1-(4-ALKANESULFONYLPHENACYL)-4-ARYLPIPERAZINES AND RELATED COMPOUNDS: A NEW SERIES OF CENTRAL DEPRESSANTS*

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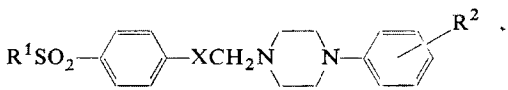
Substitution reactions of 4-methanesulfonyl-, 4-ethanesulfonyl-, 4-(2-methylpropane)sulfonyl and 4-methylthiophenacyl bromide with 1-phenyl-, 1-(4-tolyl)-, 1-(3-chlorophenyl)- and 1-(4-hydroxyphenyl)piperazine yielded amino ketones *Ia*–*VIa* and *Xa* which were partly reduced to the amino alcohols *Ib*–*IVb*, and *Xb*. Analogously, using morpholine, 1-methylpiperazine, benzylmethylamine and aniline, amino ketones *XIa*–*XIIIa* and *XVa* and amino alcohols *XIb*–*XIIIb* were obtained. Debenzylation of *XIIIa* with ethyl chloroformate gave rise to carbamate *XIVa*. Some of the compounds prepared had selective central depressant effects on mice and rats; the most interesting compound *Ia* ("mesylphenacyrazine") is evaluated clinically.

1-Arylpiperazines substituted at the strongly basic $N_{(4)}$ with another bulky residue which usually consists of a shorter aliphatic chain to which an aromatic or a heterocyclic residue is attached have been reported[1–9] as agents with a central depressant activity. Some of them are in use as psychotropic drugs or are being intensively tested; *e.g.* mepiprazol[10,11], enpiprazol[12,13], tolpiprazol, *i.e.* 1-(3-tolyl)-4-[2-(5-methyl-3-pyrazolyl)ethyl]piperazine[14], toprilidine (Hoe 757) (ref.[15]), Su-17595A (ref.[16]), MJ 1978 (ref.[17,18]) *etc.* In our recent work (ref.[19,20]) we also encountered similar 1-arylpiperazines with clear indications of central depressant activity. The subject of the present communication are first of all 1-arylpiperazines substituted at N^4 with a 4-(alkanesulfonyl)phenacyl residue (*Ia*–*VIa*). After having observed some interesting pharmacological properties in the parent compound *Ia* (VÚFB-8752, mesylphenacyrazine)[21] the preparative study was extended to a series of analogues as described here.



I, $R^1 = CH_3$, $R^2 = H$
II, $R^1 = CH_3$, $R^2 = 4\text{-}CH_3$
III, $R^1 = CH_3$, $R^2 = 3\text{-}Cl$
IV, $R^1 = CH_3$, $R^2 = 4\text{-}OH$
V, $R^1 = CH_2CH_3$, $R^2 = H$
VI, $R^1 = CH_2CH(CH_3)_2$, $R^2 = H$

In formulae: *a*, X = CO; *b*, X = CHOH

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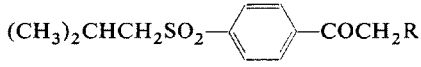
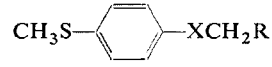
The 4-(methanesulfonyl)phenacyl bromide[22,23] and 4-(ethanesulfonyl)phenacyl bromide[23] used as starting compounds were prepared as described before. The synthesis of 4-(2-methylpropanesulfonyl)phenacyl bromide (*VIII*) started from phenyl isobutyl sulfide[24,25] which was converted in a Friedel–Crafts reaction with acetic anhydride to 4-(isobutylthio)acetophenone (see ref.[26,27]). Subsequent oxidation with hydrogen peroxide in acetic acid yielded 4-(2-methylpropanesulfonyl)acetophenone (*VII*) which reacted with bromine in acetic acid to the desired compound *VIII*. All the three 4-(alkanesulfonyl)phenacyl bromides were condensed with excess 1-phenylpiperazine[28] either in chloroform at room temperature or in benzene at an elevated temperature (method *A*), giving amino ketones *Ia*, *Va* and *VIa*. To prepare larger quantities of 1-phenylpiperazine, the heating[28] of a mixture of hydrochlorides of diethanolamine and aniline to 240°C appeared to be unsatisfactory. Hence we used a method[29] based on the reaction of N,N-bis(2-chloroethyl)amine[30,31] with aniline in boiling 1-butanol (this modification was developed by Dr K. Šindelář of this laboratory). 4-(Methanesulfonyl)phenacyl bromide was condensed with 1-(4-tolyl)piperazine[32] and with 1-(3-chlorophenyl)piperazine[32] (Method *A*), giving amino ketones *IIa* and *IIIa*. The amino ketones *Ia*–*IIIa* were reduced with sodium borohydride in aqueous methanol (method *B*) or with lithium aluminium hydride in tetrahydrofuran (method *C*) to the corresponding amino alcohols *Ib*–*IIIb*.

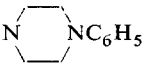


VII, R = H

VIII, R = Br



IX, R = Br

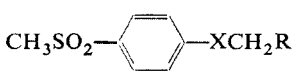
X, R = 

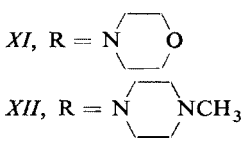
To define more accurately the structural field of activity in this series analogous methods were applied to the preparation of the methylthio analogues *Xa* and *Xb*. The starting 4-(methylthio)phenacyl bromide (*IXa*)[33,34] was prepared by bromination of 4-(methylthio)acetophenone[23,34–37] in acetic acid. 4-(Methanesulfonyl)phenacyl bromide was further condensed (mostly by method *A*) with morpholine, 1-methylpiperazine, N-benzylmethylamine[38] and aniline with the formation of amino ketones *XIa*–*XIIIa* and *XVa*. The first three were reduced to amino alcohols *XIb*–*XIIIb*. Benzylmethylamino ketone *XIIIa* was debenzylated in a reaction with ethyl chloroformate, giving rise to carbamate *XIVa*.

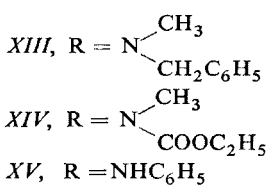
In view of the interesting character of amino ketone *Ia* we took up the biotransformation of this compound. It could have been assumed to be metabolized by the following mechanisms: *a*) reduction of the keto group with the formation of amino alcohol *Ib*, *b*) hydroxylation in the *para*-position of the benzene ring of the phenylpiperazine moiety giving rise to phenol ketone *IVa*, *c*) combination of the two mecha-

nisms giving rise to phenol alcohol *IVb*, *d*) N-oxidation, *e*) oxidative N-dealkylation giving rise to 1-phenylpiperazine and probably also to 4-(methanesulfonyl)benzoic acid, *f*) oxidative N-dealkylation of the *p*-hydroxylated metabolite giving rise to 1-(4-hydroxyphenyl)piperazine. Of the enumerated potential metabolites we mentioned already the preparation of 1-phenylpiperazine and amino alcohol *Ib*. To prepare the phenolic compounds *IVa* and *IVb*, the 1-(4-hydroxyphenyl)piperazine dihydrobromide was synthesized as described in the literature[39] and from this the base was liberated and condensed with 4-(methanesulfonyl)phenacyl bromide in a mixture of dimethylformamide and ethanol. Reduction of ketone *IVa* to alcohol *IVb* was carried out by using method *B*. 4-(Methanesulfonyl)benzoic acid was prepared by oxidation of 4-(methanesulfonyl)acetophenone[35,36] with potassium permanganate (for other methods see[40,41]). It resulted also, in a mixture with its ethyl ester[42], in an attempt to N-oxidize *Ia* with hydrogen peroxide in aqueous ethanol. Preliminary metabolic experiments with *Ia* on rats led to the detection of *Ib*, *IVb*, phenylpiperazine and 4-(methanesulfonyl)benzoic acid as metabolites[43].

The bases prepared were converted for characterization and for pharmacological testing to the corresponding salts (mostly maleates). The bases and salts are summarized with the usual experimental data in Table I.







Compounds *Ia* and *Ib* were evaluated by the pharmacological methods of general screening on oral application. They were found to be little toxic (LD_{50} about 2 g/kg for mice) and for the *in vivo* tests were used in doses of 300 mg/kg. They displayed an expressed and protracted depressant action on mice, they potentiated strikingly thiopental sleep of mice, antagonized the effect of phenmetrazine in mice, had a hypothermic effect on rats, an indication of a cataleptic effect on rats, an antihistamine effect on guinea-pigs, a hypotensive effect on rats, a vasodilatory effect on guinea-pigs and an antiarrhythmic effect on mice. For this reason, they were subjected together with several other similar arylpiperazine derivatives, to more detailed psychopharmacological tests from the point of view of the quality of their central depressant action. The results of some of these tests are shown in Table II. Here, too, the compounds were applied only orally. The table includes first of all the approximate mean lethal doses (LD_{50}) for mice. It also shows the mean effective dose (ED_{50}) in the rotating-rod test[44]. The ED_{50} values were calculated for the period of maximum effect (30—120 min after application)[45]. The next column shows the results of studying the effect of the compounds on the locomotor activity in mice for

TABLE I

1-(4-Alkanesulfonylphenacyl)-4-arylpiperazines and Analogue s

Compound[a] Method (% yield)	M.p., °C (solvent)	Formula (m.w.)	Calculated/Found			
			% C	% H	% N	% S
Ia	177—178	$C_{19}H_{22}N_2O_3S$	63·66	6·19	7·82	8·94
[b]	(ethanol–benzene)	(358·4)	63·74	6·22	7·77	9·10
Ia-M	169—170	$C_{23}H_{26}N_2O_7S$	58·22	5·52	5·90	6·75
—	(ethanol)	(474·5)	58·26	5·56	5·69	6·98
Ia-MS	216—217	$C_{20}H_{26}N_2O_6S_2$	52·85	5·76	6·16	14·11
—	(ethanol–ether)	(454·5)	52·69	5·73	5·62	13·90
IIa	145—146	$C_{20}H_{24}N_2O_3S$	64·49	6·50	7·52	8·61
A (77)	(ethanol)	(372·5)	64·44	6·60	7·27	8·58
IIa-M	165—166	$C_{24}H_{28}N_2O_7S$	59·00	5·78	5·74	6·56
—	(ethanol)	(488·5)	58·57	5·91	5·91	6·53
IIIa	163—165	$C_{19}H_{21}ClN_2O_3S$	58·08	5·39	7·13	8·16[c]
A (70)	(benzene)	(392·9)	58·24	5·34	7·19	8·36
IVa	145—147	$C_{19}H_{22}N_2O_4S$	60·94	5·92	7·48	8·56
[b]	(ethanol)	(374·4)	60·79	6·05	7·61	8·61
IVa-M	157—158	$C_{23}H_{26}N_2O_8S$	56·33	5·34	5·71	6·52
—	(aqueous ethanol)	(490·5)	56·68	5·42	6·09	7·17
Va	123—124[d]	$C_{20}H_{24}N_2O_3S$	64·49	6·50	7·52	8·61
A[e]	(ethanol)	(372·5)	64·07	6·54	7·14	8·80
Va-M	163—164	$C_{24}H_{28}N_2O_7S$	59·00	5·78	5·73	6·56
—	(ethanol)	(488·5)	58·84	5·81	5·58	6·78
VIa	130—131[f]	$C_{22}H_{28}N_2O_3S$	65·97	7·05	7·00	8·00
A (62)	(ethanol)	(400·5)	65·72	7·08	6·80	7·85
VIa-M	152—153	$C_{26}H_{32}N_2O_7S$	60·46	6·24	5·42	6·20
—	(ethanol)	(516·6)	60·12	6·15	5·36	6·36
Xa	143—144	$C_{19}H_{22}N_2OS$	69·91	6·79	8·58	9·82
[b]	(benzene–light petroleum)	(326·4)	69·86	6·86	8·77	10·00
Xa-M	163—164	$C_{23}H_{26}N_2O_5S$	62·42	5·92	6·63	7·25
	(methanol–ethanol)	(442·5)	62·22	5·95	6·15	7·31
XIa	171—172[g]	$C_{13}H_{17}NO_4S$	55·10	6·05	4·94	11·32
A (51)	(ethanol)	(283·3)	55·39	6·13	4·79	11·54
XIa-M	170—171	$C_{17}H_{21}NO_8S$	51·11	5·30	3·51	8·03
—	(ethanol)	(399·4)	51·41	5·26	3·78	8·28
XIIa	139—140[h]	$C_{14}H_{20}N_2O_3S$	56·72	6·80	9·46	10·82
A (71)	(benzene)	(296·4)	56·97	6·87	9·12	10·99

TABLE I
(*Continued*)

Compound[a] Method (% yield)	M.p., °C (solvent)	Formula (m.w.)	Calculated/Found			
			% C	% H	% N	% S
XIIa-2 HM	165—166	$C_{22}H_{28}N_2O_{11}S$	50·00	5·34	5·30	6·06
—	(ethanol)	(528·5)	49·72	5·43	5·55	6·26
XIIIa-HCl	189—190	$C_{17}H_{20}ClNO_3S$	57·69	5·70	3·96	9·06
A[e]	(ethanol–ether)	(353·9)	57·55	5·77	3·75	9·24
XVa	155—156	$C_{15}H_{15}NO_3S$	62·25	5·23	4·84	11·08
[b]	(benzene)	(289·3)	62·52	5·47	4·75	11·25
Ib	210—211	$C_{19}H_{24}N_2O_3S$	63·30	6·71	7·77	8·90
B[b]	(benzene–ethanol)	(360·5)	63·87	6·67	7·71	8·96
Ib-M	168—169	$C_{23}H_{28}N_2O_7S$	57·96	5·92	5·88	6·73
	(ethanol–ether)	(476·5)	58·26	6·02	5·68	6·97
IIb	196—197	$C_{20}H_{26}N_2O_3S$	64·14	7·00	7·48	8·56
C[b]	(ethanol)	(374·5)	64·32	7·19	7·06	8·61
IIb-M	150—151	$C_{24}H_{30}N_2O_7S$	58·75	6·17	5·71	6·54
—	(ethanol–ether)	(490·6)	58·75	6·39	5·22	6·36
IIIb	176—177[i]	$C_{19}H_{23}ClN_2O_3S$	57·78	5·86	7·10	8·12[j]
C (82)	(benzene–light petroleum)	(394·9)	58·36	5·91	6·93	8·29
IVb	199—200	$C_{19}H_{24}N_2O_4S$	60·60	6·43	7·44	8·52
B (70)	(ethanol)	(376·5)	60·73	6·46	7·48	8·32
Xb	139—140	$C_{19}H_{24}N_2OS$	69·47	7·37	8·53	9·76
C (90)	(ethanol)	(328·5)	69·98	7·60	8·26	9·42
Xb-M	162—163	$C_{23}H_{28}N_2O_5S$	62·14	6·35	6·30	7·21
—	(ethanol)	(444·5)	61·62	6·51	6·29	6·90
XIb	102—104[k]	$C_{13}H_{10}NO_4S$	54·71	6·71	4·91	11·24
B (52)	(benzene–hexane)	(285·4)	54·61	6·81	5·02	11·23
XIb-M	129—130	$C_{17}H_{23}NO_8S$	50·84	5·78	3·49	7·99
	(ethanol)	(401·4)	51·07	5·93	3·37	8·12
XIIb	131—132[m]	$C_{14}H_{22}N_2O_3S$	56·35	7·43	9·39	10·74
B (84)	(benzene–ethanol)	(298·4)	56·82	7·27	8·99	10·55
XIIb-2 HM	188—190	$C_{22}H_{30}N_2O_{11}S$	49·80	5·70	5·28	6·04
—	(ethanol)	(530·5)	49·96	5·81	5·12	6·07
XIIIb	104—105[n]	$C_{17}H_{21}NO_3S$	63·90	6·64	4·38	10·04
B (69)	(benzene–hexane)	(319·4)	64·27	6·61	4·09	10·05
XIIIb-M	174—175	$C_{21}H_{25}NO_7S$	57·91	5·79	3·22	7·36
—	(ethanol–ether)	(435·5)	58·20	5·74	3·31	7·56

which the photo-cell method of Dews was used[46]. Doses bringing about a reduction of locomotor activity to 50% of the mean control value (D_{50}) were calculated. Changes of general activity of rats were recorded in the Animex apparatus[47] after an oral dose of 5 mg/kg. The table shows the mean relative values of activity as compared with the control group. Finally, the results of interaction of the compounds tested with apomorphine in a chewing and agitation test in rats are shown according to Janssen and coworkers[48]. The compounds were usually applied in a dose of 1 g/kg *p.o.* 60 min before apomorphine. The table shows the average values of the chewing and agitation score and their statistical significance as compared with the control group (the maximum score is 9, a 0—3 scale, measurement in triplicates).

Table II shows first of all the low toxicity of the compounds prepared. To bring about ataxia (the rotating-rod test) rather high doses were required; some of the

Explanation to Table I

[a] M maleate, 2 HM di(hydrogen maleate), MS methanesulfonate, HCl hydrochloride. [b] See experimental. [c] Cl calculated 9·02%, found 9·05%. [d] UV spectrum: λ_{max} 244 nm (log ε 4·44), 282 nm (3·64); IR spectrum: 696, 748, 830 (5 and 2 adjacent Ar—H), 1150, 1290, 1310 (SO_2), 1504, 1600 (Ar), 1702 (CO—Ar), 2780 cm^{-1} (N—CH_2); NMR spectrum: δ 8·30 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2 of phenacyl), 8·10 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2 of phenacyl), 6·85—7·40 (m, 5 H, C_6H_5), 3·85 (s, 2 H, $COCH_2$), 3·23 (t, J = 5·0 Hz, 4 H, $CH_2N^4CH_2$ of piperazine), 3·14 (q, J = 7·0 Hz, 2 H, SO_2CH_2), 2·74 (t, J = 5·0 Hz, 4 H, $CH_2N^1CH_2$ of piperazine), 1·25 (t, J = 7·0 Hz, 3 H, CH_3). [e] Yield of crude product almost corresponds to the theoretical. [f] UV spectrum: λ_{max} 245 nm (log ε 4·49), 282 nm (3·66); IR spectrum: 690, 724, 755, 830 (5 and 2 adjacent Ar—H), 1150, 1290, 1320 (SO_2), 1500, 1578, 1600 (Ar), 1692 (CO—Ar), 2750 cm^{-1} (N—CH_2); NMR spectrum: δ 8·30 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2 of phenacyl), 8·10 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2 of phenacyl), 6·80—7·50 (m, 5 H, C_6H_5), 3·94 (s, 2 H, $COCH_2$), 3·25 (t, J = 5·0 Hz, 4 H, $CH_2N^4CH_2$ of piperazine), 3·00 (d, J = 6·0 Hz, 2 H, SO_2CH_2), 2·71 (t, J = 5·0 Hz, 4 H, $CH_2N^1CH_2$ of piperazine), 2·22 (m, 1 H, CH of isobutyl), 1·05 (d, J = = 6·0 Hz, 6 H, 2 CH_3). [g] UV spectrum: λ_{max} 239 nm (log ε 4·10), 277 nm (3·39); IR spectrum: 830 (2 adjacent Ar—H), 1088, 1133 (ether), 1147, 1300 (SO_2), 1571, 1592 (Ar), 1705 cm^{-1} (CO—Ar). [h] UV spectrum: λ_{max} 240 nm (log ε 4·15); IR spectrum: 770 (S—O), 838 (2 adjacent Ar—H), 1150, 1308 (SO_2), 1707 cm^{-1} (CO—Ar); NMR spectrum: δ 8·25 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2), 8·00 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2), 3·78 (s, 2 H, $COCH_2$), 3·06 (s, 3 H, SO_2CH_3), 2·56 (bs, 8 H, 4 NCH_2 of piperazine), 2·28 (s, 3 H, NCH_3). [i] IR spectrum: 680, 815, 895 (C—Cl and Ar—H), 1115 (CHOH), 1150, 1300 (SO_2), 1560, 1590 (Ar), 3340, 3500 cm^{-1} (OH). [j] Cl calculated: 8·98%, found: 8·54%. [k] IR spectrum: 768 (S—O), 875 (2 adjacent Ar—H), 1089 (CHOH), 1118, 1152, 1300 (SO_2), 3100 cm^{-1} (OH...N); NMR spectrum: δ 7·97 (d, J = = 8·5 Hz, 2 H, aromatic 3,5-H_2), 7·62 (d, J = 8·5 Hz, 2 H, aromatic 2,6-H_2), 4·84 (dd, J = 9·0; 5·0 Hz, 1 H, Ar—CH—O), *c.* 3·80 (1 H, OH), 3·75 (t, J = 4·5 Hz, 4 H, CH_2OCH_2 of morpholine), 3·04 (s, 3 H, CH_3), *c.* 2·54 (m, 6 H, 3 NCH_2). [m] UV spectrum: λ_{max} 260 nm (log ε 3·02), 265 nm (3·02), 272 nm (2·92); IR spectrum: 690, 770 (S—O), 818, 828 (2 adjacent Ar—H), 1075, 1090 (CHOH), 1150, 1300 (SO_2), 1600 (Ar), 3200 cm^{-1} (OH). [n] IR spectrum: 689, 700, 740, 779, 836 and 880 (S—O, 5 and 2 adjacent Ar—H), 1077, 1090 (CHOH), 1150, 1293 (SO_2), 1600 (Ar), 3525 cm^{-1} (OH); NMR spectrum: δ 7·82 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2), 7·45 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2), 7·25 (s, 5 H, C_6H_5), 4·72 (t, J = 8·0 Hz, 1 H, Ar—CH—O), 3·82 (bs, disappears after D_2O, 1 H, OH), 3·59 (d, 4 H, CH_2NCH_2), 2·97 (s, 3 H, SO_2CH_3), 2·30 (s, 3 H, NCH_3).

compounds were practically ineffective in this test. On the other hand, doses lower by about an order of magnitude were fully effective in the locomotor activity test. Analogously, in experiments on rats, some of the compounds inhibited the overall activity of the animals even in the relatively low dose of 5 mg/kg *p.o.* None of the compounds suppressed appreciably the apomorphine chewing of rats. All the compounds, however, depressed intensively the apomorphine-induced agitation; this result was usually statistically significant (with respect to the control group). The most interesting compound of the lot appeared to be *Ia* ("VÚFB8752") designated with the working name "mesylphenacyrazine". A more detailed testing confirmed the depressant effect of *Ia* on the CNS of mice and rats. The depressant activity is pronounced, well definable in a number of tests but also selective, without gross disturbance of motor coordination and reactivity of the nervous system to external stimuli. The effect of mesylphenacyrazine does not have the character of a sedative-hypnotic action, it differs qualitatively from the effect of neuroleptics (*e.g.* of the phenothiazine series), it differs from the anxiolytics of the 1,4-benzodiazepine series particularly in the absence of the anticonvulsant component; the compound does not

TABLE II

Pharmacological Properties of Arylpiperazine Derivatives (mg/kg, *p.o.*)

Compound[a]	Acute toxicity (mouse) LD_{50}	Rotating rod (mouse) ED_{50}	Locomotor activity (mouse) D_{50}	Total activity (rat) %[b,c]	Antiapomorphine effect score (rat)	
					chewing	agitation[c]
Ia-M	2 007	117	8·3	25$^+$	8·6	5·3$^+$
Ib-M	>1 000	73	13·6	65$^+$	8·8	6·6
IIa-M	>2 000	>500	43·3	60	8·5	4·5$^+$
IIb-M	1 500	370	47·0	103	7·4	5·0$^+$
IIIa	1 000	>500	51·7	62	7·2	5·0$^+$
IIIb	[d]	500	13·3	59	8·0[e]	5·6^{+e}
IVa-M	[d]	340	>50	97	9·0[e]	7·0[e]
IVb	[d]	200–500	>50	115	9·0[e]	6·7[e]
Va-M	>1 000	>500	15·0	53$^+$	9·0	3·2$^+$
VIa-M	[d]	>500	13·0	109	8·6	3·2$^+$
Xa-M	>2 000	>500	>50	81	9·0	5·6$^+$
Xb-M	>1 000	115	15·8	48$^+$	8·8	4·8$^+$

[a] M maleate. [b] Changes of activity recorded in the Animex apparatus are shown in per cent as compared with the control group (= 100%). [c] The asterisk designates statistical significance ($p = 0{\cdot}05$) with respect to the control group average. [d] No lethal effect even at a dose of 2 g/kg. [e] Applied in a dose of 300 mg/kg.

have the character of a central myorelaxant compound. The cataleptic effect of mesylphenacyrazine is detectable from a dose of 100 mg/kg *p.o.* but there is no clear dependence of effect on dose as the dose is increased. At 30 mg/kg *p.o.* mesylphenacyrazine has a pronounced procataleptogenic effect in interaction with perphenazine (applied per os 1 hour before either at the subcataleptic dose of 1 mg/kg or in the cataleptically active dose of 4 mg/kg). Mesylphenacyrazine (*Ia*) was offered for clinical testing as a tranquilizer with a selective depressant activity on the central nervous system and with a wide margin of safety.

Compounds which do not contain the arylpiperazine moiety in their molecules, usually lack completely the central depressant effect and their testing was restricted to a general screening. The approximate value of LD_{50} (mg/kg) for mice, the dose D (mg/kg) at which they were applied *in vivo* and the character of the effects observed are shown: *XIa* maleate, *p.o.*, 2000, 300, indication of hypoglycemic effect on rats; *XIb* maleate, *i.v.* 625, 125, slight hypotensive effect on rats; *XIIa* di(hydrogen maleate), *p.o.*, 2000, 300, slight hypoglycemic effect which, at a dose of 100 mg/kg, could not be detected any more; *XIIb* di(hydrogen maleate), *p.o.*, 2000, 300, a slight hypoglycemic effect; *XIIIa*-hydrochloride, *p.o.*, 1500, 300, at doses above D, indications of central excitation, hyperthermic effect, a short-lived incoordinating effect in the rotating-rod test in mice, increases the glucose blood level in rats; *XIIIb*-maleate, *i.v.* 110, 20, at doses above D indications of central excitation; *XVa*, *p.o.*, 2500, 300, at doses above D indications of central depression; further a hypothermic effect and potentiation of thiopental sleep in mice. With 4-(methanesulfonyl)phenacyl bromide (LD_{50} greater than 1 g/kg *p.o.* for mice) a pronounced effect was found in the rotating-rod test in mice when using large oral doses; a dose of 0·5 g/kg brings about ataxia in more than 50% animals in the experimental group. 1-Phenylpiperazine (as maleate) (LD_{50} 47 mg/kg *i.v.*, 108 mg/kg *p.o.*) has only indications of the central effects of its N^4-substitution derivatives; it has a depressant effect in the locomotor activity test (D_{50} 29·2 mg/kg *p.o.*), it causes ataxia on the rotating rod only in sublethal doses.

Practically all the compounds prepared were tested for antimicrobial effects *in vitro*, most of them being ineffective. Some antibacterial activity was found with *IIa* (maleate). The minimum inhibitory concentrations in μg/ml are shown: *Streptococcus β-haemolyticus*, 50; *Staphylococcus pyogenes aureus* (including the strain resistant to penicillin), 50; *Klebsiella pneumoniae*, 100; *Proteus vulgaris*, 50. Compounds *IVa* (maleate) and *IVb*, on the other hand, showed a specific inhibitory activity against the growth of lower fungi and yeasts: at concentrations of about 100 μg/ml they inhibit growth of *Saccharomyces pasterianus*, *Trichophyton mentagrophytes*, *Candida albicans* and *Aspergillus niger*.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected. The samples were dried *in vacuo* of an oil-pump over P_2O_5 at room temperature or at elevated temperature (maximum 100°C). The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G or in an Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a Zeiss, Jena ZKR-60 spectrometer. The homogeneity of the compounds was tested in a thin layer of silica gel. The compounds prepared in the *b* series (secondary alcohols) are all racemates.

4-(2-Methylpropanesulfonyl)acetophenone (*VII*)

Acetic anhydride (19 ml) was added dropwise over 90 min to a refluxing mixture of 90 ml CS_2 and 30·0 g phenylisobutyl sulfide[24,25] (b.p. 107—110°C/10 Torr). The mixture was refluxed for 2 h, cooled, diluted with 30 ml CS_2 and decomposed by pouring into a mixture of 250 g ice, 100 ml water and 60 ml concentrated hydrochloric acid. After separation, the aqueous phase was extracted with chloroform, the organic phases were combined, dried with $MgSO_4$ and distilled: 33·2 g (89%) 4-(isobutylthio)acetophenone, b.p. 145—148°C/1·5 Torr, m.p. 26—28°C. Literature data[26,27] on this compound are rather scanty (b.p. 180—182°C/12 Torr, or 163°C/5 Torr) and a low yield has been reported[26] when using $ZnCl_2$ instead of $AlCl_3$. 30% Hydrogen peroxide (107 ml) was added dropwise over 1 h under stirring to a solution of 32·0 g 4-(isobutylthio)acetophenone in 90 ml acetic acid so as to keep the temperature below 60°C. After warming the mixture on a water bath to 90°C an exothermic reaction took place during which (10 min) the heating was interrupted. Then it was stirred for 30 min at 95°C, after partial cooling it was diluted with 65 ml water and, after complete cooling, the product was filtered: 32·0 g (90%), m.p. 66—67°C (benzene–hexane). IR spectrum (KBr): 845 (2 adjacent Ar—H), 1155, 1270, 1295 (SO_2), 1577, 1600 (Ar), 1690 cm^{-1} (Ar—CO). For $C_{12}H_{16}O_3S$ (240·2) calculated: 59·98% C, 6·71% H, 13·34% S; found: 59·58% C, 6·85% H, 13·36% S.

4-(2-Methylpropanesulfonyl)phenacyl Bromide (*VIII*)

Bromine (18·3 g) was added dropwise over 30 min under stirring to a solution of 27·5 g *VII* in 65 ml acetic acid at room temperature. Then the mixture was slowly heated (30 min) to 50°C whereupon it became colourless. After further 10 min of stirring at this temperature, it was poured into 400 ml ice-cold water and the precipitated product was filtered after 30 min of standing, washed with water and dried in air: 35·2 g (97%) crude compound which was recrystallized from a mixture of benzene and hexane: m.p. 113—114°C. For $C_{12}H_{15}BrO_3S$ (319·2) calculated: 45·14% C, 4·74% H, 25·04% Br, 10·04% S; found: 45·17% C, 4·82% H, 25·21% Br, 9·87% S.

4-(Methylthio)phenacyl Bromide (*IXa*)

Bromine (8·5 g) was added dropwise under stirring over 30 min to a suspension of 8·3 g 4-(methylthio)acetophenone[23] (m.p. 80—81°C) in 45 ml acetic acid. In the course of further 30 min, the mixture was heated to 65°C and then poured into 250 g of a mixture of ice and water. The product was filtered, washed with water and dried: 12·0 g (98%) crude compound. It crystallizes in the form of yellowish needles from hexane and melts at 46—47°C. For C_9H_9BrOS (245·1) calculated: 44·10% C, 3·70% H, 32·60% Br, 13·08% S; found: 44·08% C, 3·67% H, 32·44% Br, 12·80% S. Ref.[33,34] report a melting point of 65·5—66·5°C for a product obtained by bromination in chloroform.

1-Phenylpiperazine

A mixture of 35·7 g N,N-bis(2-chloroethyl)amine hydrochloride[30,31], 18·7 g aniline and 150 ml 1-butanol was refluxed for 8 h. Then it was combined with 13·8 g K_2CO_3 and refluxing continued for 32 h, every 8 h adding 13·8 g K_2CO_3. After cooling, it was filtered, the solid was extracted with boiling benzene and the combined organic solutions were distilled; 20·1 g (62%), b.p. 108 to 112°C/1·3 Torr. If the reaction was carried out in boiling ethanol, the yield was 20%, in 1-propanol 40%, in 2-butoxyethanol 46%. Ref.[29] reports the b.p. of the product to be 162—164°C/22 Torr.

1-(4-Hydroxyphenyl)piperazine

A solution of 22·8 g 1-(4-hydroxyphenyl)piperazine dihydrobromide[39] (m.p. 274—275°C) in 30 ml water was mixed with 60 ml concentrated ammonium hydroxide. After 2 h standing in a refrigerator, the base was filtered, washed with water and dried: 10·8 g (90%), m.p. 218—220°C (90% ethanol). For $C_{10}H_{14}N_2O$ (178·2) calculated: 67·38% C, 7·92% H, 15·72% N; found: 67·27% C, 7·99% H, 15·96% N.

1-(4-Methanesulfonylphenacyl)-4-phenylpiperazine (*Ia*)

A. *In benzene* (method *A*): A warm solution of 27·7 g 4-(methanesulfonyl)phenacyl bromide[22,23] (m.p. 121—123°C) in 600 ml benzene was added dropwise over 20 min under stirring to a solution of 35·2 g 1-phenylpiperazine in 300 ml benzene and the mixture was refluxed for 2 h in a 70—80°C water bath. The precipitate (a mixture of the product and phenylpiperazine hydrobromide) was filtered while warm and extracted with 400 ml chloroform. The remaining solid (25·0 g) represents the quantitative yield of phenylpiperazine hydrobromide (see ref.[29]). The benzene and chloroform solutions were combined, evaporated, the residue was suspended in 200 ml ethanol, the product was filtered, washed with water and dried; 28·0 g (78%) crude base which crystallized from a large volume of a mixture of ethanol and benzene in the form of yellowish needles; m.p. 177—178°C. NMR spectrum: δ 8·30 and 8·15 (2 d, 4 H, aromatic protons of SO_2—Ar—CO), 6·80—7·50 (m, 5 H, C_6H_5), 3·90 (s, 2 H, $ArCOCH_2$), 3·25 (t, $J = 6{\cdot}0$ Hz, 4 H, $CH_2N^4CH_2$), 3·07 (s, 3 H, SO_2CH_3), 2·75 (t, $J = 6{\cdot}0$ Hz, 4 H, $CH_2N^1CH_2$).

Maleate, m.p. 169—170°C (ethanol). UV spectrum (ethanol): λ_{max} 282·5 nm (log ε 3·62), 241 nm (4·48). IR spectrum (KBr): 698, 770 (5 and 2 adjacent Ar—H), 1132, 1156, 1305, 1320 (SO_2), 1500, 1585, 1605 (Ar), 1703 (CO—Ar and CO of the maleic acid carboxyl), 2460 and 2580 cm^{-1} (COOH). Monomethanesulfonate, m.p. 216—217°C (ethanol–ether). The analyses are shown in Table I.

B. *In chloroform*: A warm-prepared solution of 168 g 4-(methanesulfonyl)phenacyl bromide in 2500 ml chloroform was added to a solution of 200 g 1-phenylpiperazine in 600 ml chloroform and the mixture was stirred for 1·5 h at room temperature. The precipitated phenylpiperazine hydrobromide (134 g) was filtered and the filtrate evaporated at reduced pressure. The residue was combined with 200 ml dimethylformamide and 500 ml ethanol, 15 ml concentrated NH_4OH was added and, after homogenization, was left in the refrigerator overnight. The product was filtered, washed with a mixture of dimethylformamide and ethanol and then with ethanol alone and dried in air; 190 g (88%) crude base melting at 168—170°C.

1-(4-Methanesulfonylphenacyl)-4-(4-hydroxyphenyl)piperazine (*IVa*)

A warm solution of 6·9 g 4-(methanesulfonyl)phenacyl bromide in 160 ml ethanol was added under stirring to a warm solution of 8·9 g 1-(4-hydroxyphenyl)piperazine in 170 ml dimethylformamide and the mixture was stirred for 4 h at room temperature. Most of the solvents were evaporated at reduced pressure and the residue was diluted with 1 liter water. After standing overnight the product was filtered, washed with water and ether, mixed with 100 ml dilute hydrochloric acid (1 : 3), filtered, suspended in 100 ml dilute NH_4OH (1 : 2), filtered, washed with water, ethanol and ether: 8·0 g (86%), m.p. 145—147°C (ethanol). UV spectrum: λ_{max} 239·5 nm (log ε 4·43), 285 nm (3·59). IR spectrum: 832 (2 adjacent Ar—H), 1155, 1305 (SO_2), 1214 (Ar—OH), 1513, 1571, 1592, 1608 (Ar), 1705 (CO—Ar), 3390 and 3460 cm^{-1} (OH). NMR spectrum (CD_3SOCD_3): δ 8·80 (bs, 1 H, OH), 8·30 and 8·09 (ABq, $J = 9{\cdot}0$ Hz, 4 H,

aromatic protons of SO_2—Ar—CO), 6·85 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of hydroxyphenyl), 6·60 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of hydroxyphenyl), 3·91 (s, 2 H, $COCH_2$), 3·25 (s, 3 H, SO_2CH_3), 2·90 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·69 (m, 4 H, $CH_2N^1CH_2$ of piperazine).

Maleate, m.p. 157—158°C (aqueous ethanol). Analyses are shown in Table I.

1-(4-Methylthiophenacyl)-4-phenylpiperazine (*Xa*)

A solution of 15·0 g *IXa* in 170 ml ether was added to a solution of 20·0 g 1-phenylpiperazine in 50 ml ether. The mixture was stirred for 2 h at room temperature and refluxed for 2 h. After cooling, it was shaken with a solution of 8·0 g NaOH in 150 ml water and the precipitated product was filtered. It was dissolved in 200 ml hot benzene, the solution was filtered and, 70 ml light petroleum was added. The mixture was cooled, this resulting in 12·0 g precipitated product. Another part was obtained by processing the mother liquor and the original ether solution; total yield 14·0 g (70%) base, m.p. 143—144°C (benzene–light petroleum).

Maleate, m.p. 163—164°C (methanol–ethanol). Analyses are shown in Table I.

Ethyl N-(4-methanesulfonylphenacyl)-N-methylcarbamate (*XIVa*)

A mixture of 13·0 g amino ketone *XIIIa* (Table I), 15·0 g ethyl chloroformate and 50 ml benzene was refluxed for 6 h. The solution was diluted with further 200 ml benzene, washed with dilute hydrochloric acid, and, after drying, evaporated at reduced pressure; 12·2 g (a practically quantitative yield): m.p. 118—119°C (ethanol). IR spectrum: 837 (2 adjacent Ar—H), 1155, 1292 ($ArSO_2$), 1500 (Ar), 1693 (CO—Ar), 1717 cm^{-1} (NCOOR). For $C_{13}H_{17}NO_5S$ (299·3) calculated: 52·16% C, 5·72% H, 4·68% N, 10·71% S; found: 52·48% C, 5·82% H, 4·57% N, 11·03% S.

N-(4-Methanesulfonylphenacyl)aniline (*XVa*)

A solution of 16·6 g 4-(methanesulfonyl)phenacyl bromide in 200 ml chloroform was added under stirring to a solution of 11·6 g aniline in 80 ml chloroform and the mixture was refluxed for 5 h. After cooling, it was shaken with 200 ml dilute hydrochloric acid (1 : 3), the acid aqueous solution was filtered and made alkaline with NH_4OH and the mixture of bases was extracted with chloroform. Aniline was removed from the residue by extraction with benzene while the desired product crystallized; 2·6 g (15%), m.p. 155—156°C (benzene). The reaction proceeded only to a small extent and a greater part of the starting 4-(methanesulfonyl)phenacyl bromide was recovered from the original chloroform solution. Analysis of the product is shown in Table I.

1-(4-Methanesulfonylphenyl)-2-(4-phenylpiperazino)ethanol (*Ib*) (Method *B*)

A solution of 4·2 g $NaBH_4$ in 40 ml water with 1 ml 20% NaOH was added dropwise over a period of 30 min to a suspension of 5·7 g *Ia* in 200 ml methanol at 45°C. The mixture was stirred for 1 h at 50°C and, after cooling, 30 ml water and 20 ml hydrochloric acid was added. After 30 min of stirring at 30—40°C, filtration removed the small fraction of the undissolved substance and the filtrate was evaporated at reduced pressure. The mixture was mixed with 150 ml water, excess NH_4OH was added and the precipitated base was filtered and recrystallized from a large volume of a mixture of benzene and ethanol; 4·20 g (74%), m.p. 210—211°C. NMR spectrum (CD_3SOCD_3): δ 7·85 (d, J = 8·0 Hz, 2 H, aromatic 3,5-H_2), 7·56 (d, J = 8·0 Hz, 2 H, aromatic 2,6-H_2), 6·60—7·45 (m, 5 H, C_6H_5), 5·25 (bs, 1 H, OH), 4·80 (t, 1 H, Ar—CH—O), 2·85 to 3·40 (m, 6 H, CH_2 in a chain and $CH_2N^4CH_2$ of piperazine), 3·12 (s, 3 H, CH_3SO_2), 2·60

(m, 4 H, $CH_2N^1CH_2$ of piperazine). Maleate, m.p. 168–169°C (ethanol–ether). Analysis is shown in Table I.

1-(4-Methanesulfonylphenyl)-2-(4-p-tolylpiperazino)ethanol (*IIb*) (Method *C*)

A solution of 7·0 g *IIa* in 200 ml tetrahydrofuran was added dropwise under stirring to a solution of 3·0 g $LiAlH_4$ in 30 ml tetrahydrofuran and the mixture was refluxed for 3 h. After cooling, 12 ml 20% NaOH was added dropwise, charcoal was added, the suspension was filtered and the filtrate was evaporated: 6·2 g (88%) crude base which was purified by crystallization from ethanol, m.p. 196–197°C. Maleate, m.p. 150–151°C (ethanol–ether). Analyses are shown in Table I.

4-(Methanesulfonyl)benzoic Acid

A. *When attempting to* N-*oxidize* Ia: A mixture of 13·2 g base *Ia* and 800 ml ethanol was combined with 15·8 ml 30% H_2O_2, the mixture was stirred for 15 min at 60–70°C and for 1 h at room temperature. The excess H_2O_2 was decomposed by 2 h of heating with a platinum foil to 60°C and, after filtration, the solution was evaporated at reduced pressure. The residue was combined with 100 ml 5% NaOH and extracted with chloroform. Acidification of the alkaline aqueous solution with hydrochloric acid led to the precipitation of 5·3 g (72%) 4-(methanesulfonyl) benzoic acid, m.p. 266–267°C (80% ethanol). For $C_8H_8O_4S$ (200·2) calculated: 48·00% C, 4·03% H; found: 47·85% C, 4·20% H.

The chloroform solution was washed with 100 ml dilute hydrochloric acid (1 : 3). Treatment of the aqueous solution with 20% NaOH and extraction with benzene led to the isolation of 2·0 g oil which, according to chromatography on a thin layer of alumina is 1-phenylpiperazine. The chloroform solution was evaporated and the residue (1·0 g) was chromatographed on a column of 25 g Al_2O_3 (activity II). Elution with benzene yielded 0·6 g substance melting at 87–88° in a capillary (benzene–hexane) which was identified as ethyl 4-(methanesulfonyl)benzoate. IR spectrum: 795 (2-adjacent Ar—H), 1 160, 1 280 (SO_2), 1 583, 1 605 (Ar), 1 725 cm^{-1} (ArCOOR). NMR spectrum: δ 8·20 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2), 7·94 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2), 4·35 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·05 (s, 3 H, SO_2CH_3), 1·39 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For $C_{10}H_{12}O_4S$ (228·2) calculated: 52·63% C, 5·30% H, 14·02% S; found: 52·78%C 5·32% H, 13·59% S. Esterification of 4-(methanesulfonyl)benzoic acid according to ref.[42] gave the ethyl ester melting at 87–88°C (capillary) which, in mixture with the compound prepared by the present procedure, melts without depression. M.p. of both substances in Kofler's block is 94–95°C; ref.[42] reports a m.p. of 95–96°C.

B. *By oxidation of* 4-(*methanesulfonyl*)*acetophenone*: A mixture of 19·8 g 4-(methanesulfonyl)-acetophenone[23,35,36] (m.p. 124–126°C), 500 ml water, 10 ml 10% NaOH and 63·5 g $KMnO_4$ was refluxed under stirring for 3 h. After cooling, 500 ml 30% solution of $Na_2S_2O_5$ was added, the decolourized mixture was filtered and the filtrate acidified with hydrochloric acid. The precipitate was filtered and the organic fraction was extracted with boiling ethyl acetate. Evaporation of the extract yielded 11·0 g (55%) acid which, after recrystallization from 90% ethanol, melts at 272–273°C. Ref.[40,41] report melting points of 266–267·5, 267–268, and 274–276°C for the compound prepared in different ways. The compound prepared according to B is identical with that prepared according to A.

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