ACTA CHEMICA SCANDINAVICA 7 (1953) 596–602

Synthetic Plant Hormones

IV. Preparation and Physiological Activity of some α-Phenoxy fatty Acids, especially Isobutyric Acids *

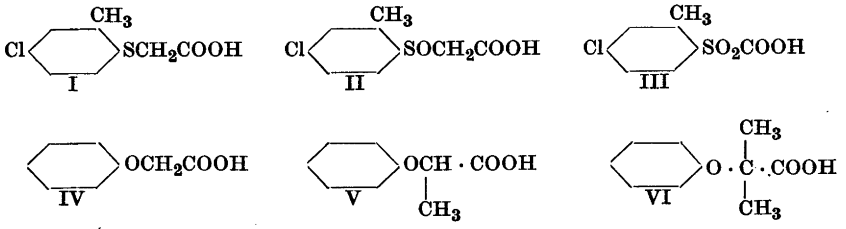
ÅKE JÖNSSON**

Organisk-kemiska Institutionen Kungl. Tekniska Högskolan, Stockholm, Sweden

Investigations of the growth promoting properties of 4-chloro-2-methylphenylsulphideacetic acid (I) and related compounds have shown that oxidation of (I) to the corresponding sulphoxide (II) does not cause any fundamental alteration in the auxin activity of the compound. However, the sulphone (III) was inactive. Using a somewhat different test, 2,4-dichlorophenylsulphideacetic acid was found to be active but both the oxidation products inactive [2].

It appeared possible that the lack of activity of the oxidised compounds might be due to a sterical blocking effect and a number of methyl substituted phenoxyacetic acids belonging to the α-phenoxypropionic and α-phenoxy*iso*-butyric acid series were therefore prepared for comparative studies of their auxin properties.

The physiological properties of these compounds have been investigated by Burström and Hansen [6] and are reported on in detail elsewhere. It was found that the phenoxyacetic (IV) and α-phenoxypropionic acid (V) derivatives



* Part III. *Acta Chem. Scand.* **6** (1950) 993.

** Bönnelyche & Thuröe AB Research Fellow 1950, 1951.

have an activity resembling that of 3-indoleacetic acid, causing inhibition of the cell elongation of wheat roots [2,3]. (Phenoxyacetic acid itself was inactive at concentrations up to 10^{-5} *M*. In a 10^{-4} *M* solution, however, it accelerated root growth.) The *α-phenoxyisobutyric acid* (VI) *derivatives strongly increased the cell elongation* [4,5]. For example, in 10^{-6} *M* solution *p*-chlorophenoxy*iso*butyric acid caused a cell (and root length) elongation of about 75 per cent [4]. Further, it was found that by using mixtures of *α-p*-chlorophenoxy*iso*butyric acid and 3-indoleacetic acid [4] or *α*-phenoxy*iso*butyric and D,L-*α*-phenoxypropionic acid [3] in suitable proportions *it was possible to alter the effect on cell elongation gradually from acceleration to inhibition.* The ratio of *α*-phenoxy*iso*butyric acid to D,L-*α*-phenoxypropionic acid which results in normal cell length was approximately 2.5 for all concentrations of the acids between 0 and 10^{-5} *M*. This indicates that phenoxy*iso*butyric acids act as true "auxin antagonists".

Table 1 summarises the results obtained with these and several other acetic acid derivatives. It appears that the introduction of *one* alkyl group into the

Table 1. Type of activity of some α-aryloxy fatty acids.

(+ = inhibits cell elongation
0 = inactive
− = accelerates cell elongation)

Acid	Type of activity	Acid	Type of activity
Phenoxyacetic acid	0[1]	*α*-Phenoxyisobutyric acid	−
p-Chloro-	+	*p*-Fluoro-	−
2.4-Dichloro-	+	*o*-Chloro-	−
2.4-Dimethyl-	+	*m*-Chloro-	−
		p-Chloro	−
D,L-*α*-Phenoxypropionic acid	+	2.4-Dichloro-	−
D,L-*p*-Chloro-	+	2.4.5-Trichloro-	−
D,L-2.4-Dichloro-	+	2.4.6-Trichloro-	−
D,L-2.4-Dimethyl-	+	2.3.4.5.6-Pentachloro-	−
		p-Bromo-	−
D,L-*α*-*p*-Chlorophenoxycaproic acid	+	*p*-Iodo-	−
		o-Methyl-	−
α-1-Naphtoxy*iso*butyric acid	−	2.4-Dimethyl-	−
α-2-Naphtoxy*iso*butyric acid	−	*p*-Amino-	0
		p-Acetamino-	0
		p-Carboxy-	0
*α-Cyclo*hexyloxy*iso*butyric acid	−	*p*-Nitro-	0

[1] In normal concentrations (up to 10^{-5} *M*). Accelerates root elongation in higher concentrations (10^{-4} *M*).

side chain of a nuclear substituted phenoxyacetic acid does not cause any reversal of the auxin activity, but that the introduction of a *gem*dimethyl group in general gives rise to compounds possessing antiauxin activity. A reservation must be made, according to Burström [3], for the possibility that several physiologically different activities are included in the general concept of "auxin activity".

Substituents in the nucleus merely modify the auxin or antiauxin activity of the parent compound and this substantiates the deduction that it is the structure of the side chain which is of paramount importance for producing the auxin or antiauxin effect. It is interesting to note that *α-cyclo*hexyloxy-*iso*butyric acid is a powerful auxin antagonist, or at least causes elongation [6] of root cells. No compounds, which does not contain at least one double bond in the nucleus has ever been found to exhibit auxin activity [7].

It would seem reasonable to assume that the *iso*butyric acids act by preventing indoleacetic acid or the auxinlike acids such as the phenoxyacetic acids or the α-phenoxypropionic acids from carrying out their normal function in the cell. The mechanism is quite obscure but it is attractive to assume that there is competition between the *iso*butyric acid and the acetic acid derivatives for an apoenzyme. Several other explanations of the effect, however, are possible.

Although the auxinlike properties of phenoxyacetic, propionic and *n*-butyric acids and related compounds, have been extensively studied in the past, the *iso*butyric acid analogues have received very little attention. Recently, however, Osborne and Wain reported that phenoxy*iso*butyric acids cause no growth responce in a number of standard tests for auxin activity [8,9]. Åberg [10] has investigated the activity of 1-naphthylmethylsulphide acetic, α(1-naphthylmethyl-sulphide) propionic and α-(1-naphthylmethyl-sulphide) *iso*butyric acid and the corresponding 2-naphthyl compounds and found, that they all antagonize 2,4-D. He has also found [11], that (+)-α-(2-naphthoxy)-propionic and (−)-α-(1-naphthoxy)propionic acid act like indole acetic acid in depressing root growth, whereas their enantiomorphs behave as auxin antagonists.

The phenoxyacetic, α-phenoxypropionic and α-phenoxycaproic acids were prepared *via* the ethyl esters in the usual way from the ethylesters of the α-chloro acids and the appropriate sodium phenolate.

The α-phenoxy *iso*butyric acids were prepared by a modification of Galimberti and Defrancheschi's [9] method from phenol, chloroform, acetone and sodium hydroxide using excess of acetone as solvent. Sometimes neutral, crystalline compounds were obtained as by-products. In a few cases they were isolated and found to be phenyl orthoformates.

2,4,6-Tribromophenol and 2,4,6-triiodophenol failed to react and these trihalogenated ethyl α-phenoxy*iso*butyrates could not be obtained by reacting ethyl α-bromo-*iso*butyrate with the dry sodium phenolates. This is obviously due to steric hindrance.

α-*p*-Aminophenoxy*iso*butyric acid was obtained by reduction of the nitro acid.

α-*p*-Bromophenoxy*iso*butyric acid was converted into its nitrile *via* the acid chloride and the amide.

EXPERIMENTAL *

Phenoxyacetic, α-phenoxypropionic and α-phenoxycaproic acids.

These acids were prepared by heating the dry sodium phenolate with an equimolecular amount of the ethyl ester of the halogenated aliphatic acid at 100° in a sealed tube for about twelve hours, followed by alkaline hydrolysis of the crude ester. With the exception of α-chlorophenoxy caproic acid they have all been reported earlier.

D,L-*α-p-chlorophenoxy caproic acid* forms colourless needles from petroleum ether: M.p. 74—75° C. (Found: Cl 14.5 %; equiv. weight 242.7 · $C_{12}H_{15}ClO_3$ requires: Cl 14.6 %; equiv. weight 243.6).

α-Aryloxy*iso*butyric acids

General procedure: Phenol (0.15 mole), sodium hydroxide (0.85 mole, pellets) and dry acetone (2.6 mole) were mixed in a three-necked flask equipped with a mechanical stirrer, a dropping funnel and a reflux condenser, and heated to boiling on a water bath. The bath was removed and chloroform (0.21 mole) was run in with stirring at such a speed that the mixture boiled gently. If the chloroform is added too rapidly the reaction may become uncontrollable. After the addition the mixture was heated under reflux with stirring for four hours. The excess acetone was destilled off, and the salt cake dissolved in water. The solution was filtered (in some instances solid, crystalline by-products remained on the filter) saturated with carbon dioxide, and extracted with ether to remove unreacted phenol. A stream of air was blown through the solution to remove dissolved ether and the acid was precipitated by acidification with dilute sulphuric acid. Most of the acids separate as crystallising oils in yields of 40—85 per cent of the theoretical. Analyses and melting points for the compounds not previously described are given in Table 2.

In the case of 2,4-dichloro- and 2,4-dimethylphenoxy*iso*butyric acids which have not been obtained crystalline the crude acid was dissolved in ether, the solution was dried and the acid was precipitated as its *cyclo*hexylamine salt by the addition of excess *cyclo*hexylamine.

Cyclohexylammoniumsalt: a) Of α-2,4-dichlorophenoxy*iso*butyric acid, M.p. 170—171° C. (Found N 4.02. $C_{16}H_{23}Cl_2NO_3$ requires N 4.02 %); b) Of α-2,4-dimethylphenoxy-*iso*butyric acid, M.p. 183—185° C. (Found C 69.8, H 9.49. $C_{18}H_{29}NO_3$ requires C 70.3, H 9.51 %.)

* All melting points uncorrected.

Table 2. Analytical data for some α-phenoxyisobutyric acids not previously described.

α-Phenoxy*iso*butyric acid	M.p. °C	Equiv. weight Found	Equiv. weight Calc.	Halogen Found	Halogen Calc.
o-Chloro-	73—74	215	214.6	16.6	16.5
m-Chloro-	58—59	216	214.6	16.4	16.5
2,4,5-Trichloro-	90—91	284	283.5	37.9	37.5
2,4,6-Trichloro-	68—70	284	283.5	37.7	37.5
2,3,4,5,6-Pentachloro-	142—143	353	352.3	50.5	50.3
p-Bromo-	132—133	259	259.0	30.7	30.9
p-Fluoro-	83—84	198	198.1	C 60.9 H 5.7	C 60.9 H 5.6
p-Iodo-	137—138	306	306.0	C 39.9 H 3.75	C 39.2 H 3.63

The neutral by-products were recrystallised from glacial acetic acid and formed long, thin needles.

Tri-o-chlorophenyl orthoformate, M.p. 129—130° C. (Found Cl 26.7 %; mol.weight 417 (Rast). $C_{19}H_{13}Cl_3O_3$ requires Cl 26.9 %; mol. weight 396.)

Tri-2,4-dichlorophenyl orthoformate, M.p. 201—202° C. (Found C 45.8; H 2.00; Cl 42.1 %; mol.weight 476 (Rast). $C_{19}H_{10}Cl_6O_3$ requires C 45.7; H 2.02; Cl 42.6 %; mol.weight 499.)

Tri-2,4,5-trichlorophenyl orthoformate, M.p. 230—231° C. (Found Cl 52.5 % mol. weight 583 (Rast). $C_{19}H_7Cl_9O_3$ requires Cl 53.0 % mol.weight 602.)

α-*p*-Carboxyphenoxy*iso*butyric acid

The methyl ester of this acid was prepared by the general procedure from methyl *p*-hydroxybenzoate and hydrolysed directly with aqueous sodium hydroxide. Prisms (from water). M.p. 170—171° C. (Found C 59.6, H 5.4 %; equiv.weight 112.1. $C_{11}H_{12}O_5$ requires C 58.9, H 5.4 %; equiv.weight 111.5.)

α-*p*-Aminophenoxy*iso*butyric acid

α-*p*-Nitrophenoxy*iso*butyric acid (22.5 g, 0.10 mole) was dissolved in a mixture of ammonia (50 ml) and water (50 ml) and reduced with ferrous hydroxide, prepared from $FeSO_4 \cdot 7H_2O$ (175 g) dissolved in water (400 ml) and precipitated with concentrated aqueous ammonia (100 ml). The reaction proceeds rapidly. The ferric hydroxide sludge was filtered off and washed thoroughly with dilute ammonia. The combined filtrate and washings were acidified with hydrochloric acid to pH 6. After cooling the crystalline precipitate was collected by filtration (11 g). Additional material was obtained by concentrating the mother liquor under reduced pressure. The total yield of sandy crystals was 15 g (77 %). M.p. 217—218° C (decomp.). Purification *via* the hydrochloride did not raise the melting point. (Found N 7.0 %, equiv.weight 195.1. $C_{10}H_{13}NO_3$ requires N 7.2 %, equiv.weight 196.3.)

N-Acetylderivative M.p. 169—170° C (from water). (Found N 5.9 %, equiv.weight 238.2. $C_{12}H_{15}NO_3$ requires N 5.9 %, equiv.weight 237.1.)

α-*p*-Bromophenoxy*iso*butyramide

α-*p*-Bromophenoxy*iso*butyric acid (26 g) was refluxed with thionylchloride (75 ml) for 2 hours on a water bath. The excess thionylchloride was distilled off, the last traces being removed in a vacuum. The residue in the flask was dissolved in dry benzene (100 ml) and saturated with dry ammonia. The precipitated ammonium chloride was filtered off and washed with benzene, and the combined filtrate and washings were evaporated to dryness, yielding a crystalline product (19.5 g) which was repeatedly recrystallised from chloroform-petroleum ether. M.p. 128° C. (Found Br 30.8 %. $C_{10}H_{12}BrNO_2$ requires Br 31.0 %.)

α-*p*-Bromophenoxy*iso*butyronitrile

α-*p*-Bromophenoxy*iso*butyramide (10.5 g) was refluxed with thionylchloride (50 ml) on a water bath for 1 hour. The excess thionylchloride was distilled off and the residue was poured on to ice. After some hours the oil was dissolved in ether, the solution washed with sodium bicarbonate solution and water, dried with potassium carbonate and fractionated under reduced pressure. Yield 6.9 g (71 %). Colourless oil. B.p. 131—132° C/10 mm (uncorrected). (Found Br 33.1 %. $C_{10}H_{10}Br$ NO requires Br 33.3 %.)

SUMMARY

Following our earlier studies on the auxin activity of aryl thiophenoxy acids and their "branched" oxidation products (sulphoxides and sulphones) a series of α-aryloxy-propionic and *iso*butyric acids have been prepared for a study of the effect of branching in the acetic acid section. As expected the compounds of the type D,L-aryl-$OCH(CH_3)COOH$ were shown to exhibit normal type of auxin activity (inhibition of root cell elongation), but those of the type aryl—$O—C(CH_3)_2COOH$ possessed marked antiauxin activity (acceleration of root cell elongation).

These studies have been supported by grants from the *P. Klason and W. Roos Funds.*

REFERENCES

1. Burström, H., Jönsson, Å., and Nilsson, G. *Acta Chem. Scand.* **6** (1952) 993.
2. Wilske, C., and Burström, H. *Physiol. Plantarum* **3** (1950) 58.
3. Burström, H. *Physiol. Plantarum* **4** (1951) 641.
4. Burström, H. *Physiol. Plantarum* **3** (1950) 277.
5. Burström, H. *Physiol. Plantarum* **4** (1951) 470.
6. Hansen, B. *Private communication.*

7. Thimann, K. V. in *Plant Growth Substances* edited by Skoog, F. University of Wisconsin Press 1951, p. 26.
8. Osborne, D. J., and Wain, R. L. *J. Hort. Sci.* **26** (1950) 60; *Science* **114** (1951) 92.
9. Wain, R. L. *J. Sci. Food Agr.* **2** (1950) 101.
10. Åberg, B. *Physiol. Plantarum* **4** (1951) 627.
11. Åberg, B. *Arkiv Kemi* **3** (1951) 549.
12. Galimberti, P., and Defrancheschi, A. *Gazz. chim. ital.* **77** (1947) 431; *Chem. Abstr.* **42** (1948) 3361i.

Received December 22, 1952.