PLANT-GROWTH SUBSTANCES: ω-ARYL- AND ω-ARYLOXY-ALKYLCARBOXYLIC ACIDS

By K. GAIMSTER

A number of carboxylic acids of the type $R\cdot[CH_2]\cdot CO_2H$ have been synthesized in connexion with studies of plant-growth activity. They include the first six or seven members of five homologous series of ω-substituted alkylcarboxylic acids, namely *o*-methoxyphenoxy-, *p*-chlorophenoxy-, 2 : 4-dichlorophenoxy-, 2 : 4 : 5-trichlorophenoxy- and 1-naphthyl-alkylcarboxylic acids; and five 1-naphthyl-alkylcarboxylic acids in which the alkyl chain is branched or otherwise modified.

The phenoxy-acids were prepared by classical methods but, for many of the 1-naphthyl acids, methods involving the use of organo-cadmium compounds were employed.

Introduction

Recent studies[1] concerning the fate in the plant of compounds having plant-growth activity have been based on the possibility that these compounds are degraded by a mechanism involving β-oxidation. Evidence for the latter has recently been reviewed by Wain.[2] A continuation of such studies led to the need for information on the plant-growth activity of a number of homologous series of ω-substituted alkylcarboxylic acids, especially of those series the first members of which were known to possess pronounced plant-growth activity.

The synthesis of the first six or seven members of five such series was thus undertaken, namely *o*-methoxyphenoxy-, *p*-chlorophenoxy-, 2 : 4-dichlorophenoxy-, 2 : 4 : 5-trichlorophenoxy- and 1-naphthyl-alkylcarboxylic acids, together with five 1-naphthyl-alkylcarboxylic acids in which the alkyl chain was branched or otherwise modified. The biological results relating to these acids have been reported and their significance discussed elsewhere.[3] The results are in full accordance with the thesis that these acids are degraded by a mechanism which involves β-oxidation.

ω-Phenoxyalkylcarboxylic acids

In the *o*-methoxyphenoxy series, the acetic[4] and propionic[5] acids have been previously prepared. In the *p*-chlorophenoxy series, the acetic,[6] propionic[7] and butyric[8] acids are known. The first seven members of the 2 : 4-dichlorophenoxy series were prepared by Synerholm & Zimmerman.[9] In the 2 : 4 : 5-trichlorophenoxy series, the acetic[10] and butyric[9] acids are known. All the acids of this type were prepared by classical methods from the appropriate phenol, using chloroacetic acid or β-bromopropionic acid respectively for the first and second members of each series. The key intermediate for higher members of each series was the appropriate ω-phenoxyalkyl bromide, which was prepared by treating the phenol with a polymethylene dibromide. From each ω-phenoxyalkyl bromide so formed, two ω-phenoxyalkylcarboxylic acids could be prepared, via the corresponding nitrile or by the malonic ester synthesis.

Of the ω-phenoxyalkyl bromides and cyanides used, the following have already been described: 1-bromo-2-*o*-methoxyphenoxyethane,[11] 1-bromo-3-*o*-methoxyphenoxypropane,[12] 1-bromo-5-*o*-methoxyphenoxypentane,[12, 13] 1-bromo-2-*p*-chlorophenoxyethane,[14] 1-bromo-3-*p*-chlorophenoxypropane,[14] 1-bromo-3-(2 : 4-dichlorophenoxy)propane,[15] 1-bromo-3-(2 : 4 : 5-trichlorophenoxy)propane,[15] and 1-cyano-3-(2 : 4-dichlorophenoxy)propane.[16] In general the intermediate ω-phenoxyalkylmalonic esters were used for the next stage without isolation in the pure state. It was noted that the chlorinated phenoxyalkylmalonic acids were more resistant to decarboxylation than were the *o*-methoxyphenoxyalkylmalonic acids. The treatment of phenoxyalkyl bromides with sodium cyanide in aqueous ethanol gave in most cases a good yield of the appropriate cyanide. It is, however, of interest from a theoretical point of view that in certain cases this reaction failed to give the expected product.

The reactions which were attempted are summarized in Table I.

In the reactions described as anomalous, none of the desired nitrile was isolated; instead, the main product was the corresponding bis-phenoxyalkane, together with some of the appropriate phenol. This suggests that a fission of the ether linkage in the phenoxy compound has

taken place. For example, treatment with sodium cyanide in 90% ethanol appears to cleave the ether linkage of 1-bromo-2-*p*-chlorophenoxyethane to form *p*-chlorophenol which, presumably, reacts with unchanged 1-bromo-2-*p*-chlorophenoxyethane to form 1 : 2-bis-(*p*-chlorophenoxy)-ethane, thus:

$$Cl{\cdot}C_6H_4{\cdot}O{\cdot}[CH_2]_2{\cdot}Br \rightarrow Cl{\cdot}C_6H_4{\cdot}OH$$
$$Cl{\cdot}C_6H_4{\cdot}OH + Cl{\cdot}C_6H_4{\cdot}O{\cdot}[CH_2]_2{\cdot}Br \rightarrow Cl{\cdot}C_6H_4{\cdot}O{\cdot}[CH_2]_2{\cdot}O{\cdot}C_6H_4{\cdot}Cl$$

In the case of 1-cyano-3-(2 : 4 : 5-trichlorophenoxy)propane, we have an intermediate example, since, although the reaction of 1-bromo-3-(2 : 4 : 5-trichlorophenoxy)propane with sodium cyanide gave a 66% yield of a product which was very largely 1-cyano-3-(2 : 4 : 5-trichlorophenoxy)propane, analysis of the latter compound gave results which were slightly low for nitrogen and slightly high for chlorine. Alkaline hydrolysis of this nitrile resulted in a 61% yield of pure 3-(2 : 4 : 5-trichlorophenoxy)propane-1-carboxylic acid, together with about 5% of 1 : 3-bis-(2 : 4 : 5-trichlorophenoxy)propane, which was, presumably, the contaminant in the nitrile.

It is of interest in this connexion to note that in the conversion of 2 : 4-dichlorophenoxymethyl chloride to the corresponding cyanide[17] some bis-(2 : 4-dichlorophenoxy)methane was always obtained even under the best conditions evolved. Under less favourable conditions for the reaction, as much as 30% of the bis-compound could be isolated.

Further work is required on this reaction before a mechanism can be suggested, but it seems that the combined electron-attracting effect of a chlorine atom or atoms in the benzene ring and of a bromine atom not further away than the γ-carbon atom is necessary before the ether linkage becomes susceptible to attack by the reagent.

ω-1-Naphthyl-alkylcarboxylic acids

In this series, the well-known substituted acetic acid is usually prepared by some modification of the method of Boessneck[18] but a variety of other methods have been used. Although a number of ways have been used for the preparation of the propionic acid, perhaps the most convenient method is that of Mayer & Sieglitz.[19] The preparation of the corresponding butyric acid has been described by a number of workers.[20, 21]

No attempt has been recorded to devise a method which would be of general application to the series except that of Manske & Ledingham,[22] who attempted to carry out a stepwise ascent of this series by reducing an acid to the corresponding alcohol by the use of sodium in ethanol followed by conversion of this alcohol to the corresponding bromide and a malonic ester synthesis to give the next higher homologue but one. Thus, by starting from the second and third members of this series, the fourth and fifth members were prepared. The analytical figures given[22] for the fourth and fifth members of the series were not, however, in very good agreement with theoretical values and the authors admitted that such a method was not suitable for making any of the succeeding members. An attempt was therefore made to devise a preparative method which would be generally applicable to the series. The method finally adopted was one based on that described for the preparation of ethyl 2-1′-naphthoylethane-1-carboxylate.[23, 24] The method is essentially the conversion of 1-naphthylmagnesium bromide to the corresponding organo-cadmium compound, which is treated with the ω-ester-acid chloride of a dibasic acid.

Table I

Reaction of ω-phenoxyalkyl bromides, $RO{\cdot}[CH_2]_n{\cdot}Br$, *with sodium cyanide*

R	*n* = 2	3	5
o-Methoxyphenyl	—	N	N
p-Chlorophenyl	A	A	N
2 : 4-Dichlorophenyl	A	N	N
2 : 4 : 5-Trichlorophenyl	—	N*	N

N = normal reaction
A = anomalous reaction

* A small amount of the anomalous product was isolated.

The keto-ester thus produced is reduced and hydrolysed to the appropriate ω-1-naphthyl-alkylcarboxylic acid. The method of choice for this hydrolysis and reduction was found to be the modification of the Wolff–Kishner reduction described by Huang-Minlon,[25] although Clemmensen reduction, preceded or followed by hydrolysis, was also used in some cases.

These steps may be represented by the following scheme:

$$C_{10}H_7\cdot[CH_2]_n\cdot MgBr \xrightarrow{CdCl_2} C_{10}H_7\cdot[CH_2]_n\cdot Cd_{\frac{1}{2}} \xrightarrow{Cl\cdot CO\cdot[CH_2]_m\cdot CO_2R} C_{10}H_7\cdot[CH_2]_n\cdot CO\cdot[CH_2]_m\cdot CO_2R \rightarrow C_{10}H_7\cdot[CH_2]_{n+m+1}\cdot CO_2H.$$

R = Me or Et

This method was successfully applied to the third, fourth, fifth and sixth members of the series. The method failed, however, when 1-naphthylmethylmagnesium chloride was used; in attempts to prepare higher homologues than the sixth member of the series, pure samples of the keto-esters could not be obtained; neither was it possible to purify the crude 1-naphthyl-alkylcarboxylic acids prepared by hydrolysis and reduction of these impure keto-esters. The ω-ester-acid chlorides were prepared by the action of thionyl chloride on the corresponding mono-ester which was itself prepared either, in the case of succinic and glutaric acids, by the action of methanol on the anhydride, or, for higher homologues, by the semi-esterification of the appropriate dicarboxylic acid. In this latter connexion, the method of working up using a chemical separation[26] was found more convenient than the method[27] based simply on fractional distillation under reduced pressure of the resulting mixture of diester, mono-ester and unchanged acid. The third member of the series of ω-1-naphthyl-alkylcarboxylic acids, namely, 3-1′-naphthylpropane-1-carboxylic acid, was also prepared by the 'ketonic' hydrolysis of the condensation product of the sodium derivative of ethyl acetoacetate with 1-bromo-2-1′-naphthylethane.

1-Naphthyl-alkylcarboxylic acids with branched or modified chain

1-1′-Naphthylpropane-2-carboxylic acid, $C_{10}H_7\cdot CH_2\cdot CHMe\cdot CO_2H$, was prepared by a method[28, 29] involving the methylation of diethyl 2-1′-naphthylethane-1 : 1-dicarboxylate; and the resulting malonic ester was hydrolysed and decarboxylated. In the author's hands, this decarboxylation showed a reluctance to go to completeness, and a pure sample of the required acid was only obtained by converting the incompletely decarboxylated material to its acid chloride, which, after purification, was converted to the acid. 3-1′-Naphthyl-2-methylpropane-1-carboxylic acid, $C_{10}H_7\cdot CH_2\cdot CHMe\cdot CH_2\cdot CO_2H$, has previously been prepared[30] by a malonic ester synthesis from 2-bromo-1-1′-naphthylpropane. However, since 1-1′-naphthylpropane-2-carbonyl chloride was available from the previous synthesis, this material was successfully converted by means of the Arndt–Eistert synthesis to the required higher homologue. 2-1′-Naphthylpropane-1-carboxylic acid, $C_{10}H_7\cdot CHMe\cdot CH_2\cdot CO_2H$, was prepared by a method[31] involving a Reformatsky reaction between methyl 1-naphthyl ketone and ethyl bromoacetate. 6-1′-Naphthyl-4-ketohexane-1-carboxylic acid, $C_{10}H_7\cdot[CH_2]_2\cdot CO\cdot[CH_2]_3\cdot CO_2H$, was prepared by hydrolysis of the corresponding ethyl ester which was an intermediate in the syntheses of the straight chain acids. 2-1′-Naphthylmethylbenzene-1-carboxylic acid, $C_{10}H_7\cdot CH_2\cdot C_6H_4\cdot CO_2H$, was prepared by Clemmensen reduction of 2-1′-naphthoylbenzene-1-carboxylic acid obtained[32] from dinaphthylcadmium and phthalic anhydride.

An attempt was made to extend to branched-chain acids the method applied to the straight-chain acids, namely, the reaction of an ester-acid chloride with an organo-cadmium compound. To this end, 2-methoxycarbonyl-2-methylpropane-1-carbonyl chloride, one of the ester-acid chlorides corresponding to *as*-dimethylsuccinic acid, was prepared. The latter acid[33] was converted via its anhydride to the monomethyl ester and thence to the ester-acid chloride. Reaction between the latter and dinaphthylcadmium took place smoothly, but the resulting keto-ester could not be obtained analytically pure. From attempts to reduce and hydrolyse this ester, no crystalline acid was obtained.

Experimental

ω-Phenoxyalkyl bromides

These were prepared by the same general method, an example of which is given below. The physical constants of the new ω-phenoxyalkyl bromides are given in Table II.

Table II

ω-Phenoxyalkyl bromides

	M.p.	B.p.	Found Ag halide %	Formula	Required Ag halide %
1-Bromo-6-*o*-methoxyphenoxyhexane	—	154–160°/0·04 mm.	*—	$C_{13}H_{19}O_2Br$	—
1-Bromo-5-*p*-chlorophenoxypentane	—	130–138°/0·4 mm.	120	$C_{11}H_{14}OClBr$	119·5
1-Bromo-6-*p*-chlorophenoxyhexane	32°	185–195°/10 mm.	109	$C_{12}H_{16}OClBr$	113
1-Bromo-5-(2 : 4-dichlorophenoxy)pentane	39–40°	135–150°/0·15 mm.	154	$C_{11}H_{13}OCl_2Br$	152
1-Bromo-5-(2 : 4 : 5-trichlorophenoxy)pentane	34–36°	211–220°/15 mm.	175	$C_{11}H_{12}OCl_3Br$	178
1-Bromo-6-(2 : 4 : 5-trichlorophenoxy)hexane	39–41°	181–200°/0·09 mm.	170	$C_{12}H_{14}OCl_3Br$	171

* Found : Br, 27·2 ; $C_{13}H_{19}O_2Br$ requires Br, 27·9%

1-*Bromo*-6-(2 : 4 : 5-*trichlorophenoxy*)*hexane.*—2 : 4 : 5-Trichlorophenol (79 g., 0·4 mole) was dissolved in a solution of potassium hydroxide (25 g.) in methanol (100 ml.), and the solution added to a stirred solution of 1 : 6-dibromohexane (390 g., 1·6 mole) in methanol. After refluxing with stirring for four hours, the suspension was filtered and the bulk of the methanol removed by distillation on the steam-bath. The residue was poured into water, the heavy oil separated, and the aqueous layer extracted with ether. The ethereal extracts and oil were combined, dried, and the ether removed. The residue was distilled to give, firstly, 306 g. of crude 1 : 6-dibromohexane as a pale yellow oil, b.p. 108–120°/10 mm., and then 100 g. (69%) of the required *bromide* as a practically colourless oil, b.p. 181–200°/0·09 mm., which solidified on cooling to colourless needles, m.p. 39–41°.

ω-Phenoxyalkyl cyanides

These nitriles were all prepared by the same general method, an example of which is given below. The physical constants of the ω-phenoxyalkyl cyanides are listed in Table III.

Table III

ω-Phenoxyalkyl cyanides

	M.p.	B.p.	Found N %	Found Cl %	Formula	Required N %	Required Cl %
1-Cyano-3-*o*-methoxyphenoxypropane	—	170–175°/10 mm.	7·25	—	$C_{11}H_{13}O_2N$	7·33	—
1-Cyano-5-*o*-methoxyphenoxypentane	—	136–145°/1 mm.	5·97	—	$C_{13}H_{17}O_2N$	6·4	—
1-Cyano-5-*p*-chlorophenoxypentane	47–48°	—	6·27	15·5	$C_{12}H_{14}ONCl$	6·28	15·9
1-Cyano-5-(2 : 4-dichlorophenoxy)-pentane	34–35°	183–187°/0·1 mm.	5·27	—	$C_{12}H_{13}ONCl_2$	5·4	—
1-Cyano-3-(2 : 4 : 5-trichlorophenoxy)-propane*	94–95°	—	4·6	40·8	$C_{10}H_8ONCl_3$	5·3	40·2
1-Cyano-5-(2 : 4 : 5-trichlorophenoxy)-pentane	47–48°	—	4·5	36·1	$C_{12}H_{12}ONCl_3$	4·78	36·4

* This material was shown to be contaminated with 1 : 3-bis-(2 : 4 : 5-trichlorophenoxy)propane ; the latter was recovered during the subsequent hydrolysis of this nitrile to the corresponding acid.

1-*Cyano*-5-(2 : 4-*dichlorophenoxy*)*pentane.*—Sodium cyanide (6 g.) in water (6 ml.) was added to 1-bromo-5-(2 : 4-dichlorophenoxy)pentane (15·6 g., 0·05 mole) in ethanol (40 ml.). The solution was refluxed overnight, the bulk of the ethanol was removed by distillation, the residue poured into water (100 ml.) and the oil which separated was extracted with ether. The ethereal solution was dried, the ether removed and the residue distilled. The required nitrile (11·3 g., 87%) was obtained as a colourless oil, b.p. 183–187°/0·09 mm., which solidified on standing to a colourless solid, m.p. 34–35°.

Anomalous reaction of ω-phenoxyalkyl bromides

(a) *Attempted preparation of* 1-*cyano*-2-p-*chlorophenoxyethane.*—1-Bromo-2-*p*-chlorophenoxyethane (23·6 g., 0·1 mole) in ethanol (40 ml.) was added over 1 hour to a stirred refluxing

solution of sodium cyanide (6 g.) in water (8 ml.). The resulting solution was refluxed with stirring for 8 hours, the bulk of the ethanol was removed by distillation and the residue was poured into water.

The pale brown granular solid which separated was filtered off, washed with water, dried at 35°, and recrystallized from benzene–light petroleum (b.p. 40–60°) to give 7·4 g. of colourless prisms, m.p. 133–134°. Recrystallization of this material from ethanol gave 6·0 g. of colourless blunt needles, m.p. 133–134°. Qualitative elementary analysis showed the absence of nitrogen and the presence of chlorine [Found: C, 59·1; H, 4·3; Cl, 24·5%; molecular weight, 280. Calc. for $C_{14}H_{12}O_2Cl_2$ (1 : 2-bis-*p*-chlorophenoxyethane): C, 59·3; H, 4·24; Cl, 25·1%; molecular weight, 283].

(b) *Attempted preparation of* 1-*cyano*-3-p-*chlorophenoxypropane.*—Sodium cyanide (6 g.) in water (8 ml.) was added over 20 minutes to a stirred refluxing solution of 1-bromo-3-*p*-chlorophenoxypropane (25 g., 0·1 mole) in ethanol (40 ml.). The resulting solution was refluxed with stirring for a further 2 hours, the bulk of the ethanol was removed by distillation and the residue was poured into water (250 ml.). The oil which separated was extracted with chloroform; evaporation of the chloroform solution left a dark brown oil which partially crystallized on standing. The crystals were filtered off, washed with light petroleum (b.p. 40–60°), and dried at 35° to give pale brown, long needles (2·9 g.), m.p. 117°. Further dilution of the filtrate with light petroleum (b.p. 40–60°) caused separation of 9·6 g. of alkali-soluble brown solid with a phenolic odour (probably largely *p*-chlorophenol).

Recrystallization of the 2·9 g. of needles from chloroform–light petroleum (b.p. 40–60°) gave colourless needles, m.p. 119°. Qualitative elementary analysis showed the presence of chlorine and a trace of nitrogen [Found: N, less than 0·4; Cl, 24·6. Calc. for $C_{15}H_{14}O_2Cl_2$ (1 : 3-bis-*p*-chlorophenoxypropane): Cl, 23·9%].

ω-Phenoxyalkylcarboxylic acids

The physical properties and methods of preparation are given in Table IV. Representative examples of the methods of preparation are given below.

5-o-*Methoxyphenoxypentane*-1-*carboxylic acid.*—1-Cyano-5-*o*-methoxyphenoxypentane (21·9 g., 0·1 mole) was refluxed for 8 hours with a solution of sodium hydroxide (15 g.) in water (18 ml.) and ethanol (50 ml.). Distillation to dryness on the steam-bath under reduced pressure gave a colourless residue which was dissolved in hot water (100 ml.). The resulting solution, after filtration, was acidified to Congo red with hydrochloric acid and cooled in ice. The pale cream solid which separated was filtered off, washed with water and recrystallized from aqueous ethanol to give 16·8 g. (77%) of the required *acid*, as colourless plates, m.p. 101–102°.

Diethyl 6-o-*methoxyphenoxyhexane*-1 : 1-*dicarboxylate.*—To a stirred refluxing solution of sodium (9 g.) in dry ethanol (200 ml.), was added diethyl malonate (90 g.) over 5 minutes, followed by 1-bromo-5-*o*-methoxyphenoxypentane (54·6 g., 0·2 mole) over 10 minutes. The solution was refluxed for a further 4 hours, the bulk of the ethanol was removed by distillation and the residue was poured into water (1 litre). The orange-coloured oil which separated was extracted with ether, the solvent removed and the residue distilled. After a forerun of diethyl malonate, 45·5 g. (66%) of the required *ester* was obtained as a colourless oil, b.p. 171–199°/0·2 mm. (Found: C, 65·6; H, 8·1. $C_{19}H_{28}O_6$ requires C, 64·8; H, 7·9%).

6-o-*Methoxyphenoxyhexane*-1-*carboxylic acid.*—Diethyl 6-*o*-methoxyphenoxyhexane-1 : 1-dicarboxylate (35·2 g., 0·1 mole) was added over 30 minutes to a boiling stirred solution of potassium hydroxide (20 g.) in water (20 ml.) and the solution was refluxed with stirring for a further 4 hours. Water (20 ml.) was added and the solution was concentrated by the removal of 25 ml. of distillate. To the boiling stirred residue was added dropwise over one hour a mixture of sulphuric acid (18 ml.) and water (50 ml.). Refluxing with stirring was continued for a further 6 hours. After being cooled in ice, the solution was extracted with ether, and the ethereal extract was washed with water and dried. Removal of the ether gave a red oil which solidified on keeping; the solid was recrystallized from aqueous ethanol to give 18 g. (72%) of a faintly grey microcrystalline powder, m.p. 55–56°; recrystallization of this material from benzene–light petroleum (b.p. 40–60°) gave 13·5 g. (54%) of the required *acid*, as colourless prisms, m.p. 61–62°.

Table IV

ω-Phenoxyalkylcarboxylic acids $RO\cdot[CH_2]_n\cdot CO_2H$

Acid	R	*n*	Synthetic route	M.p.	Crystalline form	Solvent	Found C %	Found H %	Found Cl %	Formula	Required C %	Required H %	Required Cl %
3-*o*-Methoxyphenoxypropane-1-carboxylic acid	*o*-methoxyphenyl	3	B	84–85°	prisms	(*a*)	62·8	6·9	—	$C_{11}H_{14}O_4$	62·9	6·5	—
4-*o*-Methoxyphenoxybutane-1-carboxylic acid	,,	4	C	79–80°	,,	(*a*)	63·6	7·18	—	$C_{12}H_{16}O_4$*	64·4	7·15	—
5-*o*-Methoxyphenoxypentane-1-carboxylic acid	,,	5	B	101–102°	plates	(*b*)	65·6	7·5	—	$C_{13}H_{18}O_4$	65·5	7·6	—
6-*o*-Methoxyphenoxyhexane-1-carboxylic acid	,,	6	C	61–62°	prisms	(*a*)	66·4	7·7	—	$C_{14}H_{20}O_4$	66·7	7·9	—
4-*p*-Chlorophenoxybutane-1-carboxylic acid	*p*-chlorophenyl	4	C	71°	,,	(*a*)	—	—	15·6	$C_{11}H_{13}O_3Cl$	—	—	15·5
5-*p*-Chlorophenoxypentane-1-carboxylic acid	,,	5	B	77–78°	needles	(*a*)	—	—	14·9	$C_{12}H_{15}O_3Cl$	—	—	14·7
6-*p*-Chlorophenoxyhexane-1-carboxylic acid	,,	6	C	74–75°	prisms	(*b*)	—	—	14·1	$C_{13}H_{17}O_3Cl$	—	—	13·9
7-*p*-Chlorophenoxyheptane-1-carboxylic acid	,,	7	C	110–112°	,,	(*c*)	—	—	12·8	$C_{14}H_{19}O_3Cl$	—	—	13·1
2-(2 : 4 : 5-Trichlorophenoxy)ethane-1-carboxylic acid	2 : 4 : 5-trichlorophenyl	2	A	142–144°	plates	(*a*)	—	—	39·6	$C_9H_7O_3Cl_3$	—	—	39·6
4-(2 : 4 : 5-Trichlorophenoxy)butane-1-carboxylic acid	,,	4	C	96–97°	micro-prisms	(*a*)	—	—	35·3	$C_{11}H_{11}O_3Cl_3$	—	—	35·8
5-(2 : 4 : 5-Trichlorophenoxy)pentane-1-carboxylic acid	,,	5	B	73–74°	,,	(*a*)	—	—	34·1	$C_{12}H_{13}O_3Cl_3$	—	—	34·2
6-(2 : 4 : 5-Trichlorophenoxy)hexane-1-carboxylic acid	,,	6	C	94–95°	,,	(*a*)	—	—	32·1	$C_{13}H_{15}O_3Cl_3$	—	—	32·7
7-(2 : 4 : 5-Trichlorophenoxy)heptane-1-carboxylic acid	,,	7	C	55°	,,	(*a*)	—	—	30·4	$C_{14}H_{17}O_3Cl_3$	—	—	31·3

Synthetic routes

(A) $R\cdot OH \xrightarrow{Br\cdot[CH_2]_2\cdot CO_2H} RO\cdot[CH_2]_2\cdot CO_2H$

(B) $R\cdot OH \xrightarrow{Br\cdot[CH_2]_x\cdot Br} RO\cdot[CH_2]_x\cdot Br \longrightarrow RO\cdot[CH_2]_x\cdot CN \longrightarrow RO\cdot[CH_2]_x\cdot CO_2H$

(C) $R\cdot OH \xrightarrow{Br\cdot[CH_2]_x\cdot Br} RO\cdot[CH_2]_x\cdot Br \longrightarrow RO\cdot[CH_2]_x\cdot CH[CO_2Et]_2 \longrightarrow RO\cdot[CH_2]_{x+1}\cdot CO_2H$

Solvents: (*a*) Benzene/light petroleum (b.p. 40–60°); (*b*) aqueous ethanol; (*c*) benzene

* Found: OMe, 13·6. $C_{12}H_{16}O_4$ requires OMe, 13·8.

Diethyl 4-p-*chlorophenoxybutane*-1 : 1-*dicarboxylate.* — 1-Bromo-3-*p*-chlorophenoxypropane (25 g., 0·1 mole) was treated by the method described for the preparation of diethyl 6-*o*-methoxyphenoxyhexane-1 : 1-dicarboxylate. The required *ester* (23·5 g., 61%) was obtained as a colourless oil, b.p. 132–150°/0·07 mm. (Found : Cl, 11·26. $C_{16}H_{21}O_5Cl$ requires Cl, 10·8%).

4-p-*Chlorophenoxybutane*-1-*carboxylic acid.*—Diethyl 4-*p*-chlorophenoxybutane-1 : 1-dicarboxylate (8·2 g., 0·025 mole) was treated in the manner described for the preparation of 6-*o*-methoxyphenoxyhexane-1-carboxylic acid. In this case decarboxylation did not occur. The product obtained was recrystallized from benzene–light petroleum (b.p. 40–60°), to give 4·2 g. (72%) of 4-p-*chlorophenoxybutane*-1 : 1-*dicarboxylic acid* as colourless prisms, m.p. 108–110° (Found : Cl, 13·1. $C_{12}H_{13}O_5Cl$ requires Cl, 13·0%). This acid was decarboxylated by heating for 4 hours under reduced pressure (10 mm.) in an oil-bath at 180°. On cooling, the melt solidified to a pale brown mass which was recrystallized from benzene–light petroleum (b.p. 40–60°), to give 2·3 g. (70%) of material with m.p. 65–69°. A further recrystallization from benzene–light petroleum (b.p. 40–60°) gave 1·8 g. (45%) of the required *acid* as colourless prisms, m.p. 71°.

Derivatives of ω-phenoxyalkylcarboxylic acids

p-*Bromophenacyl ester of* 3-*o*-*methoxyphenoxypropane*-1-*carboxylic acid.*—3-*o*-Methoxyphenoxypropane-1-carboxylic acid (1·9 g.) was suspended in water (5 ml.) and neutralized with 2N-sodium carbonate solution to which was added a further 0·2 g. (0·01 mole in all) of the acid. The resulting solution, which was acid to phenolphthalein, was added to a hot solution of *p*-bromophenacyl bromide (3·07 g., 0·011 mole) in ethanol (70 ml.) and the resulting solution was refluxed for 1 hour and allowed to cool.

The solid which separated was filtered off, and recrystallized from ethanol to give the required *ester* (0·65 g., 16%) as colourless micro-needles, m.p. 116–117° (Found : Br, 20·0. $C_{19}H_{19}O_5Br$ requires Br, 19·7%).

p-*Phenylphenacyl ester of* 3-*o*-*methoxyphenoxypropane*-1-*carboxylic acid.*—*p*-Phenylphenacyl bromide (3·07 g.) in ethanol (70 ml.) and 3-*o*-methoxyphenoxypropane-1-carboxylic acid (2·1 g., 0·01 mole) in sodium carbonate solution were caused to react as in the preparation of the *p*-bromophenacyl ester, to give the required *ester* (2·7 g., 67%), as colourless micro-needles (from ethanol), m.p. 135° (Found : OMe, 7·95. $C_{25}H_{24}O_5$ requires OMe, 7·7%).

ω-1-*Naphthylalkylcarboxylic acids*

Monoesters of dibasic acids

The monomethyl esters of succinic and glutaric acids were obtained by the action of methanol on the appropriate anhydride.[34] The monoethyl esters of adipic, pimelic and sebacic acids were obtained by semi-esterification of the appropriate acid.[26, 27]

Ester-acid chlorides

Treatment of the monoesters with thionyl chloride[34] gave the corresponding acid chlorides ; the properties of the three higher members are listed in Table V.

Halides used were 1-bromonaphthalene,[35] 1-chloromethylnaphthalene[36] and 1-bromo-2-1′-naphthylethane.[37]

Keto-esters

The keto-esters, whose properties and synthetic routes are summarized in Table VI, were prepared by essentially the same method, a typical example of which is described below.

Methyl-6-1′-*naphthyl*-4-*ketohexane*-1-*carboxylate.*—The apparatus consisted of a 1-litre, three-necked, round-bottom flask, fitted with a stainless-steel stirrer[38] driven by a powerful motor, reflux condenser (closed by drying tube) and dropping funnel.

2-1′-Naphthylethylmagnesium bromide was prepared in this flask from 1-bromo-2-1′-naphthylethane (47 g., 0·2 mole) and magnesium (4·8 g.) in dry ether (250 ml.). The Grignard solution was cooled in ice and anhydrous cadmium chloride (22 g., 0·12 mole) was added as rapidly as possible. The suspension was then refluxed with stirring for 1 hour, after which time a small sample was removed which gave a negative Gilman reaction.[39]

The bulk of the ether was removed by distillation and replaced by dry benzene (200 ml.) and

Table V

Ester-acid chlorides

$EtCO_2{\cdot}[CH_2]_n{\cdot}COCl$

	n	B.p.	Found Cl %	Formula	Required Cl %
4-Ethoxycarbonylbutane-1-carbonyl chloride	4	113–114°/15 mm.	18·6	$C_8H_{13}O_3Cl$	18·5
5-Ethoxycarbonylpentane-1-carbonyl chloride	5	134–136°/15 mm.	17·0	$C_9H_{15}O_3Cl$	17·2
8-Ethoxycarbonyloctane-1-carbonyl chloride	8	173–175°/15 mm.	14·6	$C_{12}H_{21}O_3Cl$	14·3

Table VI

Keto-esters $1\text{-}C_{10}H_7{\cdot}[CH_2]_n{\cdot}CO{\cdot}[CH_2]_m{\cdot}CO_2R$

Prepared by the reaction $1\text{-}C_{10}H_7{\cdot}[CH_2]_n{\cdot}Br \longrightarrow 1\text{-}C_{10}H_7{\cdot}[CH_2]_m{\cdot}(Cd)_{\frac{1}{2}} \xrightarrow{ClCO{\cdot}[CH_2]_m{\cdot}CO_2R} 1\text{-}C_{10}H_7{\cdot}[CH_2]_n{\cdot}CO{\cdot}[CH_2]_m{\cdot}CO_2R$

Name	n	m	R	B.p.	Found C %	Found H %	Found OR %	Formula	Required C %	Required H %	Required OR %
Methyl 2-1′-naphthoylethane-1-carboxylate	0	2	Me	169–180°/0·5 mm.	74·2	6·0	—	$C_{15}H_{14}O_3$	74·4	5·8	—
Methyl 3-1′-naphthoylpropane-1-carboxylate	0	3	Me	158–163°/0·1 mm.	—	—	12·1	$C_{16}H_{16}O_3$	—	—	12·1
Ethyl 4-1′-naphthoylbutane-1-carboxylate	0	4	Et	145–161°/0·07 mm.	76·0	7·22	—	$C_{18}H_{20}O_3$	76·1	7·05	—
Methyl 6-1′-naphthyl-4-ketohexane-1-carboxylate	2	3	Me	173–185°/0·08 mm.	—	—	10·8	$C_{18}H_{20}O_3$	—	—	10·9
Ethyl 7-1′-naphthyl-5-ketoheptane-1-carboxylate	2	4	Et	193–201°/0·1 mm.	—	—	12·55	$C_{20}H_{24}O_3$	—	—	14·4
Ethyl 8-1′-naphthyl-6-keto-octane-1-carboxylate	2	5	Et	201–207°/0·04 mm.	—	—	12·1	$C_{21}H_{26}O_3$	—	—	13·8
Ethyl 8-1′-naphthoyloctane-1-carboxylate	0	8	Et	145–152°/0·3 mm.	—	—	16·4	$C_{22}H_{28}O_3$	—	—	13·2

the reaction mixture was again cooled in ice. 3-Methoxycarbonylpropane-1-carbonyl chloride (24·8 g., 0·15 mole) in dry benzene (50 ml.) was added over 5 minutes, causing the separation of a solid complex which was at first sticky and difficult to stir, but which soon reverted to a granular solid. The reaction mixture was refluxed with stirring for 3 hours, cooled and poured into a mixture of ice (500 g.) and water (500 ml.). Sufficient 2N-sulphuric acid was added to bring the mixture acid to Congo red, and a small quantity of solid was removed by filtration through Hyflo. The benzene layer was separated from the filtrate and the aqueous layer was extracted with benzene (2 × 60 ml.). The combined benzene extracts were washed with water, dilute sodium bicarbonate solution, and again with water, and dried. The residue remaining after removal of the benzene was distilled under reduced pressure. The required *keto-ester* was obtained as a pale yellow oil, b.p. 170–185°/0·08 mm.

As can be seen from Table VI, some of the longer chain keto-esters were not obtained pure.

ω-1-Naphthyl-alkylcarboxylic acids

5-1′-Naphthylpentane-1-carboxylic acid.—Ethyl 4-1′-naphthoylbutane-1-carboxylate was hydrolysed by refluxing with 10% ethanolic potassium hydroxide solution. Clemmensen reduction[40] of the crude acid obtained by acidification of this reaction gave the required *acid* as colourless prisms, m.p. 70–72°, from light petroleum (b.p. 40–60°) (Found: C, 79·1; H, 7·3. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·44%).

4-1′-Naphthylbutane-1-carboxylic acid.—(*a*) By Clemmensen reduction.—Methyl 3-1′-naphthoylpropane-1-carboxylate was reduced[40] to give *methyl 4-1′-naphthylbutane-1-carboxylate* as an almost colourless oil, b.p. 164–172°/0·1 mm., which solidified on standing (Found: C, 78·6; H, 7·2. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%). Alkaline hydrolysis of this ester gave the required *acid* as colourless prisms, m.p. 87–89°, from light petroleum (b.p. 40–60°) (Found: C, 78·9; H, 7·17. $C_{15}H_{16}O_2$ requires C, 79·0; H, 7·0%).

(*b*) By Wolff–Kishner reduction.—Methyl 3-1′-naphthoylpropane-1-carboxylate was reduced[25] to give the required acid, m.p. 87–89° (no depression with the sample prepared by Clemmensen reduction).

6-1′-Naphthylhexane-1-carboxylic acid.—Methyl 6-1′-naphthyl-4-ketohexane-1-carboxylate was reduced[25] to the required *acid*, obtained as colourless microprisms, m.p. 58–60°, from light petroleum (b.p. 40–60°) (Found: C, 79·7; H, 7·8. $C_{17}H_{20}O_2$ requires C, 79·8; H, 7·7%).

3-1′-Naphthylpropane-1-carboxylic acid.—Freshly distilled ethyl acetoacetate (26 g.) followed by 1-bromo-2-1′-naphthylethane (23·5 g., 0·1 mole) was added to a refluxing solution of sodium (4·6 g.) in anhydrous ethanol (100 ml.). The turbid solution was refluxed for 4 hours and then filtered. The ethanol and most of the excess ethyl acetoacetate was distilled from the filtrate to leave an orange oil which was refluxed for 2 hours with a solution of potassium hydroxide (30 g.) in ethanol (100 ml.). The resulting solution was poured into water (1 litre). Alkali-insoluble material was removed by extracting this milky solution with ether. The resulting alkaline solution was boiled with charcoal, filtered and brought to pH 7 by the addition of hydrochloric acid. The brown tarry material was removed by filtration through Hyflo and the filtrate was acidified to Congo red with hydrochloric acid and set aside overnight.

The cream-coloured solid was filtered off, washed with water and recrystallized from 150 ml. of hot water to give the required acid as colourless needles, m.p. 106° (no depression with material which had been prepared by reduction of 2-1′-naphthoylethane-1-carboxylic acid and which melted at 109–110°).

1-Naphthyl-alkylcarboxylic acids with branched or modified chains

2-1′-Naphthylmethylbenzene-1-carboxylic acid.—2-1′-Naphthoylbenzoic acid[32] (4·5 g.) was reduced by the Clemmensen method[25] to give the required *acid* (*α-1′-naphthyl-o-toluic acid*) (1 g.) as colourless microprisms, m.p. 144–145°, from benzene (Found: C, 82·1; H, 5·4. Calc. for $C_{18}H_{14}O_2$: C, 82·4; H, 5·35%).

1-1′-Naphthylpropane-2-carbonyl chloride.—1-1′-Naphthylpropane-2-carboxylic acid[28] (6·4 g.) in dry benzene (20 ml.) was refluxed for 40 minutes with thionyl chloride (5 ml.). The benzene was removed by distillation and the residue distilled to give the required *acid chloride* (4·3 g.) as a colourless oil, b.p. 190–195°/15 mm. (Found: Cl, 14·95. $C_{14}H_{13}OCl$ requires Cl, 15·3%).

2-Methyl-3-1'-naphthylpropane-1-carboxylic acid

N-Methyl-*N*-nitrosourea[41] (17·5 g.) was added over 30 minutes in portions of about 1 g. to a stirred mixture of ether (250 ml.) in 40% aqueous potassium hydroxide (70 ml.) at 0–5°. The yellow ethereal diazomethane solution was separated, dried at 0° over potassium hydroxide and treated with a solution of 1-1'-naphthylpropane-2-carbonyl chloride (8·8 g., 0·038 mole) in dry ether (50 ml.) at 5–10°. The solution was set aside overnight and the ether was then removed by distillation under reduced pressure at 25–30° to give the crude diazoketone (8 g.) as a yellowish-brown, viscous oil. This diazoketone was dissolved in dry dioxan (60 ml.) and the resulting solution was added over 1 hour to a stirred mixture of silver oxide (1·3 g.), anhydrous sodium carbonate (3·3 g.), sodium thiosulphate (2 g.), and water (130 ml), maintained at 50–60°. The suspension was maintained at 60–70° for a further hour, cooled to 20° and acidified to Congo red with dilute nitric acid. To this was added ether (100 ml.) and the mixture was filtered through Hyflo. Ether extraction of the filtrate and evaporation of the dried ethereal extract gave a pale brown syrup (9·2 g.) which was distilled to give a pale yellow oil (4·1 g.), b.p. 220–226°/15 mm., which slowly solidified on standing. Recrystallization of this material from benzene–light petroleum (b.p. 40–60°) gave the required acid (2·0 g.) as a pale fawn micro-crystalline solid, m.p. 86–88°. Bachmann & Cortes,[30] using a different route, claim m.p. 89–91° (Found: C, 78·8; H, 7·0. Calc. for $C_{15}H_{16}O_2$: C, 78·9; H, 7·0%).

Acknowledgments

The author wishes to thank Professor R. L. Wain and Dr. H. J. Barber for their advice and interest and the Directors of May & Baker Ltd. for the generous provision of facilities.

Chemical Research Laboratories
May & Baker Ltd.
Dagenham, Essex

Received 18 November, 1955

References

[1] Fawcett, C. H., Ingram, J. M. A., & Wain, R. L., *Nature, Lond.*, 1952, **170**, 887
[2] Wain, R. L., *Ann. appl. Biol.*, 1949, **36**, 558
[3] Wain, R. L., & Wightman, F., *Proc. roy. Soc.*, 1954, [B] **142**, 525
[4] Auwers, K., & Haymann, K., *Ber. dtsch. chem. Ges.*, 1894, **27**, 2804
[5] Pfeiffer, P., Oberlin, H., & Konermann, E., *Ber. dtsch. chem. Ges.*, 1925, **58**, 1955
[6] Michael, A., *Amer. chem. J.*, 1887, **9**, 216
[7] Chakravarti, D., & Dutta, N., *J. Indian chem. Soc.*, 1939, **61**, 639
[8] Nair, C. N., & Peacock, D. H., *J. Indian chem. Soc.*, 1935, **12**, 318
[9] Synerholm, M. E., & Zimmerman, P. W., *Contr. Boyce Thomson Inst.*, 1945, **14**, 369
[10] Pokorny, R., *J. Amer. chem. Soc.*, 1941, **63**, 1768
[11] Wohl, A., & Berthold, E., *Ber. dtsch. chem. Ges.*, 1910, **43**, 2180
[12] Merck, Ger. P. 184,968
[13] Leese, C. L., & Raphael, R. A., *J. chem. Soc.*, 1950, p. 2725
[14] Gagnon, P. E., Boivin, J. L., & Giguère, J., *Canad. J. Res.*, 1950, **28, B**, 352
[15] Walker, D. F., *J. Amer. pharm. Ass.*, 1950, **39**, 396
[16] Newman, M. S., Fones, W., & Renoll, M., *J. Amer. chem. Soc.*, 1947, **69**, 718
[17] Barber, H. J., Green, M. B., & Zwartouw, H. T., *J. appl. Chem.*, 1953, **3**, 419
[18] Boessneck, P., *Ber. dtsch. chem. Ges.*, 1883, **16**, 639
[19] Mayer, F., & Sieglitz, A., *Ber. dtsch. chem. Ges.*, 1922, **55**, 1835
[20] Haworth, R. D., *J. chem. Soc.*, 1932, p. 1125
[21] Schlenk, W., Bergmann, O., & Bergmann, E., *J. Soc. chem. Ind., Lond.*, 1933, **52**, 2091
[22] Manske, R. H. F., & Ledingham, A. E., *Canad. J. Res.*, 1939, **17, B**, 14
[23] Riegel, B., Burr, J. G., Kubico, M. A., & Gold, M. H., *J. Amer. chem. Soc.*, 1948, **70**, 1073
[24] Dauben, W. G., & Tilles, H., *J. org. Chem.*, 1950, **15**, 785
[25] Huang-Minlon, *J. Amer. chem. Soc.*, 1946, **68**, 2487
[26] Brown, G. B., & Baker, B. R., *J. org. Chem.*, 1947, **12**, 162
[27] Swan, S., Oehler, R., & Buswell, R. J., *Org. Synth.*, Coll. Vol. II, p. 276
[28] Blicke, F. F., & Maxwell, C. E., *J. Amer. chem. Soc.*, 1939, **61**, 1782
[29] Fieser, L. F., & Novello, F. C., *J. Amer. chem. Soc.*, 1940, **62**, 1855
[30] Bachmann, W. E., & Cortes, G. D., *J. Amer. chem. Soc.*, 1943, **65**, 1329
[31] Boekelheide, V., & Larrabee, C. E., *J. Amer. chem. Soc.*, 1950, **72**, 1240
[32] de Benneville, P. L., *J. org. Chem.*, 1941, **6**, 462
[33] Vogel, I., *J. chem. Soc.*, 1928, p. 2019
[34] Cason, J., *Org. Synth.*, **25**, 19
[35] Clarke, H. T., & Brethen, M. R., *Org. Synth.*, Coll. Vol. I, p. 121
[36] Cambron, A., *Canad., J. Res.*, 1939, **17, B**, 10
[37] Haworth, R. D. & Mavin, C. R., *J. chem. Soc.*, 1933, p. 1014
[38] Hershberg, E. B., *Industr. Engng Chem.* [*Anal.*], 1936, **8**, 313
[39] Gilman, H., & Schulze, F., *J. Amer. chem. Soc.*, 1925, **47**, 2002
[40] Martin, E. L., *J. Amer. chem. Soc.*, 1936, **58**, 1438
[41] Arndt, F., *Org. Synth.*, Coll. Vol. II, p. 461