POTENTIAL ANTIPSYCHOTICS: 2-METHOXY, 2-METHYLTHIO-, 2-(DIMETHYLSULFAMOYL)- AND 2-TRIFLUOROMETHYL-10-PIPERAZINODIBENZO[*b,f*]THIEPINS*

K.Šindelář, A.Dlabač, J.Metyšová, B.Kakáč, J.Holubek, E.Svátek, Z.Šedivý and M.Protiva

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

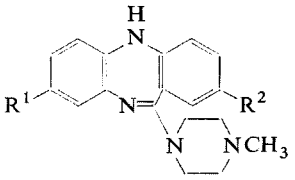
Received September 9th, 1974

In an attempt to obtain structural analogues of "clozapine" (*II*) in the series of derivatives of dibenzo[*b,f*]thiepin, the title compounds *IIIa*—*IIIe*, *IVb*, *IVc* and *V* were synthesized *via* the intermediates *VI*—*XIII*. The substituent in the ring of these compounds is shifted from the usual position 8 to 2. Like clozapine (*II*) and the chloro derivative *III* (R^1 = Cl, R^2 = H), all the compounds prepared are inactive cataleptically; in contrast with the two, however, they are less potent as central depressants.

Schmutz and coworkers[1,2] described for the dibenzo[*b,e*]-1,4-diazepine derivative *I* a high degree of cataleptic and depressant activity; a shift of the chlorine atom from position 2 (nearer the piperazine residue) to position 8, as carried out in *II*, was associated with disappearance of cataleptic activity while the central depressant activity was preserved. In view of the importance ascribed to the cataleptic effect because of its allowing to predict antipsychotic activity on the basis of experiments with animals (see ref.[3]) one could expect compound *II* ("HF-1854") to be antipsychotically inactive. On the contrary, however, it displayed a useful antipsychotic activity during preliminary clinical tests[4] and is being introduced into clinical practice under the name "clozapine" (Leponex^R)[5–9]. Using relatively high doses, the preparation is reliable in the treatment of schizophrenia when it causes much less extrapyramidal reactions than all other neuroleptics used. These surprising results lead to the tendency to consider the cataleptic effect as correlating rather with the side effects of extrapyramidal character than with the antipsychotic activity itself and hence to attempts to revise the term "neuroleptic"[10]. Clozapine contributed to the development of neurochemical studies which resulted in the finding of its enhancing the turnover of dopamine in the brain, which results in an increased level of (4-hydroxy-2-methoxyphenyl)acetic acid (*i.e.* homovanillic acid), the principal product of dopamine metabolism[11–15]. It is assumed that these properties might represent more specific predictive indicators of antipsychotic activity[16] than the hitherto employed demonstration of cataleptic, antiapomorphine and antiamphetamine activity which clozapine lacks.

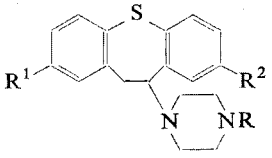
Transition from the classical neuroleptic (see *I*) to the new type of neuroleptic, *i.e.* clozapine (*II*), was accompanied from the structural point of view by the shift of the typical substituent from the usual position in the skeleton to a "quasi"-sym-

* Part LXXXIV in the series Neurotropic and Psychotropic Agents; Part LXXXIII: This Journal *40*, 1612 (1975).

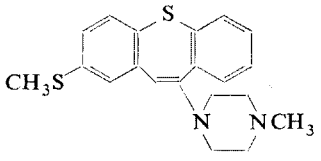


I, $R^1 = H$, $R^2 = Cl$
II, $R^1 = Cl$, $R^2 = H$

metrical one. A similar change is not possible in the molecules of those tricyclic neuroleptics where the skeleton forms a completely symmetrical formation together with the side-chain, *i.e.* in the molecules of phenothiazine and thioxanthene derivatives. On the other hand, in the present series of 10-piperazinodibenzo[*b*,*f*]thiepin neuroleptics, where positions 2 and 8 may also be considered as "quasi"-symmetrical, such an approach appears to be feasible. This series includes the well-known neuroleptically active clorotepin (octoclothepin)[17,18] (*III*, $R^1 = H$, $R^2 = Cl$) characterized pharmacologically by a high degree of central depressant and cataleptic activity and clinically by its reliable antipsychotic activity. Its 2-chloroisomer (*III*, $R^1 = Cl$, $R^2 = H$) was prepared some time ago[19,20] when it was evaluated only from the point of view of central depressant activity in the rotating-rod test in mice using intravenous application. Although it was closest to clorotepin of all the position isomers of perathiepin monochloro derivatives it had only 25% of its activity. In a recent testing after *p.o.* application it appeared, however, that on this application it has an almost two-fold greater depressant activity than clorotepin and that it is almost inactive cataleptically. This finding led to the view that in the present series of neuroleptics one will be able to find compounds with the activity profile of clozapine. The present study is the first in a series along these lines. It describes the preparation and orientation pharmacology of 2-methoxy, 2-methylthio, 2-(dimethylsulfamoyl) and 2-trifluoromethyl derivatives of perathiepin (*IIIa*, *IIIc*–*IIIe*) and further of the corresponding 2-methoxy-8-fluoro derivative *IIIb*, aminoalcohols



III, $R = CH_3$
IV, $R = CH_2CH_2CH$



V

For formulae in the series:

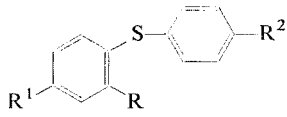
a, $R^1 = OCH_3$, $R^2 = H$
b, $R^1 = OCH_3$, $R^2 = F$
c, $R^1 = SCH_3$, $R^2 = H$
d, $R^1 = SO_2N(CH_3)_2$, $R^2 = H$
e, $R^1 = CF_3$, $R^2 = H$

IVb and *IVc* and finally of the enamine *V*. The molecules of these compounds contain in position 2 substituents that had been found in position 8 to affect favourably the degree of neuroleptic activity[21-23].

The synthesis of these compounds followed the general scheme[17,19-23], *i.e. via* the intermediates *VI*—*XIII*. Of the starting acids *VI*, the literature contains data[24] only on 2-(phenylthio)-5-(dimethylsulfamoyl)benzoic acid (*VId*) which was obtained in a reaction of 2-bromo-5-(dimethylsulfamoyl)benzoic acid[24,25] with thiophenol in dimethylformamide in the presence of potassium hydroxide and copper. Analogously (method *A*) we prepared now acid *VIb* from 2-bromo-5-methoxybenzoic acid[26] and acid *VIc* from 2-bromo-5-methylthiobenzoic acid[25]. Acid *VIa* was prepared by a reaction of sodium thiophenolate with the sodium salt of 2-bromo-5-methoxybenzoic acid[26] in dimethylformamide in the presence of copper.. Synthesis of acid *VIe* proceeded from 3-aminobenzotrifluoride which was brominated[27] to 3-amino-4--bromobenzotrifluoride; as by-product there appeared 5-amino-2-bromobenzotrifluoride[27] and a dibromo derivative which, on the basis of IR and NMR spectra, may be considered as 5-amino-2,4-dibromobenzotrifluoride (*XIV*). 3-Amino-4-bromobenzotrifluoride was converted according to data in the literature[28,29] to 2-bromo-5-trifluoromethylbenzonitrile; as by-products of the diazotization and Sandmeyer's reaction there appeared two new compounds which, on the basis of analyses and spectra, were identified as the triazene *XV* and the azobenzene *XVI*. 2-Bromo-5--trifluoromethylbenzonitrile was condensed with thiophenol in dimethylformamide in the presence of potassium hydroxide and copper; the main product obtained was 2-phenylthio-5-trifluoromethylbenzonitrile (*XVII*) and as a minor product, there was the amide *XVIII*. Acid *VIe* was obtained by alkaline hydrolysis of nitrile *XVII*.

Acids *VI* were reduced to alcohols *VII* either with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene (see ref.[30]) (method *B*) or with diborane in tetrahydrofuran (see ref.[31]) (method *C*). To convert alcohols *VII* to chlorides *VIII*, thionyl chloride in chloroform was used in the presence of pyridine (method *D*); in two cases the crude products *VIIIa*, *VIIIc* were used without characterization for further work. Preparation of nitriles *IX* from chlorides *VIII* was done in most cases through a reaction with sodium cyanide in dimethylformamide (method *E*); in the case of chloride *VIIIb* the reation with potassium cyanide in aqueous ethanol was used. In the case of preparation of nitrile *IXd* by method *E* a mixture resulted which had to be separated by chromatography on alumina, this yielding about 15% of a more polar product which, according to further processing (hydrolysis and cyclization, see below), is apparently *XIX*, *i.e.* has the structure of the alkylation product of the nitrile *IXd* by chloride *VIIId* (analogies and references in ref.[32]). Hydrolysis of nitriles *IX* to acids *X* was done with potassium hydroxide in aqueous ethanol (method *F*) throughout.

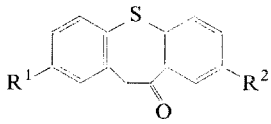
To cyclize acids *X* to ketones *XI* polyphosphoric acid in boiling toluene (method *G*) was used throughout. The same method was employed for cyclization of the crude



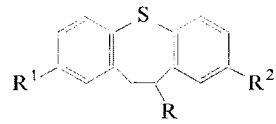
VI, R = COOH
VII, R = CH_2OH

VIII, R = CH_2Cl
IX, R = CH_2CN

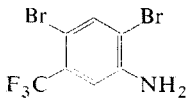
X, R = CH_2COOH



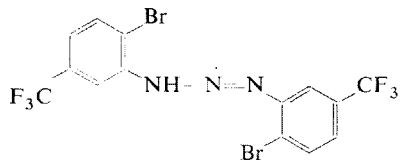
XI



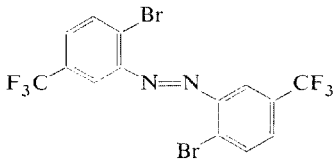
XII, R = OH
XIII, R = Cl



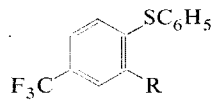
XIV



XV



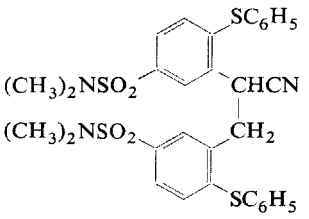
XVI



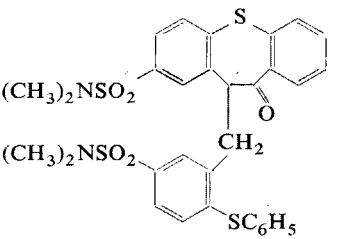
XVII, R = CN
XVIII, R = $CONH_2$

acid obtained by hydrolysis of the more polar product of preparation of nitrile *IXd* for which the structure *XIX* was suggested. A conjugated ketone (ν(CO) 1665 cm^{-1}) was obtained which in the mass spectrum contains a molecular ion $C_{31}H_{30}N_2.O_5S_4$ in agreement with analysis. On the basis of these facts the product is assigned the structure of ketone *XX*. Since method *G* yields ketone *XIe* in a low yield (most of *Xe* is recovered), an attempt was made to cyclize acid *Xe* with polyphosphoric acid alone at 145°C; the cyclization was accompanied under these conditions by hydrolysis of the trifluoromethyl group giving the keto acid *XXI* in a fine yield. When working in toluene, ketone *XIe* is formed in mixture with other compounds, two of which were isolated by chromatography. Both have the formula $C_{22}H_{16}O_2S$, both are conjugated diketones (ν(CO) 1650 and 1684, or 1665 and 1676 cm^{-1})

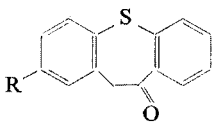
and apparently the products of interaction of acid *XXI* with toluene in the sense of a Friedel-Crafts acylation. On the basis of comparison of intensities of the bands of IR spectra of both substances belonging to the 4 adjacent Ar—H bonds, the more polar isomer, formed in a yield of about 7% was assigned the structure of the *para* derivative *XXII*, the somewhat less polar and rather minor one (about 1% yield) the structure of the ortho isomer *XXIII*. The patent application[33] mentions ketone *XIa*.



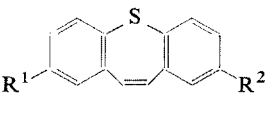
XIX



XX



XXI, R = COOH
XXII, R = 4-$COC_6H_4CH_3$
XXIII, R = 2-$COC_6H_4CH_3$



XXIV

Reduction of ketones *XI* to alcohols *XII* was done with sodium borohydride in aqueous ethanol or in a mixture of ethanol and dioxane (method *H*). To convert alcohols *XII* to chlorides *XIII*, the action of hydrogen chloride in benzene, chloroform or a mixture of the two was employed (method *J*). Only after termination of the present experimental work, a patent application was published[34] where the preparation of some of our intermediates is described without data on yield or analyses; the references are found in the appropriate sections.

The final products of this work, *i.e.* the piperazine derivatives *IIIa*–*IIIe*, *IVb* and *IVc*, were prepared by substitution reaction of chlorides *XIII* with 1-methylpiperazine or with 1-(2-hydroxyethyl)piperazine in boiling chloroform (method *K*). Reaction of ketone *XIc* with 1-methylpiperazine and titanium tetrachloride in boiling benzene (see ref.[35]) yielded the enamine *V* which was reduced with diborane (method[36]) to the dihydro derivative *IIIc*; this method represents an alternative procedure for the preparation of *III* and *IV*. As by-products of the substitution reactions according to method *K*, the elimination products *XXIV* were found, only *XXIVb* being a novel substance, all the others having been obtained[21–23] in the synthesis of analogous 8-substitution derivatives *III*. All the bases prepared here were characterized

TABLE I

2-Substituted 10-Piperazinodibenzo[*b,f*]thiepins (*III*—*V*), Intermediates (*VI*—*XIII*) and Elimination Products *XXIV*.

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% S
VIa	[b]	153—155 (aqueous ethanol)	$C_{14}H_{12}O_3S$ (260·3)	64·59 64·38	4·65 4·81	— —	12·32 12·17
VIb	*A* (78)	150—152[c] (benzene–light petroleum)	$C_{14}H_{11}FO_3S$ (278·3)	60·42 60·85	3·98 4·12	— —	11·52 11·63
VIc	*A*[b]	138·5—139·5 (benzene)	$C_{14}H_{12}O_2S_2$ (276·4)	60·84 61·08	4·38 4·28	— —	23·20 23·08
VId	*A* (81)	216—220[d] (acetonitrile)	—	—	—	—	—
VIe	*b*	166—169 (benzene–light petroleum)	$C_{14}H_9F_3O_2S$ (298·3)	56·37 55·75	3·04 2·83	19·11[e] 18·71	10·75 10·46
VIIa	*B* (95)	160/0·4[f]	$C_{14}H_{14}O_2S$ (246·3)	68·26 68·16	5·73 6·01	— —	13·02 13·08
VIIb	*B* (93)	185—190/2[g]	$C_{14}H_{13}FO_2S$ (264·3)	63·61 64·02	4·96 5·14	— —	12·13 12·20
VIIc	*B*[b] (97)	190/0·6	$C_{14}H_{14}OS_2$ (262·4)	64·08 64·39	5·38 5·72	— —	24·44 24·18
VIId	*C*[b] (96)	138—139 (benzene–light petroleum)	$C_{15}H_{17}NO_3S_2$ (323·4)	55·71 56·33	5·30 5·47	4·33 4·34	19·93 19·35
VIIe	*C* (95)	88—89·5[h] (cyclohexane–light petroleum)	$C_{14}H_{11}F_3OS$ (284·3)	59·14 59·12	3·90 3·97	20·05[e] 20·31	11·28 11·60
VIIIb	*D* (86)	165—170/1	$C_{14}H_{12}ClFOS$ (282·8)	59·46 59·79	4·28 4·32	12·54[i] 12·06	11·34 11·26
VIIId	*D*[b] (90)	110—111·5 (benzene–light petroleum)	$C_{15}H_{16}ClNO_2S_2$[j] (341·9)	52·69 53·06	4·72 4·72	4·10 3·98	18·76 18·64
VIIIe	*D* (95)	40·5—41·5[k] (light petroleum)	$C_{14}H_{10}ClF_3S$ (302·7)	55·54 55·68	3·33 3·36	18·83[e] 19·10	10·59 10·46
IXa	*E* (81)[m]	181—183/0·8	$C_{15}H_{13}NOS$ (255·3)	70·55 70·44	5·13 5·36	5·49 5·46	12·56 12·54
IXb	[b]	170—175/1	$C_{15}H_{12}FNOS$ (273·3)	65·91 66·04	4·43 4·45	5·12 5·04	11·73 11·90

TABLE I
(*Continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% S
IXc	*E*[b]	48—49 (benzene–cyclohexane)	$C_{15}H_{13}NS_2$ (271·4)	66·38 65·92	4·83 4·99	5·16 5·09	23·63 23·78
IXd	*E*[b]	105—106 (ethanol)	$C_{16}H_{16}N_2O_2S_2$ (332·5)	57·80 57·96	4·85 4·86	8·43 8·57	19·29 19·58
IXe	*E* (60)	146—148/0·5[n]	$C_{15}H_{10}F_3NS$ (293·3)	61·42 60·94	3·44 3·48	4·78 4·48	10·93 11·02
Xa	*F* (90)	114—116[o] (aqueous ethanol)	$C_{15}H_{14}O_3S$ (274·3)	65·67 65·21	5·14 4·86	— —	11·69 11·80
Xb	*F* (89)	88—90[p] (aqueous ethanol)	$C_{15}H_{13}FO_3S$ (292·3)	61·63 61·68	4·48 4·52	— —	10·97 10·77
Xc	*F*[b]	132—134 (benzene–light petroleum)	$C_{15}H_{14}O_2S_2$ (290·4)	62·04 62·50	4·86 5·13	— —	22·08 22·22
Xd[q]	*F* (85)	148·5—149·5[r] (aqueous ethanol)	$C_{16}H_{18}NO_{4.5}S_2$ (360·5)	53·31 53·61	5·03 5·01	3·89 4·01	17·79 18·16
Xe	*F* (87)	106—109[s] (aqueous ethanol)	$C_{15}H_{11}F_3O_2S$ (312·3)	57·68 57·63	3·55 3·59	18·25[e] 18·31	10·27 10·28
XIa	*G* (75)	131·5—132·5[t] (cyclohexane)	$C_{15}H_{12}O_2S$ (256·3)	70·28 70·21	4·72 4·80	— —	12·51 12·23
XIb	*G*[b] (86)	167—169 (benzene)	$C_{15}H_{11}FO_2S$ (274·3)	65·67 65·38	4·04 3·92	6·93[e] 6·64	11·69 11·85
XIc	*G* (90)	130—131[u] (ethanol)	$C_{15}H_{12}OS_2$ (272·4)	66·14 66·57	4·44 4·67	— —	23·54 23·43
XId	*G* (60)	168—169·5[v] (benzene–ethanol)	$C_{16}H_{15}NO_3S_2$ (333·4)	57·64 57·74	4·53 4·72	4·20 4·09	19·23 19·28
XIe	*G*[b]	111·5—113·5 (cyclohexane)	$C_{15}H_9F_3OS$ (294·3)	61·21 60·73	3·08 3·13	19·37[e] 19·07	10·90 11·44
XIIa	*H*[w] (87)	91—92·5[x] (benzene–light petroleum)	$C_{15}H_{14}O_2S$ (258·3)	69·74 69·90	5·46 5·76	— —	12·41 12·13
XIIb	*H*[w] (74)	83—85[y] (benzene–light petroleum)	$C_{15}H_{13}FO_2S$ (276·3)	65·20 65·09	4·74 4·95	6·88[e] 6·67	11·60 11·61
XIIc	*H*[b]	122—124 (benzene–light petroleum)	$C_{15}H_{14}OS_2$ (274·4)	65·65 65·71	5·14 5·29	— —	23·37 23·18

TABLE I
(*Continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% S
XIId	*H*[z]	139—141[aa]	$C_{16}H_{17}NO_3S_2$	57·31	5·11	4·18	19·10
	(80)	(benzene–cyclohexane)	(335·3)	57·24	5·19	3·85	18·84
XIIe	*H*[w]	127[bb]	$C_{15}H_{11}F_3OS$	60·80	3·74	19·24[e]	10·82
	(95)	(benzene–light petroleum)	(296·3)	60·43	3·59	19·07	11·15
XIIIa	*J*[b]	113—114	$C_{15}H_{13}ClOS$	65·09	4·73	12·81[i]	11·59
		(cyclohexane)	(276·8)	65·43	4·84	12·60	11·59
XIIIb	*J*[cc]	105—107[dd]	$C_{15}H_{12}ClFOS$	61·12	4·10	6·44[e]	10·88
	(95)	(benzene–light petroleum)	(294·8)	61·40	3·96	6·30	10·66
XIIIc	*J*[ee]	82—83	$C_{15}H_{13}ClS_2$	61·52	4·47	12·11	21·90
	(90)	(cyclohexane–light petroleum)	(292·9)	61·73	4·38	12·47	21·62
XIIId	*J*[ee]	141·5—142·5[ff]	$C_{16}H_{16}ClNO_2S_2$	54·30	4·56	3·96	18·12
	(80)	(benzene–cyclohexane)	(353·9)	54·51	4·74	3·78	17·99
XIIIe	*J*[gg]	76·5—78·5[hh]	$C_{15}H_{10}ClF_3S$	57·23	3·20	18·11[e]	10·19
	(80)	(light petroleum)	(314·8)	57·37	3·28	18·29	10·21
IIIa	*K*	140—142[jj]	$C_{20}H_{24}N_2OS$	70·54	7·11	8·23	9·42
	(82)	(ethanol)	(340·5)	70·56	7·46	8·19	9·40
IIIa-2MS[kk]		147·5—149·5	$C_{22}H_{34}N_2O_8S_3$	47·98	6·22	5·09	17·47
	—	(acetone)	(550·7)	47·76	6·23	5·00	17·12
IIIb	*K*	121—123[mm]	$C_{20}H_{23}FN_2OS$	67·01	6·47	7·82	8·94
	(80)	(ethanol)	(358·5)	67·20	6·61	7·87	8·60
IIIb-2MS		194—195[nn]	$C_{22}H_{31}FN_2O_7S_3$	47·98	5·67	5·09	17·47
		(ethanol–ether)	(550·7)	48·00	5·71	4·98	17·36
IIIc	*K* ([b])	102—103	$C_{20}H_{24}N_2S_2$	67·37	6·78	7·86	17·99
	(80)	(ethanol)	(356·6)	67·68	6·87	7·90	18·14
IIIc-2HM		126—128	$C_{28}H_{32}N_2O_8S_2$	57·13	5·48	4·76	10·89
		(ethanol–ether)	(588·7)	56·97	5·52	4·81	10·78
IIId	*K*	155—157[oo]	$C_{21}H_{27}N_3O_2S_2$	60·40	6·52	10·06	15·36
	(80)	(methanol)	(417·6)	60·33	6·79	9·80	15·26
IIId-MS[pp]		125—127 and 245—246 (ethanol–ether)	$C_{24}H_{37}N_3O_6S_3$ (559·8)	51·49	6·66	7·51	17·19
				51·24	6·67	7·21	17·49

TABLE I
(*Continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% S
IIIe-M	*K* (80)	151—152[qq] (acetone–ether)	$C_{24}H_{25}F_3N_2O_4S$ (494·5)	58·29 58·00	5·10 5·12	5·67 5·75	6·48 6·47
IVb	*K*[b] (86)	102—103 (cyclohexane)	$C_{21}H_{25}FN_2O_2S$[rr] (388·5)	64·92 65·12	6·49 6·96	7·21 7·18	8·26 7·93
IVb-M[q]		142—143[ss] (ethanol–ether)	$C_{25}H_{30}FN_2O_{6.5}S$ (513·6)	58·46 58·73	5·89 5·88	5·45 5·13	6·24 6·35
IVc-2HM	*K* (82)	154—156 (ethanol–ether)	$C_{29}H_{34}N_2O_9S_2$ (618·7)	56·30 56·40	5·54 5·61	4·53 4·60	10·36 10·32
V	[b]	146—147 (ethanol)	$C_{20}H_{22}N_2S_2$ (354·5)	67·76 68·18	6·25 6·36	7·90 7·50	18·09 18·25
V-MS		269—271 (ethanol)	$C_{21}H_{26}N_2O_3S_3$ (450·7)	55·97 56·21	5·82 5·85	6·22 6·16	21·35 21·43
XXIVa	*K* (10)	103—106[tt] (ethanol)	—	—	—	—	—
XXIVb	*K*[b]	81—83 (light petroleum)	$C_{15}H_{11}FOS$ (258·3)	69·74 69·53	4·29 4·08	7·36[e] 7·08	12·41 12·40
XXIVc	*K* (15)	89—91[uu] (benzene–light petroleum)	—	—	—	—	—
XXIVd	*K* (15)	153—156[vv] (ethanol)	—	—	—	—	—
XXIVe	*K* (19)	56·5—57·5[ww] (methanol)	$C_{15}H_9F_3S$ (278·3)	64·73 65·01	3·26 3·46	20·48[e] 20·68	11·52 11·60

[a] M maleate, 2 HM (di(hydrogen maleate), MS methanesulfonate, 2 MS dimethanesulfonate. [b] See Experimental. [c] IR spectrum: 835, 880 (Ar—H), 930, 1260 (COOH), 1035, 1240, 1480 (Ar—O—CH_3), 1565, 1600, 1610 (Ar), 1688 (Ar—CO), 2600 cm^{-1} (COOH). [d] Ref.[24] describes the preparation of the substance in the same way and reports a m.p. of 215—217°C (benzene). [e] Content of fluorine. [f] IR spectrum ($CHCl_3$): 820, 830, 868 (Ar—H), 1030 (CH_2OH), 1240 (Ar—O—CH_3), 1480, 1575, 1600 (Ar), 2857 (OCH_3), 3618 cm^{-1} (OH). [g] IR spectrum (film): 830, 870 (Ar—H), 1032 (CH_2OH), 1237 (Ar—O—CH_3), 1495, 1600 (Ar), 3400 cm^{-1} (OH). [h] IR spectrum: 692, 719, 751, 826, 843, 894 (Ar—H), 1038, 1066 (CH_2OH), 1141, 1176, 1333 (CF_3), 1478, 1608 (Ar), 3245, 3310 cm^{-1} (OH); patent application[34] describes the preparation of the compound by reduction of methyl ester of acid *VIe* with $LiBH_4$ in tetrahydrofuran and reports a m.p. of 84°C for the product. [i] Content of chlorine. [j] Calculated: 10·37% Cl; found: 10·15% Cl. [k] Calculated: 11·71% Cl; found: 11·44% Cl; patent application[34] describes the preparation of the compound through a reaction of *VIIe* and $SOCl_2$ in benzene and characterizes

the product as a brown-yellow oil. [m] Yield referred to the starting *VIIa* since *VIIIa* was used without characterization as a crude product. [n] Calculated: 19·43% F; found: 19·58% F; patent application[34] describes the preparation of the compound by a reaction of *VIIIe* and NaCN in dimethylsulfoxide and characterizes the product as a dark-red oil. [o] IR spectrum: 687, 738, 825, 858 (Ar—H), 952, 1242 (COOH), 1482, 1592 (Ar), 1700 cm^{-1} (R—COOH). [p] IR spectrum: 830, 863 (Ar—H), 966, 1035, 1317 (COOH), 1245 (Ar—O—CH_3), 1500, 1600 (Ar), 1710 (R—COOH), 2600, 3000 cm^{-1} (COOH). [q] Hemihydrate. [r] IR spectrum: 700, 735, 758, 830, 893 (Ar—H), 1160, 1345 (NSO_2), 1592 (Ar), 1707 (R—COOH), 2660 and 3000 cm^{-1} (COOH and H_2O); NMR spectrum: δ 10·60 (bs, disappears after D_2O, 1 H, COOH), 7·55 (d, J = 2·0 Hz, 1 H, 6-H of phenylacetic acid), 7·40 (q, J = 8·5; 2·0 Hz, 1 H, 4-H of phenylacetic acid), 7·26 (s, 5 H, C_6H_5), 7·02 (d, J = 8·5 Hz, 1 H, 3-H of phenylacetic acid), 3·84 (s, 2 H, $ArCH_2CO$), 2·60 (s, 6 H, CH_3NCH_3). [s] IR spectrum: 694, 733, 752, 826, 886 (Ar—H), 934 (COOH), 1139, 1170, 1340 (CF_3), 1237 (COOH), 1614 (Ar), 1696 (R—COOH), 2650, 2920, 3020 cm^{-1} (COOH); patent application[34] reports a m.p. of 102—103°C for a similarly prepared product. [t] UV spectrum: λ_{max} 229 nm (log ε 4·34), 249 nm (4·22), 337 nm (3·52); IR spectrum: 754, 823, 874 (Ar—H), 1253, 1288 (Ar—O—CH_3), 1570, 1588, 1598 (Ar), 1670 cm^{-1} (Ar—CO); NMR spectrum δ 8·15 (m, 1 H, 9-H), 7·42 (d, J = 9·0 Hz, 1 H, 4-H), 7·05—7·50 (m, 3 H, 6,7,8-H_3), 6·92 (d, J = 3·0 Hz, 1 H, 1-H), 6·65 (q, J = 9·0; 3·0 Hz, 1 H, 3-H), 4·25 (s, 2 H, $ArCH_2CO$), 3·70 (s, 3 H, OCH_3); the compound is mentioned in the patent application[33] without experimental details, a m.p. of 131·5°C being given. [u] UV spectrum: λ_{max} 226 nm (log ε 4·38), infl. 240 nm (4·32), 263 nm (4·22), 281 nm (4·30), 340 nm (3·60); IR spectrum: 773, 810, 828, 871 (Ar—H), 1555, 1592 (Ar), 1670 cm^{-1} (Ar—CO); NMR spectrum: δ 8·15 (m, 1 H, 9-H), 7·15—7·60 (m, 4 H, 1,6,7,8-H_4), 7·42 (d, J = 9·0 Hz, 1 H, 4-H), 6·95 (q, J = 9·0; 2·5 Hz, 1 H, 3-H), 4·25 (s, 2 H, $ArCH_2CO$), 2·40 (s, 3 H, SCH_3). [v] IR spectrum: 700, 730, 778, 815, 900 (Ar—H), 1160, 1355 (NSO_2), 1595 (Ar), 1680 cm^{-1} (ArCO); NMR spectrum: δ 8·12 (m, 1 H, 9-H), 7·00—7·90 (m, 6 H, remaining aromatic protons), 4·34 (s, 2 H, $ArCH_2CO$), 3·63 (s, 6 H, CH_3NCH_3); patent application[34] describes the preparation of the compound from the corresponding 2-aminoketone *via* the 2-(chlorosulfonyl) ketone but does not characterize the product. [w] Reaction carried out in ethanol. [x] IR spectrum: 753, 816, 870 (Ar—H), 1028 (CHOH in a cycle), 1278 (Ar—O—CH_3), 1571, 1600 (Ar), 3320, 3380 cm^{-1} (OH); NMR spectrum: δ 7·40 (d, J = 9·0 Hz, 1 H, 4-H), 7·00—7·50 (m, 4 H, 6,7,8,9-H_4), 6·80 (d, J = 3·0 Hz, 1 H, 1-H), 6·60 (q, J = 9·0; 3·0 Hz, 1 H, 3-H), 5·18 (q, J = 8·5; 4·0 Hz, 1 H, Ar—CH—O), 3·68 and 3·25 (2 dd, J = 14·0; 4·0 and 14·0; 8·5 Hz, 2 H, $ArCH_2$), 3·66 (s, 3 H, OCH_3), 2·15 (s, disappears after D_2O, 1 H, OH). [y] IR spectrum: 814, 869, 879 (Ar—H), 1027 (CHOH in a ring), 1051, 1212 (Ar—O—CH_3), 1569, 1590 (Ar), 3340 cm^{-1} (OH). [z] Reaction conducted in a mixture of ethanol and dioxane. [aa] IR spectrum: 716, 729, 768 (Ar—H), 1050 (CHOH), 1155, 1340 (NSO_2), 3280, 3350 cm^{-1} (OH); NMR spectrum: δ 7·00—7·70 (m, 7 H, aromatic protons), 5·40 (m, 1 H, Ar—CH—O), 3·66 and 3·29 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·62 (s, 6 H, CH_3NCH_3); patent application[34] describes the preparation of the compound by reduction of ketone with $NaBH_4$ in aqueous dioxane but the product is not characterized. [bb] IR spectrum: 755, 817, 834, 872 (Ar—H), 1083 (CHOH), 1124, 1167, 1326 (CF_3), 1587, 1603 (Ar), 3300, 3350 cm^{-1} (OH); patent application[34] describes a similar procedure of preparation and reports a m.p. of 122 to 123°C for the product. [cc] Reaction conducted in benzene. [dd] NMR spectrum: δ 7·35 (d, J = 9·0 Hz, 1 H, 4-H), 6·95 (q, J = 12·0; 2·5 Hz, 1 H, 9-H), 7·10—7·40 (m, 2 H, 6,7 H_2), 6·72 (d, J = = 2·5 Hz, 1 H, 1-H), 6·57 (q, J = 9·0; 2·5 Hz, 1 H, 3-H), 5·65 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·87 and 3·55 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·70 (s, 3 H, OCH_3); calculated: 12·03% Cl; found: 12·08% Cl. [ee] Reaction conducted in chloroform. [ff] Calculated: 10·02% Cl; found: 9·67% Cl; patent application[34] describes the preparation in a similar way in benzene but does not characterize the product. [gg] Reaction conducted in a mixture of ben-

by their spectra and were converted to crystalline salts. All the compounds falling within the basic synthetic scheme, *i.e. III–XIII* and *XXIV*, are summarized together with the usual experimental data in Table I.

In the form of salts, the compounds were subjected to pharmacological tests, the administration being usually *per os*, only occasionally parenterally. The acute toxicity for mice was estimated (the mean lethal dose LD_{50}). The incoordinating effect in the rotating-rod test on mice was also studied and expressed by the mean effective dose ED_{50}, this being taken as the indicator of central depressant effect. Finally, the cataleptic effect on rats (for pharmacological methods see ref.[23]) considered as an indicator of neuroleptic activity was studied. With the newly prepared compounds it has never been possible to determine the mean effective dose for the practical inactivity of these compounds in this test. The numerical data on toxicity and activity (in mg/kg) are summarized in Table II and represent values referred to the bases. For reference, the table contains also clozapine[37], further clorotepin[18] and its 2-chloro isomer (*III*, $R^1 = Cl$, $R^2 = H$)[20].

Table II shows that the new compounds resemble clozapine and the 2-chloro derivative of perathiepin (*III*, $R^1 = Cl$, $R^2 = H$) in their inactivity in the catalepsy test but differ from them in their relatively weak central depressant activity. The negative effect of the methoxy, methylthio and trifluoromethyl groups on the central depressant activity was observed by Schmutz and coworkers[1] in the series of direct clozapine analogues. The effect of the individual substituents in the "quasi"symmetrical positions 2 and 8 on the individual parameters of pharmacodynamic activity is thus not the same.

Explanation to Table I

zene and chloroform. [hh] NMR spectrum: δ 6·95–7·70 (m, 7 H, aromatic protons), 5·70 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·61 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$); calculated: 11·26% Cl; found: 11·28% Cl; patent application[34] describes the preparation in a similar way in benzene and characterizes the product as yellow crystals. [jj] IR spectrum: 751, 827, 862 (Ar—H), 1246 (Ar—O—CH_3), 1590 (Ar), 2735 cm^{-1} (NCH_3); NMR spectrum: δ 6·90–7·60 (m, 4 H, 6,7,8,9-H_4), 7·35 (d, J = 9·0 Hz, 1 H, 4-H), 6·77 (d, J = 3·0 Hz, 1 H, 1-H), 6·52 (q, J = 9·0; 3·0 Hz, 1 H, 3-H), 2·90–4·00 (m, 3 H, $ArCH_2CHAr$), 3·67 (s, 3 H, OCH_3), 2·58 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·35 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3). [kk] Monohydrate. [mm] NMR spectrum: δ 6·40–7·50 (m, 6 H, aromatic protons), 2·80 to 4·00 (m, 3 H, $ArCH_2CHAr$), 3·70 (s, 3 H, OCH_3), 2·66 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·35 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). [nn] Calculated: 3·45% F; found: 3·63% F. [oo] NMR spectrum δ 6·80–7·60 (m, 7 H, aromatic protons), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (s, 6 H, CH_3NCH_3), 2·55 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3). [pp] Solvate with C_2H_5OH. [qq] IR spectrum: 762, 833, 870 (Ar—H), 1116, 1164, 1336 (CF_3), 1450–1620 and 2200–3000 cm^{-1} (COO^-NH^+); calculated: 11·53% F; found: 11·57% F. [rr] Calculated: 4·89% F; found: 4·97% F. [ss] Calculated: 3·70% F; found 3·64% F. [tt] A m.p. of 105–106·5°C was reported previously[21] for this compound. [uu] The same m.p. was found in a previous study[21]. [vv] A m.p. of 156–158°C was reported previously[23] for this compound. [ww] NMR spectrum: δ 7·05–7·60 (m, 7 H, aromatic protons), 6·96 (s, 2 H, CH=CH); the compound was described before[22] as an oil boiling at 137°C/0·3 Torr.

The compounds prepared were tested for antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek); Table III shows the minimum inhibitory concentrations against several typical microorganisms. Mention should be made of the pronounced antibacterial, particularly antituberculosis activity of the trifluoromethyl derivative *IIIe*.

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 a temperature suitably raised (at most 100°C). The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in an Infrascan (Hilger and Watts) or in a Unicam SP 200G spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR-60 (Zeiss, Jena) spectrometer, the mass spectrum on a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was checked on a thin layer of silica gel. Preparative chromatography was done on alumina of activity II. The analyses of compounds *III*—*XIII* and *XXIV* are shown in Table I.

TABLE II

Pharmacological Effects of the Compounds Prepared (mg/kg)

Compound	Administration	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
IIIa	*p.o.*	93	14	> 50[a]
IIIb	*p.o.*	180	10·5	> 50[b]
IIIc	*p.o.*	185	14	>100[c]
IIId	*p.o.*	300	>200[d]	>100[c,e]
IIId	*i.v.*	19·5	16	—
IIIe	*p.o.*	310	12·5	>100[b]
IIIe	*i.v.*	52	8	—
IVb	*p.o.*	600	28	> 50[a]
IVc	*p.o.*	370	33	> 50[c]
V	*p.o.*	>150[f]	—	>100[g]
Clozapine[1,37]	*p.o.*	210	3·8	> 50[c]
III, $R^1 = Cl$, $R^2 = H$[20]	*p.o.*	70	1·2	>100[b]
	i.v.	36	0·23	—
Clorotepin[18]	*p.o.*	78	2·2	4·3
	i.v.	46·3	0·06	2·4[h]

[a] The dose brings about catalepsy in 2 out of 10 rats. [b] The dose brings about catalepsy in 3 out of 10 rats. [c] The dose has no cataleptic effect. [d] The dose brings about ataxia in 4 out of 10 mice 90 min after application. [e] The dose has an excitatory effect. [f] The testing was complicated by difficulties with the preparation of a suitable suspension. [g] The dose brings about catalepsy in 1 out of 10 rats. [h] Intraperitoneally.

TABLE III

Antimicrobial Activity of the Compounds Prepared *in vitro* (μg/ml)

Compound [a]	Microorganism[b]						
	1	2	3	4	5	6	7
IIIa-MS	50	50	12·5	—	—	—	—
IIIb-MS	25	25	25	—	125	—	—
IIIc-2 HM	25	25	25	125	—	—	—
IIId-MS	50	50	25	—	—	—	—
IIIe-M	12·5	12·5	6·25	125	125	—	—
IVb-M	—	—	—	—	125	—	—
IVc-2 HM	25	25	25	125	125	—	—
V-MS	—	—	25	62·5	62·5	125	62·5

[a] MS Methanesulfonate, M maleate, 2 HM di(hydrogen maleate). [b] 1 *Streptococcus β-haemolyticus*, 2 *Staphylococcus pyogenes aureus*, 3 *Mycobacterium tuberculosis* H37Rv, 4 *Saccharomyces pasterianus*, 5 *Trichophyton mentagrophytes*, 6 *Candida albicans*, 7 *Aspergillus niger*.

5-Amino-2,4-dibromobenzotrifluoride (*XIV*)

According to ref.[27], 198 g 3-aminobenzotrifluoride was brominated at 0—10°C with 155 g bromine in a mixture of 600 ml acetic acid and 120 ml ether in the presence of 12 g iron. Distillation of the crude product regenerated 58·5 g of the starting 3-aminobenzotrifluoride; 83·3 g (40% referred to conversion) 3-amino-4-bromobenzotrifluoride was obtained, b.p. 58—64°C : : 1 Torr (ref.[27] gives a b.p. of 81—82°C/5 Torr), further 66·5 g (32% referred to conversion) 5-amino-2-bromobenzotrifluoride, b.p. 80—86°C/1 Torr, m.p. 46—49°C (ref.[27] gives a b.p. of 81—84°C/0·5 Torr and m.p. 55—56°C) and finally 16·8 g (6% referred to conversion) dibromo derivative which, according to spectra, has the structure of *XIV*; b.p. 86—96°C/0·6 Torr, m.p. 47—48°C (light petroleum). Ref.[27] reports a b.p. of 113—115°C/3 Torr and m.p. 45—47°C and designates it as 5-amino-2,4-dibromo or 3-amino-2,4-dibromobenzotrifluoride. IR spectrum 888 (solitary Ar—H), 1133, 1174, 1304 (CF_3), 1482 (Ar), 1620 (Ar—NH_2), 3365 cm^{-1} (NH). NMR spectrum: δ 7·62 and 6·95 (2 s, 2 H, aromatic protons), 4·16 (bs, disappears after D_2O, 2 H, NH_2). For $C_7H_4Br_2F_3N$ (319·0) calculated: 26·36% C, 1·26% H, 50·11% Br, 17·87% F, 4·40% N; found: 26·32% C, 1·36% H, 50·14% Br, 17·89% F, 4·33% N.

2-Bromo-5-trifluoromethylbenzonitrile[28,29]

A mixture of 83·3 g 3-amino-4-bromobenzotrifluoride, 900 g ice with 70 ml concentrated H_2SO_4 was diazotized in the usual way with a solution of 24·2 g $NaNO_2$ in 40 ml water. The solution of the diazonium salt was filtered with the yield of 15·6 g yellow crystalline compound which was dissolved in chloroform, the solution was washed with a solution of soda and evaporated. The residue was recrystallized from benzene; m.p. 171—172°C. According to spectra and analysis we are dealing here with 1,3-bis(2-bromo-5-trifluoromethylphenyl)triazene (*XV*). UV spectrum: λ_{max} 240 nm (log ε 4·13), 301 nm (4·14), 348 nm (4·25). IR spectrum: 830 and 885 (2 adjacent and soli-

tary Ar—H), 1125, 1174, 1375 (Ar—CF_3), 1509, 1590, 1610 (Ar), 3310 cm^{-1} (NH). NMR spectrum: δ 10·22 (bs, disappears after D_2O, 1 H, NH), 7·79 (d, J = 2·0 Hz, 2 H, aromatic protons in positions 6,6'), 7·66 (d, J = 9·0 Hz, 2 H, aromatic protons in positions 3,3'), 7·22 (q, J = 9·0; 2·0 Hz, 2 H, aromatic protons in positions 4,4'). For $C_{14}H_7Br_2F_6N_3$ (491·1) calculated: 34·24% C, 1·44% H, 32·55% Br, 23·21% F, 8·56% N; found: 34·30% C, 1·39% H, 32·55% Br, 23·45% F, 8·79% N.

Besides this a solution of 160 g NaCN was prepared in 320 ml NH_4OH, combined with a cold solution of 200 g $CuSO_4.5\,H_2O$ in 480 ml water, with 240 ml toluene and, at a temperature below 10°C, the solution was slowly combined with a filtered solution of the diazonium salt. The mixture was stirred for 4 h at room temperature and, after standing overnight, it was steam-distilled. The distillate (4-litres) was extracted with a mixture of benzene and ether. Usual processing yielded 31·2 g (36%) 2-bromo-5-trifluoromethylbenzonitrile, b.p. 107—115°C/10 Torr, m.p. 50—51°C, in agreement with reported data[28].

Recrystallization of the distillation residue from benzene yielded 0·2 g red substance identified as 5,5'-bis(trifluoromethyl)-2,2'-dibromoazobenzene (*XVI*), m.p. 200—201°C (benzene). UV spectrum: λ_{max} 325 nm (log ε 4·23), 240 nm (4·20), 217 nm (4·42). IR spectrum: 829 and 910 (2 adjacent and solitary Ar—H), 1117, 1192, 1326 (Ar—CF_3), 1596 (Ar), 1657 cm^{-1} (N=N). For $C_{14}H_6Br_2F_6N_2$ (476·1) calculated: 35·32% C, 1·27% H, 33·57% Br, 23·95% F, 5·89% N; found: 35·56% C, 1·33% H, 33·26% Br, 24·56% F, 5·84% N.

2-(Phenylthio)-5-trifluoromethylbenzonitrile (*XVII*)

A mixture of 64·2 g 2-bromo-5-trifluoromethylbenzonitrile, 33·0 g thiophenol, 18 g KOH, 3 g Cu and 500 ml dimethylformamide was refluxed under nitrogen with stirring for 16 h. The solvent was distilled off *in vacuo*, the residue was separated between water and benzene, the mixture was filtered, the benzene layer separated from the filtrate, dried and treated by distillation; 66·4 g (93%) b.p. 127—130°C/0·15 Torr. During redistillation, the b.p. was 135—137°C/0·6 Torr. Even then the compound is not completely pure. For $C_{14}H_8F_3NS$ (279·3) calculated: 60·21% C, 2·89% H, 5·02% N; found: 60·91% C, 3·04% H, 4·48% N. Patent application (ref.[34]) describes the preparation of this compound by Sandmeyer's reaction from 3-amino-4-(phenylthio)benzotrifluoride and the product is described as a dark oil.

Besides this product, 2·8 g of a higher-boiling fraction (b.p. 178—200°C/0·6 Torr) was obtained which crystallized and was purified by crystallization from benzene, m.p. 177—177·5°C. It is 2-(phenylthio)-5-trifluoromethylbenzamide (*XVIII*). IR spectrum: 689, 713, 752, 800, 825, 858 (5 and 2 adjacent and solitary Ar—H), 1122, 1176, 1323 (Ar—CF_3), 1619 (Ar), 1645 ($CONH_2$), 3185 and 3390 cm^{-1} (NH_2). NMR spectrum (C_5D_5N): δ 9·07 and 8·72 (2 bs, 2 H, NH_2), 8·09 (d, 1 H, aromatic proton in position 6 of benzamide), 6·80—7·55 (m, 7 H, remaining aromatic protons). For $C_{14}H_{10}F_3NOS$ (297·3) calculated: 56·56% C, 3·39% H, 19·18% F, 4·71% N, 10·78% S; found: 56·53% C, 3·50% H, 19·43% F, 4·57% N, 10·84% S.

2-(Phenylthio)-5-methoxybenzoic Acid (*VIa*)

A solution of sodium methoxide which was prepared from 100 ml methanol and 7·5 g Na, was combined with 18·0 g thiophenol and 34·2 g 2-bromo-5-methoxybenzoic acid[26] (m.p. 159 to 160·5°C) in 150 ml methanol. Methanol was then distilled off from the mixture, the remnants were removed *in vacuo* at 130°C. The solid residue was combined with 6 g "molecular" copper (washed with dimethylformamide) and 250 ml dimethylformamide and the mixture was refluxed under stirring for 12 h. The dimethylformamide was then distilled *in vacuo*, the residue was dissolved in 600 ml water and, after filtration, the filtrate was acidified with hydrochloric acid; 25·8 g 67%), m.p. 149—152°C. The analytical sample melted at 153—155°C (aqueous ethanol).

2-(Phenylthio)-5-(methylthio)benzoic Acid (*VIc*) (Method *A*)

A mixture of 120 ml dimethylformamide, 17·0 g 2-bromo-5-(methylthio)benzoic acid[25] (m.p. 144—145°C), 8·5 g thiophenol, 10 g 90% KOH and 3 g Cu was heated for 14 h on a 150°C bath. Dimethylformamide was distilled off *in vacuo*, the residue dissolved in 300 ml water, the solution was filtered for removing copper and the filtrate acidified with hydrochloric acid. The separated oil was extracted with a mixture of benzene and ether and, after evaporation of the solvents, it crystallized from a small amount of benzene: 15·3 g (80%), m.p. 138·5—139·5°C (benzene).

2-(Phenylthio)-5-trifluoromethylbenzoic Acid (*VIe*)

A mixture of a solution of 66·4 g *XVII* in 350 ml ethanol and a solution of 70 g KOH in 100 ml water was refluxed for 4 h. After evaporation of ethanol the residue was diluted with water and the solution acidified with hydrochloric acid. The separated product was recrystallized from a mixture of benzene and light petroleum: 57·6 g (81%), m.p. 166—169°C. IR spectrum: 681, 704, 831, 875 (5 and 2 adjacent and solitary Ar—H), 917, 1257, (COOH), 1124, 1183, 1342 (CF_3), 1564, 1609 (Ar), 1695 (Ar—COOH), 2500, 2560, 2640 cm^{-1} (COOH). Patent application[34] reports a m.p. of 140—145°C for a similarly prepared product.

2-(Phenylthio)-5-(methylthio)benzyl Alcohol (*VIIc*) (Method *B*)

A 55% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate (84·5 g) was added under stirring to a suspension of 22·4 g *VIc* in 140 ml benzene over a period of 1·5 h. After standing overnight, the mixture was decomposed with 200 ml 15% NaOH, the benzene layer was washed with water, dried with $MgSO_4$ and evaporated; 20·7 g (97%) oily product, a sample of which was redistilled for analysis; b.p. 190°C/0·6 Torr.

2-(Phenylthio)-5-(dimethylsulfamoyl)benzyl Alcohol (*VIId*)
(Method *C*)

Sodium borohydride (1·2 g) was added to a solution of 2·82 g *VId* in 10 ml tetrahydrofuran under nitrogen. Under cooling and with stirring, a solution of 4 ml boron trifluoride etherate in 10 ml tetrahydrofuran was added dropwise (at below 20°C). The mixture was stirred for 5 h, left to stand for 48 h, decomposed with 30 ml 10% hydrochloric acid and extracted with benzene. The extract was washed with 10% NaOH and water, dried with $MgSO_4$ and evaporated; 2·59 g (96%) product of m.p. 138—139°C which did not rise on recrystallization from a mixture of benzene and light petroleum. IR spectrum: 705, 740, 763, 827 (Ar—H), 1045 (CH_2OH), 1160, 1330 (NSO_2), 1590 (Ar), 3500 cm^{-1} (OH).

2-(Phenylthio)-5-(dimethylsulfamoyl)benzyl Chloride (*VIIId*) (Method *D*)

A warm-prepared solution of 33·2 g *VIId* in a mixture of 60 ml chloroform and 10 ml pyridine was cooled to 20°C and, during an hour, 13·3 g $SOCl_2$ was added dropwise at 20—25°C. The mixture was stirred for 2 h, left to stand for 24 h, washed with water, 5% NaOH and again with water, dried with $MgSO_4$ and evaporated; 31·7 g (90%), m.p. 108·5—110·5°C. A sample was recrystallized for analysis from a mixture of benzene and light petroleum, m.p. 110—111·5°C. IR spectrum: 708, 743, 770, 835, 900 (5 and 2 adjacent and solitary Ar—H), 1174 and 1345 (NSO_2), 1590 cm^{-1} (Ar).

2-(4-Fluorophenylthio)-5-methoxyphenylacetonitrile (*IXb*)

A solution of 18·0 g *VIIIb* in 32 ml ethanol was added to a solution of 8·3 g KCN in 13 ml water and the mixture was refluxed for 7 h under stirring. After cooling, it was diluted with 250 ml water and extracted with ether. The ether solution was washed with water, dried with K_2CO_3 and evaporated. The residue was distilled: 15·5 g (89%), b.p. 170–175°C/1 Torr. NMR spectrum: δ 7·40 (d, J = 8·5 Hz, 1 H, 3-H of phenylacetonitrile), 6·60–7·10 (m, 7 H, remaining aromatic protons), 3·74 (s, 5 H, OCH_3 and CH_2CN).

2-(Phenylthio)-5-(methylthio)phenylacetonitrile (*IXc*) (Method *E*)

Crude *VIIIc* which was prepared by method *D* from 19·8 g *VIIc* was dissolved in 50 ml dimethylformamide, 5·5 g NaCN was added and the mixture was heated for 4 h on a boiling-water bath. Most of the solvent was then evaporated *in vacuo*, the residue was diluted with water and extracted with benzene. Washing, drying and distillation of the extract yielded 15·1 g (74%) product boiling at 180°C/0·3 Torr, m.p. 48–49°C (benzene–cyclohexane).

2-(Phenylthio)-5-(dimethylsulfamoyl)phenylacetonitrile (*IXd*)

Method *E* applied to 31·5 g *VIIId* yielded 35 g oily residue which was dissolved in hot ethanol, the solution was filtered with charcoal and the filtrate was evaporated. The residue (25·8 g) contains, according to thin-layer chromatography, at least 4 components. It was chromatographed on a column of 1 kg alumina. Elution with a mixture of benzene and chloroform yielded first 0·9 g starting *VIIId* (m.p. 108–111°C) and then 17·0 g (56%) product *IXd*, m.p. 105–106°C (ethanol). NMR spectrum: δ 7·74 (d, J = 2·0 Hz, 1 H, 6-H of phenylacetonitrile), 7·50 (q, J = 8·5; 2·0 Hz, 1 H, 4-H of phenylacetonitrile), 7·30 (s, 5 H, C_6H_5), 7·02 (d, J = 8·5 Hz, 1 H, 3-H of phenylacetonitrile), 3·80 (s, 2 H, CH_2CN), 2·62 (s, 6 H, CH_3—N—CH_3). On continuing the chromatography by elution with chloroform, 4·40 g oil *XIX* was obtained. The last fraction eluted from the column was alcohol *VIId* (2·20 g, m.p. 135·5–137°C).

2-(Phenylthio)-5-(methylthio)phenylacetic Acid (*Xc*) (Method *F*)

A solution of 15 g KOH in 30 ml water was added to a solution of 14·7 g *IXc* in 70 ml ethanol and the mixture was refluxed for 4 h. After evaporation of ethanol, the residue was diluted with water, the solution was filtered and the filtrate acidified with hydrochloric acid. The precipitated product was filtered and recrystallized from a mixture of benzene and light petroleum; 12·0 g (77%), m.p. 132–134°C. IR spectrum: 688, 738, 826, 862 (5 and 2 adjacent and solitary Ar—H), 946 (COOH), 1 237 (C—O), 1 545, 1 578 (Ar), 1 700 (COOH), 2 520, 2 620 and 2 720 cm^{-1} (COOH). NMR spectrum: δ 10·75 (bs, disappears after D_2O, 1 H, COOH), 6·90–7·40 (m, 3 H, 3,4,6-H_3 of phenylacetic acid), 7·07 (s, 5 H, C_6H_5), 3·73 (s, 2 H, $ArCH_2CO$), 2·38 (s, 3 H, SCH_3).

2-Methoxy-8-fluorodibenzo[*b,f*]thiepin-10(11*H*)-one (*XIb*) (Method *G*)

Toluene (50 ml) and acid *Xb* (15·0 g) were added to 150 g polyphosphoric acid. The mixture was stirred for 4 h and refluxed in a 150°C bath. After cooling, it was decomposed with ice-cold water and extracted with benzene. The extract was washed with water, 5% NaOH and water, dried with K_2CO_3 and evaporated; 12·0 g (86%), m.p. 152–156°C. Analytical sample melted at 167–169°C (benzene). UV spectrum: λ_{max} 343 nm (log ε 3·58), 252 nm (4·15), 229 nm (4·34). IR spectrum: 801, 811, 890 (2 adjacent and solitary Ar—H), 1 019, 1 249, 1 267 (Ar—O—CH_3),

1 570, 1 596 (Ar), 1 672 cm^{-1} (Ar—CO). NMR spectrum: δ 7·80 (q, J = 10·0; 3·0 Hz, 1 H, 9-H), 7·45 (d, J = 9·0 Hz, 1 H, 4-H), 7·00—7·50 (m, 2 H, 6,7-H_2), 6·89 (d, J = 3·0 Hz, 1 H, 1-H), 6·62 (q, J = 9·0; 3·0 Hz, 1 H, 3-H), 4·26 (s, 2 H, $ArCH_2CO$), 3·71 (s, 3 H, OCH_3).

2-Dimethylsulfamoyl-11-[2-(phenylthio)-5-(dimethylsulfamoyl)benzyl]dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XX*)

The oily product (4·4 g) obtained by elution with chloroform in the preparation of *IXd* was dissolved in 40 ml ethanol, 5·0 g KOH in 20 ml water was added and the mixture was refluxed for 6 h. After evaporation of ethanol, the residue was diluted with water, the liquid was washed with benzene, acidified with hydrochloric acid and the product was isolated by extraction with chloroform. After evaporation of the extract, the semisolid acid obtained was added to a mixture of polyphosphoric acid (40 g P_2O_5 and 20 ml 85% H_3PO_4) and 60 ml toluene and the mixture was refluxed under stirring for 5 h. After partial cooling, it was poured into water and extracted with benzene. The extract was washed with 10% NaOH and water, dried and evaporated. A total of 2·85 g product was obtained which was recrystallized for analysis from a mixture of benzene and ethanol, m.p. 218—220°C. IR spectrum: 690, 711, 737, 749, 756, 838, 897 (5, 4 and 2 adjacent and solitary Ar—H), 1157, 1337, 1345 (NSO_2), 1665 cm^{-1} (Ar—CO). Mass spectrum with a molecular ion of formula $C_{31}H_{30}N_2O_5S_4$ and the course of fragmentation agrees with the formulation of the compound as *XX*. For $C_{31}H_{30}N_2O_5S_4$ (638·9) calculated: 58·28% C, 4·73% H, 4·39% N, 20·08% S; found: 58·96% C, 4·95% H, 4·03% N, 19·54% S.

10-Oxo-11*H*-dibenzo[*b*,*f*]thiepin-2-carboxylic Acid (*XXI*)

Polyphosphoric acid was prepared in the usual way from 80 g P_2O_5 and 40 ml 85% H_3PO_4, 14·4 g acid *Xe* was added and the mixture was stirred for 1 h at 140—145°C. After pouring into water, a solid separated and was filtered and recrystallized from a mixture of benzene and ethanol; 9·8 g (79%), m.p. 280—283°C. UV spectrum: λ_{max} 236·5 nm (log ε 4·43), 266 nm (3·80), 289·5 nm (3·86), 325 nm (3·59). IR spectrum: 763, 815, 851 (Ar—H), 912 (COOH), 1290 (Ar—COOH), 1567, 1587 (Ar), 1675 (Ar—CO—R), 1696 (Ar—COOH), 2400—3200 cm^{-1} (COOH). NMR spectrum (C_5D_5N): δ 12·85 (bs, 1 H, COOH), 8·35 (d, J = 2·0 Hz, 1 H, 1-H), c. 8·25 (m, 1 H 9-H), 8·07 (q, J = 9·0; 2·0 Hz, 1 H, 3-H), 7·62 (d, J = 9·0 Hz, 1 H, 4-H), 7·00—7·50 (m, 3 H remaining aromatic protons), 4·29 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{10}O_3S$ (270·3) calculated 66·65% C, 3·73% H, 11·86% S; found: 66·52% C, 3·84% H, 11·63% S.

2-Trifluoromethyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIe*)

A. A mixture of polyphosphoric acid (from 80 g P_2O_5 and 40 ml 85% H_3PO_4), 200 ml toluene and 27 g acid *Xe* was processed by method *G*. 23·0 g starting *Xe* was recovered (m.p. 107—109°C) and only 2·83 g (11%; 75% referred to conversion) ketone *XIe* was obtained (m.p. 97—111°C). Analytical sample, m.p. 111·5—113·5°C (cyclohexane). UV spectrum: λ_{max} 237·5 nm (log ε 4·31), 255 nm (4·02), 278·5 nm (3·69), 325 nm (3·53). IR spectrum: 736, 756, 806, 828, 903 (4 and 2 adjacent and solitary Ar—H), 1106, 1178, 1337 (CF_3), 1594 (Ar), 1686 cm^{-1} (Ar—CO—R). NMR spectrum: 8·12 (m, 1 H, 9-H), 7·05—7·80 (m, 6 H, remaining aromatic protons), 4·34 (s, 2 H, $ArCH_2CO$). Patent application[34] described the cyclization with polyphosphoric acid at 110°C but does not report the yield; its m.p. is 103—104°C.

B. The same amount of polyphosphoric acid, 23·5 g acid *Xe* and 200 ml toluene were processed according to method *G* but the reaction period was extended to 16 h. Even under these conditions,

14·4 g *Xe* was regenerated (m.p. 105—107°C). A total of 9·2 g nonhomogeneous neutral product was obtained which was chromatographed on a column of 500 g alumina. On elution with a mixture of benzene and light petroleum, the first fraction to be eluted was 1·63 g of a semisolid substance; this was followed by 5·02 g (23%; 59% referred to conversion) ketone *XIe*, m.p. 112 to 113°C. Chloroform then eluted 0·35 g substance melting at 123—125°C (benzene–light petroleum) which was identified as 2-(*o*-toluoyl)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXIII*). UV spectrum: λ_{max} 240 nm (log ε 4·50), 301 nm (4·01). IR spectrum: 733 and 748 (two intense bands corresponding to 4 adjacent Ar—H), 793, 847, 859, 873 (2 adjacent and solitary Ar—H), 1 560, 1 591 (Ar), 1 665 (Ar_2CO), 1 676 cm^{-1} (Ar—CO—R). NMR spectrum: δ 8·12 (m, 1 H, 9-H), 7·00 to 7·90 (m, 10 H, remaining aromatic protons), 4·30 (s, 2 H, $ArCH_2CO$), 2·26 (s, 3 H, Ar—CH_3). For $C_{22}H_{16}O_2S$ (344·4) calculated: 76·73% C, 4·68% H, 9·30% S; found: 76·79% C, 4·83% H, 8·96% S.

In the following chloroform fractions 2·10 g substance was eluted which melted at 156—158°C (benzene–light petroleum) and was identified as 2-(*p*-toluoyl)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXII*). UV spectrum: λ_{max} 239·5 nm (log ε 4·48), inflexion 257·5 nm (4·35), 291·5 nm (4·11). IR spectrum: 755, 787, 834, 852, 863 (4 and 2 adjacent and solitary Ar—H), 1 590, 1 609 (Ar), 1 650 (Ar_2CO), 1 684 cm^{-1} (Ar—CO—R). NMR spectrum: δ 8·12 (m, 1 H, 9-H), 7·00—7·80 (m, 10 H, remaining aromatic protons), 4·31 (s, 2 H, $ArCH_2CO$), 2·38 (s, 3 H, Ar—CH_3). For $C_{22}H_{16}O_2S$ (344·4) calculated: 76·73% C, 4·68% H, 9·30% S; found: 77·13% C, 4·77% H, 9·07% S.

2-(Methylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIc*) (Method *H*)

A solution of 0·42 g $NaBH_4$ in 2 ml water with a drop of 20% NaOH was added dropwise over 5 min to a solution of 3·0 g *XIc* in a mixture of 40 ml ethanol and 30 ml dioxane. The mixture was refluxed under stirring for 3 h. After evaporation, the residue was diluted with 3% hydrochloric acid and extracted with chloroform. The residue obtained by processing the extract was recrystallized from a mixture of benzene and light petroleum; 2·62 g (87%), m.p. 122—124°C. IR spectrum: 758, 813, 873 (4 and 2 adjacent and solitary Ar—H), 1 000 (CHOH in the ring), 1 557, 1 582 (Ar), 3 360 cm^{-1} (OH).

2-Methoxy-10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIIIa*) (Method *J*)

Powdery $CaCl_2$ (5 g) was added to a solution of 8·7 g *XIIa* in 100 ml benzene and the suspension was saturated for 2 h under stirring with anhydrous hydrogen chloride. After standing overnight, it was filtered and the filtrate evaporated. Recrystallization of the residue from cyclohexane yielded 9·15 g (98%) product melting at 113—114°C.

2-(Methylthio)-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (*V*)

1-Methylpiperazine (15 ml) was added to a solution of 5·0 g *XIc* in 80 ml benzene and then, over a period of 5 min, a solution of 3·0 g $TiCl_4$ in 20 ml benzene was added dropwise. The mixture was refluxed for 24 h, cooled, decomposed with water, the precipitate was filtered and washed with benzene. The benzene layer of the filtrate was separated, washed with water, dried and evaporated. The residue was recrystallized from ethanol; 5·61 g (86%), m.p. 146—147°C. UV spectrum: λ_{max} 271·5 nm (log ε 4·40) infl. 315 nm (3·90). IR spectrum: 767, 782, 817 (Ar—H and CH=C), 1 545, 1 575 (Ar), 1 621 (C=C), 2 710 and 2 760 cm^{-1} (N—CH_2). NMR spectrum: δ 6·80—7·70 (m, 7 H, aromatic protons), 6·20 (s, 1 H, $ArCH{=}C$), 2·92 (t, 4 H, $CH_2N^1CH_2$), 2·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·35 (s, 3 H, SCH_3), 2·28 (s, 3 H, NCH_3). Neutralization of the base with methanesulfonic acid in a mixture of ethanol and ether yields methanesulfonate, melting at 269—271°C (ethanol).

2-(Methylthio)-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IIIc*)

Sodium borohydride (1·02 g) was added to a solution of 3·43 g enamine *V* in 50 ml tetrahydrofuran, the mixture was cooled to 5°C and, over a period of 40 min, 3·6 ml acetic acid in 10 ml tetrahydrofuran was added dropwise. The mixture was stirred for 2 h at room temperature, then further 3·6 ml acetic acid was added dropwise, the mixture was refluxed for 1 h and left to stand overnight at room temperature. Excess 10% NaOH was then added and the product was extracted with benzene. The extract was shaken several times with excess 10% hydrochloric acid. Evaporation of the benzene phase yielded a relatively high amount of ketone *XIc* (m.p. 128·5 to 129·5°C). The acid aqueous solution was made alkaline with 10% NaOH and base *IIIc* was extracted with benzene; m.p. 102—103°C (ethanol). IR spectrum: 765, 816, 894 (4 and 2 adjacent and solitary Ar—H), 1565, 1590 cm^{-1} (Ar). NMR spectrum: δ 6·75—7·70 (m, 7 H, aromatic protons), 2·90—4·00 (m, 3 H, Ar—CH_2CH—Ar), 2·58 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·40 (s, 3 H, SCH_3), 2·23 (s, 3 H, NCH_3). Neutralization of the base with maleic acid in a mixture of ethanol and ether yielded the di(hydrogenmaleate), m.p. 126—128°C (ethanol–ether).

2-Methoxy-8-fluoro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IVb*) (Method *K*)

A mixture of 4·0 g *XIIIb*, 6 ml chloroform and 5·4 g 1-(2-hydroxyethyl)piperazine was refluxed under stirring for 6 h. After evaporation of chloroform, the residue was combined with 30 ml 5% NaOH and the mixture was extracted with benzene. The extract was washed with water and 2·5N-H_2SO_4. The acid solution was separated, made alkaline with NH_4OH and extracted with benzene; 3·5 g (66%), m.p. 102—103°C (cyclohexane). NMR spectrum: δ 6·40—7·50 (m, 6 H, aromatic protons), 2·80—4·00 (m, 3 H, $ArCH_2CHAr$), 3·70 (s, 3 H, OCH_3), 3·54 (t, J = 6·0 Hz, 2 H, CH_2O), 2·91 (s, disappears after D_2O, 1 H, OH), 2·55 (m, 10 H, 5 NCH_2). The maleate crystallizes from a mixture of ethanol and ether as hemihydrate, m.p. 142—143°C.

The benzene solution after removing the basic fraction by shaking with the acid was washed with water, dried and evaporated. A small amount of 2-fluoro-8-methoxydibenzo[*b,f*]thiepin (*XXIVb*) was obtained, m.p. 81—83°C (light petroleum). NMR spectrum: δ 6·80—7·50 (m, 6 H, aromatic protons), 6·90 (s, 2 H, CH=CH), 3·70 (s, 3 H, OCH_3).

The authors are indebted to Dr M. Ryska, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, for recording and interpretation of the mass spectrum of XX, *to Mrs E. Princová for skilled technical assistance with the synthesis of the compounds, and to Mrs J. Komancová, Mr M. Čech, Mrs A. Slavíková, Miss Z. Volková, Miss J. Hrdá and Mr K. Havel (Analytical department of this Institute) for carrying out the analyses.*

REFERENCES

1. Schmutz J., Hunziker F., Stille G., Lauener H.: Chim. Therap. *2*, 424 (1967).
2. Hunziker F., Fischer E., Schmutz J.: Helv. Chim. Acta *50*, 1588 (1967).
3. Hoffmann I., Ruschig H.: *Arzneimittel; Entwicklung, Wirkung, Darstellung*, Vol. I. *Therapeutica mit Wirkung auf das Zentrale Nervensystem* (G. Ehrhart, H. Ruschig, Eds), p. 219. Verlag Chemie, Weinheim 1972.
4. Gross H., Langner E.: Wien. Med. Wochschr. *116*, 814 (1966).
5. Berzewski H., Helmchen H., Hippius H., Hoffmann H., Kanowski S.: Arzneimittel-Forsch. *19*, 495 (1969).

6. Angst J., Jaenicke U., Padrutt A., Scharfetter C.: Pharmakopsychiat. Neuro-Psychopharmakol. *4*, 192 (1971).
7. Deisenhammer E., Allahyari H., Ringswald E., Schöny W., Steiner H.: Wien. Med. Wochschr. *122*, 732 (1972).
8. Gebhardt R.: Pharmakopsychiat. Neuro-Psychopharmakol. *5*, 295 (1972).
9. Rodová A., Švestka J., Náhunek K., Češková E.: Activitas Nervosa Super. *15*, 94 (1973).
10. Stille G., Hippius H.: Pharmakopsychiat. Neuro-Psychopharmakol. *4*, 182 (1971).
11. Stille G., Lauener H.: Arzneimittel-Forsch. *21*, 252 (1971).
12. Bartholini G., Haefely W., Jalfre M., Keller H. H., Pletscher A.: Brit. J. Pharmacol. *46*, 736 (1972).
13. Andén N.-E., Stock G.: J. Pharmacol. *25*, 346 (1973).
14. Bürki H. R., Ruch W., Asper H., Baggiolini M., Stille G.: Schweiz. Med. Wochschr. *103*, 1716 (1973).
15. Stadler H., Lloyd K. G. Bartholini G.: Naunyn-Schmiedeberg's Arch. Exptl. Pathol. Pharmacol. *283*, 129 (1974).
16. Stavarz R. J., Robinson S., Sulser F., Dingell J. V.: Federation Proc. *33* (3—I), 246, Abstr. No. 244 (1974).
17. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
18. Metyš J., Metyšová J., Votava Z., Benešová O., Dlabač A., Kazdová E., Franc Z., Queisnerová M., Kraus P., Vaněček M., Hradil F., Jílek J. O., Protiva M.: Farmakoterap. Zprávy *17*, 131 (1971).
19. Protiva M., Jílek J. O., Metyšová J., Seidlová V., Jirkovský I., Metyš J., Adlerová E., Ernest I., Pelz K., Pomykáček J.: Farmaco (Pavia) Ed. Sci. *20*, 721 (1965).
20. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1852 (1968).
21. Pelz K., Jirkovský I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1985 (1968).
22. Pelz K., Jirkovský I., Metyšová J., Protiva M.: This Journal *34*, 3936 (1969).
23. Šindelář K., Metyšová J., Protiva M.: This Journal *38*, 2137 (1973).
24. Muren J. F., Bloom B. M.: J. Med. Chem. *13*, 17 (1970).
25. Künzle F., Schmutz J.: Helv. Chim. Acta *52*, 622 (1969).
26. Bachman G. B., Picha G. M.: J. Am. Chem. Soc. *68*, 1599 (1946).
27. Tarrant P., Lilyquist M. R.: J. Am. Chem. Soc. *75*, 3034 (1953).
28. Lafferty J. J., Tedeschi D. H., Zirkle Ch. L. (Smith Kline & French Laboratories): U.S. 3,133.081 (Appl. 30. XI. 1961); Chem. Abstr. *61*, 4364 (1964).
29. Inukai K., Maki Y.: Kogyo Kagaku Zasshi *68*, 315 (1965); Chem. Abstr. *63*, 2913 (1965).
30. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *39*, 3338 (1974).
31. Šindelář K., Metyšová J., Protiva M.: This Journal *37*, 1734 (1972).
32. Šindelář K., Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *39*, 3548 (1974).
33. J. R. Geigy A.-G.: Neth. Appl. 64/4.862 (Swiss Appl. 4. V. 1963); Chem. Abstr. *62*, 16 215 (1965).
34. Gerecke M., Kaplan J.-P., Kyburz E. (F. Hoffmann-La Roche & Co. AG.): Ger. Offen. 2,336.130 (31. I. 1974); Chem. Abstr. *80*, 108 576 (1974).
35. Jílek J. O., Šindelář K., Metyšová J., Metyš J., Pomykáček J., Protiva M.: This Journal *35*, 3721 (1970).
36. Bártl V., Metyšová J., Metyš J., Němec J., Protiva M.: This Journal *38*, 2301 (1973).
37. Stille G., Lauener H., Eichenberger E.: Farmaco (Pavia), Ed. Prat. *26*, 603 (1971).

Translated by A. Kotyk.