The Relationship between the Constitution and the Effect of Chemical Compounds on Plant Growth

1. 2-PHENOXYETHYLAMINE DERIVATIVES

By R. L. JONES, T. P. METCALFE and W. A. SEXTON
Imperial Chemical Industries Limited, Dyestuffs Division, Research Laboratories, Blackley, Manchester

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The discovery of the selective herbicidal effect of the substituted phenoxyacetic acids (Slade, Templeman & Sexton, 1945; Templeman & Sexton, 1946*a*) has prompted a further investigation of related compounds, with particular regard to the origin and function of 3-indolylacetic acid in green plants. The auxins of green plants exist only to a limited extent in the free state, the greater portion being present either as complexes, possibly of a proteinaceous nature, or as physiologically inactive precursors. It is generally believed that 3-indolylacetic acid in green plants, as in bacteria, originates from tryptophan, and direct evidence of this has been provided by the finding of Wildman, Ferri & Bonner (1947) that infiltration of tryptophan to spinach leaves greatly increased the amount of ether-extractable 'auxin' in a few hours. Oxygen was required in this process, and there was evidence that a carbonyl compound was an intermediate metabolite. Infiltration of 3-indolylpyruvic acid produced the same effect, but this was not so with tryptamine. It appears to have been generally assumed, without much direct evidence, that the pathway from tryptophan to 3-indolylacetic acid is the same in plants as in bacteria, proceeding through 3-indolylpyruvic acid by the route indicated in Fig. 1. It is theoretically possible, however, that the first step might be decarboxylation to tryptamine, followed by enzymic conversion to 3-indolylacetic acid, perhaps via the aldehyde. It is also possible that more than one route may operate or that different plant species use different routes. Thus, although the experiments of Wildman *et al.* (1947) using spinach may be taken as evidence against the tryptamine route, it has been shown by Skoog (1937) that tryptamine can be converted by cut surfaces of *Avena* to a substance having auxin activity. Decarboxylation of amino-acids may be inferred to

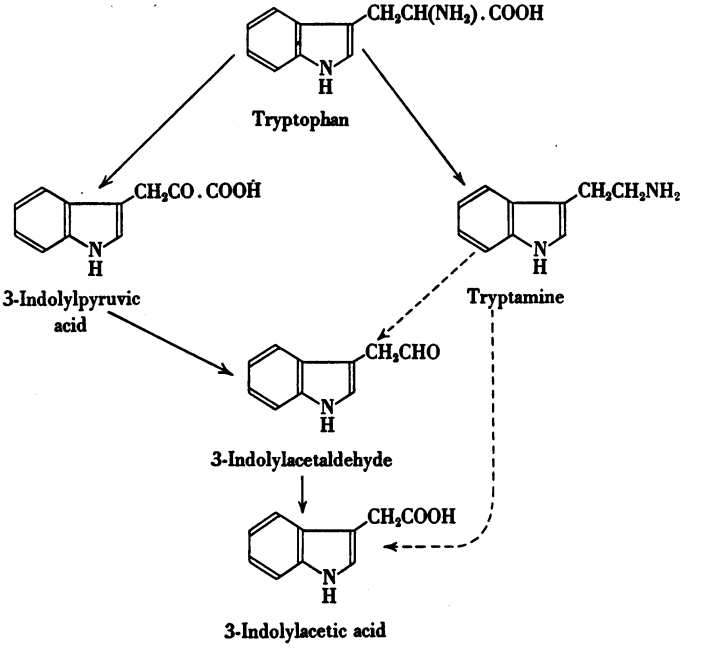


Fig. 1. Alternative pathways from tryptophan to β-indolylacetic acid.

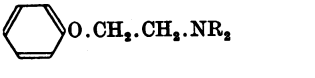
occur in plant tissue as several appropriately constituted amines have been recognized in the free state. Indeed, not only is the molecule of tryptamine discernible in such alkaloids as harmine, physostigmine and dipterine, but it has been found in the free state in certain *Acacia* species (White, 1944). From this it may be concluded that the tryptamine route to 3-indolylacetic acid is worth serious consideration, at least in certain plant species. Finally, it should be added that evidence for the occurrence in plants of 3-indolylacetaldehyde has been produced by Larsen (1944, 1947).

The work here described was based upon the following hypothesis. Plant growth is regulated, perhaps in part, through the maintenance of a critical level or concentration of 3-indolylacetic acid, and this level is maintained in a dynamic system by the balance of anabolic and catabolic processes. Degradation of 3-indolylacetic acid is known to occur in plants, for a degradative enzyme has been isolated from the pea epicotyl (Tang & Bonner, 1947). Any disturbance of this balance will result in hormonal dysfunction which may be revealed by such symptoms as epinasty, organ modification or cessation of growth. It follows from this hypothesis that the normal precursors of 3-indolylacetic acid may, by conversion to the latter compound, produce the same symptoms as 3-indolylacetic acid itself.

Tryptophan itself, although inactive by the *Avena* test for auxin (Link & Eggers, 1943) is, as stated above, convertible to auxin, and it inhibits root growth in cress (Audus & Quastel, 1947). 3-Indolylpyruvic acid is active in the *Avena* test (Kögl & Köstermans, 1935) and so, apparently, is 3-indolylacetaldehyde (Larsen, 1947). The work of Skoog (1937), already referred to, provides one piece of evidence for the conversion of tryptamine to 'auxin'. Our colleague, Dr A. Rhodes of Jealotts Hill Research Station, has found that tryptamine has a marked effect in reducing the root length of germinating cress and a much less marked effect on wheat. We have confirmed this observation (cf. also Audus & Quastel, 1947). Since certain substituted phenoxyacetic acids produce growth effects similar to those of 3-indolylacetic acid, we decided to study the problem further by moving from the indole series to the substituted 2-phenoxyethyl series, where syntheses are much more easy, and by employing the technique of seed germination.

METHODS

Preparation of compounds. The compounds selected for study were the substituted 2-phenoxyethylamines of the general formula



in which the benzene ring contained appropriate substituents and in which R was hydrogen or a hydrocarbon residue. The methods employed were conventional and are given here in outline only, details of the properties of the new compounds being given in Table 1, together with such analyses as were deemed desirable to check the purity of individual compounds or of a typical member of a series prepared by a general method.

The amines were made by interaction of the 2-phenoxyethylbromide with excess of NH_3 or the appropriate primary or secondary amine. When the latter was volatile, solutions in methanol under pressure were employed. In the case of 2-2′:4′-dichlorophenoxyethylamine a more convenient laboratory method was provided by the decomposition, by means of boiling ethanolic HCl, of the quaternary salt of the phenoxyethylbromide with hexamethylenetetramine.

Quaternary salts were prepared either by quaternization of the tertiary amines with alkyl halide or by reaction of the 2-phenoxyethylbromide with the appropriate tertiary amine. Quaternary salts of 2-phenoxyethylbromides with hexamethylenetetramine were obtained by reaction of the components in hot $CHCl_3$ solution, from which the crystalline salts separated.

Biological methods. The general requirement for this work was a rapid routine test method which would distinguish readily between active and inactive compounds without necessarily providing accurate quantitative data. Two plant species, rape and oats, were chosen as test objects, since the earlier work of Templeman & Sexton (1946*a*, *b*) had shown that several monocotyledonous species were susceptible to *iso*propyl phenylcarbamate, while some dicotyledonous species were generally the more susceptible to auxin-like herbicides, such as the substituted phenoxyacetic acids. The chosen seeds were oats (*Avena sativa*, var. White Winter) and rape (*Brassica campestris*, var. English Broad Leaved).

The seeds were allowed to germinate on agar slopes in 6 in. × ½ in. test tubes, each tube containing three rape seeds or two oat seeds. The number of tubes used was 12 for rape or oats at 100 p.p.m. and for rape at 50 p.p.m., 18 for rape at 10 p.p.m. or less and for oats at 50 p.p.m. or less. The tubes were mounted vertically in the dark at room temperature, and the root lengths measured when the rape roots were 5–6 cm. long (5–7 days) and the oats 6–7 cm. long (8–10 days). Seeds which failed to germinate were rejected, and the average root length ('average control length') of the remaining seeds was measured. With oats, the longest root produced by each seed was measured, since trial experiments had shown this to be reasonably proportionate to the combined lengths of all the roots. In the experimental tubes, the substance under test was incorporated with the agar at a concentration of 100 p.p.m. and greater dilutions were examined subsequently if necessary. The seeds were examined at the same time as the controls, and the effect of the chemical was assessed in the following way. Those substances which caused more than half the roots to be less than 50% of the average control length were characterized as 'very active' and are given two plus signs in the tables. If a substance failed to reduce half the roots to less than 50% of the average control length it was then reassessed on a basis of 80% of the average root length. If more than half the roots were reduced to 80% of the average control length, the substance was marked with one plus sign and characterized as 'active'. If it failed to reduce half the roots to 80% of the average control length, it was characterized as inactive (−).

Table 1. *New compounds synthesized*

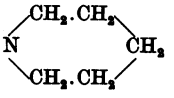
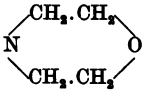
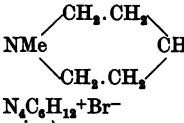
Formula	Physical characteristics	Analyses	Found (%)	Required (%)
$C_6H_5.O.CH_2.CH_2.NH_2$	Hydrochloride sinters at 180°, m.p. 210°	(Hydrochloride)	N, 8·0	8·05
p-$Cl.C_6H_4.O.CH_2.CH_2.NH_2$	Colourless oil, b.p. 152–156°/15 mm. Hydrochloride, m.p. 228°	(Hydrochloride)	N, 6·8	6·7
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NH_2$	Pale yellow oil, b.p. 174–176°/15 mm. Hydrochloride, m.p. 188–192°	(Base)	C, 46·8 H, 4·55	46·6 4·4
		(Hydrochloride)	Cl, 44·2 N, 5·8	43·8 5·8
1:3:4-$C_6H_3Me_2.O.CH_2.CH_2.NH_2$	Colourless oil, b.p. 140°/15 mm. Hydrochloride, m.p. 190°	(Hydrochloride)	N, 7·2	7·0
1:5:2-$C_6H_3MeCl.O.CH_2.CH_2.NH_2$	Colourless oil, b.p. 154–156°/15 mm. Hydrochloride, m.p. 162–164°	(Hydrochloride)	N, 6·3	6·3
2:4:5:1-$C_6H_2Cl_3.O.CH_2.CH_2.NH_2$	Colourless oil, b.p. 170°/15 mm. Hydrochloride, m.p. 237–239°	(Hydrochloride)	C, 35·2 H, 3·35	34·7 3·25
2-$C_{10}H_7.O.CH_2.CH_2.NH_2$	Hydrochloride chars at 260°	(Hydrochloride)	N, 6·5	6·3
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NHMe$	Colourless oil, b.p. 160°/15 mm.	(Hydrochloride)	N, 5·35	5·45
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2$	Colourless oil, b.p. 160–164°/12 mm. Hydrochloride hygroscopic	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NEt_2$	Liquid, b.p. 100°/0·15 mm. Hydrochloride, m.p. 127–128°	(Hydrochloride)	N, 4·5	4·7
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NHC_6H_5$	M.p. 42–44°. Hydrochloride decomposed by water, m.p. 137–140°	(Base)	C, 59·8 H, 4·8 N, 5·4	59·7 4·6 5·0
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMeC_6H_5$	Pale yellow viscous oil, b.p. 250–260°/15 mm. Insoluble in dilute HCl	—	Cl, 24·05	24·2
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.$ 	Pale yellow oil, b.p. 194–196°/15 mm. Hydrochloride, m.p. 158–160°	(Hydrochloride)	N, 4·8	4·5
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.$ 	Base: thick oil, b.p. 210–212°/15 mm. Hydrochloride, m.p. 86°	(Hydrochloride)	N, 4·45	4·5
$(2:4:1\text{-}C_6H_3Cl_2.O.CH_2.CH_2.)_2NH$	Hydrochloride, m.p. 183–185°	(Hydrochloride)	N, 3·25	3·2
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_3^+Br^-$	White crystals, m.p. 88–89°	—	C, 39·25	40·0
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2Et^+I^-$	M.p. 77–78°	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_2.CH_3^+Br^-$	M.p. 146–148°	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_3.CH_3^+Br^-$	M.p. 194°	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_5.CH_3^+Br^-$	M.p. 160–162°	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.NMe_2.(CH_2)_6.CH_3^+Br^-$	M.p. 160–162°	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_{11}.CH_3^+Br^-$	M.p. 120–124°	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NEt_3^+I^-$	—	—	—	—
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.$ 	M.p. 158–160°	—	C, 40·7 H, 4·45	40·4 4·8
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.N_4C_6H_{12}^+Br^-$ (from hexamethylenetetramine)	M.p. 164°	—	N, 13·8	13·7
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NC_5H_5^+Br^-$ (from pyridine)	M.p. indefinite (hygroscopic)	—	—	—
1:3:4-$C_6H_3Me_2.O.CH_2.CH_2.N_4C_6H_{12}^+Br^-$ (from hexamethylenetetramine)	M.p. 176–179°	—	—	—

Table 2. *Herbicidal activity of standard substances*

(The activities in Tables 2–5 are indicated by + and − signs as explained in the text, p. 144.)

. means not examined

Compound	Formula	Concentration (p.p.m.)	Activity: Rape	Activity: Oats
4-Chloro-2-methylphenoxyacetic acid	2:4:1-$C_6H_3MeCl.O.CH_2.COOH$	20	.	++
		10	.	+
		0·1	++	.
2:4-Dichlorophenoxyacetic acid	2:4:1-$C_6H_3Cl_2.O.CH_2.COOH$	0·1	++	.
2-Naphthoxyacetic acid	2-$C_{10}H_7.O.CH_2.COOH$	10	++	.
		1	++	.
*iso*Propyl phenylcarbamate	$C_6H_5.NH.COO.CHMe_2$	0·1	−	++
Tryptamine	$C_8H_6N.CH_2.CH_2.NH_2$	1·0	++	.

Basic substances were examined as their hydrochlorides, acidic substances as their Na salts, while the quaternary ammonium compounds were all neutral salts, freely soluble in water at the required concentrations. Using this method of assessment, results obtained with known herbicidal substances are given in Table 2, thereby establishing a reference standard.

RESULTS

Systematic Testing. The results of the examination of the various substances are given in Tables 3–5, which are arranged so as to emphasize relationships between structure and activity. All concentrations are expressed in parts/million (p.p.m.).

Table 3. *Effect of substitution in the benzene ring upon the herbicidal activity of 2-phenoxyethylamine*

Compound (R = $CH_2.CH_2.NH_2$)	Concentration (p.p.m.)	Activity: Rape	Activity: Oats
$C_6H_5.OR$	100	−	−
1:4-$C_6H_4(OR)_2$	10	++	−
	2	++	−
	0·1	−	−
2:4:1-$C_6H_3Cl_2.OR$	10	++	−
	2	++	−
	0·1	−	.
1:5:2-$C_6H_3MeCl.OR$	5	++	−
	1	++	−
	0·1	−	.
1:3:4-$C_6H_3Me_2.OR$	50	++	−
	10	+	−
2:4:5:1-$C_6H_3Cl_3.OR$	50	++	−
	10	−	.
2-$C_{10}H_7.OR$	10	++	−
	2	−	.
1-$C_{10}H_7.OR$	50	+	+
4:1-$C_6H_4NO_2.OR$	50	−	−

Preliminary investigations regarding mode of action. If the working hypothesis is correct, the activity of chlorinated 2-phenoxyethylamine against rape is to be attributed to its conversion to the corresponding chlorinated phenoxyacetic acid. This might conceivably be brought about through an amine oxidase similar to that found abundantly in animal sources and described by Blaschko, Richter & Schlossmann (1937), and which is inhibited competitively by *iso*propylamine derivatives of the type of ephedrine. Tryptamine is known to be a substrate for this enzyme. Accordingly, attempts were made to determine whether the activity of 2:4-dichlorophenoxyethylamine could be antagonized by ephedrine. Ephedrine itself was inactive on both species at 100 p.p.m. and at this strength it failed to antagonize the effect of 5 p.p.m. of 2:4-dichlorophenoxyethylamine.

Veldstra & Havinga (1943) have advocated the hypothesis that substances with an auxin-like activity must be constituted with a suitable nucleus (e.g. indole, naphthalene or substituted benzene) from which an acidic group projects at an angle to the plane of the nucleus. According to this hypothesis, growth regulation by the auxins is a function of the negative pole of the acidic group, which affects ionic transport. It might perhaps be expected then that a similarly constituted molecule, but with a positive instead of a negative pole, would act in a manner antagonistic to that of the naturally functioning auxin or auxin-like substance. Tests with mixtures of 2:4-dichlorophenoxyacetic acid and 2-2′:4′-dichlorophenoxyethylamine on rape, however, showed no evidence of antagonism.

In order to obtain further evidence for the hypothesis that the phenoxyethylamines functioned through conversion to the phenoxyacetic acids, certain substances were submitted in a qualitative way to the pea test for auxin activity. This test was conducted as described by Went & Thimann (1937), but since quantitative results were not required, visual inspection was substituted for measurement of angles of curvature. Solutions were examined at a range of concentrations, and the results are given in Table 6.

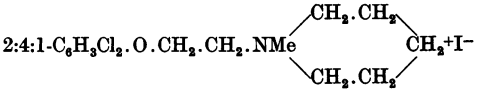
Table 4. *Effect of* N-*substitution* (*formation of secondary and tertiary amines*) *on the herbicidal activity of substituted* 2-*phenoxyacetic acids*

Compound	Concentration (p.p.m.)	Activity: Rape	Activity: Oats
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NH_2$	2	++	–
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NHMe$	50	++	–
	10	–	–
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2$	100	++	++
	50	++	+
	10	–	–
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NEt_2$	100	++	++
	50	–	+
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NH.C_6H_5$	100	++	+
	50	++	.
	10	+	.
	5	–	.
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe.C_6H_5$	100	++	–
	50	+	.
	10	+	.
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.N(CH_2.CH_2)_2CH_2$	100	++	++
	50	+	++
	20	–	.
	10	–	+
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.N(CH_2.CH_2)_2O$	50	++	++
	10	–	+
$(2:4:1\text{-}C_6H_3Cl_2.O.CH_2.CH_2.)_2NH$	50	++	++
	10	–	–
$C_6H_5.O.CH_2.CH_2.NH_2$	100	–	–
$C_6H_5.O.CH_2.CH_2.NH.C_6H_5$	100	+	+
$C_6H_5.O.CH_2.CH_2.NMe.C_6H_5$	100	–	+
2-$C_{10}H_7.O.CH_2.CH_2.NH_2$	10	++	–
	2	–	–
2-$C_{10}H_7.O.CH_2.CH_2.NH.C_6H_5$	100	–	+

DISCUSSION

Considering first the primary amines of Table 3, it is clear that those substituents in the benzene ring which favour activity against dicotyledonous species in the phenoxyacetic acid series (Templeman & Sexton, 1946*a*) also favour similar activity in the phenoxyethylamine series. The 4-chloro, 2:4-dichloro and 4-chloro-2-methyl derivatives were the most active of the compounds examined, the 2-naphthoxy compound was intermediate in activity, while the unsubstituted compound and the 4-nitro compound were inactive at the concentrations tested. In general, the amines did not appear to be quite as active as the corresponding acids. This finding constitutes evidence in favour of the hypothesis that these substances function in plant growth regulation through conversion to the phenoxyacetic acids. It has been demonstrated experimentally that they do not function as antagonists for the phenoxyacetic acids. Direct biochemical evidence for the hypothesis, however, is lacking. Blaschko *et al.* (1937) failed to find amine oxidase in certain green plants (seeds, tubers and leaves), but it does not follow from this that the enzyme is absent from germinating rape seed. It is possible, however, that a different enzyme system may be responsible for the degradation of tryptamine or the phenoxyethylamines in green plants, and this would account for our failure to antagonize the effect of 2:4-dichlorophenoxyethylamine by the amine oxidase inhibitor, ephedrine. Furthermore, the antagonism experiment would involve the question of the cell permeability of ephedrine, about which nothing is known. The failure to antagonize the effects of 2:4-dichlorophenoxyethylamine in this manner does not therefore invalidate the hypothesis concerning its mode of action. Two further facts in support are to be noted. First, the activity of 2:4-dichlorophenoxyethylamine in the pea test is of a similar nature to that of 2:4-dichlorophenoxyacetic acid though it differs quantitatively. Secondly, a preliminary observation in the

Table 5. *Herbicidal activity of quaternary derivatives of substituted 2-phenoxyethylamines*

Compound	Concentration (p.p.m.)	Activity: Rape	Activity: Oats
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_3^+Br^-$	50	−	+
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2Et^+I^-$	50	+	+ +
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_2.CH_3^+Br^-$	50	+ +	+
	10	+	.
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_3.CH_3^+Br^-$	50	+ +	+
	10	+ +	.
	5	+	.
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_6.CH_3^+Br^-$	50	+ +	−
	10	+ +	.
	5	+	.
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NMe_2.(CH_2)_{11}.CH_3^+Br^-$	50	−	−
	50	+	+ +
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NEt_3^+I^-$	50	+ +	+ +
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.N_4C_6H_{12}^+Br^-$ (*a*)	50	+ +	+
	10	+ +	−
	5	+ +	.
2:4:1-$C_6H_3Cl_2.O.CH_2.CH_2.NC_5H_5^+Br^-$ (*b*)	20	+	+ +
	10	−	−
2:4:1-$C_6H_3Me_2.O.CH_2.CH_2.N_4C_6H_{12}^+Br^-$ (*a*)	50	+ +	+
	20	+ +	−
	10	−	.
p-$Cl.C_6H_4.O.CH_2.CH_2.N_4C_6H_{12}^+Br^-$ (*a*)	50	.	+ +
	10	+ +	.
2-$C_{10}H_7.O.CH_2.CH_2.N_4C_6H_{12}^+Br^-$ (*a*)	100	.	+
	50	+	.

(*a*) From hexamethylene tetramine.
(*b*) From pyridine.

field indicated a similar physiological response of growing buttercups to both the amine and the acid. Direct experiments on the conversion of the amine to the acid in plant tissue or by plant extracts have not yet been made.

Table 6. *Results of the pea test for auxin activity*

Compound	Concentration (p.p.m.)	Effect observed
2:4-Dichlorophenoxyacetic acid	1	Equal to 3-indolylacetic acid at 5 p.p.m.
2:4-Dichlorophenoxyethylamine	10	Equal to 3-indolylacetic acid at 1 p.p.m.
Quaternary compound of hexamethylenetetramine with 2:4-dichlorophenoxyethyl bromide	100	Equal to 3-indolylacetic acid at 5 p.p.m.

Turning now to the first three compounds in Table 4 it is seen that substitution of the amino hydrogen atoms by methyl groups decreases the activity towards rape and increases the susceptibility of oats. The fully methylated compound is apparently much more active against oats than is 2:4-dichlorophenoxyacetic acid. This can be interpreted in more than one way. The relative insusceptibility of oats to the phenoxyacetic acid or the primary phenoxyethylamines might be due to the failure of these compounds to penetrate in adequate amounts to the appropriate site of action; methylation might assist such penetration, thus causing the phenoxyacetic acid to be liberated at a place which would otherwise be inaccessible to this molecule. The oat plant can, of course, respond to the phenoxyacetic acids under appropriate circumstances, for they are active in the standard *Avena* coleoptile test for auxins. It is possible, though perhaps not very likely, that methylation has the reverse effect on permeability in rape, so that the activity against germinating rape seed is reduced. This question cannot be answered until much more is known of the permeability of different plant species and tissues to organic compounds. Another possibility is that the secondary and tertiary amines function by an entirely different mechanism in which the greater susceptibility of oats is inherent. On the whole, the results given in Table 4 show that with the secondary and tertiary amines generally, there is much less

difference in the susceptibility of the two species than with the primary amines. This caused us to take the further step of examining quaternary compounds.

Amongst the quaternary compounds of Table 5, the 2:4-dichloro series will be considered first. It can be seen that as the molecular weight in the series of *n*-alkyl compounds rises, the activity against rape increases to C_6 and C_7, but the C_{12} compound is inactive. This is the familiar peak effect in an homologous series which is found in many relationships between chemical constitution and biological activity. Against oats there appears to be a maximum at C_2, though the result with the C_6 compound is anomalous. In view of the possibility that these quaternary compounds may be functioning by a mechanism bearing no particular relation to the chlorinated phenoxy nucleus, a general investigation of the activity of quaternary salts is now in progress and will be reported separately.

The quaternary compounds of hexamethylenetetramine call for special comment. Such compounds are known to decompose in boiling neutral aqueous solution with generation of aldehydes according to an oxidation-reduction reaction which has recently been discussed by Angyal & Rassack (1948), and we have evidence of decomposition at room temperature. Attempts to convert the hexamethylenetetramine derivative of 2:4-dichlorophenoxyethyl bromide into the aldehyde met with mixed success. While boiling with water definitely gave rise to some aldehydic material, as judged by the formation of a bisulphite compound, the aldehyde itself could not be isolated and appears to be unstable; compare the instability of phenoxyacetaldehyde (Pomeranz, 1894).

Under acidic conditions these hexamethylenetetramine derivatives are decomposed to the primary amines. This reaction has been found to proceed well in the case of the 2:4-dichlorophenoxy derivatives. Thus it may be argued that the hexamethylenetetramine compounds are potential precursors of the phenoxyacetic acids in living systems. In accordance with this conception, both the 2-2′:4′-dichlorophenoxyethyl and 2-2′:4′-dimethylphenoxyethyl compounds of hexamethylenetetramine are active against rape at high dilution, and indeed the former has been shown to produce the characteristic response of the substituted phenoxyacetic acids with growing buttercups. It is possible therefore that these compounds owe their activity against oats to their quaternary structure, but that their high activity against rape is due to their conversion to the acids within the living organism.

(*Note added* 8 *April* 1949.) Since this paper was submitted for publication, confirmation of our hypothesis that indolylacetic acid can arise in plants from tryptophan either through indolylpyruvic acid or through tryptamine has been presented by Gordon & Nieva (1949). These authors have demonstrated the operation of the two alternative pathways in leaves of pineapple.

SUMMARY

1. The activity of substituted β-phenoxyethylamines against germinating oat and rape seed has been studied in the laboratory.

2. In the case of the primary amines, selective activity against rape is associated with the same benzene substituents as cause activity in the phenoxyacetic acid series.

3. Substitution in the amino group tends to alter the relative susceptibility of the two species, and there is evidence that the quaternary salt derivatives operate by a different mechanism.

4. Quaternary derivatives of appropriately substituted 2-phenoxyethyl bromides with hexamethylenetetramine are particularly active against rape.

5. The results are discussed in relation to a hypothesis that phenoxyethylamines are converted by the living plant to the phenoxyacetic acids.

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