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ALKYLAMINOALKYL ARYOXYACETATES

THESIS

Presented in Partial Fulfillment of the Requirements for the Degree of Master of Science in the Graduate Department of the University of Richmond.

by

William Kenneth Easley, B. S.

The University of Richmond

August 1947

Approved by

J. Stanton Pierce

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INTRODUCTION

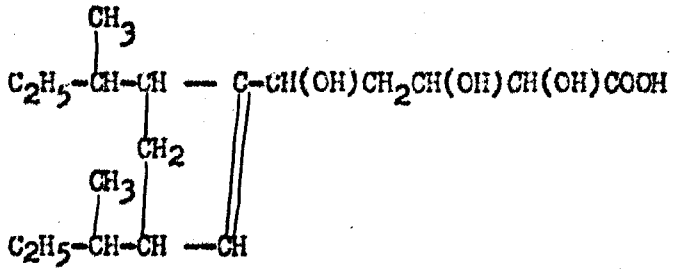
Numerous investigations into the preparation, properties, and effects of plant growth substances have been carried out. It has been shown that phenoxyacetic acids, naphthoxyacetic acids, esters, amides and salts of phenoxyacetic acids and certain substituted products of these acids are plant growth promoting substances.

It is the purpose of this work to produce esters of phenoxyacetic and naphthoxyacetic acids which contain a secondary amino group and as a result of their ability to form acid salts, such as hydrochlorides, water soluble compounds. These compounds would be readily applicable to plants in sprays.

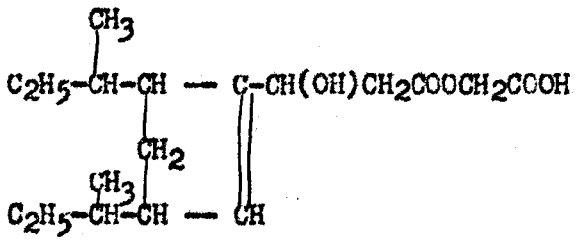
HISTORY

The study of organic compounds of known structure having growth promoting properties began in 1931 when Kögl and collaborators[1] gave a tenative formula for auxine, the substance isolated from B. coli, Rhizopus species, and yeast as $C_{18}H_{32}O_4$. This substance was also found in large quantities in human male and female urine.

Later Kögl[2] gave the structural formulas for auxin-a (I) and auxine-b (II) as follows,



I

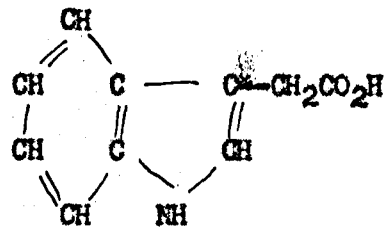


II

(1) Kögl and Smit, Proc. K. Oked. Wetensch. Amsterdam 34, 1411 (1931); C. A. 26, 2755 (1932).

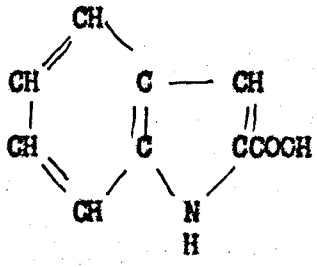
(2) Kögl and Eryxlehen, Z. physical chem. 227, 51 (1934); C. A. 29,3656[7] (1935).

and noted similarity in action between beta-indole acetic acid (III) and the auxins.

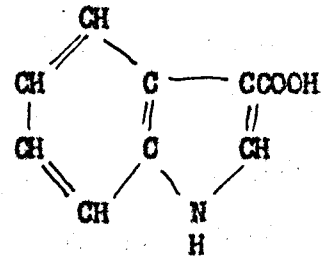


III

Further investigation carried out by Kögl and Kostermans[3] extended the list of growth substances to include 2- and 3-indolecarboxylic acid (IV and V), beta-(3-indole)-propionic acid (VI), 3-indole pyruvic acid (VII) and beta-(3-indole)-alpha-amino-propionic acid (VIII).



IV



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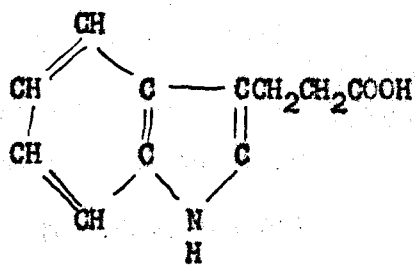
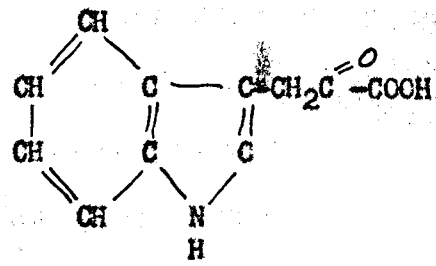
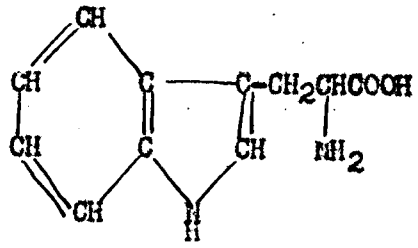


VI



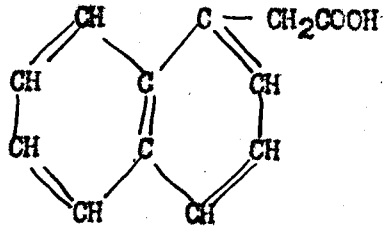
VII

(3) Kögl and Kostermans, Zeitschr. F. phys. Chem. 235, 201-16 (1935); Norman, The Botanical Gazette 107, 476 (1946).

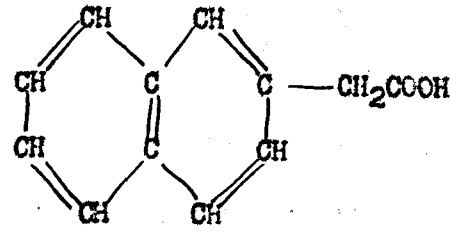


VIII

Zimmerman and Wilcoson[4] tested various nephthaleneacetic acid derivatives, for example alpha- and beta-naphthaleneacetic (IX and X) and various other arylacetic acids for activity on plants.



IX

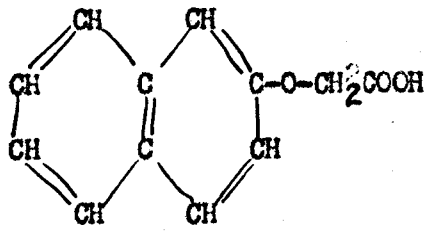


X

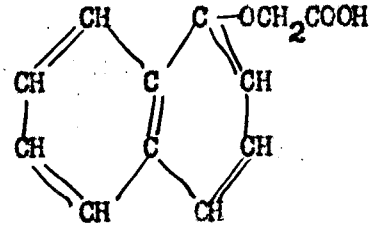
However, it was not until 1938 that beta-naphthoxyacetic acid (XI) was recognized as a growth substance by Irvine. The following year Zimmerman and associates tested alpha-nephthoxyacetic acid (XIII) among other compounds.[5]

(4) Zimmerman and Wilcoson, Conts, Boyce Thompson Inst., 7, 209-20 (1935); Norman, The Botanical Gazette, 107, 476 (1946).

(5) Gilbert, Chem. Rev. 39, 204 (1946).



XI



XII

Spica[6] in 1888 prepared alpha- and beta-naphthoxyacetic acids from the reaction of the potassium salt of chloroacetic acid with the corresponding potassium salt of the naphthol. Spitzer[7] in 1901 undertook further investigation of the reaction described by Spica and obtained beta-naphthoxacetic and in a purer condition than had Spica. He also prepared several derivatives of beta-naphthoxyacetic acid.

Phenoxyacetic acid (XIII) was first prepared in 1859 by Heintz[8], who obtained it as a product of the reaction between sodium phenoxide and the sodium salt of chloroacetic acid.

$C_6H_5-O-CH_2COOH$

XIII

(6) Spica, Gazz. Chem. Ital, 16, 438 (1886); Spitzer, Ber., 34, 3191 (1901)

(7) Spitzer, Ber., 34, 3192 (1901).

(8) Heintz, ann. d. Physik. 109, 489, 361 (1859); Beilstein 6, 161 (4th edition).

The minimum structural requirements for growth substances were postulated by Koepfli, Thimann, and Went[9] as follows: (a) ring system as nucleus, (b) double bond within ring, (c) a side chain, (d) either a carboxyl group or structure which can be converted to a carboxyl group as a component of the side chain at last one carbon from the nucleus, (e) a particular stereochemical configuration between the carboxyl group and the nucleus.

Esters and salts have been found to possess growth-promoting activity often as potent as the acids themselves and in some cases even greater than the parent compound.[10]

Previous work in the esterification of secondary amino alcohols has centered around local anesthetic and anti-spasmodic activity.

The general formula for a typical local anesthetic is

$$Ar - CO - O - (C_n - N =$$

A B C

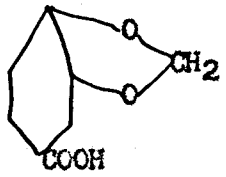
A = the acid
B = the alkanol group
C = the amino group

Among the acids used are p-amino benzoic acid, $p\text{-}NH_2\text{-}C_6H_4\text{-}COOH$, benzoic acid C_6H_5COOH, phenylacetic acid, $C_6H_5\text{-}CH_2\text{-}COOH$, alpha-phenyl propionic acid, $C_6H_5\text{-}CH(CH_3)\text{-}COOH$, p-toluic acid, $p\text{-}CH_3\text{-}C_6H_4\text{-}COOH$,

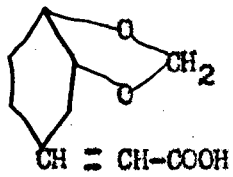
(9) Gilbert, Chem. Rev., 39, 204 (1946).

(10) Gilbert, Chem. Rev., 39, 201 (1946).

piperonylic acid (XIV) and m, p-Methylene dioxycinnamic acid (XV)[11].



XIV



XV

The alkyl chain between the acid and the nitrogen usually is made up of two or three carbon atoms which may, however, be substituted with an alkyl group such as methyl.

The amino group can be either primary[12], secondary or tertiary. Since Goldberg and Whitmore[13] have shown the secondary amino group effective in local anesthetics, derivatives of this nature have been prepared in recent years.

Pierce, Salsbury, and Fredericksen[14] prepared alkoxybenzoates of secondary amino alcohols which have the general formula of

$RO-C_6H_4-COOCH_2CH_2NHR^1.HCl$

where R can be alkyl or allyl and R^1 is alkyl.

Pierce, Salsbury, Haden and Willis[15] also prepared alkoxybenzoates of 2-monoalkyl-amino-2-methyl-1-propanol and 2-mono-alkylamino-1-

(11.) Jenkins and Hartung, The Chemistry of Organic Medicinal Products, John Wiley and Son, New York, second edition, (1943)

(12) Hartung, Munch, and Kester, J. Am. Chem. Soc. 54, 1526 (1932).

(13) Goldberg and Whitmore, J. Am. Chem. Soc. 59, 2380 (1937).

(14) Pierce, Salsbury, and Fredericksen, J. Am. Chem. Soc. 64, 1691 (1942).

(15) Pierce, Salsbury, Haden and Willis, J. Am.Chem. Soc. 64, 2884-5(1942).

butanol which have the following general formulas, respectively;

RO $C_6H_4COOC(CH_3)_2NHR^1$ R and R^1 = alkyl

RO $C_6H_4COOCH(C_2H_5)NHR'$ R and R^1 = alkyl

In 1945 Pierce, Haden, and Gano prepared for study as anti-spasmodics the phenylacetates, diphenylacetates, and phenyl alkyl acetates of beta-methyl-beta-monoalkyl amino propanols. They have the general formula of:

$C_6H_5CH(R)COOCH_2C(CH_3)_2NH(R^1).HCl$

R = C_6H_5, H, C_2H_5

R^1 = alkyl (C_3H_7 through C_6H_{13})

Norman[17] has shown that beta-(diethylamino)-ethyl-2,4-dichlorophenoxyacetate and beta-(diethylamino)-ethyl-2,4,5-trichlorophenoxyacetate possess growth activity comparable with that of 2,4-dichlorophenoxyacetic acid.

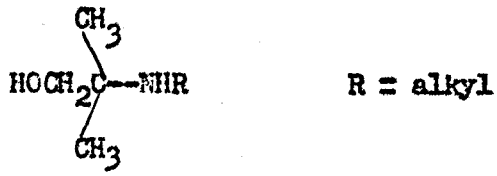
Since many of the compounds which Norman tested were extremely insoluble in water, it is the purpose of this investigation to prepare water soluble esters of beta-naphthoxyacetic and phenoxyacetic acids with 2-methyl-2-monoalkylaminopropanol.

(16) Pierce, Haden and Gano, J. Am. Chem. Soc. 67, 408-9 (1945).

(17) Norman, The Botanical Gazette, 107, 476-507 (1946).

DISCUSSION OF RESULTS

Phenoxyacetyl and beta-naphthoxyacetyl chloride were used to esterify the free base of 2-methyl-2-alkyamino-1-propanols. The possibility of amide formation was not ignored but if amide formation took place it was not to an appreciable extent. The explanation for this seems to lie in steric hindrance of the two methyl groups in the amino alcohol as shown in the following formula:



R = alkyl

Attempts to prepare 2-methyl-2-hexyl-aminopropyl phenoxyacetate hydrochloride and 2-methyl-2-propyl (and hexyl) aminopropyl beta-naphoxyacetate hydrochloride resulted in oils.

Alpha-naphthoxyacetic acid was prepared but attempts to prepare the acid chloride resulted in resin formation.

EXPERIMENTAL

Preparation of Phenoxyacetic Acid:- A typical preparation follows: one mole (94.1 g.) of phenol was placed in a five liter round bottomed flask and 160 g. of 50 per cent sodium hydroxide solution (2 moles) was added. To the resulting alkaline solution one mole (94.5 g.) of chloroacetic acid and a liter of water were added and the mixture was heated for five hours. A liter of water, 80 g. of 50 per cent sodium hydroxide solution (1 mole), and 0.5 mole (47.3 g.) of chloroacetic acid were added and the mixture was heated for four more hours. At the end of this time a liter of water was added and the resulting solution made strongly acidic by the addition of 250 ml. of concentrated hydrochloric acid. Upon cooling a solid separated from the acid solution. The solid was separated by means of suction filtration and the filtrate was discarded. The precipitate of phenoxyacetic acid was purified by recrystallization from water.

Yield, 95.9 g. (63 per cent), M. P. 91-97°

Preparation of Phenoxyacetyl Chloride:- In a typical run 0.2 mole (30.4 g.) of phenoxyacetic acid was refluxed for one hour with 0.6 mole (71.4 g.) of thionyl chloride. The reaction mixture was allowed to cool then it was placed in a claisen flask and the excess thionyl chloride removed by heating the mixture to 100° C. at a pressure of 80 mm. The crude acid chloride was used immediately without further purification.

Preparation of 2-methyl-2-propylamino-propyl Phenoxyacetate Hydrochloride:- In a typical run o.1 mole (13.1 g.) of 2-methyl-2-propylaminopropanol was placed in a 125 ml. distilling flask. To it was added 0.1 mole (17.1 g.) of phenoxyacetyl chloride in portions, the reaction mixture being shaken from time to time and cooled. After the addition of the acid chloride was complete and the initial heat of reaction had subsided, the reaction mixture was heated for 1.5 hours on a water bath. The reaction mixture was then dissolved in the minimal amount of ethyl alcohol (95 per cent) and the alcoholic solution was then poured into 500 ml. of 0.25 N sodium hydroxide solution. An oily layer formed immediately and was separated from the basic solution in a separatory funnel and dissolved in isopropyl ether. The ethereal solution was filtered and saturated with dry hydrogen chloride, precipitating a heavy oil which crystallized upon trituration with anhydrous ethyl ether. The solid product was further purified by recrystallization from a mixture of anhydrous acetone and isopropyl ether.

Yield 8.13 g. (27 per cent), M. P. 130-131°

Preparation of beta-Naphthoxyacetic Acid:- In a typical run, 100 g. of beta-naphthol was placed in a fine liter round-bottomed flask and to the beta-naphthol was added 360 g. of potassium hydroxide solution (1:2). Then to the alkaline solution an aqueous solution of 95 g. of chloroacetic acid was added. The reaction mixture was allowed to cool during which time the sodium salt of beta-naphthoxyacetic acid

separated as a solid. The precipitate was filtered with suction, dissolved in two liters of boiling water and filtered while hot from a slight residue. The filtrate was made strongly acidic by the addition of 125 ml. of concentrated hydrochloric acid. A reddish-white solid formed and was separated by suction filtration.

Yield, 67 g. (42 per cent theory) M. P. 152-154°

Preparation of beta-Naphthoxyacetyl Chloride:- In a typical preparation, 0.2 mole (40.4 g.) of beta-naphthoxyacetic acid was placed in a 500 ml. round-bottomed flask equipped with a reflux condenser and 0.6 mole (71.4 g.) of thionyl chloride was added through the condenser. The mixture was refluxed on the water bath for one hour. At the end of this time the reaction mixture was transferred to a 250 ml. Claisen flask and the excess thionyl chloride removed by heating the mixture to 100° under a pressure of 70 mm. The crude acid chloride was used in the preparation of an ester of 2-methyl-2-monoalkylaminopropanol, as previous attempts to purify the product by vacuum distillation resulted in decomposition.

Preparation of 2-Methyl-2-n-amylaminopropyl beta-naphthoxyacetate Hydrochloride:- In a typical preparation 0.08 mole (12.7 g.) of 2-methyl-2-n-amylamino-1-propanol was placed in a 125 ml. distilling flask. To the secondary amino alcohol 0.08 mole of beta-naphthoxyacetyl chloride was added in portions, with shaking and external cooling. After the addition of the acid chloride was completed and the initial heat of reaction

had subsided, the reaction mixture was heated 1.5 hours on the water bath. The reaction mixture was dissolved in the minimal amount of ethyl alcohol (95 per cent) and the alcoholic solution was poured into a liter of 0.25 N sodium hydroxide solution. An oily layer formed immediately and was separated from the basic solution and dissolved in isopropyl ether. The ethereal solution was filtered and saturated with dry hydrogen chloride, precipitating a heavy oil which crystallized upon trituration with anhydrous ethyl ether. The crystalline product was further purified by recrystallization from a mixture of anhydrous acetone and isopropyl ether.

Yield, 5.7 g. (19 per cent theory). M. P. 155-157°

TABLE OF PHYSICAL CONSTANTS

I

a-Methyl-2-alkyaminopropyl Phenoxyacetates Hydrochlorides:

$C_6H_5OCH_2COOCH_2C(CH_3)_2NHR.HCl$

R	M.P.°C. (uncor.)	Yield %	Formula	Chlorine,% Calcd.	Found	(a)
Propyl	130-131	27	$C_{15}H_{24}O_3NCl$	11.73	11.52,	11.52
Butyl	130.5-131.5	30	$C_{16}H_{26}O_3NCl$	11.23	10.81	
Amyl	146-147	26	$C_{17}H_{28}O_3NCl$	10.75	10.56	10.55

II

2-Methyl-2-alkyaminopropyl-beta-Naphoxyacetate Hydrochlorides:

beta-$C_{10}H_7OCH_2COOCH_2C(CH_3)_2NHR.HCl$

R	M.P.°C. (uncor.)	Yield %	Formula	Chlorine,% Calcd.	Found	
Butyl	160-162	22	$C_{20}H_{28}O_3NCl$	9.67	9.51	9.49
Amyl	155-157	19	$C_{21}H_{30}O_3NCl$	9.31	9.15	9.14

(a) Analyses performed by Mr. R. L. Kersey, Jr.

SUMMARY

Some 2-methyl-2-alkyaminoalkylpropyl-phenoxy and beta-naphoxy-acetates hydrochlorides have been prepared and characterized.

ACKNOWLEDGEMENT

Grateful acknowledgement is given to Dr. J. Stanton Pierce for his advice, encouragement, and constructive criticism during this investigation.

AUTOBIOGRAPHY

I, William Kenneth Easley, was born on July 19, 1921 in Morristown, Tennessee. I attended the public schools of Morristown, Tennessee and graduated from Morristown High School in May 1939. I attended Carson-Newman College for four years receiving the degree of Bachelor of Science in February 1944. During the Summer of 1943 I was a student at East Tennessee State Teachers College. From March 1944 until April 1946 I was a member of the United States Navy, being discharged with the rate of Pharmacist's Mate Second Class. From June 1946 until September 1946 I was employed as a Chemist by Tennessee Eastman Corporation at Oak Ridge, Tennessee. In September 1946 I was awarded a Graduate Assistantship at the University of Richmond where I am completing the requirements for the degree of Master of Science.

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