Phytochemistry, 1976, Vol. 15, pp. 1421–1424 Pergamon Press. Printed in England.

INHIBITORS OF THE GEOTROPIC RESPONSE IN PLANTS: A CORRELATION OF MOLECULAR STRUCTURES

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(*Received* 17 *March* 1976)

Key Word Index—*Lepidium sativum*; Cruciferae; cress; root geotropism; auxin transport inhibitors; structure activity correlation.

Abstract—Selected compounds from several groups of chemicals known to affect the root geotropic response in plants have been assessed for their effects on both stem and root geotropism in cress seedlings in order to compare their relative activities. It is suggested that a class of compound which affects geotropism can be distinguished, and that the molecular requirements for its activity can be tentatively defined. It is suggested that an *ortho* carboxylic acid function attached to an aromatic ring, which is separated by a conjugated system of atoms from a second aromatic ring, is required for high activity. Substituents on the second aromatic ring increase activity if they assist in the achievement of a minimum molecular size.

INTRODUCTION

The existence of compounds which can eliminate the gravitational response in plants has long been known [1], and the possibility recognized that an understanding of the way these chemicals act might assist in the elucidation of the mechanism of the geotropic response [2].

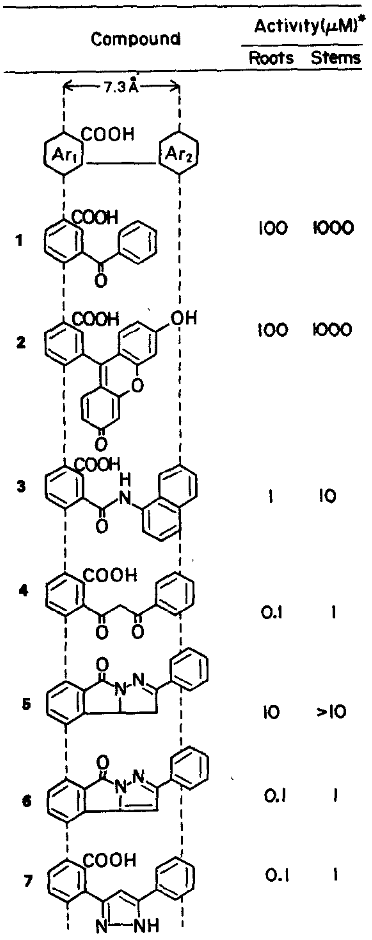
Comparison of the chemical structures of several highly active groups of compounds recently reported to affect geotropism [3–5] shows basic similarities between them, which suggests that they may act in the same way. Examination of other previously reported active compounds [1–17] also shows that at least some of them may have these same properties. Because of the different methods used to determine the effectiveness of the compounds, comparative activities between the series have been assessed by measuring the abilities of selected compounds to eliminate the geotropic response of the roots and shoots of cress seedlings.

RESULTS AND DISCUSSION

A large number of active compounds possess an *ortho* carboxyphenyl group attached by a linkage of atoms to a second aromatic ring. This is shown schematically in Fig. 1, and compounds will be discussed in terms of the diagram. Activities of other compounds of this type are shown in Tables 1–4.

The carboxylic acid function

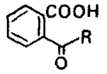
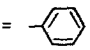
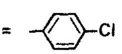
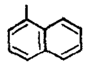
It has been shown that replacement of the carboxyl by hydrogen destroys activity and this is illustrated by compounds **1–7**, **3–7** and **4–7** in Tables 1, 3 and 4. Replacement by OH [9] as in **3–6** or placing the carboxylic function in positions other than *ortho* [9] also renders **3** inactive. Since esters [1], and pseudo esters [1,8] of **1**, e.g. **1–4**, **1–5** and esters [3,9] amides [3,9] imides [9,10] and anilides [3] of **3** and **4** retain activity as in **4–2** and **4–3**, it has been concluded that the free acid may well



*Minimum concentration causing complete loss of geotropic response.

Fig. 1. Root and stem antigeotropic activity on cress seedlings of compounds of different series.

Table 1. Root antigeotropic activity of benzoyl benzoic acids

Compound no.	Structure	Activity μM*	
			
1–1	R= 	100†	44‡
1–2	R= 	10†	3.8‡
1–3	R= 	1†	0.28‡
1–4	Methyl ester of **1–2**	100†	>36‡
1–5	Pseudo ester of **1–4**		36‡
1–6	2-Benzylbenzoic acid	>100†	>47‡
1–7	Diphenyl ketone	>100†	

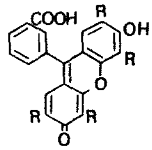
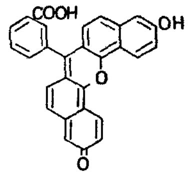
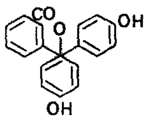
* Defined as in Fig. 1. † Present results. ‡ Calculated from ref. [7] measured on rape seedlings.

be the active form [1,3,5,9,10]. It has also been concluded that the active form of the pyrazolo *iso*-indolones is also the free acid **7** [4,5]. By similar reasoning the active form of the phenacylidene phthalide **4–8**, would be the free acid **4–1**. However, it is not known whether other acidic functions, e.g. sulphonic acid, nitramine, or isosteric groups, e.g. nitro, would be effective.

The aromatic ring Ar_1

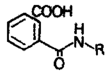
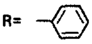
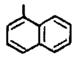
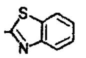
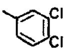
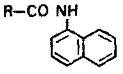
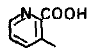
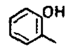
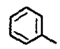
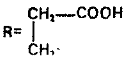
If the benzene ring is replaced by variety of non-aromatic groups, the activity is reduced at least one thousandfold [3,9]; examples of this are **3–8** and **4–9**. Replacement by pyridine [9] as in **3–5**, however, shows no decrease in activity, which suggests that other aromatic rings, as yet untried, may be similarly effective.

Table 2. Root antigeotropic activity of fluoresceins

Compound no.	Structure	Activity μM*	
			
2–1	R=H	100†	30‡
2–2	R=Br	1	15‡
2–3	R=I	1	
2–4		1§	
2–5		>100§	

* Defined as in Fig. 1. † Ref. [18]. ‡ Calculated from ref. [7]. § Present results.

Table 3. Root antigeotropic activity of aryl phthalamic acids and related compounds

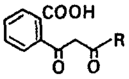
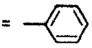
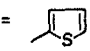
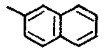
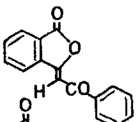
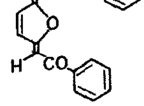
Compound no.	Structure	Activity μM*		
				
3–1	R= 	100†	100‡	10§
3–2	R= 	1	1	1
3–3	R= 		10	10
3–4	R= 	10	10	
				
3–5	R= 		1	
3–6	R= 		>100	
3–7	R= 		>100	
3–8	 $\mathrm{R}=\mathrm{CH_2{-}CH_2{-}COOH}$		>100	

* Defined as in Fig. 1. † Present results. ‡ Ref. [9] measured on lentils. § Ref. [10] measured on lentils.

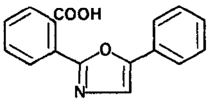
The aromatic ring Ar_2

The known active compounds have benzene, substituted benzene [3,5], naphthalene, pyridine, quinoline [9,10], benzothiazine [9] and thiophene [3] residues

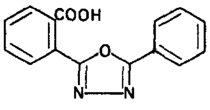
Table 4. Root antigeotropic activity of propanediones and related compounds

Compound no.	Structure	Activity μM*	
			
4–1	R= 	0.1†	0.04‡
4–2	Methyl ester of **4–1**	1†	3.5‡
4–3	*N*-methylanilide of **4–1**	10†	>2.7‡
4–4	R= 	1†	3.4‡
4–5	R= 	0.01§	
4–6	R = Me	>10†	>4.8‡
4–7	Dibenzoyl methane	>100†	
4–8		0.1†	0.04‡
4–9		>10†	>5.0‡

* Defined as in Fig. 1. † Present results. ‡ (Calculated) ref. [3]. § ref. [5].



8



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in this position, see compounds **4–4**, **4–5**, **3–3**, **3–4**. Replacing Ar_2 by aliphatic moieties, such as Me, butyl hexyl, etc., gives rise to inactive compounds [3,10], e.g. **4–6**. It is suggested, therefore, that this aromatic ring may be essential for activity.

Steric requirements.

Of the compounds unsubstituted on Ar_2, those that have a distance between the centres of their benzene rings of 7.3 Å as measured on Dreiding models, are the most active. Those where the distance is less than this, e.g. **1–1**, **2–1** and **3–1**, are significantly less active than those which fulfill the requirement, e.g. **1–3**, **2–4**, **3–2**, **4–1** and **7**. It is possible that this distance is a minimum requirement only, because derivatives of the *iso* indolones and propanediones where Ar_2 = naphthyl as in **4–5** retain activity [5]. This distance requirement is shown in Fig. 1. The effect of substituents can also be explained in steric terms. If their effect is to increase the molecular size up to the proposed minimum, then activity is increased, but if the molecule is already of that size, they have little effect. This would explain the greater activity of the substituted benzoyl benzoic acids over the parent compound [1], and the enhanced activities of eosin, erythrosin [1] and mercurorochrome [11] over the parent fluorescein, e.g. **1–1** and **1–2**; **2–1**, **2–2** and **2–3**. On the other hand, when the minimum size has already been reached, as in the propanediones **4** and diazines **7**, or, if the free acid is the active form, that the active form has reached this size, as in **5** and **6**, further substitution appears to have little effect [3,5]. This steric function of the substituents appears to be more important than their electronic properties.

In the phenyl phthalamic acid series, where the parent compound is below the minimum size, as in **3–1**, a large number of substituents, both electron donating and electron withdrawing, have been introduced on to the Ar_2 end of the molecule [9,10]. The general effect has been to increase activity [9,10] as in **3–4**, but when such substituents are placed on molecules already large enough, e.g. on 4, the general effect is to slightly reduce activity [3,5].

A further property desirable for optimum activity appears to be either conjugation or planarity between Ar_1 and Ar_2 [1,3,5]. While this requirement is as yet not well defined, it is consistent with *ortho* benzyl benzoic acid **1–6** being less active than the keto analogue **1–1**, and phenolphthalein **2–5**, being inactive, while the fluoresceins have significant activity. Reduced analogues of the propanedione **4** have also been found to be less active than the compound itself [3], and the unconjugated *iso* indolone **5** is one hundred times less active than its conjugated analogue **6**.

It is suggested therefore, that of the compounds known to affect the geotropic response, many can be classified and defined by a common set of chemical and physical parameters. The precise limits of these parameters are not yet known, and it may be that the most active compounds have yet to be discovered. It is noteworthy that some of the more active members have also been found to be potent inhibitors of auxin transport [4,13,14]. A common mechanism of action would imply that the other members of the class also have this property, and preliminary results indicate that this is indeed the case [18,19].

This correlation of structure is potentially useful because it enables the prediction of compounds which should be active. By way of example, it would be predicted that the oxazole and oxadiazole compounds **8** and **9**, recently patented as herbicides [20] should abolish root geotropism, as well as being potent inhibitors of auxin transport.*

EXPERIMENTAL

Geotropic assay. Seeds of cress (*Lepidium sativum*) were allowed to germinate on agar (0.75%) until the roots were 1 cm long. The seedlings were then transferred to the surface of agar containing the substance under test in a Petri dish. The dish was then placed on its edge such that the root tip pointed vertically upwards, and was kept in the dark at 24° for 24 hr. In untreated plants, the root tip turned downwards and the shoot grew upwards, the changes being apparent after 24 hr. With antigeotropic compounds the roots continued to grow vertically. When the gravitational response of shoots was destroyed they continued to grow downward. Each Petri dish contained four plants, and each assay was performed at least twice at each concentration starting at 100 μM and diluting tenfold until activity disappeared. Reproducibility of the assay was high.

Chemicals. The benzoyl benzoic acids were obtained by standard methods as described in ref. [7]. Fluoresceins were commercial samples except for the naphthofluorescein **2–4**, which was synthesised by the method of ref. [21]. Aryl phthalamic acids were made by standard methods [9,10]. Preparation of compounds in Table 4 [3] the *iso*indolones **5** and **6** [5] and the pyrazole **7** [5], have been previously described.

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* Note added in proof: The same authors now claim growth regulating activity for these compounds, and have included the thiazole and thiadiazole analogues as well. Amer. Pat. 3,947,263 (1976).

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