AN ATTEMPTED SYNTHESIS OF INDOLE-2-PROPIONIC ACID

and

THE OXIDATION OF m-XYLYL BROMIDE TO m-TOLUIC ACID

A Thesis submitted

by

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to the

Post-Graduate Studies Committee

of the University of Manitoba

in partial fulfillment of the

requirements for the Degree

of

Master of Science

- 1939 -

The writer wishes to acknowledge his indebtedness to Dr. E. H. Charlesworth for the suggestion of these problems and for his very kind assistance throughout the course of the investigations.

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P R E F A C E

During recent years there has been a great deal of interest taken in the action of indole derivatives as plant hormones. Since, however, no intensive investigation has been made of derivatives substituted in the 2-position, the synthesis of indole-2-β-propionic acid, with which part I of this thesis deals, was undertaken with the view to having the compound tested for its possible action as a phytohormone.

Unfortunately, after some time, it was found that, due to the poor yields obtained in several of the preparations, supplies of the necessary chemicals would be sufficient for only one run. In view of the probably indefinite results to be obtained, work was begun on a second problem.

Part II of this presentation is an account of attempts to prepare m-toluic acid by the oxidation of m-xylyl bromide.

With the exception of photochemical oxidation, all previous attempts to prepare this acid by the oxidation of m-xylene have been unsuccessful, since both methyl groups attached to the benzene nucleus are attacked by oxidizing agents, resulting in the formation of isophthalic acid. However, from a con-

sideration of similar cases, it is conceivable, theoretically at least, that were a halogen such as bromine, substituted for hydrogen in one of the methyl groups in m-xylene, this group should be attacked by oxidizing agents in preference to the unsubstituted one. Thus by choice of the proper reagent and temperature conditions, it might be possible to obtain m-toluic acid. Since it involves the use of relatively inexpensive chemicals, this method, if successful, might well be of some commercial value in the manufacture of what is now a rather expensive compound.

PART I

I N T R O D U C T I O N

(a) A Survey of Indole Derivatives as Plant Hormones

Attempts to explain the various growth phenomena of plants (correlations, tropisms, bud-inhibition, etc.) have culminated in the isolation, within the last decade, of definite chemical substances, known as auxins or growth substances, which have been shown to be the cause of the afore-mentioned responses. In addition to these naturally-occuring substances, many synthetic compounds (including various indole derivatives) have also been found to be effective as phytohormones. Since the synthesis of the acid named in the title of this thesis was undertaken with the view to having its growth-promoting activity tested, a brief review of the subject of plant hormones will be given, with particular reference to derivatives of indole. A more detailed treatment, especially from the botanical point of view will be found in excellent books written by P. Boysen Jensen,[1] and by F. W. Went and K. V. Thimann[2] and also in review papers by these same authors.[3,4]

Since the early evidence for the existence and role of auxins came through the study of tropisms, it might be of interest, before continuing with a review

of the subject, to note the application of auxins to these phenomena.

It is a well-known fact that plants, when unilaterally illuminated, will grow towards the light. Many elaborate theories were evolved to account for this but the first simple one was proposed by Blaauw, whose experiments led him to state in 1918[5] that "whenever light causes a growth reaction, unequal distribution of the light will cause unequal growth, which we call phototropism" and hence that tropisms were simply a phenomenon of differential growth. The later work of Boysen Jensen and Paal further advanced this theory, giving rise to two possible explanations; first, that phototropism might be due to increased transmission of growth-promoting substance on the dark side of the plant, or second, that it might arise from decreased transmission of growth-promoting substance on the light side. That both of these occur simultaneously was finally shown by Cholodny in 1927[6] and Went in 1928.[7] From the experiments of both of these investigators was evolved the so-called Cholodny-Went theory which is now generally accepted. It may be stated as follows: "Growth curvatures whether induced by internal or by external factors, are due to an unequal distribution of auxin between the two sides of the curving organ."[2] (p.157)

Thus unilateral illumination causes an increased concentration of auxin on the dark side of the stem with a consequent increased growth-rate of this side resulting in a curvature toward the light. Experimental proof of this principle was advanced by Went[7] who arranged coleoptiles* of a species of grass (Avena sativa) on agar blocks in such a manner that, when illuminated from one side, the auxin from the light and dark sides diffused into separate blocks. It was found that the block from the shaded side contained the greater concentration of auxin. Similarly the concentration of auxin by gravity in the under side of the plant stem accounts for its upward growth.

In the case of roots, it has been found, first by Nielsen in 1930[8] and confirmed later by others, that the action of the phytohormones is to inhibit growth. Thus the concentration of auxin on the underside of the root under the influence of gravity, causes the upper portion to develop at a relatively greater rate with a consequent downward curvature of the root.

Although the actual isolation of growth-hormones is a recent development, the idea that the phenomenon of correlation is brought about by substances

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* The coleoptile is a leaf-sheath which envelopes the growing point and first foliage leaf of the plant.

or "saps" was advanced as early as 1758 when Duhamel du Monceau[9] suggested the theory that correlation was brought about by two saps, one moving downward, the other upward, in the plant. The former was elaborated in the leaves and, after passing downward through the cortex, was used for the nutrition of the roots. If, however, this downward stream were intercepted by ringing or other means, it caused swellings, callus and root formation above the wound.

Sachs in 1880,[10] 1882,[11] and 1893[12] brought out a complete theory of such phenomena, his ideas differing, however, from the modern view by the assumption of the existence of many "specific substances" such as root-forming, flower-forming and other substances, which move in different directions through the plant. Light and gravity were assumed to affect the distribution of these special substances. It was, however, through the study of tropisms -- to which attention was directed about this time -- rather than correlations that auxin was finally isolated.

The first important work on this type of phenomena was that of C. Darwin, who showed in 1880[13] that the effects of light and gravity are perceived by the tip of the plant and that the stimulus is transmitted to the lower regions, which then react. This led him

to state that "we must, therefore, conclude that when seedlings are freely exposed to a lateral light, some influence is transmitted from the upper to the lower part, causing the latter to bend." In regard to geotropism of roots, he concluded "that it is the tip alone which is acted on, and that this part transmits some influence to the adjoining parts, causing them to curve downwards".

Although these views met with some opposition, they were completely confirmed by the work of later investigators, among the latter being P. Boysen Jensen. In addition, Boysen Jensen[14,15,16] showed that the stimulus could be transmitted across a wound gap. By cutting off the tips of Avena coleoptiles, sticking them on again with gelatin and illuminating the tip only, he found that curvature appeared not only in the tip but also in the base. From this he concluded that "the transmission of the irritation is of a material nature produced by concentration changes in the coleoptile tip". He did not, however, postulate the presence of a special growth-promoting substance.

The experiments of Boysen Jensen were repeated and extended by Paal in 1914[17] and 1919,[18] who, after excluding the possibilities of the base being influenced by scattered light, by contact stimulus, or by the

assymmetrical weight of the bending tip, confirmed Boysen Jensen's results. In addition he showed that the stimulus could be transmitted by a layer of gelatin but could not cross mica or platinum foil and also that, even without light, curvatures could be induced in the base by cutting off the tip and replacing it on one side of the stump. From these results he concluded[18] that "the tip is the seat of a growth-regulating center. In it a substance (or a mixture) is formed and internally secreted, and this substance, equally distributed over all sides, moves downwards through the living tissue. In the growing zone it causes symmetrical growth. If the movement of this correlation carrier is disturbed on one side, a growth decrease on that side results, giving rise to a curvature of the organ".

Soding, in 1923[19] and again in 1925,[20] further confirmed the theory that the growth of the coleoptile is controlled by the tip through the agency of a diffusible substance. Success in isolating this substance was not, however, achieved for several years, although Seubert in 1925[21] showed that agar containing saliva, diastase, and malt extract caused a promotion of growth.

Isolation of auxin was finally obtained by F. W. Went in 1928[22] by placing coleoptile tips on agar blocks when it was found that the active substance

diffused into the agar. Such blocks when applied to one side of decapitated coleoptile tips caused a curvature of the stem away from the agar, the degree of curvature being proportional, within limits, to the concentration of auxin. This test, later known as the "Went Avena test" has since been used in the assay of the activity of other substances. In addition, by means of this test, certain of the properties of the substance were determined. Thus it was shown to be thermo- as well as photo-stable, and readily diffusible. By allowing the substance to diffuse from agar into a series of blocks of fresh agar and then assaying the activity of each block, the diffusion coefficient could be calculated and hence the molecular weight. The value so determined was 376 -- a figure which was later found to be in fairly good agreement with that calculated for auxin A.

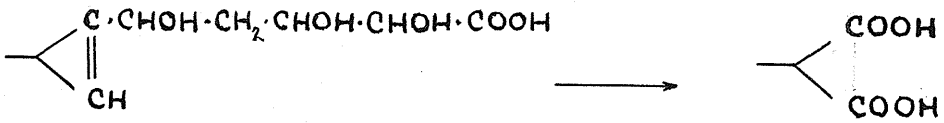
As mentioned previously, Seubert in 1925[21] had shown that growth-promoting substances may occur outside the plant. Extending these experiments, a systematic examination of animal excretions and tissues was made by Kogl and Haagen Smit in 1931,[23] and by Kogl, Haagen Smit and Erxleben in 1933.[24,25] Investigation showed that human urine was an extremely rich source of growth-substance. The bicarbonate-soluble

fraction of the ether extract of urine was extracted with petroleum ether and purified by partition between benzene and aqueous alcohol. It was then precipitated with lead acetate from weakly alkaline seventy per cent alcohol, treated with calcium hydroxide to precipitate a colored impurity, and finally heated with acid methyl alcohol. The product isolated proved, however, to be a lactone instead of the expected ester. It was then distilled in vacuo when the bulk of the active substance distilled at 125° to 130° under 0.1 millimeter pressure, yielding crystals of an acid with the molecular formula $C_{18}H_{32}O_5$, for which the name "auxin A" was proposed.

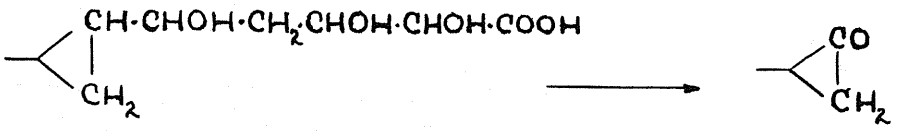
By a very similar method of purification, another active substance, auxin B, was subsequently isolated from malt and from corn germ oil by Kogl, Erxleben and Haagen Smit in 1934.[26] It proved on analysis to have the formula $C_{18}H_{30}O_4$, being isomeric with the lactone of auxin A. Its reactions showed it to be acidic in nature with an activity as a growth-promoter equal to that of the other hormone.

By a series of brilliant researches, the constitutional formulae of these two closely related compounds were determined by Kogl, Erxleben and Haagen Smit in 1933[27] and by Kogl and Erxleben in 1934[28] and 1935.[29]

Their investigations have been summarized as follows, by Went and Thimann.[2] The acid and lactone were shown to have but one double bond, and the acid to have one carboxylic group. After addition of hydrogen at the double bond, the number of hydrogen atoms in the molecule was still two short of saturation, and hence there must be one ring in the molecule. In auxin A, the remaining three oxygen atoms were found to be in hydroxyl groups, while in auxin B, one hydroxyl and one keto-group could be identified. Oxidative degredation of both auxin A and B gave rise to a C_{13} dicarboxylic acid which contained no hydroxyl groups. Similar oxidation of the hydrogenated derivative, which is biologically inactive, yielded a neutral C_{13} ketone. The oxidation has therefore carried away all the hydroxyl groups, together with a chain of five carbon atoms. From the difference between the two oxidations it is also clear that the double bond was not in the side chain which was removed. Further reasoning indicated that this side chain contained the three hydroxyl groups and the carboxyl group, and established their relative positions. Hence the oxidations must be formulated as follows, substance I being auxin A, and II dihydro-auxin A:



I III



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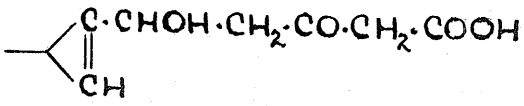
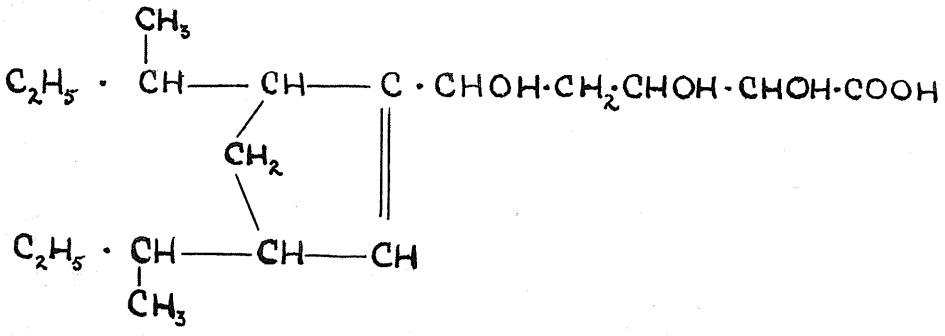
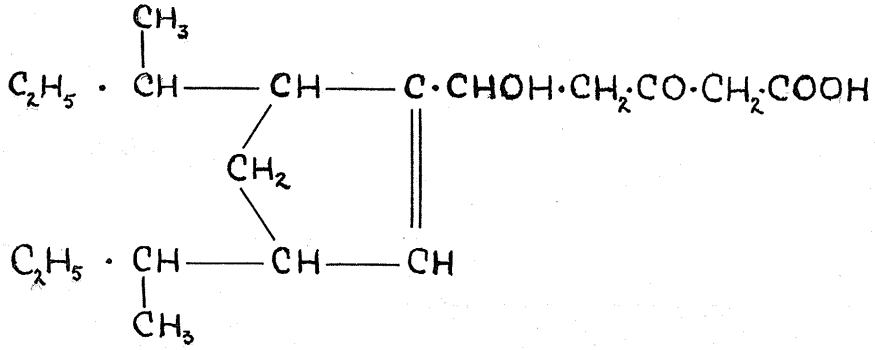


V

Since auxin B loses carbon dioxide to give a neutral ketone, it must have its keto-group in the β-position and therefore must be formulated as V. The structure of the C_{13} residue was worked out by degredation experiments, while finally the synthesis[29] of a dicarboxylic acid identical with the oxidation product III, (auxin-glutaric acid) confirmed the following formulae for auxin A and B:



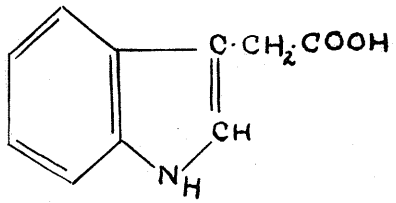
VI auxin A (auxentriolic acid)



VII auxin B (auxenolonic acid)

The development of a charcoal adsorption method for removing the active substance from urine led to the working up of larger volumes. Using this method, it was found[30] that, although two-thirds of the activity could be recovered by adsorption on charcoal and elution with 60% methyl acetate containing 5% concentrated ammonia, the subsequent steps in the usual isolation procedure failed to yield a crystalline auxin. The active substance was largely destroyed on attempting to lactonize but was finally obtained by

extraction with xylene and removal of impurities by precipitation with a mixture of barium acetate and potassium hydroxide. The filtrate yielded crystals which melted at 162° and showed high activity. This product, to which the name hetero-auxin was given, was subsequently shown to be identical with indole-3-acetic acid,* (VIII).



VIII

This identity was further supported by the fact that synthetic indole-3-acetic acid was found to have the same effect on plant growth as the naturally-occuring compound.

The discovery that a synthetic compound is active in influencing plant growth at once aroused interest in the possibility that other indole derivatives might also be active. Thus in the same paper

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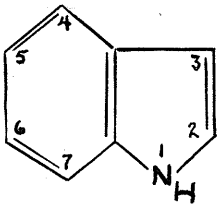
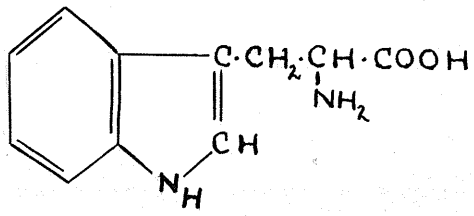
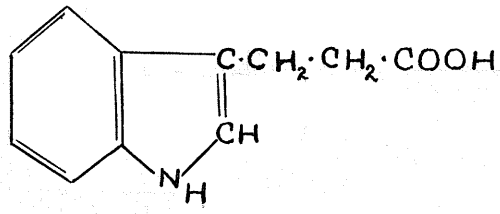


* The system of numbering the indole nucleus which will be followed in this presentation is shown at the left.

in which they recorded the isolation of hetero-auxin, Kogl, Haagen Smit and Erxleben also reported that tryptophane (indole-3-aminopropionic acid, IX), indole-3-β-propionic acid (X), indole-2-carboxylic acid and indole-3-carboxylic acid were all inert.

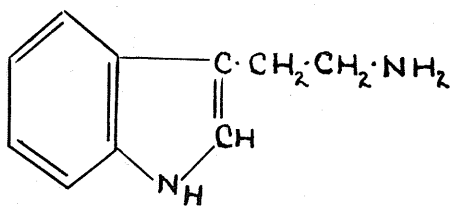


IX



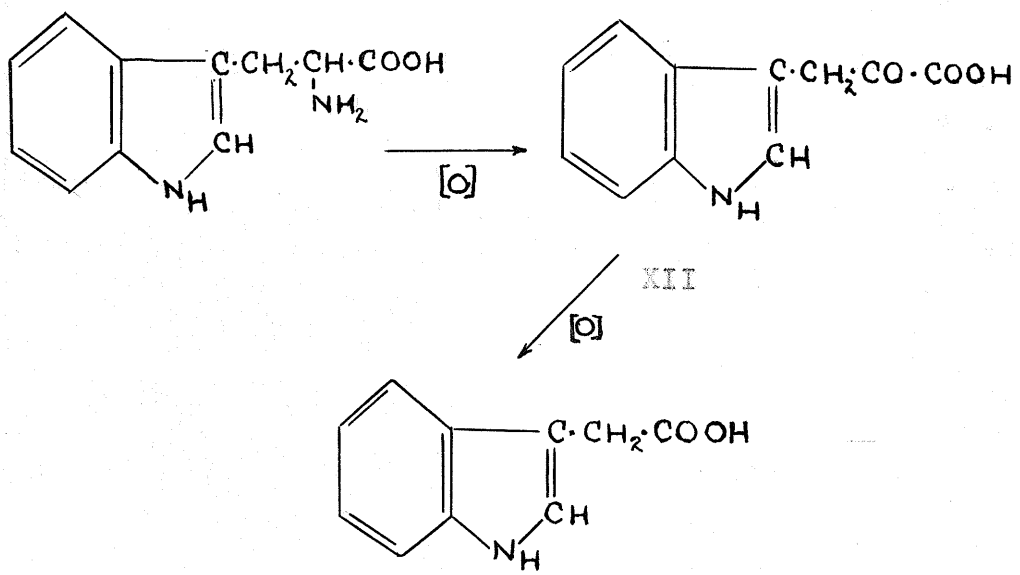
X

Since that time these derivatives have been retested and their small activities determined. It has been found[31] that if tryptophane is applied to "Avena", curvatures are produced after a lapse of two hours. F. Skoog[32] has reported that tryptamine (XI) also behaves in this manner.



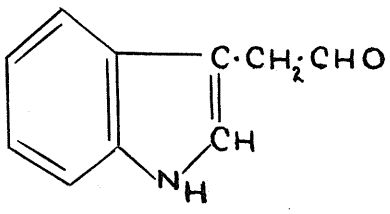
XI

Nielsen in 1928[33] had found that the medium on which Rhizopus suinus, a pathogenic fungi, had grown was rich in a substance active in producing plant curvatures. This was finally isolated by Thimann in 1935[34] and shown to be indole-3-acetic acid. It is almost certain that the mode of formation of this compound by the micro-organism is by a process of oxidative deamination of tryptophane present in the peptone used for the culture. It is presumed to take place in the following way through indole-3-pyruvic acid (XII):[2 (p.111)]



The same conversion by the plant is considered by Thimann and Went[31] to be extremely probable, thus accounting for the delayed activity. Although tryptamine (XI) does not contain a carboxylic group, it

could be oxidized to hetero-auxin (VIII) through indole-3-acetaldehyde (XIII).

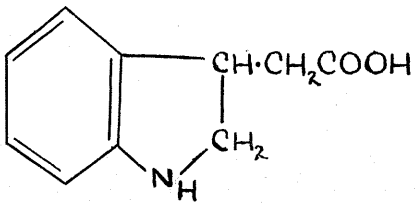


XIII

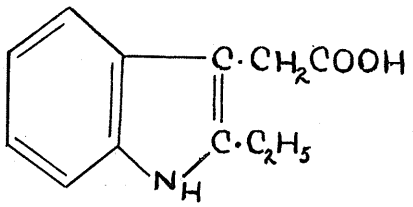
Indole-3-propionic acid has also been reported as being active by Zimmerman and Wilcoxon,[35] and by A. E. Hitchcock.[36] Its effectiveness in producing curvatures in the Went "Avena test" is, however, very much less than that of indole-3-acetic acid.

To determine the constitutional specificity of hetero-auxin, Kogl and Kostermans[37] prepared a large number of derivatives and tested them by the Avena curvature method. Among these derivatives were the methyl, ethyl, n-propyl and iso-propyl esters of indole-3-acetic acid. It was found that the methyl ester retained more than one-third of the activity of the free acid. With increasing size of the alkyl groups, the activity decreased at about the same rate, the iso-propyl ester being the least effective compound. A number of derivatives were prepared for the purpose of determining the effect of various substituents, or

other modifications on the activity of hetero-auxin. Hydrogenation of the indole ring destroyed activity since both 2,3-dihydroindole-3-acetic acid (XIV) and its methyl ester were inactive.



XIV



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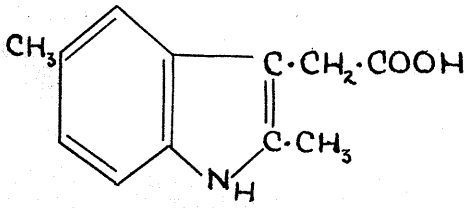
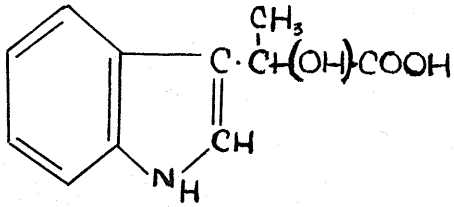
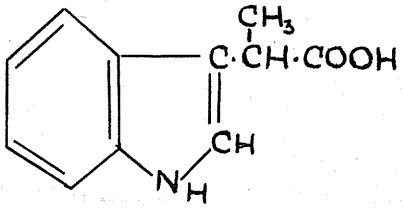


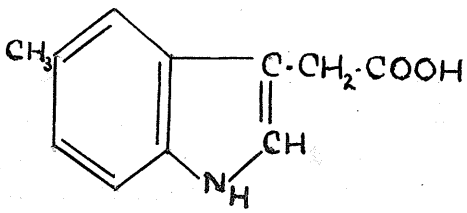
XVI



XVII



XVIII



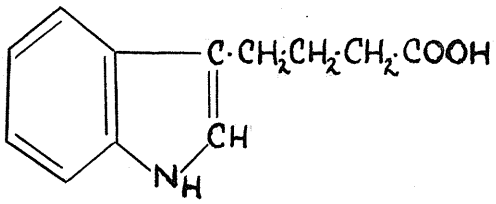
XIX

Other derivatives tested were 2-ethylindole-3-acetic acid (XV), 2,5-dimethylindole-3-acetic acid (XVI), indole-3-α-lactic acid (XVII), indole-3-pyruvic acid (XII), indole-3-α-propionic acid (XVIII), and 5-methyl-

indole-3-acetic acid (XIX) and its methyl ester. Of these only the last three were found to be active, although Haagen Smit and Went[38] have reported that 2,5-dimethylindole-3-acetic acid (XVI) is 0.002 as effective as indole-3-acetic acid.

A further list of indole derivatives was published by F. Kogl.[39] Compounds not previously reported were N-methylindole-3-acetic acid and its ethyl ester, and 2-methylindole-3-acetic acid and its methyl ester. Both of the acids were found to be effective but the esters were inactive.

A great many compounds have been tested by Zimmerman, Wilcoxon and Hitchcock of the Boyce Thompson Institute, aromatic acids and esters other than indole derivatives being found effective as plant hormones for various responsee.[35,40] In addition, a number have been reported by Manske and Leitch.[41] The new indole derivatives shown to be active are as follows: indole-3-butyric acid (XX)(now being produced commercially for use as a growth stimulant), indole-3-valeric acid (XXI), 5-methylindole-3-propionic acid (XXII), and indylene-1:3-diacetic acid (XXIII). 2-Carboxyindole-3-butyric acid (XXIV) was also tested by Zimmerman and Wilcoxon[40] but was found to be ineffective.



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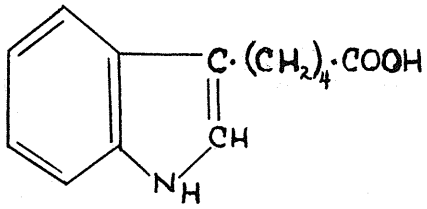
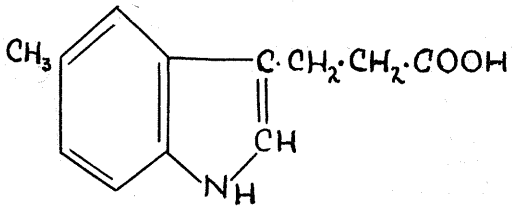


XXI



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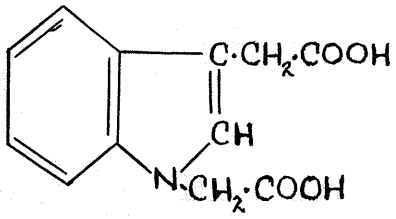

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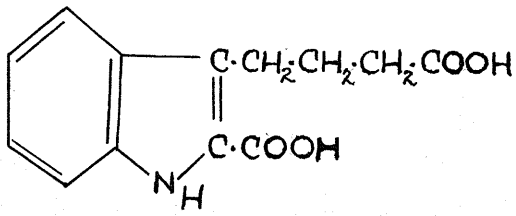
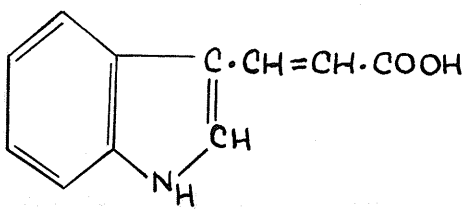
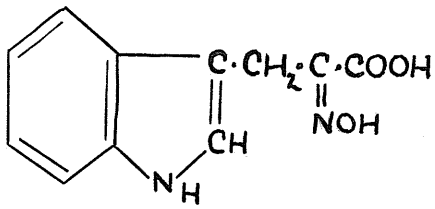


XXIV

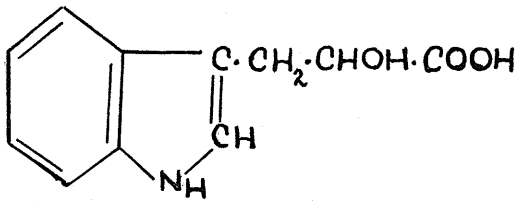
Bauguess[42] has also tested several indole derivatives, with resulting root initiation, stem bending, and bud inhibition in tomatoes, marigolds and stocks. Ones not previously mentioned in this thesis are indole-3-acrylic acid (XXV), indole-3-α-oximinopropionic acid (XXVI) and dl-indole-3-β-lactic acid (XXVII).



XXV



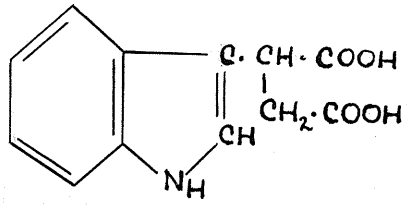
XXVI



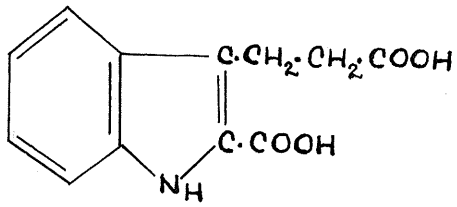
XXVII

More recently, an attempt has been made by Koepfli, Thimann and Went[43] to determine the relation between chemical structure and physiological activity and to present the minimum structural requirements for growth activity. For this purpose, a large number of compounds, among them many indole derivatives, were prepared and tested. A number of these had previously been reported by other investigators, but were tested again, since failure to promote curvatures in the "Avena" test does not necessarily imply complete inactivity in causing other plant responses. Of the derivatives examined, only the following have not been mentioned in preceding sections: indole-3-succinic

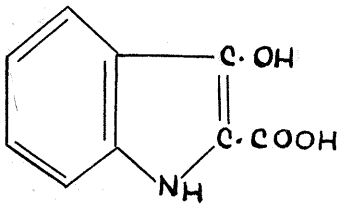
acid (XXVIII), 2-carboxyindole-3-propionic acid (XXIX), indoxylic acid (XXX), N-acetyl-3-hydroxyindole (XXXI), isatin (XXXII), 5-methoxyindole-3-propionic acid (XXXIII) and 6- and 7-methoxyindole-3-propionic acid.



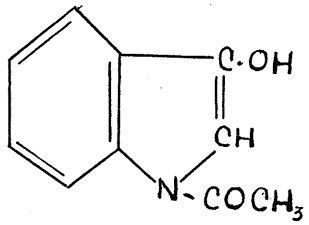
XXVIII



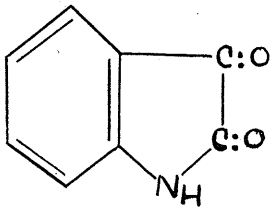
XXIX



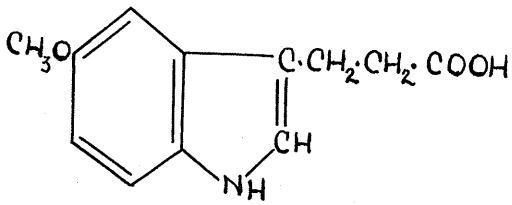
XXX



XXXI



XXXII



XXXIII

Skatole (3-methylindole) was also reported as inactive although Davies, Atkins and Hudson have found it effective in stimulating root development in willow branches.[44]

All indole derivatives which have been tested, together with the literature references, are tabulated below:

Table I.

Indole Derivatives reported Active

Derivative	Lit. Ref.
Indole-3-acetic acid	30,40,44,45
methyl ester	37,40,45
ethyl ester	37
n-propyl ester	37
isopropyl ester	37
Indole-3-propionic acid and methyl ester	36,40,41,44
Indole-3-butyric acid and methyl ester	35,40,41,45
Indole-3-valeric acid	35,40,41,43
Indole-3-pyruvic acid	37,39
Indole-3-acrylic acid	42
Indole-3-isopropionic acid	37,43
N-methylindole-3-acetic acid	39
2-Methylindole-3-acetic acid	39
5-Methylindole-3-acetic acid	37,39
Tryptophane	30,31
Tryptamine	32
5-Methylindole-3-propionic acid	35,41
Indylene-1:3-diacetic acid	35,41
Indole-3-α-oximinopropionic acid	42

Table II.

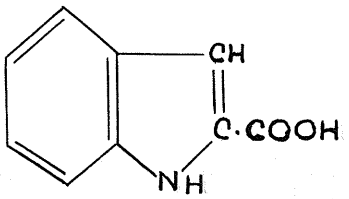
Indole Derivatives reported Inactive

Derivative	Lit. Ref.
Skatole (3-methylindole)	43
Indoxyl (3-hydroxyindole)	43
Indole-3-succinic acid	43
dl-Indole-3-β-lactic acid	42
Indole-3-α-lactic acid	37
2-Carboxyindole-3-butyric acid	35,43
Indole-2-carboxylic acid	30,39
Indole-3-carboxylic acid	30,39,43
2-Carboxyindole-3-propionic acid	43
Indoxylic acid	43
5-Methoxyindole-3-propionic acid	43
6-Methoxyindole-3-propionic acid	43
7-Methoxyindole-3-propionic acid	43
N-acetyl-3-hydroxyindole	43
Isatin	43
2,3-Dihydroindole-3-acetic acid	37,39
2-Ethylindole-3-acetic acid	37
2,5-Dimethylindole-3-acetic acid	37,39
ω-Skatolylmalonic acid	44
Ethyl N-methylindole-3-acetate	39
Methyl 2-methylindole-3-acetate	39

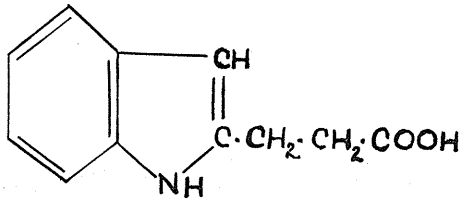
Koepfli, Thimann and Went recently undertook an intensive investigation of a large number of compounds with a view to determining the minimum structural requirements for activity as a phytohormone. From experimental evidence they conclude[43] that a compound in order to be active, must contain (1) a five- or six-membered homocyclic or heterocyclic nucleus, (2) a double bond in this ring, (3) a side chain, (4) a carboxyl group (or a group readily reduced to carboxyl) at least one carbon atom removed from the nucleus, and (5) a particular space relationship between the ring and the carboxyl group. It appeared that this question of space relationship was one of the most important since in a number of cases it was found that, while the cis-isomer was active, the trans-form was not. The most obvious difference between the cis- and trans-isomers is the distance between the carboxyl group and the nucleus, and this suggests that the growth activity of the cis-isomers is occasioned by the close proximity of the carboxyl group to the nucleus.

From a consideration of tables I and II, in which are listed all indole derivatives so far tested, it will be seen that, although derivatives with side-chains substituted in the 3-position of the indole nucleus have been thoroughly investigated, the only

mono-substituted compound tested with the substituent group in the 2-position is indole-2-carboxylic acid, (XXXIV).



XXXIV



XXXV

Activity of the latter would be excluded by number 4 of Koepfli, Thimann and Went's requirements, since the carbon atom of the carboxyl group is directly connected with the nucleus. Indole-3-β-propionic acid (XXXV), on the other hand, should fulfill all the requirements except possibly the last (5). It would therefore be of great interest to discover whether or not this substance is active as a plant hormone. It is regrettable that lack of chemicals forced the abandonment of this problem.

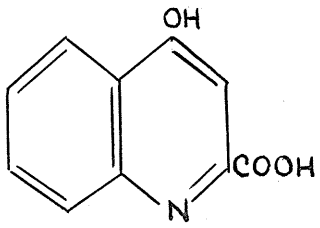
(b) A Review of Indole Derivatives in Physiological Experiments

Considerable interest has also been taken in indole derivatives in connection with experiments concerning the possibility of replacing tryptophane (indole-3-α-aminopropionic acid, IX) in the animal diet by various synthetic compounds closely related structurally to the natural substance. Such investigations are important in that they indicate the possible path of metabolism of the amino acid in the body and in addition the types of chemical reactions which the animal organism is capable of accomplishing.

The general method followed in such experiments is to feed to white rats diets deficient in the amino acid under consideration. A decreased growth rate results. The diet is then supplemented by the synthetic compound. Resumption of growth, as checked by control animals on an unsupplemented diet, indicates that the compound is being utilized and hence that either it is being converted into the amino acid or is being used in its place, i.e., is a possible intermediary product in metabolism.

When tryptophane is administered to normal rabbits, it is partially eliminated as γ-hydroxy-

quinoline-4-carboxylic (kynurenic) acid,[46] (XXXVI).



XXXVI

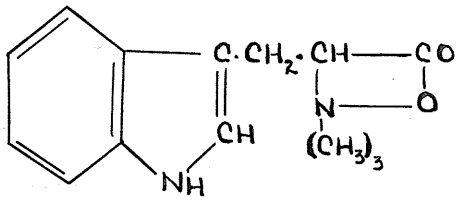
Production of this acid has also been used as a criterion in estimating the extent of utilization of indole derivatives, although it has been stated that "this substance is not a link in the chain of normal tryptophane oxidation in the animal body but rather is an end-product of a set of side reactions brought into play especially when tryptophane is administered in excess of ordinary metabolic requirements".[47]

Since the discovery of the amino acids, many synthetic compounds have been tested for their ability to replace the natural substance in the diet. The first of such experiments with tryptophane was performed by Sure in 1925,[48] who, after carrying out experiments to ascertain whether indole and alanine would condense to form tryptophane, came to the conclusion that they do not. Two years later, Jackson undertook similar, more intensive, investigations with various indole derivatives.[49] Indole-3-aldehyde

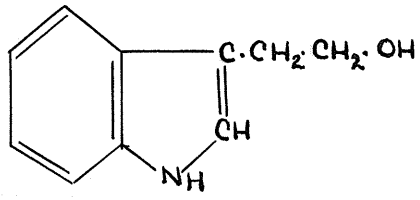
and l-indole-3-β-lactic acid were tested. The first was chosen since it had been reported that furfuraldehyde condenses with acetic acid in rabbits and dogs to give furfuracrylic acid. A similar reaction in the case of indole-3-aldehyde followed by addition of ammonia in the proper fashion would give tryptophane. The indole-lactic acid was of importance since it had been found[50] possible to replace histidine with dl-β-4-imidazole lactic acid. In neither case, however, was the growth of white rats appreciably influenced by the addition of these compounds. The active lactic acid was then subjected to the probable racemizing action of long boiling in barium hydroxide solution and tested again, when it was found that it still had no effect. Both Ichihara and Iwakura[51] and Bauguess and Berg[52] have since obtained positive results with the racemic form of indole-3-lactic acid. The latter investigators attribute Jackson's failure to incomplete racemization of the acid.

In 1929,[53] Jackson reported experiments with nine additional indole derivatives, with position 3 side-chains as follows: the betaine of tryptophane (XXXVII), indole-3-ethyl alcohol (XXXVIII), indole-3-α-benzoylaminoacrylic acid (XXXIX), methylene tryptophane (XL), indole-3-butyric acid (XX), indole-3-α-

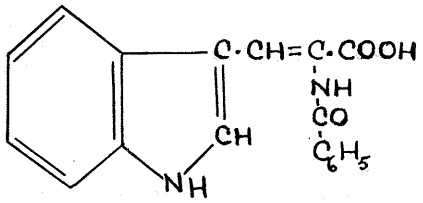
uraminopropionic acid (XLI), indole-3-propionic acid (X), indole-3-pyruvic acid (XII) and indole-3-ethylamine, (tryptamine, XI).



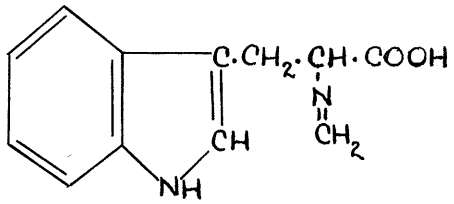
XXXVII



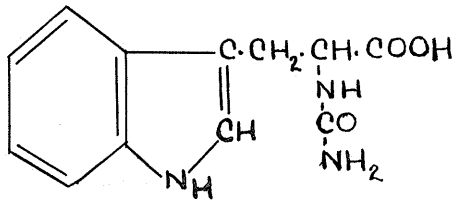
XXXVIII



XXXIX



XL



XLI

With the exception of indole-3-pyruvic acid, the derivatives employed had no appreciable influence on growth. Further brief experiments were carried out with indole-3-acetic acid, indole-3-acetonitrile and isatin but gave wholly negative results. This shows

how very specific the animal organism is in its requirements for compounds of a particular structure since it was unable to bring about the rather superficial alterations necessary to convert them to tryptophane. The fact that indole-3-pyruvic acid replaced tryptophane in the diet is in agreement with the many demonstrations in the literature of the close physiological relations between amino acids and the corresponding pyruvic acids. In this connection, it may be noted that Harrow and Sherwin[54] had previously found that imidazole pyruvic acid would to a certain extent replace histidine in the diet. In addition, Ellinger and Matsuoka[55] in 1920 reported that indole pyruvic acid gave rise to an increased kynurenic acid output.

The inactivity of indole-3-propionic acid and the activity of indole-3-pyruvic acid was confirmed by Berg, Rose, and Marvel in 1927.[56] Hence this latter acid may be regarded as a normal metabolite of tryptophane.

Indole-3-β-acrylic acid (XXV) and indole-3-β-(α-oximino)-propionic acid (XXVI) were studied by Bauguess and Berg.[52,57] Although indole-3-acrylic acid would require only the directive addition of ammonia to the double-bonded carbons to be converted into tryptophane, while the oximino compound needed only reduction