SYNTHESIS OF SEVERAL 4-HYDROXY-3,5-DIMETHOXYBENZAMIDES, THEIR O-SUBSTITUTED DERIVATIVES AND SOME RELATED COMPOUNDS AS POTENTIAL NEUROTROPIC AGENTS

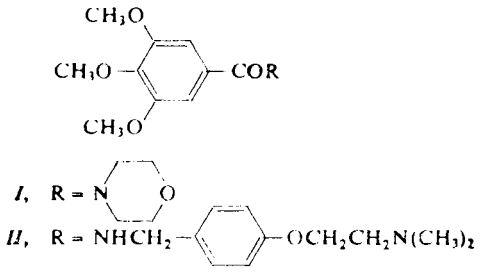
Vladimír VALENTA and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

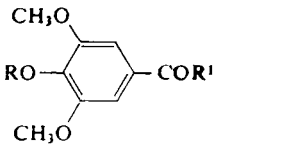
Received June 26th, 1984

Reactions of 4-benzyloxy-3,5-dimethoxybenzoyl chloride with pyrrolidine, piperidine, morpholine and 1-methylpiperazine gave the amides *IIIa*—*IIId* which were debenzylated by catalytic hydrogenation on palladium. The 4-hydroxy-3,5-dimethoxybenzamides *IVa*—*IVc* were then treated with sodium hydride and 2-dimethylaminoethyl chloride to give the O-(2-dimethylaminoethyl)amides *Va*—*Vc*. The 3,4,5-trimethoxybenzamide *IX* was prepared as a homologue of the antiemetic agent "trimethobenzamide" (*II*) and reduced to the benzylaniline derivative *X*. The substituted nicotinamide *XI* was obtained from nicotinoyl chloride and 4-(2-diethylaminoethoxy)aniline. Out of the compounds prepared the amides *IIId* and *Vc* had some anticonvulsant activity, the piperazide *IVd* revealed a significant α-adrenolytic effect and the amino ether *X* reduced the blood pressure of normotensive rats.

Investigations[1,2] in the series of 3,4,5-trimethoxybenzamides led to the discovery of "trimethozine" (*I*) which found practical use in pharmacotherapy as a tranquillizing agent[3]. 4-Alkoxy-3,5-dimethoxybenzamides with a higher alkyl in the alkoxy group proved to have anticonvulsant activity[4] and aminoalkyl 4-alkoxy--3,5-dimethoxybenzoates were found to be spasmolytic agents of the papaverine type[5]. An independent study of 4-alkoxy-3,5-dimethoxybenzamides[6] characterized these compounds as analgetics. "Trimethobenzamide" (*II*), which is used as an antiemetic agent[7,8], is also a substituted 3,4,5-trimethoxybenzamide. The purpose of the present paper was the synthesis of O-substituted syringamides, containing the aryl 2-dialkylaminoethyl ether fragment in their molecules, as potential anticonvulsant and antidepressant agents.

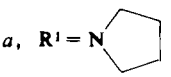


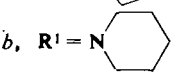
Reactions of 4-benzyloxy-3,5-dimethoxybenzoyl chloride[4] with an excess of pyrrolidine, piperidine, morpholine and 1-methylpiperazine in boiling benzene gave the amides *IIIa–IIId* in satisfactory yields which were characterized by UV and IR spectra (partly with ^{1}H NMR spectra). The piperazine derivative *IIId* was prepared also in the form of the hydrochloride. The four amides were then debenzylated by catalytic hydrogenation in ethanol at normal pressure and making use of palladium on carbon as the catalyst. The hydroxybenzamides *IVa–IVc* were obtained in high yields and characterized by spectra. In the case of the piperazine derivative there was obtained in a relatively low yield a high-melting substance whose analysis did not correspond to compound *IVd*. The mass spectrum, however, confirmed the expected composition $C_{14}H_{20}N_2O_4$. The product was then identified as the hydrochloride of compound *IVd*; the only source of hydrogen chloride was the hydrogenolysis of palladium(II) chloride which was added to the reaction mixture instead of the metal. The amides *IVa–IVc* were subjected to treatment with sodium hydride and 2-dimethylaminoethyl chloride in dimethylformamide. There resulted the oily bases *Va–Vc* which afforded crystalline hydrogen oxalates. In the cases of compounds *Va* and *Vb* the identity was confirmed by recording the mass spectra of the oxalates. For making sure the identity of compound *Vc*, the oily base was released from the oxalate and its ^{1}H NMR spectrum was recorded.

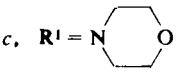


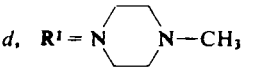
III, R = $CH_2C_6H_5$
IV, R = H
V, R = $CH_2CH_2N(CH_3)_2$

In formulae *III – V*:

a, R^1 = 

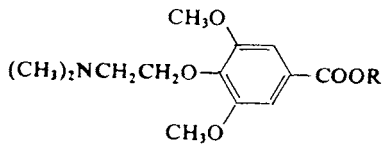
b, R^1 = 

c, R^1 = 

d, R^1 = 

An attempt at preparing compounds *Va–Vd* by a reversed sequence in which the O-(2-dimethylaminoethyl) group would be first introduced into the molecule of a 4-hydroxy-3,5-dimethoxybenzoic acid derivative, and only then the amidation would be carried out, was not successful. Methyl 4-hydroxy-3,5-dimethoxybenzoate[9,10] was transformed by a known procedure[5] to the O-(2-dimethylaminoethyl) derivative *VI* which was heated on the one hand with morpholine, and with 1-methylpiperazine on the other to 120–140°C. The expected amides *Vc* and *Vd* were not obtained; the same product resulted in both cases and was identified as the acid *VII*. The preparation of this compound by a different procedure was described in the literature[5] and the given melting point of the hydrochloride is in agreement with our value.

The free amino acid *VII* was not described. We have not an unequivocal explanation for the unexpected course of these reactions. There is probably necessary to assume the intervention of small amounts of water – either contained in the starting amines or supplied by the air moisture into the reaction mixtures which were heated for a relatively long time (7·5 – 10 h) without protection from the air. The methyl ester *VI* is probably easily hydrolyzed in the presence of bases to the acid *VII*. On the other hand its acid hydrolysis with boiling dilute hydrochloric acid, which is described in the literature[5], is evidently uneasy; we were not able to follow the literature procedure and the only product obtained was the hydrochloride of the amino ester *VI*. Also unsuccessful was the attempt to react the acid *VII* with cyclohexylamine in dichloromethane in the presence of N,N'-carbonyldiimidazole (method[11–13]): the starting acid *VII* was recovered. The acid *VII* could not be transformed to the acid chloride (or its hydrochloride) by heating with thionyl chloride in benzene like described[5]; our product was identified as the acid *VII* hydrochloride. Reaction of 4-hydroxy-3,5-dimethoxybenzoic acid[14] with two molecules of sodium ethoxide in ethanol gave the suspension of the disodium salt which was treated with an excess of 2-dimethylaminoethyl chloride at the boiling point of the mixture. An oily base was obtained in a low yield and gave the dihydrochloride crystallizing as the monohydrate. The mass spectrum and analysis of this compound proved its identity of the ester *VIII*. The literature[5] described this compound as the nonsolvated dihydrochloride with a little higher melting point than our substance; the compound was allegedly prepared from the chloride of the acid *VII*.

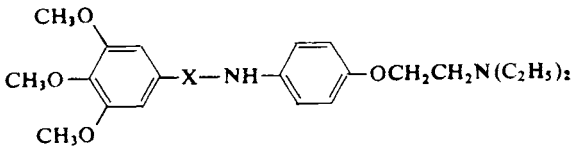


VI, R = CH_3
VII, R = H
VIII, R = $CH_2CH_2N(CH_3)_2$

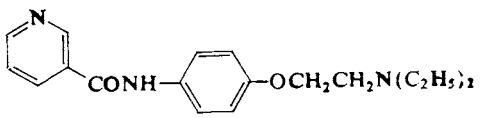
Reaction of 4-(2-diethylaminoethoxy)aniline[15] with 3,4,5-trimethoxybenzoyl chloride[16] in pyridine afforded the benzanilide *IX* which is a homologue of "trimethobenzamide" (*II*); the oily base was transformed to the hydrochloride. Reduction of the amide *IX* with lithium aluminium hydride in tetrahydrofuran gave the diamine *X* which afforded the dihydrochloride. Reaction of 4-(2-diethylaminoethoxy)aniline[15] with the crude nicotinoyl chloride hydrochloride[17] in pyridine resulted directly in the hydrochloride of the nicotinamide *XI*.

Most of the compounds prepared were pharmacologically tested in the form of salts, described in the Experimental, by methods of the general pharmacological screening.

It was searched after the following effects: (*a*) central neurotropic (discoordinating, analgetic, anticonvulsant, body temperature influencing, thiopental potentiation-influencing the spontaneous locomotor activity, antireserpine, anticataleptic, antitus, sive), (*b*) neurovegetative and peripheral neurotropic (local anaesthetic, mydriatic,



IX, X = CO
X, X = CH_2



XI

antispasmodic, antihistamine), (*c*) cardiovascular (influencing the blood pressure, adrenolytic, antiarrhythmic, peripheral vasodilating, (*d*) diuretic, antiinflammatory. First of all the acute toxicity in mice (LD_{50} in mg/kg) and the doses (D in mg/kg) used in the screening are given (*i.v.* administration): *IIId*, 125, 25; *IVb*, 300, 60; *IVd*, 400, 80; *Va*, 100, 20; *Vb*, 125, 25; *Vc*, 115, 20; *IX*, 150, 25; *X*, 55, 10; *XI*, 100, 20. In most of the tests mentioned, the compounds were ineffective in doses D. In the acute toxicity determination the first toxic symptoms with some compounds were an increase of activity and reactivity which was followed by tremor, ataxia and convulsions (*IIId*, *IVb*), with some other there was a central depression (*IVd*, *Vc*). Out of the central effects, the anticonvulsant one (towards pentetrazole) was observed with two compounds: *IIId* (ED = 125 mg/kg orally) and *Vc* (ED = 100 mg/kg orally). Compound *X* in a dose of 13 mg/kg *i.v.* prolongs the thiopental sleeping time to 350% of the control value and it exhibits anticataleptic activity in rats (against the perphenazine catalepsy) in the dose D. Three compounds decreased the blood pressure in normotensive rats: *IVd* (*i.v.* doses of 10–80 mg/kg brought about drops of the pressure by 10–35% lasting for 2–10 min), *IX* (in a dose of 15 mg/kg *i.v.* a drop of blood pressure by 60% in rabbits lasting for 1–2 min), *X* (a longer lasting drop of the pressure after the dose D). Compound *IV* had a significant α-adrenolytic effect (ED = 10 mg/kg *i.v.*) in rats.

EXPERIMENTAL

The melting points of analytical samples were determined in the 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 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with the spectrometers MS 902 (AEI) and Varian MAT-311. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were processed by drying with $MgSO_4$, Na_2SO_4 or K_2CO_3, filtration and evaporation of the filtrates under reduced pressure on a rotating evaporator.

N-(4-Benzyloxy-3,5-dimethoxybenzoyl)pyrrolidine (*IIIa*)

A stirred solution of 30 g pyrrolidine in 20 ml benzene was slowly treated with a suspension of 21·5 g 4-benzyloxy-3,5-dimethoxybenzoyl chloride[4] in 100 ml benzene, the mixture was refluxed for 3 h, diluted with 200 ml benzene, washed with water, 10% NH_4OH and water, dried with K_2CO_3 and evaporated; 19·9 g (83%) crude *IIIa*, m.p. 114–121°C. Analytical product was obtained by crystallization from 50% ethanol with filtration of the hot solution with active carbon; m.p. 121·5–123·5°C. UV spectrum: λ_{max} 257 nm (log ε 4·04). IR spectrum: 715, 762, 860 (5 adjacent and solitary Ar–H), 1 132, 1 230 (ArOR), 1 465, 1 509, 1 583, 2 990, 3 018, 3 038 (Ar), 1 622 cm^{-1} ($ArCONR_2$). For $C_{20}H_{23}NO_4$ (341·4) calculated: 70·36% C, 6·79% H, 4·10% N; found: 70·47% C, 7·03% H, 4·45% N.

N-(4-Benzyloxy-3,5-dimethoxybenzoyl)piperidine (*IIIb*)

A reaction of 11·0 g 4-benzyloxy-3,5-dimethoxybenzoyl chloride[4] with 12·7 g piperidine in 60 ml benzene was carried out similarly like in the preceding case and the mixture was similarly processed; 9·5 g (77%) crude *IIIb*, m.p. 112–120°C. Analytical sample, m.p. 121·5–122·5°C (90% methanol). UV spectrum: λ_{max} 245 nm (log ε 4·02). IR spectrum: 700, 732, 758, 767, 840, 850 (5 adjacent and solitary Ar–H), 1 130, 1 229 (ArOR), 1 467, 1 506, 1 585, 2 905, 3 018, 3 045, 3 070 (Ar), 1 626 cm^{-1} ($ArCONR_2$). For $C_{21}H_{25}NO_4$ (355·4) calculated: 70·96% C, 7·09% H, 3·94% N; found: 70·92% C, 7·17% H, 3·91% N.

N-(4-Benzyloxy-3,5-dimethoxybenzoyl)morpholine (*IIIc*)

A similar reaction of 11·4 g 4-benzyloxy-3,5-dimethoxybenzoyl chloride[4] with 10 g morpholine in 60 ml benzene gave 8·2 g (66%) crude *IIIc*, m.p. (110)–135°C. Analytical sample, m.p. 137·5 to 138°C (ethanol). UV spectrum: λ_{max} 246 nm (log ε 3·95). IR spectrum: 703, 759, 840 (5 adjacent and solitary Ar–H), 1 120, 1 238 (ROR and ArOR), 1 504, 1 585, 3 032, 3 050 (Ar), 1 626 ($ArCONR_2$), 2 815, 2 850 cm^{-1} ($ArOCH_3$). ^{1}H NMR spectrum: δ 7·30 (m, 5 H, C_6H_5), 6·55 (s, 2 H, 2,6-H_2), 4·95 (s, 2 H, $ArCH_2O$), 3·75 (s, 6 H, 2 OCH_3), 3·55 (bs, 8 H, 2 NCH_2CH_2O). For $C_{20}H_{23}NO_5$ (357·4) calculated: 67·21% C, 6·48% H, 3·92% N; found: 67·48% C, 6·60% H, 3·92% N.

1-(4-Benzyloxy-3,5-dimethoxybenzoyl)-4-methylpiperazine (*IIId*)

A similar reaction of 16·9 g 4-benzyloxy-3,5-dimethoxybenzoyl chloride[4] with 11·0 g 1-methylpiperazine in 200 ml benzene gave 13·0 g (64%) crude *IIId*, m.p. 110–116°C. Analytical sample, m.p. 117–119°C (benzene–cyclohexane–light petroleum). UV spectrum: λ_{max} 248 nm (log ε 3·95). IR spectrum: 701, 732, 758, 846 (5 adjacent and solitary Ar–H), 1 127, 1 230 (ArOR), 1 506, 1 576 (Ar), 1 629 cm^{-1} ($ArCONR_2$). ^{1}H NMR spectrum: δ 7·20–7·50 (m, 5 H, C_6H_5), 7·60 (s, 2 H, 2,6-H_2), 5·00 (s, 2 H, $ArCH_2O$), 3·80 (s, 6 H, 2 OCH_3), 3·60 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·35 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{21}H_{26}N_2O_4$ (370·4) calculated: 68·08% C, 7·07% H, 7·56% N; found: 68·05% C, 6·89% H, 7·21% N.

Hydrochloride, m.p. 231–233°C with decomposition (ethanol–ether). For $C_{21}H_{27}ClN_2O_4$ (406·9) calculated: 61·98% C, 6·69% H, 8·71% Cl, 6·88% N; found: 61·66% C, 6·89% H, 8·80% Cl, 6·87% N.

N-(4-Hydroxy-3,5-dimethoxybenzoyl)pyrrolidine (*IVa*)

A solution of 16·5 g *IIIa* in 450 ml ethanol was treated with 10 g active carbon and 2 ml solution of $PdCl_2$ containing 0·12 g Pd. The mixture was hydrogenated under normal conditions (temperature, pressure) with shaking. The theoretical consumption of hydrogen was reached within 1 h. The mixture was filtered and evaporated in vacuo; 10·7 g (89%) crude *IVa*, m.p. (150) to 165°C. Analytical sample, m.p. 170–171·5°C (75% aqueous ethanol). UV spectrum: λ_{max} 262 nm (log ε 3·94). IR spectrum: 890 (solitary Ar—H), 1 120, 1 224, 1 320 (ArOR, ArOH), 1 518, 1 580 (Ar), 1 600 ($ArCONR_2$), 2 710, 3 220 cm^{-1} (ArOH on H-bond with C=O). ^1H NMR spectrum: δ 6·85 (s, 2 H, 2,6-H_2), 5·88 (bs, 1 H, OH), 3·90 (s, 6 H, 2 OCH_3), 3·60 (bm, 4 H, CH_2NCH_2 in pyrrolidine), 1·90 (bm, 4 H, remaining 2 CH_2 of pyrrolidine). For $C_{13}H_{17}NO_4$ (251·3) calculated: 62·13% C, 6·82% H, 5·57% N; found: 62·45% C, 6·71% H, 5·52% N.

N-(4-Hydroxy-3,5-dimethoxybenzoyl)piperidine (*IVb*)

IIIb (13·8 g) was similarly hydrogenated in 400 ml ethanol using 8 g active carbon and 8 ml solution of $PdCl_2$ containing 0·5 g Pd. The crude product was crystallized from a mixture of 25 ml benzene and 2·5 ml light petroleum; 9·4 g (90%), m.p. 122–129°C. Analytical sample, m.p. 132–133·5°C (benzene–light petroleum). UV spectrum: λ_{max} 258 nm (log ε 3·84). IR spectrum: 860 (solitary Ar—H), 1 118, 1 225, 1 330 (ArOR, ArOH), 1 520, 1 587 (Ar), 1 605 ($ArCONR_2$ with C=O in H-bond), 2 810 ($ArOCH_3$), 3 120 cm^{-1} (OH). ^1H NMR spectrum: δ 6·70 (s, 2 H, 2,6-H_2), 5·90 (bs, 1 H, OH), 3·90 (s, 6 H, 2 OCH_3), 3·60 (bm, 4 H, CH_2NCH_2), 1·62 (bs, 6 H, remaining 3 CH_2 of piperidine). For $C_{14}H_{19}NO_4$ (265·3) calculated: 63·38% C, 7·22% H, 5·28% N; found: 63·25% C, 6·92% H, 5·18% N.

N-(4-Hydroxy-3,5-dimethoxybenzoyl)morpholine (*IVc*)

IIIc (6·8 g) was similarly hydrogenated in 120 ml ethanol using 4·0 g active carbon and 4 ml solution of $PdCl_2$ containing 0·24 g Pd. After filtration the solid was extracted with 100 ml boiling ethanol, the filtrates were combined and evaporated; 4·45 g (88%), m.p. 162–164°C. Analytical sample, m.p. 163·5–164·5°C (ethanol). UV spectrum: λ_{max} 260 nm (log ε 3·88). IR spectrum: 853 (solitary Ar—H), 1 124, 1 243, 1 329 (ArOR, ArOH), 1 585 (Ar), 1 607 ($ArCONR_2$ with C=O in H-bond), 2 708, 3 260 cm^{-1} (OH in H-bond). ^1H NMR spectrum: δ 6·61 (s, 2 H, 2,6-H_2), 5·75 (bs, 1 H, OH), 3·82 (s, 6 H, 2 OCH_3), 3·61 (bs, 8 H, 2 OCH_2 and 2 NCH_2 of morpholine). For $C_{13}H_{17}NO_5$ (267·3) calculated: 58·41% C, 6·41% H, 5·24% N; found: 58·33% C, 6·80% H, 5·05% N.

1-(4-Hydroxy-3,5-dimethoxybenzoyl)-4-methylpiperazine (*IVd*)

IIId (4·5 g) was similarly hydrogenated in 150 ml ethanol using 2·5 g active carbon and 2·2 ml solution of $PdCl_2$ containing 0·15 g Pd; 1·1 g (27%) hydrochloride of *IVd*, m.p. 249°C with decomposition (95% ethanol). Mass spectrum, *m/z* (%): 280 (M^+ corresponding to $C_{14}H_{20}N_2O_4$, 12%), 223 (8), 181 (31), 99 (35), 83 (60), 70 (100). For $C_{14}H_{21}ClN_2O_4$ (316·8) calculated: 53·08% C, 6·68% H, 8·84% N; found: 52·78% C, 6·88% H, 9·19% N.

N-[3,5-Dimethoxy-4-(2-dimethylaminoethoxy)benzoyl]pyrrolidine (*Va*)

A solution of 4·1 g *IVa* in 40 ml dimethylformamide was stirred, treated at 10°C with 0·43 g 93% NaH and then with 7·0 g 2-dimethylaminoethyl chloride, added dropwise. The mixture was stirred for 5 h at room temperature, allowed to stand overnight and distributed between 35 ml water and 90 ml benzene. The benzene layer was dried with $MgSO_4$ and evaporated *in vacuo*. The residue (2·4 g oil) was transformed by neutralization with 1·1 g oxalic acid dihydrate in 5·5 ml acetone and treatment with ether to the hydrogen oxalate; 2·28 g (38%), m.p. 131–133°C (acetone). Mass spectrum, *m/z*: 322 (M^+ corresponding to $C_{17}H_{26}N_2O_4$), 236, 72, 58. For $C_{19}H_{28}N_2O_8$ (412·4) calculated: 55·33% C, 6·84% H, 6·79% N; found: 55·40% C, 6·81% H, 6·76% N.

N-[3,5-Dimethoxy-4-(2-dimethylaminoethoxy)benzoyl]piperidine (*Vb*)

A solution of 6·1 g *IVb* in 60 ml dimethylformamide was treated under stirring at 10°C with 0·6 g 93% NaH and then with 9·9 g 2-dimethylaminoethyl chloride. The mixture was stirred for 5 h at 7–10°C, allowed to stand overnight, diluted with 60 ml water and extracted with benzene. Processing of the extract gave 2·8 g crude base which was transformed to the hydrogen oxalate similarly like in the preceding case; 2·1 g (22%), m.p. 143·5–144·5°C (acetone). Mass spectrum, *m/z* (%): 336 (M^+ corresponding to $C_{18}H_{28}N_2O_4$), 72 (70), 58 (100). For $C_{20}H_{30}N_2O_8$ (426·5) calculated: 56·32% C, 7·09% H, 6·57% N; found: 55·97% C, 6·91% H, 6·42% N.

N-[3,5-Dimethoxy-4-(2-dimethylaminoethoxy)benzoyl]morpholine (*Vc*)

A solution of 5·9 g *IVc* in 50 ml dimethylformamide was stirred, treated at 5°C with 0·62 g 90% NaH and then with 8·6 g 2-dimethylaminoethyl chloride. The mixture was stirred for 6 h at 12°C, allowed to stand overnight at room temperature and finally stirred for 1 h at 65°C. After cooling the solid was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in 80 ml chloroform, the solution was washed with water and 20 ml 1M-NaOH, dried with K_2CO_3 and evaporated under reduced pressure. The oily residue (5·2 g) was transformed to the hydrogen oxalate similarly like in the preceding cases; 4·6 g (50%), m.p. 141–143°C (acetone–ethanol–ether). For $C_{19}H_{28}N_2O_9$ (428·4) calculated: 53·26% C, 6·59% H, 6·54% N; found: 53·03% C, 6·68% H, 6·48% N.

A sample of the oxalate was decomposed with NH_4OH, the oily base was isolated by extraction with dichloromethane and used for recording the ^1H NMR spectrum: δ 6·58 (s, 2 H, 2,6-H_2), 4·10 (t, J = 6·0 Hz, 2 H, OCH_2 in the chain), 3·89 (s, 6 H, 2 OCH_3), 3·68 (bs, 8 H, 4 CH_2 of morpholine), 2·71 (t, 2 H, CH_2N in the chain), 2·31 (s, 6 H, CH_3NCH_3).

3,5-Dimethoxy-4-(2-dimethylaminoethoxy)benzoic Acid (*VII*)

A) A mixture of 3·0 g *VI* (ref.[5]) and 3·0 g 1-methylpiperazine was stirred for 7·5 h at 130 to 140°C. After evaporation of methylpiperazine *in vacuo* the residue was diluted with 100 ml toluene and the precipitate was filtered; 2·8 g (98%) *VII*, m.p. 218–220°C (methanol). For $C_{13}H_{19}NO_5$ (269·3) calculated: 57·98% C, 7·11% H, 5·20% N; found: 58·14% C, 6·86% H, 5·26% N. Treatment of *VII* with HCl in a mixture of methanol and ether gave the hydrochloride, m.p. 250 to 252·5°C (ethanol). Lit.[5], m.p. 249–251°C with decomposition.

B) A mixture of 2·83 g *VI* (ref.[5]) and 5·0 g morpholine was stirred and refluxed for 10 h. Morpholine was evaporated *in vacuo* and the solid residue (2·7 g, 100%) identified as *VII*, m.p. 217·5–219°C (methanol). The hydrochloride melted at 247·5–250°C.

C) A mixture of 1·9 g *VII*, 8 ml benzene and 5 ml $SOCl_2$ was refluxed for 1·5 h and evaporated *in vacuo*. The residue was diluted with 10 ml toluene and the solid was filtered; 2·2 g hydrochloride of *VII*, m.p. 245–250°C.

2-Dimethylaminoethyl 3,5-Dimethoxy-4-(2-dimethylaminoethoxy)benzoate (*VIII*)

4-Hydroxy-3,5-dimethoxybenzoic acid[14] (4·95 g) was added to a stirred solution of sodium ethoxide (1·15 g Na in 25 ml ethanol) and the formed suspension of the disodium salt was treated with 8·2 g 2-dimethylaminoethyl chloride. The stirred mixture was refluxed for 6 h, the solvent was evaporated and the residue was distributed between 50 ml 1M-NaOH and 200 ml benzene. The benzene layer was washed with water, dried and evaporated. The residue is the oily crude *VIII*; 2·0 g (24%). The dihydrochloride crystallized from wet 2-propanol as the monohydrate, m.p. 197–200·5°C. Mass spectrum, *m/z*: 340 (M^+ corresponding to $C_{17}H_{28}N_2O_5$), 296, 129 (?), 98, 72, 58, 43. UV spectrum: λ_{max} 263 nm (log ε 4·08), infl. 300 nm (3·71). IR spectrum (KBr): 866 (solitary Ar-H), 1 130, 1 228, 1 339 (ArOR, COOR), 1 509, 1 600 (Ar), 1 722 cm^{-1} (ArCOOR) For $C_{17}H_{32}Cl_2N_2O_6$ (431·4) calculated: 47·33% C, 7·47% H, 16·44% Cl, 6·49% N; found: 47·19% C, 7·62% H, 15·84% Cl, 6·30% N.

N-[4-(2-Diethylaminoethoxy)phenyl]-3,4,5-trimethoxybenzamide (*IX*)

A solution of 2·0 g 4-(2-diethylaminoethoxy)aniline[15] in 20 ml pyridine was stirred and slowly treated with 2·3 g 3,4,5-trimethoxybenzoyl chloride[16]. The spontaneously warmed mixture was allowed to stand for 12 h, pyridine was evaporated *in vacuo* and the residue was distributed between 1% NaOH and 100 ml chloroform. The chloroform layer was dried and evaporated. The residue was dissolved in ethanol and the solution treated with a slight excess of HCl in ethanol. The hydrochloride was filtered and recrystallized from a mixture of methanol and ether; 3·2 g (83%), m.p. 203°C. For $C_{22}H_{31}ClN_2O_5$ (438·9) calculated: 60·19% C, 7·12% H, 8·08% Cl, 6·38% N; found: 60·11% C, 7·12% H, 8·14% Cl, 6·51% N.

N-(3,4,5-Trimethoxybenzyl)-4-(2-diethylaminoethoxy)aniline (*X*)

Hydrochloride of *IX* (12·1 g) was decomposed with NH_4OH and the base *IX* was isolated by extraction with chloroform. *IX* (11·1 g) was dissolved in 50 ml tetrahydrofuran and the solution was dropped into a stirred suspension of 6·0 g $LiAlH_4$ in 50 ml tetrahydrofuran. The mixture was stirred and refluxed for 4 h, allowed to stand at room temperature for 12 h and then decomposed under stirring with a slow addition of 6 ml water, 6 ml 15% NaOH and 18 ml water. After 30 min stirring the solid was filtered off and washed with ether, the filtrate was dried with K_2CO_3 and evaporated *in vacuo*; 7·9 g (74%) crude oily *X*. Neutralization with HCl in a mixture of ethanol and ether and crystallization from ethanol gave 3·8 g dihydrochloride, m.p. 176–180°C. For $C_{22}H_{34}Cl_2N_2O_4$ (461·4) calculated: 57·26% C, 7·43% H, 15·37% Cl, 6·07% N; found: 57·17% C, 7·55% H, 15·13% Cl, 5·99% N.

N-[4-(2-Diethylaminoethoxy)phenyl]nicotinamide (*XI*)

A stirred solution of 12·6 g 4-(2-diethylaminoethoxy)aniline[15] in 50 ml pyridine was slowly treated with a solution of 10·7 g nicotinoyl chloride hydrochloride[17] in 70 ml pyridine and the spontaneously warmed mixture was allowed to stand for 12 h at room temperature. The suspension of the product formed was diluted with 100 ml ether and after 30 min standing the hydrochloride of *XI* was filtered, washed with ether and dried; 19·2 g (90%), m.p. 205–208°C. Analytical sample, m.p. 206–208°C (ethanol). For $C_{18}H_{24}ClN_3O_2$ (349·8) calculated: 61·79% C, 6·91% H, 12·01% N; found: 61·96% C, 6·94% H, 11·94% N.

Compounds IX–XI *were prepared by Dr I. Jirkovský in this laboratory. The authors thank Mrs M. Vlková for the help with the synthesis, Drs E. Svátek, J. Holubek, M. Ryska and Mrs A. Hrádková (Physico-chemical department of this institute) and Dr J. Protiva (Department of organic*

chemistry, Charles University, Prague) for recording and interpretation of the spectra, Drs F. Hradil, M. Bartošová and S. Wildt (affiliated unit of the institute at Pardubice-Rosice) for the pharmacological data, and finally Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Kropáčová, Mr M. Čech and Mr K. Havel (Analytical department of this institute) for carrying out the analyses.

REFERENCES

1. Vargha L., Kasztreiner E., Borsy J., Farkas L., Kuszmann J., Dumbovich B.: Biochem. Pharmacol. *11*, 639 (1962).
2. Kasztreiner E., Borsy J., Vargha L.: Biochem. Pharmacol. *11*, 651 (1962).
3. Kósa L.: Ther. Hung. *21*, 96 (1973).
4. Egyesult Gyogyszer es Tapszergyar: Neth. Appl. 66/5 460 (Hung. Appl. 22.04.65); Chem. Abstr. *67*, 32 496 (1967).
5. Kasztreiner E., Vargha L., Borsy J.: Acta Chim. Acad. Sci. Hung. *51*, 327 (1967).
6. Vacher J., Duchene-Marullaz P., Lakatos C., Farenc M. J., Busch N.: Med. Pharmacol. Exptl. *12*, 49 (1965); Chem. Abstr. *62*, 13 704 (1965).
7. Goldberg M. W., Teitel S. (Hoffmann-La Roche, Inc.): U.S. 2 789 293 (24.03.59); Chem. Abstr. *53*, 16 066 (1959).
8. Schallek W., Heise G. A., Keith E. F., Bagdon R. E.: J. Pharmacol. Exp. Ther. *126*, 270 (1959); Chem. Abstr. *53*, 20 516 (1959).
9. Hahn G., Wassmuth H.: Ber. Deut. Chem. Ges. *67*, 696 (1934).
10. Horning E. C., Parker J. A.: J. Amer. Chem. Soc. *74*, 2 107 (1952).
11. Staab H. A.: Angew. Chem. *74*, 407 (1962); Angew. Chem., Int. Ed. *1*, 351 (1962).
12. Staab H. A., Lüking M., Dürr F. H.: Chem. Ber. *95*, 1 275 (1962).
13. Červená I., Protiva M.: This Journal *49*, 1 009 (1984).
14. Bogert M. T., Coyne B. B.: J. Amer. Chem. Soc. *51*, 571 (1929).
15. Büchi J., Enézian J., Enézian G., Valette G., Pattani C.: Helv. Chim. Acta *43*, 1 971 (1960).
16. Reeve W., Sterling J. D., jr: J. Amer. Chem. Soc. *71*, 3 657 (1949).
17. Späth E., Spitzer H.: Ber. Deut. Chem. Ges. *59*, 1 479 (1926).

Translated by the author (M. P.).