BASIC AMIDES OF 2,4,5-TRICHLOROPHENOXYACETIC, 2,4,6-TRIMETHYLPHENOXYACETIC AND 4-BROMO-3,5-DIMETHYLPHENOXYACETIC ACID AND SOME RELATED COMPOUNDS; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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Reactions of methyl esters *II* of 2,4,5-trichlorophenoxyacetic (*Ia*), 2,4,6-trimethylphenoxyacetic (*Ib*) and 4-bromo-3,5-dimethylphenoxyacetic acid (*Ic*) with 2-diethylaminoethylamine, 2-morpholinoethylamine, 3-morpholinopropylamine, 1-methylpiperazine, 3-(4-methylpiperazino)propylamine, 3-[4-(2-tolyl)piperazino]propylamine and 1,4-bis(3-aminopropyl)piperazine in boiling ethanol gave the basic amides *Va–Xlc* which were isolated as hydrochlorides. Reactions of the acid chlorides *IVa* and *IVb* with 1,4-bis(2-hydroxyethyl)piperazine and 1,4-bis(3-hydroxypropyl)-piperazine in dimethylformamide resulted directly in dihydrochlorides of diesters *XIIab* and *XIIIab*. The compounds prepared have only weak CNS effects (mostly of the depressant type); they have local anaesthetic, mild hypotensive (some of them adrenolytic), antiarrhythmic and peripheral vasodilating activities.

In one of the preceding communications of this series[1] we have described the synthesis and pharmacology of several basic amides of 3,4,5-trimethoxyphenoxyacetic acid showing in addition to a mild central depressant activity some more important cardiovascular effects. The 2-diethylaminoethylamide (trimethophenoxamide) was the most active compound which was clinically tested as an antiarrhythmic agent[2]. This work was continued by synthesis of basic amides and some esters of further three trisubstituted phenoxyacetic acids which were also evaluated pharmacologically; the synthesis of these compounds is the object of the present communication.

As starting compounds of this study we selected 2,4,5-trichlorophenoxyacetic (*Ia*) (ref.[3,4]), 2,4,6-trimethylphenoxyacetic (*Ib*) (ref.[5]) and 4-bromo-3,5-dimethylphenoxyacetic acid (*Ic*). These acids were prepared by the general method[6] consisting in heating the corresponding phenols, *i.e.* 2,4,5-trichlorophenol, 2,4,6-trimethylphenol and 4-bromo-3,5-dimethylphenol[7,8], with chloroacetic acid with an excess of aqueous sodium hydroxide. After diluting with water, the little soluble sodium salts of the acids *I* crystallized and afforded the free acids by acidification. In the case of the acid

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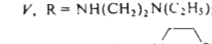
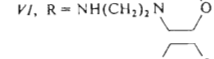
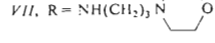
Ic this sodium salt was directly used to further work. Refluxing of the acids *Ia* and *Ib* with dimethyl sulfate and potassium carbonate in aqueous acetone gave the methyl esters *IIa* and *IIb*; the ester *IIc* was obtained similarly from the sodium salt of the acid *Ic*. A similar reaction of the acid *Ia* with diethyl sulfate led to the ethyl ester *IIIa*. Further intermediates prepared were the acid chlorides *IVa* (ref.[9]) and *IVb* obtained by treatment of the acids with thionyl chloride.

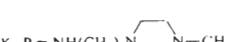
$ArOCH_2COR$

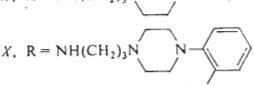
I, R = OH
II, R = OCH_3
III, R = OC_2H_5
IV, R = Cl
V, R = $NH(CH_2)_2N(C_2H_5)_2$

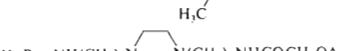


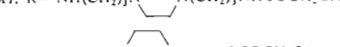


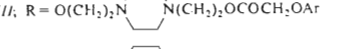


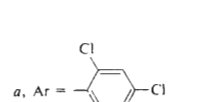


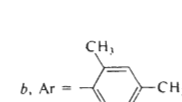


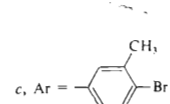












The basic amides *Va*–*XIc* were obtained by reactions of the methyl esters *II* with the following amines in boiling ethanol : 2-diethylaminoethylamine, 2-morpholinoethylamine, 3-morpholinopropylamine[1,10], 1-methylpiperazine, 3-(4-methylpiperazino)propylamine[1,11], 3-[4-(2-tolyl)piperazino]propylamine[1] and 1,4-bis(3-aminopropyl)piperazine[1,12]. The water-soluble amines were used in a moderate excess and the excessive amine was removed after the reaction by washing with water (method A). The water-insoluble tolylpiperazinopropylamine was used in equimolecular quantity or a slight excess of the ester was used and the products were precipitated directly from the ethanolic solutions as hydrochlorides by a solution of hydrogen chloride in ether (method *B*). In the preparation of the diamides *XIa*–*XIc* approximately two molecules of the esters *IIa*–*IIc* per one molecule of the amine were used and only in these cases it succeeded to prepare crystalline bases (method *C*). Reactions

of the acid chlorides *IVab* with 1,4-bis(2-hydroxyethyl)piperazine[13] and 1,4-bis(3-hydroxypropyl)piperazine[14] in dimethylformamide at 100°C resulted directly in dihydrochlorides of the diesters *XIIab* and *XIIIab* (method *D*). All the basic compounds prepared are assembled in Table I. The Experimental describes the preparation of intermediates and brings only examples of preparation of the basic compounds by methods *A* – *D*.

The substances prepared were evaluated pharmacologically using methods of the general screening; they were tested in the form of salts shown in Table I. First of all the routes of administration, values of acute toxicity in mice (LD_{50}) and the screened doses (D) (doses in mg/kg) are given: *Va*, *i.v.*, 75, 15; *Vb*, *i.v.*, 50, 10; *Vc*, *i.v.*, 75, 15; *VIa*, *i.v.*, 75, 15; *VIIa* ,*i.v.*, 125, 25; *VIIb*, *i.v.*, 100, 20; *VIIIa*, *i.v.*, 162·5, 30; *IXa* *i.v.*, 100, 20; *IXb*, *i.v.*, 100, 20; *IXc*, *i.v.*, 150, 30; *Xa*, *p.o.*, 875, 150; *Xb*, *i.v.*, 62·5, 12; *Xc*, *p.o.*, 1 500, 300; *XIa*, *p.o.*, >2 500, 300; *XIb*, *i.v.*, 50, 10; *XIc*, *p.o.*, >2 500, 300; *XIIa*, *p.o.*, 1 750, 300; *XIIb*, *p.o.*, 350, 70; *XIIIa*, *p.o.*, 2 000, 300; *XIIIb*, *p.o.*, 350, 70.

The CNS activity of the compounds is not significant. With most of them a central depressant activity (inhibition of spontaneous motility in mice) appears only in doses above D (*Vb*, *VIa*, *VIIa*, *VIIIa*, *IXa*, *IXb*, *Xc*, *XIIa*, *XIIIa*); some of them bring about excitation (increase of motility) (*Va*, *Vc*, *Xb*, *XIIb*). With some of the compounds the potentiation of the thiopental sleeping time in mice was noted at doses D (*Vb*, *Xa*, *Xc*, *XIa*) and compounds *Xa* and *XIa* had hypothermic effect in rats. The expected local anaesthetic effect in the test of infiltration anaesthesia in guinea-pigs (procaine-like) and in the test of corneal anaesthesia on the rabbit eyes (cocaine-like) was observed (*Va*, *Vc*, *VIa*, *VIIa*, *Xb*, *XIb*) and also the structurally nonspecific spasmolytic effect (papaverine-like) on the isolated rat duodenum appeared (*Vc*, *XIb*). The compounds had also some cardiovascular effects: mild hypotensive effects in normotensive rats of short duration (*Va*, *Vb*, *Vc*, *VIa*, *VIIa*, *VIIb*, *IXb*, *IXc*, *Xa*, *Xb*, *XIa*, *XIb*, *XIIIa*), α-adrenolytic effect (*Vc*, *IXc*, *Xb*), antiarrhythmic effect in mice only towards ventricular fibrillations induced with chloroform (*VIIa*, *VIIIa*), peripheral vasodilating activity evaluated by increasing the temperature of the guinea-pig's ear (*VIIb*, *Xa*, *Xc*, *XIb*, *XIIIb*), negatively inotropic effect on the isolated rabbit heart atrium (*Va*, *Vc*, *VIIa*, *VIIb*, *IXa*, *XIb*) and a mild negatively chronotropic effect (*Vb*, *IXa*). Compound *IXb* showed at the dose D a hypoglycaemic effect in rats which was confirmed also on oral administration (ED decreasing the blood sugar level by 20% was 100 mg/kg); some compounds had a mild hyperglycaemic effect (*VIIIa*, *XIc*, *XIIIa*).

Compounds *Xabc* and *XIab* showed some antimicrobial effects in the tests *in vitro* (Dr A. Šimek, bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 125 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *Xa* 12·5, *Xb* 25, *XIa* 25; *Staphylococcus pyogenes aureus*, *Xa* 12·5, *Xb* 25, *XIa* 25; *Proteus vulgaris*, *Xa* 50; *Mycobacterium tuberculosis* H37Rv, *Xa* 50, *Xb* 25, *Xc* 12·5, *XIa* 50, *XIb* 50; *Saccharomyces pasterianus*, *Xa* 125, *XIa* 125; *Trichophyton mentagrophytes*, *Xa* 125, *XIa* 125.

TABLE I

Basic amides and esters of the trisubstituted phenoxyacetic acids and their hydrochlorides

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated / Found % C	% H	% Cl	% N
Va . HCl	*A*[a] (72)	138·5—140·5 (ethanol–ether)	$C_{14}H_{20}Cl_4N_2O_2$ (390·1)	43·10 / 43·26	5·16 / 5·16	36·35 / 36·16	7·18 / 7·16
Vb . HCl[b]	*A* (84)	147—150 (ethanol–ether)	$C_{17}H_{29}ClN_2O_2 + 0{\cdot}5\ H_2O$ (337·9)	60·42 / 60·64	8·95 / 9·02	10·49 / 11·06	8·29 / 8·47
Vc . HCl	*A* (82)	179—180 (ethanol–ether)	$C_{16}H_{26}BrClN_2O_2$ (393·8)	48·80 / 48·90	6·65 / 6·74	9·00 / 8·98	7·12 / 7·07
VIa . HCl	*A* (70)	221—222 (aqueous ethanol)	$C_{14}H_{18}Cl_4N_2O_3$ (404·1)	41·59 / 41·64	4·48 / 4·44	35·09 / 35·23	6·93 / 6·78
VIIa . HCl	*A* (71)	194—197 (ethanol)	$C_{15}H_{20}Cl_4N_2O_3$ (418·2)	43·08 / 43·36	4·82 / 4·95	33·92 / 33·70	6·70 / 6·74
VIIb . HCl[c]	*A* (89)	195—198 (ethanol–ether)	$C_{18}H_{29}ClN_2O_3 + H_2O$ (374·9)	57·67 / 58·05	8·33 / 8·21	9·46 / 9·20	7·47 / 7·67
VIIIa . HCl	*A* (72)	226—230 (aqueous ethanol–ether)	$C_{13}H_{16}Cl_4N_2O_2$ (374·1)	41·74 / 41·90	4·31 / 4·27	37·91 / 38·01	7·49 / 7·04
IXa . 2 HCl[c]	*A* (90)	211—213 (95% ethanol)	$C_{16}H_{24}Cl_5N_3O_2 + H_2O$ (485·7)	39·57 / 39·93	5·40 / 5·38	36·50 / 36·14	8·65 / 8·53
IXb . 2 HCl[d]	*A* (89)	173—176 (aqueous ethanol–ether)	$C_{19}H_{33}Cl_2N_3O_2 + H_2O$ (442·4)	51·58 / 51·44	8·43 / 7·92	16·03 / 16·40	9·50 / 9·81
IXc . 2 HCl[c]	*A* (74)	216—219 (ethanol)	$C_{18}H_{30}BrCl_2N_3O_2 + H_2O$ (487·3)	44·36 / 44·56	6·62 / 6·71	14·55 / 14·18	8·62 / 8·56

Xa . HCl	*B* (94)	192—194 (ethanol)	$C_{22}H_{27}Cl_4N_3O_2$ (507·1)	52·11 52·22	5·36 5·39	27·96 27·68	8·28 8·37
Xb . 2 HCl[c]	*B* (66)	98—100 (ethanol–ether)	$C_{25}H_{37}Cl_2N_3O_2 + H_2O$ (500·5)	59·99 59·67	7·85 7·87	14·17 14·62	8·39 8·56
Xc . 2 HCl	*B*[a] (83)	204—208 (ethanol–ether)	$C_{24}H_{34}BrCl_2N_3O_2$ (547·4)	52·66 52·99	6·26 6·39	12·97 12·52	7·68 7·68
XIa	*C*[a] (88)	164—166 (ethanol–benzene)	$C_{26}H_{30}Cl_6N_4O_4$ (675·3)	46·24 47·08	4·48 4·63	31·50 31·33	8·30 8·23
XIa . 2 HCl[d]		216—219 (80% ethanol)	$C_{26}H_{32}Cl_8N_4O_4 + H_2O$ (784·2)	39·83 40·17	4·62 4·61	36·17 35·61	7·14 7·22
XIb . 2 HCl[c]	*C* (71)	206—208 (ethanol–ether)	$C_{32}H_{50}Cl_2N_4O_4 + H_2O$ (643·7)	59·70 59·31	8·14 8·12	11·02 11·36	8·70 8·71
XIc	*C* (50)	184·5—185·5 (ethanol)	$C_{30}H_{42}Br_2N_4O_4$ (682·5)	52·79 52·42	6·20 6·31	23·42[e] 23·68	8·21 8·26
XIc . 2 HCl		209·5—210·5 (ethanol–dimethylformamide)	$C_{30}H_{44}Br_2Cl_2N_4O_4$ (755·4)	47·69 47·88	5·87 6·01	9·39 9·11	7·42 7·51
XIIa . 2 HCl	*D*[a] (71)	212—214 (aqueous ethanol)	$C_{24}H_{26}Cl_8N_2O_6$ (722·1)	39·92 40·23	3·63 3·77	39·28 39·14	3·88 3·97
XIIb . 2 HCl	*D* (43)	201—203 (96% ethanol)	$C_{30}H_{44}Cl_2N_2O_6$ (599·6)	60·09 59·72	7·39 7·55	11·82 11·81	4·67 4·72
XIIIa . 2 HCl	*D* (65)	210—215[f] (aqueous ethanol)	$C_{26}H_{30}Cl_8N_2O_6$ (750·2)	41·63 41·26	4·03 4·25	37·81 37·34	3·74 3·69
XIIIb . 2 HCl	*D* (75)	204—205·5 (98% ethanol)	$C_{32}H_{48}Cl_2N_2O_6$ (627·6)	61·24 61·33	7·71 7·89	11·30 11·45	4·43 4·38

[a] See Experimental. [b] Hemihydrate. [c] Monohydrate. [d] Dihydrate. [e] Content of Br. [f] IR spectrum (KBr): 781 (C—Cl), 869 (solitary Ar—H), 1 089 ($ArOCH_2$), 1 197 (C—O of ester), 1 479, 1 586 (Ar), 1 763 (RCOOR'), 2 440 cm^{-1} (NH^+).

EXPERIMENTAL

The melting points were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 70 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra (mostly in Nujol) were recorded with a Unicam SP 200 G spectrophotometer and the ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a ZKR-60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on alumina (Brockmann, act. II). Analyses of the compounds prepared by the general methods (*A*—*D*) are included in Table I.

2,4,5-Trichlorophenoxyacetic Acid (*Ia*)

2,4,5-Trichlorophenol (80 g) was added to a solution of 22·5 g NaOH in 120 ml water, the mixture was heated to 95°C and treated under stirring over 45 min with a solution of 52 g chloroacetic acid and 22·5 g NaOH in 170 ml water. The mixture was then stirred for 2·5 h in an open flask (bath 120—135°C). The melt was heated with 500 ml water and the suspension allowed to stand overnight at room temperature. The precipitated sodium salt was filtered, dissolved in 2 250 ml water at 80°C and the solution was acidified with 5M-HCl. The precipitated product was filtered after 24 h standing, it was washed with water and dried; 75 g (74%), m.p. 149—153°C. Analytical sample, m.p. 158—160°C (benzene). IR spectrum: 680, 770 (C—Cl), 842, 878, 889 (sclitary Ar—H), 940 (COOH), 1 070 ($ArOCH_2$), 1 235, 1 253, 1 289 ($ArOCH_2$ and COOH), 1 430, 1 480, 1 590 (Ar), 1 745 cm^{-1} (COOH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ c. 13·00 (bs, 1 H, COOH), 7·80 (s, 1 H, 3-H), 7·44 (s, 1 H, 6-H), 4·91 (s, 2 H, OCH_2CO). For $C_8H_5Cl_3O_3$ (255·5) calculated: 37·61% C, 1·97% H, 41·63% Cl; found: 37·85% C, 2·09% H, 41·34% Cl. Lit.[3,4], m.p. 153°C.

2,4,6-Trimethylphenoxyacetic Acid (*Ib*)

A similar reaction of 25·2 g 2,4,6-trimethylphenol in a solution of 10·4 g NaOH in 40 ml water with a solution of 24 g chloroacetic acid and 10·4 g NaOH in 60 ml water gave 25·3 g (70%) crude product, m.p. 139—142°C. Analytical sample, m.p. 148—151·5°C (benzene). IR spectrum: 855 (solitary Ar—H), 920 (COOH), 1 070, 1 205, 1 210 ($ArOCH_2$), 1 245, 1 260, 1 300 (COOH), 1 605 (Ar), 1 710, 1 740 cm^{-1} (COOH). ^{1}H NMR spectrum: δ 10·42 (s, 1 H, COOH), 6·88 (s, 2 H, 3,5-H_2), 4·46 (s, 2 H, OCH_2CO), 2·25 (s, 9 H, 3 CH_3). For $C_{11}H_{14}O_3$ (194·2) calculated: 68·02% C, 7·26% H; found: 67·81% C, 7·20% H. Lit.[5], m.p. 131·5°C.

Methyl 2,4,5-Trichlorophenoxyacetate (*IIa*)

A stirred mixture of 51 g *Ia*, 600 ml acetone, 60 ml water and 26·6 g dimethyl sulfate was refluxed and treated over 2·5 h with 29 g K_2CO_3 in small portions. The mixture was refluxed for 8 h and allowed to stand overnight. The solid was filtered off and the filtrate evaporated under reduced pressure. The residue was combined with the filtered solid material, it was stirred with 250 ml 5% $NaHCO_3$ and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated; 36·6 g (68%) crude solid product which was crystallized from 230 ml methanol, m.p. 88—91°C. Analytical sample, m.p. 91—92°C (methanol). IR spectrum: 680, 775 (C—Cl), 865, 882 (solitary Ar—H), 1 070, 1 086 ($ArOCH_2$), 1 145, 1 245, 1 295 ($RCOOCH_3$), 1 588, 3 100 (Ar), 1 753 cm^{-1} (RCOOR'). ^{1}H NMR spectrum: δ 7·54 (s, 1 H, 3-H), 6·97 (s, 1 H, 6-H), 4·71 (s, 2 H, OCH_2CO), 3·84 (s, 3 H, OCH_3). For $C_9H_7Cl_3O_3$ (269·5) calculated: 40·11% C, 2·61% H, 39·47% Cl; found: 40·55% C, 2·82% H, 39·09% Cl.

Methyl 2,4,6-Trimethylphenoxyacetate (*IIb*)

Was prepared similarly from 29 g *Ib*, 28·5 g dimethyl sulfate and 32 g K_2CO_3 in a mixture of 375 ml acetone and 50 ml water; 21 g (68%), b.p. 135–138°C/1·3 kPa. For $C_{12}H_{16}O_3$ (208·3) calculated: 69·24% C, 7·75% H; found: 69·61% C, 7·90% H.

Methyl 4-Bromo-3,5-dimethylphenoxyacetate (*IIc*)

A stirred solution of 20·1 g 4-bromo-3,5-dimethylphenol[7,8] and 11·2 g NaOH in 40 ml water was heated to 90°C and treated over 1 h with a solution of 13·2 g chloroacetic acid in 20 ml water, added dropwise. The mixture was then stirred for 4 h in a bath of 105°C. The remaining melt was diluted with 50 ml hot water, it was stirred for 1 h at 80°C and after cooling the precipitated sodium 4-bromo-3,5-dimethylphenoxyacetate was filtered and dried; 26·6 g (95%), m.p. over 250°C. A mixture of 20 g of this salt, 200 ml methanol and 20 g dimethyl sulfate was refluxed for 10 h and evaporated *in vacuo*. The residue was partitioned by shaking between 250 ml chloroform and 100 ml 2·5M-NaOH, the chloroform solution was dried with $MgSO_4$ and evaporated. The remaining oil could be distilled (b.p. 128°C/70 Pa) but it crystallized on standing; 11·0 g (58%), m.p. 59–63°C. Analytical sample, m.p. 62–65°C (aqueous methanol). IR spectrum: 840, 860 (solitary Ar–H), 1 020, 1 100 ($ArOCH_2$), 1 180, 1 220, 1 320 ($RCOOCH_3$), 1 580 (Ar), 1 770 cm^{-1} (RCOOR'). For $C_{11}H_{13}BrO_3$ (273·1) calculated: 48·37% C, 4·80% H, 29·26% Br; found: 48·80% C, 4·97% H, 29·76% Br.

Ethyl 2,4,5-Trichlorophenoxyacetate (*IIIa*)

Was prepared similarly like *IIa* from 17 g *Ia*, 11·5 g diethyl sulfate and 10·5 g K_2CO_3 in a mixture of 170 ml acetone and 20 ml water; 11·5 g (54%), m.p. 63–66°C. Analytical sample, m.p. 66 to 67·5°C (aqueous ethanol). IR spectrum: 727 (C–Cl), 870 (solitary Ar–H), 1 090, 1 220 ($ArOCH_2$), 1 140, 1 298 (RCOOR'), 1 585 (Ar), 1 710, 1 740 cm^{-1} (RCOOR'). For $C_{10}H_9Cl_3O_3$ (283·5) calculated: 42·36% C, 3·20% H, 37·52% Cl; found: 42·65% C, 3·26% H, 37·34% Cl.

2,4,6 Trimethylphenoxyacetyl Chloride (*IVb*)

A mixture of 20·5 g *Ib*, 50 ml benzene and 31·5 ml $SOCl_2$ was refluxed for 5 h and evaporated under reduced pressure. The residue was distilled; 17·3 g (77%), b.p. 139°C/1·6 kPa. The distillate crystallized on standing, m.p. 61–62·5°C. For $C_{11}H_{13}ClO_2$ (212·7) calculated: 62·12% C, 6·16% H, 16·67% Cl; found: 62·40% C, 6·20% H, 16·69% Cl.

N-(2-Diethylaminoethyl)-2,4,5-trichlorophenoxyacetamide (*Va*) (Method *A*)

A mixture of 8·9 g *IIa*, 4·2 g 2-diethylaminoethylamine and 20 ml ethanol was refluxed for 20 h and the solvent was evaporated *in vacuo*. The residue was diluted with water and extracted with benzene. The extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in 60 ml ethanol and the solution was treated with a slight excess of a solution of HCl in ether. The hydrochloride crystallized on standing overnight; 9·3 g (72%), m.p. 138·5–140·5°C (ethanol–ether).

N-(3-[4-(2-Tolyl)piperazino]propyl)-4-bromo-3,5-dimethylphenoxyacetamide (*Xc*) (Method *B*)

A mixture of 6·9 g *IIc*, 4·7 g 3-[4-(2-tolyl)piperazino]propylamine[1] and 15 ml ethanol was refluxed for 20 h. It was then diluted with 20 ml ethanol, the solution was filtered with charcoal and the filtrate was treated with a slight excess of a solution of HCl in ether; 9·1 g (83%) dihydrochloride, m.p. 204–208°C (ethanol–ether).

1,4-Bis[3-(2,4,5-trichlorophenoxyacetamido)propyl]piperazine (*XIa*) (Method *C*)

A mixture of 17·0 g *IIa*, 6·0 g 1,4-bis(3-aminopropyl)piperazine[1,12] and 25 ml ethanol was stirred and refluxed for 24 h. Standing overnight at room temperature led to crystallization of the base which was filtered and dried; 18·8 g (88%), m.p. 162–166°C. Analytical sample, m.p. 164–166°C (ethanol–benzene). IR spectrum: 631, 751, 776 (C—Cl), 875 (solitary Ar—H), 1 050, 1 080, 1 250 ($ArOCH_2$), 1 530, 1 668 (CONH), 1 585 (Ar), 2 830 ($N—CH_2$), 3 420 cm^{-1} (NH). ^1H NMR spectrum: δ 7·55 (s, 2 H, 3,3′-H_2), 6·90–7·65 (bs, 2 H, 2 CONH), 7·05 (s, 2 H, 6,6′-H_2), 4·50 (s, 4 H, 2 $COCH_2O$), 3·43 (q, 4 H, 2 CH_2N in the chains), 2·00–2·40 (m, 12 H, 4 CH_2N of piperazine and 2 CH_2N adjacent to piperazine), 1·30–2·00 (m, 4 H, 2 CH_2 in the middle of the propane chains). Ethanolic solution of the base was neutralized with a solution of HCl in ether and the product was crystallized from aqueous ethanol; dihydrochloride dihydrate, m.p. 216 to 219°C.

1,4-Bis[2-(2,4,5-Trichlorophenoxyacetoxy)ethyl]piperazine (*XIIa*) (Method *D*)

A stirred solution of 2·38 g 1,4-bis(2-hydroxyethyl)piperazine[13] in 20 ml dimethylformamide was treated at 60°C with a solution of 7·5 g *IVa* (ref.[9]) in 20 ml dimethylformamide, added dropwise. The mixture was then stirred for 5 h at 100°C. On cooling, the dihydrochloride of the product started to crystallize which was completed by a successive addition of 40 ml ether; 7·0 g (71%), m.p. 212–214°C (aqueous ethanol).

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