The Chemistry of Plant Growth-regulators. Part II. Modification of the Side-chain of 2 : 4-Dichlorophenoxyacetic Acid.*

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The synthesis of some 2 : 4-dichlorophenoxyacetic acids modified in the side-chain and related benzo-1 : 3-dioxole-2-carboxylic acids is described. Growth-regulating properties of these compounds are briefly discussed.

It was concluded in Part I * that hydroxylation of 2 : 4-dichlorophenoxyacetic acid (2 : 4-D) in the 6-position is not a metabolic process essential before growth-regulating properties are shown. Hypotheses relating plant growth-regulating activity with the structure of the aryloxyalkanecarboxylic acids, recently reviewed by Wain (" Plant Growth Substances," Roy. Inst. Chem., London, 1953), have stressed that the $-O{\cdot}CH{\cdot}CO_2H$ system is essential and, further, have considered the significance of the configuration of the carbon atom α to the carboxyl group. Some phenoxyacetic acids modified in the side-chain have now been synthesised to test such relations.

Previous investigations of the phenoxy-acids of the type $ArO{\cdot}CHR{\cdot}CO_2H$ have been

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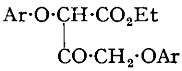
* Part I, *J.*, 1954, 565.

confined to those compounds in which R is an alkyl or aryl group (cf. Wain, *op. cit.*) and we now report the introduction of acyl and ester substituents into the α-position.

2 : 4-Dichlorophenoxymalonic acid has been synthesised but exhibits low growth-regulating activity. Such relative inactivity in a system which is readily decarboxylated by chemical processes to a phenoxyacetic acid, was unexpected; however, significant activity is shown in the following α-(2 : 4-dichlorophenoxy)-β-oxo-esters.

Claisen condensation of ethyl 2 : 4-dichlorophenoxyacetate with ethyl oxalate proceeded normally in ether, yielding ethyl 2 : 4-dichlorophenoxyoxaloacetate, which was isolated and purified as the copper salt (cf. Huntress and Olsen, *J. Amer. Chem. Soc.*, 1948, **70**, 2856, for parent compound). Self-condensation of ethyl 2 : 4-dichlorophenoxyacetate occurs in toluene and the sodio-derivative of ethyl $\alpha\gamma$-bis-(2 : 4-dichlorophenoxyacetoacetate is precipitated. This salt has unusual properties, being insoluble in water and ethyl alcohol, soluble in pyridine and hot nitrobenzene, and unaffected by cold dilute hydrochloric acid. The parent ester can be obtained by the action of hot acetic acid on the sodio-derivative, which is reprecipitated on titration with alcoholic sodium hydroxide solution (phenolphthalein). Hydrolysis with alcoholic potassium hydroxide to 2 mols. of the 2 : 4-dichlorophenoxyacetic acid confirms the structure (inset).



$$\begin{array}{l}Ar\cdot O\cdot CH\cdot CO_2Et\\ \quad\quad\;\; |\\ \quad\quad CO\cdot CH_2\cdot OAr\end{array}$$

Some benzo-1 : 3-dioxole-2-carboxylic acids have been prepared for comparison with the corresponding phenoxyacetic acids. First, in the benzodioxole system the carboxyl group is held in a fixed position to the plane of the ring and, secondly, if activity is present in some nuclear chlorinated derivatives, then resolution of such compounds would yield information on the effect of the configuration of the α-carbon atom. A low yield in the synthesis of the parent benzo-1 : 3-dioxole-2-carboxylic acid from catechol, sodium, and ethyl dichloroacetate was noted by Burger, Markees, Nes, and Yost (*ibid.*, 1949, **71**, 3307) and we have improved the yield (to 23%) by the use of a continuous-extraction process. 5-Chloro- and 4 : 6-dichloro-benzo-1 : 3-dioxole-2-carboxylic acids were also readily isolated by this method. Direct chlorination of the parent acid yielded a (?5 : 6-)dichloro-derivative. Several alternative syntheses were unsuccessfully attempted. 2 : 2-Dialkylbenzo-1 : 3-dioxoles were obtained in good yield by condensation of catechol with ketones in the presence of phosphoric oxide (Sloof, *Rec. Trav. chim.*, 1935, **54**, 995). We confirmed this procedure, for example, in the synthesis of 2 : 2-di*iso*butylbenzo-1 : 3-dioxole, but were unable to oxidise such alkyl derivatives to the carboxylic acids. Further investigations of the dioxoles were abandoned when preliminary testing of the 5-chloro-acid showed no growth-regulating activity. Rather, such results support Wain's hypothesis (*op. cit.*) of free rotation of the oxyacetate moiety.

We also synthesised *meso*-$\alpha\alpha'$-bis-2 : 4-dichlorophenoxysuccinic acid and ethyl 2 : 4-dichlorophenyl oxalate. The former, which retains the $\cdot O\cdot CH\cdot CO_2H$ grouping, might result by dehydrogenation and the latter by direct oxidation of 2 : 4-dichlorophenoxyacetic acid in the plant. Neither of these compounds showed activity. Finally, 2 : 4-dichlorophenoxyacetone has been synthesised and its lack of growth-regulating activity shows that the acid carboxyl and not the polar carbonyl group is an essential feature.

The preliminary testing procedure employed was that of effect on the elongation of the primary maize root, and the results reported above are in general agreement with current correlations between structure and activity in the aryloxyalkanecarboxylic acids. There is considerable specificity in the constitution of the single substituent allowable on the α-carbon atom. The order of inhibitive activity is $2:4:1\text{-}C_6H_3Cl_2\cdot O\cdot CH_2\cdot CO_2H \gg$ ethyl $\alpha\gamma$-bis-2 : 4-dichlorophenoxyacetoacetate $>$ $2:4:1\text{-}C_6H_3Cl_2\cdot O\cdot CH(CO_2H)_2$. The series showing high activity in this investigation is the β-keto-esters, and their enolic salts and chelate derivatives. The insolubility and non-volatility of the sodio-salt of the aceto-acetate and its ability to yield 2 : 4-dichlorophenoxyacetic acid on alkaline hydrolysis might lead to useful practical applications.

Experimental

2 : 4-*Dichlorophenoxymalonic Acid*.—Ethyl chloromalonate (19·5 g.) was added to a hot solution of sodium 2 : 4-dichlorophenoxide [from the dichlorophenol (16·3 g.) and sodium (2·3 g.)] in ethanol (100 ml.), and the mixture heated at reflux for 2 hr. Ethyl 2 : 4-dichloro-

phenoxymalonate, isolated by ether-extraction, was a colourless oil, b. p. 164—167°/2·0 mm. (slight decomp.). The crude ester was hydrolysed with excess of alcoholic potassium hydroxide solution, and the acid separated (21·5 g.), m. p. 142—144° (decomp.), on acidification. Recrystallisation from benzene–ether gave 2 : 4-*dichlorophenoxymalonic acid* (12·0 g.) as colourless needles with bitter taste and m. p. 148—149° (decomp.; inserted in bath at 146°) (Found : C, 41·0; H, 2·4. $C_9H_6O_5Cl_2$ requires C, 40·8; H, 2·3%). The acid, which is decarboxylated at the m. p., solidifies on cooling and remelts at 138° (mixed m. p. with 2 : 4-dichlorophenoxyacetic acid, m. p. 140°, is not depressed).

Ethyl 2 : 4-*Dichlorophenoxyoxaloacetate*.—This ester (170 g.), prepared from ethyl 2 : 4-dichlorophenoxyacetate (124·5 g.) and ethyl oxalate (80·3 g.) by Huntress and Olsen's method (*loc. cit.*), was a pale yellow viscous oil, soluble in dilute sodium hydroxide solution and giving a deep red colour with alcoholic ferric chloride. A *copper* derivative, prepared from the oxaloacetate (17·45 g.) in alcohol (50 ml.) with crystalline copper sulphate (8·0 g.) and sodium acetate trihydrate (8·0 g.) in water (60 ml.), was precipitated as an apple-green powder; it recrystallised from alcohol as long green needles (16·0 g.), m. p. 205°, with a reversible brown (hot)–green (cold) colour change (Found : C, 44·5; H, 3·4. $C_{28}H_{26}O_{12}Cl_4Cu$ requires C, 44·3; H, 3·5%). It is insoluble in water and light petroleum, sparingly soluble in ether, but soluble in chloroform, benzene, and acetone. Hydrolysis of the copper derivative with cold hydrochloric acid (5N) under ether yields *ethyl* 2 : 4-*dichlorophenoxyoxaloacetate*, with slight decomposition, as a pale-yellow viscous oil, $d_D^{23.5}$ 1·318, $n_D^{23.5}$ 1·5243 (Found : C, 46·1; H, 4·2. $C_{14}H_{14}O_6Cl_2$ requires C, 48·1; H, 4·0%). Better analytical figures cannot be obtained owing to partial hydrolysis; the product re-forms the copper derivative in >90% yield.

Ethyl αγ-*Bis*-2 : 4-*dichlorophenoxyacetoacetate*.—Addition of ethyl 2 : 4-dichlorophenoxyacetate (124·5 g.) to a hot solution of ethyl oxalate (80·3 g., 10% excess) and sodium ethoxide (from 11·5 g. of sodium) in toluene (100 ml.) caused rapid precipitation of a colourless salt. The reaction was forced, during 5 hr., by distillation of the ethanol–toluene azeotrope from the mixture, the theoretical quantity of ethanol (46 g.) being recovered. The dried insoluble *sodio*-derivative (73 g.), isolated after washing with toluene and water, crystallised from pyridine as small colourless prisms (Found: C, 45·5; H, 2·8; Cl, 29·5; Na, 4·7. $C_{18}H_{13}O_5Cl_4Na$ requires C, 45·6; H, 2·8; Cl, 29·9; Na, 4·9%). It gave a deep purple colour with neutral ferric chloride solution.

The sodio-compound (50 g.) was added to hot acetic acid (200 ml.) and, on cooling, *ethyl* αγ-*bis*-2 : 4-*dichlorophenoxyacetoacetate* crystallised as slender colourless needles, m. p. 99°, in almost theoretical yield [Found : C, 47·5; H, 3·3%; *M* (Rast), 446. $C_{18}H_{14}O_5Cl_4$ requires C, 47·8; H, 3·1%; *M*, 452].

Hydrolysis of the ester (11·0 g.) with excess of alcoholic potassium hydroxide gave 2 : 4-dichlorophenoxyacetic acid as colourless prisms (8·5 g., 97%), m. p. and mixed m. p. 141°. No carbon dioxide or oxalate ion was found.

Benzo-1 : 3-*dioxole*-2-*carboxylic Acid and its Chloro-derivatives*.—Catechol (11 g.) in butanol (20 ml.) was heated with hot sodium butoxide solution [from sodium (4·6 g.) in butanol (100 ml.)] under reflux in an atmosphere of hydrogen; a colourless sodium salt was precipitated. Butyl dichloroacetate (18·5 g.) was added during 10 min. Titration with standard hydrochloric acid (methyl-orange) showed 83% reaction in 1 hr. and 92·5% in 2 hr. The mixture, after hydrolysis with aqueous sodium hydroxide solution and steam-distillation to remove butanol, on acidification, yielded an acidic black polymeric oil. Continuous extraction of this product with light petroleum gave the benzo-1 : 3-dioxole-2-carboxylic acid (3·8 g.) as large colourless plates, m. p. 109° (Found : C, 57·7; H, 3·6. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·6%). Burger *et al.* (*loc. cit.*) record m. p. 104—106°.

By a similar procedure, 5-*chlorobenzo*-1 : 3-*dioxole*-2-*carboxylic acid* (2·4 g.), from 4-chlorocatechol (14·45 g.), was isolated as colourless needles, m. p. 132—33° (from light petroleum) (Found : C, 48·0; H, 2·7%; equiv., 195. $C_8H_5O_4Cl$ requires C, 47·9; H, 2·5%; equiv., 200). Similarly 4 : 6-*dichlorobenzo*-1 : 3-*dioxole*-2-*carboxylic acid* (3·0 g.) was obtained from 3 : 5-dichlorocatechol (8·95 g.), as colourless needles, m. p. 149—149·5° (from light petroleum) (Found : C, 40·7; H, 1·7. $C_8H_4O_4Cl_2$ requires C, 40·9; H, 1·7%).

The unsubstituted acid (1·0 g.) in chlorobenzene (20 ml.) was treated with chlorine (0·45 g., 1 mole) at room temperature. After extraction from the mixture with sodium hydrogen carbonate solution, a crude dichloro-acid was isolated as a brown oily solid (0·9 g.). Repeated crystallisation gave the (? 5 : 6-)*dichlorobenzo*-1 : 3-*dioxole*-2-*carboxylic acid* as colourless needles, m. p. 145° (from ethyl acetate–light petroleum) (Found : C, 41·0; H, 1·8%). Mixed m. p. with the 4 : 6-dichloro-acid (*vide supra*) was 120—128°.

2 : 2-*Di*iso*butylbenzo*-1 : 3-*dioxole*.—Catechol (5·5 g.) and di*iso*butyl ketone (3·55 g.) were condensed in the presence of phosphoric oxide (7·5 g.), according to Slooff's method (*loc. cit.*). 2 : 2-*Di*iso*butylbenzo*-1 : 3-*dioxole* was isolated as a colourless oil (2·0 g.), b. p. 73—75°/0·5 mm., d_4^{18} 0·972 (Found : C, 76·6; H, 9·2. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

Attempted oxidation of this dioxole, or of the 2 : 2-dimethyl or 2-ethyl-2-methyl compound, with potassium permanganate in water or pyridine or with chromic oxide in acetic acid failed to yield dioxole-2-carboxylic acid.

Ethyl Bis-2 : 4-*dichlorophenoxyacetate*.—A solution of sodium 2 : 4-dichlorophenoxide, from the phenol (16·3 g.) and sodium (2·3 g.) in anhydrous ethanol, was added to ethyl dichloroacetate (31·4 g., 100% excess), and the mixture heated at reflux for 8 hr.; precipitation of sodium chloride was then complete. The mixture was worked up in the usual manner and the ethereal solution, after extraction of unchanged phenol, gave *ethyl bis*-2 : 4-*dichlorophenoxyacetate* (8·25 g.) finally isolated as slender colourless needles, m. p. 77°, from ethanol (Found : C, 47·0; H, 3·1. $C_{16}H_{12}O_4Cl_4$ requires C, 46·9; H, 3·0%). The ester was identified by hydrolysis to bis-2 : 4-dichlorophenoxyacetic acid, isolated as a potassium salt, m. p. 235° (decomp.), which on acidification gave the parent acid as colourless needles, m. p. 154° (Haskelberg, *J. Org. Chem.*, 1947, **12**, 426, records m. p. 152°). No half-condensation product, *i.e.*, ethyl α-chloro-2 : 4-dichlorophenoxyacetate, could be isolated from the original reaction.

meso-αα′-*Bis*-2 : 4-*dichlorophenoxysuccinic Acid*.—Methyl *meso*-dibromosuccinate (15·2 g.) was condensed with sodium 2 : 4-dichlorophenoxide, from dichlorophenol (16·3 g.), in the usual manner, meso-αα′-*bis*-2 : 4-*dichlorophenoxysuccinic acid* (8·5 g.) being obtained as colourless plates, m. p. 255° (decomp.; inserted in bath at 252° and losing water at the m. p.) (from aqueous ethanol) (Found : C, 43·5; H, 2·3. $C_{16}H_{10}O_6Cl_4$ requires C, 43·7; H, 2·3%).

Ethyl 2 : 4-*Dichlorophenyl Oxalate*.—Ethyl chloroglyoxylate (17 g.) in carbon tetrachloride (50 ml.) was stirred with 2 : 4-dichlorophenol (16·2 g.) in 2N-sodium hydroxide (75 ml.) containing some crushed ice. After 2 min. the carbon tetrachloride layer was separated, washed with ice-cold alkali, and dried ($MgSO_4$). After evaporation of the solvent, the *ester* distilled as a colourless oil (25 g.), b. p. 146—147°/2·5 mm. It crystallised as long colourless needles, m. p. 39°, from light petroleum (Found : C, 45·5; H, 3·0. $C_{10}H_8O_4Cl_2$ requires C, 45·7; H, 3·1%).

2 : 4-*Dichlorophenoxyacetone*.—Monobromoacetone (27·4 g.) was added to a hot solution of sodium 2 : 4-dichlorophenoxide [from the phenol (32·6 g.) and sodium (4·6 g.)] in ethanol (200 ml.); precipitation of sodium bromide was complete in 2 hr. The unchanged phenol was removed by alkaline extraction, and the product isolated as a colourless liquid (25 g.), b. p. 120—124°/1·5 mm., which rapidly solidified. Recrystallisation gave 2 : 4-*dichlorophenoxyacetone* as colourless prisms, m. p. 57°, from light petroleum (Found : C, 49·2; H, 3·65. $C_9H_8O_2Cl_2$ requires C, 49·3; H, 3·7%). The 2 : 4-*dinitrophenylhydrazone* formed orange prisms, m. p. 155°, from alcohol (Found : C, 45·0; H, 2·9; N, 14·2. $C_{15}H_{12}O_5N_4Cl_2$ requires C, 45·1; H, 3·0; N, 14·0%).

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