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Some correlations of chemical constitution and plant hormone action

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NOTE TO USERS

SOME CORRELATIONS OF CHEMICAL CONSTITUTION AND PLANT HORMONE ACTION

by

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INTRODUCTION

Although the study of plant growth regulators is not a particularly new field of endeavor, this area of work has received its greatest attention during relatively recent years. Proof of this statement is realized when one considers that the number of publications on the subject has increased from fifty in 1930 to a few hundred in 1950.[1] Academic, governmental, and industrial groups all have contributed to this increased interest in the field.

The first attempts to determine the chemical nature of plant growth stimulators were made by Fitting [2,3] more than forty years ago. However, the chemistry of these substances received little further study for a number of years.

Today the available literature on the subject of plant growth substances has reached tremendous proportions. Some of the many general references, including books and review

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[1] F. Skoog, "Plant Growth Substances," University of Wisconsin Press, Madison, Wisconsin, 1951.

[2] H. Fitting, Z. Botan., 1, 1 (1909).

[3] H. Fitting, ibid., 2, 225 (1910).

articles, may be cited.[1,4,5,6,7,8,9,10,11,12,13,14,15,16] So great is the volume of the original literature, however, that no attempt has been made in most of the general works to include all the sources of original work which have contributed in one way or another to the over-all knowledge of plant growth substances. Because of the magnitude of the

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[4] F. W. Went and K. V. Thimann, "Phytohormones," The Macmillan Company, New York, N. Y., 1937.

[5] K. V. Thimann and J. Bonner, Physiol. Revs., 18, 524 (1938).

[6] F. A. Gilbert, Chem. Revs., 39, 199 (1946).

[7] K. V. Thimann in G. Pincus and K. V. Thimann, "The Hormones: Physiology, Chemistry, and Applications," Academic Press, Inc., New York, N. Y., 1948, Vol. 1, pp. 5, 75.

[8] A. G. Norman and R. L. Weintraub, Natl. Research Council, Natl. Acad. Sci., Washington, D. C., Chem.-Biol. Coordination Center, Pub. No. 206, 45 (1951).

[9] A. G. Norman, C. E. Minarik, and R. L. Weintraub, Ann. Rev. Plant Physiol., 1, 141 (1950).

[10] G. E. Blackman, W. G. Templeman, and D. J. Halliday, ibid., 2, 199 (1951).

[11] J. Bonner and R. S. Bandurski, ibid., 3, 59 (1952).

[12] J. van Overbeek, ibid., 3, 87 (1952).

[13] H. Veldstra, ibid., 4, 151 (1953).

[14] A. S. Crafts, ibid., 4, 253 (1953).

[15] V. H. Freed, J. Agr. Food Chem., 1, 47 (1953).

[16] R. L. Weintraub, ibid., 1, 250 (1953).

available literature, the present work will often contain references to general works rather than original works unless the original work has special significance in the discussion at hand. Very often the original work, though quite helpful, did not assume its present importance until later workers tied together the more or less isolated facts to give a somewhat integrated picture from a broader view. Certainly the present discussion is in no way meant to be complete, although emphasis will be placed on more recent developments which are of greatest interest from the point of view of the chemist.

The choice of compounds whose syntheses were carried out or attempted in the present work was based on the relationship of certain structural features of the desired compound to those of substances of known plant growth activity. The selection of compounds fell into three main categories. First, it was aimed to prepare some entirely new types which might be particularly effective. Second, some syntheses were carried out using models of known types but making alterations which were calculated to enhance appreciably the activity. Third, an examination was initiated of some types to throw light on the essentiality of some functional groups.

HISTORICAL

Types of Action and Test Methods

When a plant is treated with one of the many plant growth substances, it may respond in any one of a number of ways, or it may respond in several ways at the same time.[8,13] These responses may be observed as stimulation of cell elongation, initiation of roots, induction of parthenocarpy, modification of organs (formative effects), control of abscission or of bud development, and inhibition of root growth or of seed germination. As it is generally believed that stimulation of cell elongation represents the simplest morphological effect of the growth regulators, this type of action has been more extensively studied than have the other types.

When one compares the activities of different compounds, it is essential that the comparison be made of results obtained from the same test method. Failure to consider the type of response from which the results were taken can only lead to confusion, as the effects brought about by a group of compounds in one type of test may not parallel those observed in another test.

Furthermore, it is important to keep in mind in expressing the results of a given test method that the

quantitative response to a stimulating agent is described by an activity curve with a maximum, for the action at higher concentrations always becomes an inhibitory one. However, this maximal response is not attained by all compounds at the same concentration. Therefore, it is often desirable that the activities be measured at a series of concentrations in order to determine an activity curve. Sometimes it is more important to know relative activities than absolute activities; then it is particularly important that the tests be carried out under identical conditions.

Structural Requirements for Activity

A critical study of the structural features of a physiologically active compound may prove very fruitful from two points of view. In the first place, the study may lead to some interesting answers, or at least speculations, as to the mode of action. Secondly, such study is of great assistance in the search for a compound which has even more desirable characteristics to fill the needs of the problem at hand. Fortunately, compared to the situation which exists in most such studies, the compounds to be studied and the methods by which they are tested are relatively simple, and thus lend themselves to analysis rather nicely. However,

in spite of such encouragement, the present state of the study leaves much to be learned.

Following some earlier investigations[13] on the relation between structure and activity, Koepfli, Thimann, and Went[17] formulated the five structural requirements for stimulation of cell elongation which have become so well-known. These requirements consist of (a) a ring system as nucleus; (b) a double bond in this ring; (c) a side chain; (d) a carboxyl group (or a structure readily converted to a carboxyl group) on this side chain at least one carbon atom removed from the ring; and (e) a particular space relationship between the ring and the carboxyl group. Since the formulation of these requirements for activity, a large number of compounds have been tested, and the requirements have been restated in different forms.[8,18] The restatements had their basis in the fact that some compounds which met the requirements were inactive, whereas certain other compounds which failed to meet them were active.

In 1944 Veldstra[19] condensed the five requirements as set up by Koepfli and co-workers into two: (I) a basal

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[17] J. B. Koepfli, K. V. Thimann, and F. W. Went, J. Biol. Chem., 122, 763 (1938).

[18] L. J. Audus, Biol. Revs. Cambridge Phil. Soc., 24, 51 (1949).

[19] H. Veldstra, Enzymologia, 11, 97, 137 (1944).

ring system with high surface activity [(a) and (b) in the earlier theory]; and (II) a carboxyl group (or its dipole) in a very definite spatial position with respect to this ring system (out of its plane) [(c), (d), and (e) in the earlier theory].

A few years later Veldstra and Booij[20] restated the requirements as: (A) a basal ring system (nonpolar part) with high interface activity; and (B) a carboxyl group (polar part), in general a group of acidic character, in such a spatial position with respect to the ring system, that on adsorption of the active molecule to a boundary (the nonpolar part playing the most important role), this functional group will be situated as peripherally as possible. Requirement (A) was formulated on the basis of the behavior of most active compounds upon polarographic assay. Such assays indicated that the nuclear double bond probably played no part in a reversible oxidation-reduction process and that all highly active growth substances possess a high surface activity as measured by their suppression of the oxygen maximum. The basis for the formulation of requirement (B) was the fact that, along with other supporting evidence, cis-cinnamic

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[20] H. Veldstra and H. L. Booij, Biochim. et Biophys. Acta, 3, 278 (1949).

acid shows activity, whereas the isomeric trans form does not. Each of the bases for requirements (A) and (B) will be discussed individually.

In connection with requirement (A), it was believed, because highly active growth substances show high interfacial activity, that the ring system functions largely in the adsorption of the active molecule to the site of action.[13] Support of this view was given by the fact that known growth substances contain within the molecule a nonpolar (lipophilic) skeleton (L) carrying a polar (hydrophilic) carboxyl group (H). The amphipatic structure of low chemical reactivity which results from this asymmetric distribution of lipophilic and hydrophilic portions might well be expected to exert some action at such a phase boundary as a protein (enzyme) surface.

In order to study the accumulation of amphipatic substances at an interface, Paleg and Muir[21] carried out polarographic experiments simulating to some extent the primary active sites in the plant cell. In these experiments the accumulation of substances at the boundary between the rather nonpolar mercury droplet and the polar aqueous solution was studied through measurement of the extent of suppression of

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[21] L. G. Paleg and R. M. Muir, Plant Physiol., 27, 285 (1952).

the oxygen maximum. These studies showed that there was no correlation of surface activity as measured in this way with the activity of compounds as plant growth regulators.

However, although the polarographic method cannot be depended upon to distinguish between active and inactive compounds, an analysis of the results obtained by this method for a series of structurally related compounds of different growth activities shows without exception that the substances having the highest growth activity are the ones having the highest interfacial activity.[13]

Booij and Veldstra[22], in a search for a set of conditions more nearly equivalent to those present in biological structures, replaced the polarographic test with the interaction of growth substances with oleate micelles in an oleate coacervate. The results of the tests carried out in this manner indicated that the surface activity of the molecule of the substance most active in plant growth regulation is such that there is a definite balance between the hydrophilic carboxyl group and the lipophilic ring system. According to this theory, any upset of the optimal H/L balance results in decreased activity. If the side chain is made too hydrophilic, the compound will prefer the aqueous phase;

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[22]H. L. Booij and H. Veldstra, Biochim. et Biophys. Acta, 3, 260 (1949).

if the ring system is made too lipophilic, sites other than the primary ones will claim the molecule. An upset of the H/L balance in any other way would have the same effect. For example, the decrease in amphipatic nature resulting from replacing a benzene ring with a pyridine ring, or from introduction of a nuclear hydroxyl group, will lead to decreased growth activity if the original structure had an optimal H/L balance.

A comparison of the effect on the oleate coacervate of the series of normal fatty acids with that of growth substances (R-COOH) makes it possible to estimate the "aliphatic lipophily equivalent" of the various R residues.[13,23] In this way it was found that γ-indole-3-butyric acid, 1-naphthaleneacetic acid, and 2,4-dichlorophenoxyacetic acid were equivalent to octanoic acid; thus, one may say that the indole-3-propyl, 1-naphthylmethyl, and 2,4-dichlorophenoxymethyl groups correspond to the n-heptyl radical.[24] Of the compounds so far studied in the oleate coacervate, the R group of the active ones has been found to have a lipophily equivalent of C_5-C_8, with a maximum at C_7. However, the method does not differentiate, for instance, between the

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[23] H. L. Booij and H. G. Bungenberg de Jong, ibid., 3, 242 (1949).

[24] H. Veldstra, Bull. soc. chim. biol., 31, 594 (1949).

active 2,3,6-trichlorobenzoic acid and the inactive 2,4,6-trichlorobenzoic acid.[25]

Requirement (B) as given by Veldstra and Booij[20] was formulated on the basis of the great difference in plant growth activity exhibited by the isomeric cis- and trans-cinnamic acids.[19] Only the cis form is active; in fact, although the trans isomer is inactive as an auxin, it is effective in decreasing the growth response brought about by the cis isomer.[26] A study of molecular models indicates that, in contrast with the trans acid, the cis acid cannot assume a flat form because of steric hindrance involving the hydrogen atoms in the ortho positions. The trans isomer tends to take on a flat form because of conjugation effects.[27] The cis acid shows less activity in the oleate coacervate than does the trans isomer; Veldstra[13] concluded that the greater plant growth activity of the cis compound was due to its particular spatial structure. Similarly, cis-tetralideneacetic acid and cis-1-naphthaleneacrylic acid were found to be active, whereas their trans isomers are

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[25] H. Veldstra, Rec. trav. chim., 71, 15 (1952).

[26] J. van Overbeek, R. Blondeau, and V. Horne, Am. J. Botany, 38, 589 (1951).

[27] G. W. Wheland, "The Theory of Resonance," 3rd. ed., John Wiley and Sons, Inc., New York, N. Y., 1947, p. 92.

inactive.[13,19] Havinga and Nivard[28] showed by means of ultraviolet absorption spectra that the carboxyl groups of the acids probably are not in the plane of the rings.

The observed activity of 1,2,3,4-tetrahydro-1-naphthoic acid and cis-2-phenylcyclopropane-1-carboxylic acid lend further support to the three-dimensional amphipatic structure proposed as a requirement for activity.[13] The activity of 2,3,6-trichlorobenzoic acid[29] also supports this view, for ultraviolet spectra have shown that di-ortho substitution causes the carboxyl group to rotate out of the plane of the ring.[25] This, of course, does not account for the inactivity of 2,4,6-trichlorobenzoic acid.

Thimann[1] has raised the objection that on the basis of the three-dimensional amphipatic structure, one would expect a substance such as cis-cinnamic acid, with the carboxyl group fixed outside the plane of the ring, to have greater activity than a substance such as indoleacetic acid, in which the side chain is free to rotate into any one of numerous positions. Thus, the carboxyl group would spend less time in the desired position perpendicular to the ring in cis-cinnamic acid. However, Veldstra[13] has maintained

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[28] E. Havinga and R. J. F. Nivard, Rec. trav. chim., 67, 846 (1948).

[29] J. A. Bentley, Nature, 165, 449 (1950).

that the fact of the matter may be that the carboxyl group occupies the ideal position a fair share of the time when this group is not fixed; there may well be an attraction by the active sites in the cell to aid the carboxyl group in attaining this ideal position. Perhaps the flexibility of the group enables it to assume a position which is even more ideal than the position occupied by a group which is rigidly held outside the plane of the ring system.

Although an indole, naphthalene, or benzene ring constitutes the nucleus of the most active compounds, active substances are known with a wide variety of ring systems, among which should be mentioned cyclopentene, cyclohexene, anthracene, acenaphthene, fluorene, indene, indane, benzofuran, coumaran, and thianaphthene.[8] The activity of compounds containing these rings is greatly influenced, of course, by any ring substituents. It appears that the area of the naphthalene or indole ring system is most favorable; to some extent the area of certain substituted benzene rings seems to be equally favorable. Usually increasing or decreasing the size of the ring system results in decreased activity, which may be ascribed to an upset of the more nearly optimal H/L balance. When the -NH- group in the active indole-3-acetic acid is replaced with an oxygen atom or a methylene group, the resulting coumarone-3-acetic acid

or indene-3-acetic acid is found to have only 15% or 20%, respectively, of the activity of indole-3-acetic acid (pea test). Apparently, the -NH- group is highly desirable in this type of ring system. Pyridine-3-acetic acid is inactive; perhaps the introduction of lipophilic ring substituents would bring about activity.[13]

Thus far, unsaturation in the ring system has been found to be essential. It appears that when only one double bond is present, it must assume a position next to the side chain.[30]

Most growth substances have within the side chain a carboxyl group, or other group readily converted to carboxyl by chemical means, which is either attached directly to the ring or attached to the ring through such a link as the $-CH_2-$ or $-OCH_2-$ group. When there is more than one methylene group in the side chain, there is often an oscillation in the activity of the homologous compounds, depending upon whether there is an odd or even number of methylene groups.[3,13,17] In the naphthalene- and indoleacetic acid series, the compounds having an even number of carbon atoms in the side chain are more active than those having an odd number. Also, Synerholm

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[30] F. W. Went, Arch. Biochem., 20, 131 (1949).

and Zimmerman[31] found that with the 2,4-dichlorophenoxyalkanoic acids and 2-naphthoxyalkanoic acids, the propionic acids were inactive, whereas the acetic and butyric acids were active. They suggested that perhaps the higher homologues might be inactive as such, but that by β-oxidation the acids having an even number of carbon atoms might be converted to the active aryloxyacetic acids. Subsequent work[32] has given support to this view. On the other hand, β-oxidation of the acids having an odd number of carbon atoms would lead to unstable aryl carbonates.[31]

Substitution of a methyl group for one of the hydrogens in the alpha position of the acetic acid derivatives has relatively little effect, whereas replacement by a phenyl group often causes the acid to lose its activity. Substitution of both alpha hydrogens by organic radicals usually results in loss of activity. Perhaps the reduction or loss of activity brought about by these substitutions is caused by their preventing the molecule from assuming a satisfactory spatial configuration.[13]

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[31] M. E. Synerholm and P. W. Zimmerman, Contribs. Boyce Thompson Inst., 14, 369 (1947).

[32] C. H. Fawcett, J. M. A. Ingram, and R. L. Wain, Nature, 170, 887 (1952).

Types of Compounds Showing Activity

Aryloxyalkanoic acids and related compounds.- As the present work is primarily concerned with aryloxyalkanoic acids and some of their derivatives, or substances structurally similar, the discussion of these compounds will be given more consideration than will be given the other types of substances exhibiting physiological activity in plants.

So great has been the practical importance[33] of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) that the synthesis and testing of structurally related compounds has assumed vast proportions.[34,35] The results of these extensive tests have led to various theories regarding the structural requirements and mechanism of action of these compounds.

Phenoxyacetic acid, having no formative activity, may be thought of as having four sites of specificity: the ring, the ether oxygen, the methylene group, and the carboxyl group.[16]

In regard to nuclear substitution, replacement of hydrogen by halogen in certain positions gives rise to

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[33] R. H. Beatty, J. Agr. Food Chem., 1, 178 (1952).

[34] H. E. Thompson, C. P. Swanson, and A. G. Norman, Botan. Gaz., 107, 476 (1945).

[35] R. L. Weintraub, J. W. Brown, J. C. Nickerson, and K. N. Taylor, ibid., 113, 348 (1952).

compounds having growth activity. The introduction of substituents other than halogen has little or no activating effect on the molecule. Among the halogen substituents, fluorine and chlorine are approximately equal in their activating influence, bromine is less effective, and iodine is even less activating. Halogen substitution is most effective in the 4-, 2,4-, and 2,3,4- positions.[16] However, trihalogen substitution in which both the 2- and 6- positions are occupied results in loss of all activity.[36,37]

When the ether oxygen of 2,4-dichlorophenoxyacetic acid is replaced by nitrogen, the formative activity drops to about 1% of its former value; all formative activity is lost upon replacement by sulfur.[16] In a different test where the ether oxygen was replaced by sulfur, the sulfide showed weaker activity than 2,4-D; all activity was lost upon oxidation to the sulfoxide or sulfone.[13,38] There may be physiological significance in the fact that the sulfur atom in the sulfide has two unshared pairs of electrons, whereas

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[36] R. M. Muir, C. Hansch, and A. H. Gallup, Plant Physiol., 24, 359 (1949).

[37] M. E. Synerholm and P. W. Zimmerman, Contribs. Boyce Thompson Inst., 14, 91 (1945).

[38] C. Wilske and H. Burström, Physiol. Plantarum, 3, 58 (1950).

in the sulfoxide it has only one such pair, and in the sulfone it has no unshared electrons.

As was stated in the preceding section, replacement of one of the hydrogen atoms in the methylene group by a methyl radical has virtually no effect on the activity of 2,4-dichlorophenoxyacetic acid; replacement by an ethyl or larger radical produces a marked decrease in activity.[13,16] Replacement of both methylene hydrogens by methyl radicals results in an inactive compound. These facts indicate that perhaps the presence of an alpha-hydrogen is essential for activity. However, as was mentioned earlier, there is a distinct possibility that the reduction or loss of activity resulting from the substitution of organic radicals in the methylene group may be due to a steric hindrance which prevents the molecule from assuming the desired spatial configuration. Certainly the presence of an alpha-hydrogen is not a requirement for activity in all ring-type plant growth substances, for α-methylene-phenylacetic acid is as active as phenylacetic acid, and 2,3,6-trichlorobenzoic acid shows much activity.

A considerable amount of work has been done in an effort to determine, for practical and theoretical reasons, the effect of substituting various groups for carboxyl in the aryloxyalkanoic acids. The various functional

derivatives which have been studied include the ester, amide, anilide, ureide, hydrazide, nitrile, and acid chloride. Such derivatives do not necessarily have lower activity than the parent acid; in fact, the activity is sometimes greater. It is generally believed that they are hydrolyzed to the free acid, and that the free acid is the species which is directly responsible for the observed activity. However, in most instances there is no direct evidence to substantiate this view. Support for the argument that preliminary hydrolysis occurs is found in studies of the activities of optical isomers of a series of N-(2,4-dichlorophenoxyacetyl)amino acids.[16,39] In general, the D-isomers were found to be inactive, whereas the L-, or natural, isomers have about the same activity as 2,4-D. The DL-derivatives are about one-half as active as the L-isomers. This might be interpreted as an indication that cellular hydrolytic enzymes readily effect hydrolysis of the amide bond of the natural amino acids, but that a greater resistance of the unnatural forms to enzyme hydrolysis prevents their cleavage to give the active 2,4-D. On the other hand, if the argument raised by Thimann in regard to the observed activity of 1-naphthaleneacetamide is valid, and

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[39] J. W. Wood and T. D. Fontaine, J. Org. Chem., 17, 891 (1952).

if it may be carried over to amides of aryloxyacetic acids, there exists the possibility that such derivatives might be active as such, without the formation of the free acid.[1] This will be discussed further in the section dealing with the arylalkanoic acids.

Functional derivatives of 2,4-dichlorophenoxyacetic acid which can be converted to the free acid only through oxidation usually have much less formative activity than 2,4-D.[16] However, a root inhibition test showed 2,4-dichlorophenoxyethanol to have an activity of the same order of magnitude as that of the acid, although it was only slightly active in producing epinastic responses.[40] A study of a large number of substituted β-phenoxyethylamines as inhibitors for seed germination revealed that selective activity is associated with the same benzene substituents as produce activity in the phenoxyacetic acid series.[41] As a whole, however, the activities are lower than those in the acid series. Possibly the activity results through conversion of the amine to the acid. Quaternary derivatives of appropriately substituted 2-phenoxyethyl bromides with

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[40] R. B. Carroll, Contribs. Boyce Thompson Inst., 16, 409 (1952).

[41] R. L. Jones, T. P. Metcalfe, and W. A. Sexton, Biochem. J. (London), 45, 143 (1949).

hexamethylenetetramine are active as inhibitors of seed germination; possibly these compounds give rise to either aldehydes or amines in the process.[41]

Several mechanisms based on structure-activity relationships have been advanced in an effort to explain the primary reaction which leads to plant growth activity.[16]

On the basis of their work with mono-, di-, and trichlorophenoxyacetic acids, Leaper and Bishop[42] have suggested a mechanism in which the active phenoxyacetic acid is oxidized to a substituted quinone. According to this view, it is essential that there be two unsubstituted positions para to each other. (Previously other workers[36,43] had suggested that the requirements for activity as set up by Koepfli and co-workers[17] should include a free position ortho to the side chain.) In the course of plant metabolism the active compound might be oxidized to a quinone. The resulting quinone would then either take part directly in the oxidation-reduction systems that are generally associated with growth to effect the observed response, or be subjected to further degradative oxidation to give a

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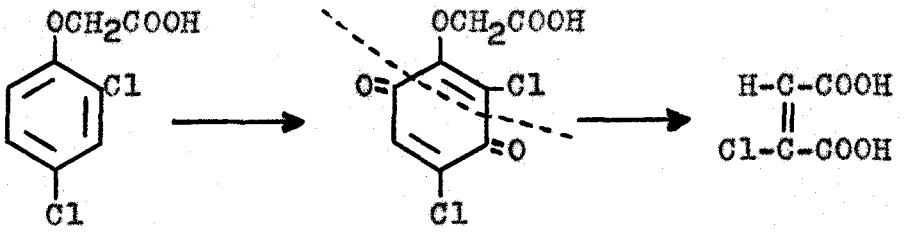
[42] J. M. F. Leaper and J. R. Bishop, Botan. Gaz., 112, 250 (1951).

[43] C. Hansch and R. M. Muir, Plant Physiol., 25, 389 (1950).

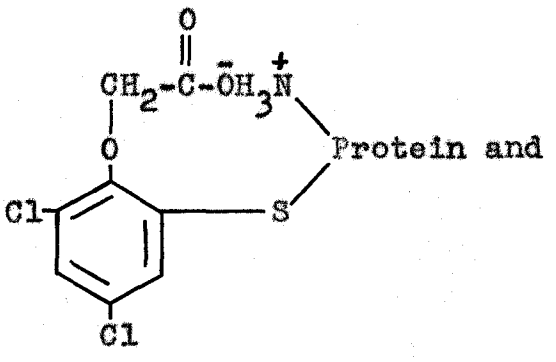
substituted maleic acid which would then act as the primary agent.



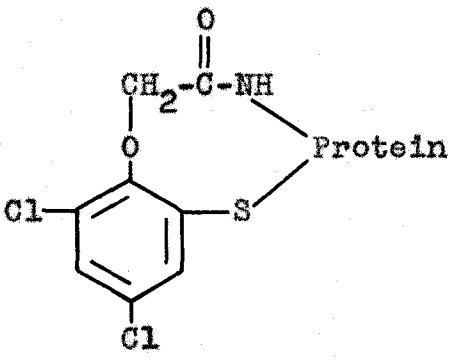
However, it appears unlikely that this mechanism offers a valid explanation, for appreciable formative activity is shown by a number of halogenated phenoxyacetic acids which do not have unsubstituted <u>para</u> positions. In disagreement with the mechanism is the observed activity of 2,3,4-trichloro-, 3,4,5-trichloro-, 4-chloro-3,5-dimethyl-, 2,3,6-trichloro-, 2,4,6-trichloro-, 2,3-dichloro-, and 2,6-dichlorophenoxyacetic acid.[16] Further evidence against this mechanism comes from the fact that no formative activity was shown by a number of quinones which were tested. Also, although chloromaleic acid itself has not been tested, the anhydride and hydrazide were found to be inactive.

A second mechanism has been postulated on the basis that an unsubstituted position <u>ortho</u> to the side chain is a requirement for activity.[36,43] In this mechanism there are two ways of explaining the inactivating effect of a

second ortho substituent.[16] This substituent may block a reaction at the ortho position itself, or it may prevent a reaction at the side chain through steric hindrance. Muir and co-workers[36,44] prefer the first explanation, for they believe that in active compounds a chemical reaction occurs at the ortho position. In addition, they believe that reaction occurs at the carboxyl group. According to this hypothesis, the compound first may react with an amino group of a protein substrate to give a substituted ammonium salt or a substituted amide. Subsequently reaction might occur at the ortho position with another part of the protein, such as a sulfhydryl group, to give a so-called cyclic ammonium salt or a cyclic amide. When 2,4-dichlorophenoxyacetic acid is the growth substance, these products may be designated as



and



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[44] R. M. Muir and C. Hansch, ibid., 26, 369 (1951).

However, this mechanism probably does not present the true picture, for some compounds substituted in both ortho positions do exhibit activity.[45] Furthermore, certain functional derivatives of some di-ortho-halogenated phenoxyacetic acids have relatively high activity. Muir and co-workers[36] have suggested that because the activity of 2,4,6-trimethylphenoxyacetic acid in cell elongation is not less than that of the unsubstituted phenoxyacetic acid, reaction of the substituted compound with the substrate may occur through a methyl group or by removal of a methyl group.

In regard to the general requirement that there be at least one hydrogen atom attached to the methylene carbon in phenoxyacetic acids,[13,16] it is important to bear in mind that when one of these hydrogens is substituted by an alkyl group, an asymmetric carbon atom results. Numerous studies have been made of the relative plant growth activity of the optical isomers formed because of this asymmetry.[13,46,47,48] These studies have indicated that there is a

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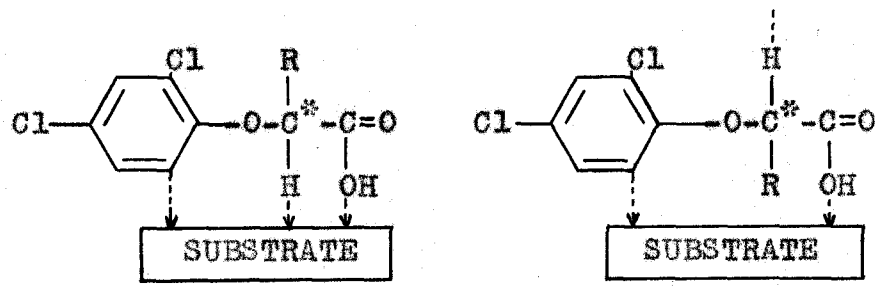
[45] K. V. Thimann, ibid., 27, 392 (1952).

[46] R. L. Wain, J. Sci. Food Agr., 2, 101 (1951).

[47] M. S. Smith and R. L. Wain, Proc. Roy. Soc. (London), B139, 118 (1951).

[48] M. S. Smith, R. L. Wain, and F. Wightman, Nature, 169, 883 (1952).

stereochemical specificity in the action of these compounds as plant growth substances. This has led to the formulation of a mechanism involving a three-point attachment of the growth regulator to the substrate.[16,47]



Active Inactive

However, Veldstra[13] contends that the stereochemical specificity emphasizes the importance of spatial configuration, as discussed earlier, rather than gives information about the nature of the contact between the growth substance and its receptor.

Arylalkanoic acids and related compounds.- The activity of phenylacetic acid is little affected by the replacement of one of the hydrogens in the methylene group with a methyl radical, whereas substitution of both hydrogens by methyl groups results in inactivation of the molecule.[17] These are the same results as were discussed earlier in regard to 2,4-dichlorophenoxyacetic acid. Substitution of both hydrogens by a methylene group, however, results in

little change of activity. Thimann's view that steric factors are probably responsible for these findings is supported by the observation that whereas DL-α-n-propyl- and α-allylphenylacetic acid are more active than the parent acid, the α-isopropyl compound is practically inactive.[49] To ascribe these observed results to changes in the lipophilly of the molecule is hardly justified, for studies of effects in the oleate coacervate show the isopropyl group to be of intermediate lipophilic character.[13]

Although 4-nitro- and 2,4-dinitrophenylacetic acid are inactive,[45] 2-nitrophenylacetic acid is as active as the parent acid, and the 3-isomer is even more active. 4-Bromophenylacetic acid is much more active than the non-halogenated compound. This indicates that 4-nitrophenylacetic acid owes its inactivity chiefly to the nature of the nitro group rather than to the 4-position which it occupies.

The introduction of a methyl group in the 4-position of cis-cinnamic acid has little effect on the activity, whereas the presence of chlorine in the 2- and 4-positions increases this activity. In the same range of concentrations 2- and 4-nitro-cis-cinnamic acid are inactive.[13] A

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[49] H. Veldstra and C. van de Westeringh, Rec. trav. chim., 70, 1113 (1951).

study of cis- and trans-1-phenylcyclopropane-2-carboxylic acid, related in a spatial sense to cis- and trans-cinnamic acid, revealed that, just as with the cinnamic acids, only the cis isomer is active.[50]

Because both naphthaleneacetic acids possess much activity, and in the event that the low activity or inactivity of some naphthalenepropionic and -butyric acids might be due to their rather great lipophilic character, a second carboxyl group was introduced in the side chain in order to see if the reduced lipophily would result in more active substances. However, such substitution led to inactive compounds.[13] When a double bond was introduced into the weakly active γ-(1-naphthalene)butyric acid to give γ-(1-naphthalene)-isocrotonic acid, related by vinylogy to 1-naphthaleneacetic acid, all activity was lost.[51] This loss of activity may have been the result of restriction of free rotation of the side chain.

In general, arylacetic acids of ring systems larger than that of naphthalene possess lower activity than do the naphthaleneacetic acids. Phenanthrene-2-acetic acid is inactive,

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[50] H. Veldstra and C. van de Westeringh, ibid., 70, 1127 (1951).

[51] C. Mentzer, Bull. soc. chim. biol., 30, 384 (1948).

its -3- isomer is very slightly active, and the -9- isomer is somewhat more active. Fluorene-9-acetic acid is inactive, and carbazole-9-acetic acid is very weakly active.[13]

A considerable amount of study has been made on the indole-3-alkanoic acids.[13] Alkyl substitution in the pyrrole nucleus of indole-3-acetic acid greatly reduces the activity; the activity is less sensitive to substitution in the benzene ring. Other work gives further support to the observation that substitution in the hetero ring brings about reduced activity; halogen substitution in the 4-, 5-, or 6-position causes only a slight decrease or even an increase in activity, whereas introduction of a substituent in the 7-position usually results in a much lower activity.[52,53,54] Findlay and Dougherty[55] found that introduction of a methoxyl group into the 5-, 6-, or 7-position of indole-3-acetic acid resulted in no loss of activity. On the other hand, the high activity of β-indole-3-propionic acid was

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[52] F. J. Stevens, J. Sci., 22, 79 (1947).

[53] F. J. Stevens and S. W. Fox, J. Am. Chem. Soc., 70, 2263 (1948).

[54] A. L. Hoffmann, S. W. Fox, and M. W. Bullock, J. Biol. Chem., 196, 437 (1952).

[55] S. P. Findlay and G. Dougherty, ibid., 183, 361 (1950).

lost upon substitution of a methoxyl group in the 5-, 6-, or 7-position.[17]

It is interesting to note that whereas lengthening of the side chain in the naphthalene series results in low activity, β-indole-3-propionic acid and γ-indole-3-butyric acid are highly active. The explanation has been advanced that perhaps the lipophilic character of indole-3-acetic acid is below maximal.[13] The complete inactivity of 2-carboxy derivatives of indole-3-alkanoic acids lends some support to this view.

Just as with the aryloxyalkanoic acids, the question arises as to whether certain functional derivatives of arylalkanoic acids are active as such or whether their activity depends on the formation of the free acid. Generally it is believed that conversion to the free acid is essential for activity, although usually there is no direct evidence for this. Salts are usually less active than the free acid. Methyl esters have about the same activity as the corresponding acid, whereas ethyl esters are usually less active. Although Kögl and Kostermans[56] believed the lower activity of the higher esters of indole-3-acetic acid to indicate that hydrolysis to the acid was a prerequisite

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[56] F. Kögl and D. G. F. R. Kostermans, Hoppe-Seyler's Z. physiol. Chem., 235, 201 (1935).

for the growth response, Thimann[1] takes a different view. He believes that hydrolysis is only necessary for transport of the substance and that, for primary activity, the ester is active as such. Also, Thimann believes that hydrolysis of amides is not a requirement for activity. His reasoning is based on the fact that although 1-naphthaleneacetamide possesses lower activity than the free acid, the curve relating activity and concentration of the amide is quite different than that of the acid. The two curves would be expected to be parallel if hydrolysis were involved. In addition, at the optimum concentration of the amide no trace of ammonia could be detected. Veldstra,[13] however, questions Thimann's conclusion in regard to the activity-concentration curves on the basis that they would be parallel only if the degree of conversion of amide to acid is independent of the concentration. Because the conversion occurs inside the cell rather than in the solution, and transport must take place, it is quite possible that the amount of acid formed varies with the concentration, thus giving a curve which differs from that of the acid. Veldstra further argues that the ammonia formed in the cell might not be detected, for it is not necessarily excreted into the solution.

A considerable amount of work has been done in an effort to determine the role of indole-3-acetaldehyde in

plant growth.[13,57] Until recently it was uncertain whether or not the aldehyde is active as such. However, in 1952 Brown, Henbest, and Jones[58,59] showed that the activity of this compound in the Avena straight growth test is equal to or less than that which would be expected from the amount of acidic material formed in the solution in the presence of coleoptile sections, indicating the aldehyde to be either inactive or inhibitory. Larsen[60] found the activity of 1-naphthaleneacetaldehyde in the Avena test to be about 11 per cent that of 1-naphthaleneacetic acid; phenylacetaldehyde was found to be 7.3 per cent as active as phenylacetic acid. There is some evidence that the aldehydes may undergo a Cannizzaro reaction to give the active acid and the inactive alcohol. On the other hand, differences in the activities of the neutral aldehydes and their corresponding acids may be due to differences in rate of penetration and distribution.[13]

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[57] P. Larsen, Ann. Rev. Plant Physiol., 2, 169 (1951).

[58] J. B. Brown, H. B. Henbest, and E. R. H. Jones, Nature, 169, 335 (1952).

[59] J. B. Brown, H. B. Henbest, and E. R. H. Jones, J. Chem. Soc., 3172 (1952).

[60] P. Larsen, Plant Physiol., 26, 697 (1951).

More study will be required before it can be stated with certainty whether or not conversion to acids is of great importance in determining the activity of certain nitriles.[13] Of considerable significance in this regard was the identification by Jones and co-workers[61] of the neutral compound from cabbage which is highly active in the Avena straight growth test as indole-3-acetonitrile. This finding disproved the belief of those who considered indole-3-acetaldehyde to be the only neutral growth-promoting substance present in plant extracts.

Both indole-3-ethanol and 1-naphthaleneethanol are weakly active.[13] Indole-3-ethylamine shows a delayed action, and 2-(1-naphthalene)ethylamine shows distinct activity. It is quite possible that the activity of these alcohols and amines results through transformation to the corresponding acids.

Arylcarboxylic acids and related compounds.- Since the introduction of substituted benzoic acids into research on plant growth substances by Zimmerman and Hitchcock[62] in 1942, a great amount of study has been made of this type of

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[61] E. R. H. Jones, H. B. Henbest, G. F. Smith, and J. A. Bentley, Nature, 169, 485 (1952).

[62] P. W. Zimmerman and A. E. Hitchcock, Contribs. Boyce Thompson Inst., 12, 321 (1942).

compound having a carboxyl group attached directly to the ring.[13] These studies have shown that the hydrophilic hydroxyl and amino groups do not give activity to the benzoic acids, whereas activity may result upon introduction of the lipophilic chloro, bromo, iodo, and methyl substituents. The effect of the nitro group depends upon its position in the ring, the greatest influence usually being shown by the substituent in the 3-position. Although activity is shown by certain ortho substituted benzoic acids, di-ortho substitution results in greater activity, provided the group is no larger than chlorine or methyl. The 2,3,6-trisubstituted acids are even more active. Substitution in the 4-position results in inactivity. These general effects of substitution are interesting, for they are very much in disagreement with the influences of similar substitution in the aryl- and aryloxyalkanoic acid series. Furthermore, for the most part, the activity of such compounds as 2,3,6-trichlorobenzoic acid is not accounted for by the theories which have been applied to the substituted alkanoic acids.

Muir and Hansch[44] extended the concept that growth activity depends on a chemical reaction at the position ortho to the side chain by assuming that in the arylcarboxylic acid series an electronegative ortho substituent such as chlorine takes part in the reaction with the

substrate. Some support for this view was found by Hansch, Muir, and Metzenberg,[63] who showed that the release of chloride ion accompanies the increased elongation of Avena coleoptile sections caused by 2,6-dichlorobenzoic acid. However, other workers[64] have questioned that this last evidence warrants the conclusion that the release of chloride ion is essentially associated with growth activity. Actually, chloride ion is released with the inactive 2,4-dichlorobenzoic acid. Also, the ortho reaction concept would lead one to expect the inactive 2,6-dibromobenzoic acid to be active. In addition, 2,6-dimethylbenzoic acid is very slightly active, 3-nitro-2,6-dimethylbenzoic acid is active, and 3-chloro-, 3-bromo-, and 3-iodo-2,6-dimethylbenzoic acid are highly active. These facts show it is unlikely that reaction occurs between the plant substrate and the inert ortho substituent to give the growth response.

Veldstra[13,25] believes that the ortho reaction concept breaks down, too, in that it does not take into account the fact that the ortho position is not the same distance from the reacting carboxyl group in the various classes of growth

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[63] C. Hansch, R. M. Muir, and R. L. Metzenberg, Jr., Plant Physiol., 26, 812 (1951).

[64] H. Veldstra and C. van de Westeringh, Rec. trav. chim., 71, 318 (1952).

substances. He contends that the active benzoic acids owe their activity to a much more specific property. Comparison of the ultraviolet absorption spectra of the active and inactive acids indicated that in active compounds substituted in the 2- and 6-positions, the di-ortho substitution suppresses the conjugation between the carboxyl group and the nucleus. Thus, whereas the carboxyl group in benzoic acid tends to be coplanar with the ring, the carboxyl group in the active benzoic acids is rotated out of the plane of the ring. Therefore, these acids assume, or are potentially able to assume, the same general spatial configuration as is characteristic of the aryl- and aryloxyalkanoic acids. In this way one can explain the activity of 1-naphthoic acid and its 1,4-dihydro and 1,2,3,4-tetrahydro derivatives. Similarly, the theory would predict 2-chloro-1-naphthoic acid to be more active than the non-halogenated acid; this prediction has been verified. However, the theory does not explain the inactivity of 2,4-dibromobenzoic acid. Therefore, the explanation has been offered[64] that perhaps the larger bromine atoms mask the carboxyl group, preventing it from carrying out its function. This same factor might account for the inactivity of 2,6-dimethoxybenzoic acid.

Veldstra[13,25] has concluded that the activity of the arylcarboxylic acids, just as that of the other plant growth substances, depends on a satisfactory H/L balance and a three-dimensional amphipatic structure. The fact that the activity of the active substituted benzoic acid, which results upon substitution of two lipophilic groups not larger than methyl or chlorine in the two ortho positions of benzoic acid, is increased upon introduction of a third group in the 3-position, indicates that the lipophily of the disubstituted compound is not sufficiently great. However, this does not explain the inactivity of 2,4,6-trichlorobenzoic acid. Apparently, unknown factors are in operation.

As with the aryl- and aryloxyalkanoic acids, derivatives of arylcarboxylic acids have received some attention as plant growth substances.[13] The activity of 2,3,6-trichlorobenzaldehyde has been reported over a range varying from very weak to greater than that of the corresponding acid. 2,6-Dichlorobenzaldehyde has been found inactive. There are indications that aryl aldehydes are not active as such, but only after conversion to the acid. Possibly their inherent activity is more of an inhibitory one. However, the problem is not settled. 1-(Hydroxymethyl)naphthalene and 1-(aminomethyl)naphthalene are inactive. On the other hand, 2,3,6-trichlorobenzyl alcohol has an activity of

the same order of magnitude as that of the corresponding acid. Of interest here is the activity of 1-(nitromethyl)-naphthalene; in its aci-form this compound has an acid group isosteric with a carboxyl.[19]

Other compounds.- A wide variety of active compounds are known which do not fit into any one of the three types of growth substances just discussed.[8,9,10,14,15,65] Many of them are best known as herbicides, some of which act through contact rather than by a true hormone mechanism. No attempt will be made to discuss these substances in this work.

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[65]D. E. Wolf, J. Agr. Food Chem., 1, 181 (1953).

EXPERIMENTAL

All melting points were determined in a copper block. All melting points and boiling points are uncorrected. Infrared spectra were taken of all new compounds and of some compounds previously reported. Thanks are due to Dr. V. A. Fassel and Messrs. M. Margoshes, R. Kross, and R. M. Hedges for taking and interpreting these spectra.

4-Chloroguaiacol.- In general, the procedure used for the preparation of this intermediate was that used by Frejka and co-workers[66] for the preparation of 4-chlorocatechol. To a solution of 101.5 g. (0.82 mole) of guaiacol in 200 ml. of dry ether in a 500-ml. three-necked flask equipped with stirrer, reflux condenser, dropping funnel, and nitrogen inlets was added, with stirring, 110.7 g. (0.82 mole) of sulfuryl chloride at a fast drip. The solution refluxed spontaneously during the addition. The sulfur dioxide and hydrogen chloride which were liberated were permitted to escape into a hood through a vacuum adapter placed in the nitrogen line. After the addition was completed, the yellow solution was stirred for 1 hour. Following distillation of the solvent in a nitrogen atmosphere, the product was

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[66] J. Frejka, B. Šefránek, and J. Zika, Collection Czechoslov. Chem. Commun., 9, 238 (1937).

distilled, also under nitrogen, to give 113.1 g. (87%) of a pale yellow, slightly turbid liquid boiling over the range 235-249°. This liquid was redistilled through a Vigreux column to give 96.7 g. (74%) of colorless product boiling at 75-82° (0.9-1.2 mm.), n^{31}_{D} 1.5556. The boiling point of 4-chloroguaiacol has been reported[67,68] previously to be 239-241.5° (757.7 mm.).

2-Methoxy-4-chlorophenoxyacetic acid.- This synthesis was carried out by the general method used by Hayes and Branch.[69] To 20.0 g. (0.50 mole) of sodium hydroxide dissolved in 100 ml. of water in a 250-ml. flask equipped with reflux condenser were added 40.0 g. (0.25 mole) of 4-chloroguaiacol and 23.6 g. (0.25 mole) of chloroacetic acid. The resulting light red solution was refluxed for 6 hours; the color of the solution became lighter during the period of refluxing. Upon cooling, the mixture became a nearly white solid mass. Upon transference to a beaker, 100 ml. of water was added, followed by the addition of 50 ml. of 1:1 hydrochloric acid. The mixture, acid to Congo Red, was

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[67] A. Peratoner and G. Ortoleva, Gazz. chim. ital., 28, I, 197 (1898) [Chem. Zentr., 69, I, 1054 (1898)].

[68] T. Jona and G. B. Pozzi, ibid., 41, I, 722 (1911) [C. A., 5, 3805 (1911)].

[69] N. V. Hayes and G. E. K. Branch, J. Am. Chem. Soc., 65, 1555 (1943).

extracted several times with a total of 1600 ml. of ether. The ethereal solution was extracted with 7500 ml. of 5% sodium carbonate, the sodium salt of the acid being only slightly soluble in the alkaline solution. Upon acidification of the alkaline solution with 1200 ml. of 1:1 hydrochloric acid, the free acid precipitated. Filtration gave 35.8 g. (66%) of nearly white solid melting at 134-140°. Recrystallization from 3000 ml. of water, with the aid of Norit, gave 29.4 g. (54%) of white platelets melting at 140-143°. Another recrystallization from 2500 ml. of water gave 27.2 g. (50%) of product melting at 141-143°.

Anal. Calcd. for $C_9H_9ClO_4$: Cl, 16.37; neut. equiv., 217. Found: Cl, 16.17, 16.33; neut. equiv., 218, 218.

In an earlier run purification of the acid by recrystallization from a 5:1 water-95% ethanol solution was attempted. This resulted in a marked lowering of the melting point and a broadening of the melting range, presumably because of slight esterification through interaction with the solvent.

2-Hydroxy-4-chlorophenoxyacetic acid.- Lederer[70] has reported the preferential cleavage of the unsubstituted methyl group in 2-methoxyphenoxyacetic acid, by treatment with hydrochloric acid or hydrobromic acid, to give 2-hydroxy-

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[70] L. Lederer, German Patent 108,241 [Chem. Zentr., 71, I, 1116 (1900)].

phenoxyacetic acid, the carboxymethyl group remaining intact.

Accordingly, a suspension of 2.17 g. (0.010 mole) of 2-methoxy-4-chlorophenoxyacetic acid in 100 ml. of concentrated hydrochloric acid (37-38%) was refluxed in a hood for 4 hours. A small amount of the solid did not dissolve in the refluxing solution. Upon cooling, white needles separated. Filtration through an acid-resistant filter paper gave 1.62 g. (75% recovery) of material melting at 127-133° with preliminary softening, identified as 2-methoxy-4-chlorophenoxyacetic acid by a mixed melting point.

Subsequent small-scale runs indicated that hydrobromic acid, under similar conditions, did effect cleavage of one of the ether linkages. Therefore, the cleavage by hydrobromic acid was repeated on a larger scale.

To 21.7 g. (0.10 mole) of 2-methoxy-4-chlorophenoxyacetic acid was added 150 ml. of 48% hydrobromic acid. (The hydrobromic acid had been distilled previously to give a nearly colorless solution boiling at 123-126°.) Upon heating, the organic acid dissolved. The solution was refluxed for 5 hours, during which time it darkened to a reddish brown. The white solid which separated from the solution on cooling was filtered through acid-resistant filter paper to give 15.6 g. (77%) of crude product melting

over the range 75-90°. Four recrystallizations from quantities of water varying from 100 to 200 ml. gave 11.3 g. (56%) of white crystals melting at 124-126°. It appeared that the solvent, perhaps as water of hydration, clung tenaciously to the crystals; for without rather prolonged drying over calcium chloride, the weight was too great and the melting point was far low.

A comparison of the infrared spectra of this product and the starting material used in its preparation indicated the presence of a phenolic hydroxyl group in the molecule of the product which was absent in the molecule of the starting compound.

Anal. Calcd. for $C_8H_7ClO_4$: Cl, 17.50. Found: Cl, 17.89, 17.84.

Lactone of 2-hydroxy-4-chlorophenoxyacetic acid.- A 15 x 125 mm. test tube containing 2.126 g. (0.01049 mole) of 2-hydroxy-4-chlorophenoxyacetic acid was heated for 1½ hours in an oil-bath maintained at 150-155°. A gas rose through the liquid as the material melted, and continued to be liberated during most of the heating period. A colorless liquid condensed near the top of the tube; the liquid at the bottom became yellowish orange. The tube was then placed in an oven at 105-110° for 2 hours, and finally allowed to cool and solidify in a desiccator containing calcium chloride.

The contents of the tube weighed 1.938 g., representing a 100.1% yield of the lactone, and melted at 58-61° with preliminary softening. This solid was digested with 50 ml. of petroleum ether (b.p. 60-70°) and filtered hot to remove 0.16 g. of undissolved tan solid melting at 114-119°, identified as 2-hydroxy-4-chlorophenoxyacetic acid by a mixed melting point. The filtrate was cooled, and from the cold solution was filtered 0.82 g. of white flakes melting at 63-65° with preliminary softening. Concentration of the mother liquor to about 10 ml., with subsequent cooling and filtering, gave an additional 0.56 g. of white flakes melting at 65-67°. This brought the total yield of recrystallized product to 71%. Another recrystallization of the second crop from 5 ml. of petroleum ether (b.p. 60-70°) raised the melting point to 67-69°.

Anal. Calcd. for $C_8H_5ClO_3$: Cl, 19.2. Found: Cl, 19.6, 19.5.

4-Chloro-o-phenylenedioxydiacetic acid (attempted).- The synthesis of this compound was attempted by a modification of the method[71,72] described earlier for the preparation of m-phenylenedioxydiacetic acid.

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[71] S. Gabriel, Ber., 12, 1639 (1879).

[72] J. V. Alphen, Rec. trav. chim., 46, 144 (1927).

To 1.58 g. (0.0078 mole) of 2-hydroxy-4-chlorophenoxyacetic acid was added 1.2 g. (0.031 mole) of sodium hydroxide dissolved in 10 ml. of water. The acid dissolved, giving a yellowish orange solution. Then 0.74 g. (0.0078 mole) of chloroacetic acid was added, and the mixture was heated over a free flame to concentrate it to a thin paste. Upon the dropwise addition of 1:1 hydrochloric acid to the warm paste, a firmer mass was formed. A total of 3 ml. of 1:1 hydrochloric acid and 20 ml. of water was added to give a white solid in a colorless solution having a pH of about 3. This solid was filtered to give 1.19 g. of material melting at 128-135° with preliminary softening; frothing of the material occurred at the melting point. A mixed melting point showed the material was not 2-hydroxy-4-chlorophenoxyacetic acid. Recrystallization from a small amount of water gave 0.40 g. of white solid which began to melt at about 128° with much preliminary softening. It appeared that a froth was gradually formed and remained until the temperature reached about 155°, at which time the froth settled to give a wet white solid which began to turn brown without melting at about 250°. No further work was done with this product.

3-Chloro-2-naphthoxyacetic acid.- This synthesis was carried out by the method used by Haskelberg[73] for preparing

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[73] L. Haskelberg, J. Org. Chem., 12, 426 (1947).

similar compounds from the corresponding phenol. Subsequent to its preparation as given here, James and Woodcock[74] reported the preparation of 3-chloro-2-naphthoxyacetic acid by essentially the same method.

To a cold solution of sodium ethoxide prepared from 60 ml. of absolute ethanol and 0.92 g. (0.040 g. atom) of sodium in a 250-ml. two-necked flask equipped with stirrer and reflux condenser fitted with a calcium chloride drying tube was added 7.2 g. (0.040 mole) of 3-chloro-2-naphthol (purchased from Chemicals Procurement Company). To the dark solution was added 6.7 g. (0.040 mole) of ethyl bromoacetate, and the mixture was refluxed with stirring for 2 hours. A solution of 5.6 g. (0.10 mole) of potassium hydroxide dissolved in 20 ml. of water was added, and refluxing and stirring were continued for 30 minutes. The slurry was dissolved in about 120 ml. of hot water; the resulting solution was acidified with 15 ml. of 1:1 hydrochloric acid, whereupon copious precipitation occurred. As the solid did not dissolve upon the addition of 100 ml. of hot water, the mixture was cooled and filtered to give 9.5 g. (100%) of gray solid melting at 175-180°. The solid was dissolved in a solution of 150 ml. of dioxane and 30 ml. of water, treated with Norit, and filtered hot. Water (560 ml.) was added to the hot solution to effect incipient cloudiness.

74P. M. James and D. Woodcock, J. Chem. Soc., 3418 (1951).

The mixture was cooled and filtered to give 7.8 g. (82%) of light tan solid melting at 182-184°. Another recrystallization from a solution of 60 ml. of dioxane and 80 ml. of water, with the aid of Norit, did not improve the purity of the product, probably largely due to the great tendency of the product to separate as an oil. Therefore, the product was recrystallized from a solution of 100 ml. of benzene and 10 ml. of dioxane to give 3.4 g. (36%) of white crystals melting at 183-185°.

Anal. Calcd. for $C_{12}H_9ClO_3$: C, 60.90; H, 3.83. Found: C, 61.08, 61.08; H, 3.95, 3.93.

James and Woodcock[74] reported the melting point of 3-chloro-2-naphthoxyacetic acid as 182-183°.

6-Bromo-2-naphthoxyacetic acid.- This compound was prepared by the method of Haskelberg[73] except that ethyl chloroacetate was substituted for ethyl bromoacetate.

In a 100-ml. flask equipped with reflux condenser and calcium chloride drying tube were placed 25 ml. of absolute ethanol and 0.69 g. (0.030 g. atom) of sodium. To the cold solution were added 6.7 g. (0.030 mole) of 6-bromo-2-naphthol (kindly provided by Dr. J. B. Campbell of E. I. du Pont de Nemours and Company) and 3.7 g. (0.030 mole) of ethyl chloroacetate. The mixture was heated, with occasional shaking, on a steam-bath for 1 hour. To the mixture was added 4.2 g. (0.075 mole) of potassium hydroxide dissolved

in 10 ml. of water. The resulting white paste was dissolved in 250 ml. of boiling water, and the free acid was precipitated by acidification of the hot solution with 20 ml. of 1:1 hydrochloric acid. From the cold solution was filtered 8.1 g. (96%) of slightly pink solid melting at 208-214° with preliminary softening. The solid was digested with 300 ml. of xylene and filtered hot, giving a slightly colored solid residue weighing 4.0 g. and melting at 223-228° with preliminary softening. From the cold filtrate was filtered 2.2 g. of slightly colored solid also melting at 223-228° with preliminary softening. As a mixed melting point indicated these two solids to be the same, they were combined and dissolved in 50 ml. of hot dioxane; the product was precipitated by the addition of 100 ml. of water to the hot solution. Filtration of the cold mixture gave 5.9 g. of slightly colored product melting at 225-228°. This solid was recrystallized by dissolving it in 50 ml. of hot dioxane and adding just sufficient water (50 ml.) to cause the formation of a precipitate. From the cold solution was filtered 5.8 g. (69%) of white solid melting at 226-229°.

Anal. Calcd. for $C_{12}H_9BrO_3$: C, 51.27; H, 3.23. Found: C, 51.05, 51.18; H, 3.32, 3.30.

Haskelberg[73] reported an 88% yield of 6-bromo-2-naphthoxyacetic acid melting at 210°.

In order to compare the preparation of the aryloxyacetic acid through its ester as given above with the direct preparation[69] employing a haloacetic acid, 6-bromo-2-naphthoxyacetic acid was synthesized by a second method.

To 6.7 g. (0.030 mole) of 6-bromo-2-naphthol and 2.8 g. (0.030 mole) of chloroacetic acid was added 2.4 g. (0.060 mole) of sodium hydroxide dissolved in 60 ml. of water. Most of the solid went into solution upon heating the mixture to the reflux temperature. The mixture was refluxed for 1 hour, copious precipitation occurring early in the reflux period. The mixture was then heated on a steam-bath for 2 hours. The resulting mixture was dissolved in 350 ml. of hot water; the alkaline solution was treated with Norit and filtered hot. The free acid was precipitated by acidification of the warm solution with 20 ml. of 1:1 hydrochloric acid. From the cold solution was filtered 6.3 g.(75%) of white solid melting at 188-216° with preliminary softening and darkening. Recrystallization from 60 ml. of a 1:2 water-dioxane solution gave 4.3 g. (51%) of nearly white solid melting at 225-228°. A mixed melting point showed the product to be the same as the 6-bromo-2-naphthoxyacetic acid prepared through the ester.

1,6-Dibromo-2-naphthoxyacetic acid (attempted).- To 9.1 g. (0.030 mole) of 1,6-dibromo-2-naphthol (kindly provided

by Dr. J. B. Campbell of E. I. du Pont de Nemours and Company) and 2.8 g. (0.030 mole) of chloroacetic acid were added 50 ml. of ethanol and 3.4 g. (0.060 mole) of potassium hydroxide dissolved in 50 ml. of water. A clear, dark-colored solution resulted upon heating the mixture to the reflux temperature. The mixture was refluxed for 3 hours to give a cloudy solution which was treated with 40 ml. of 50% ethanol, heated with Norit, and filtered hot. To the warm, colored filtrate was added 15 ml. of 1:1 hydrochloric acid; a dense red oil separated. No effort was made to purify this oil.

Haskelberg[73] prepared 1,6-dibromo-2-naphthoxyacetic acid through its ethyl ester by the reaction of 1,6-dibromo-2-naphthol with ethyl bromoacetate in a solution of sodium ethoxide. He reported a crude yield of 85%; the melting point of the recrystallized product was 178°.

2-Carboxy-4-chloronaphthoxyacetic acid (attempted).- To a solution of sodium ethoxide prepared from 1.8 g. (0.080 g. atom) of sodium and 60 ml. of absolute ethanol were added 8.9 g. (0.040 mole) of 4-chloro-1-hydroxy-2-naphthoic acid and 9.8 g. (0.080 mole) of ethyl chloroacetate. The mixture was refluxed, with occasional shaking, for 1 hour. Following the addition of 11.2 g. (0.20 mole) of potassium hydroxide dissolved in 30 ml. of water, the mixture was heated on a

steam-bath for 30 minutes. The hydrolyzed mixture was poured into 100 ml. of hot water, and to the resulting warm solution was added 30 ml. of 1:1 hydrochloric acid. The acidic mixture was cooled and filtered to give 9.6 g. (108% crude recovery) of nearly white solid melting at 217° with gas evolution, identified as 4-chloro-1-hydroxy-2-naphthoic acid by a mixed melting point.

In a second effort to synthesize this aryloxyacetic acid, an attempt was made to force the reaction by employing the higher-boiling solvent, methyl cellosolve. The reaction mixture was maintained at the reflux temperature of this solvent for 2½ hours; however, the starting phenolic compound was obtained in a 90% crude recovery following hydrolysis, acidification, and filtration.

A third attempt was made to prepare the naphthoxy compound, this time using the higher-boiling methyl cellosolve and employing the more reactive ethyl bromoacetate instead of ethyl chloroacetate. The reaction mixture was refluxed for 1 hour, hydrolyzed, acidified, and filtered to give a 101% crude recovery of starting material.

The only reference to the preparation of 2-carboxy-4-chloronaphthoxyacetic acid is the work of Bull and Fuson,[75]

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[75] B. A. Bull and R. C. Fuson, J. Am. Chem. Soc., 56, 736 (1934).

who prepared the compound by oxidation and chlorination of 2-acetonaphthoxyacetic acid, by oxidation of 4-chloro-2-acetonaphthoxyacetic acid, and by chlorination of 2-carboxy-naphthoxyacetic acid.

4'-(2,4-Dinitrophenylamino)phenoxyacetic acid (attempted).- To 5.50 g. (0.020 mole) of 2,4-dinitro-4'-hydroxydiphenylamine (kindly provided by Dr. J. B. Dickey) and 1.89 g. (0.020 mole) of chloroacetic acid was added 1.60 g. (0.040 mole) of sodium hydroxide dissolved in 60 ml. of water. The dark red mixture was heated on a steam-bath for 3 hours, then acidified with 10 ml. of 1:1 hydrochloric acid. From the acidified mixture was filtered 6.16 g. of red solid melting over the range 144-150°. If this is assumed to be the desired aryloxyacetic acid, the yield of crude product was 93%. However, one would expect the melting point of the aryloxyacetic acid to be higher than that of the parent phenol, so it is unlikely that the product was the desired compound. When the solid was dissolved in a hot solution of 35 ml. of dioxane and 15 ml. of water, no second phase separated upon cooling. The addition of 20 ml. of water resulted in the separation of a dark oil heavier than the solvent. No further work was done with this oil.

1-Aminoanthraquinone-4-oxyacetic acid (attempted).- To the cold solution prepared from 0.23 g. (0.010 g. atom)

of sodium and 20 ml. of methyl cellosolve were added 2.39 g. (0.010 mole) of 1-amino-4-hydroxyanthraquinone (kindly provided by Dr. J. B. Dickey) and 1.23 g. (0.010 mole) of ethyl chloroacetate. The mixture was refluxed for 3 hours. To the deep red mixture was added 1.4 g. (0.025 mole) of potassium hydroxide dissolved in 10 ml. of water; the resulting purple mixture was heated on a steam-bath for 30 minutes. Acidification with 15 ml. of 1:2 hydrochloric acid, followed by cooling and filtration, gave 2.36 g. (99% recovery) of dark brown solid melting over the range 187-193° with preliminary softening, identified as 1-amino-4-hydroxyanthraquinone by a mixed melting point.

In a second attempt to prepare 1-aminoanthraquinone-4-oxyacetic acid, methyl iodoacetate was substituted for ethyl chloroacetate. (The methyl iodoacetate was previously purified in a manner similar to the method used by Aronstein and Kramps.[76] Using essentially the same procedure for carrying out the reaction and isolating the product as was used in the first attempt, there was obtained an 89% recovery of crude starting material, identified by a mixed melting point.

Flavone-3-oxyacetic acid (attempted).- To a cold solution prepared from 0.46 g. (0.020 g. atom) of sodium and 60 ml. of methyl cellosolve were added 4.76 g. (0.020

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[76] L. Aronstein and J. M. A. Kramps, Ber., 14, 604 (1881).

mole) of 3-hydroxyflavone and 3.34 g. (0.020 mole) of ethyl bromoacetate. The mixture became homogeneous upon heating to the reflux temperature. The solution was refluxed with stirring for 2 hours. Then 2.8 g. (0.050 mole) of potassium hydroxide dissolved in 20 ml. of water was added, and the solution was refluxed for 20 minutes. The solution was cooled and acidified with 20 ml. of 1:2 hydrochloric acid. Filtration of the resulting mixture gave 1.06 g. (22% recovery) of pale yellow solid melting at 163-166°, identified as 3-hydroxyflavone by a mixed melting point. The filtrate was diluted with 100 ml. of water, and the mixture was extracted with two 100-ml. portions of ether. The combined ethereal extracts were washed with 50 ml. of water and dried over sodium sulfate. The solvent was distilled over a steam-bath, the last traces under the vacuum of a water aspirator, to give a liquid residue which partially solidified on standing. After rubbing on a porous plate, a sample of the residue was found to melt over the range 107-129°. When mixed with a sample of 3-hydroxyflavone, the material began to melt at 90°. The semi-solid residue was dissolved in 150 ml. of a refluxing 1:2 benzene-petroleum ether (b.p. 77-115°) solution; the hot solution was decanted from a small amount of undissolved liquid residue. Filtration of the cold mixture gave 0.83 g. of pale yellow solid melting

at 82-90°; further heating caused the liberation of a gas. Although work was discontinued on this material, it seems unlikely that it was the desired oxyacetic acid in view of the fact that its melting point was far below that of the parent hydroxy compound.

3-Pyridineoxyacetic acid (attempted).- Subsequent to the attempted synthesis of this compound as given here, Perkins[77] reported the preparation of 3-pyridineoxyacetic acid hydrochloride monohydrate by the reaction of 0.1 mole of 3-hydroxypyridine with 0.12 mole of chloroacetic acid and 0.24 mole of sodium hydroxide in water, followed by acidification of the reaction mixture. 3-Pyridineoxyacetic acid was prepared by dissolving the hydrochloride monohydrate in an equimolar solution of sodium hydroxide, with subsequent concentration. The 3-pyridineoxyacetic acid hydrochloride monohydrate decomposed without melting at 118° and melted at 180-185° (decompn.). The 3-pyridineoxyacetic acid melted at 170° (decompn.). However, Kirpal[78] previously had carried out the reaction of 1 mole of 3-hydroxypyridine with 2 moles of chloroacetic acid in alcohol to give a product melting at 185° (decompn.) to which he assigned the formula

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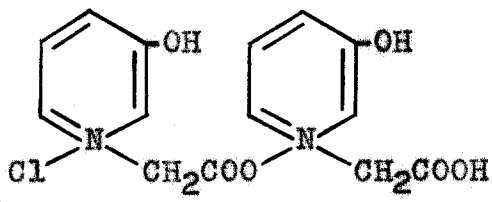
[77] R. P. Perkins, U. S. Patent 2,559,546 [C. A., 46, 1052 (1952)].

[78] A. Kirpal, Monatsh., 29, 471 (1908).



To a cold solution prepared from 2.3 g. (0.10 g. atom) of sodium and 30 ml. of methyl cellosolve was added 9.5 g. (0.10 mole) of 3-hydroxypyridine; most of the hydroxypyridine dissolved, with the liberation of a small amount of heat, to give a pink solution. Upon the addition of 16.7 g. (0.10 mole) of ethyl bromoacetate, an orange mixture resulted, and much heat was liberated. The mixture was heated on a steam-bath, with stirring, for 2 hours, whereupon the color became brown. Following the addition of 14.0 g. (0.25 mole) of potassium hydroxide dissolved in 40 ml. of water, heating on a steam-bath, with stirring, was continued for 20 minutes. The dark mixture was cooled and treated with 60 ml. of 1:1 hydrochloric acid. The acidic solution was extracted three times with 50-ml. portions of ether, and the combined ethereal extracts were washed with 30 ml. of water, then dried over sodium sulfate. Distillation of the ether gave a small amount of orange liquid residue which did not solidify on standing. A similar extraction of the aqueous layer with ethyl acetate also separated a small

amount of liquid residue. The aqueous layer was then concentrated, cooled, and filtered to give 8.1 g. of nearly white solid which darkened but did not melt when heated to 400°. The solvent was distilled from the filtrate over a steam-bath under the vacuum of a water aspirator to give a brown residue. This residue was digested with 100 ml. of refluxing ethanol, the mixture was cooled, and the solid was filtered to give 13.6 g. of nearly white solid which did not melt when heated to 400°. The filtrate was concentrated to give, upon cooling, a dark, somewhat viscous liquid containing a small amount of light-colored solid. When an attempt was made to vacuum-distill this mixture, decomposition was observed to have begun by the time the bath temperature had reached 190°.

Ethyl 3-pyridineoxyacetate.- This ester was synthesized by the general method used in the attempted preparation of the acid, the saponification not being carried out, of course.

To a cold solution of sodium ethoxide prepared from 18.4 g. (0.80 g. atom) of sodium and 400 ml. of absolute ethanol in a 1-liter three-necked flask equipped with stirrer, dropping funnel, and reflux condenser fitted with a calcium chloride drying tube, was added 76.1 g. (0.80 mole) of 3-hydroxypyridine. The 3-hydroxypyridine dissolved upon stirring; to the resulting solution was added with stirring, over a period

of about 7 minutes, 134 g. (0.80 mole) of ethyl bromoacetate. During this addition the solution became orange, much white solid precipitated, and much heat was liberated. The mixture was refluxed with stirring for 4 hours, during which time the supernatant liquid became wine red. The solvent was distilled from the mixture over a steam-bath under the vacuum of a water aspirator, and the residue was stirred with a mixture of 400 ml. of ether and 400 ml. of 5% sodium hydroxide. The aqueous layer was separated and extracted twice with 200-ml. portions of ether. The combined ethereal layers were washed twice with 100-ml. portions of water and dried over sodium sulfate. Following removal of the solvent over a steam-bath, the residue was distilled to give 17.6 g. (12%) of golden-colored liquid boiling at 96-98° (0.1 mm.). Redistillation gave 15.4 g. (11%) of colorless liquid boiling at 97-98° (0.2 mm.), $\underline{n}^{29}_{D}$ 1.5053, $\underline{d}^{28}_{4}$ 1.154.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73; $\underline{MR}_D$[79], 45.67. Found: C, 59.44, 59.50; H, 6.16, 6.24; N, 7.82, 7.92; $\underline{MR}_D$, 46.59.

When the molar refraction was calculated through use of the molar refraction of pyridine as determined experimentally, the calculated value of $\underline{MR}_D$ was increased to 45.82.

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[79]Calculated from the values for atomic refractions given in A. Weissberger, "Physical Methods of Organic Chemistry," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1949, Vol. 1, p. 1163.

1,2-Dihydro-2-keto-1-quinolineacetic acid.- To a cold solution of sodium ethoxide prepared from 2.3 g. (0.10 g. atom) of sodium and 100 ml. of absolute ethanol were added 14.5 g. (0.10 mole) of 2-hydroxyquinoline and 12.3 g. (0.10 mole) of ethyl chloroacetate. The mixture was refluxed on a steam-bath, with occasional shaking, for 1 hour. At no time did a clear solution result. To the reaction mixture containing a white solid was added 14.0 g. (0.25 mole) of potassium hydroxide dissolved in 30 ml. of water, and the resulting mixture was refluxed on a steam-bath for 10 minutes. The warm mixture was acidified with 45 ml. of 1:1 hydrochloric acid. From the cold solution was filtered 20.1 g. (99%) of white solid melting with gas evolution at 275° with preliminary softening and darkening. The solid was digested with a refluxing solution of 140 ml. of dioxane and 110 ml. of water; the mixture was cooled and filtered to give 10.5 g. (52%) of white solid melting with gas evolution at 280° with preliminary softening and darkening. The product was then digested with a refluxing solution of 140 ml. of dioxane and 250 ml. of nitrobenzene. The mixture was filtered hot to give 5.5 g. of undissolved white solid melting with gas evolution at 282° with preliminary softening and darkening. The filtrate, upon cooling, yielded 4.2 g. of white solid also melting with gas evolution at 282° with

preliminary softening and darkening, thus bringing the yield of pure material to 48%. The melting point of the 4.2 g. of solid was not increased upon an additional recrystallization from a 1:2 dioxane-nitrobenzene solution.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.75, 64.70; H, 4.45, 4.40; N, 6.98, 7.00.

Although this reaction was carried out with the hope of preparing 2-quinolineoxyacetic acid, the infrared spectrum, together with related work[80,81] on similar compounds, indicates that the product probably exists as the zwitter ion of 1,2-dihydro-2-keto-1-quinolineacetic acid. However, its structure has not been proved.

8-Quinolineoxyacetic acid and its hydrochloride (attempted).- Attempts were made to carry out these syntheses by the method of Nagel,[82] using a simplified method for the isolation of the intermediate hydrochloride.

In a 500-ml. three-necked flask equipped with stirrer, reflux condenser, and dropping funnel were placed 9.2 g. (0.40 g. atom) of sodium and 100 ml. of absolute ethanol.

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[80] A. R. Surrey, J. Am. Chem. Soc., 70, 2190 (1948).

[81] F. W. Bergstrom, Chem. Revs., 35, 77 (1944).

[82] O. Nagel, Monatsh., 18, 31 (1897).

After all the sodium had reacted, 29.0 g. (0.20 mole) of 8-hydroxyquinoline in 150 ml. of absolute ethanol was added. The mixture containing much solid was refluxed on a steam-bath for 30 minutes. The solid was all dissolved by the slow addition of 20 ml. of water to the stirred, refluxing mixture. To the resulting orange solution, with stirring and refluxing, was added 18.9 g. (0.20 mole) of chloroacetic acid dissolved in 30 ml. of 95% ethanol. The mixture was refluxed for 6 hours to give an orange solution containing a considerable amount of solid. Most of the ethanol and water was distilled over a steam-bath to give, upon cooling, an orange solid cake as a residue. One hundred milliliters of water was added, and the mixture was warmed to effect solution. The solution was cooled, and 70 ml. of 1:2 hydrochloric acid was added to give a solution having a pH of 2. This solution was extracted with 100 ml. of ether, causing the aqueous layer to become a firm mass. The ether was poured off. The aqueous layer was filtered, and the solid was washed first with a 1:1 water-ethanol solution, then with ethanol, and finally with ether. The yellow solid weighed 31.4 g. (66%, calculated as 8-quinolineoxyacetic acid hydrochloride) and began to soften at about 178°, becoming darker and finally melting at 218° with gas evolution and formation of a dark red liquid. Nagel reported that

8-quinolineoxyacetic acid hydrochloride turns brown at 205° and melts at 216°.

The yellow solid was dissolved in 120 ml. of hot water and treated with an excess of freshly precipitated silver oxide (prepared by the reaction of sodium hydroxide with silver nitrate). The mixture was stirred while heating on a steam-bath for 2 hours. The solid material, presumably silver oxide and silver chloride, was filtered from the hot solution. However, only a trace of solid, believed to be the unreacted hydrochloride, separated from the solution upon cooling, and neither extraction with ether nor removal of the water led to significant amounts of solid. Furthermore, digestion with boiling water of the residue containing the silver compounds was of no avail. Nagel reported the melting point of 8-quinolineoxyacetic acid to be 176°.

In a second attempt to prepare 8-quinolineoxyacetic acid, the intermediate hydrochloride was prepared in the same way except that sodium hydroxide was substituted for metallic sodium, and a 3:2 water-95% ethanol solution was used as solvent. In this way there was obtained a 96% yield of the supposed hydrochloride which began to turn brown at about 210° and melted at 228° with gas evolution and formation of a red liquid. This material was treated with silver oxide in the same way as in the previous trial. This time the

filtrate from the removal of the silver compounds was treated with ethanol following its concentration, resulting in the separation of a small amount of light yellow solid melting at 181° with gas evolution and formation of a red liquid. Although its melting point was in fair agreement with that reported by Nagel for 8-quinolineoxyacetic acid, the infrared spectrum showed no carbonyl band.

A third preparation of 8-quinolineoxyacetic acid hydrochloride was attempted, this time by the same method as was used in the second trial. The yield was 79% of yellow solid which began to turn brown at about 220° and melted at 230° with gas evolution and formation of a red melt. Recrystallization from a 1:1 water-95% ethanol solution gave a 61% yield of light yellow solid which began to turn brown at about 205° and melted at 226° with gas evolution and formation of a red liquid. An analysis of this material gave these results: C, 51.91, 51.76; H, 4.89, 5.00; Cl, 10.37, 10.48; N, 5.63, 5.57. Neglecting oxygen, this would require the formula $C_{10.79}H_{12.28}Cl_{0.74}N_{1.00}$. Apparently the compound was not pure. The infrared spectrum showed the presence of a carbonyl group as would be expected.

In a fourth trial employing ethyl chloroacetate instead of chloroacetic acid and sodium ethoxide instead of sodium hydroxide, thus proceeding through the ester, there was

obtained a 54% yield of the hydrochloride melting at 222° with gas evolution and formation of a red melt, and with preliminary darkening.

Methiodide of 8-quinolineoxyacetic acid (attempted).- In general, the method employed was that used by Meisenheimer and Dodonow[83] in their preparation of the methiodide of quinoline.

In a 250-ml. three-necked flask equipped with stirrer, reflux condenser, and dropping funnel were placed 100 ml. of 90% ethanol and 12.0 g. (0.050 mole) of the supposed 8-quinolineoxyacetic acid hydrochloride prepared in the third trial above. To the suspension was added slowly with stirring 7.8 g.(0.055 mole) of methyl iodide dissolved in 20 ml. of 90% ethanol. No heat effect was observed. The mixture was then refluxed with stirring for 2 hours. Some of the hydrochloride dissolved upon heating the mixture; before it had all dissolved, precipitation of another substance began. More solid precipitated upon cooling. Filtration gave 8.0 g. (46%, calculated as the desired methiodide) of short yellow needles melting at 203° with gas evolution and preliminary darkening. Recrystallization from 90 ml. of a 1:4 water-ethanol solution gave 6.5 g. of yellow solid

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[83] J. Meisenheimer and J. Dodonow, Ann., 385, 134 (1911).

melting at 205° with gas evolution and preliminary darkening. A mixed melting point with the starting 8-quinolineoxyacetic acid was 194° (decompn.). A qualitative test showed the presence of iodine; however, the infrared spectrum showed the absence of a carbonyl group. Analysis of the material gave these results: C, 48.06, 48.05; H, 3.97, 3.90; N, 5.23, 5.18. Neglecting oxygen and iodine, this corresponds to the formula $C_{10.76}H_{10.51}N_{1.00}$.

Monohydrate of the methiodide of 8-hydroxyquinoline.- Employing the same method as was used in the preceding experiment, 7.8 g. (0.055 mole) of methyl iodide dissolved in 20 ml. of 90% ethanol was added slowly, with stirring, to 7.3 g. (0.050 mole) of 8-hydroxyquinoline in 100 ml. of 90% ethanol. The solution was refluxed with stirring for 2 hours. As no solid separated from the orange solution on cooling, most of the solvent was distilled. From the cold concentrated mixture was filtered 3.7 g. of yellow solid melting over the range 70-110°. The solid was digested with 50 ml. of benzene and filtered hot to give 1.91 g. (13%) of yellow material melting at 169-171° with gas evolution. Recrystallization from 45 ml. of a 1:2 ethanol-benzene solution gave 1.61 g. (11%) of yellow product melting at 168° with gas evolution and preliminary softening.

Anal. Calcd. for $C_{10}H_{12}INO_2$: C, 39.36; H, 3.96; N, 4.59. Found: C, 39.54, 39.46; H, 4.06, 4.04; N, 4.59, 4.62.

Claus and Howitz[84] carried out the preparation of the methiodide by heating the reacting materials in a sealed tube in a water-bath without a solvent; they reported the product to darken above 140°, melting with gas evolution at 170°. Upon heating 8-hydroxyquinoline with methyl iodide in methanol at 100° in a sealed tube, Lippmann and Fleissner[85] obtained a substance melting at 143° (decompn.) which they considered to be a complex consisting of a molecule of the methiodide of 8-hydroxyquinoline associated with a molecule of the hydroiodide of 8-methoxyquinoline and two molecules of water.

In an earlier preparation of this methiodide, a 0.39% yield (mixed m.p.) was obtained by the dropwise addition of a toluene solution of methyl iodide to a refluxing solution of 8-hydroxyquinoline in toluene.

5,7-Dichloro-8-quinolineoxyacetic acid.- To a cold solution prepared from 0.46 g. (0.020 g. atom) of sodium and 30 ml. of methyl cellosolve were added 4.28 g. (0.020 mole) of 5,7-dichloro-8-hydroxyquinoline and 2.46 g. (0.020 mole) of ethyl chloroacetate. The mixture was refluxed for 3 hours, treated with 2.8 g. (0.050 mole) of potassium hydroxide

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[84] A. Claus and H. Howitz, J. prakt. Chem., [2], 42, 222 (1890).

[85] E. Lippmann and F. Fleissner, Monatsh., 10, 665 (1889).

dissolved in 10 ml. of water, and heated on a steam-bath for 30 minutes. Twenty milliliters of 1:2 hydrochloric acid was added, and, after cooling, there was filtered 4.14 g. (76%) of light gray solid melting at 208-212° with gas evolution and formation of a dark liquid. Three recrystallizations from 100-150 ml. of a 1:2 water-dioxane solution, with the aid of Norit, gave 2.13 g. (39%) of white needles melting at 219° with gas evolution, with preliminary softening and formation of an orange melt.

Anal. Calcd. for $C_{11}H_7Cl_2NO_3$: C, 48.55; H, 2.59; N, 5.15; Cl, 26.06. Found: C, 48.53, 48.50; H, 2.66, 2.60; N, 5.14, 5.12; Cl, 26.19, 26.10.

An earlier attempt to carry out the synthesis by refluxing for 5 hours a mixture of 5,7-dichloro-8-hydroxyquinoline, chloroacetic acid, and sodium hydroxide in a 1:1 water-95% ethanol solution led to a 95% crude recovery of the quinoline compound. Also, in an effort to prepare the oxyacetic acid by the method used in the successful synthesis described above, but with substitution of absolute ethanol for methyl cellosolve as the refluxing solution, there was obtained a 92% crude recovery of the hydroxyquinoline.

5,7-Dibromo-8-quinolineoxyacetic acid.- Using the procedure by which the corresponding dichloro compound was prepared, 12.1 g. (0.040 mole) of 5,7-dibromo-8-hydroxy-

quinoline and 4.9 g. (0.040 mole) of ethyl chloroacetate were added to a solution prepared from 0.92 g. (0.040 g. atom) of sodium and 60 ml. of methyl cellosolve. The mixture was refluxed for 1 hour, treated with 5.6 g. (0.10 mole) of potassium hydroxide dissolved in 20 ml. of water, and refluxed for an additional 20 minutes. Acidification with 40 ml. of 1:2 hydrochloric acid and filtration gave 12.1 g. (84%) of light gray solid melting over the range 185-195° (decompn.). One recrystallization from 140 ml. of a 1:6 water-dioxane solution, followed by three recrystallizations from 100-200 ml. of a 1:1 benzene-dioxane solution, gave 3.2 g. (22%) of white needles melting at 222-224° with gas evolution and formation of an orange melt; there was preliminary softening and darkening.

Anal. Calcd. for $C_{11}H_7Br_2NO_3$: C, 36.59; H, 1.95; N, 3.88. Found: C, 36.86, 36.99; H, 2.01, 2.00; N, 4.05, 3.94.

Nagel[82] reported the compound to melt at 203° (darkening); he obtained it as orange-yellow needles from ethanol following its preparation by treatment of 8-quinolineoxyacetic acid with bromine water.

5,7-Diiodo-8-quinolineoxyacetic acid.- To a cold solution prepared from 0.92 g. (0.040 g. atom) of sodium and 60 ml. of methyl cellosolve were added 15.9 g. (0.040 mole) of 5,7-diiodo-8-hydroxyquinoline and 6.7 g. (0.040 mole) of ethyl bromoacetate. The mixture was refluxed with stirring

for 1 hour, then treated with 5.6 g. (0.10 mole) of potassium hydroxide dissolved in 20 ml. of water, and refluxed with stirring for another 10 minutes. After cooling and acidifying with 40 ml. of 1:2 hydrochloric acid, there was filtered 10.5 g.(58%) of brown solid melting at 161° with gas evolution. The solid was digested with 300 ml. of dioxane, and the mixture was filtered hot to remove a small amount of brown solid which did not melt below 400°. The filtrate was treated with Norit, and water (300 ml.) was added to the refluxing orange solution to effect incipient cloudiness. Filtration of the cold mixture gave 6.1 g. (34%) of brownish pink solid melting at 179° (decompn.). Recrystallization from 150 ml. of a 1:2 petroleum ether (b.p. 77-115°)-dioxane solution gave 5.0 g. (28%) of slightly colored solid melting at 199° with gas evolution, formation of a red liquid, and preliminary darkening. Another recrystallization, with the aid of Norit, from the same solvent pair gave a nearly white solid with the same decomposition point.

Anal. Calcd. for $C_{11}H_7I_2NO_3$: C, 29.04; H, 1.55; N, 3.08. Found: C, 29.13, 29.20; H, 1.70, 1.65; N, 3.29, 3.31.

5-Sulfo-7-iodo-8-quinolineoxyacetic acid (attempted).- To the cold solution prepared from 1.8 g. (0.080 g. atom) of sodium and 60 ml. of methyl cellosolve were added 14.0 g. (0.040 mole) of 8-hydroxy-7-iodo-5-quinolinesulfonic acid

and 13.4 g. (0.080 mole) of ethyl bromoacetate. The mixture was refluxed with stirring for 1 hour, and 11.2 g. (0.20 mole) of potassium hydroxide dissolved in 40 ml. of water was added. The clear red solution was refluxed for 10 minutes, cooled, and acidified with 50 ml. of 1:1 hydrochloric acid. No precipitate formed upon cooling, so about half of the solvent was distilled over a steam-bath under the vacuum of a water aspirator. Filtration gave 17.9 g. of orange solid melting at 231-234° (decompn.). The solid was dissolved in a solution of 70 ml. of water and 160 ml. of dioxane. The addition of 110 ml. of acetone caused the separation of 4.3 g. of yellow solid which darkened and softened but did not melt below 400°. Concentration of the filtrate gave 2.8 g. (27%, calculated as the dihydrate of 8-hydroxy-5-quinolinesulfonic acid[86]) of yellow-orange solid melting at 310-313° (decompn.). Two recrystallizations from 90 ml. of water, with the aid of Norit, gave 1.28 g. (12%) of yellow crystals melting at 326-328° with gas evolution and formation of a dark melt.

Anal. Calcd. for $C_9H_7NO_4S \cdot 2H_2O$: C, 41.37; H, 4.24; N, 5.36; S, 12.27, water of hydration, 13.79. Found: C, 41.59, 41.71; H, 4.50, 4.43; N, 5.41, 5.44; S, 12.20, 12.23;

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[86] A. Claus and S. Baumann, J. prakt. Chem., 55, 457 (1897).

water of hydration (100° *in vacuo* over phosphorus pentoxide), 13.51, 13.50.

Concentration of the filtrate from the separation of the solid melting at 310-313° (decompn.) gave 3.3 g. of brown solid melting at 230-235° with gas evolution. This solid was not investigated further.

In a previous attempt to prepare the desired oxyacetic acid through the use of ethyl chloroacetate instead of ethyl bromoacetate, 36% of the 8-hydroxy-7-iodo-5-quinolinesulfonic acid was recovered.

α-(2,4-Dichlorophenoxy)palmitic acid.- To a cold solution of sodium ethoxide prepared from 0.69 g. (0.030 g. atom) of sodium and 60 ml. of absolute ethanol were added 4.9 g. (0.030 mole) of 2,4-dichlorophenol and 10.9 g. (0.030 mole) of ethyl *α*-bromopalmitate. The clear solution was refluxed with stirring for 3 hours, during which time a white solid separated. Four and two-tenths grams (0.075 mole) of potassium hydroxide dissolved in 20 ml. of water was added, and the mixture was refluxed for 20 minutes. Following cooling and acidification with 25 ml. of 1:2 hydrochloric acid, there was filtered 12.2 g. (98%) of white solid melting at 73-76° with preliminary softening. An attempt to recrystallize this solid from a 1:2 water-dioxane solution resulted in an oil which could not be made to

crystallize, so the oil was recovered by extraction with ether. Following removal of the ether, the solid was recrystallized from 300 ml. of a 1:3 water-95% ethanol solution to give 9.2 g. (74%) of white solid melting at 75-76° with preliminary softening.

Anal. Calcd. for $C_{22}H_{34}Cl_2O_3$: C, 63.30; H, 8.21; Cl, 16.99. Found: C, 64.50, 64.53; H, 8.85, 8.90; Cl, 14.90, 14.95.

The lack of close agreement between the calculated and experimental values in the analyses shows that the product was not pure. However, the two derivatives prepared from this crude acid as described below gave good analyses.

α-(2,4-Dichlorophenoxy)palmitamide.- By a standard procedure[87] for preparing amides, 10 ml. (0.14 mole) of thionyl chloride was added to 2.09 g. (0.0050 mole) of crude α-(2,4-dichlorophenoxy)palmitic acid. Protected from moisture, the mixture was heated on a steam-bath for 30 minutes, cooled, and poured into 30 ml. (0.45 mole) of concentrated ammonium hydroxide in an ice-bath. Filtration gave 6.3 g. of white solid which softened and darkened on heating but did not melt below 400°. Recrystallization from 350 ml. of a 2:5

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[87] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948.

water-95% ethanol solution gave 1.40 g. (67%) of white solid melting at 78-81° with formation of a cloudy liquid. The solid was dissolved in 50 ml. of ethanol and filtered hot to remove a small amount of white solid. Following the addition of 17 ml. of water to the hot solution, and cooling, the mixture was filtered to give 1.17 g. (56%) of white solid melting at 77-79°.

Anal. Calcd. for $C_{22}H_{35}Cl_2NO_2$: C, 63.45; H, 8.47; N, 3.36. Found: C, 63.47, 63.32; H, 8.63, 8.69; N, 3.06, 3.01.

α-(2,4-Dichlorophenoxy)palmitanilide.- Using a standard procedure[87] for the preparation of anilides, 4.0 ml. (0.055 mole) of thionyl chloride was added to 2.09 g. (0.0050 mole) of crude α-(2,4-dichlorophenoxy)palmitic acid. The mixture was heated on a steam-bath for 30 minutes and cooled. A solution of 4.0 ml. (0.044 mole) of aniline in 60 ml. of benzene was added, and heating on the steam-bath was continued for 10 minutes. The solid was filtered from the cold benzene solution, and the solution was washed successively with 10 ml. of water, 10 ml. of 5% hydrochloric acid, 10 ml. of 5% sodium hydroxide, and 10 ml. of water. Distillation of the solvent gave a residue which was recrystallized from 110 ml. of a 1:10 water-95% ethanol solution to give 1.00 g. (41%) of white solid melting at 72-77° with preliminary softening. Two additional recrystallizations from 35-45

ml. of a 1:10 water-95% ethanol solution gave 0.65 g. (26%) of white solid melting at 81-83°.

Anal. Calcd. for $C_{28}H_{39}Cl_2NO_2$: C, 68.28; H, 7.98; N, 2.84. Found: C, 68.28, 68.16; H, 8.09, 8.13; N, 2.64, 2.70.

Ethyl o-phenylenedioxyacetate.- This synthesis was carried out by a slight modification of the method of Christiansen and Dolliver.[88]

To a cold ethanolic solution of sodium ethoxide prepared from 46.0 g. (2.0 g. atoms) of sodium and 1500 ml. of absolute ethanol in a 3-liter three-necked flask equipped with stirrer, reflux condenser, dropping funnel, and nitrogen inlets was added 110 g. (1.0 mole) of catechol. To the dark mixture was added 157 g. (1.0 mole) of ethyl dichloroacetate, with stirring, over a period of 20 minutes. After 1 hour of stirring at room temperature, the mixture was stirred for 6 hours with refluxing. The solvent was removed over a steam-bath under the vacuum of a water aspirator, and the residue was stirred with a mixture of 600 ml. of ether and 300 ml. of 5% sodium bicarbonate. The layers were separated, and the ethereal layer was extracted with an additional 300 ml. of 5% sodium bicarbonate, then washed with 100 ml. of

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[88] W. G. Christiansen and M. A. Dolliver, J. Am. Chem. Soc., 66, 312 (1944).

water. A considerable amount of tar-like material (see DISCUSSION) remained undissolved and was separated with the aqueous layer. The ethereal solution was dried over sodium sulfate, the solvent was removed, and the dark residue was distilled to give 68.1 g. of material boiling at 81-89° (0.3 mm.). This material consisted of a colorless liquid containing some white solid identified as catechol by a mixed melting point. The distillate was extracted with two 30-ml. portions of 5% sodium bicarbonate to remove the catechol, and the organic layer was washed once with 30 ml. of water. Distillation gave 53.4 g. (28%) of colorless liquid boiling at 79-81° (0.3 mm.), $\underline{n}^{24}_{D}$ 1.5127.

In a previous trial the ethereal extract of the ester was washed with 5% sodium hydroxide[88] instead of 5% sodium bicarbonate. Subsequent distillation of the solvent in a run of the same size as that described above gave only 18.6 g. of a red liquid residue. Therefore, the aqueous layer (containing some ethanol) remaining from the ether extraction was acidified with 1:1 hydrochloric acid. The dense, dark red oil which separated was removed, the aqueous layer was extracted with ether, and the oil and ethereal extracts were combined and dried over sodium sulfate. Following removal of the solvent, the residue was vacuum-distilled to give about 48 g. of pale yellow liquid boiling over a wide range.

Redistillation through a small Todd column fitted with a spiral packing without a core gave 20.0 g. (10%) of colorless liquid boiling at 92-94° (0.7 mm.), n^{23}_D 1.5084.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; mol. wt., 194. Found: C, 61.41, 61.38; H, 5.26, 5.36; mol. wt. (cryoscopic in benzene), 169, 175.

Christiansen and Dolliver reported the boiling point of ethyl o-phenylenedioxyacetate to be 115-117° (12.5 mm.).

o-Phenylenedioxyacetamide.- A mixture of 3.9 g. (0.020 mole) of ethyl o-phenylenedioxyacetate and 20 ml. (0.30 mole) of concentrated ammonium hydroxide was shaken vigorously for 10 minutes; a solid formed very quickly after the shaking was begun, and heat was liberated. Filtration, upon cooling, gave 2.63 g. (80%) of white solid melting at 110-112°. Recrystallization from 40 ml. of water gave 2.12 g. of white flakes still melting at 110-112°.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.18, 58.18; H, 4.25, 4.32; N, 8.52, 8.53.

o-Phenylenedioxyacethydrazide.- In accordance with a general procedure,[87] 4.0 ml. (0.082 mole) of hydrazine hydrate (99-100%) was added to 3.9 g. (0.020 mole) of ethyl o-phenylenedioxyacetate. A white solid formed immediately. The mixture was heated for 10 minutes on a steam-bath; then sufficient 95% ethanol (40 ml.) was added to give a

homogeneous refluxing solution. Upon cooling, 2.15 g. (60%) of white solid melting at 182-185° was obtained. Recrystallization from 70 ml. of ethanol gave 1.80 g. (50%) of white needles melting at 185-187°. Another recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.26, 53.37; H, 4.49, 4.51; N, 15.61, 15.63.

o-Phenylenedioxyacetanilide.- The procedure employed by Hardy[89] was used for the preparation of this derivative.

To a cold solution of ethylmagnesium bromide prepared from 1.0 g. (0.041 g. atom) of magnesium, 5.0 g. (0.046 mole) of ethyl bromide, and 30 ml. of anhydrous ether, was added slowly 4.0 g. (0.043 mole) of aniline. When the evolution of ethane ceased, 3.9 g. (0.020 mole) of ethyl o-phenylenedioxyacetate was added; the mixture was warmed on a steam-bath for 10 minutes and cooled. Following acidification with 40 ml. of 1:2 hydrochloric acid, the ether was distilled over a steam-bath. Upon cooling and filtering the acidic mixture, there was obtained 3.99 g. (83%) of nearly white solid melting at 118-128°. Recrystallization from 100 ml. of a 2:3 water-95% ethanol solution gave 3.29 g. (69%) of white

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[89] D. V. N. Hardy, J. Chem. Soc., 398 (1936).

flakes melting at 135-137°. Another recrystallization from the same solvent did not raise the melting point.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.71, 69.70; H, 4.64, 4.72; N, 5.89, 5.85.

n-Butyl o-phenylenedioxyacetate.- A solution of 15.5 g. (0.080 mole) of ethyl o-phenylenedioxyacetate, 46 ml. (0.50 mole) of n-butyl alcohol, and 2 drops of concentrated hydrochloric acid was refluxed for 24 hours. After removal of the solvent over a steam-bath under the vacuum of a water aspirator, the residue was distilled to give 14.0 g. of colorless material boiling at 84-102° (0.3 mm.). This distillate contained some white solid identified as catechol (mixed m.p.), which was removed by extraction with two 5-ml. portions of 5% sodium bicarbonate. The organic layer was washed with 5 ml. of water, dried over calcium chloride, and distilled to give 10.0 g. (56%) of colorless liquid boiling at 100-102° (0.3 mm.), n^{29}_D 1.4907, d^{28}_4 1.125.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; MR_D, 56.76. Found: C, 64.30, 64.39; H, 6.56, 6.52; MR_D, 57.19.

α-(o-Phenylenedioxy)caproic acid (attempted).- During one of the preparations of ethyl o-phenylenedioxyacetate, there had been some evidence suggesting that the hydrogen atom on the carbon alpha to the carbethoxyl group might be

sufficiently acidic to form a salt in an aqueous alkaline solution, as indicated by the inability of ether extraction to remove the ester from an aqueous ethanolic solution containing sodium hydroxide. Therefore, an effort was made to see if ethyl o-phenylenedioxyacetate might undergo a reaction of the malonic ester type. The procedure used was that employed by Adams and Kamm[90] for their preparation of ethyl n-butylmalonate, except that here an attempt was made to hydrolyze the ester which might be formed.

To a cold solution of sodium ethoxide prepared from 0.46 g. (0.020 g. atom) of sodium and 20 ml. of absolute ethanol was added 3.9 g. (0.020 mole) of ethyl o-phenylenedioxyacetate. The dark mixture was treated with 2.7 g. (0.020 mole) of n-butyl bromide, and then heated on a steam-bath for 3 hours. A solution of 2.8 g. (0.050 mole) of potassium hydroxide in 20 ml. of water was added, and the mixture was refluxed for 30 minutes. Cooling and acidification gave two liquid phases, but no solid acid as had been hoped. No further study was made of this reaction.

4-Chlorocatechol.- One preparation of this intermediate was carried out by the method of Frejka and co-workers.[66] In this synthesis a 33% yield of 4-chlorocatechol melting

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[90] R. Adams and R. M. Kamm, Org. Syntheses, Coll. Vol. 1, 250 (1941).

at 87-89° was obtained by the reaction of catechol with sulfuryl chloride. Frejka and co-workers reported a 33% yield of product melting at 88°.

Another preparation of 4-chlorocatechol was carried out by the method used by Wrede and Mühlroth.[91] They obtained 4-chlorocatechol as a by-product in their synthesis of 3-chlorocatechol from catechol and sulfuryl chloride, but did not give any melting point or yield of the 4-chloro compound. The procedure used in this Laboratory differed chiefly in that the crude 4-chlorocatechol corresponding to the material they obtained as a by-product was recrystallized from a 1:1 benzene-petroleum ether (b.p. 60-70°) solution to give a 51% yield of product melting at 88-90°.

The chief difference in the reaction conditions used in the two preparations was a matter of temperature. The 33% yield of 4-chlorocatechol was obtained when the sulfuryl chloride was added to the ethereal solution of catechol at the reflux temperature; the 51% yield was obtained when the addition was carried out at -1° to +5°.

Ethyl 4-chloro-o-phenylenedioxyacetate.- The method of synthesis and isolation was that which was found more successful in the preparation of ethyl o-phenylenedioxyacetate;

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[91] F. Wrede and O. Mühlroth, Ber., 63, 1931 (1930).

it consisted of a slight modification of the method of Christiansen and Dolliver.[88]

To a cold solution of sodium ethoxide prepared from 46.0 g. (2.0 g. atoms) of sodium and 1500 ml. of absolute ethanol in a 3-liter three-necked flask equipped with stirrer, reflux condenser, dropping funnel, and nitrogen inlets, was added 145 g. (1.0 mole) of 4-chlorocatechol. To the dark mixture was added 157 g. (1.0 mole) of ethyl dichloroacetate, with stirring, over a period of 20 minutes. After stirring at room temperature for 1 hour, stirring with refluxing was continued for 6 hours. The solvent was removed over a steam-bath under the vacuum of a water aspirator, and the dark residue was stirred with a mixture of 800 ml. of ether and 400 ml. of 5% sodium bicarbonate. The ethereal layer was separated and extracted with another 400-ml. portion of 5% sodium bicarbonate, washed with two 200-ml. portions of water, and dried over sodium sulfate. The solvent was removed, and the dark residue was distilled through a Vigreux column to give 81.4 g. (36%) of yellow liquid distilling at 108-109° (0.4-0.5 mm.), $\underline{n}^{29}_{D}$ 1.5331, $\underline{d}^{28}_{4}$ 1.325.

Anal. Calcd. for $C_{10}H_9ClO_4$: Cl, 15.51; $\underline{MR}_D$,[79] 52.39. Found: Cl, 15.14, 15.14; $\underline{MR}_D$ 53.56.

Ethyl 4-chlorophenacyloxyacetate (attempted).- To 9.2 g. (0.40 g. atom) of sodium and 100 ml. of dry benzene in a

500-ml. three-necked flask equipped with stirrer, dropping funnel, reflux condenser, and nitrogen inlets was added dropwise, with stirring, 41.6 g. (0.40 mole) of ethyl glycolate. After the addition was completed, the reaction rate was increased by refluxing the mixture, which became darker. When most of the sodium had reacted, 93.6 g. (0.40 mole) of 4-chlorophenacyl bromide suspended in 200 ml. of dry benzene was added in small portions. Vigorous gas evolution took place, and refluxing occurred spontaneously. The reddish brown mixture was then stirred at room temperature for 12 hours. Water was added to dissolve any sodium bromide, and the benzene layer was separated and dried over sodium sulfate. Removal of the solvent gave a dark liquid residue which, upon distillation, yielded 3.5 g. of a nearly colorless liquid of pleasant odor boiling over the range 42-91° (0.2-0.3 mm.) and 10.8 g. (12% crude recovery) of 4-chlorophenacyl bromide (mixed m.p.) boiling at 103-112° (0.4-0.8 mm.). As there was some decomposition, the distillation was discontinued.

1-Nitro-2-(p-chlorophenoxy)ethane (attempted).- The 1-bromo-2-(p-chlorophenoxy)ethane (m.p. 38-41°) used in this attempted synthesis was prepared in 58% yield by essentially the same method as that used by Gagnon and

co-workers.[92] The bromide was allowed to react with silver nitrate by a slight modification of the method of Reynolds and Adkins.[93]

In a 300-ml. three-necked flask equipped with stirrer, reflux condenser, and dropping funnel were placed 46.2 g. (0.30 mole) of silver nitrite and 60 ml. of dry benzene. To the suspension in an ice-bath was added, with stirring, 59.0 g. (0.25 mole) of 1-bromo-2-(p-chlorophenoxy)ethane dissolved in 40 ml. of dry benzene over a period of 2 hours. The mixture was stirred for an additional 3 hours while yet in the ice-bath, then refluxed gently for 6 hours. Some reddish-brown fumes (probably nitrogen dioxide) were given off during the refluxing. A gray solid weighing 49.1 g. was filtered from the cold solution, which was then extracted with three 150-ml. portions of 5% sodium hydroxide. The aqueous solution was washed with benzene; then carbon dioxide gas was passed into the alkaline solution for 6 hours. By extraction with benzene, about 6 grams of an orange liquid, which was not investigated, was obtained from the carbonated solution. Acidification with 1:1 hydrochloric acid, followed by further extraction with benzene,

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[92] P. E. Gagnon, J. L. Boivin, and J. Giguere, Can. J. Research, 28B, 352 (1950).

[93] R. B. Reynolds and H. Adkins, J. Am. Chem. Soc., 51, 279 (1929).

gave no appreciable material upon removal of the solvent from the benzene extract.

Distillation of the solvent from the benzene solution which previously had been extracted with sodium hydroxide gave an orange liquid residue weighing 45 g. This residue was distilled to give 18.0 g. of yellow liquid boiling at 99-110° (1.1 mm.) and 13.4 g. of yellow liquid boiling at 110-120° (1.1 mm.). A qualitative test[94] for a primary nitro compound was only faintly positive for each of these distillates. Each distillate gave positive tests for chlorine and nitrogen; neither gave a positive test for bromine. Probably each fraction contained a number of by-products such as nitrite, nitrate, alcohol, and ketone ordinarily obtained in this type of reaction.[95,96,97,98]

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[94] E. Demole, J. Chem. Soc., 28, 561 (1875).

[95] H. B. Hass and E. F. Riley, Chem. Revs., 32, 373 (1943).

[96] N. Kornblum, N. N. Lichtin, J. T. Patton, and D. C. Iffland, J. Am. Chem. Soc., 69, 307 (1947).

[97] N. Kornblum, J. T. Patton, and J. B. Nordmann, ibid., 70, 746 (1948).

[98] N. Kornblum and C. Teitelbaum, ibid., 74, 3076 (1952).

2,4-Dichlorophenoxyacetaldehyde diethylacetal.- Subsequent to its preparation in this Laboratory, Drake[99] reported the preparation of 2,4-dichlorophenoxyacetaldehyde diethylacetal by the reaction of equimolar quantities of 2,4-dichlorophenol, chloroacetal, and sodium methoxide dispersed in ethanol heated under autogenous pressure at 150° for 18 hours.

One hundred fourteen grams (0.70 mole) of 2,4-dichlorophenol was dissolved in 200 ml. of diethylene glycol in a 1-liter three-necked flask equipped with stirrer, dropping funnel, nitrogen inlets, and reflux condenser through which was hung a thermometer dipping into the reaction mixture. After the addition of 17.3 g. (0.75 g. atom) of sodium, heating with stirring was carried out cautiously until all the sodium had reacted. To the mixture maintained at 195-200° was added dropwise, with stirring, 103 g. (0.67 mole) of chloroacetal over a period of 35 minutes. The dark solution containing much solid was then stirred at 195-200° for 15 hours. (In a subsequent preparation it was shown that 3 hours of heating and stirring was sufficient.) Upon cooling, 200 ml. of 5% sodium hydroxide was added, and the mixture

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[99] L. R. Drake, U. S. Patent 2,553,555 [C. A., 46, 532 (1952)].

was extracted with three 200-ml. portions of ether. The combined ethereal extracts were washed with two 200-ml. portions of water and dried over sodium sulfate. After removal of the solvent, the product was distilled through a Vigreux column to give 138 g. (74%) of nearly colorless liquid boiling at 123-127° (0.5-0.7 mm.). Redistillation gave 126 g. (67%) of colorless liquid distilling at 106-108° (0.2 mm.), $\underline{n}^{24}_{D}$ 1.5065, $\underline{d}^{26}_{4}$ 1.190.

Anal. Calcd. for $C_{12}H_{16}Cl_2O_3$: Cl, 25.40; $\underline{MR}_D$, 68.68. Found: Cl, 24.88, 24.91; $\underline{MR}_D$, 69.76.

Drake reported no yield but gave the physical constants $\underline{n}^{35}_{D}$ 1.5069, $\underline{d}^{23}_{4}$ 1.2095.

A previous attempt to carry out the synthesis in boiling water by the method of Marvel and Tanenbaum[100] resulted in a 67% recovery of chloroacetal.

2,4-Dichlorophenoxyacetaldehyde.- The hydrolysis of 2,4-dichlorophenoxyacetaldehyde diethylacetal was carried out by the method of Allen and Edens[101] in their preparation of phenylpropargylaldehyde.

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[100] C. S. Marvel and A. L. Tanenbaum, Org. Syntheses, Coll. Vol. 1, 435 (1941).

[101] C. F. H. Allen and C. O. Edens, Jr., ibid., 25, 92 (1945).

A two-phase system of 97.7 g. (0.35 mole) of 2,4-dichlorophenoxyacetaldehyde diethylacetal and 350 ml. of water containing 25 ml. of concentrated sulfuric acid was refluxed with stirring for 1 hour. The mixture was then steam-distilled for 17 hours; even after this long period of distillation, product was still coming over. From the distillate was filtered 38.5 g. (49%, calculated as 2,4-dichlorophenoxyacetaldehyde monohydrate[102]) of white solid melting at 72-77°. This solid was dissolved in 260 ml. of a 2:1 benzene-petroleum ether (b.p. 60-70°) solution; a small amount of a colorless liquid heavier than the bulk of the solution was separated and discarded when it was found to be miscible with water. As no solid separated, the solvent was removed to leave a white solid melting at 53-58° with preliminary softening. Two recrystallizations from petroleum ether (b.p. 60-70°) gave 18.0 g. (25%) of white product melting at 57-60°.

Anal. Calcd. for $C_8H_6Cl_2O_2$: Cl, 34.59. Found: Cl, 34.39, 34.45.

Pomeranz,[102] in his preparation of phenoxyacetaldehyde, steam-distilled the hydrolyzed acetal to give phenoxyacetaldehyde monohydrate, which was converted to the anhydrous aldehyde by distillation under reduced pressure.

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[102] C. Pomeranz, Monatsh., 15, 739 (1894).

In a second preparation of 2,4-dichlorophenoxyacetaldehyde by the same method as that used in the first trial there was obtained a 37% yield of product melting at 58-61° with preliminary softening and formation of a cloudy melt which became clear at 66°.

An attempt to prepare the aldehyde by acid hydrolysis of the acetal, removal of the aqueous solution, treatment of the residual white paste with sodium bisulfite reagent, and isolation and decomposition of the bisulfite addition compound gave an 18% crude yield, calculated as 2,4-dichlorophenoxyacetaldehyde monohydrate, of white solid melting at 64-70° to give a turbid liquid.

2,4-Dichlorophenoxyacetaldehyde semicarbazone.- In general accordance with a standard procedure,[87] 1.90 g. (0.017 mole) of semicarbazide hydrochloride and 2.85 g. of sodium acetate were added to 3.08 g. (0.015 mole) of 2,4-dichlorophenoxyacetaldehyde. The mixture was refluxed for 30 minutes, cooled, and filtered to give 3.90 g. (99%) of white solid melting at 176-180° (decompn.). Two recrystallizations from 50-60 ml. of a 1:2 water-95% ethanol solution gave 2.62 g. (67%) of product melting at 181-183° with gas evolution and formation of an orange liquid.

Anal. Calcd. for $C_9H_9Cl_2N_3O_2$: Cl, 27.06. Found: Cl, 26.98, 27.07.

2,4-Dichlorophenoxyacetaldehyde thiosemicarbazone.- This derivative was prepared by the method of Wilson and Burns[103] from 3.08 g. (0.015 mole) of 2,4-dichlorophenoxyacetaldehyde and 1.55 g. (0.017 mole) of thiosemicarbazide in a solution of 50 ml. of ethanol and 3 ml. of water. The mixture was refluxed for 1 hour, cooled, and filtered to give 3.14 g. (75%) of white solid melting at 151-156°. Recrystallization from 30 ml. of a 1:5 water-ethanol solution gave 2.73 g. (65%) of product melting at 155-157°.

Anal. Calcd. for $C_9H_9Cl_2N_3OS$: Cl, 25.49. Found: Cl, 25.33, 25.43.

2,4-Dichlorophenoxyacetaldehyde 2,4-dinitrophenylhydrazone.- In a modification of the method of Allen,[104] 5.6 g. (0.020 mole) of 2,4-dichlorophenoxyacetaldehyde diethylacetal and 4.0 g. (0.020 mole) of 2,4-dinitrophenylhydrazine in 200 ml. of ethanol were heated to boiling. The mixture was cooled slightly, and 4 ml. of concentrated hydrochloric acid was added. Upon heating to reflux, the solid went into solution. The mixture was refluxed for 1 hour, a copious amount of orange solid precipitating early in the reflux period. Filtration, upon cooling, gave 7.1 g.

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[103] F. J. Wilson and R. Burns, J. Chem. Soc., 121, 870 (1922).

[104] C. F. H. Allen, J. Am. Chem. Soc., 52, 2955 (1930).

(92%) of product melting at 169-173°. Recrystallization from a solution of 100 ml. of ethanol and 220 ml. of ethyl acetate gave 5.3 g. (69%) of orange solid melting at 172-174°.

Anal. Calcd. for $C_{14}H_{10}Cl_2N_4O_5$: Cl, 18.41. Found: Cl, 18.32, 18.31.

2,4-Dichlorophenoxyacetaldehyde 4-nitrophenylhydrazone.- A mixture of 5.6 g. (0.020 mole) of 2,4-dichlorophenoxyacetaldehyde diethylacetal and 3.1 g. (0.020 mole) of 4-nitrophenylhydrazine in 200 ml. of ethanol was heating to boiling to give a clear solution. After slight cooling, 4 ml. of concentrated hydrochloric acid was added. The solution was refluxed on a steam-bath, with stirring, for 10 minutes with no precipitation. The steam-bath was then replaced with a cold water-bath, and stirring was continued for an additional 50 minutes. The orange solid which separated during this cooling was filtered to give 2.62 g. (39%) of material which partially melted at about 175°. Two recrystallizations from ethanol-ethyl acetate solutions, each time with filtration of a small amount of insoluble red solid from the hot solution, gave 1.15 g. (17%) of orange solid melting at 184-186°.

Anal. Calcd. for $C_{14}H_{11}Cl_2N_3O_3$: C, 49.43; H, 3.26; N, 12.35. Found: C, 49.16, 49.28; H, 3.40, 3.34; N, 12.29, 12.40.

In an earlier attempt to prepare the 4-nitrophenylhydrazone, the reaction was carried out in the same manner as that for the preparation of the 2,4-dinitrophenylhydrazone except that the hydrochloric acid was added before heating was begun. From this reaction was obtained a 66% crude yield of glyoxal bis(4-nitrophenylhydrazone).[105] This product, after digestion with a hot ethanol-ethyl acetate solution and with hot dioxane, was recrystallized from nitrobenzene to give a dark red solid melting at 316° with gas evolution and formation of a dark liquid, and identified as glyoxal bis(4-nitrophenylhydrazone) by a mixed melting point with an authentic specimen.

In another trial, using reaction conditions identical with those employed for the preparation of the 2,4-dinitrophenylhydrazone, there was obtained a 52% yield of crude glyoxal bis(4-nitrophenylhydrazone)(mixed m.p.) melting at 306° (decompn.).

By the same procedure as was used in the reaction above where a 66% yield of the bis- compound was obtained, chloroacetal was allowed to react with 4-nitrophenylhydrazine in ethanol in the presence of hydrochloric acid to give a 66%

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[105] A. Wohl and C. Neuberg, Ber., 33, 3095 (1900).

yield of crude glyoxal bis(4-nitrophenylhydrazone)(mixed m.p.) melting at 307° (decompn.).

In the event that 2,4-dichlorophenol might be a cleavage product formed in the preparation of glyoxal bis(4-nitrophenylhydrazone) from 2,4-dichlorophenoxyacetaldehyde diethylacetal and 4-nitrophenylhydrazine, an attempt was made to find phenolic material in the solution from which the bis- compound was first isolated in 66% yield. This was done by diluting the filtrate with water, extracting it with ether, extracting the ethereal solution with 5% sodium hydroxide, and acidifying the alkaline solution with hydrochloric acid. Extraction of the acidic solution with ether, followed by drying and removal of the ether, gave a dark red liquid residue which did not solidify on standing in an ice-bath. A comparison of the infrared spectrum of this liquid with that of 2,4-dichlorophenol showed that the two substances were not the same. The spectrum of the liquid also showed that no aldehydic or ketonic carbonyl group was present.

2,4-Dichlorophenoxyacetaldehyde 2,4,6-trichlorophenylhydrazone (attempted).- In an effort to prepare this hydrazone by the same method as that used for the synthesis of the 2,4-dinitrophenylhydrazone, except that the hydrochloric acid was added before heating was begun, there was obtained

a 42% crude yield of glyoxal bis(2,4,6-trichlorophenylhydrazone)[106] melting over the range 167-175°. Recrystallization from a 3:4 ethanol-ethyl acetate solution gave pale yellow crystals melting at 189-191°, identified as glyoxal bis(2,4,6-trichlorophenylhydrazone) by a mixed melting point with an authentic specimen.

2,4-Dichlorophenoxyacetaldoxime (attempted).- By a standard procedure,[87] a mixture of 3.08 g. (0.015 mole) of 2,4-dichlorophenoxyacetaldehyde, 7.0 g. (0.10 mole) of hydroxylamine hydrochloride, 3.0 g. (0.075 mole) of sodium hydroxide, 70 ml. of water, and 100 ml. of ethanol was refluxed gently, with stirring, for 1 hour. As no solid separated upon cooling, the solution was concentrated, again cooled, and filtered to give 2.47 g. (75%, calculated as the desired compound) of white solid melting at 102-106°. Concentration of the mother liquor gave an additional 0.58 g. of white solid melting at 93-98° with preliminary softening; the melting point was increased upon admixture with a sample of the first crop. The two crops were combined and recrystallized from 260 ml. of a 1:3 ethanol-water solution to give 2.51 g. of white solid melting over the range 66-103°. Another recrystallization from the same solvent pair gave

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[106] F. D. Chattaway and L. H. Farinholt, J. Chem. Soc., 94 (1930).

2.05 g. of white solid melting over the range 69-98°. This material was not studied further.

In another attempt to prepare the oxime, a two-phase system of 5.6 g. (0.020 mole) of 2,4-dichlorophenoxyacetaldehyde diethylacetal, 100 ml. of water, and 1 ml. of hydrochloric acid was refluxed with stirring for 2 hours. The thin white paste formed upon cooling was extracted with ether. Following removal of the ether, the colorless liquid residue was refluxed with stirring for 4 hours in a mixture of 9.0 g. (0.13 mole) of hydroxylamine hydrochloride, 4.0 g. (0.10 mole) of sodium hydroxide, 50 ml. of water, and 50 ml. of ethanol. Filtration of the cold mixture gave 2.95 g. (67%, calculated as the desired oxime) of white solid melting at 99-105°. Recrystallization from 110 ml. of a 2:9 benzene-petroleum ether (b.p. 60-70°) solution gave 1.42 g. of white solid melting at 103-105°. Concentration of the mother liquor gave an additional 0.76 g. of white solid melting at 70-75°; a mixed melting point with a sample from the first crop extended over the range 70-92°. The solid melting at 103-105° was recrystallized from a solution of 100 ml. of petroleum ether (b.p. 60-70°) and 10 ml. of benzene to give 1.19 g. of long white needles melting at 113-116°. Another recrystallization from the same solvent pair caused the melting point of the solid (1.11 g.) to drop

to 111-116°. Recrystallization from 140 ml. of a 1:3 ethanol-water solution gave 1.02 g. of white needles melting at 110-115°.

Recrystallization of the solid melting at 70-75° from 15 ml. of petroleum ether (b.p. 60-70°) gave 0.65 g. of white solid melting at 73-75°. Another recrystallization from the same solvent gave 0.58 g. of material melting chiefly at 73-75° with preliminary softening; however, some of the solid did not melt until the temperature reached 96°. A final recrystallization from 80 ml. of a 1:3 ethanol-water solution gave 0.51 g. of white solid melting over the range 71-95°.

An infrared spectrum of each of these two final products (m.p. 110-115° and m.p. 71-95°) dissolved in carbon tetrachloride indicated them to be the same. However, a comparison of the spectra of the two substances in a Nujol mull showed they were not the same. This would suggest that the two substances might be dimorphic forms of the same compound; the spectra did not indicate the substances to be syn-anti isomers.

Other derivatives of 2,4-dichlorophenoxyacetaldehyde (attempted).- An effort was made to prepare a number of other aldehyde derivatives, but it was found impossible to isolate a product from any of these reactions. An attempt

to prepare the unsubstituted hydrazone from the free aldehyde by the method of Dutcher and Wintersteiner[107] met with no success. Similarly, efforts to prepare the unsubstituted phenylhydrazone,[87] the hydantoin,[108] and the bis(carboxymethyl)mercaptal,[109] each time through hydrolysis of the acetal without isolation of the intermediate aldehyde, were unsuccessful. Also, an attempt to condense nitromethane[110] with the hydrolysis product of the acetal met with failure.

4-Chlorophenoxymethyl 2-thienyl ketone (attempted).- 4-Chlorophenoxyacetyl chloride was prepared by the method of Minton and Stephen,[111] except that the reaction mixture was heated for 3 hours instead of 1½ hours, to give a 94% yield of very pale yellow liquid boiling at 120-121° (8 mm.). The Friedel-Crafts type reaction was then carried out by a modification of the method of Johnson and May.[112]

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[107] J. D. Dutcher and O. Wintersteiner, J. Am. Chem. Soc., 61, 1992 (1939).

[108] H. R. Henze and R. J. Speer, ibid., 64, 522 (1942).

[109] J. J. Ritter and M. J. Lover, ibid., 74, 5576 (1952).

[110] A. P. Phillips, ibid., 70, 452 (1948).

[111] T. H. Minton and H. Stephen, J. Chem. Soc., 121, 1598 (1922).

[112] J. R. Johnson and G. E. May, Org. Syntheses, Coll. Vol. 2, 8 (1943).

To a solution of 41.0 g. (0.20 mole) of 4-chlorophenoxyacetyl chloride, 16.8 g. (0.20 mole) of thiophene, and 200 ml. of dry thiophene-free benzene, maintained at 0-1°, was added dropwise with stirring 52.2 g. (0.20 mole) of anhydrous stannic chloride over a period of 1 hour. The ice-bath was removed, stirring was continued for 2 hours, and the solution was allowed to stand for 12 hours. Although the color had become purple, there had been no evidence of the evolution of hydrogen chloride; so the mixture was refluxed with stirring for 12 hours, and then hydrolyzed with 1:9 hydrochloric acid. A gray solid weighing 36.4 g. which softened but did not melt when heated to 400° was filtered, and the benzene layer was separated, washed with water, and dried over calcium chloride. Distillation of the solvent gave a dark solid which was recrystallized from 250 ml. of ethanol, with the aid of Norit, to give 10.9 g. (32%) of 5-chloro-3(2H)-benzofuranone[111,113] as a white solid. Recrystallization from 100 ml. of ethanol gave 10.2 g. (30%) of the white crystalline product melting at 118-120°.

Anal. Calcd. for $C_8H_5ClO_2$: C, 56.99; H, 2.99. Found: C, 56.51, 56.49; H, 3.39, 3.32.

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[113] M. L. Kalinowski and L. W. Kalinowski, J. Am. Chem. Soc., 70, 1970 (1948).

In another trial the reaction was carried out the same way except that only one-tenth as much stannic chloride was used, and the entire reaction was carried out with stirring at room temperature for a period of 5 days. Upon working up this mixture in the way described above, there was obtained a small amount of 4-chlorophenoxyacetic acid (mixed m.p.) and a dark liquid residue having the odor of an acid chloride.

4-Chlorophenoxymethyl 2-furyl ketone (attempted).- By essentially the same method as that used in the first attempted preparation of the corresponding thienyl compound, but with substitution of furan for the thiophene, there was obtained a 40% yield of 5-chloro-3(2H)-benzofuranone (mixed m.p.) melting at 114-117°.

DISCUSSION

Synthesis of Compounds

Standard procedures, often with slight modifications when the need existed, were used in most of the preparations and attempted preparations which have been described. Occasionally, such procedures were found to lead to unexpected results.

Most of the oxyacetic acids of the aromatic and heterocyclic compounds were prepared by one or both of two general procedures. In one[69] of the procedures one part of the phenolic-type compound was refluxed with one part of chloroacetic acid and two parts of sodium hydroxide in aqueous solution for three to six hours. In the other procedure[73] one part of the phenolic-type compound and one part of the alkyl haloacetate were added to a solution of one part of the sodium alkoxide in the alcohol from which the alkoxide was prepared. The mixture was heated at, or near, the reflux temperature of the alcohol for one to three hours. Two and one-half parts of concentrated aqueous potassium hydroxide were then added, and heating was continued, usually for ten to thirty minutes.

In the second procedure described above, the reaction temperature was determined by the choice of solvent. In one synthesis, the preparation of 5,7-dichloro-8-quinolineoxyacetic acid, a 76% crude yield was obtained in refluxing methyl cellosolve, whereas in refluxing absolute ethanol there was obtained a 92% crude recovery of 5,7-dichloro-8-hydroxyquinoline. The alcohol chosen in most of the trials was based on the predicted or observed reactivity of the phenolic-type compound.

Although there were not a sufficient number of oxyacetic acids prepared by both procedures to make possible an accurate comparison, the procedure using the ester gave the higher yield of a purer product in the preparation of 6-bromo-2-naphthoxyacetic acid. Also, a procedure using the ester was successful in the synthesis of 5,7-dichloro-8-quinolineoxyacetic acid, whereas the procedure employing the acid in an aqueous ethanol solution gave a 95% crude recovery of 5,7-dichloro-8-hydroxyquinoline. Of course, the higher temperature employed in the procedure using the ester is a factor which must be considered. The results obtained in the attempted preparation of 8-quinolineoxyacetic acid are not such as to warrant a comparison.

Another advantage of the method employing the ester is that, if the intermediate saponification step is not carried

out, the product may be isolated as the ester instead of the free acid. This may be of particular value in the preparation of an oxyacetate the free acid of which is amphoteric. Thus, in this Laboratory ethyl 3-pyridine-oxyacetate was prepared when an effort to synthesize the free acid failed.

No successful control trials were made to compare the effects of chlorine, bromine, and iodine as the halogen in the acid or ester.

Although no cleavage product was isolated upon boiling 2-methoxy-4-chlorophenoxyacetic acid with concentrated hydrochloric acid, refluxing 48% hydrobromic acid did effect selective cleavage to give 2-hydroxy-4-chlorophenoxyacetic acid.[70] It was not surprising that heating the hydroxy compound would lead to the lactone; Carter and Lawrence[114] have reported that distillation of 2-hydroxyphenoxyacetic acid, or its ethyl ester, gives the corresponding lactone. In view of the fact that o-phenylenedioxydiacetic acid has been prepared[114] in a similar manner from the disodium salt of catechol and sodium chloroacetate, it was disappointing to find that treatment of 2-hydroxy-4-chlorophenoxyacetic acid with chloroacetic acid in alkaline solution did not

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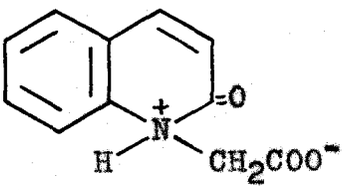
[114] W. Carter and W. T. Lawrence, J. Chem. Soc., 77, 1222 (1900).

result in a product which could be identified as 4-chloro-o-phenylenedioxydiacetic acid.

Although the structure of the product from the reaction of 2-hydroxyquinoline with ethyl chloroacetate and sodium ethoxide was not proved, the infrared spectrum and related work[80,81] would suggest the material to be 1,2-dihydro-2-keto-1-quinolineacetic acid in its zwitter ion form.



This structure would account for its high melting point and low solubility in organic solvents, as well as some of the absorption bands in the infrared spectrum that could not be explained if the substance were an oxyacetic acid.

Attempts to prepare 8-quinolineoxyacetic acid by modifications of the method of Nagel[82] proved unsuccessful. In one trial there was obtained a small amount of product melting 5° above that reported by Nagel, but the infrared spectrum showed the material to contain no carbonyl group. Furthermore, the supposed 8-quinolineoxyacetic acid hydrochloride prepared as an intermediate did not give proper analyses, although its infrared spectrum did show the presence

of a carbonyl group. An attempt to prepare the methiodide of 8-quinolineoxyacetic acid from the supposed hydrochloride led to a compound which not only gave analyses not in agreement with those required for the methiodide but also contained no carbonyl group, as determined from the infrared spectrum.

The monohydrate of the methiodide of 8-hydroxyquinoline was prepared from 8-hydroxyquinoline and methyl iodide in refluxing 90% ethanol. The melting point of the product thus obtained was in close agreement with that reported earlier[84] as prepared in a sealed tube in the absence of solvent. It melted considerably higher than did the complex product obtained by Lippmann and Fleissner,[85] who carried out the reaction in methanol.

The formation of 8-hydroxy-5-quinolinesulfonic acid in the attempted preparation of 5-sulfo-7-iodo-8-quinolineoxyacetic acid was not greatly surprising, for earlier workers[86] had reported that it resulted upon heating in water the sodium salt of 8-hydroxy-7-iodo-5-quinolinesulfonic acid.

Although α-(2,4-dichlorophenoxy)palmitic acid was not prepared in pure form, two derivatives made from the crude material gave good analyses.

An attempt to prepare ethyl o-phenylenedioxyacetate by the method of Christiansen and Dolliver[88] met with little

success. It was later found that ether extraction was not successful in removing the ethyl o-phenylenedioxyacetate from a 5% aqueous solution of sodium hydroxide containing some ethanol, for acidification of the alkaline solution, followed by ether extraction and distillation of the solvent and product, gave a 10% yield of the desired ester. This would indicate that the hydrogen on the carbon alpha to the carbethoxyl group is so acidic as to permit salt formation in the alkaline solution. Although one would expect this hydrogen to be quite "active", such a great acidity would hardly be predicted. Nevertheless, it was found that the ester could be extracted by ether from a 5% sodium bicarbonate solution to give, upon distillation, a 28% yield of product.

In view of the apparent acidity of ethyl o-phenylenedioxyacetate, an experiment was carried out to see if it might undergo a malonic ester type of reaction. Although the results of the trial did not indicate such a reaction to have occurred, they were not sufficiently conclusive to rule out the possibility that the reaction might have taken place.

In line with the observed acidity of ethyl o-phenylenedioxyacetate, it was found that the ethoxyl group could be replaced by other groups with great ease. No difficulty was

encountered in preparing the amide, hydrazide, anilide, and n-butyl ester. The fact that the amide formed in a matter of seconds, whereas prolonged periods of time are usually required for amide formation under these conditions, is particularly indicative of the ease of replacement of the ethoxyl group in this ester.

Ethyl 4-chloro-o-phenylenedioxyacetate was prepared in higher yield (36%) than was the non-chlorinated compound (28%). The higher yield of the chloro compound probably resulted from stabilization of the catechol brought about by the presence of the chlorine atom in the molecule. The relatively low yields of each of the o-phenylenedioxyacetates may be caused to a significant extent by the attachment of a $-CHClCOOC_2H_5$ group to an oxygen in one catechol molecule with subsequent reaction of the α-chloro ester thus formed with another molecule of the catechol. This, upon further condensation, would result in cyclic or linear polymers.

An attempt was made to prepare ethyl 4-chlorophenacyloxyacetate, with the plan to use it as an intermediate in the synthesis of 4-chlorostyryloxyacetic acid, a vinylog of 4-chlorophenoxyacetic acid. It was hoped that once the phenacyl compound had been prepared, subsequent reduction, dehydration, and hydrolysis would lead to the desired 4-chlorostyryloxyacetic acid. However, no ethyl 4-chloro-

phenacyloxyacetate was isolated from the reaction of 4-chlorophenacyl bromide with ethyl glycolate and sodium. This might well have been predicted, for Widman[115] has reported that phenacyl chloride reacts with sodium methoxide and with sodium ethoxide in an unexpectedly complex manner to give α- and β-chlorodiphenacyls. More recently, Berson[116] has postulated that the α- and β-bromodiphenacyls formed by treatment of phenacyl bromide with sodium ethoxide are produced through self-condensation of the phenacyl bromide in a normal Darzens type of reaction.[117]

As is usual in that type of reaction,[95,96,97,98] the attempted synthesis of 1-nitro-2-(p-chlorophenoxy)ethane from 1-bromo-2-(p-chlorophenoxy)ethane and silver nitrite resulted in a mixture of products which probably included such compounds as nitrite, nitrate, alcohol, and ketone, as well as the desired nitro compound. The simple distillation which was made was not sufficient to separate the mixture into its individual compounds.

When an attempt was made to prepare 2,4-dichlorophenoxyacetaldehyde diethylacetal from 2,4-dichlorophenol and

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[115] O. Widman, Ann., 400, 86 (1913).

[116] J. A. Berson, J. Am. Chem. Soc., 74, 5175 (1952).

[117] M. S. Newman, Org. Reactions, 5, 413 (1949).

chloroacetal in a refluxing aqueous solution of sodium hydroxide by the method of Marvel and Tanenbaum[100], 67% of the chloroacetal was recovered, and none of the desired product was isolated. These results are similar to those obtained by Autenrieth,[118] who observed that very little sodium chloride was formed when sodium phenoxide and chloroacetal were refluxed for a long time in ethanolic solution. However, Autenrieth found that the desired phenoxyacetaldehyde diethylacetal was formed upon heating an ethanolic solution of sodium phenoxide and chloroacetal in a sealed tube at 160° for two days. Similarly, Pomeranz[102] heated these same substances in a sealed tube at 200° for eight hours to obtain a 70% yield of the acetal. More recently, Rotbart[119] and Dey[120] prepared phenoxyacetaldehyde diethylacetal from sodium phenoxide and bromoacetal.

As it was not convenient to carry out a relatively large-scale preparation of 2,4-dichlorophenoxyacetaldehyde diethylacetal under pressure, the higher temperature desired was obtained by use of a high-boiling solvent. In this way the reaction of sodium 2,4-dichlorophenoxide with chloroacetal was carried out at atmospheric pressure in diethylene

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[118] W. Autenrieth, Ber., 24, 159 (1891).

[119] M. Rotbart, Ann. chim., [11], 1, 439 (1934).

[120] A. N. Dey, J. Chem. Soc., 1057 (1937).

glycol maintained at 195-200° for about three and one-half hours to give a 67% yield of the expected purified acetal. Subsequently, Drake[99] has prepared 2,4-dichlorophenoxyacetaldehyde diethylacetal by heating at 150° for 18 hours, under autogenous pressure, equimolar quantities of 2,4-dichlorophenol, chloroacetal, and sodium methoxide dispersed in ethanol.

In the present work, 2,4-dichlorophenoxyacetaldehyde was prepared by acid hydrolysis of the acetal, followed by steam distillation of the aldehyde. Experimental evidence, together with the earlier work of Pomeranz[102] on phenoxyacetaldehyde, indicates that the product obtained from the distillate was probably the monohydrate of 2,4-dichlorophenoxyacetaldehyde. Although this water of hydration was removed by recrystallization from a hydrocarbon solvent, it may be that it could have been removed more satisfactorily by vacuum distillation of the aldehyde.[102]

An attempt to isolate the aldehyde from the hydrolyzed acetal by formation of the sodium bisulfite addition compound, followed by acid decomposition of the addition product, led to what was probably an 18% yield of crude 2,4-dichlorophenoxyacetaldehyde monohydrate. This low yield of product might be due to a resistance of the acetal to hydrolysis; Rotbart[119] has reported that phenoxyacetaldehyde diethylacetal

is much more resistant to hydrolysis than is the diethylacetal of cyclohexyloxyacetaldehyde. Also, Rosenmund and Zetzsche[121] have reported that phenoxyacetaldehyde, prepared by reduction[122] of phenoxyacetyl chloride, reacts with sodium bisulfite to give an addition product corresponding to a 72% yield of the regenerated aldehyde. There is, of course, the possibility that an acid-catalyzed aldol condensation might have occurred during the acid hydrolysis of the acetal used in the present work, and that some process such as steam distillation was required to shift the equilibrium between aldehyde and aldol by continuous removal of the aldehyde as it was formed.

Although no difficulty was encountered in the preparation of the semicarbazone, thiosemicarbazone, or 2,4-dinitrophenylhydrazone of 2,4-dichlorophenoxyacetaldehyde, difficulty or failure was experienced in attempts to prepare a number of other derivatives. Attempts to prepare the hydrazone, phenylhydrazone, hydantoin, bis(carboxymethyl)mercaptal, and condensation product with nitromethane all ended in failure. With the exception of the unsubstituted hydrazone,

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[121] K. W. Rosenmund and F. Zetzsche, Ber., 56, 1481 (1923).

[122] E. Mosettig and R. Mozingo, Org. Reactions, 4, 362 (1948).

each of these preparations was attempted, following hydrolysis of the acetal, without isolation of the intermediate aldehyde. Attempts to prepare the oxime, with or without isolation of the intermediate aldehyde, led to a product which appeared to become more impure upon recrystallization. Indeed, it appeared at first that two products were being formed that might be found to be the syn and anti isomers of the aldoxime. However, the infrared spectra indicated that these products were not isomers, although they might have been dimorphic forms of the aldoxime.

Although the 4-nitrophenylhydrazone could be prepared by carefully controlling the period of time during which the acetal was refluxed with 4-nitrophenylhydrazine in ethanol containing hydrochloric acid, a longer period of refluxing, such as that used for the preparation of the 2,4-dinitrophenylhydrazone, led to the formation of the bis(4-nitrophenylhydrazone) of glyoxal. As it is known that ketones having a halogen atom on the carbon alpha to the carbonyl group do sometimes react with phenylhydrazines to give bis-phenylhydrazones of substituted glyoxals,[123,124] it was thought that perhaps the phenoxy group might play the same

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[123] S. Bodforss, Ber., 72, 468 (1939).

[124] N. Campbell and E. B. McCall, J. Chem. Soc., 2870 (1950).

role as a halogen atom. On this basis, it was expected that 2,4-dichlorophenol would be formed as a cleavage product. However, no evidence of its presence could be found.

As chloroacetal has been shown to react with phenylhydrazine to give glyoxal bisphenylhydrazone,[125] it was fully expected that it would form the bis(4-nitrophenylhydrazone) with 4-nitrophenylhydrazine; this expectation was borne out.

When the reaction of 2,4-dichlorophenoxyacetaldehyde diethylacetal with 2,4,6-trichlorophenylhydrazine was carried out, glyoxal bis(2,4,6-trichlorophenylhydrazone) was isolated.

Although sufficient study was not made of the reactions of 2,4-dichlorophenoxyacetaldehyde diethylacetal with the substituted phenylhydrazones to warrant an unquestioned conclusion, it may well be that the 2,4-dinitrophenylhydrazone of 2,4-dichlorophenoxyacetaldehyde owes its greater stability, relative to the 4-nitro and 2,4,6-trichloro derivatives, to the greater electron-attracting character of the two nitro groups.

When an attempt was made to prepare 4-chlorophenoxymethyl 2-thienyl ketone by refluxing a mixture of equimolecular quantities of 4-chlorophenoxyacetyl chloride,

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[125] E. Fischer, Ber., 26, 92 (1893).

thiophene, and anhydrous stannic chloride in benzene solution, the only substance isolated was the Friedel-Crafts intramolecular cyclization product of the acid chloride. The same compound was obtained upon substitution of thiophene with furan. No product of a Friedel-Crafts reaction was isolated when an attempt was made to prepare the thienyl compound, using one-tenth as much stannic chloride, by carrying out the reaction at room temperature for a period of five days.

Testing of Compounds

The compounds which were prepared in this work were tested, or are being tested, for formative activity. The procedure used for carrying out these tests has been described.[126] An effort has been made to have starting materials as well as the final products tested in the event that this added information might prove useful in finding the minimum structural requirements for activity. Probably some of the compounds have been tested previously, possibly by a method similar to the one used in this study.

Given in Table 1 is a list of compounds which have been, or will be, made available for testing for formative

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[126] J. W. Brown and R. L. Weintraub, Botan. Gaz., 111, 448 (1950).

Table 1

Activities of Compounds

Compound	Activity[a]
Guaiacol	---
4-Chloroguaiacol	Inactive
2-Methoxy-4-chlorophenoxy-acetic acid	Virtually no activity
2-Hydroxy-4-chlorophenoxy-acetic acid	Activity about 1% that of 2,4-D
Lactone of 2-hydroxy-4-chlorophenoxyacetic acid	Inactive
3-Chloro-2-naphthol	---
3-Chloro-2-naphthoxyacetic acid	---
6-Bromo-2-naphthol[b]	---
6-Bromo-2-naphthoxyacetic acid	Inactive
6-Bromo-2-hydroxynaphthoic acid	Inactive

[a]Those compounds for which no activity is given either have not yet been submitted from this Laboratory or have not yet been tested for formative activity.

[b]Kindly provided by Dr. J. B. Campbell of E. I. du Pont de Nemours and Company.

Table 1 (Continued)

Compound	Activity[a]
2,4-Dinitro-4'-hydroxydiphenylamine	---
2-Nitro-4-chloro-4'-hydroxydiphenylamine	---
1-Amino-4-hydroxyanthraquinone	---
1,5-Di(dimethylamino)-4,8-dihydroxyanthraquinone	---
1-Hydroxy-4-(β-cyanopropylamino)anthraquinone[c]	---
3-Hydroxypyridine	---
Ethyl 3-pyridineoxyacetate	---
2-Hydroxyquinoline	---
1,2-Dihydro-2-keto-1-quinolineacetic acid	Inactive
8-Hydroxyquinoline	---
Product from attempted preparation of 8-quinolineoxyacetic acid hydrochloride	---
Product from attempted preparation of the methiodide of 8-quinolineoxyacetic acid	---

[c]This compound, in addition to the five compounds which precede it in this Table, was kindly provided by Dr. J. B. Dickey.

Table 1 (Continued)

Compound	Activity[a]
Monohydrate of the methiodide of 8-hydroxyquinoline	---
5,7-Dichloro-8-hydroxy-quinoline	---
5,7-Dichloro-8-quinoline-oxyacetic acid	Inactive
5,7-Dibromo-8-hydroxy-quinoline	---
5,7-Dibromo-8-quinoline-oxyacetic acid	---
5,7-Diiodo-8-hydroxy-quinoline	---
5,7-Diiodo-8-quinoline-oxyacetic acid	---
8-Hydroxy-7-iodo-5-quinolinesulfonic acid	---
Dihydrate of 8-hydroxy-5-quinolinesulfonic acid	---
α-(2,4-Dichlorophenoxy)-palmitic acid[d]	---
α-(2,4-Dichlorophenoxy)-palmitamide	---
α-(2,4-Dichlorophenoxy)-palmitanilide	---
Catechol	---

[d] Impure.

Table 1 (Continued)

Compound	Activity[a]
Ethyl o-phenylenedioxyacetate	Some activity
o-Phenylenedioxyacetamide	---
o-Phenylenedioxyacethydrazide	---
o-Phenylenedioxyacetanilide	---
n-Butyl o-phenylenedioxyacetate	---
4-Chlorocatechol	Inactive
Ethyl 4-chloro-o-phenylenedioxyacetate	Activity 1% that of 2,4-D
Product from attempted preparation of 1-nitro-2-(p-chlorophenoxy)-ethane[e]	Active
Product from attempted preparation of 1-nitro-2-(p-chlorophenoxy)-ethane[f]	Active
2,4-Dichlorophenoxyacetaldehyde diethylacetal	---

[e] B.p. 99-110° (1.1 mm.); chlorine and nitrogen present, bromine absent.

[f] B.p. 110-120° (1.1 mm.); chlorine and nitrogen present, bromine absent.

Table 1 (Continued)

Compound	Activity[a]
2,4-Dichlorophenoxyacetaldehyde	---
2,4-Dichlorophenoxyacetaldehyde semicarbazone	Activity 13% that of 2,4-D
2,4-Dichlorophenoxyacetaldehyde thiosemicarbazone	Activity 4% that of 2,4-D
2,4-Dichlorophenoxyacetaldehyde 4-nitrophenylhydrazone	---
2,4-Dichlorophenoxyacetaldehyde 2,4-dinitrophenylhydrazone	Inactive
2,4-Dichlorophenoxyacetaldoxime (?)[g]	---
2,4-Dichlorophenoxyacetaldoxime (?)[h]	---
Glyoxal bis(4-nitrophenylhydrazone)	---
Glyoxal bis(2,4,6-trichlorophenylhydrazone)	---
5-Chloro-3(2H)-benzofuranone	---

[g]Low-melting product, m.p. 71-95°.

[h]Higher-melting product, m.p. 110-115°.

activity. At the time of this writing relatively few of the results of these tests have been received. Some of the results given were obtained in preliminary or orienting tests. Further tests will probably lead to more quantitative results of greater reliability.

SUMMARY

A brief survey has been made of some of the more recent literature concerned with correlations of chemical structure and plant growth activity of several types of organic compounds.

A number of new compounds, most of which bear a structural resemblance to the aryloxyalkanoic acids, have been synthesized to be tested for formative activity in plants. Included among these substances are derivatives of some heterocyclic compounds, as well as of aryloxyalkanoic and arylenedioxyalkanoic acids. In some of these compounds the functional carboxyl group has been replaced by some other group in order to study the effect of such a substitution on the compound as a plant growth regulator.

A list of compounds is given which have been, or will be, submitted for testing for formative activity. Those results which have been received at the time of this writing are included.

Attempts to acylate thiophene and furan with 4-chlorophenoxyacetyl chloride were found to result in intramolecular cyclization of the acyl chloride.

Although some derivatives of 2,4-dichlorophenoxyacetaldehyde were prepared satisfactorily, difficulty was

encountered with others. Attempts to prepare certain substituted phenylhydrazones of this aldehyde led to glyoxal bisphenylhydrazones, possibly through cleavage of the ether linkage.