Studies on Plant Growth Substances

Part XIII*. Plant Growth Activity of Substituted 1-Naphthoic Acid Derivatives**

By Koichi KOSHIMIZU, Toshio FUJITA, Tetsuo MITSUI
and Jiro KATO***

Department of Agricultural Chemistry, Kyoto University, Kyoto

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1-Naphthoic acid derivatives substituted with chlorine, bromine, methyl or nitro groups at various positions of the ring were assayed for their activities in the pea straight-growth and the callus formation tests. Their growth activities are discussed from two points of view, i.e. the spatial structure hypothesis of Veldstra and the *ortho* reaction hypothesis advanced for benzoic acid derivatives proposed by Hansch and Muir. It appears that a combination of these two views are appropriate for the present authors' results.

INTRODUCTION

The relationship between chemical structure and plant growth activity has not been investigated with substituted naphthoic acid derivatives so extensively as with the series of substituted benzoic acids¹⁾. It is reasonable expected that these two series of compounds, in which a carboxyl group is directly bound to the aromatic ring, are more or less similar to each other in their physical and chemical properties, — 1- (or 2-) naphthoic acids corresponding to 2,3- (or 3,4-) dialk(en)yl benzoic acids. Hence, studies of substituted naphthoic acids may contribute to the understanding of the structural requirement for growth promoting activity. From this viewpoint 1-naphthoic acid derivatives substituted with a chlorine, bromine, methyl or nitro group at various positions were prepared and growth activity was measured.

EXPERIMENTAL

Methods of bioassay

* Part XII by M. Inaba and T. Mitsui, This Bulletin, **20**, 42 (1956).

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*** Department of Botany, Kyoto Univ., Kyoto.

1) e.g. H. Veldstra, *Ann. Rev. Plant Physiol.*, **4**, 151 (1953).

Details of the methods of the pea straight-growth test and the callus formation test have previously been given^{2,3)}. The former is appropriate for testing weakly active growth substances.

Preparation of compounds*.

3-, 4- and 6-Nitro-1-naphthoic acids were prepared by the method of Leuck et al.⁴⁾. 3-Nitro acid, m.p. 267° (reported 270.5~271.5°⁴⁾). *Anal.* Found: C, 60.93; H, 3.53. Calcd. for C₁₁H₇O₄N: C, 60.83; H, 3.25. 4-Nitro acid, m.p. 223~224° (reported, 226°⁴⁾). *Anal.* Found: C, 60.71; H, 3.27. 6-Nitro acid, m.p. 223° (reported, 227~227.5°⁴⁾). *Anal.* Found: C, 60.54; H, 3.43.

5- and 8-Nitro-1-naphthoic acids; 1-Naphthoic acid was nitrated with concentrated nitric acid, and 5- and 8-nitro acids were separated from the mixture by recrystallization with alcohol⁵⁾. 5-Nitro acid, m.p. 239° (reported, 239°⁵⁾). *Anal.* Found: C, 60.73; H, 3.20. Calcd. for C₁₁H₇O₄N: C, 60.83; H, 3.25. 8-Nitro acid, m.p. 217° (reported, 215°⁵⁾). *Anal.* Found: C, 60.57; H, 3.18.

2-Chloro-1-naphthoic acid: 2-Hydroxy-1-naphthoic acid derived from 2-naphthol by means of the Kolbe-

2) J. Kato, *Mem. Coll. Sci. Univ. Kyoto*, **B 20**, 32 (1951).

3) J. Kato, *Physiol. Plant.*, **11**, 200 (1958).

* All melting points are uncorrected.

4) G. J. Leuck, R. P. Perkins and F. C. Whitmore, *J. Am. Chem. Soc.*, **51**, 1831 (1929).

5) A. G. Eckstrand, *J. Prakt. Chem.*, (2), **38**, 155, 241 (1888).

reaction⁶⁾ was treated with phosphorus pentachloride, and resulting chloro-naphthoic acid chloride was converted to the acid⁷⁾, m.p. 155~156° (reported, 152~153°⁷⁾, 154~155°⁸⁾). *Anal.* Found: C, 64.17; H, 3.69. Calcd. for $C_{11}H_7O_2Cl$: C, 63.94; H, 3.41.

3-, 4-, 5- and 6-Chloro-1-naphthoic acids were prepared according to the Sandmeyer-reaction from the corresponding amino acids obtained by reduction of the nitro acids⁹⁾. 3-Chloro acid, m.p. 221° (reported, 223°⁹⁾). *Anal.* Found: C, 63.76; H, 3.66; Cl, 17.08. Calcd. for $C_{11}H_7O_2Cl$: C, 63.94; H, 3.41; Cl, 17.17. 4-Chloro acid, m.p. 220~221° (reported 225°⁹⁾). *Anal.* Found: C, 64.07; H, 3.64; Cl, 16.96. 5-Chloro acid, m.p. 247° (reported, 245°⁹⁾). *Anal.* Found: C, 64.09; H, 3.40; Cl, 17.04. 6-Chloro acid, m.p. 213° (reported, 215.8~216.2°¹⁰⁾). *Anal.* Found: C, 63.89; H, 3.64.

3-, 4-, 5- and 6-Bromo-1-naphthoic acids were prepared from the amino acids, essentially in the same way as described above by means of the Sandmeyer-reaction. 3-Bromo acid, m.p. 231.5~232.5° (reported, 236°⁹⁾). *Anal.* Found: C, 52.56; H, 2.82; Br, 32.18. Calcd. for $C_{11}H_7O_2Br$: C, 52.62; H, 2.81; Br, 31.83. 4-Bromo acid, m.p. 220~221° (reported, 221°⁹⁾). *Anal.* Found: C, 52.70; H, 3.03. 5-Bromo acid, m.p. 256~257° (reported, 246°⁹⁾, 262°¹⁰⁾). *Anal.* Found: C, 52.55; H, 3.07. 6-Bromo acid, m.p. 183~184°. *Anal.* Found: C, 52.43; H, 2.83.

8-Chloro- and 8-bromo-1-naphthoic acids were prepared by treating with chlorine or bromine anhydro-8-hydroxymercuri-1-naphthoic acid¹¹⁾ obtained from naphthalic acid⁴⁾. 8-Chloro acid, m.p. 171~172° (reported, 170~170.5°¹¹⁾). *Anal.* Found: C, 63.63; H, 3.70; Cl, 17.07. Calcd. for $C_{11}H_7O_2Cl$: C, 63.94; H, 3.41; Cl, 17.17. 8-Bromo acid, m.p. 176~178° (reported, 176~179°¹¹⁾). *Anal.* Found: C, 52.83; H, 2.85; Br, 32.08. Calcd. for $C_{11}H_7O_2Br$: C, 52.62; H, 2.81; Br, 31.83.

2-Methyl-1-naphthoic acid was obtained by carbonation with carbon dioxide from 1-magnesium bromide derivative of 2-methylnaphthalene¹²⁾, m.p. 125~126° (reported, 126~127°¹²⁾). *Anal.* Found: C, 77.50; H, 5.61. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41.

3-Methyl-1-naphthoic acid; 3-Methyl-1-bromonaphthalene prepared according to Fischer et al.⁹⁾ was converted to 3-methyl-1-naphthoic acid in the same way as described above, m.p. 171~172° (reported, 171~172°⁹⁾). *Anal.* Found: C, 77.34; H, 5.58. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41.

4-Methyl-1-naphthoic acid was prepared in the same way as described in case of 2-methyl acid¹²⁾, m.p., 175~176° (reported, 175°¹²⁾). *Anal.* Found: C, 77.17; H, 5.65. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41.

6-Methyl-1-naphthoic acid was prepared by the reaction of α -furoic acid with toluene in the presence of anhydrous aluminum chloride¹³⁾, m.p. 176~177° (reported, 176.5~177°¹³⁾). *Anal.* Found: C, 77.66; H, 5.43. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41.

8-Methyl-1-naphthoic acid was prepared by the Clemmensen reduction of naphthaldehydic acid¹⁴⁾, m.p., 153° (reported, 153°¹⁴⁾). *Anal.* Found: C, 77.23; H, 6.60. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41.

RESULTS AND DISCUSSION

Activities of halogen (chlorine and bromine) substituted 1-naphthoic acids on the straight-growth of pea stem section are shown in Figs. 1 and 2. The growth activity is intensified by the substitution at positions of 2 or 8, whereas it is reduced by substitution at one of the other positions, 3- and 5-halogeno-acids being almost inactive. Essentially the same effects of halogen substitutions were also found in callus forming activity (Table I).

The order of methyl substituted 1-naphthoic acids with respect to their growth activities is similar to that of the halogeno-acid series (Fig. 3 and Table I). In this case, however, unlike 2-chloro-acid, 2-methyl acid is less active than the parent acid. All the nitro acids are less active than the parent acid, as shown in Fig. 4 and Table I.

Veldstra et al.^{1,15,16)} have affirmed that the essential requirements for a growth promoting substance are as follows: (a) the HL-balance

6) Am. Pat. 2,132,357; *Chem. Zentr.*, **1938**, II, 4312.

7) H. Rabe, *Ber.*, **22**, 392 (1889).

8) H. Veldstra, *Rec. Trav. Chim.*, **71**, 15 (1952).

9) A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer and J. Vaughan, *J. Chem. Soc.*, **1958**, 1426.

10) T. L. Jacobs, S. Winstein, R. B. Henderson, J. Bond, J. W. Ralls, D. Seymour and W. H. Florsheim, *J. Org. Chem.*, **11**, 229 (1946).

11) F. C. Whitmore and A. L. Fox, *J. Am. Chem. Soc.*, **51**, 3363 (1929).

12) F. Mayer and A. Sieglitz, *Ber.*, **55**, 1835 (1922).

13) C. C. Price, E. C. Chapin, A. Goldman, E. Krebs and H. M. Shafer, *J. Am. Chem. Soc.*, **63**, 1857 (1941).

14) R. C. Fuson and G. Munn, *J. Am. Chem. Soc.*, **71**, 1870 (1949).

15) H. Veldstra, *Enzymologia*, **11**, 97, 137 (1944).

16) H. Veldstra and H. L. Booij, *Biochim. Biophys. Acta*, **3**, 278 (1949).

FIG. 1. Activity of Chloro-1-Naphthoic Acids in the Straight-Growth of Pea Stem Section

Each point in Figs. 1~4 is the average of two runs of experiments, 10 section pieces being used for each lot in each run.

FIG. 2. Activity of Bromo-1-Naphthoic Acids in the Straight-Growth of Pea Stem Section

between the basal lipophilic ring system and the hydrophilic substituent such as the carboxyl group and, (b) definite spatial position of the hydrophilic substituent in relation to the ring system. From this viewpoint Veldstra^{8,17)} has

17) H. Veldstra, "The chemistry and mode of action of plant growth substances", Butterworths Scientific Publications, London, 1956, p. 117.

stated that the activities of substituted benzoic acids are dependent on a non-flat structure caused by the *ortho* substituent of such a size that the carboxyl group is not masked out. On the same basis he has considered that the weak activity of 1-naphthoic acid is attributable to a structure in which the carboxyl group is slightly

TABLE I. CALLUS FORMING ACTIVITY OF 1 PER CENT LANOLIN PASTE OF SUBSTITUTED 1-NAPHTHOIC ACID DERIVATIVES AND OF INDOLE-3-ACETIC ACID, DECAPITATED EPICOTYLE OF *Vicia Faba* L. BEING THE TEST OBJECT

Compound	Activity*	Compound	Activity*
1-Naphthoic acid	+	3-Nitro-	Inactive
2-Chloro-	+++	4-Nitro-	±
3-Chloro-	Inactive	5-Nitro-	Inactive
4-Chloro-	±	8-Nitro-	±
5-Chloro-	Inactive	2-Methyl-	+
6-Chloro-	+	3-Methyl-	Inactive
8-Chloro-	+++	4-Methyl-	Inactive
3-Bromo-	Inactive	6-Methyl-	Inactive
4-Bromo-	±	8-Methyl-	++
5-Bromo-	Inactive	Indole-3-acetic acid	++
6-Bromo-	+		
8-Bromo-	+++		

* Order of activity: +++, ++, +, ±.

hindered by the spatial influence of the *peri* position, and that the enhanced activities of 2-chloro-, 8-halogeno- (chloro-, bromo- and iodo-) and 8-methyl acids result from the carboxyl group being twisted more strongly by the influence of the neighbouring bulky substituent¹⁷⁾.

The present results concerning the activities of 2-chloro-, 8-halogeno- and 8-methyl-acids are in good agreement with the experimental results reported by Veldstra in spite of the different test methods. The fact that the 3-, 4-, 5- and

6-substituted halogeno- and methyl-acids are less active than the parent 1-naphthoic acid may be explained by shifts in the HL-balance, and the enhancement of the activity by the 2- and 8-substitutions may be due to the strong steric effect overcoming the suppressive effect of the shift in the HL-balance. It is, however, difficult to explain why 2-methyl acid shows a weaker activity than the parent acid, and also to point out what determines the order of activities of 3-, 4-, 5- and 6-substituted acids all of which seems to have the carboxyl group in a spatial relation similar to 1-naphthoic acid. It can be expected that the nitro substitution gives effects differing from halogen and methyl substitutions, because, by the firstnamed, the molecule becomes more lipophilic so as to make the HL-balance improper, and the carboxyl group may be less twisted in the 8-nitro acid than in the 8-halogeno- and 8-methyl acids according to the twist of the nitro group itself.

On the other hand, Muir and Hansch¹⁸⁻²⁰⁾ have advanced a hypothesis in concern of a definite chemical reaction between the auxin

18) R. M. Muir and C. Hansch, *Plant Physiol.*, **26**, 369 (1951).

19) C. Hansch, R. M. Muir and R. L. Metznerberg, *Plant Physiol.*, **26**, 812 (1951).

20) R. M. Muir and C. Hansch, *Plant Physiol.*, **28**, 218 (1953).

FIG. 3. Activity of Methyl-1-Naphthoic Acids in the Straight-Growth of Pea Stem Section

FIG. 4. Activity of Nitro-1-Naphthoic Acids in the Straight-Growth of Pea Stem Section

molecule and the cellular proteinous material. According to the above authors, at least one of the *ortho* positions of the ring to the point of attachment of the carboxyl group must be capable of reaction with an electron-rich plant substrate. Therefore, the *ortho* position must have a proper electron density and the group or atom at that position should be capable of displacement under conditions of reaction. Recently, Fukui, Nagata and Yonezawa²¹⁾ calculated the π -electron distribution of various benzoic acid derivatives by the application of a molecular orbital method, and found that a distinct parallelism exists between the indices of the reactivity at the *ortho* position and the growth activities of these compounds.

According to this hypothesis, the order of activities of the substituted acids as shown in Figs. 1, 2, 3 and 4 may reflect an order of electron density (or chemical reactivity) at a definite position of the naphthalene ring. Although the 2-position of 1-naphthoic acid, which corresponds to the *ortho* position of benzoic acid, may be capable of displacement by an electron-rich plant substrate, substitution of this position by a methyl group may lock up such a reaction.

This assumption may explain the fact that 2-methyl acid is less active than the 2-chloro-acid. Since, however, the 2-methyl acid has an activity which is only slightly lower than the parent acid, it should be admitted that the spatial requirement suggested by Veldstra, or some other unknown factors may have some effect on the activity of this acid. The relatively low activities of the nitro acid series may also be comprehended by the strong electron attracting property of the aromatic nitro group in contrast to the mesomeric electron releasing property of both halogen and methyl groups.

Thus, for the explanation of the experimental results reported above a combination of Veldstra's and Hansch-Muir's hypotheses appears to be required. In order to hold ground of the above discussions the authors have determined more precise molecular structures of the acids in question and are examining the chemical reactivity indices of definite positions of the naphthalene ring. The results will be reported elsewhere.

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21) K. Fukui, C. Nagata and T. Yonezawa, *J. Am. Chem. Soc.*, **80**, 2267 (1958).