SYNTHESIS OF 4-METHOXYPHENOXYACETIC AND 3,4,5-TRIMETHOXYPHENOXYACETIC ACID AMIDES AND HYDRAZIDES AS POTENTIAL NEUROTROPIC AND CARDIOVASCULAR AGENTS

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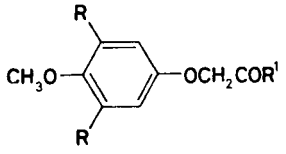
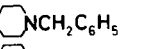
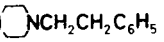
4-Methoxyphenoxyacetyl chloride, 3,4,5-trimethoxyphenoxyacetic acid and its methyl ester were reacted with 2-phenylethylamine, 1-benzylpiperazine, 1-(2-phenylethyl)piperazine, 1-(1--phenyl-2-propyl)piperazine, isopropylhydrazine, 1-aminopiperidine, and 4-aminomorpholine and afforded the amides and hydrazides *Iab—IVab* and *Vb—VIIIb*. 1-Amino-4-methylpiperazine and 1-amino-4-phenylpiperazine were transformed to the hydrazones *XV* and *XVI*, and to the quaternary salts *XVII* and *XVIII*. Pharmacological screening showed indications of thymoleptic activity with compounds *Ia—IIIa*, anorectic effect with *IIa* and *IIIb*, antiarrhythmic activity with *IIIa*, *XVII*, and *XVIII*, and myorelaxant effect with *XVII* and *XVIII*. Antimicrobial and anthelmintic effects were also noted.

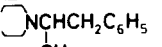
The present communication represents a continuation of our previous papers[1,2] dealing with amides of 3,4,5-trimethoxyphenoxyacetic acid and further three trisubstituted phenoxyacetic acids. The task was to search after new neurotropic and psychotropic agents (especially antidepressants) and to prepare products for testing for cadiovascular activities; the prototypes were the antidepressant agent "mefexamide", *i.e.* N-(2-diethylaminoethyl)-4-methoxyphenoxyacetamide[3], and "trimethophenoxamide", N-(2-diethylaminoethyl)-3,4,5-trimethoxyphenoxyacetamide, showing



I, $R^1 = NHCH_2CH_2C_6H_5$

II, $R^1 =$ 

III, $R^1 =$ 

IV, $R^1 =$ 

V, $R^1 = N(C_2H_5)_2$

VI, $R^1 = NH{-}NHCH(CH_3)_2$

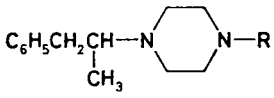
VII, $R^1 =$ 

VIII, $R^1 =$ 

In formulae *I–VIII*: *a*, R = H *b*, R = OCH_3

antiarrhythmic activity[1]. We describe here in the first line the synthesis of four new N-substituted 4-methoxyphenoxyacetamides *Ia–IVa*, corresponding 3,4,5-trimethoxyphenoxyacetamides *Ib–IVb*, and three hydrazides of the trimethoxy acid *VIb* to *VIIIb*.

The first to be prepared was N-(2-phenylethyl)-4-methoxyphenoxyacetamide (*Ia*) which was obtained by reaction of 4-methoxyphenoxyacetyl chloride[4] with a 100% excess of 2-phenylethylamine in chloroform. Similar reaction of 4-methoxyphenoxyacetyl chloride[4] with 1-benzylpiperazine[5] and 1-(2-phenylethyl)piperazine[6], which were used only in a slight escess, gave the oily bases *IIa* and *IIIa* which were converted to hydrochlorides. For preparing the further member of the series, *i.e. IVa*, 1-(1-phenyl-2-propyl)piperazine (*IX*) was needed. Literature[7] described the preparation of this product by reaction of 1-phenyl-2-propyl 4-toluenesulfonate with piperazine. We used the following synthesis: 1-Phenylpropan-2-one was reduced with sodium borohydride in ethanol (for different reduction methods, *cf.* refs[8–10]) to 1-phenylpropan-2-ol which was trasnformed by the described procedure to the 4-toluenesulfonate[10,11]. Reaction of this ester with 1-(ethoxycarbonyl)piperazine gave the carbamate *X* (its preparation by a different procedure was described[12]) which was hydrolyzed with a concentrated ethanolic solution of potassium hydroxide to give *IX*. Its reaction with 4-methoxyphenoxyacetyl chloride[4] in chloroform gave directly the hydrochloride of *IVa*.

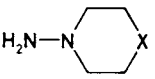


IX, R = H
X, R = $COOC_2H_5$

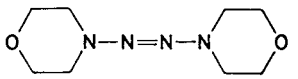
In the 3,4,5-trimethoxyphenoxyacetic acid series (*b*) it was not possible to use the acid chloride since an attempt at its preparing by reaction of the acid[13] with thionyl chloride and by the following distillation of the mixture led to cleavage of the Ar—O—CH_2 ether bond and the only characterized product obtained was identified as 3,4,5-trimethoxyphenol (ref.[14]). The free acid[13] and its methyl ester[1] were thus used as the starting materials. Reaction of the methyl ester with 2-phenylethylamine in boiling ethanol gave the amide *Ib*. The piperazides *IIb–IVb* were obtained by heating the corresponding piperazine salts of 3,4,5-trimethoxyphenoxyacetic acid to 190°C; the bases were transformed to hydrochlorides. The same method, applied to the corresponding diethylamine salt, afforded in a low yield the diethylamide *Vb*.

For further work the cyclic hydrazine derivatives *XI–XIII* were needed in addition to isopropylhydrazine[15] and 1-aminopiperidine[16,17], which were prepared by described procedures. Compounds *XI–XIII* were prepared by reduction of 4-nitroso-

morpholine[18], 1-methyl-4-nitrosopiperazine[19], and 1-nitroso-4-phenylpiperazine[20] with lithium aluminium hydride in ether (method[16,17]). The preparation of *XI* (ref.[17]), *XII* (refs[19,21]), and *XIII* (ref.[20]) was described by different methods (see references). In the preparation of *XI*, N,N'-dimorpholinodiimide (*XIV*) was isolated as a by-product. The same compound was mentioned in the literature[22] as a minor by-product of the reduction of 4-nitrosomorpholine with zinc and acetic acid.



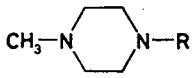
XI, X = O
XII, X = NCH_3
XIII, X = NC_6H_5

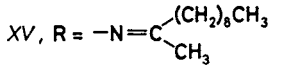


XIV

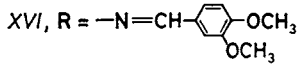
An attempt to prepare the hydrazide *VIb* by treatment of methyl 3,4,5-trimethoxyphenoxyacetate[1] with isopropylhydrazine[15] in boiling ethanol failed (no reaction); heating of both compounds without solvent to 120°C afforded the hydrazide *VIb* in satisfactory yield. The hydrazide *VIIb* was obtained by reaction of methyl 3,4,5--trimethoxyphenoxyacetate[1] with 1-aminopiperidine in a boiling mixture of butanol and toluene. *VIIIb* resulted similarly by heating a mixture of the ester with *XI* to 120°C.

Reaction of *XII* with 2-undecanone in boiling ethanol gave the hydrazone *XV* which is easily cleaved by acids. This lability made impossible the preparation of the hydrochloride; even treatment with maleic acid in ethanol at 50°C led to cleavage and *XII* dimaleate was isolated as the only product. Similar reaction of *XII* with 3,4--dimethoxybenzaldehyde afforded the hydrazone *XVI* which proved more stable and could be transformed to the maleate. Reaction of *XII* with benzyl chloride (2 molecules per one of *XII*) in ether led to the bisquaternary salt *XVII*. Similar

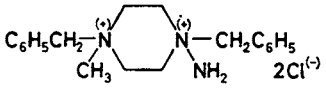




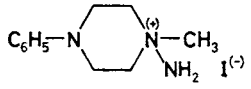
XV, R = $-N=C(CH_3)(CH_2)_8CH_3$



XVI, R = $-N=CH-C_6H_3(OCH_3)_2$



XVII



XVIII

TABLE I

Pharmacology of compounds *Ia*—*VIIIb* and *XVI*—*XVIII*

Compound	Administration	Acute toxicity LD_{50}, mg/kg	Dose screened D, mg/kg	Effects
Ia	*p.o.*	>2 500	300	*a, c, g*
Ib	*p.o.*	2 000	300	*a*
IIa	*i.v.*	80	17	*g, h, i, j, k*
IIb	*i.v.*	125	25	*l*
IIIa	*i.v.*	87·5	17	*a, b, c, d, e, f, g*
IIIb	*i.v.*	100	20	*a, m*
IVa	*i.v.*	75	15	*e, g, k, l, n, o*
IVb	*i.v.*	62	12	*a*
Vb	*i.v.*	90	18	*a, k*
VIb	*i.v.*	500	100	*a, g, k, r*
VIIb	*p.o.*	>2 500	300	*s*
VIIIb	*i.v.*	900	180	*a, k*
XVI	*i.v.*	100	20	*r, t, u, v*
XVII	*i.v.*	75	15	*a, r, t, v, w, x*
XVIII	*i.v.*	6·25	1	*t, v, x, y, z*

[a] In doses above D, inhibition of spontaneous motility and reactivity of mice, ataxia, and tremor. [b] Discoordinating effect in mice in the rotarod test. [c] Antagonization of the reserpine-induced ptosis in mice. [d] In concentrations of 0·1—0·5% complete anaesthesia in 50% guinea-pigs in the test of infiltration anaesthesia. [e] In a concentration of 10 μg/ml inhibition of the $BaCl_2$-induced contractions of the isolated rat duodenum to 50%. [f] Antiarrhythmic effect towards aconitine in rats (procainamide-like effect). [g] Anthelmintic activity towards *Hymenolepis nana.* [h] In doses above D, a mild increase of activity in mice, salivation, and piloerection. [i] Antagonization of the reserpine-induced hypothermia in mice. [j] Anorectic activity in mice at the oral dose of 85 mg/kg. Doses of 10, 20, and 40 mg/kg were inactive in this line but brought about excitation in the test of Ther. [k] Anthelmintic activity towards *Nippostrongylus brasiliensis.* [l] In doses above D, excitation in mice followed by depression, tremor, convulsions, Straub's phenomenon. [m] Anorectic activity in mice at the oral dose of 100 mg/kg (food consumption reduced to 50%). [n] In the concentration of 10 μg/ml inhibition of the acetylcholine-induced contractions of the isolated rat duodenum to 50%. [o] In the dose of 100 mg/kg *s.c.* mild antagonization of amnesia in rats which was elicited by the halothane anaesthesia (the influence on the passive avoidance reactions was followed). [p] Anthelmintic effects towards *Trichocephalus muris* and *Aspiculuris tetraptera.* In oral doses of 60 and 130 mg/kg it showed anthelmintic effect in pigs towards *Ascaris suum, Oesophagostomum dentatum, Trichocephalus suis,* and *Metastrongylus* sp. [r] After the dose D or D/2 brief and deep drops of the blood pressure in normotensive anaesthetized rats. [s] No pharmacological effects within the screening programme. [t] Significant myorelaxant effect (rat's gastrocnemius muscle) at 2 LD_{50} under artificial ventilation. [u] Mild potentiation of the thiopental sleeping-time in mice. [v] Hyperglycaemic effect in rats. [w] Sympatholytic effect in rats. [x] Mild antiarrhythmic effect in mice against ventricular fibrillations elicited by inhalation of chloroform. [y] Brief but significant rises of blood pressure in rats, sympathomimetic, and excitating effects. [z] Positive effects on the heart inotropy and frequency (isolated rabbit heart atrium).

reaction of *XIII* with methyl iodide gave the monoquaternary salt *XVIII*. Most of the compounds prepared were characterized by the IR and/or ^{1}H NMR spectra.

The substances prepared were evaluated pharmacologically using methods of the general screening (the basic compounds were mostly tested in the form of salts shown in the Experimental); the results are summarized in Table I. The central neurotropic effects are only slightly indicated. The central depressant effects appear only in high doses (higher than the screened doses D); in the dose D ataxia in mice appeared only with *IIIa* and thiopental potentiation with *XVI*. Antireserpine effects (indication of thymoleptic activity) towards ptosis were noted with *Ia* and *IIIa*; the reserpine hypothermia was antagonized with *IIa*. Compound *IIa* in higher doses exhibits some central stimulating activity and has anorectic effect in the screened dose; anorectic effect in high doses was shown also by *IIIb*. Peripheral neurotropic effects appeared also rather rarely: spasmolytic effects with *IIIa* and *IVa*, and local anaesthetic effect with *IIIa*. Compound *IVa* antagonized mildly amnesia elicited in rats by the halothan anaesthesia (the influence on the passive avoidance reactions was evaluated) (a nootropic-like effect). The influence on the cardiovascular system is manifested with some compounds (*VIb*, *XVI*, *XVII*) by drops of the blood pressure of rats after intravenous administration. The antiarrhythmic activity was indicated with *IIIa* and then with the quaternary salts *XVII* and *XVIII* whose pharmacological profile is determined by their structural onium salt character. In high doses they block transmission on the neuro-muscular junction (myorelaxant effect). Compound *XVIII* is very toxic, brings about rises of the blood pressure and has positive inotropic as well as chronotropic effects. Some of the compounds show anthelmintic activity especially against *Hymenolepis nana* and *Nippostronylus brasiliensis*. The activities were in no case of such kind that their detailed investigation would be warranted.

Antimicrobial effects *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml – unless they exceed 100 μg/ml – are given): *Streptococcus β-haemolyticus*, *Ib* 50, *IIb* 50, *IIIa* 50, *IIIb* 50, *IVa* 50, *Vb* 50; *Mycobacterium tuberculosis* H37Rv, *Ia* 50, *IIa* 100, *IIIa* 50, *IIIb* 100; *Trichophyton mentagrophytes*, *Ib* 50, *IIb* 50, *IIIa* 50, *IIIb* 50, *IVa* 50, *IVb* 50, *Vb* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in the Kofler block and were not corrected. The samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra (mostly in Nujol, ν in cm^{-1}) were recorded with a Unicam SP 200G spectrophotometer and ^{1}H NMR spectra (in C^2HCl_3, δ, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with Na_2SO_4 or K_2CO_3 and evaporated on a rotating evaporator.

1-(Ethoxycarbonyl)-4-(1-phenyl-2-propyl)piperazine (*X*)

1-Phenylpropan-2-one (67·1 g) was reduced with 10·0 g $NaBH_4$ in 120 ml ethanol and gave 62·0 g (91%) 1-phenylpropan-2-ol, b.p. 103—104°C/1·3 kPa (ref.[8], b.p. 101—102°C/1·5 kPa), which was transformed by the described procedure[10,11] to the 4-toluenesulfonate, m.p. 90—93°C (refs[10,11], m.p. 86—89°C and 91—93°C, respectively). A solution of 36·6 g 1-phenyl-2-propyl 4-toluenesulfonate in 50 ml dioxane was added over 20 min to a stirred mixture of 20·0 g 1-(ethoxycarbonyl)piperazine, 40 ml dioxane, and 17·0 g Na_2CO_3 at 40—50°C. The mixture was stirred and refluxed for 8 h, the solid was filtered off, and the filtrate was distilled; 23·5 g (68%) *X*, b.p. 147—149°C/13 Pa, which crystallized after cooling, m.p. 64—66°C. IR spectrum: 709, 742, 769 (5 adjacent Ar—H); 1 130, 1 246 (C—O in COOR); 1 500, 1 606, 3 000, 3 050 (Ar); 1 697 (NCOOR). ^{1}H NMR spectrum: 0·97 d, 3 H (CH_3 in 1-phenyl-2-propyl, J = 7·0); 1·25 t, 3 H (CH_3 in ethoxyl, J = 7·0); 2·52 t, 4 H ($CH_2N^4CH_2$ of piperazine); 2·30—3·10 m, 3 H ($ArCH_2CHN$); 3·45 t, 4 H ($CH_2N^1CH_2$ of piperazine); 4·14 q, 2 H (OCH_2, J = 7·0); 7·18 m, 5 H (C_6H_5). For $C_{16}H_{24}N_2O_2$ (276·4) calculated: 69·53% C, 8·75% H, 10·14% N; found: 69·74% C, 8·90% H, 10·32% N.

Hydrochloride was prepared by treatment of a solution of the base in ethanol with a solution of HCl in ether; m.p. 217·5°C (ethanol–ether). For $C_{16}H_{25}ClN_2O_2$ (312·8) calculated: 61·42% C, 8·06% H, 11·33% Cl, 8·96% N; found: 61·43% C, 8·25% H, 11·42% Cl, 8·94% N. In ref.[12] a different synthesis of *X* was described, b.p. 175—183°C/0·4 kPa, and the product was characterized as the hydrobromide.

1-(1-Phenyl-2-propyl)piperazine (*IX*)

A mixture of 22·5 g *X*, 30 g KOH, and 35 ml ethanol was stirred and refluxed for 3 h. After cooling, it was diluted with 120 ml water and extracted with chloroform. Processing gave 13·2 g (80%) *IX*, b.p. 106°C/13 Pa. For this compound, prepared differently, refs[7,23] gave the b.p. 120—123°C/60 Pa and 115—125°C/70 Pa, respectively.

N-(2-Phenylethyl)-4-methoxyphenoxyacetamide (*Ia*)

A stirred solution of 4·84 g 2-phenylethylamine in 20 ml chloroform was treated dropwise with a solution of 4·2 g 4-methoxyphenoxyacetyl chloride[4] in 10 ml chloroform. The reaction was exothermic and the mixture refluxed without external heating. The mixture was stirred for 4 h, allowed to stand overnight at room temperature, the precipitated 2-phenylethylamine hydrochloride (3·1 g, m.p. 220—223°C) was filtered off and washed with chloroform. The filtrate was washed with water, dried, and evaporated. The residue crystallized; 5·7 g (100%), m.p. 80—82·5°C. Analytical sample, m.p. 80—81·5°C (toluene–light petroleum). IR spectrum: 710, 760, 834 (5 and 2 adjacent Ar—H); 1 063, 1 231 ($ArOCH_3$); 1 513, 3 032 (Ar); 1 550, 1 662 (CONH); 3 335 (NH). ^{1}H NMR spectrum: 2·80 t, 2 H ($ArCH_2$); 3·58 m, 2 H (NCH_2); 3·71 s, 3 H (OCH_3); 4·38 s, 2 H (OCH_2CO); 6·64 bs, 1 H (NH); 6·75 s, 4 H (4 ArH of methoxyphenyl); c. 7·15 m, 5 H (C_6H_5). For $C_{17}H_{19}NO_3$ (285·3) calculated: 71·55% C, 6·71% H, 4·91% N; found: 71·24% C, 6·88% H, 5·20% N.

1-Benzyl-4-(4-methoxyphenoxyacetyl)piperazine (*IIa*)

A solution of 3·9 g 4-methoxyphenoxyacetyl chloride[4] in 10 ml chloroform was stirred and treated dropwise with a solution of 3·5 g 1-benzylpiperazine[5] in 10 ml chloroform, added over 5 min. The temperature rose spontaneously and brought the mixture to refluxing. It was stirred for 1·5 h, cooled, and shaken with a solution of 25 ml NH_4OH in 50 ml water. The chloroform

layer was washed with water, dried, and evaporated. The crude oily base (6·1 g) was dissolved in 15 ml ethanol and treated with a solution of HCl in ether; 4·9 g (70%) hydrochloride, m.p. 203–204°C (ethanol). IR spectrum: 710, 760, 828 (5 and 2 adjacent Ar—H); 1 050, 1 056, 1 230 ($ArOCH_3$); 1 515 (Ar); 1 660 (CON); 2 472, 2 535 (NH^+). For $C_{20}H_{25}ClN_2O_3$ (376·9) calculated: 63·73% C, 6·68% H, 9·41% Cl, 7·43% N; found: 63·68% C, 6·71% H, 9·57% Cl, 7·61% N.

1-(4-Methoxyphenoxyacetyl)-4-(2-phenylethyl)piperazine (*IIIa*)

Similar reaction of 4·85 g 4-methoxyphenoxyacetyl chloride[4] with 5·05 g 1-(2-phenylethyl)piperazine[6] in 35 ml chloroform gave 9·0 g crude base which was transformed to 9·1 g (93%) hydrochloride, m.p. 210–211·5°C (ethanol). IR spectrum: 705, 758, 830 (5 and 2 adjacent Ar—H); 1 040, 1 239 ($ArOCH_3$); 1 516, 1 600, 3 032, 3 068 (Ar); 1 660, 1 677 (CON); 2 490 (NH^+). For $C_{21}H_{27}ClN_2O_3$ (390·9) calculated: 64·52% C, 6·96% H, 9·07% Cl, 7·16% N; found: 64·86% C, 7·35% H, 9·09% Cl, 7·33% N.

1-(4-Methoxyphenoxyacetyl)-4-(1-phenyl-2-propyl)piperazine (*IVa*)

A stirred solution of 27·9 g 1-(1-phenyl-2-propyl)piperazine in 100 ml chloroform was treated over 50 min with a solution of 29·7 g 4-methoxyphenoxyacetyl chloride[4] in 60 ml chloroform. The temperature rose spontaneously to 50°C. The mixture was stirred for 1·5 h to 50–55°C, cooled to 20°C, and treated with 200 ml ether. The precipitated hydrochloride of *IVa* was filtered, washed with a mixture of ethanol and ether, and dried; 51·8 g (93%), m.p. 201·5–202·5°C (ethanol). For $C_{22}H_{29}ClN_2O_3$ (404·9) calculated: 65·25% C, 7·22% H, 8·76% Cl, 6·92% N; found: 65·44% C, 7·22% H, 8·84% Cl, 6·94% N.

N-(2-Phenylethyl)-3,4,5-trimethoxyphenoxyacetamide (*Ib*)

A mixture of 5·12 g methyl 3,4,5-trimethoxyphenoxyacetate[1], 3·02 g 2-phenylethylamine, and 15 ml ethanol was refluxed for 10 h and evaporated *in vacuo*. The solid residue (6·9 g, 100%) was recrystalized from aqueous methanol, m.p. 90–92°C and after resolidification 98°C. IR spectrum: 709, 759, 837 (5 adjacent and solitary Ar—H); 1 141, 1 151, 1 230 ($ArOCH_3$), 1 509, 1 607, 3 022, 3 060 (Ar); 1 550, 1 648 (CONH), 3 290 (NH). ^{1}H NMR spectrum: 2·82 t, 2 H ($ArCH_2$, J = 7·0); 3·60 m, 2 H (NCH_2); 3·76 s, 3 H (4-OCH_3); 3·81 s, 6 H (3,5-$(OCH_3)_2$); 4·40 s, 2 H (OCH_2CO); 6·08 s, 2 H (H-2 and H-6 of trimethoxyphenyl); 6·60 bt, 1 H (NH); 7·18 m, 5 H (C_6H_5). For $C_{19}H_{23}NO_5$ (345·4) calculated: 66·07% C, 6·71% H, 4·06% N; found: 66·30% C, 6·92% H, 3·98% N.

1-Benzyl-4-(3,4,5-trimethoxyphenoxyacetyl)piperazine (*IIb*)

A mixture of 9·6 g 3,4,5-trimethoxyphenoxyacetic acid[13] and 3·6 g 1-benzylpiperazine[5] was slowly heated in an open flask in order to reach during 30 min the temperature of 185–190°C. It was maintained at this temperature for further 30 min, cooled, dissolved in 60 ml chloroform, the solution was washed with dilute NaOH and water, dried, filtered with charcoal, and evaporated. The residue (8·3 g) was dissolved in 100 ml ethanol and the solution was treated with a slight excess of HCl in ether. Addition of further 20 ml ether led to crystallization of 6·6 g (74%) hydrochloride of *IIb*, m.p. 159–161°C (ethanol–ether). For $C_{22}H_{29}ClN_2O_5$ (436·9) calculated: 60·47% C, 6·69% H, 8·11% Cl, 6·41% N; found: 59·94% C, 7·07% H, 7·94% Cl, 6·01% N.

A sample of the hydrochloride was decomposed with NH_4OH and the base (isolated by extraction with ether) crystallized, m.p. 100—101·5°C (2-propanol). IR spectrum: 704, 742, 818 (5 adjacent and solitary Ar—H); 1 138, 1 170 ($ArOCH_3$); 1 513, 1 600, 3 030, 3 060 (Ar); 1 660 (CON). For $C_{22}H_{28}N_2O_5$ (400·5) calculated: 65·98% C, 7·05% H, 6·99% N; found: 66·11% C, 7·38% H, 6·79% N.

1-(3,4,5-Trimethoxyphenoxyacetyl)-4-(2-phenylethyl)piperazine (*IIIb*)

Was prepared similarly like *IIb* from 9·6 g 3,4,5-trimethoxyphenoxyacetic acid[13] and 3·8 g 1-(2-phenylethyl)piperazine[6]; 7·3 g (81%) hydrochloride, m.p. 176·5—177·5°C (ethanol). For $C_{23}H_{31}ClN_2O_5$ (451·0) calculated: 61·25% C, 6·93% H, 7·86% Cl, 6·21% N; found: 61·11% C, 7·12% H, 7·97% Cl, 6·19% N.

1-(3,4,5-Trimethoxyphenoxyacetyl)-4-(1-phenyl-2-propyl)piperazine (*IVb*)

Similar reaction of 6·75 g 3,4,5-trimethoxyphenoxyacetic acid[13] and 2·75 g 1-(1-phenyl-2-propyl)-piperazine gave 5·3 g (85%) *IVb* hydrochloride, m.p. 161—163°C (ethanol). For $C_{24}H_{33}ClN_2O_5$ (465·0) calculated: 61·99% C, 7·15% H, 7·62% Cl, 6·03% N; found: 61·41% C, 7·47% H, 7·60% Cl, 5·99% N.

The base, which was released from the hydrochloride by treatment with NH_4OH and isolated by extraction with ether, crystallized on standing, m.p. 96—97°C (ethanol). For $C_{24}H_{32}N_2O_5$ (428·5) calculated: 67·26% C, 7·53% H, 6·54% N; found: 67·17% C, 7·54% H, 6·33% N.

N,N-Diethyl-3,4,5-trimethoxyphenoxyacetamide (*Vb*)

A mixture of 4·8 g 3,4,5-trimethoxyphenoxyacetic acid[13] and 20 ml diethylamine was refluxed for 45 min, the excess of diethylamine was distilled off, and the residue was heated for 1·5 h to 170°C. Similar processing like in the preparation of *IIb* gave 0·6 g (10%) *Vb*, m.p. 100—100·5°C (aqueous methanol). IR spectrum (KBr): 831 (solitary Ar—H); 1 086, 1 136, 1 204, 1 242 ($ArOCH_3$); 1 513, 1 596, 3 000, 3 020 (Ar); 1 660 (CON). ^{1}H NMR spectrum: 1·13 t, 3 H and 1·21 t, 3 H (2 CH_3 of diethylamino, J = 7·0); 3·40 q, 4 H (CH_2NCH_2, J = 7·0); 3·75 s, 3 H (4-CH_3O in trimethoxyphenyl); 3·81 s, 6 H (3,5-$(CH_3O)_2$ in trimethoxyphenyl); 4·61 s, 2 H OCH_2CO); 6·21 s, 2 H (H-2 and H-6 in trimethoxyphenyl). For $C_{15}H_{23}NO_5$ (297·3) calculated: 60·58% C, 7·80% H, 4·71% N; found: 60·46% C, 7·86% H, 4·34% N.

4-Aminomorpholine (*XI*)

A solution of 22·7 g 4-nitrosomorpholine[18] in 500 ml ether was added over 3 h to a stirred solution of 10·0 g $LiAlH_4$ in 375 ml ether at 0—10°C. The mixture was stirred for 1 h at room temperature and was refluxed for 6 h. After cooling it was decomposed under stirring by slow addition of 10 ml water, 10 ml 20% NaOH, and 25 ml water, the mixture was stirred for 30 min, the solid was filtered off, and washed with ether. The filtrate was dried and distilled; 6·0 g (31%), b.p. 165—167°C/0·1 MPa. Ref.[17], b.p. 163—165°C/0·1 MPa.

The solid, which was filtered off, was extracted with 200 ml boiling ether. Evaporation of the extract gave 1·0 g N,N'-dimorpholinodiimide (*XIV*), m.p. 157—158°C (ethanol). IR spectrum: 1 070, 1 094, 1 112, 1 130 (C—O—C); 1 270, 1 690. ^{1}H NMR spectrum: 3·18 m, 8 H (2 CH_2NCH_2); 3·82 m, 8 H (2 CH_2OCH_2). For $C_8H_{16}N_4O_2$ (200·2) calculated: 47·98% C, 8·06% H, 27·98% N; found: 47·89% C, 8·20% H, 28·33% N. Ref.[22], m.p. 152°C.

1-Amino-4-methylpiperazine (*XII*)

A solution of 44 g 1-methyl-4-nitrosopiperazine[19] in 100 ml ether was added over 0·5 h to a stirred solution of 31·5 g $LiAlH_4$ in 1 000 ml ether under reflux. The mixture was refluxed for 10 h, cooled, and decomposed by slow addition of 25 ml water, 25 ml 20% NaOH, and 75 ml water, it was stirred for 30 min, the solid was filtered off, and washed with ether. The filtrate was dried and distilled; 34·3 g (88%), b.p. 67°C/1·9 kPa. Ref.[19], b.p. 172–175°C/0·1 MPa (different method).

Dimaleate, m.p. 172–173°C (98% ethanol). For $C_{13}H_{21}N_3O_8$ (347·3) calculated: 44·95% C, 6·09% H, 12·10% N; found: 44·65% C, 6·16% H, 11·85% N.

1-Amino-4-phenylpiperazine (*XIII*)

1-Nitroso-4-phenylpiperazine[20] (25 g) was similarly reduced with 10 g $LiAlH_4$ in 750 ml ether and gave 19·3 g (84%) product boiling at 128–130°C/0·13 kPa. The redistilled product (b.p. 118–120°C/70 Pa) crystallized on standing, m.p. 53–55°C. For $C_{10}H_{15}N_3$ (177·2) calculated: 67·76% C, 8·53% H, 23·71% N; found: 67·75% C, 8·60% H, 23·48% N. Ref.[20], b.p. 129–130°C/ /0·13 kPa (similar reduction in tetrahydrofuran).

Dihydrochloride, m.p. 201·5–203·5°C (97% ethanol). For $C_{10}H_{17}Cl_2N_3$ (250·2) calculated: 48·00% C, 6·85% H, 28·34% Cl, 16·80% N; found: 47·75% C, 6·92% H, 28·10% Cl, 17·14% N.

1-(3,4,5-Trimethoxyphenoxyacetyl)-2-(2-propyl)hydrazine (*VIb*)

A mixture of 7·7 g methyl 3,4,5-trimethoxyphenoxyacetate[1], 4·5 g isopropylhydrazine[15] and 0·05 g sodium methoxide was stirred and heated for 12 h under reflux to 100–120°C. After partial cooling, the melt was dissolved in 250 ml benzene, the solution was washed with water, and the basic product was extracted into 57 ml 2·5M-HCl. The aqueous solution was made alkaline with 20 ml NH_4OH and the product was extracted with benzene. Processing of the extract gave 7·9 g (88%) *VIb*, m.p. 80–81·5°C (cyclohexane–benzene). IR spectrum: 806, 883 (solitary Ar—H); 1 133, 1 152 ($ArOCH_3$); 1 510, 1 589, 1 603 (Ar); 1 537, 1 650 (CONH); 3 205, 3 225, 3 275 (NH). ^{1}H NMR spectrum: 1·04 d, 6 H (2 CH_3 of isopropyl, $J = 6·5$); 3·20 m, 1 H (N—CH); 3·78 s, 3 H (4-CH_3O of trimethoxyphenyl); 3·82 s, 6 H (3,5-$(CH_3O)_2$ of trimethoxyphenyl); 4·54 s, 2 H (OCH_2CO); 5·60–6·60 bs, 1 H (NH); 6·18 s, 2 H (H-2 and H-6 of trimethoxyphenyl). For $C_{14}H_{22}N_2O_5$ (298·3) calculated: 56·36% C, 7·43% H, 9·39% N; found: 55·94% C, 7·46% H, 9·26% N.

Hydrochloride, m.p. 180·5–182·5°C (2-propanol). For $C_{14}H_{23}ClN_2O_5$ (334·8) calculated: 50·22% C, 6·92% H, 10·59% Cl, 8·37% N; found: 50·52% C, 6·95% H, 10·42% Cl, 8·31% N.

1-(3,4,5-Trimethoxyphenoxyacetamido)piperidine (*VIIb*)

A mixture of 8·3 g methyl 3,4,5-trimethoxyphenoxyacetate[1], 3·5 g 1-aminopiperidine[17], 5 ml toluene, 25 ml butanol, and 0·05 g sodium methoxide was stirred and refluxed for 4 h. A part of the solvents (15 ml) was distilled off and the residue was cooled overnight. The separated product was filtered and crystallized from 18 ml methanol; 3·0 g (29%) *VIIb*, m.p. 156·5–158°C (methanol). IR spectrum: 806, 826, 875 (solitary Ar—H); 1 167 ($ArOCH_3$); 1 504, 1 510, 1 598, 3 008, 3 060, 3 092 (Ar); 1 530, 1 692 (CONH); 3 285 (NH). ^{1}H NMR spectrum: 1·20 to 2·00 m, 6 H (3 CH_2 in positions 3, 4, and 5 of piperidine); 2·80 bt, 4 H (CH_2NCH_2); 3·80 s, 3 H (4-OCH_3 of trimethoxyphenyl); 3·85 s, 6 H (3,5-$(OCH_3)_2$ in trimethoxyphenyl); 4·50 s, 2 H, (OCH_2CO); 6·18 s, 2 H (H-2 and H-6 of trimethoxyphenyl); 7·12 bs, 1 H (CONH—N). For

$C_{16}H_{24}N_2O_5$ (324·4) calculated: 59·24% C, 7·46% H, 8·64% N; found: 59·10% C, 7·63% H, 8·48% N.

4-(3,4,5-Trimethoxyphenoxyacetamido)morpholine (*VIIIb*)

A mixture of 7·7 g methyl 3,4,5-trimethoxyphenoxyacetate[1], 4·6 g *XI*, and 0·05 g sodium methoxide was stirred and heated under reflux for 3 h to 120—125°C. After cooling the melt was dissolved in 200 ml chloroform, the solution was washed with water, dried, and evaporated; 5·4 g (55%) *VIIIb* which was crystallized from benzene, m.p. 144·5—146·5°C. IR spectrum: 861 (solitary Ar—H); 1 000, 1 119, 1 134, 1 165, 1 230, 2 820 (R—O—R and $ArOCH_3$); 1 513, 1 610 (Ar); 1 564, 1 676 (CONH), 3 060, 3 200 (NH). ^{1}H NMR spectrum: 2·85 t, 4 H (CH_2NCH_2); 3·75 s, 3 H (4-OCH_3 of trimethoxyphenyl); 3·75—3·81 m, 4 H (CH_2OCH_2); 3·81 s, 6 H (3,5-$(OCH_3)_2$ in trimethoxyphenyl); 4·50 s, 2 H (OCH_2CO); 6·18 s, 2 H (H-2 and H-6 of trimethoxyphenyl); 7·32 bs, 1 H (NH). For $C_{15}H_{22}N_2O_6$ (326·4) calculated: 55·20% C, 6·80% H, 8·58% N; found: 55·63% C, 6·80% H, 8·72% N.

1-Methyl-4-(2-undecylideneamino)piperazine (*XV*)

A mixture of 9·0 g 2-undecanone, 5·7 g *XII*, and 20 ml ethanol was refluxed for 8 h, ethanol was slowly distilled off over the following 4 h, the residue was treated with 75 ml benzene which was slowly distilled off through a column for removing remaining water as the azeotropic mixture. The residue was distilled; 10·0 g (73%), b.p. 118—122°C/70 Pa. IR spectrum (film): 1 640 (C=N); 2 770 (CH_3—N). ^{1}H NMR spectrum: 0·86 t, 3 H (terminal CH_3 in nonyl); 1·25 bs, 14 H (7 CH_2 of nonyl adjacent to methyl); 1·91 s, 3 H (=C—CH_3); 2·19 m, 2 H (=C—CH_2); 2·27 s, 3 H (NCH_3); 2·66 m, 8 H (4 CH_2N of piperazine). For $C_{16}H_{33}N_3$ (267·4) calculated: 71·85% C, 12·44% H, 15·71% N; found: 71·75% C, 12·80% H, 15·40% N.

An attempt to transform *XV* (2·7 g) by treatment with 1·2 g maleic acid in 15 ml ethanol at 50°C to the maleate, led to 0·5 g *XII* dimaleate, m.p. 172—173°C (98% ethanol) (see above).

1-(3,4-Dimethoxybenzylideneamino)-4-methylpiperazine (*XVI*)

A mixture of 8·4 g 3,4-dimethoxybenzaldehyde, 5·7 g *XII*, 20 ml ethanol, and 3·0 g acetic acid was stirred and refluxed for 16 h, filtered with charcoal and $MgSO_4$, and the filtrate was evaporated *in vacuo*. The residue was dissolved in 200 ml chloroform, the solution was washed with 10% $NaHCO_3$ and water, dried, and evaporated. The glassy residue was dissolved in 20 ml ethanol and the solution was treated with a solution of 3·9 g maleic acid in 15 ml ethanol. Addition of 30 ml ether and standing overnight led to crystallization of 10·8 g (56%) maleate of *XVI*, m.p. 122—123°C (ethanol). For $C_{18}H_{25}N_3O_6$ (379·4) calculated: 56·98% C, 6·64% H, 11·08% N; found: 56·77% C, 6·66% H, 10·84% N.

1-Amino-1,4-dibenzyl-4-methylpiperazinium Dichloride (*XVII*)

A solution of 5·7 g *XII* in 20 ml ether was treated under stirring with a solution of 14·0 g benzyl chloride in 15 ml ether, the mixture was allowed to stand for 4 days at room temperature, diluted with 20 ml ether, and the solid product was filtered. Two crystallizations from ethanol–ether gave 7·8 g (42%) *XVII*, m.p. 235°C. For $C_{19}H_{27}Cl_2N_3$ (368·3) calculated: 61·95% C, 7·39% H, 19·25% Cl, 11·41% N; found: 61·72% C, 7·47% H, 19·30% Cl, 11·62% N.

1-Amino-1-methyl-4-phenylpiperazinum Iodide (*XVIII*)

A solution of 2·5 g *XIII* in 25 ml ether was treated with 5·7 g methyl iodide and the mixture

was allowed to stand for 3 days at room temperature. The precipitated solid was filtered and crystallized from a mixture of 60 ml ethanol and 25 ml ether; 3·5 g (57%), m.p. 165—167°C. For $C_{11}H_{18}IN_3$ (319·2) calculated: 41·39% C, 5·68% H, 39·76% I, 13·17% N; found: 41·32% C, 5·63% H, 39·73% I, 12·74% N.

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