POTENTIAL CEREBRAL STIMULANTS: ESTERS OF 2-DIMETHYLAMINOETHANOL WITH SOME LIPOPHILIC CARBOXYLIC ACIDS

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2-Dimethylaminoethyl esters of 2,2-dimethylpropanoic, heptanoic, octanoic, decanoic, hexadecanoic, cyclopentylacetic, cycloheptylacetic, 2-cyclopenthylhexanoic, (4-chlorophenoxy)-fumaric, and 2-(4-chlorophenoxy)succinic acid were prepared by reactions of the acid chlorides with 2-dimethylaminoethanol and were transformed to crystalline salts for pharmacological testing. The ester *IX* (hydrogen fumarate VÚFB-14005) was found to antagonize significantly halothan amnesia in rats and the ester *X* (hydrogen fumarate VÚFB-14004) proved to be an anticholinergic spasmolytic agent.

There is a strong evidence indicating that dysfunction in cholinergic transmission in the brain is related to memory loss associated with senile dementia and to Alzheimer's disease[1]. The findings available suggest that treatments which could enhance cholinergic synaptic transmission in the cerebral cortex and hippocampus might provide a therapeutic approach for the corresponding geriatric patients. The memory deficits associated with aging seem to be related to a presynaptic decrease in the release of acetylcholine and to postsynaptic decrease in responsiveness to acetylcholine. A direct influencing of the acetylcholine deficit in the brain by its oral or parenteral administration is not possible (i) because it does not penetrate the blood-brain barrier, (ii) due to its instability in biological media, and (iii) because of its striking peripheral pharmacological effects. The chemically closely related 2-dimethylaminoethanol (deanol) was postulated to be the possible precursor in the biosynthesis of acetylcholine in the brain[2]. There is some positive evidence in this line[3,4]; other investigations, however, could not confirm elevation of the brain acetylcholine levels after acute administration of deanol[5]. Deanol "per se" has some pharmacological activity[6] (mild central stimulant) and had been used in the form of salts (e.g. 4-acetamidobenzoate[7], N-acetyl-L-glutamate[8], pyroglutamate[9]) as antidepressant and psychostimulant. The penetration of deanol through the blood-brain barrier is poor[10]; much better in this respect are deanol esters, especially 3-cyclohexylpropio-

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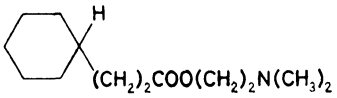
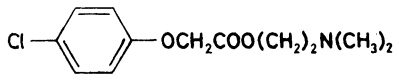
nate (*I*) (cyprodenate) (refs[11,12]) and 4-chlorophenoxyacetate (*II*) (meclofenoxate) (refs[10,13]) which found practical use as cerebral stimulants. It was explicitly stated that *II* increases choline levels in the rat brain[14]. Lipophilicity of the acids used for the esterification of deanol plays certainly an important role. This was the motive of the present communication describing first the synthesis of some title compounds.



I



II

Our attention was first devoted to 2-dimethylaminoethyl esters of aliphatic acids Such esters were earlier prepared as intermediates in the synthesis of the corresponding choline esters[15,16] whose pharmacology was studied[17]. Japanese authors[18] investigated a series of fatty acid esters of deanol from the point of view of their influence on the spontaneous locomotor activity of mice and found central depression followed by excitation. Deanol and its acetate revealed antireserpine activity oriented towards the reserpine-induced inhibition of motor activity. Most recently[19], some fatty acid esters of deanol were identified to be natural products occurring in the calf liver. Within our study, the synthesis of 2-dimethylaminoethyl esters of 2,2--dimethylpropanoic (*III*), heptanoic (*IV*) (refs[16–18]), octanoic (*V*) (refs[16–18]), decanoic (*VI*) (refs[16,17]), and hexadecanoic acid (*VII*) (refs[15–17,19]) was carried out. They were obtained by reactions of 2,2-dimethylpropanoyl chloride[20], heptanoyl chloride[21], octanoyl chloride[21], decanoyl chloride[21], and hexadecanoyl chloride[21] with a slight exess of 2-dimethylaminoethanol in chloroform at temperatures of 20–40°C (general method). The crude hydrochlorides of the amino esters formed were decomposed by dilute sodium hydroxide or with sodium hydrogen carbonate, the bases were isolated by extraction with ether and transformed to crystalline hydrogen maleates or hydrogen fumarates. The ester *VI* was also prepared by acid catalyzed "azeotropic" esterification of 2-dimethylaminoethanol with decanoic acid in boiling benzene under slow removal of the reaction water by distillation of the azeotrope with benzene. The reaction proceeded very slowly and an excess of the acid was necessary (cf. Experimental).

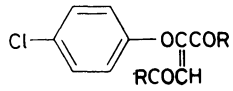
Another two esters prepared by the general method were the close analogues of *I*, i.e. the cyclopentylacetate *VIII* and the cycloheptylacetate *IX*. The starting cyclopentylacetyl chloride[22] and cycloheptylacetyl chloride[23] were obtained by described methods. The esters *VIII* and *IX* were oily and were transformed to crystalline salts (hydrochloride of the former and hydrogen fumarate of the latter), whose spectra were recorded. Cycloheptylacetic acid was prepared differently than described in the literature[23,24]. Diethyl malonate was alkylated with cycloheptyl bromide in ethanol in the presence of sodium ethoxide. Diethyl cycloheptylmalonate was

obtained and characterized. Its hydrolysis with ethanolic potassium hydroxide afforded cycloheptylmalonic acid (for different synthesis, cf. ref.[25]) which was decarboxylated in crude state by heating to 200°C and the resulting cycloheptylacetic acid was purified by distillation. The last ester prepared, which belongs to the alicyclic group, was *X*, obtained by the general method from 2-cyclopentylhexanoyl chloride[26]. The oily ester *X* was transformed to the hydrogen fumarate and its spectra were measured. The esters *III*–*X*, which were prepared by the general method, are assembled in Table I with the usual experimental data. The preparation of *IX* is described in the Experimental as an example.

$(CH_3)_2NCH_2CH_2OCOR$

III, R = $C(CH_3)_3$
IV, R = $(CH_2)_5CH_3$
V, R = $(CH_2)_6CH_3$
VI, R = $(CH_2)_8CH_3$
VII, R = $(CH_2)_{14}CH_3$
VIII, R = CH_2–cyclopentyl
IX, R = CH_2–cyclohexyl
X, R = CH(cyclopentyl)$(CH_2)_3CH_3$

With the intention to prepare bis(2-dimethylaminoethyl) 2,3-bis(4-chlorophenoxy)-succinate, the reaction of diethyl 2,3-dibromosuccinate[27,28] with sodium 4-chlorophenoxide in ethanol was carried out. After hydrolysis, a crystalline product melting at 224–226°C was obtained. The melting point value is in agreement with that given for *meso*-2,3-bis(4-chlorophenoxy)succinic acid in ref.[29]. The ^{1}H NMR spectrum, however, identified our product to be (4-chlorophenoxy)fumaric acid (*XI*) for which the melting point of 211–212°C was given[30] (cf. also ref.[31]). We have to assume that the product of ref.[29] is in fact also *XI* and that the structure mentioned was erroneously assigned. The acid *XI* was transformed by boiling with thionyl chloride in the presence of a small amount of dimethylformamide to the crude *XII* which, without purification and characterization, was esterified with 2-dimethylaminoethanol in chloroform at room temperature. The crude ester *XIII* obtained was transformed to crystalline salts (bis-(hydrogen oxalate), bis(hydrogen maleate)). The released oily base was used for recording the ^{1}H NMR spectrum which fully confirmed structure *XIII*.



XI, R = OH
XII, R = Cl
XIII, R = $OCH_2CH_2N(CH_3)_2$

2-(4-Chlorophenoxy)succinic acid (*XIV*) (ref.[32]) was the starting material for the synthesis of a further ester. It was converted by treatment with thionyl chloride to

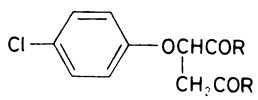
TABLE I

2-Dimethylaminoethyl esters prepared by the general method

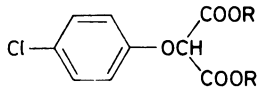
Compound[a] (% yield[b])	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
III-HF	126–128[c]	$C_{13}H_{23}NO_6$	53·96	8·01	4·84
(64)	(ethanol)	(289·3)	53·71	8·01	4·84
IV-HM[d,e]	106–109	$C_{15}H_{27}NO_6$	56·76	8·58	4·41
(100)	(ethanol–ether)	(317·4)	57·06	8·81	4·46
V-HM[d,e]	78–80·5	$C_{16}H_{29}NO_6$	57·98	8·82	4·23
(100)	(ethanol)	(331.4)	57·88	8·96	4·06
VI-HM[d,f]	63·5–66	$C_{18}H_{33}NO_6$	60·14	9·25	3·90
(78)	(ethanol–ether)	(359·5)	60·42	8·98	3·76
VII-HM[d,g,h]	87·5–90	$C_{24}H_{45}NO_6$	64·98	10·22	3·16
(94)	(ethanol)	(443·6)	65·21	10·49	3·10
VIII-HCl	168–171[i]	$C_{11}H_{22}ClNO_2$	56·04	9·41	5·94[j]
(90)	(chloroform–ether)	(235·8)	56·23	9·46	5·82
IX-HF[k]	102–104·5	$C_{17}H_{29}NO_6$	59·45	8·51	4·08
(86)	(ethanol–ether)	(343·4)	59·32	8·32	4·18
X-HF	110–112·5[l]	$C_{19}H_{33}NO_6$	61·43	8·96	3·77
(93)	(ethanol–ether)	(371·5)	61·14	8·71	3·59

[a] HF hydrogen fumarate, HM hydrogen maleate; [b] The yields per the crude oily bases given. [c] ^{1}H NMR spectrum (CD_3SOCD_3) : 1·20 s, 9 H ($C(CH_3)_3$); 2·55 s, 6 H ($N(CH_3)_2$); 3·02 t, 2 H (CH_2N, J = 5·0); 4·25 t, 2 H (OCH_2, J = 5·0); 6·52 s, 2 H (CH=CH of fumaric acid); 11·40 bs, 2 H (2 × COOH). [d] Refs[16,17] mentioned the compound (without characterization) as an intermediate; [e] ref.[18] deals with the pharmacology of the hydrochloride (not haracterized); [f] ref.[42] mentioned the compound without data on synthesis and characterization. [g] The base was prepared similarly in ether[15], b.p. 187°C/0·4 kPa. [h] The compound was isolated from calf liver and characterized only by spectra and chromatography. A sample was synthesized from the acid chloride and 2-dimethylaminoethanol in dichloromethane. [i] IR spectrum: 1 190, 1 749 (RCOOR'); 1 470, 2 480, 2 530, 2 593 (NH^+). [j] Calculated: 15·04 % Cl; found: 15·15 % Cl. [k] See Experimental. [l] MS spectrum: 255 (M^+, $C_{15}H_{29}NO_2$); IR spectrum: 1 734 (RCOOR'); 2 460 (NH^+); ^{1}H NMR spectrum (CD_3SOCD_3) : 0·80 bt, 3 H (CH_3 of butyl); 1·00–2·20 m, 16 H (4 × CH_2 and CH of cyclopentyl, 3 × CH_2 of butyl, and CHCO); 2·45 s, 6 H ($N(CH_3)_2$; 2·85 t, 2 H (CH_2N, J = 6·0); 4·20 t, 2 H (OCH_2, J = 6·0); 6·55 s, 2 H (CH=CH of maleic acid); 11·50 bs, 2 H (2 × COOH of maleic acid).

the crude *XV* which was esterified with 2-dimethylaminoethanol in chloroform to give *XVI*. The oily base afforded the crystalline bis(hydrogen oxalate). The attempts to prepare bis(2-dimethylaminoethyl) 4-chlorophenoxymalonate were unsuccessful. Diethyl chloromalonate[33] was treated with sodium 4-chlorophenoxide in ethanol and gave *XVII* (cf. ref.[34]) which was hydrolyzed with aqueous sodium hydroxide to *XVIII* (cf. ref.[35]). The identity of *XVII* and *XVIII* was corroborated by the ^{1}H NMR spectra. An attempt to prepare the mentioned ester by "azeotropic" esterification of *XVIII* in boiling xylene and in the presence of a small amount of 4-toluenesulfonic acid proceeded with concomitant decarboxylation and afforded *II* which was characterized as the crystalline hydrochloride (its melting point is identical with that of the product described in ref.[13]). The ^{1}H NMR spectrum of the released base confirmed structure *II* for the product. An attempt to prepare the desired diester by transesterification of *XVII* with 2-dimethylaminoethanol in distilling toluene (with the addition of a catalytic amount of sodium hydride) gave also only *II* which was isolated as the hydrogen oxalate. The same product was obtained by reaction of the "crude chloride of *XVIII*" with 2-dimethylaminoethanol in chloroform; in this case we assume that the decarboxylation proceeded already during the treatment of *XVIII* with boiling thionyl chloride.



XIV, R = OH
XV, R = Cl
XVI, R = $OCH_2CH_2N(CH_3)_2$

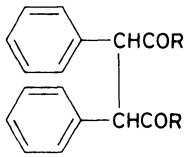


XVII, R = C_2H_5
XVIII, R = H

The last part of this study deals with derivatives of *meso*-2,3-diphenylsuccinic acid[36] and was carried out in connection with our previous work in series of antispasmodic[37] and myorelaxant agents[38]. The acid chloride *XIX* (ref.[39]) was reacted with 2-diethylaminoethanol and with 2-(1-piperidinyl)ethanol and gave the oily esters *XX* and *XXI* which were converted to crystalline dihydrochlorides. Reaction of *XX* with methyl iodide in methanol gave the diquaternary salt *XXI*. The dihydrochloride of *XX* and the salt *XXII* were described in ref.[40]. Treatment of *XIX* with 2-(methylthio)ethanol[41] and reaction of the crude product with methyl iodide gave the crystalline disulfonium salt *XXIII*. Reaction of *XIX* with 2-(diethylamino)ethylamine in benzene gave directly the dihydrochloride of *XXIV*.

Compounds *III*–*X*, *XIII*, and *XVI* were pharmacologically tested in the form of salts described in the Experimental and in Table I; the doses given were calculated per bases. The testing proceeded on the one hand within a general pharmacological screeening program, and in the test of amnesia, elicited in rats by the halothan

anaesthesia (the influence on the passive avoidance responses was evaluated), on the other.



XIX, R = Cl
XX, R = $OCH_2CH_2N(C_2H_5)_2$
XXI, R = $OCH_2CH_2N^{(+)}$⟨⟩
XXII, R = $OCH_2CH_2N^{(+)}(CH_3)(C_2H_5)_2$ $I^{(-)}$
XXIII, R = $OCH_2CH_2S^{(+)}(CH_3)_2$ $I^{(-)}$
XXIV, R = $NHCH_2CH_2N(C_2H_5)_2$

Acute toxicity in mice on intravenous administration (unless otherwise stated). LD_{50} in mg/kg: *III*, 75; *IV*, 150; *V*, 150; *VI*, 87·5; *VII*, 225; *VIII*, 62·5; *IX*, 75; *X*, 62·5; *XIII*, 85; *XVI*, 2 500 orally. The doses i.v. (unless stated otherwise) in mg/kg used in the screening: *III*, 15; *IV*, 30; *V*, 30; *VI*, 17; *VII*, 45; *VIII*, 12; *IX*, 15; *X*, 12; *XIII*,17; *XVI*, 300 p.o.

Test of amnesia: The doses of 100 mg/kg s.c. of compounds *III*–*VIII* and *XVI* showed only indication of effect (on the border of statistical significance); *IX* and *X* antagonized significantly the halothan amnesia. The most active compound *IX* had a significant effect in the dose of 20 mg/kg s.c. (threshold doses 5 and 10 mg/kg s.c.).

Influence on the spontaneous motor activity of mice: compound *IV* in the dose of 10 mg/kg s.c. had central stimulant effect (increase of motility).

Hypotensive effects in normotensive anaesthetized rats after doses D (i.v.): brief and deep drops of the blood pressure were observed with *V*, *VII*, *IX*, and *XIII*.

Antiacetylcholine spasmolytic effect on the isolated rat duodenum: reduction of the acetylcholine contractions to 50% of the control value was brought about by the following compounds in concentrations (mg/l) given: *VIII*, 10; *IX*, 10; *X*, 0·1–1·0.

In conclusion, compound *IX* (hydrogen fumarate VÚFB-14005) antagonized significantly halothan amnesia in rats (a nootropic-like effect) and compound *X* (hydrogen fumarate VÚFB-14004), having a mild effect against halothan amnesia had a clear anticholinergic spasmolytic effect on the isolated rat duodenum.

EXPERIMENTAL

The melting points 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 a suitably elevated tempera-

ture. The UV spectrum (in methanol, λ_{max} in nm (log ε)) was recorded with a Unicam SP 700 spectrophotometer, IR spectra (in Nujol, ν in cm^{-1}) with a Unicam SP 200G spectrophotometer, ^1H NMR spectra (δ in ppm, J in Hz) with a CW-NMR spectromter Tesla BS487C (80 MHz), and the mass spectrum (m/z) with MS 902 (AEI) spectrometer. Thin-layer chromatography (TLC) on silica gel (Silufol) was used for checking the homogeneity of the products. The extracts were processed by drying (Na_2SO_4 or K_2CO_3) and by evaporation under reduced pressure.

Diethyl Cycloheptylmalonate

Diethyl malonate (45·3 g) was added dropwise to a stirred solution of sodium ethoxide (from 6·5 g Na and 150 ml ethanol), 100 ml ethanol were distilled off, and the residue was treated with 50 g cycloheptyl bromide. The mixture was stirred for 1 h at room temperature, allowed to stand overnight, and refluxed for 16 h (bath temperature 110°C). The remaining ethanol was distilled off. the residue was diluted with 100 ml water and the mixture was extracted with ether. Processing of the extract and distillation of the residue gave 50·5 g (70%) of the product boiling at 119–125°C/0·25 kPa. Analytical sample, b.p. 121°C/0·25 kPa. ^1H NMR spectrum ($CDCl_3$): 1·29 t, 6 H (2 × CH_3, J = 7·0); 1·40–2·50 m, 13 H (6 × CH_2 and CH of cycloheptyl); 3·25 d, 1 H (COCHCO, J = 8·0); 4·20 q, 4 H (2 × OCH_2, J = 7·0). For $C_{14}H_{24}O_4$ (256·3) calculated: 65·59% C, 9·44% H; found: 65·88 C, 9·48% H.

Cycloheptylacetic Acid

A mixture of 49·3 g diethyl cycloheptylmalonate and of a solution of 92·6 g KOH in 275 ml ethanol was stirred and refluxed for 3 h, ethanol was evaporated, the residue was dissolved in water, the solution was washed with ether, and acidified with hydrochloric acid. The separated crude cycloheptylmalonic acid was extracted with ether. Processing of the extract gave 42·4 g of a solid product melting at 163°C (ref.[25], m.p. 164·5°C, different synthetic method). Without purification this product was decarboxylated by heating to 200–210°C. After termination of CO_2 formation, the residue was subjected to fractional distillation in vacuo; 9·5 g (32%) of cycloheptylacetic acid boiling at 125–127°C/1·3 kPa. Refs[23,24], b.p. 161°C/2 kPa and 165°C/2·5 kPa, respectively.

2-Dimethylaminoethyl Cycloheptylacetate (*IX*) (General Method)

A stirred solution of 4·8 g 2-dimethylaminoethanol in 10 ml chloroform was treated under cooling (ice and water) with 8·4 g cycloheptylacetyl chloride[23], added dropwise (temperature 20–25°C). The mixture was stirred for 30 min at room temperature and then heated under reflux for 5 h to 70–80°C. After standing overnight chloroform was evaporated, the solid residue (crude hydrochloride of *IX*) was decomposed with saturated $NaHCO_3$, and the oily ester was extracted with ether. Processing of the extract gave 9·4 g (86%) of the crude oily *IX*. This base (9·05 g) was neutralized with 4·6 g fumaric acid in 8 ml boiling ethanol. Treatment with ether and standing overnight gave 10·8 g of hydrogen fumarate, m.p. 102–104·5°C (ethanol–ether). ^1H NMR spectrum (CD_3SOCD_3): 1·00–2·10 m, 13 H (6 × CH_2 and CH of cycloheptyl); 2·22 d, 2 H (CH_2CO); 2·50 s, 6 H ($N(CH_3)_2$); 2·90 t, 2 H (CH_2N, J = 5·0); 4·25 t, 2 H (OCH_2, J = 5·0); 6·58 s, 2 H (CH=CH of fumaric acid); 10·38 bs, 2 H (2 × COOH of fumaric acid). The analysis is included in Table I.

2-Dimethylaminoethyl Decanoate (*VI*)

A) Reaction of 8·3 g 2-dimethylaminoethanol with 15·3 g decanoyl chloride[21] in 20 ml

chloroform according to the general method gave 17·0 g (78%) of crude *VI* which was transformed to the hydrogen maleate, m.p. 63·5–66°C (ethanol–ether) (cf. Table I).

B) A mixture of 32·1 g decanoic acid, 8·3 g 2-dimethylaminoethanol, 1 drop of H_2SO_4, and 100 ml benzene was boiled, wet benzene was slowly distilled off through a column and was substituted with dry benzene. The reaction proceeded for 25 h and its course was checked by TLC. Benzene was evaporated, the residue was decomposed with 150 ml 4% NaOH, and the product was extracted with ether. Processing of the extract gave 8·9 g (39%) of crude oily *VI*. The hydrogen maleate was prepared, melted at 63·5–66°C, and was identical with that obtained under *A* (cf. Table I).

2-(4-Chlorophenoxy)fumaric Acid (*XI*)

4-Chlorophenol (25·7 g) was added at 80°C to a solution of sodium ethoxide, prepared from 4·6 g Na and 100 ml ethanol, and the mixture was stirred for 15 min. After cooling to 25–32°C, a solution of 33·2 g diethyl 2,3-dibromosuccinate[27,28] was added dropwise over 35 min under stirring. The suspension formed was stirred for 6 h at room temperature and for 8 h at30–40°C. After standing for a week it was refluxed for 2 h. The composition of the reaction mixture (TLC) did not change any more. Ethanol was distilled off, the residue was diluted with 200 ml water and the mixture was extracted with ether. Processing of the extract gave 26·5 g residue which was hydrolyzed by heating with 150 ml 2·5M-NaOH to 100°C for 2·5 h. After cooling the solution was washed with ether and acidified at 30–40°C with 80 ml 5M-HCl (to pH 1). The precipitated yellowish solid was filtered after standing overnight, washed with water, and crystallized from a mixture of 550 ml water and 20 ml 5M-HCl; 10·4 g (43%) of *XI*, m.p. 224–225°C with decomposition (change of crystal modification at 150–170°C). Ref.[30], m.p. 211–212°C (different method). UV spectrum: infl. 275 (3·46), infl. 282 (3·42). IR spectrum: 819, 830, 840 (2 adjacent Ar–H); 929, 1 292, 1 710, 2 560, 2 685 (COOH); 1 218 (ArOC=C); 1 492, 1 592 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 6·47 s, 1 H (C=CHCO); 6·91 d, 2 H (H-2 and H-6, J = 8·5); 7·35 d, 2 H (H-3 and H-5, J = 8·5); 12·75 bs, 2 H (2 × COOH). For $C_{10}H_7ClO_5$ (242·6) calculated: 49·50% C, 2·91% H, 14·61% Cl; found: 48·10% C, 2·96% H, 14·53% Cl.

Bis(2-dimethylaminoethyl) 2-(4-Chlorophenoxy)fumarate (*XIII*)

A mixture of 6·6 g *XI*, 25·2 g $SOCl_2$, and 0·1 ml dimethylformamide was stirred for 15 min at 45–50°C and then refluxed for 2 h. The excess of $SOCl_2$ was removed by distillation, the last traces by distillation with 25 ml toluene in vacuo. The oily residue (crude *XII*) was dissolved in 30 ml chloroform and the stirred solution was treated dropwise with 3·16 g 2-dimethylaminoethanol. After standing overnight at room temperature the mixture was washed with dilute NH_4OH and the base was extracted with 3 × 25 ml 1M-H_2SO_4. The acid solution was filtered with active carbon, the base was released with NH_4OH and extracted with chloroform. Processing gave 4·6 g (44%) of crude oily *XIII*.

Bis(hydrogen oxalate), m.p. 167–168°C (95% ethanol). For $C_{22}H_{29}ClN_2O_{13}$ (564·9) calculated: 46·77% C, 5·17% H, 6·27% Cl, 4·96% N; found: 46·54% C, 5·42% H, 6·57% Cl, 4·66% N.

Bis(hydrogen maleate), m.p. 140–142°C (ethanol–ether). For $C_{26}H_{33}ClN_2O_{13}$ (617·0) calculated: 50·61% C, 5·39% H, 5·75% Cl, 4·54% N; found: 50·64% C, 5·68% H, 5·45% Cl, 4·57% N.

The oily base, released from the maleate, was used for recording the ^{1}H NMR spectrum ($CDCl_3$): 2·20 s and 2·28 s, 12 H (2 × $N(CH_3)_2$); 2·50 t and 2·65 t, 2 and 2 H (2 × CH_2N); 4·15 t and 4·40 t, 2 and 2 H (2 × OCH_2); 5·20 s, 1 H (C=CHCO); 7·05 d, 2 H (H-2 and H-6, J = 8·5); 7·38 d, 2 H (H-3 and H-5, J = 8·5).

Bis(2-dimethylaminoethyl) 2-(4-Chlorophenoxy)succinate (*XVI*)

A mixture of 5·2 g *XIV* (ref.[32]), 25 g $SOCl_2$, and 0·1 ml dimethylformamide was refluxed for 2·5 h, the excess of $SOCl_2$ was removed by distillation and then by distillation with 25 ml toluene in vacuo. The residue (the crude *XV*) was dissolved in 35 ml chloroform and the solution was treated with 3·74 g 2-dimethylaminoethanol. The mixture was allowed to stand for 48 h at room temperature, diluted with 35 ml chloroform, washed with 10% NH_4OH and water, dried, filtered with active carbon, and evaporated; 6·2 g (77%) of crude oily *XVI*.

Bis(hydrogen oxalate), m.p. 144·5–145·5°C (dioxane–ether). For $C_{22}H_{31}ClN_2O_{13}$ (567·0) calculated: 46·60% C, 5·51% H, 6·25% Cl, 4·94% N; found: 46·84% C, 5·81% H, 6·04% Cl, 4·66% N.

Diethyl (4-Chlorophenoxy)malonate (*XVII*)

4-Chlorophenol (32·2 g) was added to a solution of sodium ethoxide, prepared from 5·75 g Na and 150 ml ethanol, the mixture was stirred for 10 min at 40°C and was treated dropwise at 25–27°C over 20 min with 52·6 g diethyl chloromalonate[33]. It was stirred for 9 h at 40–50°C, after cooling the separated solid was filtered off and the filtrate was evaporated. The residue was dissolved in 150 ml ether, the solution was washed with 0·25M-NaOH and water, dried, and distilled; 47·9 g (67%) of *XVII*, b.p. 161–163°C/27 Pa. ^{1}H NMR spectrum ($CDCl_3$): 1·26 t, 6 H (2 × CH_3, J = 7·0); 4·24 q, 4 H (2 × OCH_2, J = 7·0); 5·08 s, 1 H (OCHCO); 6·81 d, 2 H (H-2 and H-6, J = 8·0); 7·18 d, 2 H (H-3 and H-5, J = 8·0). For $C_{13}H_{15}ClO_5$ (286·7) calculated: 54·45% C, 5·27% H, 12·37% Cl; found: 54·48% C, 5·39% H, 12·19% Cl. Ref.[34] mentioned a similar method of synthesis but the product was not characterized.

(4-Chlorophenoxy)malonic Acid (*XVIII*)

A mixture of 14·3 g *XVII* and 45 ml 2·5M-NaOH was stirred and refluxed for 2 h. After cooling to 20°C the solution was acidified with 2·5M-HCl. After standing overnight the precipitated product was filtered, washed with water, and dried in vacuo; 8·3 g (72%) of *XVIII*, m.p. 160°C (water). Ref.[35], m.p. 145–147°C. IR spectrum: 833 (2 adjacent Ar–H); 902, 1 276, 1 730, 2 680, infl. 3 060 (COOH); 1 238 (ArOR); 1 497, 1 590 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 5·32 s, 1 H (OCHCO); 6·90 d, 2 H (H-2 and H-6, J = 8·5); 7·30 d, 2 H (H-3 and H-5, J = 8·5); 12·50 bs, 2 H (2 × COOH). For $C_9H_7ClO_5$ (230·6) calculated: 46·87% C, 3·06% H, 15·38% Cl; found: 47·06% C, 2·95% H, 15·60% Cl.

2-Dimethylaminoethyl (4-Chlorophenoxy)acetate (*II*)

A) A mixture of 7·6 g *XVIII*, 15·5 g 2-dimethylaminoethanol, 0·5 g 4-toluenesulfonic acid, and 50 ml xylene was distilled for 5 h through a column and the wet xylene was substituted with dry xylene. After cooling the solution was washed with 1M-NaOH and water, dried, and evaporated in vacuo. The residue was dissolved in ethanol and treatment with HCl in ether gave 5·3 g (55%) of *II* hydrochloride, m.p. 137·5–139·5°C (ethanol). The analysis was in agreement with $C_{12}H_{17}Cl_2NO_3$. Ref.[13], m.p. 135–139°C.

B) A mixture of 20·5 g *XVII*, 65 g 2-dimethylaminoethanol and 65 ml toluene was treated with 0·55 g NaH and distilled for 10 h through a column (the distilate was substituted with fresh toluene). Toluene and the excess of 2-dimethylaminoethanol were distilled off in vacuo, the residue was dissolved in 150 ml benzene, the solution was washed with water, dried, filtered with active carbon, and evaporated. The residue was distilled in vacuo giving 2·1 g of the only homogeneous fraction boiling at 144–145°C/10 Pa which was identified as *II*.

Bis(hydrogen oxalate), m.p. 175–176°C (acetone–ethanol–ether). For $C_{14}H_{18}ClNO_7$ (347·8) calculated: 48·35% C, 5·22% H, 10·20% Cl, 4·03% N; found: 48·50% C, 5·24% H, 10·23% Cl, 3·90% N.

The released oily base was used for recording the ^{1}H NMR spectrum ($CDCl_3$): 2·20 s, 6 H ($N(CH_3)_2$); 2·51 t, 2 H (CH_2N, J = 6·0); 4·21 t, 2 H ($COOCH_2$, J = 6·0); 4·58 s, 2 H (OCH_2CO); 6·78 d, 2 H (H-2 and H-6, J = 8·5); 7·18 d, 2 H (H-3 and H-5, J = 8·5).

C) A mixture of 4·6 g *XVIII*, 25 g $SOCl_2$, and 0·2 ml dimethylformamide was refluxed for 2·5 h, the excess of $SOCl_2$ was removed by distillation and by evaporation with 25 ml benzene in vacuo, and the oily residue was dissolved in 30 ml chloroform. The solution was treated with 3·56 g 2-dimethylaminoethanol and the mixture was allowed to stand overnight at room temperature. It was diluted with 30 ml chloroform, washed with dilute NH_4OH and water, dried, and evaporated. The remaining oily base (4·9 g) was transformed to the bis(hydrogen oxalate) (5·0 g, 72%), melting at 167–170°C with decomposition. Crystallization from a mixture of ethanol, acetone, and ether gave the salt melting at 175–176°C, identical with that under *B*.

Bis(2-diethylaminoethyl) *meso*-2,3-Diphenylsuccinate (*XX*)

A mixture of 1·5 g *XIX* (refs[39,40]) and 2·28 g 2-diethylaminoethanol was heated for 15 min to 120°C. After cooling it was decomposed with 20 ml water and extracted with ether. Processing of the extract gave 1·8 g (79%) of *XX*, b.p. 205–210°C/0·13 kPa (m.p. 57°C). This base was transformed to the dihydrochloride in ethanol by treatment with HCl in ether, m.p. 212°C (ethanol). Ref.[40], m.p. 206°C. For $C_{28}H_{42}Cl_2N_2O_4$ (541·6) calculated: 62·10% C, 7·81% H, 13·09% Cl, 5·17% N; found: 62·18% C, 8·11% H, 12·92% Cl, 5·30% N.

The dimethiodide (*XXII*) was prepared from the base (1·8 g) by treatment with 6·65 g methyl iodide in 5 ml methanol; the mixture was allowed to stand for 48 h at 0°C, 2·0 g (70%) of *XXII*, m.p. 220°C (ethanol). Ref.[40], m.p. 225–226°C.

Bis(2-(1-piperidinyl)ethyl) *meso*-2,3-Diphenylsuccinate (*XXI*)

A mixture of 1·5 g *XIX* (refs[39,40]) and 2·58 g 2-(1-piperidinyl)-ethanol was heated for 30 min to 130°C. After cooling it was diluted with 30 ml water and extracted with ether. Processing of the extract gave 1·8 g (75%) of the crude oily *XXI* which was transformed to the dihydrochloride, m.p. 231°C (ethanol). For $C_{30}H_{42}Cl_2N_2O_4$ (565·6) calculated: 63·70% C, 7·48% H, 12·54% Cl, 4·95% N; found: 63·40% C, 7·65% H, 12·60% Cl, 4·79% N.

Bis(2-(methylthio)ethyl) *meso*-2,3-Diphenylsuccinate Dimethiodide (*XXIII*)

A mixture of 0·92 g *XIX* (refs[39,40]), 3 ml benzene, and 0·55 g 2-(methylthio)ethanol[41] was refluxed for 2 h, volatile components of the mixture were evaporated in vacuo, and the residue was distilled; 0·90 g (72%) of bis(2-(methylthio)ethyl) *meso*-2,3-diphenylsuccinate, b.p. 220–225°C/0·13 kPa (m.p. 104°C). This intermediate (0·73 g) was dissolved in 1 ml boiling methyl iodide and the solution was allowed to stand for 48 h at room temperature; 1·06 g (85%) of *XXIII*, m.p. 180°C (70% aqueous ethanol). For $C_{24}H_{32}I_2O_4S_2$ (702·5) calculated: 41·03% C, 4·59% H, 36·13% I, 9·13% S; found: 40·95% C, 4·28% H, 36·07% I, 9·06% S.

N,N′-Bis(2-diethylaminoethyl)-*meso*-2,3-diphenylsuccinamide (*XXIV*)

A stirred solution of 3·06 g *XIX* (refs[39,40]) in 25 ml benzene was treated dropwise over 45 min at 10°C with a solution of 2·32 g 2-(diethylamino)ethylamine in 20 ml benzene. The mixture was allowed to stand for 12 h at room temperature and the crystallized dihydrochloride of *XIV*

was filtered and recrystallized from ethanol; 3·5 g (66%), m.p. 253°C (ethanol). For $C_{28}H_{44}Cl_2 . N_4O_2$ (539·6) calculated: 62·32% C, 8·22% H, 13·14% Cl, 10·38% N; found: 62·02% C, 8·49% H, 13·00% Cl, 10·29% N.

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