NEUROTROPIC AND PSYCHOTROPIC AGENTS. LVI.*

SULFOXIDES, N-OXIDES AND SULFONES DERIVED FROM NEUROLEPTIC 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*]THIEPINS

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Received May 4th, 1972

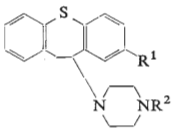
Oxidation of aqueous solutions of methanesulfonates of 10-piperazino-10,11-dihydrodibenzo-[*b,f*]thiepin derivatives *I*—*III*, *V* and *VII* with excess hydrogen peroxide at room temperature yielded the corresponding sulfoxides (*X*, *XI*) or disulfoxides (*XII*, *XIV*, *XV*). Oxidation of the aminosulfides *I*—*III*, *VI* and *VII* and further of aminosulfoxides *X*—*XII* with a slight excess of hydrogen peroxide in 95% ethanol at room temperature results selectively in N-oxides *XVI*—*XXIII*. The sulfone *XXVII* was obtained by oxidation of 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin to *XXVI* and by its substitution reaction with 1-methylpiperazine; this was oxidized further to the N-oxide *XXVIII*. The disulfides *III* and *VII* are selectively oxidized at the methylthio group in position 8 to the monosulfoxides *VIII* and *IX* with the aid of an acid solution of potassium bromide and bromate. The sulfoxides and N-oxides prepared here are mostly potential metabolites of the neuroleptics perathiepin (*I*), octoclothepin (*II*), methiothepin (*III*) and oxyprothepin (*VII*); compounds *X*, *XI*, *XIII* and *XVII* were shown to be metabolites. From the pharmacodynamic point of view, all the S- and N-oxidations result in a decrease of central depressant as well as of cataleptic activity.

In connection with the systematic studies of neuroleptic 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins we were interested in the products of their S- and N-oxidation as potential neuroleptics or tranquilizers, as well as potential metabolites of the parent compounds.

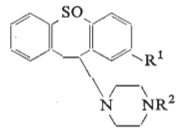
Firstly, we took up the oxidation of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin ("perathiepin")[1] (*I*) and its 8-chloro derivative ("octoclothepin")[2] (*II*) by hydrogen peroxide in acetic acid. It was found that when using an equivalent amount of the oxidizing agent at room temperature oxidation does not take place while when using excess reagent at higher temperature the piperazine residue is split off and the tricyclic fragment is oxidized to dibenzo[*b,f*]thiepin-5,5-dioxide[1]. The oxidation of sulfides *I* and *II* to the sulfoxides *X* and *XI* was then solved by using sodium periodate as the oxidizing agent[1-3]; analogously, it was possible to oxidize the 8-nitro derivative of *I* (ref.[3,4]). In parallel with the present work, the oxidation of sulfide *I* was studied by Fouche[5-7] who succeeded in oxidizing it with excess hydrogen peroxide in acetic acid at room temperature, obtaining a low yield of sulfoxide *X*. The sulfoxide *X* was identified as one of the metabolites of perathiepin (*I*) in human urine[8,9]. Similarly, sulfoxide *XI* was identified in the

* Part LV: This Journal *38*, 115 (1973).

urine as one of the metabolites of octoclothepin[8,10] (*II*), just as in rat urine after administration of ^{35}S-octoclothepin[11].



I, $R^1 = H$, $R^2 = CH_3$
II, $R^1 = Cl$, $R^2 = CH_3$
III, $R^1 = SCH_3$, $R^2 = CH_3$
IV, $R^1 = Cl$, $R^2 = H$
V, $R^1 = SCH_3$, $R^2 = H$
VI, $R^1 = Cl$, $R^2 = (CH_2)_3OH$
VII, $R^1 = SCH_3$, $R^2 = (CH_2)_3OH$
VIII, $R^1 = SOCH_3$, $R^2 = CH_3$
IX, $R^1 = SOCH_3$, $R^2 = (CH_2)_3OH$



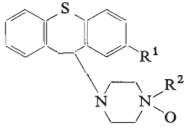
X, $R^1 = H$, $R^2 = CH_3$
XI, $R^1 = Cl$, $R^2 = CH_3$
XII, $R^1 = SOCH_3$, $R^2 = CH_3$
XIII, $R^1 = Cl$, $R^2 = H$
XIV, $R^1 = SOCH_3$, $R^2 = H$
XV, $R^1 = SOCH_3$, $R^2 = (CH_2)_3OH$

Now the oxidation reactions in this group of compounds were studied in greater detail[12,13] and it was possible to solve the preparation of practically all the combinations of products oxidized at the atoms of sulfur and/or nitrogen. It was found at first that for the preparation of sulfoxides from the corresponding sulfides the method of choice is the oxidation of aqueous solutions of salts of the corresponding aminosulfides with excess hydrogen peroxide at room temperature ("method A"). Most suitable for this purpose are the methanesulfonates[14] which are readily water-soluble. In this way, the first to be prepared were again sulfoxides *X* and *XI*, using oxidation of sulfides *I* and *II*. The 8-methylthio derivative ("methiothepin"[15]) (*III*) is oxidized under the given conditions at both sulfide functions and yields the disulfoxide *XII*. Oxidation of the sulfidic functions to sulfoxides gives rise to new centres of asymmetry in the molecules so that probably mixtures of stereo-isomers are formed. We did not attempt to separate these mixtures or to identify the configuration of the products, some of which being probably not fully homogeneous.

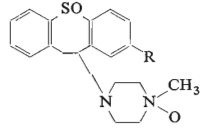
The secondary amine *IV* ("noroctoclothepin")[16] which itself is a metabolite of octoclothepin[10,11] was oxidized to the sulfoxide *XIII* with sodium periodate in aqueous methanol. The sample obtained made it possible to identify another metabolite of octoclothepin (*II*) in the urine of patients after administration of this drug[10]. The secondary amine[16] *V* corresponding to methiothepin (*III*) was oxidized by method A to the disulfoxide *XIV*. The disulfoxides *XII* and *XIV* can be considered as potential metabolites of methiothepin (*III*). Method A was also used for the oxidation of the N-(3-hydroxypropyl) derivative *VII* ("oxyprothepin")[16–21]; the disulfoxide *XV* formed is a potential metabolite of oxyprothepin.

For the transformation of bases *I*–*III* to the N-oxides *XVI*–*XVIII* the selective method was found to be oxidation with a slight excess of hydrogen peroxide in 95%

ethanol at room temperature ("method B") (for the technique see[22,23]; for the localization of the oxygen atom at the terminal nitrogen see the analogy in[22,24]). The IR spectra of the highly polar products which crystallize almost always as hydrates, exhibit a N-oxide band at 960–973 cm^{-1} while the sulfoxide band is missing. All the three N-oxides (*XVI–XVIII*) are potential metabolites of neuroleptic agents *I–III*; in the case of octoclothepin N-oxide (*XVII*) it was actually demonstrated that it is a metabolite in humans after application of octoclothepin[10] (*II*). These N-oxides are apparently the intermediate products of metabolic N-demethylation of the starting bases[8–11] *I–III*. Method B was further used for the transformation of N-(3-hydroxypropyl) bases[16] *VI* and *VII* to the N-oxides *XIX* and *XX* and finally for the N-oxidation of sulfoxides *X–XII* to the N,S-dioxides *XXI* and *XXII*, or to the N,S,S'-trioxide *XXIII*. These oxides are also potential metabolites of the principal aminosulfides *I–III* and *VI–VII* but have not been demonstrated as such so far. Compounds which are simultaneously N-oxides and sulfoxides (*e.g. XXII*) possess in their IR spectrum a N-oxide band (973 cm^{-1}) plus a sulfoxide one (1022 cm^{-1}). With increasing number of the oxygen functions, the polarity of the products increases, the compounds being soluble in water even in the form of bases; their crystallization is more difficult (this is caused by the nonhomogeneity of the products due to increasing numbers of centres of asymmetry) and solvatation of the products is a common phenomenon.



XVI, $R^1 = H$, $R^2 = CH_3$
XVII, $R^1 = Cl$, $R^2 = CH_3$
XVIII, $R^1 = SCH_3$, $R^2 = CH_3$
XIX, $R^1 = Cl$, $R^2 = (CH_2)_3OH$
XX, $R^1 = SCH_3$, $R^2 = (CH_2)_3OH$

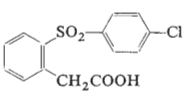


XXI, R = H
XXII, R = Cl
XXIII, R = $SOCH_3$

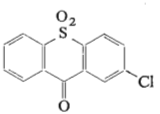
The preparation of the monosulfoxides *VIII* and *IX* was facilitated by the observation that, whereas octoclothepin (*II*) does not react with an acid solution of potassium bromate and bromide, oxyprothepin (*VII*) is oxidized by this agent. This could be used for developing a potentiometric titration method of estimating the base *VII*. This observation showed the great difference between the reactivity of the sulfur atoms in the diphenylsulfide fragment and in the methylphenylsulfide residue. Bromate-bromide oxidation ("method C") was then used for the preparation of *VIII* and *IX* from sulfides *III* and *VII*. Similarly, when an equivalent of periodic acid was used ("method D") the oxidation of the methanesulfonates of bases *III* and *VII* in aque-

ous solution proceeded selectively at the methylthio group, giving rise to the monosulfoxides *VIII* and *IX*.

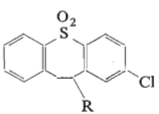
As mentioned above, the oxidation of aminosulfide *I* with excess hydrogen peroxide in boiling acetic acid does not result in the corresponding sulfone but rather in a destruction of the molecule by splitting off the methylpiperazine residue[1]. A similarly conducted oxidation of 11*H*-dibenzo[*b*,*f*]thiepin-10-one does not stop at the 11*H*-dibenzo[*b*,*f*]thiepin-10-one 5,5-dioxide which would be a usable intermediate but leads directly to dibenzo[*b*,*f*]thiepin-10,11-dione 5,5-dioxide[1,25]. Mirwald[25] attempted without success to prepare this monoketosulfone by cyclization of 2-(benzenesulfonyl)phenylacetic acid. Oxidation of 2-(4-chlorophenylthio)phenylacetic acid[2] with excess hydrogen peroxide in warm acetic acid gave 2-(4-chlorobenzenesulfonyl)-phenylacetic acid (*XXIV*) which was subjected to treatment with polyphosphoric acid but the attempt to cyclize it to the unknown 8-chloro-11*H*-dibenzo[*b*,*f*]thiepin-10-one 5,5-dioxide was also unsuccessful; a minute yield of the neutral lower homologue of the desired compound was detected (2-chlorothioxanthone 10,10-dioxide[26,27]; *XXV*). Its origin might consist in 2-(4-chlorobenzenesulfonyl)phenylglyoxylic acid, which would not be unexpected to arise during oxidation of 2-(4-chlorophenylthio)phenylacetic acid. The path to the desired octoclothepin 5,5-dioxide (*XXVII*) was opened only when it became possible to oxidize 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[2] with hydrogen peroxide in hot acetic acid to the sulfone *XXVI*. The subsequent substitution reaction with 1-methylpiperazine led then smoothly to the desired aminosulfone *XXVII*. Preparation of the analogous 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin 5,5-dioxide had been solved in the meantime[6,28,29]: 10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin was oxidized with 4-nitroperbenzoic acid to the corresponding chlorosulfone which was processed by a substitution reaction with 1-methylpiperazine. Our aminosulfone was then transformed by method B to the corresponding sulfone N-oxide *XXVIII*.



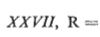
XXIV



XXV



XXVI, R = Cl

XXVII, R = 

XXVIII, R = 

All the piperazine derivatives prepared (*VIII*—*XXIII*, *XXVII*, *XXVIII*) are shown with the usual experimental data in Table I. In the experimental section we show only examples of methods A—D and the compounds that were prepared by other methods. The important bands

TABLE I

Piperazine Derivatives *VIII*—*XXIII*, *XXVII* and *XXVIII*

Compound[a] (method)	M.p., °C (solvent)	Formula (m.w.)	Calculated/Found				
			% C	% H	% N	% Cl	% S
VIII-M	152—153[b]	$C_{24}H_{28}N_2O_5S_2$	58·99	5·78	5·73	—	13·12
(*C*)	(acetone–ether)	(488·6)	58·98	5·96	5·64	—	12·90
VIII-M	167—170[b]	$C_{24}H_{28}N_2O_5S_2$	58·99	5·78	5·73	—	13·12
(*D*)	(ethanol–acetone –ether)	(488·6)	59·08	5·94	5·69	—	12·91
IX-2 HCl—H_2O	184—187[b]	$C_{22}H_{34}Cl_2N_2O_3S_2$	52·06	6·35	5·52	13·97	12·63
(*C*)	(aqueous ethanol)	(507·5)	51·48	6·14	5·42	13·63	12·62
IX-2 HCl—2 H_2O	150·5—153	$C_{22}H_{34}Cl_2N_2O_4S_2$	50·28	6·52	5·33	13·49	12·20
(*C*)	(chloroform)	(525·6)	50·57	6·61	5·31	13·28	12·07
IX-2 HCl—H_2O	180—185[b]	$C_{22}H_{32}Cl_2N_2O_3S_2$	52·06	6·35	5·52	13·97	12·63
(*D*)	(aqueous ethanol)	(507·5)	51·75	6·32	5·08	14·25	12·63
X[c]	166—168	$C_{19}H_{22}N_2OS$	69·92	6·79	8·58	—	9·82
(*A*)	(acetone)	(326·4)	69·73	6·63	8·48	—	9·86
XI[d]	172—174	$C_{19}H_{21}ClN_2OS$	63·23	5·87	7·76	9·82	8·88
(*A*)	(acetone)	(360·9)	63·05	5·91	7·55	10·00	8·84
XI-M	199—201	$C_{23}H_{25}ClN_2O_5S$	57·91	5·28	5·87	7·43	6·72
	(ethanol–ether)	(477·0)	57·99	5·51	5·94	7·45	6·82
XII[e]	195—197	$C_{20}H_{24}N_2O_2S_2$	61·84	6·23	7·21	—	16·48
(*A*)	(acetone)	(388·4)	61·78	6·31	6·69	—	16·23
XII-M	205—206	$C_{24}H_{28}N_2O_6S_2$	57·14	5·59	5·55	—	12·70
	(aqueous ethanol)	(504·5)	57·01	5·65	5·37	—	12·50
XIII-M[f]	175—176	$C_{22}H_{23}ClN_2O_5S$	57·07	5·00	6·05	7·66	6·93
	(ethanol)	(462·9)	56·98	5·16	6·02	7·83	6·78
XIV[g]	201—204	$C_{19}H_{22}N_2O_2S_2$	60·95	5·92	7·48	—	17·10
(*A*)	(ethanol)	(374·4)	60·57	5·89	6·94	—	17·00
XIV-M	170—172	$C_{23}H_{26}N_2O_6S_2$	56·32	5·34	5·71	—	13·05
	(ethanol–ether)	(490·5)	56·00	5·53	5·42	—	12·99
XV-H_2O	80—85[h]	$C_{22}H_{30}N_2O_4S_2$	58·64	6·71	6·22	—	15·23
(*A*)	(chloroform)	(450·6)	58·36	6·30	5·16	—	14·62
XVI-2 H_2O[i]	110—112	$C_{19}H_{26}N_2O_3S$	62·96	7·23	7·73	—	8·84
(*B*)	(benzene)	(362·5)	63·00	7·24	7·46	—	9·05
XVI-2 HCl—0·5 H_2O	178—182	$C_{19}H_{25}Cl_2N_2O_{1·5}S$	55·88	6·17	6·86	17·36	7·85
	(ethanol–ether)	(408·4)	56·47	6·19	7·22	17·32	8·14
XVII-H_2O[f]	129—131	$C_{19}H_{23}ClN_2O_2S$	60·22	6·12	7·39	9·35	8·46
(*B*)	(benzene)	(378·9)	60·24	6·26	7·10	9·03	8·25
XVII-HCl	198—200	$C_{19}H_{22}Cl_2N_2OS$	57·43	5·58	7·05	17·85	8·07
	(ethanol)	(397·4)	57·59	5·75	7·04	17·94	8·33

TABLE I
(*Continued*)

Compound[a] (method)	M.p., °C (solvent)	Formula (m.w.)	Calculated/Found				
			% C	% H	% N	% Cl	% S
XVIII-2 HCl—H_2O	176—178	$C_{20}H_{28}Cl_2N_2O_2S_2$	51·83	6·09	6·04	15·30	13·83
(*B*)	(ethanol)	(463·5)	52·59	6·09	5·79	15·46	13·72
XIX-H_2O[j]	156—159	$C_{21}H_{27}ClN_2O_3S$	59·63	6·44	6·62	8·38	7·58
(*B*)	(benzene)	(423·0)	59·68	6·39	6·70	8·19	7·51
XIX-2 HCl—0·5 H_2O	155—158	$C_{21}H_{28}Cl_3N_2O_{2\cdot5}S$	51·80	5·80	5·75	21·85	6·58
	(ethanol)	(486·9)	51·96	5·83	5·39	21·36	6·86
XX-2 HCl—H_2O[k]	152—154	$C_{22}H_{32}Cl_2N_2O_3S_2$	52·06	6·35	5·52	13·97	12·63
(*B*)	(ethanol)	(507·5)	51·47	6·28	5·26	13·62	12·56
XXI-2 HCl—H_2O	185—188	$C_{19}H_{26}Cl_2N_2O_3S$	52·65	6·04	6·46	16·36	7·40
(*B*)	(acetone)	(433·4)	52·79	5·78	6·36	16·09	7·32
XXII-1·5 H_2O[m]	150—153	$C_{19}H_{24}ClN_2O_{3\cdot5}S$	56·50	5·99	6·93	8·78	7·94
(*B*)	(acetone)	(403·9)	56·78	6·13	6·46	8·45	7·80
XXII-2 HCl	203—207	$C_{19}H_{23}Cl_3N_2O_2S$	50·73	5·15	6·22	23·65	7·13
	(ethanol–ether)	(449·8)	50·79	5·32	6·08	23·26	7·38
XXIII-HCl—H_2O	238—243	$C_{20}H_{27}ClN_2O_4S_2$	52·33	5·93	6·10	7·72	13·97
(*B*)	(aqueous ethanol)	(459·0)	52·69	5·64	6·03	7·36	13·97
XXVII[f]	168—169	$C_{19}H_{21}ClN_2O_2S$	60·54	5·61	7·43	9·41	8·51
	(ethanol)	(376·9)	60·25	5·71	7·36	9·39	8·53
XXVII-M	198—200	$C_{23}H_{25}ClN_2O_6S$	56·04	5·11	5·68	7·19	6·50
	(aqueous ethanol)	(493·0)	55·99	5·19	5·62	7·27	6·69
XXVIII-H_2O[n]	203—206	$C_{19}H_{23}ClN_2O_4S$	55·53	5·64	6·82	8·63	7·80
(*B*)	(water)	(410·9)	55·64	5·67	6·50	8·48	7·86
XXVIII-2 HCl	180—188	$C_{19}H_{23}Cl_3N_2O_3S$	48·99	4·97	6·01		6·88
	(ethanol–ether)	(465·8)	48·88	5·19	5·50		6·98

[a] M maleate. [b] The difference in the melting points of products obtained by different methods may be accounted for by the somewhat different composition of the stereoisomeric mixtures formed. Using the amorphous base *VIII*, liberated from the maleate in the usual way, the NMR spectrum was measured: δ 8·10 (mcs, 1 H in position 9 of the aromatic ring), 7·00—7·80 (m, 6 H, the remaining aromatic protons), 3·00—4·10 (m, 3 H in $ArCH_2CHAr$), 2·65 (s, 3 H in $SOCH_3$), 2·26 (s, 3 H in $N—CH_3$), 2·20—3·00 (m, 8 H, CH_2 groups of piperazine), [c] Yield 95%. NMR spectrum: δ 7·85 (m, 2 H in *o*-positions to SO), 7·10—7·70 (m, 6 H, other aromatic protons), 4·26 (dd. 1 H, J = 9·0 and 5·0 Hz, CH—N), 2·90—380· (m, 2 H in $ArCH_2$), 2·55 (m, 8 H of piperazine), 2·30 (s, 3 H in $N—CH_3$). Ref.[5–7] report for the base prepared by a different procedure, a m.p. of 161°C. In earlier work[1,3] periodate was used for oxidation and the product was characterized in the form of crystalline maleate. [d] Yield 64%. [e] NMR spectrum: δ 8·20 (m, 1 H in position 4 of the aromatic ring), 8·00 (d, J = 8·0 Hz, 1 H in position 6 of the aromatic ring), 7·50 to 7·88 (m, 2 H in positions 7 and 9 of the aromatic ring), 7·27 (m, 3 H in positions 1, 2 and 3 of the aromatic ring), 4·30 (dd, J = 9·0 and 5·0 Hz, 1 H in CH—N), 2·90—3·85 (m, 2 H in $ArCH_2$),

of the IR spectra of most of the piperazine derivatives prepared here are shown in Table II. Most of the compounds prepared were tested as salts by using two basic pharmacological tests applied for an orientation evaluation of potential neuroleptics. The results are summarized in Table III, the numerical values referring to the corresponding base. The table shows the administration way, values of acute toxicity (LD_{50}) for mice, the mean effective dose (ED_{50}) in the

TABLE II

IR Spectra of Piperazine Derivatives (Nujol), cm^{-1}

Compound	ν(SO)	Compound	ν(NO)	H_2O
VIII-M[a]	1 060	*XVI*-2 H_2O	970	1 695, 3 360
IX	1 065	*XVII*-H_2O	973	1 675, 3 400
X	1 030, 1 080	*XIX*-H_2O	963	1 685, 3 290
XI	1 033	*XX*-2 HCl—H_2O	960	3 360
XII	1 030, 1 048	*XXII*-1·5 H_2O[b]	973	1 682, 3 490
XIII	1 033, 1 072	*XXVIII*-H_2O[d]	972	1 675, 3 480
XIV	1 030, 1 086			
XV-H_2O[c]	1 030, 1 040			

[a] Maleate. [b] ν(SO) 1 022 cm^{-1}. [c] H_2O 1 655 cm^{-1}. [d] $\nu(SO_2)$ 1 162, 1 302 cm^{-1}.

2·68 (s, 3 H in $SOCH_3$), about 2·55 (m, 8 H of CH_2 groups of piperazine), 2·28 (s, 3 H in N—CH_3). [f] See the experimental. [g] NMR spectrum: δ 8·22 (mcs, 1 H in position 9 of the aromatic ring), 7·5—8·5 (m, 2 H in positions 4 and 6 of the aromatic ring), 7·0—7·5 (m, 4 H, other aromatic protons), 4·25 (m, 1 H in CH—N), 3·37 (m, 2 H in $ArCH_2$), 2·90 (m, 4 H, CH_2 groups of piperazine adjacent to NH), about 2·60 (m, 4 H, the remaining two CH_2 groups of piperazine), 2·66 (s, 3 H in $SOCH_3$), 1·84 (bs, 1 H in NH). [h] The product is a residue after evaporation which could not be made to crystallize. [i] Yield 63%. UV spectrum: λ_{max} 229 nm (log ε 4·08), 258 nm (3·90), 264 nm (3·87). NMR spectrum (hexadeuteriodimethyl sulfoxide, 6%): δ 6·90—7·90 (m, 8 H, aromatic protons), 4·0 (deformed triplet, 1 H in CH—N), 2·55—4·0 (m, CH_2 groups of piperazine and $ArCH_2$), 3·03 (s, 3 H in N—CH_3). [j] Yield 67%. UV spectrum: λ_{max} 234 nm (log ε 4·20). NMR spectrum (hexadeuteriodimethyl sulfoxide, 6%): δ 6·95—7·80 (m, 7 H, aromatic protons), 3·92 (bs, 1 H in CH—N), 2·55—3·80 (m, CH_2 groups of piperazine, of the side chain and $ArCH_2$), 3·46 (s, 1 H in OH, disappears after deuterization). [k] UV spectrum: λ_{max} 277 nm (log ε 4·04). [m] Yield 75%. UV spectrum: λ_{max} 258 nm (log ε 3·95), 265 nm (3·97). NMR spectrum (hexadeuteriodimethyl sulfoxide, 6%): δ 7·25—7·9 (m, 7 H, aromatic protons), about 4·30 (t, 1 H in CH—N), 2·60—3·80 (m, CH_2 groups of piperazine and $ArCH_2$), 3·08 (s, 3 H in N—CH_3). [n] Yield 68%. UV spectrum: λ_{max} 242 nm (log ε 4·22). NMR spectrum (hexadeuteriodimethyl sulfoxide): δ 7·7—8·05 (m, 3 H, aromatic protons in positions 6, 7 and 9), 7·4—7·64 (m, 4 H, remaining aromatic protons), 4·24 (deformed triplet, 1 H in CH—N), 3·53 (s, disappears on deuterization, H_2O), 2·97 (s, 3 H in N—CH_3), 2·60—3·40 (m, 10 H of the CH_2 groups of piperazine and $ArCH_2$).

rotating-rod test in mice (disturbance of motor coordination) and finally the mean effective doses (ED_{50}) in the catalepsy test in rats. The table includes for the sake of comparison all the parent compounds *I*— *VII*, from which products of S- and N-oxidation were prepared.

TABLE III

Pharmacological Properties of Derivatives of 10-Piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin

Compound	Application	Acute toxicity LD_{50} mg/kg	Rotating rod ED_{50} mg/kg	Catalepsy[a] ED_{50} mg/kg
I	*i.v.*	42·3	0·187	10
II	*i.v.*	46·3	0·06	2·4
III	*i.v.*	51	0·094	2·0
IV	*p.o.*	120	5·6	30·0
V	*p.o.*	68	>10	>25
VI	*i.v.*	49	0·18	1·0
VII	*i.v.*	44	0·11	0·62
VIII	*i.v.*	10·2	0·41	4·2
IX	*i.v.*	10·0	2·0	6·5
X	*i.v.*	17·5	1·8	>10
XI	*i.v.*	10	0·36	4·8
XII	*i.v.*	64	4·8	>10
XIII	*p.o.*	115	50	>50
XIV	*i.v.*	27·5	>10	>10
XVI	*i.v.*	35·3	2·4	>10
XVII	*i.v.*	72	2·5	5·5
XVIII	*i.v.*	60	0·74	3·3
XIX	*i.v.*	80	2·1	2·0
XX	*i.v.*	36	2·2	8·8
XXI	*i.v.*		50	>10
XXII	*i.v.*	185	11	>10
XXIII	*i.v.*	185	6·2	>10
XXVII	*i.v.*	10·5	2·2	16
XXVIII	*i.v.*	170	50	>10

[a] If an *i.v.* application is indicated for the given compound, intraperitoneal application was used for the catalepsy test.

The results permit the following conclusions to be drawn for the relations between structure and activity or toxicity: *1*) All the S- and N-oxidations result in a decrease of the central-depressant as well as cataleptic activity. *2*) Mono-S-oxidation at the sulfur atom in position 5 results in a decrease of the depressant activity to 10—20%, that of the cataleptic activity to 50% (pair *II* and *XI*) and, at the same time, in a con-

siderable increase in toxicity. *3*) Mono-S-oxidation at the sulfur atom in the methylthio group in position 8 results with the N-methyl derivative in a decrease of the depressant activity to 25% and that of the cataleptic activity by 50% (pair *III*, *VIII*), with the N-(3-hydroxypropyl) derivative to a decrease in both directions to 10% (pair *VII*, *IX*). At the same time, toxicity is increased considerably. *4*) The S-oxidation in position 5 together with the methylthio group in position 8 results in practically complete inactivation (pair *III*, *XII*). *5*) The N-oxidation preserves the toxicity practically intact, it decreases the central depressant activity approximately to 10% while the cataleptic effect is influenced relatively little, *viz.* to 30–50%. The N-oxides *XVII*–*XX* and particularly *XVIII* and *XIX* may be designated as relatively active neuroleptics with the ratio of depressant and cataleptic activity shifted toward cataleptic in comparison with the amines *II*, *III*, *VI* and *VII*. *6*) Simultaneous S^5- and N-oxidation results in a marked decrease of toxicity together with a practical suppression of central activity (*XXI*–*XXIII*). *7*) S-Oxidation in position 5 to the sulfone stage results in increased toxicity and substantial decrease of depressant as well as cataleptic activity (pair *II*, *XXVII*). *8*) Simultaneous N-oxidation results in detoxication and practical inactivation from the point of view of central activity (*XXVIII*). *9*) The N-demethylated compounds *IV* and *V* are themselves rather little effective (particularly cataleptically); their S-oxidation results in complete inactivation.

Compound *XIII* showed a pronounced antihistamine effect in the aerosol test with guinea-pigs after oral administration (PD_{50} 0·52 mg/kg). In the histamine detoxication test in guinea-pigs it is relatively little effective (PD_{50} 1 mg/kg *p.o.*). The same substance in an oral dose of 5 mg/kg antagonizes with statistical significance the effect of serotonin in rats *in vivo*. Compound *XXVII* has also an antihistamine activity; in the histamine detoxication test in guinea-pigs it shows a PD_{50} of 0·47 mg/kg when administered subcutaneously.

EXPERIMENTAL

The melting points of the preparations were determined in Kofler's block; the samples were dried in the usual way. The UV spectra in methanol were recorded in a Unicam SP 700 spectrophotometer, the IR spectra in Nujol in a Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform, unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer.

8-Chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin 5-Oxide (*XI*) (Method A)

A mixture of 11·7 g base[2] *II*, 120 ml water and 4·0 g methanesulfonic acid was dissolved by heating. After filtration and cooling, 90 ml 28% H_2O_2 were added and the mixture was left for 12 h at room temperature. It was then filtered with charcoal, the solution made alkaline with aqueous ammonia and the base extracted with benzene. Treatment of the extract yielded a residue (7·8 g, 64%): m.p. 172–174°C (acetone). UV spectrum: λ_{max} 232 nm inflex (log ε 4·14). Maleate, m.p. 199–201°C (ethanol–ether). The product is apparently more homogeneous than the substance prepared earlier[2] by oxidation of *II* with periodic acid (ref.[2] reported a m.p. of the maleate as 186–188°C).

8-Chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin 5-Oxide (*XIII*)

A mixture of 2·0 g base[16] *IV*, 0·7 ml concentrated HCl, 20 ml methanol and 4 ml water was combined under stirring with a solution of sodium periodate, prepared from 1·60 g HIO_4 and 0·28 g NaOH in 10 ml water. The mixture was left for 48 h at room temperature and then evaporated at reduced pressure. From the residue, the basic product was isolated in the usual way (2·1 g glassy substance). Maleate, m.p. 175—176°C (decomp., ethanol). The base liberated by decomposition of the maleate is amorphous. UV spectrum: λ_{max} 233·5 nm (log ε 4·20).

8-Chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin N-Oxide (*XVII*) (Method B)

A solution of 3·45 g base *II* in 18 ml 95% ethanol was combined with 2 ml 25% H_2O_2, the mixture was left for 12 h at room temperature, refluxed for 3 h and heated for another hour with platinum foil[23]. The solution was evaporated at reduced pressure, the residue mixed with 50 ml water and the crystallizing base monohydrate was filtered; 3·4 g, m.p. 129—131°C (benzene). UV spectrum: λ_{max} 256 nm (log ε 4·00), 265 nm (4·01). The NMR spectrum (hexadeuteriodimethylsulfoxide): δ 7·25—7·90 (m, 7 H of aromatic rings), 4·00 (t, 1 H of CH—N), 2·60—3·80 (m, CH_2 groups of piperazine and $ArCH_2$ and H_2O), 3·08 (s, 3 H of N—CH_3). Hydrochloride, m.p. 198—200°C (ethanol).

8-Methanesulfinyl-10-[4-(3-hydroxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IX*)

A. *Oxidation with bromate-bromide* (Method C): 15 ml acetic acid and 5 ml 20% HCl were added to a solution of 2·50 g methanesulfonate of base[16] *VII* in 15 ml water. Under stirring, this was followed by a dropwise addition of 10·3 ml 1M-$KBrO_3$ (10 ml contain 2·0 g KBr). The mixture was left for 1 h at room temperature, made alkaline with aqueous ammonia and extracted with benzene. After evaporation of the extract, 2·26 g of a glassy basic residue was obtained. Dihydrochloride-monohydrate was prepared by neutralization of the base in ethanol with the aid of an ether solution of hydrogen chloride; m.p. 184—187°C (aqueous ethanol). Dihydrochloride-dihydrate was obtained by neutralization of the base in chloroform with ethanolic hydrogen chloride and free evaporation; m.p. 150·5—153°C (ethanol). B. *Oxidation with periodic acid* (Method D): 0·5 ml methanesulfonic acid and a solution of 2·30 g HIO_4 in 8 ml water were added to a solution of 4·96 g methanesulfonate of base[16] *VII* in 35 ml water. The solution was left for 15 h at room temperature, was filtered, the filtrate made alkaline with aqueous ammonia and the glassy base (4·1 g) was isolated by extraction with benzene. Dihydrochloride-monohydrate, m.p. 180—185°C (aqueous ethanol) does not depress the m.p. in mixture with the product prepared according to *A*. With both products one can distinguish microscopically two types of crystals — we may be dealing here with two racemates crystallizing together.

2-(4-Chlorobenzenesulfonyl)phenylacetic Acid (*XXIV*)

200 ml 27% H_2O_2 were added under stirring to a solution of 50·0 g 2-(4-chlorophenylthio)phenylacetic acid[2] in 350 ml acetic acid. The mixture was heated for 2 h to 70°C, after 2 h of standing it was diluted with 150 ml water and the crystalline product filtered after 12 h: 44·0 g (79%), m.p. 170—171°C (ethanol). UV spectrum: λ_{max} 240 nm (log ε 4·22), inflex 270 nm (3·34). IR spectrum: 746 and 757 (1,2-C_6H_4), 831 (1,4-C_6H_4), 946, 1 708, 2 560, 2 645 and 2 735 (COOH), 1 160 and 1 312 cm^{-1} (SO_2). The NMR spectrum (CF_3CO_2H): δ 8·20 (s, 1 H in *o*-position toward the acetic acid residue), 7·15—8·00 (m, 7 H of the remaining aromatic protons), 4·14 (s, 2 H in $ArCH_2COO$). For $C_{14}H_{11}ClO_4S$ (310·8) calculated: 54·11% C, 3·57% H, 11·41% Cl, 10·32% S;

found: 54·00% C, 3·50% H, 11·52% Cl, 10·30% S. An attempt was made to cyclize this acid (8·0 g) with the aid of polyphosphoric acid (40 g) at 230°C (3 h). The neutral product isolated in the usual way (3·8 g) was chromatographed on alumina (120 g, activity II). Elution with benzene yielded 1·16 g of fractions which partly crystallized: 0·07 g, m.p. 226—228°C. For $C_{13}H_7ClO_3S$ (278·7) calculated: 56·02% C, 2·53% H, 12·72% Cl, 11·50% S; found: 56·39% C, 2·64% H, 12·69% Cl, 11·40% S. According to analysis and the melting point we are dealing here with 2-chlorothioxanthone 10,10-dioxide (*XXV*). Ref.[26,27] give values of 222° and 226°C.

8,10-Dichloro-10,11-dihydrodibenzo[*b,f*]thiepin 5,5-Dioxide (*XXVI*)

100 ml 25% H_2O_2 were added dropwise over 30 min under stirring to a suspension of 30·0 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2] in 400 ml acetic acid at 60°C. The mixture was stirred for 5 h at 70°C, filtered while hot and the filtrate was evaporated at reduced pressure to crystallization: 25·0 g (76%), m.p. 140—142°C (acetone). UV spectrum: λ_{max} 270 nm (log ε 3·37), 278 nm (3·33), 285 nm (3·07). IR spectrum: 710, 769, 770 and 779 (1,2-C_6H_4), 826 and 856 (1,2,4-C_6H_3), 1115 and 1298 (SO_2), 1153 and 1580 cm^{-1} (Ar). For $C_{14}H_{10}Cl_2O_2S$ (313·2) calculated: 53·69% C, 3·21% H, 22·64% Cl, 10·24% S; found: 53·55% C, 3·26% H, 22·75% Cl, 10·51% S.

8-Chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin 5,5-Dioxide (*XXVII*)

A mixture of 30 ml chloroform, 20·0 g *XXVI* and 30·0 g 1-methylpiperazine was refluxed for 10 h, evaporated at reduced pressure and the residue was combined with 200 ml water and extracted with 200 ml benzene. The extract was shaken with 100 ml 3M-HCl, after 1 h of standing the mixture was filtered, the crystalline hydrochloride was suspended in the acid-aqueous phase, separated from the filtrate, the suspension was diluted with 100 ml water, made alkaline with aqueous ammonia and the crude base was extracted with benzene. After treatment of the extract, a total of 6·20 g (25%) of an amorphous base was obtained — this was converted in the usual way to the maleate, m.p. 198—200°C (aqueous ethanol). Decomposition of the maleate with aqueous ammonia and extraction with benzene yielded the base, m.p. 168—169°C (ethanol), NMR spectrum: δ 7·2—8·2 (m, 7 H, aromatic protons), 3·8—4·2 (m, 2 H in $ArCH_2$), 3·1—3·3 (split doublet, 1 H of CH—N), 2·4—2·8 (deformed triplet, 8 H of piperazine), 2·28 (s, 3 H in N—CH_3).

The antihistamine effect of XIII *and* XXVII *was assayed by Dr J. Metyš at the pharmacological department of this institute. The NMR spectra were recorded and interpreted by Dr B. Kakáč and Dr J. Holubek at the physico-chemical department. The analyses were carried out in the analytical department (headed by Dr J. Körbl) by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Mrs A. Slavíková and Mrs J. Hrdá.*

REFERENCES

1. Jilek J. O., Svátek E., Metyšová, J. Pomykáček J., Protiva M.: This Journal *32*, 3186 (1967).
2. Jilek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
3. Protiva M., Jílek J., Adlerová E., Metyšová J.: Czechoslov. Pat. 130.741 (Appl. 29. XI. 1966); Chem. Abstr. *73*, 56 125 (1970).
4. Adlerová E., Ernest I., Metyšová J., Protiva M.: This Journal *33*, 2666 (1968).
5. Fouche J. C. L. (Rhone-Poulenc S. A.): French Pat. 1,505.342 (Appl. 16. XII. 1965); Belg. Pat. 685.839; Austrian Pat. 265.283.

6. Fouche J. C. L. (Rhone-Poulenc S. A.): US-Pat. 3, 509.154 (French Appl. 23. VIII. and 16. XII. 1965); Neth. Appl. 66/11.458; Chem. Abstr. *67*, 100 151 (1967).
7. Fouche J. C. L. (Rhone-Poulenc S. A.): French Pat. 5416 M (Appl. 8. III. 1966); Chem. Abstr. *71*, 30 503 (1969).
8. Queisnerová M., Svátek E., Macek K., Metyšová J.: Activitas Nervosa Super. 10 (*3*), 335 (1968).
9. Queisnerová M., Svátek E., Macek K., Metyšová J.: Českoslov. farm. *17*, 248 (1968).
10. Queisnerová M., Svátek E., Metyšová J.: Biochem. J. *114*, 339 (1969).
11. Franc Z., Horešovský O., Pelc B., Francová V., Kraus P.: Biochem. Pharmacol. 19 (*4*), 1443 (1970).
12. Jílek J. O., Metyšová J., Protiva M.: Symposium *Chemie Ústí 1970* (20. V. 1970); Abstracts, p. 18.
13. Jílek J. O., Metyšová J., Protiva M.: Chim. Therap. 5 (*5*), 368 (1970).
14. Jílek J. O., Šindelář K., Pomykáček J., Horešovský O., Pelz K., Svátek E., Kakáč B., Holubek J., Metyšová J., Protiva M.: This Journal *38* 115 (1973).
15. Pelz K., Jirkovský I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1895 (1968).
16. Jílek J. O., Pomykáček J., Metyšová J., Protiva M.: This Journal *36*, 2226 (1971).
17. Protiva M., Jílek J. O., Metyšová J.: Activitas Nervosa Super. *13*, 184 (1971).
18. Metyšová J., Metyš J.: Activitas Nervosa Super. *13*, 185 (1971).
19. Kazdová E., Metyšová J., Dlabač A.: Activitas Nervosa Super. *13*, 186 (1971).
20. Likovský Z., Votava Z.: Activitas Nervosa Super. *13*, 187 (1971).
21. Dlabač A., Metyš J., Metyšová J.: Activitas Nervosa Super. *13*, 188 (1971).
22. Gauch R., Hunziker F., Lehner H., Michaelis W., Schindler O.: Farmaco (Pavia), Ed. Prat. *24*, 92 (1969).
23. Cope A. C., Towle P. H.: J. Am. Chem. Soc. *71*, 3423 (1949).
24. Jílek J., Protiva M., Metyšová J., Pomykáček J. (Spofa): Belg. Pat. 759.999 (Czechoslov. Appl. 10. XII. 1969); German. Offen. 2,060.903; Chem. Abstr. *75*, 63 646 (1971).
25. Mirwald L.: *Thesis.* Universität des Saarlandes, Saarbrücken 1961.
26. Ullmann F., Lehner A.: Ber. *38*, 739 (1905).
27. Gilman H., Diehl J. W.: J. Org. Chem. *24*, 1914 (1959).
28. Fouche J. C. L. (Société des Usines Chimiques Rhone-Poulenc): French Pat. 1,478.355 (Appl. 23. VIII. 1965).
29. Fouche J. C. L. (Société des Usines Chimiques Rhone-Poulenc): French Pat. 4888 M (Appl. 22.XI. 1965); Chem. Abstr. *69*, 67 427 (1968).

Translated by A. Kotyk.