POTENTIAL NEUROLEPTICS OF THE ORTHOPRAMIDE SERIES; SYNTHESIS OF N-SUBSTITUTED 5-(AMINOSULFONYL)-2-METHOXYBENZAMIDES

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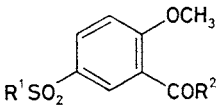
The mixed anhydride of 5-(aminosulfonyl)-2-methoxybenzoic acid (*VII*) and monoethyl carbonate reacted with benzylamine, 1-methylpiperazine, and 1-benzylpiperazine to give the 5-(aminosulfonyl)-2-methoxybenzamides *II*, *IV*, and *V*. Heating the ethyl ester *X* with 4-amino-1-methylpiperidine resulted in the amide *III*. Reaction of 5-(chlorosulfonyl)-2-methoxybenzoyl chloride (*XI*) with 1-benzylpiperazine afforded 5-(4-benzylpiperazinosulfonyl)-2-methoxybenzoic acid 4-benzylpiperazide (*VI*). Compounds *II*—*VI* are analogues of the antidopaminergic and antiemetic agent sulpiride (*I*) but only the benzylpiperazides *V* and *VI* showed indications of psychotropic activity of the neuroleptic type.

Neuroleptic agents of the orthopramide (*o*-anisamide, more generally benzamide) series represent a relatively new type of atypical antipsychotic drugs[1-3]. The best known substance, belonging to this type, is N-(1-ethyl-2-pyrrolidinylmethyl)-5-(aminosulfonyl)-2-methoxybenzamide (*I*) (sulpiride) which was first shown to be a potent inhibitor of apomorphine-induced vomiting in dogs[4] and was, therefore, considered a useful antiemetic. A more profound knowledge of its CNS pharmacology[5] and biochemical pharmacology[6-8] led, however, to recognition of its antidopaminergic character and its successful introduction into the pharmacotherapy of schizophrenia[9-14]. The antidopaminergic activity of sulpiride (*I*) was found to be stereoselective, the effects being connected with the (−)-enantiomer[15-17]. The affinity of sulpiride (*I*) to the striatal neuroleptic receptors enabled the use of [^{3}H]-sulpiride as a ligand for these receptors[18]. In connection with our systematic investigations in the group of tricyclic neuroleptic agents[19,20] we considered it worthwhile to synthesize the sulpiride analogues *II*—*VI* for pharmacological testing. The corresponding experiments are being described in the present communication.

The principal intermediate, used in the synthesis of compound *I* and analoues was 5-(aminosulfonyl)-2-methoxybenzoic acid (*VII*) which was prepared from 2-methoxybenzoic acid by chlorosulfonation and by subsequent ammonolysis[21], *i.e. via* the sulfonyl chloride *VIII* (ref.[22]). The acid *VII* was esterified with methanol or ethanol to give the esters *IX* and *X* (ref.[23]); the ethyl ester *X* has now also been obtained by ester exchange from the methyl ester *IX*. The chloride *XI* was obtained



I, $R^1 = NH_2$; $R^2 = NHCH_2$-(1-ethyl-2-pyrrolidinyl)

II, $R^1 = NH_2$; $R^2 = NHCH_2C_6H_5$

III, $R^1 = NH_2$; $R^2 = NH$-(4-methyl-1-piperazinyl)

IV, $R^1 = NH_2$; $R^2 = N$-(4-methyl-1-piperazinyl)

V, $R^1 = NH_2$; $R^2 = N$-(4-benzyl-1-piperazinyl)

VI, $R^1 = R^2 = N$-(4-benzyl-1-piperazinyl)

VII, $R^1 = NH_2$; $R^2 = OH$

VIII, $R^1 = Cl$; $R^2 = OH$

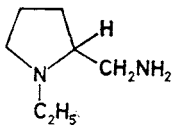
IX, $R^1 = NH_2$; $R^2 = OCH_3$

X, $R^1 = NH_2$; $R^2 = OC_2H_5$

XI, $R^1 = R^2 = Cl$

XII, $R^1 = R^2 = NH_2$

by treatment of the acid *VIII* with thionyl chloride[22]. A patent[24] described the transformation of methyl 2-methoxybenzoate[24] by chlorosulfonation and subsequent ammonolysis to the methyl ester *IX*; in our hands, the crystalline product obtained in a poor yield was identified as the diamide *XII*. It was mentioned in the literature[25] as one of the metabolites of sulpiride (*I*) and as the starting product of one sulpiride synthesis[26]. For preparing a sample of sulpiride (*I*) as the standard for pharmacological investigation[8] we heated a mixture of the methyl ester *IX* with an equimolecular amount of (1-ethyl-2-pyrrolidinylmethyl)amine (*XIII*). In patent literature the synthesis of compound *I* by slightly different procedures was described from the methyl ester *IX* (refs[24,27,28]), ethyl ester *X* (ref.[29]), and the corresponding butyl ester[21,30] (mostly in solvents). The starting amine *XIII* was obtained from 1-ethyl-2-(nitromethylene)pyrrolidine[31] by hydrogenation on Raney nickel under pressure (7 MPa) at 85°C; the described hydrogenation[31] at normal pressure and 30°C was found to proceed too slowly.



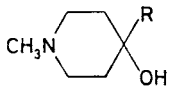
XIII

The amidation by heating the mixture of ethyl ester *X* with benzylamine to 100°C proceeded very sluggishly; the addition of a small amount of sodium methoxide had not much influence; the benzylamide *II* was obtained after 10 h in the yield of 5% only. For this reason, the mixed anhydride of the acid *VII* with monoethyl carbonate was prepared *in situ* by treatment of the acid *VII* with triethylamine and ethyl chloroformate in dichloromethane, and was subjected to the action of benzylamine; under these conditions the benzylamide *II* was obtained in the yield of 29%. Heating the ethyl ester *X* with 4-amino-1-methylpiperidine[32,33] to 120–130°C

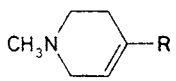
gave 54% of the amide *III*. A series of similar amides was described in a patent[34] but the N-methyl compound *III* was not included. The 4-methylpiperazide *IV* was prepared from the acid *VII* and 1-methylpiperazine in dichloromethane by the method using the mixed anhydride of the acid *VII* with monoethyl carbonate; the yield was again only 29%. Several piperazides of the acid *VII* have very recently been described[35]; the N-methyl compound *IV* has not been prepared. Reaction of the mentioned mixed anhydride with 1-benzylpiperazine in a mixture of dichloromethane and dioxane afforded the 4-benzylpiperazide *V*, obtained previously by different methods[22,35]. Its hydrogen oxalate and hydrochloride were prepared, the latter appearing in two crystalline forms (A, m.p. 180–184°C; B, m.p. 242–243·5°C). An attempt to follow a procedure[22] described for the preparation of compound *V*, consisting in treatment of the dichloride *XI* (ref.[22]) with 1-benzylpiperazine in chloroform, and in the subsequent ammonolysis, led to a mixture which was chromatographed on silica gel. The most polar fraction was the compound *V*, obtained in a moderate yield. The least polar product was identified to be the bis(4-benzylpiperazide) *VI* which was prepared for comparisn from the dichloride *XI* (ref.[22]) by treatment with a 100% exess of 1-benzylpiperazine in chloroform and fully characterized.

In connection with the present work some further potential intermediates were synthesized. 1-Methyl-4-phenylpiperidin-4-ol (*XIV*) (ref.[36]) was subjected to the Ritter reaction[37] with sodium cyanide in a mixture of acetic and sulfuric acid. A mixture was obtained which was separated by chromatography on alumina; the only characterized product to be isolated was identified as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (*XVII*), *i.e.* product of elimination. Its preparation by different procedures was described previously (refs[38,39]). It was clear that compound *XVI* was not the only product of the Ritter reaction and that the other product (probably *XIX*) escaped during the isolation procedure. For this reason, the reaction was repeated and the crude product was hydrolyzed with potassium hydroxide in boiling ethanol. The mixture of bases obtained was separated by chromatography on alumina. The olefinic amine *XVI* was eluted as the least polar product; the most polar (and major) product was an oily base which afforded the oxalate. The mass spectrum confirmed the elemental composition $C_{12}H_{18}N_2$ expected for the base *XVIII* but the whole procedure proved too inefficient as to serve as the basis for further work. Another attempt started from 1-(ethoxycarbonyl)-4-piperidone[40] which was treated with n-butylmagnesium bromide in ether and gave the hydroxy carbamate *XX*. Its hydrogenolysis with sodium dihydridobis(2-methoxyethoxo)aluminate (*cf.*[41]) afforded 4-butyl-1-methylpiperidin-4-ol (*XV*) obtained previously[42] by a different procedure. The subsequent Ritter reaction (*cf.*[43]) with hydrogen cyanide *in situ* gave the elimination product *XVII* as the only characterized one (ref.[42]). In the last attempt, *p*-tolunitrile[44] was brominated with N-bromosuccinimide (method[45]) to 4-(bromomethyl)-benzonitrile (ref.[46]). This compound was transformed by treatment with dimethyl-

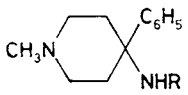
amine in ether to 4-(dimethylaminomethyl)benzonitrile (*XXI*) (ref.[47]). The reduction to the diamine *XXII* (ref.[47], different method) was accomplished successfully with sodium dihydridobis(2-methoxyethoxo)aluminate (*cf.*[41]) in a mixture of benzene and toluene.



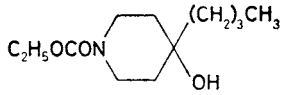
XIV, R = C_6H_5
XV, R = $(CH_2)_3CH_3$



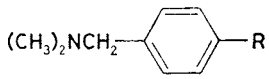
XVI, R = C_6H_5
XVII, R = $(CH_2)_3CH_3$



XVIII, R = H
XIX, R = CHO



XX



XXI, R = CN
XXII, R = CH_2NH_2

Compounds *II*, *III*, *V*, and *VI* (the last three in the form of salts described in the Experimental) were subjected to a preliminary pharmacological screening. They were administered orally (all doses were calculated *per* bases). In the rotarod test in mice doses of 500 mg/kg were administered: compound *III* was inactive, *V* showed ataxia in 30% of animals, *VI* elicited ataxia in 100% of animals (for sulpiride, ED_{50} = = c. 500 mg/kg). The same doses were administered in the test of inhibition of the climbing behaviour of mice which was induced by apomorphine (2 mg/kg *s.c.*): compounds *II* and *III* were inactive, *V* was active in 40% animals, and *VI* was also significantly active (for sulpiride, PD_{50} = 340 mg/kg (ref.[8])). For estimating the influence on the adrenaline toxicity in mice, the doses of 250 mg/kg were administered: compounds *II*, *III*, *V*, and *VI* were inactive. The same doses were used for establishing the influence on the lethal action of noradrenaline in rats: compounds *II*, *III*, and *V* were inactive, compound *VI* protected 40% of the animals. In conclusion, only the benzylpiperazides *V* and *VI* showed indications of psychotropic activity of the neuroleptic type.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler 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 8 000 spectrophotometer, IR spectra (in Nujol) with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $C^2H_3.SOC^2H_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with MCH 1320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3, and evaporated under reduced pressure on a rotating evaporator.

Ethyl 5-(Aminosulfonyl)-2-methoxybenzoate (*X*)

A stirred mixture of 80·0 g *IX*, 600 ml ethanol, and 6 ml H_2SO_4 was refluxed for 12 h. Approximately 300 ml of the solvent were distilled off through a column, the residue was cooled to 6°C, the crystalline product was filtered, and thoroughly washed with ice-cold water. Drying *in vacuo* gave 82·6 g (98%) *X*, m.p. 148–151°C. Ref.[23], m.p. 150°C.

5-(Aminosulfonyl)-2-methoxybenzamide (*XII*)

A cooled and stirred solution of 35 g methyl 2-methoxybenzoate[24] in 50 ml chloroform was treated dropwise over 1 h with 100 g chlorosulfonic acid at 15–18°C. The mixture was stirred for 30 min at 20°C, for 2 h at 35–40°C, and poured with stirring to 350 g ice. The organic layer was separated, the aqueous one extracted with chloroform, and the combined chloroform solutions were dried and partly evaporated *in vacuo* (6·7 kPa, 38°C). The cooled residue was dropped with stirring to 350 ml NH_4OH at 20–25°C (external cooling). The layers were separated and evaporated *in vacuo*. Whereas the organic layer contained only 0·6 g inhomogeneous oil, the aqueous layer gave 6·0 g (12%) *XII*, m.p. 245–246°C (aqueous ethanol). UV spectrum λ_{max}, nm (log ε): 236 (4·06), 290 (3·36). IR spectrum ν, cm^{-1}: 790, 820, 860 (2 adjacent and solitary Ar—H), 1 160, 1 325 (SO_2NH_2), 1 560, 1 579 (Ar), 1 646 ($ArCONH_2$), 3 360, 3 470 (NH_2). ^1H NMR spectrum: 8·30 (d, J = 2·0 Hz, 1 H, 6-H), 7·91 (dd, J = 8·0; 2·0 Hz, 1 H, 4-H), 7·70 (bs, 2 H, $CONH_2$), 7·30 (bs, 2 H, SO_2NH_2), 7·25 (d, J = 8·0 Hz, 1 H, 3-H), 3·99 (s, 3 H, OCH_3). For $C_8H_{10}N_2O_4S$ (230·2) calculated: 41·74% C, 4·38% H, 12·17% N, 13·90% S; found: 41·73% C, 4·41% H, 12·23% N, 13·60% S.

(±)-2-(Aminomethyl)-1-ethylpyrrolidine (*XIII*)

1-Ethyl-2-(nitromethylene)pyrrolidine[31] (280 g) was dissolved at 65°C in 6·6 l methanol, 65 g Raney nickel were added, and the mixture was hydrogenated in an autoclave with stirring at 85°C and at the pressure of 7 MPa H_2. After 5 h the reaction was finished and a sample did not show the presence of the starting compound (TLC). The catalyst was filtered off, washed with methanol, and the filtrate was distilled using a column *in vacuo* of approximately 1·3 kPa; 173 g (76%) *XIII*, b.p. 55°C/1·3 kPa. Gas chromatographic analysis showed the content of 99·75%. Ref.[13], b.p. 58–60°C/2·1 kPa or 66–68°C/4·0 kPa.

(±)-N-(1-Ethyl-2-pyrrolidinylmethyl)-5-(aminosulfonyl)-2-methoxybenzamide (*I*)

A mixture of 12·8 g *XIII* and 24·5 g *IX* (ref.[23]) was stirred and heated for 30 min to 100°C. After this time it solidified and was maintained at 100°C for 2·5 h without stirring. The cooled

melt was dissolved in 100 ml 1M-HCl, the clear solution was cooled to 10°C, the precipitated hydrochloride of *I* was filtered, and washed with 50% aqueous ethanol. The solid was dissolved in 100 ml water at 80–90°C, the solution was filtered while hot with active carbon, the filtrate was cooled to 40°C, and treated under stirring with 8·0 ml NH_4OH (final pH 10). The precipitated base *I* was filtered after cooling to 10°C, it was washed with ice-cold water, and dried *in vacuo*; 25·6 g (75%), m.p. 173·5–177°C. Analytical sample, m.p. 178·5–179·5°C (50% aqueous ethanol). UV spectrum λ_{max}, nm (log ε): 230 (4·23), 288·5 (3·37). IR spectrum ν, cm^{-1}: 825, 893 (2 adjacent and solitary Ar—H), 1 146, 1 170, 1 330 (SO_2NH_2), 1 245 ($ArOCH_3$), 1 510 (Ar), 1 550, 1 640 (CONHR), 3 380 (NH). ^1H NMR spectrum: 8·35 (bt, 1 H, CONH), 8·30 (d, J = 2·0 Hz, 1 H, 6-H), 7·90 (dd, J = 8·0; 2·0 Hz, 1 H, 4-H), 7·30 (d, J = 8·0 Hz, 1 H, 3-H), 7·30 (bs, 2 H, SO_2NH_2), 3·99 (s, 3 H, OCH_3), 1·10 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl), 1·40–3·70 (m, 11 H, 3 CH_2N, CH_2CH_2CH of pyrrolidine). Ref.[30], m.p. 178°C.

Hydrochloride, m.p. 225–227°C (water). For $C_{15}H_{24}ClN_3O_4S$ (377·9) calculated: 47·67% C, 6·40% H, 9·38% Cl, 11·12% N, 8·49% S; found: 47·62% C, 6·53% H, 9·43% Cl, 11·25% N, 8·55% S.

Methanesulfonate, m.p. 161–163·5°C (ethanol). For $C_{16}H_{27}N_3O_7S_2$ (437·5) calculated: 43·92% C, 6·22% H, 9·60% N, 14·66% S; found: 44·11% C, 6·40% H, 9·45% N, 14·59% S.

N-Benzyl-5-(aminosulfonyl)-2-methoxybenzamide (*II*)

A) A mixture of 6·46 g *X* and 2·75 g benzylamine was stirred for 5 h at 100°C. Because a sample of the mixture did not show any noticeable progress of the reaction (TLC), 0·1 g sodium methoxide were added and the heating was continued for further 5 h. After cooling, the mixture was diluted with ethanol and allowed to crystallize overnight. The solid was filtered and crystallized from ethanol; 0·4 g (5%), m.p. 198–200°C. UV spectrum λ_{max}, nm (log ε): 289 (3·43), infl. 230 (4·26). IR spectrum ν, cm^{-1}: 698, 740, 840, 905 (5 and 2 adjacent, and solitary Ar—H), 1 010, 1 245 ($ArOCH_3$), 1 175, 1 345 (SO_2NH_2), 1 483, 1 585, 3 030 (Ar), 1 560, 1 620 (ArCONHR), 3 280, 3 360 (NH, NH_2). ^1H NMR spectrum: 8·76 (bt, J = 6·0 Hz, 1 H, CONH), 8·15 (d, J = = 2·5 Hz, 1 H, 6-H), 7·87 (dd, J = 8·5; 2·5 Hz, 1 H, 4-H), 7·25 (bs, 7 H, C_6H_5 and SO_2NH_2), 7·20 (d, J = 8·5 Hz, 1 H, 3-H), 4·48 (d, J = 6·0 Hz, 2 H, $ArCH_2N$), 3·90 (s, 3 H, OCH_3). For $C_{15}H_{16}N_2O_4S$ (320·4) calculated: 56·23% C, 5·03% H, 8·75% N, 10·01% S; found: 56·17% C, 5·11% H, 8·41% N, 9·81% S.

B) A suspension of 9·1 g *VII* (ref.[21]) in 200 ml dichloromethane was treated with 4·05 g triethylamine, after 30 min stirring at room temperature, the mixture was cooled to −5°C, and treated with stirring with 5·0 g ethyl chloroformate added dropwise. The mixture was stirred for 1 h at −5°C and then treated dropwise with a solution of 3·8 g benzylamine in 15 ml dichloromethane, added over 15 min. It was stirred for 30 min at 0°C and allowed to stand overnight at room temperature. The solvent was evaporated, the residue stirred with 100 ml 1 : 5 dilute NH_4OH, the solid was filtered, and crystallized from ethanol; 3·3 g (29%) *II*, m.p. 198 to 200°C. The product was identical with that obtained according to *A*. Acidification of the ammoniacal aqueous filtrate recovered 4·1 g starting *VII*. The yield of *II per* conversion was thus 53%.

N-(1-Methyl-4-piperidinyl)-5-(aminosulfonyl)-2-methoxybenzamide (*III*)

A mixture of 13·0 g *X* (ref.[23]) and 5·70 g 4-amino-1-methylpiperidine[33] was heated for 5 h to 100°C, 0·1 g NaH were added and the mixture was heated for additional 6 h to 120–130°C. After cooling, the solid melt was refluxed with a mixture of 150 ml ethanol and 50 ml water, the

suspension was cooled, and the solid was filtered, 8·8 g (54%); m.p. 307–308°C (aqueous ethanol). Mass spectrum (heating to 330°C), *m/z*: 327 (M^+ corresponding to $C_{14}H_{21}N_3O_4S$), 98 (base peak), 97. IR spectrum *ν*, cm^{-1}: 838, 890 (2 adjacent and solitary Ar—H), 1 140, 1 310 (SO_2NH_2), 1 240 ($ArOCH_3$), 1 530, 1 629 (ArCONHR), 1 580 (Ar), 3 180 (NH, NH_2). For $C_{14}H_{21}N_3O_4S$ (327·4) calculated: 51·35% C, 6·47% H, 12·83% N, 9·80% S; found: 51·86% C, 6·54% H, 12·31% N, 9·75% S.

Methanesulfonate, m.p. 237–240°C and after new crystallization by further heating remelting at 256–258°C (95% ethanol). For $C_{15}H_{25}N_3O_7S_2$ (423·5) calculated: 42·54% C, 5·95% H, 9·92% N, 15·14% S; found: 42·35% C, 5·93% H, 10·13% N, 15·23% S.

5-(Aminosulfonyl)-2-methoxybenzoic Acid 4-Methylpiperazide (*IV*)

A suspension of 4·6 g *VII* (ref.[21]) in 100 ml dichloromethane was treated with 2·4 g triethylamine, and stirred for 30 min at room temperature. After cooling to −5°C, it was treated dropwise with 2·6 g ethyl chloroformate, and stirred for 1 h at −5°C. A solution of 2·4 g 1-methylpiperazine in 7·5 ml dichloromethane was then added over 15 min, and the mixture was stirred for 30 min at 0°C. After standing overnight at room temperature, the mixture was decomposed with 100 ml 0·5M-HCl, the acid aqueous layer was washed with dichloromethane and was made alkaline with 50 ml 2M-NaOH. The hydrophilic product could not be extracted with dichloromethane or chloroform. For this reason, the aqueous alkaline solution was evaporated *in vacuo*, the residue was extracted by a boiling mixture of 200 ml ethanol and 50 ml benzene, the solid (NaCl) was filtered off, the filtrate was evaporated *in vacuo*, and the hygroscopic residue, dissolved in 25 ml chloroform (with 1 ml methanol) was chromatographed on 150 g neutral Al_2O_3 (activity II). Elution with chloroform, containing 1% methanol, gave 1·8 g (29%) *IV*, m.p. 191–191·5°C (ethanol). UV spectrum λ_{max}, nm (log *ε*): 229 (4·18), 276·5 (3·21), 283 (3·20). IR spectrum *ν*, cm^{-1}: 816, 890 (2 adjacent and solitary Ar—H), 1 150, 1 335 (SO_2NH_2), 1 270 ($ArOCH_3$), 1 490, 1 575, 1 597 (Ar), 1 609 (ArCONRR'), 2 685 (CH_2—N, CH_3—N), 3 220 (NH_2). ^1H NMR spectrum: 7·79 (dd, J = 8·0; 2·0 Hz, 1 H, 4-H), 7·55 (d, J = 2·0 Hz, 1 H, 6-H), 7·25 (bs, 2 H, SO_2NH_2), 7·20 (d, J = 8·0 Hz, 1 H, 3-H), 3·88 (s, 3 H, OCH_3), 3·62 and 3·12 (2 bm, 2 + 2 H, $CH_2N^1CH_2$ of piperazine), c. 2·30 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·19 (s, 3 H, NCH_3). For $C_{13}H_{19}N_3O_4S$ (313·4) calculated: 49·82% C, 6·11% H, 13·41% N, 10·23% S; found: 49·81%C, 6·24% H, 13·73% N, 10·16% S.

5-(Aminosulfonyl)-2-methoxybenzoic Acid 4-Benzylpiperazide (*V*)

A suspension of 6·9 g *VII* (ref.[21]) in a mixture of 70 ml dichloromethane and 55 ml dioxane was treated with 3·7 g triethylamine, and the mixture was refluxed for 15 min. After cooling to −10°C, 3·9 g ethyl chloroformate were added dropwise and the mixture was stirred for 30 min at −10°C. 1-Benzylpiperazine (5·3 g) was slowly added at −5°C, the mixture was stirred for 1 h at 0°C and for 8·5 h at room temperature. The precipitated solid was filtered, dissolved in 50 ml water, the solution was evaporated *in vacuo*, and the residue (8·5 g inhomogeneous oil) was chromatographed on a column of 400 g neutral Al_2O_3 (activity II). Chloroform eluted 3·5 g oil and chloroform with 2% methanol afforded 1·7 g (15%) crystalline solid melting at 180–190°C. Recrystallization from ethanol led to pure *V*, m.p. 189–190°C. UV spectrum: λ_{max}, nm (log *ε*): 277·5 (3·25), 284 (3·23), infl. 229 (4·26). IR spectrum *ν*, cm^{-1}: 700, 743, 825, 895 (5 and 2 adjacent, and solitary Ar—H), 1 025, 1 260, 1 275 ($ArOCH_3$), 1 135, 1 160, 1 324, 1 335 (SO_2NH_2), 1 480, 1 495, 1 602, 3 080 (Ar), 1 630 (ArCONRR'), 2 810 (OCH_3, N—CH_2), 3 190, 3 340 (NH_2). ^1H NMR spectrum: 7·82 (dd, J = 8·5; 2·5 Hz, 1 H, 4-H), 7·60 (d, J = 2·5 Hz, 1 H, 6-H), 7·28 (bs, 7 H, C_6H_5 and SO_2NH_2), 7·18 (d, J = 8·5 Hz, 1 H, 3-H), 3·85 (s, 3 H, OCH_3), 3·60 and 3·12

(2 bm, 2 + 2 H, $CH_2N^1CH_2$ of piperazine), 3·48 (s, 2 H, $ArCH_2N$), 2·30 (bm, 4 H, $CH_2N^4CH_2$ of piperazine). Refs[22,35], m.p. 189°C and 186–187°C, respectively.

Hydrogen oxalate, m.p. 138–142°C (ethanol). For $C_{21}H_{25}N_3O_8S$ (479·5) calculated: 52·60% C, 5·26% H, 8·76% N, 6·69% S; found: 52·62% C, 5·41% H, 8·96% N, 7·00% S.

Hydrochloride: Crystal form A, m.p. 180–184°C (ethanol–ether). For $C_{19}H_{24}ClN_3O_4S$ (425·9) calculated: 53·56% C, 5·68% H, 8·33% Cl, 9·87% N, 7·53% S; found: 53·81% C, 5·87% H, 8·11% Cl, 9·76% N, 7·45% S. Crystal form B, m.p. 242–243·5°C (ethanol); found: 53·62% C, 5·61% H, 8·32% Cl, 10·06% N, 7·39% S.

5-(4-Benzylpiperazinosulfonyl)-2-methoxybenzoic Acid 4-Benzylpiperazide (*VI*)

A) A stirred solution of 8·9 g 5-(chlorosulfonyl)-2-methoxybenzoyl chloride (*XI*) (ref.[22]) in 30 ml chloroform was treated over 1 h with a solution of 12·3 g 1-benzylpiperazine in 12 ml chloroform. The mixture was stirred for 1 h without heating and refluxed for 30 min. After cooling, 7·5 g Na_2CO_3 were added, the mixture was refluxed for further 30 min and stirred at room temperature for 2·5 h. After standing overnight, the solid was filtered off, the filtrate was evaporated *in vacuo*, and the residue was crystallized from 50 ml ethanol; 8·4 g (46%) *VI*, m.p. 100 to 104°C (ethanol). Mass spectrum, *m/z* (composition, %): 548·2414 (M^+ corresponding to $C_{30}H_{36}N_4O_4S$, calculated 548·2457, 1·5%), 457 ($C_{23}H_{29}N_4O_4S$, 3), 402 ($C_{20}H_{24}N_3O_4S$, 3·5), 308 (2·5), 175 ($C_{11}H_{15}N_2$, 100), 146, 132, 91. For $C_{30}H_{36}N_4O_4S$ (548·7) calculated: 65·67% C, 6·61% H, 10·21% N, 5·84% S; found: 65·34% C, 7·01% H, 9·98% N, 5·70% S.

Maleate, m.p. 206–207°C (90% ethanol–ether). For $C_{38}H_{44}N_4O_{12}S$ (780·8) calculated: 58·45% C, 5·68% H, 7·18% N, 4·11% S; found: 58·06% C, 5·86% H, 7·21% N, 4·30% S.

B) A stirred solution of 8·8 g 1-benzylpiperazine in 10 ml chloroform was treated dropwise over 1 h with a solution of 13·5 g *XI* (ref.[22]) at 0–10°C. The mixture was slowly added to a stirred solution of 20 ml NH_4OH in 20 ml water at 10–20°C. After 15 min stirring at this temperature, the mixture was heated, and refluxed for 30 min. After standing overnight, the chloroform layer was separated, evaporated, and the residue (21·5 g; TLC: mixture of 5 substances) was chromatographed on a column of 300 g silica gel. Chloroform eluted 3·0 g (11%) *VI* (m.p. 100–104°C), identical with the product obtained under *A*. Elution with chloroform, containing 10% methanol, yielded 2·8 g (14%) *V*, m.p. 185–189°C (ethanol).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (*XVI*)

A stirred solution of 5·73 g *XIV* (ref.[36]) in 11 ml acetic acid was slowly treated at 22°C with 4·3 g NaCN. A mixture of 12 ml H_2SO_4 and 10 ml acetic acid was added over 15 min (temperature rose spontaneously to 50°C) and the mixture was stirred for 6 h without heating or cooling. Under cooling it was poured into 100 ml water, the mixture was made alkaline with 60 ml 40% NaOH, and extracted with ether. Processing of the extract gave 4·2 g inhomogeneous oil which was chromatographed on 180 g neutral Al_2O_3 (activity II). Elution with benzene, containing 10% chloroform, gave 3·3 g (64%) oil which slowly crystallized from light petroleum, m.p. 37–38°C, and was shown to be *XVI*. UV spectrum: λ_{max}, nm (log ε): 245·5 (4·12). ^1H NMR spectrum (C^2HCl_3): 7·25 (m, 5 H, C_6H_5), 6·00 (bm, 1 H, 5-H), 3·08 (bm, 2 H, 6,6-H_2), 2·59 (m, 4 H, 2,2,3,3-H_4), 2·38 (s, 3 H, NCH_3). Refs[38,39], m.p. 33°C and 40–42°C, respectively.

4-Amino-1-methyl-4-phenylpiperidine (*XVIII*)

The Ritter reaction was similarly carried out from 5·73 g *XIV* (ref.[36]) and 5·9 g NaCN in the presence of 22 ml acetic acid and 16 ml H_2SO_4. The crude product (5·8 g mixture of at least

3 components) was refluxed for 3 h with a solution of 18 g KOH in 20 ml ethanol. After cooling it was diluted with 60 ml water and extracted with ether. Processing of the extract gave 4·9 g oily mixture which was chromatographed on 300 g neutral Al_2O_3 (activity II). Elution with benzene, containing 10% chloroform, gave successively 0·4 g *XVI* (m.p. 33–37°C), 0·5 g *XIV* (m.p. 110°C, ref.[36]), and 2·8 g (49%) oily *XVIII* which was transformed by neutralization with oxalic acid dihydrate in ethanol to the sesquioxalate, m.p. 208–210°C (85% ethanol). Mass spectrum, *m/z* (%): 190·1460 (M^+ corresponding to $C_{12}H_{18}N_2$, calculated 190·1470, 5%), 173 (100), 172 (44), 144, 130, 96 (42), 71 (20), 70 (22). For $C_{15}H_{21}N_2O_6$ (325·4) calculated: 55·36% C, 6·53% H, 8·61% N; found: 54·92% C, 6·78% H, 8·46% N.

4-(n-Butyl)-1-(ethoxycarbonyl)piperidin-4-ol (*XX*)

Reaction of 11·7 g Mg and 65·7 g n-butyl bromide in 160 ml ether afforded the n-butylmagnesium bromide solution, which was diluted with 500 ml ether, and treated under stirring with a solution of 65·8 g 1-(ethoxycarbonyl)-4-piperidone[40] in 60 ml ether. The mixture was stirred for 2 h, decomposed with 300 ml 10% NH_4Cl, and the separated organic layer was dried and distilled; 47·4 g (54%), b.p. 128–138°C/93 Pa. A sample for analysis was redistilled and the middle fraction was used; b.p. 135°C/93 Pa. IR spectrum ν, cm^{-1}: 1 096 (tert. C—OH), 1 247, 1 278 (C—O of ester), 1 675 (NCOOR), 3 440 (OH). ^1H NMR spectrum (C^2HCl_3): 4·10 (q, J = 7·0 Hz, 2 H, OCH_2), 3·00–3·90 (m, 4 H, CH_2NCH_2), 1·85 (bs, 1 H, OH), c. 1·50 (m, 10 H, remaining 5 CH_2 groups), 1·21 (t, J = 7·0 Hz, 3 H, CH_3 in ethoxyl), 0·90 (def. t, 3 H, CH_3 of butyl). For $C_{12}H_{23}NO_3$ (229·3) calculated: 62·85% C, 10·11% H, 6·11% N; found: 62·37% C, 9·84% H, 6·43% N.

4-(n-Butyl)-1-methylpiperidin-4-ol (*XV*)

A stirred solution of 29·9 g *XX* in 150 ml benzene was slowly treated with 100 g 50% solution of sodium dihydridobis(2-methoxyethoxo)aluminate in toluene. The mixture was stirred for 6 h at 60°C, decomposed by slow addition of 100 ml 2·5M-NaOH and 40 ml water, and the product was isolated by extraction with benzene. Processing of the extract and distillation of the residue gave 17·1 g (59%) *XV*, b.p. 114–116°C/2·0 kPa. Redistilled analytical sample had the b.p. 112°C/1·6 kPa. ^1H NMR spectrum (C^2HCl_3): 2·20 (s, 3 H, NCH_3), 1·90 (bs, disappears after ^2H_2O, 1 H, OH), 0·89 (def. t, 3 H, CH_3 of butyl). For $C_{10}H_{21}NO$ (171·3) calculated: 70·12% C, 12·36% H, 8·18% N; found: 70·09% C, 12·35% H, 8·06% N. Ref.[42], b.p. 110–120°C/1·73 kPa.

4-(n-Butyl)-1-methyl-1,2,3,6-tetrahydropyridine (*XVII*)

The Ritter reaction of 5·1 g *XV* and 5·9 g NaCN in 22 ml acetic acid and 16 ml H_2SO_4 was carried out similarly like in the preceding cases. The crude product (4·7 g inhomogeneous oil) was subjected to fractional distillation *in vacuo*; 1·2 g (26%) *XVII*, b.p. 72°C/1·33 kPa. Ref.[42], b.p. 84–87·5°C/1·3 kPa. The base was transformed by neutralization with oxalic acid dihydrate in ethanol and by the addition of ether to the hydrogen oxalate, m.p. 117·5–120°C (2-propanol–ether). Mass spectrum, *m/z* (%): 153·1521 (M^+ corresponding to $C_{10}H_{19}N$, calculated 153·1517, 21%), 152 (18), 110 (16), 96 (100), 68 (32), 67 (16), 45 (23). ^1H NMR spectrum: 11·15 (bs, COOH of oxalic acid), 5·35 (bm, 1 H, 5-H), 3·60 (bm, 2 H, 6,6-H_2), 3·20 (t, J = 6·0 Hz, 2 H, =C—CH_2 in butyl), 2·78 (s, 3 H, NCH_3), 0·86 (def. t, 3 H, CH_3 of butyl). For $C_{12}H_{21}NO_4$ (243·3) calculated: 59·24% C, 8·70% H, 5·76% N; found: 59·23% C, 8·58% H, 5·69% N.

4-(Bromomethyl)benzonitrile

A stirred solution of 11·7 g *p*-tolunitrile[44] in 50 ml tetrachloromethane was slowly treated with

18·1 g N-bromosuccinimide and 0·85 g dibenzoyl peroxide, and the mixture was refluxed for 7 h. After cooling, the solid was filtered off and extracted repeatedly with tetrachloromethane. The extracts were combined with the filtrate, evaporated, and the residue was crystallized from ethanol; 10·1 g (52%),m.p. 112–115°C. Ref.[46], m.p. 115–116°C.

4-(Dimethylaminomethyl)benzonitrile (*XXI*)

The reaction of 9·8 g 4-(bromomethyl)benzonitrile with 10 ml dimethylamine (cooled to −10°C) in 350 ml ether was carried out according to the described procedure[47], and gave 6·5 g (81%) *XXI*, b.p. 84°C/93 Pa. Ref.[47], b.p. 78–82°C/7–13 Pa.

Hydrochloride, m.p. 260–264°C with decomposition (ethanol). For $C_{10}H_{13}ClN_2$ (196·7) calculated: 61·06% C, 6·66% H, 18·03% Cl, 14·25% N; found: 61·08% C, 6·59% H, 18·01% Cl, 14·68% N.

4-(Dimethylaminomethyl)benzylamine (*XXII*)

A stirred solution of 5·4 g *XXI* in 15 ml benzene was treated over 1 h with 50 ml 52% sodium dihydrodobis(2-methoxyethoxo)aluminate in toluene, diluted with 90 ml benzene. The mixture was refluxed for 1 h, cooled, and decomposed under cooling with 32 ml 2M-NaOH, added dropwise over 2 h. After dilution with 50 ml benzene, the organic layer was dried and evaporated. Distillation of the residue *in vacuo* gave 4·4 g (79%) *XXII*, b.p. 82–84°C/80 Pa. Ref.[47], b.p. 92–96°C/13 Pa.

Dihydrochloride, m.p. 278–281°C with decomposition (ethanol). For $C_{10}H_{18}Cl_2N_2$ (237·2) calculated: 50·64% C, 7·65% H, 29·90% Cl, 11·81% N; found: 50·42% C, 7·23% H, 29·85% Cl, 12·02% N.

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REFERENCES

1. Kaiser C. in the book: *Burger's Medicinal Chemistry*, 4th ed. (M. E. Wolff, Ed.), Part III, p. 944. Wiley, New York 1981.
2. Jenner P., Marsden C. D.: Life Sci. *25*, 479 (1979).
3. Jenner P., Marsden C. D.: Neuropharmacology *20*, 1285 (1981).
4. Justin-Besancon L., Thominet M., Laville C., Margarit J.: C. R. Acad. Sci., D *265*, 1253 (1967); Chem. Abstr. *68*, 11323 (1968).
5. Valzelli L., Bernasconi S.: Psychopharmacologia *26*, 255 (1972).
6. Kato R., Sato Y., Shimomura K.: J. Pharmacol. *5* (Suppl. 2), *48*, 48 (1974).
7. O'Connor S. E., Brown R. A.: Gen. Pharmacol. *13*, 185 (1982); Chem. Abstr. *97*, 49077 (1982).
8. Metyšová J., Valchář M.: Activ. Nerv. Super. *26*, 27 (1984).
9. Burchard J. M., Gross L., Kempe P.: Int. J. Clin. Pharmacol. Ther. Toxicol. *6*, 266 (1972).
10. Toru M., Shimazono Y., Miyasaka M., Kokubo T., Mori Y., Nasu T.: J. Clin. Pharmacol. *12*, 221 (1972).
11. Eckman F.: Arzneim.-Forsch. *24*, 993 (1974).
12. Cassano G. B., Castrogiovanni P., Conti L., Bonollo L.: Curr. Ther. Res. *17*, 189 (1975).

13. Mielke D. H., Galland D. M., Roniger J. J., Kessler C.: Psychopharmacol. Bull. *13* (3), 40 (1977).
14. Cassano G. B., Castrogiovanni P., Conti L., Bonollo L.: Psychopharmacol. Bull. *13* (3), 41 (1977).
15. Hofmann M., Jommi G. C., Montefusco O., Tonon G. C., Spano P. P., Trabucchi M.: J. Neurochem. *32*, 1547 (1979).
16. Jenner P., Clow A., Reavill C., Theodorou A., Marsden C. D.: J. Pharm. Pharmacol. *32*, 39 (1980).
17. De Maio D., Ferrario M., Oppizzi G., Scieghi G.: *12th CINP Congress, Göteborg, June 1980*; Abstracts, p. 236. Pergamon Press, Oxford 1980.
18. Freedman S. B., Poat J. A., Woodruff G. N.: Neuropharmacology *20*, 1323 (1981); Chem. Abstr. *96*, 193237 (1982).
19. Protiva M.: Pharm. Ind. *32*, 923 (1970).
20. Protiva M.: Respharma *1985* (Dec.), 41.
21. Lange F. W., Mueller J. (Chemisches Laboratorium Fritz–Walter Lange): Ger. Offen. 2,253,463 (Appl. 31.10.72); Chem. Abstr. *81*, 91342 (1974).
22. Liebenow W., Grafe I. (Ludwig Heumann & Co.): Ger. Offen. 2,721,643 (Appl. 13.05.77); Chem. Abstr. *90*, 103673 (1979).
23. Yousef A. F., Abou-Ouf A. A., El-Gendy M. A.: Acta Chim. Hung. *69*, 81 (1971).
24. Lieber G. (Microsules Argentina S. A.): Ger. Offen. 2,305,632 (Argentina Appl. 10.04.72); Chem. Abstr. *80*, 14838 (1974).
25. Sugnaux F. R., Benakis A.: Eur. J. Drug Metab. Pharmacokinet. *3*, 235 (1978); Chem. Abstr. *91*, 32595 (1979).
26. Shimizu S., Takano H. (Nippon Iyakuhin Kaihatsu Kenkyusho Y. K.; Sankei Yakuhin K. K.): Japan. Kokai Tokkyo Koho 79 154,756 (Appl. 26.05.78); Chem. Abstr. *93*, 26259 (1980).
27. Zoni G., Bellani P. (Italfarmaco S.p.A.): Ger. Offen. 2,459,221 (Ital. Appl. 21.12.73); Chem. Abstr. *83*, 178806 (1975).
28. Kosary J., Kasztreiner E., Farkas L., Borvendeg J., Eggenhofer J., Pap V., Balogh T., Somogyi G., Orban E. *et al.* (Alkaloida Vegyeszeti Gyar): Ger. Offen. 2,613,394 (Hung. Appl. 28.03.74); Chem. Abstr. *86*, 5309 (1977).
29. Mauri F. (Gaver S. A.): Can. 965.425 (Swiss Appl. 18.07.73); Chem. Abstr. *83*, 79070 (1975).
30. Bulteau G., Acher J., Monier J. C. (Société d'Etudes Scientifiques et Industrielles de l'Ile-de--France): Ger. Offen. 2,507,989 (Fr. Appl. 05.03.74); Chem. Abstr. *84*, 30875 (1976).
31. Kamiya A., Hashimoto M. (Société d'Etudes Scientifiques et Industrielles de l'Ile-de-France): Ger. Offen. 1,966,195 (Japan Appl. 19.08.68); Chem. Abstr. *77*, 48223 (1972).
32. Tomita K.: J. Pharm. Soc. Jpn. *71*, 1053 (1951); Chem. Abstr. *46*, 5044 (1952).
33. Brookes P., Terry R. J., Walker J.: J. Chem. Soc. *1957*, 3165.
34. Spickett R. G. W., Moragues Mauri J., Prieto Soto J. (Antonio Gallardo, S. A.): Ger. Offen. 2,513,136 (Brit. Appl. 21.03.74); Chem. Abstr. *84*, 30908 (1976).
35. Botré C., Botré F., Jommi G., Signorini R.: J. Med. Chem. *29*, 1814 (1986).
36. McElvain S. M., Safranski J. C., jr: J. Am. Chem. Soc. *72*, 3134 (1950).
37. Krimen L. I., Cota D. J.: Org. React. *17*, 213 (1969).
38. Büchi J., Prost M., Eichenberger H., Lieberherr R.: Helv. Chim. Acta *35*, 1527 (1952).
39. Schmidle C. J., Mansfield R. C.: J. Am. Chem. Soc. *78*, 425 (1956).
40. Šindelář K., Rajšner M., Červená I., Valenta V., Jílek J. O., Kakáč B., Holubek J., Svátek E., Mikšík F., Protiva M.: Collect. Czech. Chem. Commun. *38*, 3879 (1973).
41. Štrouf O., Čásenský B., Kubánek V.: *Sodium Dihydridobis(2-methoxyethoxo)aluminate (SDMA), A Versatile Organometallic Hydride*, pp. 146, 172. Academia, Prague 1985.

42. McElvain S. M., Berger R. S.: J. Am. Chem. Soc. *77*, 2848 (1955).
43. Zagorevskii V. A., Lopatina K. I.: Zh. Obshch. Khim. *33*, 2525 (1963).
44. Clarke H. T., Read R. R.: Org. Synth., Coll. Vol. I, 514 (1946).
45. Schmid H., Karrer P.: Helv. Chim. Acta *29*, 573 (1946).
46. Banse G.: Ber. Dtsch. Chem. Ges. *27*, 2161 (1894).
47. Bardsley W. G., Crabbe M. J. C., Shindler J. S., Ashford J. C.: Biochem. J. *127*, 875 (1972); Chem. Abstr. *77*, 58128 (1972).

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