8-ALKYL AND 8-CYCLOALKYL-10-PIPERAZINODIBENZO[*b,f*]THIEPINS*

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Proceeding from 4-ethyl, 4-isopropyl, 4-n-butyl, 4-n-octyl, 4-cyclopropyl and 4-cyclopentyl thiophenols, the corresponding 8-substituted dibenzo [*b, f*] thiepin-10(11*H*)-ones *XIV* were synthesized *via* the intermediates *IX—XIII*. The ketones *XIV* were further converted to the 10-piperazino derivatives of the 10,11-dihydro series *I—VI* and further to enamines *VII*. Starting from the cyclopropyl acid *IXe*, the cyclopropyl analogue (*XXVII*) of the neuroleptic chlorprothixene was synthesized in three steps. The piperazine derivatives *Ia*, *Ib*, *Ie*, *IIa*, *IIb* and *VIIb* were found to be very effective neuroleptics with a high degree of central depressant and cataleptic activity.

In the present pharmacochemical research of 8-substitution derivatives of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*] thiepin which are generally neuroleptically active, relatively little attention has been devoted so far to alkyls as 8-substituents. The synthesis of the 8-methyl derivative (*I*, $R^1 = CH_3$) and of the 8-tert-butyl derivative (*I*, $R^1 = C(CH_3)_3$) (ref.[1]) has been described, the first of these having been found to be a four-fold more potent central depressant than chlorpromazine, the second of these being slightly weaker than chlorpromazine. At the same time, in the phenothiazine series of neuroleptics with a similarly localized substituent of alkyl type, only the ethyl derivative[2] "ethylisobutrazine" found practical application while in the thioxanthene series of 2-alkyl derivatives of prothixene the isopropyl derivative was found to be most effective here[3]. For this reason we thought it useful to extend the information on the 8-alkyl derivatives of this series and we started to work with the 8-ethyl, 8-isopropyl, 8-n-butyl and 8-n-octyl derivatives *Ia—Id*. The study included two representatives of the series of 8-cycloalkyl derivatives, *viz*. the 8-cyclopropyl derivative *Ie* and the 8-cyclopentyl derivative *If*. In a number of cases, the principal N-methyl derivatives *I* were supplemented with further N-substitution analogues *II—VI* and further with the 10-unsaturated analogues, the enamines *VII*.

During synthesis of *I—VII* we generally adhered to the usual scheme[1], using the corresponding 4-substituted thiophenols as the starting compounds. The thiophenols were condensed in the first step with 2-iodobenzoic acid[4] in the presence of potassium

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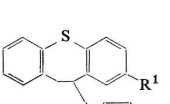
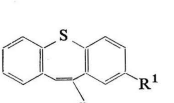
hydroxide to the corresponding 2-(4-subst. phenylthio)benzoic acids *IX* (method *A*). The second step consisted in the reduction of these acids with sodium bis(2-metho-



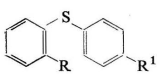


I, R = CH_3
II, R = $(CH_2)_3OH$
III, R = $COOC_2H_5$
IV, R = H
V, R = $(CH_2)_3OCO(CH_2)_6CH_3$
VI, R = $(CH_2)_3OCO(CH_2)_{10}CH_3$

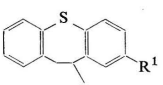
VII, R =
VIII, R = H

In all formulae: *a*, $R^1 = CH_2CH_3$; *b*, $R^1 = CH(CH_3)_2$; *c*, $R^1 = (CH_2)_3CH_3$; *d*, $R^1 = (CH_2)_7CH_3$; *e*, R^1 =  ; *f*, R^1 =

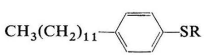
xyethoxy)dihydroaluminate[5] to the 2-(4-subst. phenylthio)benzyl alcohols *X* (method *B*). In a further step, these alcohols were converted by treatment with thionyl chloride (method *C*) to the 2-(4-subst.phenylthio)benzyl chlorides *XI* which were refluxed with aqueous-ethanolic potassium cyanide (method *D*) giving the nitriles *XII*. Alkaline hydrolysis of these nitriles (method *E*) then yielded the 2-(4-subst.phenylthio) phenylacetic acids (*XIII*). Cyclization to the 8-subst.dibenzo[*b*,*f*]thiepin-10(11*H*)-ones (*XIV*) was usually carried out by heating with polyphosphoric acid (method *F*). Ketones were reduced with sodium borohydride in aqueous ethanol (method *G*) to alcohols *XV* which were treated with hydrogen chloride in benzene (method *H*) to yield the chlorides *XVI*. Substitution reactions of these chlorides with 1-methylpiperazine, 1-(3-hydroxypropyl)piperazine[6], or with 1-ethoxycarbonylpiperazine[7] (method *J*) resulted in the piperazine derivatives *I*–*III*. The substitution reactions were accompanied by elimination reactions giving rise to 2-substituted dibenzo[*b*,*f*]thiepins (*VIII*) which were in most cases isolated and characterized. Alkaline hydrolysis of carbamates *III* (method *K*) yielded secondary amines *IV*. With a view to the possibility of obtaining a protracted effect by esterification of alcohols of type *II* with fatty acids containing a longer chain[8], reaction of alcohols *II* with capryloyl[9] and lauroyl chlorides[10] in benzene (method *L*) was used for the preparation of esters *V* and *VI*. Reactions of ketones *XIV* with 1-methylpiperazine and titanium tetrachloride in benzene (method *M*) led to enamines *VII* (ref.[11–13]). The experimental section shows only examples of preparations using the above general methods. All the compounds prepared are included together with the usual experimental data in Table I.



IX, R = COOH
X, R = CH_2OH
XI, R = CH_2Cl
XII, R = CH_2CN
XIII, R = CH_2COOH



XIV, R = =O
XV, R = —OH
XVI, R = —Cl



XVII, R = H

XVIII, R =

In the ethyl series (*a*) we proceeded from the described 2-(4-ethylphenylthio)-benzoic acid[3] (*IXa*) and used the above general reactions. Only in the case of cyclization of *XIIIa* with polyphosphoric acid to the ketone *XIVa* a modified method was used, consisting in the presence of toluene as solvent for the organic reaction components (method *F-1*). In the isopropyl series (*b*) the starting compound was 4-isopropyl-thiophenol[1] which had been obtained by reduction of 4-isopropylbenzenesulfonyl chloride[1] with phosphorus and iodine in boiling acetic acid (method[14]). This was then[3] transformed to acid *IXb*. The ketone *XIVb* was obtained in approximately the same yield with method *F* at 150°C as with method *F-1*. Likewise, in the n-butyl series (*c*) the starting 4-n-butylthiophenol[1] was obtained by reduction of 4-(n-butyl)-benzenesulfonyl chloride[1] with lithium aluminium hydride in ether. 2-(4-n-Butyl-phenylthio)benzoic acid (*IXc*) has been reported previously[3]. Ketone *XIVc* has been obtained by the *F-1* method. The other compounds of this series were prepared by application of general methods.

Synthesis of the n-octyl derivative *Id* was motivated differently from the preparation of other compounds of this series. Preliminary tests of the ethyl derivative *Ia* and of the n-butyl derivative *Ic* showed that with extension of the alkyl chain in position 8 the central activity decreased. On the other hand, the antimicrobial activity rose (Table III), this raising the interest in compounds with a longer alkyl in the given position. In the n-octyl series (*d*) the preparation of the starting 4-n-octylthiophenol has been described in the literature[15] but here we used also the novel procedure, *viz.* reduction of 4-(n-octyl)benzenesulfonyl chloride[16] with phosphorus and iodine in acetic acid. The work in this series was rather complicated by the highly lipophilic character of all the intermediates which decreased the yields and complicated the isolation. For reducing the acid *IXd* to the alcohol *Xd* we used lithium aluminium hydride in ether[1]. Cyclization of acid *XIIId* was carried out by method *F* at 160 to 170°C; the ketone *XIVd* was characterized as crystalline 2,4-dinitrophenylhydrazone.

The attempt at preparing the analogous n-dodecyl derivative was motivated similarly to the work in the n-octyl series but the work was not completed because of the extremely lipophilic character of the intermediates. n-Dodecylbenzene[17] was chlorosulfonated and the crude 4-(n-dodecyl) benzenesulfonyl chloride was reduced with phosphorus and iodine in acetic acid to the novel 4-n-dodecylthiophenol (*XVII*) which was converted in a poor yield by method *A* to the acid *XVIII*.

TABLE I

Dibenzo[*b,f*]thiepins (*I—VIII*) and Intermediates of Their Synthesis (*IX—XVI*)

Compound[a,b]	Method (yield %)	B. p.,°C/Torr or m. p.,°C (solvent)	Formula (m. w.)	Calculated/Found			
				% C	% H	% S	% N (Cl)
IXd	*A*	111—112[c]	$C_{21}H_{26}O_2S$	73·64	7·65	9·36	—
	(90)	(ethanol)	(342·5)	73·39	7·82	9·41	
XVIII	*A*	90·5—91·5[d]	$C_{25}H_{34}O_2S$	75·33	8·60	8·04	—
	(25)	(ethanol)	(398·6)	75·36	8·70	7·91	
IXe	*A*[e]	192—194	$C_{16}H_{14}O_2S$	71·08	5·22	11·86	—
	(80)	(aqueous ethanol)	(270·3)	71·25	5·21	11·94	
IXf	*A*	208—209[f]	$C_{18}H_{18}O_2S$	72·45	6·08	10·75	—
	(77)	(aqueous ethanol)	(298·4)	72·20	6·11	10·94	
Xa	*B*	160—163/1·7[g]	$C_{15}H_{16}OS$	73·73	6·60	13·12	—
	(89)		(244·3)	73·87	6·65	12·70	
Xb	*B*[e]	156—160/1·5	$C_{16}H_{18}OS$	74·37	7·02	12·41	—
	(94)		(258·4)	74·58	7·12	12·32	
Xc	*B*	175—180/0·5	$C_{17}H_{20}OS$	74·95	7·40	11·77	—
	(92)		(272·4)	74·81	7·52	11·50	
Xd	[e]	195/0·4	$C_{21}H_{28}OS$	76·78	8·59	9·76	—
			(328·5)	76·56	8·80	9·60	
Xf	*B*	212—216/2[h]	$C_{18}H_{20}OS$	76·01	7·09	11·27	—
	(82)		(284·4)	75·70	6·96	10.97	
XIa	*C*	170/2·5	$C_{15}H_{15}ClS$	68·55	5·75	12·20	13·49
	—		(262·8)	68·47	5·79	12·03	13·80
XIb	*C*	163—165/2	$C_{16}H_{17}ClS$	69·42	6·19	11·58	12·81
	(87)		(276·8)	69·32	6·16	11·62	13·07
XIc	*C*	133—138/2	$C_{17}H_{19}ClS$	70·20	6·58	11·03	12·19
	—		(290·8)	70·07	6·57	10·92	12·21
XId	*C*	190—193/0·5	$C_{21}H_{27}ClS$	—	—	9·24	—
	—		(346·9)			9·44	
XIf	*C*[e]	180—182/1	$C_{18}H_{19}ClS$	71·38	6·32	10·59	11.71
	(80)		(302.9)	71·71	6·38	10·50	11·51
XIIa	*D*	185—188/2·5	$C_{16}H_{15}NS$	—	—	12·66	5·53
	(62)		(253·4)			12·00	5·22
XIIb	*D*[e]	158—162/1	$C_{17}H_{17}NS$	76·36	6·40	11·99	5·24
	(86)		(267·4)	76·74	6·53	11·68	4·86
XIIc	*D*	195—200/2	$C_{18}H_{19}NS$	76·82	6·81	11·39	4·98
	(84)		(281·4)	76·81	6·87	11·25	4·41

TABLE I
(*Continued*)

Compound[a,b]	Method (yield %)	B. p., °C/Torr or m. p., °C (solvent)	Formula (m. w.)	Calculated/Found % C	% H	% S	% N (Cl)
XIIf	*D* (80)	190–195/2·5[i]	$C_{19}H_{19}NS$ (293·4)	77·79 77·60	6·53 6·49	10·91 11·04	4·77 4·81
XIIIa	*E*[e] (83)	96–99 (aqueous ethanol)	$C_{16}H_{16}O_2S$ (272·4)	70·55 70·70	5·92 6·03	11·77 11·96	—
XIIIb	*E* (86)	111–113[j] (aqueous ethanol)	$C_{17}H_{18}O_2S$ (286·4)	71·29 71·34	6·33 6·35	11·20 11·13	—
XIIIc	*E* (92)	84–85 (aqueous ethanol)	$C_{18}H_{20}O_2S$ (300·4)	71·96 72·23	6·71 6·78	10·67 10·70	—
XIIId	*E*	68–68·5[k] (aqueous ethanol)	$C_{22}H_{28}O_2S$ (356·5)	74·11 74·67	7·92 8·02	8·99 9·12	—
XIIIe	[e]	122–125·5 (aqueous ethanol)	$C_{17}H_{16}O_2S$ (284·4)	71·81 71·57	5·67 5·71	11·27 11·58	—
XIIIf	*E* (92)	106–107[m] (aqueous ethanol)	$C_{19}H_{20}O_2S$ (312·4)	73·04 73·16	6·45 6·45	10·26 9·97	—
XIVa	*F-1* (90)	190/2·5[n]	$C_{16}H_{14}OS$ (254·3)	75·55 75·09	5·55 5·61	12·61 12·41	—
XIVb	*F*[e] (76)	167–170/1·5	$C_{17}H_{16}OS$ (268·4)	76·08 76·40	6·01 6·05	11·95 11·96	—
XIVc	*F-1*[e] (82)	190–195/2	$C_{18}H_{18}OS$ (282·4)	76·55 76·55	6·42 6·50	11·35 11·00	—
XIVd-DFH	*F* —	177·5–178·5[o] (ethanol–acetone)	$C_{28}H_{30}N_4O_4S$ (518·6)	64·84 64·56	5·83 6·01	6·18 6·43	10·80 10·90
XIVe	[e]	76·5–77 (cyclohexane)	$C_{17}H_{14}OS$ (266·4)	76·65 76·76	5·30 5·50	12·04 12·12	—
XIVe-DFH		244·5–245·5[p] (dimethyl-formamide–ethanol)	$C_{23}H_{18}N_4O_4S$ (446·5)	61·86 61·85	4·06 4·25	7·18 7·35	12·55 12·82
XIVf	*F-1* (60)	212–215/2[q]	$C_{19}H_{18}OS$ (294·4)	77·51 77·72	6·16 6·41	10·89 10·72	—
XVa	*G* (92)	87–88[r] (benzene–light petroleum)	$C_{16}H_{16}OS$ (256·4)	74·96 74·95	6·29 6·22	12·51 12·43	—
XVb	*G* (86)	87–88[s] (light petroleum)	$C_{17}H_{18}OS$ (270·4)	75·51 75·37	6·71 6·80	11·86 11·71	—

TABLE I
(*Continued*)

Compound[a,b]	Method (yield %)	B. p., °C/Torr or m. p., °C (solvent)	Formula (m. w.)	Calculated/Found			
				% C	% H	% S	% N (Cl)
XVc	*G*[e] (82)	62—63 (benzene–light petroleum)	$C_{18}H_{20}OS$ (284·4)	76·01 76·16	7·09 7·08	11·27 11·28	—
XVe	*G* (98)	105—107[t] (cyclohexane)	$C_{17}H_{16}OS$ (268·4)	76·08 75·91	6·01 6·22	11·95 11·73	—
XVf	*G* (95)	77—81[u] (light petroleum)	$C_{19}H_{20}OS$ (296·4)	76·98 76·77	6·80 6·77	10·82 11·00	—
XVIb	*H* (93)	66—68[v] (light petroleum)	$C_{17}H_{17}ClS$ (288·8)	70·69 70·82	5·93 6·07	11·10 11·28	12·28 12·48
XVIe	*H*[e] (97)	76·5—77 (cyclohexane)	$C_{17}H_{15}ClS$ (286·8)	71·18 70·52	5·27 5·43	11·18 10·95	12·36 12·13
Ia	*J* (72)	96—98 (acetone)	$C_{21}H_{26}N_2S$ (338·5)	74·51 74·22	7·74 7·90	9·47 9·62	8·28 8·14
Ia-MS	—	190—192 (ethanol)	$C_{22}H_{30}N_2O_3S_2$ (434·6)	60·80 59·91	6·96 7·00	14·76 14·92	6·44 6·35
Ib	*J*[c] (91)	118—120 (benzene–light petroleum)	$C_{22}H_{28}N_2S$ (352·5)	74·95 74·45	8·00 8·11	9·09 9·23	7·95 8·22
Ib-2MS	—	203—206 (ethanol)	$C_{24}H_{36}N_2O_6S_3$ (544·7)	52·91 52·62	6·66 6·70	17·66 17·52	5·14 5·01
Ic-MS[w]	*J* (72)	171—173[x] (ethanol–ether)	$C_{24}H_{35}N_2O_{3.5}S_2$ (471·7)	61·11 61·15	7·48 7·39	13·59 13·53	5·94 5·56
Id-M	*J* (51)	127—130[y] (ethanol–ether)	$C_{31}H_{42}N_2O_4S$ (538·7)	69·11 68·87	7·85 7·84	5·95 6·44	5·21 5·07
Id-2HM	—	151—152·5 (ethanol–ether)	$C_{35}H_{46}N_2O_8S$ (654·8)	64·20 64·35	7·08 7·20	4·90 5·10	4·27 4·11
Ie-M	*J* (78)	168—170[z] (ethanol)	$C_{26}H_{30}N_2O_4S$ (466·6)	66·93 67·08	6·48 6·50	6·87 7·04	6·00 5·90
If-2MS[w]	*J* (61)	203—205 (ethanol)	$C_{26}H_{39}N_2O_{6.5}S_3$ (579·8)	53·86 54·10	6·78 6·74	16·59 16·61	4·83 4·63
IIa	*J* (93)	71—73[aa] (benzene–light petroleum)	$C_{23}H_{30}N_2OS$ (382·6)	72·21 72·11	7·90 7·96	8·38 8·00	7·32 7·07

TABLE I
(*Continued*)

Compound[a,b]	Method (yield %)	B. p., °C/Torr or m. p., °C (solvent)	Formula (m. w.)	Calculated/Found			
				% C	% H	% S	% N (Cl)
IIa-2MS[bb]	—	128—130 (ethanol–ether)	$C_{25}H_{42}N_2O_9S_3$ (610·8)	49·16 50·02	6·93 6·61	15·75 15·70	4·59 5·00
IIa-2HM[w]	—	153—155 (ethanol)	$C_{31}H_{39}N_2O_{9.5}S$ (623·7)	59·63 59·78	6·30 6·35	5·14 5·24	4·49 4·49
IIb-2MS	*J* (94)	185—186 (ethanol)	$C_{26}H_{40}N_2O_7S_3$ (588·8)	—	—	16·34 16·20	4·76 4·83
IIc	*J* (74)	92—94[cc] (benzene–light petroleum)	$C_{25}H_{34}N_2OS$ (410·6)	73·12 73·10	8·35 8·39	7·81 7·85	6·82 6·46
IIc-2HM	—	103—107 (ethanol)	$C_{33}H_{42}N_2O_9S$ (642·7)	61·66 61·77	6·59 6·53	4·99 5·57	4·36 4·23
IIf-2MS[w]	*J* (82)	188—189 (ethanol)	$C_{28}H_{43}N_2O_{7.5}S_3$ (623·8)	53·90 54·07	6·94 7·14	15·42 15·65	4·49 4·45
IIIa-M	*J* (70)	188—190 (ethanol)	$C_{27}H_{32}N_2O_6S$ (512·5)	63·27 63·15	6·29 6·32	6·25 6·52	5·47 5·47
IIIb-M	*J* (68)	176—179 (ethanol)	$C_{28}H_{34}N_2O_6S$ (526·6)	63·86 63·81	6·51 6·53	6·08 6·00	5·32 5·32
IIIf[dd]	*J* (76)	90—93[ee] (benzene)	$C_{28}H_{34}N_2O_2S$ (462·6)	72·70 72·38	7·41 7·44	6·92 7·05	6·06 5·71
IVa	*K*[e] (84)	113—114 (acetone)	$C_{20}H_{24}N_2S$ (324·4)	74·04 73·86	7·46 7·49	9·86 9·91	8·64 8·38
IVa-M	—	159—161 (ethanol)	$C_{24}H_{28}N_2O_4S$ (440·5)	65·43 65·76	6·40 6·68	7·28 7·62	6·36 6·07
IVb	*K* (93)	160—163[ff] (benzene)	$C_{21}H_{26}N_2S$ (338·5)	74·51 74·43	7·74 7·85	9·47 9·44	8·28 7·98
IVf-2HM	*K* (97)	143—146 (acetone)	$C_{31}H_{36}N_2O_8S$ (596·7)	62·40 62·18	6·08 6·10	5·37 5·57	4·69 4·67
Va-2HM	*L*[e] —	144—146 (acetone)	$C_{39}H_{52}N_2O_{10}S$ (740·9)	63·22 63·32	7·07 7·07	4·33 4·44	3·78 3·81
Vb-2HM	*L* —	146—148 (acetone)	$C_{40}H_{54}N_2O_{10}S$ (754·9)	63·64 63·43	7·21 7·40	4·25 4·69	3·71 3·39
Vc-2HM	*L* —	113—115 (acetone)	$C_{41}H_{56}N_2O_{10}S$ (768·9)	64·04 64·28	7·34 7·34	4·17 4·40	3·64 3·67

TABLE I
(*Continued*)

Compound[a,b]	Method (yield %)	B. p., °C/Torr or m. p., °C (solvent)	Formula (m. w.)	Calculated/Found			
				% C	% H	% S	% N (Cl)
VIa-2HM	*L*	126–128	$C_{43}H_{60}N_2O_{10}S$	64·80	7·59	4·02	3·51
	—	(acetone)	(797·0)	64·63	7·67	4·14	3·46
VIIb-MS[w]	*M*	210–212	$C_{23}H_{31}N_2O_{3.5}S_2$	60·62	6·86	14·08	6·15
	—	(ethanol–ether)	(455·6)	60·88	6·92	14·58	6·07
VIIc	*M*[e]	140–141	$C_{23}H_{28}N_2S$	75·77	7·74	8·80	7·68
	—	(benzene)	(364·5)	76·13	7·91	9·06	7·91
VIIc-M	—	197–200	$C_{27}H_{32}N_2O_4S$	67·47	6·71	6·67	5·83
		(ethanol)	(480.6)	67·35	6·71	7·02	5·67
VIIf-MS[gg]	*M*	204–208	$C_{25}H_{34}N_2O_4S_2$	61·21	6·99	13·05	5·71
	—	(ethanol)	(490·5)	61·60	6·97	13·30	5·47
VIIIa	*J*	170–173/2	$C_{16}H_{14}S$	—	—	13·45	—
	—		(238·3)			12·86	
VIIIb	*J*[e]	177–180/1·5	$C_{17}H_{16}S$	80·90	6·39	12·71	—
	—		(252·4)	80·52	6·52	12·56	
VIIIc	*J*	150–160/1·7[hh]	$C_{18}H_{18}S$	81·15	6·81	12·04	—
	—		(266·4)	80·77	7·07	11·71	
VIIIe	*J*	72–73[ii]	$C_{17}H_{14}S$	81·55	5·64	12·81	—
	—	(light petroleum)	(250·3)	81·39	5·93	12·51	
VIIIf	*J*	200/0·5[jj]	$C_{19}H_{18}S$	81·96	6·52	11·52	—
	—		(278·4)	81·92	6·56	10·75	

[a] The intermediate nitrile *XIId*, alcohol *XVd* and chlorides *XVIa*, *XVIc*, *XVId* and *XVIf* could not be obtained in the crystalline form and were used in the crude state. They are not included in the table. [b] DFH 2,4-dinitrophenylhydrazone, MS methanesulfonate, M maleate, HM hydrogen maleate. [c] IR spectrum (KBr): 745 (4 vicinal aromatic C—H), 810 (2 vicinal aromatic C—H), 912 (COOH), 1 250 (CO), 1 550 and 1 582 (Ar), 1 670 cm^{-1} (ArCOOH); NMR spectrum: δ 11·75 (bs, disappears after D_2O, 1 H, COOH), 8·18 (m, 1 H, aromatic 6-H), 7·54 (d, J = 9·0 Hz, 2 H, aromatic 2′,6′-H_2), 7·27 (d, J = 9·0 Hz, 2 H, aromatic 3′,5′-H_2), c. 7·21 (m, 2 H, aromatic 4,5-H_2), 6·80 (m, 1 H, aromatic 3-H), 2·65 (t, J = 7·0 Hz, 2 H, $ArCH_2$), c. 1·60 (m, 2 H, CH_2 in the vicinity of terminal methyl), 1·30 (bs, 10 H, remaining CH_2 groups of octyl), 0·88 (t, 3 H, CH_3). [d] UV spectrum: λ_{max} 222 nm (log ε 4·40), 256 nm (395), 276 nm (3·73), 317 nm (3·54); IR spectrum: 736 (4 vicinal aromatic C—H), 810 (2 vicinal aromatic C—H), 1 562, 1 585 (Ar), 1 674 cm^{-1} (ArCOOH). [e] See experimental section. [f] UV spectrum: λ_{max} 222 nm (log ε 4.41), 254 nm (4·01), 273 nm (3·76), 311 nm (3·58); IR spectrum (KBr): 740 (4 vicinal aromatic C—H), 810 (2 vicinal aromatic C—H), 920, 1 254 (COOH), 1 560, 1 588 (Ar), 1 730, 2 560, 2640, 3 100–3 200 cm^{-1} (COOH). [g] IR spectrum: 755 (4 vicinal aromatic C—H), 825 (2 vicinal aromatic C—H), 1 030

(CH_2OH), 1590 (Ar), 3380 cm^{-1} (OH). [h] NMR spectrum: δ 7·10—7·60 (m, 8 H, aromatic protons), 4·72 (bs, 2 H, $ArCH_2O$), 2·90 (m, 1 H, Ar—CH of cyclopentyl), 2·33 (bs, disappears after D_2O, 1 H, OH), 1·50—2·20 (m, 8 H, 4 CH_2 of cyclopentyl). [i] IR spectrum (film): 758 (4 vicinal aromatic C—H), 820 (2 vicinal aromatic C—H), 1590 (Ar), 2255 cm^{-1} (R—CN). [j] IR spectrum: 758 (4 vicinal aromatic C—H), 828 (2 vicinal aromatic C—H), 928, 1238, 1710 and 3100 cm^{-1} (COOH). [k] IR spectrum: 760 (4 vicinal aromatic C—H), 820 (2 vicinal aromatic C—H), 940 (COOH), 1240 (C—O), 1700 cm^{-1} (COOH); NMR spectrum: δ 10·40 (bs, disappears after D_2O, 1 H, COOH), 6·90—7·50 (m, 8 H, aromatic protons), 3·80 (s, 2 H, $ArCH_2CO$), 2·52 (t, J = 7·0 Hz, 2 H, $ArCH_2$ of octyl), c. 1·55 (m, 2 H, CH_2 in the vicinity of terminal methyl), 1·23 (bs, 10 H, remaining CH_2 groups of octyl), 0·85 (t, 3 H, CH_3). [m] IR spectrum: 755, 768 (4 vicinal aromatic C—H), 818, 828 (2 vicinal aromatic C—H), 945, 1238 (COOH), 1570, 1593 (Ar), 1710, 2560, 2730 and 3150 cm^{-1} (COOH). [n] UV spectrum: λ_{max} 241 nm (log ε 4.29); IR spectrum: 747, 766 (4 vicinal aromatic C—H), 830 (2 vicinal aromatic C—H), 880 (solitary aromatic C—H), 1600 (Ar), 1670 cm^{-1} (Ar—CO). [o] UV spectrum: λ_{max} 254 nm (log ε 4·31), 356 nm (4·44); IR spectrum: 740, 760 (4 vicinal aromatic C—H), 840 (2 vicinal aromatic C—H), 909 (solitary aromatic C—H), 1340, 1518 (NO_2), 1540, 1595 (Ar), 1620 (C=N), 3310 cm^{-1} (NH); NMR spectrum: δ 11·90 (bs, disappears after D_2O, 1 H, NH), 9·18 (d, J = 3·0 Hz, 1 H, aromatic proton between nitro groups), 8·35 (mcd, J = 9·0; 3·0 Hz, 1 H, another aromatic proton in the vicinity of NO_2), 8·02 (d, J = 9·0 Hz, 1 H, aromatic proton in *m*-position toward NO_2 groups), 7·00—7·80 (m, 7 H, remaining aromatic protons), 4·19 (s, 2 H, $ArCH_2$ in a ring), 2·58 (t, 2 H, $ArCH_2$ of octyl), c. 1·50 (m, 2 H, CH_2 adjacent to the terminal methyl), 1·24 (bs, 10 H, remaining CH_2 groups of octyl), 0·85 (t, 3 H, CH_3). [p] UV spectrum (ethanol): λ_{max} 228 nm (log ε 4·63), 251 nm (4·67), infl. 281 nm (4.37); IR spectrum: 760 (4 vicinal aromatic C—H), 842 and 833 (2 vicinal aromatic C—H), 860 (solitary aromatic C—H), 1330 and 1510 (NO_2), 1590 (Ar), 1610 (C=N), 3310 cm^{-1} (NH). [q] UV spectrum: λ_{max} 244 nm (log ε 4·26), 340 nm (3.47); IR spectrum (film): 748 (4 vicinal aromatic C—H), 828 (2 vicinal aromatic C—H), 875 (solitary aromatic C—H), 1288 (CO), 1594 (Ar), 1673 cm^{-1} (ArCO); NMR spectrum: δ 8·13 (d, J = 3·0 Hz, 1 H, aromatic 9-H), 7·00—7·80 (m, 6 H, remaining aromatic protons), 4·35 (s, 2 H, $ArCH_2CO$), 2·95 (m, 1 H, Ar—CH of cyclopentyl), 1·40—2·20 (m, 8 H, 4 CH_2 of cyclopentyl). [r] IR spectrum (KBr): 749 (4 vicinal aromatic C—H), 826 (2 vicinal aromatic C—H), 899 (solitary aromatic C—H), 1052 (CHOH), 3380 cm^{-1} (OH). [s] NMR spectrum: δ 6·90—7·70 (m, 7 H, aromatic protons), 5·10—5·50 (m, dd after D_2O, 1 H, Ar—CH—O), 3·20—3·90 (dd, 2 H, $ArCH_2$ in a ring), 2·40—3·30 (m, 1 H, Ar—CH of isopropyl), 2·08 (bs, disappears after D_2O, 1 H, OH), 2·21 and 2·11 (2 s, 2 CH_3). [t] IR spectrum (KBr): 758 (4 vicinal aromatic C—H), 830 (2 vicinal aromatic C—H), 862 (solitary aromatic C—H), 1060 (CHOH), 1605 (Ar), 3400 cm^{-1} (OH); NMR spectrum: δ 7·05—7·70 (m, 6 H, aromatic protons in positions 1, 2, 3, 4, 6, 9), 6·90 (mcd, J = 9·0; 2·5 Hz, 1 H, aromatic 7-H), 5·33 (m, dd after D_2O, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·76 and 3·32 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$ in a ring), 2·16 (d, disappears after D_2O, 1 H, OH), 1·85 (m, 1 H, Ar—CH of cyclopropyl), 0·50—1·10 (m, 4 H, 2 CH_2 of cyclopropyl). [u] IR spectrum: 751 (4 vicinal aromatic C—H), 820 (2 vicinal aromatic C—H), 900 (solitary aromatic C—H), 1015 (CHOH), 3240 cm^{-1} (OH). [v] NMR spectrum: δ 6·90—7·70 (m, 7 H, aromatic protons), 5·80 (dd, J = 6·0; 8·0 Hz, 1 H, Ar—CH—Cl), 3·45—4·20 (m, 2 H, $ArCH_2$ in a ring), 2·50—3·10 (m, 1 H, Ar—CH of isopropyl), 1·17 (d, J = 7·0 Hz, 6 H, 2 CH_3). *w* Hemihydrate. [x] NMR spectrum (CD_3SOCD_3): δ 6·80—7·70 (m, 7 H, aromatic protons), 3·80—4·20 (m, 1 H, Ar—CH—N), 2·00—3·60 (m, 12 H, 2 $ArCH_2$ and 4 CH_2 of piperazine), 2·31 (s, 3 H, NCH_3), 1·35 (m, 4 H, 2 CH_2 of butyl), 0·82 (t, 3 H, C—CH_3). [y] NMR spectrum of base: δ 6·70—7·55 (m, 7 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·58 (m, 4 H, $CH_2N^1CH_2$ of piperazine), c. 2·50 (2 H, $ArCH_2$ of octyl), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·24 (s, 3 H, NCH_3), c. 1·50 (m, 2 H, CH_2 in the vicinity

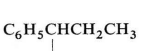
of the terminal methyl), 1·23 (bs, 10 H, remaining CH_2 groups of octyl), 0·85 (t, 3 H, C—CH_3) [z] NMR spectrum of base: δ 6·50—7·10 (m, 7 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3), 1·80 (m, 1 H, Ar—CH of cyclopropyl), 0·50—1·10 (m, 4 H, 2 CH_2 of cyclopropyl). [aa] IR spectrum (KBr): 761 (4 vicinal aromatic C—H), 822 (2 vicinal aromatic C—H), 899 (solitary aromatic C—H), 1067 (C—OH), 2779, 2840 (NCH_2), 3215 and 3450 cm^{-1} (OH); NMR spectrum: δ 6·75—7·60 (m, 7 H, aromatic protons), c. 4·00 (bs, 1 H, OH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·78 (t, J = 7·0 Hz, 2 H, CH_2O), c. 2·58 (m, 12 H, $ArCH_2$ and 5 NCH_2), 1·70 (m, 2 H, middle CH_2 of hydroxypropyl), 1·15 (t, J = 8·0 Hz, 3 H, C—CH_3). [bb] Dihydrate. [cc] IR spectrum (KBr): 760 (4 vicinal aromatic C—H), 828 (2 vicinal aromatic C—H), 888 (solitary aromatic C—H), 1070 and 1130 (CH_2OH), 2770 (NCH_2), 3190 cm^{-1} (OH). [dd] Solvate with 1/3 benzene molecule. [ee] NMR spectrum: δ 6·85—7·65 (m, 7 H, aromatic protons), 4·11 (q, 2 H, $COOCH_2$), 3·00—3·95 (m, 3 H, $ArCH_2CHAr$), 3·40 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), c. 2·00 (m, 1 H, Ar—CH of cyclopentyl), 1·68 (m, 8 H, 4 CH_2 of cyclopentyl), 1·24 (t, 3 H, C—CH_3). [ff] NMR spectrum: δ 7·56 (d, J = 2·5 Hz, 1 H, aromatic 9-H), 7·00—7·50 (m, 5 H, aromatic protons in positions 1, 2, 3, 4, 6), 6·94 (q, J = 9·0; 2·5 Hz, 1 H, aromatic 7-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), c. 3·00 (m, 1 H, Ar—CH of isopropyl), 2·76 and 2·64 (2 m, 8 H, 4 CH_2 of piperazine), 1·52 (s, 1 H, NH), 1·18 (d, J = 7·0 Hz, 6 H, 2 CH_3). [gg] Monohydrate. [hh] UV spectrum: λ_{max} 260 nm (log ε 4·24), 285·5 nm (3·60); IR spectrum: 745 (4 vicinal aromatic C—H), 785 (*cis*-CH=CH), 820 (2 vicinal aromatic C—H), 888 (solitary aromatic C—H), 1590 cm^{-1} (Ar); NMR spectrum: δ 7·05—7·60 (m, 7 H, aromatic protons), 7·05 (s, 2 H, ArCH=CHAr), 2·55 (t, J = 7·0 Hz, 2 H, $ArCH_2$), 1·45 (m, 4 H, C—CH_2CH_2—C of butyl), 0·88 (t, 3 H, CH_3). [ii] UV spectrum: λ_{max} 222 nm (log ε 4·49), 262·5 nm (4·42), 297·5 nm (3·66); NMR spectrum: δ 6·80—7·50 (m, 7 H, aromatic protons), 6·90 (s, 2 H, ArCH=CHAr), 1·50—2·00 (m, 1 H, Ar—CH of cyclopropyl), 0·50—1·10 (m, 4 H, 2 CH_2 of cyclopropyl). [jj] UV spectrum: λ_{max} 258 nm (log ε 4·22), 284 nm (3·70); IR spectrum (film): 750 (4 vicinal aromatic C—H), 788 (*cis*-CH=CH), 822 (2 vicinal aromatic C—H), 880 (solitary aromatic C—H), 1590 cm^{-1} (Ar); NMR spectrum: δ 7·00—7·60 (m, 9 H, aromatic and olefinic protons), 2·92 (m, 1 H, Ar—CH of cyclopentyl), 1·69 (m, 8 H, 4 CH_2 of cyclopentyl).

Investigation in the cyclopropyl series (*e*) was attractive because of the similarity of cyclopropyl with isopropyl (the favourable effect of which on activity was confirmed in this series) as well as because of lack of reports on this substituent's effect on the aromatic ring on the neuroleptic activity in other series; the 2-cyclopropyl derivatives of the phenothiazine series, *e.g.* the cyclopropyl analogue of chlorpromazine, had been described in patent literature[18,19] but were generally designated as coronary dilatants, spasmolytics and compounds with a central depressant activity. At the same time it was to be expected that the instability of the cyclopropane ring might make some of the synthetic steps rather difficult.

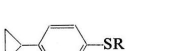
The starting compound used was cyclopropylbenzene which had been prepared according to Corbin and coworkers[20] by an intramolecular debromination of 1,3-dibromo-1-phenylpropane with the aid of a Zn-Cu-couple[21]. The authors carried out the reaction at 7—9°C. We observed while working in larger batches that under these conditions the reaction does not proceed with a low concentration of the dibromo derivative while after reaching higher concentrations it may

have the tendency to proceed too vigorously. It was found here that this difficulty can be overcome by working at 50°C. At the same time, the dibromo derivative must be added dropwise and very slowly to the mixture of the Zn-Cu-couple and dimethylformamide to maintain the low concentration of the starting compound. If it is added more rapidly an intermolecular debromination in the more reactive α-positions takes place as documented by the identification of *meso*-3,4-diphenylhexane (*XIX*) (ref.[22]) in one of the experiments (debromination in the terminal positions probably takes place only during processing the reaction mixture).

Cyclopropylbenzene was converted by bromination at −70°C selectively and in a high yield to 4-cyclopropylbromobenzene[23] (see also ref.[24]). The compound reacts with magnesium in ether smoothly to the Grignard reagent (ref.[25]) which reacts with sulfur, giving rise to the novel 4-cyclopropylthiophenol (*XX*). Preparation of the analytically pure compound appeared to be difficult and hence the product was characterized by gentle oxidation to the crystalline di(4-cyclopropylphenyl) disulfide (*XXI*). Application of method *A* to the crude thiol *XX* yields readily the acid *IXe*. In view of the fact that during homologization of acid *IXe* to acid *XIIIe* by the usual procedure difficulties could be expected (particularly with method *C*), a modified procedure was preferred[26]: the thiol *XX* was converted to the acid *XIIIe* by direct condensation with 2-(2-iodophenyl)acetic acid[26,27]. Attempts at cyclization of *XIIIe* by the usual methods, *i.e.* with the aid of sulfuric acid, polyphosphoric acid, hydrofluoric acid or phosphorus pentoxide in toluene or xylene were not successful, apparently due to the instability of the cyclopropane ring in these media. On the other hand, cyclization proceeds relatively readily in trifluoroacetic anhydride[28–30]. Even in this case, the product formed is not homogeneous but chromatography on alumina permits the isolation of about 50% of the desired crystalline ketone in a pure state, the identity having been confirmed by analysis and spectra and finally by conversion to the 2,4-dinitrophenylhydrazone. In further steps of synthesis of *Ie* we used methods *G*, *H* and J. During treatment of alcohol *XVe* (method *H*) with hydrogen chloride no damage to the cyclopropane ring was observed.

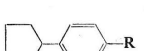


XIX



XX, R = H

XXI, R = S



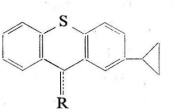
XXII, R = SO_2Cl

XXIII, R = SO_2NH_2

XXIV, R = SH

In the cyclopentyl series (*f*) the starting compound was cyclopentylbenzene, obtained best by a Friedel–Crafts reaction of benzene with cyclopentanol[31]. The usual chlorosulfonation yielded the novel 4-cyclopentylbenzenesulfonyl chloride (*XXII*) which was converted for characterization to the sulfonamide *XXIII*. Reduction of the sulfonyl chloride with lithium aluminium hydride yielded 4-cyclopentylthiophenol (*XXIV*) which was processed further by application of general procedures.

The above 2-(4-cyclopropylphenylthio)benzoic acid (*IXe*) was used for the synthesis of the hitherto unknown cyclopropyl analogue of the neuroleptic chlorprothixene[32]. Cyclization with the aid of trifluoroacetic anhydride yielded 2-cyclopropylthioxanthone (*XXV*) which reacted with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran to the tertiary alcohol *XXVI*. Its dehydration with boiling 20% sulfuric acid gave rise to the olefin *XXVII*, probably as a mixture of geometric isomers. Repeated crystallization of hydrogen maleate yielded a probably homogeneous compound but its configuration at the double bond cannot be determined.



XXV, R = =O

XXVI, R = $\diagup\!\!\diagdown^{OH}_{(CH_2)_3N(CH_3)_2}$

XXVII, R = =$CH(CH_2)_2N(CH_3)_2$

Most of the prepared piperazine derivatives *I*, *II*, *IV* and *VII* and the thioxanthene derivative *XXVII* were tested pharmacologically with a view to the assumed central depressant and neuroleptic activity (for methods see ref.[33]) in the form of salts, the values shown referring to bases. The results obtained are shown in Table II which inculdes as standards octoclothepin (*I*, R^1 = Cl) *i.e.* 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (for parenteral administration as methanesulfonate[5], for oral application as maleate[34]), and further chlorprothixene, *i.e. cis*-2-chloro-9-(3-dimethylaminopropylidene)thioxanthene[35] (*p.o.* as hydrochloride, parenterally as methanesulfonate[32]). Besides tests of acute toxicity for mice, the compounds were evaluated in the rotating-rod test (effect on motor coordination) in mice and for assessing the neuroleptic activity their cataleptic effect in rats was examined. The results are shown in the table as the usual mean lethal doses LD_{50} as well as in the form of the mean effective doses (ED_{50}), in mg/kg throughout.

Table II shows that ethyl, isopropyl and cyclopropyl are suitable 8-substituents from the point of view of central depressant and cataleptic activity in the series of neuroleptic 10-piperazinodibenzo[*b,f*]thiepins. Highly effective are especially N-methyl derivatives *I*, N-(3-hydroxypropyl) derivatives *II* and enamines *VII*. In the rotating rod test, none of the compounds exceeds the effect of octoclothepin even if some of them are almost equal to it (*Ia*, *Ie*, *IIa*). On the other hand, in the catalepsy test, it is surpassed by a number of compounds (*Ia*, *Ib*, *IIa*, *IIb*, *VIIb*) and others are almost equal to it (*Ie*, *IIf*). In contrast with octoclothepin, some compounds display a dissociation of the depressant from the cataleptic activity in favour of the latter which makes them to potential neuroleptics with decreased depressant activity. Of the highly effective compounds, this dissociation is best exhibited by the enamine of the isopropyl series (*VIIb*) which is 4 times weaker as a depressant but 14 times more

effective as a cataleptic than octoclothepin. Of the medium-potent compounds the hydroxyl derivative of the isopropyl series *IIb* is 8 times weaker as a depressant and more than twice more effective as a cataleptic than octoclothepin. The cyclopropyl analogue of chlorprothixene (compound *XXVII*) retains some depressant activity but is completely ineffective cataleptically. It cannot be excluded, however, that the compound tested actually belongs to the practically inactive *trans* series.

Esters *Vb* and *Vc* in the form of di(hydrogen maleates) have been tested so far by methods of general pharmacological screening at the affiliated unit of this institute at Rosice n/L (Dr J. Němec). Both were applied *p.o.* Their LD_{50} are greater than 1 g/kg and the compounds were applied *in vivo* in doses of 300 (*Vb*) or 200 (*Vc*) mg/kg. Both bring about signs of central depression, have cataleptic, antiamphetamine, and hypothermic activity and they potentiate thiopental narcosis. Further they display an antihistamine effect and, at higher doses, they depress the blood pressure and are antiinflammatory. In general, they thus behave also as neuroleptics.

TABLE II

Pharmacological Properties of Prepared Compounds

Compound	Acute toxicity[a] LD_{50}		Rotating rod[a] ED_{50}		Catalepsy[a] ED_{50}	
	i.v.[b]	*p.o.*[b]	*i.v.*	*p.o.*	*i.p.*[b]	*p.o.*
OCT[c]	46	78	0·06	2·2	2·4	4·3
Ia	54	—	0·088	—	0·72	—
Ib	28	—	0·18	—	1·0	—
Ic	—	250	—	9·6	—	17·0
Ie	—	86	—	2·5	—	4·8
If	47	—	0·8	—	4·2	—
IIa	47	—	0·074	—	0·56	—
IIb	29	—	0·45	—	1·0	—
IIc	—	275	—	12·0	—	38·0
IIf	37	—	0·6	—	3·2	—
IVa	—	160	—	3·7	—	9·6
VIIb	35	—	0·25	—	0·17	—
VIIc	—	200	—	7·2	—	8·2
VIIf	—	—	0·9	—	—	—
CPTX[d]	38	217	0·11	5·2	2·6	23·0
XXVII	—	<200[e]	—	11·0	—	$>50·0$[f]

[a] All values in mg/kg. [b] *i.v.* intravenously, *i.p.* intraperitoneally, *p.o. per os.* [c] Octoclothepin. [d] Chlorprothixene. [e] The dose shown was lethal for 4 out of 5 animals. [f] The dose shown caused catalepsy in 1 out of 10 rats.

TABLE III
Antimicrobial Activity of Prepared Compounds *in vitro*

Compound[a,b]	1[c]	2	3	4	5	6	7	8	9	10
Ia-MS	12·5	12·5	12·5	12·5	—	12·5	62·3	62·3	125	125
Ib-2MS	12·5	12·5	12·5	12·5	—	3·1	125	62·3	125	125
Ic-MS	3·2	3·2	3·2	3·2	—	25	31·2	31·2	125	31·2
Id-M	12·5	12·5	12·5	12·5	50	25	125	125	—	—
Ie-M	25	25	25	25	—	12·5	125	125	—	—
If-2MS	6·2	6·2	6·2	6·2	—	12·5	62·3	62·3	125	125
IIa-MS	50	50	50	50	—	25	125	125	—	125
IIb-MS	25	25	25	25	—	12·5	—	—	—	—
IIc-2HM	3·2	3·2	3·2	3·2	—	25	62·3	62·3	125	125
IIf-2MS	6·2	6·2	6·2	6·2	—	12·5	62·3	62·3	125	125
IVa-M	12·5	12·5	12·5	12·5	—	12·5	62·3	62·3	125	125
VIIb-MS	—	—	—	—	—	12·5	62·3	62·3	62·3	62·3
VIIc-M	3·2	3·2	3·2	3·2	—	25	62·3	62·3	125	62·3
VIIf-MS	—	—	—	—	—	—	62·3	62·3	62·3	125
XXVII-M	12·5	12·5	12·5	12·5	—	6·2	125	125	—	—

[a] Minimum inhibitory concentration in μg/ml. Unless a numerical value is given, the compound at 125 μg/ml causes no inhibition. [b] MS methanesulfonate, M maleate, HM hydrogen maleate. [c] *Streptococcus* β-*haemolyticus*, 2 *Streptococcus* β-*haemolyticus* WARD, 3 *Staphylococcus pyogenes aureus*, 4 *Staphylococcus pyogenes aureus* penicillin-resistant, 5 *Klebsiella pneumoniae*, 6 *Mycobacterium tuberculosis* H37Rv. 7 *Saccharomyces pasterianus*, 8 *Trichophyton mentagrophytes*, 9 *Candida albicans*, 10 *Aspergillus niger*.

In view of the antimicrobial activity of other derivatives of 10-piperazinodibenzo[*b,f*]thiepins[36] the compounds described here were tested at the bacteriological department of this institute (Dr A. Šimek, Dr J. Turinová) *in vitro* for their inhibitory activity toward 14 representative types of microorganisms. Table III shows the minimum found inhibitory concentrations in μg/ml. It should be noted that all the compounds up to a concentration of 125 μg/ml were inactive toward *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella typhi abdominalis* and *Proteus vulgaris*. Table III shows the 8-n-butyl derivatives (*Ic*, *IIc*, *VIIc*) and the 8-cyclopentyl derivatives (*If*, *IIf*) to be relatively highly bacteriostatic, particularly toward cocci; they are more potent than the corresponding ethyl, isopropyl and cyclopropyl derivatives. This led to the preparation of the 8-n-octyl derivative *Id* but this was found again to be less effective. Hence the assumption of possible dissociation of central from antimicrobial activity with extending the alkyl chain in position 8 was not confirmed.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried for 8 h at a suitable temperature (100°C maximum) at oil-pump vacuum over P_2O_5. The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated

otherwise) in a Unicam SP 200 G or in an Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer. The mass spectrum was obtained in a MS 902 (AEI) mass spectrometer.

4-Cyclopentylbenzenesulfonyl Chloride (*XXII*)

Chlorosulfonic acid (285 g) was added dropwise under stirring at 4—8°C over a period of 45 min to a solution of 90 g cyclopentylbenzene[31] (b.p. 114—116°C/25 Torr) in 300 ml chloroform. The mixture was stirred for another hour at 10°C and then decomposed with ice and water. The product was isolated by extraction with chloroform. A total of 90 g (60%) crude sulfonyl chloride was obtained (residue), a sample of which was recrystallized for analysis from light petroleum; m.p. 52—54°C. IR spectrum: 838 (2 vicinal aromatic C—H), 1 180 and 1 385 (SO_2Cl), 1 595 cm^{-1} (Ar). NMR spectrum: δ 8·00 (mcd, 2 H, aromatic protons in the vicinity of SO_2Cl), 7·50 (mcd, 2H, remaining aromatic protons), 2·85—3·35 (m, 1H, CH—Ar), 1·25—2·40 (m, 8H, CH_2 groups of cyclopentane). For $C_{11}H_{13}ClO_2S$ (244·7) calculated: 53·98% C, 5·35% H, 14·49% Cl, 13·10% S; found: 53·87% C, 5·32% H, 14·54% Cl, 12·92% S.

4-Cyclopentylbenzenesulfonamide (*XXIII*)

A mixture of 1·5 g sulfonyl chloride *XXII* and 15 ml concentrated aqueous ammonia was heated under stirring for 20 min to 65—70°C and then left for 2 h at room temperature. The precipitated product was filtered and recrystallized from aqueous ethanol; m.p. 124—125°C. NMR spectrum: δ 7·89 (mcd, 2H, $J = 9{\cdot}0$ Hz, aromatic protons in the vicinity of SO_2NH_2), 7·38 (mcd, $J = 9{\cdot}0$ Hz, 2H, remaining aromatic protons), 5·24 (s, 2H, SO_2NH_2), 3·00 (m, 1H, CH—Ar), 1·50—2·30 (m, 8H, $4CH_2$ of cyclopentane). For $C_{11}H_{15}NO_2S$ (225·3) calculated: 58·63% C, 6·71% H, 6·22% N, 14·23% S; found: 59·00% C, 6·74% H, 6·31% N, 14·49% S.

Cyclopropylbenzene

A. Crude 1-phenyl-1,3-dibromopropane[20] (69·5 g) was added dropwise under stirring at about 50°C over the period of 60 min to a mixture of 125 ml dimethylformamide and the Zn—Cu-couple (prepared from 32 g zinc and 100 ml 2% solution of cupric sulfate)[21]. The mixture was processed according to ref.[20] and a total of 23·9 g (84%) product was obtained: b.p. 58—62°C/7 Torr.

B. A double batch was carried out at 58—60°C and 1-phenyl-1,3-dibromopropane was added dropwise over 30 min. The mixture was decomposed with water[20], steam-distilled and the product was isolated by extraction with ether. After distilling off the cyclopropylbenzene a residue of 10·6 g was obtained, m.p. 90—92°C (cyclohexane). According to analysis and NMR spectrum we are dealing here with *meso*-3,4-diphenylhexane (*XIX*) with a reported[22] m.p. of 92—93°C. NMR spectrum: δ 7·25 (m, 10H, aromatic protons), 2·55 (m, 2H, CH—CH), c. 1·30 (m, 4H, $2CH_2$), 0·48 (t, $J = 7{\cdot}0$ Hz, 6H, $2CH_3$). For $C_{18}H_{22}$ (238·4) calculated: 90·70% C, 9·30% H; found: 90·70% C, 9·56% H.

4-Isopropylthiophenol

A solution of 700 g crude 4-isopropylbenzenesulfonyl chloride[3] in 800 ml acetic acid was added dropwise over 1 h to a boiling mixture of 1320 ml acetic acid, 300 g red phosphorus and 17 g iodine and the mixture was refluxed under stirring for 3 h. After cooling, it was combined slowly with 400 ml water, the mixture was refluxed for 1 h and, after cooling, it was poured into 10 l icecold

water. The product was isolated by extraction with chloroform and redistilled; 424 g (87%), b.p. 100–103°C/12 Torr. For a product prepared differently a b.p. of 104°C/15 Torr was reported[3].

4-n-Octylthiophenol

Similarly to the preceding case, 127 g crude 4-n-octylbenzenesulfonyl chloride[16] was reduced with 24 g red phosphorus and 19 g iodine in 160 ml boiling acetic acid. Analogous treatment (extraction with benzene) led to 63·4 g (64%) product boiling at 124–130°C/0·3 Torr. Literature[15] reports a b.p. of 136–137°C/2·3 Torr. for the compound prepared differently.

4-n-Dodecylthiophenol (*XVII*)

n-Dodecylbenzene[17] (29·6 g; b.p. 186–190°C/15 Torr) was added dropwise under stirring over 45 min to 26 ml chlorosulfonic acid at 5–10°C, the mixture was stirred for 4 h at room temperature and then was left to stand overnight. After decomposition with ice and water the crude 4-(n-dodecyl)benzenesulfonyl chloride (35 g) was isolated by extraction with ether and evaporation of the extract. The total amount of the product was then reduced similarly to preceding cases with the aid of 6·4 g red phosphorus and 3·4 g iodine in 45 ml boiling acetic acid. Analogous treatment yielded 17·7 g (68%) product boiling at 177–181°C/0·7 Torr. For analysis, a redistilled middle fraction was used; b.p. 162–163°C/0·6 Torr. For $C_{18}H_{30}S$ (278·5) calculated: 77·63% C, 10·86% H, 11·51% S; found: 77·30% C, 10·83% H, 11·46% S.

4-n-Butylthiophenol

A solution of 23·2 g crude 4-n-butylbenzenesulfonyl chloride[3] in 200 ml ether was added dropwise over 1 h to a suspension of 9·45 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 2 h. After cooling, 150 ml water-saturated ether was added, followed with 400 ml 2·5M-HCl. After filtration, the ether phase was separated, the aqueous phase was extracted with ether, the ether solutions were dried with $MgSO_4$ and distilled; 9·0 g (55%), b.p. 130–135°C/30 Torr, or 120–125°C/20 Torr. For a compound prepared differently ref.[3] reported a b.p. of 119°C/14 Torr.

4-Cyclopentylthiophenol (*XXIV*)

As in the preceding case, 194 g sulfonyl chloride *XXII* was reduced with 75 g $LiAlH_4$ and the almost theoretical yield (130 g) of a crude residue was used for further work. Sample for analysis was distilled; b.p. 165°C/25 Torr. For $C_{11}H_{14}S$ (178·2) calculated 74·13% C, 7·92% H, 17·96% S; found: 74·14% C, 7·81% H, 17·61% S.

4-Cyclopropylthiophenol (*XX*)

A Grignard reagent was prepared from 6·4 g Mg and 49·4 g 4-cyclopropylbromobenzene[23] (b.p. 102°C/7 Torr) in 140 ml ether, using several drops of 1,2-dibromoethane for initiating the reaction. The preparation of the reagent took 9 h. After dilution with 80 ml ether the solution was combined over 4 h at room temperature with 6·5 g sulfur flowers. The suspension was stirred for 1 h at room temperature and then refluxed for 1 h. After standing overnight it was diluted with 100 ml ether and slowly poured into 280 ml water and 50 ml hydrochloric acid. Processing of the ether layer yielded 17·5 g (47%) product boiling at 110–116°C/12 Torr, which, even after redistillation, does not yield satisfactory analytical values. However, it was processed further without difficulties. For $C_9H_{10}S$ (150·2) calculated: 71·95% C, 6·71% H, 21·34% S; found: 72·73% C, 6·83% H, 20·38% S.

Di(4-cyclopropylphenyl)disulfide (*XXI*)

Thiol *XX* (1·5 g) was added to 15 ml 1M-NaOH and, under stirring at 5°C, this was followed with 1·1 ml 30% H_2O_2 in 9 ml water. The precipitate formed was filtered, washed with water and dried; 1·2 g (81%), m.p. 71–72·5°C (light petroleum). IR spectrum (KBr): 823 (2 vicinal aromatic C–H), 1 498 and 1 600 cm^{-1} (Ar). NMR spectrum: δ 7·44 (d, J = 9·0 Hz, 4H, aromatic protons in the vicinity of S), 7·00 (d, J = 9·0 Hz, 4H, remaining aromatic protons), 1·45–2·10 (m, 2H, 2CH–Ar), 0·40–1·15 (m, 8H, $4CH_2$ of cyclopropyls). For $C_{18}H_{18}S_2$ (298·5) calculated: 72·43% C, 6·07% H, 21·50% S; found: 72·59% C, 6·12% H, 21·45% S.

2-(4-Cyclopropylphenylthio)benzoic Acid (*IXe*) (Method *A*)

Thiol *XX* (7·5 g) was added to a solution of 10·8 g KOH in 110 ml water at 50°C, the mixture was stirred for a while and then 0·45 g "molecular" copper and 12·5 g 2-iodobenzoic acid[4] was added and the mixture was refluxed under stirring for 7 h. It was filtered while hot with charcoal and the filtrate was cooled and acidified with 2·5M-HCl. The precipitated product was filtered, washed with water and recrystallized from aqueous ethanol; 10·6 g (80%), m.p. 192–194°C. IR spectrum (KBr): 734 (4 vicinal aromatic C–H), 815 (2 vicinal aromatic C–H), 1252 (C–O), 1672 cm^{-1} (Ar–COOH). NMR spectrum: δ 12·00 (bs, disappears after D_2O, 1H, COOH), 8·16 (m, 1H, aromatic 6-H), 7·50 (d, J = 9·0 Hz, 2H, aromatic 2′,6′-H_2), 7·13 (d, J = 9·0 Hz, 2H, aromatic 3′, 5′-H_2), c. 7·10 (m, 2H, aromatic 4,5-H_2), 6·80 (m, 1H, aromatic 3-H), 1·90 (m, 1H, CH–Ar), 0·60–1·20 (m, 4H, $2CH_2$ of cyclopropane). The analytical data are shown in Table I.

2-(4-Isopropylphenylthio)benzyl Alcohol (*Xb*) (Method *B*)

770 ml of a 70% benzene solution of sodium bis(2-methoxyethoxy)dihydroaluminate were added dropwise under stirring over 2 h to a solution of 362 g acid *IXb* (ref.[3]) in 2800 ml benzene. The temperature rose spontaneously to 40°C. The mixture was stirred for 3 h at room temperature and then decomposed under external cooling by adding dropwise 2 000 ml 10% NaOH. The benzene phase was separated and the aqueous one extracted with more benzene. Usual treatment of the organic phases yielded 324 g (94%) product boiling at 170–170·5°C/1·5–2 Torr. IR spectrum: 752 (4 vicinal aromatic C–H), 822 (2 vicinal aromatic C–H), 1015 (CH_2OH), 1360 (isopropyl), 1590 (Ar), 3370 cm^{-1} (OH). The analytical data are shown in Table I.

2-(4-n-Octylphenylthio)benzyl Alcohol (*Xd*)

Acid *IXd* (6·85 g) was added in parts under stirring to a suspension of 2·0 g $LiAlH_4$ in 40 ml ether and the mixture was refluxed for 6 h. It was cooled, decomposed by adding dropwise 7·5 ml water and 2 ml 20% NaOH, stirred for 30 min, the solid was filtered, the filtrate was dried with Na_2SO_4 and evaporated. A total of 5·8 g (88%) crude product was obtained, the sample of which was redistilled for analysis; b.p. 195°C/0·4 Torr. The analytical data are shown in Table I.

2-(4-Cyclopentylphenylthio)benzyl Chloride (*XIf*) (Method *C*)

$SOCl_2$ (18 g) was added dropwise under stirring at room temperature over a period of 15 min to a solution of 28·4 g alcohol *Xf* in 40 ml benzene and the mixture was refluxed for 30 min. After evaporation of excess $SOCl_2$ and benzene the product was distilled; 24·2 g (80%), b.p. 180–182°C/1 Torr or 210–215°C/3 Torr. The analytical data are shown in Table I.

2-(4-Isopropylphenylthio)phenylacetonitrile (*XIIb*) (Method *D*)

A solution of 18·6 g chloride *XIb* in 35 ml ethanol was added to a solution of 9·1 g KCN in 13 ml water and the mixture was refluxed for 7 h. After cooling, it was diluted with 200 ml water and the product was isolated by extraction with ether; 15·5 g (86%), b.p. 158–162°C/1 Torr. NMR spectrum: δ 7·15–7·70 (m, 8H, aromatic protons), 3·84 (s, 2H, $ArCH_2CN$), 2·86 (d, J = 7·0 Hz, 1H, Ar—CH), 1·21 (d, J = 7·0 Hz, 6H, $2CH_3$). The analytical data are shown in Table I.

2-(4-Ethylphenylthio)phenylacetic Acid (*XIIIa*) (Method *E*)

A mixture of 123 g nitrile *XIIa*, 850 ml ethanol and 136 g KOH in 125 ml water was refluxed for 5 h. After partial cooling, it was diluted with 1 250 ml water (50°C), the mixture was filtered with charcoal and the filtrate made acid with excess dilute hydrochloric acid. The precipitated acid was filtered, washed with water and recrystallized from aqueous ethanol; 110 g (83%), m.p. 96–99°C. IR spectrum (KBr): 745 (4 vicinal aromatic C—H), 823 (2 vicinal aromatic C—H), 930, 1 244, 1 407, 1 692 and 2 600 cm^{-1} (COOH). The analytical data are shown in Table I.

2-(4-Cyclopropylphenylthio)phenylacetic Acid (*XIIIe*)

Thiol *XX* (9·7 g) was added to a solution of 13·8 g KOH in 140 ml water at 40°C, the mixture was stirred for 5 min, 0·9 g "molecular" copper and 16·2 g 2-(2-iodophenyl)acetic acid[26,27] was added and the mixture refluxed under stirring for 4 h. After standing overnight, 0·3 g copper was added and refluxing continued for 7 h. It was filtered while hot with charcoal and the filtrate was made acid with hydrochloric acid at 70°C to pH 1. The precipitated product was filtered, washed with water and dried; 16·8 g (96%), m.p. 122–122·5°C (aqueous ethanol). IR spectrum ($CHCl_3$): 820 (Ar—H), 1 492 and 1 590 (Ar), 928, 1 235 and 1 705 cm^{-1} (COOH). NMR spectrum: δ 7·31 (s, 4H, aromatic protons in positions 3, 4, 5, 6), 7·25 and 7·00 (2d, J = 9·0 Hz, 4H, aromatic protons in positions 2′, 3′, 5′, 6′), 3·80 (s, 2H, $ArCH_2COO$), 1·80 (m, 1H, Ar—CH), 0·50–1·15 (m, 4H, $2CH_2$ of cyclopropane). The analytical data are shown in Table I.

8-Isopropyldibenzo[*b,f*]thiepin-10(11H)-one (*XIVb*) (Method *F*)

Acid *XIIIb* (14·3 g) was added at 100°C to 30 g polyphosphoric acid and the mixture was heated under stirring for 2 h to 150°C. After cooling, 60 ml benzene was added and the mixture decomposed under cooling with 60 ml water. The product was isolated by extraction with benzene, the extract was washed with 5% NaOH and water, dried with K_2CO_3 and evaporated. The crude product was distilled; 10·2 g (76%), b.p. 167–170°C/1·5 Torr. UV spectrum: λ_{max} 242·5 nm (log ε 4·33), 335 nm (3·63), infl. 265 nm (4·07). IR spectrum (film): 748 (4 vicinal aromatic C—H), 838 (2 vicinal aromatic C—H), 1 290 (C—O), 1 360 (isopropyl), 1 584 (Ar), 1 675 cm^{-1} (Ar—CO). The analytical data are shown in Table I.

8-n-Butyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XIVc*) (Method *F-1*)

Acid *XIIIc* (60 g) was added to a hot mixture of 540 g polyphosphoric acid and 180 ml toluene and the mixture was refluxed under stirring for 2 h. After cooling, 500 ml benzene was added and decomposed with 750 ml ice-cold water. The organic phase was washed with water and 5% NaOH (acidification of the alkaline solution recovered 12·0 g acid *XIIIc*), dried with K_2CO_3 and processed by distillation; 37 g (82%), b.p. 190–195°C/2 Torr. UV spectrum: λ_{max} 241 nm (log ε 4·29), 334 nm (3·55). IR spectrum: 745, 752 (4 vicinal aromatic C—H), 828 (2 vicinal aromatic C—H),

870 (solitary aromatic C—H), 1075 and 1288 (C—O), 1595 (Ar), 1670 cm^{-1} (Ar—CO). NMR spectrum: δ 8·06 (d, J = 2·5 Hz, 1H, aromatic 9-H), 7·00—7·30 (m, 6H, remaining aromatic protons), 4·34 (s, 2H, $ArCH_2CO$), 2·59 (t, J = 7·0 Hz, 2H, $ArCH_2$ of butyl), c. 1·45 (m, 4H, $C—CH_2CH_2—C$ of butyl), 0·88 (t, 3H, CH_3). The analytical data are shown in Table I.

8-Cyclopropyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIVe*)

A mixture of 80 ml trifluoroacetic anhydride and 13·2 g acid *XIIIe* was stirred for 4 h at room temperature. After standing overnight, 6 ml benzene were added and the mixture refluxed for 7 h, diluted with 25 ml benzene and decomposed with 1 l 12% $NaHCO_3$. The mixture was extracted with benzene and the extract was evaporated. The residue was dissolved in benzene and chromatographed on a column of alumina (300 g, activity II). Elution with benzene yielded 6·8 g (55%) *XIVe*, m.p. 82—86°C; after recrystallization from cyclohexane, m.p. 85—86°C. UV spectrum: λ_{max} 242·5 nm (log ε 4·39), 260 nm (4·15), 342 nm (3·60). IR spectrum (KBr): 755 (4 vicinal aromatic C—H), 842 (2 vicinal aromatic C—H), 878 (solitary aromatic C—H), 1475 and 1600 (Ar), 1670 cm^{-1} (Ar—CO). NMR spectrum: δ 8·06 (d, J = 2·5 Hz, 1H, aromatic 9-H), 7·63 (d, J = 9·0 Hz, 1H, aromatic 6-H), 7·21 (mcd, J = 9·0; 2·5 Hz, 1H, aromatic 7-H), 7·25—7·90 (m, 4H, remaining aromatic protons), 4·40 (s, 2H, $ArCH_2CO$), 1·88 (m, 1H, Ar—CH), 0·50—1·15 (m, 4H, $2CH_2$ of cyclopropane). The analytical data are shown in Table I.

8-n-Butyl-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVc*) (Method *G*)

A solution of 11·4 g $NaBH_4$ with 0·65 ml 20% NaOH in 65 ml water was added dropwise over 1 h under stirring to a solution of 29·0 g ketone *XIVc* in 400 ml ethanol, the mixture was refluxed for 4 h, the ethanol was evaporated at reduced pressure, the residue was diluted with 400 ml water and the product was extracted with benzene. The extract was washed with water, 5% NaOH, dried and evaporated. The residue crystallized from a mixture of benzene and light petroleum; 24 g (82%), m.p. 62—63°C. IR spectrum (KBr): 743 (4 vicinal aromatic C—H), 820 (2 vicinal aromatic C—H), 867 and 882 (solitary aromatic C—H), 1047 (CHOH), 992, 1465 (Ar), 3280 and 3330 cm^{-1} (OH). NMR spectrum: δ 6·80—7·60 (m, 7H, aromatic protons), 5·25 (m, dd after D_2O, J = 9·0; 4·0 Hz, 1H, Ar—CH—O), 3·73 and 3·28 (2dd, J = 14·0; 4·0 Hz and 14·0; 4·0 Hz, 2H, $ArCH_2$ in a ring), 2·53 (t, J = 7·0 Hz, 2H, $ArCH_2$ of butyl), 2·15 (d, disappears after D_2O, 1H, OH), 1·42 (m, 4H, $C—CH_2CH_2—C$ of butyl), 0·88 (t, 3H, CH_3). The analytical data are shown in Table I.

8-Cyclopropyl-10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XVIe*) (Method *H*)

Powder $CaCl_2$ (5 g) was added to a solution of 6·9 g alcohol *XVe* in 90 ml benzene and the suspension was saturated at room temperature with anhydrous HCl for 3 h. After standing overnight, it was filtered and the filtrate was evaporated at reduced pressure. The residue crystallized from cyclohexane; 7·10 g (97%), m.p. 76·5—77°C. NMR spectrum: δ 7·05—7·90 (m, 6H, aromatic protons in positions 1, 2, 3, 4, 6 and 9), 6·90 (mcd, J = 9·0; 2·5 Hz, 1H, aromatic proton in position 7), 5·85 (dd, J = 9·0; 4·0 Hz, 1H, Ar—CH—Cl), 4·02 and 3·65 (2dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2H, $ArCH_2$ in the ring), 1·85 (m, 1H, Ar—CH of cyclopropane), 0·50—1·10 (m, 4H, $2CH_2$ of cyclopropane). The analytical data are shown in Table I.

8-Isopropyl-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*] thiepin (*Ib*) (Method *J*)

1-Methylpiperazine (7·5 g) was added to a solution of 7·2 g chloride *XVIb* in 8 ml chloroform and the mixture was refluxed for 6 h. After evaporation of the chloroform the residue was dissolved

in 100 ml benzene, the solution was washed with 2·5M-NaOH and with water. The base was then transferred by shaking with 3 times 70 ml 1·25M-H_2SO_4 to the aqueous phase. Evaporation of the separated benzene phase and distillation of the residue yielded a small amount of 2-isopropyldibenzo[*b,f*]thiepin (*VIIIb*), b.p. 177—180°C/1·5 Torr. UV spectrum: λ_{max} 221 nm (log ε 4·43), 261 nm (4·39), 297 nm (3·72). IR spectrum: 746 (4 vicinal aromatic C—H), 786 (*cis*-CH=CH), 826 (2 vicinal aromatic C—H), 880 (solitary aromatic C—H), 1061, 1553, 1589 cm^{-1} (Ar). NMR spectrum: δ 7·00—7·60 (m, 7H, aromatic protons), 6·99 (s, 2H, olefinic CH=CH), 2·80 (m, 1H, Ar—CH of isopropyl), 1·18 (d, J = 7·0 Hz, 6H, $2CH_3$). The analytical data are shown in Table I.

The acid aqueous phase was made alkaline with excess aqueous NH_4OH and the liberated base was isolated by extraction with benzene; 8·0 g (91%). It crystallized on standing, m.p. 118 to 120°C (benzene–light petroleum). NMR spectrum: δ 7·55 (d, J = 2·5 Hz, 1H, aromatic 9-H), 7·00—7·50 (m, 5H, aromatic protons in positions 1, 2, 3, 4, 6), 6·93 (mcd, 1H, aromatic 7-H), 3·00—4·00 (m, 3H, Ar—CH_2CH—Ar), c. 3·00 (obscured m, 1H, Ar—CH of isopropyl), 2·64 (m, 4H, $CH_2N^1CH_2$ of piperazine), 2·51 (m, 4H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3H, NCH_3), 1·18 (d, J = 7·0 Hz, 6 H, 2 CH_3 of isopropyl). Further data are in Table I.

8-Ethyl-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin (*IVa*) (Method *K*)

A mixture of 12·0 g carbamate *IIIa*, 17 ml ethanol and 8·4 g KOH was refluxed for 3 h in a 120°C bath. It was then cooled, dissolved in 60 ml water and extracted with benzene. After washing and drying of the extract, the benzene was evaporated and the residue recrystallized from 12 ml ethanol; 8·2 g (84%), m.p. 113—114°C (acetone). NMR spectrum: δ 7·00—8·50 (m, 7H, aromatic protons), 2·95—4·00 (m, 6 H, $ArCH_2CHAr$, $ArCH_2$ and NH), 2·30—2·95 (m, 8 H, CH_2 groups of piperazine), 1·14 (t, 3 H, C—CH_3 of ethyl). Further data are contained in Table I.

8-Ethyl-10-[4-(3-capryloyoxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Va*) (Method *L*)

Capryloyl chloride[9] (10·5 g, b.p. 105°C/35 Torr) was added to a solution of 11·4 g aminoalcohol *IIa* in a mixture of 60 ml benzene and 20 ml chloroform, the mixture was stirred and left to stand for 4 days at room temperature. It was then heated for 1 h to 60°C, cooled, 100 ml water was added, made alkaline with ammonia and extracted with benzene. Processing of the extract yielded the crude base which was dissolved in 35 ml acetone and neutralized with a solution of 6·9 g maleic acid in 25 ml acetone. A total of 13·0 g (59%) crystalline di(hydrogen maleate) was obtained; m.p. 144—146°C (acetone). The analytical data are shown in Table I.

8-n-Butyl-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*VIIc*) (Method *M*)

1-Methylpiperazine (15 g) was added to a solution of 8·5 g ketone *XIVc* in 70 ml benzene, followed over a period of 5 min with a solution of 3·0 g $TiCl_4$ in 20 ml benzene. The mixture was refluxed under stirring for 24 h. After cooling, it was decomposed with 100 ml water, the inorganic fraction was filtered and the filtrate processed by benzene extraction. Washing of the extract with water and evaporation yielded the crude base, which was recrystallized from benzene; 6·2 g (57%), m.p. 140—141°C. NMR spectrum: δ 7·00—7·65 (m, 7 H, aromatic protons), 6·34 (s, 1 H, Ar—CH=C), 3·00 and 2·55 (2 m, 10 H, $ArCH_2$ of butyl and 4 CH_2 of piperazine), 2·36 (s, 3 H, NCH_3), 1·40 (m, 4H, C—CH_2CH_2—C of butyl), 0·90 (t, 3 H, CH_3 of butyl). Further data are included in Table I.

2-Cyclopropylthioxanthone (*XXV*)

A mixture of 11·4 g acid *IXe* and 100 g trifluoroacetic anhydride was stirred for 5 h at 35°C. After standing overnight, 120 ml of benzene was added and the mixture was stirred for 8 h at 35°C. After cooling, it was decomposed by pouring into 500 ml 10% $NaHCO_3$, 100 ml benzene was added, followed with 30 ml 5M-NaOH. After separation, acidification of the alkaline layer recovered 4·1 g acid *IXe*. The benzene layer was washed with water, dried with Na_2SO_4 and evaporated. A total of 3·8 g (57%) crude product melting at 95—98°C was obtained. For analysis it was recrystallized from a mixture of benzene and light petroleum, m.p. 104—106°C (change of the crystal modification at 95°C). The mass spectrum shows a molecular ion at $m/e = 252$ which corresponds to the assumption; the fragmentation is in agreeement with the expected structure. For $C_{16}H_{12}OS$ (252·3) calculated: 75·15% C, 4·80% H, 12·71% S; found: 76·07% C, 5·01% H, 12·80% S.

2-Cyclopropyl-9-(3-dimethylaminopropyl)thioxanthene-9-ol (*XXVI*)

Reaction of 0·8 g Mg and 4·06 g 3-dimethylaminopropyl choride in 15 ml tetrahydrofuran produced a Grignard reagent, using a grain of iodine and several drops of 1,2-dibromoethane for initiating the reaction. The preparation of the reagent took 3 h. After cooling, a suspension of 4·0 g ketone *XXV* in 25 ml tetrahydrofuran was added and the mixture was left to stand for 3 days at room temperature. It was then decomposed with 100 ml 20% NH_4Cl and extracted with benzene. Processing of the extract yielded 4·7 g (87%) crude product which was recrystallized for analysis from a mixture of cyclohexane and light petroleum, m.p. 123—125·5°C. IR spectrum ($CHCl_3$): 770 (4 vicinal aromatic C—H), 820 (2 vicinal aromatic C—H), 900 (solitary aromatic C—H), 1020 (C—OH), 1596 (Ar), 2630 and 2700 cm^{-1} (OH in a hydrogen bond at N). NMR spectrum: δ 8·02 (m, 1 H, aromatic 8-H), 7·75 (d, $J = 3{\cdot}0$ Hz, 1 H, aromatic 1-H), 7·10—7·60 (m, 4 H, aromatic protons in positions 4, 5, 6, 7), 6·98 (mcd, $J = 9{\cdot}0$; 3·0 Hz, 1 H, aromatic 3-H), 2·40 (s, 6 H, 2 N—CH_3), 1·60—2·40 (m, 5 H, Ar—CH of cyclopropyl and CH_2—C—CH_2N of the side chain), 0·50—1·40 (m, 6 H, 2 CH_2 of cyclopropyl and C—CH_2—C of the side chain). For $C_{21}H_{25}NOS$ (339·5) calculated: 74·29% C, 7·42% H, 4·12% N, 9·46% S; found: 73·82% C, 7·69% H, 4·08% N, 9·23% S.

2-Cyclopropyl-9-(3-dimethylaminopropylidene)thioxanthene (*XXVII*)

A mixture of 125 ml water, 35 g H_2SO_4 and 8·25 g aminoalcohol *XXVI* was refluxed for 2 h, cooled, made alkaline with NH_4OH and the product was isolated by extraction with chloroform. The crude base (7·8 g) was converted by neutralization with maleic acid (2·9 g) in 2-propanol to the crystalline hydrogen maleate (9·2 g) which, after several recrystallizations from a mixture of 2-propanol and ether melted at 140—143°C. UV spectrum: λ_{max} 231 nm (log ε 4·55), 271·5 nm (4·18), 329·5 nm (3·50). IR spectrum (KBr): 755 (4 vicinal aromatic C—H), 835 (2 vicinal aromatic C—H), 892 (solitary aromatic C—H), 1460 (Ar), 1528 and 1615 (COO^-), 2460 cm^{-1} (NH^+). For $C_{25}H_{27}NO_4S$ (437·5) calculated: 68·62% C, 6·22% H, 3·20% N, 7·33% S; found: 68·28% C, 6·52% H, 3·24% N, 7·31% S.

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