EXTENSION-GROWTH ACTIVITIES OF SOME *CYCLO*PROPANE DERIVATIVES, A NEW CLASS OF ANTIAUXIN

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Summary

2,3-Dihydrobenzofur-2,3-yleneacetic acid, 1,2-dihydro-1,2-naphthyleneacetic acid, and *cis*- and *trans*-2,3-dihydrothionaphthen-2,3-yleneacetic acid have been shown to competitively inhibit auxin-induced growth of *Avena* coleoptile sections, and thus are antiauxins. *trans*-2-Phenyl*cyclo*propanecarboxylic acid, 2,3-dihydrothionaphthen-2,3-yleneacetic acid dioxide, and 1,2-3,4-tetrahydronaphth-1,2-3,4-di(yleneacetic acid) were inactive towards coleoptile growth.

The structural difference between these antiauxins and related auxins is discussed with reference to structural requirements for antiauxin activity.

I. INTRODUCTION

The molecules of many substances possessing auxin activity contain the following structural features: (1) a ring system, (2) a double bond in a ring, (3) a side chain on one of the doubly bound carbon atoms, (4) an unsubstituted carbon atom *ortho* to the side chain, (5) a carboxyl group (or a structure equivalent to a carboxyl group) on this side chain, (6) a particular space relationship between the ring and the carboxyl group (Thimann 1951).

McRae and Bonner (1953) have shown that molecules lacking in one of the features (4), (5), or (6) above, but with all other features intact, will competitively inhibit auxin-induced extension growth and thus qualify for definition as antiauxins (Tukey *et al.* 1954). In this study, molecules in which the double bond requirement (2) is replaced by a *cyclo*propane ring are investigated for growth activity in the *Avena* section extension test. Other molecules, in which a double bond in the side chain of an auxin has been replaced by a *cyclo*propane ring, have also been investigated. The *cyclo*propane ring is a strained structure and, in this situation, is probably the closest structural approach to a double bond that can be made. Most of the *cyclo*propane derivatives used here have been synthesized by the addition of ethyl diazoacetate to carbon–carbon double bonds of heterocyclic systems (Badger *et al.* 1958; Badger, Rodda, and Sasse 1958); unfortunately no addition product is formed with indole and thus the *cyclo*propane analogue of 3-indolylacetic acid (IAA) could not be tested.

II. MATERIALS

Samples of the following compounds have been supplied by Professor G. M. Badger, University of Adelaide:

(I*a*) *cis*-2-phenyl*cyclo*propanecarboxylic acid, m.p. 105°C (lit., m.p. 105°C).

(I*b*) *trans*-2-phenyl*cyclo*propanecarboxylic acid, m.p. 88–90°C (lit., m.p. 91°C).

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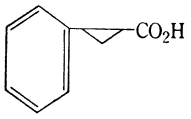
(II) 2,3-dihydrobenzofur-2,3-yleneacetic acid, m.p. 182°C (lit., m.p. 181°C).

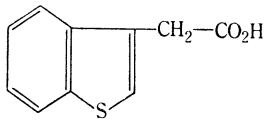
(III) 1,2-dihydro-1,2-naphthyleneacetic acid, m.p. 164°C (lit., m.p. 165–166°C).

(IV) 1,2-3,4-tetrahydronaphth-1,2-3,4-di(yleneacetic acid), m.p. 282°C (lit., m.p. 286°C).

(V) 3-thionaphthenylacetic acid, m.p. 108–110°C (lit., m.p. 109°C).



cis (Ia); trans (Ib)



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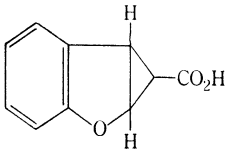

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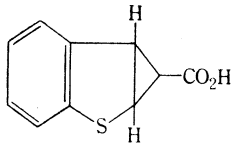
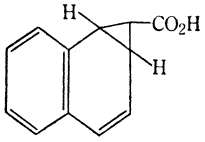


cis (VIa); trans (VIb)



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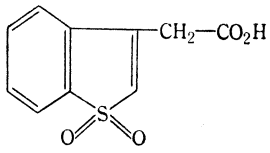

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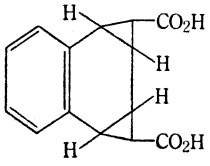

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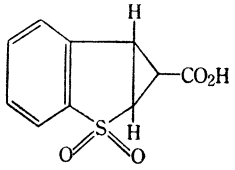

(VIII)

(VI*a*) *cis*-2,3-dihydrothionaphthen-2,3-yleneacetic acid, m.p. 182°C (lit., m.p. 182°C).

(VI*b*) *trans*-2,3-dihydrothionaphthen-2,3-yleneacetic acid, m.p. 145–148°C (lit., m.p. 148°C).

(VII) 3-thionaphthenylacetic acid dioxide, m.p. 265°C (lit., m.p. 267°C).

(VIII) 2,3-dihydrothionaphthen-2,3-yleneacetic acid dioxide, m.p. 241°C (lit., m.p. 241°C).

All samples were tested for homogeneity by paper chromatography in butanol–ammonium carbonate, using methyl red as indicator. Only *trans*-2-phenyl*cyclo*propanecarboxylic acid was slightly contaminated. The geometrical

configurations of the two 2,3-dihydrothionaphthen-2,3-yleneacetic acids have not been unequivocally proven. But Badger, Rodda, and Sasse (1958) present evidence for the acid, m.p. 148°C, being the *trans*-acid. In other cases the isomer present could not be specified, but all samples contained only one isomer.

III. Methods

Series of concentrations of the above substances were tested alone and in mixtures with a series of concentrations of IAA in the *Avena* coleoptile section extension test. The method of McRae and Bonner (1953) was followed except in the following details: in preliminary tests, the growth of 3-mm coleoptile sections

Table 1

AVENA COLEOPTILE SECTION EXTENSION IN SOLUTIONS OF THE TEST COMPOUNDS LISTED

Increments in section length are expressed as a percentage of the increment obtained in buffer plus sucrose alone. The latter increment was approximately 10 per cent. of the original length

Compound under Test (formula number)	Concentration (M):								
	3×10^{-7}	6×10^{-7}	10^{-6}	3×10^{-6}	5×10^{-6}	10^{-5}	3×10^{-5}	5×10^{-5}	10^{-4}
I*a*			100	140		220	320		290
I*b*			100	100		90	110		140
II	90		100	60		110	80		60
III	100		100	90		40	80		70
IV						100			100
V	110	130	160	230		430			
VI*a*			110			102			60
VI*b*	90		100	120		70	90		70
VII					90	110		85	100
VIII	80		120	120		120	120		120

over 20 hr was measured, and in tests for use in kinetic studies, 6-mm sections were grown for 10 hr, during which period growth was proportional to time. The methods for the treatment of results have also been fully described by McRae and Bonner (1953).

IV. Results

In Tables 1 and 2 are shown the results of preliminary tests to establish the general nature of the growth activity of the substances.

trans-2-Phenyl*cyclo*propanecarboxylic acid (I*b*), 2,3-dihydrothionaphthen-2,3-yleneacetic acid dioxide (VIII), and 1,2-3,4-tetrahydronaphth-1,2-3,4-di(yleneacetic acid) (IV) were found not to influence coleoptile section extension or the extra extension induced by added IAA. 3-Thionaphthenylacetic acid dioxide (VII) at 10^{-4}M slightly inhibited IAA-induced growth and it has been shown also to inhibit seed germination (Schlesinger and Mowry 1951). *cis*-2-Phenyl*cyclo*propanecarboxylic acid (I*a*) and 3-thionaphthenylacetic acid (V) promoted coleoptile section growth,

thus confirming previous claims (Crook, Davies, and Smith 1937; Veldstra and van de Westeringh 1951), based on other test tissues, that these substances were auxins.

2,3-Dihydrobenzofur-2,3-yleneacetic acid (II), 1,2-dihydro-1,2-naphthyleneacetic acid (III), and *cis*- and *trans*-2,3-dihydrothionaphthen-2,3-yleneacetic acid (VI*a* and VI*b*) were inactive alone (Table 1) and inhibited IAA-induced growth (Table 2). The four substances were then tested with IAA under the conditions required for the application of the kinetic treatment of McRae and Bonner (1953) to the growth results. As is shown in Figure 1, the criteria for competitive inhibition of IAA-induced growth were met for each substance. These substances can thus be called antiauxins.

TABLE 2

AVENA COLEOPTILE SECTION EXTENSION IN SOLUTIONS OF MIXTURES OF THE TEST COMPOUNDS LISTED AND IAA

Increments in section length are expressed as a percentage of the increment obtained in buffer plus sucrose and IAA of the appropriate concentration. In an optimal concentration of IAA the increment was approximately 800 per cent. of the increment in the absence of IAA

Compound under Test (10^{-4}M)	IAA Concentration (M):							
	5×10^{-8}	10^{-7}	2×10^{-7}	3×10^{-7}	5×10^{-7}	8×10^{-7}	10^{-6}	5×10^{-6}
I*b*	120		105		105			90
IV		95	100	100	105		95	90
VII		90	75		70	85	85	95
VIII	100			85	110			105

V. DISCUSSION

It has been shown that replacement of a double bond, adjacent to the side chain, in the auxins 1-naphthylacetic acid, 3-thionaphthenylacetic acid, and 3-benzfuranylacetic acid by a *cyclo*propane ring produces antiauxins (III, VI*a*, VI*b*, II). Of the two *cyclo*propane derivatives (IV, VIII) that did not exhibit antiauxin activity, one was not an analogue of an auxin (VII) and the growth activity of the other parent compound, 1,4-naphthyldiacetic acid, has not been investigated. If the replacement of the double bond by a *cyclo*propane ring had been the only structural change that had occurred, then another instance of the creation of antiauxins by the elimination of one structural feature essential for auxin activity could be added to those discussed by McRae and Bonner (1953). But in the *cyclo*propane derivatives, the carboxyl group was attached to a fused ring carbon atom rather than a side chain carbon atom and the *ortho* hydrogen atoms were not equivalent to those in the parent auxin molecules.

McRae and Bonner (1953) found that weak auxins could competitively inhibit IAA-induced growth, but there is no evidence for the substances II, III, VI*a*, or VI*b* being auxins (Table 1).

Some auxins such as *cis*-cinnamic acid have a double bond in the side chain. The replacement of this double bond by a *cyclo*propane ring produces another auxin, *cis*-2-phenyl*cyclo*propanecarboxylic acid, as has been demonstrated here for *Avena* sections and by Veldstra and van de Westeringh (1951) for split pea epicotyls.

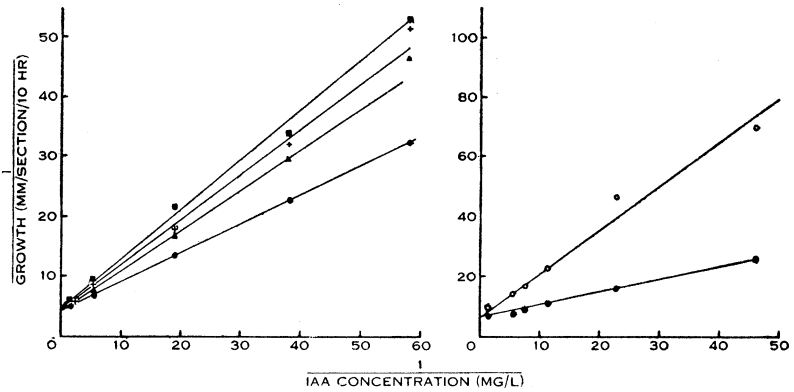

Fig. 1.—Inhibition of 3-indolylacetic acid (IAA)-induced *Avena* section growth by some *cyclo*propane derivatives. Data plotted according to Lineweaver-Burk treatment as a test for competitive inhibition, which requires intersection of the lines at the vertical axis. The greater the slope of the lines the greater has been the inhibition of IAA-induced growth. The treatments were:

- ● IAA alone.
- ▲ IAA plus 2,3-dihydrobenzofur-2,3-yleneacetic acid (II), 5×10^{-5}M.
- \+ IAA plus *trans*-2,3-dihydrothionaphthen-2,3-yleneacetic acid (VI*b*), 5×10^{-5}M.
- ■ IAA plus 1,2-dihydro-1,2-naphthyleneacetic acid (III), 2×10^{-5}M.
- ○ IAA plus *cis*-2,3-dihydrothionaphthen-2,3-yleneacetic acid (VI*a*), 2×10^{-4}M.

This result might suggest that, in a side chain, a double bond and a *cyclo*propane ring are equivalent. This is not supported by the finding that replacement of the double bond in the antiauxin *trans*-cinnamic acid by a *cyclo*propane ring produces the growth-inactive *trans*-2-phenyl*cyclo*propanecarboxylic acid.

VI. Acknowledgments

Thanks are due to Professor G. M. Badger, who, with his colleagues, synthesized the compounds. I am particularly grateful to Dr. Jenneth M. Sasse for checking the purity of the samples.

VII. References

Badger, G. M., Christie, B. J., Rodda, H. J., and Pryke, J. M. (1958).—Polynuclear heterocyclic systems. XIII. The reaction of ethyl diazoacetate with naphthalene and its heterocyclic analogues. *J. Chem. Soc.* **1958**: 1179–84.

Badger, G. M., Rodda, H. J., and Sasse, J. M. (1958).—The reaction of ethyl diazoacetate with thionaphthen. *J. Chem. Soc.* **1958**: 4777–9.

CROOK, E. M., DAVIES, W., and SMITH, N. E. (1937).—Synthetic plant growth hormones. *Nature* **139**: 154–5.

MCRAE, D. H., and BONNER, J. (1953).—Chemical structure and antiauxin activity. *Physiol. Plant.* **6**: 485–510.

SCHLESINGER, A. H., and MOWRY, D. T. (1951).—Benzothiophenes and their 1-dioxides. *J. Amer. Chem. Soc.* **73**: 2614–16.

THIMANN, K. V. (1951).—The synthetic auxins: relation between structure and activity. In "Plant Growth Substances." (Ed. F. Skoog.) (Univ. of Wisconsin Press.)

TUKEY, H. B., WENT, F. W., MUIR, R. M., and VAN OVERBEEK, J. (1954).—Nomenclature of chemical plant regulators. *Plant Physiol.* **29**: 307–8.

VELDSTRA, H., and VAN DE WESTERINGH, C. (1951).—Plant growth regulators XX. Structure-activity (5). 2-Phenylcyclopropane-1-carboxylic acids. *Rec. Trav. Chim. Pays-Bas* **70**: 1127–35.