BASIC AMIDES OF 3,4,5-TRIMETHOXYPHENOXYACETIC ACID; SYNTHESIS AND PHARMACOLOGY OF TRIMETHOPHENOXAMIDE AND ANALOGUES*

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Reactions of methyl 3,4,5-trimethoxyphenoxyacetate (*II*) with ammonia and amines resulted in amides *V*—*XIV*, some of which in high doses showed central depressant effects. Their cardiovascular effects (antiarrhythmic, adrenolytic, hypotensive) proved more important. The 2-diethylaminoethylamide *VIII* ("trimethophenoxamide") proceeded after thorough pharmacological and toxicological studies to clinical trials as an antiarrhythmic agent. 3,4,5-Trimethoxyphenol, 3,4,5-trimethoxyphenoxyacetic acid (*I*) and its methyl ester *II* were further used to prepare the 2-diethylaminoethyl ester *IV*, hydrazide *XV*, acetone derivative *XVI*, and the mescaline analogue *XVIII*. The mentioned effects were also found for some of the starting aminonitriles and N-(aminoalkyl)piperazines *XIXa*—*XXIIIab*.

The synthesis of a series of basic esters and amides of substituted phenoxyacetic acids was described in 1960 (ref.[1]) and the products were characterized as neurostimulants and regulators of brain metabolism. One of these substances was 2-dimethylaminoethyl *p*-chlorophenoxyacetate ("meclophenoxate") which proved in the meantime its usefulness in the treatment of cerebrovascular disorders, states of mental confusion (especially in gerontopsychiatry) and of delirium tremens[2,3]. Two additional products, *i.e.* N-(2-diethylaminoethyl)amides of *p*-chlorophenoxyacetic ("clofexamide") and *p*-methoxyphenoxyacetic acid ("mefexamide"), were described as antidepressants of a specific activity profile, having simultaneously local anaesthetic, analgetic and antiinflammatory activities[4—9]. In this communication we describe our experimental work in this series of compounds in which we started from the first mentioned paper[1]; our studies proceeded in two phases: the first one in 1964 to 1966 (ref.[10]), the second in 1970—1. After the conclusion of our experiments, a series of papers on potential drugs in the group of basic derivatives of substituted phenoxyacetic acids appeared (*e.g.*[11—14]).

3,4,5-Trimethoxyphenoxyacetic acid (*I*) was the starting material of our investiga-

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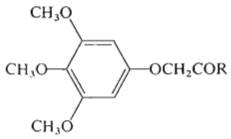


I, R = OH
II, R = OCH_3
III, R = OCH_2CH_3
IV, R = $OCH_2CH_2N(C_2H_5)_2$
V, R = NH_2
VI, R = $NHCH_2C_6H_5$

VII, R = 

VIII, R = $NHCH_2CH_2N(C_2H_5)_2$

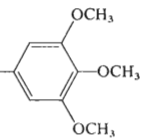
IX, R = $NH(CH_2)_2N$ 

X, R = $NH(CH_2)_3N$ 

XI, R = $NH(CH_2)_3N$ 

XII, R = $NH(CH_2)_3N$ 

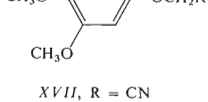
XIII, R = $NH(CH_2)_3N$ 

XIV, R = $NH(CH_2)_3N$  $(CH_2)_3NHCOCH_2O$ 

XV, R = $NHNH_2$
XVI, R = CH_3

tion, its synthesis having been described by us earlier[15]. Reaction of this acid with dimethyl sulfate and potassium carbonate yielded the methyl ester *II* which was used as intermediate for further synthetic work. In an attempt to prepare the 2-diethylaminoethyl ester *IV* by reaction of acid *I* with sodium ethoxide in ethanol and by the following treatment with 2-diethylaminoethyl chloride, the ethyl ester *III* was isolated as the sole product; the primarily formed *IV* underwent evidently transesterification with ethanol. The ethyl ester *III* was also obtained in an attempt to prepare the diethylamide by reaction of methyl ester *II* with diethylamine in ethanol; instead of aminolysis transesterification took place again. 2-Diethylaminoethyl ester *IV* was then obtained in low yield from the acid *I*, dicyclohexylcarbodiimide and 2-diethylaminoethanol in dichloromethane. Amides *V*–*XIV* were prepared by reactions of methyl ester *II* with ammonia and the corresponding amines; the most usual modifications of the procedure were reactions of the components in boiling ethanol (method *A*) or in 1-butanol at 110°C (method *B*). The hydrazide *XV* was obtained in a similar manner.

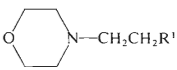
Reaction of 3,4,5-trimethoxyphenol[16,17] with bromoacetone in the presence of potassium carbonate resulted in 3,4,5-trimethoxyphenoxyacetone (*XVI*), characterized in the form of oxime and 2,4-dinitrophenylhydrazone. In a similar manner, 3,4,5-trimethoxyphenol and chloroacetonitrile gave 3,4,5-trimethoxyphenoxyacetonitrile (*XVII*), reduced with lithium aluminium hydride in a poor yield to 2-(3,4,5-trimethoxyphenoxy)ethylamine (*XVIII*). The same compound was obtained more satisfactorily by a similar reduction of the amide *V*. This mescaline analogue *XVIII* was already mentioned by Woolley[18] in a pharmacological paper dealing with serotonin agonists and antagonists; two synthetic ways leading to the amine *XVIII* (one of them using reduction of amide *V*) were indicated in this paper in a flow-sheet without experimental data.



XVII, R = CN
XVIII, R = CH_2NH_2

Amines used in the synthesis of amides *VIII*–*XIV* were prepared by conventional procedures. Morpholine, 1-methylpiperazine, 1-phenylpiperazine[19], 1-(2-tolyl)piperazine[20] and piperazine were treated with acrylonitrile (method *C*) to give nitriles *XIXa* (ref.[21]), *XXa* (ref.[22–24]), *XXIa* (ref.[25–27]), *XXIIa* (ref.[25]), and *XXIIIa*

(ref.[28]). Their reduction with lithium aluminium hydride in ether (method *D*) led to amines *XIXb* (ref.[21,29]), *XXb* (ref.[22–24,30]), *XXIb* (ref.[26,31]), and *XXIIb*. The amine *XXIIIb* was obtained from the nitrile *XXIIIa* by hydrogenation on Raney nickel under pressure[32] (for another method see[33]). All the compounds prepared are summarized in Table I; the table includes data on hydrochlorides of the intermediates *XIXab – XXIIIab*.



XIX

a, $R^1 = CN$
b, $R^1 = CH_2NH_2$

TABLE I

3,4,5-Trimethoxyphenoxyacetic Acid Derivatives, Some Related Compounds and Intermediates

Compound[a]	Method (yield, %)	M.p., °C (Solvent) or b.p., °C/Torr	Formula (Mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
II	[b]	79–81 (methanol)	$C_{12}H_{16}O_6$ (256·2)	56·24 56·30	6·29 6·27	— —	— —
III	[b]	51–52 (dibutyl ether) 148–150/2	$C_{13}H_{18}O_6$ (270·3)	57·77 57·78	6·71 6·69	— —	— —
IV	[b]	182–184/1	$C_{17}H_{27}NO_6$ (341·4)	59·81 59·75	7·97 7·70	4·10 4·02	— —
IV-HM	[b]	72–74 (ethanol–ether)	$C_{21}H_{31}NO_{10}$ (457·5)	55·13 55·17	6·83 6·53	3·06 3·09	— —
V	[b]	124–125 (methanol)	$C_{11}H_{15}NO_5$ (241·2)	54·76 55·05	6·27 6·38	5·81 6·06	— —
VI	[b]	98–99 (methanol)	$C_{18}H_{21}NO_5$ (331·4)	65·24 64·97	6·39 6·38	4·23 4·16	— —
VII	[b]	108–109 (benzene–ether)	$C_{15}H_{21}NO_6$ (311·3)	57·86 57·81	6·80 6·77	4·50 4·50	— —
VIII-HCl	*A*[b] (78)	157–158 (ethanol)	$C_{17}H_{29}ClN_2O_5$ (376·9)	54·17 54·17	7·76 7·98	7·43 7·72	9·41 9·26
IX-HCl[c]	*B*[b] (53)	155–157 (ethanol)	$C_{17}H_{28}ClN_2O_{6,5}$ (399·9)	51·06 51·17	7·06 7·14	7·01 7·16	8·86 9·10

TABLE I
(*Continued*)

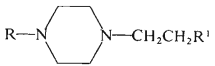
Compound[a]	Method (yield, %)	M.p., °C (Solvent) or b.p., °C/Torr	Formula (Mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
X-HCl	*A* (90)	191—194 (ethanol)	$C_{18}H_{29}ClN_2O_6$ (404·9)	53·39 53·34	7·22 7·50	6·92 6·82	8·76 9·03
XI-2 HCl	*A* (76)	235—237·5 (90% ethanol–ether)	$C_{19}H_{33}Cl_2N_3O_5$ (454·4)	50·22 49·91	7·32 7·64	9·25 9·07	15·61 15·34
XII-2 HCl	*A* (60)	143—145 (ethanol–ether)	$C_{24}H_{35}Cl_2N_3O_5$ (516·4)	55·81 55·63	6·83 6·92	8·14 8·05	13·73 13·83
XIII-2 HCl	*B* (77)	177—180[d] (ethanol)	$C_{25}H_{37}Cl_2N_3O_5$ (530·5)	56·60 56·20	7·03 7·15	7·90 7·89	13·37 13·54
XIV	*A* (40)	151·5—153·5[e] (ethanol–petroleum ether)	$C_{32}H_{48}N_4O_{10}$ (648·7)	59·24 59·70	7·46 7·62	8·64 8·52	— —
XIV-2 HCl[f]	—	227·5—228·5 (90% ethanol–ether)	$C_{32}H_{54}Cl_2N_4O_{12}$ (757·7)	50·72 51·00	7·18 7·39	7·40 7·46	9·36 9·39
XV	[b]	141—143 (ethanol)	$C_{11}H_{16}N_2O_5$ (256·3)	51·55 51·74	6·29 6·22	10·93 11·08	— —
XVI-oxime	[b]	90—92 (aqueous methanol)	$C_{12}H_{17}NO_5$ (255·3)	— —	— —	5·49 5·58	— —
XVI-DPH	[b]	164—167 (ethanol)	$C_{18}H_{20}N_4O_8$ (420·4)	51·43 51·21	4·79 4·82	13·33 13·71	— —
XVII	[b]	150—154/0·4 50—52 (aqueous methanol)	$C_{11}H_{13}NO_4$ (223·2)	59·18 59·12	5·87 5·94	6·27 5·99	— —
XVIII	[b]	160—162/5	—	—	—	—	—
XVIII-HCl[c]	—	175—177 (95% ethanol–ether)	$C_{11}H_{19}ClNO_{4.5}$ (272·7)	48·43 48·70	7·02 7·05	5·14 4·61	13·00 13·18
XIXa	*C*[21] (97)	125—128/10[g]	—	—	—	—	—
XIXa-HCl		219—221 (ethanol)	$C_7H_{13}ClN_2O$ (176·6)	47·49 47·77	7·42 7·37	15·86 15·77	20·07 20·30
XIXb	*D*[29] (83)	102—108/15[h]	—	—	—	—	—
XXa	*C*[22] (76)	139—142/22[i]	—	—	—	—	—
XXa-2 HCl	—	216—220 (ethanol)	$C_8H_{17}Cl_2N_3$ (226·2)	42·49 42·57	7·58 7·62	18·58 18·62	31·35 31·52

TABLE I
(*Continued*)

XXb	D^{23} (70)	104–108/6[j]	—	—	—	—	—
XXb-3 HCl	—	244–246[k] (ethanol)	$C_8H_{22}Cl_3N_3$ (266·7)	36·03 36·08	8·32 8·35	15·76 15·89	39·89 39·87
XXIa	C^{25} (93)	70–71[l] (90% ethanol)	—	—	—	—	—
XXIa-2 HCl	—	200–204 (ethanol–ether)	$C_{13}H_{19}Cl_2N_3$ (288·2)	54·17 54·25	6·65 6·66	14·58 14·48	24·60 24·82
XXIb	*D* (74)	39–45 132–134/0·2[m]	—	—	—	—	—
XXIb-2 HCl	—	246–248[n] (95% ethanol–ether)	$C_{13}H_{23}Cl_2N_3$ (292·2)	53·43 53·57	7·93 8·18	14·38 14·53	24·26 24·36
XXIIa	C^{b} (81)	78·5–79 (ethanol)	—	—	—	—	—
XXIIa-HCl	—	219–222 (ethanol)	$C_{14}H_{20}ClN_3$ (265·8)	63·26 63·11	7·59 7·91	15·81 15·64	13·34 13·48
XXIIb	D^{b} (91)	129/0·15	$C_{14}H_{23}N_3$ (233·3)	72·06 72·08	9·93 9·95	18·01 17·60	— —
XXIIb-2 HCl	—	259–261 (ethanol)	$C_{14}H_{25}Cl_2N_3$ (306·3)	54·90 54·70	8·23 8·38	13·72 13·80	23·15 23·29
XXIIIa	C^{28} (78)	64–66[o] (benzene)	—	—	—	—	—
XXIIIa-2 HCl	—	221 (90% ethanol)	$C_{10}H_{18}Cl_2N_4$ (265·2)	45·29 45·27	6·84 6·82	21·13 21·06	26·74 26·36
XXIIIb	Ref.[32] (58)	110–112/0·1[p]	—	—	—	—	—
XXIIIb-4 HCl	—	258–259[q] (ethanol–ether)	$C_{10}H_{28}Cl_4N_4$ (346·2)	34·69 34·40	8·16 8·35	16·18 15·62	40·97 40·03

[a] HM hydrogen maleate, DPH 2,4-dinitrophenylhydrazone. [b] See Experimental. [c] Hemihydrate. [d] IR spectrum (nujol): 750, 828 (4 adjacent and solitary Ar—H), 1135, 1160, 1230 ($ArOCH_3$), 1506, 1598 (Ar), 1575, 1650 (RCONHR'), 2400 (NH^+), 3220 cm^{-1} (NH of amide). [e] IR spectrum (nujol): 890 (solitary Ar—H), 1120, 1160, 1240 ($ArOCH_3$, $ArOCH_2$), 1512, 1598 (Ar), 1536, 1679 (RCONHR'), 3300 cm^{-1} (NH of amide); ^{1}H-NMR spectrum: δ 7·45 (bs, 2 H, 2 NHCO), 6·21 (s, 4 H, 4 Ar—H), 4·47 (s, 4 H, 2 OCH_2), 3·80 and 3·85 (2 s, 18 H, 6 OCH_3), 3·45 (q, J = 6·0 Hz, after D_2O t, 4 H, 2 CH_2NCO), 2·44 (m, 12 H, $CH_2N\langle^{CH_2CH_2}_{CH_2CH_2}\rangle NCH_2$), 1·70 (m, 4 H, 2 C—$CH_2$—C in the propane chain). [f] Dihydrate. [g] Ref.[21] reports a b.p. of 149°C :

Most of the substances prepared were evaluated pharmacologically using methods of the general screening (the basic compounds were tested in the form of salts shown in the Experimental and in Table I); the results are summarized in Table II. Most of the substances are relatively little toxic. The most toxic one is the (2-tolyl)piperazine derivative *XIII* showing the character of an adrenolytic agent. The central neurotropic activity is only slightly indicated. For 10 compounds, signs of central depression (decreased motility after high doses, potentiation of thiopental, hypothermic effect) could be observed; basic nitriles *XIXa*, *XXIa* and *XXIIa* are the most active in this line. After administration of high doses of *XXa* and *XXIIa*, increased motility of mice was observed; at the same time, however, these compounds potentiate the thiopental effect. Other types of neurotropic effects appear only in isolated cases: local anaesthetic (*XIII*), mydriatic (*XXIa*), myorelaxant (arylpiperazinopropylamines *XXIb*, *XXIIb*). Cardiovascular activity of the products seems to be more important. All of the arylpiperazine derivatives (*XII*, *XIII*, *XXIa*, *XXIIa*, *XXIIb*) have clear or even significant adrenolytic activity. Most of the compounds tested show a hypotensive effect in normotensive rats which is weak and of short duration with some of the compounds, with other ones significant and relatively protracted (most active are the adrenolytic arylpiperazine derivatives *XII*, *XIII*, *XXIa* and *XXIIa*). Some of the compounds displayed antiarrhythmic activity, especially the basic amides *VIII*, *XI* and *XIV*. With compound *VIII*, this effect was comparable with that of procainamide[34] and compound *VIII* under the name of "trimethophenoxamide" underwent detailed pharmacological, toxicological and later clinical testing.



XX, R = CH_3 — *a*, R^1 = CN
XXI, R = C_6H_5 — *b*, R^1 = CH_2NH_2
XXII, R = 2-$C_6H_4CH_3$
XXIII, R = $CH_2CH_2R^1$

Trimethophenoxamide was subjected to acute toxicity tests in several species with various routes of administration. The estimated LD_{50} values in mg/kg are given: mice, *i.v.* 180, oral 465; rats, *i.v.* 220, oral 1760. To rabbits and cats, the sub-

: 20 Torr. [h] Ref.[29] reports a b.p. of 100—102°C/16 Torr. [i] Ref.[22] reports a b.p. of 134—136°C : : 13 Torr. [j] Ref.[23,30] report the values of b.p. 52°C/0·3 Torr, and 113°C/17 Torr. respectively. [k] Ref.[30] reports a m.p. of 249—250°C. [l] Ref.[25] reports a m.p. of 71·3—72·1°C. [m] Ref.[26] reports a b.p. of 139—140°C/0·4 Torr. [n] Ref.[31] reports a m.p. of 253—255°C. [o] Ref.[28] reports a m.p. of 65—66°C. [p] Ref.[32] reports a b.p. of 123—123·5°C/1·5 Torr. [q] Ref.[33] reports a m.p. over 300°C.

TABLE II

Pharmacology of 3,4,5-Trimethoxyphenoxyacetic Acid Derivatives and Intermediates

Compound[a]	Code Number	Administration	Acute toxicity LD_{50} mg/kg	Dose screened D mg/kg	Effects
IV	VÚFB-5054	*i.v.*	525	50	*b, c, d*
V	VÚFB-5022	*i.v.*	650	100	*e*
VI	VÚFB-5067	*p.o.*	>2 500	300	*f*
VII	VÚFB-5049	*i.v.*	600		*g*
VIII	VÚFB-5021	*i.v.*	175		*h*
IX	VÚFB-8988	*i.v.*	500	100	*e, i*
X	VÚFB-8780	*i.v.*	375	75	*e*
XI	VÚFB-8781	*i.v.*	150	30	*e, j*
XII	VÚFB-8783	*i.v.*	25	5	*i, k, l*
XIII	VÚFB-8784	*i.v.*	17·5	3·5	*i, k, l, m, n*
XIV	VÚFB-8779	*i.v.*	90	18	*e, i, o*
XV	VÚFB-5029	*i.v.*	680		*p*
XIXa	VÚFB-8733	*i.v.*	750	150	*b, e, l, o, q*
XXa	VÚFB-8979	*i.v.*	375	75	*b, e, r*
XXb	VÚFB-8786	*i.v.*	225	45	*e*
XXIa	VÚFB-8980	*i.v.*	220	55	*b, i, k, l, s, t*
XXIb	VÚFB-8990	*i.v.*	75	15	*e, u*
XXIIa	VÚFB-8981	*i.v.*	125	25	*b, k, l, q, r, t*
XXIIb	VÚFB-8785	*i.v.*	60	12	*e, l, v*
XXIIIa	VÚFB-8978	*i.v.*	450	90	*e, j, q*
XXIIIb	VÚFB-8982	*i.v.*	150	30	*g*

[a] In the case of basic compounds, salts described in Table I were used in pharmacological and toxicological experiments. [b] At dose *D* it prolongs the thiopental sleep in mice. [c] Significant coronary dilating effect (isolated perfused rat heart). [d] Antiarrhythmic activity equalling that of procainamide. [e] Slight and bried drop of blood pressure in normotensive rats. [f] Significant diuretic effect in mice within 2 h after administration. [g] No typical effects in a wide range of doses. [h] Trimethophenoxamide; pharmacological and toxicological data see in the General part. [i] In doses higher than *D* central depression in mice. [j] Slight antiarrhythmic effect in mice against chloroform-induced fibrillation. [k] Significant drop of blood pressure of prolonged duration in normotensive rats. [l] Significant adrenolytic effect in rats (antagonizes the adrenaline-induced rise of blood pressure). [m] A slight locally anaesthetic effect on rabbit cornea. [n] Papaverine-like spasmolytic effect against barium chloride contractions of the isolated rat duodenum. [o] Anti-

stance was administered only orally and the lethal doses showed a great scattering: rabbits, 1 000 – 1 600; cats, 25 – 500. The oral toxicity of trimethophenoxamide for mice and rats is practically identical with that of procainamide (LD_{50} 525, and 1950 mg/kg, respectively). On intravenous administration, trimethophenoxamide is approximately half as toxic as procainamide (LD_{50} 99, and 110 mg/kg, respectively). On oral administration, rats are significantly more resistant against trimethophenoxamide than mice. This was the reason for using mice in chronic toxicity tests. Trimethophenoxamide and procainamide were administered orally for 3 months at two dosage levels: 40 and 120 mg/kg daily. Neither of the agents elicited (even in the higher dose) changes which would suggest organ damages (histological examinations). A further chronic trial was carried out in beagle dogs, to which both agents (2 groups) were administered intravenously for 5 weeks in a daily dose of 40 mg/kg. After the termination of the trial, haematological investigation did not show any damage to the blood count after trimethophenoxamide; a slight relative lymphopenia was observed after procainamide. Biochemical findings did not show differences in comparison with the controls.

The attention was then concentrated to the antiarrhythmic action of trimethophenoxamide. This effect was proved in vitro on isolated guinea-pig and rabbit hearts with electrostimulation, as well as in vivo on cats with arrhythmia elicited also by electrostimulation or by high doses of adrenaline or ouabaine. Procainamide was again used as standard. The activities of both agents were approximately equal on the isolated guinea-pig heart and in the influence on the fibrillation threshold in cats. Trimethophenoxamide was more active than procainamide in the influence on adrenaline arrhythmia. In its action on the duration of the refractory phase in rabbits, trimethophenoxamide appeared to be by 50% less active than procainamide. Several methods were used for evaluating the influence of trimethophenoxamide on the coronary circulation (isolated guinea-pig heart according to Langendorff, changes in blood perfusion of isolated guinea-pig myocardium evaluated conductometrically, and also in experiments in guinea-pigs *in situ*, influence on the coronary flow in dogs, influence on the experimental infarct elicited by administration of a com-

arrhythmic activity in mice against chloroform-induced fibrillation and in rats against aconitine-induced arrhythmias. [p] Has not the character of a monoamine oxidase inhibitor: no antireserpine effect in mice at 5 mg/kg *i.v.* (rather slight potentiation), no monoamine oxidase inhibition in vitro on the rat brain preparation, does not influence tryptamine convulsions in rats at 5 mg/kg *i.v.*, no anorectic effect in mice at 40 mg/kg *i.v.*, slight stimulation in mice on the rotating rod at 150 mg/kg *i.v.*, does not influence the duration of thiopental sleep in mice at 25 mg/kg *i.v.* [q] Slight hypothermic effect in rats. [r] In doses higher than *D* signs of central excitation in mice. [s] Mydriatic effect in mice. [t] Peripheral vasodilation (rabbit's ear) of short duration. [u] Significant myorelaxant effect (rat's gastrocnemius muscle) at 2 LD_{50} under artificial ventilation. [v] Like under *u* but at the dose *D*.

bination of vasopressin and thrombin in rats). None of the tests used proved a coronary constrictive activity. On the contrary, results obtained with the isolated heart indicate that trimethophenoxamide in high doses enhances the coronary flow. This increase is accompanied by a negative inotropic effect; both of these effects, however, appeared only at high concentrations of the substance in the perfusion solution, which cannot be attained by therapeutic doses. Trimethophenoxamide was further evaluated from the point of view of its influence on the blood pressure and some further circulatory parameters (effect on blood pressure in anaesthetized rats and dogs, nonanaesthetized rabbits, effect on microcirculation in rat mesenterium). High intravenous doses of trimethophenoxamide and procainamide (*e.g.* ,75 mg/kg) bring about a sudden and deep drop in blood pressure as well as death of the anaesthetized rats; doses under 3·7 mg/kg are practically without effect on blood pressure. An oral dose of 1 g/kg brings about only a mild drop in the blood pressure. For nonanaesthetized rabbits, the threshold dose causing a drop of the blood pressure by 10% in comparison with the initial values is 25 mg/kg *i.v.*; this hypotension is of short duration (5 min). In anaesthetized dogs, a dose of 10 mg/kg *i.v.* brings about a drop in the systolic as well as diastolic pressures by 15% and this drop remains for 1 – 2 min. A double dose has only a slightly higher hypotensive effect. At the same time the heart rate is increased by 15% and the duration of tachycardia is identical with the duration of hypotension. After these doses, there are no visible changes in the ECG. The microcirculation in the rat mesenterium remained likewise unchanged when 0·5 – 1% solutions were used. In the test of infiltration local anaesthesia on guinea-pigs, trimethophenoxamide produced an effect approaching 25% of that of procainamide. From the point of view of the CNS effects, trimethophenoxamide proved to be practically indifferent: doses of 2·5 – 35 mg/kg *i.v.* do not influence the behaviour of mice on the rotating rod, the dose of 5 mg/kg *i.v.* does not influence the thiopental sleep in mice (the dose of 25 mg/kg slightly shortens the duration of the sleep), the substance has no antireserpine effect (10 mg/kg *i.v.* administered simultaneously with reserpine does not influence the eyelid ptosis in mice), after doses of 5 mg/kg *i.v.* there is no alteration of tryptamine convulsions in rats, there is no anticonvulsant effect, in an oral dose of 40 mg/kg the substance has no anorectic effect in mice. On isolated rat ductus deferens, trimethophenoxamide did not show a typical α-adrenergic activity. Antihistamine and antiinflammatory activities are likewise absent. On the basis of the evaluation carried out, clinical trials of trimethophenoxamide as a potential antiarrhythmic were recommended[35]. Simultaneously with pharmacological and toxicological studies, a pharmacokinetic investigation was carried out[36].

Clinical trials of trimethophenoxamide in the treatment of cardiac rhythm disorders proceeded at the Institute of Cardiovascular Diseases, Prague (Dr. K. Bergmann, Dr O. Horák) and at the Internal Department, Faculty Hospital 2, Charles University, Prague (Dr A. Struppl, Dr J. Mrázová). The agent was administered to a total of 30 patients with various types of cardiac rhythm disorders. In paroxysmal types

of arrhythmias, it was administered preventively in the form of 2 tablets (containing 250 mg each) daily for 1–4 months. For heterotopic rhythms and ventricular arrhythmias, it was used for short periods in the pushed dosage of 8–10 tablets (2·0–2·5 g) during 24 h; in these cases, the administration was either discontinued after attaining a positive effect or the therapy was continued with a maintenance range of doses. Clearly positive effects were observed in all cases of ectopic ventricular rhythms. Supraventricular arrhythmias were influenced to a lesser extent, and completely unchanged remained the simple sinus tachycardias as well as all chronic cases of cardiac rhythm disorders. The most important side effect of the treatment was hypotension occurring in 25% of the patients, which was independent of the doses used. For this reason and further on the basis of a comparison with procainamide, in which trimethophenoxamide did not show any clear advantages, the clinical trials were discontinued and the projects for therapeutic use of the agent abandoned.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 0·5 Torr over P_2O_5 at room temperature or at 77°C. The IR spectra (in KBr or in Nujol) were recorded on a Unicam SP 200G spectrophotometer and ^{1}H-NMR spectra (in $CDCl_3$) on a ZKR-60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of alumina (Brockmann, act. II). Analyses of the compounds prepared are shown in Table I.

Methyl 3,4,5-Trimethoxyphenoxyacetate (*II*)

3,4,5-Trimethoxyphenoxyacetic acid[15] (*I*, 242 g) was dissolved in a mixture of 2·5 l acetone, 126·5 g dimethyl sulfate and 300 ml water at room temperature, the mixture was slowly treated with 139 g anhydrous K_2CO_3 and then refluxed under stirring for 5 h. Acetone was evaporated, the residue diluted with 1·1 l 5% $NaHCO_3$ and the mixture extracted with chloroform. The extract was dried with $MgSO_4$ and evaporated. There were obtained 240 g (90%) of a product with m.p. 78–82°C which is suitable for further work. For analysis, the product was recrystallized from methanol, m.p. 79–81°C. IR spectrum (KBr): 1 161 (C—O), 1 230 ($ArOCH_3$), 1 570, 1 600 (Ar), 1 746 cm^{-1} (RCOOR').

Ethyl 3,4,5-Trimethoxyphenoxyacetate (*III*)

A. Acid *I* (12·1 g) was added to a boiling solution of sodium ethoxide (1·2 g Na, 100 ml ethanol) and the solution obtained was treated with 13·0 g 2-diethylaminoethyl chloride. The mixture was refluxed for 2 h. After cooling, the precipitated NaCl was filtered off and the filtrate evaporated under reduced pressure. The residue was diluted with excess of 3% $NaHCO_3$ and the mixture extracted with chloroform. The extract was washed with 10% NaCl, dried with K_2CO_3 and distilled; 13·4 g (99%) neutral compound with a b.p. of 148–150°C/2 Torr; m.p. 51–52°C (dibutyl ether).

B. A mixture of 50 g *II*, 3·0 g diethylamine and 20 ml ethanol was heated with stirring for 2 h to 60°C. The volatile components were evaporated under reduced pressure and the residue was crystallized from aqueous ethanol, m.p. 51–53°C. The product is identical with that obtained according to *A*.

2-Diethylaminoethyl 3,4,5-Trimethoxyphenoxyacetate (*IV*)

A solution of 10·0 g *I* in 50 ml dichloromethane was slowly treated with a solution of 9·0 g N,N′-dicyclohexylcarbodiimide in 50 ml dichloromethane. After standing for 2 h, the solid was filtered, the filtrate treated with a solution of 2·5 g 2-diethylaminoethanol in 30 ml pyridine and the mixture left for 12 h at room temperature. Dichloromethane was then distilled off and the residue was heated for 4 h to 80°C. Pyridine was evaporated in vacuo, the residue diluted with chloroform and the basic product extracted with 5% hydrochloric acid. The acid aqueous solution was made alkaline with Na_2CO_3 and the product isolated by extraction with chloroform; 3·8 g (27%), b.p. 182–184°C/1 Torr. Neutralization with maleic acid in ethanol and addition of ether yielded the hydrogen maleate with a m.p. of 72–74°C (ethanol–ether).

3,4,5-Trimethoxyphenoxyacetamide (*V*)

II (2·56 g) was dissolved in 100 ml ethanol saturated with NH_3 and the mixture kept 2 h at room temperature. Ethanol was then evaporated and the residue crystallized from methanol; 2·26 g (94%), m.p. 124–125°C. IR spectrum (KBr): 847 (solitary Ar—H), 1131 ($CONH_2$), 1238 ($ArOCH_3$), 1510, 1600 (Ar), 1660, 1690 ($CONH_2$), 2835 (OCH_3), 3374 and 3494 cm^{-1} (NH_2 of amide).

N-Benzyl-3,4,5-trimethoxyphenoxyacetamide (*VI*)

A mixture of 10·0 g *II* and 4·0 g benzylamine was heated briefly to 190°C and the melt crystallized from ethanol; 12·0 g (93%), m.p. 98–99°C.

3,4,5-Trimethoxyphenoxyacetomorpholide (*VII*)

A mixture of 5·0 g *II* and 30 ml morpholine was refluxed for 2 h. Volatile components were evaporated under reduced pressure, the residue decomposed with 5% Na_2CO_3 and extracted with chloroform. The extract was washed with 3M-HCl and water, dried with K_2CO_3 and evaporated. The residue was crystallized from a mixture of benzene and ether; 3·0 g (49%), m.p. 108–109°C.

N-(2-Diethylaminoethyl)-3,4,5-trimethoxyphenoxyacetamide (*VIII*)
(Method *A*)

A mixture of 25·6 g *II*, 11·8 g 2-diethylaminoethylamine and 570 ml ethanol was refluxed with stirring for 2 h. Ethanol was evaporated under reduced pressure, the residue dissolved in 140 ml ethanol and the solution acidified under stirring with a solution of hydrogen chloride in ether. After standing overnight at 0–5°C, the precipitated hydrochloride of the product was filtered; 29·3 g (78%), m.p. 146–153°C. The analytical sample was obtained by crystallization from ethanol, m.p. 157–158°C.

N-(2-Morpholinoethyl)-3,4,5-trimethoxyphenoxyacetamide (*IX*) (Method *B*)

A mixture of 12·8 g *II*, 25 ml 1-butanol and 5·9 g 2-morpholinoethylamine was stirred and heated to 110°C for 8 h, butanol was evaporated, the residue dissolved in chloroform and the solution washed with water. The chloroform solution was dried with K_2CO_3, evaporated, the residue dissolved in 50 ml ethanol, the solution filtered with charcoal and the filtrate acidified with a solution of HCl in ether. Standing and cooling led to precipitation of 10·5 g (53%) hydrochloride hemihydrate with a m.p. of 149—155°C. Analytical product, m.p. 155—157°C (ethanol).

3,4,5-Trimethoxyphenoxyacetohydrazide (*XV*)

A solution of 4·2 g *II* and 1·5 g 80% hydrazine hydrate in 15 ml ethanol was refluxed for 2 h. By standing, 3·5 g (83%) of a product were obtained, m.p. 141—143°C (ethanol).

3,4,5-Trimethoxyphenoxyacetone (*XVI*)

A boiling mixture of 5·5 g 3,4,5-trimethoxyphenol[16], 70 ml acetone and 4·2 g K_2CO_3 was treated dropwise with a solution of 5·2 g bromoacetone in 25 ml acetone. The mixture was stirred and refluxed for 4 h. After the evaporation of acetone, the residue was diluted with 40 ml 2·5% Na_2CO_3 and the product isolated by extraction with chloroform; 6·2 g (86%) oil. The crude product gave the oxime melting at 90—92°C (aqueous methanol) and the 2,4-dinitrophenylhydrazone, m.p. 164—167°C (ethanol).

3,4,5-Trimethoxyphenoxyacetonitrile (*XVII*)

A mixture of 3·0 g 3,4,5-trimethoxyphenol[16], 80 ml acetone, 2·0 g chloroacetonitrile and 4·0 g K_2CO_3 was stirred and refluxed for 4 h. After the evaporation of acetone, the residue was decomposed with 100 ml 5% Na_2CO_3 and extracted with chloroform. Processing of the extract gave 3·2 g (88%) product with a b.p. of 150—154°C/0·4 Torr. The distillate solidified to yellow needles crystallizing from aqueous methanol and melting at 50—52°C (sealed capillary).

2-(3,4,5-Trimethoxyphenoxy)ethylamine (*XVIII*)

A. A solution of 7·6 g *V* in 100 ml tetrahydrofuran was dropped under stirring to a solution of 5·0 g $LiAlH_4$ in 100 ml tetrahydrofuran; the mixture was refluxed for 8 h. After standing overnight, the mixture was decomposed by a slow addition of 5 ml water, 5 ml 15% NaOH and 15 ml water. The precipitated solid was filtered off, washed with benzene, and the filtrate was dried with K_2CO_3 and distilled; 4·8 g (67%), b.p. 160—162°C/5 Torr. The base was neutralized with an ethanolic solution of HCl giving the hydrochloride which crystallized from a mixture of 95% ethanol and ether as a hemihydrate, m.p. 175—177°C.

B. XVII (6·9 g) was similarly reduced with 3·4 g $LiAlH_4$ in 100 ml tetrahydrofuran. A similar processing yielded only 1·6 g (23%) of the base, b.p. 160—165°C/5 Torr, identical with the product prepared according to *A*.

1-(2-Cyanoethyl)-4-(2-tolyl)piperazine (*XXIIa*) (Method *C*)

1-(2-Tolyl)piperazine[20] (58·3 g) was stirred and treated over a period of 45 min with 19·5 g acrylonitrile; the temperature rose spontaneously to 80°C. The mixture was stirred for 2 h and left overnight. The solid product was mixed with petroleum ether and filtered; the crude product

was recrystallized from ethanol, 61·0 g (81%), m.p. 78·5–79°C. Ref.[25] reports for the base a m.p. of 78·4–79°C. Neutralization of the base in ethanol with a solution of HCl in ether gave the monohydrochloride, m.p. 219–222°C (ethanol).

1-(3-Aminopropyl)-4-(2-tolyl)piperazine (*XXIIb*) (Method *D*)

Nitrile *XXIIa* (59 g) was added in small portions under stirring to a suspension of 17 g $LiAlH_4$ in 550 ml ether. The mixture was refluxed for 7 h and after standing overnight decomposed dropwise with 15 ml water, 15 ml 20% NaOH and 50 ml water. The precipitated solid was filtered and washed with ether. The filtrate was dried with K_2CO_3 and processed by distillation; 53 g (91%), b.p. 129°C/0·15 Torr. ^{1}H-NMR spectrum: δ c. 7·01 (m, 4 H, Ar—H), 2·90 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·65 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50–3·00 (m, 4 H, remaining 2 NCH_2), 2·25 (s, 3 H, Ar—CH_3), 1·70 (m, 2 H, C—CH_2—C in the propane chain), 1·27 (s, 2 H, NH_2). Similarly as in foregoing cases, the dihydrochloride was prepared, m.p. 259–261°C (ethanol).

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