

FURTHER STUDIES ON THE SYNTHESIS OF AMINO ACIDS

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fulfillment of the requirements for the
degree of Doctor of Philosophy

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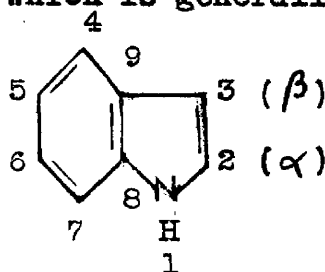
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INTRODUCTION

In 1866, Baeyer and Knop (1), in the course of a study of the structure of indigo, reduced isatin and obtained two products, $C_8H_7NO_2$ and C_8HN_7O (dioxindole and oxindole), which they regarded as hydroxy derivatives of C_8H_7N ; they named the latter 'indole', to show its derivation from indigo. The work was continued by Baeyer and Emmerling (2), who proposed in 1869 the formula which is generally accepted:



This structure was suggested largely as a result of synthetic methods of preparation of the compound by fusion of nitrocinnamic acid with iron filings and sodium hydroxide, and by the action of lead peroxide upon azocinnamic acid.

A system of nomenclature was devised by Baeyer (3), and used by Fischer (4), in order to differentiate the derivatives of indole. This system was cumbersome, involving independent numerical designations for each ring. Current practice is to use numbers, with the nitrogen atom as 1, assignment of numbers to the positions in the formula as shown above. The 2- and 3-positions are occasionally referred to as the α - and β -positions, respectively.

Indole derivatives occur widespread in many natural products. Indole itself has been obtained, usually in small amounts, by extraction from naturally occurring materials by methods which suggest that the in-

dole so obtained is in many cases the result of breakdown of its derivatives. Various plants have yielded indole, among them the following: Robinia pseudacacia (5), the jasmines (6, 7, 8), certain citrus plants (9), and orange blossoms (10). The usual procedure is to extract the blossoms repeatedly with a suitable solvent, followed by distillation of the extract. In this way, Hesse and Zeitschel (10) obtained about 0.1 per cent of indole from orange-blossom oil, while Hesse (7) isolated 2.5 percent from jasmine. Herter (11) also found indole in the wood of Celtis reticulosa.

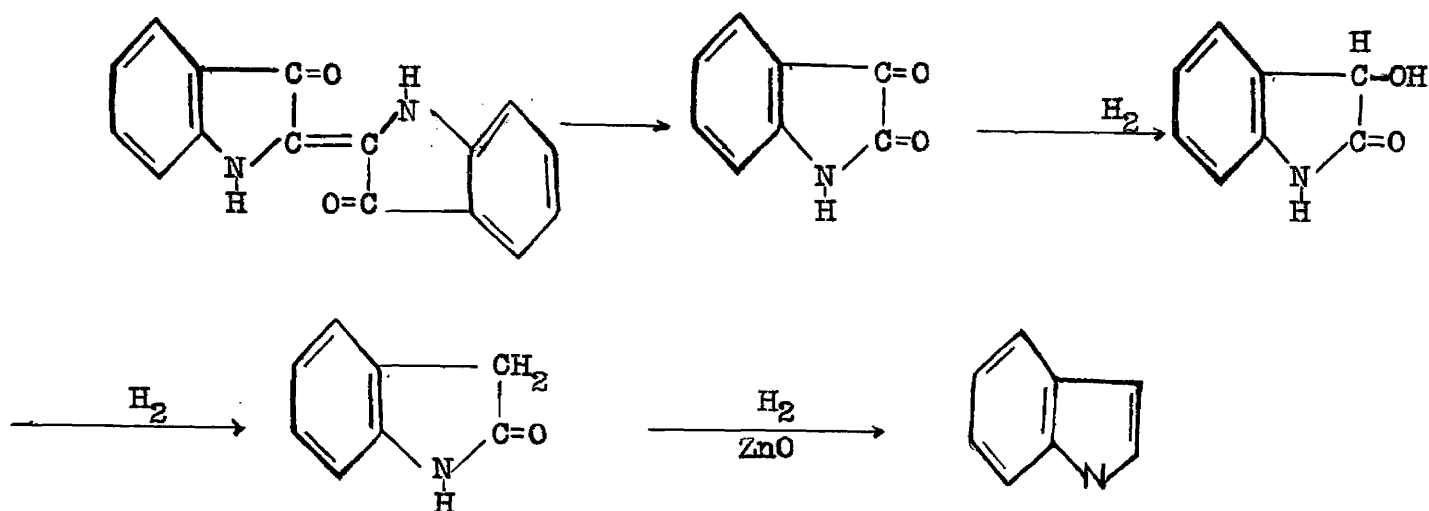
Indole has been isolated from the liver and pancreas (12), the brain (13), and bile (14).

It is also found frequently after putrefactive processes have taken place. It is found in the animal body wherever pus formation occurs (15), in the putrefaction of milk (16), of blood fibrin (17, 18, 19), of albumin (20), and possibly of vegetable protein (7). The formation of indole is presumably the result of the decomposition of tryptophan in these cases of putrefaction of protein material. Formation of indole from albumin may be stopped by the addition of lactose, but other sugars have varying effects upon its production (21, 22).

Indole has also been isolated from coal tar, appearing in the fraction boiling between 240° and 260° C. (23), from which it may be isolated as its solid sodium or potassium derivative after treatment with sodium or potassium hydroxide, or sodium amide. Homologues of indole can also be obtained from coal tar (24). Molasses tar has also yielded some of the base (25).

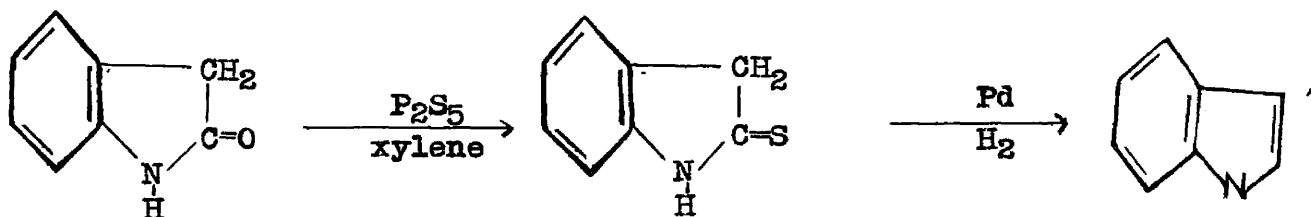
Indole was first prepared synthetically by Baeyer (26); he oxidized indigo to obtain isatin, reduced the isatin to dioxindole using zinc dust,

and further reduced oxindole to indole by passing its vapors over hot zinc oxide.



He also prepared it by reducing 2,3-dichloroindole to indole (27).

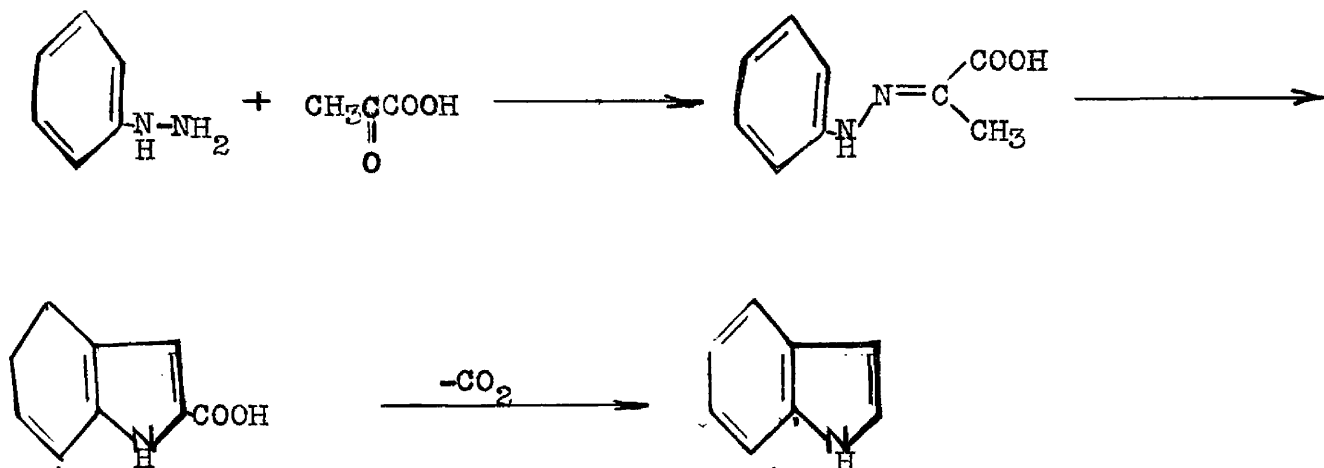
Indoxyl, reduced by sodium amalgam, by zinc dust and alkali (28), or catalytically (29), yielded indole. Dihydroindole was obtained by the electrolytic reduction of the sulfur analog of oxindole; this in turn yielded indole upon being dehydrogenated (30).



In the preparation of synthetic indigo by the method involving the fusion of phenylglycine or its o-carboxylic acid with sodium hydroxide, if the melt was 'over-melted' a small amount of indole was obtained (31). This melt also yielded indole when a metal such as sodium or iron was added at $300^\circ C$. (32). Vorländer and Apelt (28) obtained a fairly good yield of indole by adding sodium amalgam or zinc dust to the alkaline melt of indoxylic acid at $60-70^\circ C$.

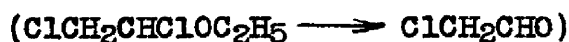
More generally applicable methods of synthesis of indole and its

derivatives involve ring closures to form the pyrrole side ring. Among these various methods, the Fischer procedure is the most versatile for the preparation of derivatives. This method, discovered by Fischer and Jourdan (33) in 1883, involves in general the loss of ammonia from phenylhydrazones. Thus, the phenylhydrazone of pyruvic acid yielded indole-2-carboxylic acid (34) and this upon decarboxylation gave indole:



The Fischer indole reaction fails, however, for the direct preparation of indole itself. According to the general scheme of the reaction it should be formed from the phenylhydrazone of acetaldehyde, but this is not realized.

Other syntheses, which like the Fischer synthesis involve ring closure by the reaction of a carbon group with the ortho position, are as follows: Berlinerblau (35) employed aniline and α, β -dichloroethyl ether according the following scheme:



Also, Prud'homme (36) used a somewhat analogous procedure with aniline and ethylene dibromide as the initial reactants:



Polikier (37) heated the dianilide of tartaric acid with zinc chloride to obtain indole; dianilinosuccinanilide was found as the first intermediate. The calcium salt of phenylglycine heated with excess of calcium formate gave indole in very small yield (38), the product being isolated as the picrate. Distilling *o*-chloro-*o*-chloroacetanilide with zinc dust yielded small amounts of indole (39). Baeyer found that indole was formed when vapors of ethylaniline were led through hot tubes (40).

A rather large number of methods have been described in which ring closure is accomplished by reaction of an alkyl group, attached to the benzene ring in the *o*- position to a nitro group, an amino group, or a substituted amino group. Gluud (41, 42) synthesized *o*-aldehydophenylglycine and, by heating the compound in acetic anhydride containing sodium acetate, effected ring closure and decarboxylation of the intermediate indole-2-carboxylic acid. Verley (43) treated *N*-aldehydo-*o*-toluidine with sodium amide and obtained indole. The distillation of oxal-*o*-toluic acid with zinc dust, or dry distillation of the barium salt, gave indole (44). Also, *N*-methyl-*o*-toluidine, dropped on reduced nickel at 300-330° C., produced small yields of indole (45, 46, 47); other alkyltoluidines (48) also yielded indoles.

A series of methods involving substituted cinnamic acids, styrenes, stilbenes, and analogous compounds as starting materials are described in the literature. Lipp's indole synthesis involves the heating of *o*-amino-*o*-chlorostyrene with sodium ethylate (49). Weermann (50, 51, 52) prepared indole by the use of *o*-nitro-cinnamide as follows:

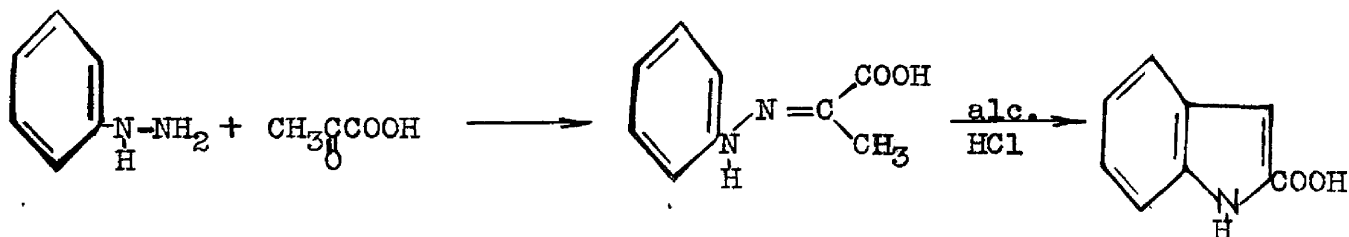


A quantitative yield of indole was reported when *o,o'*-diaminostilbene hydrochloride was heated under reduced pressure (53, 54). Baeyer and Emmerling (2) and Beilstein and Kuhlberg (55), prepared indole from *o*-nitrocinnamic acid. Reduction of *o*-nitrophenylacetaldehyde yielded indole (51). Also, *o*-nitrophenylpyruvic acid has been converted into indole-2-carboxylic acid (56, 57, 58). Pschorr and Hoppe (59) prepared 2-aminoindole from *o*-nitrophenylacetic acid; this was converted into indole by reduction with sodium and alcohol. Indole may also be obtained from *o,w*-dinitrostyrene (60, 61). Walter (62) prepared it by treating acetylated *o*-aminocinnamic acid with fuming hydrochloric acid at high temperatures. Some indole is obtained from *o*-aminophenylpropionic acid (63).

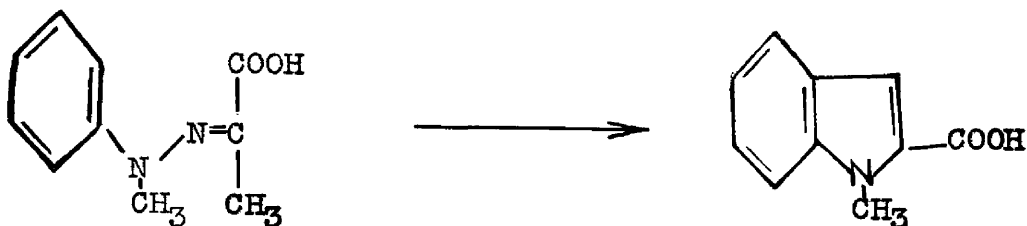
A variety of pyrogenic methods have also been reported. In some of these cases rather strenuous treatment is involved, and for many the yields are not good. In summary, however, the following examples are cited: Morgan (64) provided one of the earliest syntheses of indole by his fusion of carbostyryl with alkali. Hofmann and Königs (65) obtained indole and quinoline from the high-temperature treatment of tetrahydroquinoline or methyltetrahydroquinoline. Fusion of albumin with potassium hydroxide yielded indole (66, 67, 68). Also, indole-2-carboxylic acid (69), and quinoline-2,3-dicarboxylic acid (70), when heated with calcium carbonate gave indole. Ketodihydrobenzene-*p*-

thiazine (71), with a red-hot mixture of zinc and copper powders yielded some indole. Acetylene and aniline (72) passed over metallic or oxide catalysts formed indole. Fileti (73) obtained indole by passing the vapor of cumidine over hot lead oxide, and by distilling skatole over hot porcelain chips. Widmann (74) distilled 3-nitro-4-isopropenylbenzoic acid with lime and obtained a small yield of indole. Tripyrroline (75) and pyrrole (76) have also been converted into indole.

Although the Fischer method may be applied indirectly to the preparation of indole, it finds its chief usefulness in the synthesis of many and varied indole derivatives. The method is in itself very versatile, but it is made even more general by the preparation of otherwise unattainable phenylhydrazones from diazonium salts by the method of Japp and Klingemann (77, 78). In general, Fischer's synthesis may be described as involving the elimination of ammonia from phenylhydrazones, and may be accomplished with the phenylhydrazones of most carbonyl compounds the structures of which allow ring closures to occur:



In 1883, Fischer and Jourdan (33) found that when they boiled the methylphenylhydrazone of pyruvic acid with alcoholic hydrogen chloride, they obtained a compound which analyzed for $\text{C}_{10}\text{H}_9\text{O}_2\text{N}$ in about 5 per cent yield. Fischer and Hess (79) investigated this compound further and found it to be an indole derivative, formed as follows:



This work was continued by Fischer, who found that zinc chloride was a better catalyst for the reaction, allowing a wider range of applicability (80). The procedure employed by Fischer may be described by citing his preparation of 2-methylindole; this he accomplished by mixing acetone phenylhydrazone with five times its weight of anhydrous zinc chloride, and by heating the mixture to about 200°. A yield of 60 per cent of 2-methylindole was obtained. In an analogous manner, Fischer obtained a 35 per cent yield of skatole from propionaldehyde phenylhydrazone (4).

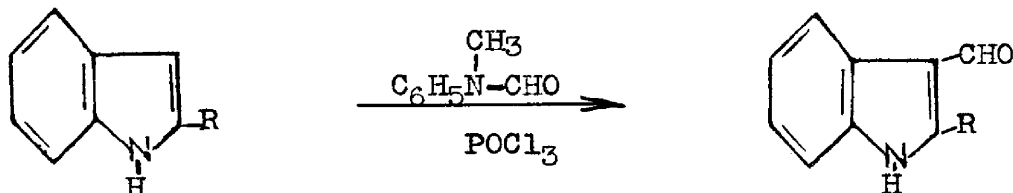
Since the time of this early work a number of changes have been introduced into the method, with improvements in the yields. Thus it was found (34) that by the use of an inert solvent such as methylnaphthalene, and by keeping the temperature below 150°, acetone phenylhydrazone gave a 75 per cent yield of 2-methylindole, propionaldehyde phenylhydrazone an 80 per cent yield of skatole, and the phenylhydrazone of pyruvic acid gave a 60 per cent yield of indole-2-carboxylic acid.

Also, the large amounts of zinc chloride used by Fischer were shown to be unnecessary (81), and other salts were found to be effective. The reaction was found to proceed in the presence of 1 per cent of zinc chloride; cuprous chloride, cuprous bromide, or platinum chloride, cobalt chloride, nickel chloride, etc. (82), may also be used. Besides these, a number of other catalysts have been employed: nickel, cobalt, and powdered copper (82), concentrated sulfuric acid (83, 84, 86), alcoholic sulfuric acid (85) and alcoholic zinc chloride (86). Grignard

reagents have also been used (87).

The ease of indole formation from the various phenylhydrazones varied irregularly; with some, the reaction occurred extremely readily. For example, Plancher (86) and Jenisch (88) found that the methylphenylhydrazones of isopropyl methyl ketone and isopropyl phenyl ketone would undergo ring closure even at room temperature in the presence of alcoholic zinc chloride. Acetaldehyde phenylhydrazone would be expected to yield indole, but this reaction did not occur. Phenylhydrazones of β -ketoesters more commonly produced pyrazolones.

Indole-3-aldehydes can be prepared from indoles having a replaceable hydrogen at the 3-position, by reaction with N-methylformanilide in the presence of condensing agents such as phosphorous oxychloride (89):



Certain indoles will also undergo the Gattermann and Hoesch aldehyde synthesis (90).

Indole-3-aldehyde was first obtained, along with harman, by Hopkins and Cole (91) as a result of treatment of tryptophan with ferric chloride. Later, Ellinger (92, 93) prepared the aldehyde by treatment of indole with chloroform and potassium hydroxide; 3-chloroquinoline was also obtained in this reaction. Boyd and Robson (94) effected its preparation through the action of zinc cyanide upon 2-carbethoxyindole.

Skatole may be synthesized, by the Fischer method (95, 96, 83) from the phenylhydrazone of propionaldehyde, from 3-nitrocumic acid (97), indigo (98), aniline and glycerol (99), and o-acetylanilidoacetic acid

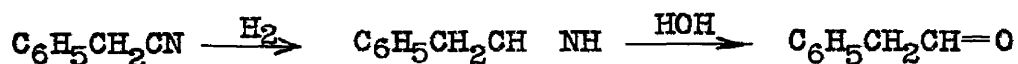
ethyl ester (100), as well as from other sources.

The Fischer method may be used for the preparation of 2-methylindole, employing the phenylhydrazone of acetone (4). Other methods of preparation involved aniline and monochloroacetone (101), dihydromethylketole (102), o-amidophenylacetone (103), and acetylated o-toluidine (104).

PURPOSE OF THE WORK AND DISCUSSION OF RESULTS

In view of the fact that most of the syntheses reported in the literature for indole and its derivatives suffer from being tedious, complicated and, more often than not, productive of small yields, an investigation was undertaken to find not only more direct intermediates for the synthesis of indole, but such intermediates whose derivatives might lead to physiologically active and useful indole compounds; and it was hoped that general reactions might be explored for the synthesis of a series of such compounds for pharmacological study.

A casual remark suggested that benzyl cyanide may be hydrogenated to the imine which in turn may be readily hydrolyzed to phenylacetaldehyde.



A study of this reaction showed that it is simple to perform, proceeds smoothly, and the products may be easily isolated. Once it had been established that this reduction of a cyanide to the aldehyde is possible, it was felt that if *o*-nitrobenzyl cyanide were hydrogenated in a similar manner, indole would be obtained. The steps of the expected hydrogenation are shown:

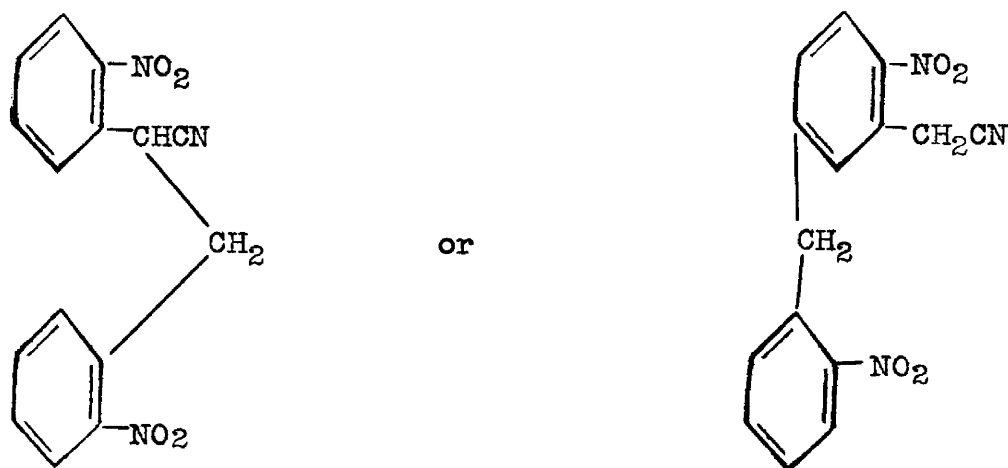




In a similar manner substituted *o*-nitrobenzyl cyanides would be expected to form the corresponding substituted indoles:



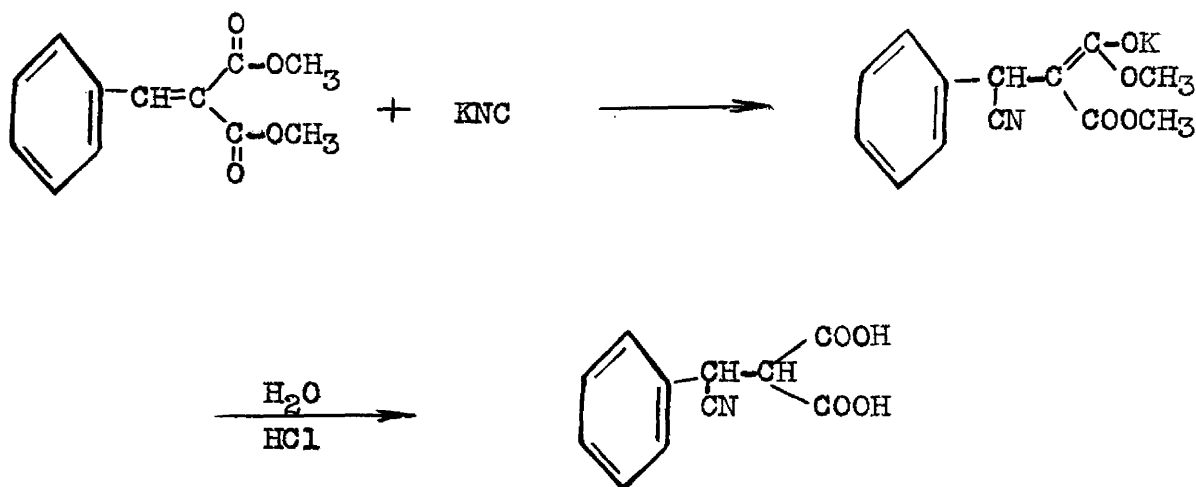
With this in mind, numerous syntheses were attempted with an eye to preparing *o*-nitrobenzyl cyanide. All methods of direct nitration of benzyl cyanide failed to produce the *o*-nitro derivative in quantities sufficient for further investigation. Treating *o*-nitrobenzyl chloride with potassium cyanide gave no *o*-nitrobenzyl cyanide, although Bamberger (105) indicated that small yields may be expected; the reaction proceeded according to Bamberger to give mainly a condensation product with either one of the structures shown below:



An attempt was made to prepare 2,4-dinitrobenzyl cyanide by direct nitration, and use it in these reactions to obtain an aminoindole. However, vigorous nitration caused hydrolysis of the cyano group to carboxyl, and 2,4-dinitrophenyl acetic acid was the only reaction product isolated.

Since all indications were that the preparation of *o*-nitrobenzyl cyanide in large quantities was so difficult as to be impractical, a different approach was investigated.

The synthesis of β -cyano ketones, esters and nitriles through the action of potassium isocyanide on the corresponding α,β -ethylenic ketones, esters and nitriles is a general reaction. It proceeds through the formation of enolates, or iminolates, by 1,4-addition of potassium isocyanide to the conjugated system of the unsaturated compounds, the metal uniting with carbonyl oxygen or cyano nitrogen.



In 1937, Michael and Weiner (106) reported their investigations into the mechanism of this reaction, using dimethyl benzal malonate. By treating this compound with potassium isocyanide, they were able to obtain quantitative yields of the potassium enol β -cyanobenzylmalonic ester. Acidification of the latter resulted in a yield of 100 per cent of β -cyanobenzylmalonic ester. Methyl benzalcyanoacetate also was found to follow the above reaction quantitatively.

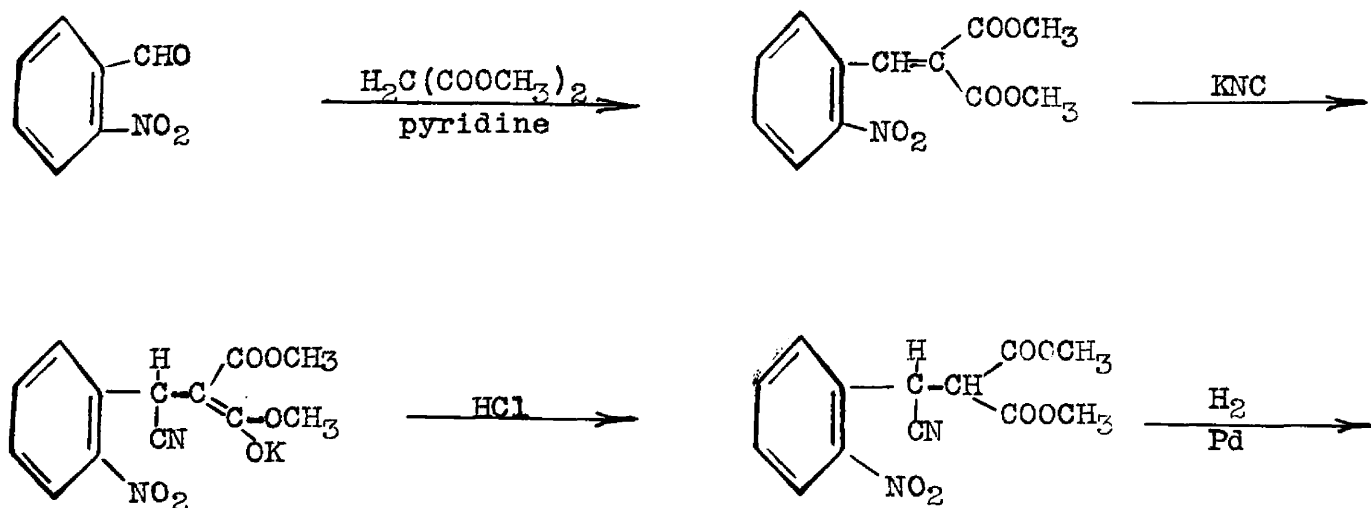
Benzal malonic ester contains a malonic ester group, without the essential α -hydrogen necessary to yield an enolate; the carbonyl oxygen of a carbomethoxy group has, however, a developed affinity for the slightly neutralized potassium atom of the isocyanide and a strong attraction exists between it and the respective, unsaturated oxygen. Further, the β -unsaturated carbon of the ester shows the necessary free chemical energy and affinity, i.e., the chemical potential, to unite with the cyano group. The first formed, cyclic, polymolecule passes over into the β -cyano enolate:

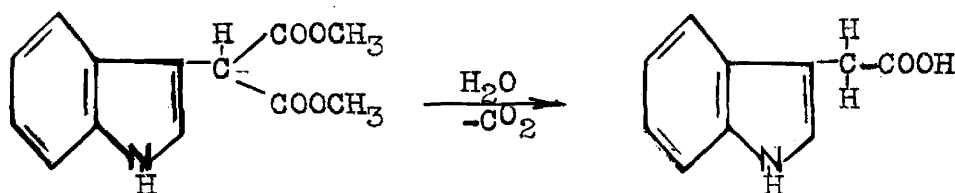


The β -unsaturated carbon has a far more developed affinity for the carbon than the nitrogen of the addendum and the introduction of the decidedly negative cyano group leads to a far better neutralized enolate than would the basic isocyano group.

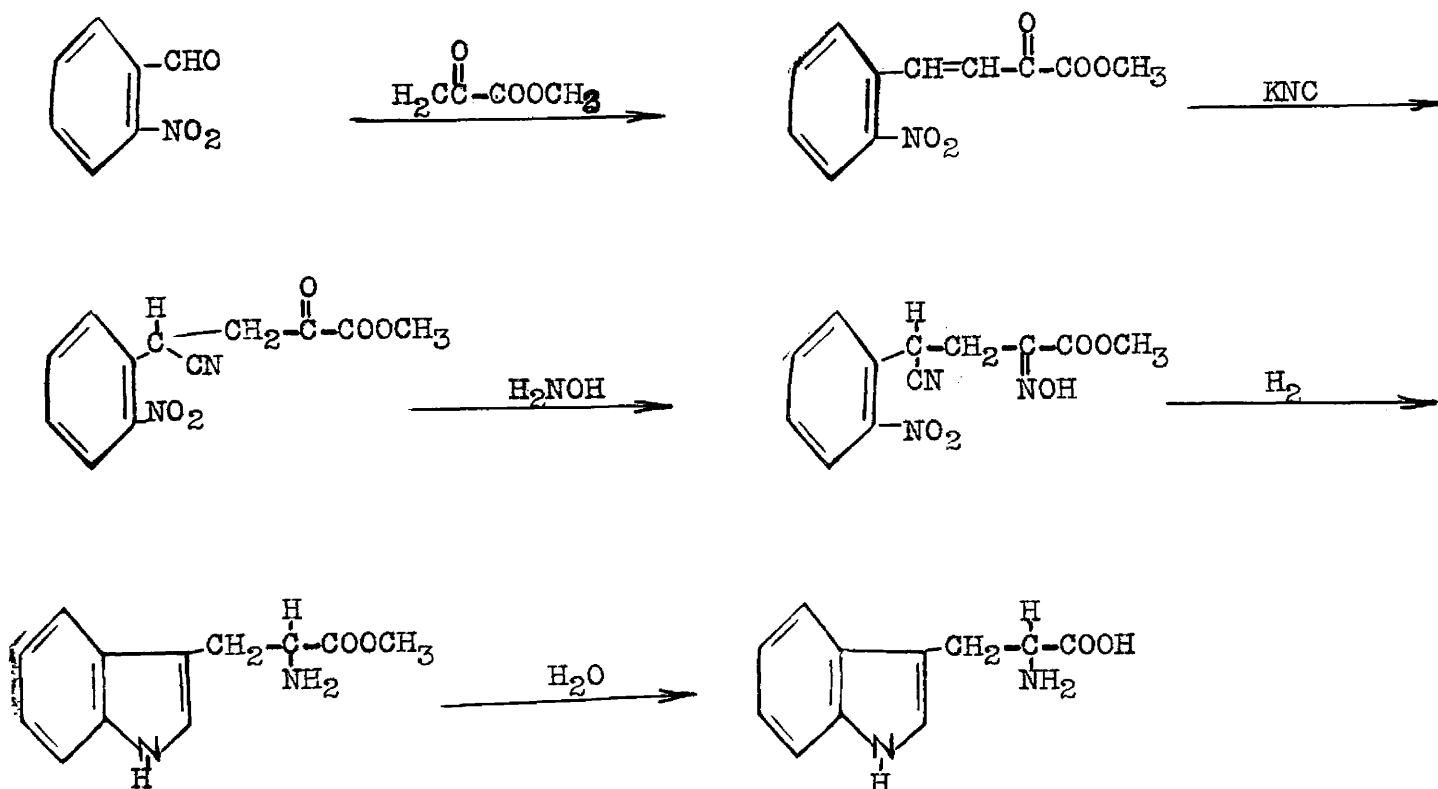
Fumaric ester, citraconic ester and benzalacetophenone gave the expected addition product but the reaction proceeded further, forming complicated condensation products.

Michael's apparent success with this addition reaction led to the thought of a procedure for preparing indole-acetic acid by catalytic reduction. The plan was to prepare the *o*-nitro derivative of β -cyano-benzylmalonic ester and form the indole nucleus by simultaneous reduction and condensation of the nitro and cyano groups. Hydrolysis and decarboxylation of this compound would give indole-acetic acid.





If this could be accomplished, it was felt that the possibility of preparing tryptophan in like manner was not too remote. Here it is necessary to condense *o*-nitrobenzaldehyde with methyl pyruvate, follow this with the Michael condensation, production of the ketoxime, hydrogenation to form the indole nucleus, and hydrolysis to tryptophan.



In order to become familiar with these reactions the work of Michael was repeated in the course of the present investigation and his results were substantially duplicated. By allowing potassium isocyanide to react with dimethyl benzalmalonate, as described by Michael, a quantitative yield of potassium enol β -cyanobenzylmalonic ester was isolated. Unfor-

tunately, as discussed later, it was found that the reaction is not so general as Michael's report would lead one to believe.

For the synthesis of dimethyl o-nitrobenzalmalonate, o-nitrobenzaldehyde was desired.

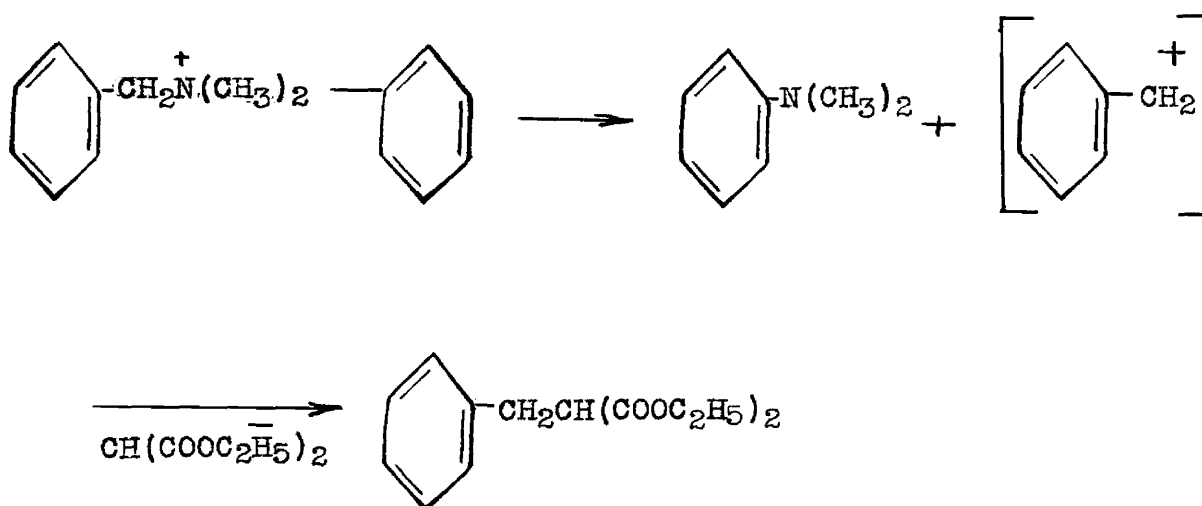
Although there are, in the literature, a variety of methods for the preparation of o-nitrobenzaldehyde, all report small yields. The aldehyde, besides being extremely sensitive to heat, light and air, also undergoes autooxidation. This instability makes its isolation most difficult. Of all the syntheses carried out during these investigations, none yielded o-nitrobenzaldehyde in significant amounts.

Therefore, in the hope that a more stable compound would be formed, m-bromo-o-nitrobenzaldehyde was prepared. The presence of bromine in the molecule was felt to be of no disadvantage, as it would be expected to split off during the catalytic hydrogenation (Cf. 107). No difficulties were encountered in the synthesis of this compound. However, all attempts to form the Knoevenagel condensation product with malonic ester proved to be unsuccessful.

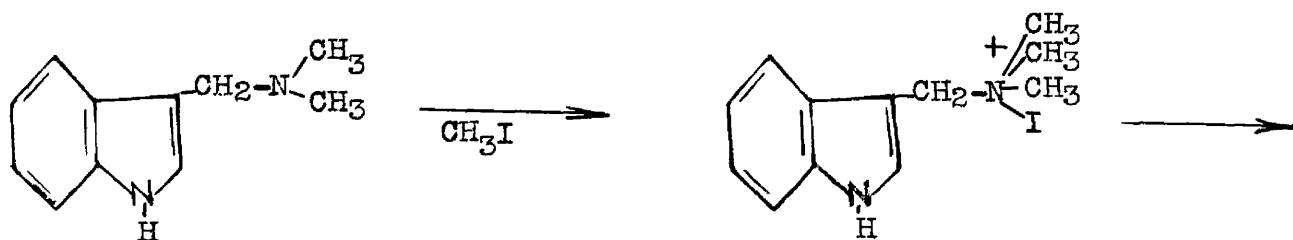
In preliminary experiments to test the application of the Michael condensation to the compounds concerned here, it was found that apparently the reaction is not so general as is indicated in Michael's report (106). Methyl cinnamate and methyl o-nitrocinnamate apparently reacted as was to be expected when the usual conditions were observed. Although it appeared that in each case the potassium enolate could be obtained, the subsequent acidification invariably led to the isolation of the original material, with the liberation of hydrocyanic acid. It appears that the cyano compounds, if formed in these cases, are quite unstable, in the presence of acids. Thus, it would seem that there are limitations

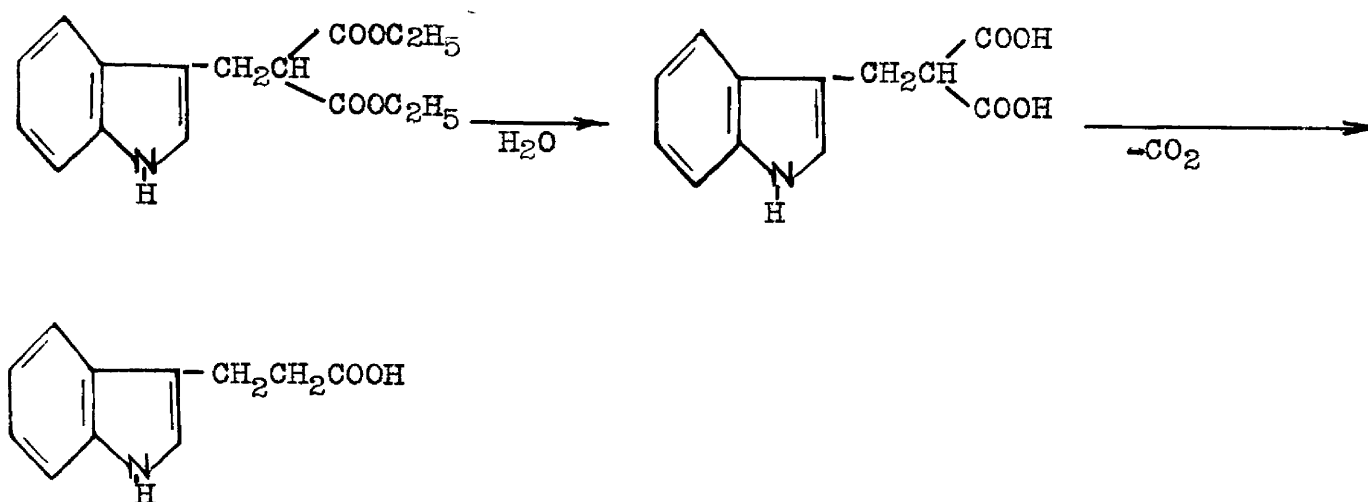
to the reaction which are not at first obvious to the investigator.

In a study of the action of quaternary ammonium salts containing a benzyl group on sodium derivatives of acetoacetic ester and malonic ester, Snyder et al (108) found, contrary to the previous literature, that carbon-alkylation occurs. Sodiaoacetoacetic ester reacted with benzyldimethylphenyl ammonium chloride in boiling ethanol to produce about 60 per cent yields of crude ethyl α -benzylacetoacetate. Under the same conditions the sodium derivative of malonic ester reacted with the salt to give a yield of about 40 per cent of diethyl benzylmalonate. The reactions probably proceed by an ionic path.

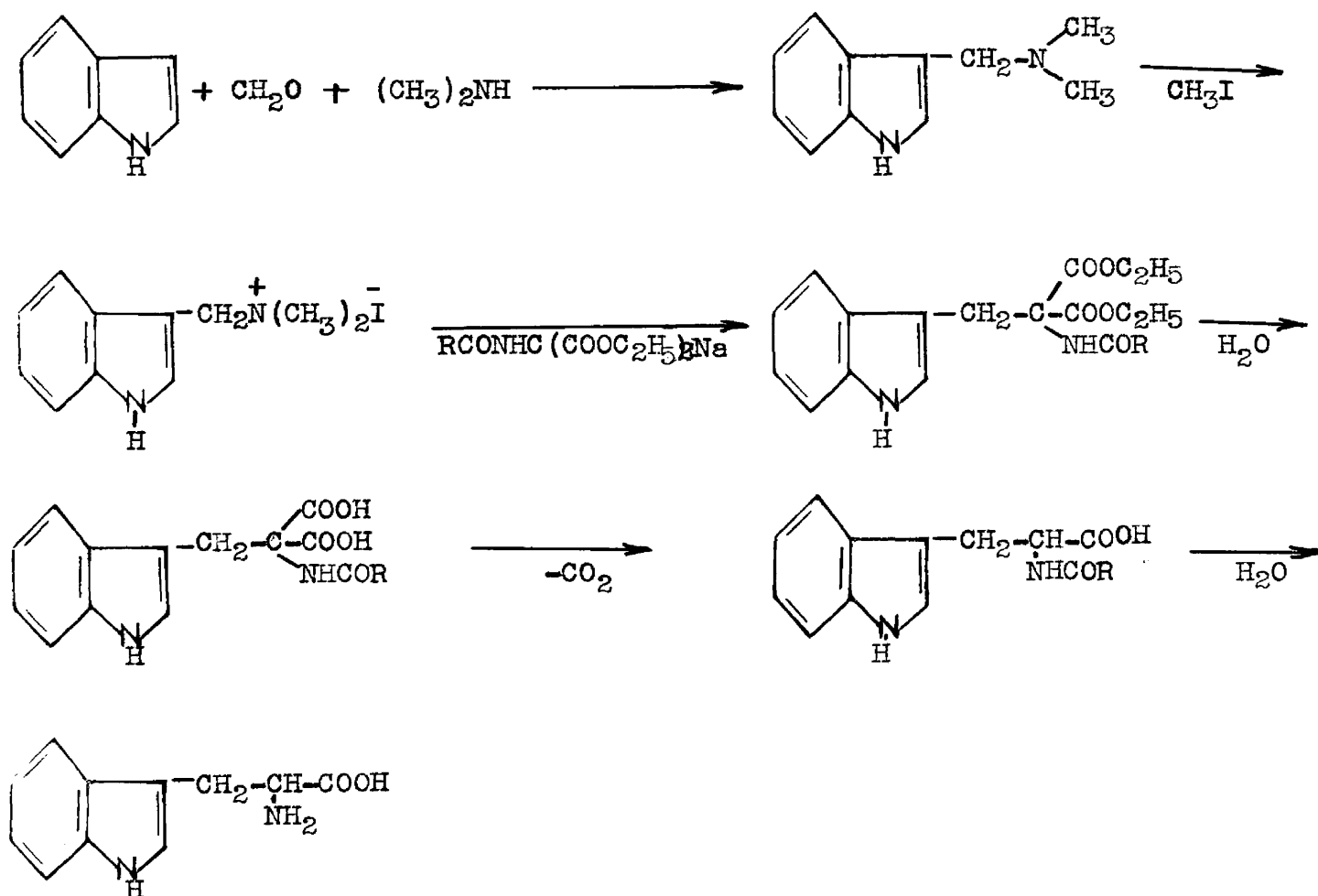


Gramine, 3-dimethylaminomethylindole, can be prepared readily from indole, (109), and it is converted easily to quaternary ammonium salts, such as the methiodide. By condensing gramine methiodide with sodio-malonic ester, subsequent hydrolysis and decarboxylation Snyder was able to obtain β -(3-indole)-propionic acid in good yields.



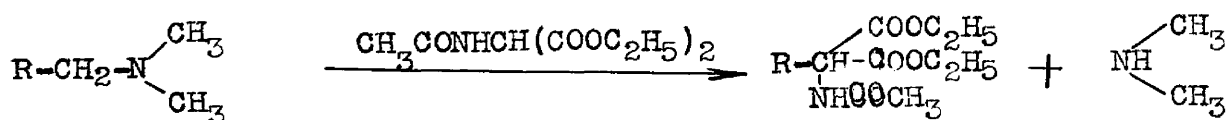


The high yields obtained in these reactions suggested to Snyder and Smith, (110), that dl-tryptophan might be prepared by condensation of gramine methiodide with an alkali derivative of an acylaminomalonic ester. By using ethyl sodioacetaminomalonate the yield of tryptophan, based on indole, was about 45 per cent.



Simultaneously Albertson et al (111), reported the use of acetamido- and benzamidomalonic esters, obtaining an over-all yield of 35 per cent based on indole.

During an extended investigation of carbon alkylation with gramine methiodide, Howe et al (112) observed that gramine condenses with malonic ester to yield ethyl α -carbethoxy- β -(3-indole)-propionate in much the same way as the methiodide condenses with sodiomalonic ester. This observation prompted the study of the condensation of gramine with acetaminomalonic ester. Although Mannich bases (β -dialkylamino ketones) have been condensed with β -keto esters in the presence of sodium ethoxide in ethanol (113) unsatisfactory yields of ethyl α -acetamido- α -carbethoxy- β -(3-indolyl)-propionate were obtained from gramine and acetaminomalonic ester with the same condensing agent. Better yields were obtained when the reactants were heated to 165° or when solutions of the reactants in pyridine or dioxane were heated to boiling. The presence of a small amount of a basic catalyst such as sodium methylate, sodium carbonate or sodium hydroxide was beneficial. The best results, 90 per cent, were obtained when the reactants were refluxed in an inert solvent such as toluene, dioxane or xylene in the presence of a small amount of powdered sodium hydroxide. With these modifications the over-all yield of dl-tryptophan from indole was 66 per cent.



It has been found by Albertson et al (114) that it is unnecessary and undesirable to use gramine methiodide in the condensation. When

ethyl iodide was added slowly to a warm solution of gramine and ethyl sodioacetamidomalonate in absolute ethanol, the desired product was isolated in a yield of 73%. Since it was possible to recover 16% of the gramine in a state of purity suitable for re-use, the yield based on the consumed Mannich base was actually 86 per cent. Furthermore, the reaction in dry ethyl alcohol was over in about seven to eight hours whereas the dioxane procedure required about thirty-six hours for completion. Saponification of the ethyl α -acetamido- α -carbethoxy- β -(3-indolyl)-propionate to the free dicarboxylic acid was quantitative. Simultaneous decarboxylation and deacetylation gave a yield of dl-tryptophan of 61 per cent which is not as good as was realized by the alkaline degradation of the ester as reported by Snyder.

When the less expensive methyl sulfate was substituted for ethyl iodide in the above condensation, the yield was 72 per cent with a 10 per cent recovery of gramine.

Since dimethylalkylamine, a product of the reaction, forms quaternary salts with the alkylating agents, the gramine is incompletely converted to the methosulfate or ethiodide. When two moles of methyl sulfate are used, the demands of both the volatile and Mannich base are satisfied and the latter then reacts completely. When this technique was followed the reaction was over in four hours at room temperature and the yield of ethyl α -acetamido- α -carbethoxy- β -(3-indolyl)-propionate increased to 95 per cent.

The attempt also was made to carry out the synthesis of the amino acid with ethyl benzamidomalonate but the yields in some of the steps were so low as to render the procedure impractical.

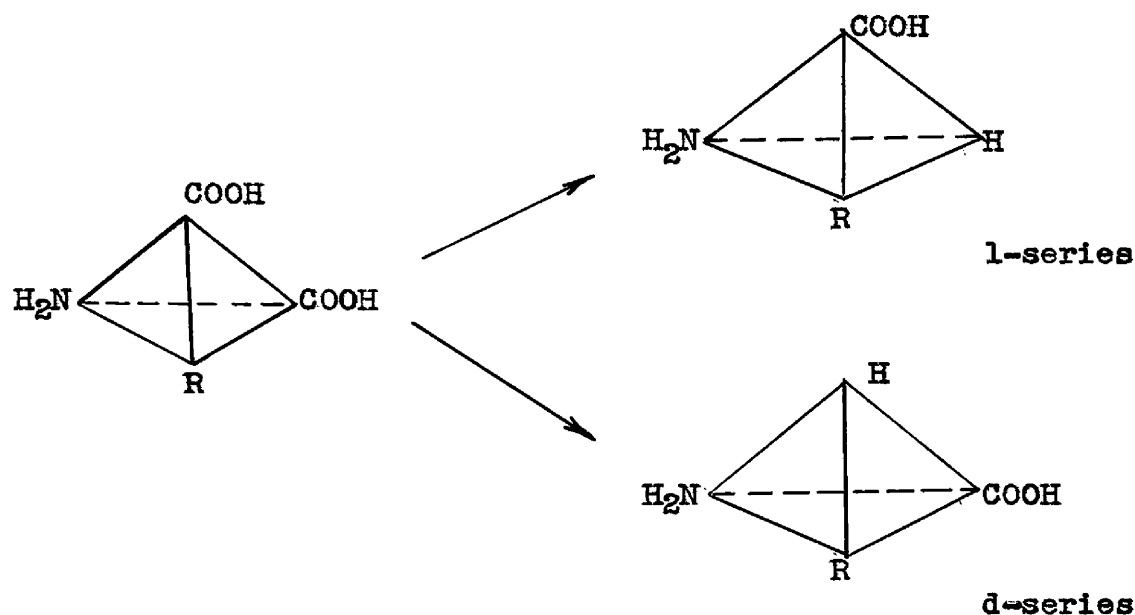
This work prompted the idea of using, instead of an acylaminomalonic

ester, the benzyl- or dibenzylaminomalonic ester, thus obviating the hydrolysis of the acyl group. In order to alkylate aminomalonic ester, it is necessary to block the amino group to prevent any possible reaction between it and sodium. Therefore, dibenzyl amine must be used, as the monobenzylamino derivative would not satisfy this condition. Although there is every indication the reaction between bromomalonic ester and dibenzyl amine should yield dibenzylaminomalonic ester, it was found that the reaction does not proceed as expected, but that apparently unsaturation occurs. Even though a quantitative yield of dibenzyl amine hydrobromide is obtained when twice the theoretical amount of dibenzylamine is used no dibenzylaminomalonic ester can be isolated, and the reaction product responds positively to tests for unsaturation. This interesting observation was not further investigated.

However, if malonic ester is first alkylated and then brominated, a compound is obtained which can be treated with monobenzyl amine to produce the alkyl derivative of benzylamino malonic ester. In this case, the substance in question does not undergo unsaturation, and one of the amino hydrogen atoms remains free. Benzyl-benzylamino-malonic ester was prepared according to this method, and the benzyl group then was removed by catalytic hydrogenation (Cf. 115). Saponification of the reduction product gave benzylaminomalonic acid. Mattocks (116) prepared p-nitrobenzylaminomalonic acid by this method. From the ease with which these reactions occur, it appears that this may well be a general method of preparation of those amino acids whose carbon nucleus is unaffected by bromination.

The alkylated aminomalonic acids of general structure, $R-\overset{\text{COOH}}{\underset{\text{NH}_2}{\text{C}}}-\text{COOH}$, should prove of considerable interest to the chemist interested in pro-

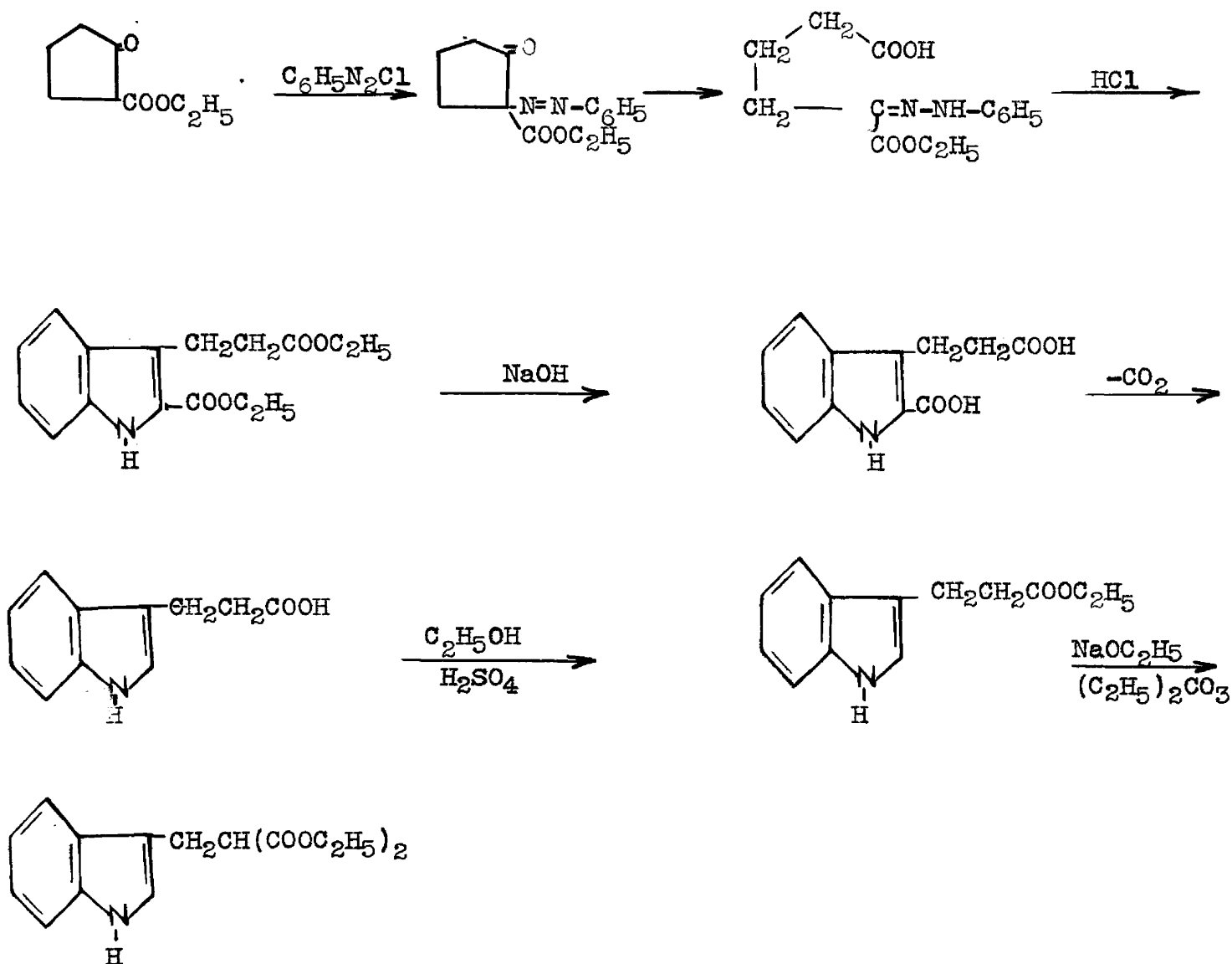
teins and amino acids, for on selective or asymmetric decarboxylation they should open up a means to the synthesis of either the d- or the l-series. E. g.,



Such asymmetric decarboxylations have been tried without much success in the laboratory, but enzymic decarboxylases appear more encouraging. Feeding experiments with malonic acids, analogous to the essential amino acids, ought to give a clue to their biological availability and value.

Indole and compounds containing the indole nucleus are extremely sensitive to the action of mineral acids, polymerizing to tars almost immediately. This sensitivity is borne out by the attempt of Smith and Sogn (117) to prepare tryptophan from ethyl α -keto-cyclopentanone carboxylate. This was coupled with diazotized aniline. The azo compound obtained was subjected to hydrolytic cleavage whereby the phenylhydrazone of ethyl hydrogen α -keto-adipate resulted and action of acid on the latter caused a Fischer indole synthesis to occur with production of ethyl β -(2-carbethoxy-indole-3)-propionate. This diester was hydrolyzed by action of alkali to the diacid, which was decarboxylated and the

product esterified to ethyl β -(3-indolyl)-propionate. The ester was readily carbethoxylated to ethyl α -carbethoxy- β -(3-indolyl)-propionate.

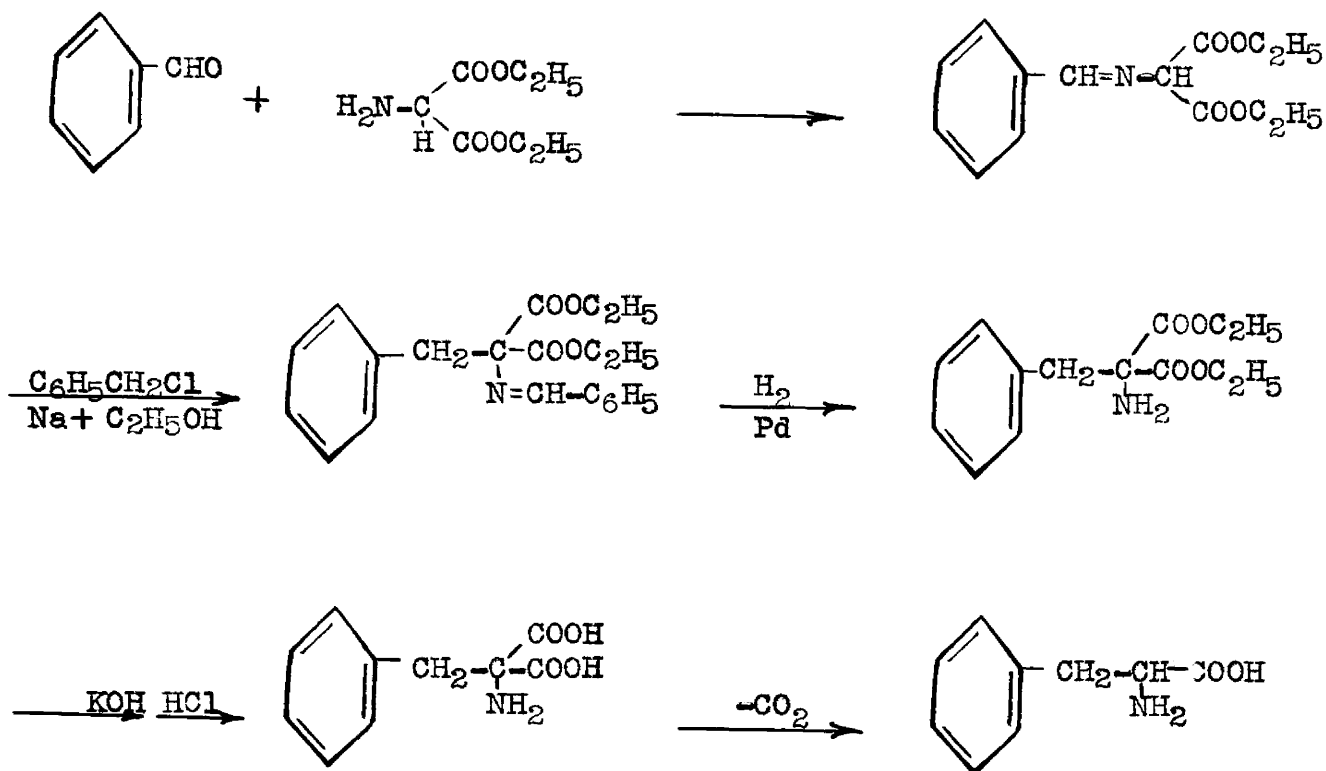


Bromination of this compound, in various solvents, and in the presence of potassium acetate as a buffer, led to no definite bromo compound. The bromine reacted readily, and hydrobromic acid was evolved, but the removal of the solvent left a residue of an oil which could not be crystallized, nor could this crude bromo compound be aminated by action of ammonia. The product was an oily substance, often colored, from which no solid material could be obtained. Attempts to hydrolyze the bromination product by action of acids led to nothing but black, tarry material.

Attempts were made by Smith and Sogn to alkylate phthalimidomalonic ester with β -chloropropionic aldehyde acetal. It was hoped that the phenylhydrazone of the resulting aldehyde compound would, by a Fischer indole synthesis, lead directly to dl-tryptophan. However, no alkylation could be achieved; either no reaction at all occurred, or else the reaction mixture developed dark spots which rapidly spread throughout the mass and only tarry decomposition products resulted.

In view of the successful method of alkylation of acylamidomalonic ester developed by the investigations of Snyder, Albertson, and their coworkers, as described, the question arose whether during the alkylation of aminomalonic ester the amino group may not be equally well protected by formation of a Schiff's base. For this purpose the benzal-amino intermediate should prove most valuable, since one would expect to remove it by catalytic hydrogenolysis (Cf. 115) under conditions which should not affect the stability of the indole nucleus.

In order to test the practicability of this route, malonic ester was treated with benzaldehyde in benzene solution to form the Schiff base. This was isolated as an oil, and without further purification, was alkylated with benzyl chloride. The benzyl-benzalaminomalonic ester so obtained was then subjected to catalytic hydrogenation during which 81 per cent of the calculated quantity of hydrogen was taken up. The reaction product was saponified and decarboxylated, yielding a solid whose N-benzoyl derivative melted somewhat lower than that previously reported for phenyl alanine (118). The reactions involved are illustrated below:



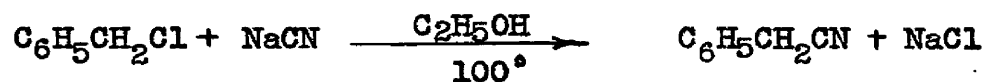
A similar alkylation, using gramine, as described by Albertson et al (114) was attempted, but in the limited experiments performed on this reaction, the results were negative, and insufficient intermediates did not permit further investigation. Despite this, it is believed that the encouraging results obtained using benzyl chloride as the alkylating agent indicate that an intensive study of the reaction conditions has possibilities of solving the problem and adding another variation to the synthesis of amino acids.

EXPERIMENTALPreparation of catalyst

To 3 gm. of Norite or blood charcoal was added 0.3 gm. of palladium chloride crystals and this mixture was shaken in an atmosphere of hydrogen until saturated. The solution was filtered and the palladinized charcoal was washed successively with water and alcohol. The catalyst was dried in a vacuum desiccator over sulfuric acid before use.

Preparation of benzyl cyanide

Benzyl cyanide was prepared according to the directions of Adams and Thal (119), as follows:

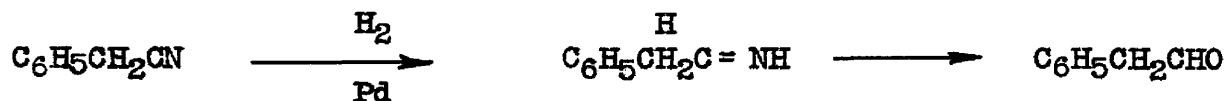


Into a one liter round-bottomed flask, fitted with a stopper holding a reflux condenser and a separatory funnel, were placed 100 gm. (2 moles) of powdered sodium cyanide (96-98% pure) and 90 cc. of water. The mixture was warmed on a water bath in order to dissolve most of the sodium cyanide, and then 200 gm. (1.6 moles benzyl chloride (b.p. 175-180°) in 200 gm. of 95% ethanol were added through the separatory funnel in the course of one-half to three-quarters of an hour. The mixture was then heated under a reflux condenser on the steam bath for four hours, cooled, and filtered with suction to remove most of the sodium chloride. The filtered salt was washed with a small portion of alcohol in order to remove any benzyl cyanide which may have been mechanically held.

The liquid was then transferred to a one liter distilling flask, and as much alcohol as possible was removed on the steam bath. The res-

idual liquid was steam-distilled, condensing in the distillate as a heavy, pale yellow oil. The distillate was cooled, extracted with ether to remove all of the benzyl cyanide, and the ethereal solution was dried over anhydrous sodium sulfate. The ether was distilled off on a water bath, and the remaining benzyl cyanide was then distilled through a fractionating column, boiling at 135-140° at 38 mm. A yield of 121 gm. was obtained, corresponding to 65% of the theoretical.

Catalytic hydrogenation of phenylacetonitrile



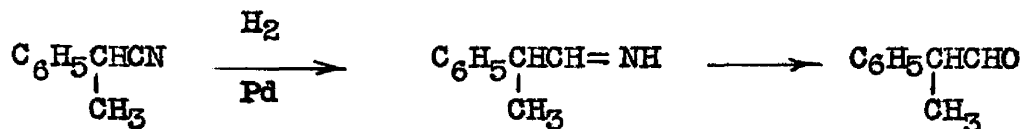
The hydrogenation of benzyl cyanide was run with 6 gm. (0.051 mole) of benzyl cyanide, 36 cc. of alcoholic hydrochloric acid (0.1 gm./cc.) and the 10% palladium-charcoal catalyst (prepared as described on page 27) in a total volume of 150 cc. of 70% ethanol. The catalyst was freshly prepared, and not thoroughly dried. A total of 1120 cc. (half of the amount calculated to reduce the benzyl cyanide completely to phenethylamine) of hydrogen was taken up within four hours, when the hydrogenation was discontinued.

The catalyst was filtered from the alcoholic mixture, and the alcohol was removed by distillation under reduced pressure. The residual liquid was steam-distilled. The colorless oil appearing in the distillate was extracted with ether, the ethereal solution was dried over anhydrous sodium sulfate, and the ether was then distilled off, leaving 3.5 gm. (58% theory) of a colorless oil, with a rose-like odor.

The oil was distilled under reduced pressure, b. 85°/10 mm. (120) and the 2,4-dinitrophenyl hydrazone was prepared, m. 118°. From these data it was established that the product was phenylacetaldehyde.

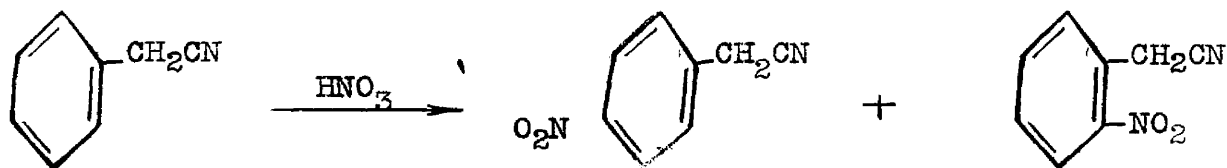
Catalytic hydrogenation of α -phenylpropionitrile

The α -phenylpropionitrile was obtained through the courtesy of Dr. Louise Kelley of Goucher College.



Six gm. (0.045 mole) of α -methylbenzyl cyanide, in 150 cc. of 70% ethanol, was reduced in the presence of two equivalents of hydrogen chloride and the 10% palladium-charcoal catalyst. The isolation procedure was identical with that for phenylacetaldehyde (page 28). The 4 gm. (60% yield) of aromatic yellow oil, hydratropaldehyde obtained distilled, b.₁₉ 95°, and the semicarbazone prepared, m. 152° (121).

Mononitration of benzyl cyanide

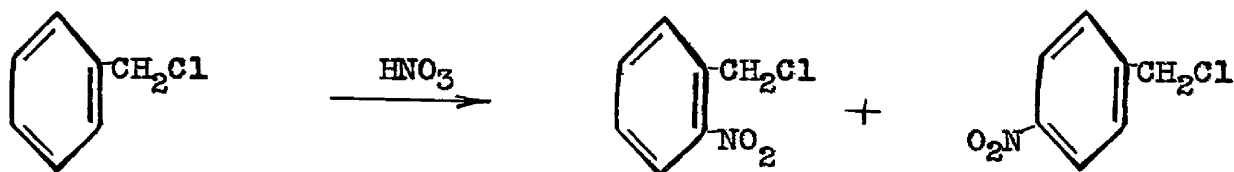


The nitration of benzyl cyanide was carried out as follows: Fifteen cc. of fuming nitric acid (s. gr. 1.50) was placed in a 50 cc. beaker and the acid was cooled in an ice-salt bath with stirring to 0° C. Then 2 gm. (0.017 mole) of benzyl cyanide was added dropwise, keeping the mixture well stirred throughout the addition. After all of the benzyl cyanide had been added, the reaction mixture was stirred for fifteen minutes longer, and then slowly poured over crushed ice. The white precipitate which formed was filtered with suction and recrystallized from hot 80 per cent ethanol. The yield was 1.5 gm. (60% theory), m. 116° (122), and all the properties were those of the p-nitrobenzyl cyanide.

In several of the runs a small amount of a yellow oil, which crystallized on standing, was obtained, but the yield of this product was considered insignificant.

This procedure was repeated in a series of nitrations, increasing the temperature of the reaction mixture by 5° each time, from 0° to 45° C., but no o-nitrobenzyl cyanide could be isolated in any case. The yield of the para compound was consistently the same.

Nitration of benzyl chloride



Into 197 gm. (1.56 moles) of benzyl chloride was cautiously dropped a mixture of 312 gm. of fuming nitric acid and 160 gm. of acetic anhydride. This addition required about two hours for completion. The temperature was kept at 30° and at no time exceeded 35°.

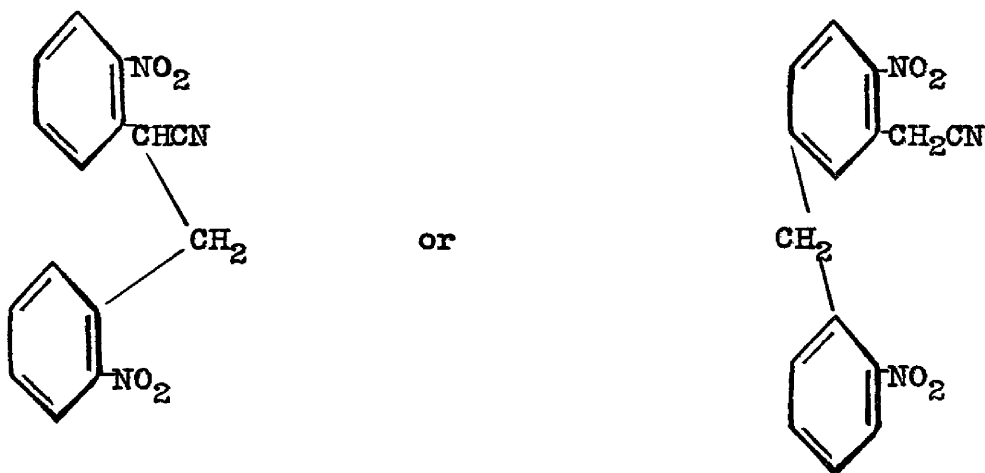
The reaction mixture was then poured over cracked ice, causing an orange oil to separate. This was extracted with benzene, the benzene layer was washed free from acid with distilled water, dried over anhydrous sodium sulfate and distilled under reduced pressure. Any unchanged benzyl chloride distilled at 80°/15 mm. At 125°-140°/15 mm. a yellow oil, the o-nitrobenzyl chloride, was obtained, the p-isomer distilling at 145-160°/15 mm. The latter crystallizes on cooling to room temperature, m. 71° (123). A yield of 21 gm. (8% of the theoretical amount) of the o-nitrobenzyl chloride was obtained in this manner.

Attempted preparation of o-nitrobenzyl cyanide

Twenty-one grams (0.12 mole) of o-nitrobenzyl chloride dissolved in 21 gm. of 95% ethanol was slowly added to 7 gm. (0.14 mole) of sodium cyanide dissolved in a small amount of water. This was refluxed on a water bath for six hours. A brown tarry mass resulted. On pouring into 150 cc. of water, there occurred separation of a brown oil, which was extracted with 200 cc. of boiling water and filtered. The aqueous filtrate was allowed to evaporate spontaneously. No cyanide was isolated.

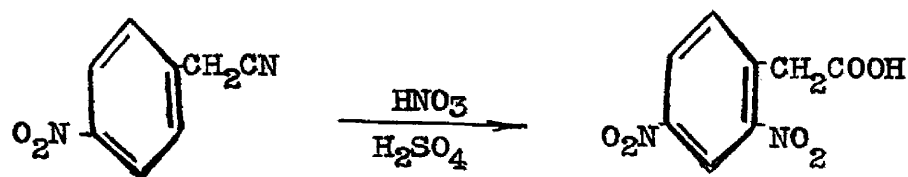
Reaction of o-nitrobenzyl chloride with sodium cyanide

Bamburger (105) reported that he obtained small yields of o-nitrobenzyl cyanide when o-nitrobenzyl chloride was treated with sodium cyanide, but the chief product was a condensation product with either of the following two formulas:



This synthesis was attempted in these laboratories and the results were substantially confirmed except that no o-nitrobenzyl cyanide could be isolated.

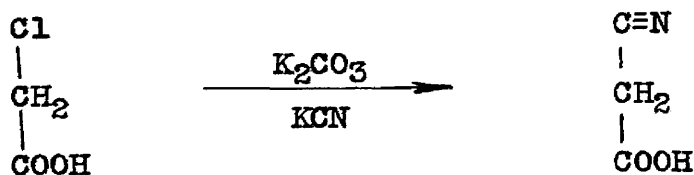
Nitration of p-nitrobenzyl cyanide

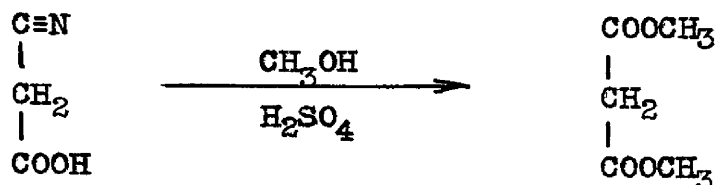


To a cooled mixture of 15 cc. of fuming nitric acid (s. gr. 1.50) and 15 cc. conc. sulfuric acid, was added drop-wise with stirring 2 gm. of p-nitrobenzyl cyanide. After the addition was complete, the reaction mixture was gradually heated to 55°-60° C., and kept there for thirty minutes. It was then cooled and poured over crushed ice. The resulting fine, yellow precipitate was filtered with suction, washed with hot water, in which it was slightly soluble, and recrystallized from 80% ethanol. Pale yellow needles were obtained, which melted at 175° C., liberating a gas. It appears that hydrolysis had occurred, and that the product was 2,4-dinitrophenyl acetic acid which Borsche (124) reports as melting at 179-180° with decomposition. No dinitrobenzyl cyanide was recovered from the reaction mixture.

Preparation of dimethyl malonate

The procedure employed for the preparation of dimethyl malonate was identical with that given by McElvain (126) for the diethyl ester, using an equivalent amount of methyl alcohol in place of ethanol.





In a large porcelain evaporating dish was dissolved 376 gm. (4 moles) of monochloroacetic acid in water, and the solution, warmed to 50°, was neutralized with 300 gm. (2.17 mole) dry solid potassium carbonate. Two hundred and eighty gm. (4.3 moles) of pure granular potassium cyanide was then added. The addition of the last portion caused vigorous boiling, due to the formation of cyanoacetic acid. The entire operation was carried out under a hood.

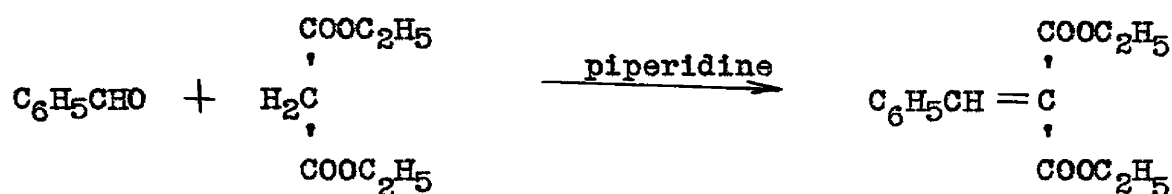
After addition was complete, the reaction mixture was stirred with a thermometer while being concentrated, using two bunsen burners, until the temperature was 125°. It was then stirred with a spatula while cooling. Stirring must be continued, or otherwise a hard mass is formed which can hardly be powdered. The solid was now rapidly and thoroughly broken up in a large mortar, transferred to a 5-l flask fitted with a reflux condenser. With thorough shaking, there was added 200 cc. of absolute methanol and then gradually, a cooled mixture of 800 cc. of absolute methanol and 600 cc. of conc. sulfuric acid.

The pasty mass was heated for two hours with frequent shaking on a water bath under the hood, well cooled, and shaken with 1600 cc. of water. Undissolved salt was removed by filtration and washed several times with ether, which was then used to extract the aqueous filtrate. The latter was then thoroughly extracted with two further lots of ether and the combined ether extracts shaken with conc. sodium carbonate solution until no longer acid.

The ethereal solution was dried over anhydrous sodium sulfate, the ether removed, and the dimethyl malonate distilled under reduced pressure. A yield of 139 gm. (26.3 theory), b. 181° (127) was obtained.

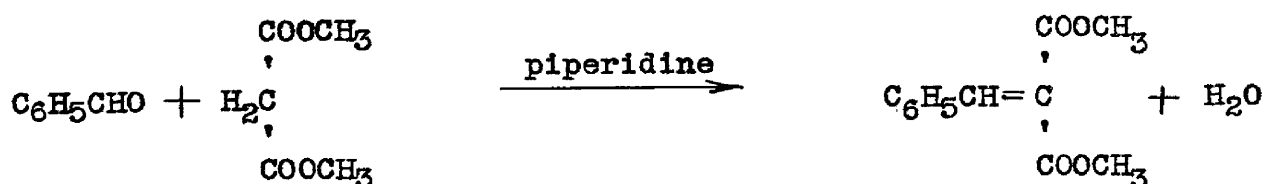
Preparation of diethyl benzalmalonate

The condensation of diethyl malonate and benzaldehyde to yield diethyl benzalmalonate was carried out according to the directions of Knoevenagel (125), as illustrated in the following equation:



One hundred gm. (0.6 mole) of diethyl malonic ester were mixed with 70 gm. (0.6 mole) of freshly distilled benzaldehyde in a 200 cc. flask, gradually mixed with 2 gm. of piperidine at room temperature and allowed to stand in a well-stoppered container for two days. To complete the reaction, the mixture was heated for twelve hours on a water bath. The condensation product was washed, after the addition of ether, with dilute acid and then water, dried over anhydrous sodium sulfate and distilled, boiling 175-186 at 11 mm. The yield obtained was 73 gm., corresponding to 50% of the theoretical.

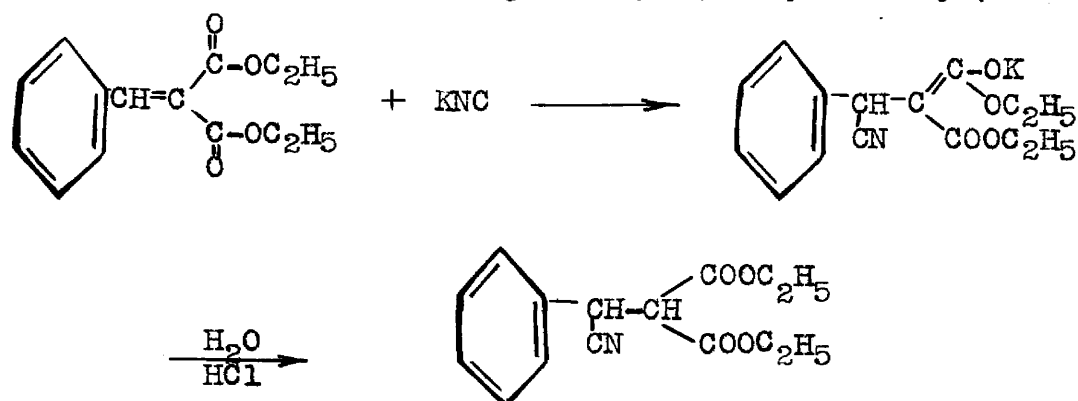
Preparation of dimethyl benzalmalonate



The procedure followed was identical with that for the diethyl derivative, as described on page 34. The yield of dimethyl benzalmalonate was 98 gm. (75% theory), b. 171°/10 mm. (123).

Michael condensation with diethyl benzalmalonate

The equation given below outlines the procedure, according to Michael (106), for preparing diethyl (α -cyanobenzyl) malonate.



Six gm. (0.025 mole) of diethyl benzalmalonate was added to a suspension of 1.6 gm. (0.0246 mole) of potassium cyanide in 20 cc. of boiling absolute ethanol and the mixture refluxed until all of the salt dissolved. One-half of the solvent was distilled off. On cooling, a pink solid appeared. This was dissolved in dry ether, but it could not be crystallized from the ether, owing to its extreme solubility in it. The substance is very soluble in all of the ordinary organic solvents and does not crystallize from them.

Another attempt was made to obtain the desired cyano compound by following Michael's alternate method. Six gm. (0.025 mole) of diethyl benzalmalonate was dissolved in 50 cc. of ethanol and a solution of 1.6 gm. (0.0246 mole) of potassium cyanide in 20 cc. of water was added. The solution was allowed to stand for ten minutes, 3 cc. conc. hydrochloric acid was added, and then the reaction mixture was allowed to stand for twenty-four hours. It was then diluted with enough water to cause precipitation of an oil, which was extracted with ether. The ethereal

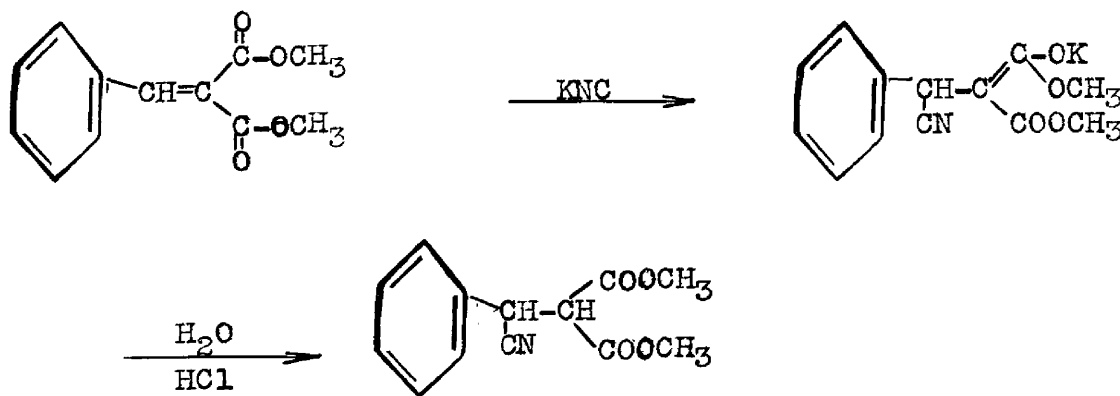
solution was dried over anhydrous sodium sulfate and the ether was removed by distillation. The residue was dissolved in absolute ethanol, and on cooling in a carbon dioxide-alcohol bath, white crystals were obtained in the solution. These could not be removed as they melted immediately on being removed from the freezing bath.

It was strongly felt that in both of these experiments the substances obtained were identical. However, in view of the fact that the isolation and purification were so difficult, use of this compound was abandoned in favor of the dimethyl benzalmalonate.

Since Michael obtained the α -cyano derivative in 100 per cent yields, it was thought that the solution obtained above would be practically pure. This was reduced catalytically, but it formed a sticky mass with the charcoal. These reduction experiments should be repeated with some modifications, such as, perhaps, first shaking the alcoholic solution of the condensation product with activated charcoal before using the catalyst.

Michael condensation with dimethyl benzalmalonate

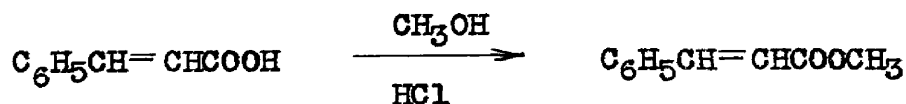
The preparation of dimethyl (α -cyanobenzyl)malonate was carried out as directed by Michael (106), as illustrated below:



Five and one-half grams (0.025 mole) of dimethyl benzalmalonate was added to a suspension of 1.63 g. (0.025 mole) of potassium isocyanide in 20 cc. of boiling absolute methanol. The salt dissolved immediately. One-half of the solvent was distilled off, which resulted in the separation of a voluminous white, crystalline potassium compound. One hundred cc. of dry ether was added and the mixture cooled in an ice bath. The solid which formed was filtered, washed repeatedly with dry ether and dried in vacuo at 100°. The yield was 7.0 g. (100% of the theoretical amount).

The potassium compound was suspended in ether, dilute acid was added and the mixture was shaken until solution was complete. The dried solution was freed of ether and the colorless residual oil was dissolved in an equal volume of methyl alcohol and cooled to -20°, when it completely solidified, the yield being 6.0 g., or 100%. The compound was recrystallized by dissolving in the minimum volume of methyl alcohol at room temperature and cooling in a freezing mixture. It separated in rosettes of needles, m. 47.5-48.5°.

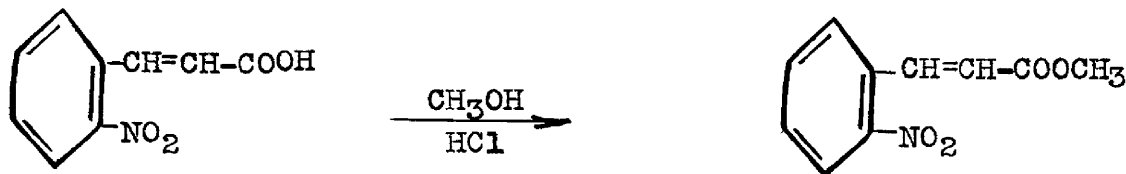
Preparation of methyl cinnamate



To 150 cc. of absolute methanol containing 8 gm. of hydrochloric acid was added 37 gm. (0.25 moles) of cinnamic acid, and the mixture refluxed for several hours. The alcohol was removed by distillation under reduced pressure, and the residual liquid immersed in an ice-bath, when crystallization occurred. The crystals of methyl cinnamate after drying weighed 36.5 gm. (97% yield) m. 36°, which agrees with that described for the ester by Weger (128).

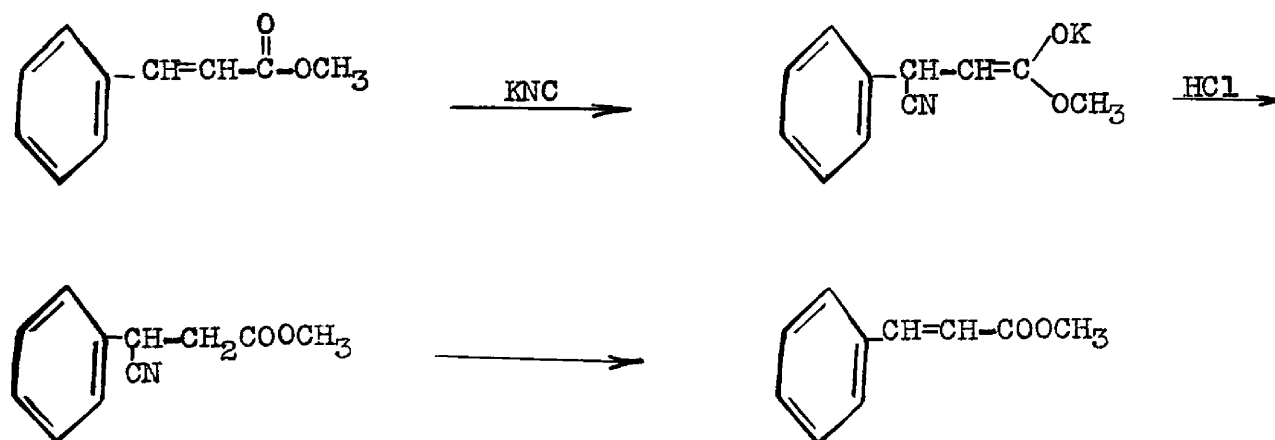
Preparation of methyl o-nitrocinnamate

The o-nitrocinnamic acid used in this experiment was obtained through the courtesy of Mr. B. Sussman.



Ten gm. (0.055 mole) of o-nitrocinnamic acid and 150 gm. of absolute methanol containing 6 gm. of hydrochloric acid were heated on a water-bath under a reflux condenser until solution was complete. Almost all of the alcohol was distilled off and the solution was cooled, when yellow plate-like crystals formed, weight 7.7 gm. (72% yield). These on recrystallization from methanol melted at 73° (55).

Michael condensation with methyl cinnamate



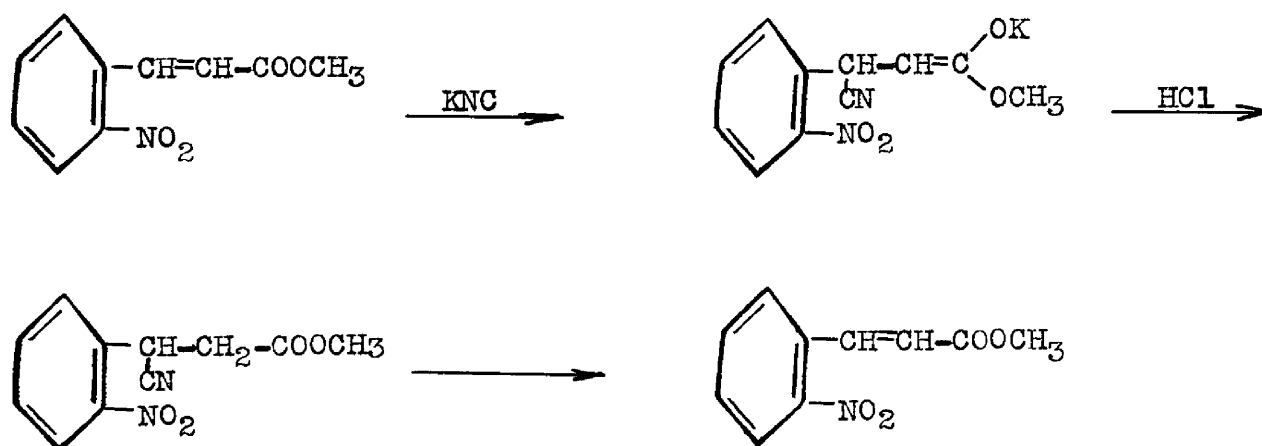
A mixture of 6.5 gm. (0.04 moles) of methyl cinnamate, 2.6 gm. (0.04 moles) of potassium isocyanide (dried over phosphoric anhydride in a vacuum desiccator) and 50 cc. of absolute methanol were refluxed for three hours on a water-bath, or until most of the potassium isocyanide had dissolved. That part of the latter which did not go into solution

was filtered off. The filtrate was concentrated to one-half its volume. It was then cooled in an ice-salt bath, and 80 cc. of dry ether was added. The liquid became milky and was further cooled in the ice-box, during which time white crystals formed. This suggested that the reaction probably proceeded as anticipated. The white precipitate was suspended in ether and dilute hydrochloric acid was added until solution was complete. The ether layer was dried overnight in the ice box over anhydrous sodium sulfate.

On evaporation of the ether a white solid remained. It was recrystallized from petroleum ether, forming white, fluffy needles, m. 133° , weight 5 gm. There was no depression in the melting point when mixed with known cinnamic acid.

Apparently the condensation took place as expected, but the product formed appears to be unstable in the presence of acid.

Michael condensation with methyl o-nitrocinnamate

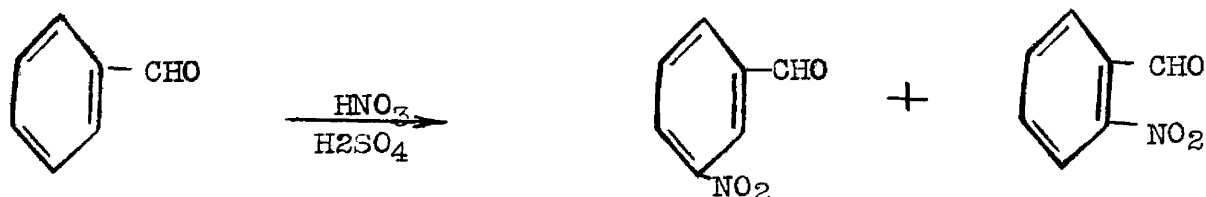


Four gm. (0.02 moles) of methyl o-nitrocinnamate was dissolved in 80 cc. of absolute methanol with slight heating, and 1.3 gm. (0.02 moles) of potassium cyanide was added. The cyanide dissolved in about five

minutes to give a slightly darker yellow solution. The reaction mixture was allowed to stand for three hours, when 0.6 cc. (one equivalent) of conc. hydrochloric acid was added. A white precipitate formed and was removed by filtration. On concentration of the filtrate, and cooling, a further white precipitate was obtained, the total weight of solids being 3.7 gm. Investigations of the properties of the precipitates showed that they were, in each case, the original ester. As with methyl cinnamate the reaction apparently occurred, but the product was unstable in acid medium.

Nitration of benzaldehyde

In a personal communication Eastman Kodak and Co. report that during the synthesis of m-nitrobenzaldehyde 4 per cent of the product is the ortho-isomer. Zenitz (107), during his study of the nitration of propiophenone, found that low temperature reactions favored the formation of o-nitropropiophenone. It was for these reasons that the nitration of benzaldehyde was studied, with the hope that appreciable amounts of o-nitrobenzaldehyde might be obtained.

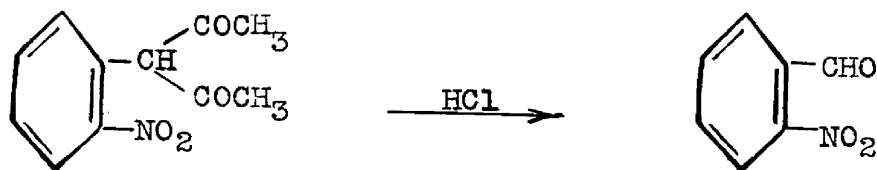


A nitration mixture was prepared by carefully adding 300 cc. of cooled, fuming nitric acid to 700 cc. of well-cooled conc. sulfuric acid. The acid solution was cooled to 10° C., and then 212 gm. (2 moles) of benzaldehyde was added dropwise with stirring. The temperature during the addition was kept between 15-20° C. After addition of the benzaldehyde was complete, stirring was continued for one-half hour, and then

the mixture was poured over cracked ice. The yellow solid which formed was removed by filtration, and crystallized from hot 95% ethanol. The crystallization was allowed to proceed overnight in the ice box. A very hard, yellow, crystalline mass was deposited at the bottom of the container, with a layer of a yellow-orange oil, also not too alcohol-soluble, above it. The crystals, on separation from the alcoholic mixture, and after drying, weighed 150 gm., m. 58.5° C., and were pure m-nitrobenzaldehyde. Lippmann (129) described this compound as thin needles, mp. 58° . Addition of water to the filtrate from this crystallization resulted in the separation of a further quantity of yellow-orange oil. Further cooling of either this oil or the oil obtained in the original crystallization above, yielded more of the m-nitrobenzaldehyde. This procedure was repeated a number of times, each time more meta compound being obtained, the yield totaling 210 gm. (69% theory. The oil remaining was at first thought to be o-nitrobenzaldehyde, but its derivatives on purification gave all evidence of being those of the m-nitrobenzaldehyde. It appeared that the oil was merely the meta derivative of benzaldehyde, with sufficient impurities, perhaps including a minute amount of o-nitro benzaldehyde, to lower its melting point sufficiently to liquify it.

This procedure was repeated many times, varying both the temperature of the nitration, and the ratio of nitric to sulfuric acid in the nitration mixture, but without any appreciable difference in results. It is felt that nitration of benzaldehyde in this manner, unless tremendous quantities are used, (in the laboratory) is not a practical method of preparing o-nitro benzaldehyde.

Preparation of o-nitrobenzaldehyde from the diacetate



A suspension of 40 gm. (0.18 mole) of o-nitrobenzaldiacetate (prepared by Sussman according to the directions of Johnson (130) in a mixture of 325 cc. of concentrated hydrochloric acid, 348 cc. of water, and 62 cc. of ethanol was refluxed with stirring for one and one-half hours. The mixture was then cooled to 0°, the solid filtered with suction and washed with water, and then steam-distilled. The o-nitrobenzaldehyde, which distilled as an oil, was recovered from the aqueous distillate by cooling. The solid o-nitrobenzaldehyde was removed and dried; weight 8 gm., m. 44° C. (130).

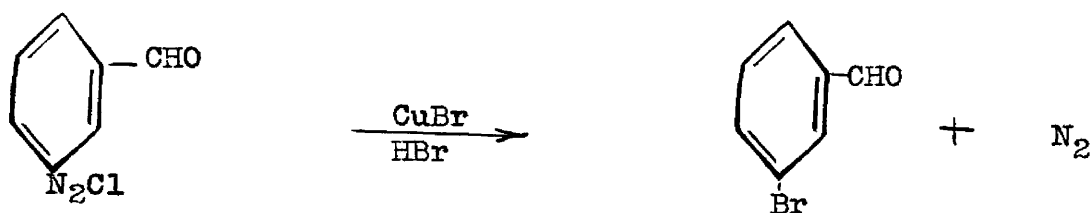
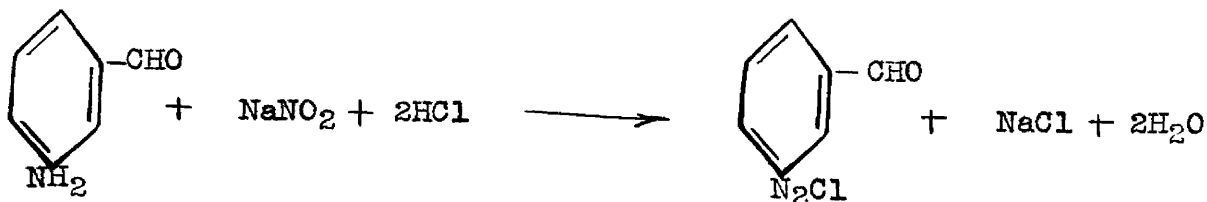
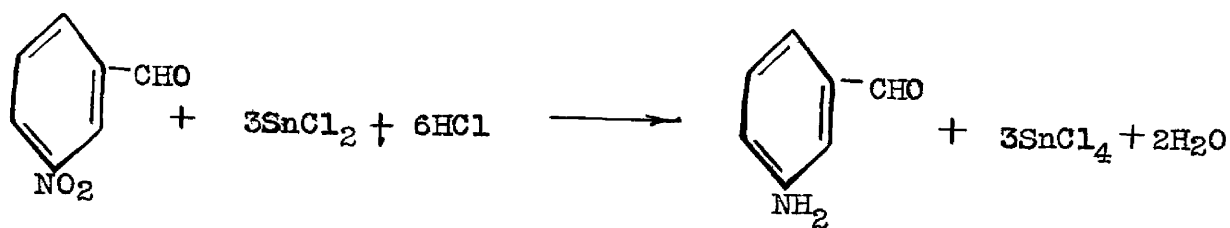
Knoevenagel condensation on o-nitrobenzaldehyde

A Knoevenagel condensation was run in the usual manner (page 34), using o-nitrobenzaldehyde and dimethyl malonate. A dark brown tar resulted, from which no product could be isolated.

Mattocks (116), in his condensation of p-nitrobenzaldehyde with diethyl malonate obtained a high yield of the bis compound, rather than the diethyl p-nitrobenzalmalonate. A similar reaction may perhaps occur when o-nitrobenzaldehyde is used. However, further investigation of this reaction was considered to be impractical.

Preparation of m-bromo-benzaldehyde

m-Bromobenzaldehyde was prepared as directed by Buck et al. (131).



. A solution of 450 g. (2 moles) of stannous chloride crystals (C.P.) in 600 cc. of concentrated hydrochloric acid was placed in a 3-l. beaker provided with an efficient mechanical stirrer and cooled in an ice bath. When the temperature of the solution had fallen to 5°, 100 g. (0.66 mole) of m-nitrobenzaldehyde (m. 52-55°) was added in one portion. The temperature rose slowly at first, reaching 25-30° in about five minutes, then it rose very rapidly to about 100°. Stirring must be vigorous or the reaction mixture may be forced out of the beaker. During the reaction the m-nitrobenzaldehyde dissolved, and an almost clear solution was obtained. The solution was cooled in an ice-salt mixture until the temperature had fallen to about 2°. During the cooling, orange-red crystals separated and a pasty suspension resulted.

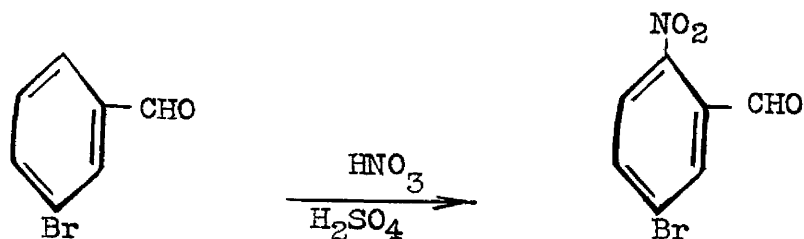
A 250-cc. separatory funnel was fixed so that its stem extended below the surface of the pasty suspension. A solution of 46 g. (0.67 mole)

of sodium nitrite in 150 cc. of water was placed in the funnel and was slowly added to the well-stirred mixture until it showed a positive starch-iodide test for nitrous acid. The temperature of the mixture was maintained between 0° and 5° throughout the addition of the nitrite solution, which required about 90 minutes. Usually, all but 5-8 cc. of the nitrite solution was added before a positive test for nitrous acid appeared.

During the latter part of the diazotization of the aminobenzaldehyde, a hot solution of cuprous bromide was prepared. In a 5-l. round-bottomed flask, 189 g. of copper sulfate and 91 g. of sodium bromide were dissolved in 600 cc. of hot water, and to this solution was added a solution of 41 g. of sodium metabisulfite and 27 g. of sodium hydroxide in 300 cc. of water. The final temperature of the resulting cuprous bromide solution should be about 75° .

The diazonium solution was added to the hot cuprous chloride solution while the latter was shaken by hand but was not cooled. After the solutions were thoroughly mixed, 200 cc. of 48% hydrobromic acid was added and the mixture allowed to stand overnight. The reaction mixture was steam distilled to separate the m-bromobenzaldehyde, which was collected practically completely in the first 1.5 l. of distillate. The m-bromobenzaldehyde was removed from the aqueous distillate by extraction with two 150-cc. portions of ether, and the ethereal solution was dried with 10-15 g. of anhydrous calcium chloride. After being decanted from the drying agent, the ether was distilled, and the residual liquid was distilled under reduced pressure. The m-bromobenzaldehyde boiled at $93-98^{\circ}/8\text{mm}$. The yield was 80 g., or 65% of the theoretical amount.

Nitration of m-bromobenzaldehyde



A mixture of 75 cc. of fuming nitric acid and 75 cc. of concentrated sulfuric acid was cooled to 0° with stirring. Ten gm. (0.054 moles) of *m*-bromobenzaldehyde was slowly added through a separatory funnel, the temperature not being allowed to exceed 5° . The syrupy liquid was poured over cracked ice, the white precipitate was filtered and dried over phosphoric anhydride in a vacuum desiccator. A quantitative yield of 12 gm. was obtained. Further crystallization from petroleum ether gave long, yellowish, fluffy needles, *m.* 74° (132).

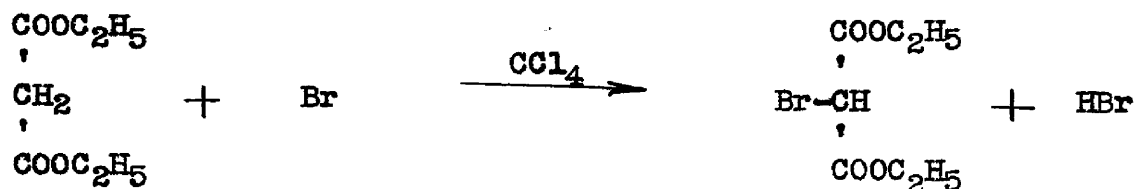
The phenylhydrazone was prepared according to the directions given by Einhorn et al (132). One gram of the aldehyde in alcoholic solution was treated with 0.5 g. of phenylhydrazine. The hydrazone soon formed and was recrystallized from alcohol in dark red needles, *m.* 180° , establishing the identity of the compound as 2-nitro-5-bromobenzaldehyde.

Knoevenagel condensation of 2-nitro-5-bromobenzaldehyde.

A condensation of 2-nitro-5-bromobenzaldehyde and dimethyl malonate was attempted, according to the directions of page 34. However, a black-brown tar resulted, from which it was impossible to extract any well-defined product, with any of the usual organic solvents or their combinations.

Preparation of diethyl bromomalonate

Palmer and coworkers (133) prepared diethyl bromomalonate as follows:

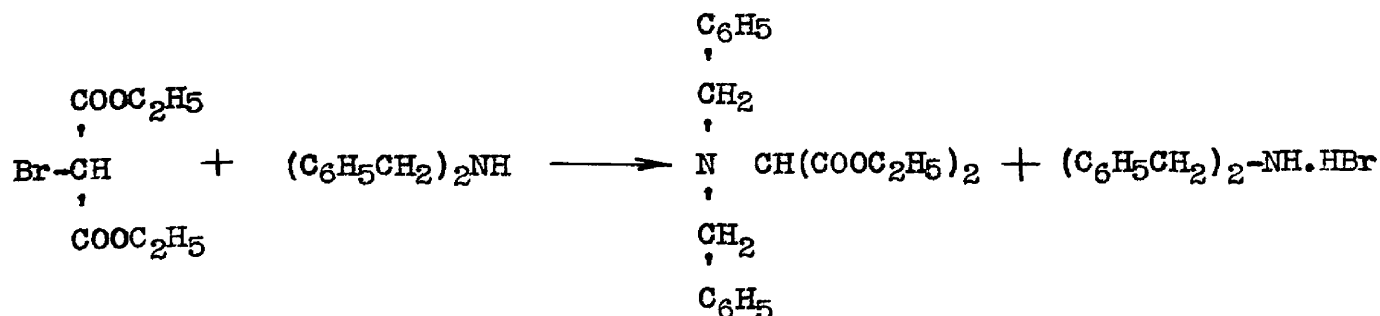


A one liter three-necked flask was fitted with a stirrer, a reflux condenser with a tube to a gas trap for absorption of hydrogen bromide, and a separatory funnel with a long stem almost touching the blades of the stirrer. In the flask was placed 160 gm. (one mole) of freshly distilled diethyl malonate and 150 cc. of carbon tetrachloride. In the separatory funnel was placed 53 cc. (165 gm., 1.03 moles) of dry bromine. The stirrer was started and the bromine introduced at a slow constant rate, enough to keep the color of the reaction mixture orange. After addition of the bromine, the reaction mixture was refluxed on a water-bath until there was no further evolution of hydrogen bromide (several hours are required).

The mixture was cooled, and washed five times with 50 cc.-portions of 5% sodium carbonate solution. It was then dried by shaking with anhydrous sodium sulfate, and distilled under reduced pressure. The fraction boiling at 126-130°/15 mm. was collected; weight 182 gm. (76% yield).

Reaction between diethyl bromomalonate and dibenzylamine

The reaction did not take place as expected.



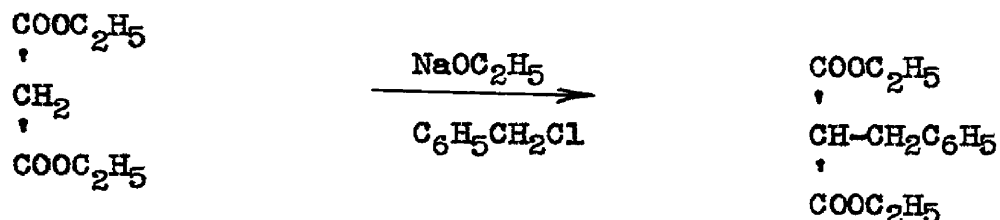
In a 500 cc. three-necked flask equipped with a mechanical stirrer, a reflux condenser and a hot water bath was placed 23.8 g. (0.1 mole) of diethyl bromomalonate, 39.4 g. (0.2 mole) of dibenzylamine and 75 cc. of absolute ethanol. The solution was refluxed for about eight hours. After one hour of refluxing, white crystals began to form in the reaction mixture. When the reaction was complete, these were collected on a filter, and the alcohol removed from the filtrate by distillation under reduced pressure. After cooling the residue ether was added to precipitate completely the crystals, whose total weight was 52 g., m. $255-6^{\circ}$, identifying them as dibenzylamine hydrobromide (134). The ethereal solution was washed several times with water to insure complete removal of the hydrobromide, and then dried over anhydrous sodium sulfate. Distillation of the ether left a residue of an oil weighing 35 g., calculated yield, 35.5 g. The product was thought to be diethyl dibenzylaminomalonate. However, hydrogenation of this product did not yield diethyl aminomalonate, as would be expected. On standing for extended periods of time in the laboratory in a cork-stoppered flask at room temperature, the oil gradually deposited crystals. When these were removed and washed with ether, they melted at 266° . When mixed with known dibenzylamine hydrobromide, there was no depression in the melting point. If to a solution of the oil in dry ether or benzene, dry hydrochloric acid was added, a precipitation of dibenzylamine hydrochloride resulted.

A repetition of the reaction gave a product which showed evidences of unsaturation.

Since the product obviously was not the expected diethyl dibenzylaminomalonate, it was not further investigated.

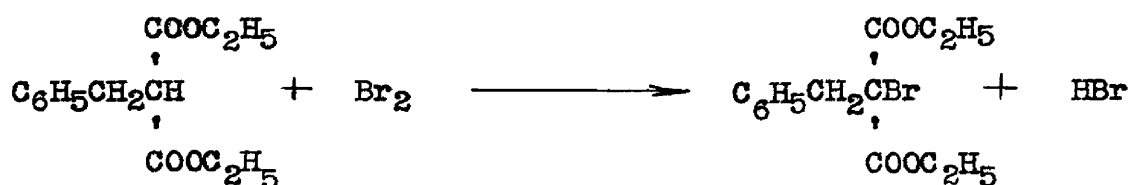
Preparation of diethyl benzylmalonate

Diethyl benzylmalonate was prepared according to the directions of Marvel et al (135).



To 500 cc. of absolute ethanol in a one liter three-necked flask equipped with a dropping funnel, a reflux condenser, a mechanical stirrer, and an oil bath, was added 23 gm. (1 gm. atom) of sodium cut in small slices. When all the sodium had reacted, a calcium chloride tube was placed on the condenser and 166 gm. (1 mole) of diethyl malonate were added through the separatory funnel in a steady stream. This was followed by the dropwise addition of 126.4 gm. (1 mole) of benzyl chloride over a period of about one and one-half hours. The mixture was refluxed, with stirring, until neutral to moist litmus paper (about three hours). The reflux condenser was then exchanged for a downward condenser and the alcohol distilled off until almost 500 cc. was collected. The residue was then treated with not more than 400 cc. of water and shaken. The ester layer was dried over anhydrous sodium sulfate and distilled. The fraction boiling at 145-155° C./4mm. was collected and weighed 122 gm. (49% yield).

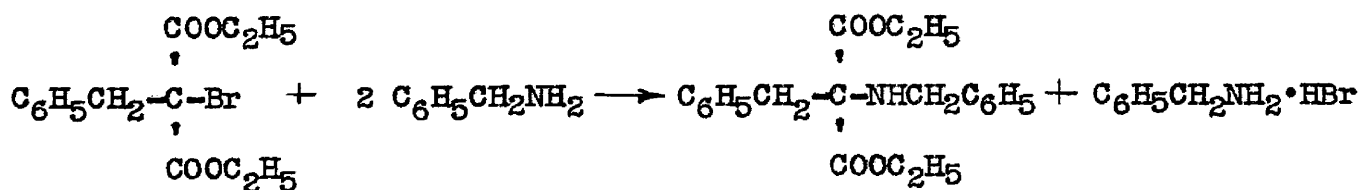
Bromination of diethyl benzylmalonate



Into a 500-cc. three-necked flask equipped with a mechanical stirrer, a dropping funnel and a reflux condenser, was placed 62.5 gm. (0.25 moles) of diethyl benzylmalonate, 20 gm. of pyridine (0.25 mole) in 75 cc. of carbon tetrachloride. To this solution, with stirring and occasional cooling, was added 13.8 cc. of bromine (0.26 mole). As the bromination proceeded the temperature rose slightly and an orange precipitate of pyridine hydrobromide resulted. After all of the bromine had been added this precipitate was removed by filtration. After drying the weight was 40 gm. (theoretical yield).

The filtrate was washed four times with 25 cc.-portions of a 5% sodium carbonate solution, and dried over anhydrous sodium sulfate. The carbon tetrachloride was removed by reduced pressure distillation. The remaining oil was washed with dilute hydrochloric acid until free of any traces of pyridine, and then several times with water, and again dried over anhydrous sodium sulfate. The final oily product weighed 52.3 gm. (50% of the theoretical).

Reaction of diethyl benzyl- α -bromomalonate with benzylamine

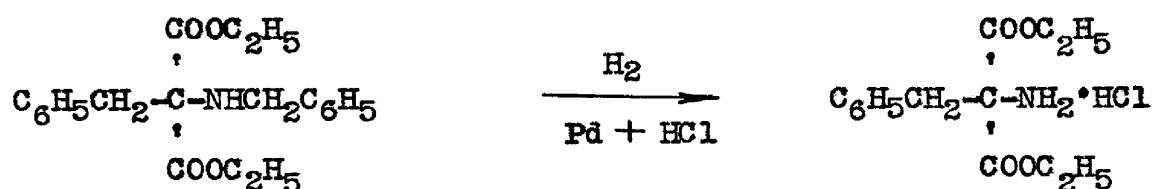


Into a 500 cc., three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a hot-water bath, was placed 16.4 gm. (0.05 mole) of the oil obtained above (presumably diethyl benzyl- α -bromomalonate), 10.7 gm. (0.1 mole) of benzylamine, and 75 cc. of absolute ethanol. The solution was refluxed for six or seven hours. White crystals of benzylamine hydrobromide separated out of solution and were filtered off. The alcohol was removed from the filtrate under reduced

pressure and ether was added to the cooled residue. There was further precipitation of the white crystals, the all-over yield of which was 6 gm., m. 204° (136).

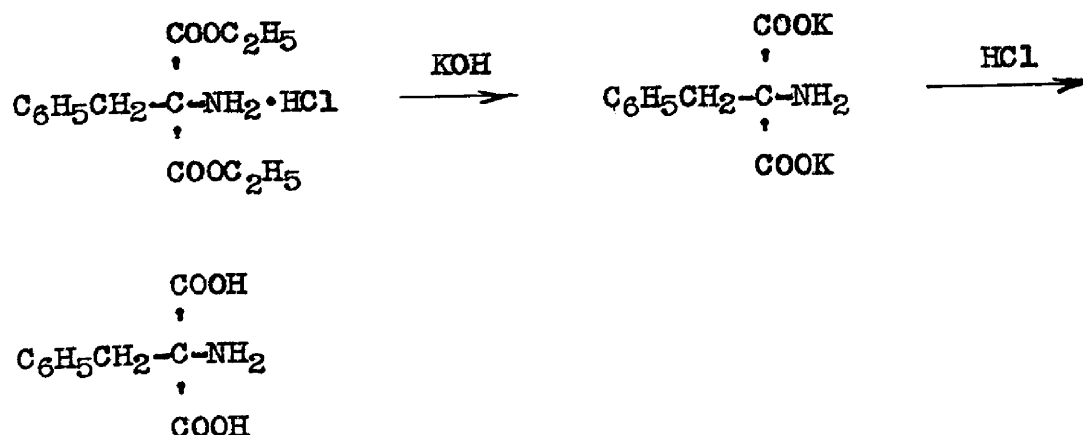
The ethereal solution was washed with water, dried over anhydrous sodium sulfate, and the ether removed. The oily residue could not be crystallized from the usual organic solvents. At the temperature of a carbon-dioxide-acetone bath, crystals formed, but melted before reaching room temperature. The oil weighed 13 gm. (73% theory).

Hydrogenation of diethyl benzyl-benzylaminomalonate



Thirty-five and one-half gm. (0.1 mole) of diethyl benzyl-benzylaminomalonate was hydrogenated in the usual way using a palladium catalyst in absolute ethanol. Treatment of the reduction product in the ordinary manner yielded 7.5 gm. (31% yield, calculated as diethyl benzylaminomalonate) of white crystals, m. 179°.

Saponification of diethyl benzyl-aminomalonate



Saponification of the compound obtained above was carried out as follows: Into a 500-cc. three-necked flask equipped with a mechanical stirrer and a reflux condenser, was placed 6 gm. (0.025 mole) of diethyl benzyl-aminomalonate in 75 cc. of absolute ethanol. The solution was stirred and 2.8 gm. (0.05 mole) of solid potassium hydroxide was added. As the alkali dissolved, a pale yellow solid, presumably the monopotassium salt, precipitated. This dissolved in the solvent as the reaction proceeded, and the reaction mixture was refluxed with stirring for about three hours. At the end of this time, the condenser was placed in a downward position, and the alcohol was removed by distillation, water being added periodically to prevent the mass from solidifying. The contents of the flask were then cooled in an ice bath, and with stirring, concentrated hydrochloric acid was added until the reaction mixture was acid to Congo red paper, and then an additional 10 cc. of acid was added. The white solid which formed was recrystallized from 95 per cent ethanol, weighed 2 gm., m. 255° .

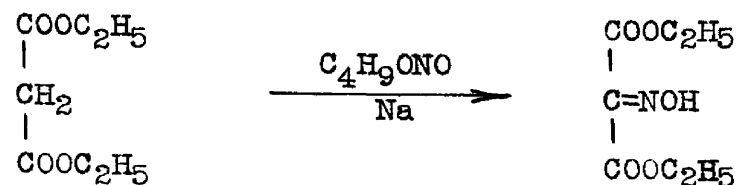
Mixed m. with phenylalanine	205°
Benzoyl derivative	m. 100°

Nitrogen

found (Kjehldahl)	calculated for $C_{10}H_{11}O_4N$
7.20	6.7
7.25	calculated for $C_9H_{11}O_2N$
	(Phenylalanine)
	8.5

Preparation of isonitrosomalonic ester

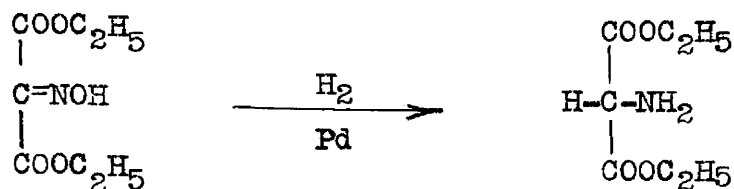
Isonitrosomalonic ester was prepared as directed by Barry (137).



In a liter three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel was placed 300 cc. of absolute ethanol. Twenty-three gm. (one gm. atom) of clean sodium was dissolved in the alcohol, followed by 166 gm. (one mole) of ethyl malonate. After the flask had been immersed in a cold water bath, 116 gm. of n-butyl nitrite, previously dried over anhydrous sodium sulfate, was slowly added with effective stirring, causing the white precipitate of sodio-malonic ester to dissolve with the formation of a thick, clear, orange-yellow colored solution. The ethanol and butanol were removed under reduced pressure, and the residue was treated with 300 gm. of crushed ice and 200 cc. of 6N sulfuric acid (15% by weight); the isonitrosomalonic ester separated as a reddish-yellow oil. This was extracted with ether and the ether extract was washed with a saturated solution of sodium bicarbonate, dried over anhydrous sodium sulfate and the ether distilled. The fraction distilling at 145-155°/10 mm. was collected, weight 60 gm. (34% theory). At lower pressures the yield is reportedly higher, but such conditions were not available during the present investigation.

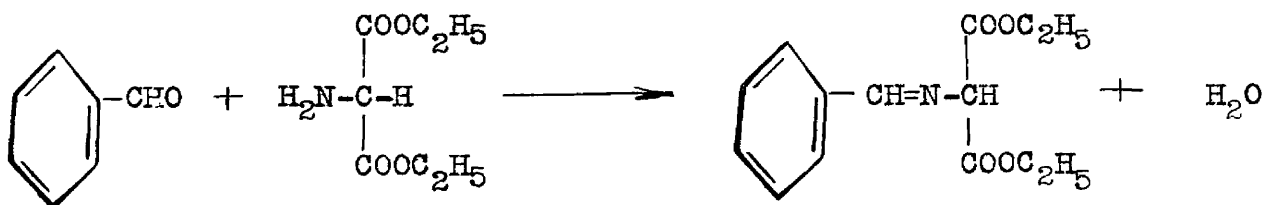
Hydrogenation of diethyl isonitrosomalonate

The hydrogenation of diethyl isonitrosomalonate to diethyl aminomalonate was carried out according to the direction of Barry (137).



Twenty gm. (0.1 mole) of isonitrosomalonic ester were dissolved in 125 cc. of absolute ethanol, and hydrogenated under 115 lbs. pressure, using the palladium catalyst. After nine hours, the theoretical quantity of hydrogen (65 lbs.) had reacted. The reaction mixture was filtered to remove the catalyst, and the filtrate was allowed to evaporate in a vacuum desiccator over sulfuric acid. The pale yellow oil, diethyl aminomalonate, remaining was distilled, and the fraction boiling at 100-110°/6 mm. was collected; weight, 8 gm. (50% theory).

Preparation of diethyl benzalaminomalonate



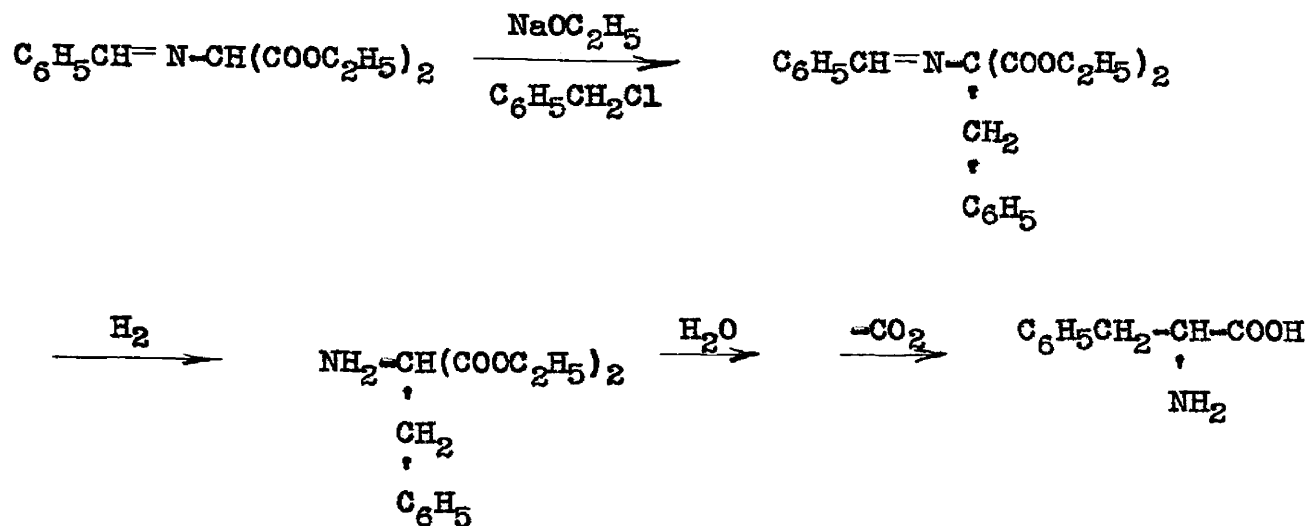
Into a small separatory funnel was placed 8 gm. (0.045 mole) of diethyl aminomalonate, 4.7 gm. (0.045 mole) of benzaldehyde and 10 cc. of benzene, the mixture was well-shaken and allowed to stand overnight. The liquid became very cloudy, and a portion of the water formed in the reaction had separated. The addition of a small amount of anhydrous sodium sulfate removed the remainder of the water, and the benzene layer became clear. The benzene was distilled, leaving a yellow oil, presumed to be the Schiff base.

An attempt was made to prepare the hydrochloride, as a means of

purification and identification, but all the usual methods of preparation lead to a gelatinous mass which could be neither filtered, nor dried, nor treated in any way to yield a sample satisfactory for analysis.

Preparation of diethyl benzyl-benzalaminomalonate and its hydrogenation

The following reactions were tried:



The results, although not conclusive, are encouraging.

In a 250 cc. round-bottom three-necked flask fitted with a reflux condenser, a mechanical stirrer, and a separatory funnel, was dissolved 1 gm. (0.05 mole) of clean sodium in 75 cc. of absolute ethanol, and 13 gm. (0.05 mole) of diethyl benzalaminomalonate was added. This mixture was heated on an oil bath to gentle refluxing, with stirring, and 6 gm. (0.047 mole) of benzyl chloride was slowly added through the separatory funnel. Refluxing and stirring were continued until the reaction mixture was no longer alkaline. The salt which was precipitated during the course of the reaction was in the colloidal state, and could not be removed by filtration. The reaction mixture was concentrated on a water-bath until all of the alcohol was evaporated. Water was then added to dissolve the salt, and the orange oil which was thrown out of solution

by the water was extracted with ether. The ethereal solution was dried over calcium chloride, and the ether removed by distillation. The orange oil remaining weighed 7 gm.

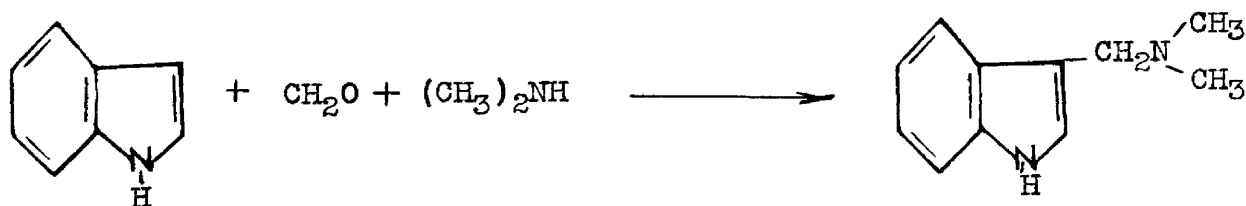
A hydrogenation in the usual manner with 3.5 gm. (0.01 mole) of this oil (previously shaken with Nuchar to remove any catalytic poisons which might be present) was carried out. Only 81 per cent of the theoretical quantity of hydrogen reacted, indicating that this percentage was the purity of the ester being reduced. The solvent was removed under reduced pressure, leaving a brownish-orange oil as the product.

No attempt at purification of this oil was made, but it was saponified immediately. The oil was refluxed with dilute hydrochloric acid for three hours, any unreacted oil being removed by filtration at the end of this time. The filtrate, while hot, was treated with 28 per cent ammonium hydroxide until the solution was yellow to methyl red. A greenish-white solid precipitated. A volume of alcohol equal to three times that of the acidic mixture was added, and the flask cooled. The solid was removed and recrystallized from 65 per cent ethanol.

The N-benzoyl derivative melted at 120° , and there was an insufficient quantity for analysis. The reported m. of this compound, N-benzoyl phenylalanine, is 188° (118).

Preparation of gramine

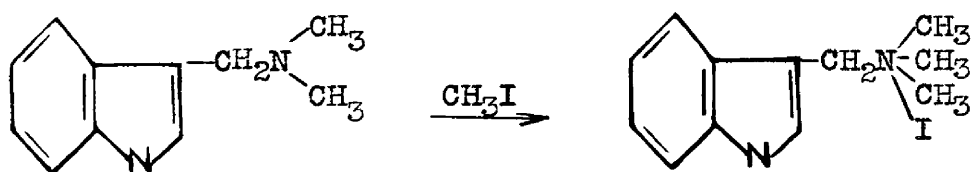
Following the directions given by Snyder et al (108), gramine was prepared as described below.



To 235 cc. of a 23% solution of dimethylamine (equivalent to 1.05 moles), at 5°, was added 140 gm. (2.33 moles) of glacial acetic acid. The mixture was cooled to 5°, and 80 gm. of 40% formalin (equivalent to 1.0 mole of formaldehyde), at 5°, was added. The mixture was agitated mildly and poured into a flask containing 117.2 gm. (1.0 mole) of indole. The flask was shaken occasionally until the indole had dissolved. The temperature of the mixture rose to 56° during this period. After standing overnight, the mixture was then added slowly to a stirred solution of 140 gm. (3.5 moles) of sodium hydroxide in one liter of water. The resulting suspension was cooled in an ice-bath for two hours. The gramine was collected by filtration, pressed dry, washed with three 100-cc. portions of water, and dried in an oven at 65° to constant weight. A theoretical yield of 174 gm. was obtained, m. 127-128°.

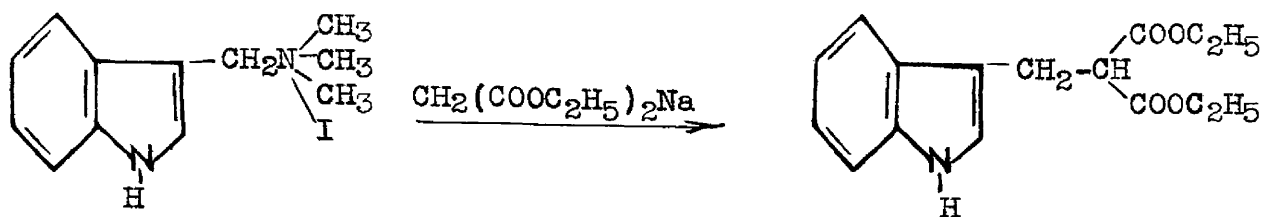
Preparation of gramine methiodide

Gramine methiodide was obtained in the manner described by Snyder et al (108).



To a solution of 43.5 (0.25 mole) of gramine in 188 cc. of absolute ethanol were added 39 gm. of methyl iodide over a period of about one-half hour. The mixture was allowed to stand at room temperature overnight and then at 0° overnight. The product was collected by filtration and washed with three 25 cc.-portions of absolute ethanol, and three 25 cc.-portions of dry ether. The dried product weighed 62 gm. (78% theory).

Preparation of ethyl α -carbethoxy- β -(3-indole)-propionate



The sodium derivative of malonic ester was prepared by stirring for thirty hours a mixture of 2.3 gm. (0.1 mole) of powdered sodium, 120 cc. of toluene and 40 gm. (0.25 moles) of diethyl malonate. To the resulting paste was added 35 gm. (0.11 mole) of gramine methiodide. This mixture was heated, with stirring, for two hours with the oil-bath at 110°, and for four hours with the oil-bath at 145°. The cooled mixture was stirred with three 100 cc.-portions of water. The combined aqueous washings were extracted with three 100 cc.-portions of ether and the ether extracts were added to the organic layer from the first extraction. The solution was dried, and the solvents and excess malonic ester were removed by distillation, first from a steam bath and finally at 5 mm. pressure. The residual red liquid was poured slowly into 150 cc. of petroleum ether with cooling and stirring. The solid which soon formed was collected and after drying, weighed 16 gm. m. 58°, which agreed with the results obtained by Snyder et al (108).

Reaction between gramine and diethyl benzalaminomalonate

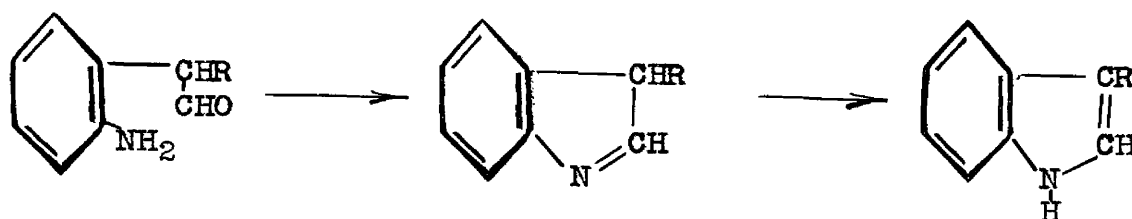
An alkylation of diethyl benzalaminomalonate with gramine was attempted following the procedure employed by Howe and coworkers (112) with an alkylamidomalonic ester.

To a boiling solution of 84 cc. of xylene and 0.6 gm. of powdered sodium hydroxide, in a 500-cc. three-necked flask fitted with a mechanical stirrer and a reflux condenser, was added 4.3 gm. (0.025 mole) of gramine and 6.5 gm. (0.025 mole) of diethyl benzalaminomalonate, and the mixture was stirred and refluxed for five hours.

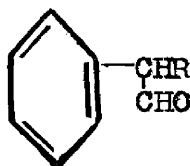
The reaction mixture was then filtered through a preheated funnel, and the filtrate was allowed to cool to room temperature and then was kept in the ice box overnight. Pale yellow crystals formed, which on recrystallization melted at 127° , and gave no depression of the melting point when mixed with known gramine.

SUMMARY

1. A review covering the natural occurrence and the laboratory syntheses of indole is presented.
2. An investigation was initiated to determine the feasibility of preparing indole and its derivatives according to the following proposed general reaction:

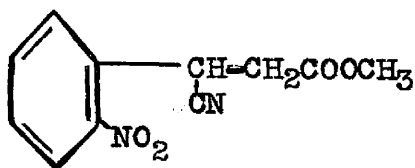


It is not difficult to prepare compounds of type



for both benzyl cyanide and α -methylbenzyl cyanide may be hydrogenated to the imino stage and readily converted into the corresponding aldehydes, $C_6H_5CH_2CHO$ and $C_6H_5CH(CH_3)CHO$, respectively. Other benzyl cyanide derivatives may be readily prepared, and it is expected that they may be converted with equal ease into the corresponding aldehydes. However, the introduction of an amino group into the o-position of these compounds presents a difficulty which has not yet been solved. The nitration of benzyl cyanide, benzyl chloride or benzaldehyde yields little or none of the desired o-nitro derivatives to serve as desirable intermediates.

3. The condensation of potassium isocyanide with α, β -ethylenic compounds, according to the procedure of Michael, was studied to determine its applicability to methyl cinnamate and to methyl *o*-nitrocinnamate; the latter reaction would be expected to yield



It is regrettable that apparently this condensation is more limited in scope than was anticipated.

4. A study was made of reactions which depend, in effect, on the alkylation of aminomalonic ester for the synthesis of intermediates from which amino acids may be readily obtained. It was hoped to protect the amino group, during the alkylation, by

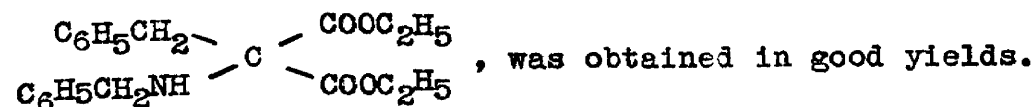
(a) dibenzyl

(b) benzal

Unfortunately the dibenzylaminomalonic ester, $(C_6H_5CH_2)_2NCH(COOC_2H_5)_2$, was not obtained when dibenzylamine was allowed to react with bromomalonic ester.

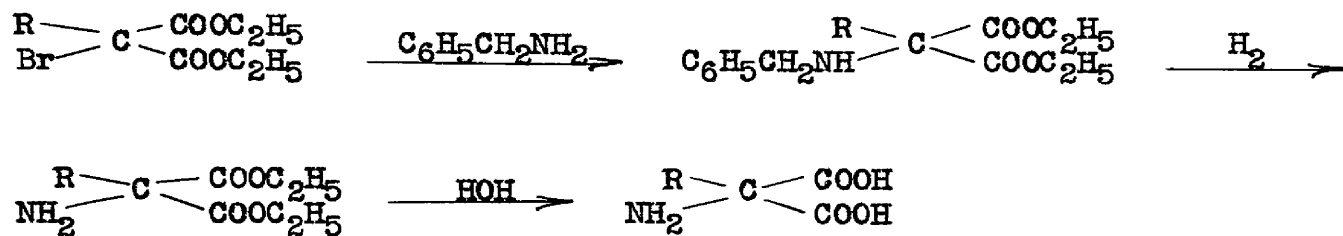
Experiments in which the alkylation of benzalaminomalonic ester, $C_6H_5CH=N-CH(COOC_2H_5)_2$, was tried were inconclusive; the indications, however, are encouraging and the reaction merits further investigation.

5. A study was initiated into the synthesis of α -amino- α -alkylmalonic acids. Benzyl bromomalonic ester, $C_6H_5CH_2-CH(Br)-COOC_2H_5$, was treated with benzylamine; α -benzyl- α -benzylaminomalonic ester,



Hydrogenolysis of the N-benzyl group yielded α -benzyl- α -aminomalonic

ester, from which the corresponding acid, $\begin{matrix} \text{C}_6\text{H}_5\text{CH}_2 \\ \text{NH}_2 \end{matrix} \text{C} \begin{matrix} \text{COOH} \\ \text{COOH} \end{matrix}$, was obtained by saponification. These results suggest that the reaction



may be broadly useful in making available an extended series of α -alkyl- α -aminomalonic acids.

In view of the fact that acids of this type, $\begin{matrix} \text{R} \\ \text{NH}_2 \end{matrix} \text{C} \begin{matrix} \text{COOH} \\ \text{COOH} \end{matrix}$, differ sterically from the L-amino acids found naturally only by having a labile carboxyl group in the α -position, they should prove of considerable interest to the chemist interested in physiological processes and nutrition.

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