SYNTHESIS OF SEVERAL COMPOUNDS RELATED TO 1-(4-METHYLSULFONYLPHENACYL)-4-PHENYLPIPERAZINE AND THEIR PHARMACOLOGICAL SCREENING

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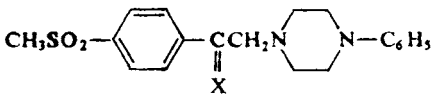
The title compound *I* was transformed to its oxime *II*, hydrazone *III*, and semicarbazone *IV*. 1-(4-Methylsulfonylphenyl)-2-(4-phenylpiperazino)ethanol (*V*) was esterified by the corresponding acid chlorides in pyridine to give the acetate *VI*, propionate *VII*, benzoate *VIII*, and 4-nitrobenzoate *IX*. Reactions of 4-(methylsulfonyl)phenacyl bromide, its 4-(ethylsulfonyl), and 4-(2-methylpropylsulfonyl)analogues with diethanolamine afforded instead of the expected substitution products *X* the hemiacetals *XI*—*XIII*, *i.e.* 2-hydroxy-4-(2-hydroxyethyl)-2-(4-alkylsulfonylphenyl)morpholines. The products were subjected to the pharmacological and microbiological screening; compounds *II*—*IV* and *VI*—*IX* have more or less the character of tranquillizers, the hemiacetals *XI*—*XIII* have some antimicrobial activity *in vitro*. Compound *XIII* showed, surprisingly, a positively inotropic effect, and its methiodide *XIV* a peripheral myorelaxant effect.

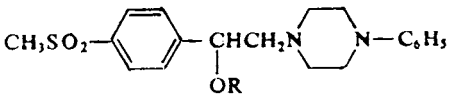
In a previous communication[1] we described the synthesis of 1-(4-methylsulfonylphenacyl)-4-phenylpiperazine (*I*, mesylphenacyrazine) which showed properties of a selective central depressant agent and entered clinical trials (for references, *cf.*[2]). In the meantime its general pharmacology was summarized[3], its effect on sleep cycles in rats was compared with that of phenobarbital[4], pharmacokinetics and metabolism in rats were described[5]. An experimental study on healthy volunteers and a short-term clinical trial with psychotics proved for mesylphenacyrazine hypno-sedative properties of a mild intensity[6,7]; clinical trials were discontinued after having found a rather high incidence of side effects[8]. For concluding the experimental work in the series of mesylphenacyrazine derivatives and analogues a few further compounds were synthesized and tested which is described in the present communication.

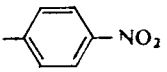


I, X = O
II, X = NOH
III, X = N-NH$_2$
IV, X = N-NHCONH$_2$

In the first line three simple derivatives of compound *I* were prepared. Reaction of the base *I* (ref.[1]) with hydroxylamine hydrochloride in boiling ethanol in the presence of pyridine gave directly the oxime (*II*) hydrochloride which was transformed by treatment with an ethanolic solution of methanesulfonic acid to the methanesulfonate of *II*. An attempt to reduce the hydroximino group to the acetamido one by heating with zinc and acetic acid (*cf.*[9]) led to a hydrogenolytic cleavage and to isolation of 1-phenylpiperazine[1] (in the form of maleate). Reaction of compound *I* (ref.[1]) with aqueous (80% or 35%) hydrazine hydrate in boiling ethanol afforded the hydrazone *III*; its salts (methanesulfonate, maleate) were not stable and decomposed during crystallization. Treatment of compound *I* (ref.[1]) with semicarbazide (freshly released from the hydrochloride) in a boiling mixture of ethanol and pyridine gave the semicarbazone *IV*; its salts showed the same instability like in the case of compound *III*.

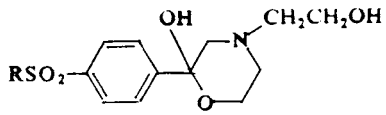
The alcohol *V* (ref.[1]), corresponding to *I* and identified as its metabolite[5], was esterified with acetyl chloride, propionyl chloride, benzoyl chloride and 4-nitrobenzoyl chloride in boiling pyridine and gave the esters *VI*–*IX*; for pharmacological testing the bases were transformed to the maleates. The hydrochloride of *V* was also prepared.



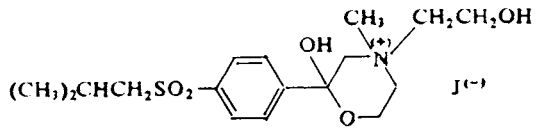
V, R = H
VI, R = $COCH_3$
VII, R = $COCH_2CH_3$
VIII, R = COC_6H_5
IX, R = CO–  –NO_2

4-(Methylsulfonyl)phenacyl bromide[10,11], 4-(ethylsulfonyl)phenacyl bromide[11] and 4-(2-methylpropylsulfonyl)phenacyl bromide[1] were subjected to treatment with diethanolamine in boiling chloroform. Crystalline bases were obtained corresponding by their composition (analyses) to the expected amino ketones *X*. Their UV and IR spectra, however, excluded the possibility of the presence of the conjugated keto group and in general of any carbonyl group at all. They had then to be formulated as the hemiacetals *XI*–*XIII* similarly like the products of reactions of phenacyl bromide with N-substituted ethanolamines[12,13]. Their hydrochlorides were prepared in the presence of water (in fact even by evaporation of solutions in excessive hydrochloric acid to dryness) which made possible the hydrolysis of the hemiacetals to ketones *X*; the spectra of the hydrochlorides, however, proved again the absence of the keto group. It must be concluded that the hemiacetals are extremely stable and that the hydrochlorides correspond also to formulae *XI*–*XIII*. The same type of structure (*XIV*) was assigned to the methiodide prepared from the base *XIII*.

X



XI, R = CH_3
XII, R = CH_2CH_3
XIII, R = $CH_2CH(CH_3)_2$



XIV

The compounds prepared were evaluated by methods of the general pharmacological screening either in the form of bases or in the form of salts, described in the Experimental; oral or parenteral administration was used. First of all acute toxicity was estimated in mice (values of LD_{50} in mg/kg and the way of administration given); doses (D in mg/kg) used in the screening are also given: *II*, 250, *i.v.*, 50; *III*, 2 000, *p.o.*, 300; *IV*, >2 500, *p.o.*, 300; *VI*, 2 500, *p. o.*, 300; *VII*, >2 500, *p.o.*, 300; *VIII*, 2 500, *p.o.*, 300; *IX*, >2 500, *p.o.*, 300; *XI*, 800, *i.v.*, 150; *XII*, 750, *i.v.*, 150; *XIII*, 400, *i.v.*, 80; *XIV*,12·5, *i.v.*, 2·5. In doses higher than D compounds *II*–*IV* and *VI*–*IX* have central depressant activity, decrease the activity and reactivity of mice, bring about ataxia and ptosis; compounds *XI* and *XII*, on the other hand, increase the activity, bring about the Straub reaction and ataxia on the basis of excitation. Some typical effects manifested in doses D or in lower doses (all doses in mg/kg): Anticonvulsant effect towards pentetrazole in mice; *II*, ED = 100–250 *p.o.*; *IV*, ED = = 50–100 *p.o.* Significant inhibition of the spontaneous motility in mice was brought about at doses D by compounds *III*, *IV*, *VI*–*VIII*. In the rotarod test in mice ataxia was brought about by the following oral doses: *VI*, 100–300; *VII*, 100; *VIII*, 300. Compounds *VI*–*IX* in oral doses of 100–300 mg/kg had hypothermic effect in rats (reduced the rectal temperature by 1°C). Thiopental sleeping time in mice was prolonged to 200% of the control value by the following oral doses: *VI*, 10–50; *VII*, 10; *IX*, 100. Compound *VII* showed the antiamphetamine effect in the dose D (protected 100% mice from the lethal effect of a standard dose of amphetamine). Compound *XIII* in a concentration of 50 μg/ml had a positively inotropic effect on the isolated rabbit atrium. The rather toxic quaternary salt *XIV* in a dose equal to 2 LD_{50} *i.v.* (the

animal connected to a respiratory pump) had a significant myorelaxant effect on the gastrocnemius muscle of the rat.

The compounds were also tested for antimicrobial activity *in vitro* (species, compound, and the minimum inhibitory concentration in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *XI* 100, *XIII* 100, *XIV* 50; *Staphylococcus pyogenes aureus*, *XI* 100, *XII* 100, *XIII* 100, *XIV* 100; *Pseudomonas aeruginosa*, *XI* 100, *XII* 100, *XIII* 100, *XIV* 100; *Proteus vulgaris*, *XI* 50, *XII* 50, *XIII* 50, *XIV* 100; *Mycobacterium tuberculosis* H37Rv, *XI* 100, *XIV* 100; *Saccharomyces pasterianus*, *XI* 100, *XII* 100, *XIII* 100, *XIV* 100; *Trichophyton mentagrophytes*, *II* 50, *XI* 100, *XII* 100, *XIII* 100, *XIV* 100.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G or Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in $C^2H_3SOC^2H_3$ unless stated otherwise) with a *ZKR* 60 (Zeiss, Jena) or Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on alumina or silica gel.

1-(4-Methylsulfonylphenacyl)-4-phenylpiperazine Oxime (*II*)

A) *Hydrochloride*: A mixture of 3·6 g *I* (ref.[1]), 1·0 g $NH_2OH.HCl$, 10 ml ethanol and 10 ml pyridine was refluxed for 2 h, the solution was evaporated *in vacuo*, the residue mixed with 5 ml, water, allowed to stand overnight, filtered and dried; 3·4 g (83%), m.p. 187–203°C. Analytical sample, m.p. 190–193°C with decomposition (ethanol). UV spectrum: λ_{max} 250 nm (log ε 4·39). IR spectrum: 700, 760, 792, 803 (5 and 2 adjacent Ar—H), 1 152, 1 308 (SO_2), 1 500, 1 604, 3 040 (Ar), 1 620 (C=N), 2 575 (NH^+), infl. 3 160 cm^{-1} (OH). ^{1}H NMR spectrum: δ 13·15 (bs, 1 H, NOH), 8·19 (d, J = 8·5 Hz, 2 H, 3,5-H$_2$ in phenacyl), 7·98 (d, J = 8·5 Hz, 2 H, 2,6-H$_2$ in phenacyl), 6·80–7·40 (m, 5 H, C_6H_5), 4·60 (bs, 2 H, CH_2N in the chain), 3·00–4·00 (m, 8 H, 4 CH_2N of piperazine), 3·25 (s, 3 H, CH_3SO_2). For $C_{19}H_{24}ClN_3O_3S$ (409·9) calculated: 55·67% C, 5·90% H, 8·65% Cl, 10·25% N, 7·82% S; found: 55·79% C, 5·88% H, 8·64% Cl, 10·41% N, 8·10% S.

B) *Methanesulfonate*: A suspension of 5·0 g *II*.HCl in 50 ml boiling ethanol was treated with 3·5 g methanesulfonic acid, the mixture was refluxed for 10 min and the solution formed was allowed to stand overnight; 3·6 g (62%) methanesulfonate hemihydrate, m.p. 177–180°C. Analytical sample, m.p. 182–185°C with decomposition (ethanol). For $C_{20}H_{27}N_3O_6S_2 . 0{\cdot}5\ H_2O$ (478·6) calculated: 50·19% C, 5·89% H, 8·78% N, 13·40% S; found: 50·26% C, 5·88% H, 8·60% N, 13·59% S.

C) *Cleavage with* Zn *and acetic acid*: A mixture of 7·5 g *II*.HCl, 100 ml acetic acid and 13·0 g Zn was refluxed for 4·5 h, allowed to stand overnight and filtered. The filtrate was evaporated *in vacuo*, the residue was dissolved in 100 ml water, the solution was filtered with active carbon and the filtrate was made alkaline with 20% NaOH. The separated solid was filtered off, the filtrate was neutralized with acetic acid and evaporated *in vacuo*. The residue was extracted with chloroform, the extract was evaporated, the residue (4·8 g oil) was dissolved in ethanol and the boiling solution was treated with 3·0 g maleic acid. The solution obtained was cooled and treated with

ether; 2·3 g 1-phenylpiperazine maleate, m.p. 145 – 147°C (ethanol–ether), identified by comparison with the maleate prepared from the authentic 1-phenylpiperazine[1]. For $C_{14}H_{18}N_2O_4$ (278·3) calculated: 60·42% C, 6·52% H, 10·07% N; found: 60·71% C, 6·45% H, 10·04% N.

1-(4-Methylsulfonylphenacyl)-4-phenylpiperazine Hydrazone (*III*)

A mixture of 10·0 g *I* (ref.[1]), 250 ml ethanol and 25 ml 80% $N_2H_4.H_2O$ was stirred and refluxed for 30 min. Most of ethanol was evaporated *in vacuo* and the residue was allowed to crystallize in a refrigerator; 7·6 g (73%), m.p. 172—177°C. Analytical sample, m.p. 185—188°C (ethanol). UV spectrum: λ_{max} 247 nm (log ε 4·20), 298 nm (4·12). IR spectrum: 700, 774, 784 (5 and 2 adjacent Ar-H), 1 162, 1 318 (SO_2), 1 500, 1 589, 3 035 (Ar), 1 604 (C=N), 3 130, 3 375 cm^{-1} (NH_2). ^1H NMR spectrum: δ 7·85 (s, 4 H, ArH of phenacyl), 7·65 (bs, 2 H, NH_2), 6·70—7·30 (m, 5 H, C_6H_5), 3·60 (s, 2 H, CH_2N in the chain), 3·14 (s, 3 H, CH_3SO_2), 3·08 (bs, 4 H, CH_2N^4. .CH_2 of piperazine), 2·54 (bs, 4 H, $CH_2N^1CH_2$ of piperazine). For $C_{19}H_{24}N_4O_2S$ (372·5) calculated: 61·27% C, 6·49% H, 15·04% N, 8·61% S; found: 60·89% C, 6·58% H, 15·17% N, 8·68% S.

1-(4-Methylsulfonylphenacyl)-4-phenylpiperazine Semicarbazone (*IV*)

Semicarbazide hydrochloride (17·0 g) was rubbed together with 17·0 g sodium acetate and the mixture was extracted with 170 ml boiling ethanol. The undissolved NaCl was filtered off, the filtrate was treated with a warm solution of 6·0 g *I* (ref.[1]) in 75 ml pyridine and the mixture was refluxed for 2 h. It was filtered while hot, the filtrate was evaporated *in vacuo*, the residue was diluted with 50 ml ethanol and the precipitated product was filtered after cooling; 4·0 g (58%), m.p. 209—211°C(ethanol). UV spectrum: λ_{max} 225 nm (log ε 4·37), 249 nm (4·33), 290 nm (4·34). IR spectrum: 697, 762, 784 (5 and 2 adjacent Ar—H), 1 143, 1 152, 1 312 (SO_2), 1 495, 1 503, 1 579, 1 600 (Ar), 1 688 ($NHCONH_2$), 3 250, 3 325, 3 400, 3 460 cm^{-1} (NH, NH_2). ^1H NMR spectrum: δ 8·14 and 7·85 (ABq, J = 8·5 Hz, 2 + 2 H, 4 ArH of phenacyl), 6·70 to 7·30 (m, 5 H, C_6H_5), 6·62 (bs, 3 H, $NHCONH_2$), 3·79 (s, 2 H, CH_2N in the chain), 3·19 (s, 3 H, CH_3SO_2), 3·10 (bs, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (bs, 4 H, $CH_2N^1CH_2$ of piperazine). For $C_{20}H_{25}N_5O_3S$ (415·5) calculated: 57·81% C, 6·06% H, 16·85% N, 7·72% S; found: 57·84% C, 6·21% H, 16·93% N, 7·73% S.

1-(4-Methylsulfonylphenyl)-2-(4-phenylpiperazino)ethanol Hydrochloride (*V*.HCl)

A mixture of 10·0 g *V* (ref.[1]) and 250 ml benzene was saturated with HCl, the precipitated product was filtered and crystallized from water: 11·0 g (100%), m.p. 221—224°C with decomposition. For $C_{19}H_{25}ClN_2O_3S$ (396·9) calculated: 57·49% C, 6·35% H, 8·93% Cl, 7·05% N, 8·08% S; found: 57·41% C, 6·29% H, 8·71% Cl, 6·89% N, 8·20% S.

1-(4-Methylsulfonylphenyl)-2-(4-phenylpiperazino)ethyl Acetate (*VI*)

A solution of 5·2 g *V* (ref.[1]) in 50 ml pyridine was stirred and treated dropwise at 50°C with 2·2 g acetyl chloride and the mixture was refluxed for 2 h. After cooling it was poured into 700 ml cold water, the product separating first as an oil crystallized, was filtered, dissolved in 120 ml benzene, the solution was filtered with charcoal and the filtrate was evaporated. The residue was dissolved in 30 ml warm benzene and crystallization was induced by treatment with cyclohexane; 4·60 g (79%), m.p. 126—127°C. Mass spectrum, *m/z*: 402 (M^+ corresponding to $C_{21}H_{26}$. .N_2O_4S), 343, 175 ($C_{11}H_{15}N_2$). IR spectrum (KBr): 695, 701, 769, 775 (5 and 2 adjacent Ar— -H), 1 154, 1 313 (SO_2), 1 249 (C—O of ester), 1 508, 1 602, 3 010, 3 033, 3 053, 3 090 (Ar),

1 724 cm^{-1} (RCOOR'). For $C_{21}H_{26}N_2O_4S$ (402·5) calculated: 62·67% C, 6·51% H, 6·96% N, 7·96% S; found: 63·32% C, 6·64% H, 6·89% N, 7·88% S.

Maleate hemihydrate, m.p. 147—148°C (96% ethanol–chloroform). For $C_{25}H_{30}N_2O_8S + 0{\cdot}5\ H_2O$ (527·6) calculated: 56·90% C, 5·92% H, 5·30% N; found: 56·75% C, 5·85% H, 5·07% N.

1-(4-Methylsulfonylphenyl)-2-(4-phenylpiperazino)ethyl Propionate (*VII*)

A solution of 7·2 g *V* (ref.[1]) in 70 ml pyridine was similarly reacted with 2·5 g propionyl chloride and similar processing of the mixture gave 7·1 g (87%) product which crystallized from a mixture of benzene and hexane, m.p. 116—117°C. IR spectrum (KBr): 765, 786, 836 (5 and 2 adjacent Ar—H), 1 149, 1 309 (SO_2), 1 500, 1 600, 3 000, 3 050, 3 080 (Ar), 1 730 cm^{-1} (RCOOR'). ^1H NMR spectrum (C^2HCl_3): δ 7·94 (d, J = 8·5 Hz, 2 H, 3,5-H_2 in sulfonylphenyl), 7·57 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in sulfonylphenyl), 7·25 (m, 2 H, 2,6-H_2 in phenyl-N), 6·88 (m, 3 H, remaining ArH), 6·02 (dd, J = 8·0; 5·0 Hz, 1 H, Ar—CH—O), 3·12 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 3·04 (s, 3 H, CH_3SO_2), 2·50—2·90 (m, 6 H, 3 CH_2N^1 of piperazine and in the chain), 2·44 (q, J = 7·0 Hz, 2 H, CH_2CO), 1·19 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{22}H_{28}N_2O_4S$ (416·5) calculated: 63·43% C, 6·78% H, 6·72% N, 7·70% S; found: 63·72% C, 6·60% H, 6·48% N, 7·93% S.

Maleate sesquihydrate, m.p. 150—151°C (96% ethanol–chloroform). For $C_{26}H_{32}N_2O_8S + 1{\cdot}5\ H_2O$ (559·6) calculated: 55·81% C, 6·29% H, 5·01% N, 5·73% S; found: 56·13% C, 5·84% H, 4·99% N, 5·71% S.

1-(4-Methylsulfonylphenyl)-2-(4-phenylpiperazino)ethyl Benzoate (*VIII*)

A solution of 5·2 g *V* (ref.[1]) in 50 ml pyridine was treated with 2·43 g benzoyl chloride and the mixture was heated for 1·5 h to 70—80°C. After cooling it was poured into 600 ml water, the oily product was separated by decantation, it was dissolved in 250 ml benzene, the solution was dried with Na_2SO_4 and evaporated. The residue crystallized after the addition of 1 ml benzene and 1 ml hexane; 4·80 g (73%), m.p. 123—125°C. Analytical sample, m.p. 128—129°C (benzene–hexane). Mass spectrum, *m/z*: 464 (M^+ corresponding to $C_{26}H_{28}N_2O_4S$). UV spectrum: infl. at 250 nm (log ε 4·06). IR spectrum: 700, 719, 771, 780 (5 and 2 adjacent Ar—H), 1 159, 1 319 (SO_2), 1 281 (C—O of ester), 1 501, 1 609, 3 065, 3 095 (Ar), 1 720 cm^{-1} (ArCOOR). For $C_{26}H_{28}N_2O_4S$ (464·6) calculated: 67·21% C, 6·08% H, 6·03% N, 6·90% S; found: 67·41% C, 6·20% H, 6·20% N, 7·10% S.

Maleate, m.p. 195—196°C (aqueous ethanol). For $C_{30}H_{32}N_2O_8S$ (580·6) calculated: 62·06% C, 5·56% H, 4·82% N, 5·52% S; found: 62·22% C, 5·49% H, 4·82% N, 5·72% S.

1-(4-Methylsulfonylphenyl)-2-(4-phenylpiperazino)ethyl 4-Nitrobenzoate (*IX*)

The crude base (9·0 g) was prepared similarly like in the preceding case from 9·0 g *V* (ref.[1]) and 5·2 g 4-nitrobenzoyl chloride in 70 ml pyridine, dissolved in 40 ml chloroform and the solution was chromatographed on a column of 210 g neutral Al_2O_3 (activity II). Elution with chloroform gave in the first fractions an almost homogeneous product which was purified by crystallization from a mixture of benzene and hexane; 6·4 g (51%), m.p. 84—85°C. Mass spectrum, *m/z*: 509 (M^+ corresponding to $C_{26}H_{27}N_3O_6S$). UV spectrum: λ_{max} 252 nm (log ε 4·38). IR spectrum: 702, 730, 781 (5 and 2 adjacent Ar—H), 1 160, 1 320 (SO_2), 1 284 (C—O of ester), 1 532 ($ArNO_2$), 1 610 (Ar), 1 723 cm^{-1} (ArCOOR). ^1H NMR spectrum (C^2HCl_3): δ 8·32 and 8·15 (ABq, J = 8·0 Hz, 2 + 2 H, 4 ArH of nitrobenzoyl), 7·95 (d, J = 8·0 Hz, 2 H, 3,5-H_2

in sulfonylphenyl), 7·60 (d, J = 8·0 Hz, 2,6-H_2 in sulfonylphenyl), 6·70–7·20 (m, 5 H, C_6H_5), 6·25 (dd, 1 H, Ar—CH—O), 3·00 (s, 3 H, CH_3SO_2), 2·50–3·20 (m, 10 H, 5 CH_2N). For $C_{26}H_{27}N_3O_6S$ (509·6) calculated: 61·28% C, 5·34% H, 8·25% N, 6·29% S; found: 61·97% C, 5·44% H, 7·94% N, 6·27% S.

Maleate hemihydrate, m.p. 175–176°C (aqueous ethanol). For $C_{30}H_{31}N_3O_{10}S + 0{\cdot}5\ H_2O$ (634·6) calculated: 56·80% C, 5·07% H, 6·62% N, 5·05% S; found: 56·85% C, 5·04% H, 6·56% N, 5·20% S.

2-Hydroxy-4-(2-hydroxyethyl)-2-(4-methylsulfonylphenyl)-morpholine (*XI*)

A stirred solution of 22·0 g diethanolamine in 20 ml chloroform was treated dropwise with a solution of 27·7 g 4-methylsulfonylphenacyl bromide[10] in 250 ml chloroform and the mixture was refluxed for 16 h. After cooling 100 ml water were added, the mixture was stirred for 30 min and the precipitated product was filtered, washed with water and chloroform, and dried; 23·0 g (75%), m.p. 146–148°C. Analytical sample, m.p. 149–150°C (ethanol). IR spectrum: 776, 790, 835 (2 adjacent Ar—H), 1 045 (CH_2OH), 1 075 (C—OH), 1 120 (C—O—C), 1 157, 1 315 (SO_2), 1 600 (Ar), 2 740 (N—CH_2), 3 270 cm^{-1} (OH). For $C_{13}H_{19}NO_5S$ (301·3) calculated: 51·82% C, 6·36% H, 4·65% N, 10·64% S; found: 51·78% C, 6·97% H, 4·56% N, 10·60% S.

The *hydrochloride* was prepared by dissolving 6·0 g base and 2·1 ml hydrochloric acid in 100 ml ethanol and by evaporation of the solution *in vacuo*. The residue was crystallized from a mixture of 90% ethanol and ether, m.p. 156–157°C. IR spectrum: 840 (2 adjacent Ar—H), 1 058 (CH_2.OH), 1 110 (C—OH), 1 145(C—O—C), 1 156, 1 293, 1 303, 1 312 (SO_2), 1 492, 1 600, 3 030 (Ar), 2 755 (NH^+), 3 110, 3 275 cm^{-1} (OH). For $C_{13}H_{20}ClNO_5S$ (337·7) calculated: 46·22% C, 5·97% H, 10·49% Cl, 4·15% N, 9·49% S; found: 46·18% C, 6·26% H, 10·64% Cl, 4·16% N, 9·37% S.

2-(4-Ethylsulfonylphenyl)-2-hydroxy-4-(2-hydroxyethyl)morpholine (*XII*)

A similar reaction of 11·6 g 4-ethylsulfonylphenacyl bromide[11] with 8·5 g diethanolamine in 170 ml boiling chloroform and similar processing of the mixture gave 5·60 g (45%) *XII*, m.p. 134 to 138°C. Analytical sample, m.p. 137–138°C (ethanol–hexane). IR spectrum: 802 (2 adjacent Ar—H), 1 050 (CH_2OH), 1 138 (C—OH, C—O—C, SO_2), 1 302, 1 320 (SO_2), 3 282 cm^{-1} (OH). ^1H NMR spectrum: δ 7·85 (s, 4 H, ArH), 3·24 (q, 2 H, CH_2SO_2), 1·06 (t, 3 H, CH_3), 2·00–4·50 (m, remaining 5 CH_2 and 2 OH). For $C_{14}H_{21}NO_5S$ (315·4) calculated: 53·31% C, 6·71% H, 4·44% N, 10·17% S; found: 53·31% C, 6·92% H, 4·20% N, 10·03% S.

The *hydrochloride* was prepared by suspending 5·2 g base in a mixture of 40 ml ethanol and 6 ml water, acidification with 2·5 ml hydrochloric acid and by evaporation *in vacuo*. The solid residue was crystallized from aqueous ethanol, m.p. 160–161°C. IR spectrum: 840 (2 adjacent Ar—H), 1 060 (CH_2OH), 1 143 (C—OH, C—O—C, SO_2), 1 276 (OH), 1 306 (SO_2), 1 595, 1 612, 3 030 (Ar), 3 170, 3 310, 3 440 cm^{-1} (OH). For $C_{14}H_{22}ClNO_5S$ (351·8) calculated: 47·79% C, 6·30% H, 10·08% Cl, 3·98% N, 9·11% S; found: 47·45% C, 6·40% H, 10·21% Cl, 4·32% N, 9·14% S.

2-Hydroxy-4-(2-hydroxyethyl)-2-[4-(2-methylpropylsulfonyl)phenyl]morpholine (*XIII*)

A mixture of 24·0 g 4-(2-methylpropylsulfonyl)phenacyl bromide[1], 270 ml chloroform, and 16·0 g diethanolamine was refluxed for 16 h. After cooling the solution was washed with water, dried with Na_2SO_4 and evaporated *in vacuo*. The residue (33 g oil) was dissolved in a mixture

of 150 ml benzene and 30 ml ether and the solution was shaken with a solution of 25 ml hydrochloric acid in 200 ml water. The separated hydrochloride was filtered, dissolved in 400 ml warm water and the solution was combined with the aqueous layer of the filtrate. The solution obtained was washed with benzene, filtered with charcoal and partly evaporated *in vacuo*. The residue was allowed to crystallize in a refrigerator; 15·5 g (52%) hydrochloride monohydrate, m.p. 135–137°C. Analytical sample, m.p. 139–140°C (aqueous ethanol–ether). UV spectrum: λ_{max} 265 nm (log ε 3·04), 271·3 nm (3·01), infl. 259 nm (2·91). IR spectrum (KBr): 790 (2 adjacent Ar—H), 1 075 (CH_2OH), 1 155 (C—OH, C—O—C, SO_2), 1 300 (SO_2), 3 325 cm^{-1} (OH). For $C_{16}H_{26}ClNO_5S + H_2O$ (397·9) calculated: 48·29% C, 7·09% H, 8·91% Cl, 3·52% N, 8·06% S; found: 48·54% C, 7·26% H, 9·02% Cl, 3·58% N, 8·29% S.

The above hydrochloride (1·5 g) was suspended in 25 ml water, the suspension was made alkaline with NH_4OH and the base was extracted with chloroform. Processing of the extract gave the oily base which crystallized from a mixture of ethanol and some hexane, m.p. 101 to 102 C. UV spectrum: λ_{max} 259 nm (log ε 2·98), 264 nm (3·07), 271 nm (3·01), infl. 252 nm (2·92). IR spectrum: 798, 832 (2 adjacent Ar—H), 1 052 (CH_2OH), 1 158 (C—OH, C—O—C, SO_2), 1 308, 1 320 (SO_2), 3 285 cm^{-1} (OH). ^{1}H NMR spectrum (C^2HCl_3): δ 7·90 (s, 4 H, ArH), 3·80–4·50 (m, 2 H, disappears after ^2H_2O, 2 OH), 3·65 (t, 4 H, 2 CH_2O), 2·00–3·10 (m, 9 H, 3 CH_2N, SO_2CH_2CH), 1·00 (d, J = 6·0 Hz, 2 CH_3). For $C_{16}H_{25}NO_5S$ (343·4) calculated: 55·94% C, 7·34% H, 4·08% N, 9·34% S; found: 55·77% C, 7·55% H, 3·99% N, 9·26% S.

2-Hydroxy-4-(2-hydroxyethyl)-4-methyl-2-[4-(2-methylpropylsulfonyl)phenyl]morpholinium Iodide (*XIV*)

A solution of 9·0 g *XIII* in a mixture of 50 ml ethanol and 20 ml ether was treated with 3·8 g methyl iodide and the mixture was allowed to stand for 3 days at room temperature. It was evaporated *in vacuo* and the residue was crystallized from a mixture of 15 ml ethanol and 25 ml ether; 7·0 g (50%), m.p. 153–155°C. The product is a 1 : 1 solvate with ethanol. UV spectrum: λ_{max} 265 nm (log ε 3·10), 272 nm (3·07), infl. 260 nm (2·97). IR spectrum (KBr): 782, 840 (2 adjacent Ar—H), 1 080 (CH_2OH), 1 158 (C—OH, SO_2), 1 300 (SO_2), 3 380 cm^{-1} (OH). For $C_{17}H_{28}INO_5S + C_2H_6O$ (531·4) calculated: 42·94% C, 6·43% H, 23·88% I, 2·64% N, 6·04% S; found: 42·76% C, 6·12% H, 24·13% I, 2·88% N, 6·65% S.

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