POTENTIAL TRANQUILIZING AGENTS: 1-(4-AMINOSULFONYL-PHENACYL)-4-METHYL(AND PHENYL)PIPERAZINES*

Z.J.VEJDĚLEK, J.METYŠ, J.NĚMEC and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

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Reactions of 4-ethylbenzenesulfonyl chloride with dimethylamine, diethylamine, N-methylbenzylamine, pyrrolidine, piperidine and morpholine led to sulfonamides *IIIa—f* which were oxidized with potassium permanganate to the corresponding 4-(aminosulfonyl)acetophenones (*IV*). Bromination yielded 4-(aminosulfonyl)phenacyl bromides *V* which underwent substitution reactions with 1-methylpiperazine and 1-phenylpiperazine to diaminoketones *I* and *II*. The central depressant activity of these compounds in experiments on rats and mice was rather low; relatively highest activity was found with phenylpiperazine derivatives *IIa* and *IIe*.

In a previous communication of this series[1] we described the synthesis and the selective central depressant activity of 1-(4-alkanesulfonylphenacyl)-4-arylpiperazines, in particular of the parent 1-(4-methanesulfonylphenacyl)-4-phenylpiperazine[2,3] which, after pharmacological[4-6], toxicological[7,8], pharmacokinetic and metabolic[9] studies is now being tested clinically under the name of "mesylphenacyrazine"[10]. The present paper deals with the close structural analogues of mesylphenacyrazine where the alkanesulfonyl group is replaced with an aminosulfonyl one. The compounds have the general formulas *I* and *II* where the R substituent is the residue of dimethylamine, diethylamine, N-methylbenzylamine, pyrrolidine, piperidine and morpholine.

In the synthesis of *I* and *II*, the starting compound was 4-ethylbenzenesulfonyl chloride[11,12] which was treated with excess amounts of the above secondary amines to obtain 4-ethylbenzenesulfonamides *IIIa—f*. The literature knows only the N,N-dimethyl derivative *IIIa* which was obtained by a reaction of 4-ethylbenzenesulfonyl chloride with excess aqueous solution of dimethylamine[13]. In analogy (method *A*), other sulfonamides *III* with the exception of *IIIc* were prepared. *IIIc* was synthesized y an analogous reaction in benzene. The ethylbenzene derivatives *III* were oxidized with potassium permanganate in aqueous acetone in the presence of magnesium nitrate (method *B*) to 4-(tert-aminosulfonyl)acetophenones *IV*. This was the method used previously for preparing[13,14] the N,N-dimethyl derivative *IVa*. Ref.[15] described the

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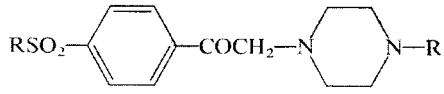
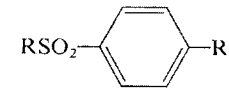
preparation of the N,N-diethyl derivative *IVb* but using a principally different procedure. The next step was the bromination of acetophenones *IV* to phenacyl bromides *V* with bromine in acetic acid (method *C*); this was described before[13,14] in connection with the preparation of *Va*. Substitution reactions of phenacyl bromides *V* with excess 1-methylpiperazine and 1-phenylpiperazine[1] were carried out in a benzene solution (method *D*). The bases obtained (*I* and *II*) were converted to crystalline maleates. All the compounds prepared are summarized in Table I. The experimental section includes only examples of preparations by the various general methods.



I. $R^1 = CH_3$
II. $R^1 = C_6H_5$

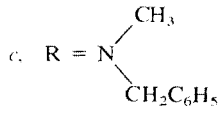


III. $R^1 = CH_2CH_3$
IV. $R^1 = COCH_3$
V. $R^1 = COCH_2Br$

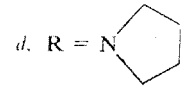
In formulas *I* – *V*:

a. $R = N(CH_3)_2$

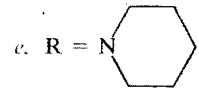
b. $R = N(C_2H_5)_2$



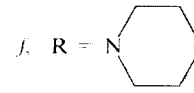
c. $R = N(CH_3)(CH_2C_6H_5)$



d. $R =$ pyrrolidin-1-yl



e. $R =$ piperidin-1-yl



f. $R =$ morpholin-4-yl

Maleates of the piperazine derivatives *I* and *II* were evaluated in psychopharmacological tests with a view to the expected central depressant activity, partly also by methods of general pharmacological screening. The results of the tests are shown in Table II. The psychopharmacological tests used were the same as those with mesylphenacyrazine and its analogues[1]. In the rotating rod test the ability of female mice with administered substances to maintain balance for 1 min on a horizontal rotating rod was examined. The mean effective dose ED_{50} was calculated for the period of maximum effect (30–120 min after application). For studying the effect of the substances on locomotor activity of mice the photo-cell method was employed (for the technique see ref.[1]). Rats were used to examine the total activity, recorded in an Animex apparatus, following administration of the compounds in a *p.o.* dose of 5 mg/kg. Table II shows further the results of interaction of the compounds tested with apomorphine in the chewing and agitation tests in rats; the compounds tested were applied in a dose of 1 g/kg *p.o.* 60 min before apomorphine.

Table II demonstrates the low toxicity of the compounds tested. An incoordinating effect was found only in traces so that only in the case of *IIa* and *IIb* (phenylpiperazine derivatives) was it possible to calculate the mean effective dose. Likewise, in the highly sensitive test of effect on locomotor activity the compounds tested are practically inactive; the D_{50} dose could be determined only for compound *IIa*. On the other

TABLE I

1-(4-Aminosulfonylphenacyl)piperazines and Intermediates

Compound[a] (method)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
			% C	% H	% N	% S
IIIb (*A*[b])	50—51 (benzene–hexane)	$C_{12}H_{19}NO_2S$ (241·3)	59·73 59·56	7·93 8·20	5·80 5·67	13·28 13·25
IIIc *b*	71—72 (hexane)	$C_{16}H_{19}NO_2S$ (289·4)	66·40 66·52	6·62 6·86	4·84 4·63	11·08 11·18
IIId (*A*)	75—76[c] (benzene–hexane)	$C_{12}H_{17}NO_2S$ (239·3)	60·23 59·96	7·16 7·48	5·85 5·79	13·39 13·65
IIIe (*A*)	60—61 (hexane)	$C_{13}H_{19}NO_2S$ (253·3)	61·63 61·46	7·56 7·81	5·53 5·45	12·65 12·62
IIIf (*A*)	114—115 (ethanol)	$C_{12}H_{17}NO_3S$ (255·3)	56·45 56·35	6·71 6·97	5·48 5·50	12·56 12·78
IVb (*B*)	70—71 (tetrachloromethane)	$C_{12}H_{17}NO_3S$ (255·3)	56·45 56·28	6·71 6·91	5·48 5·39	12·56 12·56
IVc (*B*[d])	101—102[e] (tetrachloromethane–benzene)	$C_{16}H_{17}NO_3S$ (303·4)	63·34 63·18	5·65 5·89	4·62 4·57	10·57 10·83
IVd (*B*)	136—137[f] (tetrachloromethane–benzene)	$C_{12}H_{15}NO_3S$ (253·3)	56·90 56·45	5·97 5·99	5·53 5·46	12·65 12·63
IVe (*B*)	112—113[g] (tetrachloromethane–hexane)	$C_{13}H_{17}NO_3S$ (267·3)	58·40 58·70	6·41 6·65	5·25 5·26	11·99 12·07
IVf (*B*[b])	155—156 (tetrachloromethane–benzene–ethanol)	$C_{12}H_{15}NO_4S$ (269·3)	53·50 53·30	5·62 5·75	5·20 5·12	11·91 11·95
Vb (*C*)	79—80[h] (benzene–hexane)	$C_{12}H_{16}BrNO_3S$[i] (334·2)	43·12 43·08	4·83 5·00	4·19 4·27	9·59 9·38
Vc (*C*)	107—109 (benzene–light petroleum)	$C_{16}H_{16}BrNO_3S$[j] (382·3)	50·26 49·98	4·22 4·50	3·66 3·54	8·39 8·27
Vd (*C*)	114—116 (benzene–hexane)	$C_{12}H_{14}BrNO_3S$[k] (332·2)	43·38 42·75	4·26 4·26	4·21 4·17	9·65 9·67
Ve (*C*[b])	81—83 (benzene–hexane)	$C_{13}H_{16}BrNO_3S$ (346·2)	— —	— —	4·04 3·82	9·27 9·10
Vf (*C*)	125—126[m] (benzene–hexane)	$C_{12}H_{14}BrNO_4S$ (348·2)	— —	— —	4·02 4·31	9·21 9·56
Ib (*D*)	96—97 (ethanol–hexane)	$C_{17}H_{27}N_3O_3S$ (353·5)	57·75 57·88	7·70 8·10	11·89 11·60	9·07 8·93

TABLE I
(*Continued*)

Compound[a] (method)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
			% C	% H	% N	% S
Ib-2M	171—172 (ethanol)	$C_{25}H_{35}N_3O_{11}S$ (585·6)	51·26 50·99	6·03 6·32	7·18 7·12	5·48 5·36
Id-2M[n] (*D*)	158—160 (ethanol)	$C_{25}H_{35}N_3O_{12}S$ (601·6)	49·90 50·07	5·87 5·97	7·00 7·35	—
Ie (*D*)	136—137[o] (benzene–hexane)	$C_{18}H_{27}N_3O_3S$ (365·5)	59·14 59·56	7·45 7·32	11·50 11·27	8·77 8·75
Ie-2M	169—170 (aqueous ethanol)	$C_{26}H_{35}N_3O_{11}S$ (597·6)	52·25 52·31	5·91 6·09	7·03 7·13	5·36 5·41
If (*D*)	151—152[p] (benzene–hexane)	$C_{17}H_{25}N_3O_4S$ (367·5)	55·55 55·67	6·86 7·25	11·44 11·54	8·73 8·87
If-2M	165—167 (ethanol)	$C_{25}H_{33}N_3O_{12}S$ (599·6)	50·07 49·91	5·55 5·99	7·01 7·17	5·34 5·08
IIa (*D*[b])	148—150 (ethanol)	$C_{20}H_{25}N_3O_3S$ (387·5)	61·99 61·96	6·50 6·33	10·84 10·44	8·27 8·29
IIa-M	162—163 (ethanol)	$C_{24}H_{29}N_3O_7S$ (503·6)	57·24 56·75	5·81 5·96	8·34 8·20	6·37 6·45
IIb-M (*D*)	160—162 (ethanol)	$C_{26}H_{33}N_3O_7S$ (531·6)	58·74 58·83	6·26 6·46	7·90 7·71	6·03 6·26
IIc (*D*)	118—120[q] (benzene–light petroleum)	$C_{26}H_{29}N_3O_3S$ (463·6)	67·36 67·31	6·31 6·56	9·06 8·76	6·92 6·88
IIc-M	161—162 (ethanol)	$C_{30}H_{33}N_3O_7S$ (579·7)	62·16 62·28	5·74 5·84	7·25 6·99	5·53 5·38
IId (*D*)	118—120[r] (ethanol)	$C_{22}H_{27}N_3O_3S$ (413·5)	63·90 63·66	6·58 6·81	10·16 10·19	7·75 7·98
IId-M[n]	158—160 (ethanol)	$C_{26}H_{33}N_3O_8S$ (547·6)	57·10 57·53	6·08 6·49	7·66 7·46	5·85 5·80
IIe[s] (*D*)	138—139[t] (benzene)	$C_{29}H_{35}N_3O_3S$ (505·6)	—	—	8·31 8·06	6·32 6·15
IIe-M	172—173 (ethanol)	$C_{27}H_{33}N_3O_7S$ (543·6)	59·65 59·66	6·12 6·42	7·73 7·45	5·90 6·02
IIf (*D*)	162—164[u] (benzene)	$C_{22}H_{27}N_3O_4S$ (429·5)	61·51 61·78	6·34 6·63	9·78 9·50	7·47 7·12
IIf-M[v]	167—169 (ethanol)	$C_{26}H_{34}N_3O_{9.5}S$ (572·6)	54·52 54·57	6·00 6·31	7·34 7·54	5·60 5·86

hand, only *IIe* depresses with statistical significance the total activity of rats. None of the compounds tested depressed appreciably the apomorphine chewing of rats. On the contrary, practically all the compounds included in the table depress apomorphine-caused agitation; only in the case of *IIe* is this effect statistically significant. Signs of central depression, manifested by a hypothermic effect in rats and by prolongation of thiopental sleep in mice were displayed by *Id*, *If* and *IIa*. Compound *IIa* appears to be the most interesting one of the whole series; it had an antiamphetamine effect, a sign of a cataleptic effect and a relatively high antihistamine effect in the histamine detoxication test in guinea-pigs. Some of the compounds display signs of effect

[a] M maleate. [b] Experimental. [c] NMR spectrum: δ 7·84 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of benzenesulfonamide), 7·39 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of benzenesulfonamide), 3·20 (t, J = 6·0 Hz, 4 H, CH_2NCH_2), 2·72 (q, J = 7·0 Hz, 2 H, CH_2 of ethyl), 1·71 (t, J = 6·0 Hz, 4 H, remaining 2 CH_2 of pyrrolidine), 1·23 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). [d] In this case it was necessary to separate the mixture of *IIIc* and *IVc* by chromatography on a column of alumina (activity II) using elution with benzene; the first fractions contained the less polar *IIIc* (recovery about 60%), the following fractions yielded *IVc* in a yield of about 10%. [e] IR spectrum: 706, 725, 790 (5 and 2 adjacent Ar—H), 1169, 1348 (NSO_2), 1502, 1574, 1600 (Ar), 1698 cm^{-1} (Ar—CO). [f] UV spectrum (C_2H_5OH): λ_{max} 249 nm (log ε 4·11), infl. 286 nm (3·13); IR spectrum ($CHCl_3$): 835 (2 adjacent Ar—H), 1162, 1350 (NSO_2), 1570, 1595 (Ar), 1690 cm^{-1} (Ar—CO); NMR spectrum: δ 8·30 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of acetophenone), 8·00 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of acetophenone), 3·34 (t, J = 7·0 Hz, 4 H, CH_2NCH_2), 2·68 (s, 3 H, $COCH_3$), 1·80 (t, J = 7·0 Hz, 4 H, remaining 2 CH_2 of pyrrolidine). [g] IR spectrum: 839 (2 adjacent Ar—H), 1170, 1342 (NSO_2), 1573, 1600 (Ar), 1691 cm^{-1} (ArCO). [h] IR spectrum: 835 (2 adjacent Ar—H), 1160, 1197, 1340 (NSO_2), 1575, 1595 (Ar), 1705 cm^{-1} (Ar—CO). [i] Calculated. 23·91% Br; found: 24·11% Br. [j] Calculated: 20·91% Br; found: 20·96% Br. [k] Calculated: 24·05% Br; found: 24·33% Br. [m] UV spectrum: λ_{max} 253 nm (log ε 4·09); IR spectrum: 832 (2 adjacent Ar—H), 725, 1175, 1352 (NSO_2), 1708 cm^{-1} (Ar—CO). [n] Monohydrate. [o] ^{1}H-NMR spectrum: δ 8·14 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of phenylene), 6·84 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of phenylene), 3·80 (s, 2 H, CO . . CH_2N), 3·00 (t, 4 H, $CH_2N^1CH_2$ of piperazine), c. 2·55 (m, 8 H, 4 NCH_2 of piperazine and piperidine), 2·30 (s, 3 H, NCH_3), c. 1·52 (m, 6 H, remaining 3CH_2 of piperidine). [p] ^{1}H-NMR spectrum: δ 8·30 and 7·90 (2 d, J = 9·0 and 9·0 Hz, 4 H, aromatic protons), 3·80 (s, 2 H, CO . . CH_2N), 3·75 (t, 4 H, CH_2OCH_2), 3·00 (t, 4 H, CH_2NCH_2 of morpholine), 2·57 (bs, 8 H, 4 NCH_2 of piperazine), 2·30 (s, 3 H, NCH_3). [q] UV spectrum: λ_{max} 251 nm (log ε 4·37); IR spectrum: 740, 763, 835 (5 and 2 adjacent Ar—H), 1167, 1343 (NSO_2), 1508, 1605 (Ar), 1700 (Ar—CO), 2710 cm^{-1} (CH_2—N). [r] IR spectrum ($CHCl_3$): 1162, 1347 (NSO_2), 1493, 1595 (Ar), 1685, 1697 (Ar—CO), 2760 cm^{-1} (N—CH_2); ^{1}H-NMR spectrum: δ 8·30 and 7·98 (2 d, J = 9·0 and 9·0 Hz, 4 H, protons of phenylene), 6·80—7·55 (m, 5 H, C_6H_5), 3·98 (s, 2 H, $COCH_2N$), 3·24 (m, 8 H, $CH_2N^4CH_2$ of piperazine and CH_2NCH_2 of pyrrolidine), 2·75 (m, 4 H, CH_2N^1 . . CH_2 of piperazine), 1·76 (m, 4 H, remaining 2 CH_2 of of pyrrolidine). [s] Solvate with benzene. [t] ^{1}H-NMR spectrum: δ 8·06 and 7·70 (2 d, J = 9·0 and 9·0 Hz, 4 H, protons of phenylene), 7·23 (s, C_6H_6), 6·70—7·30 (m, 5 H, C_6H_5), 3·80 (s, 2 H, $COCH_2N$), 3·20 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·90 (m, 4 H, CH_2NCH_2 of piperidine), 2·70 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 1·50 (m, 6 H, remaining 3 CH_2 of piperidine). [u] IR spectrum: 747, 802, 836 (5 and 2 adjacent Ar—H), 1119 (C—O—C), 1172, 1354, (NSO_2), 1500, 1600 (Ar), 1704 cm^{-1} (Ar—CO). [v] Sesquihydrate.

TABLE II

Pharmacological Properties of Maleates of Piperazine Derivatives *I* and *II*. Values in mg/kg, *p. o.* application, unless stated otherwise (for methods see ref.[1]).

Compound	Acute toxicity for mice LD_{50}, g/kg	Rotating rod in mice ED_{50}	Locomotor activity in mice[a] D_{50}	Total activity in rats %[b,c]	Antiapomorphine effect in rats[d] chewing	Antiapomorphine effect in rats[d] agitation[c]	Other effects
Ib	0·175[e]	[f]	—	—	—	—	[g]
Id	1·0—2·0[h]	>500[i]	[j]	102	8·6	4·6	[k]
Ie	0·175[e]	[f]	—	—	—	—	[m]
If	2·5	[n]	—	—	—	—	[o]
IIa	1·5—2·0[p]	370	36·2	116	9·0	7·8[q]	[r]
IIb	>2·0[s]	195	>50	116	8·4	4·2	—
IIc	>2·0[t]	>500[u]	[j]	137	8·4	5·4	—
IId	1·0—2·0[v]	>500[w]	[j]	101	8·8	4·2	—
IIe	>2·0[t]	[x]	[j]	51*	9·0	3·2*	—
IIf	>2·0[s]	>500[w]	>50	82	8·0	4·2	—
MSP[y]	2·0	117	8·3	25*	8·6	5·3*	—

[a] D_{50} brings about a reduction of locomotor activity by 50% of the control. [b] Changes of activity recorded in an Animex apparatus are shown in % in comparison with the control group (= 100%). [c] The asterisk indicates statistical significance ($p < 0{\cdot}05$) as compared with the mean value of the control group. [d] The average values of chewing and agitation scores are shown together with the statistical significance (asterisk) as compared with the control group; the maximum score amounts to 9 (scale 0—3, three measurements). [e] Intravenously. [f] Inactive at an *i.v.* dose of 35 mg/kg. [g] At 175 mg/kg, it increases blood sugar level of rats by 20%. [h] At 1·0 g/kg, it is not lethal, a dose of 2·0 g/kg represents the LD_{100}. [i] The dose of 500 mg/kg causes ataxia in 40% animals. [j] Ineffective at the highest dose applied (50 mg/kg). [k] At 100—300 mg/kg it depresses blood pressure of normotensive rats by at least 10% of the starting value; at 1—10 μg/ml, it inhibits acetylcholine contractions of rat duodenum by 50% in an *in vitro* test (approximately matching adiphenine); at 100—300 mg/kg, it decreases body temperature (measured *in recto*) of rats by 1°C; at a dose of 10—25 mg/kg it prolongs thiopental sleep of mice to twice the control value; at 100—300 mg/kg it shows an antiarrhythmic effect toward aconitine in rats. [m] At 35 mg/kg *i.p.* it prolongs statistically the survival of an asphyctic mouse myocard. [n] Ineffective at 300 mg/kg. [o] At 100—300 mg/kg it depresses the rat body temperature by 1°C; at a dose of 10—25 mg/kg it prolongs thiopental sleep in mice to twice the control value; at 100—300 mg/kg it has an antiarrhythmic effect toward aconitine in rats. [p] The doses shown bring about an intense CNS depression. A higher dose causes death of 80% animals. [q] Practically the same score was displayed by the control group. [r] At 25 mg/kg it decreases the blood pressure of normotensive rats by at least 10% of the initial value and prolongs thiopental sleep of mice to twice the control value; at 300 mg/kg it increases the blood sugar level of rats by 20%; at 100—300 mg/kg it decreases the body temperature of rats by at least 1°C and inhibits significantly mouse motility in known surroundings; at a dose of

on the cardiovascular system (a slight hypotensive and antiarrhythmic effect of *Id*, *If* and *IIa*). As to the central effects, none of the new compounds matches the properties of mesylphenacyrazine[1-10].

Of the intermediates, compound *IIId* was evaluated pharmacologically and found to be of low toxicity for mice (LD_{50} = 2·5 g/kg p.o.). In tests done *in vivo* it was applied at a dose of 300 mg/kg, being inactive in most of the tests' At 100–250 mg/kg *p.o.* it prolongs thiopental sleep of mice to twice the control value, thus suggesting a depressant activity.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* using an oil pump, over P_2O_5 at room temperature or at a higher temperature not exceeding 100°C. The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G or in an Infrascan (Hilger and Watts) spectrophotometer and the NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was checked in a thin layer of silica gel. The analyses of all the compounds *I–V* are shown in Table I.

N,N-Diethyl-4-ethylbenzenesulfonamide (*IIIb*) (Method *A*)

4-Ethylbenzenesulfonyl chloride[11,12] (50·0 g, b.p. 145°C/16 Torr) was added dropwise over a period of 45 min under stirring at 10–15°C to a solution of 53·0 g diethylamine in 50 ml water. The mixture was stirred for 30 min at 40°C. After cooling, the separated oil was isolated by extraction with chloroform. The extract was dried with Na_2SO_4 and evaporated at reduced pressure. A total of 57·0 g (92%) crude product was obtained. The analytical sample was obtained by crystallization from a mixture of benzene and hexane, m.p. 50–51°C. In analogy, sulfonamides *IIId–f* were prepared in almost theoretical yields (as crude products).

N-Benzyl-N-methyl-4-ethylbenzenesulfonamide (*IIIc*)

4-Ethylbenzenesulfonyl chloride[11,12] (50·0 g) was added dropwise under stirring over a period of 40 min at 10–15°C to a solution of 61·0 g N-methylbenzylamine in 200 ml benzene and the mixture was heated for 30 min to 40°C, cooled, and the precipitated N-methylbenzylamine hydrochloride was filtered and washed with benzene. The filtrate was evaporated and the remaining oil crystallized on standing in a refrigerator. It was combined with 120 ml light petroleum, filtered,

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5 mg/kg it protects 50% guinea-pigs from the lethal effect of 5 mg histamine/kg, applied intrajugularly; at 100 mg/kg it protects 50% mice from the lethal effect of amphetamine (30 mg/kg, *i.p.*); at doses above 300 mg/kg it shows signs of cataleptic effect in rats. [s] A dose of 2·0 g/kg is lethal for 40% animals. [t] At the dose shown it is not lethal for mice. [u] The dose shown causes ataxia in 20% animals. [v] A dose of 1·0 g/kg has no lethal effects, a dose of 2·0 g/kg is lethal for 80% animals. [w] The dose shown causes ataxia in 30% animals. [x] Ineffective even at the highest dose of 500 mg/kg. [y] Mesylphenacyrazine[1-10].

and washed with some light petroleum; 56·6 g (81%), m.p. 71—72°C (hexane). ^{1}H-NMR spectrum: δ 7·83 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of phenylene), 7·40 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of phenylene), 7·32 (s, 5 H, C_6H_5), 4·10 (s, 2 H, $ArCH_2N$), 2·72 (q, J = 8·0 Hz, 2 H, CH_2 of ethyl), 2·55 (s, 3 H, NCH_3), 1·25 (t, J = 8·0 Hz, 3 H, CH_3 of ethyl).

4-(Morpholinosulfonyl)acetophenone (*IVf*) (Method *B*)

A solution of 62 g *IIIf* (Table I) in 700 ml acetone was added dropwise under stirring over a period of 90 min at 50°C to a solution of 38 g $KMnO_4$ and 100 g $Mg(NO_3)_2 . 6 H_2O$ in 600 ml water. The mixture was stirred for 2 h at 50°C, combined with 16 g solid $KMnO_4$ and heated for 3 h to 50°C. After cooling, the precipitated MnO_2 was filtered, washed with warm acetone and ethanol and the filtrate was evaporated at reduced pressure. The residue (50 g) represents a mixture of *IIIf* and *IVf*. Double crystallization from a mixture of equal parts of tetrachloromethane and benzene yielded 14·8 g (23%) homogeneous *IVf*, m.p. 150—152°C. The analytical product melts at 155—156°C (benzene–tetrachloromethane–ethanol). UV spectrum: λ_{max} 246·5 nm (log ε 4·11). IR spectrum: 848 (2 adjacent Ar—H), 1178, 1355 (NSO_2), 1575, 1602 (Ar), 1702 cm^{-1} (Ar—CO). Compounds *IVa—e* were prepared analogously and with similar yields.

4-(Piperidinosulfonyl)phenacyl Bromide (*Ve*) (Method *C*)

Five drops of bromine were added to a suspension of 10·0 g *IVe* (Table I) in 50 ml acetic acid and the mixture was stirred for 40 min at room temperature until decolorization. The remaining bromine (of the original amount of 6 g) was then added over a period of 30 min and the mixture left to stand for 20 min. Then it was poured into 250 ml ice-cold water. The precipitated product was filtered, washed with water and dried in air; 12·0 g (93%), m.p. 68—70°C. An analytical sample was obtained by crystallization from a mixture of benzene and hexane, m.p. 81—83°C. IR spectrum: 825 (2 adjacent Ar—H), 1173, 1344 (NSO_2), 1705 (Ar—CO), 2859 cm^{-1} (N—CH_2). The other phenacyl bromides *V* were prepared similarly in yields exceeding 90%.

1-[4-(Dimethylaminosulfonyl)phenacyl]-4-phenylpiperazine (*IIa*) (Method *D*)

A solution of 7·50 g *Va* (ref.[13,14]) in 250 ml hot benzene was added dropwise under stirring to a solution of 7·96 g 1-phenylpiperazine[1] in 40 ml benzene. The mixture was stirred for 1 h at room temperature, heated for 10 min to 50°C and the precipitated hydrobromide of 1-phenylpiperazine was filtered while hot. The precipitate was extracted with 150 ml boiling benzene and filtered again. The combined benzene filtrates were evaporated at reduced pressure, yielding 9·60 g (theoretical amount) of a crude base, m.p. 125—130°C. Analytical sample was obtained by crystallization from ethanol, m.p. 148—150°C. UV spectrum: λ_{max} 251 nm (log ε 4·36), IR spectrum (Nujol): 694, 740, 766, 830 (5 and 2 adjacent Ar—H), 1170, 1346 (NSO_2), 1600 (Ar), 1706 (Ar—CO), 2700 and 2780 cm^{-1} ($CH_3—N—CH_3$). Neutralization of the solution of base *IIa* in chloroform with a solution of maleic acid in ethanol yielded the crystalline maleate, m.p. 162—163°C (ethanol). In analogy, other bases *I* and *II* were prepared in yields exceeding 90%.

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