm (4·11), 337·5 nm (3·64); IR spectrum (Nujol): 755, 821, 897 (4 and 2 adjacent and solitaryAr—H), 1597 (Ar), 1678 cm^{-1} (CO—Ar); ^{1}H-NMR spectrum (Tesla 80 MHz) indicates the substance to be a mixture of two stereoisomers in a ratio of about 1 : 1: δ 8·05 and 7·92 (2 mcs, 1 H, 9-H), 7·59 (m, 1 H, 4-H), 7·00—7·50 (m, 5 H, remaining aromatic protons), c. 4·80 (m, 1 H, Ar—CH—CO), 1·60—3·00 (m, 5 H, CH_2CHCH_2), 2·15 and 2·10 (2s, 6 H, CH_3NCH_3), 0·95 (d, J = 6·0 Hz, 3 H, C—CH_3). [h] Hemihydrate. [i] IR spectrum (Nujol): 743, 807, 859 (4 and 2 adjacent and solitary Ar—H), 1023 (CHOH), 3250 cm^{-1} (O—H...N); ^{1}H-NMR spectrum: δ 7·75 (mcs, J = 2·0 Hz, 1 H, 1-H), 7·38 (d, J = 9·0 Hz, 1 H, 4-H), c. 7·00—7·50 (m, 5 H, remaining aromatic protons), 5·35 (s, 1 H, 11-H), 3·58 (t, J = 7·0 Hz, 1 H, 10-H), 2·35 (s, disappears after D_2O, 1 H, OH), 2·34 (t, J = 6·0 Hz, 2 H, CH_2N), 2·25 (s, 6 H, CH_3NCH_3), 1·70 (m, 2 H, remaining CH_2). [j] Hydrogen maleate. [k] Monohydrate. [l] IR spectrum: 753, 821 (Ar—H), 1108 (CHOH), 1473 (Ar), 2495, 2600 (NH^+), 3330 cm^{-1} (OH). [m] IR spectrum (Nujol): 747, 774, 810, 883 (4 and 2 adjacent and solitary Ar—H), 1550, 1575 (Ar), 2460, 2480, 2520, 2570 cm^{-1} (NH^+). [n] For measuring further spectra, the base was liberated (oil); UV spectrum: λ_{max} 223 nm (log ε 4·41), 259·5 nm (4·27), infl. 283 nm (3·73); ^{1}H-NMR spectrum: δ 7·00—7·60 (m, 7 H, aromatic protons), 6·95 (s, 1 H, olefinic CH), 2·20—3·05 (m, 4 H, CH_2.CH_2), 2·25 (s, 6 H, CH_3NCH_3). [o] IR spectrum (Nujol): 750, 828, 840, 878 (4 and 2 adjacent and solitary Ar—H), 1465, 1550, 1579 (Ar), 1620 (C=C conjugated), 2480, 2635 (NH^+), 3435 cm^{-1} (OH, H_2O). [p] Picrate.

amine and of methyl chloride, apparently due to thermal decomposition. The molecular ion *m/e* 301 corresponds to $C_{17}H_{16}ClNS$. Chemical identification of the two quaternary salts was achieved by heating with an aqueous solution of potassium hydroxide (method *J*) when Hoffmann's degradation took place and when olefinic amines *IXd* and *IXe* were obtained and found to be identical with the products of dehydrochlorination of chlorides *VIIId* and *VIIIe*.

All the analyzed products are summarized in Table I together with the usual experimental data. The experimental section shows examples of the general methods used and further descriptions of synthetic procedures differing from the general methods *A*–*J*.

The hydrochlorides of most of the bases prepared and quaternary chlorides *X* and *XI* were orientatively evaluated by methods of general pharmacological screening. The list shows the method of administration in tests *in vivo*, an orientation value of the mean lethal dose LD_{50} in mg/kg for mice and finally dose D in which the compound was applied to obtain the first information *in vivo* (if it was not effective in the given test it was not tested further): *Id*, *p.o.*, 750, 150; *Ie*, *p.o.*, 1000, 200; *If*, *i.v.* 25, 5; *IVd*, *i.v.* 70, 12; *IVe*, *i.v.*, 40, 8; *Vd*, *i.v.*, 62·5, 12; *Ve*, *i.v.*, 62·5, 12; *VId*, *i.v.* 25, 5; *VIe*, *i.v.* 75, 15; *VIf*, *i.v.* 25, 5; *IXd*, *i.v.* 25, 5; *IXe*, *i.v.* 30, 6; *X*, *i.v.* 4, 1; *XI*, *i.v.* 6·25, 1.

Effects on the CNS are restricted mainly to amino ketones *I*, amino alcohols *VI* and amino olefins *IX*. Most of these compounds suppress motility of mice in known surroundings (the dose in mg/kg is shown at which motility was significantly inhibited): *Id*, 100 *p.o.*; *Ie*, 200 *p.o.*; *VId*, 5 *s.c.*; *VIe*, 15 *s.c.*; *IXd*, 5 *s.c.*; *IXe*, 6 *s.c.* A pronouncedly depressant effect in this test was displayed by the quaternary salt *X* (1 *s.c.*). On the other hand, the basic nitrile *IVd* was the only one to show an excitatory effect (12 *s.c.*). An incoordinating effect in the rotating-rod test in mice is displayed only at high doses so that only with amino ketone *Ie* was it possible to determine the mean effective dose (200 mg/kg *p.o.*). The potentiating effect on thiopental sleep in mice (dose in mg/kg, which prolongs thiopental sleep to twice the control value) was displayed by amino ketones *I*, nitriles *IV* and one of the olefinic amines: *Id* and *Ie*, 5–10 *p.o.*; *IVd* 1–2·5 *i.v.*; *IVe* 5–8 *i.v.*; *IXd* 5 *i.v.* A hypothermic effect (doses in mg/kg which bring about a drop of rectal temperature in rats by 1°C) was found only with amino ketones: *Id*, 25–50 *p.o.*; *Ie*, 25 *p.o.* It was surprising to find a cataleptic effect for rats (the mean effective doses in mg/kg are shown, on *i.p.* application): *VIe*, 15; *IXd*, 5; *IXe*, 6. With amino ketones *Id* and *Ie* a pronounced antireserpine effect on mice was observed, which supplements a previous finding on this type of compounds[2,5]. A significant antagonism with the hypothermic effect of reserpine in mice is observed at low doses (*Id*, 10 mg/kg *p.o.*; *Ie*, 2·5–5 mg/kg *p.o.*) while to antagonize reserpine ptosis, substantially greater doses are required (*p.o.*., mg/kg; *Id*, 150; *Ie*, 50). With both these substances an anticonvulsant effect in mice was observed, both toward pentetrazol (doses in mg/kg *p.o.*, which significantly antagonize the convulsant effect of pentetrazol: *Id*, 50–100; *Ie*, 25–50) and toward the electro-shock (doses in mg/kg *p.o.* which in 50% animals prevent the convulsions of hind legs due to an electric shock: *Id*, 150; *Ie*, 100). Amino ketone *Ie* at the high dose of 200 mg/kg *p.o.* displayed an analgesic effect in Haffner's test (dose which has an analgesic effect in 50% of the animals used).

Among the other neurotropic effects one should mention the antiacetylcholine effect of *If*, *Vd*, *VId,e,f*, *IXd,e*, *X* and *XI* in an *in vitro* test using isolated rat duodenum. All these compounds at concentrations between 1 and 10 μg/ml inhibit acetylcholine contractions by 50%. A structurally less specific effect toward barium chloride contractions of isolated rat duodenum was displayed at the same concentrations with *If*, *IVd,e*, *VId,f* and *IXd,e*. With all the three compounds

a mydriatic effect on mice was found (doses in mg/kg are shown which dilate the pupil by 100%): *Id*, 100—150 *p.o.*; *Ie*, 50—100 *p.o.*; *IVd* > 12 *i.p.* A myorelaxing effect on rat gastrocnemius muscle was displayed only by the quaternary salt *X* and that at a dose greater than LD_{50} during artifical ventilation (10 mg/kg *i.v.*); at the same dose, it antagonizes completely muscle contractions caused by electric stimulation. The locally anaesthetic effect in the test of infiltration anaesthesia in guinea-pigs (concentration causing complete anaesthesia in 50% animals is shown) as well as in the corneal anaesthesia test in rabbit eye (concentrations like in the preceding case) was found with three substances at equal concentrations for both tests: *If*, 0·5%; *IVe*, 1% (irritates); *VIf*, 0·1—0·5%. An antihistamine effect in an *in vivo* test in guinea pigs where detoxication of histamine is followed (doses in mg/kg which protect 50% animals from the lethal effect of 5 mg/kg histamine applied intrajugularly are shown) was observed with amino ketones *I*, amino alcohols *VI*, olefinic amines *IX* and both quaternary salts; *Id*, 1—5 *p.o.*; *Ie*, 5—25 *p.o.*; *If*, 1—2·5 *s.c.*; *VId* < < 1 *s.c.*; *VIe* < 10 *s.c.*; *IXd* < 1 *s.c.*; *IXe* 3 *s.c.*, *X* < 1 *s.c.*; *XI* < 1 *s.c.* Compound *IXd* was also studied in the histamine aerosol test in guinea-pigs; a dose of 5 mg/kg *i.p.* applied 15 min before exposure to the aerosol showed only a slight protective effect for 30% animals (Dr J. Metyš). The cardiovascular effects of the compounds tested were not particularly significant. Of those applied *p.o.*, only *Ie* at a dose of 100—200 mg/kg brings about a decrease of blood pressure of normotensive rats by 10%. Of those applied *i.v.* at doses D only *VIf* brings about a brief drop and *IXe* a brief and deep drop of blood pressure of normotensive rats. Some of the compounds displayed an adrenolytic effect on rats (the *i.v.* doses in mg/kg are shown decreasing adrenaline pressure response by 50%): *VIe*, 15; *IXd*, 2·5—5; *IXe*, 3—6; *XI*, 1. Three of the compounds showed an antiarrhythmic effect in rats (doses in mg/kg which inhibit significantly the occurrence of arrhythmias after aconitine): *Ie*, 100—200 *p.o.*; *VIe*, 5—15 *i.v.*; *IXe*, 6 *i.v.* Most of the compounds tested showed a negatively inotropic effect in a preparation of isolated rabbit atrium (concentrations in μg/ml which depress inotropy by 25%): *If*, 5—50; *IVd*, 25—50; *Vd*, 10—25; *Ve*, 25—50; *VId*, 10—25; *VIe*, 5—50; *IXd*, 10—25; *IXe*, 5—25. The heartbeat frequency remains unaffected with some of the compounds (*IVd*, *Vd*) while with others it is depressed by 25% at the same concentrations (*If*, *VId*, *VIe*, *IXd*, *IXe*) and finally with one it is increased by 25% at the concentration shown (*Ve*). A sole compound, the quaternary salt *X*, has a positive inotropic effect (at 10—25 μg/ml it increases inotropy by 25%) while it has no effect on heartbeat frequency. With some of the compounds a significant effect on the survival of mouse myocardium during asphyxia found at the doses shown (mg/kg): *Id*, <100 *p.o.*; *Ie*, 200 *p.o.*; *VId*, 2—5 *i.p.* Four compounds had a diuretic effect on mice on oral application (the doses in mg/kg increase diuresis by 100% as compared with the control): *If*, 25; *IVd*, <60; *Vd*, 50; *Ve*, 25—60. Only with *Ie* was an indication of antiinflammatory activity found on using kaolin arthritis with rats as an inflammation model; at a dose greater than 200 mg/kg *p.o.* the compound inhibits significantly the development of edema of rat hind leg after injection of a kaolin suspension.

Pharmacodynamically most interesting are the amino ketones *Id* and *Ie* which, in various tests, have the character of central depressants (motility, ataxia, hypothermia, potentiation of thiopental sleep) but, because of their pronounced antireserpine effect, they must be considered as thymoleptics with a typical sedative component (type of amitriptyline and prothiadene). They are also anticonvulsant, antihistaminic, mydriatic and partly analgesic. Amino alcohols *VI* lack more pronounced central effects but possess a number of structurally less specific neurotropic effects: spasmolytic (toward acetylcholine and barium chloride), adrenolytic, antihistamine and locally anaesthetic. In the aspects mentioned they resemble olefinic amines *IX* which,

moreover, possess a clear central depressant and, first of all, a cataleptic effect whereby they resemble neuroleptics. Of the quaternary salts *X* and *XI*, pharmacodynamically most interesting is *X* which has central depressant, a myorelaxant and a positively inotropic effect. Both quaternary salts have clearly antihistamine and antiacetylcholine effects. On intravenous application they are rather toxic.

Some of the compounds prepared were tested at the Research Institute for Biofactors and Veterinary Drugs at Pohoří—Chotouň (director Dr B. Ševčík) for coccidiostatic and anthelminthic activity. The coccidiostatic effect was tested in a battery test in chickens infected with oocysts of *Eimeria tenella*; Compounds *Id* and *IVd* had a pronounced effect, compounds *IVe* and *Ve* a clear effect. An anthelminthic effect was observed using the roundworm *Nippostrongylus brasiliensis* — pronounced with *Id* and *Ve*, clear with *IVd* and suggested with *IVe*. *Id* was then tested at the Helminthological Institute, Slovak Academy of Sciences, Košice; it was found to be potent against another species, *Trichocephalus muris* (70—90% efficiency of the mebendazol standard).

All the compounds prepared were evaluated by Dr J. Turinová and Dr A. Čapek (Bacteriological department of this institute) *in vitro* as to their antimicrobial activity toward a standard set of microorganisms. The results are shown in the form of minimum inhibitory concentrations in Table II. All the compounds were ineffective against *Pseudomonas aeruginosa*, *Escherichia coli*,

TABLE II

Antimicrobial Activity of the Dibenzo[*b*,*f*]thiepin Derivatives and Intermediates in *vitro* (minimum inhibitory concentration in μg/ml)

Compound[a]	Microorganism[b]							
	1	2	3	4	5	6	7	8
Id	50	—	50	25	—	125	—	—
Ie	50	—	50	25	—	125	—	—
If	—	—	50	40	100	12·5	100	100
IVd	50	—	50	25	—	—	—	—
IVe	50	—	50	25	—	—	—	—
VId	—	—	—	25	100	100	100	50
VIe	100		—	50	100	50	100	100
VIf	—	—	—	25	100	50	—	100
IXd	25	25	25	25	50	25	100	100
IXe	25	25	25	25	100	25	100	100
X	—	—	100	—	100	100	100	—
XI	—	—	100	—	100	50	100	—

[a] The compounds were tested in the form of salts listed in Table I. [b] 1 *Streptococcus β-haemolyticus*, 2 *Streptococcus faecalis*, 3 *Staphylococcus pyogenes aureus*, 4 *Mycobacterium tuberculosis* H37Rv, 5 *Saccharomyces pasterianus*, 6 *Trichophyton mentagrophytes*, 7 *Candida albicans*, 8 *Aspergillus niger*.

and *Proteus vulgaris* which are not included in the Table. Most of the compounds are somewhat inhibitory against cocci, mycobacteria, yeasts and fungi.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 0·5 Torr over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra in $CDCl_3$ in a ZKR-60 (Zeiss, Jena) spectrometer (unless stated otherwise) and the mass spectra in a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was tested by chromatography on thin layers of silica gel (Silufol). Analyses of all the compounds are shown in Table I.

2-[2-(4-Chlorophenylthio)phenyl]-4-methyl-5-dimethylaminovaleronitrile (*IVf*) (Method *A*)

Sodium amide (2·76 g, 80% purity) was added under stirring at 60°C over a period of 15 min to a solution of 12·9 g *IVa* (ref.[8]) and 7·05 g 2-methyl-3-dimethylaminopropyl chloride[9] in 50 ml toluene. The mixture was refluxed under stirring for 3 h and, after partial cooling, it was decomposed by adding 50 ml water. The toluene layer was washed with water and shaken with 100 ml 10% hydrochloric acid. The acid aqueous solution was made alkaline with 10% NaOH to pH 9 and the product was extracted with ether; 16·2 g (91%) oily base. Neutralization of the base in an ethanolic solution with hydrogen chloride in ethanol with a little ether yielded a hydrochloride which, even after a repeated crystallization from 2-propanol, melts diffusely, m.p. 179 to 187°C and which probably represents a mixture of two racemates. IR spectrum: 760, 825 (4 and 2 adjacent Ar—H), 1580, 1596 (Ar), 2495, 2535, 2615, 2640 (NH^+), 2975 cm^{-1} (CH_2). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 10·80 (bs, 1 H, NH^+), 7·10—8·00 (m, 8 H, aromatic protons), 4·62 (t, J = 7·0 Hz, 1 H, Ar—CH), c. 3·00 (m, 2 H, CH_2N), 2·63 (s, 6 H, CH_3NCH_3), c. 2·00 (m, 3 H, CH_2CH—C—$N^{(+)}$), 1·01 (d, J = 6·0 Hz, 3 H, C—CH_3).

2-[2-(4-Chlorophenylthio)phenyl]hexanamide (*Vb*)

Sodium amide (3·9 g) was added in parts to a 70°C solution of 12·95 g *IVa* (ref.[8]) and 14·0 g n-butyl bromide in 40 ml toluene and the mixture was refluxed for 6 h. After 12 h of standing at room temperature it was decomposed with water, the toluene layer was washed several times with water, dried and evaporated *in vacuo*. The residue (1·50 g crude oily nitrile *IVb*) was dissolved in 75 ml ethanol, combined with 12 g KOH in 40 ml water and refluxed for 3 h. The ethanol was evaporated at reduced pressure and the residue was extracted with ether. Processing of the extract yielded 10·5 g (62%) crude product which was recrystallized for analysis from ethanol: m.p. 115—118°C. IR spectrum (Nujol): 772, 825 (4 and 2 adjacent Ar—H), 1645 ($CONH_2$), 3170 and 3380 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 7·10—7·70 (m, 4 H, aromatic protons of *o*-phenylene), 7·27 and 7·08 (ABq, J = 9·0 Hz, 4 H, aromatic protons of *p*-phenylene), 5·85 and 5·40 (2 bs, 2 H, NH_2), 4·06 (t, J = 7·0 Hz, 1 H, Ar—CH—CO), 1·00—2·20 (m, 6 H, 3 CH_2), 0·78 (t, 3 H, CH_3).

2-[2-(4-Chlorophenylthio)phenyl]-5-dimethylaminovaleramide (*Ve*) (Method *B*)

A solution of 34 g KOH in 100 ml water was added to a solution of 40 g hydrochloride *IVe* in 200 ml ethanol and the mixture was refluxed for 3 h. After evaporation of ethanol *in vacuo* the

residue was diluted with water and extracted with ether. Processing of the exctract yielded 26 g (69%) compound melting at 97–99°C. The analytical sample melted at 98–99°C (ethanol–ether). IR spectrum: 739, 756, 813 (4 and 2 adjacent Ar—H), 1647 ($CONH_2$), 2760, 2780, 2815 (CH_3.NCH_3), 3185 and 3390 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 6·80–7·50 (m, 8 H, aromatic protons), 5·85 and 5·46 (2 bs, 2 H, NH_2), 4·04 (t, J = 7·0 Hz, 1 H, Ar—CH—CO), 2·06 (s, 6 H, CH_3NCH_3), 1·85–2·30 (m, 2 H, CH_2N), 1·00–1·60 (m, 4 H, remaining 2 CH_2). Neutralization of the base with ethanolic hydrogen chloride yielded a hydrochloride melting at 184–186°C (ethanol–ether).

11-(n-Butyl)-8-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Ib*) (Method *C*)

Polyphosphoric acid (30 g; stock acid prepared from 150 ml 80% H_3PO_4 and 300 g P_2O_5) was combined under stirring at 120°C with 6·0 g *Vb* and the mixture was heated for 7 h at 130°C. After cooling to 60°C it was decomposed with ice and water under stirring and the product was extracted with ether. The extract was washed with water and 5% Na_2CO_3, dried with Na_2SO_4 and evaporated: 4·9 g (87%) crude product which was recrystallized from ethanol (filtration with active charcoal): m.p. 73–76°C. UV spectrum: λ_{max} 230 nm (log ε 4·31), 241-5 nm (4·30), infl. 262·5 nm (4·10), 338 nm (3·70). IR spectrum: 755, 822, 910 (4 and 2 adjacent and solitary Ar—H), 1585 (Ar), 1678 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum: δ 8·06 (mcs, J = 3·0 Hz, 1 H, 9-H), 6·90–7·70 (m, 6 H, remaining aromatic protons), 4·65 (dd, J = 8·0; 6·0 Hz, 1 H, Ar—CH—CO), 1·10–2·30 (m, 6 H, 3 CH_2), 0·89 (t, J = 5·0 Hz, 3 H, CH_3).

11-Benzyl-8-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Ic*)

Like in the preceding case, 12·0 g *Vc* was cyclized with 100 g polyphosphoric acid at 140°C for 6 h. A total of 10·0 g neutral product was obtained which was shown to be nonhomogeneous by chromatography on Silufol. It was dissolved in benzene and chromatographed on a column of 500 g silica gel. The first fractions eluted with benzene contained 5·0 g (44%) less polar homogeneous product which crystallized; m.p. 130–131°C (ethanol) and was identified as ketone *Ic*. UV spectrum: λ_{max} 262 nm (log ε 4·09), 338 nm (3·65). IR spectrum: 700, 750, 820, 902 (5, 4 and 2 adjacent and solitary Ar—H), 1680 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum (Tesla BC-487, 80 MHz): δ 8·00 (mcs, J = 3·0 Hz, 1 H, 9-H), 7·00–7·70 (m, 11 H, remaining aromatic protons), 5·12 (dd, J = 8·0; 5·0 Hz, 1 H, Ar—CH—CO), 3·92 and 3·25 (2 dd, J = 14·0; 8·0 and 14·0; 5·0 Hz, 2 H, $ArCH_2$).

On continuing the chromatography, benzene eluted 4·4 g (39%) homogeneous noncrystalline product, apparently 2-[2-(4-chlorophenylthio)phenyl]indan-1-one (*XII*). ^{1}H-NMR spectrum: (Tesla 80 MHz): δ 8·75 (mcd, J = 8·0; 2·5 Hz, 1 H, 7-H of indanone), 6·90–7·60 (m, remaining aromatic protons), 4·42 (dd, J = 8·0; 5·0 Hz, 1 H, Ar—CH—CO), 3·58 and 3·00 (2 dd, J = 16·0; 8·0 and 16·0; 5·0 Hz, 2 H, $ArCH_2$).

8-Chloro-11-(2-dimethylaminoethyl)dibenzo[*b*,*f*]thiepin-10(11H)-one (*Id*)

Like in the preceding cases, 12·0 g hydrochloride *Vd* was cyclized with 50 g polyphosphoric acid, for 4 h at 130°C. After standing overnight, it was decomposed with ice and water, the base was liberated with 20% NaOH and isolated by extraction with ether. Processing of the extract yielded 7·2 g (70%) product which was recrystallized for analysis from ether; m.p. 107–108°C. The mass spectrum displays a molecular ion at m/e 331, corresponding to $C_{18}H_{18}ClNOS$. UV spectrum: λ_{max} 223 nm (log ε 4·28), 241 nm (4·30), infl. 265 nm (4·03), 340 nm (3·59). IR spectrum: 747,

764, 782, 823, 856, 903 (4 and 2 adjacent and solitary Ar—H), 1577 (Ar), 1670 (Ar—CO), 2780 and 2830 cm^{-1} ($N(CH_3)_2$). ^{1}H-NMR spectrum: δ 8·03 (mcs, J = 2·0 Hz, 1 H, 9-H), 6·90—7·70 (m, 6 H, remaining aromatic protons), 4·75 (m, 1 H, Ar—CH—CO), 2·20—3·00 (m, 4 H, 2 CH_2), 2·20 (s, 6 H, $N(CH_3)_2$). Neutralization with hydrogen chloride in ethanol and addition of ether yielded a hydrochloride melting at 275°C under decomposition (ethanol). Ref.[3] describes the preparation of the compound in a different way and reports for the base a m.p. of 108—109°C.

cis-10-Benzyl-2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-ol (*VIc*) (Method *D*)

A solution of 0·5 g $NaBH_4$ in 6 ml water, made alkaline with a drop of 10% NaOH was added dropwise over a period of 10 min to a boiling solution of 1·9 g *Ic* in 60 ml ethanol. The mixture was refluxed under stirring for 4·5 h. Ethanol was evaporated *in vacuo*, the residue was diluted with 50 ml water and extracted with ether. Processing of the extract yielded 1·6 g (84%) crude product which was recrystallized from ether; m.p. 51—53°C. IR spectrum: 690, 743, 810 (Ar—H), 1028, 1035, 1058, 1064, 1109 (CHOH in a ring), 1578, 1600, 3025, 3060 (Ar), 3420, 3520 cm^{-1} (OH). ^{1}H-NMR spectrum (Tesla 80 MHz): δ 6·90—7·60 (m, 7 H, aromatic protons of the tricycle), 7·20 (s, 5 H, C_6H_5), 4·90 (bs, after D_2O s, 1 H, 10-H), 4·35 (m, 1 H, 11-H), 2·80—3·50 (m, 2 H, $ArCH_2$), 1·60 (bs, disappears after D_2O, 1 H, OH).

cis-2-Chloro-10-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-ol (*VIe*)

Like in the preceding case, 20 g ketone *Ie* was reduced with the aid of 1·2 g $NaBH_4$ in 80 ml ethanol and 15 ml water. Processing of the mixture yielded an ether extract (100 ml ether), a partial evaporation of which and standing resulted in a total of 14·0 g (70%) product melting at 142—147°C, melting after recrystallization from ether at 145—147°C (modification *A*). IR spectrum (Nujol): 750, 775, 830, 840, 890 (4 and 2 adjacent and solitary Ar—H), 1024 (CHOH), 3150 cm^{-1} (OH in hydrogen bond). ^{1}H-NMR spectrum: δ 7·55 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·32 (d, J = 9·0 Hz, 1 H, 6-H), 7·04 (mcd, J = 9·0; 2·0 Hz, 1 H, 7-H), 7·10—7·50 (m, 4 H, remaining aromatic protons), 5·11 (s, 1 H, 10-H), 3·85 (bs, disappears after D_2O, 1 H, OH), 3·74 (t, J = 7·0 Hz, 1 H, 11-H), 2·15 (t, J = 6·0 Hz, 2 H, CH_2N), 2·05 (s, 6 H, CH_3NCH_3), 1·52 (m, 4 H, remaining 2 CH_2). Crystallization of a compound obtained in a similar way from ethanol yielded a lower-melting modification *B* with m.p. 113—116°C which crystallizes from ether to modification *A*. On the other hand, modification *A* (stable) cannot be converted to modification *B* by crystallization from ethanol. In chromatography on Silufol both modifications have the same R_F. Neutralization of modification *A* with maleic acid in ethanol and addition of ether yielded hydrogen maleate, m.p. 156—159°C.

trans-2-Chloro-10-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-ol (*VIIe*) (Method *E*)

A solution of 1·0 g modification *A* of alcohol *VIe* in 15 ml 30% sulfuric acid was refluxed for 2 h. After cooling, it was made alkaline with 40% NaOH and the product was isolated by extraction with ether; 0·8 g (80%) product melting at 123—130°C, after crystallization from ether at 132 to 134°C. In mixture with the two modifications of alcohol *VIe* the compound markedly depresses the melting point but during chromatography on Silufol the R_F of both isomers is identical. IR spectrum: 748, 763, 820, 870, 880 (4 and 2 adjacent and solitary Ar—H), 1100 (CHOH in a ring), 1599 (Ar), 2805 (CH_2, CH_3), 3125 cm^{-1} (OH).

trans-10-Benzyl-2,11-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIIc*)

Thionyl chloride (0·83 g) was added to a solution of 1·05 g *VIc* in 20 ml toluene and the mixture was left for 12 h at room temperature. The volatile fractions were evaporated *in vacuo* and the residue was recrystallized from 2-propanol; 0·80 g (80%), m.p. 43–45°C.

trans-2,11-Dichloro-10-(2-dimethylaminoethyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIId*) (Method *F*)

Thionyl chloride (1·35 g) was added dropwise to a solution of 2·0 g *VId* in 45 ml toluene and the mixture was refluxed for 30 min. After standing overnight, the precipitated hydrochloride was filtered; 1·7 g (73%) melting at 178–183°C (ethanol–ether).

10-Benzyl-2-chlorodibenzo[*b*,*f*]thiepin (*IXc*)

A solution of 4·17 g $SOCl_2$ in toluene (10 ml) was added dropwise at room temperature to a solution of 8·1 g crude *VIc* in 50 ml toluene. The mixture was refluxed for 30 min and the volatile fractions were then evaporated *in vacuo*. The residue (7·7 g) represents practically the theoretical yield of olefin *IXc*, m.p. 96–97°C (ethanol). UV spectrum: λ_{max} 259 nm (log ε 4·31), 283 nm (4·28). ^{1}H-NMR spectrum: δ 7·20 (s, 5 H, C_6H_5), 7·00–7·80 (m, 8 H, remaining aromatic protons and olefinic 10-H), 3·80 (bs, 2 H, $ArCH_2$).

trans-10-Benzyl-2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-ol (*VIIc*)

A solution of 1·0 g KOH in 20 ml water was added to a solution of 1·0 g *VIIIc* in a mixture of 20 ml ethanol and 10 ml acetone. The mixture was refluxed for 3 h and the volatile fractions were evaporated *in vacuo*. The residue was diluted with water and the product was isolated by extraction with ether; 0·9 g (95%), m.p. 141–142·5°C (cyclohexane–light petroleum).

10-Benzyl-2-chloro-11-ethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIII*)

A solution of 4·0 g KOH in 20 ml ethanol was added to a solution of 4·5 g *VIIIc* in a mixture of 60 ml ethanol and 20 ml benzene and the mixture was refluxed for 2 h. After cooling, the precipitated KCl was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with water and the product was extracted with ether; 4·0 g (87%), m.p. 105–106°C (2-propanol). The product probably represents a mixture of *cis*- and *trans* isomers. IR spectrum: 709, 763, 770, 828 (Ar—H), 1096 (Ar—C—O—R), 1570, 1596, 1613, 3010, 3065, 3100 cm^{-1} (Ar). ^{1}H-NMR spectrum (Tesla 80 MHz): δ 6·50–7·50 (m, 12 H, aromatic protons), 5·25 (m, 1 H, 10-H), 3·00 to 3·70 (m, 5 H, 11-H, $ArCH_2$ and OCH_2), 1·30 (t, 3 H, CH_3). The mass spectrum contains a molecular ion *m/e* at 380·0992 which supports the composition $C_{23}H_{21}ClOS$; there are intensive fragments at *m/e* 289, 261, 245 and 231.

11-Chloro-1-methyl-2,3,3a,12b-tetrahydro-1*H*-pyrrolo[2,3-*m*]dibenzo[*b*,*f*]thiepin Methochloride (*X*) (Method *H*)

1-Methylpiperazine (1·5 g) was added to a solution of 1·6 g hydrochloride *VIIId* in 10 ml chloroform and the mixture was left for 48 h at room temperature. It was then shaken with 20 ml water and the layers separated. Evaporation of the chloroform layer yielded 0·15 g oil. On standing of the aqueous layer a product crystallized which was filtered and combined with another product

which was obtained by crystallization of the concentrated filtrate; 1·1 g (72%), m.p. 166—167°C (ethanol). According to analysis it is monohydrate of *X*. The mass spectrum contains a molecular ion at *m/e* 301, corresponding to $C_{17}H_{16}ClNS$. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·04 (mcs, J = 2·5 Hz, 1 H, 12-H), 7·10—7·95 (m, 6 H, remaining aromatic protons), 5·55 (d, J = 11·0 Hz, 1 H, 12b-H), 4·65 (m, 1 H, 3a-H), c. 3·95 (m, 2 H, $CH_2N^{(+)}$), c. 2·80 (m, 2 H, CH_2 in position 3), 3·45 and 2·84 (2 s, 6H, $CH_3N^{(+)}CH_3$). Reaction of the compound with an equivalent of picric acid in hot water results in the precipitation of picrate, m.p. 228—236°C (ethanol).

2-Chloro-10-(3-dimethylaminopropyl)dibenzo[*b*,*f*]thiepin (*IXe*)

A. Method *G*: A solution of 2·0 g KOH in 20 ml ethanol was added to a solution of 1·5 g hydrochloride *VIIIe* in 30 ml ethanol and the mixture was refluxed for 1 h. After cooling, the precipitated KCl was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with 50 ml water and the product was isolated by extraction with ether; 1·0 g (73%) oil. Neutralization with hydrogen chloride in ethanol and addition of ether yielded a hydrochloride which was crystallized from a mixture of ethanol and ether; m.p. 215—217°C. The base was liberated from the hydrochloride sample by adding NH_4OH and extracted with ether; it is oily and was used as such for recording the spectra. UV spectrum: λ_{max} 223 nm (log ε 4·47), 258·5 nm (4·36), infl. 280 nm (3·82). ^{1}H-NMR spectrum (Tesla 80 MHz): δ 6·70—7·50 (m, 8 H, aromatic protons and olefinic 11-H), 2·75 (bt, 2 H, =C—CH_2), 2·26 (t, 2 H, CH_2N), 2·10 (s, 6 H, CH_3NCH_3), 1·60 (m, 2 H, remaining CH_2 group).

B. Method *J*: 12-Chloro-1-methyl-1,2,3,4,4a,13b-hexahydropyrido[2,3-*m*]dibenzo[*b*,*f*]thiepin methochloride (monohydrate) (*XI*-H_2O) (1·0 g) and 50 ml 20% aqueous solution of KOH was refluxed for 2 h. After cooling and standing overnight, a base precipitated which was extracted with ether and neutralized with hydrogen chloride in ethanol to convert it to a hydrochloride (0·7 g, 75%) which was precipitated by an addition of ether; m.p. 210—212°C (ethanol–ether). In a mixture with the product according to *A* it melts without depression. The R_F of the base on Silufol is identical with that of the base according to *A*.

The authors are indebted to Dr N. Ryska, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, for measuring and interpreting the mass spectra. Thanks are due to Mrs J. Komancová, Mrs J. Hrdá, Mrs V. Šmídová, Mrs A. Slavíková, Mr M. Čech, Mrs Z. Volková and Mr J. Komínek (analytical department of this institute) for carrying out the analyses.

One of the authors (M. P.) is indebted to Dr K. Bláha, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague, for a stimulating discussion.

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Translated by A. Kotyk.